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SUMMARY WITH CRITICAL APPRAISAL

Acetylcysteine for Patients Requiring Secretion Clearance: A Review of Guidelines

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Abbreviations

AARC	American Association of Respiratory Care
ATS	American Thoracic Society
CHEST	American College of Chest Physicians
COPD	Chronic obstructive pulmonary disease
CTS	Canadian Thoracic Society
ERS	European Thoracic Society
GRADE	Grading of Recommendations Assessment, Development and Evaluation
NAC	N-acetyl cysteine or acetyl cysteine
NICE	National Institute of Health Care and Excellence
VA/DoD	Department of Veterans Affairs and Department of Defense

Context and Policy Issues

Mucus secretion clearance is a defense mechanism used by the lung to protect itself from pathogens and particles present in the inhaled air.[1,2] Mucus traps pathogens and particles in inhaled air, and is usually cleared from the lungs and airways by airflow and ciliary hairs.[2] Impaired mucous clearance results in abnormal lung function.[3]

Mucus is a viscoelastic gel-like substance and consists of glycoproteins known as mucins, mixed with other proteins, lipids and water.[2] In healthy individuals, mucus has low viscosity and elasticity and is easily cleared, however in certain lung diseases the mucus has higher viscosity and elasticity and is not easily cleared. Pharmacologic treatments for impaired mucous secretion clearance include agents such as isotonic saline, hypertonic saline, and mucolytics such as dornase alpha, and acetylcysteine (also known as N-acetylcysteine [NAC]). NAC hydrolyzes the disulfide bonds of mucus proteins to decrease mucus viscosity, thereby facilitating its clearance.[4] NAC is used as a treatment option in various conditions in which there are problems with clearance of lung mucosal secretions (such as chronic obstructive pulmonary disease [COPD], chronic bronchitis, and intubated or post-operative patients).[1,4-7]

A recent CADTH report[8] reviewed the clinical effectiveness and safety of use of NAC for patients requiring mucous clearance. It reported that relevant clinical effectiveness and safety data for NAC compared with other treatment modalities were sparse and no definitive conclusions were possible. For NAC compared with placebo, safety data in terms of adverse events, hospitalization, atelectasis, and mortality were variable or sparse, and definitive conclusions were not possible. The purpose of this report is to review the evidence-based guidelines regarding the use of acetylcysteine for patients requiring mucous secretion clearance.

Research Questions

1. What are the evidence-based guidelines regarding the administration of acetylcysteine for mucous secretion clearance?

Key Findings

Six relevant guidelines were identified. Three guidelines suggest the use of oral acetylcysteine (NAC) for patients with chronic obstructive pulmonary disease (weak or conditional recommendations based on low- or moderate-quality evidence). The remaining

three guidelines did not indicate the strength of the recommendations. Of these, one guideline does not recommend for or against the use of NAC preparations, because of insufficient evidence; one guideline recommends against the use of NAC for acute cough; And one guideline does not recommend the use of aerosolized NAC for hospitalized patients, and patients with neuromuscular disease, respiratory muscle weakness or impaired cough.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were acetylcysteine and mucus or mucous secretions. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and May 17, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients, in any setting, requiring mucous secretion clearance.
Intervention	Nebulized or oral acetylcysteine; nebulized acetylcysteine in combination with saline
Comparator	Not applicable
Outcomes	Guidelines for appropriate use and place in therapy
Study Designs	Evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included evidence-based guidelines were critically assessed using Appraisal of Guidelines for Research and Evaluation II (AGREE II).[9] Summary scores were not calculated for the included guidelines, rather, the strengths and limitations of each individual guideline were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 323 citations were identified in the literature search. Following screening of titles and abstracts, 316 citations were excluded and seven potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 11 potentially relevant articles, five publications were excluded for various reasons, and six evidence-based guidelines met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized and additional details are provided in Appendix 2, Table 2

