Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Inhaled Mucolytics as Preventative Therapy

Specific Care Question

Does the preventative use of inhaled mucolytic therapy improve patient outcomes in hospitalized mechanically ventilated pediatric patients, particularly regarding mechanical ventilation days, intensive care unit length of stay, and hospital length of stay?

Rationale for Question Asked

Inhaled mucolytic agents are used to thin secretions, mainly when mucus buildup is a concern, to promote airway clearance (Goetz, 2022; Linssen et al., 2020; Rubin, 2015). N-acetylcysteine, dornase alfa, and hypertonic saline are three mucolytic agents referenced in the literature used in infants and children on mechanical ventilation (Goetz, 2022; Linssen et al., 2020; Rubin, 2015; Sathe et al., 2015; Strickland et al., 2015). In 2015, the American Association for Respiratory Care (AARC) established guidelines to assist respiratory therapists in decision-making for airway clearance therapies (Strickland et al., 2015). The AARC clinical practice guideline recommends against the routine use of inhaled mucolytic therapy in hospitalized infants and children due to the lack of evidence to support its use (Strickland et al., 2015). However, despite the cost associated with administering the therapy and the lack of evidence for preventative use, inhaled mucolytic therapies continue to be prescribed for infants and children requiring mechanical ventilation to prevent ventilator-associated pneumonia (Antalová et al., 2022; Goetz et al., 2022; Linssen et al., 2020; Rubin, 2015; Strickland et al., 2015). This review aimed to investigate the impact on the outcomes of mechanical ventilation days, length of intensive care unit (ICU) stay, and hospital length of stay when inhaled mucolytic therapy is used to prevent ventilator-acquired pneumonia. Additionally, the outcome of the associated cost to administer the therapy was explored when available in the literature.

The intent of this review is not to provide a clinical recommendation but to summarize evidence to inform clinical decisions. Such decisions should consider not only this evidence but also benefits, harms, value, feasibility, and acceptability.

Overview of the Evidence

Two randomized controlled trials (RCT) and three quality improvement (QI) studies were identified to investigate the routine use of inhaled mucolytic therapies to prevent ventilator-associated pneumonia in infants and children (Ezzeldin et al., 2018; Fleming et al., 2023; Gillis et al., 2021; Shein et al., 2016; Tester et al., 2020).

Overall, the certainty of the body of evidence was very low. The body of evidence was assessed to have serious indirectness and serious risk of bias. Each of the RCTs investigated the effect of treatment on the outcome of mechanical ventilation days (Ezzeldin et al., 2018; Shein et al., 2016). However, the information could not be pooled due to the clinical and statistical heterogeneity between studies (see Table 1). Differences in patient characteristics and the methods used for reporting results limited the ability to conduct a meta-analysis. The clinical heterogeneity between studies may explain the variance in the direction of effect for the outcome of mechanical ventilation days. Additionally, Shein et al. (2016) was the only trial to also investigate the effect of treatment on the outcomes of ICU stay and hospital length of stay. However, the trial had a limited number of participants by which to assess these outcomes. Each study was assessed to have limitations and concerns regarding the risk of bias (see Figure 1).

The three quality improvement studies identified investigated inhaled mucolytic therapy use (inhaled hypertonic saline, N-acetylcysteine, or dornase alfa) following the implementation of guidelines and policies detailing parameters for use (Fleming et al., 2023; Gillis et al., 2021; Tester et al., 2020). The studies varied in the inhaled mucolytic therapy selected for de-implementation (see Table 2). All three studies investigated the change in frequency of inhaled mucolytic therapy administration and cost-associated factors such as staff utilization or medication expenditures before and after the intervention. Each of the studies reported cost savings due to either a reduction of staff time utilized to administer the therapy or a reduction in medication expenditures following the implementation of guidelines and policies detailing the parameters for inhaled mucolytic therapy.

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Table 1
Included RCT Studies

