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RESPIRATORY INFECTIONS

Management of Australian Adults with Bronchiectasis in Tertiary Care: Evidence-Based or Access-Driven?

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Abstract

Purpose Australian data regarding the management of patients with bronchiectasis is scarce. We sought to compare the management of adults with bronchiectasis attending tertiary Australian centres with recent national and international guidelines.

Methods The Australian Bronchiectasis Registry is a centralised database of patients with radiologically confirmed bronchiectasis unrelated to cystic fibrosis recruited from 14 tertiary Australian hospitals. We excluded children (<18 years) and those with incomplete data, leaving 589 adults for cross-sectional analyses. We compared the proportion of patients receiving certain therapies, as compared to the proportion eligible for those treatments according to the current guidelines and baseline clinical information available from the registry.

Results Pulmonary rehabilitation was attended by 22%, although it was indicated in 67% of the cohort. Airway clearance was undertaken in 52% of patients, although 71% reported chronic productive cough. Sputum bacterial culture results were available for 59%, and mycobacterial culture results were available for 29% of the cohort. Inhaled antibiotics were used in half of potentially eligible patients. Despite guideline recommendations against routine use, inhaled corticosteroids were used in 48% of patients. Long-term macrolides were used in 28% of participants.

Conclusions Discrepancies exist between guideline recommendations and real-world treatment of bronchiectasis in Australia, even in tertiary centres. These findings suggest the need for increased patient referral to pulmonary rehabilitation, increased attention to airway clearance, increased collection of sputum samples (especially for mycobacterial culture) and rationalisation of inhaled corticosteroid use. These findings encourage a review of treatment access and will inform ongoing education to promote evidence-based care for people living with bronchiectasis.

Keywords Bronchiectasis · Treatment · Guidelines · Registry · Australia

Introduction

Bronchiectasis is gaining recognition as an important chronic lung disease of increasing prevalence with a high burden of symptoms and health care utilisation [1-5]. Chronic productive cough is the clinical hallmark of bronchiectasis, however disease aetiology is diverse and patients are markedly heterogeneous in terms of symptom burden and disease severity [6].

Once considered to be an "orphan disease", bronchiectasis was largely ignored in research [7, 8]. Treatment strategies have been extrapolated, often empirically, from other airways diseases such as asthma and chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF)—a distinct monogenetic and well-defined subcategory of bronchiectasis [8, 9]. Such empiric extrapolation may be misguided; when randomised controlled trials of therapies efficacious in CF have been performed in bronchiectasis patients, these have often been poorly tolerated [10, 11] or overtly deleterious [12].

Against this historical background, there has been a recent upsurge in bronchiectasis research activity and clinical trials, with variable results [8]. The evidence for prophylactic macrolide antibiotics to reduce exacerbations in patients with bronchiectasis and frequent exacerbations is now robust [13-17]. In contrast, recent large trials of inhaled

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antibiotics [18-21] and mucolytics [22] did not meet their primary endpoints, despite statistically and clinically significant improvement in certain subgroups. This has led experts to advocate for clinical phenotyping of patients with bronchiectasis to enable personalised treatment, and to minimise the effects of disease heterogeneity in clinical trials by targeting certain phenotypes most likely to benefit [8].

The recent publication of updated national [23-25] and inaugural international bronchiectasis management guidelines [26] shows the momentum towards an evidence base, which still remains limited for some recommendations. Nevertheless, these guidelines serve as syntheses of the available literature and important tools to guide management decisions. Unfortunately, access to guideline-recommended medications is limited even at tertiary bronchiectasis centres, as no regulatory authority worldwide has licensed any therapy specifically for bronchiectasis. By contrast, many medications for asthma and COPD are readily available with a prescription in Australian pharmacies and are subsidised by the Australian government.

The Australian Bronchiectasis Registry (ABR) was established in 2015. In addition to demographics, baseline characteristics and eventually longitudinal outcomes, the ABR provides the opportunity to study treatment patterns. The aim of this study was to assess whether management of adult bronchiectasis patients at Australian tertiary centres conforms to current management guidelines.

