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Pharmacotherapy interventions in ventilator care bundles for preventing VAP in adults: A literature review

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Abstract

Care bundles have been introduced into practice to prevent ventilator-associated pneumonia (VAP) in critically ill adults. The Institute for Healthcare Improvement (IHI) proposed a worldwide implementation of the "IHI ventilator bundle" consisting of interventions to reduce the rate of VAP. Updates to these clinical practice bundles occur based on new evidence yet change within institutions is lagging. This review aims to discuss the latest updates in clinical evidence on the pharmacotherapy included in these bundles to aid institutional quality improvement measures.
The 2022 Society for Healthcare Epidemiology (SHEA) practice recommendations for preventing VAP were used to identify key pharmacotherapy interventions that are commonly incorporated into hospital care bundles. Three interventions were focused on for this review: (1) Multimodal sedation and analgesia strategies; (2) Oral care with chlorhexidine; and (3) Stress ulcer prophylaxis. A comprehensive literature search was conducted utilizing PubMed, focusing on MeSH terms involving the interventions identified for further review. Literature published from August 2021 to September 2024 was focused on for this project. Findings from these studies were reviewed, summarized, and compared alongside the corresponding 2022 SHEA/IDSA/APIC update recommendations to either reinforce or challenge current VAP bundle practices.

This literature review identified a correlation with the pharmacotherapy interventions recommended in the 2022 SHEA/IDSA/APIC update on current VAP bundle practices. The findings support the preferential use of non-benzodiazepine sedatives associated with better clinical outcomes. Additionally, chlorhexidine for oral care with toothbrushing is not recommended due to a lack of strong evidence supporting its effectiveness in reducing VAP rates. Conflicting evidence regarding stress-ulcer prophylaxis remains, warranting the need for further high-quality studies to draw definitive conclusions. Overall, healthcare facilities should ultimately continue to prioritize quality improvement and stay informed on the latest recommendations to effectively prevent VAP.

Keywords: Ventilator associated pneumonia, ventilator bundle, sedation, stress ulcer prophylaxis

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Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia developing in patients who have received mechanical ventilation for at least 48 hours. [1] VAP is potentially a severe complication in these patients who are already critically ill with high morbidity and mortality. [2] As a result, VAP care bundles are a concept that acute care hospitals were introduced to VAP prophylaxis in critically ill patients.

In December 2004, the Institute for Healthcare Improvement (IHI) proposed the worldwide implementation of the "IHI Ventilator Bundle" which consisted of four interventions: (1) head of bed elevation by 30 to 45 degrees, (2) daily sedation vacation and assessment of readiness to extubate, (3) peptic ulcer disease (PUD) prophylaxis, and (4) deep vein thrombosis (DVT) prophylaxis. Subsequently, in 2010, the IHI added a fifth intervention: (5) daily oral care with chlorhexidine. [3]

Updates to these clinical practice bundles occur based on new evidence over the years. Nonetheless, changes within institutions are lagging. This comprehensive literature review aims to discuss and explore the latest updates in clinical evidence on the pharmacotherapy included within the VAP care bundles to aid institutional quality improvement measures.

Methods

The SHEA/IDSA/APIC practice recommendation on "strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and non-ventilator hospital-acquired pneumonia in acute-care hospitals" is a 2022 update with significant contributions from representatives of multiple organizations. [4] Sponsored by the Society of Healthcare Epidemiology (SHEA), it is a product of a collaboration between SHEA, the Infectious Diseases Society of America (IDSA), the American Hospital Association (AHA), the Association for Professionals in Infection Control and Epidemiology (APIC), and The Joint Commission.

The purpose of the SHEA/IDSA/APIC 2022 update was to highlight practical recommendations for assisting acute care hospitals in implementing strategies to prevent ventilator-associated pneumonia. Interventions were defined as either "essential practices," "additional approaches," "generally not recommended," or "definitively not recommended." "Essential practices" are recommendations that all acute care hospitals should implement. On the other hand, "additional approaches" are recommendations that can be considered in hospitals where their healthcare-associated infection prevention programs (HAIs) are not controlled following the adoption of essential practices. Within the SHEA/IDSA/APIC 2022 update, some of the critical interventions identified include: (1) daily sedation interruption, (2) daily assessment of readiness to extubate, (3) daily oral care with chlorhexidine; (4) feeding, (5) head of bed elevation by 30 to 45 degrees, (6) stress ulcer prophylaxis, among others.