Study Design

Six relevant evidence-based guidelines[11-16] were identified. A single group or a combination of groups were involved in the production of these guidelines. These groups were the American Association of respiratory Care (AARC), American Thoracic Society (ATS), American College of Chest Physicians (CHEST), Canadian Thoracic Society (CTS), European Thoracic Society (ERS), National Institute of Health Care and Excellence (NICE), and the Department of Veterans Affairs and Department of Defense (VA/DoD). In five guidelines,[12-16] it was mentioned that a systematic review was conducted to identify evidence. In the sixth guideline,[11] there was no explicit mention of a systematic review in the guideline document, but the associated guidelines manual[17] indicates requirement for a systematic literature review. The guideline development groups included healthcare professionals and methodologists for two guidelines,[13,15] healthcare professionals and a patient for the third guideline,[12] and subject area experts for the fourth guideline.[16] The fifth guideline[11] did not explicitly mention the guideline development group but the associated guidelines manual indicated that the group comprised experts in relevant areas as well as lay persons. The sixth guideline[14] did not report on the composition of the guideline development group. Four guidelines[12,13,15,16] graded the recommendations and details of the methods used are presented in Appendix 2,Table 2; two guidelines[11,14] did not present grading of recommendations.

Country of Origin

Countries indicated for the first author of the guideline document or of the guideline development group were Canada,[12,15] the UK,[11,13] and the US.[14,16] One guideline[11] was dated 2019, two guidelines[12,13] were dated 2017; two guidelines[14,15] were dated 2015, and one guideline[16] was dated 2014.

Population

The target population was patients with COPD in four guidelines,[12,13,15,16] and patients with acute cough in the fifth guideline.[11] The target population for the sixth guideline[14] was hospitalized patients without cystic fibrosis; patients with neuromuscular disease, respiratory muscle weakness, or impaired cough; and post-operative patients. The intended users of the guidelines were health care professionals, patients and their caregivers;[11] healthcare professionals, respiratory educators, and healthcare decision makers;[12] or

primary care providers.[16] In the remaining three guidelines,[13-15] the intended users were not explicitly mentioned, but appear to be individuals involved in treatment COPD patients for two guidelines;[13,15] and individuals involved with airway clearance therapy for one guideline.[14]

Interventions and Comparators

The six guidelines had broad objectives and considered several treatment options, one of which was acetylcysteine.

Outcomes

The guidelines presented recommendations regarding the use of NAC. The outcomes considered in five guidelines were cough and lung function in one guideline,[11] exacerbation, hospitalization, adverse events, and quality of life in one guideline;[13] sputum characteristics, airway clearance, and lung function in one guideline;[14] exacerbation in one guideline;[15] and dyspnea and adverse events in one guideline;[16] and in the sixth guideline[12] outcomes considered were not explicitly mentioned.

Summary of Critical Appraisal

Critical appraisal of the included guideline reports is summarized below and details are presented in Appendix 3, Table 3.

In the six included guideline reports[11-16] the scope and purpose were stated, the target users of the guideline were explicitly stated or implied, and the recommendations were clearly presented. In four reports,[12,13,15,16] the guideline development group was described and included relevant professional groups, and in two reports[11,14] the guideline development group was not described. A systematic search for evidence was mentioned in five reports[12-16] and not mentioned in one report.[11] Criteria for selecting the evidence were stated in four reports [12,13,15,16] and not stated in two reports [11,14] Recommendations were formulated based on consensus in four guidelines,[12-14,16] by voting in one guideline,[15] and methods were not reported for one guideline.[11] Conflicts of interest were declared and addressed in three guidelines,[12,15,16] conflicts of interest were declared but methods for addressing conflicts were not stated in one guideline,[14] and conflicts of interest were not mentioned in two guidelines.[11,13] Of note, one guideline[11] did not report details of the procedures used for guideline development in the guideline report, but according to their methods manual[17] a rigorous procedure (similar to the AGREE II criteria) was required.

Summary of Findings

Relevant recommendations are summarized below and associated details are presented in Appendix 4, Table 4.

Guidelines

Six relevant guideline reports[11-16] were included. Of the six included guidelines, three guidelines[12,13,15] graded the recommendations and three guidelines[11,14,16] did not present grades for the recommendations.

The NICE guideline[11] does not recommend the use of NAC for treating patients with acute cough associated with an upper respiratory tract infection or acute bronchitis. The CTS guideline[12] and the CHEST/CTS guideline[15] suggest the use of oral NAC to prevent acute exacerbations in patients with moderate to severe COPD (Grade 2B, i.e., weak

recommendation, moderate-quality evidence). The ERS/ATS guideline[13] suggests the use of oral mucolytics to prevent acute exacerbations in patients with moderate to severe COPD (conditional recommendation, low-quality evidence). The VA/DoD guideline[16] reports that there was insufficient evidence to recommend for or against the use of NAC for stable COPD patients who continue to experience respiratory symptoms, and mentions that reporting strength of recommendations is not applicable in this case.

