



## On-demand vs. routine nebulisation in ventilated ICU patients



Among ICU patients receiving invasive ventilation, on-demand nebulisation was not inferior to routine nebulisation of acetylcysteine with salbutamol, according to results of a randomised clinical trial (NEBULAE) published online in JAMA.

Use of nebulised mucolytics may provide benefit in ICU patients receiving invasive ventilation, but evidence is limited. Because of its ability to hydrolyse and break the disulfide bonds in mucin, acetylcysteine is one of the most commonly used mucolytics. To avoid a possible increase of airway resistance, acetylcysteine is frequently combined with a bronchodilator. Bronchodilators can further improve mucus clearance through an increase in small airways diameter.

The Preventive Nebulisation of Mucolytic Agents and Bronchodilating Drugs in Intubated and Ventilated Intensive Care Unit Patients (NEBULAE) randomised clinical trial was conducted to test whether a strategy of on-demand nebulisation of acetylcysteine or salbutamol is noninferior to using routine nebulisation of acetylcysteine with salbutamol with respect to days ventilator-free and alive at day 28.

The trial included 922 adult patients receiving invasive ventilation who were expected to not be extubated within 24 hours at seven ICUs in the Netherlands. Patients were randomly assigned to receive on-demand nebulisation of acetylcysteine or salbutamol (based on strict clinical indications,  $n = 471$ ) or routine nebulisation of acetylcysteine with salbutamol (every 6 hours until end of invasive ventilation,  $n = 473$ ). The primary outcome was the number of ventilator-free days at day 28, with a noninferiority margin for a difference between groups of  $-0.5$  days. Secondary outcomes included length of stay, mortality rates, occurrence of pulmonary complications, and adverse events.

The study's key findings include:

- At 28 days, patients in the on-demand group had a median 21 (IQR, 0-26) ventilator-free days, and patients in the routine group had a median 20 (IQR, 0-26) ventilator-free days (1-sided 95% CI,  $-0.00003$  to  $\infty$ ).
- There was no significant difference in length of stay or mortality, or in the proportion of patients developing pulmonary complications, between the two groups.
- Adverse events (13.8% vs. 29.3%; difference,  $-15.5\%$  [95% CI,  $-20.7\%$  to  $-10.3\%$ ];  $P < .001$ ) were more frequent with routine nebulisation and mainly related to tachyarrhythmia (12.5% vs. 25.9%; difference,  $-13.4\%$  [95% CI,  $-18.4\%$  to  $-8.4\%$ ];  $P < .001$ ) and agitation (0.2% vs. 4.3%; difference,  $-4.1\%$  [95% CI,  $-5.9\%$  to  $-2.2\%$ ];  $P < .001$ ).

"Among ICU patients receiving invasive ventilation who were expected to not be extubated within 24 hours, on-demand compared with routine nebulisation of acetylcysteine with salbutamol did not result in an inferior number of ventilator-free days," the authors explain. "On-demand nebulisation may be a reasonable alternative to routine nebulisation."

A noninferiority design for this study was chosen because, as the authors note, routine nebulisation could be considered standard of care (at least in the Netherlands) and because it was hypothesised that a strategy in which nebulisation needed strict indications would reduce the number of nebulisation-related adverse effects, while not or only slightly affecting duration of ventilation.

This study also has several limitations. Because of the nature of the intervention tested, attending nurses and physicians could not be blinded to the intervention, and the authors say "this could be a major concern, since this knowledge could have affected adjunctive treatment and study findings." However, no differences in adjunctive respiratory care as provided by nurses were noted between the two groups. In addition, the results of this trial cannot be extrapolated to other mucolytic and bronchodilating drugs.

Source: [JAMA](#)

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