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Review on strategies to minimize the appearance of multi-drug resistant organism

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Abstract

Background: The use of antibiotic drugs (ABX) in hospitals, and especially in intensive care units (ICU), is widespread. The early administration of ABX therapy can improve survival rates. The influence and impact of the ABX are observed in the patients who receive them (clinical response, course) and in the ecosystem surrounding the patient (hospital flora).

Aim of the review: The objective of this review is to identify strategies that reduce or limit the appearance and transmission of multidrug-resistant microorganisms. This identification can then develop a rational use of the ABX plan in the ICU.

Method: The following databases were queried; Medline, Embase, The Cochrane Library, and the Centre for Reviews and Dissemination (University of York), asking the questions in PICO format to evaluate the efficacy and safety of several interventions: A) Therapeutic de-escalation; B) Cycling of ABX and; C) Early antibiotic treatment.

Results: A) In therapeutic de-escalation of 98 studies identified, three studies that met the inclusion criteria were analyzed. B) Two studies comparing antibiotic cycling versus other interventions were selected. C) No studies have been found with sufficiently robust methodological designs that address the ABX early treatment. There is no strong evidence to indicate which of the different antibiotic interventions (therapeutic de-escalation, cycling of ABX and preemptive treatment) is more effective in reducing antibiotic resistance in ICU patients. There is insufficient evidence that de-escalation of antimicrobial agents is effective against resistance. In patients admitted to the ICU with a low prevalence of

fluoroquinolones resistance, increased exposure to this class of antibiotics, using antibiotic cycling, increases the emergence of resistant strains.

Conclusion: Despite the fact that no prospective studies were identified in this SR, rationale and day-to-day clinical practice experience suggest that multidisciplinary participation of different specialists in ABX's Infection and Policy Commission (or the ABX Commission), or the Pharmacy and Therapeutics Committee, might improve the development and application of these strategies.

Keywords: Drug resistance, Cross infection, Anti-bacterial agents, Intensive care units

Introduction

The use of antibiotic drugs (ABX) in hospitals, and especially in intensive care units (ICU), is widespread. The early administration of ABX therapy can improve survival rates (Mok et al., 2014). The influence and impact of the ABX are observed in the patients who receive them (clinical response, course) and in the ecosystem surrounding the patient (hospital flora). This impact is especially visible in the critically ill patients in the endemic flora of the ICU (Alvarez Lerma et al., 2010).

Treatment with broad-spectrum ABX is generally used for early treatment, since it has been shown that preemptive treatment, with the appropriate ABX, reduced mortality rates. This approach may expose individuals to excessive use of ABX and therefore, the selection of resistance to these pathogens (Silva et al., 2013).The European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) estimated that each year 25,000 Europeans die as a direct consequence of a multidrug-resistant infection (ECDC/EMA, 2009).

In Spain, as some projects in other European Member States (e.g. the Netherlands (Schuts et al., 2016)), the National Action Plan on Antimicrobial Resistance (AEMPS, 2018) was nationally coordinated in 2014 by the Spanish Agency of Medicines and Medical Devices, together with six Ministries, with the objective of minimizing the impact of antimicrobial resistance and how to be addressed jointly from the human and veterinary health. The importance of the ABX as part of the pharmacotherapy arsenal is unquestionable, hence the importance of improving the management of the knowledge about them.

Health and social care practitioners have to make clinical decisions daily. Compatible update of knowledge and health care is a complicated task, and Clinical Practice Guidelines (CPG) are useful tools to facilitate decision-making. Initiatives such as the Program for Optimizing the use of Antimicrobials (PROA) in Spanish hospitals (Rodriguez-Bano et al., 2012) can contribute to improve policy of ABX, and minimize the emergence of resistance in microorganisms. Within the framework of the ICU it emphasizes the "Zero resistance" programme (Garnacho Montero et al., 2015).

One of the lines of work, typically proposals from hospital pharmacy services, is the sequential therapy, but there are interventions whose evidence is not proven and that should be evaluated. These include the therapeutic de-escalation, and cycling of ABX and preemptive treatment. The objective of this review is to identify strategies that reduce or limit the appearance and cross transmission of multidrug-resistant organisms in order to make rational use of the ABX.

