

Review Article

Efficacy of Intermittent and Continuous Subglottic Secretion Drainage in Ventilator-Associated Pneumonia Reduction among Critically Ill Ventilated Patients: An Integrative Review

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Abstract: Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in critical care settings and affects between 9%-27% of mechanically ventilated patients for more than 48 or 72 hours. One of the strategies that reduce the VAP incidence is subglottic secretion drainage (SSD) through a lumen attached to a specialised endotracheal tube. This integrative review aims to investigate the efficacy of intermittent and continuous SSD in reducing VAP among critically ill ventilated patients. A systematic electronic search was conducted via CINAHL, PUBMED, MEDLINE and COCHRANE using the key terms. A manual search was also conducted through the references of retrieved studies, Scopus, and Google Scholar. Sixteen relevant primary articles were identified; twelve studies were conducted on general ICU populations examining intermittent subglottic drainage (ISD) and continuous aspiration of subglottic secretions (CASS) while four other studies were undertaken in cardiothoracic ICUs investigating CASS. No studies were found concerning the efficacy of ISD in this setting. Current evidence has revealed that ISD and CASS appear to be effective in general ICU settings while CASS did show significant reduction among the cardiothoracic ICU population. It was found that ISD appears to be safer in terms of tracheal damage despite the concerns of secretion pooling. This integrative review concluded that ISD and CASS appears to be effective methods in reducing VAP incidence among general ICU populations. Further research is needed to investigate both methods among cardiothoracic patients. A large randomised controlled trial is also required to compare the two settings and to determine the optimal frequency and suction pressure that could minimise complications.

Keywords: Subglottic secretion drainage, ventilator-associated pneumonia, critically ill ventilated patients

INTRODUCTION

Hospital-acquired infection (HAI) or nosocomial infection, is a confronting clinical issue associated with treatment provided in any hospital setting [1]. HAI has a profound economic burden on health organisations and leads to increased morbidity and mortality among affected patients [1, 2]. It has been reported that hospital-acquired pneumonia (HAP) is the second most common type of HAI in health care facilities; however, it is the most recurrent one in

critical care settings and correlates with high mortality varying from approximately 15% to 57% [2]. ICU is a critical care setting where a variety of critically ill patients admitted with different life-threatening conditions are highly prone to contracting HAP. This is because that such patients require a range of life-saving interventions and intensive treatments in order to maintain normal body functions of body systems and to ensure their safety [3]. Mechanical ventilation (MV) is the intervention used to aid and substitute spontaneous

breathing and ventilation when patients' respiratory systems are compromised. This interference is implemented through two main types, which are invasive or non-invasive ventilation using specific instruments for each [4]. Most critically ill patients require invasive mechanical ventilation (IMV) in which mechanical ventilators are connected to an ETT linked to the trachea through the oropharynx cavity [4]. IMV is often effective at maintaining and saving patients' lives; however, it increases the vulnerability of ventilated patients to potential complications such as pulmonary barotrauma, acute lung injury, diaphragm atrophy and ventilator associated pneumonia (VAP) [1, 5].

VAP is a subtype of HAP and results from ventilator support following intubation. Its incidence increases with prolonged mechanical ventilation [3]. It has been reported that critically ill patients undergoing support from mechanical ventilators are at increased risk of developing VAP by 1% to 3% per day of ventilation [6]. The prevalence of VAP among mechanically ventilated patients is broadly ranged due to the disparity in diagnostic standards and definitions [7]. According to Klompas, Branson [8], The Society of Healthcare Epidemiology of America (SHEA) reported that 10%-20% of patients receiving MV develop VAP. The incidence has also been stated to range between 9%-27% and between 20%-70% of mechanically ventilated patients [9, 10].

According to the Centres for Disease Control and Prevention [11], VAP remains a contributing factor for morbidity and mortality in critical care settings despite collaborative efforts to control it. The mortality rate associated with VAP is varied; Safdari, Yazdannik [9] stated that crude mortality rate of VAP among ventilated patients is approximately 25%-50%. It is reported in another research paper that the crude mortality rate ranges from 25%-76% when VAP is caused by high-risk microbial agents [12]. This nosocomial infection is also a substantial determinant of increased length of stay, duration of MV and subsequently the financial burden on healthcare facilities [13]. The estimated cost to healthcare organisations per incidence of VAP has been found to range from \$10,000 to \$ 13,000 USD [5, 14]. VAP also has a further longitudinal economic impact, as the cost increases with utilisation of healthcare resources after ICU.

There has been debate around the accurate and consistent definition of VAP due to the non-specific findings that could be overlapped with other pulmonary diseases in ventilated patients [15]. Variability has also increased due to inconsistency of the guidelines implemented in different health organisations in terms of duration of MV at which VAP could occur [3]. The American Thoracic Society & Infectious Diseases

Society of America [16] defined VAP as pneumonia that occurs after 48 hours of MV and is characterised by the signs of systematic infection, including fever and altered white blood cell counts, the manifestation of new or progressive infiltrate on chest radiographs, and alterations in sputum features. The definition of VAP in CDC guidelines has the same clinical and radiological characteristics, but with a different time frame claiming that VAP could occur within 48 hours following intubation [11]. Kalanuria, Zai [3] also argued that VAP is an infection that develops between 48 to 72 hours after tracheal intubation and MV, and similar clinical features could be established.

Onset time is also a variable determinant of VAP definition in terms of categorisation, which involves two forms; early and late onset VAP. The incidence of VAP occurring within 96 hours of intubation refers to early-onset VAP, while late-onset VAP occurs within the first 10 days and is associated with poorer prognosis [12]. However, Waters and Muscedere [13] stated that early-onset VAP develops within five days of MV, while its occurrence after five days is referred to as late-onset VAP that results in detrimental outcomes. Definition of VAP can also differ based on the diagnostic method, as there have been no gold standard criteria for diagnosing such a severe infection [7]. Nevertheless, there are three main clinical methods through which diagnosis of VAP is usually carried out, namely laboratory results of microbiology, radiological features, and clinical signs of an ongoing infection, which may be unreliable due to the variability of clinician interpretation [12].

The American Thoracic Society & Infectious Diseases Society of America [16] recommended the use of endotracheal aspirate (ETA) and bronchoalveolar lavage (BAL) as diagnostic techniques for VAP confirmation. In addition, the Clinical Pulmonary Infection Score (CPIS) is considered a valid tool and was recommended by CDC. It incorporates clinical, microbiological, physiological and radiological findings to facilitate the diagnosis of VAP; The values of CPIS range between 0 and 12, and a total score of ≥ 6 correlates with the presence of VAP [7, 15]. Although such a valid tool's sensitivity and specificity is more than 90% [4], the diagnostic criteria remain debatable.

Endotracheal intubation followed by prolonged MV remains the main risk factor for VAP development [4]. Another potential risk factor is associated with extrinsic bacterial contamination of MV equipment, such as contaminated condensate in ventilator circuits that might be aspirated through the ETT [17]. ETT cuff can create a mechanical distal obstacle for the contaminated subglottic secretions that pool above the cuff and reduce gross aspiration [13]. However, it does not always ensure secured sealing due to the possibility

of insufficient inflation, and folds formation between the cuff surface and the tracheal mucosa, leading to micro-aspiration, which increases the chance of VAP occurring [18, 19].

The pathogenesis of VAP is mainly two main subsequent mechanisms: colonisation of the respiratory tract and aspiration of colonised secretions. The presence of the ETT is considered a foreign body that contributes to VAP, as its surface gets colonised by bacteria that then contaminate secretions [4, 20]. This is related to biofilm formation, which is characterised by aggregation of microorganisms on the ETT within hours of intubation, and acts as a reservoir for bacteria that create resistance against antimicrobial agents [12]. Endotracheal intubation also violates natural defence mechanisms, including cough reflex and mucociliary clearance of secretions, and facilitates a direct connection between the upper and the lower respiratory tract [21]. This causes the secretions to accumulate in the upper respiratory tract and become colonised by pathogenic virulent organisms, as well as translocate into the lower airways. These secretions pool over the ETT cuff, and subsequently leak down to the lung via a hydrostatic gradient [18].

The causative microbial agents of VAP mostly include two common aerobic organisms, gram-negative bacilli and gram-positive organisms [3]. Early-onset VAP is caused by pathogens that are sensitive to antimicrobial agents, including gram-positive organisms such as *Staphylococcus aureus*, and gram-negative bacilli such as *Klebsiella pneumoniae* and *Escherichia coli* [22]. In contrast, Late VAP infection is caused by multi-drug resistant (MDR) gram-negative bacilli, including the methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, and *Acinetobacter* spp, and is mostly accompanied by with poor prognosis [22]. According to Rewa and Muscedere [19], onset time (early or late onset VAP) and type of causative pathogens are considered risk factors that determine the VAP prognosis. Systematic antibiotic therapy remains the mainstay for treating VAP, and a broad-spectrum antibiotic is primarily chosen for all potential gram-positive and gram-negative bacteria [3]. Microbiology confirmation can assist in selecting the best antibiotic for the identified infectious agents, and checking the CPIS score while undergoing treatment is recommended to track the effectiveness of antibiotic therapy [19].

