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New Technologies and Advances in Infection Prevention (A Marr, Section Editor)

New Strategies to Prevent Ventilator-Associated Pneumonia: What to Do for Your Patients

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Abstract

The current rates of ventilator-associated pneumonia (VAP) are falling, in large part, as a result of effective prevention strategies. However, the application and efficacy of VAP prevention is being challenged by efforts to replace VAP surveillance with monitoring for ventilator-associated complications (VAC), which include many non-infectious processes. VAP prevention is based on interrupting pneumonia pathogenesis by avoiding the inoculation of contaminated oral secretions into the lower respiratory tract. This starts by using non-invasive ventilation in place of endotracheal intubation whenever possible, placing all tracheal and gastric tubes through the mouth and not the nose, and making daily efforts to liberate patients from mechanical ventilation. Intervention strategies to avoid microaspiration of oral contents to the lung have focused on the use of modified respiratory therapy equipment. This includes endotracheal tubes with subglottic secretion drainage channels, endotracheal tube cuffs made of special materials and of special shape, adaptation of endotracheal tube materials to prevent the development of biofilm, cleaning tubes with biofilm removal devices, and using devices to maintain endotracheal tube cuff pressure. Decontamination of oral secretions with chlorhexidine is commonly incorporated, as part of routine oral care, in many patients. The use of 24 h of prophylactic antibiotics after emergent intubation is also a valuable strategy, but controversy about selective digestive and selective oral decontamination persists, because of concerns about the emergence of antibiotic resistance, particularly in ICUs with high baseline rates of resistance. Other interventions are of less certain benefit, such as post-pyloric feeding, elevation of the head of the bed, and use of probiotics. This review makes

recommendations about which current prevention strategies have the greatest potential to reduce the frequency of VAP.

Introduction

In recent years, the frequency of ventilator-associated pneumonia (VAP) has been declining, which is a reflection of the efficacy of current prevention efforts. Most notably, the widespread use of "ventilator bundles" has been a major benefit for patients treated in the ICU. However, a number of controversies about prevention have developed during this time, in part, as a consequence of the absence of a gold standard for diagnosing VAP. Consequently, when loose definitions for VAP from the Centers for Disease Control (CDC) have been applied, using some subjective criteria, there has been the emergence of the "zero VAP" era, with many hospitals reporting the elimination of this infection, possibly in response to the threat of public reporting of VAP rates, and of making VAP a non-reimbursable illness [1]. While there is no doubt that ventilator bundles can be successful, it is unlikely that they were able to eliminate VAP, and more realistically, they can reduce VAP rates by 50–60 % [2]. In response to the perception that many hospitals were "gaming the system" when they reported little of no VAP events, the CDC developed the concept of monitoring for "ventilator-associated conditions" (VAC), which has been shown in many studies to have little overlap with VAP or even infectious lung disease [3]. Thus, today, VAP prevention remains important and useful, while arguably, there is no reliable method to monitor VAP rates or to report them accurately. In addition, with the new focus on VAC, there may be a move away from monitoring the real frequency of nosocomial lung infections, acquired during mechanical ventilation.

While the efficacy of ventilator bundles seems well established, other preventive strategies have emerged, based on an understanding of VAP pathogenesis. Many of these have focused on respiratory therapy devices (endotracheal tube material, endotracheal tube cuff size, pressure and shape, airway humidification systems, airway suction systems) and the role of bacteria in the gastrointestinal tract to serve as a source of VAP pathogens. One such strategy, selective digestive decontamination (SDD) is a highly controversial approach, used in some European ICUs that have a low baseline rate of intrinsic antibiotic resistance, and is a concern because of its use of prophylactic topical (oral and intestinal) and systemic antibiotics [4]. At a time when many ICUs are dealing with rising rates of infection by multidrug resistant (MDR) pathogens and are trying to control the overuse of antibiotics, one recent review concluded that SDD was the only VAP prevention strategy that reduced mortality, and urged more use of this antibiotic-based approach [5]. The response to this recommendation has been mixed, but many, who work in ICUs with high rates of MDR pathogens, have not been willing to use the SDD prevention approach. The issue has been further complicated by the finding that selective oral decontamination (SOD) using topical oral antibiotics, without systemic or intestinal antibiotics, is almost as effective as SDD [6]. One additional strategy, the use of oral chlorhexidine, has also been effective to prevent VAP, without exposing patients to antibiotics, and in some hospitals, it has been added to ventilator bundles, as an alternative to both SOD and SDD.