Data and Methods:

Strategies to minimize the emergence of multidrug-resistant organisms in ICU with policy measures of ABX that address: A)

Therapeutic de-escalation, B) Cycling of ABX, and C) Early antibiotic treatment. Other strategies, to reduce cross transmission of multidrug-resistant organisms in ICU, are also addressed, such us: 1) preventive isolation or 2) active surveillance for patients in the early identification of Methicillin-resistant *Staphylococcus aureus* (MRSA) on asymptomatic carriers of other multidrug-resistant microorganisms.

Therefore, this review is focused to identify interventions that might help to prevent resistance to antimicrobials, in the hospital and ICU, to reduce morbidity and mortality by antimicrobial-resistant organisms.

The following databases were searched until January 2018: Medline (via PubMed), Embase, The Cochrane Library and the Centre for Reviews and Dissemination, and University of York. We used the controlled vocabulary thesaurus (MeSH or Emtree), used for indexing articles for PubMed, Cochrane and CRD (MeSH) or Embase (Emtree), as appropriate, as well as searching by free language terms for each construct of the research question, disaggregated in its PICO form (Patient, Intervention, Comparison, and Outcome). Comprehensive and updated (2008-2018) search strategies, including comprehensive search terms (i.e. resistance antibiotic AND intensive care unit). The literature search, (can be found in the supplementary material, which is available to authorized users) with the ATC classification group J01 (WHO, 2017), is described in the flow diagram in Figure 1. The results were also accompanied by a manual search on UpToDate® (Waltman, MA) and grey literature findings.

Inclusion and exclusion criteria were established a priori. We have included studies, which related interventions allowing estimators or comparative information on reduction, elimination of the appearance, or cross transmission of multidrug-resistant microorganisms to ABX. Studies reporting interventions on reducing resistance levels, for various classes of antibiotics, such as aminoglycosides or quinolones, were excluded.

Systematic reviews (SR) that do not provide quantitative data on the results of the interventions of interest and articles without abstract were excluded. It is used as filter design studies, selecting those which are clinical practice guidelines (CPG), randomized clinical trials (RCT), and economic evaluation studies.

Results

A) De-escalation therapy

Of 98 identified studies, we have analyzed 3 studies that met the criteria of inclusion: 1 SR (Silva et al., 2013), 1 RCT (Kim et al., 2012), and 1 CPG (Dellinger et al., 2013). The SR, despite identifying several studies, discards them for being uninteresting interventions or clinical conditions not relevant to the review.

The study done by Kim et al., 2012 shows statistically significant differences in favour of de-escalation in terms of the adequacy of the ABX and against the de-escalation in the time of occurrence of multi-drug resistant organism, primarily due to MRSA; HR = 3.84 (95% CI: 1.06; 13.9). Mortality, duration of the ABX, stay in ICU or adverse treatment, showed no statistically significant differences. Dellinger et al., 2013 were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence, and include in the international CPG: 1) the need to identify pathogens and apply more efficient ABX treatment, 2) reduction of the spectrum of antibiotic coverage, and 3) the reduction of the duration of the ABX treatment.

This decreases the chances that the patient develops infections by multi-resistant pathogens and the beginning of a pattern of broad-spectrum

treatment ABX to increase the effectiveness of the treatment and improve health outcomes.

B) Cycling of ABX

Two studies were selected (Nijssen et al., 2010; Martinez et al., 2006) that compare ABX cycling to other interventions. The first, a period of cycling's three months, gets 14 crops with Enterobacteriaceae resistant to third generation cephalosporin's (3GCRE) for every 1,000 patients per day to risk. This data is the same as during the baseline period, observation of the ICU. During the three months of not cycling (reducing exposure to beta-lactams and introduction of fluoroquinolones), there are 18 crops with (CPG) for every 1,000 patients per day to risk. During the three months of cycling, isolated 2.5 (CPG) resistant to fluoroquinolones (FRE) for every 1,000 patients per day to risk, being the similar results of the baseline period (2.1 FRE 1,000 patients day to risk) in contrast with the period of not cycling, which they have 8.3 FRE for every 1,000 patients per day at risk (Nijssen et al., 2010).