Avoiding endotracheal intubation or replacing it with non-invasive devices is the simplest and best method to reduce VAP incidence as such an approach helps maintain the natural host defences against microbial agents [12]. However, IMV is inevitable in most critical cases. Thus, shortening MV duration and extubating patients earlier through the weaning process

including daily sedation interruption can reduce the risk of developing VAP [4]. In addition, numerous isolated preventative strategies that target bacterial colonisation and micro-aspiration avoidance have demonstrated a reduction in VAP prevalence. They are mainly categorised into pharmacological interventions (prophylactic antimicrobial therapy, and oral chlorhexidine), and non-pharmacological interventions (body positioning, ETT cuff pressure control, silver-coated ETT, and ETT with SSD) [17, 23]. Commencing prophylactic short-term antibiotics and using silver coated ETTs upon intubation was found to be effective in decreasing biofilm formation and minimising the occurrence of early-onset VAP [24]. Elevating the head of the bed to 30-45 degrees was also found to minimise gastro-oesophageal reflux and thus reduce oral colonisation, along with the use of oral chlorhexidine [12]. In addition, using ETT with SSD to remove the colonised subglottic secretions, and controlling cuff pressure as a confounding factor, helped reduce micro-aspiration [17, 25].

These pathogenic-tailored strategies cannot stand alone to effectively reduce the incidence of VAP. Therefore, incorporating them into practice with consideration of infection control standards such as proper hand hygiene and wearing gloves could result substantially better outcomes [26]. Although many organisations including CDC and IDSA recognize these methods as VAP preventative strategies, their guidelines are inconsistent in terms of VAP bundles of routine care due to controversial evidence [23].

Unlike conventional ETTs, specialised ETTs involves a separate dorsal lumen that allows for SSD, and a new cuff designed to minimise folds created against tracheal mucosa in order to reduce leakage of contaminated subglottic secretions (Figure 1) [27]. SSD is a technique in which subglottic secretions are aspirated through two main methods: CASS or ISD. CASS is performed at a constant pressure connected to the wall suction, while ISD is conducted through either intermittent pressure or manual aspiration, using syringes, at a certain frequency [12]. Maintaining adequate cuff pressure along with effective oral decontamination should be considered prior to performing SSD to ensure better effectiveness [25]. This strategy has been recognised by the American Association of Critical Care Nurses (AACN), ATS and CDC as a VAP preventative method in ICUs, but is not been included in the routine VAP care bundle because of lacking solid data about its effectiveness, and of its association with the use of the modified ETT, which is not widely used despite its availability since 1992 [27, 28].

There have been different issues associated with this tube, including its costs and patient selection.

According to Depew and McCarthy [27], the cost-benefit ratio of procedures is a substantial factor when determining whether to implement them. It has been claimed that the ETT with SSD is estimated to cost \$15 per intubation and VAP incidence reduction is not guaranteed [27]. However, it is argued that VAP has been estimated to cost about \$1000 per incidence [14]. Speroni, Lucas [29] investigated the cost-effectiveness of this modified tube compared to the standard one and found that it could contribute in a substantial reduction in incidence of VAP and, subsequently, result in savings. Therefore, the cost can justify the benefit of reducing the incidence of VAP and the associated financial burden. Identifying and selecting patients who require MV for more than 48-72 hours upon intubation, especially in emergency situations, remains a challenge for clinicians, and is considered a significant obstacle for introducing this type of ETT as a routine practice upon intubation [30].

The current literature has supported the use of ETT-SSD as a VAP preventive measure. A multicentre randomised controlled trial (RCT) conducted on 333 adult ventilated patients revealed that VAP rate was reduced in the group with ETTs that allowed for SSD, compared to those with standard ETTs (14.8% and 25.6%, respectively) [26]. In a systematic review and meta analysis, Muscedere, Rewa [30] also compared the effectiveness of both tubes by synthesising the results of a range of RCTs published since 1992, and found that using ETTs with SSD resulted in a significant reduction in VAP of about 50%. Therefore, since 1992, research has addressed the effectiveness of using the modified ETT with SSD compared to the conventional one in reducing VAP, as a primary end point, and the associated outcomes, including duration of MV and mortality rate.

There is a lack of research that seeks to address and compare the effectiveness of the methods (CASS and ISD) through which the subglottic secretion aspiration is applied, and to investigate techniques and confounding factors such as suction pressure and ETT cuff pressure to better reduce the chance of developing VAP and maintain patients' safety. To the author's knowledge, no existing systematic or integrative reviews have been undertaken to explore the functions of ISD and CASS that were used in the previous studies when the modified ETT were compared to the standard one. This approach investigates the findings of primary relevant studies to evaluate the strength of evidence in order to ensure the best clinical practice, and identify gaps for future research. Therefore, the aim of this integrative review is to investigate the efficacy of intermittent and continuous subglottic secretion drainage in reducing the VAP incidence among critically ill ventilated patients through addressing the following questions:

Q1: Does intermittent and continuous subglottic secretion drainage reduce the incidence of ventilator-associated pneumonia among critically ill ventilated patients?

Q2: Is intermittent subglottic secretion drainage more safe than continuous aspiration in terms of tracheal mucosa injury and micro-aspiration?

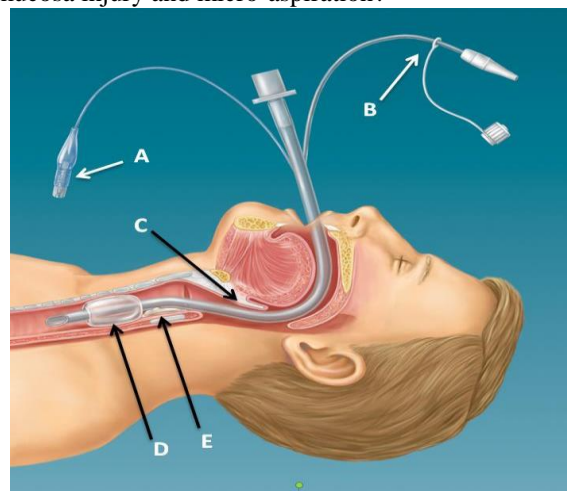


Fig-1. Specialized Endotracheal Tube with Subglottic Secretion Drainage (SSD)

- A:** lumen for inflating and deflating the cuff
- B:** lumen for SSD
- C:** Epiglottis
- D:** ETT cuff
- E:** Space where subglottic secretions pool and accumulate, and location of SSD orifice.

METHODS

The integrative literature review was chosen to be the framework conducting this review as it allows the reviewers and researchers to expand their search by combining a range of both experimental and non-experimental primary data, and to obtain a broader and holistic understanding of the topic being investigated [31]. This comprehensive methodology also helps explore the existing literature on a particular topic through the inclusion of primary relevant studies, identifies gaps in research for potential improvement, and evaluates strength in evidence [31]. According to Souza, Silva [32], such a method provides a rigorous and systematic six-stage process: formulating the issue, searching literature, data collection from identified articles, analysis of studies, discussion of results and integrative review presentation. Consistent with these stages, the review issue was initially identified the issue and the literature was explored to obtain a variety of relevant primary articles which their results were then analysed and discussed.

Search Strategy

A comprehensive electronic search was conducted in all searches using a range of databases

including CINAHL, PUBMED, MEDLINE, and COCHRANE. The aim of using different databases was to obtain broad and relevant literature that addressed the topic and answered the research question. The search was limited to the adult group of patients, English language, human, and peer reviewed articles that were published from 1992 to the present, as the SSD has been available since 1992. A manual search was also undertaken through locating studies from reference lists of identified articles, and searching for them in the databases of Google Scholar, Scopus, and Web of Science. This helped obtain further research that was not found during the electronic search for the review topic.

Following a preliminary search survey of the topic being explored, three primary search terms and MeSH headings were identified “ventilator-associated pneumonia”, “subglottic secretion drainage” and “critically ill ventilated patients”. Keywords that comprised each search terms were then established for the purpose of exploring the topic as broadly as possible. These keywords included glott*, subglottic, drainage, aspiration, suction* and secretions; vent*, ventilator-associated pneumonia, lung infection, nosocomial infection, respiratory infection, and hospital-acquired infection; ventilated patients, intensive care patients, and critical care patients. Using the chosen databases, the keywords of each term were then combined with either “AND” or “OR”, and the search outcomes for each primary search term were subsequently combined with “AND”. Searching for keywords of “vent”, “glott” and “suction” was undertaken with an asterisk (*) in order to search for all possible related words, such as ventilation, ventilator, ventilate, glottis, glottis, suctioning, and suction. Since SSD is not specific practice for nurses and can be implemented by other healthcare providers, including respiratory therapists (RTs), the search was not confined to a certain group of healthcare practitioners.

