

REVIEW

N-acetylcysteine in paediatrics: a review of efficacy, safety and dosing strategies in respiratory care

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Abstract

N-acetylcysteine (NAC) is widely used for its mucolytic, antioxidant, anti-inflammatory and synergistic antibacterial properties in the treatment of respiratory diseases. NAC and other mucolytics and mucoactive medications are frequently employed in the adult population and in paediatric settings to improve mucus clearance in conditions such as cystic fibrosis, bronchiolitis, pneumonia, and both chronic and acute bronchitis, with varying degrees of success. This narrative review evaluates the efficacy and safety of NAC in paediatric acute and chronic respiratory diseases, synthesizing data from clinical trials, observational studies and real-world evidence, with a particular focus on optimizing dosing based on patient-specific characteristics. Numerous studies indicate that oral NAC doses of 20 mg/kg/day for acute conditions and 200 mg three times daily for chronic conditions are generally effective and well tolerated in children. However, most participants in these studies were older than 9 years, resulting in a lack of literature-based evidence for the optimal dosing in younger children over 2 years of age. Given the significant weight variations within this age group, weight-based dosing is recommended to en-

sure appropriate drug exposure and optimize treatment benefits. Weight-based dosing adjustments and patient monitoring may help optimize treatment outcomes and reinforce the overall positive safety and tolerability profile in paediatric settings. NAC is a valuable therapeutic agent for paediatric respiratory diseases, particularly in older children. In younger patients, weight-adjusted dosing and careful monitoring for potential adverse effects may help maximize efficacy and maintain its favourable tolerability profile.

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Keywords: bronchitis, children, cystic fibrosis, mucolytic agents, N-acetylcysteine, over-the-counter drugs, paediatrics, respiratory diseases.

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Introduction

N-acetylcysteine (NAC), a derivative of L-cysteine, is a well-established mucolytic, antioxidant and anti-inflammatory agent used in the management of acute and chronic respiratory diseases.¹ Initially developed as a mucolytic, its ability to reduce disulphide bonds in mucus glycoproteins facilitates secretion clearance, improving mucociliary function and airway patency.² Beyond its direct mucolytic activity, NAC enhances mucociliary transport³ and modulates mucus production at the epithelial level, highlighting its combined mucolytic and mucoregulatory properties.⁴ NAC also promotes

glutathione synthesis, conferring antioxidant protection against oxidative stress-induced lung injury.² Furthermore, NAC modulates inflammatory pathways by inhibiting NF- κ B activation and neurokinin A release, thereby reducing pro-inflammatory cytokine production.⁵⁻⁸

NAC potentiates antibiotic efficacy by disrupting biofilms and exerting direct antimicrobial effects.^{9,10} In vitro, NAC synergistically potentiates antibiotics against multidrug-resistant bacteria, including *Acinetobacter baumannii* and *Klebsiella pneumoniae*, enhancing colistin activity and potentiating beta-lactams by altering bacterial morphology.^{9,11,12} It also improves penicillin efficacy against some Gram-negative pathogens¹³ and disrupts

Staphylococcus aureus biofilms, achieving $\geq 90\%$ reduction with antibiotics.¹⁴

In vivo, NAC mitigates infection-related organ damage and inflammation, improving antimicrobial outcomes.^{15–17} Clinical studies associate NAC with reduced 30-day mortality in infections caused by multidrug-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii*.¹¹ Blasi et al.¹⁰ highlight its role in respiratory infections, particularly in chronic bronchitis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF).¹⁰ Paediatric studies suggest that NAC accelerates recovery when combined with antibiotics.^{18–21}

Together, these mechanisms contribute to the overall therapeutic efficacy of NAC, suggesting that its benefits extend beyond its traditional role as a mucolytic and result from a complex interplay of mucoregulatory, anti-infective, antioxidant and anti-inflammatory actions.¹ In paediatric populations, NAC is commonly prescribed for conditions such as bronchitis, bronchiolitis, pneumonia and CF. However, its efficacy and safety profile may vary across age groups, formulations and routes of administration. In this respect, dosage recommendations may also differ depending on the country in which the product is authorized. Some countries recommend maintaining the same dosage from the age of 2 years onwards, whilst others introduce a cut-off age of 6–7 years to increase the dosage. However, because body weight varies significantly between 2 and 6–7 years, and again from 6–7 to 12 years, these broad age-based dosing categories may potentially lead to sub-optimal treatment.

Implementing more precise, age-adjusted and weight-adjusted dosing regimens could further optimize the efficacy and tolerability of the drug. Whilst oral and inhaled mucolytics generally have a favourable safety profile in older children, their use in infants under 2 years is not recommended because of reports of paradoxical bronchorrhea, airway congestion and respiratory distress.^{22,23} In addition, these drugs can cause an increase in bronchial secretions in children under the age of 2 years, who may have difficulty eliminating them through coughing.²⁴ These concerns have led to regulatory restrictions in some countries, underscoring the particular vulnerability of the very-young paediatric population and the importance of continued focus on optimal dosage within the medical community.

Given its well-established tolerability profile, NAC shows promise for managing mucus hypersecretion in children, particularly in the context of acute infections, which are highly prevalent in this age group. This narrative review synthesizes the current evidence on NAC in paediatric

respiratory diseases, addressing its pharmacokinetics, mechanisms of action, clinical efficacy and safety considerations, whilst also considering weight-based dosing regimens. By evaluating data from controlled trials, observational studies and real-world evidence, we aim to clarify the role of NAC in paediatric respiratory care and identify gaps for future research.

Methods

This is a narrative review of the literature conducted using PubMed/MEDLINE and Google Scholar. The following keywords were used for the literature search: (“N-acetylcysteine” AND “pharmacokinetics”) OR (“N-acetylcysteine” AND “mechanism of action”) OR (“N-acetylcysteine” AND “anti-inflammatory”) OR (“N-acetylcysteine” AND “antioxidant”) OR (“N-acetylcysteine” AND “cytoprotective”) OR (“N-acetylcysteine” AND “pediatric” AND “respiratory disease”). The search covered the period from January 1964 to June 2025, in line with the earliest available studies and the most recent evidence. Articles were initially screened by title and abstract for relevance, followed by a full-text review. Additionally, the reference lists of selected articles were examined to identify further relevant literature.

Pharmacokinetics of NAC

NAC is a synthetic derivative of the naturally occurring amino acid L-cysteine, characterized by its thiol group, which serves as a precursor for glutathione synthesis, a key antioxidant in cellular defence mechanisms.²⁵ NAC can be administered orally, intravenously or via inhalation, with each route influencing its pharmacokinetic profile differently.²

Inhalational administration of NAC may achieve higher airway concentrations, potentially enhancing its mucolytic effects. However, its broader use in nebulized form is limited by its low intrinsic reducing activity and short half-life in the airways.

For respiratory diseases, the usual daily oral dose for adults in clinical practice ranges from 600 to 1200 mg, although higher doses have been explored based on clinical context.^{26–31} Following oral administration, NAC is rapidly absorbed in the small intestine, achieving peak plasma concentrations within 1–2 hours.^{32,33} NAC undergoes extensive first-pass metabolism in the liver, converting it primarily into L-cysteine, which is then utilized for glutathione synthesis.²⁵ After oral administration of 400 mg of NAC, the terminal half-life is approximately 6 hours.³⁴ Because of this first-pass effect and rapid cellular uptake, the oral bioavailability of NAC is notably low, ranging from 4% to 10%.^{34,35}

The elimination half-life of NAC varies depending on the route of administration and patient population. Intravenous delivery bypasses first-pass metabolism in the liver and intestinal wall, allowing more rapid attainment of therapeutic concentrations, as seen in its use for paracetamol poisoning.³⁶ In healthy adults, intravenous NAC (600 mg) has a terminal half-life of approximately 2.3 hours, with virtually no detectable plasma levels after 12 hours.³⁵

NAC is primarily excreted renally, with about 30% of the administered dose recovered in the urine,³⁵ whilst faecal excretion accounts for approximately 3%.^{2,37}

In paediatric patients, differences in pharmacokinetics and pharmacodynamics compared with adults require dosing adjustments to ensure optimal drug efficacy and safety.^{38,39}

Mechanism of action of NAC

NAC exerts its therapeutic effects through multiple mechanisms, primarily involving its mucolytic, antioxidant and anti-inflammatory properties.⁴⁰ As an acetylated precursor of L-cysteine, NAC plays a pivotal role in maintaining cellular redox homeostasis and modulating inflammatory pathways.⁴⁰

NAC is widely recognized for its mucolytic properties, particularly in respiratory diseases characterized by excessive mucus production such as CF, COPD and idiopathic pulmonary fibrosis.⁴⁰ The mucolytic effect of NAC is multifactorial, combining direct and indirect mechanisms that facilitate mucus clearance. Its primary mucolytic action stems from its ability to cleave disulfide bonds within high-molecular-weight glycoproteins (mucins), which are responsible for mucus viscosity and elasticity.² During inflammatory processes, mucins undergo oxidative modifications, leading to abnormal disulfide cross-linking that thickens the mucus and impairs mucociliary clearance.^{25,41} By reducing these disulfide linkages through its thiol group, NAC decreases mucus viscosity, facilitating its removal from the airways and improving airflow.^{25,41} NAC also enhances mucociliary transport, providing a dual mucolytic mechanism of action that improves secretion clearance.³ Additionally, evidence suggests that NAC modulates mucus production at the epithelial level by modulating MUC5AC and MUC5B expression and reducing goblet cell numbers, reinforcing its role as both a mucolytic and mucoregulatory agent.⁴

