



Thoracic Society of Australia and New Zealand

CHRONIC SUPPURATIVE LUNG DISEASE AND BRONCHIECTASIS

IN CHILDREN AND ADULTS
IN AUSTRALIA AND NEW ZEALAND

Clinical Practice Guideline

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ABBREVIATIONS

c-HRCT	Chest high-resolution computed tomography	NTM	Non-tuberculous mycobacteria
CF	Cystic fibrosis	NTHi	Non-typeable <i>Haemophilus influenzae</i>
COPD	Chronic obstructive pulmonary disease	NZ	New Zealand
CSLD	Chronic suppurative lung disease	<i>Pa</i>	<i>Pseudomonas aeruginosa</i>
FEV ₁	Forced expiratory volume in 1 second	QoL	Quality of life
ICS	Inhaled corticosteroids	RCT	Randomised controlled trial
HTLV-1	Human T-cell lymphotropic virus 1	rhDNase	Recombinant human deoxyribonuclease
MDCT	Multi-detector computed tomography		

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ABSTRACT

- Guidelines for managing chronic suppurative lung disease (CSLD) and bronchiectasis in Australian and New Zealand children and adults were updated (latest search date Oct 2013) based on systematic reviews, multi-disciplinary meetings and a modified Delphi process.
- Diagnosis of bronchiectasis requires a chest high-resolution computed tomography scan, preferably using multi-detector scans. Child-specific criteria and protocols are recommended.
- CSLD/bronchiectasis should be diagnosed early and appropriate investigation and treatment instigated. This includes planned coordination of care among healthcare providers, and specialist evaluation to confirm diagnosis, investigate aetiology, assess baseline severity and to develop individualised management plans, including self-management when appropriate.
- Consider a chest CT scan in adults with severe COPD and those with recurrent exacerbations.
- Intensive treatment seeks to improve symptom control, reduce exacerbation frequency, preserve lung function, optimise quality of life and enhance survival.
- All exacerbations require treatment.
- Antibiotic selection is based upon lower airway culture results, local antibiotic susceptibility patterns, clinical severity and patient tolerance. Patients with severe exacerbations and/or not responding to outpatient therapy are hospitalised for more intensive treatments, including intravenous antibiotics.
- Ongoing care requires monitoring for complications and co-morbidities.
- Airway clearance manoeuvres and regular exercise are encouraged, nutrition optimised, environmental pollutants (including tobacco smoke) avoided and vaccines administered following national immunisation schedules.
- Long-term antibiotics, inhaled corticosteroids, bronchodilators and mucoactive agents may be individualised, but are not recommended routine therapy.
- Before starting macrolides in selected patients, collect sputum for mycobacterial cultures and perform an electrocardiogram.
- Although Indigenous people living in rural-remote regions provide particular challenges, the objective of delivering best practice treatment remains paramount.

INTRODUCTION

Since the previous guidelines on managing chronic suppurative lung disease (CSLD) and bronchiectasis,^{1,2} the increasing trend in the health burden of CSLD/bronchiectasis has been recognised in both Indigenous and non-Indigenous settings in Australia, New Zealand (NZ) and worldwide.^{2,3,4,5} However, delays in diagnosis still occur in children⁶ and adults.^{5,7} It is likely that many with bronchiectasis remain undiagnosed and untreated, risking premature and accelerated pulmonary decline.² This guideline presents an update from previous recommendations^{1,2} for managing CSLD/bronchiectasis (unrelated to cystic fibrosis, CF) in children and adults in Australia and NZ, including urban and rural-remote Indigenous people. Readers are referred to the former guideline² for previously used references and definitions. This update provides an overview, targeted at primary and secondary care, and is not intended for individualised specialist care. As with all guidelines, it does not substitute for sound clinical judgement, particularly when addressing such a phenotypically heterogeneous condition as bronchiectasis.⁸ Table-1 outlines the process undertaken by the writing group. The recommendations are also published in the Medical Journal of Australia.⁹

OBJECTIVES

1. To increase awareness of CSLD/bronchiectasis in children and adults;
2. To encourage earlier and improved diagnosis and management of CSLD/bronchiectasis;
3. To present an updated guideline relevant to Australian and New Zealand settings.

BACKGROUND ON BRONCHIECTASIS AND CSLD

There remain little data on the incidence and prevalence of CSLD/bronchiectasis (NZ incidence in children aged ≤ 14 -years=3.7/100,000;¹⁰ prevalence in Central Australian Indigenous people: children aged ≤ 15 -years=1470/100,000 based on community data;² adults=103/100,00 based on adults were hospitalised¹¹). Recently published Australian annual hospitalisation rates for bronchiectasis as a principal diagnosis demonstrate a steady increase between 1998–99 to 2011–12 (14 to 21 per 100,000 population respectively) (www.aihw.gov.au/bronchiectasis). The increasing trend is a worldwide phenomenon with some countries reporting childhood fatalities,⁵ and a growing appreciation of economic cost.³ Recent data in a Central Australian adult hospitalised cohort reported 34.2% of the cohort died (over ensuing 5-10 years) at a median age of 42.5-years.¹¹