This article explores the current commonly used VAP prevention strategies and the controversies surrounding VAP prevention.

What to Monitor and Prevent: VAP or VAC?

Most of the literature in the past has focused on preventing VAP. In general, VAP has been defined using clinical criteria including the presence of a new or progressive lung infiltrate, fever, leukocytosis or leukopenia, purulent sputum, altered mental status, worsening oxygenation, and culture evidence of an etiologic pathogen [7]. Some of these criteria are subject to interpretation and manipulation, and the lack of objective

criteria may in part be responsible for some hospitals reporting low or zero rates of VAP. In one study, Skrupsky et al. used the National Health Safety Network (NHSN) definition of VAP, applied by an infection surveillance team, using an administrative data base, and compared the findings with a definition based on clinical criteria and the decision to use antibiotic therapy (the ACCP definition). In a group of 2060 patients, the NHSN definition only identified 12 with VAP, while the ACCP definition identified 83 episodes. All of the 83 patients identified by the ACCP definition received antibiotic therapy, and 73 had microbiologic confirmation of their pneumonia. These findings illustrate how easily the NHSN definitions, using administrative data and infection surveillance, can be manipulated to underestimate the frequency of VAP [8]. This findings is probably not unique, and Klompas has pointed out that under the pressure of public reporting, hospitals can report falsely low rates of VAP, simply by avoiding aggressive diagnostic testing [1].

However, with the awareness of the subjective and manipulable definitions of VAP, the CDC has proposed replacing VAP surveillance, with recording rates of VAC, likely replacing one problem definition with another. VAC is viewed as being "objective" and can be recognized rapidly by electronic chart review, in as short as 3.5 min in one study [9]. In addition, the presence of VAC, as is true for VAP, is associated with an increased mortality, compared to patients without this illness. The diagnosis of VAC specifically excludes any evaluation of the chest radiograph and requires the following criteria: at least two calendar days of stable or decreasing oxygen requirements on the ventilator, followed by at least 2 days of an increase in FiO_2 of >0.2 or PEEP ≥3 cm water. If the VAC is accompanied by fever or white blood cell abnormalities, and the starting of new antibiotics, then, the patient has an infection-related ventilator-associated complication (IVAC). Based on the presence of purulent sputum and quantitative microbiologic cultures of lower respiratory tract samples, the IVAC patients can be further classified as possible or probable VAP [3]. One of the obvious problems with this definition is that it depends on ventilator settings and not on oxygenation per se. Previous studies have shown that changes in the PaO_2/FiO_2 ratio reflect the time course of VAP, but the VAC definition does not measure this physiologic parameter, but rather how the ventilator is set (presumably because this latter value can be measured in an automated fashion for simplicity). Thus, it is easy to manipulate the VAC definition by either not allowing the 2-day periods of stability required in the definition or by manipulating the ventilator oxygen settings in ways to avoid satisfying the definition of VAC. The similarities and differences of VAP and VAC are summarized in Table 1.

Several studies have illustrated the problems with using the VAC definition as a proxy for VAP. Muscedere et al. applied the VAC definition to 1320 ventilated patients and found VAC in 139 patients, but only 39 of these patients had VAP. On the other hand, they identified 148 patients with VAP, and 109 did not satisfy the definition of VAC [10••]. In this population, they applied several VAP prevention strategies including using only oral intubation, changing of heat moisture exchangers (HMEs) only every 7 days or when soiled, changing closed