NAC functions as both a direct and indirect antioxidant. The direct antioxidant effect arises from its thiol group, which scavenges reactive oxygen and nitrogen species,

including hydrogen peroxide, hydroxyl radical, superoxide, hypochlorous acid and nitrogen dioxide.^{41–45} The indirect antioxidant effects of NAC are more pronounced and involve replenishing intracellular glutathione levels.² Upon deacetylation, NAC provides cysteine, the rate-limiting substrate for glutathione synthesis.⁴⁶ Glutathione is a critical antioxidant that neutralizes reactive species and serves as a substrate for various antioxidant enzymes, including glutathione peroxidase and glutaredoxin.⁴⁷ By enhancing glutathione biosynthesis, NAC restores redox balance in cells, protecting them from oxidative damage, particularly in conditions such as acute exacerbations of COPD, where glutathione levels are depleted.^{48,49} Beyond glutathione replenishment, additional mechanisms have been proposed to explain the potential role of NAC in redox balance, including its ability to enhance plasma antioxidant activity by restoring the Cys34 residue of human serum albumin,⁵⁰ and its contribution to modest increases in hydrogen sulfide and sulfane sulfur species within cells.⁵¹

In addition to its antioxidant properties, NAC exhibits significant anti-inflammatory activity.⁴⁰ It inhibits the activation of NF- κ B, a central transcription factor in the inflammatory response.^{5–8} NF- κ B regulates the expression of pro-inflammatory cytokines, such as TNF, IL-1 β and IL-6.⁶ By blocking NF- κ B translocation and activation, NAC suppresses the release of these cytokines and reduces the expression of cyclooxygenase 2, matrix metalloproteinases and intercellular adhesion molecules, contributing to its broad anti-inflammatory profile.⁵² Additionally, NAC inhibits neurokinin A release in lipopolysaccharide-stimulated human bronchi, thereby diminishing the increase in IL-6.^{53,54}

Beyond its mucolytic, antioxidant and anti-inflammatory roles, NAC also exerts cytoprotective effects by stabilizing proteins and DNA through its reducing capacity, potentially offering protective effects against genotoxicity, cell apoptosis and malignant transformation.²⁵

The therapeutic potential of NAC in respiratory and systemic diseases arises from its multifaceted mechanisms; its combined actions make NAC an effective agent in managing conditions characterized by mucus hypersecretion, oxidative stress and inflammation.

Cough and airway mucus hypersecretion in paediatric respiratory diseases: the role of mucolytics

Acute and chronic respiratory diseases pose a significant global health burden, with an increasing preva-

lence amongst children.⁵⁵ Distinct factors, such as early allergen sensitization, frequent viral infections and improved survival of preterm infants with bronchopulmonary dysplasia, contribute to recurrent respiratory issues, increasing the risk of acute illnesses transitioning into chronic conditions.⁵⁵ Amongst these, acute respiratory tract infections are particularly common, affecting school-age children five to eight times per year, with each episode lasting 7–9 days.⁵⁶ Cough is the primary symptom, often persisting beyond 10 days in half of the cases and lasting over 3 weeks in 10% of children, significantly disrupting sleep and causing parental anxiety.⁵⁷ Consequently, parents frequently seek over-the-counter and prescription medications to alleviate their child's cough.

A key feature of paediatric respiratory diseases is airway mucus hypersecretion, observed in conditions such as CF, bronchiolitis, pneumonia, and acute and chronic bronchitis.⁵⁸ Although paediatric mucus pathophysiology is less studied than in adults, available evidence suggests similar mechanisms, including goblet cell hyperplasia, sub-mucosal gland hypertrophy and airway mucus plugging.⁵⁸ Excessive mucus accumulation exacerbates cough, impairs breathing and, in severe cases, can obstruct airways. Given these complications, mucolytics have significant therapeutic potential for treating cough associated with respiratory infections in children. These agents effectively reduce mucus viscosity without increasing its volume, facilitating airway clearance.⁵⁹ Moreover, the antioxidant, anti-infective and anti-inflammatory properties of NAC may accelerate recovery, while its ability to disrupt biofilms and inhibit bacterial adhesion may reduce the risk of secondary infections.^{10,40}

Efficacy and safety of NAC in children

Included studies

Most of the research on the efficacy and safety of NAC in children, as with many studies on mucoactive agents, was conducted prior to the implementation of Good Clinical Practice guidelines⁶⁰ in 1997. These guidelines introduced internationally recognized ethical and scientific standards for clinical trials. Nevertheless, the studies included in this review generally adhered to well-established methodologies, as evidenced by the consistency of study endpoints, supporting their overall robustness.

This review compiles data from 20 controlled and 8 uncontrolled clinical trials, encompassing a total of 1438 paediatric patients, as well as real-world evidence

from retrospective studies, representing an additional 143 paediatric patients. These studies evaluated NAC across a range of acute and chronic respiratory conditions. Specifically, 20 clinical trials investigated oral NAC, 3 examined intramuscular administration and 5 evaluated nebulized NAC. Amongst real-world studies, two evaluated nebulized NAC, and one investigated bronchoalveolar lavage (BAL) containing NAC. Detailed information on each study is provided in Tables 1–3.

Efficacy profile of NAC in paediatric acute respiratory conditions

Controlled clinical studies

Randomized placebo-controlled studies

Fiocchi et al.⁶¹ conducted a randomized, double-blind, placebo-controlled trial to investigate the effectiveness of NAC in treating paediatric patients with acute lower respiratory tract infections, including bronchitis and tracheitis (Table 1). The study included 100 children (bronchitis ($n=48$) and tracheitis ($n=52$)), divided equally between those receiving NAC syrup (20 mg/kg/day in three divided doses) and those receiving a placebo over a 28-day period. The NAC group had a mean age of 7.3 ± 3.4 years and an average weight of 23.9 ± 11.3 kg, whilst the placebo group had a mean age of 6.7 ± 3.0 years and an average weight of 25 ± 11.1 kg. Antibiotics were prescribed when necessary.

The study evaluated treatment outcomes based on respiratory parameters, cough severity and productivity, and spirometric assessments when feasible.⁶¹ Results demonstrated that NAC was more effective in alleviating symptoms and improving respiratory findings, particularly in children with more severe bronchial infections. Subgroup analysis revealed that, in children with bronchitis, NAC significantly reduced thoracic wet noises and improved both cough symptoms and productivity compared with placebo ($p < 0.05$) (Figure 1A). Mean cough scores, classified on a scale from 0 (absent) to 3 (notable), decreased from 2.15 to 0.08 in the NAC group ($p < 0.001$), whilst in the placebo group they were reduced from 2.19 to 0.48 ($p < 0.001$). In cases of tracheitis, NAC led to a significant improvement in cough symptoms relative to placebo (cough severity: $p < 0.05$; cough productivity: $p = 0.05$), with a marked reduction in thoracic wet noises compared with pre-treatment levels ($p < 0.01$) (Figure 1B). In contrast, the reduction in thoracic wet noises in the placebo group during the treatment period was not statistically significant (Figure 1B).

Amongst patients with bronchitis, the frequency of positive changes in thoracic wet noises and cough produc-

Table 1. Controlled clinical studies on NAC in paediatric respiratory diseases.

Study	Design/control type	Study and control drugs	Treatment duration	Number of participants by arm and age	Diagnosis	Efficacy results
Acute respiratory disease						
Fiocchi et al. ⁶¹	Randomized, double-blind, placebo-controlled study	NAC 20 mg/kg/day (oral) versus placebo	28 days	100 children; mean age 7 years	Bronchitis, tracheitis	NAC significantly reduced cough severity, improved lung function and thoracic wet noises
Biscatti et al. ²¹	Randomized, double-blind, placebo-controlled study	NAC (oral) 100 mg/day (<2 years), 200 mg/day (2–4 years), 300 mg/day (>4 years) versus antibiotics alone	6 days	50 children aged 1–12 years	Pneumonia, bronchitis, tracheitis	NAC treatment led to a faster resolution of fever and thoracic abnormalities
Hashemian et al. ⁶³	Randomized, placebo-controlled study	NAC 1200 mg/day (oral) versus placebo	7 days	52 children aged 8–18 years	Moderate COVID-19	NAC significantly improved oxygen saturation and reduced hospital stay duration
Trastotenojo et al. ⁶⁴	Double-blind, placebo-controlled study. Details on randomization unavailable	NAC 100 mg TID (oral) versus placebo	5 days	60 children aged 2 months to 13 years	Bronchopneumonia, asthma, bronchiolitis, tuberculosis	NAC improved cough and dyspnoea over time
Bellomo et al. ⁶⁵	Randomized, active-controlled study	NAC (oral or IM) 300 mg/day (<2 years), 600 mg/day (>2 years) versus standard treatment	8 days	50 children aged 6 months to >2 years	Acute bronchitis, pneumonia	NAC improved fever, dyspnoea, thoracic auscultation findings and cough. NAC showed comparable efficacy orally and IM

(Continued)

Table 1. (Continued)