Bronchiectasis can be misdiagnosed or co-exist with other chronic respiratory diseases. When present the prognosis is worse e.g. mortality increases in those with both chronic obstructive pulmonary disease (COPD) and bronchiectasis (hazard ratio=2.54; 95%CI 1.16-5.56).⁴ Since between 29-50% of people with COPD¹ and as many as 40% of newly referred patients with difficult to control asthma and a chronic cough have bronchiectasis,¹² it is likely that many with chronic respiratory symptoms due to CSLD/bronchiectasis remain undiagnosed. Also, complications and co-morbidities associated with bronchiectasis extend beyond the respiratory system and include cardiac and psychological effects.²



DEFINITIONS AND THEIR LIMITATIONS

The definitions of CSLD and bronchiectasis include overlapping symptoms and signs, which are not specific for each condition and were defined previously.^{1,2} New evidence and justification for including CSLD are described in recent papers.^{13,14}

Recommendation-1

- 1a. Bronchiectasis is a clinical syndrome in a child or adult with the symptoms and/or signs in Box-1 and presence of characteristic radiographic features on chest high-resolution computed tomography (c-HRCT).
- 1b. CSLD is a clinical syndrome in children with the symptoms and/or signs outlined in Box-1, but who lack a radiographic diagnosis of bronchiectasis.

GRADE-Strong

Box-1

Recurrent (≥ 3 episodes) wet or productive cough, each lasting for >4 -weeks, with or without other features, e.g. exertional dyspnoea,

- symptoms of airway hyper-responsiveness,
- recurrent chest infections,
- growth failure,
- clubbing,
- hyperinflation or chest wall deformity.

In children, triggers for referral to a specialist include one or more of the following:

- (i) persistent wet cough not responding to 4-weeks of antibiotics,
- (ii) ≥ 3 episodes of chronic (>4 -weeks) wet cough per year responding to antibiotics,
- (iii) a chest radiograph abnormality persisting >6 -weeks after appropriate therapy.

INVESTIGATIONS OF A PATIENT WITH CSLD/BRONCHIECTASIS

RADIOLOGY

c-HRCT remains the diagnostic gold standard. However, c-HRCT reconstructed from a multi-detector (MDCT) scan is substantially more sensitive than conventional c-HRCT.¹⁵ As children are at greater risk from radiation-induced cancers later in life,^{2,16} the c-HRCT protocol must ensure the lowest possible radiation exposure to obtain adequate assessment. As the key radiographic criteria of broncho-arterial ratio in people without lung disease is age-dependent,¹⁷ child-specific criteria¹⁸ are recommended.

Recommendation-2

- 2a. Patients with symptoms and/or signs suggestive of bronchiectasis require a c-HRCT to confirm the diagnosis and to assess severity and extent of bronchiectasis.

- 2b. In children, seek specialist advice before ordering a c-HRCT and child-specific criteria should be used.
- 2c. In both adults and children, MDCT scans with HRCT reconstruction is the preferred technique to diagnose bronchiectasis.

GRADE-Strong; Evidence-Moderate

AETIOLOGY

Several causative and associated factors are described for CSLD/bronchiectasis (Table-2). Identifying aetiology (Box-2) and disease severity can influence management, including treatment intensity.² Investigations for specific causes of CSLD/bronchiectasis are recommended, even though many patients lack an identifiable aetiology.² Bronchoscopy is generally indicated in children who are unable to expectorate and adults with localised disease.¹⁹ Given the implications of bronchiectasis for managing people with COPD⁴, a new recommendation is included.

Recommendation-3

Consider a c-HRCT in adults with COPD and either ≥ 3 exacerbations per year, very severe disease ($FEV_1 < 30\%$ predicted or requiring domiciliary oxygen) or whose sputum contains organisms atypical for COPD (i.e. *Aspergillus* species, *Pseudomonas aeruginosa* (*Pa*) or non-tuberculous mycobacteria, NTM).

GRADE-low; Evidence-low

SEVERITY

In addition to routine clinical data (cough, sputum, exacerbation rate, well-being, etc) and radiological assessment, objective tests provide information about disease severity and prognosis.

Lung function: Although spirometry is classically obstructive, a restrictive pattern is also recognised. Spirometry and lung volume measurements should be assessed at diagnosis and spirometry performed at each review, even though they can be relatively insensitive in mild disease and in children.² Accelerated deterioration in lung function may occur.^{20,21,22} If serial pulmonary function measurements indicate disease progression, a step-up in therapy is recommended. Paediatric studies show that spirometric volumes can stabilise and even improve,^{14,23} while in adults with moderate-severe bronchiectasis, mortality risk is associated with degree of lung function impairment.²⁴ Other assessments, including complex pulmonary function and the 6-minute walk tests, are sometimes used for determining functional impairment, but these are not discussed further.