Methods

The ABR is a multicentre prospective observational registry of patients with radiologically confirmed bronchiectasis—abnormal bronchial dilatation on computed tomography chest (CT-chest) scan—that is not due to CF. The registry has national ethical approval (Protocol No X16-0382, Project no HREC/15/CRGH/225). ABR recruitment began in March 2016. Patients were recruited from 14 sites across the Australian mainland which are predominantly large metropolitan centres with expertise in bronchiectasis management.

At enrolment, participants' baseline data were collected by hand-searching all available hospital and outpatient records, including electronic medical records. Data collected included demographics as well as symptoms and spirometry when clinically stable, history of exacerbations and usual treatments in the baseline period of up to one year prior to enrolment. The most recent CT-chest report was collected. The results of any prior airway cultures and aetiological laboratory tests were recorded. Any previous records pertaining to pulmonary rehabilitation were gathered; fields collected were: attended, not referred, patient refused, patient failed to attend, and patient not fit due to comorbidities.

Baseline registry data were exported in August 2018 for analysis. To allow focus on the treatment of adult patients and comparison with adult treatment guidelines, children (<18 years) were excluded from this analysis, as were the patients with incomplete data (defined as the absence of CT-chest scan details and spirometry).

Descriptive statistics were used to characterise the demographics and disease features of the cohort. Data were not normally distributed and thus results are presented as median and interquartile range (IQR). Cross-sectional analysis of baseline data was performed to assess the proportion of patients receiving certain respiratory treatments and was compared to the proportion of the cohort in which the treatment was indicated, according to the most current Australian and international (European) guidelines [23, 26] and the patients' baseline clinical information available from the ABR. Data were analysed in StataSE Version 15.1.621.

Results

The cohort for analysis comprised 589 adults, predominantly recruited from six tertiary sites across the states of New South Wales (303 patients) and Queensland (272 patients), which represent the major bronchiectasis centres in Eastern Australia. Key demographic and clinical findings are summarised in Table 1. The cohort were predominantly Caucasian (86%) females (71%) with a median age of 71 years, interquartile range (IQR) 64–77. Most patients (78%) had never smoked cigarettes. Disease aetiology was predominantly idiopathic (32.5%) or post-infective (28%). COPD was listed as the aetiology of bronchiectasis in 3.5%, and asthma was listed as the aetiology of disease in 3.5%. Most patients (84%) had moderate or severe bronchiectasis according to the Bronchiectasis Severity Index which is a validated disease-specific composite severity score predictive of mortality and morbidity [27]. Almost one third (29%) of patients had a respiratory-related hospitalisation in the year preceding enrolment. Nearly one-quarter (23%) displayed the frequent exacerbator trait defined as three or more exacerbations in the year preceding enrolment.

Table 2 summarises the Australian and European bronchiectasis management guideline recommendations and compares the proportion of Australian adult patients receiving treatments with the proportion who were eligible for those treatments as per the guidelines.

Pulmonary rehabilitation was attended by 22% of participants, despite 67% being likely to benefit based on a reduced exercise tolerance (modified Medical Research Council dyspnoea score of > 0). The most common reason for non-attendance was recorded as a lack of referral in 73% of patients.

Table 1 Australian adult bronchiectasis cohort—baseline demographic and clinical characteristics

	Results Med (IQR) or n (%)	Data available n
Age (years)	71 (64–77)	589
Female	420 (71%)	589
Never smoked cigarettes	451 (78%)	581
Symptoms		
Limited effort tolerance[a]	393 (69%)	570
Daily cough with sputum	416 (71%)	589
Spirometry		499
FEV_1%pred	75 (57–91)	
FVC %pred	84 (71–97)	
Airflow obstruction[b]	168 (34%)	
Radiology		563
Number of affected lobes	3 (2–5)	
Presence of cystic dilatation	81 (14%)	
Microbiology		
Bacterial cultures		345
P. aeruginosa (ever)	119 (35%)	
P. aeruginosa (chronic)[c]	49 (14%)	
H. influenzae (ever)	60 (17%)	
H. influenzae (chronic)	15 (4%)	
Mycobacterial cultures		169
NTM (ever)	40 (24%)	
NTM (chronic)	15 (9%)	
Exacerbations in the last year		
Total exacerbations	1 (0–2)	557
Respiratory hospitalisation	166 (29%)	580
≥3 exacerbations	128 (23%)	580
Multidimensional disease severity		290
Mild (BSI score 0–4)	46 (16%)	
Moderate (BSI score 5–8)	76 (26%)	
Severe (BSI score ≥9)	168 (58%)	

n number of participants for whom data are available, *FEV_1* Forced Expiratory Volumes in 1 s as percent of predicted (GLI-2012), *FVC* forced vital capacity, *LLN* lower limit of normal (GLI-2012), *NTM* non-tuberculous mycobacteria, *BSI* Bronchiectasis Severity Index

