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Ventilator-Associated Pneumonia Prevention

We Still Have a Long Way to Go!

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In this issue of *CHEST* (see page 890), Hurley[1] performed a multilevel random effects analysis examining topical antibiotics (TAs) for the prevention of ventilator-associated pneumonia (VAP). Because TA use can confer herd protection in the ICU similar to vaccination programs in the community, contextual influences resulting from a population-based intervention cannot be estimated from a single trial. However, multilevel random effects analysis allows the estimation of contextual effects. Hurley[1] found that the baseline incidence of VAP derived from observational studies was lower (23.7%; 95% CI, 20.6%-27.2%) than that in studies of TAs using concurrent control groups that either did or did not receive topical placebo (38% [95% CI, 29%-48%] vs 33% [95% CI, 20%-50%], respectively). This observed contextual influence could potentially inflate the apparent effect of TAs, especially within studies using topical placebo. The clinical importance of this observation is illustrated by investigations showing that TAs can promote the emergence of antimicrobial resistance and increase the burden of resistance genes in the gut biome of patients in the ICU.[2,3] Without knowing the overall influence of TAs on antimicrobial resistance progression and clinical outcomes, their routine use cannot be endorsed, especially in areas where antibiotic resistance is already a clinically important problem.

Hurley's[1] analysis also emphasizes the importance of continuing to investigate VAP as well as other ICU-acquired infections to optimize strategies for their prevention and treatment. There has been a sense in the United States that VAP is a vanishing condition, with reported mean national rates within medical and surgical ICUs of 1.9 and 3.8 per 1,000 ventilator-days, respectively.[4] This is in stark contrast to rates of VAP reported internationally in excess of 20 per 1,000 ventilator-days.[4] Moreover, a recent prospective surveillance study of VAP conducted in the United States, Europe, South America, and Asia found the rates of VAP, and more importantly VAP due to *Pseudomonas aeruginosa*, to be similar across continents (VAP rates, 13.5%, 19.4%, 13.8%, and 16.0%, respectively; *P aeruginosa* VAP rates, 4.1%, 3.4%, 4.8%, and 4.6%, respectively).[5] Furthermore, prior antimicrobial use and a high proportion of antimicrobial resistance in the community or hospital unit, both common exposures globally, were identified as risk factors for both VAP due to multiple drug-resistant pathogens and colonization with *P aeruginosa*.[5]

One of the most important explanations for the discrepancy regarding previously reported rates of VAP between the United States and the rest of the world is the method of surveillance used. We previously showed that the Centers for Disease Control and Prevention surveillance method markedly underestimated the occurrence of microbiologically confirmed VAP.[6] This had led the Centers for Disease Control and Prevention to adopt a new method of ICU surveillance that uses ventilator-associated conditions (VACs) to monitor the quality of ICU care.[7] The concern with shifting away from VAP as an important disease process within the ICU setting is that it may result in a reduced emphasis on the prevention of VAP and could have unforeseen consequences, especially as more and more VAP is caused by antibiotic-resistant pathogens.[8] Moreover, simply changing ICU surveillance to VACs does not guarantee that the quality of ICU care will improve. The simple criteria used to define VACs (changes in positive end-expiratory pressure and F_{IO_2} after periods of stability) exposes these surveillance criteria to "definitional gaming," whereby hospitals may

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manipulate their rates of VACs by adjusting their use of positive end-expiratory pressure and FIO_2.

The continued need to focus on improved methods for the prevention of VAP, as opposed to simply switching to alternative surveillance methods, is also illustrated by several recent studies examining the inability of the VAC criteria to identify VAP. Muscedere et al[9] retrospectively applied VAC criteria to data from a prospective time-series study in which VAP clinical practice guidelines were implemented in 11 ICUs. Of 1,320 patients evaluated, a VAC developed in 139 (10.5%), an infection-related VAC (IVAC) developed in 65 (4.9%), and VAP developed in 148 (11.2%). The statistical agreement (κ) between VAP and VAC was 0.18 and between VAP and IVAC, 0.19. Notably, Muscedere et al[9] found that increased adherence to VAP prevention guidelines during the study was associated with decreased VAP and VAC rates but no change in IVAC rates. In a recent prospective observational study, we also observed poor sensitivity of the VAC criteria for the detection of VAP (sensitivity, 25.9%; 95% CI, 16.7%-34.5%).[10] More importantly, we observed that VAP was the most common cause of VACs, and the majority of VACs were adjudicated to be nonpreventable events. These findings suggest that efforts aimed at simply improving or stabilizing oxygenation indexes during mechanical ventilation may not have an impact on the occurrence of VAP or other infection-related complications associated with mechanical ventilation.