Microbiology: Surveillance of airway or sputum microbiology helps guide antibiotic therapy in CSLD/bronchiectasis, especially if there is deterioration or inadequate response to current treatment. The most common pathogens in children are non-typeable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae* and *Moraxella catarrhalis*.²⁵ In adults, *Pa* and NTHi predominate.²⁶ About 25-45% of airway samples fail to grow pathogenic bacteria. As disease progresses the microbiota change, often with *Pa* appearing in more advanced disease and predicting a worse prognosis.²⁶ *Aspergillus* and NTM species are detected in some adults with bronchiectasis, although their pathogenic role is uncertain.²⁶ Nonetheless, NTM has been implicated in exacerbations and pulmonary deterioration.² Readers are referred to new diagnostic and classification guidelines for aspergillosis-related issues.²⁷ Molecular and sequencing based-studies^{28,29} have highlighted the abundance (up to 83%) of anaerobic bacteria and the complexity of the pulmonary microbiome, but the clinical implications remain uncertain. Meanwhile in Central Australian Indigenous adults, when compared with non-infected individuals, human T-cell lymphotropic virus (HTLV)-1 is associated with both an increased risk of developing bronchiectasis and a worse outcome.¹¹ While the background prevalence of HTLV-1 in the Central Australian Indigenous population is 7.2-13.9%, 18 (72%) of 25 patients with bronchiectasis tested in the Alice Springs Hospital were HTLV-1 seropositive.¹¹

Other tests: Pulmonary arterial hypertension complicates severe bronchiectasis.^{11,30} In advanced



disease, chronic or nocturnal hypoxemia is common and selected patients require arterial blood gas, an echocardiogram and overnight oxygen assessment.

Recommendation-4

Obtaining further history for specific underlying causes may determine subsequent investigation and management. History should include:

- History suggestive of cystic fibrosis (family history, pancreatitis, chronic gastrointestinal symptoms, male infertility);
- Underlying immune deficiency or ciliary dyskinesia (recurrent sinusitis, extrapulmonary infections, including discharging ears and severe dermatitis, and male infertility);
- Recurrent aspiration (cough and/or choking with feeds/meals, post-bariatric surgery, may be occult); and
- Inhaled foreign body

GRADE-Strong; Evidence-Moderate

Recommendation-5

Perform or refer for baseline investigations (Box-2).

GRADE-Strong; Evidence-Moderate

Box-2

Minimum investigations are:

- Full blood count and major immunoglobulin classes G, A, M, E
- Sweat test in all children and selected adults - (see below)
- Culture airway secretions, including specialised cultures for mycobacteria, particularly non-tuberculous mycobacteria (NTM) in sputum-producing patients
- Spirometry and lung volumes (when aged >6-years)
- Aspergillus serology.

In addition consider the following after discussion with a specialist:

- Exhaled fractional nasal nitric oxide, nasal ciliary brushings and/or genetic testing for primary ciliary dyskinesia
- Sweat test and/or extended CFTR gene mutation testing (adults aged <50 years or in those with episodes of pancreatitis, bowel obstruction, heat prostration and in patients with co-existent liver disease or male infertility)
- Bronchoscopy for foreign body, airway abnormality and specimens for culture of respiratory pathogens, including mycobacteria
- Assessment for aspiration (primary or secondary)
- Additional immunological tests (neutrophil function tests and lymphocyte subsets, IgG subclasses, antibody responses to vaccines)
- HIV, HTLV-1
- Echocardiogram especially in adults (when concerned about pulmonary hypertension).

Recommendation-6

Obtain further history to determine markers of severity, impact of illness, co-morbidities and modifiable risk factors. History should include: frequency of exacerbations and hospitalisations, degree of effort limitation, exposure to tobacco smoke and other pollutants, childhood history and housing.

GRADE-Strong; Evidence-low

MANAGEMENT (TABLE-3)

Early and effective management reduces short and long-term morbidity.^{23,31} In children, airway injury is superimposed upon the physiological changes involving lung growth and development.³² With appropriate treatment, lung disease complicating primary immunodeficiency should not deteriorate.^{23,33} In a Melbourne adult cohort, longer duration of chronic productive cough was related to poorer lung function,⁸ while in children longer duration of wet cough before treatment was associated with worse c-HRCT scores.³⁴

Recommendation-7

Aim to optimise general well-being, symptom control, lung function, quality of life (QoL), and reduce exacerbation frequency and prevent excessive decline in lung function. This may require intensive medical therapy.

GRADE-Strong; Evidence-High

EXACERBATIONS

Exacerbations impair QoL,²³ increases airway and systemic inflammation,³⁵ result in hospitalisation, and are an independent predictor of lung function decline.^{22,36} Symptoms include >72-hours of increased cough, change in sputum (volume, viscosity, purulence), breathlessness, haemoptysis and/or constitutional upset (malaise, tiredness).^{37,38,39} In children, exacerbations are defined clinically (increased cough, altered cough and/or sputum characteristics) with or without elevated serum biomarkers (e.g. C-reactive protein).³⁹

Recommendation-8

Develop treatment plans for exacerbations for each patient, linking them to primary healthcare and specialist or hospital facilities. When appropriate, this includes individualised and self-initiated management action plans.