Inclusion and exclusion criteria

A range of inclusion and exclusion criteria were specified in order to narrow the large number of articles initially produced through searching, which included both primary and secondary research. In addition, these criteria guided the screening and eligibility process of identified articles so only primary articles pertinent to the research topic and research were used.

Inclusion criteria

- Studies that used SSD as the main intervention, and VAP as a primary outcome measure, which is the variable of interest.
- Studies that combined SSD with other preventative strategies.

Exclusion criteria

- Studies that did not examine the VAP as the variable of interest.
- Studies with inadequate information about the method of SSD and did not specify the implemented technique.

Search outcomes

The PRISMA flow diagram was followed to conduct the screening and eligibility process using the inclusion and exclusion criteria, in order to report the most relevant primary research for this review (Figure 2).

The preliminary electronic search through databases produced 513 articles, while the manual search generated 8 articles, yielded in a total of 521 articles. The numbers were reduced to 118 research papers after removing duplicates obtained from searching the databases. The screening process was then conducted by reviewing the titles and abstracts against inclusion and exclusion criteria. As a result, 97 articles were excluded as they were either secondary research, conference proceedings, qualitative research, without full text or irrelevant to the primary intervention and outcome measure specified in the inclusion criteria.

At this stage, 21 full text primary and quantitative articles remained, which were then assessed for eligibility. Of these, a further 5 studies were excluded due to different reasons. Two studies contained insufficient information about methods or techniques used for SSD while another 3 studies did not examine the VAP as a variable of interest. Subsequently, a total of 16 relevant studies, which included 10 RCTs, 3 retrospective cohort studies and 3 quasi-experimental studies, were retained and appraised.

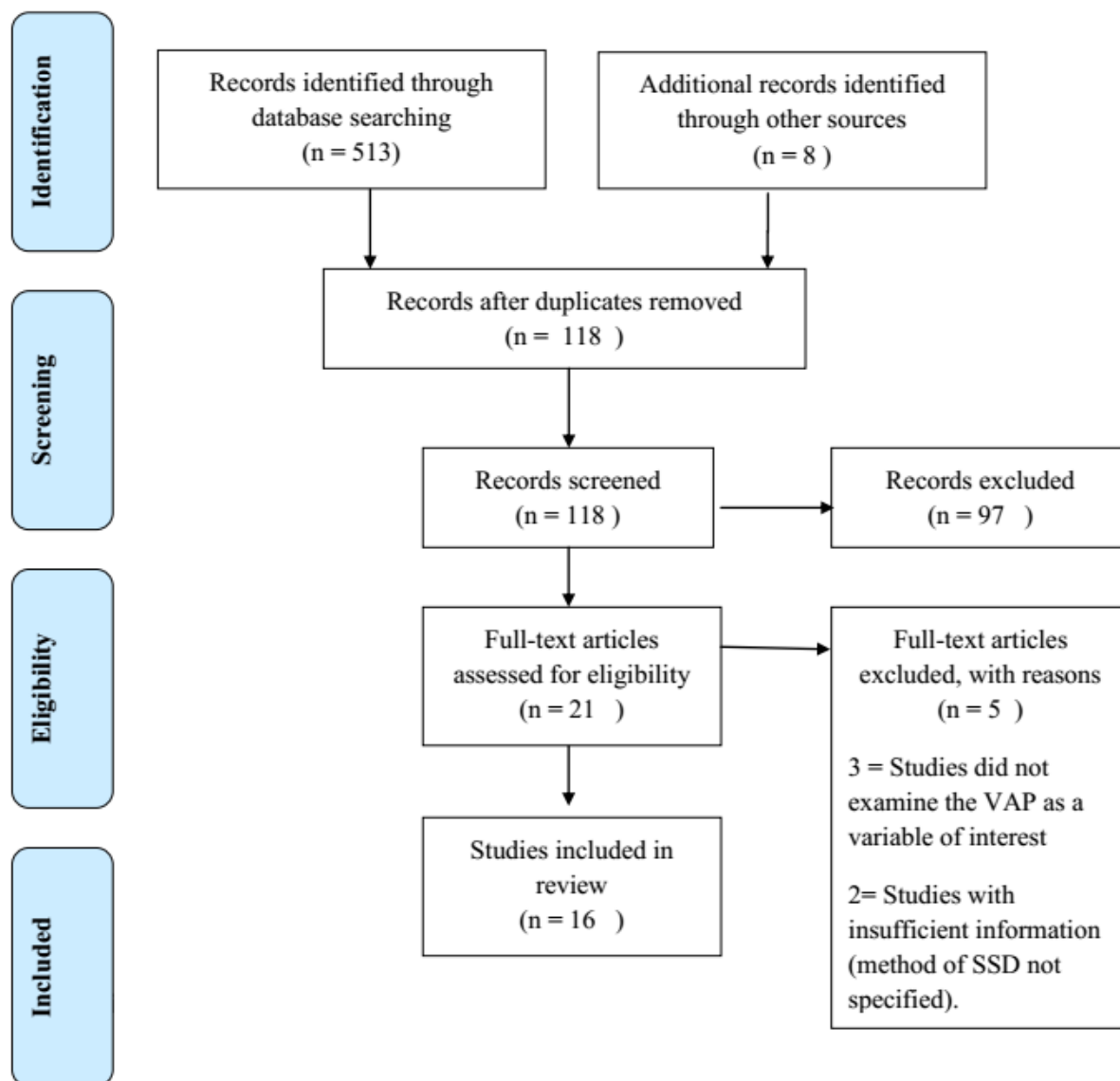


Fig-2: Search Process and Numerical Outcomes

Quality Appraisal of Studies

Quality appraisal is an effective approach that systematically investigates the reliability and relevance of identified research in certain areas. A Critical Appraisal Skill Program (CASP) is a tool that helps assess the quality and strength of different methodologies and designs of primary quantitative and qualitative research articles through a specific checklist of questions that targets methods and results [33].

In this integrative review, two CASP checklists were used to critically appraise the identified primary studies, which included 10 RCTs, 3 retrospective cohort studies, and 3 quasi-experimental studies. All 16 studies addressed the focussed primary intervention (SSD) and the primary outcome (VAP) in a variety of critically ill patients recruited from different settings. VAP incidence was measured in all studies and the results

were clearly reported. The RCTs had similarities in many aspects such as patient baseline characteristics and eligibility criteria; however, randomisation and allocation methods were varied when patients were randomly allocated into two groups of control and intervention. Healthcare practitioners, who involved in the studies, were not blind due to the nature of intervention, while the microbiologist and radiologist were blind to the intervention arm during the diagnosis process. In the cohort studies, patients were divided into intervention and control groups and their follow-up was complete. Authors also identified an important confounding factor (ETT cuff) in the method. This quality appraisal resulted in retaining all 16 studies which then were described in Table 1.

FINDINGS

The findings of the 16 articles that are described and analysed in Table 1 will be further elucidated and synthesised under relevant themes in order to achieve the aim of this integrative review and address the research question. There were main commonalities between studies in terms of the confounding variable (cuff pressure), diagnosis measures, blindness, allocation concealment, and enrolment criteria.

These studies were primarily conducted on two different populations of general ICU and cardiothoracic ICU patients. The distinction between the two populations was the focus on studying the effectiveness of subglottic aspiration on VAP incidence among the homogeneous sample of cardiac patients who could be extubated early, and among the general ICU heterogeneous patients who may stay on MV for a longer period of time. The methods of implementation for the subglottic drainage varied in the studies as some used the intermittent subglottic drainage (ISD) while others used continuous aspiration of subglottic secretion (CASS), and each one involved different techniques. In addition, some studies considered addressing the cost-effectiveness of using such a preventive strategy in terms of antibiotic use associated with VAP reduction.

Therefore, the findings will be synthesised and analysed within three relevant themes: ICU population, types of implementation, and cost-effectiveness. All 16 articles will be addressed in the first theme (12 studies in general ICUs and 4 studies in cardiothoracic ICUs). They will also be used to synthesise the findings about the types of implementation; 9 studies addressed ISD while 7 studies addressed CASS. Only three studies considered addressing the cost-effectiveness.

