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MAJOR ARTICLE

Unusually High Incidences of *Pseudomonas* Bacteremias Within Topical Polymyxin–Based Decolonization Studies of Mechanically Ventilated Patients: Benchmarking the Literature

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Background. Topical polymyxin (PM)–based regimens to decolonize patients receiving prolonged mechanical ventilation (MV) have been widely studied. However, paradoxical bacteremia incidences remain unexplained.

Methods. The literature was searched for studies of topical PM–based regimens used to decontaminate MV patients reporting incidences of overall and *Pseudomonas* bacteremia data. In addition, observational groups without any intervention and trials of various interventions other than topical PM (non-PM studies) served to provide external benchmarks and additional points of reference, respectively. The bacteremia incidences were extracted from the control and intervention (component) groups of these studies and compared with metaregression using generalized estimating equation methods.

Results. The summary odds ratio derived from studies of topical PM–based interventions against overall bacteremia was 0.60 (95% confidence interval [CI], 0.53–0.69). Benchmark incidences per 100 MV patients for overall (mean, 8.9%; 95% CI, 6.9% to 10.9%) and *Pseudomonas* (mean, 0.7%; 95% CI, 0.5% to 1.1%) bacteremia were derived from 16 observational studies. By contrast, among 17 studies of topical PM, the mean incidences among control groups for overall (mean, 15.3%; 95% CI, 11.5% to 20.3%) and *Pseudomonas* (mean, 1.6%; 95% CI, 0.9% to 3.1%) bacteremia were both higher, whereas these incidences in the intervention groups for both topical PM and non-PM studies were in each case more similar to the respective benchmarks. These paradoxical incidences cannot readily be explained in metaregression models.

Conclusions. Paradoxically, despite an apparent prevention effect of topical PM–based methods against bacteremia overall, the incidences of *Pseudomonas* bacteremia within the component groups of these studies are unusually high vs literature-derived benchmarks.

Keywords. bacteremia; intensive care; *Pseudomonas*; polymyxin; selective digestive decontamination.

Topical polymyxin (PM) is a common component within selective oral decontamination and selective digestive decontamination (SOD/SDD) regimens. The evidence in support of SDD/SOD vs other methods of infection prevention toward preventing intensive care unit (ICU)–acquired infections among patients receiving mechanical ventilation (MV) appears compelling [1–4].

SDD/SOD achieve apparent reductions in incidences of bacteremia and ventilator-associated pneumonia (VAP) that are typically >50% [1–4]. Moreover, the apparent reduction in Gram-negative bacteremia is also >50% [5, 6]. By contrast, reductions achieved with other infection prevention methods are generally <50% in this patient group [7–10]. Some decontamination strategies are undergoing reappraisal as a result of uncertain benefit and safety concerns in the MV population [9].

The mechanisms underlying this apparent reduction are of great interest. However, 4 aspects of the SDD/SOD studies complicate their interpretation. First, there is a multiplicity of study designs and end points of interest among these studies [11]. Second, the incidences of VAP [12] and bacteremia [13] among studies of SDD/SOD are unusually and unaccountably high vs incidences in comparable patient populations. Third, the relative effects of the parenteral vs topical components of SDD/SOD remain to be clarified, and, confusingly, several control and intervention groups among the SDD/SOD studies received protocolized parenteral antibiotic prophylaxis (PPAP).

Finally, the possibility of contextual effects, including that topical antibiotic use might alter the ICU microbiome, (the Stoutenbeek postulates) needs to be considered [14]. For example, there are several reports of the use of either topical PM or SDD/SOD aimed at achieving control of ICU outbreaks of multiresistant Gram-negative bacteria [15–17]. On the other hand, there is concern regarding the emergence of Gram-negative bacteria

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resistant to PM and other antibiotics resulting from their widespread use [18–20]. Of note, these contextual effects will not be apparent within individual studies examined in isolation [21].

Bacteremia offers a more objective end point than VAP. Moreover, *Pseudomonas* bacteremias are of particular interest [22]. *Pseudomonas* is an important cause of ICU-acquired bacteremia, and polymyxin is a key antibiotic with activity against it. The objective of this analysis is to benchmark the incidences of *Pseudomonas* bacteremia across a broad range of studies of the MV patient population and to model the associations between the topical PM vs the PPAP components of the SDD/SOD regimens on these end points.