When the explanatory model is adjusted by type of ICU, age of the patient, gravity - APACHE II, indication of admission, and reason of contacts, not cycling for 3 months in ICU (reduction of beta-lactam and introduction of fluoroquinolones), increases the speed of appearance of FRE in 4.1 times with regard to the cycling of ABX (adjusted HR = 4.1 [95% CI: 1.4; 11.9]) (Nijssen et al., 2010). The Group of Martinez et al. (2006) analyzed along 8 months, in two ICU, a pattern of cycling of ABX with another mixed pattern that was administered to patients, as they enter consecutively to analyze the emergence of resistance in gram-negative enteric Bacilli.

They found that the prevalence of resistance acquired during two periods of study was highest during the mixed period than during the period of cycling (9% vs. 3% respectively, p = 0.01) for Pseudomonas aeruginosa and specifically, for cefepime. No statistically significant differences for other bacilli can be seen on Enterobacteriaceae (Martinez et al., 2006).

C) Preemptive treatment

No studies have been found with robust enough methodological designs that address the preemptive treatment. Study designs were not enable to provide robust evidence about preemptive treatment (De Waele et al., 2003; Piarroux et al., 2004).

Cross transmission

We found 5 studies, of which 3 are SR (Lam et al., 2012; Pammi et al., 2011; Backman et al., 2008) and 2 RCT (Huang et al., 2013; Climo et al., 2013). A SR evaluates the effectiveness of the measures of oral hygiene in reducing colonization of *Staphylococcus aureus* (Lam et al., 2012) and given that only 3 of the 15 studies included in the review had been done with ICU patients with mechanical ventilation (MV), results of the three studies were displayed (Pedreira et al. 2009; Scannapieco et al., 2009; Fourrier et al., 2000) with broader objectives.

In all three studies, part of the intervention consists of performing oral hygiene with chlorhexidine in critically ill patients with MV. Results from the Paediatric ICU show no difference on colonization of oropharyngeal, duration of the MV, length of stay in ICU, or isolation of multidrug-resistant bacteria (Pedreira et al. 2009). A second study with adult patients showed a significant reduction in the number of isolates by culture *Staphylococcus aureus* versus placebo at 2 and 4 days of admission to ICU with MV. There was no statistically significant difference in the occurrence of pneumonia, or it has been observed that interventions at the time delayed the onset of pneumonia

(Scannapieco et al., 2009).

The work done in France excludes study to toothless patients and select patients with exclusively medical processes all with MV. Oral isotonic serum bicarbonate and oropharyngeal suction cleaning 4 times a day improve in a statistically significant way to more nosocomial infection (NI) that the application of gel with chlorhexidine associated with 0.2% in teeth and gums with sterile glove 3 times daily (p = 0.018). The application of chlorhexidine is also associated with a reduction in the number of ventilation-associated pneumonia (VAP) (p < 0.05) (Fourrier et al., 2000).

The SR of Pammi et al. 2011 sought to analyze the effect of isolation measures in reducing the cross transmission of *Candida* from infants colonized or infected. No evidence was found supporting or not of isolation measures, both individually and in group, in ICU of infants (Pammi et al., 2011).

A SR identified which aims to evaluate the relationship between hand hygiene interventions and the incidence of NI (Backman et al., 2008). In addition to 35 studies, one included is a RCT in Paediatric ICU selected (except kidney) solid organ transplant patients. Observed hand washing with chlorhexidine before and after each patient contact or the use of robe and latex gloves non sterile with each patient contact, reduce the incidence of NI ICU in a statistically significant way between the previous year and the 6 months after the interventions (4.9/100 days vs. 2.2/100); p = 0.0004. Statistically significant differences were not found in NI average in transplanted between groups (Slota et al., 2001).