It is unlikely that VAP will disappear as an important clinical complication of respiratory failure. Available data suggest that its occurrence is relatively uniform globally and that most of the pathogens associated with VAP are antibiotic resistant, requiring broad-spectrum antimicrobials.[5,8] Given this set of circumstances, it seems logical to continue to develop enhanced strategies for the prevention of VAP. Simply increasing the use of well-established and validated prevention bundles can reduce the occurrence of VAP and seems to represent a relatively simple first step.[9] TAs may still play a role in the prevention of VAP. The question is how best to apply TAs and what type of TA would be optimal for use in VAP prevention. There is increasing interest in the use of aerosolized antibiotics for the treatment and prevention of VAP to include the use of novel combinations that have an enhanced ability to minimize the development of resistance.[11] Additionally, topical administration of antiseptic agents through the endotracheal tube could contribute to lowering the rates of antibiotic-resistant VAP if cost-effective approaches for their use can be developed.[12]

In the meantime, what should ICU clinicians and investigators do? First, they should support efforts within their own ICUs aimed at preventing VAP and other hospital-acquired infections through the use of bundles or other prevention programs. Second, antimicrobial stewardship principles should be universally promoted throughout the hospital aimed at minimizing the emergence of antibiotic resistance. Finally, research efforts focused on developing novel and effective approaches for the prevention, rapid diagnosis, and effective treatment of VAP and other antibiotic-resistant infections should be encouraged.

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Ventilator-Associated Pneumonia Prevention Methods Using Topical Antibiotics

Herd Protection or Herd Peril?

James C. Hurley, MBBS, DMedSci, MEpi, PhD

Ventilator-associated pneumonia (VAP) develops in approximately 20% of patients in the ICU receiving prolonged mechanical ventilation (MV). Among the range of methods for preventing VAP, the evidence base for topical antibiotics (TAs), including selective digestive decontamination, appears to be the most compelling. However, several observations are puzzling, and the contextual influence resulting from concurrent use of both topical placebo and TA within an ICU remains untested. As with herd protection conferred by vaccination, contextual influences resulting from a population-based intervention cannot be estimated at the level of a single trial. Estimating contextual effects requires multilevel random-effects methods. In this way the dispersion in VAP incidence across groups from 206 studies, as cited in various-source systematic reviews, was calibrated. The benchmark mean VAP incidence derived from 49 observational groups of patients receiving MV is 23.7% (95% CI, 20.6%-27.2%). In contrast, for 20 and 15 concurrent control groups from the TA evidence base that did vs did not receive topical placebo, respectively, this incidence is 38% (95% CI, 29%-48%) and 33% (95% CI, 20%-50%). This contextual influence remains significant in a meta-regression model adjusted for group-level variables, such as within a trauma ICU context. The mean VAP incidence for five other categories of control groups from the broader evidence base is within four percentage points of the benchmark. The contextual effect of TA is paradoxic, peculiar, potent, perfidious, and potentially perilous. The TA evidence base requires reappraisal to consider this herd peril.

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ABBREVIATIONS: CRCDBT = concurrent randomized controlled double-blind trial; MV = mechanical ventilation; SDD = selective digestive decontamination; TA = topical antibiotic; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) develops in approximately 20% of patients in the ICU receiving prolonged mechanical ventilation (MV).[1-8] Moreover, the estimated attributable mortality rate of VAP is 13%.[9] Bacterial colonization originating partially from either the GI or the upper respiratory tracts and partially from cross-colonization

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within the ICU precedes the development of VAP (Fig 1). Hence, there are multiple potential sites at which this progression from colonization through to VAP might be disturbed.

