

SPECIAL ARTICLE

Guidelines for the prevention of ventilator-associated pneumonia and their implementation. The Spanish ‘‘Zero-VAP’’ bundle



F. Álvarez Lerma^a, M. Sánchez García^{b,*}, L. Lorente^c, F. Gordo^d, J.M. Añón^e, J. Álvarez^f, M. Palomar^g, R. García^h, S. Ariasⁱ, M. Vázquez-Calatayud^j, R. Jam^k

^a Servicio de Medicina Intensiva, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain

^b Servicio de Medicina Intensiva, Hospital Clínico San Carlos, Madrid, Spain

^c Servicio de Medicina Intensiva, Hospital Universitario de Canarias, San Cristóbal de La Laguna, Santa Cruz de Tenerife, Spain

^d Servicio de Medicina Intensiva, Hospital Universitario del Henares, Coslada, Madrid, Spain

^e Servicio de Medicina Intensiva, Hospital Virgen de la Luz, Cuenca, Spain

^f Servicio de Cuidados Intensivos, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain

^g Servicio de Medicina Intensiva, Hospital Universitario Arnau de Vilanova, Lérida, Spain

^h Servicio de Anestesia y Reanimación, Hospital Universitario de Basurto, Bilbao, Vizcaya, Spain

ⁱ Servicio de Medicina Intensiva, Hospital Universitario de Getafe, Getafe, Madrid, Spain

^j Servicio de Medicina Intensiva, Clínica Universidad de Navarra, Pamplona, Navarra, Spain

^k Servicio de Medicina Intensiva, Centro Hospitalario Parc Taulí, Sabadell, Barcelona, Spain

Received 11 November 2013; accepted 16 December 2013

Available online 1 March 2014

KEYWORDS

Ventilator-associated pneumonia;
Intensive care unit;
Mechanical ventilation;
Prevention bundle;
Guidelines;
Safety assurance

Abstract

Background: ‘‘Zero-VAP’’ is a proposal for the implementation of a simultaneous multimodal intervention in Spanish intensive care units (ICU) consisting of a bundle of ventilator-associated pneumonia (VAP) prevention measures.

Methods/design: 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. In addition to guidelines for VAP prevention, the ‘‘Zero-VAP’’ Project incorporates an integral patient safety program and continuous online validation of the application of the bundle. For the latter, VAP episodes and participation indices are entered into the web-based Spanish ICU Infection Surveillance Program ‘‘ENVIN-HELICS’’ database, which provides continuous information about local, regional and national VAP incidence rates. Implementation of the guidelines aims at the reduction of VAP to less than 9 episodes per 1000 days of mechanical ventilation.

A total of 35 preventive measures were initially selected. A task force of experts used the Grading of Recommendations, Assessment, Development and Evaluation Working Group

* Corresponding author.

E-mail addresses: miguel.sanchez@salud.madrid.org, miguelsanchez.areachip@wanadoo.es (M. Sánchez García).

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 that safely avoid or reduce time on ventilator, and discouraging 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).

Discussion: We present the Spanish VAP prevention guidelines and describe 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 the distinct features of ‘‘Zero VAP’’.

© 2013 Elsevier España, S.L. and SEMICYUC. All rights reserved.

PALABRAS CLAVE

Neumonía asociada a la ventilación mecánica;
Unidad de cuidados intensivos;
Ventilación mecánica;
Haz de prevención;
Directrices;
Control de la seguridad

Paquete de medidas para la prevención de la neumonía asociada a la ventilación mecánica y su aplicación en las UVI españolas. El Proyecto «Neumonía Zero»

Resumen

Antecedentes: «Neumonía Zero» es una propuesta de aplicación de una intervención multimodal simultánea en las unidades de cuidados intensivos españolas que consiste en un paquete de medidas preventivas de la neumonía asociada a la ventilación mecánica (NAVM).

Métodos/diseño: Se trata de una iniciativa de las sociedades españolas de Medicina Intensiva y Enfermería Intensiva. El proyecto cuenta con el apoyo del Ministerio de Sanidad y la participación es voluntaria. Además de las directrices para la prevención de la NAVM, el proyecto «Neumonía Zero» incluye un programa integral de seguridad del paciente y una validación continua «online» de la aplicación de las medidas. Para ello se introducen los episodios de NAVM y los índices de participación en la base de datos en red del programa «ENVIN-HELICS» de vigilancia de las infecciones en las unidades de cuidados intensivos españolas, que ofrece información continua acerca de las tasas de incidencia de NAVM a nivel local, autonómico y nacional. La aplicación de «Neumonía Zero» pretende reducir las NAVM a menos de 9 episodios por cada 1.000 días de ventilación mecánica.