Table 1: Description and Analysis of The Studies

Author & Year	Setting	Participants	Study Design	Intervention & control groups	Diagnostic Criteria	Outcomes	Themes	Comments
1 Damas <i>et al.</i> , [34]	Five general ICUs of a University Hospital.	352 intubated patients and expected to require ventilation for ≥ 48 hours.	Randomised control trial.	Continuous Aspiration of subglottic secretion (CASS) (n=170) vs control group (n=182). CASS was implemented by wall suction pressure (100-150 mmHg).	VAP was microbiologically confirmed through quantitative bacterial culture from an endotracheal specimen, after it was suspected by radiological and clinical features.	CASS resulted in a significant reduction of VAP, as it occurred in 15 patients (8.8%) of SSD group, and 32 patients (17.6%) of control group (p=0.018). There was a reduction of DDDs of antibiotic use in the intervention group by 7.1%.	General ICU population. Types (CASS) Cost-effectiveness	Single blind and multicentre RCT. Tracheal mucosa damage associated with CASS.
2 Hudson <i>et al.</i> , [6]	Cardiothoracic ICU of a cardiac surgery centre and university research hospital.	4880 ventilated patients followed cardiac surgery and expected to require ventilation for ≥ 48 hours.	Retrospective cohort study.	Continuous Aspiration of subglottic secretion (CASS) (n=2450) vs Control group (n=2430). CASS was implemented by wall suction pressure (NS).	VAP was diagnosed through the radiological and microbiological approaches.	The implementation of CAAS after cardiac surgery in ICU was associated with a decreased incidence of VAP. VAP was 1.9% in the CASS group and 5.6% in the control group (p<0.0001).	Cardiothoracic ICU population. Types (CASS)	Single centre study. SSD lumen flushing to prevent occlusion. Report tracheal mucosa damage.
3	Medical-surgical	1135 ICU trauma	Retrospective cohort study.	Intermittent Subglottic	VAP diagnosis was carried out by	SSD group had lower VAP	General ICU population	Single centre study.

Hubbard <i>et al.</i> , [25]	(general) ICU.	patients intubated for more than 48 hours.		drainage (ISD) (n=468) vs control group (n=667). ISD was implemented by wall suction pressure (100 mmHg every 20s	quantitative broncho-alveolar lavage (BAL).	incidence (5.7% vs 9.3 % standard ETT), decreased MV days (12 vs 1), and decreased ICU length of stay (13 vs 16).	Types (ISD; wall suction pressure).	Tracheal mucosa damage.
4 Lorente <i>et al.</i> , [41]	Medical-surgical (general) ICU of the University Hospital of the Canary Islands.	656 patients who required MV for ≥ 48 hours.	Quasi-experimental study.	Intermittent Subglottic drainage (ISD) (n=415) vs control group (n=241). ISD was implemented by manual aspiration (10 ml syringe hourly).	Confirmation of VAP was done after clinical suspicion, through quantitative culture of ETA.	The incidence of VAP was lower in the ISD group with continuous control of cuff pressure (CCCP) compared with the standard group (P < .001).	General ICU population. Types (ISD; manual aspiration).	Single blind study. Continuous control of cuff pressure at certain pressure considering tracheal damage.
5 Lorente <i>et al.</i> , [42]	General ICU in Spain.	284 patients expected to undergo mechanical ventilation for more than 48 h.	Quasi-experimental study.	Intermittent subglottic secretion (ISD) (n=134) vs control group (n=150). ISD was implemented by manual aspiration (10 ml syringe hourly).	VAP was confirmed by quantitative culture of ETA after the radiological features and clinical signs were established.	The combination of ISD and continuous pressure control had further significant influence on VAP incidence.	General ICU population. Types (ISD; manual aspiration).	Single blind study. Continuous control of cuff pressure at certain pressure considering tracheal damage.
6 Granda <i>et al.</i>	. Cardiothoracic ICU of a cardiac surgery centre.	1399 Patients after major heart surgery	Quasi-experimental study.	Continuous Aspiration of subglottic	VAP was confirmed through ETA and if CPIS	The VAP incidences was measured before	Cardiothoracic ICU population. Types (CASS)	Single blind study.

<i>al.</i> , [45]	.	expected to be ventilated for ≥ 48 hours.		secretion (CASS) (before CASS, n=401; after CASS, n=998). CASS was implemented by wall suction pressure (100-150 mmHg).	scores were more than 6.	and after the intervention – per 1000 days-and reported as (23.92 vs 16.46 (P 1/4 0.04, respectively). There was a reduction of DDDs of antibiotic use in the intervention group, saving costs of \$ 3.945 per month.	Cost-effectiveness	Tracheal mucosa injury
7 Juneja <i>et al.</i> , [10]	General ICU of a tertiary care hospital, .	311 patients who required MV for ore than 72 hours.	Retrospective cohort study.	ISD group (n=150) vs control group (n=161). ISD was done by wall suction pressure 120 mmHg every20s.	VAP was diagnosed by CPIS tool.	The ISD reduces the incidence of VAP. VAP incidence was 7.8% in SSD group and 14.1% in control group.	General ICU population. Types (ISD; wall suction pressure).	Single centre study. Minimal tracheal damage
8 Lacherade <i>et al.</i> , [26]	Four French Medical-surgical (general) ICUs.	333 patients requiring MV for ≥ 48 h.	Randomized control trial.	Intermittent subglottic secretion (ISD) (n=169) vs control group (n=164). ISD was implemented by manual aspiration (10 ml syringe hourly).	Quantitative culture from tracheal aspirate used to confirm VAP, after clinical suspicion.	VAP was found in 25 patients (14.8%) of the SSD group, and 42 patients (25.6) of the control group (p=0.02). Early-onset VAP 2 (1.2%) vs. 10 (6.1%). Late-Onset VAP 23 (18.3%) vs. 32 (33%).	General ICU population. Types (ISD; manual aspiration).	Multicentre trial. Single blind RCT. Secretions pooling.

<p>9 Bouza <i>et al.</i>, [43]</p>	<p>A single cardiothoracic ICU.</p>	<p>714 patients, who were ventilated for more than 48 h.</p>	<p>Randomized Control trial.</p>	<p>Continuous Aspiration of subglottic secretion (CASS) (n=331) vs control group (n=359). CASS was implemented by wall suction pressure (100-150 mmHg).</p>	<p>VAP was microbiologically confirmed by quantitative bacterial culture, following clinical suspicion.</p>	<p>CASS minimizes the incidence of VAP. The result of VAP incidence for CASS group and control group was (26.7% vs 47.5%, respectively) p=0.04. There was a reduction of DDDs of antibiotic use in the intervention group compared to control group (1206 vs.1877, respectively).</p>	<p>Cardiothoracic ICU population. Types (CASS) Cost-effectiveness</p>	<p>Single blind RCT. Tracheal damage</p>
<p>10 Lorente <i>et al.</i>, [37]</p>	<p>A single medical–surgical (general) ICU.</p>	<p>280 patients who were expected to be on MV for ≥24 h.</p>	<p>Randomized control trial.</p>	<p>Intermittent Subglottic drainage (ISD) (n=140) vs control group (n=140). ISD was implemented by manual aspiration (10 ml syringe hourly).</p>	<p>Confirmation of VAP after clinical suspicion, after quantitative culture of tracheal aspirate.</p>	<p>ISD reduces the early and late-onset VAP. VAP occurred in 11 (7.9%) patients receiving SSD and 31(22.1%) in the control group (p=0.001). Early-onset VAP 5(3.6%) vs 15 (10.7%); Late-onset VAP 6 (9.5%) vs 16 (26.7%).</p>	<p>General ICU population. Types (ISD; manual aspiration).</p>	<p>Single blind study. Secretions pooling</p>
<p>11</p>	<p>General ICU of a French</p>	<p>18 medical ICU patients</p>	<p>Randomized control trial.</p>	<p>Continuous Aspiration of</p>	<p>VAP confirmed by quantitative</p>	<p>Tracheal colonization and</p>	<p>General ICU population.</p>	<p>Single blind RCT.</p>

Girou <i>et al.</i> , [38]	University Hospital.	on MV for >5 days.		subglottic secretion (CASS) (n=8) vs control group (n=10). CASS was implemented by wall suction pressure (-30 mmHg).	culture of tracheal secretion after clinical suspicion.	incidence of VAP was not significantly modified by continuous SSD. 7 episodes of VAP occurred the SSD group and 6 episodes in control group.	Types (CASS).	Secretion pooling and micro-aspiration
12 Smulders <i>et al.</i> , [40]	Medical–surgical (general) ICU.	150 patients on MV for ≥72 h.	Randomized control trial.	Intermittent Subglottic drainage (ISD) (n=75) vs control group (n=75). ISD was implemented by wall suction pressure (100mmHg every 20 seconds).	VAP was diagnosed by clinical and radiological features. .	ISD reduces the incidence of VAP. The results of VAP incidence in the SSD group and control group were (4% vs 16%, respectively; P=0.014).	General ICU population. Types (ISD; wall suction pressure).	Single blind RCT. Injurious tracheal mucosa
13 Kollef <i>et al.</i> , [44]	Cardiothoracic ICU.	343 patients expected to be on MV after cardiac surgery.	Randomized control trial.	Continuous Aspiration of subglottic secretion (CASS) (n=160) vs control group (n=183). CASS was implemented by wall suction pressure (less than 20 mmHg).	VAP was diagnosed by clinical and microbiological approach. .	VAP was found in 8(5.0%) patients of CASS group and 15(8.2%) of control group; P=0.238.	Cardiothoracic ICU population Type (CASS).	Single blind RCT. Secretions pooling and potential micro-aspiration.
14	General ICU of a university	39 critically ill patients with	Randomised control trial.	Intermittent Subglottic	VAP was diagnosed and	There was a reduction on	General ICU population.	Single blind RCT.