The AARC guideline[14] does not recommend the routine use of aerosolized NAC for airway clearance in hospitalized patients without cystic fibrosis. The guideline also does not recommend use of mucolytics for treating atelectasis in post-operative patients, or the use of aerosolized agents to improve airway clearance in patients with neuromuscular disease, respiratory muscle weakness, or impaired cough.

Limitations

The guideline reports did not always explicitly present information regarding some of the quality assessment criteria indicated in the quality assessment tool (AGREE II). According to the guideline development manual or reports referred to by these groups, rigorous procedures are a requirement for developing the guidelines, however it was difficult to definitively ascertain to what extent these were followed, as the information was not explicitly presented in the included publications. The recommendations in the included guideline reports do not explicitly mention mucous clearance. Some recommendations do not specifically mention the type of NAC (i.e., oral or aerosolized) and some recommendations mention the general term mucolytics rather than NAC specifically. It is unclear if all the NAC formulations on which the recommendations were based are those that are available in Canada, hence generalizability of the recommendations to the Canadian setting is unclear.

The evidence informing the recommendations was generally of low or moderate quality, or was insufficient to recommend for or against the use of NAC. One guideline development group was common to two guideline reports,[12,15] hence the recommendations in the two reports are not exclusive to a particular group or groups. Findings need to be interpreted with caution, considering these limitations.

Conclusions and Implications for Decision or Policy Making

Six relevant evidence-based guidelines[11-16] were identified regarding the use of NAC for patients potentially requiring mucous secretion clearance. Three guidelines[12,13,15] suggest the use of oral NAC for patients with COPD (weak or conditional recommendations based on low- or moderate-quality evidence). The strength of the recommendations was not reported for the remaining guidelines. Of these, one guideline[16] does not recommend for or against the use of NAC preparations, because of insufficient evidence; one guideline[11] recommends against the use of NAC for acute cough; and the last guideline[14] recommends against the use of aerosolized NAC for hospitalized patients and patients with neuromuscular disease, respiratory muscle weakness or impaired cough. Evidence informing the recommendations on treatment with NAC was of limited quality or sparse.

A review of guidelines by Miravitlles et al.[18] did not meet the inclusion criteria for this current report, because the methodology was unclear. However, this review may provide some useful insights in terms of guidelines regarding the use of NAC in different countries. According to a table presented in this review, guidelines from England and Wales, Poland, and Russia recommend the use of NAC; guidelines from the Czech Republic recommend

the use of NAC in case of frequent exacerbations, bronchitis, COPD, and bronchiectasis; guidelines from Germany recommend NAC only for viscous secretions; guidelines from Spain recommend NAC as second-line treatment; guidelines from Sweden and France did not recommend NAC; and guidelines from Finland did not recommend NAC for long-term use. Italy and Portugal did not present any recommendations with respect to NAC.

In conclusion, use of oral NAC was suggested for COPD in three guidelines; and for the other disease conditions, NAC was not recommended or the recommendation was neither for nor against it.