A wide range of VAP prevention methods have been studied. Sixteen systematic reviews[10-25] contain abstracted VAP incidence data for 157 groups across a broad evidence base of VAP prevention methods. In addition, three systematic reviews contain abstracted VAP incidence data for 49 groups from observational studies.[4-6]

The methods of VAP prevention can be broadly classified into nonantibiotic-based methods delivered through either the gastric route,[10-14] the airway route,[15-20] or the oral care route[21-23] and various antibiotic-based methods.[23-26] The gastric route methods include various types of stress ulcer prophylaxis (two systematic reviews,[10,11] 17 studies), enteral feeding (one systematic review,[12] eight studies), and probiotics (two systematic reviews,[13,14] 10 studies). The various airway route methods include secretion drainage (two systematic reviews,[15,16] 24 studies), inspired air humidification (one systematic review, 12 studies),[17] secretion management by body posturing (two systematic reviews,[18,19] 16 studies), and programmed circuit changes (one systematic review,[20] two studies). The oral care methods (three systematic reviews,[21-23] 16 studies) studied were of various antiseptics, such as chlorhexidene and tooth brushing.

On the other hand, antibiotic-based methods, such as selective digestive decontamination (SDD), are based on the administration of antibiotics to the oropharynx topically through a nasogastric tube to the stomach and possibly parenterally. These studies are summarized in three systematic reviews (40 studies)[23-25] and a meta-analysis[26] and can be further classified into those in which control groups were concurrent with the study group and received no placebo, concurrent and received placebo alone, concurrent and received up to 5 days of parenteral antibiotics routinely (duplex studies), and nonconcurrent.

The evidence base for topical antibiotics (TAs) appears the most compelling. In meta-analyses of studies of TAs

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both with concurrent[23-26] and with nonconcurrent[26] control groups, the apparent reduction in VAP incidence is $>50\%$, whereas in studies of methods of VAP prevention other than TAs the reduction is $<50\%$.[10-20]

The challenges to study design in the evaluation of these various VAP prevention methods are several.[26-28] First, there are presumably unknown risk factors for VAP in addition to the known risk factors, such as admission for trauma.[27-29] Second, multiple definitions for VAP are available, and which is the most objective and unambiguous is debatable.[30] Some studies have avoided VAP as a study end point altogether.[31]

These two challenges are optimally controlled within a concurrent randomized controlled double-blind trial (CRCDBT) study design. First, the randomized assignment of patients to concurrent control and intervention groups minimizes bias arising from confounding in that all risk factors for the study end point, whether known or unknown, are distributed randomly between the groups. Second, concealing group allocation through the use of a matching placebo minimizes observer bias resulting from diagnostic ambiguity. Third, in defining the evidence base and in deriving summary estimates, studies with these attributes are graded with a higher quality of study design and are preferentially included over unblinded studies and studies that use historic control groups.

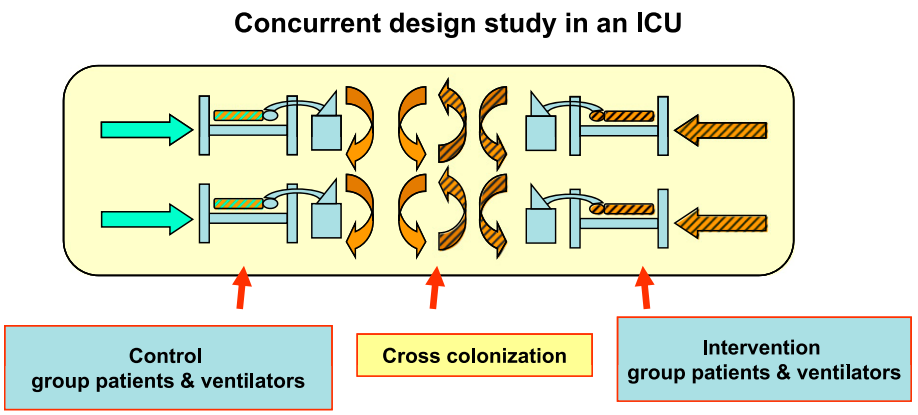

Figure 1 – *Schematic of control and intervention patients receiving mechanical ventilation in an ICU. Color coding within horizontal arrows represent different colonizing flora, and circular arrows represent contextual effects resulting from cross-colonization.*

For studies of TA, there are two additional considerations.[27,32,33] Does the placebo used to achieve study blinding within a CRCDBT have any effect on the study end points? Is there any contextual effect resulting from a change in the colonizing flora within an ICU resulting from a unit-wide intervention with TAs (Fig 1)? Common TA regimens include polymyxin and an aminoglycoside. The use of SDD results in decreased colonization with aerobic gram-negative bacilli at the oropharynx but increased colonization with gram-positive bacteria such as *Staphylococcus aureus*.[34-36] This increased colonization is also reflected in a higher proportion of *S aureus* among VAP isolates.

