

Cough in Children and Adults: Diagnosis, Assessment and Management n(CICADA) Australian Chronic Cough Position Statement Update

Update undertaken from
March 2021 - June 2022

Contents

Contents..... 1

Updated Position Statement - Introduction.....	4
1. Introduction	5
2. Overview of chronic cough	6
3. Chronic cough in children.....	16
4. Chronic cough in adults	26
5. Important causes of adult chronic cough	33
6. Adult unexplained/refractory chronic cough	36
Conclusion	55
References.....	56

List of tables

Table 1: Population exposures and associations with chronic cough	10
---	----

Table 2: Probability based diagnosis in children	22
Table 3: Significant conditions not to be missed in children.....	23
Table 4: Summary strength of recommendations for the efficacy of treatment of cough in association with the conditions in children.....	24
Table 5: Conditions associated with chronic cough in adults	29
Table 6: Evidence summaries for treating specific diseases that lead to chronic cough in adults	40
Table 7: Summary strength of recommendations for the efficacy of treatment of cough in association with the conditions in adults	51

List of figures

Figure 1: Definitions of chronic cough for clinical practice.....	6
Figure 2: Preventive strategies in children and adults.....	12
Figure 3: Algorithm for diagnosis and assessment of a child with chronic cough.....	18
Figure 4: "Red flags" and "cough pointers" in children.....	22
Figure 5: Diseases and/or exposures causing chronic cough.....	27
Figure 6: "Red flags" and "cough pointer" in adults.....	27
Figure 7: Algorithm for diagnosis and assessment of adult chronic cough.....	28

Updated Position Statement - Introduction

The objective of Updating the CICADA Position Statement is to address Priority Areas 3: Diagnosis, management, and care (Knowledge translation) of the National Strategic Action Plan for Lung Conditions (2019). A key action within this priority area is the ongoing revision, dissemination and implementation of evidence-based clinical practice guidelines and tools for lung conditions.

The first version of the CICADA Position Statement - CICADA: Cough in Children and Adults: Diagnosis and Assessment, Australian Cough Guidelines summary statement – was led by Prof Peter Gibson and Prof Anne Chang in collaboration with relevant clinicians and academics representing a multidisciplinary approach. For this second version of the guidelines a similar multidisciplinary expert committee was established that included clinicians, academics, allied health experts and consumers.

Expert Committee Membership

Co-Chairs: Assoc Prof Julie Marchant and Prof Peter Wark

Topic Leads:

- **Overview including prevalence and risk factors** – Dr Jennifer Perret
- **Neurophysiology and Future directions** – Prof Stuart Mazzone*
- **Overall approach to diagnosis assessment** (including cultural safety and security and the role of a multidisciplinary team approach) – A/Prof Andre Schultz
- **Children** – Prof Anne Chang*
- **Adults** – Prof Peter Wark

Committee and Working Group Members

- Assoc Prof Anne Vertigan*
- Prof Anne Holland
- Prof Sheree Smith
- Prof Shyamali Dharmage
- Prof Maree Toombs
- Adj Assoc Prof Debbie Rigby
- A/Prof Johnson George
- Dr Helen Petsky
- Dr Danielle Wurzel
- Dr Jennifer Mann
- Dr Kerry-Ann O'Grady
- Assoc Prof Emma Kennedy
- Dr David King
- Dr Jonathan Pham
- Mrs Lesley Versteegh
- Rebecca Dingle (Consumer member)
- Naomi Fitzakerley (Consumer member)
- Mearon O'Brien (LFA Guidelines Manager)

**Original authors from CICADA Summary Statement 2010*

Guidelines Development Process

From Jan 2021 to December 2022 members of the CICADA committee regularly convened (email, face-to-face, virtual meetings) to undertake extensive literature review and discuss recommendations. The committee included several working groups (children, adult, epidemiology and prevention, overall approach) who undertook systematic searches for relevant literature: published since 2010 (last CICADA update),¹ including but not limited to “all RCTs, systematic reviews, guidelines, position statements in any setting.” Databases searched included OVID-Medline, PubMed, Cochrane and EMBASE. Search results were then screened (total 6395 abstracts); a total of 277 new studies were included in this statement. The search strategies, PRISMA diagrams are included in the Technical report.

The recommendations use the principles of evidence-based medicine² and the GRADE approach to guide recommendations to inform the strength of the evidence: strong, weak, or no specific recommendation.³

The implications of strong recommendation are: for patients – most people in your situation would want the recommended course of action and only a small proportion would not, suggest request discussion if the intervention is not offered; for clinicians – most patients should receive this 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 – some 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 their values and preferences; for policy makers – policy making will require substantial debate.

1. Introduction

Cough is a common symptom that leads to medical consultation and results in significant health care costs. Cough can be caused with a wide range of diseases some of which can have serious health implications. Guidelines seek to standardise and assist in diagnosis, investigation, and management of cough.^{4,5} CICADA (Cough in Children and Adults: Diagnosis, Assessment and Management) is an Australian position statement for the clinical assessment and management of chronic cough first published in 2010.¹ In this updated position statement the burden of chronic cough, including the disproportionate burden in our First Nations population is highlighted, in addition to current updated approaches to assessment and management.

Recommendations for the initial assessment of chronic cough, particularly in primary care, are explored. The initial assessment for chronic cough relies on history and examination to elicit any “red flags” that may indicate an underlying disease or systemic exposure (Figure 4 children,

Figure 6 adults). Diagnostic probability-based management algorithms are important clinical decision tools^{6,7} and are presented for both children (Figure 3) and adults (Figure 7). Initial assessment in children and adults should always include a chest X-ray (CXR) and spirometry (when age >6 years).⁵⁻⁷ As high-quality evidence exists that the common aetiologies of chronic cough in children and adult are not the same,⁸ we will discuss the diagnostic causes

and management of paediatric and adult chronic cough separately in this updated statement.

Definitions of chronic cough

In both adults and children, estimating the duration of cough is critical in assessment.^{6,7} In children a chronic cough is defined as a daily cough for >4-weeks.⁶ Whereas in adults a chronic cough is a daily cough of >8-weeks.⁷ The initial assessment for chronic cough relies on a thorough history and examination to elicit any “red flags”, indicators that may signal an underlying disease or systemic exposure.⁹

In children, “specific cough” refers to a cough that occurs with a condition known to be associated with or cause a chronic cough. In children in whom there is a chronic cough without a defined cause the term “non-specific cough” is used. In children this usually undergoes spontaneous remission.⁸

The definitions in the adult literature are subtly different. Similar to children, most chronic cough is associated with a specific condition, that can be treated. Where cough persists despite optimal treatment of or exclusion of conditions known to be associated with cough, it is termed Refractory Chronic Cough (RCC). If no identifiable cause for the cough can be determined, it is termed Unexplained Chronic Cough (UCC), this is estimated to occur in 10% adults with chronic cough.⁵

Figure 1: Definitions of chronic cough for clinical practice

Cough a protective respiratory behaviour of forced expulsive manoeuvre of air, usually against a closed glottis, which is associated with a characteristic sound.

Acute cough: cough lasting up to 2 weeks

In children:

Protracted acute cough: cough lasting 2 to 4 weeks

Chronic cough: cough lasting more than 4 weeks

In adults:

Protracted acute cough: cough lasting 2 to 8 weeks

Chronic cough: cough lasting more than 8 weeks

2. Overview of chronic cough

Neurophysiology

Cough is an important airway defensive response, needed to keep the airways clear of foreign material or obstruction. However, cough can become a troublesome and unwanted symptom of many diseases.¹⁰ The act of coughing is a complex neurophysiological process that involves sensory, motor and integration divisions of the nervous system. Understanding this complexity relies on an appreciation that not all coughs are the same. For instance, cough can be an uncontrollable reflex response to an irritant stimulus in the airways, an example of this is the accidental inhalation of food or liquid during eating where an almost instantaneous and uncontrollable coughing bout serves to clear the airways of the inhaled substances.¹¹ However, cough can also be a purely voluntary act devoid of any peripheral sensory stimulus.^{11,12} For many, especially with troublesome coughing, their cough lays somewhere in between these two extremes where sensory detection of an airway stimulus

results in the perception of an irritation in the airways, clinically referred to as an urge-to-cough, which in turn elicits a cough response under varying levels of behavioural control.^{12,13}

Adding to the complexity is the discovery that two different sensory nerve pathways exist for initiating cough in response to airway irritant stimuli.^{10,14-16} Each of these pathways possess specialised receptors and ion channels that detect and transduce different types of cough stimuli. The first pathway is responsive to mechanical stimuli and rapid changes in the acidity of the airways, for example when food or other particulate matter enters the airways or when acidic gastric contents are aspirated. This pathway is particularly effective at evoking uncontrollable reflex coughing and may also be important for cough in diseases where there is an excess of mucous mechanically distorting the airway lining. The second pathway is specialised for a variety of chemical stimuli, such as the components of cigarette smoke, other environmental inhalants, and a wide variety of chemical mediators of inflammation. This pathway can elicit reflex coughing when the stimulus level is high, but additionally allows for the perception of niggly and irritating sensations in the airways, common in people with airways inflammation, which promotes behavioural coughing.

The two cough sensory nerve pathways send inputs to the brainstem. Here the information can be integrated with the brainstem networks that control breathing, reconfiguring the normal breathing pattern into a cough motor pattern which is sent to the muscles of respiration via phrenic, intercostal, laryngeal and abdominal motor neuron pathways.¹⁷⁻²⁰ This is the mechanism for a purely reflex cough. Alternatively, sensory inputs can ascend to the higher brain where they are integrated to encode for airway sensations and generate the urge-to-cough.^{12,19,21,22} Arising from the higher brain are a variety of regulatory pathways, including those for volitional cough induction, volitional cough suppression and placebo cough suppression,^{12,23} and the balance of their activity is an important for behavioural modulation of coughing.²⁴ It is also via these higher brain networks that presumably some of the comorbidities of chronic cough arise, including the cognitive impacts on mood leading to anxiety and depression.

In the disease setting, excessive coughing is thought to result from both a sensitization of the peripheral and brainstem pathways encoding for cough as well as a diminished capacity to engage higher brain processes that ordinarily help to control coughing.^{10,25,26} For example, sensory nerves in the airways and lungs can become more responsive to stimuli through the process of peripheral sensitization whereby mediators of inflammation act on the nerve fibres to lower their activation threshold or to change their expression of ion channels and receptors involved in nerve activation.¹⁶ Within brainstem integration sites, excessive peripheral sensory input leads to neuronal and glial cell changes that amplify further the peripheral inputs, a process called central sensitization.^{25,27} These hypersensitivities manifest clinically as coughing in response to innocuous stimuli (such as perfumes, laughing or eating dry crumbly food)¹⁰ and are demonstrable in patients with functional brain imaging.²⁶ Some patients with chronic cough also show reduced ability to volitionally suppress cough evoked by inhaled chemical stimuli²⁸, which again has been shown with brain imaging to be related to their inability to activate a cough suppression network in the brain.²⁶ Coughing is highly susceptible to placebo regulation through neural process that also regulate other clinically relevant conditions, such as chronic pain. This is important in practice, as many cough suppressant drugs struggle to demonstrate clinical efficacy over placebo in controlled trials.^{29,30}

Overall prevalence

Adults

In 2015, the overall global prevalence of “chronic cough” in adults was estimated to be 9.6% (95%CI: 7.6-11.7%), which was highest in Oceania (18.1%).³¹ However, epidemiological studies in general European adult populations that used stricter definitions found a 10-year incidence of new onset chronic cough and of chronic productive cough for >3 months duration from age 20-44 years at baseline to be 4.6% and 4.0% respectively.³² The prevalence of chronic cough (regardless of phlegm production) gradually increases to peak in the 6th decade and has been estimated to occur in 3% of never smokers, 4% of former smokers and 8% of current smokers across all adult age ranges.³³ Overall, chronic cough presents more commonly in middle-aged women.^{5,34,35}

The prevalence of chronic bronchitis in adults, which has a more specific definition than productive chronic cough, was 6.1% in a middle-aged general Australian population (aged 41-45 years),³⁶ compared with adult populations of Japan (1.7%),³⁷ Canada (<4%)^{38,39} and USA (5%). The prevalence of chronic bronchitis also increased with age,⁴⁰ with similar variation by smoking status.^{36,40}

Australian studies that specifically report chronic cough separately to chronic bronchitis are limited. Only one study was identified in the initial search criteria that reported chronic cough in Australian adults (prevalence 8.8%).⁴¹ Those data were collected between 2002 – 2008 in 1335 adults who were enrolled in a larger cohort in 1968 in Tasmania and they represented 15% of the original study population.⁴¹ There were no studies identified that reported chronic cough prevalence in Aboriginal and Torres Strait Islander adults.

Children

In children, a systematic review of the duration of symptoms post presentation to primary care or emergency department for respiratory infections found cough had not resolved in 10% by day 25.⁴² In a UK study of 179 children aged 5 to 16 years who had been coughing for 14 days or more, 37% had evidence of recent pertussis infection),⁴³ 62.3% of children were still coughing after 8 weeks (positive pertussis serology: 85%, negative pertussis serology: 49%). The proportion still coughing at 4 weeks was not reported. In children, a systematic review of the duration of symptoms post presentation to primary care or emergency department for respiratory infections found cough had not resolved in 10% by day 25.⁴² In a cross-sectional study of 385 children aged 6-15 years with HIV in Zimbabwe, 54% had a chronic cough of > 1 month duration.⁴⁴ Chronic productive cough without asthma diagnosis or symptoms was reported in 21.5% of 377 Alaskan Native/American Indian children aged 10-18 years in a school-based study in 1997 however the study did not define cough duration.^{44,45}

A study of 191 children aged < 7 years in four remote First Nations community in Western Australia between July 2018 and May 2019 reported chronic wet cough was present in 21 (11%) and unknown in 27 (14%).⁴⁶ In a single clinic setting in a remote Western Australian First Nations community,⁴⁷ 3.6% of children aged 0 – 8 years presenting to the clinic over a six month period had a record of chronic wet cough in their medical records; those data were not collected for children presenting for non-respiratory illnesses. In 180 First Nations children aged <5 years presenting to primary care in an urban setting in Queensland for any reason, 24% of children had a history of cough lasting more than 4 weeks in the previous 12 months.⁴⁸ In 12 month follow-up of these children, 25.7% (70/272) of episodes of acute respiratory illnesses with cough resulted in cough persisting beyond 4 weeks. These findings are similar to

a study of 839 children aged <15 years presenting to an Australian tertiary paediatric emergency department with cough as symptom.⁴⁹ Cough lasting >28 days was reported by parents/carers at time of presentation in 7.5% of children. At day 28 post presentation, 171/839 (20.4%, 95% CI 17.7 to 23.1) had persistent cough, irrespective of duration at baseline. In a prospective study of 509 children with cough aged < 15 years enrolled in both primary care and emergency departments in Queensland, 23% had persistent cough at day 28.⁵⁰ In a separate analysis of 362 children aged <5years from that same study,⁵¹ 33% reported a history of cough >4 weeks in the previous 12 months, 14.6% had a cough duration at baseline of >28 days and 26.2% were classified as having chronic cough at day 28.

In summary the prevalence of chronic cough in Australian children presenting with cough to emergency departments is 7.5%⁴⁹ while the prevalence of chronic wet cough approximates 13% for children of Indigenous communities.⁴⁶

Risk factors

Chronic cough is one of the most common presentations to general practice and referrals to respiratory specialists.

It is increasingly appreciated that chronic cough substantially impacts health-related quality-of-life and is especially distressing when it interferes with speech or causes urinary stress incontinence in women.⁵² Embarrassment and possible stigmatization can occur when coughing in public places (especially during the recent COVID-19 pandemic), and depression and anxiety as co-morbidities are common in chronic cough. Cough syncope is a serious consequence from severe acute bouts of coughing that could result in physical injury and motor vehicle accidents.

While chronic cough can arise from intense and persistent stimulation of a normal cough reflex (e.g. inhalation of a foreign body), it is more typically precipitated by a cough trigger in individuals with a heightened cough sensitivity reflex, or associated with specific conditions that feature cough as a presenting symptom.

Cough triggers can include upper respiratory tract infections (URTIs,) physical exercise, speaking on the telephone, pollens, subfreezing air and certain chemical triggers (e.g. exhaust fumes, poor indoor air, cigarette smoke, strong odours).⁵³

In a general population setting, the most common risk factors of chronic cough in adults include: female sex, asthma and gastroesophageal reflux disease (GORD) for never smokers; abdominal obesity, low income and asthma for former smokers; and the presence of airflow limitation for current smokers.³³ Some evidence suggests that a bidirectional relationship between chronic cough and chronic pain exists,⁵⁴ consistent with the concept of cough hypersensitivity in some individuals which will be discussed further in [cough hypersensitivity section](#).

Most observational studies included in the systematic search were not longitudinal (other than to assess response to trials of treatment), especially involving paediatric populations. The appropriate duration of chronic cough and chronic bronchitis was confirmed for all included studies, except as indicated by 'bronchitic symptoms' (

Table 1).

