Ventilator-Associated Pneumonia: Preventing the Inevitable

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Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in patients in intensive care units (ICU). Because of its association with unwanted clinical outcomes, preventive measures have been studied intensively in the past 25 years. Unfortunately, a large amount of clinical trials yielded disappointingly few clear-cut answers. Furthermore, because of the difficulties in reliably diagnosing VAP, we should be very reluctant in embracing measures that have been associated with VAP reductions in small-sized studies, but with no benefits on patient outcome documented in sufficiently powered well-designed trials. Only topical antimicrobial prophylaxis (either alone in the oropharynx or in combination with intestinal decontamination) has been demonstrated to improve patient outcome resulting from prevention of VAP. However, this was demonstrated in not-so-average circumstances-in ICUs with extremely low levels of antibiotic resistance. Despite the obvious challenges with using antibiotics as preventive measures, careful evaluation of these strategies in settings with higher drug-resistance levels is now justified, and future studies should be designed to demonstrate outcome benefits rather than reductions in VAP rates.

Intensive care units (ICUs) are the hot zones of nosocomial infections and antibiotic resistance. Many patients experience immune paralysis induced by an acute and severe disease, many have underlying immunodeficiency and/or significant comorbidity, and most of them need invasive devices, such as intubation and intravascular devices that bypass first-line host defences. As a result, ICU patients are extremely prone to infection. Furthermore, the obvious necessity of antibiotic treatment increases selection of antibiotic-resistant pathogens and amplifies the risk of cross-transmission. ICU physicians are, therefore, daily facing the difficult task to counter this unwanted sequence of events. Because we have to accept that patients will remain critically ill when admitted to an ICU and that they will continue to have underlying diseases, the possibilities to break this chain are to reduce the use of invasive devices, to prevent infection, and to minimize the occurrence of cross-transmission.

VENTILATOR-ASSOCIATED PNEUMONIA

The most frequently occurring ICU-acquired infection is pneumonia, or so-called ventilator-associated pneumonia (VAP). In a 1-day point-prevalence survey in 1417 ICUs worldwide in 2007, the prevalence of respiratory tract infection was 64% among all patients infected (1). Compared with patients not developing VAP, patients developing VAP have higher mortality rates in the ICU and hospital, stay longer in the ICU and hospital, and generate more costs for treatment. For all these reasons, prevention of VAP has held a prominent position on the research agenda of intensive care medicine in the past 25 years, with an ultimate goal of improving patient outcome, preferably by reducing mortality. Less ambitious but still highly relevant goals would be reductions in the duration of stay in health care settings or of antibiotic use.
<table>
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<th>Intervention</th>
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<th>Total no. of patients in the study</th>
<th>RRR of VAP, % (95% CI)</th>
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<td>Head-of-bed elevation</td>
<td>Drakulovic et al (7)</td>
<td>87</td>
<td>78 (7–95)</td>
<td>35 (-47 to 71)</td>
<td>Single-center Spanish study interrupted after interim analysis and with feasibility of placing patients in a 45° position evaluated once daily; control patients were treated in complete supine position</td>
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<td>Van Nieuwenhoven et al (8)</td>
<td>221</td>
<td>22 (-42 to 57)</td>
<td>3 (-46 to 35)</td>
<td>Multi-center study in the Netherlands. With frequent evaluation of patient position (every 60 s), but the pursued position of 45° could not be realized (mean, ~30°); control patients received standard care, corresponding to a 10° 15° position</td>
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<td>Subglottic aspiration</td>
<td>Valles et al (11)</td>
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<td>43 (-1 to 68)</td>
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<td>Smulders et al (10)</td>
<td>150</td>
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<td></td>
<td>Lacherade et al (9)</td>
<td>333</td>
<td>42 (10–63)</td>
<td>-6 (-37 to 18)</td>
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<td>Silver-encoated tubes</td>
<td>Kollef et al (14)</td>
<td>1,932</td>
<td>34 (1–68)</td>
<td>-14 (-34 to 3)</td>
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<td>Probiotics</td>
<td>Knight et al (15)</td>
<td>259</td>
<td>30 (-41 to 65)</td>
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<td>Klarin et al (16)</td>
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<td>70 (-170 to 97)</td>
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<td>Morrow et al (17)</td>
<td>138</td>
<td>47 (14–67)</td>
<td>18 (-63 to 58)</td>
<td>Single-center study in the United States</td>
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<td>Topical antibiotics (SDD and SOD)</td>
<td>Krueger et al (25)</td>
<td>546</td>
<td>80 (41–93)</td>
<td>24 (-9 to 47)</td>
<td>Statistically significant reduction in ICU mortality was observed in the subgroup of patients with APACHE II score of 20–29 (RRR, 49; 95% CI, 13–70).</td>
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<td>De Jonge et al (24)</td>
<td>934</td>
<td>NA</td>
<td>35 (13–57)</td>
<td>Single-center trial in the Netherlands, involving 2 units with SDD executed in 1 unit, without cross-over; incidence of VAP was not determined</td>
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<td>De Smet et al (30)</td>
<td>5,939</td>
<td>NA</td>
<td>13 (3–28) a11 (1–26) a</td>
<td>Multi-center, cluster-randomized, cross-over study in the Netherlands, in which SDD and SOD were compared with standard care (no SDD and no SOD); incidences of VAP were not determined</td>
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<td>Chlorhexidine oropharyngeal decontamination</td>
<td>Fourrier et al (34)</td>
<td>228</td>
<td>-8 (-127 to 48)</td>
<td>-29 (-106 to 19)</td>
<td>Concentration of chlorhexidine was .12%</td>
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<td>Koeman et al (33)</td>
<td>42 (-9 to 69)</td>
<td>-29 (-81 to 9)</td>
<td>Concentration of chlorhexidine in vaseline-based paste was 2%; difference in VAP occurrence was statistically significant in time-dependent analysis</td>
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<td>Segers et al (36)</td>
<td>991</td>
<td>NA</td>
<td>-29 (-148 to 90)</td>
<td>Single-center study of oro- and nasopharyngeal chlorhexidine (12%) decontamination in cardiosurgical patients; most infections occurred after extubation</td>
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<td></td>
<td>Iseganan Kollef et al (37)</td>
<td>709</td>
<td>20 (-13 to 56) a</td>
<td>-22 (-54 to 11) a</td>
<td>Multi-center study of an oral paste with an antimicrobial peptide, which appeared to marginally effective in oropharyngeal decontamination</td>
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Abbreviations: CI, confidence interval; NA, not applicable; RRR, relative risk reduction; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination.