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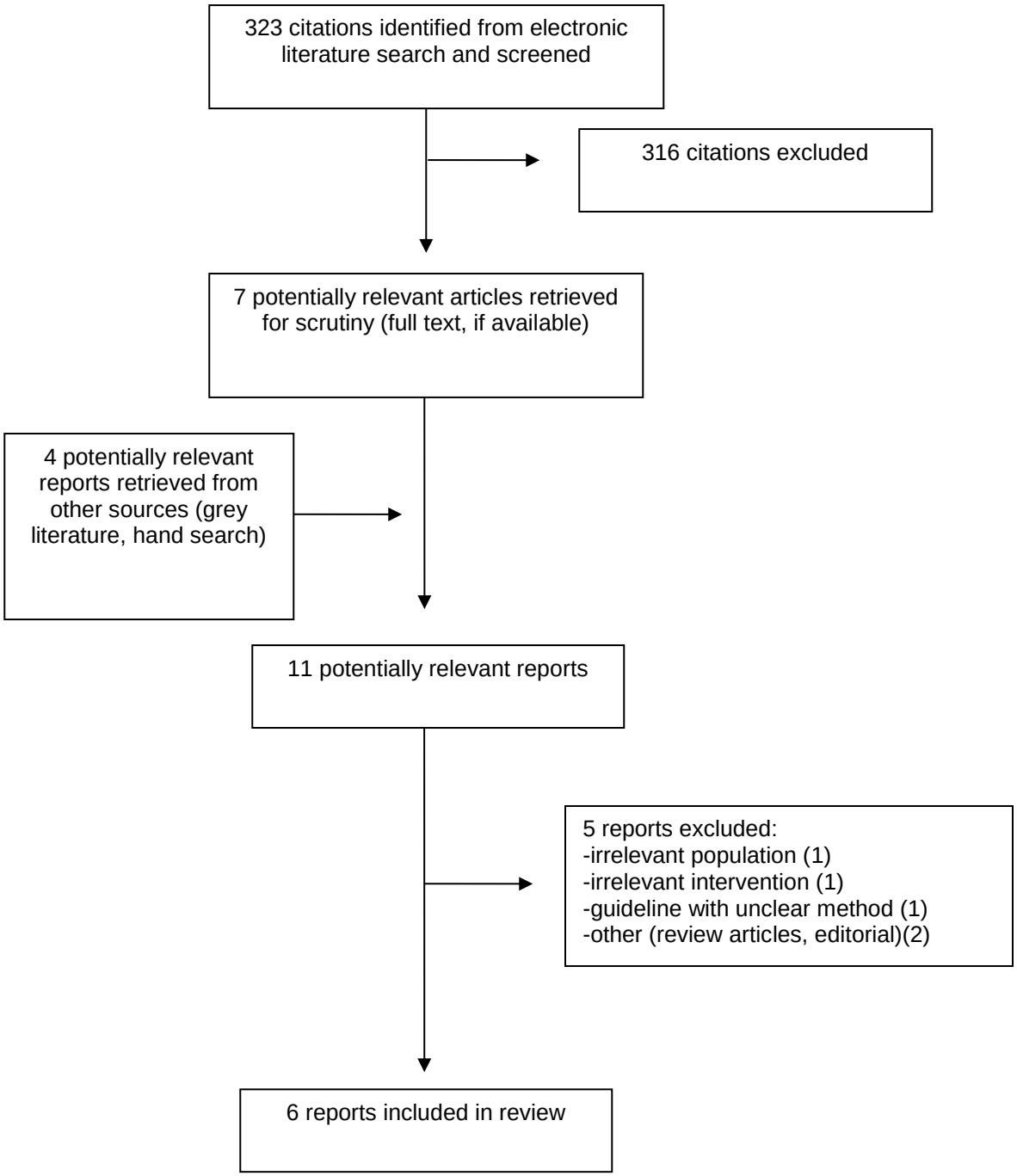
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
NICE,[11] 2019, UK						
Intended users: Health care professionals; People with acute cough, their families and care-givers Target population: Patients with acute cough	Mucolytics (including NAC), beta-2-agonists, corticosteroids, antibiotics, and self care	Productive cough, dyspnea, lung function, and adverse events	The guideline document did not specifically report on the methodology used to develop the guidelines. However details regarding the guideline development process and GDG are available in the NICE guideline development manual.[17] According to the manual, a systematic review is conducted to identify relevant evidence, the quality of the evidence is assessed using GRADE, and recommendations are formulated using formal consensus methods such as Delphi and nominal group techniques, and consensus development conferences. Also, according to the manual, GDG comprises practitioners (specialist and generalists), service or care providers, and at least two lay members such as patients or their caregivers.			
CTS (Bourbeau),[12] 2017, Canada						
Intended users: Respirologist, internist, primary care physician, pharmacist, nurse practitioner, respiratory educator, and healthcare decision maker. Target population: Patients with stable COPD as well as those with concomitant asthma.	Mucolytics (including NAC), and other agents such as beta-2-agonists, anti-muscarinics (or anticholinergics), corticosteroids, and phosphodiesterase-4-inhibitors.	Dysnea, exercise tolerance, physical activity, health status, exacerbations	The method used for the development of the guideline was based on the CTS guideline production methodology.[19] A systematic literature review was undertaken.	Recommendations were classified using GRADE, as adapted for use by CHEST (details in CHEST/CTS [Criner],[15] shown below)	Recommendations were based on scientific evidence and expert-informed opinion and were formulated based on majority consensus The GDG comprised 10 respirologists, two primary care physicians, one pharmacist, and one patient with COPD	Externally reviewed; published in a peer-reviewed journal

