Keele University
Impact Accelerator Unit

Keele Critically Appraised Topic (CAT Form)

Clinical Question:

In preterm and neonatal patients, what is the incidence of harm for those receiving mucoactive nebulisers compared to those receiving usual care?

Clinical bottom line

The incidence of harm appears to be low for those receiving nebulised mucoactive drugs in the preterm and neonatal population however, there is a lack of high-quality evidence on this subject. Based on the available literature, our clinical practice remains unchanged as there is insufficient evidence to support routine use of nebulised mucoactive drugs in this patient group at this time.

Plain language summary

In our neonatal unit, some babies struggle with thick, sticky mucus in their lungs. In older children and adults, medication can be given as a mist by a nebuliser machine to loosen this mucus. Because babies, especially those born early, are very sensitive to treatments, it is important to carefully study any new therapy before using it widely to check it is safe.

We found that there has been very little research on whether these medicines are safe or helpful when given by nebuliser. The studies that do exist are quite small and not of high quality. Overall, they suggest that giving these medicines as a mist seems to be safe, with

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very few side effects reported. Some problems, like changes in heart rate or low oxygen levels, have been linked to these medicines when utilised in other forms (for example, when put directly into a breathing tube), but not when given by nebuliser.

This means we cannot yet recommend using these medicines routinely for very young babies. More research is needed before we can be sure they work well and are completely safe in this group.

Why is this important?

Within our own clinical practice there have been several neonatal patients with secretion retention issues due to thick and tenacious secretions. Common practice within our paediatric and adult patients would be to utilise nebulised mucoactive drugs such as hypertonic saline or recombinant human deoxyribonuclease (rhDNase) to help loosen secretions. Currently this is difficult within our neonatal population due to the lack of nebulisation equipment and practical difficulties in delivering the nebulisers. Nebulised mucoactive drugs are only used in a few cases where other therapies have already failed and following discussion with the multidisciplinary team. This question would help us determine if it is worthwhile investing in nebulisation equipment and if nebulised mucoactive drugs are a viable and safe adjunct to aid secretion clearance in this patient population.

Search timeframe (e.g. 2013-2013)

2011-2025

This timeframe was selected to capture advances in neonatal care, particularly improved outcomes for extremely preterm infants, while excluding older studies that may not reflect current practices.

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Search criteria

Population Intervention Comparison Outcomes (PICO) themes	**Description**	**Search terms**
Population and Setting E.g. adults with OA, primary care	Neonates (infants up to 44 weeks gestational age) This reflects the mix of preterm and term infants as seen on our neonatal unit	Preterm infants (less than 37 weeks) Neonates Newborn up to 1 month premature
Intervention or Exposure (i.e. what is being tested) e.g. manual therapy	Nebulised mucoactive drugs	nebuliser nebulizer nebulizer treatment aerosol treatment aerosol
Comparison, if any e.g. usual care, leaflet	Usual care	
Outcomes of interest e.g. Visual analogue scale, Range of motion	Safety Effectiveness – deposition of drug Improved outcome – e.g. resolution of CXR findings, improved respiratory function, decreased length of stay	Harm Adverse events negative effects negative impacts negative outcomes negative consequences efficiency productivity therapy or treatment effect

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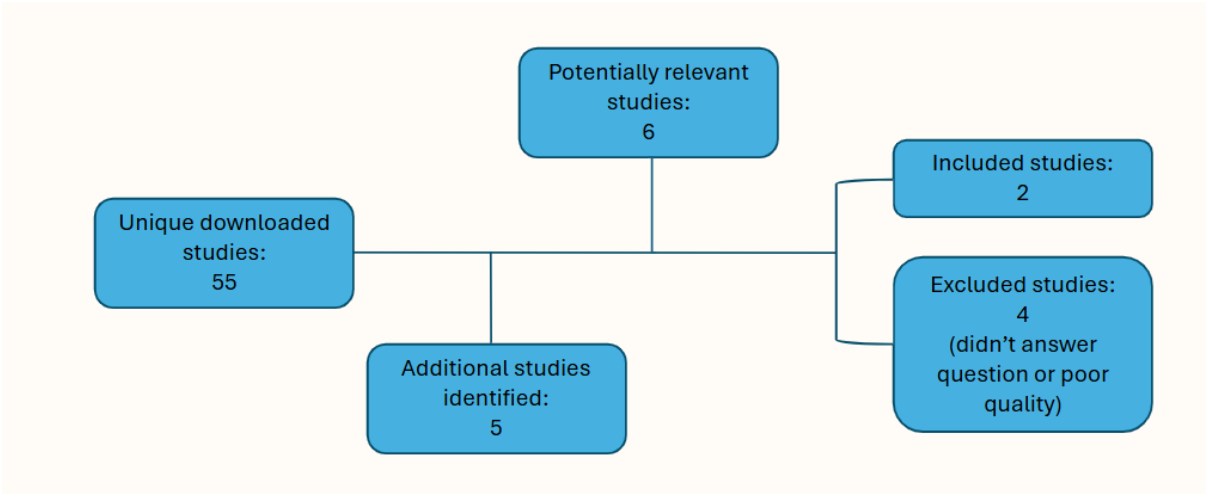
		length of stay improved respiratory function chest x-ray resolution
Types of studies e.g. Randomised Controlled Trails, Systematic reviews	All	

Databases searched

- Cochrane Library
- Directory of Open Access Journals
- EBSCOhost
- Embase
- Gale Health and Wellness
- Gale OneFile: Health and Medicine
- HMIC Health Management Information Consortium
- Ovid Emcare
- PubMed
- Web of Science

Date of search

10.09.2025



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Results of the search:

There were fifty-five unique downloaded studies. Further searches and discussion with colleagues revealed an additional five papers. There were six potentially relevant studies. There were two included and their critical appraisal is included in Table 1. There were four excluded studies.