The SHEA/IDSA/APIC 2022 update on practice recommendations for preventing ventilator-associated pneumonia was utilized to identify critical pharmacotherapy interventions commonly incorporated into hospital care bundles. Out of the six key interventions previously mentioned, three interventions were focused on for this review:

1. **Multimodal sedation and analgesia**
2. **Daily oral care with chlorhexidine**
3. **Stress ulcer prophylaxis**

In addition, the SHEA/IDSA/APIC 2022 update's intended population was adults, children, and neonates. However, this literature review will only discuss and focus on practice recommendations to prevent ventilator-associated pneumonia in adult patients.

A comprehensive literature search was conducted utilizing PubMed, focusing on MeSH terms involving the three interventions identified for further review. Because the supporting evidence to the SHEA/IDSA/APIC 2022 update was searched up until August 2021, literature published from August 2021 to September 2024 was focused on for this project. Findings from these studies were reviewed, summarized, and compared alongside the corresponding SHEA/IDSA/APIC 2022 update recommendations to either reinforce or challenge current VAP bundle practices.

SHEA/IDSA/APIC 2022 Update's Recommendations & Supporting Evidence

Multimodal sedation & analgesia strategies

Defined as an "essential practice,"

"It is recommended to preferentially use multimodal strategies and medications other than benzodiazepines to manage agitation (Quality of Evidence: High)."

These recommendations are based on the SCCM 2018 practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. The guidelines are a result of extensive research and expert consensus in the field. They recommend using a multimodal approach with the use of analgesics for pain, reassurance for anxiety, and antipsychotics, dexmedetomidine, and/or propofol for agitation. [3] Two meta-analyses also showed that dexmedetomidine and propofol are associated with a shorter duration of mechanical ventilation and ICU length of stay compared to benzodiazepines. [6-8]

Oral care with chlorhexidine

Defined as an "essential practice,"

"It is recommended to provide daily oral care with toothbrushing without chlorhexidine (Quality of Evidence: Moderate)."

Two studies, one being a meta-analysis, showed that daily toothbrushing significantly lowers ventilator-associated pneumonia rates, shorter duration of mechanical ventilation, and length of stay in the ICU. [9-10] However, there is a significant controversy surrounding the use of chlorhexidine in oral care. Several meta-analyses of randomized controlled trials and observational studies suggest that oral care with chlorhexidine may increase mortality rates in mechanically ventilated patients. [11-13] Other studies have shown unclear conclusions on the impact of oral care with chlorhexidine on pneumonia rates, duration of mechanical ventilation, or ICU length of stay. [14-15] This controversy is primarily due to the unblinded nature of many of these systematic reviews, which then had a lack of association between oral care with chlorhexidine and ventilator-associated pneumonia rates when they were restricted to double-blinded studies.

Stress ulcer prophylaxis

Defined as "definitively not recommended",

"It is strongly recommended that stress ulcer prophylaxis should not be used routinely in mechanically ventilated patients."

This clear recommendation against routine use guides healthcare professionals in their practice. Five meta-analyses have shown that while stress ulcer prophylaxis lowers the risk of gastrointestinal bleeding, it has no significant impact on pneumonia rates, length of stay in the ICU, and mortality. [16-20]

New Literature Since the SHEA/IDSA/APIC 2022 Update

Multimodal sedation & analgesia strategies

One meta-analysis, a comprehensive review of 23 randomized controlled trials, can significantly contribute to the understanding of sedation methods in the ICU. It compared the outcomes of adult patients admitted to the ICU who were given either propofol or midazolam. These outcomes included length of stay in the ICU, duration of mechanical ventilation, and time until extubation. The study's findings revealed that propofol was associated with a reduced ICU stay, mechanical ventilation time, and time until extubation. As such, the authors concluded that sedation with propofol, compared to midazolam, is associated with improved clinical outcomes in the ICU. [21]