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
ERS/ATS (Wedzicha),[13] 2017, UK						
Intended users: Not mentioned explicitly; appear to be individuals involved with prevention of COPD exacerbations Target population: Patients with COPD	Mucolytics and other agents such as beta-2-agonists, anti-muscarinics, roflumilast, and fluroquinolones	Exacerbation, hospitalization, quality of life, adverse events, mortality, sputum production, lung function	A systematic literature review was undertaken	Recommendations were classified as conditional or strong. A conditional recommendation for an intervention indicates that the panel was uncertain that the desirable consequences of the intervention outweigh the undesirable consequences. A strong recommendation for an intervention indicates that the panel was certain that the desirable consequences of the intervention outweigh the undesirable consequences.	Recommendations were based on iterative consensus GDG comprised 11 clinicians with experience in COPD management and research, two methodologists, and one clinician-methodologist	Reviewed and approved by all panel members before submission
AARC (Strickland),[14] 2015, US						
Intended users: Not mentioned explicitly; appear to be individuals prescribing airway clearance therapy Target population: Hospitalized patients without	Mucolytics (including NAC), and other agents such as beta agonists, anti-cholinergics, saline (normal and hypertonic)	Airway clearance, oxygenation, hospital stay, sputum properties, quality of life, atelectasis, adverse events	Recommendations were based on a systematic review and clinical experience.	Recommendations were not graded.	As high-quality evidence was not available, a formal guideline development process was not used. Composition of GDG was not reported	Externally reviewed; published in a peer-reviewed journal

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
CF; patients with NMD, respiratory muscle weakness, or impaired cough; and post-operative patients						
CHEST/CTS (Criner),[15] 2015, Canada						
Intended users: Not mentioned explicitly; appear to be individuals involved with prevention of COPD exacerbations Target population: Patients with COPD	Mucolytics (including NAC); and other agents such as beta agonists, anti-cholinergics, and non pharmacological therapies and vaccinations	Exacerbations, emergency department visits, hospital admission, unscheduled physician visit	A systematic literature review was undertaken The recommendation and its associated grade were based on information from the evidence review.	Recommendations were graded using the CHEST grading system. Grades 1A, 1B, and 1C indicate strong recommendations based on high-quality, moderate-quality, and low- or very-low-quality evidence respectively. Grades 2A, 2B, and 2C indicate weak recommendations based on high-quality, moderate-quality, and low- or very-low-quality evidence respectively.	Recommendations were drafted by three panelists, sent to all the panelists and finalized by voting. The expert panel comprised experts in pulmonology and respiratory therapy (a chair from CHEST, a vice-chair from CTS, eight panelists from CHEST and nine from CTS). A methodologist was involved in study selection, data extraction, and quality review.	Externally reviewed; published in a peer-reviewed journal
VA/DoD,[16] 2014, US						
Intended users: Primary care providers Target population:	NAC, and other agents such as beta-2-agonists, anti-muscarinics, corticosteroids, and	Exacerbation, dyspnea, hospitalization, lung function, adverse events.	It was stated that the methodology used for developing the guidelines followed the process	When applicable, recommendations were classified based on the GRADE system as described	Recommendations were based on consensus Strength of the recommendations were	The final drafts of VA/DoD guidelines are submitted for

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Patients with COPD	phosphodiesterase-4-inhibitors, and non-pharmacological therapies and vaccination		described in the VA/DoD Guideline for Guidelines.[20] A systematic review was conducted.	in VA/DoD Guideline for Guidelines.[20]	stated where applicable GDG comprised of Guideline Champions (Champions), and subject matter experts from within the VA and DoD (Work group). Further details were not presented; however a participant list was included in the Appendix and comprised individuals with credentials such as MD, PhD, PharmD, MPH, RN.	independent review (according to the VA/DoD Guideline methods)