Table 1: Population exposures and associations with chronic cough

Causative agent	
Cigarette smoking	<p>Cigarette smoking is a frequent cause of incident chronic bronchitis,³⁵ and productive cough typically increases with daily intensity and cumulative pack-year history.⁵⁵ A smoking-related chronic cough could motivate smokers to quit the habit, but for some people, a transient increase in cough due to the normalization of previous airway desensitization from cigarette use can occur⁵ and productive cough typically increases with daily intensity and cumulative pack-year history.⁵⁵ A smoking-related chronic cough could motivate smokers to quit the habit, but for some people, a transient increase in cough due to the normalization of previous airway desensitization from cigarette use can occur.³⁴</p> <p>Having a label of “smoker’s cough” could deter health care professionals from considering referral for post-bronchodilator spirometry to confirm complications such as COPD and obstructive chronic bronchitis,⁵⁶ despite recommendations to do so by guidelines.^{57,58}</p> <p>Patients in psychiatric hospitals have high smoking rates (43-88%), with approx. one-half and one-third of middle-aged patients reporting chronic cough and chronic bronchitis respectively.⁵⁹</p>
Marijuana smoking	<p>Cannabis/marijuana use is likely to be related to respiratory symptoms, but the strength of evidence is low due to inherent difficulties obtaining accurate exposure information and heterogeneity of the cough outcome (e.g. cough most days for 3 months versus >6 coughs/day).^{60,61} A pooled estimate from two prospective studies was 2.04-fold (95%CI: 1.02-4.06) and 3.84-fold (1.62-9.07) increase in the relative risk for cough and sputum production respectively.⁶¹</p>
Vaping	<p>There is limited evidence for an association between nicotine vaping and bronchitic symptoms in senior high school students and graduates.^{62,63} Some association was seen between cannabis vaping and bronchitic symptoms.⁶³</p>
Occupational exposures	<p>In adults, occupational exposures contribute substantially to obstructive lung diseases and account for 13%, 14% and 16% of adult chronic bronchitis, COPD, and asthma respectively (95%CI range 0.06-0.22).⁶⁴ In prospective observational studies,^{32,65} incident chronic phlegm production was associated with exposure to metals (with cough), mineral dusts (especially coal), gases/fumes/solvents (especially men) and pesticides (especially women). Modest increases in risk of productive chronic cough from these occupational inhalant exposures have been seen for smokers but not non-smokers.⁶⁶ The prevalence of chronic bronchitis in coal miners increases with job duration and cumulative dust exposure.⁶⁷</p>

	<p>Among farmers, positive associations with chronic bronchitis have varied according to work with different livestock trades including dairy cattle, swine and horses.⁶⁸ In a systematic review, pesticide use was associated with chronic bronchitis (pooled OR 1.27; 95%CI: 1.23-1.31 I²=43%, n=6) without difference between insecticides and herbicides, however, the chronic bronchitis definition was not standardized.⁶⁹</p> <p>Among chefs, frying food using gas compared with electric stoves/plates/grills and for more than half the workday was associated with a 2.4-fold increase in risk for chronic bronchitis.⁷⁰ Increased bronchitic symptoms has recently been reported for employees in the coffee roasting industry who “worked near flavouring” (but the definition was not standardized).⁷¹</p>
Air pollutants	<p>In the context of increasing urbanization in Australian cities, heavy outdoor air pollution from industry and traffic sources can trigger a dry cough,⁵ and trigger cough among children with asthma,⁷² although associations are modest across general populations.^{73,74,5} and trigger cough among children with asthma,⁷² although associations are modest across general populations.^{73,74}</p> <p>Despite the success of public health policy in reducing smoking rates, chronic cough related to passive SHS exposure is still commonly reported for susceptible children⁷⁵ and increases the risk of productive chronic cough for adults.⁷⁶</p> <p>Firefighters exposed to metropolitan fires (and bushfire smoke) could be at increased risk for chronic bronchitis and associated COPD/emphysema.⁷⁷ Indoor and outdoor woodfire smoke exposure is an ongoing public health issue in Australian states that have adopted a high usage of wood-fire heaters. Biomass fuel burning is a strong risk factor for chronic bronchitis in houses that are poorly ventilated, which could be relevant to Indigenous Australians of rural/remote communities (no refs).</p> <p>Some evidence suggests that higher domestic levels of endotoxin from bedding and bedroom floors may be associated with chronic bronchitis in a general population without asthma.⁷⁸</p>
Potential paediatric predictors	<p>Non-independent predictors of chronic cough in young children in a paediatric hospital setting in QLD Australia (<6 years, 30% Indigenous) included: age <12 months; gestational age <37 weeks; underlying asthma/prior wheeze; and childcare attendances especially if continuous.⁵¹</p>
Obesity and/or diabetes	<p>While not classically associated with chronic cough, there could be a complex interplay as central obesity can worsen chronic cough, asthma and reflux-related cough are more severe in the obese, and obesity-related obstructive sleep apnoea and type II diabetes/metabolic dysfunction might increase chronic cough risk.^{79,80} Modest evidence that obesity could be associated with incident chronic cough.³⁵ Type II diabetes might be associated with -chronic bronchitis ever: a higher prevalence was seen (27.6% compared with 16.7% in</p>

	general population), but associations were not consistent across age-strata. ⁸¹
--	--

Abbreviations: CI = Confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio

Prevention of Chronic Cough

Assessment of the potential risk factors discussed in the previous section and modification of such exposures is essential to the optimal management of chronic cough. A summary of potential modifiable risk factors for prevention for chronic cough in children and in adults are displayed in

Figure 2 below.

Figure 2: Preventive strategies in children and adults

For children and adults:

Immunizations: pneumococcus, H. influenzae, B. pertussis

Avoidance of airway irritants

- Cigarette smoke, wood-fire smoke
- Fumes, strong odours, subfreezing air
- For those susceptible, animals, pollens

Public health education, policy, and advocacy

- To reduce smoking rates even further
- To phase out woodfire heaters

Knowledge transfer to patients and GPs

- Assess for red flags (Table 4 children, Table 7 adults)
- Early clinical review if chronic cough develops post-acute respiratory infection⁴⁹
- Early and adequate treatment of a chronic wet cough in children to minimize complications of protracted bacterial bronchitis such as asthma/wheeze and bronchiectasis^{82,83}

Additionally, for adults:

Workplace education about hazard minimization for workers of high-risk occupations

Supporting GPs to consider other diagnoses beyond "a smoker's cough"

- Pre-emptive spirometry with bronchodilator reversibility to confirm a diagnosis of asthma
- Pre-emptive spirometry referral to confirm a diagnosis of COPD ⁵⁶⁻⁵⁸
- Pre-emptive management of obesity and type II diabetes
- Pre-emptive detection of early lung cancer and laryngeal cancer

Abbreviations: COPD = Chronic obstructive pulmonary disease; B. pertussis = *Bordetella pertussis*; GP = General practitioner; H. influenzae = *Haemophilus influenzae*

Addressing chronic cough in Aboriginal and Torres Strait Islander people in Australia

Australian First Nations people are disproportionately affected by chronic lung conditions such as protracted bacterial bronchitis and bronchiectasis that typically present with chronic wet cough. Of note, there is a profound mortality gap of 22 years between First Nations and non-First Nations Australians with bronchiectasis.⁸⁴

Due to multiple factors, chronic wet cough in children of Australian First Nations heritage is often incorrectly considered normal by both families and health practitioners.⁴⁷ First Nations Australians who have been symptomatic since childhood are more likely to have significantly poorer clinical outcomes – suggesting that poorly managed respiratory illness in childhood can have serious flow-on effects into adulthood.⁸⁵ Timely detection and optimal management of children with chronic wet cough is, therefore, an essential element of primary and secondary disease prevention.

Focused Strategies

A systematic review of studies published in the past decade has highlighted potential strategies in combatting chronic wet cough in this population:

Addressing environmental factors (*Level of evidence: good; Strength of recommendation: strong*) Observational data has suggested that air quality (including airborne particulate matter and bacteria) may be associated with increased prevalence of chronic wet cough. In particular, dry weather, dusty conditions and second-hand cigarette smoke exposure have been proposed as environmental risk factors.⁴⁶

Culturally secure health information to facilitate detection of chronic wet cough (*Level of evidence: satisfactory; Strength of recommendation: strong*) Timely treatment of chronic wet cough in childhood is essential to avoid complications such as bronchiectasis. Accurate history taking, which is critical for the detection of chronic wet cough, is facilitated in First Nations settings by the provision of appropriate health information in a culturally secure way. Community engagement at a local level can also help to improve health literacy and promote early healthcare-seeking by families, in a manner that is culturally and linguistically appropriate.⁴⁷

Targeted education of clinicians (*Level of evidence: satisfactory; Strength of recommendation: strong*) Research into clinicians working with First Nations communities has identified challenges to managing chronic wet cough - including limited training and inappropriate normalisation of cough in children by healthcare practitioners.⁸⁶ Targeted education and training of clinicians has been shown to improve physician assessment of chronic cough and appropriate antibiotic prescription.⁴⁷

Utilising chronic cough management algorithms (*Level of evidence: excellent; Strength of recommendation: strong*) Two randomised controlled trial of Australian children, including children of First Nations descent, has demonstrated the effectiveness of management algorithms for chronic cough, as compared to usual care.^{50,87} Written decision-aids may be particularly useful for clinicians working in resource-limited healthcare settings or remote areas with little or no access to specialist care.

Role of the multidisciplinary team

Healthcare models for the treatment of chronic cough vary and the optimal model of care is yet to be determined. The diagnosis and management of chronic cough may at times require a multidisciplinary approach including respiratory medicine, otorhinolaryngology, gastroenterology. In cases where occupational exposure or allergy is suspected, an occupational physician or allergist may facilitate diagnosis and management. After a complete diagnostic workup, referral to a speech and language therapist should be considered for those patients who do not respond to medical therapy.⁸⁸

Paediatric aerodigestive clinics and adult-centred multidisciplinary chronic cough clinics have been established with the goal of reducing the number of separate referrals, facilitating timely diagnosis, and reducing the total number of invasive diagnostic procedures.⁸⁹⁻⁹³ One retrospective medical record review suggested that a tripe endoscopy procedure, performed by an otolaryngologist, pulmonologist and gastroenterologist might be a useful diagnostic approach for patients with chronic cough.⁸⁹ Further research is required to determine the impact of multidisciplinary chronic cough services on patient outcomes. Such specialist clinics are not yet available to all patients in Australia, and the role of the general practitioner in coordinating multi-specialist and allied health care remains crucial.

Future directions

Recent advances in basic and clinical cough research are impacting the diagnosis, assessment and treatment of troublesome coughing.

Basic studies of cough neurophysiology in animals have led to the development of several new antitussive medicines that are now in advanced clinical trial. This notably includes molecules that block the P2X3 and P2X2/3 ATP receptors.⁹⁴ One candidate molecule, Gefapixant, recently met phase III trial primary end points for the treatment of refractory and unexplained chronic cough and is now moving forward into licensing for these conditions.⁹⁵ Another, Camplipixant is currently in phase III trial (results not yet available). Several other P2X3 antagonists were investigated in phase II trials^{94,96} but advancement of these programs has been discontinued. Trials with centrally acting compounds, Orvepitant and Aprepitant, that act on brain neurokinin 1 receptors have also demonstrated some clinical benefit,⁹⁶ notably including in patients with cough associated with lung cancer (Aprepitant) and future studies are planned (for Orvepitant) in other difficult to treat cough cohorts, including IPF. Recently, the opioid analgesic nalbuphine also demonstrated efficacy in IPF cough.⁹⁷

Cough reflex testing with capsaicin has been a cornerstone for preclinical animal and human research into cough sensitivity. Based on reflex testing in animals, several other molecules were predicted to be efficacious in human with chronic cough but failed in clinical trial. This includes molecules acting at TRPV1, TRPV4 and sodium channels, central nicotinic receptors and NMDA receptors (reviewed in⁹⁶). Although disappointing, these investigations have led to a clearer understanding of the value of preclinical research into cough mechanisms in patients. It is now recognised that the results of cough challenge testing are not predictive of therapeutic efficacy of antitussive compounds but rather an extremely valuable tool to assess appropriate drug target engagement. This is refining the pipeline for translating research into practice and allowing for improved dosing strategies in clinical trials. Preclinical and clinical trial studies are also facilitated by the use of a range of validated questionnaires and patient reports of subjective severity and treatment outcomes.^{10,98} Interestingly, improvements in the actual number of cough events per day doesn't always translate to improved patient reports of their cough, and vice versa. This supports the multi-dimensional nature of cough and underpins a major challenge in developing efficacious treatments. These subjective tools are not commonly utilised in clinical practice but can provide an important insight into cough severity and management.

New variations of cough challenge testing, including with different tussive substances and the use of cough reflex suppression testing, are demonstrating an under-appreciated heterogeneity in cough stimulus responsivity in patients as well as identifying new mechanisms underpinning chronic cough.^{28,99,100} These observations, along with a lack of uniformity in the therapeutic benefits of antitussives in recent clinical trials and other preclinical and clinical observations have led to the proposal that distinct patient cough endotypes exist.¹⁰¹ To date

there are no available biomarkers to conclusively define these endotypes, but their existence will have important implications for therapeutic management. Accordingly, there is a growing acceptance in the field that a more personalised approach to medical care will be required, rather than a single drug that treats all troublesome cough.¹⁰

3. Chronic cough in children

Diagnosis and assessment

The initial assessment for chronic cough seeks to characterize the condition using history, elicit any alarm symptoms known as “red flags” or findings (Figure 4) that might indicate a serious underlying disease, and then to identify whether there is a specific disease present that is associated with chronic cough (termed specific cough).

Specific cough

Specific cough refers to a cough that occurs with a condition known to be associated with or cause a chronic cough. Identification of the many different conditions that are associated with chronic cough forms the basis of specific treatment and further investigation. These conditions can be identified by a probability based diagnostic approach (Table 2), consideration of important conditions not to be missed (Table 3), and by reviewing cough pointers, an approach which has been validated in children.¹⁰² Methods for systematic and objective cough assessment are also available and at present are mainly used in research settings or specialised cough clinics.¹⁰³

Management

The management of chronic cough is based around addressing the common issues of environmental exposures and patient or parental concerns, followed by institution of specific therapy. Children are differentiated from adults when considered appropriate in the knowledge that while they share similarities, there are also substantial differences.⁸

Environmental exposures: Tobacco smoke exposure, both active and environmental, is a significant trigger for cough. Cessation of parental smoking can successfully reduce cough in children.¹⁰⁴ [Grade: Strong] Other potentially relevant exposures include certain forms of home heating and respiratory irritants such as particulates and proximity to high level of road traffic. Angiotensin converting enzyme inhibitor (ACEI) use may be associated with persistent cough, which is more frequent in adults (c.f. children).¹⁰⁵ Management consists of evaluation of the risks and benefits of ACEI therapy and cessation if appropriate.