[a]modified Medical Research Council dyspnoea scale score > 0

[b]Airflow obstruction—FEV_1/FVC < LLN (GLI-2012)

[c]defined as ≥2 airway cultures positive for the same pathogen in the two years prior to and three months after enrolment

Regular airway clearance was documented in 52% of patients and was indicated in 71% on the basis of daily cough with sputum production. In those performing regular airway clearance, the most common methods were active cycle of breathing technique and/or a clearance device. More than one technique was used in 25% of patients. Regular exercise was used as the sole clearance technique in 14% of patients.

Long-term oral antibiotics for exacerbation prophylaxis were used in 35% of the cohort and were indicated in 26% on the basis of ≥3 pulmonary exacerbations or ≥2 respiratory-related hospitalisations in the year preceding enrolment. Macrolides accounted for 81% of prophylactic antibiotics used. Long-term inhaled antibiotics were used in 4% of patients, whereas they were indicated in 8% of patients on the basis of chronic *P. aeruginosa* (defined as ≥2 cultures positive for *P. aeruginosa* within the two years prior to and three months after enrolment).

Within the cohort, 48% were using inhaled corticosteroids (ICS). Of those receiving ICS, use was indicated in only 57% on the basis of physician-reported asthma or severe COPD (FEV_1 < 50% of predicted) with ≥2 exacerbations in the preceding year (Table 3). Inhaled bronchodilators were used in 59% of the cohort of whom 67% met the indications for bronchodilator treatment on the basis of asthma, COPD, or use of inhaled mucolytics or antibiotics (Table 4).

Discussion

We report the largest multicentre Australian study of bronchiectasis management, using data from the ABR. This study demonstrates that guideline-recommended treatments are underutilised in patients attending Australian tertiary bronchiectasis centres, whereas more easily accessible therapies such as ICS and bronchodilators are likely overused, despite a limited evidence base in bronchiectasis. These findings highlight an opportunity to improve the evidence-based management of patients with bronchiectasis in Australia and the need for further large trials of therapies which are used widely but without high-level evidence.

Pulmonary rehabilitation is strongly recommended for those with impaired exercise capacity in all current guidelines, and is supported by high quality evidence [23-26]. Pulmonary rehabilitation is safe, improves exercise capacity and quality of life [28, 29], may reduce exacerbations [30] and is valued by patients with bronchiectasis [26]. A recent study has demonstrated that compared to patients with COPD, those with bronchiectasis have similar completion rates and derive a similar magnitude of benefit from pulmonary rehabilitation [31]. However, less than one-quarter of the ABR cohort had attended pulmonary rehabilitation, despite the majority experiencing a reduced exercise tolerance. The predominant reason for non-attendance was recorded as a lack of referral. These findings are similar to those reported from the European Bronchiectasis Registry where variability in referral and access were key barriers [32].

Additionally, only half of the ABR cohort undertook regular airway clearance, despite most having a daily productive cough. Airway clearance remains a crucial component of bronchiectasis management and is strongly recommended

Table 2 Management in the Australian adult bronchiectasis cohort compared with treatment guidelines (n = 589)