Inicialmente, se seleccionaron 35 medidas de prevención. Un grupo de expertos utilizó la metodología del Grading of Recommendations, Assessment, Development and Evaluation Working Group para crear una lista de 7 recomendaciones básicas «obligatorias» (formación y entrenamiento en el manejo de la vía aérea, higiene estricta de manos en el manejo de la vía aérea, control de la presión del neumotaponamiento, higiene bucal con clorhexidina, posición semiincorporada, fomento de medidas que de forma segura eviten o reduzcan la duración de la ventilación mecánica, y desaconsejar los cambios programados de tubuladuras, humidificadores y tubos endotraqueales) y 3 medidas adicionales «muy recomendables» (descontaminación selectiva del tubo digestivo, aspiración de las secreciones subglóticas y un breve curso de antibióticos intravenosos).

Debate: Presentamos las directrices españolas para la prevención de la NAVM y describimos la metodología utilizada para seleccionar y aplicar las recomendaciones y la estructura organizativa del proyecto. En comparación con recomendaciones convencionales, el programa de seguridad asociado, el registro de datos «online» y los sistemas de control del cumplimiento, además de la existencia de un objetivo predefinido, son características distintivas de «Neumonía Zero».

© 2013 Elsevier España, S.L. y SEMICYUC. Todos los derechos reservados.

Background

Ventilator-associated pneumonia (VAP) is the most frequent ICU-acquired infection.¹⁻³ It is associated with significant increases in the 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’’)^{3,2} shows stable VAP

incidence densities of approximately 15 episodes per 1000 days of mechanical ventilation for the years 2000–2009 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 2006–2008, from as low as 2.1 in pediatric medical-surgical ICUs to 10.7 episodes per 1.000 days in burn units¹.

Recently, the implementation of “bundles” of effective measures, compared to individual interventions, has been proposed to reduce the incidence of catheter-related

bloodstream infections²¹ and VAP.²² In Spain, a highly successful bacteraemia prevention bundle, named “Zero Bacteraemia”, was started and implemented by the Spanish Society of Intensive Care Medicine (SEMICYUC) in 2008²³ under the auspices and financial support of the World Health Organization and the Quality Assurance Agency of the Spanish Ministry of Health (QAA). The “Zero-VAP” Project uses the organizational structure and methodology created for “Zero-Bacteraemia”. In this article we describe the methods applied to identify the recommendations to be included in the “Zero-VAP” bundle and to accomplish