GRADE-Strong; Evidence-Low

ANTIBIOTICS

High bacterial loads in the airways of patients with CSLD/bronchiectasis are associated with increased respiratory symptoms, more frequent exacerbations and elevated inflammatory markers.³⁵ Consequently, antibiotic therapy to reduce bacterial load has a central management role.^{31,35} A recent review of the use of antibiotics in people with bronchiectasis is available.⁴⁰

(i) Acute exacerbations

Depending upon the severity, short-term oral antibiotics and ambulatory care are usually tried first for acute exacerbations.⁴¹ More severe episodes require intravenous antibiotics combined with intensified physiotherapy and other airway clearance methods, including nebulised therapy.⁴¹ While robust evidence is lacking, a 2-week antibiotic course is generally recommended.^{31,42} Response to therapy includes reduced sputum volume and purulence, and improved cough character (wet to dry or cessation of cough), general well-being, QoL and markers of systemic inflammation (C-reactive protein), microbial clearance, and 'return to baseline' state.^{31,35,41}

(ii) Pseudomonas aeruginosa eradication

Chronic *Pa* infection in CSLD/bronchiectasis is associated with advanced disease and deteriorating clinical outcomes.⁴³ A small retrospective study reported that when first isolated, *Pa* can be eradicated with intravenous antibiotics followed by 3-months of oral and inhaled anti-pseudomonal antibiotic therapy.⁴³ While eradication was accompanied by reduced exacerbation rates, additional studies are needed to demonstrate any sustained clinical benefit.



(iii) Long-term suppression

The goal of long-term oral or inhaled antibiotic therapy is to reduce bacterial load and airway inflammation when sustained eradication of lower respiratory pathogens is not possible. Trials of long-term oral beta-lactam and inhaled antibiotics provide conflicting results for a clinical benefit, with the best evidence being provided for benefit by a randomised controlled trial (RCT) on inhaled gentamicin. In contrast, recent randomised placebo-controlled trials of macrolides for 6-24 months duration report exacerbations were reduced by 33-64% and in some instances improved QoL and lung function.^{13,37,38,44,45} Nevertheless, additional studies are required to establish their overall role and safety in CSLD/bronchiectasis, particularly concerning the clinical implications of developing antibiotic resistance.^{46,47} Macrolides should be avoided in those receiving Class IA/III anti-arrhythmic agents, if there is a prolonged QTc interval or as a single agent when NTM are cultured.⁴⁷ New inhaled antibiotic formulations (e.g. ciprofloxacin, amikacin) are currently undergoing clinical trials to determine if they have a role in managing non-CF bronchiectasis.

Recommendation-9

Base antibiotic selection (Box-3) on lower airway culture results [sputum, bronchoscopy washings (adults and older children) or bronchoalveolar lavage (young non-expectorating children)] when available, local antibiotic susceptibility patterns, clinical severity and patient tolerance, including allergy.

GRADE-Strong; Evidence-Moderate

Box-3		
	Mild-moderate exacerbation (oral therapy)[^]	Moderate to severe exacerbation (IV therapy)[^]
Initial empiric therapy [*]	Children: amoxicillin, amoxicillin-clavulanate Adults: amoxicillin, amoxicillin-clavulanate or doxycycline [†] Children and adults: ciprofloxacin if <i>P. aeruginosa</i> in recent cultures.	Children and adults: ampicillin, cefotaxime or ceftriaxone (amoxicillin, amoxicillin-clavulanate, or cefuroxime [‡]) Children and adults: piperacillin-tazobactam, ticarcillin-clavulanate, or ceftazidime + tobramycin [§] if severe or <i>P. aeruginosa</i> in recent cultures.
Specific pathogens		
<i>H. influenzae</i> β -lactamase-ve	amoxicillin	ampicillin (amoxicillin [‡])
β -lactamase +ve	amoxicillin-clavulanate or doxycycline [†]	cefotaxime or ceftriaxone (amoxicillin-clavulanate or cefuroxime [‡]),
<i>S. pneumoniae</i>	amoxicillin	benzylpenicillin G, ampicillin (amoxicillin [‡])
<i>M. catarrhalis</i>	amoxicillin-clavulanate	cefotaxime or ceftriaxone (amoxicillin-clavulanate, or cefuroxime [‡])
<i>S. aureus</i>	di-/flucloxacillin	flucloxacillin
MRSA	seek specialist advice [¶]	seek specialist advice [¶]
<i>P. aeruginosa</i>	ciprofloxacin (max 14 days)	Children and adults: piperacillin-tazobactam, ticarcillin-clavulanate, or ceftazidime + tobramycin [§]
NTM	seek specialist advice [¶]	seek specialist advice [¶]

^{*}In addition to clinical severity, initial empiric therapy is also guided by previous lower airway culture results (sputum, BAL/bronchoscopy washings), local antibiotic susceptibility patterns and prior responses to antibiotic treatments. In children too young to expectorate sputum and when no previous lower airway culture results are available, prescribed empiric antibiotic therapy should be active against *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*.

^Seek local specialist advice if a history of antibiotic hypersensitivity or severe adverse antibiotic effects exists and when serious drug interactions may occur. Aminoglycosides, macrolides and fluoroquinolones in particular should be used with care in the elderly. †Doxycycline is used only in adults and adolescents; ‡Available only in New Zealand; §Although treating *P. aeruginosa* bacteraemia with combined beta-lactam and aminoglycoside antibiotic therapy provides no additional clinical benefit and is associated with more adverse events than using a single beta-lactam agent, the role of single beta-lactam therapy for non-bacteraemic *P. aeruginosa* pneumonia and other respiratory infections is unproven. Combination therapy should still be used when multi-resistant *P. aeruginosa* strains are detected. ¶Specialist advice is required for treating MRSA in accordance with local susceptibility patterns and infection control policies. The decision of when to treat NTM and what agents to use is complicated by the high levels of antibiotic resistance shown by these strains and the need for prolonged therapeutic courses involving multiple drug combinations that risk serious toxicity and drug interactions.