Author (year)	Study Type	Population	Participants	Intervention	Control	Results
Ezzeldin et al. (2018)	RCT	Hospitalized premature newborns, gestational age between 24 and 36 weeks, requiring mechanical ventilation	*N* = 100	• Nebulized hypertonic saline (4 mL per application, twice daily), in addition to the routine bundle for prevention of ventilator-associated pneumonia (*n* = 50)	• Routine bundle components for prevention of ventilator-associated pneumonia without nebulized hypertonic saline (*n* = 50)	• Neonates in the nebulized mucolytic group required fewer days on the ventilator[a] (nebulized mucolytic group, 10.7 ± 8.6; standard care group, 16.9 ± 3.4, *p* < .001)
Shein et al. (2016)	RCT	Hospitalized mechanically ventilated pediatric patients (< 18 years of age)	*N* = 18	• 3 mL of 3% hypertonic saline, four times daily via nebulizer (*n* = 9)	• 3 mL of 0.9% saline, four times daily via nebulizer (*n* = 9)	• Duration of mechanical ventilation was longer for children treated with prophylactic hypertonic saline[b] (hypertonic saline, 208.1 [IQR 136.3 – 3.19.8] hours; placebo, 129.5 [IQR 74.4 – 146.1] hours, *p* = .03) • Duration of ICU care did not significantly differ between the prophylactic hypertonic saline and the placebo groups[b] (hypotonic saline, 12, [IQR 9 – 17] days; placebo, 8 [IQR 6 – 12.5] days, *p* = .08) • Hospital length of stay did not significantly differ between the prophylactic hypertonic saline and the placebo groups[b] (hypertonic saline, 17 [IQR 16 – 22.5] days; placebo, 15 [IQR 9 – 22.5] days, *p* = .45)

Note. [a]Data is presented as mean, standard deviation. [b]Data is presented as median, interquartile range (IQR)

Figure 1

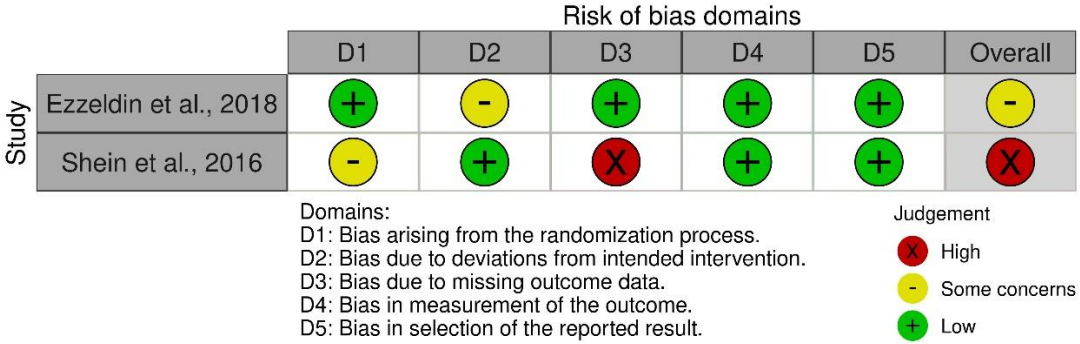

Table 2

Included QI Studies

Author (year)	Study Type	Population	Setting	Intervention	Outcomes	Results
Fleming et al. (2023)	QI	Hospitalized, mechanically ventilated patients (age not specified)	ICU; Milwaukee, WI	• *Pre-Intervention:* Obtained baseline data for 3% hypertonic saline and N-acetylcysteine administration for each ICU. Developed a policy enabling respiratory therapists to discontinue nebulized mucolytic therapy if	• Number of administered 3% hypertonic saline and/or N-acetylcysteine nebulizer treatments • Time measured in full-time employees required for 3% hypertonic saline and/or N-acetylcysteine administration	• When comparing baseline to post-policy activation periods, monthly mean 3% hypertonic saline and/or N-acetylcysteine treatments were reduced from 3,565.2 ± 596.4 to 547.5 ± 284.3; p <.001 • The monthly mean number of full-time employees administering 3% hypertonic saline and/or N-acetylcysteine treatments was reduced from 5.1 ± 0.86 to 0.8 ± 0.41, p <.001

				treatment indications are not met • *Intervention*: Enacted the nebulized mucolytic therapy de-implementation policy using a change management education strategy • *Post-Intervention*: Collected and analyzed data post-policy activation		
Gillis et al. (2021)	QI	Hospitalized, mechanically ventilated children	Pediatric ICU; Columbus, OH	• *Pre-Intervention*: Reviewed evidence and created a clinical pathway to reduce dornase alfa use • *Intervention*: Plan-Do-Study-Act (PDSA), Cycle 1: Educated staff and implemented clinical pathway and electronic medical record order PDSA, Cycle 2: Limited daily dosing, updated clinical pathway and electronic medical record order, and	• Number of medication new starts defined as any first course for the specific medication, or any new medication starts for the same patient following discontinuation for > 48 hours • Total number of medication doses • Days on mechanical ventilation defined as per 100 patient days	• New dornase alfa starts per 100 patient days decreased by 53% (pre-intervention, 1.17; first cycle, 0.55) after the first PDSA Cycle, and further decreased to 0.25 following the second PDSA Cycle (post-intervention) • Total doses of dornase alfa per 100 patient days decreased by 75% (pre-intervention, 16; first cycle, 4) after the first PDSA Cycle. Total doses remained the same at 4 per 100 patient days through December 2019. • New N-acetylcysteine starts occurred more than twice as often following clinical pathway implementation • Total doses of N-acetylcysteine per 100 patient