AARC = American Association for Respiratory Care; ATS = American Thoracic Society; CF = cystic fibrosis; CHEST = American College of Chest Physicians; CTS = Canadian Thoracic Society; DoD = Department of Defense; ERS = European Respiratory Society; GDG = Guideline Development Group; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NAC = acetylcysteine; NICE National Institute of Health and Care Excellence; NMD = neuromuscular disease; VA = Department of Veteran's Affair; VA/DoD = Department of Veterans Affairs/ Department of Defense.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Guidelines using AGREE II[9]

Item	Guideline					
	NICE,11 2019, UK	CTS12 (Bourbeau), 2017, Canada	ERS/ATS13 (Wedzicha), 2017, UK	AARC14 (Strickland), 2015, US	CHEST/ CTS15 (Criner), 2015, Canada	VA/DoD,16 2014, US
Domain 1: Scope and Purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	y	y	y	y	y	y
2. The health question(s) covered by the guideline is (are) specifically described.	n	y	y	n	y	y
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	y	y	y	y	y	y
Domain 2: Stakeholder Involvement						
4. The guideline development group includes individuals from all relevant professional groups.	Not stated	y	y	Not stated	y	y
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Not stated	y	Not stated	Not stated	Not stated	y
6. The target users of the guideline are clearly defined.	y	y	y (implied)	y (implied)	y (implied)	y
Domain 3: Rigour of Development						
7. Systematic methods were used to search for evidence.	Not stated	y	y	y	y	y
8. The criteria for selecting the evidence are clearly described.	Not stated	y	y	Not stated	y	y
9. The strengths and limitations of the body of evidence are clearly described.	Not stated	y	y	Not stated	y	y
10. The methods for formulating the recommendations are clearly described.	Not stated	y	y	y	y	y
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	y	Not stated	y	y	y	y
12. There is an explicit link between the recommendations and the supporting evidence.	y	Not stated	y	y	y	y
13. The guideline has been externally reviewed by experts prior to its publication.	Not stated	y	Unclear	y	y	y

Item	Guideline					
	NICE,11 2019, UK	CTS12 (Bourbeau), 2017, Canada	ERS/ATS13 (Wedzicha), 2017, UK	AARC14 (Strickland), 2015, US	CHEST/ CTS15 (Criner), 2015, Canada	VA/DoD,16 2014, US
14. A procedure for updating the guideline is provided.	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Domain 4: Clarity of Presentation						
15. The recommendations are specific and unambiguous.	y	y	y	y	Y	y
16. The different options for management of the condition or health issue are clearly presented.	y	y	y	Not stated	Y	y
17. Key recommendations are easily identifiable.	y	y	y	y	y	y
Domain 5: Applicability						
18. The guideline describes facilitators and barriers to its application.	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
20. The potential resource implications of applying the recommendations have been considered.	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
21. The guideline presents monitoring and/or auditing criteria.	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Domain 6: Editorial Independence						
22. The views of the funding body have not influenced the content of the guideline.	Not stated	y	Not stated	Not stated	Not stated	Not stated
23. Competing interests of guideline development group members have been recorded and addressed.	Not stated	y	Not stated	Two of the six authors had association with industry	y	y

AARC = American Association for Respiratory Care; ATS = American Thoracic Society; CHEST = American College of Chest Physicians; CTS = Canadian Thoracic Society; ERS = European Respiratory Society; VA/DoD = Department of Veterans Affairs/ Department of Defense; n = no; y = yes (i.e., criteria were met).