Study	Design/control type	Study and control drugs	Treatment duration	Number of participants by arm and age	Diagnosis	Efficacy results
Camurri et al. ⁶⁶	Randomized, active-controlled study	NAC 300 mg /day (oral) versus bromhexine 48 mg/day (oral)	10 days	32 children, aged 2–11 years	Acute bronchitis	Both treatments improved symptoms; bromhexine had better efficacy
Chen et al. ⁶⁷	Randomized, active-controlled study	NAC 300 mg BID or TID (10% solution, nebulized) + budesonide 0.25–0.5 mg BID (nebulized) versus budesonide alone	14 days	120 children, mean age 7.3 years	<i>Mycoplasma Pneumoniae</i> pneumonia	NAC led to faster resolution of cough, fever, and rales and reduced inflammatory markers
Xue et al. ⁶⁸	Randomized, active-controlled study	NAC 300 mg BID (10% solution, nebulized) versus ambroxol 300 mg BID (nebulized)	7 days	98 children, aged 2–6 years	Pneumonia	NAC led to faster resolution of fever, cough, and lung rales and improved both lung function and inflammatory markers
Seidita et al. ⁶⁹	Active-controlled study	NAC 300 mg /day (oral) versus sobrerol 100 mg TID (oral)	3 days	40 children, aged 3–12 years	Bronchitis, pharyngo-tracheobronchitis	Both treatments were effective, sobrerol had slightly better sputum viscosity reduction
Liu et al. ⁷¹	Active-controlled study	NAC 300 mg BID (10% solution, nebulized) versus ambroxol 30 mg BID (nebulized)	14 days	120 children, aged 1–7 years	Bronchial pneumonia	NAC was more effective in reducing symptoms and improving immune function

(Continued)

Table 1. (Continued)

Study	Design/control type	Study and control drugs	Treatment duration	Number of participants by arm and age	Diagnosis	Efficacy results
Chronic respiratory disease						
Mitchell & Elliott ⁷²	Randomized, crossover, double-blind, placebo-controlled study	NAC 200 mg TID (oral) <i>versus</i> placebo	Two 3-month periods	20 children, mean age 10.8 years	CF	No significant difference in lung function vs placebo
Stafanger et al. ⁷³	Randomized, crossover, double-blind, placebo-controlled study	NAC 200 mg TID (<30 kg) or 400 mg BID (>30 kg) (oral) <i>versus</i> placebo	Two 3-month periods	54 children; mean age 9.5 (CF), 29.7 (PCD) years	CF (n=41), PCD (n=13)	NAC improved lung function in patients with CF during peak infection seasons. No significant effects were observed in patients with PCD
Stafanger et al. ⁷⁴	Randomized, crossover, placebo-controlled study	NAC 200 mg TID (<30 kg) or 400 mg BID (>30 kg) (oral) <i>versus</i> placebo	3 months	52 children, mean age 15.8 years	CF with chronic <i>Pseudomonas aeruginosa</i> infection	NAC led to significant lung function improvement in severely ill patients with CF (PEFR <70%)
Ratjen et al. ⁷⁵	Randomized, parallel group, double-blind, placebo-controlled study	NAC 200 mg TID <i>versus</i> ambroxol 30 mg TID <i>versus</i> placebo	3 months	36 children, mean age 13.9 years	CF	No significant difference in lung function, though the placebo group exhibited a trend toward greater decline
Gotz et al. ⁷⁶	Randomized, crossover, double-blind, placebo-controlled study	NAC 9.5 mg/kg (oral) <i>versus</i> placebo	14 days	21 children	CF	Both treatments led to global improvements, with no clear difference between them
Baran et al. ⁷⁷	Randomized, crossover, double-blind, placebo-controlled study	NAC 19.4 mg/kg (oral) <i>versus</i> placebo	15 days	6 children	CF	NAC improved FEV ₁ , PEFR and maximal expiratory flow

(Continued)

Table 1. (Continued)

Study	Design/control type	Study and control drugs	Treatment duration	Number of participants by arm and age	Diagnosis	Efficacy results
Rudnik et al. ⁷⁸	Open-label, controlled study	NAC 50 mg BID or 200 mg TID (oral)	4 weeks	58 children, aged 2 months to 16 years	Chronic lung diseases	NAC led to clinical improvements in 89% of patients, with slight lung function improvement in one subset
Steil et al. ⁷⁹	Open-label, crossover study	NAC 10–30 mg/kg/day (oral) versus carbocysteine	3–6 months	22 children	CF	NAC improved lung function in children with baseline FVC <75%
Baldini et al. ⁸⁰	Active-controlled study	NAC 200–300 mg/day (oral) versus ambroxol 30 mg/day	10 days	28 children, aged 2–13 years	Spastic bronchitis	Both treatments were effective, ambroxol showed faster symptom relief
Dietzsch et al. ⁸¹	Active-controlled study	NAC 10% (nebulized) followed by L-arginine hydrochloride 5% (nebulized)	NAC pre-treatment duration is unknown 4–10 weeks (L-arginine hydrochloride)	24 children, aged 2–12 years	CF	NAC demonstrated superior mucolytic effects. L-arginine hydrochloride should not be used to treat children with CF

BID, *bis in die*; CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IM, intramuscular; NAC, N-acetylcysteine; PCD, primary ciliary dyskinesia; PEFR, peak expiratory flow rates; TID, *ter in die*.

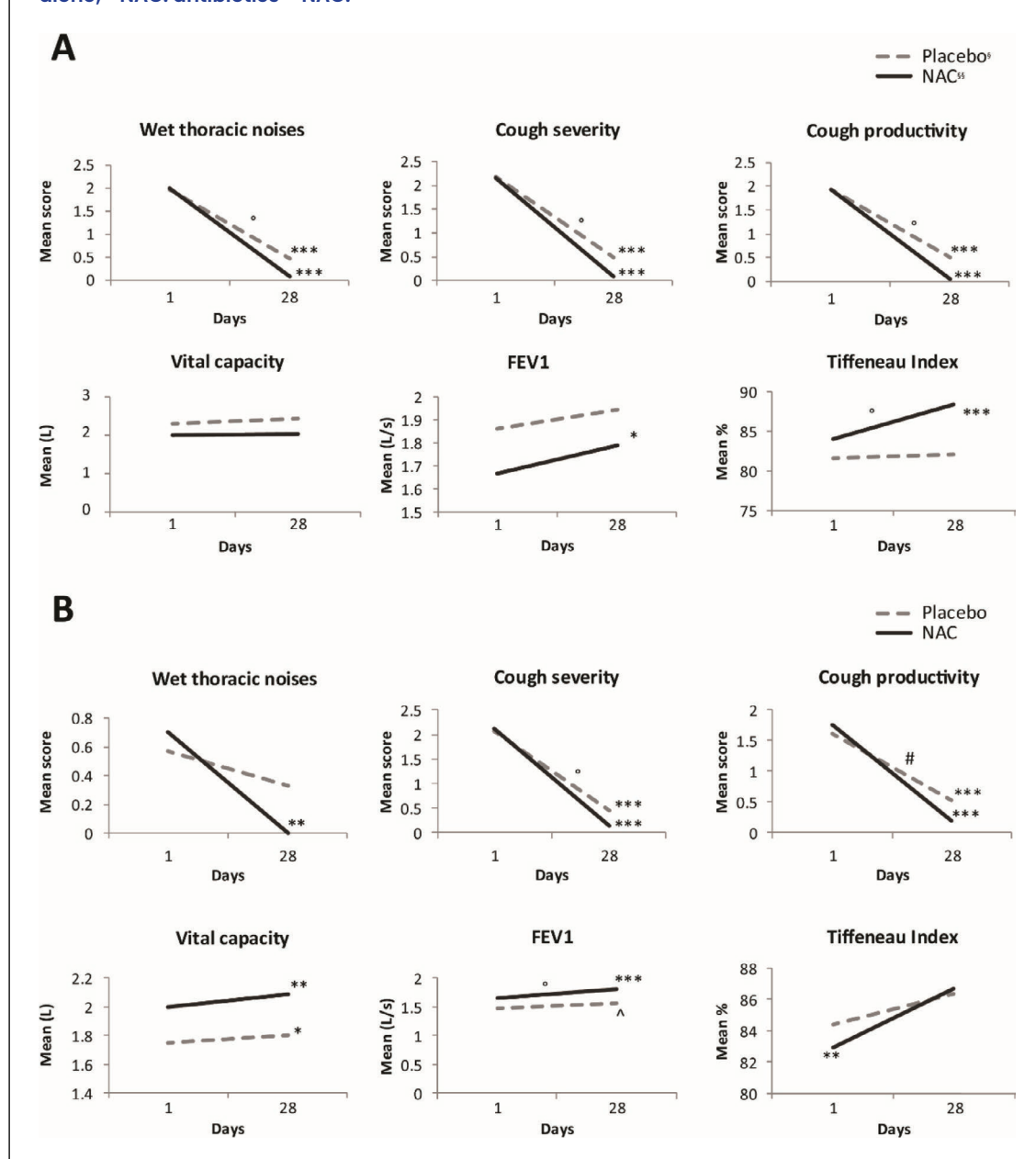
tivity was significantly higher in the NAC group by the end of the second week of treatment ($p<0.05$). However, this significance disappeared by the end of the treatment period, suggesting an earlier onset of efficacy with NAC. In contrast, for patients with tracheitis, data on positive modification were available only at the end of treatment, with statistical significance limited to thoracic wet noises ($p<0.01$).⁶¹

