



# The effect of reintubation on ventilator-associated pneumonia and mortality among mechanically ventilated patients with intubation: A systematic review and meta-analysis



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## ABSTRACT

**Objectives:** This meta-analysis summarized the risks that reintubation impose on ventilator-associated pneumonia (VAP) and mortality.

**Background:** Extubation failure increases the probability of poor clinical outcomes pertaining to mechanical ventilation.

**Methods:** Literature published during a 15-year period was retrieved from PubMed, Web of Knowledge databases, the Embase (Excerpta Medica database), and the Cochrane Library. Data involving reintubation, VAP, and mortality were extracted for a meta-analysis.

**Results:** Forty-one studies involving 29,923 patients were enrolled for the analysis. The summary odds ratio (OR) between VAP and reintubation was 7.57 (95% confidence interval [CI] = 3.63–15.81). The merged ORs for mortality in hospital and intensive care unit were 3.33 (95% CI = 2.02–5.49) and 7.50 (95% CI = 4.60–12.21), respectively.

**Conclusions:** Reintubation can represent a threat to survival and increase the risk of VAP. The risk of mortality after reintubation differs between planned and unplanned extubation. Extubation failure is associated with a higher risk of VAP in the cardiac surgery population than in the general population.

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## Introduction

Mechanical ventilation via an endotracheal tube is a ubiquitous life-support method applied to various patients experiencing respiratory failure, including those with chronic obstructive pulmonary disease (COPD), neuromuscular disease, cardiovascular disease, and trauma.<sup>1</sup> The ultimate aim of ventilation support is for

it to be discontinued, with the patient regaining spontaneous breathing. Complications can be experienced when using extubation, with the reinstatement of mechanical ventilation being associated with two types of weaning: planned and unplanned extubation. A planned extubation is implemented promptly by the physician or nurse after a weaning-readiness assessment and successful spontaneous breathing trial (SBT).<sup>2</sup> The extubation failure rate reportedly ranges between 2% and 25% among patients experiencing planned extubation.<sup>3</sup> Unplanned extubation refers to the premature removal of the endotracheal tube such as due to the behavior of the mechanically ventilated patient (deliberate unplanned extubation) or an unintentional disconnection during nursing and medical-care (accidental extubation). The incidence of unplanned extubation reportedly accounts for 0.3–14% of all intubated patients, and 60% of these patients need reintubation.<sup>4</sup>

Numerous studies have verified that extubation failure increases the probability of poor clinical outcomes pertaining to mechanical

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ventilation, such as a greater need for tracheotomy, longer stay in the intensive care unit (ICU), increases in the rates of ventilator-associated pneumonia (VAP) and mortality, and increased medical expenditure.<sup>1,4–33</sup> However, there are also contradictory reports of reintubation not being correlated with VAP or mortality.<sup>7,34–43</sup> A previous pooling analysis by He et al confirmed that reintubation was a risk factor for VAP in patients who had ever undergone cardiac surgery.<sup>44</sup>

The current meta-analysis involved a large population that received invasive mechanical ventilation via an endotracheal tube for various reasons. The objectives of this study were as follows: (1) quantifying the risk of VAP after reintubation among patients with and without experience of cardiac surgery, and (2) ascertaining the effect of reintubation after planned or unplanned extubation on the risk of mortality.

## Methods

### Literature search strategy

PubMed, Web of Knowledge databases, the Embase (Excerpta Medica database), and the Cochrane Library were searched for literature published between January 1990 and July 2015 that contain pre-specified key phrases to identify the potential link between reintubation and VAP or mortality. The following word restrictions were applied when retrieving articles: (“ventilator-associated pneumonia” or “VAP” or “pneumonia, ventilator-associated” or “hospital mortality” or “ICU mortality”) and (“reintubation” or “extubation” or “extubation failure”) and “mechanical ventilation.” Two of the authors independently screened the references using these key phrases, and some additional relevant articles were retrieved manually. After eliminating duplicated articles, the authors selected the potentially eligible studies according to their abstracts or titles. The inclusion criteria were summarized as follows: (1) patients older than 14 years, (2) original research, (3) patients received invasive mechanical ventilation via an endotracheal tube, and (4) one of the clinical conditions (VAP or death in hospital or ICU) after reintubation was recorded. When articles shared the same data, the article with the most information was included. The full text of the selected papers was read as described in the next section. The detailed exclusion criteria are summarized as follows: (1) article published in a language other than English, (2) data not available, (3) planned extubation or unplanned extubation before reintubation is not clear, or (4) not all patients received invasive mechanical ventilation via endotracheal tube.