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
NICE,[11] 2019, UK	
Evidence: Evidence was obtained from a systematic review including 6 RCTs involving children with acute upper and lower respiratory tract infection. Mucolytics (oral NAC or oral carbocisteine) were significantly better than placebo for reducing cough at 6 to 7 days, but not at the end of treatment (28 days). There were no significant differences between mucolytics and placebo with respect to productive cough and lung function. As the benefits of mucolytics were unclear the committee agreed they should not be offered to adults or children **Recommendation:** "Do not offer a mucolytic (for example acetylcysteine or carbocisteine) to treat an acute cough associated with an upper respiratory tract infection or acute bronchitis." (*p6*)	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
CTS (Bourbeau),[12] 2017, Canada	
Evidence: No evidence was presented in the document, however, seven references were mentioned. The key messages were based on scientific evidence, and expert-informed opinion. **Recommendation:** "We suggest treatment with oral N-acetylcysteine (600 mg po BID) to prevent AECOPD for patients with chronic bronchitis, a history of at least one exacerbation in the previous year, and on long-acting inhaled therapy (Grade 2B)." (*p230*)	**Strength of Evidence:** Moderate quality **Strength of Recommendation:** Weak
ERS/ATS (Wedzicha),[13] 2017, UK	
Evidence: Evidence was obtained from one systematic review (with four relevant RCTs); and two additional RCTs. Of the 6 RCTs on mucolytic agents, four RCTs were on NAC, one RCT was on ambroxol, and one RCT was on carbocisteine. Mucolytic therapy reduced the likelihood of hospitalization. The effect on COPD exacerbations varied depending on the assessment method. Mucolytic therapy reduced the risk of exacerbations when assessed as number of exacerbations per patient-year and showed no effect when assessed as proportion of patients who remained exacerbation-free. There was no evidence that mucolytic therapy increased adverse events or altered quality of life. The beneficial effect of mucolytic therapy on COPD exacerbations was mainly observed with high dose mucolytic therapy, such as 600 mg NAC, twice daily. **Recommendation:** "For patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we	**Strength of Evidence:** Low-quality **Strength of Recommendation:** Conditional

Evidence and Recommendations	Strength of Evidence and Recommendations
suggest treatment with an oral mucolytic agent to prevent future exacerbations (conditional recommendation, low quality of evidence)." (*p4*)	
AARC (Strickland),[14] 2015, US	
Evidence: For hospitalized patients without CF: Findings from a systematic review indicated that the evidence on the use of pharmacologic agents to improve airway clearance and change sputum properties, compared to usual care was weak and insufficient, hence use of such agents could not be recommended. One RCT involving male patients with chronic bronchitis or asthmatic bronchitis found that with NAC there was decrease in sputum viscosity (assessed subjectively) but no change in pulmonary function or sputum volume when compared with isoproterenol. For post-operative patients: Evidence was obtained from two RCTs, and two non-randomized studies. Findings were inconsistent. For patients with NMD, respiratory muscle weakness, or impaired cough: No RCT or other studies were identified on inhaled pharmacological agents to improve airway clearance in these patients. **Recommendations:** For hospitalized adults and pediatric patients without CF: "Routine use of aerosolized N-acetylcysteine to improve airway clearance is not recommended." (*p1072*) For post-operative adult and pediatric patients: "Mucolytics cannot be recommended for use in the treatment of atelectasis due to insufficient evidence." (*p1074*) For adult and pediatric patients with NMD, respiratory muscle weakness or impaired cough: "The use of aerosolized agents to change sputum physical properties or improve airway clearance cannot be recommended for patients with NMD or weakness due to insufficient evidence." (*p1073*)	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
CHEST/CTS (Criner),[15] 2015, Canada	
Evidence: Evidence was obtained from three relevant RCTs on COPD patients. Overall there was a decrease in exacerbation rates for treatment with oral NAC compared with placebo and NAC appeared to be well tolerated. **Recommendation:** “For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, we suggest treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD (Grade 2B). (*p900*)	**Strength of Evidence:** Moderate-quality **Strength of Recommendation:** Weak

Evidence and Recommendations	Strength of Evidence and Recommendations
VA/DoD,[16] 2014, US	
Evidence: One RCT involving COPD patients and comparing NAC with placebo was mentioned. The guideline authors reported that with NAC there were no apparent major adverse events and when compared to placebo, NAC showed no improvement in dyspnea. The authors concluded that confidence in the available evidence was weak. **Recommendation:** "There is insufficient evidence to recommend for or against the use of N-acetylcysteine (NAC) preparations available in the US in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Strength of recommendation not applicable)" (*p34*)	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not applicable

AARC = American Association for Respiratory Care; AECOPD = acute exacerbation of COPD; ATS = American Thoracic Society; BID = twice daily; CF = cystic fibrosis; CHEST = American College of Chest Physicians; COPD = chronic obstructive pulmonary disease; ERS = European Respiratory Society; NAC = acetylcysteine; NMD = neuromuscular disease; RCT = randomized controlled trial; VA/DoD = Department of Veterans Affairs/ Department of Defense.