That TAs could engender a contextual effect within the ICU was postulated in the original 1984 study of SDD by Stoutenbeek et al.[37] According to the authors, studying SDD within a concurrent trial design was not appropriate because

> …in the first place it was considered likely that having heavily contaminated controls next to decontaminated patients might adversely affect the potential beneficial results. Secondly, a reduction in the number of contagious patients by applying SDD in half of them, might reduce the acquisition, colonisation and infection incidence in the not SDD treated control group [Stoutenbeek postulates 1 and 2]. (p. 186)[37]

Hence, to avoid these contextual effects, the study by Stoutenbeek et al[37] and others[31] were intentionally nonconcurrent in design.

A more readily recognizable example of a contextual effect is the indirect effect of vaccination programs in a population contributing to herd immunity. In the clinical evaluation of new vaccines, herd protection will be inapparent in a comparison of event rates at the level of analysis of any single CRCDBT.[38] Testing for herd protection requires cluster randomized trials.

The objectives of this commentary are to test the two Stoutenbeek postulates and to demonstrate the potential application of multilevel analysis to a critical care research question using random-effects methods and the VAP evidence base as an example. The search strategy and selection criteria used in deriving the studies included in this calibration are as follows. Systematic reviews published from January 1981 to June 2013 were identified through searches of PubMed, the Cochrane database, and Google Scholar using the terms "ventilator associated pneumonia," "mechanical ventilation," "systematic review," and "meta-analysis." Studies were sourced exclusively from these systematic reviews, with the exception of 15 studies of SDD with nonconcurrent control groups. To enable tests of postulates 1 and 2, these studies with nonconcurrent control groups have been sourced here as done previously[26] because they are not included elsewhere. All studies and data are listed in e-Tables 1 to 5. Characteristics of the studies cross-referenced with e-Tables 1 to 5 are presented in Table 1.

Estimating the contextual effects within studies requires a calibration of the observed event rate among the control groups of these studies vs an external reference or benchmark range using random-effects methods. The event rates of the intervention groups from these studies are of secondary interest and are calibrated separately. The concepts underlying the multilevel analysis used in this study to enable a calibration of postulates 1 and 2 follow a five-step method. First, a benchmark of VAP incidence is derived from systematic reviews of VAP incidence in patients receiving MV under observation from studies without any study intervention.[5-7] Second, the systematic reviews of the various VAP prevention methods are used as the source of both the studies and, where possible, the data on which the calibration is based.[10-25] Sourcing the studies and the VAP incidence data from the systematic reviews helps to provide a clearly constituted evidence base and an objective and transparent source of VAP incidence for the studies. Because the interest is in the contextual effect of group membership, these data need to be from groups on an as-treated rather than intention-to-treat basis where possible.

Third, the VAP incidence proportions are transformed to logits and logit variances. This step serves two purposes. On the logit scale, the 95% CI for proportions are symmetrical and confined within the interval of 0% to 100%. Additionally, the logit transformation enables the inferential property of the proportion to be retained. For example, the inference of the proportion 4 of 10 is different from the proportion 400 of 1,000 in that the proportion with the larger denominator has greater precision as reflected in a smaller variance.

Fourth, summary logits and associated summary 95% CIs using random-effects methods can be derived by meta-analysis with the metan command in STATA 12.0 (StataCorp LP), which, in turn, are back-transformed onto the percentage scale.[39,40] The benchmark range of VAP incidence is the summary and 95% CIs derived in this way using the observational groups. Likewise, a summary and 95% CI of VAP incidence can be derived for each of the various categories of control and intervention groups from the evidence base. All these 95% CIs are derived by random-effects methods and are