Metz <i>et al.</i> , [39]	Hospital.	expected duration of MV ≥ 3 days.		drainage (ISD) (n=25) vs control group (n=14). ISD was implemented by manual aspiration (20 ml syringe every 3 hour).	confirmed by tracheal secretions or Broncho-alveolar lavage (BAL) after radiological and clinical suspicion,	VAP incidence and bacterial colonisation.	Types (ISD; manual aspiration).	Prolonged Interval of manual aspiration-potential subglottic secretions pooling.
15 Valles <i>et al.</i> , [36]	A Spanish medical-surgical (general) ICU.	190 patients expected to receive MV for ≥ 72 h	Randomised control trial.	Continuous Aspiration of subglottic secretion (CASS) (n=76) vs control group (n=77). CASS was implemented by wall suction pressure (100-150 mmHg).	VAP was confirmed by the quantitative culture of secretions obtained through Broncho-alveolar lavage (BAL), after clinical suspicion.	The result showed that the use of CASS reduced the incidence of VAP (19.9 episodes in CASS group vs 39.6 episodes in control group).	General ICU population. Types (CASS).	Single Blind RCT. Tracheal mucosa injury.
16 Mahul <i>et al.</i> , [35]	Medical surgical (general) ICU.	145 patients expected to need MV for ≥ 72 h.	Randomised control trial.	Intermittent subglottic drainage (ISD) (n=70) vs control group (n=75). ISD was implemented by manual aspiration (10 ml syringe hourly).	A Broncho-alveolar lavage (BAL) was performed if an infiltrate appeared on chest X-ray to confirm VAP.	ISD showed a twice decreased incidence of VAP in ISD group (13% vs 29.1%, control group);	General ICU population. Types (ISD; manual aspiration).	Single blind RCT. Secretions pooling.

ICU Population

Of the 16 identified studies that examined the effectiveness of intermittent and continuous subglottic aspiration on VAP incidence, 12 were conducted on general ICU populations (Table 1; studies: 1,3,4,5,7,8,10,11,12,14,15 and 16) while only 4 were carried out on cardiothoracic ICU populations (Table 1; studies: 2,6,9 and 13).

a. General ICU Patient Population

The 12 articles included a range of study designs: 8 RCTs, 2 retrospective cohort studies and 2 quasi-experimental studies that were undertaken in different centres and on varied sample sizes. These studies examined the association between the incidence of VAP, as a primary outcome, and the draining of subglottic secretions either continuously or intermittently, among that population.

Incidence of VAP

A randomized controlled trial conducted by Mahul, Auboyer [35] was the first study to examine the incidence of VAP on a general ICU population by implementing ISD as a preventative strategy. This is because the endotracheal tube with SSD was first made available in 1992. Although this single centre study enrolled a relatively small sample size ($n=145$), the VAP occurrence showed a significant reduction among the intervention group, by nearly half, when the subglottic secretions were intermittently drained in comparison to the control group (13% and 29%, respectively). Valles, Artigas [36] supported these findings in a single centre RCT that used a different method of SSD on a total of 190 mechanically ventilated ICU patients who were equally allocated into intervention and control groups; each group had 95 patients. This study revealed a significant association between continuous subglottic aspiration and the incidence of VAP associated with gram-positive cocci; VAP was reduced by 14%.

Three RCTs conducted by Damas, Frippiat [34], Lacherade, De Jonghe [26] and Lorente, Lecuona [37] showed a significant relationship between the use of SSD and early and late-onset VAP among the general ICU population. In a single centre trial, Lorente, Lecuona [37] found a significant reduction in both early and late-onset VAP incidence among the intervention group compared to the control group when the subglottic secretions were intermittently aspirated; early onset-VAP was 3.6% versus 10.7%, respectively while late-onset-VAP was 9.5 versus 26.7%, respectively, whereas a recent multicentre trial that was conducted on a large sample ($n=333$) revealed a similar trend of significant difference in early and late-onset VAP between the two groups (see Table 1) [26]. A most recent multicentre study that recruited a larger sample size ($n=352$) of general ICU populations showed

consistent findings in the reduction of early and late-onset VAP incidence among the intervention group when the secretions were continuously aspirated [34]. VAP was microbiologically diagnosed in all three studies by an expert panel who were blind to the intervention using CPIS; this could contribute in decreasing detection bias regarding VAP incidence. Two of the studies were multicentre trials, so their findings could be generalised.

However, Girou, Buu-Hoi [38] contradicted these findings and failed to reveal any statistically significant difference in the VAP incidence between the intervention and control groups when the same technique was implemented (5 episodes versus 6 episodes, respectively). Another two RCTs showed consistent findings in regard to VAP incidence among the intervention group who received ISD and were recruited from a general ICU [39, 40]. While Metz, Linde [39], who enrolled only 39 patients, found no statistically significant effect of this method on subglottic colonisation and the incidence of VAP, Smulders, van der Hoeven [40] noted in their RCT that the VAP incidence also had a similar statistical trend in the intervention group. Although these three single centre RCTs showed insignificant reductions, their sample sizes, claimed by the authors as a limitation, may have precluded any firm conclusion about effectiveness of ISD.

In another study design, two recent retrospective cohort studies (Table 1; studies: 3 and 7) that were carried out in two different general ICU settings on a large sample of cohorts revealed a significant reduction in the incidence of VAP with intermittent aspiration of subglottic secretions. Juneja, Javeri [10] conducted their study on a heterogeneous sample of ICU patients and confirmed a significantly lower incidence of VAP in the intervention group, whereas Hubbard, Veneman [25] investigated the occurrence of VAP among a group of trauma patients and concluded that VAP was significantly decreased in patients who received subglottic drainage. Despite the fact that data were retrospectively obtained from the ICU patients files, which may pose a concern of selection bias, the conclusions reached by studies validated the findings of earlier RCTs that reported a substantial decrease in VAP incidences among the general ICU population.

In two quasi-experimental studies (Table 1; studies 4 and 5), the incidence of VAP was investigated on different large samples ($n=284$ and $n=656$) from single ICUs whose subglottic secretions were intermittently aspirated, along with the use of continuous cuff pressure control system as a confounding variable. Both studies revealed a further influence and benefit of combining these approaches

because it not only resulted in a reduction in VAP incidences among the intervention group, which was diagnosed by assessors blind to the intervention, but also decreased the possibility of secretion leakage into the lungs (micro-aspiration) [41, 42]. Even though such a study design lacks randomisation, their findings were consistent with other RCTs.

b. Cardiothoracic ICU patient population

The four studies carried out on cardiothoracic surgical patients involved 2 RCTs, 1 retrospective cohort study, and 1 quasi-experimental study (Table 1; studies: 2,6,9 and 13). All studies examined the VAP incidence when subglottic secretions were continuously drained among such a group of patients.

Incidence of VAP

Bouza, Perez [43] and Kollef, Skubas [44] conducted two different single centre RCTs to examine VAP incidence reduction on cardiothoracic patients with the use of continuous subglottic aspiration. Bouza, Perez [43] recruited a large sample of such patients (n=714) and revealed a significant reduction in VAP incidence, by nearly half, among the intervention group; VAP was diagnosed by a blinded investigator and showed a reduction by 20%. This blindness could avoid detection bias in VAP incidences. However, Kollef, Skubas [44] conducted their study on 343 patients who underwent cardiac surgery and found no significant difference in VAP incidence between the intervention and control groups (5% and 8.2%, respectively; P=0.238). This conclusion was consistent with a quasi-experimental study that revealed no strong association between using continuous aspiration and the occurrence of VAP in patients who underwent cardiac surgery [45]. A recent retrospective study by Hubbard, Veneman [25] that was undertaken on a homogeneous sample of cardiothoracic patients also failed to show any significant decrease in the incidence of VAP. Nevertheless, the retrospective approach may pose a concern regarding selection bias, and therefore compromise the reliability and generalizability of findings.