Work done with 74 ICU adults in the United States, included 74,256 patients and compared between different interventions (screening and isolation, specific decolonization and universal decolonization) to reduce the transmission of MRSA and other pathogens acquired in ICU. To compare interventions with the baseline period (prior to the implementation of interventions), a statistically significant reduction is observed of positive cultures for MRSA acquired in ICU (p = 0.01), as well as bacteraemia caused by others pathogens acquired in ICU (p <; 0.001). Statistically significant differences for bacteraemia by MRSA acquired in ICU are not observed both to compare between periods and between groups. Comparing between groups, universal decolonization was the intervention that reduced the occurrence of positive cultures for MRSA and ICU-acquired bacteraemia by other pathogens more effectively (Huang et al., 2013).

A multicenter RCT, with the participation of 9 ICU (a total of 7,727 patients) assessed the utility of body hygiene through cleaning wipes, with chlorhexidine gluconate 2%, to reduce the risk of acquiring multiresistant organisms and bacteraemia nosocomial in critically ill patients. The duration of the intervention period decreased, in a statistically significant way, a 23% NI MRSA and Vancomycin-resistant *Enterococcus* (VRE), a 28% nosocomial bacteraemia, 31% primary bacteraemia, and 53% bacteraemia, associated to central venous catheter. A reduction of 90% of fungaemia is also described, associated with central venous catheter (Climo et al., 2013).

Antimicrobial stewardship guidelines and initiatives previously published by the Infectious Disease Society of America (IDSA), e.g. IDSA and Society for Healthcare Epidemiology of America (SHEA) jointly published Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship, in Clinical Infectious Diseases (January 2007 vol. 44 no. 2 159-177) for developing institutional programs to enhance antimicrobial stewardship, an activity that includes appropriate selection, dosing,

route, and duration of antimicrobial therapy. A brief summary related to "Infections and antimicrobial resistance in the intensive care unit: Epidemiology and prevention", found on UpToDate®, is adapted with permission on table 1: Summary of recommendations for preventing ventilator -associated pneumonia (VAP) in adult patients (SHEA/IDSA).

Discussion

Studies of quality capable of sustaining analyzed ABX policy measures have been searched and identified. It would be necessary to design prospective research studies that can establish a causal relationship between the policy measures of ABX and the emergence of multidrug-resistant organisms in ICUs reduction. Studies with more robust designs that allow you to determine if oral hygiene in critically ill patients with MV's more 48 hours has a clinically relevant impact is required. As antimicrobial stewardship Pharmacist, you can make prospective audit and feedback, if you review the information and recommend that the prescribing team narrow therapy.

Antibiotics should be discontinued within 48 hours after surgery. It is necessary to carry out studies that allow determining the clinical impact of the role of isolation measures in patients, colonized or infected by Candida. There is no doubt of the importance of interventions to improve hand hygiene to reduce the incidence of NI in critically ill patients. Universal decolonization in critically ill patients reduce bacteraemia, prevents the realization of surveillance test, reduces the number of isolates of contact, and decreases the chances of transmission of infection to other patients. The personal hygiene of critically ill patients with chlorhexidine-impregnated wipes reduces the transmission of bacteria resistant to other patients.

Therapeutic de-escalation consists in initiating ABX therapy with broad-spectrum empirical therapy, with the aim of increasing the chances of covering the probable infectious agent. Subsequently, a broad spectrum treatment change is performed. De-escalation should occur with respect to culture data or clinical judgment. Empiric use of combination therapy should not be administered for longer than 3-5 days if de-escalation to a single agent is appropriate. Empiric antimicrobials should cover likely pathogens according to suspected location of infection and risk of multidrug-resistant pathogens. Other considerations in choosing appropriate antimicrobials include the patient's history of drug allergy or intolerance, recent antibiotic use, comorbidities, and antimicrobial susceptibility patterns in the community and hospital. Consider discontinuing antimicrobials in 7-10 days unless there is slow response, undrainable foci, immunosuppression, or multidrug-resistant pathogens.

Blood cultures will be negative in most patients, despite a bacterial of fungal origin of sepsis. Clinical judgment is needed when considering discontinuation of antimicrobials. According to the results of the microbiological studies, a treatment with a more adjusted antimicrobial spectrum by one of the following two pathways: 1) change of ABX, and; 2) Interrupt an antibiotic combination. An additional strategy to shorten the duration of ABX treatment (Alvarez Lerma et al., 2010; Silva et al., 2013). Crop performance is a prerequisite for the use of antibiotic de-escalation in critically ill patients, although the decision to reduce the intensity of treatment should be based on the patient's clinical course (Silva et al., 2013). Therapeutic de-escalation aims to achieve adequate antibiotic coverage through the use of ABX in a targeted manner, reducing the spectrum of empirical coverage and reducing selective

pressure on the patient's flora as well as the ecosystem in which the latter remains.

