Subglottic secretion drainage for preventing ventilator-associated pneumonia: an overview of systematic reviews and an updated meta-analysis

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Subglottic secretion drainage is an effective measure to reduce mortality and VAP incidence, despite not improving the duration of mechanical ventilation or length of stay in ICU and/or hospital. http://bit.ly/2PeJLR1

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ABSTRACT Although several guidelines recommend subglottic secretion drainage as a strategy for prevention of ventilator-associated pneumonia (VAP), its use is not widespread. With the aim to assess the effectiveness of subglottic secretion drainage for preventing VAP and to improve other outcomes such as mortality, duration of mechanical ventilation and length of stay in the intensive care unit (ICU) or hospital, an electronic search of the Cochrane Library, MEDLINE, Web of Science and Embase was undertaken. Nine systematic reviews with meta-analysis (in the overview of reviews) and 20 randomised controlled trials (in the updated meta-analysis) were included. In the overview of reviews, all systematic reviews with meta-analysis included found a positive effect of subglottic secretion drainage in the reduction of incidence of VAP. In the updated meta-analysis, subglottic secretion drainage significantly reduced VAP incidence (risk ratio (RR) 0.56, 95% CI 0.48–0.63; I^2=0%, p=0.841) and mortality (RR 0.88, 95% CI 0.80–0.97; I^2=0%, p=0.888).

This is the first study that has found a decrease of mortality associated with the use of subglottic secretion drainage. In addition, subglottic secretion drainage is an effective measure to reduce VAP incidence, despite not improving the duration of mechanical ventilation and ICU and/or hospital length of stay.

Since publication of this article, it has been found that there is an error in the analysis presented in figure 3. This is indicated in the correction notice published in volume 31, issue 163 of the *European Respiratory Review*, and fully clarified by the authors in their correspondence to the editor published in the same issue (https://doi.org/10.1183/16000617.0013-2022)

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Introduction

Ventilator-associated pneumonia (VAP) is a hospital-acquired pneumonia developed in intubated patients receiving mechanical ventilation for ⩾48 h [1]. VAP is among the highest incidence hospital-acquired infections in intensive care units (ICU) affecting one-third of patients with mechanical ventilation and having an attributable mortality of 4.6–13% [2, 3]. The high incidence and mortality attributable to VAP are associated with increased resource utilisation burden generating a high economic cost to healthcare systems. Thus, cost-effective interventions that minimise the incidence of this adverse event are needed [4].

The necessary use of the endotracheal tube is one of the main risk factors for the development of VAP. It interferes with the normal protective upper airway reflexes, reduces effective coughing, causes irritation of the respiratory mucosa, increases the amount of mucus and promotes microaspiration of contaminated oropharyngeal secretions [5]. This microaspiration is the main mechanism for the entry of bacteria into the lower airway [6, 7], which could lead to VAP, depending on the quantity and virulence of aspirated bacteria and the patient's defence mechanisms [8].

Subglottic secretion drainage (SSD) has been studied extensively as a strategy for VAP prevention in such a way that >20 randomised controlled trials (RCTs) and several meta-analyses have assessed the effectiveness of this technique to reduce incidence of VAP. Nevertheless, although several guidelines recommend its use, the use of SSD is not widespread, probably due to the weakness of the quality of evidence [9–12].

For these reasons, the aim of this study was to synthesise the available evidence providing an overview of systematic reviews about the effectiveness of SSD to reduce VAP, length of stay in ICU and/or hospital, duration of mechanical ventilation and mortality. Additionally, an updated meta-analysis was conducted, which aimed to provide updated evidence about this topic.

Methods

This overview of systematic reviews and the updated meta-analysis were registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42019123699). The updated meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [13], and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [14] were followed.

Data sources and search methods

An electronic search of the Cochrane Library, MEDLINE (*via* PubMed), Web of Science and Embase (*via* Scopus) was undertaken, from inception to July 17, 2019, to identify systematic reviews with meta-analysis and RCTs that aimed to assess the effectiveness of SSD to prevent VAP.