Types of Implementation

There have been two main types of implementation, Intermittent subglottic drainage (ISD) and continuous aspiration of subglottic secretions (CASS), addressed in the 16 articles. Of which, 9 studies examined the ISD (Table 1; studies: 3,4,5,7,8,10,12,14, and 16) whereas the other 7 studies focused on CASS (Table 1; studies: 1,2,6,9,11,13, and 15).

a. Intermittent Subglottic Drainage

The 9 articles that examined the influence of intermittent secretion drainage (ISD) on the incidence of VAP through the implementation of different

techniques, included 5 RCTs, 2 retrospective cohort studies, and 2 quasi-experimental studies. There were two techniques by which the subglottic secretions were intermittently drained: manual aspiration (6 studies: 4,5,8,10,14, and 16) and wall suction pressure (3 studies: 3,7, and 12).

Manual aspiration

This type of draining was performed in 6 studies (4 RCTs and 2 quasi-experimental studies) through the connection of a syringe to the SSD lumen and aspiration of the subglottic secretions at certain intervals. It was implemented along with adjusting the cuff pressure as a confounder to minimise the chances of pooled secretions leaking into the lungs between the manual aspirations.

Lacherade, De Jonghe [26], Lorente, Lecuona [37] and Mahul, Auboyer [35] found in their RCTs a significant association between implementing ISD, using manual aspiration with syringes at a certain frequency, and the incidence of VAP among intubated patients. While Lacherade, De Jonghe [26] and his colleagues, in a multicentre trial with a large heterogeneous sample, found a significant reduction in early and late-onset VAP by more than 11% in the intervention group when the subglottic secretions were manually aspirated every one hour by a 10 ml syringe in addition to maintaining the cuff pressure between 20-30 cmH₂O, Lorente, Lecuona [37] revealed findings consistent with the use of similar procedures in their RCT undertaken in a single ICU; VAP incidence between the intervention and control group was 7.9% versus 22.1%, respectively. These two RCTs supported the first RCT carried out by Mahul, Auboyer [35] to investigate the impact of ISD using manual aspiration on the incidence of VAP which showed a similar significant trend of VAP reduction; VAP incidence decreased by nearly half in the ISD group. Nevertheless, Metz, Linde [39] contradicted these findings when they examined VAP through aspirating the subglottic secretions every 3 hours using a 20 ml syringe, as they failed to report any significant difference between the groups. Implementing this technique every 3 hours may impact the reliability of findings because it could allow the secretions to pool and then leak into the lungs, causing VAP.

In another study design, Lorente, Lecuona [41] and Lorente, Lecuona [42] conducted quasi-experimental studies on two different samples using a 10 ml syringe to manually aspirate the subglottic secretions every one hour and found a significant decrease in the incidence of VAP among the intervention groups. Both studies adjusted the cuff pressure, as an important confounding variable, at a certain pressure by using a continuous controlled system, claiming that such an approach ensures

consistent pressure that reduces secretion leakage into the lower respiratory tract and minimises tracheal mucosa injury. This continuous controlled system was firstly introduced in these studies and showed a further benefit and influence when it was combined with manual aspiration.

Wall suction pressure

This technique was implemented in 3 studies which investigated the effectiveness of ISD on incidence of VAP, using wall suction at certain pressures and frequencies, concerning tracheal damage. The cuff pressure was also maintained and monitored every 4H to maintain adequate deflation. The studies included 1 RCT, and 2 retrospective cohort studies.

Smulders, van der Hoeven [40] assessed the VAP incidence among 150 mechanically ventilated patients in a single ICU and failed to reveal or report a significant incidence of VAP in the ISD group in comparison to the control group when the subglottic secretions were intermittently drained with wall suction pressure of more than 100mmHg every 20 seconds for a duration of 8 seconds. Such a relatively small size may affect the detection of significant results. However, two recent retrospective cohort studies carried out by Hubbard, Veneman [25] and Juneja, Javeri [10] showed a significant association between ISD using wall suction pressure and the incidences of VAP. While Juneja, Javeri [10] found that VAP incidence reduced significantly with the use of wall suction pressure of 100 mmHg every 20 seconds, Hubbard, Veneman [25] noted, in a larger sample size (n=1135), similar findings when they intermittently drained subglottic secretions by using wall suction pressure of 120 mmHg with 20-second intervals and 10-second durations. Both studies reported that cuff pressure stayed between 20-30 cmH₂O as per the data retrospectively obtained from patients' files. Despite the fact that retrospective studies may pose a concern in regard to selection bias, consistency among the findings could strengthen the reliability of such findings.

b. Continuous Aspiration of Subglottic Secretions

Seven studies used continuous aspiration of subglottic secretions (CASS) as a preventative strategy in order to assess its effectiveness on VAP reduction among intubated patients (Table 1; studies: 1,2,6,9,11,13 and15). The SSD lumen was continuously kept connected to the wall suction pressure in all 7 studies because the subglottic secretions had to undergo constant aspiration at a certain pressure that could prevent tracheal damage. The cuff pressure was maintained and monitored frequently; it serves as confounding variable that assisted in reducing secretion leakage. At the same time, permeability of the SSD lumen was also checked. Of the 7 studies, there were 5

RCTs, 1 quasi-experimental study, and 1 retrospective cohort study.

Wall suction pressure

Bouza, Perez [43], Damas, Frippiat [34] and Valles, Artigas [36] concluded in their RCTs' findings that the implementation of CASS through a constant wall suction negative pressure between 100 -150 mmHg was significantly effective in the reduction of VAP among ventilated patients. All authors kept the cuff pressure between 20-30 mmHg to ensure effective sealing and adequate inflation that would potentially reduce micro-aspiration. Valles, Artigas [36] monitored the cuff pressure every 4 hours while Bouza, Perez [43] and Damas, Frippiat [34] performed it once per shift. The patency of the SSD lumen was also checked, and 10 ml of distilled H₂O was administered if the subglottic was negative.

Damas, Frippiat [34] conducted a multicentre trial on a large number of ICU patients (352) and found that only 8.8% of the intervention group developed VAP compared to 17.6% in the control group whereas Bouza, Perez [43], in a larger sample size, revealed a statistically significant reduction in VAP incidence by 20.8% among the intervention group (26.7% CASS group vs. 47.5% control group; P=0.04). These findings supported the conclusion of the RCT undertaken in a single centre by Valles, Artigas [36], who found a similar trend of VAP incidence in the CASS group despite the fact that there was no difference between the groups in terms of gram-negative colonisation in the subglottic area.

In contrast, another 2 RCTs, and a retrospective cohort and quasi-experimental studies (Table 1; studies: 2,6,11 and 13), showed no statistically significant difference in the incidence of VAP when the subglottic secretions were continuously aspirated by wall suction pressure. These studies maintained the confounding variable (cuff pressure) between 20-30 mmHg, and monitored this variable during every shift, and performed the procedure at various suction pressures. No study reported the permeability assessment of SSD lumen. Girou, Buu-Hoi [38] assessed the association between the continuous system of subglottic aspiration with a negative pressure of -30 mmHg and VAP incidence on a total of 18 intubated patients and failed to reveal any significant reduction in the occurrence of VAP. A large sample RCT conducted by Kollef, Skubas [44], who used CASS at a low suction pressure that did not exceed 20mmHg, supported this finding. They found that this procedure did not influence VAP incidence to a significant degree in the intervention group when compared to the control group (5% and 8.2%, respectively). However, the small sample recruited in Girou, Buu-Hoi [38]'s study may precluded firm conclusion, and the insufficient pressure

used in both studies to aspirate the subglottic secretions could caused secretions to pool above the ETT, permitting micro-aspiration and increasing the chance of developing VAP.

A recent retrospective cohort study concluded that there were an insignificant decrease in VAP among the CASS group connected to the continuous draining system with a pressure set as per the guidelines (unspecified) [6]. Granda, Barrio [45] found, in their quasi-experimental study, consistent results that revealed no significant difference in VAP incidences before and after the continuous aspiration that was performed with a negative pressure between 100-150 mmHg.

Cost-effectiveness

Of the 16 articles, only 3 studies addressed the effectiveness of using an endotracheal tube with CASS on antibiotic use and cost savings (Table 1; studies 1,6 and 9). Of these, there were 2 RCTs, and 1 quasi-experimental study.