Notably, in patients with bronchitis, respiratory function tests revealed that NAC significantly increased forced expiratory volume in 1 second (FEV₁; expressed in L/s) ($p<0.05$) and the Tiffeneau index (FEV₁/vital capacity ×

100) ($p<0.001$) at the end of treatment compared with baseline, whilst no such improvements were seen with placebo. In patients with tracheitis, both NAC and placebo improved vital capacity and FEV₁; however, the improvements were more statistically significant in the NAC group, with FEV₁ being the only parameter that differed significantly between the two treatments.⁶¹

A subsequent analysis of the study by Fiocchi et al.,⁶¹ conducted by Chalumeau et al.,⁶² combined the results from the bronchitis and tracheitis subgroups and reanalysed them using standardized statistical methods to ensure consistency across studies. Results indicated that NAC

Figure 1. Efficacy of N-acetylcysteine (NAC) in reducing respiratory symptoms in children with bronchitis (A) and tracheitis (B). Comparisons between day 28 and day 1 were conducted by the authors in the original paper⁶¹ using paired *t*-tests (**p*<0.05; ***p*<0.01; ****p*<0.001). Differences in change from day 1 to day 28 between the NAC and placebo groups were analysed by the authors in the original paper⁶¹ using independent *t*-tests (°*p*<0.05; #*p*=0.05; ^*p*=0.02). §Placebo: antibiotics alone; §§NAC: antibiotics + NAC.

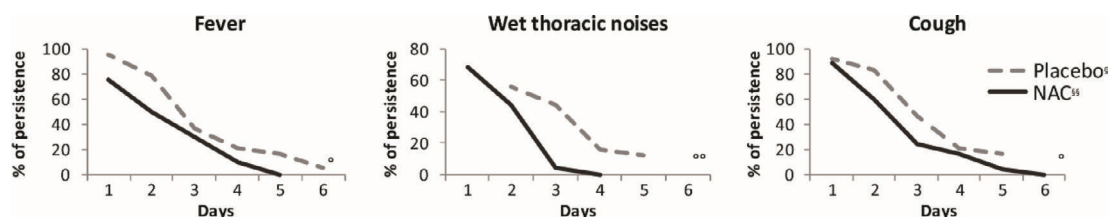


reduced the risk of thoracic semeiological alterations by 83% (risk ratio 0.17, 95% CI 0.03–0.99).⁶² The risk difference for these alterations at the end of treatment was –14% (95% CI –25% to –3%), with a number needed to treat to benefit of 8 (95% CI 4–34). Whilst NAC reduced the occurrence of productive cough, this effect was not statistically significant (risk difference –8%, 95% CI –20% to 3%).⁶²

In another randomized, double-blind, placebo-controlled trial, Biscatti et al.²¹ evaluated the adjunctive use of oral NAC in paediatric patients with acute respira-

tory infections, including pneumonia (*n*=18), bronchitis (*n*=28) and tracheitis (*n*=4) (Table 1). Fifty children were randomly assigned to receive either antibiotics alone (*n*=25) or antibiotics combined with NAC (*n*=25). NAC dosing was age-dependent: 100 mg/day for children under 2 years, 200 mg/day for those aged 2–4 years and 300 mg/day for children over 4 years. Treatment was administered orally for 6 days. Clinical efficacy was assessed based on changes in fever, thoracic auscultation findings, dyspnoea and cough. Children receiving NAC showed a more rapid resolution of fever and

Figure 2. Efficacy of N-acetylcysteine (NAC) in reducing respiratory symptoms in children with acute respiratory infections (modified from Biscatti et al.²¹). Comparisons between persistence curves were conducted by the authors in the original paper²¹ using the Wilcoxon test ([°] $p=0.05$; ^{°°} $p=0.005$). [§]Placebo: antibiotics alone; ^{§§}NAC: antibiotics + NAC.



thoracic abnormalities than those treated with antibiotics alone (Figure 2).²¹

Hashemian et al.⁶³ conducted a randomized study with 58 paediatric patients (aged 8–18 years) with moderate COVID-19 symptoms. Participants received either oral NAC (1200 mg/day) or placebo for 7 days alongside the national COVID-19 treatment protocol (Table 1). C-reactive protein (CRP) levels, white blood cell (WBC) count, serum creatinine, oxygen saturation, hospital stay duration and clinical symptoms were assessed. All measured variables in both groups showed significant improvement by the end of the study. NAC significantly improved oxygen saturation ($p=0.001$) and reduced hospital stays ($p=0.001$) compared with the placebo group. Whilst changes in CRP and WBC were not statistically significant, the NAC group exhibited a lower mortality rate (0%) than the placebo group (7.4%), although this difference was not significant ($p=0.491$).⁶³

Trastotenojo et al.⁶⁴ conducted a double-blind, placebo-controlled clinical study evaluating the efficacy of oral NAC in paediatric patients with various respiratory conditions, including bronchopneumonia (20 NAC, 18 placebo), bronchial asthma (5 NAC, 4 placebo), bronchiolitis (3 NAC, 2 placebo) and tuberculosis (2 NAC, zero placebo) (Table 1).⁶⁴ Notably, whilst the study is described as double-blind and placebo-controlled, randomization is not explicitly reported. The study initially enrolled 60 children aged between 2 months and 13 years, but six cases were excluded due to two deaths and four discharges without consent. The final analysis included patients treated with NAC (100 mg three times daily for 5 days) alongside standard therapies such as antibiotics and bronchodilators when necessary. Clinical outcomes were evaluated through assessments of cough, dyspnoea, auscultation findings, blood tests and chest X-rays. In children with bronchopneumonia, no significant differences were observed between the NAC and placebo groups when compared head-to-head at individual time points. However, when analysing

the overall treatment progression, NAC showed statistically significant improvements over time, particularly between days 1, 3, 5 and 7 ($p<0.05$), an effect not seen in the placebo group. Amongst patients with bronchopneumonia complicated by sub-acute cor pulmonale, significant improvement with NAC was recorded only on day 7 ($p<0.05$). In cases of bronchial asthma, NAC did not yield statistically significant changes at any single time point. Nonetheless, when considering the cumulative treatment effect, analysis of cough across the entire study period in both bronchopneumonia and bronchial asthma revealed a significant reduction in severity in the NAC group compared with placebo ($p<0.05$). Dyspnoea in bronchopneumonia NAC-treated patients improved rapidly, with significant differences noted at days 1, 3 and 7 ($p<0.05$). Given the small sample sizes, statistical analysis was not feasible for patients with bronchiolitis and tuberculosis.⁶⁴ These findings suggest that, whilst NAC may not have shown a clear advantage over placebo at individual daily time points, its beneficial effects became more apparent when evaluating overall treatment progression. Notably, the longer NAC was administered, the greater the observed improvement, reinforcing its potential cumulative therapeutic benefit over time.⁶⁴

Randomized active-controlled studies

Bellomo et al.⁶⁵ conducted an open, randomized comparative study evaluating the efficacy of intramuscular *versus* oral NAC in 50 paediatric patients with acute bronchitis ($n=20$) or pneumonia ($n=30$), including 35 children under the age of 2 years (Table 1). Patients were divided into two groups: 25 received oral NAC (Fluimucil, 100 mg sachet or 10% solution), whilst the other 25 were administered intramuscular NAC (300 mg/3 mL).⁶⁵ Both groups received concomitant antibiotics (streptomycin and thiamphenicol). Dosages were age-adjusted: children under 2 years received 300 mg/day (oral or intramuscular) and children over 2 years received 600 mg/day. The treatment lasted up to 8 days. Clinical outcomes, including fever, dyspnoea, thoracic auscultation findings and cough, were assessed. NAC demon-

strated comparable effectiveness via both administration routes, with marked improvements in all evaluated parameters.⁶⁵

Camurri et al.⁶⁶ conducted a randomized controlled trial involving 32 children aged 2–11 years with acute bronchitis, comparing oral NAC (300 mg/day) with bromhexine (48 mg/day) over 10 days (Table 1). Both treatments improved clinical symptoms, but bromhexine demonstrated superior therapeutic efficacy.⁶⁶

Chen et al.⁶⁷ investigated the combined use of aerosolized NAC and budesonide in 120 children with *Mycoplasma pneumoniae* pneumonia (Table 1). The experimental group (mean age 7.27±2.47 years) received both NAC and budesonide (aerosolized budesonide, dose: 0.25–0.5 mg; frequency: 10 min/session, twice daily; oxygen flow rate: 5 L/min) and NAC (3 mL/session, two to three times per day), whilst the control group (mean age: 7.02±2.58 years) received budesonide alone.⁶⁷ After 2 weeks of treatment, the NAC group experienced faster resolution of cough, fever and rales. Additionally, significant reductions in inflammatory markers (IL-6, TNF and CRP) were observed in the NAC group compared with controls. The total effective rate in the NAC group was 98.33%, surpassing the 93.33% observed in the control group.⁶⁷

