Guidelines and Implementation of ventilator-associated pneumonia prevention measures.

The Spanish “Zero-VAP” bundle

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Abstract

Objective. “Zero-VAP” is a proposal for implementation of a simultaneous multimodal intervention in Spanish intensive care units (ICU), consisting of a bundle of ventilator-associated pneumonia (VAP) prevention measures. Implementation of the guidelines aims at the reduction of VAP to less than 9 episodes per 1000 days of mechanical ventilation.

Methods. A total of 35 preventive measures were selected and a task force of experts used the Grading of Recommendations Assessment, Development and Evaluation Working Group methodology to generate a list of 7 basic “mandatory” recommendations (education and training in airway management, strict hand hygiene for airway management, cuff pressure control, oral hygiene with chlorhexidine, semi-recumbent positioning, promoting measures which safely avoid or reduce time on ventilator, discourage scheduled changes of ventilator circuits, humidifiers and endotracheal tubes) and 3 additional “highly recommended” measures (selective decontamination of the digestive tract, aspiration of subglottic secretions, and a short course of iv antibiotic).

An initiative of the Spanish Societies of Intensive Care Medicine and of Intensive Care Nurses, the project is supported by the Spanish Ministry of Health and participation is voluntary.

Additionally, the “Zero-VAP” Project incorporates an integral patient safety program for identification of errors and establishment of quality improvement objectives. VAP episodes and participation indices are entered into the web-based Spanish ICU Infection Surveillance Program “ENVIN-HELICS” data base, which provides continuous information about local, regional and national VAP incidence rates.

This article presents VAP-prevention guidelines and describes the methodology used for the selection and implementation of the recommendations and the organizational structure of the project. Compared to conventional guideline documents, the associated safety assurance program, the online data recording and compliance control systems, as well as the existence of a pre-defined objective are distinct features of "Zero VAP".

286 words

Keywords: prevention, ventilator-associated pneumonia, intensive care unit, VAP prevention bundle, safety assurance,

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent ICU-acquired infection (1-3). It is associated with significant increases in length of stay, healthcare costs and both crude and attributed mortality (4-7).Therefore, potential functional, mechanical and pharmacological prevention measures of VAP have frequently been investigated, classified and recommended in accordance with updated available evidence and feasibility (8-17). Questionnaires, however, repeatedly report that knowledge, implementation and adherence to guidelines are low among nurses and physicians working in ICUs internationally (18-20).

The Spanish annual April to June ICU National Nosocomial Infection Surveillance Study (Estudio Nacional de Vigilancia de Infección Nosocomial,"ENVIN") (2;3) shows stable VAP incidence densities of approximately 15 episodes per 1000 days of mechanical ventilation for the years 2000 to 2009 in more than 100 ICUs. These figures compare negatively with other national surveillance programs. The United States National Healthcare Safety Network reports mean VAP incidence rates of 3.7 for 2006 to 2008, from as low as 2.1 in pediatric medical-surgical ICUs to 10.7 episodes per 1.000 days in burn units (1).

Recently, the implementation of "bundles" of effective measures, compared to individual interventions, has been proposed to reduce the incidence of catheter-related bloodstream infections (21) and VAP (22). In Spain, a highly successful bacteremia prevention bundle, named "Zero Bacteremia", was started and implemented by the Spanish Society of Intensive Care Medicine (SEMICYUC) in 2008 (23) under the auspices and financial support of the World Health Organization and the Quality Assurance Agency of the Spanish Ministry of Health (QAA) (24). The "Zero-VAP" Project uses the organizational structure and methodology created for "Zero-Bacteremia". In this article we describe the methods applied to identify the recommendations to be included in the "Zero-VAP" bundle and to accomplish implementation in Spanish ICUs. We also refer to the systems used to monitor compliance

and to register the data generated during the project and describe the associated quality assurance program.

METHODS

Structure and Organization

SEMICYUC and the Spanish Society of Intensive Care Nurses (SEEIUC) lead and coordinate the technical aspects of “Zero-VAP” by means of a working contract. The QAA hierarchically involves the 17 regional healthcare authorities and the hospital directors of the participating ICUs and promotes the Project through co-financing with the regional healthcare authorities, nation-wide coordination, dissemination and follow-up. For every autonomous region, as well as in every ICU, an intensivist and an intensive care nurse coordinate “Zero-VAP” at their respective level.

A national task force with members of SEMICYUC and SEEIUC selected the prevention measures and is in charge of the management of the Project.

The VAP prevention bundle, the objectives and the tools for implementation and control of the Project were presented at a national meeting and subsequently at regional and local meetings.