a At day 14.
PREVENTION OF VAP

Key in the pathogenesis of VAP is colonization of the upper respiratory tract (oropharynx and trachea) with potentially pathogenic microorganisms, such as Enterobacteriaceae, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Even more important than colonization (actually a condition sine qua non) is intubation. The widespread use of noninvasive ventilation in patients with chronic obstructive pulmonary disease and hypercapnia or with acute heart failure in the last decennium has prevented many episodes of intubation and, probably, many episodes of VAP. The same seems to account for strategies reducing the duration of intubation, such as daily interruption of sedation (3), protocolized weaning (4), or both (5). However, the efficacy of these measures in preventing VAP is unknown. Considering that the daily risk for developing VAP is not constant but peaks in the first week (6), reducing the exposure risk at the end of the intubation period may not greatly reduce the occurrence of VAP.

If intubation cannot be avoided and will last for several days, the likelihood of colonization of the upper respiratory tract with potentially pathogenic microorganisms is high, as is the likelihood of aspiration of these pathogens into the lower respiratory tract, where they can cause pulmonary inflammation. In addition to reducing the time at risk, efforts to prevent VAP have been based on preventing aspiration of potentially pathogenic microorganisms and preventing colonization with potentially pathogenic microorganisms of the upper respiratory tract. Until recently, both concepts seemed to be mutually exclusive; interventions either aimed to prevent aspiration, but accepted colonization with potentially pathogenic microorganisms, or aimed to modulate colonization, with no attempts to prevent aspiration.

PREVENTING ASPIRATION

There are 3 options to prevent aspiration in intubated patients, while accepting colonization with potentially pathogenic microorganisms in the upper respiratory and stomach (Table 1). The practice of placing patients in a semi-recumbent position has been widely advocated. However, its popularity is based on the results of a single randomized trial involving 86 patients that was interrupted after interim analysis (7). In that study, the intervention consisted of placing half of the patients in a complete supine (180°) position and the other patients in a position with head elevation of 45°. Although the incidence of VAP was dramatically reduced in the supine-treated patients (relative risk reduction of 78%), receiving intragastric nutrition in this position was an equally important risk factor. Moreover, the feasibility of the semi-recumbent position was poorly determined, because the position was only measured once daily. In the only other randomized evaluation of this strategy, 112 patients received standard care, which appeared to be a head elevation of ~10° during the first week in the ICU (8). In that study, head-of-bed elevation was measured automatically every 60 s. However, the pursued head elevation of 45° in the other 109 patients appeared to not be feasible, despite study conditions, and the mean position that was achieved (~30) was not associated with a lower incidence of VAP. Therefore, from these studies, we can conclude that treatment in complete supine position should be avoided, especially when patients receive enteral nutrition, but we cannot discern whether mean positions of 10° and 30° change the occurrence rate of VAP. A mean position of 45° is unrealistic.
Prevention of microaspiration of secretions originating from the upper respiratory tract that accumulate above the cuff of the endotracheal tube has also been attempted. When evaluated as a single intervention, the use of specifically designed endotracheal tubes, allowing continuous aspiration of subglottic secretions, was associated with reductions of VAP occurrence in 3 randomized studies involving ICU patients (9–11) and in 2 randomized studies involving cardio surgical patients (12, 13). Among ICU patients, relative risk reductions ranged from 42% to 75%, but all studies were underpowered to demonstrate improvements in patient outcome.