TABLE 1] Characteristics of Studies

Characteristic	Observational (No Intervention)	Nonantibiotic Studies			TA Studies			
		Gastric	Airway	Oral Care	Nonconcurrent	Duplex[a]	Concurrent and Without Topical Placebo	Concurrent and With Topical Placebo
Supplemental material[b]	e-Table 1	e-Table 2	e-Table 3	e-Table 4	e-Table 5	e-Table 5	e-Table 5	e-Table 5
Publication y, range	1986-2007	1989-2012	1988-2010	2000-2012	1987-2011	1991-1997	1987-2007	1974-2007
Studies[c]	49	34	58	13	14	7	16	20
Studies with < 90% of patients receiving > 48 h MV	3	2	0	2	3	0	3	0
Bronchoscopic sampling for VAP diagnosis[d]	18	4	16	2	5	1	2	6
Trauma ICUs[e]	7	16	9	2	1	3	4	9
EU[f]	25	18	27	6	10	6	14	15
Patients per study group	264 (175-452)	56 (30-82)	51 (26-99)	53 (31-96)	72 (55-84)	46 (41-125)	50 (39-92)	51 (32-126)
Days of ventilation	11 (7-15)	9 (7-15)	10 (8-12)	13 (8-15)	9 (7-15)	9 (7-15)	10 (8-12)	13 (8-15)
VAP incidence per 100 patients								
Observational								
Mean (95% CI)	24 (21-27)	…	…	…	…	…	…	…
No. studies	49	…	…	…	…	…	…	…
Control								
Mean (95% CI)	…	26 (20-33)	26 (21-31)	27 (18-38)	27 (14-44)	27 (14-46)	33 (20-50)	38 (29-48)
No. studies	…	36	58	11	10	7	15	20
Intervention								
Mean (95% CI)	…	18 (14-22)	17 (14-21)	16 (12-21)	9 (4-16)	14 (6-28)	10 (8-14)	17 (12-24)
No. studies	…	37	59	19	12	7	18	20

Data are presented as counts or median (interquartile range) unless otherwise indicated. EU = European Union; MV = mechanical ventilation; TA = topical antibiotic; VAP = ventilator-associated pneumonia.

[a]All control group patients from duplex studies received up to 5 d of parenteral antibiotics routinely.

[b]The VAP incidence data were sourced from 16 systematic reviews[10-25] and one meta-analysis.[26]

[c]Several studies had more than one or no control or intervention groups. Hence, the number of groups does not equal the number of studies.

[d]Bronchoscopic vs tracheal sampling for VAP diagnosis.

[e]Trauma ICU arbitrarily defined as an ICU with > 50% of admissions for trauma.

[f]No. studies originating from a member state of the EU as of 2010 or from Switzerland or Norway.

more conservative (wider) than those derived by fixed-effects methods.[41] These random-effects methods are integral to multilevel methods because they enable the variance estimates derived at one level to be used in deriving the summary estimates at the higher level. With random effects, the underlying assumption is that the observed proportions (logits) used in estimating the benchmark range are simply a random sample from a potentially infinite set of such proportions (logits) that could have been sampled. The alternative is the fixed-effects presumption with an expectation that the underlying proportion is uniform across all studies, which is implausible here given the broad range of VAP definitions, populations, study designs, and interventions within the various studies.

Fifth, this benchmark is used as the basis for calibrating the dispersion in VAP incidence in control and, separately, intervention groups from studies of the various methods to prevent VAP. This is done most simply as a display of summary mean and 95% CIs derived from the various categories of control and intervention groups (Fig 2). Additionally, it is possible to estimate the numbers of outlier groups in a scatter plot (Fig 3) or funnel plot[27] and to visually assess symmetry in a caterpillar plot.[33] A comparison of group-level factors can be undertaken as a random-effects meta-regression with adjustment for known confounders (Table 2, e-Table 6).[42,43]

In this way, the benchmark of VAP incidence derived using 49 groups from nonintervention studies is 23.7% (95% CI, 20.6%-27.2%; 95% prediction interval, 8.3%-51.6%). For comparison, the mean VAP incidence reported in large US,[7] French,[8] Canadian,[44] Chinese,[45] and literature-derived[2,27] multicenter databases of groups of patients receiving MV were all $<26\%$. With one exception, the magnitude of the difference in mean VAP incidence for all categories of control groups vs the benchmark is <4 percentage points (Fig 2A, Table 1). Of note, for studies of TA-based VAP prevention methods that used topical placebo to achieve study blinding, the difference between the mean VAP incidence in the control groups vs the benchmark (14 percentage points) not only exceeds four percentage points but also is greater than the magnitude of the difference in mean VAP incidence of the corresponding TA intervention groups vs the benchmark (seven percentage points). Moreover, the dispersion in the mean VAP incidence across the various categories of control groups within the studies of TAs is 11 percentage points, which not only exceeds that of all other categories of control groups but also equals that among all categories of intervention groups