The search strategy was "ventilator-associated pneumonia" AND ("subglottic secretion" OR "subglottic aspiration" OR "subglottic drainage" OR "subglottic suctioning" OR "endotracheal intubation" OR "endotracheal tube" OR "endotracheal cuff") AND ("meta-analysis" OR "systematic review" OR "randomised controlled trial"). There were no date or language restrictions. In addition, the reference list of published full-text articles and systematic reviews were manually scanned for relevant studies (meta-analyses and RCTs).

Selection criteria and data extraction

The inclusion criteria for the overview of systematic reviews with meta-analysis were 1) population: adult patients admitted to ICUs; 2) type of study: systematic reviews with meta-analysis of RCTs; 3) type of intervention: use of endotracheal tubes that allow SSD for VAP prevention compared with the standard endotracheal tube or non-SSD control group; 4) primary outcome: VAP incidence; and 5) secondary outcomes: ICU and/or hospital mortality, duration of mechanical ventilation, ICU and/or hospital length of stay and time to VAP.

Additionally, the identified independent RCTs that aimed to assess the effectiveness of SSD to prevent VAP in adults admitted to ICUs were selected and reviewed for an updated meta-analysis. Studies in children or paediatric ICUs and studies with inconsistent or insufficient data were excluded. Abstract publications were also excluded.

Two independent reviewers (DPP-C and AH-A) conducted both the selection of studies and data extraction. Duplicate studies and irrelevant titles were removed. Disagreements were solved by discussion, and if disagreement persisted, a third reviewer solved the conflict (VM-V). Reviewers were not blinded to authors, journals or institutions.

Data from the included systematic reviews with meta-analysis were extracted through a standard data extraction form; the original studies were used when specific data were missing. The following data from each included systematic review were extracted: 1) first author's name; 2) year of publication; 3) number of

included RCTs and participants; 4) study aim; 5) eligibility criteria (details of the included participants and details of the intervention studied); 6) data for the risk ratio (RR) for dichotomous outcomes (VAP incidence and mortality) and mean differences for continuous outcomes (duration of mechanical ventilation, ICU and/or hospital length of stay and time-to-VAP); and 7) any additional methodological information of potential importance, such as the assessment of methodological quality, risk of bias, limitations and quality of evidence.

Additionally, each RCT was reviewed for necessary data; when some data were not available, each systematic review with meta-analysis in which that study was included was also reviewed to acquire any missing data. The following data were extracted from each included article: 1) first author's name; 2) year of publication; 3) study name and study aim; 4) participant characteristics (number, age); 5) intervention characteristics (SSD method, co-interventions in the intervention group, VAP prevention bundle); and 6) VAP incidence, ICU and/or hospital length of stay, duration of mechanical ventilation, time to VAP and mortality both in the control and intervention groups.

Quality assessment

Two authors (DPP-C and AH-A) independently rated the methodological quality and the quality of evidence of each outcome of the systematic reviews with meta-analysis, and the risk of bias of the RCTs included.

Overview of reviews

Methodological quality of included reviews

The Assessment of Multiple Systematic Reviews (AMSTAR-2) tool was used to assess the methodological quality of each included review [15]. This tool consists of 16 items in total with simple response categories. These items include, among others, the presence of a protocol, comprehensiveness of the literature search and assessment of the risk of bias of the individual studies included in the systematic review.

Quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was used to assess the quality of the evidence related to the key outcomes when the reviews did not provide a GRADE assessment [16]. This system uses the following criteria to assign a quality level to a body of evidence [14]: 1) high (randomised trials or double-upgraded observational studies); 2) moderate (downgraded randomised trials or upgraded observational studies); 3) low (double-downgraded randomised trials or observational studies); 4) very low (triple-downgraded randomised trials, downgraded observational studies or case series/case reports).

Additionally, some factors which can increase and/or decrease the quality of evidence were considered: 1) limitations of the studies, such as the likelihood of bias (downgraded once if <75% of the included studies were at low risk of bias); 2) inconsistency including unexplained heterogeneity or inconsistency of results (downgraded once when the I^2 statistic was >50%); 3) indirectness, such as indirect population, intervention, control or outcomes; 4) imprecision manifested in wide confidence intervals; and 5) high probability of publication bias, which was downgraded once if there was evidence or high likelihood of publication bias [14, 17, 18].