Xue et al.⁶⁸ randomized 98 children aged 2–6 years with pneumonia to receive either atomized inhalation of NAC (3 mL: 300 mg dissolved in 3 mL of 0.9% sodium chloride solution) or ambroxol hydrochloride (300 mg/tablet, one tablet dissolved in 3 mL of 0.9% sodium chloride solution) (Table 1). Solutions were added to the mask atomizer and connected to the oxygen device with an adjusted oxygen flow rate of 6–8 L/min, twice a day for 1 week.⁶⁸ The mean age of the NAC and ambroxol groups was 5.28±1.03 and 5.34±1.12 years, respectively. The NAC group showed a higher treatment efficacy, with faster resolution of fever, cough and lung rales ($p<0.05$). Post-treatment inflammatory markers, including CRP and procalcitonin, were significantly lower in the NAC group ($p<0.05$), whilst lung function parameters (forced vital capacity (FVC), FEV₁, FEV₁/FVC) improved ($p<0.05$). Additionally, serum immunoglobulin levels (IgA, IgG and IgM) and complement protein C3 were higher in the NAC group.⁶⁸

Non-randomized active controlled studies

Seidita et al.⁶⁹ compared oral sobrerol to oral NAC in 40 children aged 3–12 years with acute respiratory diseases, including bronchitis and pharyngo-tracheobronchitis (Table 1). Sobrerol was administered as granules in single-dose sachets (100 mg) three times daily for 3 days. NAC granules were given at a dose of 300 mg per day for 3 days. Clinical parameters and biological data, in-

cluding the rheological analysis of expectorate, were assessed at both baseline and the conclusion of the treatment course. Both treatments were effective over a 3-day course, with sobrerol demonstrating slightly better reductions in sputum viscosity and superior tolerability compared with NAC.⁶⁹ Notably, regulatory agencies have recently limited sobrerol use by reducing the recommended treatment duration to 3 days for all formulations because of reports of adverse neurological reactions in certain patients.⁷⁰

Liu et al.⁷¹ compared the effects of NAC and ambroxol hydrochloride in 120 children with bronchial pneumonia. The study included 58 children in the NAC group (mean age 4.6 years, range 1–7 years) and a control group of 62 children who received ambroxol hydrochloride (Table 1).⁷¹ NAC was administered by diluting 3 mL of NAC with approximately 3 mL of 10% sodium chloride, whilst ambroxol hydrochloride was prepared by dissolving one tablet of ambroxol in 3 mL of 0.9% sodium chloride. Both solutions were delivered via an atomizer mask connected to an oxygen device. The oxygen flow rate was adjusted to 7 L/min, and atomized inhalation was performed twice daily. Each session involved 3 mL of NAC or 2 mL of ambroxol per inhalation. The treatment was administered over two courses, with each course lasting 1 week. The primary endpoints included the disappearance time of key symptoms such as fever, cough, asthma, lung rales and the overall duration of hospitalization. Immune function markers, including IgA, IgG and IgM, and complement proteins C3 and C4, were measured both before and after treatment. The NAC group exhibited a significantly higher effective rate compared with the ambroxol group (94.83% versus 82.26%; $p<0.05$). The disappearance times for fever, cough, asthma, lung rales and abnormal lung X-ray findings were significantly shorter in the NAC group compared with the control group ($p<0.05$). Both treatments resulted in significant increases in IgA, IgG and IgM levels post-treatment ($p<0.01$) but the NAC group showed significantly higher increases in IgA and IgG compared with the ambroxol group ($p<0.01$). Furthermore, quality-of-life metrics, including physiological functioning, somatic pain, general health status and vitality scores, were significantly higher in the NAC group compared with the control group.⁷¹

Uncontrolled or retrospective clinical studies

Bellomo et al.¹⁸ conducted a study involving 39 children aged 2 months to 11 years with severe bronchopulmonary infections (Table 2). Participants received an antibiotic-mucolytic combination of thiamphenicol glycinate (22–40 mg/kg/day) and acetylcysteine (10–18 mg/kg/day),

Table 2. Uncontrolled clinical studies on NAC in paediatric respiratory diseases.

Study	Study and control drugs (dose, route, regimen)	Treatment duration	Number of participants by arm and age	Diagnosis	Efficacy results
Acute respiratory disease					
Bellomo et al. ¹⁸	IM combination of NAC 10–18 mg/kg/day + thiamphenicol glycinate 22–40 mg/kg/day	4–18 days	39 children, aged 2 months to 11 years	Bronchopulmonary infections	The combination of NAC and thiamphenicol glycinate led to rapid resolution of fever, dyspnoea, cough and improved chest X-ray findings
Santangelo et al. ¹⁹	NAC 20–30 mg/kg/day (IM) + cefuroxime	5–10 days	103 children, aged 2 months to 11 years	Lower respiratory tract infections	NAC led to a significant improvement in 97% of children, with microbiological clearance of pathogenic strains
Chronic respiratory disease					
Ribeiro et al. ⁸²	NAC 10–50 mg/kg/day (oral)	7–110 days	80 children, aged 23 days to 11 years	Chronic lung conditions	NAC led to clinical improvements in 88% of children and radiological resolution in 82% of cases
Szekely et al. ⁸³	NAC 100 mg TID (oral)	37 days	20 children, aged 6–12 years	Chronic bronchitis	NAC led to reduced mucosal inflammation in 50% of patients and decreased or stopped mucus hypersecretion in all patients
Nikolic et al. ⁸⁴	NAC 100–200 mg TID (oral) + antibiotics	4 days	20 children, aged 3–14 years	Recurrent febrile bronchitis	NAC shortened symptom duration and improved lung function in non-allergic children
Dietzsch et al. ⁸⁵	NAC 100 mg TID (<8 years) or 200 mg TID (≥8 years) (oral)	6 months	42 children stable for 8–10 years whilst receiving inhalation therapy with NAC	CF	NAC transition from inhaled to oral therapy resulted in stable or improved lung function in 56% (bronchoscopy) and 69% (lung function tests) of patients
Stephan et al. ⁸⁶	NAC 50 mg TID (<2 years) or 200 mg TID (>2 years) (oral)	2 years	63 children, aged 2–20 years, who had received at least 1 year of inhalation therapy with Mesna or NAC	CF	NAC showed comparable efficacy between oral and inhaled administration in improving sputum clearance, chest X-ray findings and growth parameters
Reas et al. ⁸⁷	NAC 5 mL of 20% solution (1 g) BID (nebulized)	10 weeks to 38 months	28 children, aged 7–22 years	CF	NAC improved pulmonary function, favoured linear growth and weight gain, increased exercise capacity, and decreased respiratory workload

BID, bis in die; CF, cystic fibrosis; IM, intramuscular; NAC, N-acetylcysteine; TID, ter in die.

administered by intramuscular injection for 4–18 days.¹⁸ All patients showed a rapid and complete remission of fever (2.61 days), dyspnoea, including signs of cyanosis (2.42 days), cough (5.41 days) and chest auscultation positivity (5.16 days). X-ray findings confirmed the rapid and complete therapeutic effect of the combination. The authors report increased efficacy and rapidity compared with previous experience with thiamphenicol alone, despite the severity of the disease in this study.¹⁸

Santangelo et al.¹⁹ evaluated the clinical outcomes of 103 children aged 2 months to 11 years diagnosed with lower respiratory tract infections treated with a combination of cefuroxime and intramuscular NAC (20–30 mg/kg/day) for 5 to 10 days (Table 2). Positive clinical responses were observed in 100 patients, with complete symptom resolution in 58 cases and marked improvement in 42 others. Chest X-rays confirmed recovery or significant improvement across these patients. Microbiological analysis showed that none of the 72 pathogenic strains isolated prior to treatment were detectable at the end of therapy, suggesting a potential adjunct antimicrobial effect of NAC.¹⁹

Zanasi et al.²⁰ conducted an open, retrospective study involving 59 children aged 3–14 years with acute upper respiratory tract infections accompanied by wet cough (Table 3). The study compared clinical outcomes in children treated with oral antibiotics (amoxicillin or a

macrolide) versus those receiving nebulized mucoactive agents (sobrerol or NAC).²⁰ The group treated with mucolytics demonstrated significantly greater improvements in clinical symptoms, such as cough severity and sputum clearance, compared with the group treated with antibiotics.²⁰

Efficacy profile of NAC in chronic paediatric respiratory conditions

Controlled clinical studies

Randomized placebo-controlled studies

Mitchell and Elliott⁷² conducted a crossover, randomized, double-blind, placebo-controlled study to evaluate the potential of oral NAC in preventing pulmonary deterioration in children with CF (Table 1). Twenty paediatric patients (mean age 10.8±5.9 years) received either NAC (200 mg three times daily) or placebo, alongside standard physiotherapy and additional treatments such as antibiotics, aerosolized mucolytics, pancreatic enzymes and vitamin E supplementation, when indicated. The study design consisted of two 3-month treatment periods, separated by a 2-week washout. During the first period, patients were assigned to receive either NAC or placebo, and in the second period, they were switched to the alternate treatment. Efficacy was assessed

Table 3. Real-world evidence on NAC in paediatric respiratory diseases.