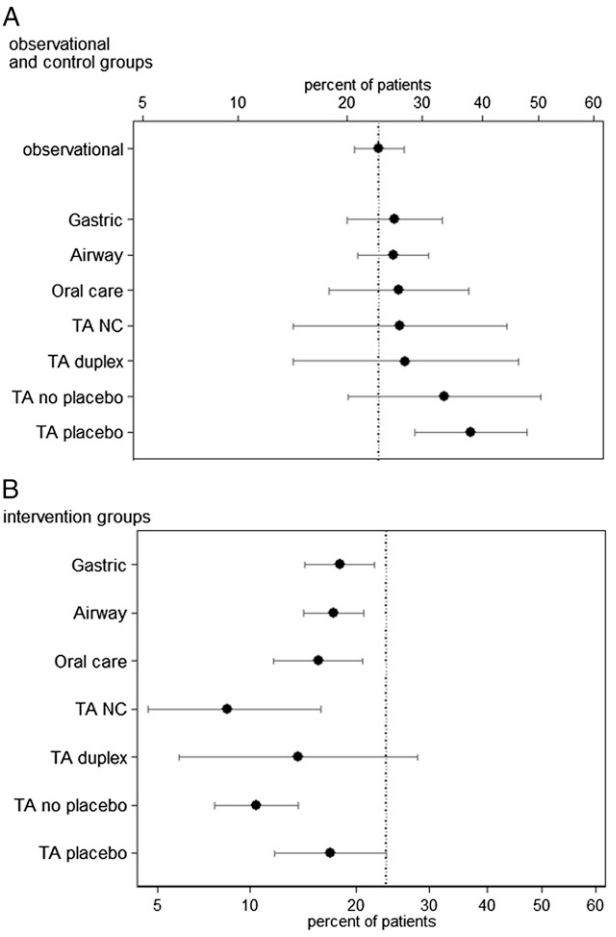

Figure 2 – *Category-specific mean ventilator-associated pneumonia incidence and 95% CIs. A, Observational and control groups. B, Intervention groups. The dashed line shows the summary mean ventilator-associated pneumonia incidence derived from the observational studies. Note that the x-axis is a logit scale. NC = nonconcurrent; TA = (studies of) topical antibiotic.*

(Fig 2B, Table 1). This overdispersion among the control groups of studies of TA is puzzling given that there are 41 different TA and nonantibiotic regimens among these intervention groups in the broader evidence base. The dispersion of VAP incidence of groups located within the 95% prediction interval of the benchmark is unusual (Figs 3A, 3B) in that among studies of TA in which topical placebo was concurrently used, the dispersions in VAP incidence among the intervention and control groups are each skewed but in opposite directions.

In a random-effects meta-regression with adjustments for known confounders (Table 2), the magnitude of the contextual influence on VAP incidence within a control group concurrent to a TA group is similar in magnitude and opposite in direction to the direct effect of the TA intervention itself and similar in magnitude to the contextual effect of being in a trauma ICU. The apparent neutral contextual effect in control groups of duplex