METHODS

The objectives here are 3-fold:

- to develop benchmarks for overall and *Pseudomonas* bacteremias among published observational studies of patients receiving MV;
- to survey and compare the incidences of overall and *Pseudomonas* bacteremias within the component (control and intervention) groups decanted from these studies of topical PM–based interventions vs these external benchmarks;
- to model by metaregression the contextual (or group-level) effects of membership of the component groups within these studies. In all 3 objectives, a composite of studies of interventions that were other than topical PM (non-PM) provide additional points of reference.

Being an analysis of published work, ethics committee review of this study was not required.

Study Selection and Decant of Groups

The literature search and study decant used here (Figure 1) is in 6 steps; the first 3 recapitulate the search as described previously [13]. These 6 steps are detailed in Figure 1 (numbered arrows).

Outcomes of Interest

The *Pseudomonas* bacteremia incidence is the number of patients with *Pseudomonas* bacteremia per 100 patients receiving prolonged MV. One topical PM study [5] had reported a composite count of glucose-nonfermenting gram-negative rod (GNF-GNR) bacteremias instead of a separate count of *Pseudomonas* bacteremias, and this count is used as a surrogate count of *Pseudomonas* bacteremia.

The bacteremia incidences were expressed as a proportion, using the number of MV patients with prolonged (>24 hours) stay in the ICU as the denominator. In addition, the following were also extracted where available: the proportion of admissions for trauma, the incidence proportion of bacteremia overall. Other parameters extracted were the mean length of ICU stay for each patient group and whether the group was exposed to PPAP.

Effect Sizes: Direct

The study-specific and overall summary effect sizes and associated 95% confidence intervals for each of the PM and non-PM interventions against bacteremia overall were calculated using the DerSimonian-Laird random-effect methods of meta-analysis using the "metan" command [24] in Stata 14.2 (Stata Corp., College Station, TX).

Survey of Bacteremia

Caterpillar plots of the overall and *Pseudomonas* bacteremia incidence data were generated to facilitate a visual survey. These were generated as follows. Each bacteremia incidence datum for each group was logit-transformed to generate caterpillar plots using the "metan" command. For *Pseudomonas* bacteremia, this transformation proceeds as follows; with the number of MV patients as the denominator (D), the number of patients with *Pseudomonas* bacteremia as the numerator (N), and R being the *Pseudomonas* bacteremia proportion (N/D), the logit(*Pseudomonas* bacteremia) is log(N/(D-N)) and its variance is 1/(D*R*(1-R)). Note that for any group with a 0 event rate (N = 0), the addition of the continuity correction (ie, N + 0.5) is required to avoid indeterminate transformations of the logit proportion and its variance. For each bacteremia type, the benchmark is the summary incidence as derived in the caterpillar plot of the observational studies. This benchmark is used as a reference line in the respective plots of the component groups from the PM and non-PM studies.

Metaregression

Metaregression models for overall and *Pseudomonas* bacteremia incidence data were undertaken by 2 different methods. First, metaregression was undertaken of the bacteremia proportion data using generalized estimating equation methods. As an alternative method, the calculated logits and logit variances were analyzed using random effects methods with the "metareg" command [25]. Each metaregression model incorporates group-level factors, with predictors being the type of study, observational or intervention, with type of intervention being non-PM or topical PM, and with type of component group being membership in an observational group, a control group, or an intervention group. Within the topical PM studies, the SDD/SOD interventions, that is, exposure to topical PM and exposure to PPAP, were factorized. Other factors were whether the proportion receiving MV was less than 90% for the group and the group mean length of ICU stay. These predictor variables were entered into each model without any preselection step.

RESULTS

Characteristics of the Studies

Of the 38 studies identified by the search (Figure 1), 33 were sourced from the previous search [13] and 5 were sourced from elsewhere (Table 1). The majority of studies were published between 1990 and 2010, and a minority originated from trauma ICUs (Supplementary Data).