Study	Design/Control type	Study and control drugs (dose, route, regimen)	Number of participants by arm and age	Diagnosis	Efficacy results
Acute respiratory disease					
Zanasi et al. ²⁰	Open, retrospective study	NAC or sobrerol (nebulized) versus antibiotics	59 children, aged 3–14 years	Acute upper respiratory infections with a wet cough	Mucolytics were more effective than antibiotics in improving cough severity and sputum clearance
Chronic respiratory disease					
Kumar et al. ⁸⁸	Case series	NAC 1.5–2.5 mL of 20% solution (300–500 mg) BID (nebulized)	2 children, aged 1 and 7 years	Plastic bronchitis	NAC led to significant improvement, with patients remaining asymptomatic at follow-up
Wang et al. ⁸⁹	Retrospective cohort study	NAC + budesonide versus ambroxol + budesonide versus budesonide alone added to BAL fluid medication	82 children	Refractory <i>Mycoplasma pneumoniae</i> pneumonia	BAL-coupled NAC + budesonide led to significantly lower levels of serum lactate dehydrogenase and serum ferritin levels, better clinical efficacy, and lung imaging improvements

BAL, bronchoalveolar lavage; BID, *bis in die*; NAC, N-acetylcysteine.

through peak expiratory flow rates (PEFR), sputum viscosity and cough frequency. No significant differences were observed in PEFR between the NAC and placebo groups, and no adverse effects were reported in either group. Four patients withdrew for reasons unrelated to NAC treatment.⁷²

Stafanger et al.⁷³ performed a crossover, randomized, double-blind, placebo-controlled study to evaluate oral NAC in patients with CF and primary ciliary dyskinesia (PCD) (Table 1). The study included 41 patients with CF (mean age 9.5 years) and 13 patients with PCD (mean age 29.7 years).⁷⁴ NAC dosing was weight-based: 200 mg three times daily for those under 30 kg and 400 mg twice daily for those over 30 kg. The treatment was administered alongside bronchodilators over two 3-month periods. Patients received either NAC or placebo in the first period and were switched to the alternate treatment in the second period, followed by a 3-month follow-up. The effects were assessed using a subjective clinical score, along with evaluations of weight, sputum bacteriology, blood leukocyte count, sedimentation rate, specific antimicrobial antibody titres, lung function parameters and ciliary function measurements. In patients with CF, NAC improved lung function during autumn, when lower airway infections were most prevalent but no significant effects were observed in patients with PCD.⁷³

Stafanger et al.⁷⁴ extended their research with a crossover, randomized, placebo-controlled trial in 52 patients with CF (mean age 15.8 years) with chronic *Pseudomonas aeruginosa* infection (Table 1). Patients received oral NAC (200 mg three times daily for those under 30 kg and 400 mg twice daily for those over 30 kg) or placebo along with standard CF therapy for 3 months.⁷⁴ The effects were assessed through a subjective clinical score as well as evaluations of weight, sputum bacteriology, blood leukocyte count, sedimentation rate, titres of specific antimicrobial antibodies, lung function parameters and in vitro nasal ciliary function. Whilst no significant differences in lung function or clinical scores were observed overall, patients with more severe CF, defined by PEFR below 70% of predicted values, showed significant improvements in PEFR, FVC and FEV₁ during NAC treatment.⁷⁴

Ratjen et al.⁷⁵ conducted a parallel-group, randomized, double-blind study comparing oral NAC (200 mg three times daily), ambroxol (30 mg three times daily) and placebo in 36 children with CF (mean age 13.9 years) (Table 1). Over a 3-month period, lung function was evaluated using body plethysmography, trapped air determination and maximal expiratory flow-volume curves. Whilst no significant differences were found amongst the groups, the placebo group showed a tendency toward greater

impairment in lung function, suggesting a potential protective effect of NAC or ambroxol.⁷⁵

Gotz et al.⁷⁶ performed a crossover, randomized, double-blind, placebo-controlled study evaluating the effects of oral NAC (9.5 mg/kg) in 21 paediatric patients with CF over 14 days. The study evaluated sputum production, cough and pulmonary function (Table 1). Both treatment and placebo periods showed global improvement, but no clear distinction was made in the therapeutic efficacy of NAC.⁷⁶

Baran et al.⁷⁷ conducted a crossover, randomized, double-blind, placebo-controlled study in six children with CF, comparing oral NAC (19.4 mg/kg) with placebo over 15 days (Table 1). Whilst subjective symptoms and chest findings worsened during placebo treatment, NAC led to improvements in FEV₁, PEFR and maximal expiratory flow.

Non-randomized controlled studies

Rudnik et al.⁷⁸ conducted an open, controlled study to evaluate the efficacy of oral NAC in children with chronic lung diseases (Table 1). The study involved 58 children across three cohorts, with the primary group consisting of 46 children aged from 2 months to 16 years, more than half of whom were under 5 years of age.⁷⁸ NAC was administered at doses ranging from 50 mg twice daily to 200 mg three times daily, adjusted according to age, over a 4-week period. Efficacy was evaluated through clinical assessments, lung auscultation, chest X-rays, blood gas analysis and bronchoscopies performed before and after treatment. In the first group, 41 of the 46 children showed clinical improvement. Seventeen children experienced complete resolution of symptoms, including the disappearance of auscultatory changes and wheezing, whilst 24 exhibited moderate improvement. Chest X-rays confirmed radiological improvements in 15 children, with reductions in peribronchial congestion and peripheral emphysema. Seven children showed improvements across all evaluated parameters; however, five children exhibited no improvement following NAC treatment.⁷⁸

In the second cohort of six children, lung function tests did not demonstrate significant differences before and after treatment.⁷⁸ Nevertheless, compared with the two control groups – one comprising children treated with Mesna inhalations and the other with 0.45% saline inhalations – the NAC-treated children showed marginally better values in small airway function and airway resistance. However, these differences were not statistically significant. Similarly, regional lung function analysis revealed no substantial changes post-treatment.⁷⁸

The third cohort, also comprising six children, underwent biochemical evaluations of protein levels in bron-

chial secretions.⁷⁸ Results showed a significant decrease in secretory IgA and α 1-antichymotrypsin levels in the bronchi, along with an increase in serum IgA, IgG and α 1-antitrypsin levels following NAC treatment. Bronchial examinations assessing mucosal inflammation indicated that children treated with inhalation therapies, such as Mistabron or hydrocortisone, showed better therapeutic outcomes than the NAC group.⁷⁸

Steil et al.⁷⁹ conducted a crossover, open-label study comparing the efficacy of oral NAC and carbocysteine in 22 children with CF. NAC was administered at doses ranging from 10 to 30 mg/kg to 20 patients, whilst the remaining patients received carbocysteine (500–750 mg/day) (Table 1). The treatment duration varied between 3 and 6 months. In patients with baseline FVC below 75%, NAC significantly improved lung function. Specifically, 12 patients exhibited an increase in mean FVC from 59.5% to 75.5% following NAC treatment.⁷⁹

Baldini et al.⁸⁰ conducted an active-controlled study comparing the efficacy of ambroxol and NAC in 28 children aged 2 to 13 years (mean age 7 years, 3 months) diagnosed with spastic bronchitis (Table 1).⁸⁰ Fourteen patients received ambroxol (30 mg/day), whilst the other 14 were treated with NAC (200–300 mg/day). The treatment was administered orally for 10 days. Efficacy was assessed by evaluating sputum volume and viscosity, ease of expectoration, cough severity, dyspnoea and bronchial sounds at baseline, day 5, and at the end of treatment. Both treatments resulted in clinical improvement; however, ambroxol demonstrated a more rapid onset of action, with patients experiencing earlier symptom relief compared with those treated with NAC.⁸⁰

Dietzsch et al.⁸¹ conducted a comparative study evaluating the mucolytic effects of NAC inhalations versus L-arginine hydrochloride aerosols in 24 children with CF aged 2–12 years (Table 1). Clinical evaluations included bronchoscopic, spirometric, scintigraphic and chemical analyses to determine the efficacy of each treatment. NAC inhalations demonstrated superior mucolytic effects compared with L-arginine hydrochloride. The percentage of days with cough increased from 2.9% during the first NAC inhalation period to 23.1% during the L-arginine hydrochloride inhalation period, and then dropped to 9.8% during the second NAC inhalation period.⁸¹

Uncontrolled or retrospective clinical studies

Ribeiro et al.⁸² conducted an open, non-controlled study evaluating the efficacy of oral NAC in 80 paediatric patients with various chronic lung conditions (Table 2). The patients ranged in age from 23 days to 11 years (mean

age 2.9 years), with 33 children under 1 year, 34 between 1 and 6 years, and 13 between 6 and 11 years.⁸² The diagnoses included bronchiectasis ($n=8$), bronchiolopathy ($n=4$), pseudobronchiectasis ($n=6$), CF ($n=2$), atelectasis ($n=15$), chronic bronchitis ($n=1$), lung abscesses ($n=1$) and combined pathologies ($n=30$). NAC was administered orally at doses of 10–50 mg/kg/day for durations ranging from 7 to 110 days (mean duration: 26.7 days), after other treatments, such as antibiotics, corticosteroids and bronchodilators, had failed. Clinical and radiological outcomes were categorized as excellent, good or poor, whilst treatment acceptance and safety were rated as good, moderate or poor. Amongst the 67 patients who completed treatment, 88% and 82% showed good clinical and radiological outcomes, respectively, including resolution of peribronchial congestion and peripheral emphysema.⁸²