				repeated staff education • *Post-Intervention*: Conducted a post-intervention mucolytic utilization analysis		days remained unchanged after the intervention • New hypertonic saline starts increased from 0.28 to 4.15 per 100 patient days and remained at 4.15 through the second PDSA Cycle • Total doses of hypertonic saline use increased from 4.37 to 38.84 doses per 100 patient days. • Mechanical ventilation days per 100 patient days decreased following clinical pathway implementation • Reduction of dornase alfa utilization resulted in a cumulative and sustained 59% mucolytic cost reduction (pre-intervention, $2183.08; post-intervention, $885.77)
Tester et al. (2020)	QI	Hospitalized, mechanically ventilated children (*N* = 74)	Pediatric ICU and Pediatric Cardiac ICU; Durham, NC	• *Pre-intervention*: Obtained data for children admitted between February 1, 2015, and through October 31, 2015 (*n* = 51) • *Intervention*: Implemented unit-specific dornase alfa utilization guideline on November 1, 2015 • *Post-Intervention*: Collected data	• Number of dornase alfa doses administered in the pediatric intensive care unit and pediatric cardiac ICU before and after guideline implementation • Number of patients for whom an alternative mucolytic agent (e.g., hypertonic saline and acetylcysteine) was used • Number of doses of acetylcysteine and hypertonic saline administered	• Following guideline implementation, the number of dornase alfa doses decreased by 77.6% (pre-guideline, 1067 doses; post-guideline, 239 doses) • Following guideline implementation, the number of acetylcysteine doses decreased by 33.2% (pre-guideline, 1169 doses; post-guideline, 781 doses) • Following guideline implementation, the number of hypertonic saline doses decreased by 49.1% (pre-guideline, 912 doses; post-guideline, 464 doses)

	following guideline implementation from December 1, 2015, through August 31, 2016. (*n* = 23)	• Change in cost following guideline implementation • Difference in the pediatric ICU length of stay • Difference in the pediatric cardiac ICU length of stay	• Before guideline implementation, the cost associated with mucolytic therapy was $116,794.26. Following guideline implementation, the cost was $29,086.50, resulting in a difference of $87,707.76. • Following guideline implementation, the average length of stay in either the pediatric ICU (pre-, 3.59 days; post-, 2.95 days) or the pediatric cardiac ICU (pre-, 3.21 days; post-, 3.22 days) did not statistically differ (*p* = .064) • The difference in total length of stay between time periods was statistically significant (pre-, 16.22 days; post-,13.14 days; *p* = .042)	

Identification of Studies
Search Strategy and Results

#23 **#22** NOT (‘**animal model’**/de OR ‘**animal tissue’**/de OR ‘**case report’**/de OR ‘**case study’**/de OR ‘**nonhuman**’/de)
#22 **#21** AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim OR [young adult]/lim AND [07-01-2010]/sd NOT [25-07-2024]/sd
#21 **#15** AND **#20**
#20 **#16** AND **#19**
#19 **#17** AND **#18**
#18 ‘**inhalational drug administration’**/exp OR ‘**nebulizer**’/exp OR ‘**aerosolized**’ OR ‘**inhaled’** OR ‘**nebulized**’ OR ‘**inhalation**’ OR ‘**nebulizer**’
#17 ‘**mucolytic agent’**/exp OR ‘**mucoactive**’ OR ‘**mucolysis**’/ exp OR ‘**mucolytic**’ OR mucokinetics OR ‘**hypertonic saline’**