	Patients treated *n* (%)	Patients eligible *n* (%)	Guideline recommendation
Pulmonary rehabilitation	131 (22)	393 (67)[a]	Strong recommendation if exercise tolerance impaired [23, 26]
Regular airway clearance	306 (52)	416 (71)[b]	Strong [23] or conditional [26] recommendation for those with chronic productive cough or difficulty with sputum expectoration
Active cycle of breathing	224 (38)		
Clearance device	212 (36)		
Exercise for clearance	147 (25)		
Postural drainage	71 (12)		
Percussion	22 (4)		
Autogenic drainage	4 (1)		
Inhaled mucolytics	104 (18)	–	Weak recommendation if difficulty expectorating sputum despite optimal airway clearance [23, 26]
Hypertonic saline	83 (14)		
Isotonic saline	21 (4)		
Mannitol	1 (<1)		
Long-term oral antibiotic	206 (35)	153 (26)[c]	Conditional [23, 26] recommendation for macrolides in patients with frequent and/or severe exacerbations
Macrolide	166 (28)		
Azithromycin	80 (14)		
Erythromycin	51 (9)		
Clarithromycin	18 (3)		
Roxithromycin	17 (3)		
Tetracycline	22 (4)		
Other antibiotic class	18 (3)		
Long-term inhaled antibiotic	24 (4)	49 (8)[d]	Strong [23] or conditional [26] recommendation if frequent exacerbations and/or chronic *P. aeruginosa*
Colistin	11 (2)		
Aminoglycoside	6 (1)		
Other inhaled antibiotic	7 (1)		
Inhaled corticosteroid	283 (48)	202 (34)[e]	Strong [23] or conditional [26] recommendation **against** routine use of ICS and bronchodilators, unless indicated for COPD or asthma. SABA recommended prior to other inhaled therapies [26]
Inhaled bronchodilators	347 (59)	280 (48)	
Long-acting β-agonist	292 (50)	216 (37)	
Short-acting β-agonist	221 (38)	280 (48)	
Muscarinic antagonist	87 (15)	216 (37)	

ICS inhaled corticosteroid, *SABA* Short-acting β-agonist

[a]Modified Medical Research Dyspnoea Scale score of > 0

[b]daily sputum expectoration; – unable to ascertain due to limitations of registry data

[c] ≥ 3 exacerbations or ≥ 2 respiratory-related hospitalisations in the preceding year [23]

[d]conservative estimate based on chronic *P. aeruginosa* (≥2 positive cultures)

[e]patients with physician-reported 'Asthma' or those with severe COPD and ≥ 2 exacerbations per year

Table 3 Appropriateness of inhaled corticosteroid (ICS) use in the Australian adult bronchiectasis cohort (n = 589)

	ICS indicated[a]		Total (*n* %)
ICS use	No (%)	Yes (%)	
No	263 (86)	43 (14)	306 (52)
Yes	*123 (43)*	160 (57)	283 (48)

Italicised cell indicates likely inappropriate use of ICS

ICS Inhaled corticosteroid

[a]Patients with asthma (physician-reported) or those with severe COPD and ≥ 2 exacerbations per year

by the current guidelines [23, 24] as it is safe, inexpensive and improves sputum expectoration and quality of life [33]. These findings highlight the opportunity for clinicians to encourage adherence with airway clearance and to refer regularly to respiratory physiotherapists and pulmonary rehabilitation. They also serve as a prompt to investigate barriers to patient participation in pulmonary rehabilitation and airway clearance, including access to services and equity of access when compared to cystic fibrosis-related bronchiectasis.

A further area of discrepancy between guidelines and practice appears to be the use of inhaled antibiotics in patients with chronic *P.aeruginosa,* as only half of suitable

Table 4 Appropriateness of inhaled bronchodilator use in the Australian adult bronchiectasis cohort ($n = 589$)

Bronchodilator use	Bronchodilators indicated[a]		Total (*n* %)
	No (%)	Yes (%)	
No	195 (81)	47 (19)	242 (41)
Yes	*114 (33)*	233 (67)	347 (59)

Indications for bronchodilators include asthma (physician-reported), COPD, or prior to use of inhaled mucolytics or antibiotics

Italicised cell indicates likely inappropriate use of inhaled bronchodilator

[a]Includes inhaled long and short-acting β-agonists and muscarinic antagonists

patients received treatment. Chronic *P. aeruginosa* infection is associated with increased mortality, hospitalisations, exacerbations and poorer quality of life in patients with bronchiectasis [34, 35]. Inhaled antibiotics reduce bacterial load [36-38] and bronchial inflammation [39] and, therefore, may ameliorate the cycle that contributes to bronchiectasis pathogenesis and progression. Meta-analyses of smaller trials showed reduced exacerbation frequency [36, 37], and recent larger phase 3 trials found trends towards reduced exacerbations, although the findings were not statistically significant [18-20]. Guidelines recommend inhaled antibiotics for patients with frequent exacerbations and/or chronic *P. aeruginosa* [23-26]. Accurately determining what proportion of the study cohort were chronically colonised by *P. aeruginosa* is hindered by suboptimal rates of sputum collection; however, based on a conservative estimate (two or more isolations of *P. aeruginosa* in respiratory tract specimens*)* only half of eligible patients were receiving inhaled antibiotics.