The GRADEpro GDT software (www.gradepro.org) was used to perform the "summary of findings" tables from each systematic review included.

Updated meta-analysis

Risk of bias assessment

Risk of bias was evaluated according to the PRISMA recommendations [19]. The methodological quality of studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias [20]. This tool evaluates the risk of bias according to six domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other biases. In this quality assessment tool, each domain is considered as low risk, unclear risk or high risk of bias.

Data synthesis

Overview of reviews

For this section, data from the included systematic reviews with meta-analysis were extracted and presented in an "overview of reviews" table.

Appropriate effect sizes were used, presenting RR for VAP incidence and mortality, and mean differences for duration of mechanical ventilator, ICU and/or hospital length of stay and time to VAP. When the systematic reviews with meta-analysis did not report the suitable effect size, the original data presented was used to calculate it.

Updated meta-analysis

Standardised mean differences (SMD) and 95% confidence intervals for duration of mechanical ventilation and ICU and/or hospital length of stay, and the RR for VAP incidence and mortality were calculated between groups (intervention *versus* control) in each study and pooled using the Mantel–Haenszel fixed-effects model [21] or the DerSimonian–Laird random-effects model [22] depending on heterogeneity (fixed-effects model for I^2<50% and random-effects model for I^2>50%).

Heterogeneity was assessed using the I^2 statistic, and the following values were used for interpretation: low (0–40%); moderate (30–60%); substantial (50–90%) and considerable (75–100%); the corresponding p-values were also considered [14]. Sensitivity analyses were conducted by deleting each study from the model, and the pooled analyses were recalculated without each study to assess its influence on the overall SMD or RR. To test the presence of publication bias, a funnel plot and Egger's test were used [23].

In addition, an exploratory analysis was performed to analyse whether the technique used to diagnose VAP (bronchoalveolar lavage or protected specimen brushed *versus* endotracheal aspiration) could influence the overall effect size.

Statistical analyses were performed using STATA software (version 14; StataCorp, College Station, TX, USA).