Methodology for the selection of VAP prevention measures

Thirty-five interventions were derived from published clinical trials, guidelines, systematic reviews and meta-analyses. They were classified as “functional”, “mechanical” or “pharmacological”(Table 1) and evaluated independently by teams of at least two members of the task force using the Grading of Recommendations Assessment, Development and Evaluation Working Group methodology (25;26) (http://www.gradeworkinggroup.org/) (Table 2). After reaching agreement on individual “strongly recommended” VAP-specific prevention measures, inclusion of 8 debated interventions was resolved by quantitative

assessment of the members of the panel, considering 1) the quality of the evidence (10 points), 2) its safety (5 points), and its feasibility in Spanish ICUs (5 points) (Table 3). Finally, feasibility and cost criteria were applied, as recommended (27), and it was agreed to generate a group of 7 “basic mandatory” and 3 “highly recommended” measures (Table 4).

Basic mandatory measures

1. Education and training in airway management (aspiration of bronchial secretions). A systematic review including 26 studies (28) suggests that educational interventions are associated with significant reductions in nosocomial infection rates, although a causal relation cannot be established due to limitations in study design. Several studies show significant reductions in VAP incidence after implementation of educational programs (29;30) and simple clinical protocols, including emphasis on strict hand hygiene (31). Although the quality of evidence for educational interventions for airway management is “moderate”, the strength of this recommendation was classified as “strong” because of its significant association with the prevention of VAP, no major threats for safety, and low cost of implementation.

The educational program to be implemented at the beginning of the project also strongly discourages routine endotracheal instillation of saline and reinforces single-use utensils.

2. Strict hand hygiene with alcohol solutions before airway management. Observational studies (32) report reductions in nosocomial infection rates and methicillin-resistant *Staphylococcus aureus* (MRSA) infection after promoting hand-washing. Hand-washing before and after patient contact and the use of gloves was introduced in 2004 as a proven measure for the prevention of VAP and other nosocomial infections (9). It is now firmly established as a fundamental component of standard clinical practice (19). The use of gloves does not preclude the obligation of hand-washing with alcohol solutions before and after management of the artificial airway.

3. *Oral hygiene with chlorhexidine.* Chlorhexidine has been recommended for MRSA skin decolonization (33;34) and VAP prevention (9;10;15). Three of 5 meta-analyses (35-39) show significant reductions of VAP incidence rates with oropharyngeal chlorhexidine. The most recent meta-analysis (39) favours chlorhexidine (OR 0.56, 95%CI 0.44 – 0.73), although 6 of the 10 trials were negative. The variable effect of chlorhexidine seems to be related to its limited microbiological effect, which, while reducing oropharyngeal carriage with *S. aureus*, leaves Gram-negative colonization largely unaffected (40). Efficacy may also be related to the local concentrations of chlorhexidine. A trial administering a high concentration 2% solution showed a significant reduction of VAP, although 10% of patients in the test group developed irritation of the oral mucosa (38). Chlorhexidine has apparently no risk of inducing cross resistance to antibiotics. However, chlorhexidine-resistant strains of MRSA may substitute susceptible strains shortly after initiating routine chlorhexidine application (41;42). Up to 63% of European strains actually express plasmid-borne *qacA*/*B* genes coding for multidrug efflux pumps (43), which confer chlorhexidine resistance in MRSA.

Oral hygiene with aqueous chlorhexidine solutions (0.12 to 2%) should be performed every 8 hours. Before its application, cuff pressure should be above 20 cmH_2O. Formal training of nurse's aides, responsible for this procedure in most ICUs, will be done.

4. Control and maintenance of cuff pressure. Although included in guidelines (44), this recommendation is based on the results of a small single-centre, non-comparative study (45) suggesting that a cuff pressure level below 20 cmH_2O is associated with an increased risk of VAP in patients not receiving systemic antibiotics. A recent randomized trial, comparing continuous monitoring of cuff pressure with intermittent or non-scheduled measurements (46), did not confirm this association in spite of a significant difference in the incidence of cuff pressures below 20 cmH_2O.The panel considered that routine checks of cuff pressure is a simple low cost standard clinical procedure, also controlling for

inappropriately high pressures and should be scheduled at 8 hour intervals and set at 20-30 cmH_2O before oral application of chlorhexidine.