Table 1. A comparison of VAC versus VAP

	VAP	VAC
Chest radiograph	New or progressive infiltrate	Not used in the definition
Oxygenation	Worsening, by either PaO_2/FiO_2 ratio or ventilator settings	Not directly measured. Uses ventilator settings as a surrogate
Fever	Part of the criteria for diagnosis	Not for VAC, but for IVAC
Other clinical features: altered mental status, purulent sputum	Part of the criteria for diagnosis	Not for VAC or IVAC. Purulent sputum is used in the definition of pneumonia in IVAC patients
Time needed to diagnose	Can take a long time for chart review	Can be automated and done in <5 min
Role of respiratory cultures	Needed for the diagnosis	Only useful in IVAC patients to distinguish possible from probable VAP
Impact on mortality	Associated with increased mortality	Associated with increased mortality
Relation to infection	Is intended to be an infectious illness	Can be caused by infectious and non-infectious illnesses
Able to manipulate the rate and "game the system"	Some components are subjective and can be manipulated	The "objective" criteria can be manipulated, such as ventilator settings

suction systems per patient and not daily, mouth care, and daily assessment for spontaneous awakening and breathing trials. The authors found that in multivariate analysis, the use of VAP prevention efforts had no statistical impact on the development of VAC or IVAC. Similarly, Lilly et al. evaluated 8408 mechanically ventilated patients and found that the VAC definition detected <1/3 of patients with VAP, and that 93 % of patient with VAC did not satisfy the CDC definition of VAP [11]. Boyer et al. further examined this issue by looking at 1209 patients ventilated for at least 2 days [12•]. They found 67 with VAC, with the diagnoses being IVAC in 50.7 %, ARDS in 16.4 %, pulmonary edema in 14.9 %, and atelectasis in 9 %. They concluded that at most, 37 % of episodes of VAC were preventable.

The major concern with the VAC definition is that, as shown from the above, it has little direct relationship to VAP, and the strategies for VAP prevention do not always prevent VAC, even if they can prevent VAP. Damas and colleagues randomized 352 patients to subglottic secretion drainage (SSD)-adapted endotracheal tubes or standard care and found that SSD led to a significant reduction in VAP (from 17.6 to 8.8 %), but had no impact on the rate of VAC, which was approximately 22 % [13]. On the other hand, the use of spontaneous awakening and breathing trials was shown to reduce the frequency of VAC, but not the rate of VAP [14]. Thus, if the goal is to reduce the frequency of VAP, it is likely that measuring VAC is not entirely relevant, and that strategies to prevent VAP will not necessarily prevent VAC and vice versa. Several recent editorials have emphasized that the VAC definition cannot be used to guide antibiotic use in the aICU, and that we only do not currently know what strategies can reduce the rate of VAC, but the strategies to prevent VAP, may not impact VAC [15]. As one editorial stated, until we have more data

about the preventability of VAC, the methods for prevention, and the relation of VAC rates to quality of care, we should probably reconsider the value of measuring VAC [16].

Ventilator Bundles

Much of the reduction in VAP in the past few years can probably be attributed to the application of ventilator bundles. Each hospital may have its own version of interventions for ventilated patients that can improve care and are "bundled" together, but the Institute for Healthcare Improvement (IHI) has developed a bundle that is the current standard of care. The IHI bundle includes the following: daily interruption of sedation with daily weaning trials, elevation of the head of the bed, deep venous thrombosis prophylaxis, intestinal bleeding prophylaxis, and often some form of oral care [17]. With application of a multi-element bundle, there should be a benefit, but it would be unrealistic to expect VAP rates to fall to zero. In one study, Bouadma and colleagues developed a prevention bundle that included head of the bed elevation, hand hygiene, maintenance of endotracheal tube cuff pressure >20 cm of water, orogastric (not nasogastric) tubes, oral chlorhexidine, and minimal tracheal suctioning. They compared a 45-month period without the bundle to a 30-month period with the bundle and only found a 43 % reduction in VAP rates, even with high compliance with the bundle elements [2]. Thus, reduction to a rate of zero was not possible.

The benefit of ventilator bundles has been shown in many studies, but Chahoud et al. recently performed a systematic review of the topic [18]. They identified 22 studies, including 13 multicenter studies and 9 in single centers, with all but 2 using a pre and post intervention, retrospective design. The mean number of bundle elements in the studies was 5.3, but half used a 4-element IHI bundle. Seventeen of 29 studies reporting VAP rates showed a drop, and also a drop in days on mechanical ventilation and ICU length of stay, but no impact on mortality. While these data are optimistic about the impact of applying a bundle, Ding et al. looked at the use of this type of intervention in community hospital ICUs and found no impact on VAP rates, even with high bundle compliance, using any of a number of VAP definitions, but there was a drop in mortality that they felt was due to other factors, and not from changes in VAP rates or from the use of the bundles [19]. In addition, the use of bundles also had no impact on the rates of VAC and IVAC.