The cycling of ABX consists of the determined alternation of ABX by which the use of an ABX or specific ABX class is restricted for a certain period of time to be reintroduced subsequently (Sandiumenge et al., 2003). Other authors describe cycling as the periodic substitution of one class of ABX by another class or the combination of ABX that present a spectrum of similar activity, but do not share the same mechanism of resistance (Alvarez Lerma et al., 2010). It is intended to minimize the occurrence of bacterial resistance to the ABX in use, reducing the selective pressure exerted on the microbial flora (Sandiumenge et al., 2003).

Preemptive treatment is the administration of ABX in some patients before clinical signs of infection appear. The application of this concept to critically ill patients is based on the identification of patients at risk of infections associated with high mortality, such as systemic fungal infections (Alvarez Lerma et al., 2010).

Having information on the quality of antibiotic prescription can help identify problems and implement strategies to improve this prescription; the European Surveillance of Antimicrobial Consumption (ESAC) has developed a group of indicators of antibiotic use in outpatients with the objective to measure the quality of the use of antibiotics and thus improve their use (Coenen et al., 2007).

Conclusion

Despite the fact that no prospective studies were identified in this SR, rationale and day-to-day clinical practice experience suggest that multidisciplinary participation of different specialists in ABX's Infection and Policy Commission (or the ABX Commission), or the Pharmacy and Therapeutics Committee, might improve the development and application of these strategies.

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Conflicts of interest:

The authors declare no potential conflicts of interest.

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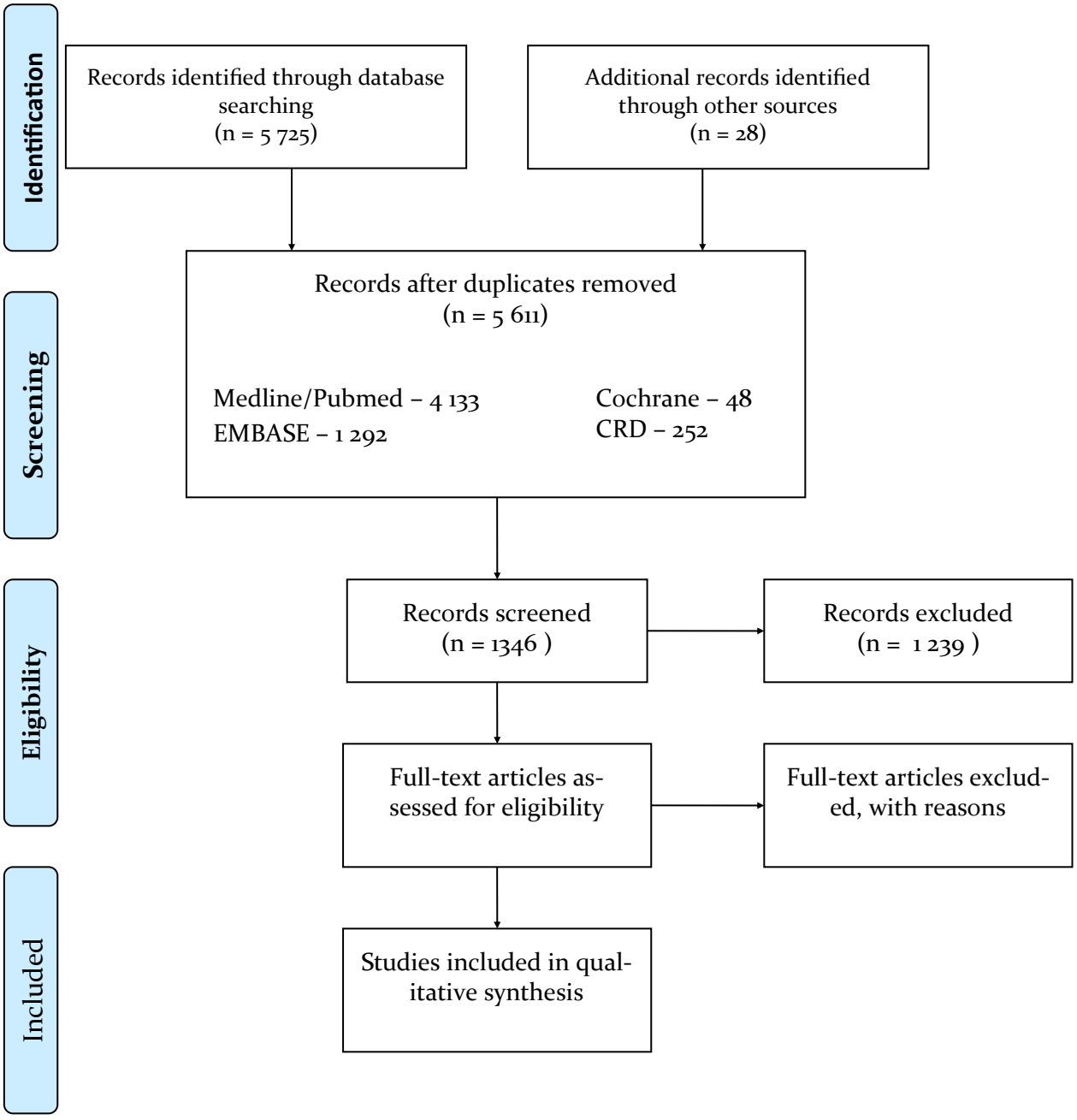
PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 1. Summary of recommendations for preventing ventilator-associated pneumonia (VAP) in adult patients — Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA)