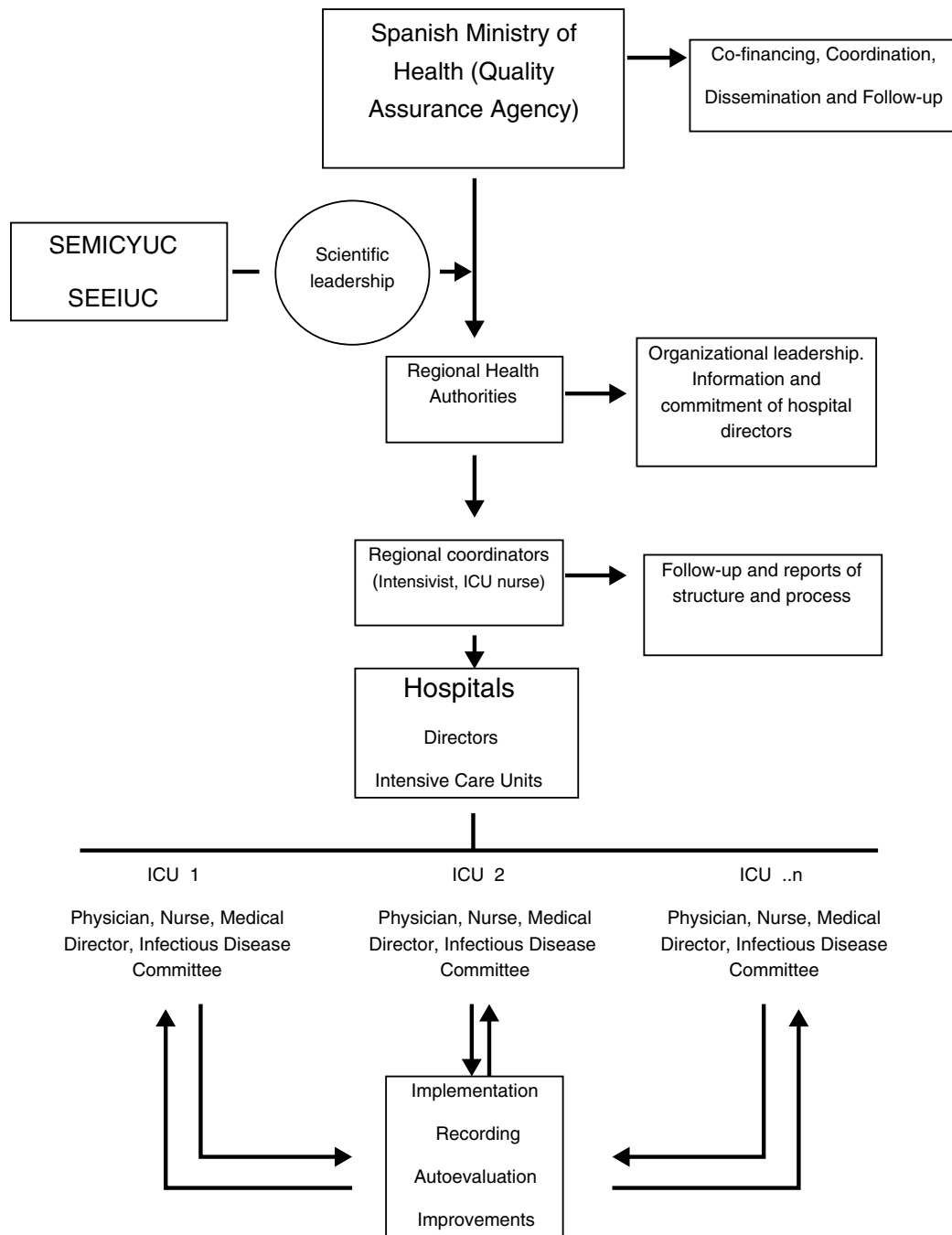


Figure 1 Organizational scheme of the “Zero VAP” Project. (SEMICYUC: Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias. SEEIUC: Sociedad Española de Enfermería Intensiva y Unidades Coronarias).

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 and design

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 (Fig. 1). For every Spanish autonomous region, as well as in every ICU, an intensivist and an intensive care nurse coordinate "Zero-VAP" at their respective level. The definitions of the European CDC²⁴⁻²⁶ for VAP and tracheobronchitis have been adopted and are available in the user's manual of ENVIN-HELICS.³ In brief, the presence of these features suggest VAP: two or more serial chest X-rays or CT scans with a suggestive image for patients with underlying cardiac or pulmonary disease, or one definitive chest X-ray or CT scan in patients without underlying cardiac or pulmonary disease, with fever $>38^{\circ}\text{C}$ and/or leucocytosis $\geq 12,000\text{ WBC}/\text{mm}^3$ or leucopenia $\leq 4000\text{ WBC}/\text{mm}^3$, and at least one of the following: (1) new onset purulent sputum or change of character of sputum; (2) cough, dyspnea or tachycardia; (3) suggestive auscultation or (4) worsening gas exchange. VAP episodes were additionally stratified according to the microbiological sampling diagnostic method employed. The target of reduction of VAP to less than 9 episodes per 1000 days of mechanical ventilation was chosen because compared to the period 2000–2009 and the most recent results it represents reductions of 40% and 25%, respectively.³

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

The VAP prevention bundle, the objectives and tools for implementation and control of "Zero-VAP" were presented at a national meeting and subsequently at regional and local meetings. The "Zero-VAP" guidelines are an extension of ENVIN-HELICS, which collects epidemiological data from all patients admitted to participating ICUs from April 1st to June 30th yearly since 1994 and does not require ethics committee approval. Viewed as a quality improvement initiative, neither the Spanish Ministry of Health nor the regional healthcare authorities requested evaluation of the project by local or regional ethics committees.

Selection of ventilator-associated pneumonia 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

Table 1 Classification of VAP prevention methods.

Functional

1. Semi-recumbent position
2. Strict hand hygiene with alcohol-based gels or solutions before airway management
3. Education and training in aspiration of bronchial secretions
4. Daily sedation vacation and assessment of weaning and extubation
5. Availability of weaning protocols
6. Early tracheostomy
7. Non-invasive mechanical ventilation
8. Microbiological surveillance of cross-contamination and infection
9. Instillation of normal saline prior to endotracheal suctioning
10. Ventilator tubing change
11. Route of endotracheal intubation. Orotracheal vs. nasotracheal
12. Type of airway humidification. Preference of heat moisture exchanger or heated humidifier
13. Physiotherapy
14. Positive end-expiratory pressure (PEEP) of 5–8 cmH₂O vs. Zero end-expiratory pressure (ZEEP) in patients without lung injury
15. Enteral feeding: route of administration and gastric residual volumes. Use of prokinetics