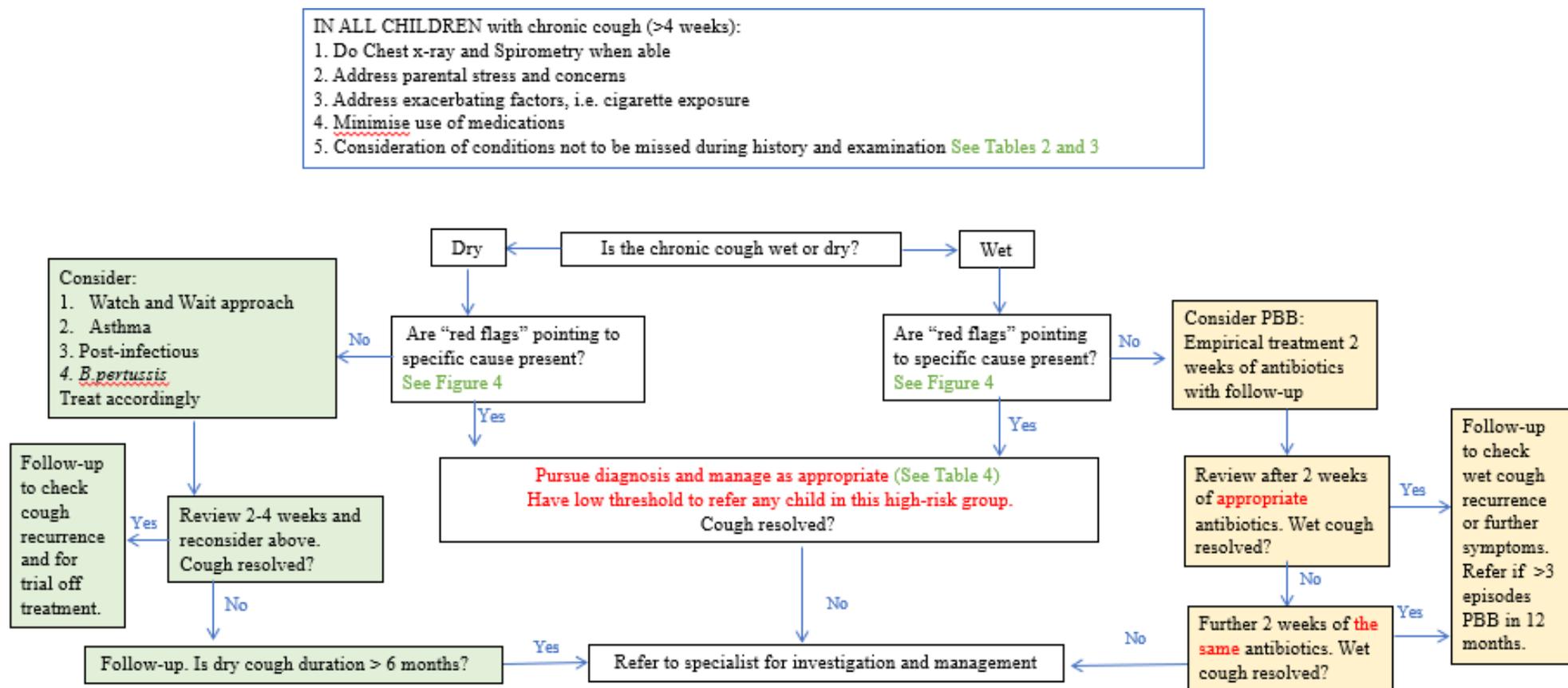
Patient/parental concerns: Patients and their carers have significant concerns and fears in relation to the aetiology, and outcome of the cough and the presence of a serious underlying disease.⁶ Providing information on the possible cough aetiology, time course for resolution of cough, and expected management may help reduce anxiety.¹⁰⁶ Education is most effective when combined with a medical consultation.¹⁰⁷ Written information without health professional consultation has only modest benefits.^{108,6} Providing information on the possible cough aetiology, time course for resolution of cough, and expected management may help reduce anxiety.¹⁰⁶ Education is most effective when combined with a medical consultation.¹⁰⁷ Written information without health professional consultation has only modest benefits.¹⁰⁸

Use of management algorithm

There is high quality evidence that using children-specific cough management algorithms improves clinical outcomes as shown in a systematic review that focused on chronic cough managed by specialists.⁹ These findings were recently confirmed in another RCT where the

cough management algorithm was applied when community-based children transitioned from acute cough to chronic cough at the 4-week timepoint.⁵⁰ The steps in the child-specific cough algorithms are largely based on assessment of cough characteristics and pointers⁹ and management targeted to the underlying aetiology⁶ rather than an empirical treatment. Such an approach has also been suggested by position statements/guidelines from other countries^{6,75,109-111} but not all. Figure 3 shows the CICADA paediatric algorithm, adapted from international ones.^{6,110,112}

Figure 3: Algorithm for diagnosis and assessment of a child with chronic cough



Specific cough- lower airway diseases

Protracted bacterial bronchitis

This condition is considered in children with chronic wet cough in the absence of other specific cough diagnoses or “red flags”/cough pointers.¹⁰⁹ CXR and spirometry are usually normal. Medium-term (2 to 4 weeks) antibiotic treatment (typically amoxicillin-clavulanate if no history of allergy) should lead to complete cough resolution^{83,113} [GRADE: Strong]. The diagnosis can only be definitive when patients become asymptomatic with treatment.^{82,109,114} A significant proportion of children with PBB have ongoing symptoms at 5-year follow-up, including bronchiectasis in 9.6%, hence these children need careful follow-up and specialist referral if recurrent episodes >3 per year or treatment fails (Figure 3).¹¹⁵

Asthma

Asthma is considered as a cause of chronic cough if the cough is episodic and associated with other features such as: expiratory wheeze and/or exertional dyspnoea, a cough with an obstructive ventilatory pattern on lung function testing, particularly if bronchodilator responsive. Other suggestive features but less definitive include presence of exercise induced cough or atopy. The diagnosis should be confirmed by spirometry with a positive bronchodilator response, or a positive bronchial provocation challenge. Treatment is according to current asthma management guidelines and involves education and self-management, inhaled bronchodilators and inhaled corticosteroids. Treatment is expected to be effective within 2-4 weeks [GRADE: Strong]. In children, chronic cough without the above features is seldom due to asthma and inhaled corticosteroids are not indicated unless there are positive features to suggest asthma. When used, the trial period should be of a defined limited duration in order to confirm or refute the hypothesised diagnosis.¹¹² Fractional exhaled nitric oxide (FeNO) is increasingly advocated as a biomarker for eosinophilic-related lung disease, predominantly asthma but in the interpretation of studies involving FeNO levels in patients, clinicians need to be cognizant of the many factors that influence these levels beyond clinical disease.¹¹⁶ FeNO levels alone cannot be used to diagnose asthma in children.¹¹⁶ Using FeNO levels alone for diagnosing and managing children with chronic cough without other cough pointers is yet to be clearly defined.⁶

Specific cough- upper airway disorders

Allergic rhinitis

Allergic rhinitis can be diagnosed by eliciting signs and symptoms of nasal inflammation: nasal itching, nasal blockage, nasal discharge, conjunctivitis and nocturnal snoring. Relevant allergenic triggers can be identified by measuring allergen specific IgE using skin prick test or RAST testing with allergens limited to likely exposures or by exclusion of specific allergen. Indiscriminate use of a large number of allergens should not be undertaken. Treatment of allergic rhinitis follows current evidence-based management guidelines [Grade: Weak].^{117,118} In children, anti-histamines have not been shown to be efficacious.^{6,119}

Post-nasal drip/upper airway cough syndrome: The evidence that postnasal drip (discharge) is a significant cause of cough in children is tenuous and when present, likely reflect co-existing upper airway disease. Some paediatric studies reported ‘upper airways cough syndrome’ as the aetiology of chronic cough^{8,75} but we did not find quality RCTs on therapies for upper airway disorders on children with non-specific cough. Clinicians are referred to guidelines for

managing allergic rhinitis but there are no data specific for cough in these updated guidelines.^{117,118}

Chronic rhinosinusitis

Chronic cough may occur concurrently in children with chronic rhinosinusitis.^{120,121} However, any association between rhinosinusitis and cough does not necessarily indicate cause. Notably, the respiratory bacterial causes of chronic rhinosinusitis and PBB in children are identical and so is the treatment recommendations for prolonged antibiotics (~2-3 weeks of amoxicillin-clavulanate as first line).^{109,120,121} While there is currently insufficient data, this raises whether the chronic wet cough in children with chronic rhinosinusitis is actually caused by PBB.

As CT-defined abnormality consistent with sinusitis is common (up to 50%)¹²² in asymptomatic children, it is unsurprising that the American Academy of Pediatrics (AAP) acute bacterial rhinosinusitis guideline recommends undertaking sinus CT only when orbital or central nervous complications are suspected (i.e., not routinely). The Infectious Diseases Society of America (ISDA)¹²¹ and USA Otolaryngologists' consensus statement,¹²⁰ also does not recommend routine radiological assessment.

Obstructive sleep apnoea

Obstructive sleep apnoea has been increasingly recognized to be associated with chronic cough in adults and, to a limited extent also in, children.¹²³ OSA is suggested by a history of snoring associated with witnessed apnoeas, sleep disturbance or sweating at night, excessive daytime sleepiness, failure to thrive (in infants), obesity, large tonsils, or nasal blockage. The diagnosis is confirmed by polysomnography. However, the association between cough and OSA is very weak as there is a paucity of data. In children with OSA and cough, the OSA itself should be treated rather than attributing OSA as the cause of the chronic cough in children.

Gastro-oesophageal reflux disease (GORD)

Chronic cough may represent an extraesophageal manifestation of GORD although controversies to cause and effect exists. In paediatric cohorts, GORD is not commonly identified as the cause of chronic cough.⁸ Also, there is little current convincing evidence that GORD is a common cause of isolated chronic cough (i.e., without GI related GORD symptoms) but proving causality is difficult.^{124,125} Data from paediatric GOR-specific evidenced-based guidelines from the UK National Institute for Health and Care Excellence¹²⁶ and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.¹²⁷ Data from paediatric GOR-specific evidenced-based guidelines from the UK National Institute for Health and Care Excellence¹²⁶ and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition¹²⁷ were consistent with findings of USA CHEST guidelines.^{8,112,128} Thus, like other chronic guidelines,^{6,75,128} CICADA recommends against empirical treatment for GORD in children with chronic cough or fundoplication for the treatment of isolated cough in children (Table 4). When symptoms of GORD are present, paediatric GORD guidelines^{126,127} should be used.

Tic and Somatic cough syndrome

Tic (habit cough) and Somatic cough syndrome (psychogenic cough) are characterised by a continuous, excessive dry barking/honking cough in a child with no "red flags" in history or

examination. The key indicator is that cough is absent in sleep. Treatment involves suggestion therapy without further investigation.^{129,130}

Non-specific cough in children

Non-specific cough is a chronic dry cough that is not associated with any of the cough pointers or cough associated diagnoses. Investigation with CXR and spirometry is normal. Most patients with non-specific cough undergo spontaneous resolution or improvement⁸ but they need to be reviewed to ensure that no new cough pointers emerge later. The management of non-specific cough adopts the approach of counsel, watch, wait and review [GRADE: Strong], and addresses parental stress and concerns [GRADE: Strong]. At each review, look out for specific pointers/"red flags"(Figure 4). CICADA recommends against use of narcotic cough suppressants¹³¹ in children [GRADE: Strong].

Figure 4: “Red flags” and “cough pointers” in children

<p>dyspnoea (at rest or exertional)</p> <p>recurrent episodes of chronic or wet or productive cough</p> <p>recurrent pneumonia</p> <p>chest pain</p> <p>haemoptysis</p> <p>systemic symptoms: fever, weight loss, growth failure</p> <p>neurodevelopmental abnormality</p> <p>feeding difficulties (including choking/vomiting)</p> <p>stridor and other respiratory noises</p> <p>abnormal clinical respiratory examination (e.g. crackles, digital clubbing)</p> <p>abnormal systematic examination (e.g. growth failure)</p> <p>abnormal chest X-ray</p> <p>abnormal lung function</p> <p>co-existing chronic diseases (e.g. immunodeficiency, syndromes)</p>
--

Table 2: Probability based diagnosis in children

Probability based Diagnosis of Chronic Cough in children	
If the <u>examination, chest x-ray and spirometry are normal</u> , the most common diagnoses or exposures associated with chronic cough are:	
Common diagnoses	<p>Protracted bacterial bronchitis (if wet/productive cough and no other systemic symptoms or signs¹⁰⁹)</p> <p>Asthma (if other respiratory symptoms are present)⁸</p>
Exposures	<p>Respiratory infection (post-infectious cough, including pertussis)</p> <p>Tobacco smoke or e-cigarettes/vaping and other pollutants (active, environmental) can exacerbate cough BUT are rarely the cause</p>

Table 3: Significant conditions not to be missed in children

Significant conditions not to be missed in children with chronic cough	
Condition	Examples of typical symptoms
Protracted bacterial bronchitis	Wet/productive cough and no other systemic symptoms or signs ¹⁰⁹
Asthma	Recurrent wheeze and/or dyspnoea responsive to β_2 agonists
Tic (habit cough) and somatic cough syndrome (psychogenic cough)	Continuous, excessive dry cough with no signs of physical disease. Stops when asleep or distracted.
Congenital airway abnormalities	Symptoms commencing in infancy/early childhood
Recurrent aspiration	Choking or coughing with feeds
Foreign body inhalation	Symptoms commenced after choking episode
Chronic infection	<i>Tuberculosis: Focal signs, weight loss, lymphadenopathy, contact history</i> <i>Lung Abscess: Fever and local signs</i> <i>Pertussis: Dry cough, contact history, paroxysms in unvaccinated children</i>
Bronchiectasis, chronic suppurative lung disease, cystic fibrosis	Wet cough not responding to 4 weeks of antibiotics or recurring,
Chronic atelectasis	Focal signs on auscultation
Interstitial lung disease	Diffuse inspiratory crepitations +/- growth failure +/- hypoxia

Table 4: Summary strength of recommendations for the efficacy of treatment of cough in association with the conditions in children

Recommendations for Children	Level of evidence*	Strength of recommendation†
Cessation of parental smoking to reduce cough	Good	Strong
COUGH WITH ALLERGIC RHINITIS Treatment according to current rhinitis management guidelines involving topical nasal corticosteroid, antihistamines, and allergen management.	Poor	Weak
COUGH WITH OBSTRUCTIVE SLEEP APNEA Tonsillectomy and adenoidectomy in children	Poor	Weak
COUGH WITH ASTHMA Treatment according to current asthma management guidelines and involves education and self-management, inhaled bronchodilators and inhaled corticosteroids. If empirical treatment is used, review in 2-4 weeks	Good	Strong
COUGH WITH PROTRACTED BACTERIAL BRONCHITIS The use of medium-term (2 to 4 weeks) antibiotics for protracted bacterial bronchitis.	Excellent	Strong
COUGH WITH GORD Treatment(s) for GORD should <u>not be used</u> when there are no gastro-intestinal clinical features of GORD and paediatric GORD guidelines should be used to guide treatment and investigations.	Good	Weak
In children the use of laparoscopic fundoplication for the treatment of chronic cough	Poor	Strong recommendation against
Nonspecific or Refractory Cough for children		
Address patient/parental stress and concerns	Poor	Strong
Address exacerbating factors e.g. tobacco smoke exposure	Good	Strong
Minimise use of medications other than demulcents, i.e. honey if no contraindications (young age) exist	Good	Strong
Adopt counsel, watch, wait and review approach	Excellent	Strong
Empiric trial of inhaled corticosteroid therapy	Poor	No recommendation

Recommendations for Children	Level of evidence*	Strength of recommendation†
Empiric trial of proton pump inhibitors	Good	Strong recommendation against
Speech pathology techniques designed to relieve glottal constriction during inspiration and to recognise and alter response to precipitants.	Poor	No recommendation
Antitussive therapy with narcotic	Good	Strong recommendation against

Notes: *NHMRC additional levels of evidence and grades of recommendations for developers of guidelines.² †The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to grade the strength of recommendations.³

4. Chronic cough in adults

Diagnosis and assessment of chronic cough in adults

A cough lasting more than 8-weeks in adults is not normal. It may indicate more serious underlying disease that requires investigation and treatment. Unlike in children, the presence of chronic cough in adults is not likely to resolve, with most experiencing persistence of cough up to a year later.¹³² It is not appropriate to take a wait and watch approach. Unexplained chronic cough is disabling and adversely affects the lives of sufferers.¹³³

The assessment of chronic cough in adults includes a history^{5,134} to define the duration and characteristics of the cough (sputum production, cough hypersensitivity, triggers) to elicit any “red flags” to suggest underlying disease (Figure 6).^{5,134}

We recommend a CXR, and spirometry followed by use of a probability-based management algorithm (Figure 7) considering the most important or frequent conditions based on probability.

For each cause, key aspects of history and investigations, are summarised in Table 5. Always ask about exposure to cigarette smoking, vaping and occupational hazards (lungfoundation.com.au). It is important to remember that more than one process may be present and contributing to chronic cough.