With the application of bundles, most studies have shown that the rate of VAP has declined, but the bundle is most effective if it is implemented with daily monitoring of compliance, often in the form of a checklist, with a dedicated team member recording compliance with each bundle element [20]. In many studies, the benefit of the bundle is directly related to the rate of compliance with all its elements. For example, Berenholtz and colleagues used the IHI bundle in 112 ICUs for 30 months and reported a 71 % drop in VAP rates, with a good

correlation between bundle compliance and observed VAP rates [21]. In another study, the authors developed a real-time dashboard to monitor bundle compliance and found that there was little impact of the ventilator bundle until its implementation was monitored closely [22]. Once monitoring was done, compliance increased from 23 to 83 %, and VAP rates fell from 19.5 to 9.2 VAPs per 1000 ventilator days.

When bundles are introduced, it may be difficult to have the ICU implement all of the elements at the same time. Perez-Granda et al. demonstrated the feasibility of sequential addition of four bundle elements, over a 35-month period [23]. They saw a drop in VAP rate from 23.9/1000 ventilator days at baseline to 13.5 /1000 ventilator days, 35 months later when all four elements had been added. The design included education and training about VAP in the first 10 months, followed by 13 months of the addition of subglottic secretion drainage, followed by the addition of an inclinometer to measure the angle of the head of the bed for 7 months, and then 5 months of the addition of oral care with chlorhexidine. The greatest drop in VAP rates occurred with the addition of the inclinometer, but the authors felt that the study design did not allow them to identify which element was most important. Rello and colleagues tried to define which bundle elements were most important in a study involving the use of a five element bundle in five Spanish ICUs [24]. They compared 149 patients in the baseline period to 885 after implementation and found that the VAP rate fell from 15.5 to 11.7 %, and that there was a reduction in the duration of mechanical ventilation and in late onset VAP, with full bundle compliance, but not with incomplete application of the bundle elements. However, they found that the reduction in VAP was related to hand hygiene, control of endotracheal tube cuff pressure, oral care, and control of sedation, but that avoiding ventilator circuit changes had no impact on the rate of VAP.

Elevation of the head of the bed to greater than 45° at all times has been a part of most bundles, out of a belief that this intervention can prevent reflux and aspiration of gastric contents into the lung. However, the optimal angle of elevation has not been carefully determined, and it is possible that lower degrees of elevation would be as effective. In addition, it is difficult to actually achieve elevation of the head of the bed to 45°, since this is often not feasible, especially in hypotensive patients who are often kept supine. In one randomized trial from the Netherlands, 112 patients were assigned to the semirecumbent position, with the goal of elevation to 45°, while 109 patients received standard care with head elevation to 10° [25]. The investigators found that both groups had similar frequencies of VAP. Most importantly, in 85 % of the study time, patients in the intervention group did not achieve elevation to 45°, with an average elevation on day 1 of 28° and on day 7 of 22.6°. In contrast, the control group had an elevation of 10° on day 1 and 16° on day 7. The failure of head elevation to impact VAP may have been the result of the impracticality of elevation to the target angle, and the observation that standard of care involves a modest degree of head elevation. One recent observation has led to questions about the logic of this entire approach. While head of the bed elevation

may prevent gastric aspiration, there are animal studies that suggest that the opposite strategy, keeping the animal head down, in the lateral Trendelenburg position, may promote respiratory secretion drainage and prevent proximal airway colonization from leading to distal infection. Li Bassi et al. demonstrated in a porcine model that Pseudomonas colonization of the endotracheal tube does not propagate distally, when the animals were maintained in the lateral Trendelenburg position [26••]. These observations have led to an ongoing randomized trial, the Gravity VAP study (personal communication from Antoni Torres, Barcelona), in which patients are being maintained in the head down position as a VAP prevention strategy.