Mechanical

1. Endotracheal tube cuff pressure monitoring
2. Subglottic secretion drainage
3. Polyurethane-cuffed endotracheal tubes
4. Polyurethane-cuffed endotracheal tubes with subglottic secretion drainage
5. Silver-coated endotracheal tubes
6. High-volume, low-pressure endotracheal tube cuff
7. Small caliber feeding tubes
8. Aspiration of tracheobronchial secretions with closed vs. open systems
9. Endotracheal tube biofilm removal device (Mucus Shaver[®])
10. Kinetic bed therapy
11. Airway filters
12. Water-soluble gel lubrication of the endotracheal tube
13. Tooth brushing

Pharmacological

1. Selective decontamination of the digestive tract
2. Selective oropharyngeal decontamination
3. Short course of intravenous antibiotic
4. Oral hygiene with chlorhexidine
5. Nebulized antibiotics
6. Antibiotic cycling
7. Probiotics

Grading of Recommendations Assessment, Development and Evaluation Working Group methodology^{27,28} (<http://www.gradeworkinggroup.org/>) (Table 2). Inclusion of 8 debated interventions was resolved by quantitative assessment by the 11 members of the panel, considering (1) the quality of

Table 2 Definitions of quality of evidence and category of recommendation according to the Grading of Recommendations Assessment, Development and Evaluation Working Group.^{27,2,8}

Quality of evidence

High. Further research is very unlikely to change our confidence in the estimate of effect

Moderate. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low. Any estimate of effect is very uncertain

Degree of recommendation

Strong. Indicating a judgment that most well informed people would make

Weak. Indicating a judgment that a majority of well-informed people would make but a substantial minority would not

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,²⁹ based on which groups of 7 “basic mandatory” and 3 “highly recommended” measures (Table 4) were generated.

Surveillance and control of compliance

Several systems for the 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.
2. *Provision 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-line³ and continuously monitored for number and category of ICU-HCW successfully completing the tests. Coordinators in each unit have access to this registry and report to the regional coordinators.

Table 4 Quality of evidence of individual components of the VAP prevention bundle. All interventions were categorized as “highly recommended”.

Intervention	Quality of evidence
<i>Basic mandatory</i>	
1. Education and training in appropriate airway management	Moderate
2. Strict hand hygiene for airway management	Moderate
3. Cuff pressure control	Moderate
4. Oral hygiene with chlorhexidine	Moderate
5. Semi-recumbent positioning. Avoid 0°, if possible	Moderate
6. Promote procedures and protocols which safely avoid or reduce time on ventilator	Moderate
7. Avoid scheduled change of ventilator circuit, humidifiers and endotracheal tubes	High
<i>Highly recommended measures</i>	
1. Selective Decontamination of the Digestive Tract or Selective Decontamination of the Oropharynx	High
2. Aspiration of subglottic secretions	High
3. Short course of intravenous antibiotic	High

3. *Evaluation of compliance.* The web-based 6-monthly compliance registry consists of 3 quality indicators, which were arbitrarily selected because of the ease of monitoring: (1) cuff pressure control prior to oral hygiene, (2) the use of chlorhexidine for oral hygiene, and (3) the number of monthly meetings and activities related to the Project. The previous registry for “Zero Bacteremia”²³ remains active: (1) a checklist for the insertion of vascular catheters, (2) chlorhexidine skin disinfection, (3) availability of a vascular catheter insertion cart, (4) achievement 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. The optional “highly recommended” measure(s) implemented at each ICU will be captured from the general database (SDD) and from a structured questionnaire (subglottic aspiration

Table 3 Mean individual score of measures categorized as “strong” recommendation.

	Efficacy	Adverse events	Feasibility	Total
Aspiration of subglottic secretions	70	35	31	136
Avoid filter and tubing changes	76	38	39	171
Semi-recumbent positioning. Avoid 0°	56	36	34	126
Monitoring and control of cuff pressure	61	35	40	136
Oral hygiene with chlorhexidine	74	44	45	163
SDD	88	36	26	150
SOD	86	38	26	150
Short course of intravenous antibiotic	72	30	37	139

and short course of iv antibiotic) to allow for a separate comparative statistical analysis.

Database

“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 meeting the definition of VAP. In addition, monthly information about risk factors, including total patient-days and ventilated patient-days, is provided. If a patient develops VAP, a database 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 are recorded automatically in the “Zero VAP” database, 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.

Detailed educational slide presentations for every component of both “basic mandatory” and “highly recommend” measures can be freely accessed at <http://hws.vhebron.net/Neumonia-zero/>.