5. *Semi-recumbent positioning. Avoidance of 0º supine positioning*. The physiologic rationale behind semi-recumbent positioning is that it may favor spontaneous ventilation and reduce aspiration of contaminated gastric content. Its effect on VAP prevention has not been validated in unstable patients or patients with increased intra-abdominal pressure and results of randomized trials vary (47;48). A meta-analysis (49) using a random effects model to compensate for significant heterogeneity observed a non-significant reduction in the incidence of VAP (OR 0.59,95%CI 0.15-2.35) in patients in a semi-recumbent 45º position. A recent well-conducted randomized trial (50) enrolling 232 patients with tetanus was negative, with 20.8% (39.2 episodes per 1000 days of ventilation) patients developing VAP in supine position and 25% (38.1 episodes) in semi-recumbence (OR 0.79, 95%CI 0.39–1.57, p=0.46). Differing study results prevent establishing a firm recommendation to elevate backrests to 45º. However, it is recommended to avoid 0º supine positioning in patients receiving enteral feeding and with no contraindication.

6. Promote procedures and protocols which safely avoid or reduce duration of mechanical ventilation. Effective interventions aimed at avoiding or shortening duration of endotracheal intubation are associated with reductions of VAP. Therefore, protocols for non-invasive mechanical ventilation (NIMV) in acute exacerbations of chronic obstructive pulmonary disease (COPD), for weaning or for sedation promoting lower infusion doses or its daily interruption should be available.

NIMV appears to be associated with reduced mortality and VAP (relative risk 0.29, 95%CI 0.19-0.45) when used as weaning strategy in patients with COPD after extubation (51).

A recent systematic review (52) suggests that the use of weaning protocols is associated with a reduced duration of mechanical ventilation. However, significant heterogeneity

between studies and the absence of data on VAP preclude grading of evidence of this potentially preventive measure.

To our knowledge, no study evaluating the effect of daily sedation vacation on VAP incidence as end-point has been performed. Two landmark trials evaluating daily interruption of sedation did not mention comparative VAP rates, although both found significant reductions in duration of mechanical ventilation (53;54). Therefore, the quality of the evidence of VAP prevention by reducing sedation could not be appropriately graded. A detailed sedation protocol was deemed to be beyond the scope of the Project.

Based on the available data, the panel decided to issue a generic recommendation for the availability of updated weaning and sedation protocols and for the use of NIMV in selected patient populations, to reduce duration of mechanical ventilation.

7. *Avoidance of elective changes of ventilator circuits, humidifiers and endotracheal tubes*.

Planned ventilator circuit changes may increase cost and the risk of VAP and should not be performed, as has already been recommended (8;11). A systematic review (55) confirms that 48 h circuit changes compared to 7days almost doubles the risk of VAP (OR 1.93, 95%CI 1.08-3.44). It is concluded that the practice of planned ventilator circuit changes should be abandoned.

Heat-moisture exchangers (HME) have been suggested to be associated with lower incidence of VAP than heated humidifiers (HH) (56). A recent meta-analysis does not confirm this effect (57) and, therefore, HH should be reserved for individual cases at increased risk of airway obstruction. The adequate frequency of change of HME has not been established. The results of prospective before-after studies and randomized trials indicate that prolonging the duration of HMEs from 24 to 48 h (58;59), to 5 days (60), and even to 7 days (61),reduces costs and does not increase VAP.

Highly recommended measures

*1. Selective Decontamination of the Digestive Tract(SDD) or Selective Oropharyngeal Decontamination (SOD).*This intervention aims at the reduction of endogenous infections by preventing or eradicating the aero-digestive carrier state with potentially pathogenic flora. The SDD protocol includes administration of a short 2 to 5-day course of a third generation cephalosporin and topical antibiotics administered as a paste to the oral mucosa and as a solution via nasogastric tube. The topical antimicrobials are non-absorbable to maintain high luminal gut concentrations and prevent development of resistance. This strategy has no effect on exogenous infections, which are caused by direct inoculation, although it may reduce cross-transmission. SDD is associated with reductions of VAP of approximately 70% in 60 randomized trials and 15 meta-analyses. A recent individual patient meta-analysis (62) calculated an odds ratio of 0.28 (95%CI 0.20-0.38) for development of VAP. SDD is also associated with significant reductions in bacteremia (OR 0.73, 95%CI 0.59-0.9) (63) and mortality (OR 0.75, 95%CI 0.65-0.87) (62). Although concerns about development of resistance during SDD have been voiced, the most recent and biggest randomized multicenter trials demonstrate significant reductions of incidence rates of multi-drug resistant bacteria (MDR)(64-66). SOD, studied in 9 controlled trials (67), drastically reduces VAP risk (OR 0.17, 95%CI 0.17-0.43), although not mortality, nor gastro-intestinal carriage with MDR (65;66).