Bouza, Perez [43], using an RCT, found a lower daily defined antibiotic doses (DDDs) with implementation of CASS among the intervention group when compared to the control group (1206 vs.1877, respectively). This finding was supported by Damas, Fripiat [34] who revealed similar findings regarding the total number of antibiotic days; 1696 in the CASS group and 1965 in the control group. In addition, Granda, Barrio [45] reported a decrease in the daily use of antimicrobial agents in the intervention group (CASS group), resulting in cost savings of \$ 3.945 per month.

DISCUSSION

VAP is considered the most common nosocomial infection in critical care settings and its pathogenesis mainly undergoes two subsequent processes: colonisation of the respiratory tract and aspiration of colonised secretions down to the lung [3]. Subglottic colonised secretions that pool above the ETT cuff are considered to be a main contributor to aspiration and incidence of VAP. To avoid these consequences, subglottic secretions could be drained, whether intermittently or continuously, through the SSD lumen attached to the modified ETTs in mechanically ventilated patients [27].

A range of primary studies have focused on the effectiveness of using the ETT with SSD compared to the standard tube on VAP incidence in both general and cardiothoracic ICU settings. The available systematic reviews and meta-analyses conducted by Dezfulian, Shojania [46] and Muscedere, Rewa [30] have analysed the results of the RCTs published since 1992 and compared the two tubes in relation to the incidence of VAP; however, the availability of primary research that addresses and compares the ISD and CASS, and the

empirical evidence on their efficacy is lacking. In addition, no known systematic or integrative reviews have been carried out to investigate these methods implemented in the available research. The use of this approach to evaluate the methods of SSD could contribute in evaluating the strength in evidence to ensure the best clinical practice. Therefore, this integrative review has investigated the available primary research examining the efficacy of ISD and CASS in VAP reduction among critically ill ventilated patients.

During the screening of 118 research studies obtained after removing the duplicates. The author excluded 97 studies because most of these were not presented as full texts and it was difficult to extract sufficient information about the implementation of SSD methods. Other studies included secondary research that provided general information about the SSD, pooled results from a number of primary studies (systematic reviews), and qualitative research that, naturally, fail to provide empirical evidence. A further five articles were removed from the remaining 21 articles; 2 of them did not specify the methods of SSD and this could, potentially, under or overestimate the efficacy of the intervention while 3 articles did not investigate VAP as the variable of interest.

The findings of this review that were synthesized under the relevant themes revealed variability in VAP reduction with the use of SSD as a pathogenic-tailored strategy. The effectiveness of SSD appears to have been examined more among ICU populations than those were admitted to cardiothoracic ICUs. The outcomes of the incidence of VAP were inconsistent in regards to the efficacy of SSD examined on general ICU patients in the 12 studies (Table 1; studies 1,3,4,5,7,8,10,11,12,14,15, and16). The five RCTs (Table 1; studies 1, 8, 10, 15, and 16) showed a significant reduction in VAP, including early and late onset VAP, among SSD groups. Two of these were multicentre trials conducted by Lacherade, De Jonghe [26] and Damas, Fripiat [34], who recruited large sample sizes (n= 333; n= 352; respectively); this could contribute to wider generalizability and applicability in terms of the findings results. Although data were retrospectively collected in two studies (Table 1; studies 3 and 7) and this may pose a concern of selection bias, their findings were consistent with the conclusion of these RCTs.

In addition, findings were supported by 2 recent quasi-experimental studies (Table 1; studies 4 and 5) that showed a further VAP reduction, especially with the combination of a continuous cuff pressure system, to be a confounding variable. Such a study design lacks randomisation; however; recruiting large sample sizes in these studies could strengthen their

results. Zheng, Lin [47] carried out a study in an ICU setting and found a consistent trend of VAP reduction when subglottic secretions were intermittently aspirated (SSD group=30% vs. Control group=51.6%; $p < 0.5$). Similarly, the incidence of VAP was reduced by 21.5% when subglottic secretions were continuously drained, revealing a significant reduction [48]. In addition, a systematic review by Muscedere, Rewa [30] analysed the pooled results of studies that examined both ISD and CASS and concluded that SSD reduced VAP by 50% and recommended its use in clinical practice. Only three single centre studies included in this review (Table 1; studies 11, 12, and 14) failed to show a significant difference in the development of VAP between the intervention and control group. Nevertheless, the relatively small sample size of these studies, which was claimed by the authors as a limitation, may compromise the reliability and generalizability of findings. Therefore, it seems that most of the studies included in this review and the other two supporting trials that were undertaken in general ICU settings had a consensus about the significance effect of SSD on VAP reduction among general ICU populations.

In regards to the cardiothoracic ICU population, 4 studies were conducted to investigate the effectiveness of SSD on VAP among such a population. Surprisingly, all of those studies used continuous aspiration to drain the subglottic secretions. Three studies (Table 1; studies 3, 6, and 13) found an insignificant association between the use of this method and the occurrence of VAP in this population. Of which, one collected the data retrospectively, presenting a concern of selection bias (Table 1; study 3), while another quasi-experimental study (Table 1; study 6) lacked randomisation. Thus, this might weaken the findings which, then, could not be generalised in cardiothoracic ICU settings. In contrast, only a single blind RCT by Bouza, Perez [43] showed a significant reduction, by nearly half, among the SSD group. Although this study was single blind due to the nature of intervention, the authors recruited a large sample of patients ($n=714$) and allocated patients into two groups through a concealed method. This reduces the bias and causes the findings to be more reliable. Apart from those studies included in this review, the author identified no further studies in the literature concerning this population.

Due to the scarcity of studies that examine the ISD among the cardiothoracic population and the mere one study showing significant findings from CASS, it is difficult to assert the efficacy of SSD, as a VAP preventative strategy, among such a population. The author believes that those patients are often extubated early and they are almost homogeneous in their characteristics, which could make it difficult to detect a

significant difference between the intervention and control group. Despite the fact that general ICU populations are heterogeneous in their characteristics and have further comorbidities, and more compromised physical health than cardiothoracic ICU patients, it has been concluded that ISD and CASS were effective in general ICU settings and could be feasibly be applicable into clinical practice. However, a large multicentre RCT is required to compare the two settings with ISD and CASS to determine SSD efficacy among both populations.

In terms of the types of implementation, the findings showed that ISD can be conducted through either manual intermittent aspiration using a syringe or wall suction pressure at varied suction pressures and frequencies, whereas CASS was implemented by using continuous wall suction pressure at varied suction pressures. Inconsistent results were obtained from the articles with regard to VAP incidences when the subglottic secretions were intermittently and continuously drained.

The six articles that addressed manual aspiration as a technique of ISD (Table 1; studies 4,5,8,10,14, and 16) revealed consistent outcomes of VAP incidence in all cases except for one RCT (Table 1; study 14) that failed to show any significant reduction in VAP among the intervention group. Those studies that showed a significant trend of reduction in VAP used 10 ml syringes, hourly, to aspirate the secretions (Table 1; studies 4,5,8,10,16). Of these studies, both the multicentre trial conducted by Lacherade, De Jonghe [26] and the study which recruited large sample size ($n=280$) by Lorente, Lecuona [37] were consistent with the first RCT undertaken by Mahul, Auboyer [35], who found a reduction in VAP by 16%. Although the two recent quasi-experimental studies (Table 1; studies 4 and 5) lacked randomisation, they applied the same procedure and supported the findings of these RCTs. Therefore, the consistency of the results in regards to using the same technique at a constant frequency could strengthen their reliability and applicability. A study conducted by Safdari, Yazdannik [9] investigated ISD and showed supportive results; VAP was significantly reduced among the ISD group compared to the control group (26.3 vs 47.4%, respectively). The only study that contradicted these findings was the one undertaken by Metz, Linde [39], who implemented manual aspiration with a different frequency (every 3 hours). However, recruiting a small sample size ($n=39$) may compromise the generalizability of results while aspirating the colonised secretions at such a frequency could allow the secretions to pool above the ETT cuff, increasing the chance of micro-aspiration.

The draining of subglottic secretions through intermittent wall suction pressure has been addressed in 3 studies (Table 1; studies 12, 3, and 7) and revealed inconsistent findings in terms of VAP incidence among ISD groups. Every study implemented the procedure at a certain suction pressure (100 mmHg) and the same frequency (every 20 second); however, they differ in the duration of suction. Data were retrospectively collected in 2 studies (Table 1; studies 3 and 7) and such a study design raises the concern of selection bias, which may weaken the results; nevertheless, their conclusions were consistent in terms of obtaining significant reduction in the incidence of VAP with the implementation of this technique. The single centre RCT that Smulders, van der Hoeven [40] conducted recruited a relatively small sample size and did not find any significant data; however, conducting a single centre study with a small amount of participants may limit the generalizability of the findings to other settings. The main issue with this technique appears to be the potential tracheal mucosa injury associated with the duration and frequency of suction due to the fact that the subglottic secretions might not be accumulated within few seconds. Suys, Nieboer [49] reported in their study that the intermittent wall suction pressure with excessive frequency and suction duration may cause tracheal injuries in intubated patients with few subglottic secretions.