In a retrospective study that also compared propofol and midazolam, it was found that the 28-day mortality rate of patients treated with midazolam was 30.8%, compared to 25.5% for the propofol group (OR 1.421, 95% CI 1.118-1.806, $P < 0.001$). Thus, propofol shows a lower mortality rate compared to midazolam in patients on sedation. [22] Similarly, in a retrospective analysis that compared dexmedetomidine versus propofol versus midazolam, midazolam had a higher mortality rate. The risk of death was 1.43 times higher in mechanically ventilated patients prescribed midazolam than those prescribed propofol. There were, however, no differences in the occurrence of ventilator-associated pneumonia, thus concluding that there was no protective effect of these three sedatives on ventilator-associated pneumonia in mechanically ventilated patients. [23]

In a more complex retrospective cohort study, the authors compared midazolam, propofol, and dexmedetomidine as both monotherapy and combination therapy on the prognosis of ICU patients receiving continuous mechanical ventilation. The studied outcomes included the incidence of ventilator-associated pneumonia, in-hospital mortality, and duration of mechanical ventilation. Separate groups were compared for their outcomes as either midazolam alone, propofol alone, dexmedetomidine alone, the combination of midazolam and dexmedetomidine, the combination of propofol and dexmedetomidine, and the combination of all three sedatives. Following the study, they concluded that dexmedetomidine alone may present favorable prognostic options for ICU patients with mechanical ventilation, with a lower risk of ventilator-associated pneumonia compared to all other interventions. [24]

Oral care with chlorhexidine

A retrospective study assessed whether the authors' modified ventilator-associated pneumonia care bundles lowered the risk of ventilator-associated pneumonia in neurosurgical patients. The ventilator-associated pneumonia care bundle was adjusted within the cohort group by increasing the frequency of intermittent endotracheal tube cuff pressure monitoring to six times daily (control group: four times daily) and reducing oral care with 0.12% chlorhexidine to three times daily (control group: four times daily). Following the study, ventilator-associated pneumonia decreased significantly in the cohort group compared to the control group (0.88/1000 vs. 6.84/1000 ventilator days, P = 0.036). Although two interventions were implemented within this study simultaneously, it was concluded that modifying the ventilator-associated pneumonia care bundle is significantly effective in lowering ventilator-associated pneumonia rates in critically ill neurosurgical patients. This then implies that reducing the frequency of oral care with chlorhexidine plays a significant role in reducing the incidence of ventilator-associated pneumonia. [25]

A meta-analysis of 48 randomized, double-blinded controlled trials aimed to determine whether the benefits of chlorhexidine for oral care outweighs its adverse effects. The study found no association between the use of oral chlorhexidine and lower ventilator-associated pneumonia rates, but it did report a significant increase in mortality. Based on these findings, the authors recommended against the routine use of chlorhexidine for oral care in mechanically ventilated patients due to the lack of robust evidence supporting its benefits. [26]

A meta-analysis of 22 randomized controlled trials investigated the efficacy of different oral chlorhexidine concentrations in preventing ventilator-associated pneumonia complications in ICU patients. The study found that chlorhexidine did not show any significant advantage over the control group in reducing the incidence of ventilator-associated pneumonia, all-cause mortality, duration of mechanical ventilation, and length of stay in the ICU. As a result, the study concluded that the routine use of chlorhexidine for oral decontamination is not recommended, as it does not significantly reduce pneumonia rates in critically ill patients. [27]

One meta-analysis showed opposing evidence that the use of chlorhexidine reduces the incidence of ventilator-associated pneumonia. It assessed ten randomized controlled trials investigating chlorhexidine's efficacy in preventing ventilator-associated pneumonia. The intended population was mechanically ventilated patients for at least 48 hours. Outcomes of this meta-analysis included incidence of ventilator-associated pneumonia, all-cause mortality, difference in days of mechanical ventilation, and length of stay in the ICU. Following the study, it was noted that the oral application of chlorhexidine reduced the incidence of ventilator-associated pneumonia (RR 0.73, 95% CI 0.55-0.97). However, it did not significantly increase all-cause mortality (RR 1.13, 95% CI 0.96-1.32). Overall, chlorhexidine proved effective in preventing ventilator-associated pneumonia, but conclusions on mortality rates cannot be drawn due to a very low quality of evidence.[28]