A total of 63 component groups were decanted from these 38 studies, with 18 groups from observational studies (Supplementary Table 1), 10 groups from studies of various

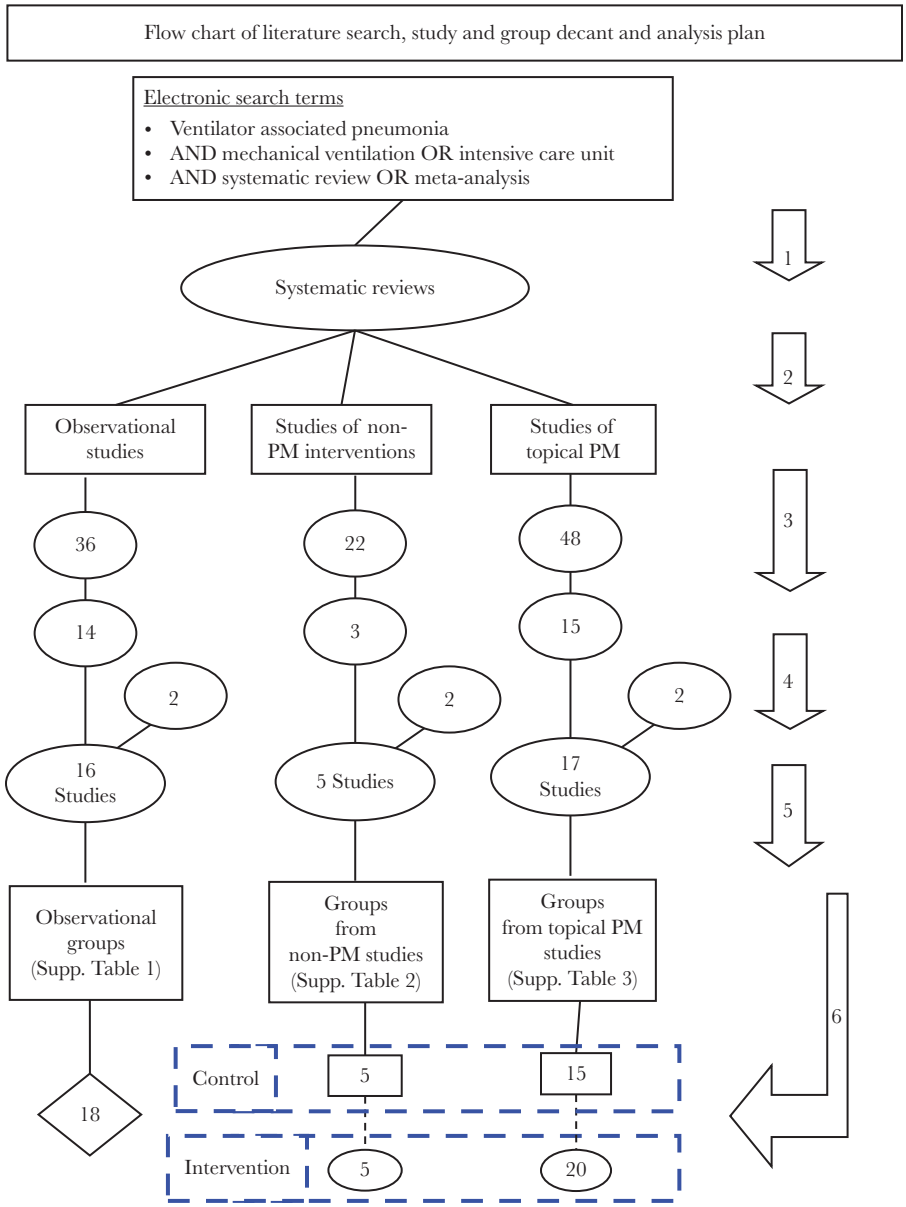

Figure 1. Search method, screening criteria, and resulting classification of eligible studies, and subsequent decant of component groups. The 6 numbered arrows are as follows: (1) An electronic search of PubMed, The Cochrane database, and Google Scholar for systematic reviews containing potentially eligible studies was undertaken using the following search terms: "ventilator associated pneumonia," "mechanical ventilation," "intensive care unit," each combined with either "meta-analysis" or "systematic review," through December 2017. (2) The systematic reviews were then searched for studies of patient populations requiring prolonged (>24 hours) intensive care unit (ICU) admission in 1 of 3 categories: studies in which there was no intervention (observational studies), studies with topical polymyxin (PM)-based interventions in any formulation, and studies of non-PM interventions (non-PM). The studies of non-PM methods of ventilator-associated pneumonia (VAP) prevention encompass a broad range of methods delivered via the gastric route, the airway route, or the oral care route. (3) The studies were screened against the following eligibility criteria. Inclusion criteria: studies in which incidence data for *Pseudomonas* bacteremia together with overall bacteremia were extractable as an incidence proportion with the denominator being the numbers of patients receiving mechanical ventilation (MV) with an ICU stay of at least 24 hours. Exclusion criteria: studies limited to patients with acute respiratory distress syndrome, studies in which fewer than 50% of patients received MV, and studies of topical antibiotics in the context of an ICU outbreak. Studies in a language other than English were included when the required data had been abstracted in an English language systematic review. Due to the absence of eligible studies of topical PM undertaken in Asia and Central and South America, together with the significant worldwide variation in *Pseudomonas*-associated VAP [23], studies from these regions were excluded from this analysis. (4) A hand search was undertaken for additional studies not identified within systematic reviews. (5) All eligible studies were then collated, and any duplicate studies were removed and separated into groups of patients receiving MV from studies without a VAP prevention method (observational groups) or studies of non-PM or PM interventions. (6) The component groups were decanted from each study as either observational, control, or intervention groups. Within studies of topical PM, any group receiving a formulation of topical PM was regarded as an intervention group, and all other groups were regarded as control groups.