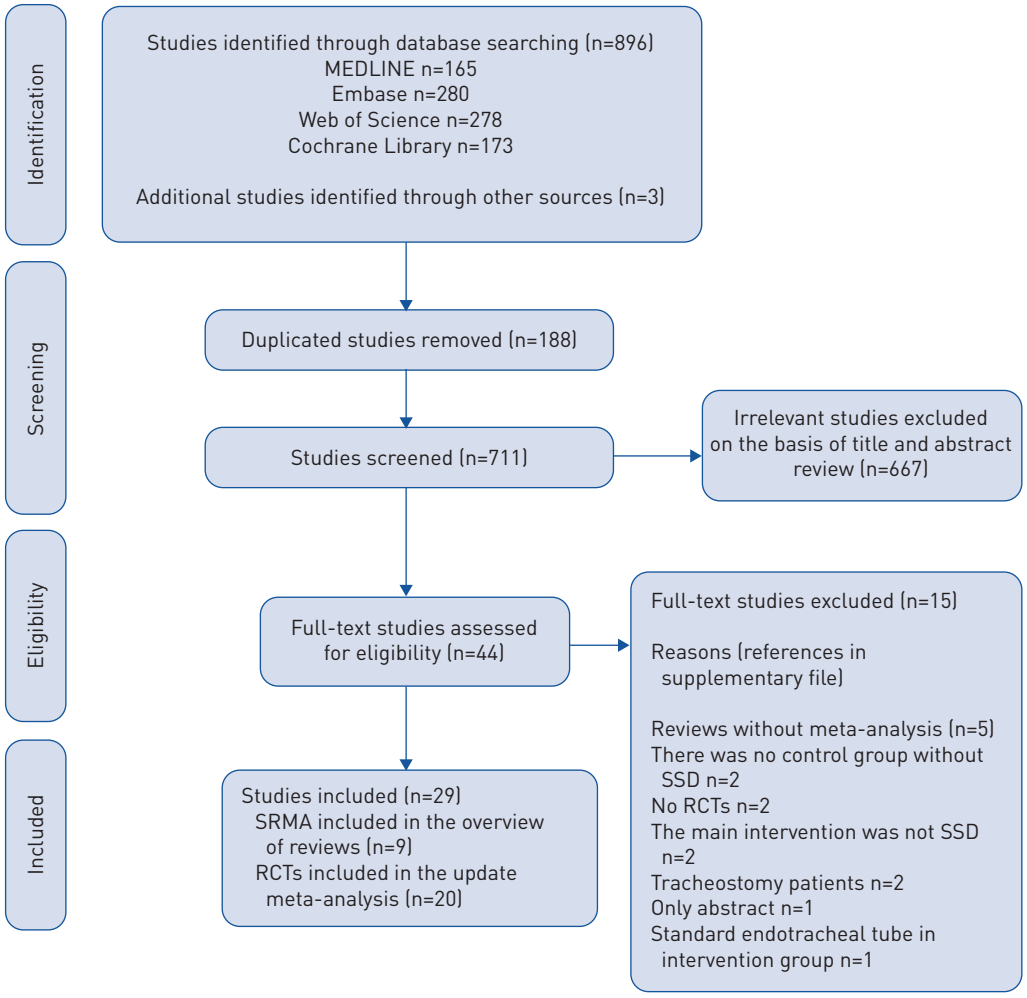

FIGURE 1 Literature search: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. SRMA: systematic reviews with meta-analysis; RCT: randomised controlled trial; SSD: subglottic secretion drainage.

Results

Details of the search screening process are presented in figure 1, and the reasons for excluding the 15 remaining full-text studies are shown in the supplementary material. Finally, 29 studies were included: nine systematic reviews with meta-analysis in the overview of reviews [24–32] and 20 RCTs in the updated meta-analysis [33–52].

Overview of reviews

Systematic reviews with meta-analysis characteristics

Supplementary table S1 shows the characteristics of the systematic reviews with meta-analysis included. Nine systematic reviews with meta-analysis that investigated the use of SSD for VAP prevention were included. These systematic reviews with meta-analysis were published between 2005 and 2018, and included 31 876 adults across 20 unique RCTs.

Two systematic reviews with meta-analysis excluded RCTs in which, in addition to using the SSD technique, other co-interventions were carried out in the experimental group [27, 28]. One systematic review with meta-analysis excluded RCTs in which the primary outcome was not VAP micro-organisms [32].

Outcome measures

An overview of the results of the included systematic reviews is provided in supplementary table S2. All included systematic reviews with meta-analysis reported data concerning VAP incidence. The RR of the SSD intervention on the reduction of VAP incidence ranged from 0.52 (95% CI 0.43–0.64) to 0.59 (95% CI 0.48–0.75), showing a significant decrease in incidence in all included systematic reviews with meta-analysis.

Four systematic reviews with meta-analysis reported the RR for overall mortality [24, 26, 28, 30], three reported the RR for ICU and hospital mortality separately [25, 27, 29], and one did not report the RR for mortality [31]; nevertheless, no review found a significant effect of SSD in reducing mortality.

The effect of SSD on the reduction of ICU and/or hospital length of stay was significant in four reviews [24, 28, 29, 31] ranging from 1.4 (95% CI −2.1–−0.08) to 4.27 (95% CI −7.36–−1.18) days fewer in the SSD group than in the non-SSD group.

The use of SSD shortened the duration of mechanical ventilation between 3.29 (95% CI −4.53–−2.05) and 1.08 (95% CI −2.04–−0.12) days, although some reviews did not find a significant reduction in the number of mechanical ventilation days [26, 27].

Additionally, five systematic reviews with meta-analysis [25, 27, 28, 30, 31] reported data for the time-to-VAP outcome, showing that the SSD intervention delayed the appearance of VAP between 2.66 (95% CI 1.06–4.26) and 4.04 (95% CI 2.6–5.47) days.