Recommendation-10

When *Pa* is first detected, consider discussion with a specialist in this field regarding suitability for eradication.

GRADE-Weak; Evidence-Low

Recommendation-11

In patients not requiring parenteral antibiotics for an acute exacerbation, oral antibiotics are prescribed for at least 10-days based on available airway microbiology results. Close follow-up to assess treatment response is necessary.

GRADE-Strong; Evidence-Low

Recommendation-12

Inadequate response should prompt repeat of lower airway cultures and assessment of whether parenteral antibiotic therapy and hospitalisation are needed.

GRADE-Strong; Evidence-Moderate

Recommendation-13

Patients failing oral antibiotic therapy for an acute exacerbation should receive intensive airway clearance strategies and parenteral antibiotics based upon the latest lower airway culture results. Close follow-up is required.

9a. In children, this requires supervised treatment for at least 10-14 days.

9b. In adults, IV antibiotics should be for at least 5-days and often followed by oral antibiotics. Conversion from IV to oral antibiotics depends upon appropriate oral alternatives and if effective adjunct therapies, such as airway clearance strategies can be maintained in an ambulatory care setting and ongoing outpatient review.

GRADE-Strong; Evidence-Moderate

Recommendation-14

Long-term oral antibiotics should not be prescribed routinely. Macrolides (or other antibiotics) can be considered for a therapeutic trial over a limited period (e.g. up to 12-24 months) in selected patients [e.g. frequent exacerbations (≥ 3 exacerbations and/or ≥ 2 hospitalisations in the previous 12-months)]. Before commencing macrolides; (a) Seek respiratory/infectious diseases specialist advice, (b) ensure NTM infection is excluded in patients capable of providing a sputum specimen, and (c) perform an ECG in adults for assessment of QTc.

GRADE-Strong; Evidence-Moderate

Recommendation-15

Long-term nebulised antibiotics should not be prescribed routinely. Consider a therapeutic trial in children and adults with frequent exacerbations and/or *Pa* infection.

GRADE-Strong; Evidence-Moderate



BRONCHODILATORS AND CORTICOSTEROIDS

Those with CSLD/bronchiectasis may have co-existent asthma with wheeze and/or dyspnoea responsive to beta-2 agonist medications. Reports on asthma symptoms in those with CSLD/bronchiectasis vary from 11 to 46%.² While some studies ascribe asthma as a cause of bronchiectasis, it is more likely asthma was misdiagnosed initially or co-existed with CSLD/bronchiectasis.^{6,12} When present, asthma therapies should be used in accordance with asthma guidelines.

Inhaled corticosteroids (ICS) provide, at best, a modest benefit in CSLD/bronchiectasis.⁴⁸ A study published⁴⁹ after the current Cochrane review⁴⁸ also found no significant differences between those receiving ICS compared to placebo. Combined ICS-long acting beta-agonist (compared to high-dose ICS) improved dyspnoea and cough with no effect on exacerbations.⁵⁰ Furthermore, ICS in adults with chronic respiratory disease risk NTM infection.⁵¹

Recommendation-16

Inhaled and oral corticosteroids should not be prescribed routinely unless there is an established diagnosis of co-existing asthma or COPD.

GRADE- Strong; Evidence-Low for oral corticosteroids, moderate for ICS

Recommendation-17

Inhaled bronchodilators should not be prescribed routinely and used only on an individual basis.

GRADE- Strong; Evidence- Low

MUCOLYTICS AND MUCOACTIVE AGENTS

Mucoactive agents include mannitol, iso- and hyper-tonic saline. While early short-term trials were promising, longer-term RCTs found that both hypertonic saline⁵² and mannitol⁵³ conferred little advantage over isotonic saline and placebo respectively. In contrast, recombinant human deoxyribonuclease (rhDNase), a widely used mucolytic in CF, is harmful in adults with CSLD/bronchiectasis and is associated with increased exacerbations and hospitalisations, and more rapid FEV₁ decline.⁵⁴

Recommendation-18

rhDNase is contraindicated in CSLD/bronchiectasis.

GRADE- Strong; Evidence-High

Recommendation-19

Mucoactive agents, including hypertonic saline and mannitol, are currently not recommended routinely. Consider a therapeutic trial in children and adults with frequent exacerbations.

GRADE-Weak; Evidence-Moderate

AIRWAY CLEARANCE TECHNIQUES, EXERCISE AND PULMONARY REHABILITATION

Despite lacking a robust evidence-base, airway clearance techniques are standard treatment in people with CSLD/bronchiectasis. Available studies suggest airway clearance techniques are beneficial, with improved QoL and exercise capacity, and reduced cough and sputum volumes.^{55,56} Given the variety of airway clearance techniques and increased efficacy when individualised therapy is utilised,⁵⁷ specific respiratory expertise should be sought.

Pulmonary rehabilitation is a multidisciplinary treatment, including exercise training, self-management education, psychosocial and nutritional intervention.⁵⁸ Small short-term RCTs including whole body exercise training have shown improvements in symptoms, exercise tolerance and QoL.⁵⁹ Unless specific contraindications exist, physical activity should be encouraged.



Recommendation-20

Airway clearance techniques are recommended and respiratory physiotherapist's advice should be sought. Individualise airway clearance therapy.