The implementation of SDD and SOD requires collaboration of several hospital departments, like critical care, microbiology and pharmacy and is not commercially available. Therefore, although the panel considered the quality of the evidence favoring SDD to be “high” and strongly recommends its use, it was not categorized as a basic mandatory measure.

In order to facilitate its implementation, the instructions for manufacture, administration and surveillance are provided.

2. Continuous aspiration of subglottic secretions (CASS). A meta-analysis (68) found that CASS significantly reduces early-onset VAP (EO-VAP) in patients exceeding 3 days of intubation (risk ratio for all episodes 0.51, 95%CI 0.37-0.71, for EO-VAP 0.38, 95%CI 0.16-0.88), although it does not prevent colonization or infection of the respiratory tract with *Enterobacteriaceae* or *Pseudomonas aeruginosa*. Duration of mechanical ventilation and ICU-stay were reduced by 2 days (95%CI 1.7-2.3) and 3 days (95%CI 2.1-3.9), respectively, with no effect on mortality. A recent randomized trial in patients undergoing major heart surgery (69) was negative. A post-hoc sub-group analysis of patients ventilated more than 48 hours found significant reductions of cumulative incidence of VAP (26.7% vs. 47.5%, relative risk 0.40, 95%CI 0.16-0.99; p=0.04), ICU length-of-stay (7 vs. 16.5 days, p=0.01) and antibiotic use, with no effect on mortality. No adverse events attributed to CASS have been reported in humans, although evidence of widespread injury to tracheal mucosa and submucosa was documented after 72 hours of CASS in sheep (70).

As for SDD, CASS is not widely available and expensive. Instructions for its use are provided.

3. *Short course (2-3 days) of systemic antibiotic therapy.* A short course of intravenous cephalosporin was added to topical antibiotics in the SDD protocol in order to prevent primary endogenous, mainly respiratory tract, infection in severe trauma patients (71;72). Patients with decreased level of consciousness are at particularly high risk, typically including severe trauma, severe head trauma, stroke, cardiac arrest and metabolic or drug-related central nervous system depression. A small randomized controlled trial (73) showed a significant reduction of the incidence of VAP from 36% to 18% associated with administration of only 2 doses of cefuroxime 1,5 g/12 h. In a double-blind randomized multicenter trial 3 doses of ceftriaxone 2 g/24 hours were associated with a significant reduction of primary endogenous VAP from 51.3% to 14.3% (74). Intravenous antibiotics have shown to be protective (45) and are therefore recommended, similar to surgical

prophylaxis, in the aforementioned patient population, although they do not reduce late infections, morbidity or mortality.

In patients with decreased level of consciousness a short 47 to 72 h course of intravenous cefuroxime, ceftriaxone or amoxicillin-clavulanate should be considered.

Surveillance and control of compliance

Several systems for surveillance of adhesion to the Project and compliance of the proposed measures have been established.

1. *Participation in the web based "ENVIN-HELICS" registry*. ICUs are committed to enter data required for calculation of incidence density of VAP. Participation of 202 units (76% of Spanish ICUs) has remained constant since "Zero VAP" started in April 2011 (Figure 2).

2. P*rovision of education and training to healthcare workers (HCW)*. Two educational modules about VAP prevention and patient safety, with their corresponding examinations, are freely accessible on-line and continuously monitored for number and category of ICU-HCW successfully completing the tests. Coordinators in each unit have access to this register and report to the regional coordinators.

3. *Evaluation of compliance*. The web-based 6-monthly compliance registry consists of 3 quality indicators: 1) cuff pressure control prior to oral hygiene, 2) use of chlorhexidine for oral hygiene, and 3) number of monthly meetings and activities related to the Project. The previous registry for "Zero Bacteremia" (23) remains active: 1) checklist for insertion of vascular catheters, 2) chlorhexidine skin disinfection, 3) availability of vascular catheter insertion cart, 4) accomplishment of daily objectives, 5) meeting with hospital directors and 6) "learning from errors" meetings. Information about how many indicators are accomplished is available on-line.

Data base

"Zero VAP" data are recorded through a specific adaptation of the "ENVIN-HELICS" web page (http://hws.vhebron.net/Neumonia-zero/). Participating ICUs record data of patients with VAP meeting the definition of the ENVIN-HELICS registry (2;75;76). In addition, monthly information about risk factors, including total patient-days and ventilated patient-days, is provided. If a patient develops VAP, a data base entry is created with information on demographics, risk factors, severity at ICU admission, underlying conditions, comorbidity, diagnostic criteria, microbiological sampling procedures, etiology and clinical course. Patients entered in the "ENVIN-HELICS" surveillance program (http://hws.vhebron.net/envin-helics/) are recorded automatically in the "Zero VAP" data base, with no additional intervention being required.