Table 1- Detail of included studies

First author, year and type of study	**Population and setting**	**Intervention or exposure tested**	**Study results**	**Assessment of quality and comments**
McGoven 2021 Literature review	Mix of preterm and term infants Literature search completed in May 2021 Cochrane and Medline databases searched	Identifying evidence reviewing safety analysis of preterm infants receiving rhDNase with atelectasis, both nebulised and instilled Studies included if objectively measuring clinical improvement following rhDNase with a control In the studies included chest x-ray (CXR) changes and clinical	95 studies screened, 8 identified and discussed, only 2 randomised controlled trials (RCTs) included following inclusion criteria The two studies included a total of 30 preterm infants and 13 term infants Limited evidence From RTC's included improvement in CXR scored	Poor quality case studies included with limited evidence and population size Variation in dosage and delivery method Clear inclusion/ exclusion criteria Studies look primarily at clinical outcomes not harm or safety

		parameters were used as objective outcomes	compared to control No serious adverse effects reported Desaturations and bradycardias were noted but only when instilled 2 cases of increased atelectasis, and 1 case of increased secretion retention, however in this case rhDNase not used alongside chest physiotherapy	
First author, year and type of study	**Population and setting**	**Intervention or exposure tested**	**Study results**	**Assessment of quality and comments**
Boogaard 2007 Literature review	Mixture of ages (children 0-18 years, including preterm) MEDLINE database and Cochrane library utilised,	Aim of review was to summarize published literature on mucoactive agents most frequently used and studied in children with non-cystic fibrosis lung disease, this is,	Total of 34 relevant articles retrieved, 21 articles reported RCTs, 22 reported uncontrolled clinical observations Authors suggest that use of mucoactive	Predominantly uncontrolled observations that suggest beneficial effects of mucoactive agents in different lung disease Likely effect of publication

	search strategy fully broken down in method section	N-acetylcysteine (NAC) and other sulfhydryl compounds, rhDNase, and hypertonic saline (HTS). Focused on literature reporting effects of mucoactive agents on clinical outcome measures e.g. length of stay, symptom severity, and chest radiographs	drugs should be in conjunction with effective airway clearance to minimise risk of mucus plugging and improve effectiveness **NAC and other Sulfhydryl compounds:** The few published RCTs in non-cystic fibrosis patients were of crossover design and short duration. They showed no effects at all or futile effects of doubtful clinical significance. No reports of harm Potential drawback of inhaled NAC is risk of bronchospasm in patients with airway hypersensitivity Observational studies reported cyanotic spells and asphyxia	bias, as uncontrolled observations of unfavourable findings are rarely published Discusses both instilled and nebulised mucolytics – at points unclear as to method of delivery For most disease no RCTs have been conducted to confirm or refute these positive findings Studies look primarily at clinical outcomes not harm or safety Larger studies needed to confirm results

			after intratracheal and oral NAC respectively (outside of scope of CAT as instilled not nebulised) **RhDNase:** - One RTC showed reduction in length of stay on intensive care unit (ITU) and lower incidence of atelectasis in post-operative ventilated patients. - Oral administration of RhDNase often associated with temporary desaturations. (outside scope of practice as not nebulised) **HTS:** Three small RCTs in infants with respiratory syncytial virus (RSV) bronchiolitis (all completed by the same	

			research group). - They reported a beneficial effect on length of stay and symptoms.	

Summary

Evidence on this topic is limited, with most available studies being small, observational and of low quality. This is likely due to the small population of preterm and neonatal patients available for recruitment.

The preterm and neonatal population is at particularly high risk of rapid clinical deterioration and is highly sensitive to medical interventions due to global developmental immaturity. It is, therefore, essential to understand potential harm associated with any intervention. Regarding harm, there were a small number of cases reported of cyanotic or bradycardic episodes related to the use of N-acetylcysteine and rhDNase. However, this was related to incidences of the drug being administered orally or instilled into the endotracheal tube as opposed to nebulisation. Most of the studies reported no significant adverse events to the nebulisation of mucoactive drugs. It was noted by the authors of one review that mucoactive drugs should be used alongside effective airway clearance techniques to minimise risk of mucus plugging.

The studies found looked at a mixture of preterm and term infants, whilst this is a good reflection of our own neonatal unit population, it should be noted that due to anatomical and physiological difference between these patient groups it would have been beneficial to be able to split this question further into specific preterm and term populations. Unfortunately, many of the studies did not give a full breakdown of patients' gestational ages or contained a mix of patient ages, therefore, this was not possible. We have tried to specify for each included paper if it applies to preterm, term or a mixed population.

During this literature search and service development project guidance was sought from Emma Foulerton (Lead Physiotherapist within the West Midlands Neonatal network) with clinical expertise in respiratory neonatal Physiotherapy.

Implications for practice

The incidence of significant harm following nebulised mucoactive drugs appears to be low however, there are only a few, low quality studies carried out on the neonatal population, therefore further evidence is essential. Although outside the scope of this

CAT review it is worthwhile to note that there were reports of bradycardia, cyanotic episodes and increased airway resistance related to the instillation of N-acetylcysteine and rhDNase in this patient group.

What would you post on social media?

No high-quality evidence around incidence of harm using mucoactive nebulisers in preterm and neonatal patients.

CAT image	Evidence quality	Checkbox
	Good quality evidence to support use....	☐
	Insufficient and poor-quality evidence OR substantial harms suggest intervention used with caution after discussion with patient...	x
	No good quality evidence, do not use until further research is conducted OR Good quality evidence to indicate that harms outweigh the benefits....	☐

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Acknowledgements

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