Basic mandatory measures

1. *Education and training in airway management* (aspiration of bronchial secretions). A systematic review including 26 studies³⁰ 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^{31,32} and simple clinical protocols, including emphasis on strict hand hygiene.³³ 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 specific care practices taught in the educational program to be implemented at the beginning of the project are freely available at <http://hws.vhebron.net/Neumonia-zero/>.
2. *Strict hand hygiene with alcohol solutions before airway management*. Observational studies³⁴ 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 were introduced in 2004 as proven measures 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^{35–38} and VAP prevention.^{9,10,15} Four of 6 meta-analyses^{39–44} show significant reductions of VAP incidence rates with oropharyngeal chlorhexidine. A recent meta-analysis⁴³ favors 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.⁴⁵ 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.⁴² Chlorhexidine apparently has no risk of inducing cross-resistance to antibiotics. However, chlorhexidine-resistant strains of MRSA may substitute susceptible strains shortly after initiating routine chlorhexidine application.^{46,47} Up to 63% of European strains actually express plasmid-borne *qacA/B* genes coding for multidrug efflux pumps,⁴⁸ which confer chlorhexidine resistance in MRSA.

Oral hygiene with aqueous chlorhexidine solutions (0.12–2%) should be performed every 8 h. Before its application, cuff pressure should be above 20 cmH₂O. 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 the guidelines,⁴⁹ this recommendation is based on the results of a small single-centre, non-comparative study⁵⁰ suggesting that a cuff pressure level below 20 cmH₂O 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,⁵¹ did not confirm this association in spite of a significant difference in the incidence of cuff pressures below 20 cmH₂O. 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 h intervals and set at 20–30 cmH₂O before oral application of chlorhexidine.
5. *Semi-recumbent positioning. Avoidance of 0° 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.^{52,53} A meta-analysis⁵⁴ 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 45° position. A recent well-conducted randomized trial⁵⁵ 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 45°. However, it is recommended to avoid 0° supine positioning in patients receiving enteral feeding and with no contraindication.

6. *Promoting procedures and protocols that 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 a weaning strategy in patients with COPD after extubation.⁵⁶

A recent systematic review⁵⁷ 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 the duration of mechanical ventilation.^{58,59} 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 the 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 review⁶⁰ confirms that 48 h circuit changes compared to 7 days almost double 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).⁶¹ A recent meta-analysis does not confirm this effect⁶² 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,^{63,64} to 5 days,⁶⁵ and even to 7 days,⁶⁶ 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 the 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-analysis⁶⁷ calculated an odds ratio of 0.28 (95%CI 0.20–0.38) for the development of VAP. SDD is also associated with significant reductions in bacteraemia (OR 0.73, 95%CI 0.59–0.9)⁶⁸ and mortality (OR 0.75, 95%CI 0.65–0.87).⁶⁷ Although concerns about the development of resistance during SDD have been voiced, the most recent and biggest randomized multicentre trials demonstrate significant reductions of incidence rates of multi-drug resistant bacteria (MDR).^{69–71} SOD, studied in 9 controlled trials,⁷² drastically reduces VAP risk (OR 0.17, 95%CI 0.17–0.43), although not mortality, or gastro-intestinal carriage with MDR.^{70,71}

The implementation of SDD and SOD requires the collaboration of several hospital departments, such as critical care, microbiology and pharmacy and neither the antimicrobial paste nor the oral solution is 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-analysis⁷³ 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*. The duration of mechanical ventilation and that of 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 a major heart surgery⁷⁴ was negative. A post hoc sub-group analysis of patients ventilated more than 48 h 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 h of CASS in sheep.⁷⁵

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.^{76,77} This measure has been evaluated separately for the prevention of VAP, without concomitant administration of topical antimicrobials, and was therefore included in the bundle for those ICUs not implementing the complete SDD protocol.

Patients with decreased level of consciousness are particularly at a high risk of primary endogenous VAP, typically including severe trauma, severe head trauma, stroke, cardiac arrest and metabolic or drug-related central nervous system depression. A small randomized controlled trial⁷⁸ showed a significant reduction of the incidence of VAP from 36% to 18% associated with the administration of only 2 doses of cefuroxime 1.5 g/12 h. In a double-blind randomized multicentre trial, 3 doses of ceftriaxone 2 g/24 h were associated with a significant reduction of primary endogenous VAP from 51.3% to 14.3%.⁷⁹ Intravenous antibiotics have shown to be protective^{50,80} and are therefore recommended, similar to surgical prophylaxis, in the aforementioned patient populations, although they do not reduce late infections, morbidity or mortality.

In patients with decreased level of consciousness, a short 48–72 h course of intravenous cefuroxime, ceftriaxone or amoxicillin-clavulanate should be considered.

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,^{8,10,49,9,11–15} 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 extends the value of this initiative beyond that of its 7 “basic” and 3 “highly recommended” or other published “conventional” guidelines.