Quality assessment

Only one review presented a rating for the certainty levels of evidence and the strength of recommendations using the GRADE tool [25].

The methodological quality and the quality of the evidence of the remaining included systematic reviews with meta-analysis were assessed. The quality of evidence for each outcome in each systematic review with meta-analysis is shown in supplementary table S3. The main limitations decreasing the level of evidence were not reporting the I^2 value to assess heterogeneity or the I^2 value was >50%; not assessing publication bias; and not assessing the risk of bias of the RCTs included or when <75% of included RCTs were reported as having a low risk of bias.

The methodological quality evaluation applying the AMSTAR-2 tool showed that the main critical domains were the absence of a protocol registered before beginning the review (only one registered a previous protocol) [25]; the absence of justification for excluding studies (only three studies provided a list of excluded studies) [26, 28, 29]; and not assessing/reporting the risk of bias [27, 28] or the publication bias of the included studies [28, 32] (supplementary table S4).

Updated meta-analysis

Studies characteristics and participants

The 20 RCTs included were published between 1992 and 2017, and comprised 3684 adults receiving mechanical ventilation and admitted to ICUs [33–52]. The sample size of the studies ranged from 18 to 690 participants, including patients with neurological damage [35], cardiothoracic surgical patients [36, 43] and patients admitted to general and medical-surgical ICUs (supplementary table S5).