Therefore, the assessment of chronic cough in adults should:

- Determine the duration and character of cough. Is chronic cough present?
- Elicit any “red flag” findings that may indicate serious underlying disease (Figure 6)
- Determine by history and relevant investigations if there is/are specific disease(s) or systemic exposure present that is associated or triggering chronic cough (Table 5)
- Optimally manage specific diseases associated with cough (Table 6 and Table 7)
- Determine if there is refractory or unexplained chronic cough and refer to a cough specialist¹³⁵

Other important characteristics of cough have emerged from a better understanding of the neurobiology of the cough reflex and are valuable to obtain from history when describing cough in adults.⁵ Troublesome cough is associated with an increased urge to cough, this has been described as an airway irritation or itch not relieved by coughing.¹³⁴

Where cough persists despite optimal treatment of diagnosed conditions it is termed refractory chronic cough. If no identifiable cause for the cough can be determined, it is termed unexplained chronic cough.⁵ Unexplained chronic cough is increasingly being recognised as an important chronic health condition in its own right, estimated to occur in 10% of adult chronic cough.¹³⁶

Figure 5: Diseases and/or exposures causing chronic cough

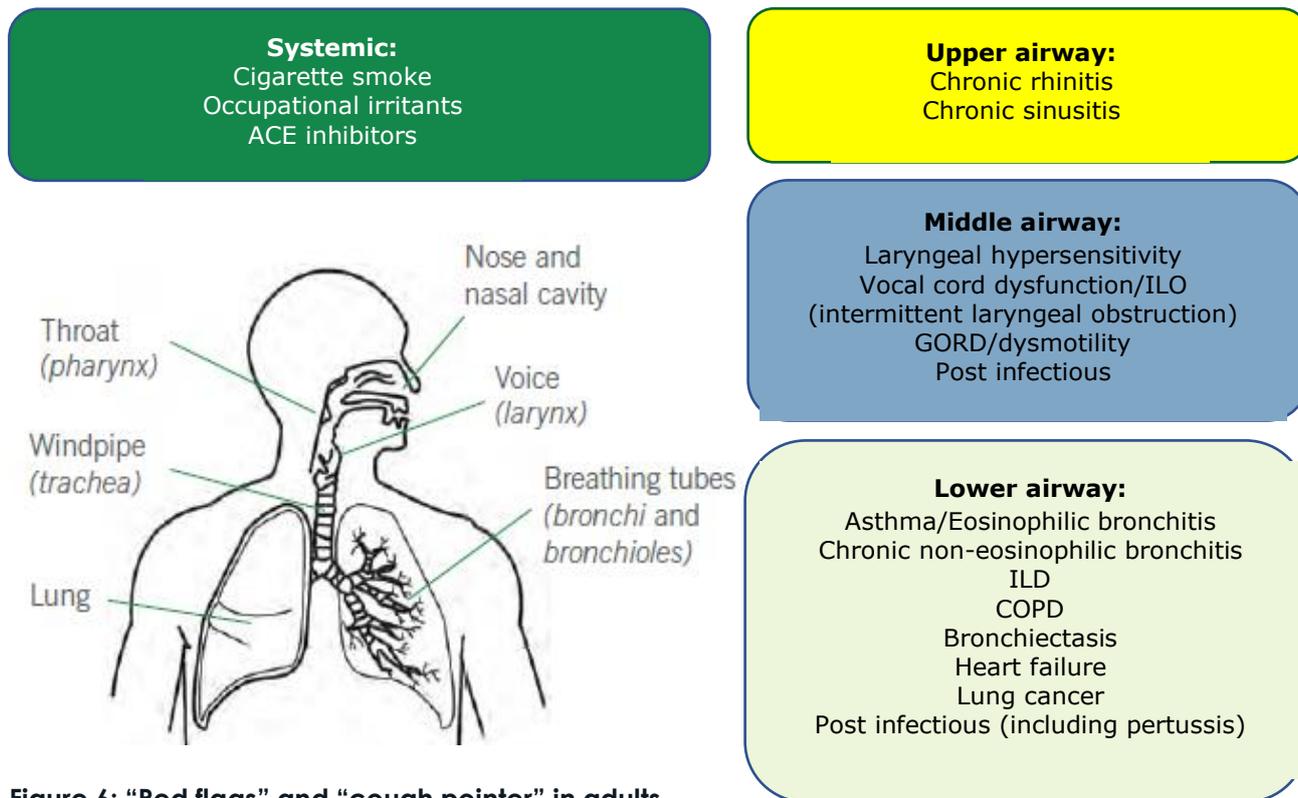


Figure 6: “Red flags” and “cough pointer” in adults

- Haemoptysis
- History of smoking/vaping (especially new cough, altered cough, cough with voice disturbance)
- Prominent dyspnoea, especially at rest or at night
- Substantial sputum production
- Hoarseness of voice
- Systemic symptoms: fever, weight loss
- Swallowing difficulties (including choking or vomiting)
- Recurrent pneumonia
- Abnormal clinical respiratory examination (e.g. crackles, wheeze, digital clubbing)
- Abnormal chest x-ray

Note: These symptoms all suggest serious underlying lung disease may be present. Further investigations such a CT chest should be considered, and referral considered

Figure 7: Algorithm for diagnosis and assessment of adult chronic cough

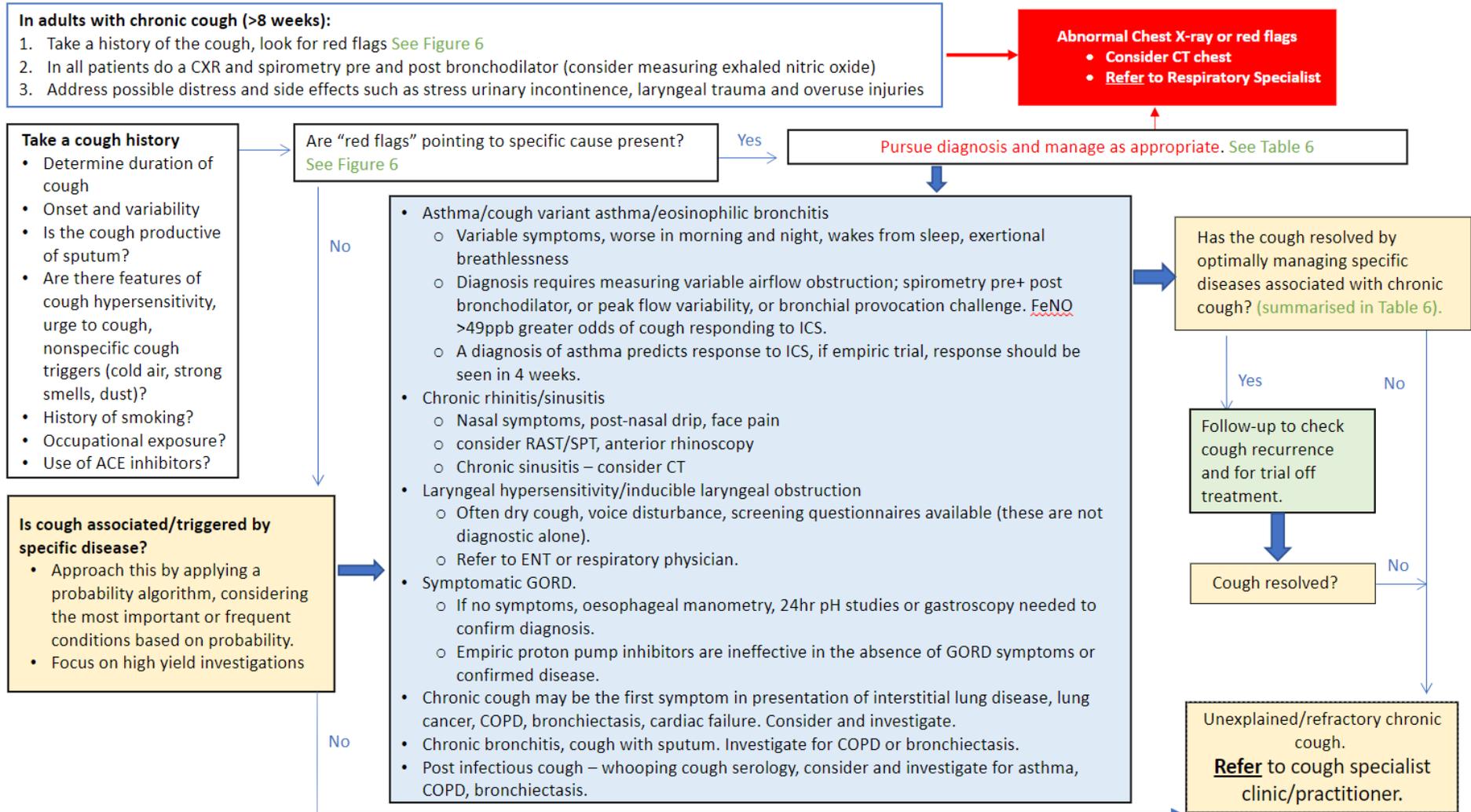


Table 5: Conditions associated with chronic cough in adults

Condition	History, key features	Investigations	Guidelines on diagnosis
Chronic rhinitis	Nasal obstruction (variable or persistent), loss of smell, nasal discharge, present in 88%	RAST/SPT Anterior rhinoscopy	ASCIA Information for Health Professionals: CRSwNP Position Paper ¹³⁷
Chronic sinusitis	Nasal obstruction, and at least one other symptom including nasal discharge, postnasal drip and reduction or loss of sense of smell and facial pain	RAST/SPT CT Sinuses	ASCIA Information for Health Professionals: CRSwNP Position Paper ¹³⁷
Laryngeal hypersensitivity	Hypersensitive cough reflex Allotussia	Laryngeal Hypersensitivity Questionnaire	
Vocal cord dysfunction/ Inspiratory Laryngeal Obstruction (ILO)	Inspiratory dyspnoea Throat tightness May also have dysphonia and sensation of choking and suffocation	Functional laryngoscopy Laryngeal CT Flattened inspiratory flow volume loops Questionnaires are not suitable for diagnosis	
GORD/dysmotility	Cough with heartburn or reflux symptoms	Oesophageal manometry	Chronic Cough Due to Gastroesophageal Reflux in

	cough associated with meals	pH-metry for resistant cases	Adults: CHEST Guideline and Expert Panel Report ¹³⁸
Post infectious	Persisting bouts of coughing, following acute respiratory illness	<i>B.Pertussis</i> serology CT chest	
Asthma Cough variant asthma Eosinophilic bronchitis without asthma	Cough with wheeze and dyspnoea Cough as the only symptom	Spirometry (bronchodilator reversibility) Elevated FeNO Peak flow variability Bronchial provocation challenge Reversible airflow limitation as for asthma Elevated FeNO Bronchial provocation challenge to rule out No evidence of variable airflow obstruction Elevated FeNO May require induced sputum to rule out	Australian Asthma Handbook – Making a diagnosis ¹³⁹

Chronic non-eosinophilic bronchitis	Sputum production without airflow obstruction.	Spirometry: pre/post bronchodilator to exclude asthma and COPD Consider bronchiectasis and need for HRCT chest	The COPD-X Plan: Section C- Case finding and confirm diagnosis ¹⁴⁰
Interstitial lung disease (ILD)	Presence of dyspnoea	HRCT chest History (exposures, serology)	Diagnosis and Management of idiopathic pulmonary fibrosis: TSANZ position paper ¹⁴¹
Chronic obstructive pulmonary disease (COPD)	Exertional dyspnoea, sputum production, history of smoking/exposure to other noxious agents	Spirometry (post-bronchodilator FEV1/FVC <0.7)	The COPD-X Plan: Section C- Case finding and confirm diagnosis ¹⁴⁰
Bronchiectasis	Sputum production, chronic bronchial infection	HRCT chest	Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. Thoracic Society of Australia and NZ guidelines ¹⁴²

Congestive cardiac failure	Dyspnoea, peripheral oedema, crackles +/-wheeze on auscultation	ECG, CXR Biomarkers (BNP or NT-BNP) Echocardiography Cardiac CT.	National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 ¹⁴³
Lung cancer	Haemoptysis, dyspnoea, chest pain, smoking history, constitutional symptoms	CXR, CT chest Bronchoscopy PET scan	Cancer Council Australia Clinical practice guidelines for the treatment of lung cancer ¹⁴⁴

Abbreviations: ASCIA = Australasian Society of Clinical Immunology and Allergy; COPD = Chronic obstructive pulmonary disease; CT = computerized tomography; CXR = Chest X-ray; ECG = electrocardiogram; FEV = Forced expiratory volume; GORD = Gastro-oesophageal reflux disease; HRCT = High-resolution computed tomography; ILO = Inspiratory Laryngeal Obstruction; PET = Positron emission tomography; RAST/SPT = Radioallergosorbent testing/Skin prick test; TSANZ = Thoracic Society of Australia and New Zealand

5. Important causes of adult chronic cough

Asthma/ Eosinophilic bronchitis/Cough-variant asthma

Eosinophilic airway inflammation is found with 30 to 50% of adult patients with chronic cough¹⁴⁵⁻¹⁴⁷ and may reflect asthma, cough-variant asthma or eosinophilic bronchitis. This reflects its importance in the diagnostic work up of these patients. Asthma has been demonstrated in 24 to 32% of adults with chronic cough.¹⁴⁶ In asthma, cough is a frequent symptom associated with chest tightness, wheeze and breathlessness. The symptoms are often variable, they may be seasonal, are often worse at night or in the early morning and may be associated with allergic disease.¹³⁹ Asthma diagnosis is defined by the presence of variable airflow obstruction as measured by spirometry, peak flow monitoring or bronchial hyperresponsiveness,^{137,139,148,149,145-147} and may reflect asthma, cough-variant asthma or eosinophilic bronchitis. This reflects its importance in the diagnostic work up of these patients.

Cough variant asthma has been regarded as a sub type of asthma though is much less common and presents solely with cough without dyspnoea or wheeze. In cough variant asthma there is normal spirometry without bronchodilator variability but there is evidence of airway hyperresponsiveness on bronchial provocation challenge and it responds to treatment of asthma.¹⁵⁰

Finally, there are those with chronic cough and eosinophilic bronchitis, defined as an increase in lower airway eosinophils that is not associated with airflow obstruction (patients have normal spirometry) or bronchial hyperresponsiveness on bronchial provocation challenge.^{146,147} Traditionally this could only be diagnosed in research settings by directly measuring airway eosinophils on induced sputum limiting the ability to diagnose this disorder outside of specialist clinics. The measurement of exhaled nitric oxide (FeNO) has been proposed as a surrogate marker of eosinophilic airway inflammation, it can be performed in clinical settings and has been investigated for its role in the diagnosis of chronic cough and asthma. A systematic review of 15 studies in 2187 adults with chronic cough assessed its ability as a diagnostic test for cough variant asthma and eosinophilic bronchitis.⁵ It was found to have good diagnostic accuracy in predicting cough variant asthma, with an area under the curve of 0.87 (95% CI 0.83 to 0.89), with higher specificity than sensitivity, but its ability to predict eosinophilic bronchitis without asthma was lower, area under the curve 0.81 (95% CI 0.77 to 0.84).⁵ The review concluded it could be a useful test to diagnose cough variant asthma, together with other measures of lung function. A subsequent study found FeNO may have better diagnostic accuracy for cough variant asthma in those with allergic rhinitis.¹⁵¹ Elevated blood eosinophils ($>0.3 \times 10^9/\text{mL}$) has been shown as a good predictor for airway eosinophilia in asthma,^{5,152} The review concluded it could be a useful test to diagnose cough variant asthma, together with other measures of lung function. A subsequent study found FeNO may have better diagnostic accuracy for cough variant asthma in those with allergic rhinitis.¹⁵¹ Elevated blood eosinophils ($>0.3 \times 10^9/\text{mL}$) has been shown as a good predictor for airway eosinophilia in asthma,¹⁵² but its role to predict cough variant asthma and eosinophilic bronchitis is unclear.

As asthma is commonly associated with chronic cough we recommend spirometry, including pre- and post-bronchodilator, be undertaken in the initial assessment of all patients with chronic cough. Treatment of asthma, according to current management guidelines ([Australian Asthma Handbook – Making a diagnosis](#)¹³⁹) has been shown to improve chronic cough [GRADE: Strong].

Chronic bronchitis/Chronic obstructive pulmonary disease/Bronchiectasis

Chronic bronchitis in the setting of chronic obstructive pulmonary disease (COPD) is well described and defined by the presence of chronic cough with sputum production.¹⁵³ Chronic bronchitis can also occur without evidence of COPD, bronchiectasis or a smoking history.^{154,155} A large US-based population study of people with chronic cough and sputum production for at least three months of the last two consecutive years, but with no evidence of airflow obstruction, found chronic bronchitis was more common in ever smokers and in these individuals it was also associated with an increased risk in loss of lung function.¹⁵⁴ In those who were never smokers while it was not associated with loss of lung function it was associated with hospitalisation for respiratory disease and increased mortality.¹⁵⁴ A large Danish study similarly found chronic bronchitis to be present in never smokers and associated with adverse outcomes.¹⁵⁵ The aetiology of chronic bronchitis without COPD, asthma or smoking remains unclear. An Italian based population study found it was more likely to be in those who are smokers but there is also an association with alcohol use, hypertension and physical inactivity.¹⁵⁶ It is also associated with urbanisation, exposure to airborne pollutants and biomass fuel.¹⁵⁷ The international BOLD study showed that chronic bronchitis was associated with older age, less education, current smoking, occupational exposure to fumes, self-reported diagnosis of asthma or lung cancer and family history of chronic lung disease.⁴⁰ Others have confirmed that chronic productive cough associated with COPD and asthma is linked to more frequent exacerbations and worse outcomes.¹⁵⁸

In chronic bronchitis associated with COPD and asthma (see section above) it is recommended to treat these underlying disorders [GRADE: Strong]. Recent up-to-date Australian guidelines for COPD management exist ([The COPD-X Plan: Section C- Case finding and confirm diagnosis](#)¹⁴⁰). In current smokers, recommend smoking cessation. Non-smoking adults with chronic bronchitis without airflow obstruction should be investigated for underlying lung disease such as bronchiectasis. Treatments trialled have included mucolytics and/or macrolide antibiotics but the evidence for their use is scarce [GRADE: Weak]. As there have been no trials using other classes of antibiotics for chronic bronchitis, they are not recommended [GRADE: Weak].

Interstitial lung disease (ILD)

Cough that has been reported in up to 80% of people with ILD¹⁵⁹ is often severe, leads to a significantly impaired quality of life and is associated with worse clinical outcomes.¹⁶⁰ Guideline based management for ILD is recommended ([Diagnosis and Management of idiopathic pulmonary fibrosis: TSANZ position paper](#)¹⁴¹) [GRADE: Weak].

Laryngeal hypersensitivity/Intermittent Laryngeal Obstruction (ILO)/Vocal cord dysfunction

Several well-defined clinical syndromes comprise laryngeal dysfunction and often have overlapping symptoms.¹⁶¹ They can also be associated with intermittent laryngeal obstruction (ILO) which describes an inappropriate, transient, reversible narrowing of the larynx in response to external triggers. ILO is an important cause of chronic cough and dyspnoea and can mimic asthma.¹⁶² Speech pathology management including education, vocal hygiene training, breathing techniques and psychoeducational counselling are effective in reducing symptoms [GRADE: Strong].