Summary descriptive statistics are available on-line for every individual unit, which may directly access its data on a daily basis. Local results are displayed together with the corresponding regional and national values.

DISCUSSION

The last decade has witnessed the publication of rigorous and comprehensive guidelines for the prevention of VAP, generated with ever improving and transparent methodologies (8-15;77), which have provided detailed reviews of the literature and thoughtful recommendations. The Spanish “Zero VAP” Project, developed under the leadership of SEMICYUC, has several additional differential features, which in our opinion extend the value of this initiative beyond that of its 7 “basic” and 3 “highly recommended” or other published “conventional” guidelines.

Beyond the usual physician-lead recommendations, this project was developed from its earliest phases in collaboration with the Spanish critical care nurses (SEEIUC), who participated actively in all theoretical and practical aspects of its design, training, implementation, adherence, compliance, quality assurance and coordination. The active role and identification of the nurses with the initiative was considered to be an essential element for success.

“Zero-VAP” is an interventional program incorporated in 2011 to a firmly established observational ICU infection surveillance program, which the Working Group for Infectious Diseases of SEMICYUC initiated in 1994. Only for the 2011 April-to-June surveillance period, results from 167 ICUs and 18,821 patients are available. The huge amount of epidemiological data and surveillance experience accumulated over 17 years in 150,000 patients by Spanish intensivists and critical care nurses constitute a solid historical control group providing the adequate baseline reference data. “Zero-VAP” may therefore be viewed as a huge, multicenter, “before-after” study, where the efficacy of a VAP-prevention bundle is prospectively evaluated.

The establishment of an organizational structure and contractual commitment involving the Spanish Ministry of Health, regional authorities, hospital directors, and regional and site medical and nurse coordinators is another differential characteristic of “Zero-VAP”, with the objective to guarantee continued adherence and quality. In addition, continuous monitoring of compliance will also allow validating the prevention package and some of its individual measures.

Compared to conventional guidelines, “Zero-VAP” is a bundle of interventions with a pre-defined objective. The reduction of the national VAP incidence rate by 25% and to less than 9 episodes per 1000 days of mechanical ventilation is a simple and clear quantitative target.

Finally, the validation for efficacy and safety of expert recommendations in “real life” situations, even if these are produced by the best of methodologies, seems to be becoming more and more important. It may even be argued that future guidelines should be accompanied by evaluation for adequacy and safety, i.e. internal validity, before widespread implementation of recommendations. Performance of randomized trials before implementation of guidelines has recently been proposed (78). In addition, the results of implementing recommendations, i.e. external validity, should ideally be assessable on a continuous basis, similar to phase IV or post-marketing studies of new antimicrobial compounds, thus allowing for early detection of adverse outcomes. “Zero-VAP”, through its continuous on-line recording of results and incorporated patient safety and quality improvement program, has efficient incorporated tools to detect and correct errors and to implement modifications or improvements, thereby also guaranteeing future adherence to recommendations.

The weaknesses of “Zero-VAP” are related to the “study” design and to the absence of site monitoring. Compared to an ideal multicenter, randomized-control trial, the current project has only a historic control group and confounding variables cannot be definitively excluded. Also, underreporting of VAP episodes may start to occur if during the project candidate VAP

episodes are evaluated with stricter criteria than in previous practice. Although a desirable "fringe benefit" of the project, this effect may falsely improve the results of implementation of the VAP prevention bundle. Unfortunately, the financial support of the project doesn't cover site monitoring to detect VAP episodes which are not reported but treated as such with antimicrobials. Monitoring of more than 200 ICUs would require allocation of important economic resources.

In summary, we present "Zero-VAP", the Spanish national VAP prevention bundle, with its organizational structure involving several levels of the healthcare administration and provide a detailed description of the methodology used for selecting the components of the bundle. Online tools put in place facilitate implementation and adherence and measure compliance and the effect of the bundle on the incidence of VAP in Spanish ICUs. "Zero-VAP" also promotes the development of a culture of safety assurance in ICUs.

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Figure legends

Figure 1. Organizational scheme of the “Zero VAP” Project. (SEMICYUC: Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias. SEEIUC: Sociedad Española de Enfermería Intensiva y Unidades Coronarias.)

Figure 2. Control panel of compliance and follow-up of the “Zero VAP” Project.

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