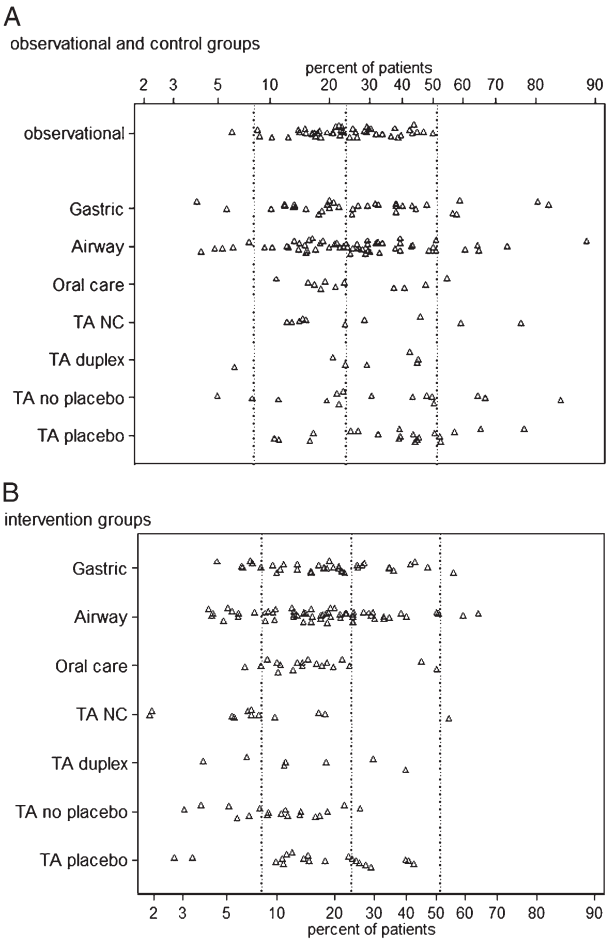

Figure 3 – *Scatter plots of ventilator-associated pneumonia incidence. A, Observational and control groups. B, Intervention groups. The center dashed line shows the summary mean ventilator-associated pneumonia incidence derived from the observational studies together with the 95% prediction intervals (right and left dashed lines). Note that the x-axis is a logit scale. See Figure 2 legend for expansion of abbreviations.*

studies is likely explainable by the routine study use of parenteral antibiotics in these groups. In a random-effects meta-regression of the intervention groups with likewise adjustments, the magnitude of the contextual influence of TA on VAP incidence is significantly less in the context of concurrent vs nonconcurrent TA study designs (e-Table 6).

Elsewhere, several additional paradoxic findings emerged from meta-regressions of the proportions of *S aureus* and *Pseudomonas aeruginosa* among the VAP isolates of SDD studies.[42,43] First, the mechanism for the profound effect of SDD on VAP incidence is difficult to explain on the basis of its antibacterial effect. Although SDD formulations usually include polymyxin and an aminoglycoside, two antibiotics that both have antipseudomonal activity, this cannot account for the preventive effect of SDD on VAP.[42] Indeed, within the context of the SDD studies, the magnitude of the statistically significant increase in the incidence of *S aureus* among control groups receiving topical placebo is greater than the magnitude of the statistically insignificant decrease in the incidence of *P aeruginosa* among the intervention groups receiving SDD.[43] In contrast, within the context of the studies of oral care methods, topical placebo has no significant influence on the overall incidence of VAP or on the proportions of either *S aureus* or *P aeruginosa* among the VAP isolates.[43]

One final paradoxic observation has emerged from a recent meta-analysis of the effect of SDD on the prevalence of antibiotic-resistant bacteria within studies of SDD.[46] It was found that polymyxin-resistant gram-negative bacteria (OR, 0.58; 95% CI, 0.46-0.72), third-generation cephalosporin-resistant gram-negative bacteria (OR, 0.33; 95% CI, 0.20-0.52), and vancomycin-resistant enterococci (OR, 0.73; 95% CI, 0.51-1.05) were less common among recipients of SDD than among the comparator groups. The study authors conceded that their findings seemed to contradict the well-established relation between antimicrobial use and selection of antimicrobial resistance.[46]

In comparing the mean VAP proportions for control groups vs the corresponding intervention groups (Table 1), the ratio is $<50\%$ for the studies of methods of VAP prevention other than antibiotics in each case and $>50\%$ for the various categories of TA methods. These estimates broadly correspond to the summary effect size estimates in the systematic reviews from which these studies and the data were drawn. In relation to postulates 1 and 2, the VAP incidence in intervention groups was higher in TA studies for which the control groups were concurrent vs nonconcurrent (e-Table 6), as per postulate 1. However, the VAP incidence was significantly higher vs the benchmark in control groups concurrent with TA groups, contrary to postulate 2.

A multilevel analysis is inherently observational, which is both a study strength because there is no direct method for estimating a contextual effect and a limitation because it cannot explain why any single group may appear to be a statistical outlier. Moreover, being conducted at the group level rather than at the patient level, multilevel analysis is unable to estimate or control for the impact of unmeasured and unknown patient-level risk factors for VAP. However, it is unlikely that such unidentified patient-level risk factors would be able to account for the discrepancies noted here. Such a putative risk factor would need to be consistently stronger for VAP than, for example, trauma (which increases the risk for VAP by up to fivefold[28,29]) yet also be profoundly

TABLE 2] Logit VAP Incidence From Observation and Control Groups: Random-Effects Regression Models