GORD/Airway Reflux

The prevalence of chronic cough associated with GORD in adults varies depending on the definition. When this requires the demonstration of acid reflux the prevalence is low;¹⁶³ however, definitions based on symptoms or oesophageal dysmotility are more frequently associated with chronic cough. A systematic review identified 9 RCTs that treated patients with acid suppression and no symptomatic GORD. Only two trials reported a reduction in cough frequency or severity, limited to those with abnormal 24-hour pH monitoring.¹⁶⁴ CICADA recommends against acid suppressive therapy without a history of reflux, or evidence of reflux on objective testing¹³⁸ [GRADE: Strong against].

Chronic rhinosinusitis

Chronic rhinitis has been described in 12% of people from the UK with a diagnosis of chronic cough and is one of the most commonly associated diseases.¹³⁶ It can be associated with and without nasal polyps and maybe allergic and not allergic.¹³⁴ Chronic rhinosinusitis is associated with nasal obstruction, occurring in 95% of patients, and at least one other symptom including nasal discharge, post nasal drip (89%), and reduction or loss of sense of smell (58%) and facial pain (60%). Facial pain rarely occurs as an isolated symptom.^{136,165} It can be associated with and without nasal polyps and maybe allergic and not allergic.¹³⁴ Chronic rhinosinusitis is associated with nasal obstruction, occurring in 95% of patients, and at least one other symptom including nasal discharge, post nasal drip (89%), and reduction or loss of sense of smell (58%) and facial pain (60%). Facial pain rarely occurs as an isolated symptom.¹⁶⁵ Treatment of chronic rhinosinusitis follows current evidence-based management guidelines ([ASCIA Information for Health Professionals: CRSwNP Position Paper](#)¹³⁷). Intranasal corticosteroids are the first line therapy although evidence they improve chronic cough is weak [GRADE: Weak]. A systematic review of antihistamines¹⁶⁶ (10 placebo-controlled trials in chronic rhinitis, asthma or cough associated with allergy) found treatment led to improved cough symptom scores, though the effect appeared greatest in those with allergy [GRADE: Weak].

Cough hypersensitivity syndrome

Cough hypersensitivity has been proposed as a term to describe excessive coughing triggered by low levels of thermal, mechanical or chemical exposure. These triggers are often minor such as a change in temperature talking and laughing or strong smells.^{5,134} The term hypertussia has been used to define excessive coughing to these stimuli.⁵ Troublesome cough is associated with an increased urge to cough, this has been described as an airway irritation or itch not relieved by coughing.¹³⁴ Cough hypersensitivity can be the result of multiple aetiologies and can be associated with a large range of triggers that are important to define (

Figure 5).⁵

Management of chronic cough in adults

The management of chronic cough in adults involves diagnosis following the probability-based algorithm (Figure 7) and optimal management of the specific disease associated with chronic cough. Table 6 highlights the level of evidence for each of these treatments and our CICADA current strength of recommendation for the therapy in the treatment of cough. It highlights the large gaps in our current knowledge of management of chronic cough in adults.

6. Adult unexplained/refractory chronic cough

Where cough persists despite optimal treatment of diagnosed conditions it is termed refractory chronic cough (RCC). If no identifiable cause for the cough can be determined, it is termed unexplained chronic cough (UCC), estimated to occur in 10% adult chronic cough⁵ and is clinically important.¹³⁶ RCC and UCC are disabling conditions and people should be referred to clinic or a specialist with an interest in chronic cough. A multidisciplinary approach from specialist health providers with expertise in chronic cough will assist in this process. In the case of unexplained and refractory chronic cough, advanced investigations and management options that include off label treatment options should be considered. In addition, there are now emerging specific antitussive therapies. A specialist cough clinic should engage actively in clinical trials and offer these to patients. The role of speech pathology and antitussive therapies in RCC and UCC are discussed below.

Role of speech pathology in UCC and RCC

There are two RCTs of speech and language therapy in adults with chronic refractory cough. Vertigan et al. demonstrated that a 2-month treatment significantly reduced cough score compared to placebo treatment (self-reported scale 2–10 points) (mean difference 2.8 points, 95% CI 1.3–4.0).¹⁶⁷ While Chamberlain Mitchell et al. used a weekly intervention for 4 weeks and demonstrated benefits over placebo for cough-specific quality of life (LCQ; 1.53 points, 95% CI 0.21–2.85 points) and objective cough frequency (fold change) (0.59, 95% CI 0.36–0.95).¹⁶⁸

Speech pathology is appropriate for cough that is refractory to medical management. The evidence is strong, and the recommendation is strong. It is recommended that patients have assessment by respiratory medicine or otolaryngology before considering speech pathology intervention.

Speech pathology involves four components:

- Education (e.g. no physiological benefit from cough, capacity for voluntary control)
- Vocal hygiene training (e.g. hydration, reduce phonotraumatic vocal behaviours, reduce laryngeal irritants)
- Symptom control exercises (e.g. PVFM release, cough control breathing)
- Psychoeducational counselling.

Antitussive therapeutic trials for UCC and RCC

For many of these agents a trial of treatment may be appropriate under the supervision of chronic cough clinic or specialist. The trial should be of sufficient duration to establish efficacy and where possible objective measures of cough severity should be used, these include; cough severity scales, the cough severity diary, quality of life measures (Leicester cough questionnaire (LCQ), cough specific quality of life questionnaire), objective cough recording devices and cough reflex sensitivity challenges.¹⁶⁹

Neuromodulators

In a systematic review of eight publications of neuromodulators including amitriptyline, gabapentin, pregabalin and baclofen, only two were RCTs (one each for amitriptyline and gabapentin).¹⁷⁰ Improvements in cough specific quality of life reported in the two RCTs, cough severity was reduced. Cough symptoms decreased in the other studies. Another systematic review identified three RCTs investigating gabapentin, amitriptyline and baclofen. Cough-related quality of life scores suggested greater improvement with gabapentin and amitriptyline compared with control.¹⁷¹ Cough frequency and severity improved with baclofen and gabapentin compared with placebo.

A trial of amitriptyline, gabapentin, or pregabalin could be considered, although the evidence weak.

Brain penetrant NK-1 receptor antagonists (e.g. aprepitant, orvepitant) may be a promising treatment for cough. In an open-label, phase 2, pilot clinical trial daily treatment with 30 mg orvepitant for 4 weeks resulted in statistically significant and clinically relevant improvement in objective cough frequency, QoL, and perception of cough severity and frequency in patients with long-term CRC.¹⁷² Orvepitant was safe and well-tolerated. Larger, randomized, controlled studies of orvepitant are underway.

Acid suppressive therapy

A systematic review identified 9 randomised controlled trials (8 proton pump inhibitors, 1 ranitidine) treated patients with acid suppression and no symptomatic gastroesophageal reflux. Only two trials reported a statistically significant reduction in cough frequency and/or severity. These findings may only be limited to those with abnormal 24-hour pH monitoring.¹⁶⁴ The evidence of strong and the recommendation is strong against the empiric use of acid suppressive therapy for chronic cough without a history of reflux, or without evidence of reflux on objective testing such as 24-hour pH monitoring.

Opioids

A single-blind crossover study of levodropropizine and dihydrocodeine, an opioid antitussive agent, on respiratory centre output in patients with chronic cough and no evidence of airway obstruction found that levodropropizine does not affect the ventilatory response to carbon dioxide in subjects with chronic cough and normal carbon dioxide sensitivity, suggesting the lack of any depressant central action.¹⁷³ A single RCT of low-dose morphine (5–10 mg twice daily) compared to placebo in 27 adults with chronic refractory cough found reduced cough severity (self-reported scale 0–9 points) (mean difference –1.96 points, 95% CI –1.09– –2.11 points) and improving quality of life (LCQ) (mean difference 2 points, 95% CI 0.93–3.07 points) but there was no change in cough sensitivity on cough challenge.¹⁷⁴

In reference to low dose morphine the evidence that it reduces cough is strong but the recommendation for its use is weak limited to short term trials, with concerns and limitations in place for the long-term use of opioids.

Inhaled corticosteroids and leukotriene receptor antagonists

Asthma and eosinophilic bronchitis, comprise a large proportion of people with chronic cough and the difficulty of diagnosing eosinophilic inflammation have meant that inhaled corticosteroids (ICS) are often trialled in chronic cough. The ERS chronic cough guideline recommends conditionally, despite the low quality of evidence for a short-term trial of ICS be considered.⁵ We recommend every effort should be made to diagnose asthma, as this predicts response to ICS. A 2018 RCT¹⁷⁵ assessed response to inhaled beclomethasone or placebo in 146 adults where asthma had been excluded, outcomes were the asthma control questionnaire, which includes symptoms of cough, they found that those with an elevated FeNO >39ppB were most likely to respond. A randomized, open-label, controlled pilot study¹⁷⁶ assessed 30 adults from a cough clinic having excluded asthma, they stratified treatment based on FeNO >30ppB, if FeNO low they received LTRA, if high OCS or LTRA, ICS were able to be used.⁵ The primary outcome was 2-hour cough recording and LTRA reduced this irrespective of FeNO, OCS also reduced cough, but this was a small complex trial, confounded by the use of ICS. A randomised controlled, parallel group and multi-centre trial¹⁷⁷ treated adults with chronic cough in an open label trial with either inhaled fluticasone or a LTRA, both arms demonstrated an improvement in cough scores and FeNO. In the case of ICS, the evidence for use in chronic cough the recommendation is weak and may be limited to those with an elevated FeNO, though the cut-point for this is unclear. In terms of LTRA their evidence for their use is weak and may be independent of FeNO. We recommend every effort should be made to diagnose asthma, as this predicts response to ICS.

Macrolide antibiotics

In a double blind RCT, adults in a cough clinic were randomised to Azithromycin 500mg/d for 3 days then 250mg three times a week for 8 weeks or placebo, they excluded people with bronchiectasis, but not asthma.¹⁷⁸ It was powered to detect a change in LCQ >2, MCID 1.13. There was a clinically important and statistically significant improvement in LCQ score in the azithromycin group from 10.2 to 12.6 (mean change, 2.4; 95% CI, 0.5 to 4.2; P ¼ .01), not seen in the placebo group (mean change, 0.7; 95% CI, 0.6 to 1.9), but not cough sensitivity. There was 11 of 21 subjects in the azithromycin group (52%) had a clinically significant improvement in their LCQ score. The effect was limited to those with asthma and maintained at 8 weeks, change 6.19 (4.1 to 8.3) p<0.01 Outside of those with asthma there is no evidence to support azithromycin as a treatment for chronic cough.

Treatments for refractory chronic cough under investigation

The limitations for treatment of refractory chronic cough are clear. A number of emerging therapies are under current investigation.

Aberrant activity through the vagus nerve, with signalling through purigenic P2 ligand-gated ion channels (P2X) and G-protein-coupled receptors (P2Y) is strongly implicated in unexplained chronic refractory chronic cough. Several agents have proceeded through to phase 2 and 3 clinical trials that target these receptors. At the current time, none of these ion channel inhibitors are currently available for clinical use in Australia outside of the setting of clinical trials. Gefapixant, P2X₃ receptor antagonist, that is directed against ATP gated ion

channels found on sensory C-fibres of the vagus nerve at this stage is the most advanced of these agents in progressing through clinical trials. ATP-evoked cough was significantly inhibited by gefapixant 100 mg, a P2X3 receptor antagonist, demonstrating peripheral target engagement. Cough count and severity were reduced in CC patients.¹⁰⁰ Two large double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials, recruited subjects with either refractory chronic cough that was persistent despite treatment of underlying conditions or unexplained chronic cough, they also needed to have moderate to severe active symptoms. gefapixant 45 mg twice per day showed significant reductions in 24-h cough frequency compared with placebo at week 12 (18.5% [95% CI 32.9–0.9]; p=0.041) and at week 24 (14.6% [26.1–1.4]; p=0.031).⁹⁵ Gefapixant 15 mg twice per day did not show a significant reduction in cough frequency versus placebo. The most common adverse events of gefapixant were related to taste disturbances.

A number of other experimental agents are under investigation for unexplained refractory chronic cough. For further details in regard these agents as well as the ion channel inhibitors we refer readers to the following publications.^{179,180}

Table 6: Evidence summaries for treating specific diseases that lead to chronic cough in adults

Condition	Treatment	Clinical significance	Level of evidence*	Strength of recommendation that treatment improves chronic cough [‡] (Strong, weak, no evidence)
Upper				
Chronic rhinitis	Nasal Douche	Saline irrigation (nasal douching) may reduce patient-reported disease severity compared with no saline irrigation at up to three months in adults with allergic rhinitis, with no reported adverse effects.	<i>Satisfactory</i>	No evidence
	Saline nasal spray	The beneficial effect of saline appears to outweigh drawbacks due to minor side effects for the majority of patients. Saline is not as effective as an intranasal steroid.	<i>Satisfactory</i>	No evidence
	Intranasal corticosteroids	<p>Intranasal corticosteroids reduce nasal symptoms, sneezing, eye irritation and improve quality of life compared with placebo when measured at up to three months.¹⁸¹ There is specific information on cough alone.</p> <p>The evidence is less clear that they improve outcomes in non-allergic chronic rhinitis.¹⁸²</p>	<i>Good</i>	Weak

	Intranasal antihistamine nasal spray	Intranasal antihistamines have been shown to reduce patient-reported disease severity in chronic rhinitis, they are more efficacious than the oral antihistamines. ¹⁸³	<i>Good</i>	<i>Weak or no evidence</i>
	Combination corticosteroid and antihistamine nasal spray	Combination intranasal corticosteroids and intranasal antihistamines has an additive effect on efficacy to reduce patient-reported disease severity in chronic rhinitis. ¹⁸⁴ Intranasal corticosteroid plus oral antihistamine has similar efficacy to intranasal corticosteroid alone, greater efficacy than oral antihistamines alone or placebo in reducing nasal symptoms for allergic rhinitis patients. Intranasal corticosteroid plus intranasal antihistamine are significantly superior to either therapy given alone, or placebo. ¹⁸⁵	<i>Good</i>	<i>Weak or no evidence</i>
	Anticholinergic nasal spray	Intranasal anticholinergics reduce rhinorrhoea associated with allergic and nonallergic rhinitis, with little, if any, effect on the symptoms of congestion and sneezing.	<i>Satisfactory</i>	<i>No evidence</i>
	Leukotriene receptor antagonists (LTRAs)	Montelukast is more effective than placebo in treating the symptoms of allergic rhinitis while the combined therapy of montelukast and an oral antihistamine is superior to either montelukast or an oral antihistamine alone. ¹⁸⁶ There were no differences between intranasal corticosteroids± leukotriene receptor antagonist mono-therapy on composite nasal symptom score, total daytime symptom score, total night time symptom score, disease-specific QoL and adverse events. ¹⁸⁷	<i>Satisfactory</i>	<i>No evidence</i>

	Inhaled capsaicin	Capsaicin appears to have beneficial effects on nasal symptoms up to 36 weeks after treatment and may be an option in the treatment of idiopathic non-allergic rhinitis.	<i>Good</i>	<i>Weak</i>
	House dust mite avoidance strategies	Use of acaricides (chemicals which kill mites) and extensive bedroom-based environmental control programmes may be of some benefit in reducing rhinitis symptoms. Isolated use of house dust mite impermeable bedding is unlikely to prove effective.	<i>Poor</i>	<i>Weak</i>
Chronic sinusitis	Intranasal steroids	There is improvement for all symptoms, a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhoea. ¹⁸¹	<i>Good</i>	<i>Weak</i>
	Large volume (150 mL) saline rinse	There is some benefit of daily, large-volume (150 mL) saline irrigation with a hypertonic solution when compared with placebo, but the quality of the evidence is low for ≥ 3 months of treatment. There is no benefit of a low-volume (5 mL) nebulised saline spray over intranasal steroids.	<i>Satisfactory</i>	<i>Weak</i>
	Short-course oral steroids	At the end of the 2-3 week treatment course there is an improvement in health-related quality of life and symptom severity in patients with chronic rhinosinusitis with nasal polyps taking oral corticosteroids. At three to six months after the end of the oral steroid treatment period, there is little or no improvement in health-related quality of life or symptom severity. ¹⁸⁸	<i>Satisfactory</i>	<i>No evidence</i>

	Monoclonal antibody therapy	In patients with severe chronic rhinosinusitis and nasal polyposis, and using intranasal steroids: Dupilumab improves disease-specific quality of life nasal symptoms and disease severity on CT compared to placebo. Mepolizumab improves nasal symptoms and disease-specific quality of life	<i>Good</i>	<i>No evidence</i>
	Topical or systemic antifungal therapy	At the end of at least four weeks treatment, patients using antifungals (topical or systemic) did not have a better quality of life or less severe symptoms than patients who used placebo or had no treatment. ¹⁸⁹	<i>Poor</i>	<i>No evidence</i>
	Antibiotics	A modest improvement in disease-specific quality of life may be seen in adults with chronic rhinosinusitis without polyps receiving three months of a macrolide antibiotic. ¹⁹⁰	<i>Poor</i>	<i>Weak</i>
Middle				
Laryngeal hypersensitivity	Speech pathology management including education, vocal hygiene training, cough suppression, and psychoeducational counselling.	Generally effective if patients are able to adhere to the treatment program. ^{167,168}	<i>Good</i>	<i>Strong</i>