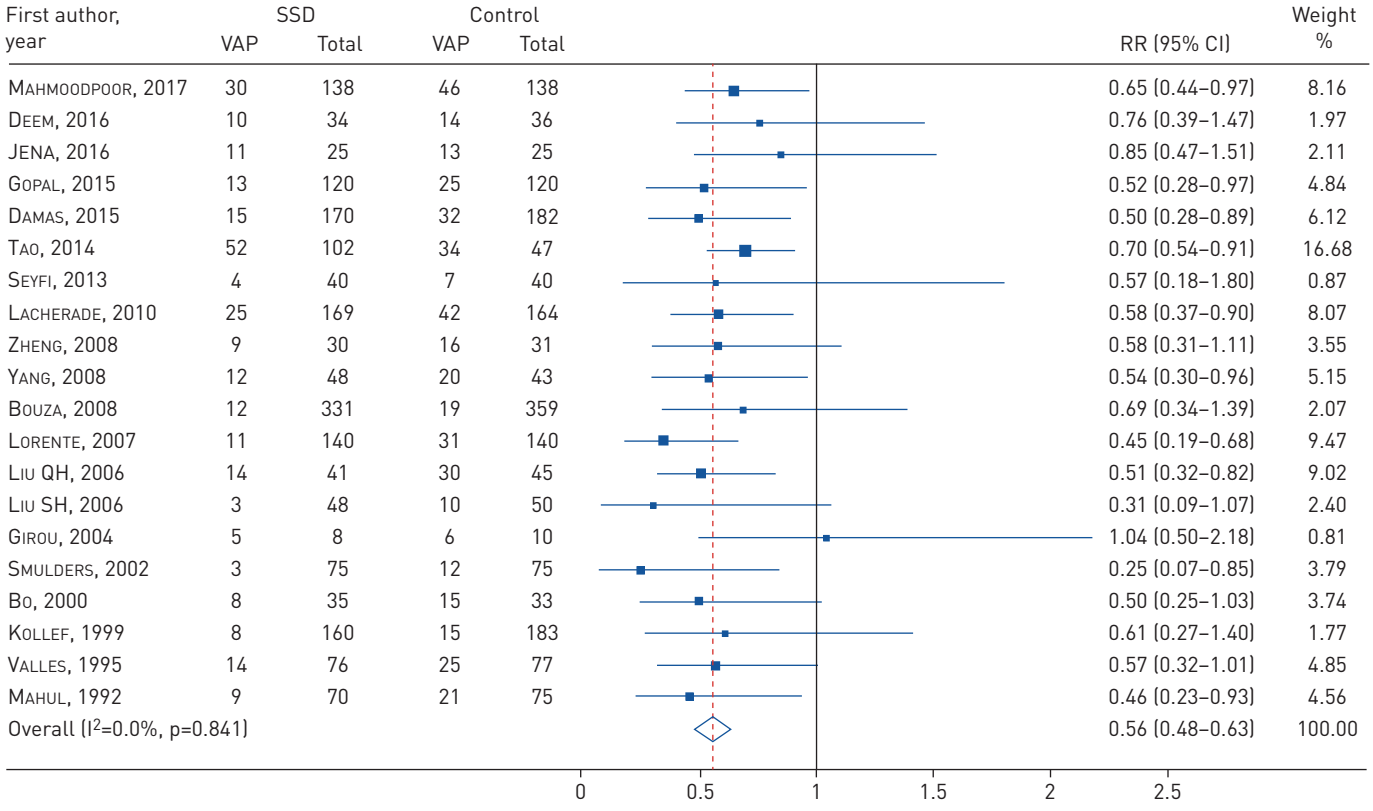

FIGURE 2 Forest plot comparing subglottic secretion drainage (SSD) *versus* non-SSD on the incidence of ventilator-associated pneumonia (VAP). RR: risk ratio.

Pooled estimates, sensitivity analysis, publication bias

VAP incidence

All RCTs provided data for VAP incidence; SSD significantly reduced VAP incidence (RR=0.56, 95% CI 0.48–0.63; I^2=0%, p=0.841) (figure 2). In the sensitivity analysis, when each study was removed, the results remained consistent across all exclusions.

Secondary outcomes

A significant difference was detected between the SSD intervention and non-SSD in mortality (RR 0.88, 95% CI 0.80–0.97; I^2=0%, p=0.888) (figure 3). Nevertheless, there was no association found between the use of the SSD technique and the decrease in ICU length of stay (SMD −0.12, 95% CI −0.26–0.03; I^2=67.4%, p=0.002), hospital length of stay (SMD −0.06, 95% CI −0.14–0.03; I^2=10.6%, p=0.348) and duration of mechanical ventilation (SMD −0.07, 95% CI −0.20–0.07; I^2=62.4%, p=0.003) (supplementary figure S1).

Time-to-VAP outcomes were not pooled because the only two new RCTs included in the updated meta-analysis did not report data regarding this outcome, which does not change the data presented in the previously published meta-analysis [25].

For the mortality outcome, the sensitivity analysis showed significant reductions after excluding the studies by Vallés *et al.* [51] and Liu *et al.* [45].

For all outcomes, both visual inspection of the funnel plot and Egger's test did not show substantial asymmetry, indicating the absence of publication bias.

The exploratory analysis performed to analyse whether the technique used to diagnose VAP (bronchoalveolar lavage or protected specimen brushed *versus* endotracheal aspiration) could influence the overall effect size showed that the use of SSD conveys a significant reduction in VAP in both subgroups, irrespective of the technique used to diagnose VAP.

Risk of bias assessment

Risk of bias is summarised in supplementary figure S2. 13 studies had a low risk of bias in the random sequence generation domain; however, only four had a low risk of bias in the allocation concealment item.