This discrepancy is not surprising given that access to inhaled antibiotics for bronchiectasis is extremely limited. Even at tertiary centres, access requires an application to the hospital's drug committee and hospital-based funding, which may discourage their prescription. Use of inhaled antibiotics is also challenging due to adverse reactions, particularly bronchospasm which can occur in 10–30% of patients using inhaled aminoglycosides [20, 37, 40]. Nebuliser education and a supervised test dose can also be practically difficult in the clinic. Additionally, concerns exist regarding antibiotic resistance following trials which showed an increase in minimum inhibitory concentration of *P. aeruginosa* isolates after inhaled antibiotic use [11, 18-20]. Nevertheless, inhaled antibiotics appear to be underused in the ABR cohort. This finding requires reflection in view of the clear negative prognostic implications of chronic *P. aeruginosa* infection and frequent exacerbations in bronchiectasis [34, 35, 41].

Rates of respiratory specimen culture were suboptimal in the ABR cohort. Standard bacterial culture results were available in 59% of the cohort, and mycobacterial culture results were available in only 29% of participants. Surveillance sputum cultures should be performed at least once in the year in patients with bronchiectasis [25]. This allows subsequent exacerbations to be treated with prompt and appropriate pathogen-directed treatment, and allows new *P. aeruginosa* infection to be detected and possibly eradicated. Furthermore, patients with chronic *P. aeruginosa* airway infection who are at higher risk of bronchiectasis complications can be identified, monitored closely and given additional treatment (for example, inhaled antibiotics) [23-26]. Mycobacterial cultures are recommended at the time of diagnosis, prior to long-term macrolide therapy, and with deterioration [25]. Nontuberculous mycobacteria (NTM) are increasingly prevalent in patients with bronchiectasis, and have the potential to cause progressive inflammatory lung disease that is amenable to treatment [42]. Furthermore, *M. abscessus* has the potential for person-to-person transmission and is a contraindication to lung transplant in many centres, necessitating strict infection control procedures [42]. Therefore, as detection of certain organisms (particularly *P. aeruginosa* and NTM) affects future diagnostic, management and infection control decisions, increased sputum collection for bacterial and mycobacterial surveillance cultures is clearly necessary.

ICS are widely available as government-subsidised medications, however they are not routinely recommended in patients with bronchiectasis unless concomitant asthma or COPD is present [23, 26]. Nevertheless, half of ABR participants were using ICS and within this group use was indicated in only 57%, on the basis of physician-reported "asthma" or COPD with severe airflow obstruction and frequent exacerbations [43]. Although ICS are easily accessible, there is insufficient evidence of benefit [44] in patients with bronchiectasis and the potential for harm through increased risk of pneumonia and mycobacterial infection [45, 46]. Bronchodilators are similarly recommended for patients with concomitant asthma, COPD, and/or those on inhaled mucolytics or antibiotics [23, 26]. In our cohort, bronchodilators were used in 59%, but were only indicated in two-thirds of those on treatment. Our findings suggest overuse of ICS and bronchodilators in patients with bronchiectasis. They focus attention on the challenge of diagnosing and managing airways diseases which can coexist and which frequently have overlapping clinical presentations [45], and may suggest clinician reluctance to de-escalate treatment. These findings lend weight to the argument for a holistic treatable traits approach and rationalisation of ICS and bronchodilator use in the bronchiectasis population, whilst highlighting the need for large studies of these therapies in patients with bronchiectasis.