### Data extraction

Data on the patients’ fundamental characteristics, comparison groups, extubation strategy, definition of extubation failure, and study design were collected from each publication selected for inclusion in this review. Regarding statistical analyses, the following data needed to be collected from each report: number of subjects in two subgroups, rates of extubation failure and extubation success, and counts of VAP cases and deaths in the ICU and hospital. For a small number of articles with missing data, the authors were contacted by email to obtain the original data sets.

### Quality assessment

Study quality was evaluated by separate two investigators using the Newcastle–Ottawa Scale (NOS), which is exclusively used in nonrandomized studies.<sup>45</sup> The three dimensions of selection, comparability, and result (with a highest score of 9) were measured

using the NOS. Any discrepancies were resolved by discussion. The papers whose NOS scores exceeded 7 were considered to describe high-quality studies, while a score of 5 or 6 was considered to reflect a moderate-quality study. High- and moderate-quality studies were ultimately included in this meta-analysis.

### Data analysis

The associations of reintubation with the risks of VAP and mortality were investigated. Odds ratio (OR) with 95% confidence interval (CI) values were used to quantify the relationships. Heterogeneity among pooled studies was tested using the  $I^2$  statistic: a fixed-effects model was used if  $I^2 < 50\%$ , otherwise a random-effects model was applied. pre-specified stratified analyses were implemented when estimating the hazard of VAP and mortality separately. Sensitivity analysis was also performed by removing individual studies in turn to determine how each study influenced the overall hazard assessment. Data were imported into specialized systematic review software (Review Manager 5) and a meta-analysis was conducted. A probability value of less than 0.05 was considered to be indicative of statistical significance. Publication bias was evaluated using the Begg rank correlation test and the Egger linear regression test.<sup>46,47</sup> These two tests were implemented using the R software (version 3.1.3), with the presence of publication bias implied when  $P < 0.05$ .

## Results

### Literature search and study selection

Initially 724 papers were identified using the keywords in our pre-specified literature retrieval process. After deleting duplicated articles, 444 records remained for further selection. After removing clearly irrelevant studies based on reading the title and abstract of each paper, 66 potentially pertinent articles remained. Among them, 3 articles were not published in English, 12 articles had incomplete data, 6 articles had ambiguous descriptions of planned or unplanned extubation, 2 studies involved noninvasive mechanical ventilation, 1 included individuals who didn’t receive mechanical ventilation via endotracheal tube, and 1 combined VAP and tracheobronchitis as one clinical outcome. This ultimately left 41 articles for inclusion in the meta-analysis. Fig. 1 shows a flow-chart of the process used to select the literature and the study entry criteria.

### Study characteristics and quality assessment

In total, 41 studies that involved 29,923 patients were included in our study. The basic characteristics are presented in Table 1. All of the articles that achieved a score of at least 5 points in the NOS appraisal were included in the meta-analysis. The included articles described 23 prospective cohort studies, 9 retrospective cohort studies, 3 randomized control trials, and 6 case–control studies. Among these 41 studies, 16 studies were related to VAP, 14 provided data on hospital mortality, and 20 provided data on ICU mortality. Moreover, 18 studies were conducted in Europe, 9 in the US, 6 in Asia, 4 in South America, 1 in Australia, and 3 in multiple continents. The method used to ascertain exposure factors and outcomes differed among the studies, with most using medical records, some using structured interviews blinded to the group divisions, while others used self-reports. Adjustment for potential confounders varied across studies, and most risk appraisals were adjusted for age, sex, duration of mechanical ventilation, length of stay in the ICU, Sequential Organ Function Assessment (SOFA) score at admission, Glasgow Coma Scale (GCS) score at admission, Acute

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