There was variability in the findings obtained from the 7 articles (Table 1; studies 1,2,6,9,11,13, and 15) that examined the efficacy of CASS through the wall suction pressure on incidence of VAP. The three RCTs (Table1; studies 1,9, and 15) that showed a significant reduction in VAP incidence implemented the CASS with a constant negative pressure of 100-150, maintained the cuff pressure (confounding variable) between 20-30 cmH₂O, which is claimed to be effective for sealing, and performed flushing to ensure the patency of the SSD lumen. One study was a multicentre trial with a large sample size (n=352) that was conducted by Damas, Fripiat [34], who found lower incidence of VAP among the CASS group when compared to the control group (8.8% vs 17.6%; respectively); this could contribute to wider generalizability of the findings. The other 2 single centre RCTs revealed the same trend of VAP reduction; Bouza, Perez [43] recruited larger number of participants (n=714) and found a reduction of 20% while Valles, Artigas [36] found a reduction of 19.5%. The consistency in the procedure and conclusions of these studies could strengthen the results. These findings are consistent with the result of RCT conducted by Yang, Qiu [48] who found a significant reduction in VAP incidence with the use of CASS of 21% among the intervention group. In addition, when a continuous oral suction was connected to 100 mmHg in an RCT by Chow, Kwok [50], the VAP incidence was significantly reduced.

The other four studies, which included 2 RCT (Table 1; studies 11 and 13), 1 retrospective study (Table1; study 2) and 1 quasi-experimental study (Table 1; study 6) failed to show any significant difference in VAP incidences between the CASS group and the control group. Every study reported the potential associated complications, including the occlusion of the SSD lumen and tracheal mucosa damage. Such issues could compromise the efficacy of CASS and the safety of patients. Both Kollef, Skubas [44] and Girou, Buu-Hoi [38] conducted a single centre RCT that recruited a small sample size and used inadequate pressure to aspirate that subglottic secretions; this could allow for micro-aspiration and may not reveal strong evidence that can be generalized. In addition, the quasi experimental study lacked effective randomisation and did not specify the suction pressure and this may could compromise the reliability of findings while the veracity of the retrospective study findings could be impacted by the potential selection bias. Berra, De Marchi [51] conducted a randomised animal study on 30 sheep to investigate the efficacy of CASS and found marginal decreases in the bacterial colonisation of the lungs, and widespread damage to the tracheal mucosa of the sheep. Although CASS ensures continuous aspiration that minimize the pooled colonised secretions, it was reported that up to 50% of ventilated patients who received CASS experienced injurious prolapse of the tracheal mucosa [49]. This raises a concern regarding the ethical issues associated with compromising patients' safety; however, providing effective training about the proper technique and procedure could assist in minimising the mucosal damage and ensuring patient safety [52].

The findings were consistent in regards to the cost-effectiveness of the use of CASS investigated in the three studies, among which were 2 RCTs (Table1; studies 1 and 9) and 1 quasi-experimental study (Table1; study 6). They showed lower daily antibiotic doses associated with a reduction in VAP incidences among the intervention group, which resulted in saving costs. Although the findings concluded by Granda, Barrio [45] might be impacted by selection bias, they were consistent with the other 2 RCTs. One RCT by Damas, Fripiat [34] was a multicentre trial with a large sample size and that could both strengthen and generalize the results. Two cost-analysis studies by Shorr and O'Malley [53] and Speroni, Lucas [29] showed similar findings, revealing that the use of CASS is an effective strategy that could result in VAP reduction and subsequently save costs in terms of antibiotics use. Although the literature supports the use of this modified tube in which the SSD can be implemented as it has been found to be cost-effective, The identification of patients who require MV for more than 48-72 hours and will benefit from SSD remains a

barrier to using this tube widely in routine practice [30]. However, establishing a protocol for using this tube upon incubation can overcome such an obstacle and introduce this into routine clinical practice. Mareiniss, Xu [54] stated that non-operative and emergency intubation, as well as admission with critical neurological issues and acute kidney injuries appear to be the most cases associated with ventilation for more than 48 or 72 hours.

This review sought to determine the efficacy of continuous and intermittent SSD in reducing VAP among critically ventilated patients and has resulted in providing recommendations for clinical practice. It appears that ISD and CASS are effective and can be applied in general ICU settings. However, implementing ISD with manual aspiration appears to be safer in terms of mitigating tracheal damage despite the concern of secretion pooling above the cuff. Healthcare professionals need to be cautious with these issues when implementing these methods in ventilated patients. In addition, their inclusion in VAP bundle guidelines could be recommended in general ICU settings; however, further research is needed.

The findings of this review have also identified many gaps in current research. First, research needed to examine the ISD on cardiothoracic ICU patients as there was no current research has been found addressing its effectiveness among this population. Second, further research is needed to confirm the efficacy of SSD among the general ICU population, and a large multicentre RCT would be warranted to compare the two populations to determine the efficacy of SSD in both general and cardiothoracic ICUs. Third, no trial was carried out to compare the two types of SSD (ISD and CASS), so a multicentre trial is required to determine which of the two types is superior in terms of effectiveness of the two types in terms of effectiveness and complications. Fourth, further research is needed to investigate whether manual aspiration is more effective than wall suction pressure when the subglottic secretions are intermittently aspirated to ensure better and safe practises. Fifth, the findings of this review indicate the necessity for future research to identify the best frequency and suction pressure of ISD, and to determine the appropriate suction pressure of CASS in order to ensure optimal and safe procedures that improve health care and maintain patient safety. Finally, the conclusions of the three articles that addressed cost-effectiveness need to be supported by further research to further confirm the cost savings in terms of antibiotic use.

The findings of this integrative review highlight the variability of methodological quality in articles examining the influence of ISD and CASS on VAP. The analysis was also impeded by a range of

limitations in the study designs such as retrospective data and quasi-experimental designs that pose a concern in regard to selection bias, a lack of randomisation, a small sample size, and the inability to avoid the awareness of health care worker to the intervention arm due to the nature of interventions. Nevertheless, the expert panel that diagnosed VAP through a microbiological approach were blind to the intervention implemented in the studies; this could reduce the detection bias. In addition, there was a lack of multicentre studies, as only two studies of the 16 articles were multicentre RCTs; this could compromise the generalizability of findings. Most of the included trials, especially those that were undertaken in general ICU settings, enrolled heterogeneous population, contributing to the possibility of differing the risk ratios across the studies. The variability of the ventilation duration (48 or 72 hours) that were required for enrolment in the studies was also inconsistent due to the inconsistency of the VAP definition recognised by different guidelines. However, the findings of articles with such design limitations are substantiated by high-quality studies. In addition, those studies have reflected ongoing research in this practice, seeking evidence for the best clinical practice.

One of this review's strength lies in the fact that it has included primary studies with different designs that has been conducted since 1992 on both populations. This covers the period in which the SSD was first available to the present day, and only exclude studies that did not specify the methods of SSD, to avoid the over or underestimation of intervention efficacy, and those did not examine the VAP as a primary endpoint. Nevertheless, it was limited to investigating the VAP incidence rather than including the secondary outcomes that could result in obtaining a broader understanding.

CONCLUSION

The aim of this integrative review was to investigate the efficacy of intermittent and continuous subglottic secretion drainage in reducing ventilator-associated pneumonia among critically ill ventilated patients. Findings revealed inconsistent findings about the efficacy of ISD and CASS on VAP incidences among general ICU populations, but the majority of studies showed the same trend of significance for both methods, indicating their efficacy in VAP reduction among those patients. In regards to cardiothoracic ICUs, the use of CASS has resulted in an insignificant reduction in VAP incidences among cardiothoracic populations except one study showed significant findings, while no study exist that have studies ISD. Thus, the efficacy of SSD as preventative strategy among cardiothoracic ICU populations need to be further investigated. ISD can be implemented through manual aspiration and wall suction pressure, and the

findings revealed a variability in outcomes. Nevertheless, manual aspiration appears to be effective and has fewer complications such as mucosal injury, despite the potential secretion pooling associated with its use. Additionally, an inconsistency in findings was seen in the studies that addressed CASS; however, most of them showed its positive influence on VAP incidence. Tracheal mucosa damage was the main concern raised in these studies. CASS was also found to be cost-effective in terms of reducing the antibiotic daily use associated with VAP incidence reduction. Although the current studies provide promising and potential benefits of ISD and CASS, further well-designed and robust research is required to tackle the gaps identified in this review to obtain further strong evidence for best clinical practice.

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