Another meta-analysis of four studies compared the usage of Chlorhexidine and povidone-iodine among adult patients admitted to the ICU to prevent ventilator-associated pneumonia. Three of those studies showed that povidone-iodine decreased ventilator-associated pneumonia compared to a placebo group, although it was not statistically significant (RR 0.61, 95% CI 0.25-1.47). One of those four studies showed that povidone-iodine demonstrated a decreased rate of ventilator-associated pneumonia compared to chlorhexidine, but the difference was also not statistically significant (RR 1.50, 95% CI 0.46-4.87). This suggests a potential for povidone-iodine in preventing ventilator-associated pneumonia, sparking hope for future research and the development of effective interventions. [29]

Stress ulcer prophylaxis

Literature evidence regarding the use of pharmacotherapy for stress ulcer prophylaxis in mechanically ventilated patients has been limited since the SHEA/IDSA/APIC 2022 update. Of note, there has been a new 2024 update to the Society of Critical Care Medicine (SCCM)/American Society of Health-System Pharmacists guideline for preventing stress-related gastrointestinal bleeding in critically ill adults. They recommend stress ulcer prophylaxis in critically ill adults with certain risk factors for upper gastrointestinal bleeding. Such risk factors include coagulopathy, shock, chronic liver disease, and possibly those who are undergoing neurocritical care. However, mechanical ventilation alone is not a potential risk factor and does not necessitate stress ulcer prophylaxis. This is due to the lack of firm evidence surrounding its use in this population, similar to the SHEA/IDSA/APIC 2022 update. [30]

The SCCM/ASHP 2024 guidelines equally prefer proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) as pharmacotherapy options to be given intravenously or orally. This preference supports a more retrospective analysis comparing the use of these drug

therapies in mechanically ventilated patients. The study showed no statistically significant difference in both risk of ventilated-associated pneumonia and all-cause mortality with proton pump inhibitors compared to histamine-2 receptor antagonists. [23]

Unrelated to ventilator-associated pneumonia care bundles, a randomized controlled trial observed whether proton pump inhibitors are beneficial or harmful as stress ulcer prophylaxis in critically ill patients undergoing invasive ventilation. The studied populations were adult patients undergoing invasive ventilation and received intravenous pantoprazole 40 mg daily versus a matching placebo. The study outcomes included drug efficacy, clinically significant upper gastrointestinal bleeding in the ICU at 90 days, and all-cause mortality at 90 days. Among those who had undergone invasive ventilation, pantoprazole resulted in a lower risk of clinically significant upper gastrointestinal bleeding than the placebo group, with no significant effect on mortality. [31]

Table 1 Summary of new literature since the SHEA/IDSA/APIC 2022 update on multimodal sedation & analgesia strategies

Literature	Design	Interventions	Clinical Outcomes	Results/Conclusion
Garcia, et al. (2021) [21]	Meta-analysis; 23 RCTs	Propofol vs. midazolam	• ICU LOS • MV duration • Time until extubation	Sedation with propofol, compared to midazolam, is associated with improved clinical outcomes in the ICU.
Sun, et al. (2022) [22]	Retrospective analysis	Propofol vs. midazolam	• 28-day mortality rate	The 28-day mortality rate was 30.8% for the midazolam group versus 25.5% for the propofol group (OR 1.421, 95% CI 1.118-1.806, P <0.001)
Kong, et al. (2022) [23]	Retrospective analysis	Dexmedetomidine vs. propofol vs. midazolam	● Mortality rate ● VAP rate	The risk of mortality was 1.43 higher in the midazolam group than in the propofol group. There were no differences in VAP rates between the three sedatives, thus there is no protective effect on VAP
Shi, et al. (2024) [24]	Retrospective analysis	Midazolam alone vs. propofol alone vs. dexmedetomidine alone vs. midazolam plus dexmedetomidine vs. propofol plus dexmedetomidine vs. combination of all three	● VAP rate ● Mortality rate ● MV duration	Dexmedetomidine alone presents with favorable outcomes with a lower risk of VAP than all other interventions

Table 2 Summary of new literature since the SHEA/IDSA/APIC 2022 update on oral care with chlorhexidine