Modifications of the Endotracheal Tube and Other Respiratory Therapy Devices

An important part of the pathogenesis of VAP is aspiration of contaminated oropharyngeal secretions into the lower respiratory tract. This can happen in non-intubated patients, but the process is facilitated by the presence of an endotracheal tube which provides direct access into the lower respiratory tract. Ordinarily, the endotracheal tube cuff can prevent oropharyngeal secretions from reaching the lower respiratory tract, but the seal is imperfect. A number of prevention strategies have been developed to prevent microaspiration around the endotracheal tube cuff (Table 2) [27].

Our approach is to use specially designed endotracheal tubes that have a suction port above the cuff and allow for the suctioning of subglottic secretions that pool above the cuff. These subglottic secretion drainage (SSD) tubes have successfully prevented VAP [28]. The use of SSD tubes has generally been effective in reducing VAP rates. Damas et al. randomized 352 patients to have the SSD tube inserted, but only half the patients had the suction port used [13]. Use of the SSD suction system led to a reduction in VAP from 17.6 to 8.8 %, along with a reduction in ventilator days and antibiotic days. As discussed above, these benefits occurred with no impact on the rate of VACs. In spite of their benefit, these tubes are not routinely used because the suction port can

Table 2. Targets in respiratory therapy devices that have been included in clinical trials of VAP prevention

Avoidance of an endotracheal tube with non-invasive ventilation
Site of endotracheal tube insertion: mouth vs. nose
Ventilator circuit tubing: avoid manipulation
Circuit humidification: heat moisture exchange device vs. heated humidifier
Endotracheal tube cuff composition and shape: polyurethane vs. polyvinylchloride, cylindrical vs. conical
Endotracheal tube suction devices: closed vs open suction systems
Endotracheal tubes with subglottic secretion channels
Endotracheal tube cuff pressure: continuous pressure maintenance devices
Endotracheal tube composition changed to prevent biofilm formation: silver inner surface
Endotracheal tube inner surface cleaning devices to remove biofilm: Mucus Shaver
Conversion of an endotracheal tube to a tracheostomy

easily become obstructed, the inner lumen diameter is reduced to allow room for the suction device but there may be problems with routine endotracheal suctioning when the inner lumen is reduced in size, and the tube itself can injure the airway epithelium [29].

The cuff itself can be modified to prevent the leakage of oropharyngeal secretions into the lung, because some cuffs, made of polyvinylchloride, allow the formation of "channel folds" that can allow secretions to move through the folds and below the cuff into the lower respiratory tract. Specially designed high volume, low pressure cuffs made of ultrathin polyurethane may avoid fold formation. In addition, changing the cuff to a conical shape may also enhance sealing with the trachea to avoid secretion microaspiration. The theory of changing the material used to make the endotracheal tube cuff is appealing, but much of the data has been collected in vitro and has demonstrated reduced leakage around certain cuffs in laboratory conditions. In a recent, multicenter randomized trial, there was no benefit to changing the cuff shape or material composition. In that study, Philippart et al. assigned 148 patients to use a cylindrical polyvinyl chloride (PVC) cuff, 144 a cylindrical polyurethane cuff (PUC), 150 a conical PVC cuff, and 162 a conical PUC cuff [30•]. The study reported no difference in VAP rates or tracheal colonization for any of the groups. Over 90 % of the patients had monitoring and adjustment of cuff pressure every 6 h. Tracheal colonization rates were similar in all the groups.

Another way to prevent leakage of secretions into the lung is to promote cuff sealing by the addition of PEEP at low levels. The simple application of 5 cm of PEEP can promote sealing and changes the cuff to a more conical shape [27]. One randomized trial did show that the application of 5–8 cm of PEEP reduced the rate of VAP from 25.4 to 9.4 % [31]. Some of the ventilator bundles discussed above have focused on promoting cuff sealing by maintaining cuff pressure between 20 and 30 cm H_2O to avoid aspiration around the cuff, and several studies have shown the value of using devices that monitor cuff pressure and automatically keep the cuff inflated to a pre-determined level of pressure. Two recent studies have compared the use of a continuous cuff pressure control system with standard cuff care, with the goal of preventing VAP [32, 33]. In one study, Nseir et al. randomized 122 patients and aimed to keep the cuff pressure at 25 cm H_2O in all patients, but one group got standard care, while the other had continuous control of cuff pressure. The intervention group had less documented gastric aspiration, as measured by pepsin levels in tracheal secretions [32]. In addition, the continuous control approach reduced the frequency of VAP from 26.2 to 9.8 %. In another study, Lorente et al. randomized 284 patients to intermittent or continuous cuff pressure control [33]. They found that continuous control, along with the use of an SSD tube, was protective against the development of VAP.