Recommendation	Rationale	Intervention	Quality of evidence
Basic practices	Good evidence that the intervention decreases the average duration of mechanical ventilation, length of stay, mortality, and/or costs; benefits likely outweigh risks	Use noninvasive positive pressure ventilation in selected populations	High
		Manage patients without sedation whenever possible	Moderate
		Interrupt sedation daily	High
		Assess readiness to extubate daily	High
		Perform spontaneous breathing trials with sedatives turned off	High
		Facilitate early mobility	Moderate
		Utilize endotracheal tubes with subglottic secretion drainage ports for patients expected to require greater than 48 or 72 hours of mechanical ventilation	Moderate
		Change the ventilator circuit only if visibly soiled or malfunctioning	High
		Elevate the head of the bed to 30 to 45°	Low*
Special approaches	Good evidence that the intervention improves outcomes but insufficient data available on possible risks	Selective oral or digestive decontamination	High¶
	May lower VAP rates but insufficient data to determine impact on duration of mechanical ventilation, length of stay, or mortality	Regular oral care with chlorhexidine	Moderate
		Prophylactic probiotics	Moderate
		Ultrathin polyurethane endotracheal tube cuffs	Low
		Automated control of endotracheal tube cuff pressure	Low
		Saline instillation before tracheal suctioning	Low
		Mechanical tooth brushing	Low
Generally not recommended	Lowers VAP rates but ample data suggest no impact on duration of mechanical ventilation, length of stay, or mortality	Silver-coated endotracheal tubes	Moderate
		Kinetic beds	Moderate
		Prone positioning	Moderate
	No impact on VAP rates, average duration of mechanical ventilation, length of stay, or mortalityΔ	Stress ulcer prophylaxis	Moderate
		Early tracheotomy	High
		Monitoring residual gastric volumes	Moderate
		Early parenteral nutrition	Moderate
No recommendation	No impact on VAP rates or other patient outcomes, unclear impact on costs	Closed/in-line endotracheal suctioning	Moderate

** There are very little data on head-of-bed elevation, but it is classified as a basic practice because of its simplicity, ubiquity, low cost, and potential benefit.*

¶ There are abundant data on the benefits of digestive decontamination but insufficient data on the long-term impact of this strategy on antimicrobial resistance rates.

Δ May be indicated for reasons other than VAP prevention.

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