## Table 4: Summary of Recommendations in Included Guidelines

| Evidence and Recommendations | Strength of Evidence and Recommendations |
|---|---|
| NICE,[11] 2019, UK | |
| **Evidence:**<br>Evidence was obtained from a systematic review including 6 RCTs involving children with acute upper and lower respiratory tract infection.<br>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.<br>As the benefits of mucolytics were unclear the committee agreed they should not be offered to adults or children<br><br>**Recommendation:**<br>"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<br><br>**Strength of Recommendation:** Not reported |
| CTS (Bourbeau),[12] 2017, Canada | |
| **Evidence:**<br>No evidence was presented in the document, however, seven references were mentioned. The key messages were based on scientific evidence, and expert-informed opinion.<br><br>**Recommendation:**<br>"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<br><br>**Strength of Recommendation:** Weak |
| ERS/ATS (Wedzicha),[13] 2017, UK | |
| **Evidence:**<br>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.<br><br>**Recommendation:**<br>"For patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we | **Strength of Evidence:** Low-quality<br><br>**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:**<br>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.<br><br>For post-operative patients: Evidence was obtained from two RCTs, and two non-randomized studies. Findings were inconsistent.<br><br>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.<br><br>**Recommendations:**<br>For hospitalized adults and pediatric patients without CF: "Routine use of aerosolized N-acetylcysteine to improve airway clearance is not recommended." (*p1072*)<br><br>For post-operative adult and pediatric patients: "Mucolytics cannot be recommended for use in the treatment of atelectasis due to insufficient evidence." (*p1074*)<br><br>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<br><br>**Strength of Recommendation:** Not reported |
| CHEST/CTS (Criner),[15] 2015, Canada | |
| **Evidence:**<br>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.<br><br>**Recommendation:**<br>“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<br><br>**Strength of Recommendation:** Weak |

| Evidence and Recommendations | Strength of Evidence and Recommendations |
|---|---|
| VA/DoD,[16] 2014, US | |
| **Evidence:**<br>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.<br><br>**Recommendation:**<br>"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<br><br>**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.