This study has a number of limitations. Due to the exclusion of patients with incomplete data, this paper largely represents non-indigenous patients attending tertiary bronchiectasis centres on the east coast of Australia. The registry does not collect information regarding drug intolerances or contraindications to therapies. The physician diagnosis of 'asthma' as collected by the registry does not require evidence of variable airflow limitation [47]; therefore the proportion of patients with asthma and hence those using ICS appropriately may be *overestimated*. Similarly, due to the suboptimal collection of respiratory specimens for microbiology, it is likely that the proportion of patients with *P. aeruginosa* (particularly chronic *P. aeruginosa*) was underestimated, and the gap between treatment eligibility and use may be wider than that observed. Finally, this analysis was cross-sectional in nature. In the future, the ABR aims to improve data completeness, expand recruitment to a broader range of sites, communities and health providers and collect longitudinal data. Despite the limitations, existing registry data from tertiary centres provide clear and important messages relevant to the primary, secondary and tertiary care of patients with bronchiectasis in Australia.

In conclusion, while adult participants from the ABR are patients with a high severity of disease and symptom burden managed by tertiary bronchiectasis centres, there are obvious gaps between guideline recommendations and practice. This study highlights the need for increased patient referral and participation in pulmonary rehabilitation, which is supported by high-level evidence of benefit in patients with bronchiectasis. Barriers and access to pulmonary rehabilitation and respiratory physiotherapy services for patients with bronchiectasis in Australia need to be studied. These results should prompt clinicians to regularly collect airway samples for bacterial and mycobacterial cultures, and to consider and advocate for access to prophylactic antibiotics wherever suitable. Finally, these data encourage clinicians to rationalise the use of inhaled corticosteroids and bronchodilators in bronchiectasis, reserving them for selected patients with concomitant asthma or COPD. These findings from the ABR highlight an opportunity to improve the holistic management of Australians living with bronchiectasis and serve as encouragement for clinicians and health services to continually review their practice in light of the emerging evidence base.

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References

1. Quint JK, Millett ERC, Joshi M, Navaratnam V, Thomas SL, Hurst JR, Smeeth L, Brown JS (2016) Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J 47(1):186–193. https://doi.org/10.1183/13993003.01033-2015
2. Bibby S, Milne R, Beasley R (2015) Hospital admissions for non-cystic fibrosis bronchiectasis in New Zealand. N Z Med J 128(1421):30–38
3. Ringshausen FC, de Roux A, Pletz MW, Hämäläinen N, Welte T, Rademacher J (2013) Bronchiectasis-associated hospitalizations in Germany, 2005–2011: a population-based study of disease burden and trends. PLoS ONE 8(8):e71109. https://doi.org/10.1371/journal.pone.0071109
4. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots R (2012) Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. Chest 142(2):432–439
5. Weycker D, Edelsberg J, Oster G, Tino G (2005) Prevalence and economic burden of bronchiectasis. Clin Pulm Med 12(4):205–209. https://doi.org/10.1097/01.cpm.0000171422.98696.ed
6. Flume PA, Chalmers JD, Olivier KN (2018) Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet 392(10150):880–890. https://doi.org/10.1016/S0140-6736(18)31767-7
7. Bell SC, Elborn JS, Byrnes CA (2018) Bronchiectasis: Treatment decisions for pulmonary exacerbations and their prevention: pulmonary exacerbations in bronchiectasis. Respirology 23(11):1006–1022. https://doi.org/10.1111/resp.13398
8. Chalmers JD, Chotirmall SH (2018) Bronchiectasis: new therapies and new perspectives. Lancet Respir Med 6(9):715–726. https://doi.org/10.1016/S2213-2600(18)30053-5
9. Serisier DJ (2014) The evidence base for non-CF bronchiectasis is finally evolving. Respirology 19(3):295–297. https://doi.org/10.1111/resp.12247
10. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, Abuan T, Tully H, Van Dalfsen J, Wells CD, Quan J (2000) Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. Am J Respir Crit Care Med 162(2 Pt 1):481–485. https://doi.org/10.1164/ajrccm.162.2.9910086
11. Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, Boersma WG, De Soyza A, Shao L, Zhang J, Haas L, Lewis SA, Leitzinger S, Montgomery AB, McKevitt MT, Gossage D, Quittner AL, O'Riordan TG (2014) Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med 2(9):738–749. https://doi.org/10.1016/S2213-2600(14)70165-1
12. O'Donnell AE, Barker AF, Ilowite JS, Fick RB (1998) Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. Chest 113(5):1329–1334. https://doi.org/10.1378/chest.113.5.1329
13. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EHJ, Koppers RJH, van der Werf TS, Boersma WG (2013) Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 309(12):1251–1259. https://doi.org/10.1001/jama.2013.1937
14. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD (2013) Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 309(12):1260–1267. https://doi.org/10.1001/jama.2013.2290

15. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, Storey L, Ashton T (2012) Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 380(9842):660–667. https://doi.org/10.1016/S0140-6736(12)60953-2
16. Wu Q, Shen W, Cheng H, Zhou X (2014) Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. Respirology 19(3):321–329. https://doi.org/10.1111/resp.12233
17. Zhuo G-Y, He Q, Xiang-Lian L, Ya-Nan Y, Si-Te F (2014) Prolonged treatment with macrolides in adult patients with non-cystic fibrosis bronchiectasis: meta-analysis of randomized controlled trials. Pulm Pharmacol Ther 29(1):80–88. https://doi.org/10.1016/j.pupt.2014.02.002
18. Aksamit T, De Soyza A, Bandel TJ, Criollo M, Elborn JS, Operschall E, Polverino E, Roth K, Winthrop KL, Wilson R (2018) RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J 51(1):1702053. https://doi.org/10.1183/13993003.02053-2017
19. De Soyza A, Aksamit T, Bandel T-J, Criollo M, Elborn JS, Operschall E, Polverino E, Roth K, Winthrop KL, Wilson R (2018) RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J 51(1):1702052
20. Haworth CS, Bilton D, Chalmers JD, Davis AM, Froehlich J, Gonda I, Thompson B, Wanner A, O'Donnell AE (2019) Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. Lancet Respir Med
21. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D (2014) Inhaled colistin in patients with bronchiectasis and chronic pseudomonas aeruginosa infection. Am J Respir Crit Care Med 189(8):975–982. https://doi.org/10.1164/rccm.201312-2208OC
22. Bilton D, Tino G, Barker AF, Chambers DC, De Soyza A, Dupont LJA, O'Dochartaigh C, van Haren EHJ, Vidal LO, Welte T, Fox HG, Wu J, Charlton B, Investigators BS (2014) Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax 69(12):1073–1079. https://doi.org/10.1136/thoraxjnl-2014-205587
23. Chang AB, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, Holland AE, O'Mara P, Grimwood K, Alison J, Cull C, Currie B, Gardner I, Holmes P, Hunter C, Kolbe J, Maclennan C, McDonald M, Morris P, Nicolson C, Petsky H, Pillarisetti N, Reynolds E, Serisier D, Thein F, van Asperen P, Voss L, Wong C (2015) Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. Med J Aust 202(1):21–24. https://doi.org/10.5694/mja14.00287
24. Martínez-García MÁ, Máiz L, Olveira C, Girón RM, de la Rosa D, Blanco M, Cantón R, Vendrell M, Polverino E, de Gracia J (2018) Spanish guidelines on treatment of bronchiectasis in adults. Arch Bronconeumol (Engl Edn) 54(2):88–98
25. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn JS, Floto RA, Grillo L, Gruffydd-Jones K, Harvey A, Haworth CS (2019) British Thoracic Society guideline for bronchiectasis in adults. Thorax 74(Suppl 1):1–69
26. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K (2017) European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 50(3):1700629
27. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, Poppelwell L, Salih W, Pesci A, Dupont LJ, Fardon TC, De Soyza A, Hill AT (2014) The bronchiectasis severity index an international derivation and validation study. Am J Respir Crit Care Med 189(5):576–585. https://doi.org/10.1164/rccm.201309-1575OC
28. Lee AL, Hill CJ, McDonald CF, Holland AE (2017) Pulmonary rehabilitation in individuals with non-cystic fibrosis bronchiectasis: a systematic review. Arch Phys Med Rehab 98(4):774–782
29. Mandal P, Sidhu M, Kope L, Pollock W, Stevenson L, Pentland J, Turnbull K, Mac Quarrie S, Hill A (2012) A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. Respir Med 106(12):1647–1654
30. Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, Rautela L, Stirling RG, Thompson PJ, Holland AE (2014) The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis—a randomised controlled trial. Respir Res 15(1):44