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#16 '**acetylcysteine'**/exp OR '**n-acetylcysteine'** OR '**ambroxol**'/exp OR '**dornase alfa'**/exp
#15 '**venilated patient'**/exp OR '**endotracheal intubation'**/exp OR '**artificial airway'** OR '**mechanical ventilation'** OR '**mechanical ventilator'**/exp OR '**mechanically ventilated'** OR intubated OR '**ventilator associated pneumonia'**/exp OR '**mechanical ventilation time'**/exp
#14 **#5** AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim OR [young adult]/lim OR pediatr*) AND [07-01-2010]/sd NOT [25-07-2024]/sd
#13 **#5** AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim OR [young adult]/lim OR pediatr*
#12 **#1** AND **#4**
#11 **#2** AND **#3**
#10 '**inhalational drug administration'**/exp OR '**nebulizer**'/exp OR '**aerosolized**' OR '**inhaled**' OR '**nebulized**' OR '**inhalation**' OR '**nebulizer**'
#9 '**sodium chloride'**/exp OR saline or '**mucolytic agent'**/exp OR '**mucoactive**' OR '**mucolysis**'/exp OR '**mucolytic**' OR mucokinetics OR '**acetylcysteine**'/exp OR '**n-acetylcysteine'** OR '**ambroxol**'/exp
#8 '**ventilated patient'**/exp OR '**endotracheal intubation'**/exp OR '**artificial airway'** OR '**mechanical ventilation'** OR '**mechanical ventilator'**/exp OR '**mechanically ventilated'** OR intubated OR '**ventilator associated pneumonia'**/exp/dm_pc OR '**mechanical ventilation time'**/exp
#7 '**nebulized hypertonic saline to prevent ventilator associated pneumonia in premature infants, a randomized trial'** OR (nebulized AND hypertonic AND ('**saline**'/exp OR saline) AND to AND prevent AND ('**ventilator**'/exp OR ventilator) AND associated AND ('**pneumonia**'/exp OR pneumonia) AND in AND ('**premature**'/exp OR premature) AND infants, AND, AND a AND randomized AND ('**trial**'/exp OR trial))
#6 **#5** AND ([adolescent]/lim OR [child]/lim OR [infant/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim OR [young adult]/lim
#5 **#1** and **#4**
#4 **#2** and **#3**
#3 **'inhalational drug administration'**/exp OR **'nebulizer'**/exp OR **'aerosolized'** OR **'inhaled'** OR **'nebulized'** OR **'inhalation'** OR **'nebulizer'**
#2 **'mucolytic agent'**/exp OR **'mucoactive'** OR **'mucolysis'**/exp OR **'mucolytic'** OR mucokinetics OR **'acetylcysteine'**/exp OR **'n-acetylcysteine'** OR **'ambroxol'**/exp
#1

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'ventilated patient'/exp OR **'endotracheal intubation'**/exp OR '**artificial airway'** OR **'mechanical ventilation'** OR **'mechanical ventilator'**/exp OR **'mechanically ventilated'** OR **intubated** OR **'ventilator associated pneumonia'**/exp/dm_pc OR **'mechanical ventilation time'**/exp

Search Dates: July 1, 2010-July 24, 2024
Records identified through database searching *n* = 3
Additional records identified through other sources *n* = 3
Records excluded due to not answering PICOT question *n* = 1

Question Originator
Respiratory Care
Findings from this review were presented with the question originators and H. Escobar, MD, on September 10, 2024.

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Characteristics of Intervention Studies
Ezzeldin et al. (2018)

Methods	Randomized Control Trial, open label

Participants	**Participants:** Premature newborns between the ages of 24 – 36 weeks requiring endotracheal intubation and mechanical ventilation
	
	Setting: Neonatal ICU, Cairo, Egypt, 2012 to 2014
	
	Randomized into the study: *N* = 115
	• **Group 1, Nebulized hypertonic saline** *n* = 57
	• **Group 2, Standard care:** *n* = 58
	
	Completed Study: *N* = 100
	• **Group 1, Nebulized hypertonic saline:** *n* = 50
	• **Group 2, Standard care:** *n* = 50
	
	Gender, females (as defined by researchers):
	• **Group 1:** *n* = 25 (50%)
	• **Group 2:** *n* = 29 (58%)
	
	Race/ethnicity or nationality (as defined by researchers):
	• Not reported or provided
	
	Age, mean in weeks, (standard deviation)
	• **Group 1:** 31.2 (±2.9)
	• **Group 2:** 31.2 (±3.1)
	
	Inclusion Criteria:
	• Indications for mechanical ventilation including:
	  ○ Respiratory distress syndrome of prematurity
	  ○ Meconium aspiration syndrome
	  ○ Transient tachypnea of the newborn
	
	Exclusion Criteria:
	• Newborns with:
	  ○ Confirmed pneumonia prior to intubation
	  ○ Acute renal failure
	  ○ Hypernatremia
	  ○ Major congenital anomalies
	
	Power Analysis: Sample size was calculated based on the primary outcome. The error rate was set at *p* = .05 and power at 80%