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

“Zero-VAP” is an interventional program incorporated into a firmly established observational ICU infection surveillance program, ENVIN-HELICS,³ which the Working Group for Infectious Diseases of SEMICYUC initiated in 1994. ENVIN-HELICS yearly collects data from ICU patients staying > 24 h and who are admitted during the surveillance period, which spans from April 1st to June 30th. The ever increasing number of participating ICUs reached 173 in 2012. The huge amount of epidemiological data and surveillance experience accumulated over 18 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,

multicentre, “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.⁸¹ 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 multicentre, randomized, control trial, the current project has only a historic control group, and confounding variables cannot be definitively excluded. Also, although pre-defined diagnostic criteria exist, 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 does not cover site monitoring to detect VAP episodes that 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.

Funding

The Spanish Ministry of Health provided financial support for the meetings of the task force.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgements

This manuscript is dedicated to the memory of Dr. María Jesús López Pueyo.

We thank Yolanda Agra (QAA) and the regional healthcare authorities for their commitment, allocation of resources and organizational support of "Zero VAP". The regional and local medical and nurse coordinators deserve mentioning for their outstanding efforts and commitment. Our thanks go also to the intensivists and critical care nurses of the participating units, whose dedication to the implementation of the proposed measures was decisive in actually making "Zero VAP" possible.

References

- Edwards JR, Peterson KD, Mu Y, Banerjee S, Allen-Bridson K, Morrell G, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control*. 2009;37:783–805.
- Olaechea PM, Insausti J, Blanco A, Luque P. Epidemiology and impact of nosocomial infections. *Med Intensiva*. 2010;34:256–67.
- Estudio Nacional de Vigilancia de Infección Nosocomial en UCI (ENVIN-UCI) 2001–2009; 2012. Available from: URL: <http://hws.vhebron.net/envin-helics/>
- Beyersmann J, Kneib T, Schumacher M, Gastmeier P. Nosocomial infection, length of stay, and time-dependent bias. *Infect Control Hosp Epidemiol*. 2009;30:273–6.
- Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165:867–903.
- Muscudere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. *Clin Infect Dis*. 2010;51 Suppl. 1:S120–5.
- Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis*. 2011;11:30–8.
- Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on ventilator-associated pneumonia. *Eur Respir J*. 2001;17:1034–45.
- Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep*. 2004;53(RR-3):1–36.
- Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med*. 2004;141:305–13.
- Masterton RG, Galloway A, French G, Street M, Armstrong J, Brown E, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2008;62:5–34.
- Muscudere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. *J Crit Care*. 2008;23:126–37.
- Coffin SE, Klompas M, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol*. 2008;29 Suppl. 1:S31–40.
- Torres A, Ewig S, Lode H, Carlet J. Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med*. 2009;35:9–29.
- Rello J, Lode H, Cornaglia G, Masterton R. A European care bundle for prevention of ventilator-associated pneumonia. *Intensive Care Med*. 2010;36:773–80.
- Lorente L, Blot S, Rello J. New issues and controversies in the prevention of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2010;182:870–6.
- American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388–416.
- Ricart M, Lorente C, Diaz E, Kollef MH, Rello J. Nursing adherence with evidence-based guidelines for preventing ventilator-associated pneumonia. *Crit Care Med*. 2003;31:2693–6.
- Cason CL, Tynner T, Saunders S, Broome L. Nurses' implementation of guidelines for ventilator-associated pneumonia from the Centers for Disease Control and Prevention. *Am J Crit Care*. 2007;16:28–36.
- Labeau S, Vandijck D, Rello J, Adam S, Rosa A, Wenisch C, et al. Evidence-based guidelines for the prevention of ventilator-associated pneumonia: results of a knowledge test among European intensive care nurses. *J Hosp Infect*. 2008;70:180–5.
- Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355:2725–32.
- Venkatram S, Rachmale S, Kanna B. Study of device use adjusted rates in health care-associated infections after implementation of bundles in a closed-model medical intensive care unit. *J Crit Care*. 2010;25:174–8.
- Palomar M, Alvarez-Lerma F, Riera A, Diaz MT, Torres F, Agra Y, et al. Impact of a National Multimodal Intervention to Prevent Catheter-Related Bloodstream Infection in the ICU: The Spanish Experience. *Crit Care Med*. 2013;41:2364–72.
- Surveillance of Nosocomial Infections in Intensive Care Units. Hospital in Europe Link for Infection Control through Sureveillance (HELICS); 2013 (Version 6.1. September 2004). Available from: URL: <http://www.ecdc.europa.eu/IPSE/protocols/icu.protocol.pdf>
- Estella A, Alvarez-Lerma F. Should the diagnosis of ventilator associated pneumonia be improved? *Med Intensiva*. 2011;35:578–82.
- Hansen S, Sohr D, Geffers C, Astagneau P, Blacky A, Koller W, et al. Concordance between European and US case definitions of healthcare-associated infections. *Antimicrob Resist Infect Control*. 2012;1:28.
- Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–6.

29. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, et al. Incorporating considerations of resources use into grading recommendations. *BMJ*. 2008;336:1170–3.
30. Safdar N, Abad C. Educational interventions for prevention of healthcare-associated infection: a systematic review. *Crit Care Med*. 2008;36:933–40.
31. Salahuddin N, Zafar A, Sukhyani L, Rahim S, Noor MF, Hussain K, et al. Reducing ventilator-associated pneumonia rates through a staff education programme. *J Hosp Infect*. 2004;57:223–7.
32. Zack JE, Garrison T, Trovillion E, Clinkscale D, Coopersmith CM, Fraser VJ, et al. Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. *Crit Care Med*. 2002;30:2407–12.
33. Baxter AD, Allan J, Bedard J, Malone-Tucker S, Slivar S, Langill M, et al. Adherence to simple and effective measures reduces the incidence of ventilator-associated pneumonia. *Can J Anaesth*. 2005;52:535–41.
34. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Infection Control Programme*. *Lancet*. 2000;356:1307–12.
35. Rodriguez-Bano J, Bischofberger C, Alvarez-Lerma F, Asensio A, Delgado T, Garcia-Arcal D, et al. Surveillance and control of methicillin-resistant *Staphylococcus aureus* in Spanish hospitals. A GEIH-SEIMC and SEMPSPH consensus document. *Enferm Infecc Microbiol Clin*. 2008;26:285–98.
36. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
37. Climo MW, Yokoe DS, Warren DK, Perl TM, Bolon M, Herwaldt LA, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. *N Engl J Med*. 2013;368:533–42.
38. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. 2013;368:2255–65.
39. Beraldo CC, Andrade D. Oral hygiene with chlorhexidine in preventing pneumonia associated with mechanical ventilation. *J Bras Pneumol*. 2008;34:707–14.
40. Gastmeier P, Geffers C. Prevention of ventilator-associated pneumonia: analysis of studies published since 2004. *J Hosp Infect*. 2007;67:1–8.
41. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. *Crit Care Med*. 2007;35:595–602.
42. Tantipong H, Morkhareonpong C, Jaiyindee S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. *Infect Control Hosp Epidemiol*. 2008;29:131–6.
43. Carvajal C, Pobo A, Diaz E, Lisboa T, Llauro M, Rello J. Oral hygiene with chlorhexidine on the prevention of ventilator-associated pneumonia in intubated patients: a systematic review of randomized clinical trials. *Med Clin (Barc)*. 2010;135:491–7.
44. Labeau SO, Van d V, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. *Lancet Infect Dis*. 2011;11:845–54.
45. Scannapieco FA, Yu J, Raghavendran K, Vacanti A, Owens SI, Wood K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. *Crit Care*. 2009;13:R117.
46. Edgeworth JD, Yadegarfar G, Pathak S, Batra R, Cockfield JD, Wyncoll D, et al. An outbreak in an intensive care unit of a strain of methicillin-resistant *Staphylococcus aureus* sequence type 239 associated with an increased rate of vascular access device-related bacteremia. *Clin Infect Dis*. 2007;44:493–501.
47. Batra R, Cooper BS, Whiteley C, Patel AK, Wyncoll D, Edgeworth JD. Efficacy and limitation of a chlorhexidine-based decolonization strategy in preventing transmission of methicillin-resistant *Staphylococcus aureus* in an intensive care unit. *Clin Infect Dis*. 2010;50:210–7.
48. Mayer S, Boos M, Beyer A, Fluit AC, Schmitz FJ. Distribution of the antiseptic resistance genes *qacA*, *qacB* and *qacC* in 497 methicillin-resistant and -susceptible European isolates of *Staphylococcus aureus*. *J Antimicrob Chemother*. 2001;47:896–7.
49. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388–416.
50. Rello J, Sonora R, Jubert P, Artigas A, Rue M, Valles J. Pneumonia in intubated patients: role of respiratory airway care. *Am J Respir Crit Care Med*. 1996;154:111–5.
51. Valencia M, Ferrer M, Farre R, Navajas D, Badia JR, Nicolas JM, et al. Automatic control of tracheal tube cuff pressure in ventilated patients in semirecumbent position: a randomized trial. *Crit Care Med*. 2007;35:1543–9.
52. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet*. 1999;354:1851–8.
53. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, Joore HC, van Schijndel RJ, van dT I, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med*. 2006;34:396–402.
54. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. *J Crit Care*. 2009;24:515–22.
55. Loan HT, Parry J, Nga NT, Yen LM, Binh NT, Thuy TT, et al. Semi-recumbent body position fails to prevent healthcare-associated pneumonia in Vietnamese patients with severe tetanus. *Trans R Soc Trop Med Hyg*. 2012;106:90–7.
56. Burns KE, Adhikari NK, Keenan SP, Meade MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev*. 2010:CD004127.
57. Blackwood B, Alderdice F, Burns KE, Cardwell CR, Lavery G, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database Syst Rev*. 2010:CD006904.
58. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342:1471–7.
59. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371:126–34.
60. Han J, Liu Y. Effect of ventilator circuit changes on ventilator-associated pneumonia: a systematic review and meta-analysis. *Respir Care*. 2010;55:467–74.
61. Kola A, Eckmanns T, Gastmeier P. Efficacy of heat and moisture exchangers in preventing ventilator-associated pneumonia: meta-analysis of randomized controlled trials. *Intensive Care Med*. 2005;31:5–11.
62. Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Impact of passive humidification on clinical outcomes of mechanically ventilated patients: a meta-analysis of randomized controlled trials. *Crit Care Med*. 2007;35:2843–51.
63. Daumal F, Colpart E, Manoury B, Mariani M, Daumal M. Changing heat and moisture exchangers every 48 hours does not increase