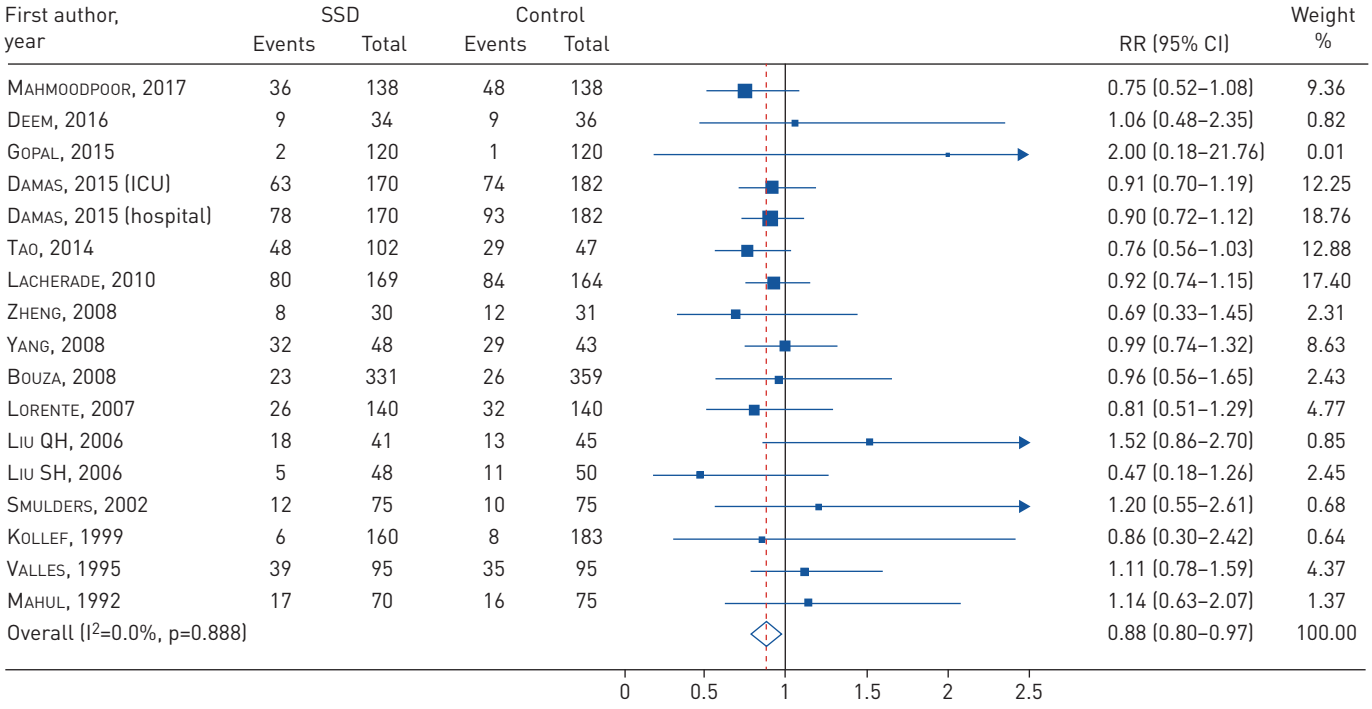

FIGURE 3 Forest plot comparing subglottic secretion drainage (SSD) *versus* non-SSD on mortality. RR: risk ratio; ICU: intensive care unit.

Eight studies had a low risk of bias in the blinding of personnel and outcome assessment, while four studies had a low risk of bias in all domains [33, 34, 37, 40].

Discussion

This work comprises an overview of nine systematic reviews with meta-analysis and an updated meta-analysis examining the effectiveness of SSD in reducing VAP incidence, ICU and/or hospital length of stay, duration of mechanical ventilation and mortality. SSD significantly reduced the incidence of VAP in all systematic reviews with meta-analysis and in the updated meta-analysis, but the results were not statistically significant for ICU and/or hospital length of stay and duration of mechanical ventilation. Nevertheless, contradictory results were observed regarding mortality between the overview of reviews and the updated meta-analysis results, with a significant trend towards less mortality being found in the updated meta-analysis.

One potential reason for such discordance in mortality could be a lack of power to detect significant effects, as Caroff *et al.* pointed out [26, 53]. Interestingly, as sample size increases in our updated meta-analysis (3200 *versus* 3684), a trend towards a decrease in mortality is seen, reaching statistical significance, which may suggest a true effect. Independently, a large epidemiological study concluded that even if the strategies for VAP prevention did not decrease mortality, which could be influenced by many factors or confounders, they provided advantages to patients, their families and the healthcare system [54].