Szekely et al.⁸³ performed an open, non-controlled study on 20 children aged 6–12 years diagnosed with chronic bronchitis (Table 2). Participants received oral NAC (100 mg three times daily) for 37 days. Bronchoscopic examinations were conducted on day 7 and at the end of treatment to evaluate mucosal inflammation and hypersecretion. NAC led to regression of mucosal inflammation in 10 patients, complete cessation of hypersecretion in 18 patients and decreased hypersecretion in 2 patients. Histological examinations revealed no significant changes in mucosal structure.⁸³

Nikolic et al.⁸⁴ investigated the role of oral NAC in 20 children aged 3–14 years with recurrent febrile bronchitis (Table 2). NAC (100–200 mg three times daily) was administered alongside antibiotics during acute bronchitis episodes for 4 days.⁸⁴ Clinical monitoring was conducted daily or every other day. NAC shortened the duration of throat catarrh and bronchitis symptoms. In children with simple or recurrent catarrhal bronchitis, vital capacity and pulmonary flow returned to normal but no changes were observed in those with bronchial allergies.⁸⁴

Dietzsch et al.⁸⁵ conducted an open, non-controlled study in 42 children with CF who had been stable for 8–10 years on inhalation therapy with NAC before transitioning to oral NAC therapy for 6 months (Table 2). Children under 8 years received 100 mg of NAC three times daily, whilst those over 8 years received 200 mg three times daily. Efficacy was evaluated through bronchoscopy and pulmonary function testing performed before and after the course of oral treatment. Oral NAC therapy resulted in worsened bronchoscopic findings in 44% of patients, no change in 22% and improvements in 34%. Lung function improved in 18%, remained unchanged in 51% and worsened in 31% of cases. Over-

all, 56% of patients showed improvement or remained stable based on bronchoscopy and 69% based on lung function tests. Seven children discontinued oral NAC due to exacerbations and resumed inhalation therapy. The study concluded that, whilst oral NAC could not fully replace inhalation therapy, it was effective in 50–60% of patients.⁸⁵

Stephan et al.⁸⁶ conducted a multicentre, non-controlled study evaluating oral *versus* inhaled NAC in 63 patients with CF aged 2–20 years over 2 years (Table 2). Prior to enrolment, all patients had received at least 1 year of inhalation therapy with Mesna or NAC. Oral NAC dosages were 50 mg three times daily for children under 2 years and 200 mg three times daily for those aged 2 years and older. The study lasted 2 years. Oral NAC was at least as effective as inhaled NAC in improving sputum clearance, chest X-ray findings and growth parameters (weight and height percentiles).⁸⁶

Reas et al.⁸⁷ evaluated the efficacy of nebulized NAC in 28 paediatric patients with CF aged 7–22 years (Table 2). Patients received 5 mL of a 20% NAC solution via aerosol inhalation twice daily for 10 weeks to 38 months, following a 6-week control period. Spirometric parameters, chest X-ray changes and clinical outcomes were assessed. NAC improved pulmonary function, including increases in vital capacity, decreases in functional residual capacity, improved air distribution and greater respiratory flow rates. Clinical improvements included enhanced exercise capacity, linear growth and weight gain. The effectiveness of NAC depended on adequate bronchial drainage, with some patients requiring additional mist-tent therapy overnight.⁸⁷

Kumar et al.⁸⁸ reported a case series of two paediatric patients with recurrent plastic bronchitis, a rare condition characterized by the formation of obstructive endobronchial casts (Table 3). A 1-year-old girl and a 7-year-old boy experienced repeated episodes of respiratory distress, with bronchoscopy revealing membrane-like casts. The younger patient was treated post-surgery with inhaled bronchodilators, nebulized NAC (1.5 mL, 20% solution, twice daily), chest physiotherapy and systemic steroids for 5 days. After improvement, she was discharged on a maintenance regimen of inhaled salbutamol (as needed), nebulized NAC and inhaled budesonide (100 µg twice daily). She remained asymptomatic at the 12-month follow-up. The older child received inhaled bronchodilators, budesonide (400 µg) with long-acting beta-agonists and nebulized NAC (2.5 mL, 20% solution, twice daily). He showed significant improvement in respiratory symptoms and was asymptomatic at the 9-month follow-up on maintenance budesonide (200 µg) and nebulized NAC.⁸⁸

Wang et al.⁸⁹ conducted a retrospective cohort study evaluating the efficacy of BAL with adjunctive medications in 82 paediatric patients with refractory *Mycoplasma pneumoniae* pneumonia (Table 3). All patients received standard care, which included intravenous azithromycin, expectoration therapy and nebulizer inhalation. Based on adjunctive therapy during BAL, they were divided into three groups: budesonide alone, ambroxol + budesonide and acetylcysteine + budesonide. The primary endpoints were changes in laboratory parameters, improvements in lung imaging, overall clinical efficacy and the incidence of adverse events. Laboratory parameters improved significantly from baseline in all three groups, with no significant post-treatment differences in WBC count, CRP or erythrocyte sedimentation rate amongst them. Serum lactate dehydrogenase and serum ferritin levels differed significantly across the three groups ($p < 0.001$) and were significantly lower in the acetylcysteine + budesonide group ($p < 0.001$). Lung lesion imaging showed superior absorption rates in the acetylcysteine + budesonide group, and overall clinical efficacy was higher than in the other groups.⁸⁹

Safety profile of NAC in paediatric respiratory conditions

In the majority of studies included in this review, both oral and inhaled NAC demonstrated a favourable safety profile, with no or minimal adverse events reported. This low incidence of adverse effects was consistently observed across various studies.^{19,21,63–66,72,75,76,79,80,83,85,90} In other studies, the incidence of adverse events in NAC-treated groups was comparable to that observed in control groups,^{67,68,89} with the exception of the study by Baran et al.,⁷⁷ where gastrointestinal discomfort was noted. Importantly, these events were not severe enough to warrant treatment discontinuation. Moreover, Liu et al.⁷¹ observed that the occurrence of adverse reactions in the NAC group was significantly lower than in the control group, further supporting the agent's favourable safety profile.

Despite the overall good tolerance of NAC, there were isolated instances in which adverse reactions led to treatment discontinuation. For example, in two studies, a small number of patients experienced adverse effects severe enough to warrant withdrawal.^{74,82} In one of these studies, 21 patients were excluded for various reasons, including 9 from the NAC group.⁷⁴ One patient developed Quincke's oedema and another experienced an exanthema, both of which resolved after discontinuing NAC.⁷⁴ Additional exclusions were due to abdomi-

nal pain, diminished cough productivity combined with increased frequency, and poor cooperation.⁷⁴ Baran et al.⁷⁷ reported that two patients withdrew from their study: one during the washout period and the other during the drug treatment phase because of severe bronchial obstruction and bacterial exacerbation, respectively. Two studies reported bronchoconstriction induced by inhaled NAC in children older than 2 years with bronchial asthma.^{91,92} As a consequence, 11 (31%) children were withdrawn from one of these studies; this side-effect was primarily attributed by the authors to the high concentration (20%) of acetylcysteine.⁹² In contrast, no such effect was reported in another study using a lower concentration (10%).⁹³

Although NAC is generally well tolerated in older children, safety concerns have been reported in infants and toddlers under 2 years of age, including paradoxical bronchial congestion, increased respiratory distress, a case of pleuropneumonia and one fatal case of pulmonary oedema.^{22,23} These events led to hospitalization in most cases, suggesting that mucolytics, including NAC, should be used with caution in patients under 2 years old. These safety concerns provide important context for age-specific therapeutic considerations.

Discussion

The findings synthesized in this review highlight the efficacy and safety of NAC in paediatric respiratory conditions, emphasizing the importance of dosage optimization based on the route of administration, patient age and disease severity. Variations in dosing regimens, particularly in younger children, in whom clinical judgment often guides treatment, underscore the need for ongoing efforts to optimize dosing strategies, given the unique vulnerability of the paediatric population.

Numerous studies have demonstrated the efficacy and safety of oral NAC in treating both acute and chronic respiratory conditions in children over 2 years of age.^{21,61,65,66,73–76,78,79,86,94} In acute settings, such as bronchitis and tracheitis, Fiocchi et al.⁶¹ reported that administering NAC syrup at a dose of 20 mg/kg/day in three divided doses significantly improved respiratory symptoms, particularly by reducing thoracic wet noises and improving cough productivity. The treatment exhibited an early onset of action, with noticeable improvements observed by the second week of therapy.⁶¹ Similarly, Biscatti et al.²¹ employed age-adjusted dosing – 100 mg/day for children under 2 years, 200 mg/day for those aged 2 to 4 years, and 300 mg/day for children over 4 years – and found that oral NAC accelerated the resolution of fever and thoracic abnormalities compared with antibiotic

therapy alone. These findings suggest that moderate oral doses of NAC are effective in managing acute respiratory conditions in children.

Steil et al.⁷⁹ observed improvement in respiratory parameters in children with CF treated with oral NAC at 10–30 mg/kg/day. However, the study's methodological limitations warrant a cautious interpretation of these findings.