non-PM methods of VAP prevention (Supplementary Table 2), and 35 groups from studies of topical PM (Supplementary Table 3). Six studies had more than 1 observational, control, or intervention group. The majority of groups from studies of topical PM methods had less than 70 patients per group, vs more than 100 patients in the majority of all remaining groups.

Table 1. Characteristics of Studies[a]

	Observational Studies	Studies of VAP Prevention	
	(No Intervention)	Nonpolymyxin Studies	Topical Polymyxin Studies
Study characteristics			
Sources	Table S1	Table S2	Table S3
No. of studies	16	5	17
Origin from systematic review[b]	4	3	10
LOS <5 d, No.[c]	5	0	3
MV for >48 h for <90%[d]	5	2	3
Trauma ICUs[e]	2	0	6
Use of PPAP in control group	0	0	5
Study publication year (range)	1988–2014	1999–2016	1984–2014
Group characteristics			
No. of patients per study group, median (IQR)[f]	327 (178–893)	114 (30–164)	61 (54–185)
Bacteremia prevention effect size			
Summary odds ratio (95% CI); No.	NA	0.82 (0.53 to 1.25); 5 Supplementary Figure 1	0.60 (0.53 to 0.69); 16 Supplementary Figure 2
Study characteristics			
Bacteremia incidence per 100 patients, mean (95% CI), %; No.			
Cohort	8.9[g] (6.9 to 10.9); 18 Supplementary Figure 3		
Control	NA	6.1 (1.7 to 19.8); 5 Supplementary Figure 4	15.3 (11.5 to 20.3); 15 Supplementary Figure 5
Intervention	NA	6.9 (2.7 to 16.8); 5 Supplementary Figure 4	9.5 (7.3 to 12.1); 20 Supplementary Figure 5
Pseudomonas bacteremia incidence per 100 patients, mean (95% CI), %; No. of groups			
Cohort	0.7[h] (0.5 to 1.1); 18 Supplementary Figure 6		
Control		0.2 (0.04 to 1.8); 5 Supplementary Figure 7	1.6[i] (0.9 to 3.1); 15 Supplementary Figure 8
Intervention		0.8 (0.3 to 2.2); 5 Supplementary Figure 7	1.3 (0.7 to 2.4); 20 Supplementary Figure 8

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MV, mechanical ventilation; PPAP, protocolized parenteral antibiotic prophylaxis; VAP, ventilator-associated pneumonia.

[a]Several studies had more than 1 control and/or intervention group. Hence the number of groups does not equal the number of studies.

[b]Studies that were sourced from 16 systematic reviews (references in the Supplementary Data).

[c]Mean length of stay for the group of less than 5 days.

[d]Studies for which less than 90% of patients were reported to receive >48 hours of MV.

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

[f]Data are median and interquartile range for numbers in the observation and control groups.

[g]This is the overall bacteremia benchmark, as derived in Supplementary Figure 3.

[h]This is the *Pseudomonas* bacteremia benchmark, as derived in Supplementary Figure 6.

[i]Recalculation of mean *Pseudomonas* bacteremia incidence and 95% CI after exclusion of the topical and parenteral ofloxacin arm of [26] gave 1.3 (0.6 to 2.7).