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Interventions	**Both:** Each infant had a chest X-ray within 48 hours of enrollment. A complete blood count and C-reactive protein level were obtained for each infant per unit protocol. Infants in the intervention and standard care groups received the routine bundle to prevent ventilator-associated pneumonia. A second chest X-ray was completed 72 hours following mechanical ventilation. A third chest X-ray was completed after one week of mechanical ventilation. Following the unit protocol, the newborns were extubated when showing signs of stability. • **Group 1, Nebulized hypertonic saline:** Each infant received 4 mL of hypertonic saline over 3 minutes twice daily via an ultrasonic nebulizer system for 10 days or until the newborn was extubated as an adjunctive therapy to the routine bundle for prevention of ventilator-associated pneumonia. Each infant was closely observed while receiving the treatment to monitor for side effects of cough, wheezing, or bronchospasms. • **Group 2, Standard care:** Each infant received only the routine bundle to prevent ventilator-associated pneumonia. Specifics were not provided regarding the routine bundle for prevention. *Note*. The routine bundle was established based on a prospective surveillance study published by Rosenthal et al. (2012). The routine bundle consisted of: ○ Active surveillance of ventilator-associated pneumonia ○ Adherence to hand hygiene guidelines ○ Performance of daily assessments of readiness to wean and use of weaning protocols ○ Performance of regular oral care with an antiseptic solution ○ Use of noninvasive ventilation whenever possible and minimization of the duration of ventilation ○ Preferable use of orotracheal instead of nasotracheal intubation ○ Removal of the condensate from ventilator circuits and keeping the ventilator circuit closed during condensate removal ○ Change of the ventilator only when visibly soiled or malfunctioning ○ Avoidance of gastric overdistension ○ Avoidance of histamine receptor 2-blocking agents and proton pump inhibitors ○ Use of sterile water to rinse reusable respiratory equipment
Outcomes	**Primary outcome(s):** • Ventilator-associated pneumonia rates, defined as infants experiencing clinical deterioration requiring escalated intervention such as: ○ Increased oxygen supplementation ○ Worsening blood gas associated with radiographic evidence of pneumonia ○ White blood cell count elevation ○ Increased C-reactive protein ○ Positive endotracheal cultures **Secondary outcome(s)** • Days on mechanical ventilation* • Occurrence of pneumothorax or pleural effusion

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	• Positive bacterial cultures from endotracheal tube aspirate or blood • Serum sodium levels to monitor for hypernatremia **Safety outcome(s):** • None reported *Outcomes of interest to the CMKC CAT development team

Notes	**Results:**
	• Fifteen infants expired within 72 hours from study inclusion and were not included in the statistical analysis (nebulized mucolytic group, *n* = 7; standard care group, *n* = 8).
	• The rate of ventilator-associated pneumonia was 37% (*n* = 35) overall, 18% in the nebulized mucolytic group (*n* = 9), and 52% in the standard care group (*n* = 26; *RR* = 0.35, 95%CI [0.18, 0.66], *p* = .001).
	• Neonates in the nebulized mucolytic group required fewer days on the ventilator (nebulized mucolytic group, 10.7 ± 8.6; standard care group, 16.9 ± 3.4, p < .001)
	• Neonates in the nebulized mucolytic group had fewer incidences of pneumothorax and pleural effusion, though a higher incidence of lobar collapse.
	  ○ Pneumothorax: nebulized mucolytic group, *n* = 18 (16%); standard care group, *n* = 11 (22%); *RR* = 0.73, 95%CI [0.32, 1.65], *p* =0.44
	  ○ Pleural effusion: nebulized mucolytic group, *n* = 2 (4%); standard care group, *n* = 7 (14%); *RR* = 0.29, 95%CI [0.06, 1.30], *p* = .11
	  ○ Lobar collapse: nebulized mucolytic group, *n* = 3 (6%); standard care group, *n* = 0 (0%); *RR* = 7.0, 95%CI [0.37, 132.1], *p* =.19
	• Positive tracheal aspirate cultures were less prevalent in the intervention group (nebulized mucolytic group, *n* = 11 (22%); standard care group, *n* = 32 (64%); *RR* = 0.34, 95%CI [0.20, 0.60], *p* < .001)
	• Positive blood cultures were less prevalent in the intervention group (nebulized mucolytic group, *n* = 9 (18%); standard care group, *n* = 20 (40%); *RR* = 0.45, 95%CI [0.23, 0.89], *p* = .02)
	• The study was not powered for secondary outcomes.
	
	Limitations (reported by authors):
	• The study was not double-blinded, as the researchers could not identify a "safe placebo" for nebulized hypertonic saline.
	• The study was not powered for secondary outcomes.
	
	Limitations (perceived by reviewer):
	• The study was a convenience sample occurring within a single institution
	• Baseline data was obtained for 115 participants meeting inclusion criteria. However, analysis was provided only for infants completing the study. While the participant loss was comparable between groups, concerns were raised regarding potential bias and certainty in effect estimates for some outcomes.