31. Patel S, Cole AD, Nolan CM, Barker RE, Jones SE, Kon S, Cairn J, Loebinger M, Wilson R, Man WD (2019) Pulmonary rehabilitation in bronchiectasis: a propensity-matched study. Eur Respir J 53(1):1801264
32. Walker P, Herrero B, Spinou A, Dimakou K, Blasi F, Ringshausen F, De Soyza A, Vendrell M, Goeminne P, Boersma W (2018) Variability in access and referral to pulmonary rehabilitation in European bronchiectasis patients enrolled in the EMBARC registry. Eur Respiratory Soc.
33. Lee AL, Burge AT, Holland AE (2015) Airway clearance techniques for bronchiectasis. Cochrane Database Syst Rev 11:CD008351
34. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD (2015) A comprehensive analysis of the impact of pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc 12(11):1602–1611. https://doi.org/10.1513/AnnalsATS.201506-333OC
35. Araújo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon TC, Obradovic D, Stone G, Trautmann M, Davis A (2018) The independent contribution of *Pseudomonas aeruginosa* infection to long-term clinical outcomes in bronchiectasis. Eur Respir J 51(2):1701953
36. Yang JW, Fan LC, Lu HW, Miao XY, Mao B, Xu JF (2016) Efficacy and safety of long-term inhaled antibiotic for patients with noncystic fibrosis bronchiectasis: a meta-analysis. Clin Respir J 10(6):731–739. https://doi.org/10.1111/crj.12278
37. Brodt AM, Stovold E, Zhang L (2014) Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. Eur Respir J 44(2):382–393
38. Xu L, Zhang F, Du S, Yu Q, Chen L, Long LH, Li YM, Jia AH (2016) Inhaled antibiotics in non-cystic fibrosis bronchiectasis: a meta-analysis. Pharmazie 71(9):491–498. https://doi.org/10.1691/ph.2016.6590
39. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT (2012) Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 186(7):657–665. https://doi.org/10.1164/rccm.201203-0487OC
40. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D (2014) Inhaled colistin in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. Am J Respir Crit Care Med 189(8):975
41. Chalmers JD, Aliberti S, Filonenko A, Shteinberg M, Goeminne PC, Hill AT, Fardon TC, Obradovic D, Gerlinger C, Sotgiu G, Operschall E, Rutherford RM, Dimakou K, Polverino E, De Soyza A, McDonnell MJ (2018) Characterization of the "frequent exacerbator phenotype" in Bronchiectasis. Am J Respir Crit Care Med 197(11):1410–1420. https://doi.org/10.1164/rccm.201711-2202OC
42. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, Leitch A, Loebinger MR, Milburn HJ, Nightingale M, Ormerod P, Shingadia D, Smith D, Whitehead N, Wilson

R, Floto RA (2017) British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 72:1–64. https://doi.org/10.1136/thoraxjnl-2017-210927
43. Yang IA, Brown JL, George J, Jenkins S, McDonald CF, McDonald VM, Phillips K, Smith BJ, Zwar NA, Dabscheck E (2017) COPD-X Australian and New Zealand guidelines for the diagnosis and management of chronic obstructive pulmonary disease: 2017 update. Med J Aust 207(10):436–442
44. Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB (2018) Inhaled corticosteroids for bronchiectasis. Cochrane Database Syst Rev 5:CD000996
45. Polverino E, Dimakou K, Hurst J, Martinez-Garcia M-A, Miravitlles M, Paggiaro P, Shteinberg M, Aliberti S, Chalmers JD (2018) The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions. Eur Respir J 52(3):1800328. https://doi.org/10.1183/13993003.00328-2018
46. Liu VX, Winthrop KL, Lu Y, Sharifi H, Nasiri HU, Ruoss SJ (2018) Association between Inhaled corticosteroid use and pulmonary nontuberculous mycobacterial infection. Ann Am Thorac Soc 15(10):1169–1176
47. Global Initiative for Asthma (2017) Global strategy for asthma management and prevention.

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