	Neuromodulators	Can be beneficial in select patients. There are side effects which should be discussed with the patient. ¹⁹¹	<i>Good</i>	<i>Strong (in selected patients)</i>
Vocal cord dysfunction(VCD)/ILO	Speech pathology management including education, vocal hygiene training, PVFM release and psychoeducational counselling.	Generally effective if patients are able to adhere to the treatment program.	<i>Good</i>	<i>Strong</i>
	Inspiratory muscle strength training	Low quality evidence. Results in decrease in perceived dyspnoea.	<i>Poor</i>	<i>Weak</i>
	Botulinum Toxin Injections	Can reduce VCD symptoms in patients who have failed speech pathology intervention. The effect size is unclear.	<i>Poor</i>	<i>Weak</i>
	Low dose amitriptyline	Unclear with the current level of evidence. One study reported VCD cessation in 53/62 patients.	<i>Poor</i>	<i>Weak</i>
GORD/dysmotility	PPI therapy has been used to treat patients with unexplained chronic cough, in association with GORD and found no improvement compared to placebo.	Acid lowering treatments should be used primarily to treat GORD symptoms. Improvement in cough may be a bonus in some patients.	<i>Good</i>	<i>Strong, against PPI for cough alone.¹⁹²</i>

Lower

Asthma	Inhaled corticosteroid treatments. ¹⁹³	Improve asthma symptoms, including cough, lung function, exacerbation frequency and HRQOL.	<i>Excellent</i>	<i>Strong</i>
	LTRA	Montelukast has been shown to improve asthma symptoms including cough but is not as effective as inhaled corticosteroids.	<i>Good</i>	<i>Weak</i>
	Beta-2 agonists	Recommended as treatment as in asthma, though evidence limited to small, short term studies.	<i>Good</i>	<i>Strong</i>
Cough Variant asthma ¹⁹³	LTRA	Recommended as treatment as in asthma, though evidence limited to small, short term studies. Duration of treatment is unclear.	<i>Satisfactory</i>	<i>Strong</i>
	Inhaled corticosteroids			
	LTRA	Recommended as treatment as in asthma, though evidence limited to small, short term studies. Duration of treatment is unclear. Has been used alone and in combination with inhaled corticosteroids for chronic cough though evidence is limited to small, short term studies. Effect in cough may be independent of FeNO.		
Eosinophilic bronchitis ¹⁹³	Inhaled corticosteroids		<i>Satisfactory</i>	<i>Strong</i>

	LTRA		<i>Satisfactory</i>	<i>Weak</i>
Chronic bronchitis without airflow obstruction	Mucolytic therapies	A systematic review of 10377 subjects with chronic bronchitis, included studies where COPD was not confirmed and so may have included subjects without airflow obstruction, found that treatment with including N-acetylcysteine, carbocysteine, erdosteine, and ambroxol, given at least once daily reduced the frequency of exacerbations requiring antibiotics. ¹⁹⁴	<i>Poor</i>	<i>Weak</i>
	Bronchial Rheoplasty		<i>Poor</i>	<i>Weak</i>
	Macrolide antibiotics	<p>An open label trial of 30 subjects with chronic bronchitis, with and without airflow obstruction where treated with bronchial rheoplasty with improvements in symptoms of cough and sputum production for up to 12 months.¹⁹⁵</p> <p>A small open, uncontrolled trial in 30 adults with chronic productive cough, showed improvement in cough and sputum following 12 weeks treatment with azithromycin 250mg/day.¹⁹⁶</p> <p>In the setting of acute exacerbations of people with chronic bronchitis, a systematic review demonstrated a lower incidence of treatment failure with</p>	<p><i>Poor</i></p> <p><i>Poor</i></p>	<p><i>Weak</i></p> <p><i>Weak</i></p>

		azithromycin, compared to amoxicillin and amoxicillin clavulanic acid. There was no placebo.		
	Inhaled long acting muscarinic agent	A small open label Japanese study of 13 patients with that included 5 with chronic bronchitis without airflow obstruction demonstrated an improvement in symptoms of cough and sputum. ¹⁹⁷	Poor	Weak
ILD	<p>Treatment depends on the underlying type of ILD, but may include anti-fibrotic therapies for progressive fibrotic ILD, or immunosuppressive therapies for ILDs with an immunological cause.</p> <p>There are no specific treatments for cough in ILD. Uncontrolled evidence suggests that pirfenidone, an anti-fibrotic therapy, may reduce cough in IPF.⁵</p>		Poor	Weak
COPD	Guideline-based COPD care including smoking cessation, optimising function through medications and pulmonary rehabilitation, as well as prevention and treatment of exacerbations. ¹⁴⁰		Excellent	Strong

	Combination of inhaled corticosteroids (ICS) and long-acting bronchodilator may reduce cough severity, but pneumonia risk related to ICS use should be considered. ¹⁴⁰		<i>Good</i>	<i>Weak</i>
Bronchiectasis	Guideline-directed care includes treatment of exacerbations with a 14-day courses of antibiotics, regular airway clearance and exercise, and pulmonary rehabilitation. ^{142,198}		<i>Good</i>	<i>Weak</i> ⁵⁶
Systemic				
Smoking cessation	Cessation of nicotine containing cigarettes or e-cigarettes increases cough sensitivity in the short term.	Enhanced cough sensitivity to capsaicin challenge ¹⁹⁹ follows smoking cessation of cigarettes and vaping devices.	<i>Satisfactory</i>	<i>Strong</i>
	Cigarette smoke cessation reduces cough in the long term	In people with COPD and chronic bronchitis smoking cessation led to short term worsening of cough, but at 30 days post-cessation, substantial improvement in cough, phlegm and dyspnoea. ²⁰⁰ In 2408 smokers with daily cough and sputum, at 1 year, smoking cessation substantially reduced cough	<i>Excellent</i>	<i>Strong</i>

		and sputum, improvements were also seen in those who reduced smoking. ²⁰¹		
Environmental exposures, avoidance reduces cough	Identification of occupational and environmental causes of chronic cough offers opportunity for exposure control and prevention. ²⁰²	Expert panel report	<i>Satisfactory</i>	<i>Weak</i>

<p>Angiotensin containing enzyme (ACE) inhibitor</p> <p>Cessation of ACE inhibitors</p>	<p>The incidence of chronic cough reported with ACE inhibitor use is 1.5 to 4%. In one pooled analysis only 3.1% ceased therapy for cough.²⁰³</p> <p>Cessation of ACE inhibitors for cough</p>	<p>Cough improves with cessation in the majority of cases. In small cases series cessation of cough took 3 days up to 4 weeks to occur.²⁰⁴</p> <p>In another study, cough resolved spontaneously in 27% and did not recur in the next 13 months.²⁰⁵</p> <p>Another small case series ACE inhibitor was successfully reintroduced after the cough resolved.²⁰⁶</p>	<p><i>Satisfactory</i></p> <p><i>Poor</i></p> <p><i>Poor</i></p>	<p><i>Strong</i></p> <p><i>Strong</i></p> <p><i>Weak</i></p>
---	---	--	--	--

Abbreviations: ACE = Angiotensin-converting-enzyme; COPD = Chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; ILD = Interstitial lung disease; ILO = Inducible laryngeal obstruction; IPF = Idiopathic pulmonary fibrosis; LTRA = Leukotriene receptor antagonists; PPI = Proton pump inhibitors; VCD = Vocal Cord Dysfunction

Notes: * NHMRC (National Health and Medical Research Council) additional levels of evidence and grades for recommendations for developers of guidelines.² †The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to grade the strength of recommendations.³

Table 7: Summary strength of recommendations for the efficacy of treatment of cough in association with the conditions in adults

Recommendations for ADULTS with chronic cough	Level of evidence*	Strength of recommendation#
<p>COUGH WITH ALLERGIC RHINITIS</p> <p>Treatment according to current rhinitis management guidelines¹⁸⁸ involving nasal corticosteroid spray, nasal antihistamine spray, combination corticosteroid/antihistamine nasal spray.</p>	Good	Weak
<p>COUGH WITH CHRONIC RHINOSINUSITIS</p> <p>Treatment according to current chronic sinusitis management guidelines ¹⁸⁸ involving nasal corticosteroid spray, large volume saline irrigation, long term antibiotic therapy (macrolide; three months)</p>	Poor/Good	Weak
<p>COUGH WITH LARYNGEAL HYPERSENSITIVITY</p> <p>Treatment with speech pathology management</p>	Good	Strong
<p>COUGH WITH VOCAL CORD DYSFUNCTION/INTERMITTENT LARYNGEAL OBSTRUCTION</p> <p>Treatment with speech pathology management</p>	Good	Strong
<p>COUGH WITH GORD/DYSMOTILITY</p> <p>Treatment(s) for GORD in adults with cough alone and no other symptoms of GORD with PPI therapy. When other symptoms of GORD use appropriate clinical guidelines.²⁰⁰</p>	Good	Strong against use PPI for cough alone

<p>COUGH WITH ASTHMA</p> <p>Treatment according to current asthma management guidelines¹⁸¹ and involves education, inhaled bronchodilators, inhaled corticosteroids</p> <p>The use of leukotriene receptor antagonists – alone or with inhaled corticosteroids</p>	<p>Excellent/ Good</p> <p>Good</p>	<p>Strong</p> <p>Weak</p>
<p>COUGH WITH EOSINOPHILIC BRONCHITIS</p> <p>Treatment with inhaled corticosteroids</p> <p>The use of leukotriene receptor antagonists – alone or with inhaled corticosteroids</p>	<p>Satisfactory</p> <p>Satisfactory</p>	<p>Strong</p> <p>Weak</p>
<p>COUGH WITH CHRONIC BRONCHITIS WITHOUT AIRFLOW OBSTRUCTION</p> <p>The use of mucolytic therapy and/or macrolide antibiotic therapy</p>	<p>Poor</p>	<p>Weak</p>
<p>COUGH WITH INTERSTITIAL LUNG DISEASE</p> <p>Treatment according to current ILD guidelines</p>	<p>Poor</p>	<p>Weak</p>
<p>COUGH WITH COPD</p> <p>Treatment according to current COPD management guidelines and involves education and self-management, smoking cessation, pulmonary rehabilitation and treatment of exacerbations.</p> <p>Addition of combination inhaled long-acting bronchodilators and corticosteroids may reduce cough severity.</p>	<p>Excellent</p> <p>Good</p>	<p>Strong</p> <p>Weak</p>

<p>COUGH WITH BRONCHIECTASIS</p> <p>Treatment according to current bronchiectasis management guidelines and involves and treatment of exacerbations with 14 days antibiotics, regular airway clearance and pulmonary rehabilitation.</p>	Good	Weak
<p>Unexplained chronic cough in ADULTS</p>		
<p>An empiric treatment trial supervised by a specialist cough clinic using validated, objective measures of cough severity (cough severity scales, the cough severity diary, QoL measures LCQ, cough specific quality of life questionnaire), objective cough recording devices and cough reflex sensitivity challenges)</p>	Satisfactory	Weak
<p>Cessation of smoking, nicotine containing cigarettes or e-cigarettes</p>	Excellent	Strong
<p>Identify and minimise environmental/occupational exposures</p>	Satisfactory	Weak
<p>Cessation of Angiotensin containing enzyme (ACE) inhibitors</p>	Satisfactory	Strong
<p>Speech and language therapy</p>	Excellent	Strong
<p>Inhaled corticosteroids or leukotriene antagonist empiric treatment trial</p>	Poor	Weak
<p>Macrolide antibiotics</p>	Satisfactory	Weak recommendation against

Acid suppressive therapy, proton pump inhibitors or H2 antagonists empiric treatment trial	Excellent	Strong recommendation against
Neuromodulators (amitriptyline, gabapentin, pregabalin) treatment trial	Satisfactory	Weak
Opioids empiric treatment trial	Satisfactory	Weak recommendation against

Abbreviations: COPD = chronic obstructive pulmonary disease; GORD = Gastro-oesophageal reflux disease; H2 = Histamine-2 (receptor antagonists); ILD = Interstitial lung disease; LCQ = Leicester cough questionnaire; PPI = Proton pump inhibitors; QoL = Quality of life

Notes:

* NHMRC (National Health and Medical Research Council) additional levels of evidence and grades for recommendations for developers of guidelines.² †The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to grade the strength of recommendations.³

Conclusion

Cough is the most common symptom leading to medical consultation. Chronic cough results in significant healthcare costs, impairs quality of life and may indicate the presence of a serious underlying condition. We have presented an updated position statement on cough management in the clinical consultation.

Main recommendations

Assessment of children and adults requires a focused history of the chronic cough to elicit any “red flag” cough pointers that may indicate an underlying disease. Further assessment with examination should include a chest radiograph and spirometry (when age >6 years). Separate paediatric and adult diagnostic management algorithms should be followed. Management of the underlying condition(s) should follow specific disease guidelines, as well as address adverse environmental exposures and patient/carer concerns. Aboriginal and Torres Strait Islander adults and children should be considered high-risk groups.

Management priorities

- *Algorithms for assessment and diagnosis of adult and paediatric chronic cough are recommended*
- *High quality evidence supports the use of that using child-specific chronic cough management algorithms to improve clinical outcomes but none exists in adults*
- *Identify “red flags” that indicate serious underlying conditions that require investigation or referral*
- *Early and effective treatment of chronic wet/productive cough in children is critical*
- *Culturally specific strategies for facilitating the management of chronic cough in First Nations populations are presented*
- *If the chronic cough does not resolve or is unexplained, the patient should be referred to a respiratory specialist or cough clinic*

References

1. Gibson PG, Chang AB, Glasgow N, et al. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. 2010.
2. National Health and Medical Research Council (NHMRC). NHMRC levels of evidence and grades for recommendations for developers of guidelines. [https://www.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20\(2009\).pdf](https://www.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20(2009).pdf) 2009.
3. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of clinical epidemiology* 2013; **66**(7): 719-25.
4. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS. Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. *Chest* 2016; **149**(1): 27-44.
5. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; **55**(1).
6. Chang AB, Oppenheimer JJ, Irwin RS. Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report. *Chest* 2020; **158**(1): 303-29.
7. Irwin RS, French CL, Chang AB, Altman KW. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. *Chest* 2018; **153**(1): 196-209.
8. Chang AB, Oppenheimer JJ, Weinberger M, Grant CC, Rubin BK, Irwin RS. Etiologies of Chronic Cough in Pediatric Cohorts: CHEST Guideline and Expert Panel Report. *Chest* 2017; **152**(3): 607-17.
9. Chang AB, Oppenheimer JJ, Weinberger M, Weir K, Rubin BK, Irwin RS. Use of Management Pathways or Algorithms in Children With Chronic Cough: Systematic Reviews. *Chest* 2016; **149**(1): 106-19.
10. Chung KF, McGarvey L, Song W-J, et al. Cough hypersensitivity and chronic cough. *Nature Reviews Disease Primers* 2022; **8**(1): 45.
11. Ando A, Farrell MJ, Mazzone SB. Cough-related neural processing in the brain: A roadmap for cough dysfunction? *Neuroscience & Biobehavioral Reviews* 2014; **47**: 457-68.
12. Stuart BM, Leonie JC, Ayaka A, Gary FE, Michael JF. Investigation of the Neural Control of Cough and Cough Suppression in Humans Using Functional Brain Imaging. *The Journal of Neuroscience* 2011; **31**(8): 2948.
13. Hegland KW, Bolser DC, Davenport PW. Volitional control of reflex cough. *Journal of Applied Physiology* 2012; **113**(1): 39-46.
14. Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Udem BJ. Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. *The Journal of Physiology* 2004; **557**(2): 543-58.
15. Chou Y-L, Mori N, Canning BJ. Opposing effects of bronchopulmonary C-fiber subtypes on cough in guinea pigs. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 2017; **314**(3): R489-R98.
16. Mazzone SB, Udem BJ. Vagal Afferent Innervation of the Airways in Health and Disease. *Physiological Reviews* 2016; **96**(3): 975-1024.
17. Driessen AK, Farrell MJ, Dutschmann M, Stanic D, McGovern AE, Mazzone SB. Reflex regulation of breathing by the paratrigebral nucleus via multiple bulbar circuits. *Brain Structure and Function* 2018; **223**(9): 4005-22.
18. Driessen AK, McGovern AE, Behrens R, Moe AAK, Farrell MJ, Mazzone SB. A role for neurokinin 1 receptor expressing neurons in the paratrigebral nucleus in bradykinin-evoked cough in guinea-pigs. *The Journal of Physiology* 2020; **598**(11): 2257-75.
19. Farrell MJ, Bautista TG, Liang E, Azzollini D, Egan GF, Mazzone SB. Evidence for multiple bulbar and higher brain circuits processing sensory inputs from the respiratory system in humans. *The Journal of Physiology* 2020; **598**(24): 5771-87.
20. Shannon R, Baekey DM, Morris KF, Nuding SC, Segers LS, Lindsey BG. Production of reflex cough by brainstem respiratory networks. *Pulmonary Pharmacology & Therapeutics* 2004; **17**(6): 369-76.
21. Alice EM, Alexandria KD, David GS, et al. Distinct Brainstem and Forebrain Circuits Receiving Tracheal Sensory Neuron Inputs Revealed Using a Novel Conditional Anterograde Transsynaptic Viral Tracing System. *The Journal of Neuroscience* 2015; **35**(18): 7041.
22. Mazzone SB, McLennan L, McGovern AE, Egan GF, Farrell MJ. Representation of Capsaicin-evoked Urge-to-Cough in the Human Brain Using Functional Magnetic Resonance Imaging. *American Journal of Respiratory and Critical Care Medicine* 2007; **176**(4): 327-32.