The inner surface of the endotracheal tube may contain a biofilm that supports the growth of pathogenic bacteria. This biofilm is a mixture of mucus and airway secretions, inflammatory cells and their byproducts, bacteria, and bacterial exoproducts. The biofilm becomes a hazard when bacteria that colonize the lower respiratory tract are aerosolized or migrate proximally, to the endotracheal tube, where they can proliferate to large numbers in the absence of host defenses. Then, during routine suctioning, this infected biofilm can become dislodged and embolize back into the lung. Several approaches have been developed to address this issue. First, the endotracheal tube inner surface can be

modified, and recently, endotracheal tubes with a silver coating on the interior surface have been developed. This lining releases silver cations that have an antibacterial effect, and can reduce the impact of the biofilm. A recent meta-analysis evaluated the available clinical studies and concluded that silver-coated tubes reduce the rate of VAP (from 7.8 to 4.5 % in one large trial of 1509 patients), and that the benefit is greatest in the first 10 days of mechanical ventilation [34]. In spite of these findings, these tubes are rarely used because of their high cost and the belief that current rates of VAP are lower than the rates observed in the trials, as a result of routine use of ventilator bundles now, that were not used routinely during the clinical trial of the silver tube.

Another approach to reducing the impact of the biofilm is to physically remove it. There are a number of innovative devices that can clean the inner surface of the endotracheal tube, but one of the simpler approaches involves the "mucus shaver." This device is an inflatable balloon with shaving rings on the outside. It is inserted into the endotracheal tube, beyond the distal tip, and then inflated, and the mucus is removed by the outer shaving rings of the balloon. It has been tested in sheep and has demonstrated efficacy in cleaning the inside of the tube in humans, but there are no data about its ability to prevent VAP [29, 35].

Excessive manipulation of ventilator circuits may be harmful and may inoculate bacteria that are growing in the circuits, into the lung. Thus, the current standard of care is not to change ventilator circuits unless soiled. Other respiratory therapy manipulations have also been studied for their impact on VAP. There is not consensus on the optimal humidification system, but some studies have suggested a lower rate of VAP with the use of heat moisture exchangers (HME), rather than heated humidifiers, but no guidelines have recommended one approach over the other [36, 37]. Similarly, there are not strong data to prefer a closed suction system over an open suction device. Some studies have suggested that early removal of the endotracheal tube and replacement with a tracheostomy could reduce the frequency of VAP, but this too has not been a consistent finding, and early tracheostomy is not thought be an effective VAP prevention strategy.

Decontamination of the Oropharynx and GI Tract: Antibiotics and Chlorhexidine

Another way to prevent the aspiration of contaminated oral and gastric contents into the lung is to eliminate bacteria from these sites with antibiotics or antibacterial agents. To eliminate oral contamination, chlorhexidine oral care has become a widely applied component of ventilator bundles. However, most of the evidence of benefit came from studies of cardiac surgery patients, where it led to a reduction in VAP rates [38]. However, the generalizability of these findings is questionable, since most of these patients had a short duration of mechanical ventilation. Klompas et al. performed a meta-analysis that questioned the benefits of oral chlorhexidine from a number of perspectives [38]. First, they found a reduction in VAP only in post cardiac surgical patients, but not in non-cardiac surgical patients, and particularly not in double-blind trials. In addition, there was a non-significant trend to increased mortality with

the use of chlorhexidine in non-cardiac surgical patients, raising concerns that aspiration of this material could be harmful to the lung.

Another approach to VAP prevention is the provision of aggressive dental care to intubated patients. A group of Brazilian investigators randomized 254 patients to routine oral care ($n = 127$, with oral chlorhexidine) or aggressive dental care ($n = 127$, with oral chlorhexidine, plus a dental surgeon 4–5 times per week, tooth brushing, tongue scraping, caries repair, and tooth extraction when needed) [39]. At baseline, many patients had poor oral hygiene, with over half having gingivitis, and nearly 30 % with caries. In the study, oral chlorhexidine was used in both groups, at 2 % for unconscious patients and 0.12 % for alert patients, since the bitter taste precluded using the higher concentration in alert patients. VAP rates were significantly reduced, although there was no mortality impact, with aggressive oral care.