Literature	Design	Interventions	Clinical Outcomes	Results/Conclusion
Triamvisit, et al. (2021) [25]	Retrospective analysis	Modified VAP care bundle in cohort group: ● Increased Intermittent endotracheal tube cuff pressure monitoring 6x/day (control: 4x/day) ● Reduced oral care with 0.12% chlorhexidine 3x/day (control: 4x/day)	● VAP rate	VAP rate decreased significantly in the cohort group compared to the control group (0.88/1000 vs. 6.84/1000 ventilator days, P = 0.036)

Vieira, et al. (2022) [26]	Meta-analysis; 48 RCTs	Oral care with chlorhexidine vs. control group	● VAP rate ● Mortality rate	There was no association between oral chlorhexidine and lower VAP rates There was a report of a significant increase in mortality in the oral chlorhexidine group
De Cassai, et al. (2024) [27]	Meta-analysis; 22 RCTs	Different concentrations of oral chlorhexidine vs. control group	● VAP rates ● All-cause mortality ● MV duration ● ICU LOS	Chlorhexidine had no significant advantage over the control group in reducing the incidence of clinical outcomes
Cruz, et al. (2023) [28]	Meta-analysis;10 RCTs	Oral chlorhexidine vs. control group	● VAP rate ● All-cause mortality ● MV duration ● ICU LOS	Chlorhexidine significantly reduced the incidence of VAP (RR 0.73, 95% CI 0.55-0.97) It did not significantly increase all-cause mortality (RR 1.13, 95% CI 0.96-1.32
Emami, et al. (2023) [29]	Meta-analysis; 4 RCTs	Oral chlorhexidine vs. povidone-iodine	● VAP rate	3 studies showed a nonsignificant decrease in VAP rate in the povidone-iodine group compared to a placebo group 1 study showed a nonsignificant decrease in VAP rate in the povidone-iodine group compared to the chlorhexidine group

Abbreviations: VAP, ventilator-associated pneumonia; RCT, randomized controlled trial; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay

Table 3 Summary of new literature since the SHEA/IDSA/APIC 2022 update on stress ulcer prophylaxis

Literature	Design	Interventions	Clinical Outcomes	Results/Conclusion
MacLaren, et al. (2024) [30]	Updated 2024 SCCM/ASHP guidelines			Recommend SUP in patients with risk factors for UGIB (coagulopathy, shock, chronic liver disease, neurocritical care) Due to low to moderate evidence, mechanical ventilation alone is not a potential risk factor and thus does not necessitate SUP
Kong, et al. (2022) [23]	Retrospective analysis	PPI vs. H2RA	● VAP rate ● All-cause mortality	There was no statistically significant difference in both outcomes with PPI compared to H2RA
Cook, et al. (2024) [31]	RCT	Pantoprazole vs. placebo	● Drug efficacy ● Clinically significant UGIB at 90 days ● All-cause mortality at 90 days	Pantoprazole resulted in a significantly lower risk of clinically significant UGIB compared to placebo with no significant effect on mortality

Abbreviations: SCCM, Society of Critical Care Medicine; ASHP, American Society of Health-System Pharmacists; SUP, stress ulcer prophylaxis; UGIB, upper gastrointestinal bleeding; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; RCT, randomized controlled trial

Conclusion

This comprehensive review of literature between August 2021 and September 2024 identified a strong correlation with the pharmacotherapy interventions recommended in the SHEA/IDSA/APIC 2022 update on current VAP care bundle practices.

The findings support the preferential use of non-benzodiazepine sedatives associated with better clinical outcomes, including ICU length of stay, mechanical ventilation duration, time until extubation, and all-cause mortality. A multimodal approach should continue to be implemented in addition to daily sedation vacations and assessment of readiness to extubate.

Due to chlorhexidine's controversial conclusions on its impact on ventilator-associated pneumonia rates and the possibility of increased mortality, routine oral care with chlorhexidine is not recommended. Oral care, including toothbrushing but without chlorhexidine, is considered an essential practice. However, other options, such as povidone-iodine, have been studied to provide improved clinical outcomes compared to chlorhexidine.

Conflicting evidence regarding stress ulcer prophylaxis remains. Consequently, this warrants further high-quality studies to draw definitive conclusions on its effectiveness in mechanically ventilated patients. Nonetheless, stress ulcer prophylaxis may be indicated for reasons other than ventilator-associated pneumonia prevention.

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