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Fleming et al. (2023)

Methods	Quality Improvement
Participants	**Participants:** Hospitalized and mechanically ventilated patients **Setting:** Intensive care units within a 700-bed academic medical center, in Milwaukee, WI, between June 1, 2020 and August 31, 2022 **Number enrolled into the study:** • Not reported **Gender (as defined by researchers):** • Not reported **Race/ethnicity or nationality (as defined by researchers):** • Not reported **Age (as defined by researchers):** • Not reported **Inclusion Criteria:** • Patients without an American Association for Respiratory Care (AARC) Clinical Practice Guideline treatment indication receiving nebulized mucolytic therapy **Exclusion Criteria:** • Patients with an AARC Clinical Practice Guideline treatment indication
Interventions	**Both**: Collected data on nebulized 3% hypertonic saline and/or N-acetylcysteine administration and other nebulized treatments as surrogate control during the three time periods. • **Pre-intervention:** Obtained baseline data from the electronic medical record to capture 3% hypertonic saline and/or N-acetylcysteine administration for each intensive care unit. Developed and requested approval for a policy enabling respiratory therapists to discontinue nebulized mucolytic therapy if treatment indications are not met. Presented policy, baseline data, and AARC Clinical Practice Guideline to Medical Executive Committee (June 1, 2020 through June 30, 2021) • **Intervention**: Established and enacted a nebulized mucolytic therapy de-implementation policy using a change management education strategy. Collected data on the frequency of nebulizer orders and treatments (July 1, 2021 through September 30, 2021) • **Post-intervention:** Collected and analyzed data post-policy activation (October 1, 2021 through August 31, 2022)
Outcomes	**Primary outcome(s):** • Number of administered 3% hypertonic saline and/or N-acetylcysteine nebulizer treatments • Respiratory therapist time measured in full-time employees required for 3% hypertonic saline and/or N-acetylcysteine administration **Secondary outcome(s):** • Not reported **Safety outcome(s):** • Not reported *Outcomes of interest to the CMKC CAT development team
Results	**Results:**

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	• When comparing baseline to post-policy activation periods, monthly mean 3% hypertonic saline and/or N-acetylcysteine treatments were reduced from 3,565.2 ± 596.4 to 547.5 ± 284.3; p <.001 • The monthly mean number of full-time employees administering 3% hypertonic saline and/or N-acetylcysteine treatments was reduced from 5.1 ± 0.86 to 0.8 ± 0.41, p <.001 • The monthly mean 3% hypertonic saline and/or N-acetylcysteine orders declined from 370.0 ± 46.9 to 93.8 ± 31.5 **Limitations:** • As the study focused on nebulized mucolytic therapy practices, specifics about the study population were lacking. • The study did not define their patient population

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Critically Appraised Topic (CAT): Inhaled Mucolytics as Preventative Therapy

Gillis et al. (2021)

Methods	Quality Improvement

Participants	**Participants:** Children requiring mechanical ventilation
	
	Setting: PICU, Nationwide Children's Hospital, Columbus, OH, between January 2017 through December 2019
	
	Number enrolled into the study:
	• Not reported
	
	Gender, males (as defined by researchers):
	• Not reported
	
	Race/ethnicity or nationality (as defined by researchers):
	• Not reported
	
	Age (as defined by researchers):
	• Not reported
	
	Inclusion Criteria:
	• Receiving hypertonic saline (3%), N-acetylcysteine, or dornase alfa
	
	Exclusion Criteria:
	• Children with:
	  ○ Cystic fibrosis
	  ○ Plastic bronchitis in the context of sickle cell disease
	  ○ Sever hypoxemia with an oxygenation index > 15
	• Children undergoing recruitment maneuvers while supported on extracorporeal membrane oxygenation (ECMO)

Interventions	• **Pre-intervention:** A multidisciplinary team reviewed the evidence regarding inhaled mucolytic therapy and created a clinical pathway to reduce the use of dornase alfa use
	• **Intervention:**
	  ○ Plan-Do-Study-Act (PDSA), Cycle 1: Educated staff and implemented clinical pathway and electronic medical record order
	  ○ PDSA, Cycle 2: Limited dosing to twice daily, updated the clinical pathway and electronic medical record order, repeated staff education
	• **Post-intervention:** Conducted a post-intervention mucolytic utilization analysis

Outcomes	**Primary outcome(s):** • Tabulation of medication new starts defined as any first course for the specific medication, or any new medication starts for the same patient following discontinuation for > 48 hours • Tabulation of medication total doses • Days on mechanical ventilation defined as per 100 patient days* • Monthly patient days **Secondary outcome(s):** • Not reported **Safety outcome(s):** • Not reported *Outcomes of interest to the CMKC CAT development team

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Critically Appraised Topic (CAT): Inhaled Mucolytics as Preventative Therapy