Factor	Coefficient[a]	95% CI	*P* Value
Groups from observational studies (reference group)	−1.18	−1.43 to −0.94	< .001
Nonantibiotic studies			
Gastric	−0.04	−0.41 to 0.33	.83
Airway	0.07	−0.24 to 0.38	.67
Oral care	0.18	−0.36 to 0.72	.51
TA studies			
Nonconcurrent	0.36	−0.20 to 0.93	.21
Duplex	0.02	−0.63 to 0.68	.95
Placebo not used[b]	0.51	0.02 to 0.99	.04
Placebo used[c]	0.44	0.01 to 0.87	.05
Mode of diagnosis[d]	−0.06	−0.32 to 0.21	.67
Trauma ICU[e]	0.54	0.26 to 0.82	.001
< 90% MV[f]	−0.70	−1.19 to −0.21	.006

SDD = selective digestive decontamination. See Table 1 legend for expansion of other abbreviations.

[a]For each model, the reference group is the observational study (benchmark) group, and the coefficient equals the difference in logits from 0 (a logit equal to 0 equates to a proportion of 50%; a logit equal to −1.23 equates to a proportion of 22.6%); the other coefficients represent the difference in logits for groups positive for that factor vs the reference group.

[b]Repeating the analysis with omission of six TA studies for which intervention groups received non-SDD regimens resulted in this coefficient being 0.49 (95% CI, −0.057 to 1.00; *P* = .052).

[c]Repeating the analysis with omission of six TA studies for which intervention groups received non-SDD regimens resulted in this coefficient being 0.55 (95% CI, 0.07-1.02; *P* = .03).

[d]Diagnosis of VAP using bronchoscopic vs tracheal-based sampling.

[e]Trauma ICU arbitrarily defined as an ICU for which > 50% of admissions were for trauma.

[f]Groups for which < 90% of patients received > 24 h of MV.

unevenly distributed, predominating in the groups of the TA studies that used topical placebo vs other groups within the broader evidence base examined here. Although most of the SDD studies came from European countries, there is no obvious reason why these studies might systematically differ to account for the results here.

The possible influence of studies that were unpublished or otherwise missing remains to be considered. However, previous testing for possible publication bias indicated that this deficit would need to be > 400 control groups with a VAP incidence of < 47% to normalize the skewed distribution in VAP incidences among the control groups within the SDD evidence base alone.[27]

Additional studies of TA other than SDD regimens have been included here, although there are too few to enable an assessment of whether the contextual effect differs for SDD vs non-SDD TA. Repeating the meta-regression with these studies excluded does not materially change the findings (Table 2, e-Table 6).

The mechanism for the contextual effect on VAP incidence arising within studies of TAs identified here can be postulated as follows. First, in the intervention group, TA directly increases the colonization pressure with gram-positive bacteria such as *S aureus*,[47] which increases the risk for cross-infection in an ICU.[48,49] Indeed, SDD interventions are known to have complex ecologic effects.[50] Second, the application of TA in the intervention groups and placebo paste in the control groups of up to four times daily in these studies could have been vehicles for inapparent cross-colonization and infection both to and from the patients in each study. Because *S aureus* accounts for approximately 20% of VAP isolates, only a minority of the increase could be accounted for by this isolate. However, this cross-infection mechanism is a more logical explanation for the paradoxic observations noted previously in relation to the apparent "reduction" in resistant bacteria with TA.[46]

Conclusions

Multilevel methods using random effects will have increasing applications in medicine, particularly in the context of critical care. Examples of such applications to diagnostic and prognostic tests are described elsewhere.[51,52]

A calibration of VAP incidence within the component groups of the broader evidence base of VAP prevention

methods enables validation of the Stoutenbeek postulates. There is a potent and perfidious contextual effect within the CRCDBTs of TA that increases the VAP incidence by as much as 14 percentage points in both concurrent intervention and control groups. These contextual effects could explain several otherwise puzzling and paradoxic observations within these studies.

This contextual effect is inapparent without the use of multilevel modeling methods. Of concern, this contextual effect on the control group has the potential to inflate the apparent effect of TA within studies having a CRCDBT design and more so for studies ranked highly on the basis of two study design attributes: randomization of concurrent patients and observer blinding achieved with topical placebo use. In the development of any therapy but especially a preventive intervention, the first imperative is to demonstrate no harm, which has yet to be done with respect to the evaluation of TA as a method of VAP prevention.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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