GRADE-Strong; Evidence-Moderate

Recommendation-21

Adults with bronchiectasis and exercise limitation should receive pulmonary rehabilitation.

GRADE-Strong; Evidence-Moderate

Recommendation-22

Regular physical activity is recommended for children and adults with CSLD/bronchiectasis.

GRADE-Strong; Evidence-Low

NUTRITION

Poor nutrition (both macro and micro-nutrition) compromises innate and adaptive immunity. Studies in other chronic respiratory diseases⁶⁰ indicate that poor nutrition may be a risk factor for respiratory exacerbations in CSLD/bronchiectasis. Vitamin-D deficiency has been associated with poorer outcomes,⁶¹ but the evidence for this is low.

Recommendation-23

Assess and optimise nutritional status.

GRADE-Strong; Evidence-Moderate

MINIMISE FURTHER LUNG INJURY

Environmental pollutants,⁶² including tobacco smoke, exacerbate chronic respiratory disorders and constitute an additional risk factor for those with CSLD/bronchiectasis.

Recommendation-24

Promote elimination of smoking, including second-hand smoke exposure.

GRADE-Strong; Evidence-High

Recommendation-25

Promote avoidance of environmental airborne pollutants.

GRADE-Strong; Evidence-Low

CO-MORBIDITIES

Patients with CSLD/bronchiectasis have increased rates of co-morbidity, including chronic sinusitis, gastro-oesophageal reflux, 'asthma-like' disease and depression. It is unknown whether these co-morbidities increase the frequency and/or severity of exacerbations or worsen lung injury.

Recommendation-26

Regularly monitor and manage complications and co-morbidities (Box-4). When present, these are managed following standard guidelines.

GRADE-Strong; Evidence-Moderate



Box-4**Regular review consists of:**

At least an annual review in adults and 6-monthly in children. A multi-disciplinary team is preferable, especially at the initial evaluation. The review includes assessment of:

- (a) severity, which includes oximetry and spirometry
- (b) sputum culture (when available) for routine bacterial and annual mycobacterial culture
- (c) management of possible complications and comorbidities, particularly for gastro-esophageal reflux disease/aspiration, reactive airway disease/asthma, COPD, otorhinolaryngeal disorders, urinary incontinence, mental health and dental disease. Less commonly patients require assessments for sleep disordered breathing and cardiac complications.
- (d) Adherence to therapies and knowledge of disease processes and treatments

OTHER TREATMENTS

Various other treatments are available, but with little supportive data (Table-3). Current management strategies have reduced the need for surgical interventions, which carry a small but significant risk of morbidity and mortality. Lung transplantation should be considered in those with end-stage lung disease.

Recommendation-27

Although surgery is not indicated normally, there may be circumstances requiring assessment by a multi-disciplinary team expert in CSLD/bronchiectasis care.

GRADE-Strong; Evidence-moderate

PUBLIC HEALTH ISSUES, PREVENTION AND APPROPRIATE HEALTH CARE DELIVERY

The socioeconomic determinants of health, including their impact upon CSLD/bronchiectasis cannot be addressed adequately here. Immunisations that prevent acute respiratory infections, such as pertussis, influenza and pneumococcal vaccines, are recommended despite the lack of specific high-level evidence for CSLD/bronchiectasis.⁶³

Delivery of chronic disease programmes requires comprehensive and highly-skilled primary healthcare services. Education of primary healthcare providers should focus upon identifying children and adults for appropriate referral and high-quality local management. Like other chronic illnesses, individualised and multi-disciplinary case management operating within an inter-professional framework is optimal.⁶⁴ Clinical deterioration should prompt early referral for specialist care. Those with moderate or severe disease are best managed by a multi-disciplinary approach to chronic care. In a pilot RCT, a self-management programme (within a multidisciplinary team) improved QoL and health-management elements.⁶⁵

Indigenous children and adults with CSLD/bronchiectasis who live in rural-remote regions provide particular challenges for the delivery of care. In asthma, including local Indigenous workers improves outcomes,⁶⁶ but there are no data specific for bronchiectasis.

Recommendation-28

Immunise according to National Immunisation Schedules. Ensure timely annual influenza immunisation and that pneumococcal vaccines are administered following national guidelines.

GRADE-Strong; Evidence-Moderate



Recommendation-29

Coordinated care by health care providers is necessary. Specialist evaluation is recommended if bronchiectasis is suspected to confirm diagnosis, investigate aetiology, assess severity and to develop management plans. Those with moderate or severe disease are best managed using a multi-disciplinary approach to chronic care with individualised case management. Clinical deterioration should prompt early referral to services with CSLD/bronchiectasis expertise.

GRADE-Strong; Evidence-low

Recommendation-30

Specialist review should be undertaken for patients with moderate disability or progressive lung disease. This includes consideration for lung transplantation.

GRADE-Strong; Evidence-Low

Recommendation-31

Providing healthcare for Indigenous people in rural-remote regions requires flexible and adaptive arrangements. However, it should not alter the objective of delivering best practice treatment to this population.

GRADE-Strong; Evidence-Low

Recommendation-32

Given the high prevalence of CSLD/bronchiectasis in Indigenous Australians, Māori and Pacific Island children and adults, a high index of suspicion with early diagnostic investigation and institution of best practice treatment should be established. Interpreters and local health-workers should be available for education regarding disease and management.