Results	**Results:** • New dornase alfa starts per 100 patient days decreased by 53% (pre-intervention, 1.17; first cycle, 0.55) after the first PDSA Cycle, and further decreased to 0.25 following the second PDSA Cycle (post-intervention) • Total doses of dornase alfa per 100 patient days decreased by 75% (pre-intervention, 16; first cycle, 4) after the first PDSA Cycle. Total doses remained unchanged at 4 per 100 patient days through December 2019. • New N-acetylcysteine starts occurred more than twice as often following clinical pathway implementation • Total doses of N-acetylcysteine per 100 patient days remained unchanged after the intervention • New hypertonic saline starts increased from 0.28 to 4.15 per 100 patient days and remained at 4.15 through the second PDSA Cycle • Total doses of hypertonic saline use increased from 4.37 to 38.84 doses per 100 patient days. • Mechanical ventilation days per 100 patient days decreased following clinical pathway implementation • Reduction of dornase alfa utilization resulted in a cumulative and sustained 59% mucolytic cost reduction (pre-intervention, $2183.08; post-intervention, $885.77) **Limitations:** • Dornase alfa prescribing reduction was the focus of the intervention, despite also reporting the prescribing practices of N-acetylcysteine and hypertonic saline

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Critically Appraised Topic (CAT): Inhaled Mucolytics as Preventative Therapy

Shein et al. (2016)

Methods	Randomized Control Trial, pilot
Participants	**Participants:** Children < 18 years of age intubated for less than 12 hours **Setting:** Pediatric Intensive Care Unit, Rainbow Babies and Children's Hospital, Cleveland, OH, between October 2013 and May 2014. **Randomized into study:** *N* = 18 • **Group 1, Nebulized hypertonic saline:** *n* = 9 • **Group 2, Nebulized normal saline (placebo):** *n* = 9 **Completed Study:** *N* = 14 • **Group 1:** *n* = 6 • **Group 2:** *n* = 8 **Gender, females (as defined by researchers):** • **Group 1:** *n* = 2 (22%) • **Group 2:** *n* = 3 (33%) **Race/ethnicity or nationality (%):**

Race Demographics by Group

Race	Hypertonic Saline (*n* = 9)	Placebo (Normal Saline) (*n* = 9)
African American, *n* (%)	5 (56%)	4 (44%)
Caucasian, *n* (%)	3 (33%)	5 (56%)
Other, *n* (%)	1 (11%)	0 (0%)

Age, median in weeks, (IQR)
- **Group 1:** 12.7 (5.6 - 32.6)
- **Group 2:** 26.0 (3.1 – 174.2)

Inclusion Criteria:
- Children with an expected duration of mechanical ventilation > 48 additional hours
- Children < 12 hours since endotracheal intubation

Exclusion Criteria:
- Children participating in a different research study
- Children with:
  - Cystic fibrosis
  - Status asthmaticus
  - Pulmonary hemorrhage
  - Pulmonary contusion

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	○ Pre-existing tracheostomy • Children requiring home use of positive-pressure ventilation or oxygen therapy • Children with adverse reactions to nebulized hypertonic saline or albuterol • Children who had a previous prescription of mucolytic therapy by the clinical team during the hospitalization **Power Analysis:** The power analysis was not fully described. The sample size of approximately 20 was selected a priori to detect a 1.2-day difference in mechanical ventilation duration. The information reported was based on a previous study (Riethmueller et al., 2006).
Interventions	**Both:** Demographics, baseline sodium level, and indication for mechanical ventilation were collected at enrollment. The Pediatric Risk of Mortality III score was calculated. Ventilator parameters, dead space, end-tidal partial pressure of CO_2 and SpO_2, and the presence of wheezing were documented before the study drug administration and again within 60 minutes following administration. For each administration, a respiratory therapist temporarily suspended mechanical ventilation and subsequently manually ventilated the child with the flow-inflating bag/nebulizer apparatus. Albuterol (2.5 mg) co-administration was mandated only for those children who had wheezing following a prior dose of the study drug. The study drug was continued until extubation or for a maximum of 7 days of treatment. Nebulization was deferred if the child was concurrently hemodynamically unstable per the clinician team or on high-frequency oscillatory ventilation, F_iO_2 > 0.75 or positive end-expiratory pressure (PEEP) > 11 cm H_2O. • **Group 1, Prophylactic hypertonic saline:** 3 mL of 3% hypertonic saline via nebulization four times daily • **Group 2, Normal saline:** 3 mL of 0.9% saline via nebulization four times daily
Outcomes	**Primary outcome(s):** • Duration of mechanical ventilation (hours)* **Secondary outcome(s)** • Duration of ICU care (days)* • Hospital length of stay (days)* • Reintubation within 24 hours **Safety outcome(s):** • Not reported *Outcomes of interest to the CMKC CAT development team
Notes	**Results:** • Duration of mechanical ventilation was longer for children treated with prophylactic hypertonic saline (hypertonic saline, 208.1 [IQR 136.3 – 3.19.8] hours; placebo, 129.5 [IQR 74.4 – 146.1] hours, *p* = .03) • Duration of ICU care did not significantly differ between the prophylactic hypertonic saline and the placebo groups (hypotonic saline, 12, [IQR 9 – 17] days; placebo, 8 [IQR 6 – 12.5] days, *p* = .08) • Hospital length of stay did not significantly differ between the prophylactic hypertonic saline and the placebo groups (hypertonic