Studies have explored the use of higher oral NAC doses in the treatment of chronic respiratory diseases such as CF. Mitchell and Elliott⁷² Ratjen et al.,⁷⁵ and Stafanger et al.,^{73,74} administered 200 mg three times daily to older children with CF (mean ages 10.8 years,⁷⁴ 13.9 years,⁷⁵ 9.5 years,⁷³ and 15.8 years⁷⁴). Additionally, Stafanger et al.^{73,74} provided 400 mg twice daily to children weighing >30 kg. The studies reported mixed results regarding improvement in lung function. Mitchell and Elliott⁷² found no significant changes in PEFR, whilst Ratjen et al.⁷⁵ reported a trend toward greater lung function impairment in the placebo group compared with those treated with NAC and ambroxol. In their first study, Stafanger et al.⁷³ observed lung function improvements specifically during autumn, coinciding with a higher prevalence of lower airway infections. However, in a subsequent study, they found that children with more severe disease (PEFR <70% of predicted values) experienced significant improvements in lung function, including increases in PEFR, FVC and FEV₁.⁷⁴ This suggests that higher doses of NAC may be particularly beneficial in cases of advanced disease; however, efficacy appears to vary based on disease severity and baseline lung function.

Unlike oral administration, inhaled and nebulized NAC offers the advantage of delivering higher concentrations directly to the airways, potentially enhancing its mucolytic effects. This route has shown promising results in both acute and chronic settings.^{20,68,71,88,95,96} These studies typically used 3 mL of a 10% NAC solution, administered two to three times daily, which appeared effective whilst minimizing the risk of bronchospasm.^{20,68,71,88,95,96} Some studies^{67,68,71} reported faster symptom resolution and reductions in inflammatory markers in children with pneumonia treated with aerosolized NAC compared with budesonide and ambroxol, respectively.

Despite its efficacy, NAC use, particularly via inhalation, has in some cases been associated with bronchospasm and paradoxical respiratory worsening in certain paediatric populations. In particular, high-concentration (20%) solutions appear to carry the greatest risk,⁹² especially in children with asthma or pre-existing airway hyperreactivity, and are therefore neither indicated nor authorized for mucolytic use, whilst lower concentrations (10%) are generally much better tolerated.^{67,68,95} Notably, the Italian

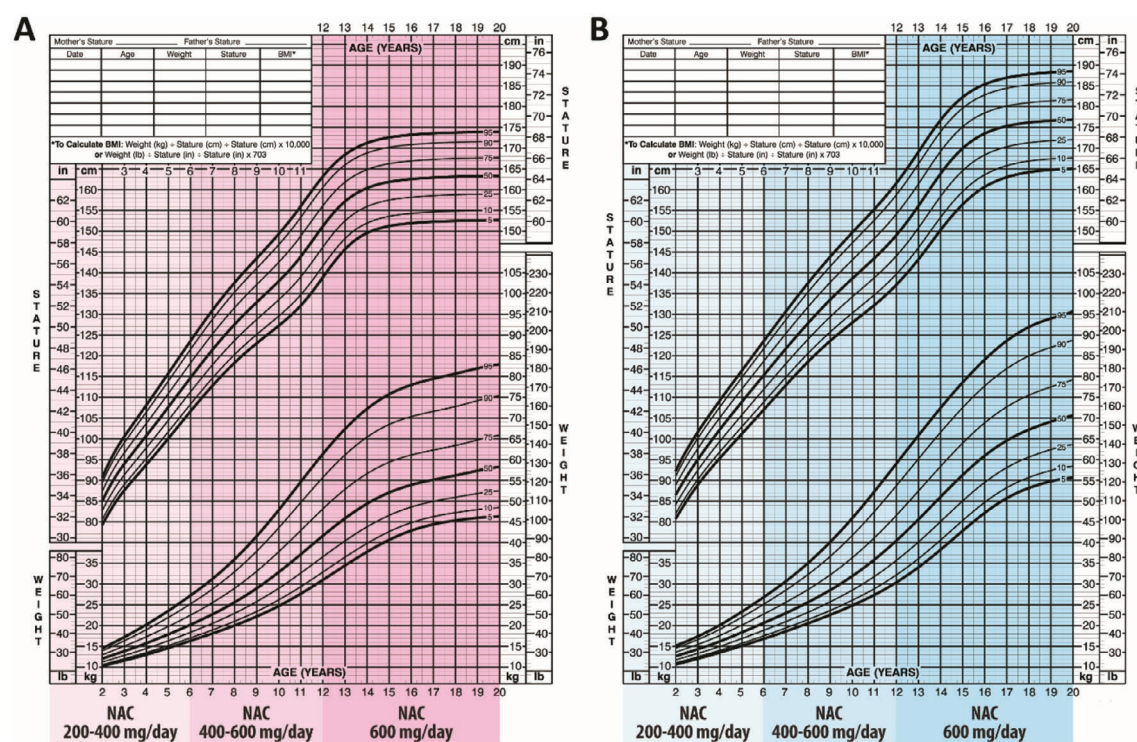
Society of Pediatric Allergy and Immunology (SIAIP) advises against prescribing mucolytics to children with bronchial asthma, aligning with recommendations from major international guidelines, including the Global Initiative for Asthma,⁹⁷ American Thoracic Society⁹⁸ and British Thoracic Society.^{99,100}

Solid evidence supports the use of oral NAC at an optimal dosage of 200–600 mg/day in children over 2 years of age, with variations depending on the country and the specific therapeutic use. The treatment demonstrates excellent tolerability and a strong safety profile.^{66,72,73,75,85,86,94} Notably, Hashemian et al.⁶³ reported no side-effects with 1200 mg/day oral NAC in older children (mean age 10.8–11.3 years) with moderate COVID-19. However, these results should be interpreted with caution because of the small sample size ($n=25$). Notably, formulation and palatability issues of oral NAC can affect adherence. Fiocchi et al.⁶¹ noted that 4% of patients discontinued treatment due to vomiting, likely related to the unpleasant taste of NAC syrup. Improving the taste and formulation of oral NAC could enhance adherence and overall treatment outcomes, particularly in younger children who may be more sensitive to unpleasant flavours.

Infants under 2 years of age have been described as more vulnerable to mucolytic-related adverse events, which may include paradoxically increased bronchorrhea and acute respiratory distress during respiratory tract infections.^{22,23} These risks may be dose-dependent and are likely influenced by anatomical and physiological differences in infants.^{22,101} Such concerns led French and Italian drug agencies to restrict the licenses for NAC and carbocysteine in children under 2 years, advising against their routine administration in this age group.^{22,101} This regulatory action underscores the particular vulnerability of the paediatric population and highlights the importance of careful, evidence-based dosing practices.²²

According to the Centers for Disease Control and Prevention growth charts (Figure 3), the median weight of a 4-year-old child is approximately 16 kg, whereas a 9-year-old weighs around 29 kg.^{102,103} Administering the same dose across this broad age and weight range disproportionately exposes younger, lighter children to higher per-kilogram doses. Given substantial weight fluctuations between ages 2 and 12 years, particularly from 2 to 6–7 years and again from 6–7 to 12 years, weight-adjusted dosing and age-defined cut-offs would optimize both efficacy and tolerability (Figure 3).

Figure 3. Stature-for-age and weight-for-age growth chart for girls¹⁰² (A) and boys¹⁰³ (B) aged 2–20 years with recommended N-acetylcysteine (NAC) age-based oral dosage. Source: Centers for Disease Control and Prevention. Reference to specific commercial products, manufacturers, companies or trademarks does not constitute their endorsement or recommendation by the U.S. Government, Department of Health and Human Services or Centers for Disease Control and Prevention.



Tailoring doses according to age group and symptom severity can maximize therapeutic benefits whilst minimizing the required dosage and the risk of side-effects.

Evidence on the utility and safety of NAC in infants under 2 years of age is limited. Studies by Naz et al.⁹⁵ and Pandey et al.⁹⁶ provide a basis for further investigation, supporting the safety and efficacy of nebulized NAC in treating acute viral bronchiolitis even in very young children. Nonetheless, its routine administration under 2 years of age needs to be carefully evaluated.

Some long-term studies are available in paediatric patients with chronic respiratory conditions. Stephan et al.⁸⁶ reported no adverse effects with either oral or inhalation therapy using NAC in paediatric patients with CF over a 2-year period. They concluded that oral NAC therapy does not cause the side-effects sometimes observed with inhaled medications and recommended oral NAC as a viable alternative to inhalation therapy for long-term CF management.⁸⁶ Similarly, in the study by Reas et al.,⁸⁷ nebulized NAC was well tolerated over the 3-year follow-up in patients with CF, with no observed long-term toxic effects. However, Dietzsch et al.⁸⁵ observed lower efficacy of oral NAC compared with nebulized NAC in paediatric patients with CF, suggesting that oral therapy should be considered as a substitute for inhalation only

in selected cases. NAC has been historically used in therapeutic protocols for chronic conditions, such as CF, with no documented recommendations against its use, even over extended treatment periods.^{25,86,87}

Furthermore, the combination of NAC with other agents, such as budesonide (as seen in the studies by Chen et al.⁶⁷ and Wang et al.⁸⁹), shows promise in enhancing therapeutic outcomes. Exploring synergistic effects and optimizing combination regimens could broaden the utility of NAC in paediatric respiratory care.

Conclusion

NAC has been extensively studied in the paediatric population and represents a valuable therapeutic option for young patients with respiratory conditions, demonstrating well-documented efficacy in both acute and chronic settings. A weight-based dosing approach may enhance treatment optimization, particularly in younger children. Future research should further investigate dose-response relationships, long-term safety, potential synergistic effects, and the development of new formulations to improve tolerability, palatability and adherence as well as to support tailored therapeutic strategies that maximize benefits whilst minimizing risks.

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