One of the most controversial approaches to VAP prevention is the use of prophylactic antibiotics, either systemically or topically. However, in patients who present to the hospital with coma and require urgent intubation, there may be a benefit to a single dose of systemic antibiotics to prevent early onset VAP, related to aspiration during the intubation process. In fact, Rello and colleagues have observed that patients who were on systemic antibiotics at the time of urgent intubation had a reduced rate of early onset pneumonia [40]. Valles et al. did a comparative cohort study of patients with neurologic illness and coma (Glasgow coma score or 8 or less), with 71 getting one dose of antibiotics (ceftriaxone, levofloxacin, or ertapenem) within 4 h of intubation and 58 controls [41••]. There was a significant reduction in early onset VAP (odds ration [OR] = 0.11) and less total VAP, but no impact on mortality with the use of antibiotics. Based on these observations, it may be worthwhile to consider a single dose of systemic antibiotics in all patients undergoing emergent intubation, since they are likely to aspirate during the intubation process.

Selective digestive decontamination (SDD) uses a combination of systemic antibiotics, along with multiple topical, non-absorbable, antimicrobial agents (such as polymyxin, tobramycin, and amphotericin) applied as a paste to the oropharynx and as a slurry (via nasogastric tube) into the stomach, in an effort to eliminate any infections incubating at the time of admission (with the systemic antibiotics) and to prevent subsequent infection by eliminating all bacteria in the gastrointestinal tract or oropharynx, that could be aspirated into the lung. Selective oral decontamination (SOD) uses only the oral paste, without the intestinal or systemic antibiotics. With SDD, a systemic antibiotic, such as cefotaxime, is used for the first 4 days to target primary endogenous infection, incubating at the time of admission, which account for 55 % of ICU infections. The topical antimicrobials are aimed at secondary endogenous infections that result from preceding oropharyngeal or intestinal colonization, and which account for about 30 % of nosocomial ICU infection. The remaining 15 % are secondary, exogenous infections, without preceding colonization, and they are eliminated by focusing on infection control. One of the largest studies of SDD was conducted in the Netherlands by DeSmet et al. [6]. Although it showed a mortality benefit of SDD in a cluster randomized trial in 13 ICUs, there are several concerns: the study was not blinded, the study groups were not well matched, mortality benefit could only be shown after statistical correction for differences between study groups, specific infection rates (such as VAP) were not reported, and SOD was almost as effective as SDD.

The concern with SDD is that in spite of reports of efficacy in reducing VAP rates, and maybe mortality, there may be a long-term risk of selecting for antimicrobial resistance in individual patients and in the ICU in general. Some data suggest that after cessation of SDD, there may be a rebound in gram-negative resistance, implying that the organisms are not eliminated by SDD, but simply suppressed, and a reservoir of organisms remains [42]. In addition, other observations suggest that the odds ratio for acquiring hospital acquired infection rises to 1.5 after the patients who received SDD or SOD leave the ICU [43].

Currently, SDD and SOD (other than oral chlorhexidine) are not widely used, in spite of their benefit on mortality [5]. This may relate to the above concerns about resistance emergence with the widespread use of preventive antibiotics. Most of the studies of SDD have been done in countries like the Netherlands, which have low rates of antimicrobial resistance. Thus, use in the setting of low resistance rates may have little relevance to use in ICUs with high rates of antimicrobial resistance, and the impact of SDD on resistance emergence in these types of ICUs remains unknown. In fact, given the efficacy of other preventive measures, particularly the ventilator bundle, with the use of oral chlorhexidine, it is uncertain if SDD and SOD have an additional incremental benefit that outweighs the risk of increasing rates of antimicrobial resistance, since the large SDD studies were conducted without the routine use of ventilator bundles.