GRADE-Strong; Evidence-Moderate



TABLE 1- METHODS

Recommendations were based upon the available evidence (Table-3). Principles of evidence-based medicine and the revised GRADE⁶⁷ approach to guideline development were used to categorise recommendations into: strong, weak, or no specific recommendation.⁶⁷

The implications of a strong recommendation are:

- For patients—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered.
- For clinicians—most patients should receive the recommended course of action.
- For policy makers—the recommendation can be adopted as a policy in most situations.

The implications of a weak recommendation are:

- For patients—most people in your situation would want the recommended course of action, but many would not
- For clinicians—you should recognise that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences
- For policy makers—policy making will require substantial debate

The level of evidence provided by GRADE is:

- High=Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate=Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low=Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low = Any estimate of effect is very uncertain.

When relative risk was not available in publications, the decision to upgrade the evidence was based primarily on the likelihood of whether further research would have an effect on the recommendation.

An updated search (from a previous search in July 2009²) was conducted in Aug-Oct 2013. This was undertaken by the writing group (for assigned recommendations) and independently performed by AC using the text-word 'bronchiectasis' or 'suppurative lung disease' and 'controlled trials' in the Pubmed and Cochrane Central Library databases. Only full papers published in English were retrieved. Recommendations were updated and finalised by complete agreement by the writing group. The assigned evidence level (defined above) of recommendations was also agreed in consensus. This document and a summary table were then circulated to the entire group for assessment using the GRADE descriptors.⁶⁷ Strength of recommendations were assigned by formal voting rules⁶⁸ and agreement with a statement by >75% of the group was defined *a priori* as consensus.

This document and a truncated version (for publication in the MJA) were then submitted to the TSANZ education committee led by Prof Peter Wark and reviewed externally. After amendments, the truncated version was submitted to the MJA^{5764} where it also underwent external independent reviews, in accordance with this Journal's processes. Further minor amendments were made and reviewed by the writing group. As the recommendations were unaltered, we did not repeat the GRADE process with the expanded group. The writing group has no financial conflicts of interest and thus responds to the eight items of guideline panel review outlined by Lenzer and colleagues.⁷⁰

TABLE 2- AETIOLOGIES AND FACTORS ASSOCIATED WITH BRONCHIECTASIS (IN ALPHABETICAL ORDER)

- Congenital causes (eg. Monier-Kuhn, Young's syndrome)
- COPD/smoking
- Cystic fibrosis
- Mucociliary dysfunction (eg. primary ciliary dyskinesia)
- Immune deficiency (primary or secondary eg. hypogammaglobulinaemia, lung and bone marrow transplantation, malignancy, HIV/AIDS)
- Pulmonary fibrosis and pneumoconiosis (eg. silicosis) – causes traction bronchiectasis
- Post obstructive (eg. foreign body)
- Post-infectious (eg. tuberculosis, adenovirus, recurrent pneumonia)
- Recurrent small volume aspiration (from upper airway secretions or gastric contents)
- Systemic inflammatory diseases (eg. rheumatoid arthritis, sarcoidosis)



TABLE 3- POSSIBLE INTERVENTIONS FOR THE MANAGEMENT OF CSLD AND BRONCHIECTASIS

ANTIBIOTICS (BY TYPE)	EVIDENCE TYPE/STUDY	SUMMARY OF RESULTS	NOTES
General	Cochrane review, other systematic review*	Generally beneficial. See text	
Macrolides	DB RCTs for 6-24 months ^{13,37,38,44*}	Exacerbations reduced significantly in Rx arm (by 33-64%). Also improvement in weight in children, ¹³ and QoL, ³⁷ sputum ⁴⁴ , PFT parameters ³⁷ and lung function decline ⁴⁴ in some, but not all studies, in adults ³⁸	All studies reported increased antibiotic resistance. However, despite harbouring more macrolide-resistant bacteria, acute non-pulmonary infections requiring antibiotics were reduced by 50% in the Rx group. ¹³
Nebulised aminoglycosides	Cross-over DB RCT (tobramycin, 30 patients with <i>Pa</i> , 6-months each). [*] New RCT (single blinded 12-month gentamicin 80mg bd) ^{71 *}	Reduced number and days of hospitalisation in tobramycin arm. Improved exercise capacity, sputum purulence, QoL, reduced exacerbations in gentamicin arm. No effect on lung function or sputum volume. ⁷¹	Antibiotic resistance increased in <i>Pa</i> , some patients poorly tolerated nebulised tobramycin. [*]
Nebulised ciprofloxacin	DB RCT (42 adults with <i>Pa</i> , mixture of liposomal and free ciprofloxacin, alternating 28-day cycles on and off therapy for 6 mths ⁷²	Reduced the odds of an antibiotic treated exacerbation by 80%	Well tolerated, though product taste problematic
Nebulised colistin	DB RCT (144 adults with <i>Pa</i> , colistin 1 million units bid for up to 6mths). ⁷³	Reduced sputum <i>Pa</i> load, improved QoL after 6 mths	Failed to achieve primary endpoint of increased time to exacerbation
Short term (<1 month)	Several cohort studies, [*] Cochrane review ⁷⁴	General clinical improvement. No RCTs (but studies in progress ⁷⁵)	
Medium term (1-11 months)	Cochrane review*, (+ see macrolide section)	Improvement with amoxicillin and macrolides (see above). Adults with <i>Pa</i> -reduced hospitalisation but no change in QoL [*]	
Long term (≥ 12 months)	RCTs (+ see macrolide section)	Adults with <i>Pa</i> had reduced hospitalisation frequency and days. [*] Reduced general disability in those taking tetracycline compared to placebo [*]	