23. Leech J, Mazzone SB, Farrell MJ. Brain Activity Associated with Placebo Suppression of the Urge-to-Cough in Humans. *American Journal of Respiratory and Critical Care Medicine* 2013; **188**(9): 1069-75.
24. Janssens T, Silva M, Davenport PW, Van Diest I, Dupont LJ, Van den Bergh O. Attentional Modulation of Reflex Cough. *Chest* 2014; **146**(1): 135-41.
25. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. *The Lancet Respiratory Medicine* 2013; **1**(5): 414-22.
26. Ayaka A, David S, Marcus M, Louis I, Stuart BM, Michael JF. Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. *Thorax* 2016; **71**(4): 323.
27. Alexandria KD, Anna-Claire D, Fionnuala TL, et al. Perspectives on neuroinflammation contributing to chronic cough. *European Respiratory Journal* 2020; **56**(4): 2000758.
28. Peter SPC, Hannah VF, Richard DT, Caroline JJ, Surinder SB. Impaired cough suppression in chronic refractory cough. *European Respiratory Journal* 2019; **53**(5): 1802203.
29. Dicpinigaitis PV, Morice AH, Birring SS, et al. Antitussive Drugs—Past, Present, and Future. *Pharmacological Reviews* 2014; **66**(2): 468.
30. Eccles R. Placebo and Side Effects Confound Clinical Trials on New Antitussives. *Lung* 2021; **199**(4): 319-26.
31. Song WJ, Chang YS, Faruqi S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* 2015; **45**(5): 1479-81.
32. Lytras T, Kogevinas M, Kromhout H, et al. Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey. *Occup Environ Med* 2019; **76**(4): 222-9.
33. Colak Y, Nordestgaard BG, Laursen LC, Afzal S, Lange P, Dahl M. Risk Factors for Chronic Cough Among 14,669 Individuals From the General Population. *Chest* 2017; **152**(3): 563-73.
34. Morice AH, Jakes AD, Faruqi S, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014; **44**(5): 1149-55.
35. Arinze JT, de Roos EW, Karimi L, Verhamme KMC, Stricker BH, Brusselle GG. Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. *ERJ Open Res* 2020; **6**(2).
36. Dharmage SC, Perret JL, Burgess JA, et al. Current asthma contributes as much as smoking to chronic bronchitis in middle age: a prospective population-based study. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 1911-20.
37. Omori H, Higashi N, Nawa T, Fukui T, Kaise T, Suzuki T. Chronic Cough and Phlegm in Subjects Undergoing Comprehensive Health Examination in Japan - Survey of Chronic Obstructive Pulmonary Disease Patients Epidemiology in Japan (SCOPE-J). *Int J Chron Obstruct Pulmon Dis* 2020; **15**: 765-73.
38. Evans J, Chen Y, Camp PG, Bowie DM, McRae L. Estimating the prevalence of COPD in Canada: Reported diagnosis versus measured airflow obstruction. *Health Rep* 2014; **25**(3): 3-11.
39. Villarreal MABD, Blackwell DL, Jen A. 2019 Tables of Summary Health Statistics for U.S Adults: 2018 National Health Interview Survey. National Center for Health Statistics. Accessed Aug 2021.
40. Mejza F, Gnatiuc L, Buist AS, et al. Prevalence and burden of chronic bronchitis symptoms: results from the BOLD study. *Eur Respir J* 2017; **50**(5).
41. Alif SM, Dharmage SC, Benke G, et al. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age. *Thorax* 2017; **72**(11): 990-7.
42. Thompson M, Vodicka TA, Blair PS, et al. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ* 2013; **347**: f7027.
43. Harnden A, Grant C, Harrison T, et al. Whooping cough in school age children with persistent cough: prospective cohort study in primary care. *BMJ* 2006; **333**(7560): 174-7.
44. McHugh G, Rylance J, Mujuru H, et al. Chronic Morbidity Among Older Children and Adolescents at Diagnosis of HIV Infection. *J Acquir Immune Defic Syndr* 2016; **73**(3): 275-81.
45. Lewis TC, Stout JW, Martinez P, et al. Prevalence of asthma and chronic respiratory symptoms among Alaska Native children. *Chest* 2004; **125**(5): 1665-73.
46. Laird P, Totterdell J, Walker R, Chang AB, Schultz A. Prevalence of chronic wet cough and protracted bacterial bronchitis in Aboriginal children. *ERJ Open Res* 2019; **5**(4).
47. Laird P, Walker R, Lane M, Totterdell J, Chang AB, Schultz A. Recognition and Management of Protracted Bacterial Bronchitis in Australian Aboriginal Children: A Knowledge Translation Approach. *Chest* 2021; **159**(1): 249-58.
48. Hall KK, Chang AB, Anderson J, Dunbar M, Arnold D, O'Grady KF. Characteristics and respiratory risk profile of children aged less than 5 years presenting to an urban, Aboriginal-friendly, comprehensive primary health practice in Australia. *J Paediatr Child Health* 2017; **53**(7): 636-43.

49. O'Grady KF, Drescher BJ, Goyal V, et al. Chronic cough postacute respiratory illness in children: a cohort study. *Arch Dis Child* 2017; **102**(11): 1044-8.
50. O'Grady KF, Grimwood K, Torzillo PJ, et al. Effectiveness of a chronic cough management algorithm at the transitional stage from acute to chronic cough in children: a multicenter, nested, single-blind, randomised controlled trial. *Lancet Child Adolesc Health* 2019; **3**(12): 889-98.
51. Au-Yeung YT, Chang AB, Grimwood K, et al. Risk Factors for Chronic Cough in Young Children: A Cohort Study. *Front Pediatr* 2020; **8**: 444.
52. French CL, Crawford SL, Bova C, Irwin RS. Change in Psychological, Physiological, and Situational Factors in Adults After Treatment of Chronic Cough. *Chest* 2017; **152**(3): 547-62.
53. Lätti AM, Pekkanen J, Koskela HO. Persistence of chronic cough in a community-based population. *ERJ Open Res* 2020; **6**(2).
54. Arinze JT, Verhamme KMC, Luik AI, Stricker B, van Meurs JBJ, Brusselle GG. The interrelatedness of chronic cough and chronic pain. *Eur Respir J* 2021; **57**(5).
55. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med* 2011; **11**: 36.
56. Vestbo J. Chronic bronchitis: so much more than just a smoker's cough. *Int J Tuberc Lung Dis* 2014; **18**(7): 760.
57. The Royal Australian College of General Practitioners, Guidelines for preventive activities in general practice. 9th edn, updated. East Melbourne, Vic: RACGP, 2018.
58. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Accessed 29-09-2020. 2020.
59. Lores L, Monje A, Bergada M, Arellano E, Rodríguez-Larrea J, Miravittles M. Prevalence of smoking in a psychiatric hospital and its relationship with respiratory symptoms and the prevalence of COPD. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 2797-804.
60. Gracie K, Hancox RJ. Cannabis use disorder and the lungs. *Addiction* 2021; **116**(1): 182-90.
61. Ghasemiesfe M, Ravi D, Vali M, et al. Marijuana Use, Respiratory Symptoms, and Pulmonary Function: A Systematic Review and Meta-analysis. *Ann Intern Med* 2018; **169**(2): 106-15.
62. McConnell R, Barrington-Trimis JL, Wang K, et al. Electronic Cigarette Use and Respiratory Symptoms in Adolescents. *Am J Respir Crit Care Med* 2017; **195**(8): 1043-9.
63. Braymiller JL, Barrington-Trimis JL, Leventhal AM, et al. Assessment of Nicotine and Cannabis Vaping and Respiratory Symptoms in Young Adults. *JAMA Netw Open* 2020; **3**(12): e2030189.
64. Blanc PD, Annesi-Maesano I, Balmes JR, et al. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *Am J Respir Crit Care Med* 2019; **199**(11): 1312-34.
65. Sood A, Shore X, Myers O, Assad N, Pollard C, Cook LS. Among All Miners, Coal Miners Demonstrate a Disproportionately High Prevalence of Obstructive Spirometric Abnormality and Chronic Bronchitis. *J Occup Environ Med* 2019; **61**(4): 328-34.
66. Skaaby S, Flachs EM, Lange P, et al. Chronic productive cough and inhalant occupational exposure—a study of the general population. *Int Arch Occup Environ Health* 2021.
67. Go LHT, Cohen RA. Coal Workers' Pneumoconiosis and Other Mining-Related Lung Disease: New Manifestations of Illness in an Age-Old Occupation. *Clin Chest Med* 2020; **41**(4): 687-96.
68. Sigsgaard T, Basinas I, Doekes G, et al. Respiratory diseases and allergy in farmers working with livestock: a EAACI position paper. *Clin Transl Allergy* 2020; **10**: 29.
69. Pourhassan B, Meysamie A, Alizadeh S, Habibian A, Beigzadeh Z. Risk of obstructive pulmonary diseases and occupational exposure to pesticides: a systematic review and meta-analysis. *Public Health* 2019; **174**: 31-41.
70. Svedahl SR, Hilt B, Svendsen K. Work environment factors and respiratory complaints in Norwegian cooks. *Int Arch Occup Environ Health* 2020; **93**(2): 205-12.
71. Harvey RR, Fechter-Leggett ED, Bailey RL, et al. The Burden of Respiratory Abnormalities Among Workers at Coffee Roasting and Packaging Facilities. *Front Public Health* 2020; **8**: 5.
72. Urman R, Eckel S, Deng H, et al. RISK EFFECTS OF NEAR-ROADWAY POLLUTANTS AND ASTHMA STATUS ON BRONCHITIC SYMPTOMS IN CHILDREN. *Environ Epidemiol* 2018; **2**(2).
73. Hooper LG, Young MT, Keller JP, et al. Ambient Air Pollution and Chronic Bronchitis in a Cohort of U.S. Women. *Environ Health Perspect* 2018; **126**(2): 027005.
74. Doiron D, Bourbeau J, de Hoogh K, Hansell AL. Ambient air pollution exposure and chronic bronchitis in the Lifelines cohort. *Thorax* 2021.
75. Marseglia GL, Manti S, Chiappini E, et al. Chronic cough in childhood: A systematic review for practical guidance by the Italian Society of Pediatric Allergy and Immunology. *Allergol Immunopathol (Madr)* 2021; **49**(2): 133-54.
76. Pelkonen MK, Laatikainen TK, Jousilahti P. The relation of environmental tobacco smoke (ETS) to chronic bronchitis and mortality over two decades. *Respir Med* 2019; **154**: 34-9.

77. Schermer TR, Malbon W, Morgan M, Smith M, Crockett AJ. Chronic respiratory conditions in a cohort of metropolitan fire-fighters: associations with occupational exposure and quality of life. *Int Arch Occup Environ Health* 2014; **87**(8): 919-28.
78. Mendy A, Salo PM, Cohn RD, Wilkerson J, Zeldin DC, Thorne PS. House Dust Endotoxin Association with Chronic Bronchitis and Emphysema. *Environ Health Perspect* 2018; **126**(3): 037007.
79. Guilleminault L. Chronic cough and obesity. *Pulm Pharmacol Ther* 2019; **55**: 84-8.
80. Wu TD, Fawzy A, Brigham E, et al. Association of Triglyceride-Glucose Index and Lung Health: A Population-based Study. *Chest* 2021.
81. De Santi F, Zoppini G, Locatelli F, et al. Type 2 diabetes is associated with an increased prevalence of respiratory symptoms as compared to the general population. *BMC Pulm Med* 2017; **17**(1): 101.
82. Kantar A, Chang AB, Shields MD, et al. ERS statement on protracted bacterial bronchitis in children. *Eur Respir J* 2017; **50**(2).
83. Ruffles TJC, Goyal V, Marchant JM, et al. Duration of amoxicillin-clavulanate for protracted bacterial bronchitis in children (DACs): a multi-centre, double blind, randomised controlled trial. *Lancet Respir Med* 2021.
84. McCallum GB, Chang AB. 'Good enough' is 'not enough' when managing indigenous adults with bronchiectasis in Australia and New Zealand. *Respirology* 2018; **23**(8): 725-6.
85. King PT, Holdsworth SR, Farmer M, Freezer N, Villanueva E, Holmes PW. Phenotypes of adult bronchiectasis: onset of productive cough in childhood and adulthood. *Copd* 2009; **6**(2): 130-6.
86. Laird P, Walker R, Lane M, Chang AB, Schultz A. We won't find what we don't look for: Identifying barriers and enablers of chronic wet cough in Aboriginal children. *Respirology* 2020; **25**(4): 383-92.
87. Chang AB, Robertson CF, Van Asperen PP, et al. A multicenter study on chronic cough in children : burden and etiologies based on a standardized management pathway. *Chest* 2012; **142**(4): 943-50.
88. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax* 2006; **61**(12): 1065-9.
89. Fracchia MS, Diercks G, Cook A, et al. The diagnostic role of triple endoscopy in pediatric patients with chronic cough. *Int J Pediatr Otorhinolaryngol* 2019; **116**: 58-61.
90. Greifer M, Santiago MT, Tsirilakis K, Cheng JC, Smith LP. Pediatric patients with chronic cough and recurrent croup: the case for a multidisciplinary approach. *Int J Pediatr Otorhinolaryngol* 2015; **79**(5): 749-52.
91. Patton CM, Lim KG, Ramlow LW, White KM. Increasing Efficiency in Evaluation of Chronic Cough: A Multidisciplinary, Collaborative Approach. *Qual Manag Health Care* 2015; **24**(4): 177-82.
92. Rotsides JM, Krakovsky GM, Pillai DK, et al. Is a Multidisciplinary Aerodigestive Clinic More Effective at Treating Recalcitrant Aerodigestive Complaints Than a Single Specialist? *Ann Otol Rhinol Laryngol* 2017; **126**(7): 537-43.
93. Skinner ML, Lee SK, Collaco JM, Lefton-Greif MA, Hoch J, Au Yeung KJ. Financial and health impacts of multidisciplinary aerodigestive care. *Otolaryngology - Head and Neck Surgery (United States)* 2016; **154**(6): 1064-7.
94. Dicipinigitis PV, McGarvey LP, Canning BJ. P2X3-Receptor Antagonists as Potential Antitussives: Summary of Current Clinical Trials in Chronic Cough. *Lung* 2020; **198**(4): 609-16.
95. McGarvey LP, Biring SS, Morice AH, et al. Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *The Lancet* 2022; **399**(10328): 909-23.
96. Mazzone SB, McGarvey L. Mechanisms and rationale for targeted therapies in refractory and unexplained chronic cough. *Clinical Pharmacology & Therapeutics* 2021; **109**(3): 619-36.
97. Maher TM, Avram C, Bortey E, et al. Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis. *NEJM Evidence* 2023; EVIDoaa2300083.
98. Zhang M, Sykes DL, Brindle K, Sadofsky LR, Morice AH. Chronic cough—the limitation and advances in assessment techniques. *Journal of Thoracic Disease* 2022; **14**(12): 5097.
99. Holt KJ, Belcher J, Smith JA. Novel capsaicin cough endpoints effectively discriminate between healthy controls and patients with refractory chronic cough. *Respiratory Medicine* 2023; **208**: 107142.
100. Morice AH, Kitt MM, Ford AP, et al. The effect of gefapixant, a P2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. *European Respiratory Journal* 2019; **54**(1).
101. Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. *The Lancet Respiratory medicine* 2018; **6**(8): 636-46.