Finally, silver-encoated tubes have been used to prevent bacteria originating from the upper respiratory tract from reaching distal lung tissue. Silver has broad-spectrum antimicrobial activity in vitro, reduces bacterial adhesion to devices in vitro, and reduces biofilm formation in animal models. In a placebo-controlled randomized study involving 2003 patients, silver-encoated endotracheal tubes were associated with a relative risk reduction of VAP of 48% but not with any beneficial effects on patient outcome (14).

MODULATION OF COLONIZATION

The alternative approach to prevent VAP is to modulate colonization of the upper respiratory tract and intestinal tract (eg, with probiotics, antiseptics, or antibiotics) without using the specific devices designed to reduce microaspiration. Several small single-center studies evaluated the effects of probiotics, either administered through the nasogastric tube (15), in the oropharynx (16), or combining both forms of application (17). In the largest (138 patients) study, application of *Lactobacillus rhamnosus* GG to the oropharynx and through the nasogastric tube was associated with a relative risk reduction of VAP of 47%; however, the study was underpowered to demonstrate benefits in patient outcome (17).

TOPICAL ANTIBIOTICS

Most experience has been derived from studies using non-absorbable antibiotics to prevent VAP, although its use has been controversial since the first study evaluating its efficacy in 1984 (18). The underlying idea of this approach, selective decontamination of the digestive tract (SDD), was that topical application of antimicrobial agents (usually polymyxin, tobramycin, and amphotericin B) in the oropharynx and through the nasogastric tube would selectively eradicate (and prevent) carriage with potentially pathogenic microorganisms without disrupting the anaerobic flora. The latter was assumed also to protect against colonization with potentially pathogenic microorganisms—a principle called colonization resistance. In most studies, patients also received a 4-day course of cefotaxim to treat any respiratory tract infection incubating at the time of ICU admission. As an alternative to SDD, researchers have used the oropharyngeal component only (ie, selective oropharyngeal decontamination [SOD]) (19). Statistically significant reductions in the incidence of VAP have been reported from multiple individual studies, although these beneficial effects were not universal (20–22). However, improvement of patient outcome was only sporadically reported from individual studies (23, 24) and, sometimes, in subgroups only (25). In meta-analyses, SDD, but not SOD, was associated with lower mortality rates (26). Nevertheless, apart from the Netherlands, where SDD was studied most intensely, topical antibiotic treatment for VAP prevention was not considered to be a safe and effective infection control measure (27). Questions about safety addressed the potential for antibiotic-induced selection of multidrug-resistant pathogens, as had been reported in some settings (20, 28, 29).

In the largest study to date (a multicenter, cluster-randomized, cross-over study involving 5939 patients in the Netherlands), SDD and SOD were associated with 13% and 11% reductions in day-28 mortality, compared with standard care (30). Furthermore, overall systemic antibiotic use (which included the 4 days of cefotaxim treatment in all patients receiving SDD) was ~10% lower in patients receiving SDD or SOD, and these patients tended to have shorter durations of stay in the ICU and the hospital. In earlier studies, both on SDD and SOD, relative risk reductions of VAP of ~60% were reported (19, 26), and therefore, it is very likely that the observed benefits in patient outcome resulted from VAP prevention. Therefore, together with the results from a previous large SDD study in the Netherlands (24) and the results from multiple smaller, single-center studies, these data provide the strongest (and to our knowledge only) evidence that modulation of colonization reduces the incidence of VAP and that VAP prevention improves patient outcome.