ANTIBIOTICS (BY TYPE)	EVIDENCE TYPE/STUDY	SUMMARY OF RESULTS	NOTES
Anti-inflammatories			
Oral NSAIDs	Cochrane review*	No RCTs	Cohort study, 25mg tds indomethacin for 28 days reduced neutrophil chemotaxis, but no change in sputum albumin, elastase, MPO
Inhaled indomethacin	Cochrane review*	RCT in 25 adults (some had CSLD). Reduced sputum and improved dyspnoea score	
Mucolytics			
Bromhexine	Cochrane review*	Studies only in acute phase	Not universally available
rhDNase	Systematic review*	Increased exacerbation rate and accelerated FEV ₁ decline	
Airway clearance			
Respiratory physiotherapy (Airway clearance techniques)	Cochrane review ⁵⁵	5 small cross-over short term studies (4 in adults, one in children). Improvements in QoL, cough-related measures and sputum.	No harm detected
Inhaled hyperosmolar agents	Cochrane review, RCTs using 6% HS (uni-centre ⁵²) and mannitol (multi-centre ⁵³), and systematic review ⁷⁶	No paediatric RCT. ⁷⁶ Adults: Mannitol conferred minimal benefit at 12-weeks, sputum expectoration in the placebo-group was significantly less than mannitol group. No effect on exacerbation frequency, QoL, spirometry, microbiological and inflammatory parameters. ⁵³ 6% HS over 12-months provided no advantage over isotonic saline in exacerbation, QoL, FEV ₁ ⁵²	82 had HRCT scans showed reduced mucous plugging in mannitol group. ⁵³

ANTIBIOTICS (BY TYPE)	EVIDENCE TYPE/STUDY	SUMMARY OF RESULTS	NOTES
Asthma therapies			
ICS	Cochrane review* plus new RCT ⁴⁹	Cochrane: No difference in any outcome when only placebo RCTs were included. Reduced exacerbation rate occurred in adults with <i>Pa</i> . RCT: 400 mcg budesonide conferred no benefit. ⁴⁹	Limited applicability in children as high ICS doses used and children are less likely to have <i>Pa</i> .
ICS-LABA	Cochrane review ⁵⁰	In stable state, ICS-LABA (compared to high dose ICS), improved dyspnoea and cough-free days, but no effect on QoL, exacerbations or lung function	
Oral cortico-steroids	Cochrane review*	No RCTs	No data*
Anti-cholinergics	Cochrane review*	No RCTs	No data*
Beta ₂ agonist	Cochrane review*	No RCTs	No data*
LTRA	Cochrane review*	No RCTs	No data*
Physical training and pulmonary rehabilitation	Cochrane review and RCT which was included in Cochrane as an abstract (data changed)* New RCT ⁵⁹	Pulmonary rehabilitation improved shuttle test results ⁵⁹ and QoL. ⁵⁹ No additional advantage of simultaneous inspiratory muscle training	
Oxygen (domiciliary)	No data as sole therapy*	Consider data from COPD showing benefit in survival*	
Surgery	Cochrane review*	No RCTs. Cohort studies suggest a benefit in selected cases.*	Reduced exacerbation rate similar to medically treated group.* Adverse events of surgery*
Ventilation for acute respiratory failure	Retrospective study ⁷⁷	Comparison of non-invasive ventilation (NIV) to mechanical ventilation. NIV failure rate of 33%. Mortality of 25%.	

ANTIBIOTICS (BY TYPE)	EVIDENCE TYPE/STUDY	SUMMARY OF RESULTS	NOTES
Vaccines			
Pneumococcal conjugate and polysaccharide vaccines	Cochrane review*	No RCTs	Advocated as vaccines pneumococcal and influenza reduce infection risk.
Influenza vaccines	Cochrane review*	No RCTs	
Acupuncture	RCT*	Improved QoL, but not in sputum or 6 min walking test.	
Model of follow- up			
Nurse led	Cochrane review*	No difference in exacerbations, but increased hospital admissions in nurse led compared to doctor led care.	Increased health care cost implications
Self-management program within a multi-disciplinary model	RCT ⁶⁵	Uni-centre RCT. Intervention group improved elements of self-care (eg exercise, medications) and QoL, no effect on lung function ⁶⁵	

*No new data based on updated searches on Pubmed (Sept-Oct 2013)-see paper² for references ie only new references are included here; COPD=chronic obstructive pulmonary disease; DB=double blind; FEV₁=forced expiratory volume in 1-second; HS=hypertonic saline; ICS=inhaled corticosteroids; LABA=long-acting beta-agonist; LTRA=leukotriene receptor antagonist; MPO=myeloperoxidase; NSAIDs=non-steroidal anti-inflammatory drugs; *Pa*=*Pseudomonas aeruginosa*; QoL=quality of life; RCT=randomised controlled trial; Rx=treatment.



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