	saline, 17 [IQR 16 – 22.5] days; placebo, 15 [IQR 9 – 22.5], p = .45) • Re-intubation rates did not significantly differ between the prophylactic hypertonic saline and the placebo groups (hypertonic saline, *n* = 1 (11%); placebo, *n* = 0 (0%), p > .99) • Four children withdrew from the study (*p* = .58, between groups). Two children met one of the three a priori stopping rules (a desaturation episode within 30 minutes of study drug administration to SpO_2 <80% that does not resolve within 2 minutes), and two children were removed due to coughing (one by an attending physician and one by a parent). **Limitations (reported by authors)**: • Sample size was smaller than prior prospective or postoperative cohort studies found in the literature. • The study was not powered for primary or secondary outcomes. • The study population is representative of a more heterogeneous cohort than the cohorts identified in the literature • Despite randomization, illness severity at baseline varied between groups. Children who received the hypertonic saline had more unfavorable radiographic findings and pulmonary disease at enrollment. **Limitations (perceived by reviewer):** • Four children were withdrawn from the study creating an imbalance between the experimental and comparator groups. Methods did not report on how the missing outcome data was managed when analyzing results and how the imbalance may have impacted outcomes.

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Critically Appraised Topic (CAT): Inhaled Mucolytics as Preventative Therapy

Tester et al. (2020)

Methods	Quality Improvement
Participants	**Participants:** Children who are critically ill **Setting:** Pediatric intensive care unit (ICU) and pediatric cardiac ICU at Duke University Hospital (Durham, NC) between February 1, 2015 through August 31, 2016 **Number enrolled into the study:** *N* = 74 • **Pre-intervention, Pre-guideline implementation:** *n* = 51 • **Post-intervention, Guideline implementation:** *n* = 23 **Gender, males (as defined by researchers):** • Not reported **Race/ethnicity or nationality (as defined by researchers):** • Not reported **Age (as defined by researchers):** • Not reported **Inclusion Criteria:** • Children admitted to the pediatric ICU or pediatric cardiac ICU • Children receiving at least one dose of dornase alfa during the data collection period **Exclusion Criteria:** • Children with a medical history or suspicion of cystic fibrosis
Interventions	Both: The data collected included the child's primary diagnosis, the reason for the use of dornase alfa, hospital length of stay, ICU length of stay, the dose and frequency of dornase alfa use, the number of doses of dornase alfa per child, the date of initiation of acetylcysteine, hypertonic saline, or dornase alfa, and associated costs for the mucolytic therapy administration. • **Pre-intervention:** Completed retrospective chart review obtaining data for children admitted between February 1, 2015, and through October 31, 2015. • **Post-intervention:** Collected data following unit-specific dornase alfa utilization guideline implementation on November 1, 2015. The data was collected from December 1, 2015 through August 31, 2016.
Outcomes	**Primary outcome(s):** • Number of dornase alfa doses administered in the pediatric ICU and pediatric cardiac ICU before and after guideline implementation **Secondary outcome(s):** • Number of patients where an alternative mucolytic agent (e.g., hypertonic saline and acetylcysteine) was used • Number of doses of acetylcysteine and hypertonic saline administered • Change in cost following guideline implementation • Difference in the pediatric ICU length of stay* • Difference in the pediatric cardiac ICU length of stay* **Safety outcome(s):** • Not reported

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	*Outcomes of interest to the CMKC CAT development team
Results	**Results:** • Following guideline implementation, the number of dornase alfa doses decreased by 77.6% (pre-guideline, 1067 doses; post-guideline, 239 doses) • Following guideline implementation, the number of acetylcysteine doses decreased by 33.2% (pre-guideline, 1169 doses; post-guideline, 781 doses) • Following guideline implementation, the number of hypertonic saline doses decreased by 49.1% (pre-guideline, 912 doses; post-guideline, 464 doses) • Before guideline implementation, the cost associated with mucolytic therapy was $116,794.26. Following guideline implementation, the cost was $29,086.50 resulting in a difference of $87,707.76. • Following guideline implementation, the average length of stay in either the pediatric ICU (pre-, 3.59 days; post-, 2.95 days) or the pediatric cardiac ICU (pre-, 3.21 days; post-, 3.22 days) did not statistically differ (p = .064) • The difference in total length of stay between time periods was statistically significant (pre-, 16.22 days; post-, 13.14 days; p = .042) **Limitations:** • The time period for data collection was limited to 9 months • Dornase alfa prescribing reduction was the focus of the intervention, despite also reporting the prescribing practices of N-acetylcysteine and hypertonic saline

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