The questions now are whether these benefits outweigh the potential adverse effects (eg, selection of antibiotic resistance) and whether these findings can be translated to other settings. The 11% and 13% reduction in day-28 mortality correspond to absolute mortality reductions of 2.9% and 3.5%, respectively. This may seem low, but it should be noted that all patients receiving mechanical ventilation who have an expected stay in the ICU of >48 h are eligible for these interventions, instead of a highly selected population, as in other intervention studies (14, 17). Moreover, to my knowledge, there are few other infection prevention measures with documented outcome improvement in ICU patients. Therefore, under the circumstances tested (ie, in ICUs in the Netherlands), the concept of oropharyngeal decontamination (with or without intestinal decontamination and standard intravenous prophylaxis for 4 days) was beneficial, at low costs, for many patients.

To what extent were the 13 participating ICUs different from units in other countries? With regard to other preventive
measures for VAP, the 13 ICUs practiced the semi-recumbent positioning of patients, aiming at a position of head elevation of 30°, but subglottic aspiration, silver-encoated tubes, and oropharyngeal care with chlorhexidine were not performed in any of the ICUs. From an ecological perspective, however, the units probably differ from ICUs in other countries: among 5939 patients studied during 2004–2006, there was 1 patient infected with methicillin-resistant *S. aureus*, 8 patients colonized with vancomycin-resistant enterococci, and 29 patients with *Clostridium difficile* infection (30). Twelve percent of 398 episodes of ICU-acquired bacteremia were caused by highly drug-resistant microorganisms, most of which were resistant to third-generation cephalosporins, and not a single patient was colonized (or infected) with carbapenemase-producing *Klebsiella pneumoniae* (M. Bonten, personal communication). On the third Tuesday of each month, all patients present in the units (including those who were not eligible for SDD or SOD) were screened for carriage of antibiotic-resistant gram-negative bacteria, and the prevalence of bacteria resistant to ceftazidime, gentamicin, and ciprofloxacin was 1.4%, 1.0%, and .5% during standard treatment, SOD, and SDD, respectively (30). When analyzed longitudinally, the point-prevalence of intestinal carriage was lowest during SDD for all 3 antibiotics, but the prevalence of ceftazidime resistance was higher after SDD (mean, 15%) than it was before SDD (mean, 6%) (31). In the respiratory samples, resistance levels for all 3 antibiotics were lowest during SDD and SOD (4%–6%), and were equally high before and after the intervention (mean, 10%). These data have been interpreted as proof that “antibiotics are not benign in critically ill patients” (32, page 427) and that Dutch physicians will, when using SDD, soon face the same resistance problems as their American and other European colleagues (32).

On the basis of the findings in the Dutch multicenter study and an earlier single-center study (24), SDD and SOD are currently used in most (if not all) ICUs in the Netherlands. Whether these interventions will be equally beneficial in ICUs with higher rates of antibiotic resistance remains to be determined. However, because these approaches are currently the only interventions with documented improvement of patient outcome, it seems prudent to carefully evaluate SDD and SOD in such settings. Naturally, this should be done with detailed microbiological monitoring. To date, there are insufficient data to reject the possibility that these measures will not be effective in settings with higher levels of antibiotic resistance, compared with Dutch ICUs. It is even possible that these infection prevention measures are more beneficial in ICUs with higher levels of resistance, because infections caused by antibiotic-resistant bacteria have been associated with higher attributable mortality than infections caused by susceptible bacteria. Nonantibiotic approaches for achieving the same preventive effects, such as the use of chlorhexidine oropharyngeal decontamination, might offer an attractive alternative. However, 2 relatively small multicenter ICU studies have yielded nonconclusive findings on VAP prevention, which might have been related to the different concentrations of chlorhexidine (2% and .12%) that were used (33, 34). Furthermore, a head-to-head comparison of oropharyngeal decontamination with topical antibiotics and chlorhexidine has never been performed. Nevertheless, the addition of this intervention to the Institute for Health Improvement bundle is not unrealistic.

**CONCLUSION**

Twenty-five years of clinical trials on VAP prevention in ICUs yielded disappointingly few clear-cut answers. Zero tolerance to VAP is an attractive credo; however, because of the pathogenesis of the disease, it is extremely difficult to imagine that any intervention will completely prevent VAP. Furthermore, because of the difficulties in reliably diagnosing VAP, we should be very reluctant to embrace measures that have been associated with VAP reductions in small-sized studies but with no benefits on patient outcome documented in sufficiently powered well-designed trials (35). Topical antimicrobial prophylaxis (either
alone in the oropharynx or in combination with intestinal decontamination) is the only measure that currently fulfills these requirements, albeit in not-so-average circumstances. In light of the continuously increasing problems with antibiotic resistance, especially in ICUs, it seems odd to conclude, but antibiotics do more than cause resistance. Careful evaluation of these strategies should be done, including the comparison of oropharyngeal decontamination with antibiotics to chlorhexidine, in other settings.

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References