102. Chang AB, Oppenheimer JJ, Irwin RS, et al. Managing chronic cough as a symptom in children and management algorithms: CHEST guideline and expert panel report. *Chest* 2020; **158**(1): 303-29.
103. Boulet LP, Coeytaux RR, McCrory DC, et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. *Chest* 2015; **147**(3): 804-14.
104. Brand PL, Duiverman EJ. [Coughing and wheezing children: improvement after parents stop smoking]. *Ned Tijdschr Geneeskd* 1998; **142**(15): 825-7.
105. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129**(1 Suppl): 169S-73S.
106. Butler CC, Kinnersley P, Hood K, et al. Clinical course of acute infection of the upper respiratory tract in children: cohort study. *BMJ* 2003; **327**(7423): 1088-9.
107. Fitzmaurice DA. Written information for treating minor illness. *BMJ* 2001; **322**(7296): 1193-4.
108. Little P, Somerville J, Williamson I, et al. Randomised controlled trial of self management leaflets and booklets for minor illness provided by post. *BMJ* 2001; **322**(7296): 1214-6, 7.
109. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis: CHEST Guideline and Expert Panel Report. *Chest* 2017; **151**(4): 884-90.
110. Alsubaie H, Al-Shamrani A, Alharbi AS, Alhaider S. Clinical practice guidelines: Approach to cough in children: The official statement endorsed by the Saudi Pediatric Pulmonology Association (SPPA). *Int J Pediatr Adolesc Med* 2015; **2**(1): 38-43.
111. Bergamini M, Kantar A, Cutrera R, Interest Group IPC. Analysis of the Literature on Chronic Cough in Children. *Open Respir Med J* 2017; **11**: 1-9.
112. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Use of Management Pathways or Algorithms in Children With Chronic Cough: CHEST Guideline and Expert Panel Report. *Chest* 2017; **151**(4): 875-83.
113. Marchant JM, Petsky HL, Morris PS, Chang AB. Antibiotics for prolonged wet cough in children. *Cochrane Database Syst Rev* 2018; **7**(7): Cd004822.
114. Chang AB, Oppenheimer JJ, Weinberger M, Rubin BK, Irwin RS. Children With Chronic Wet or Productive Cough--Treatment and Investigations: A Systematic Review. *Chest* 2016; **149**(1): 120-42.
115. Ruffles TJ, Marchant JM, Masters IB, et al. Outcomes of protracted bacterial bronchitis in children: A 5-year prospective cohort study. *Respirology* 2021; **26**(3): 241-8.
116. Turner SW, Chang AB, Yang IA. Clinical utility of exhaled nitric oxide fraction in the management of asthma and COPD. *Breathe (Sheff)* 2019; **15**(4): 306-16.
117. Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol* 2017; **119**(6): 489-511 e41.
118. Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol* 2017; **140**(4): 950-8.
119. Song DJ, Song WJ, Kwon JW, et al. KAAACI Evidence-Based Clinical Practice Guidelines for Chronic Cough in Adults and Children in Korea. *Allergy Asthma Immunol Res* 2018; **10**(6): 591-613.
120. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2014; **151**(4): 542-53.
121. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis* 2012; **54**(8): e72-e112.
122. Diamant MJ, Senac MO, Jr., Gilsanz V, Baker S, Gillespie T, Larsson S. Prevalence of incidental paranasal sinuses opacification in pediatric patients: a CT study. *J Comput Assist Tomogr* 1987; **11**(3): 426-31.
123. Teoh L, Hurwitz M, Acworth JP, van Asperen P, Chang AB. Treatment of obstructive sleep apnoea for chronic cough in children. *Cochrane Database Syst Rev* 2011; (4): Cd008182.
124. de Benedictis FM, Bush A. Respiratory manifestations of gastro-oesophageal reflux in children. *Arch Dis Child* 2018; **103**(3): 292-6.
125. Chang AB, Connor FL, Petsky HL, et al. An objective study of acid reflux and cough in children using an ambulatory pHmetry-cough logger. *Arch Dis Child* 2011; **96**(5): 468-72.
126. (NICE) NifHaCE. NICE Guideline: Gastro-oesophageal reflux disease in children and young people 2015. <https://www.nice.org.uk/guidance/ng1> (accessed 19 August 2018).
127. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **66**(3): 516-54.
128. Chang AB, Oppenheimer JJ, Kahrilas PJ, et al. Chronic Cough and Gastroesophageal Reflux in Children: CHEST Guideline and Expert Panel Report. *Chest* 2019; **156**(1): 131-40.

129. Weinberger M. The habit cough: Diagnosis and treatment. *Pediatric Pulmonology* 2018; **53**(5): 535-7.
130. Vertigan AE, Murad MH, Pringsheim T, et al. Somatic cough syndrome (previously referred to as psychogenic cough) and tic cough (previously referred to as habit cough) in adults and children. *Chest* 2015; **148**(1): 24-31.
131. Gardiner SJ, Chang AB, Marchant JM, Petsky HL. Codeine versus placebo for chronic cough in children. *Cochrane Database Syst Rev* 2016; **7**(7): Cd011914.
132. Lätti AM, Pekkanen J, Koskela HO. Persistence of chronic cough in a community-based population. *ERJ Open Research* 2020; **6**(2).
133. Won H-K, Lee J-H, An J, et al. Impact of chronic cough on health-related quality of life in the Korean adult general population: the Korean National Health and Nutrition Examination Survey 2010–2016. *Allergy, asthma & immunology research* 2020; **12**(6): 964.
134. McGarvey L, Gibson PG. What Is Chronic Cough? Terminology. *J Allergy Clin Immunol Pract* 2019; **7**(6): 1711-4.
135. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med* 1996; **156**(9): 997-1003.
136. Hull JH, Langerman H, Ul-Haq Z, Kamalati T, Lucas A, Levy ML. Burden and impact of chronic cough in UK primary care: a dataset analysis. *BMJ Open* 2021; **11**(12): e054832.
137. ASCIA Information for Health Professionals: CRSwNP Position Paper 2021. https://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Position_Paper_CRSwNP_2021.pdf (accessed).
138. Kahrilas PJ, Altman KW, Chang AB, et al. Chronic Cough Due to Gastroesophageal Reflux in Adults: CHEST Guideline and Expert Panel Report. *Chest* 2016; **150**(6): 1341-60.
139. Australian Asthma Handbook - Diagnosing asthma in adults. 2020. <https://www.astmahandbook.org.au/diagnosis/adults/making-a-diagnosis> Version 2.1).
140. Yang IA GJ, McDonald CF, McDonald V, O'Brien M, Smith B, McNamara R, Zwar N, Dabscheck E. . The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2021. www.copdx.org.au
141. Jo HE, Prasad JD, Troy LK, et al. Diagnosis and management of idiopathic pulmonary fibrosis: Thoracic Society of Australia and New Zealand and Lung Foundation Australia position statements summary. *Med J Aust* 2018; **208**(2): 82-8.
142. Chang AB, Bell SC, Torzillo PJ, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. *Medical Journal of Australia* 2015; **202**(1): 21-4.
143. Atherton JJ, Sindone A, De Pasquale CG, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. *Heart Lung Circ* 2018; **27**(10): 1123-208.
144. Party CCALCGW. Clinical practice guidelines for the treatment of lung cancer. . cited 2022 Mar 30. https://wiki.cancer.org.au/australia/Guidelines:Lung_cancer.
145. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. *Lancet* 1989; **1**(8651): 1346-8.
146. Carney IK, Gibson PG, Murree-Allen K, Saltos N, Olson LG, Hensley MJ. A systematic evaluation of mechanisms in chronic cough. *Am J Respir Crit Care Med* 1997; **156**(1): 211-6.
147. Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129**(1 Suppl): 116s-21s.
148. Australian Medicines Handbook 2020 (online). 2020 July. <https://amhonline.amh.net.au/>.
149. 2021 GINA Report. 2021. www.ginasthma.org.
150. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979; **300**(12): 633-7.
151. Chen LC, Zeng GS, Wu LL, et al. Diagnostic value of FeNO and MMEF for predicting cough variant asthma in chronic cough patients with or without allergic rhinitis. *J Asthma* 2021; **58**(3): 326-33.
152. Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015; **70**(2): 115-20.
153. Kim V, Crapo J, Zhao H, et al. Comparison between an alternative and the classic definition of chronic bronchitis in COPD Gene. *Ann Am Thorac Soc* 2015; **12**(3): 332-9.
154. Balte PP, Chaves PHM, Couper DJ, et al. Association of Nonobstructive Chronic Bronchitis With Respiratory Health Outcomes in Adults. *JAMA Intern Med* 2020; **180**(5): 676-86.
155. Çolak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. *Eur Respir J* 2019; **54**(3).
156. Ferrari M, Piccinno E, Marcon A, et al. Chronic bronchitis without airflow obstruction, asthma and rhinitis are differently associated with cardiovascular risk factors and diseases. *PLoS One* 2019; **14**(11): e0224999.

157. Miele CH, Jaganath D, Miranda JJ, et al. Urbanization and Daily Exposure to Biomass Fuel Smoke Both Contribute to Chronic Bronchitis Risk in a Population with Low Prevalence of Daily Tobacco Smoking. *Copd* 2016; **13**(2): 186-95.
158. Hughes R, Rapsomaniki E, Janson C, et al. Frequent productive cough: Symptom burden and future exacerbation risk among patients with asthma and/or COPD in the NOVELTY study. *Respiratory Medicine* 2022; **200**: 106921.
159. Ryerson CJ, Abbritti M, Ley B, Elicker BM, Jones KD, Collard HR. Cough predicts prognosis in idiopathic pulmonary fibrosis. *Respirology* 2011; **16**(6): 969-75.
160. Lee J, White E, Freiheit E, et al. Cough-specific quality of life predicts disease progression among patients with interstitial lung disease: data from the pulmonary fibrosis foundation patient registry. *Chest* 2022; **162**(3): 603-13.
161. Vertigan AE, Bone SL, Gibson PG. Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. *Respirology* 2013; **18**(6): 948-56.
162. Halvorsen T, Walsted ES, Bucca C, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. *European Respiratory Journal* 2017; **50**(3).
163. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux: clinical, diagnostic, and pathogenetic aspects. *Chest* 1993; **104**(5): 1511-7.
164. Kahrilas PJ, Howden CW, Hughes N, Molloy-Bland M. Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease. *Chest* 2013; **143**(3): 605-12.
165. Dietz de Loos DA, Hopkins C, Fokkens WJ. Symptoms in chronic rhinosinusitis with and without nasal polyps. *Laryngoscope* 2013; **123**(1): 57-63.
166. Lee J-H, Lee JW, An J, et al. Efficacy of non-sedating H1-receptor antihistamines in adults and adolescents with chronic cough: A systematic review. *World Allergy Organization Journal* 2021; **14**(8): 100568.
167. Vertigan AE, Theodoros DG, Gibson PG, Winkworth A. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax* 2006; **61**(12): 1065-9.
168. Mitchell SAC, Garrod R, Clark L, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017; **72**(2): 129-36.
169. Birring SS, Spinou A. How best to measure cough clinically. *Current opinion in pharmacology* 2015; **22**: 37-40.
170. Cohen SM, Misono S. Use of specific neuromodulators in the treatment of chronic, idiopathic cough: a systematic review. *Otolaryngology--Head and Neck Surgery* 2013; **148**(3): 374-82.
171. Wei W, Liu R, ZhangTong Y, Qiu Z. The efficacy of specific neuromodulators on human refractory chronic cough: a systematic review and meta-analysis. *Journal of Thoracic Disease* 2016; **8**(10): 2942.
172. Smith J, Allman D, Badri H, et al. The Neurokinin-1 Receptor Antagonist Orvepitant Is a Novel Antitussive Therapy for Chronic Refractory Cough: Results From a Phase 2 Pilot Study (VOLCANO-1). *Chest* 2020; **157**(1): 111-8.
173. Mannini C, Lavorini F, Zanasi A, Saibene F, Lanata L, Fontana G. A randomized clinical trial comparing the effects of antitussive agents on respiratory center output in patients with chronic cough. *Chest* 2017; **151**(6): 1288-94.
174. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007; **175**(4): 312-5.
175. Price DB, Buhl R, Chan A, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *The Lancet Respiratory Medicine* 2018; **6**(1): 29-39.
176. Sadeghi MH, Wright CE, Hart S, Crooks M, Morice A. Phenotyping patients with chronic cough: evaluating the ability to predict the response to anti-inflammatory therapy. *Annals of Allergy, Asthma & Immunology* 2018; **120**(3): 285-91.
177. Kodaka N, Nakano C, Hatanaka N, et al. The Efficacy Of Pranlukast, A Leukotriene Receptor Antagonist, In The Treatment Of Chronic Cough. B69 AIRWAY STRUCTURE AND FUNCTION: American Thoracic Society; 2012: A3564-A.
178. Hodgson D, Anderson J, Reynolds C, et al. The effects of azithromycin in treatment-resistant cough: a randomized, double-blind, placebo-controlled trial. *Chest* 2016; **149**(4): 1052-60.
179. Morice A, Dicpinigaitis P, McGarvey L, Birring SS. Chronic cough: new insights and future prospects. *Eur Respir Rev* 2021; **30**(162).

180. Roe NA, Lundy, F.T., Litherland, G.J. McGarvey, L.P.A. Therapeutic Targets for the Treatment of Chronic Cough. *Curr Otorhinolaryngol Rep* 2019; **7**: 116-28.
181. Chong LY, Head K, Hopkins C, Philpott C, Schilder AG, Burton MJ. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. *Cochrane Database of Systematic Reviews* 2016; (4).
182. Segboer C, Gevorgyan A, Avdeeva K, et al. Intranasal corticosteroids for non-allergic rhinitis. *Cochrane Database of Systematic Reviews* 2019; (11).
183. Juel-Berg N, Darling P, Bolvig J, et al. Intranasal corticosteroids compared with oral antihistamines in allergic rhinitis: A systematic review and meta-analysis. *American Journal of Rhinology & Allergy* 2017; **31**(1): e19-e28.
184. Kaliner MA, Berger WE, Ratner PH, Siegel CJ. The efficacy of intranasal antihistamines in the treatment of allergic rhinitis. *Annals of Allergy, Asthma & Immunology* 2011; **106**(2): S6-S11.
185. Feng S, Fan Y, Liang Z, Ma R, Cao W. Concomitant corticosteroid nasal spray plus antihistamine (oral or local spray) for the symptomatic management of allergic rhinitis. *European Archives of Oto-Rhino-Laryngology* 2016; **273**: 3477-86.
186. Krishnamoorthy M, Mohd Noor N, Mat Lazim N, Abdullah B. Efficacy of montelukast in allergic rhinitis treatment: a systematic review and meta-analysis. *Drugs* 2020; **80**: 1831-51.
187. Seresirikachorn K, Mullol J, Limitlaohaphan K, Asvapoositkul V, Snidvongs K. Leukotriene receptor antagonist addition to intranasal steroid: systematic review and meta-analysis. *Rhinology* 2021; **59**(1): 2-9.
188. Head K, Chong LY, Hopkins C, Philpott C, Burton MJ, Schilder AG. Short-course oral steroids alone for chronic rhinosinusitis. *Cochrane database of systematic reviews* 2016; (4).
189. Head K, Sharp S, Chong LY, Hopkins C, Philpott C. Topical and systemic antifungal therapy for chronic rhinosinusitis. *Cochrane Database of Systematic Reviews* 2018; (9).
190. Head K, Chong LY, Piomchai P, et al. Systemic and topical antibiotics for chronic rhinosinusitis. *Cochrane Database of Systematic Reviews* 2016; (4).
191. Ryan NM, Biring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2012; **380**(9853): 1583-9.
192. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database of Systematic Reviews* 2011; (1).
193. Côté A, Russell RJ, Boulet L-P, et al. Managing chronic cough due to asthma and NAEB in adults and adolescents: CHEST guideline and expert panel report. *Chest* 2020; **158**(1): 68-96.
194. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2019; (5).
195. Valipour A, Fernandez-Bussy S, Ing AJ, et al. Bronchial rheoplasty for treatment of chronic bronchitis. Twelve-month results from a multicenter clinical trial. *American Journal of Respiratory and Critical Care Medicine* 2020; **202**(5): 681-9.
196. Martin MJ, Lee H, Clayton C, et al. Idiopathic chronic productive cough and response to open-label macrolide therapy: An observational study. *Respirology* 2019; **24**(6): 558-65.
197. Saito Y, Azuma A, Morimoto T, et al. Tiotropium ameliorates symptoms in patients with chronic airway mucus hypersecretion which is resistant to macrolide therapy. *Internal Medicine* 2008; **47**(7): 585-91.
198. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; **50**(3).
199. Dicipinigitis PV. Effect of tobacco and electronic cigarette use on cough reflex sensitivity. *Pulmonary pharmacology & therapeutics* 2017; **47**: 45-8.
200. Etter J-F. Short-term change in self-reported COPD symptoms after smoking cessation in an internet sample. *European Respiratory Journal* 2010; **35**(6): 1249-55.
201. Pisinger C, Godtfredsen NS, Jørgensen T. Smoking reduction and cessation reduce chronic cough in a general population: the Inter99 study. *The Clinical Respiratory Journal* 2008; **2**(1): 41-6.
202. Tarlo SM, Altman KW, Oppenheimer J, et al. Occupational and environmental contributions to chronic cough in adults: chest expert panel report. *Chest* 2016; **150**(4): 894-907.
203. Pinto B, Jadhav U, Singhai P, Sadhanandham S, Shah N. ACEI-induced cough: A review of current evidence and its practical implications for optimal CV risk reduction. *Indian Heart Journal* 2020; **72**(5): 345-50.
204. Lip GY, Zarifis J, Beevers M, Beevers D. Duration of cough following cessation of ACE inhibitor therapy. *American journal of hypertension* 1995; **8**(1): 98-.
205. Reisin L, Schneeweiss A. Spontaneous disappearance of cough induced by angiotensin-converting enzyme inhibitors (captopril or enalapril). *The American journal of cardiology* 1992; **70**(3): 398-9.

206. Sato A, Fukuda S. A prospective study of frequency and characteristics of cough during ACE inhibitor treatment. *Clinical and Experimental Hypertension* 2015; **37**(7): 563-8.