Several guidelines recommend the use of SSD as part of a care bundle to prevent VAP [10–12, 55, 56]; however, this preventive measure is not widely used. Since those patients undergoing prolonged mechanical ventilation seem to benefit more from SSD, one reason for underusing SSD (along with a higher economic cost) could be the absence of factors allowing accurate prediction of prolonged mechanical ventilation. Moreover, it has been suggested that re-intubation with SSD may represent a risk factor for VAP [57, 58]. Regarding the cost of SSD, several cost-effectiveness studies have compared costs associated with the use of SSD endotracheal tubes *versus* standard endotracheal tubes among intubated patients [59–61]. Although specialised endotracheal tubes that allow SSD have a cost approximately seven times greater than conventional endotracheal tubes, all cost-effectiveness studies concluded that the SSD is a cost-effectiveness VAP preventive strategy [60, 61]. Another reason for the underuse of SSD as a VAP preventive strategy could be that improvements in other outcomes are not observed alongside the decreased VAP rates.

Our updated meta-analysis did not find a significant reduction in the duration of mechanical ventilation associated to the use of SSD. A review addressing this issue [53] concluded that because the use of SSD

reduces the mortality risk associated to VAP in 10% (an estimated mortality rate of 5–9% would be reduced by 0.5–0.9%), a sample size of tens of thousands would be necessary to reach statistical significance and thus demonstrate that SSD could reduce ICU and hospital mortality. According to this, although our updated meta-analysis provides a greater sample than those previously published, it may also be underpowered to obtain statistical significance. In addition, heterogeneity in the duration of mechanical ventilation is far greater than in mortality, thus implying that a larger sample size is needed to have enough statistical power. Nevertheless, consistent with the results found regarding mortality, the meta-analysis shows a trend towards a reduction in the duration of mechanical ventilation (along with ICU and/or hospital length of stay). In addition, other confounders such as different VAP preventive measures, treatments and patient's characteristics (comorbidities, age, main pathology, *etc.*) could influence this relationship.

In general, the capacity of SSD to reduce ICU and/or length of stay based on quality evidence is considered scarce. Some reviews have showed a significant decrease of ICU length of stay in the SSD group; nevertheless, these reviews had low levels of quality of evidence, which limits the reliability of the results [28–31]. In our updated meta-analysis, neither ICU nor hospital length of stay showed any improvement associated to the use of SSD.

Time to VAP was significantly increased in the SSD group in some systematic reviews; nevertheless, again, the GRADE quality of evidence was poor (low or very low for four studies [27, 28, 30, 31] and moderate for one [25]).

Our work has several limitations. First, the quality of evidence was only reported in two out of nine systematic reviews with meta-analysis. Second, the methodological quality of the systematic reviews with meta-analysis varied, ranging from critically low to high, although the majority had a low to moderate quality. Third, there was a wide heterogeneity in the population and in the type of ICUs included in the RCTs. Fourth, different diagnostic VAP criteria, such as quantitative cultures, bronchoalveolar lavage or clinical and radiologic criteria were used in the RCTs included. This could have a negative influence in terms of heterogeneity in our meta-analysis. Fifth, the use of SSD along with other VAP preventive measures did not allow us to distinguish the individual effect of SSD to prevent VAP. Moreover, these VAP bundles and/or co-interventions were different in the included studies, potentially representing a source of heterogeneity. Sixth, although a subgroup analysis by SSD techniques could be feasible in this meta-analysis, it was disregarded because recent meta-analyses [25, 62] did not report any differences between continuous and intermittent SSD to prevent VAP. Finally, due to the nature of the intervention, it could not be blinded for health staff, so only some RCTs were partially blinded.

The major strength of the present study is its development according to the Cochrane methodology and the PRISMA guidelines. Additionally, we provided a GRADE level of evidence for all included outcomes when the systematic reviews with meta-analysis did not provide a GRADE assessment. Moreover, a protocol of this overview was previously registered in PROSPERO. Finally, an updated meta-analysis including the most recent RCTs was performed, mainly yielding similar results to those obtained in previous meta-analysis but also finding a significant reduction in mortality associated to the use of SSD practice.

Conclusion

This overview provides an updated synthesis of available evidence about the use of SSD to prevent VAP, which found SSD to be an effective measure to prevent VAP and reduce mortality. However, since improvements in other outcomes such as the duration of mechanical ventilation and ICU and/or hospital length of stay were not observed alongside VAP rate improvements, further high-quality studies are necessary to elucidate the potential contribution of SSD in medical care.

Conflict of interest: None declared.

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