Other Prevention Strategies

It is beyond the scope of this review to discuss every available VAP prevention strategy. However, there are a number of interventions that have already become an accepted part of ICU patient care, and that have an impact on the occurrence of VAP. For example, since endotracheal intubation itself is part of pneumonia pathogenesis, the use of non-invasive positive pressure ventilation (NIPPV) whenever possible, as an alternative to mechanical ventilation, is an indirect way to prevent nosocomial pneumonia. In some patients, the insertion of tubes (endotracheal or gastric) through the nose may lead to obstruction of sinus drainage and the development of nosocomial sinusitis. In some instances, bacteria from the infected sinuses can migrate down the nasally inserted tube, into the lung and lead to pneumonia. Thus, insertion of gastric and tracheal tubes through the mouth and not the nose can also help reduce the rate of VAP. Although enteral feeding is preferable to total parenteral nutrition, it is important to avoid the aspiration of gastric contents into the lung. This can be achieved by placing feeding tubes into the post-pyloric area and by avoiding large gastric residual volumes of feeding. This can be accomplished by holding feeding if gastric residual volume is high, or by feeding in a continuous fashion and not with large volume boluses.

Elevation of gastric pH can promote overgrowth with gram-negative bacteria. For this reason, there had been an interest in avoiding the use of antacids and gastric acid suppressive therapy for intestinal bleeding prophylaxis. Several studies had shown the benefit of intestinal bleeding prophylaxis with sucralfate rather than the other alternatives [36]. However, with attention to many of the other issues related to gastric feeding and volume, this choice of bleeding prophylaxis has become less important. One way to avoid intestinal overgrowth

Table 3. Prevention strategies for VAP: recommendations

Should be used in all patients
Non-invasive ventilation when possible
Insert gastric and endotracheal tubes through the mouth
Change ventilator circuits only when soiled and with each new patient
Ventilator bundles: define the appropriate elements for each ICU
Oral care: possibly with chlorhexidine
24 h of prophylactic antibiotics for patients undergoing urgent intubation
Consider using in most patients
Monitoring or continuous maintenance of endotracheal tube pressure
Post-pyloric feeding
Prophylactic PEEP of 5–8 cm water
Closed suction catheter systems
Need more data before routine use
Ideal head position: elevated vs. lateral Trendelenburg
Endotracheal tube biofilm removal: Mucus Shaver or other devices, once available
Subglottic secretion drainage tube
Selective digestive or selective oral decontamination regimen
Probiotics into the gastrointestinal tract
Early tracheostomy
Polyurethane and conical endotracheal tube cuffs
Silver-coated endotracheal tube

with potentially pathogenic bacteria is to repopulate the intestines with normal flora, by the use of probiotics put into the intestinal tract of ICU patients. Probiotics, which can include *Lactobacillus* species, promote the restoration of normal intestinal flora, by interfering with the growth of pathogenic organisms. Several trials of probiotics have been conducted and have been able to reduce the rate of VAP, but without an impact on mortality [44]. Although they are not widely used, one recent analysis concluded that probiotics are a potentially cost-effective intervention [45].

Summary

The current rates of VAP are falling, in large part, as a result of effective prevention strategies. Although controversies about VAP diagnosis remain, and the relationship between VAP and VAC is uncertain, there are a number of prevention strategies that seem to be effective (Table 3). These include the routine use of a ventilator bundle that focuses on daily interruption of sedation and weaning trials. Other effective prevention strategies include the use of non-invasive ventilation, in place of endotracheal intubation whenever possible, and insertion of all tubes through the mouth and not the nose. Patients should also have careful attention to oral care (possibly with oral chlorhexidine), maintenance of endotracheal tube cuff pressure to avoid oropharyngeal secretions from reaching the lung, possible use of PEEP to promote endotracheal tube cuff sealing in the trachea, and consideration of 24 h of prophylactic antibiotics for patients undergoing emergent intubation. Once cleaning devices that remove the biofilm from the interior of the endotracheal tube become

widely available, they are also likely to be valuable. Other interventions are of less certain benefit, such as post-pyloric feeding, elevation of the head of the bed, use of subglottic secretion drainage tubes, and use of probiotics. Using endotracheal tube cuffs with novel shape and composition has great theoretical benefit, but has not been shown in clinical trials to reduce VAP rates. Finally, interventions such as selective digestive decontamination and early tracheostomy remain controversial as VAP prevention strategies.

Compliance with Ethical Standards

Conflict of Interest
The author declares that he has no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the author.

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