- the incidence of nosocomial pneumonia. *Infect Control Hosp Epidemiol.* 1999;20:347–9.
64. Djedaini K, Billiard M, Mier L, Le Bourdelles G, Brun P, Markowicz P, et al. Changing heat and moisture exchangers every 48 hours rather than 24 hours does not affect their efficacy and the incidence of nosocomial pneumonia. *Am J Respir Crit Care Med.* 1995;152 Pt 1:1562–9.
 65. Davis Jr K, Evans SL, Campbell RS, Johannigman JA, Luchette FA, Porembka DT, et al. Prolonged use of heat and moisture exchangers does not affect device efficiency or frequency rate of nosocomial pneumonia. *Crit Care Med.* 2000;28:1412–8.
 66. Thomachot L, Leone M, Razzouk K, Antonini F, Vialet R, Martin C. Randomized clinical trial of extended use of a hydrophobic condenser humidifier: 1 vs. 7 days. *Crit Care Med.* 2002;30:232–7.
 67. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *Cochrane Database Syst Rev.* 2009:CD000022.
 68. Silvestri L, van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. *J Hosp Infect.* 2007;65:187–203.
 69. De Jonge E, Schultz MJ, Spanjaard L, Bossuyt PM, Vroom MB, Dankert J, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet.* 2003;362:1011–6.
 70. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med.* 2009;360:20–31.
 71. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. *Lancet Infect Dis.* 2011;11:372–80.
 72. Silvestri L, van Saene HK, Zandstra DF, Viviani M, Gregori DSDD. SOD, or oropharyngeal chlorhexidine to prevent pneumonia and to reduce mortality in ventilated patients: which manoeuvre is evidence-based? *Intensive Care Med.* 2010;36:1436–7.
 73. Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. *Am J Med.* 2005;118:11–8.
 74. Bouza E, Perez MJ, Munoz P, Rincon C, Barrio JM, Hortal J. Continuous aspiration of subglottic secretions in the prevention of ventilator-associated pneumonia in the postoperative period of major heart surgery. *Chest.* 2008;134:938–46.
 75. Berra L, De Marchi L, Panigada M, Yu ZX, Baccarelli A, Kolobow T. Evaluation of continuous aspiration of subglottic secretion in an in vivo study. *Crit Care Med.* 2004;32:2071–8.
 76. Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF. A new technique of infection prevention in the intensive care unit by selective decontamination of the digestive tract. *Acta Anaesthesiol Belg.* 1983;34:209–21.
 77. Baxby D, van Saene HK, Stoutenbeek CP, Zandstra DF. Selective decontamination of the digestive tract: 13 years on, what it is and what it is not. *Intensive Care Med.* 1996;22:699–706.
 78. Sirvent JM, Torres A, El Ebiary M, Castro P, de Batlle J, Bonet A. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med.* 1997;155:1729–34.
 79. Sánchez García M, Cambronero Galache JA, Lopez DJ, Cerda CE, Rubio BJ, Gomez Aguinaga MA, et al. Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled, multicenter trial. *Am J Respir Crit Care Med.* 1998;158:908–16.
 80. Valles J, Peredo R, Burgueno MJ, Rodrigues de Freitas AP, Millan S, Espasa M, et al. Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated. *Chest.* 2013;143:1219–25.
 81. Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis.* 2011;11:181–9.