Of the 5 non-PM studies, 1 examined a sinusitis management protocol among MV patients, and the other 4 examined various chlorhexidine-based decontamination methods of infection prevention among MV patients. Among the 17 studies of topical PM methods there, were 4 main types of topical PM–containing regimens. Among the 35 component groups of these 17 studies, PPAP was used within 5 control and 14 intervention groups. One 3-arm topical PM study included both a topical PM arm and an ofloxacin-amphotericin arm [26]. The study by de Smet et al [5] of topical PM intervention did not provide a count of *Pseudomonas* bacteremia and the count of glucose-nonfermenting gram-negative rods (GNF-GNR) bacteremias was used [5].

Bacteremia Overall

The study-specific effect sizes of the non-PM and topical PM interventions against overall bacteremia incidence are presented as forest plots in Supplementary Figures 1 and 2. The effect sizes of the non-PM and topical PM interventions, expressed as summary odds ratios, were nonsignificant and significant, respectively (Table 1).

The overall bacteremia incidence benchmark was 8.9% (6.9%–10.9%) (Table 1; Figure 2). For 3 of the 4 categories of component group, the exception being the category of control groups from studies of topical PM, the mean overall bacteremia incidence was within 3 percentage points of this benchmark. In

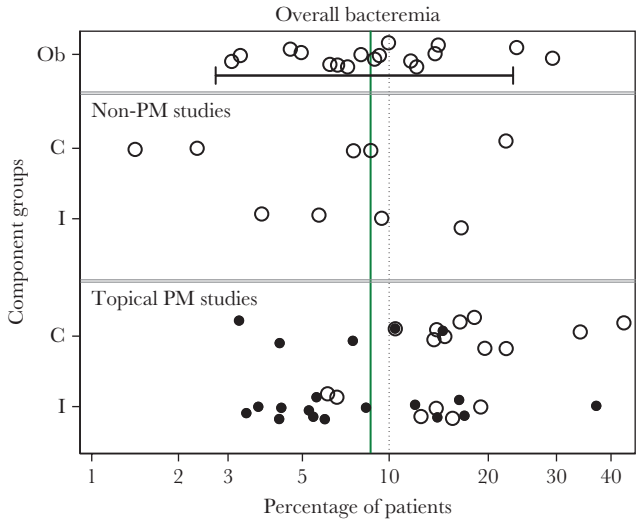

Figure 2. Incidence of overall bacteremia vs benchmark. The figure displays the bacteremia incidence for the component (C, control; I, intervention) groups of studies of either nonpolymyxin (non-PM)- or topical PM–based methods vs the respective benchmark being the summary mean (central solid vertical line) derived from the observational studies (Ob, observational) and associated 95% prediction limits (horizontal error bar). Incidences from groups that received PPAP are displayed as solid circles, and all other incidences are displayed as open circles. These data are displayed in more detail as caterpillar plots in Supplementary Figures 3–5.

a metaregression model adjusting for all the group-level factors, as detailed in Table 2, membership of a control group within a study of topical PM was the strongest association with overall bacteremia incidence. The strength of this association exceeded the magnitude of that associated with exposure to PPAP.

Pseudomonas Bacteremia

The *Pseudomonas* bacteremia incidence benchmark was 0.7% (0.5%–1.1%) (Table 1; Figure 3). By contrast, the mean *Pseudomonas* bacteremia incidence for control groups from studies on topical PM was 1.6% (0.9%–3.1%). After excluding the control group from de Smet et al [5] (for which a *Pseudomonas* bacteremia incidence was not available) and the ofloxacin arm of Verwaest et al [26], there were 16 *Pseudomonas* bacteremias among 1090 patients (1.5%) of 13 control groups from 13 studies of PM methods. By contrast, there were only 3 *Pseudomonas* bacteremias among 1072 patients (0.28%) of 10 component groups of 5 studies of non-PM methods.

In a metaregression model adjusting for all the group-level factors, as detailed in Table 2, membership of either a control or an intervention group within a study of topical PM was positively associated with *Pseudomonas* bacteremia incidence. The magnitude of each of these factors was greater than the magnitude of any other factor in this model, including that associated with exposure to PPAP.

DISCUSSION

This analysis benchmarks the incidences of overall and *Pseudomonas* bacteremias in the component groups of studies of SDD/SOD that included topical PM within the intervention.

Table 2. Metaregression Models[a,b]

	Overall bacteremia			*Pseudomonas bacteremia*		
Factor	Coef	95% CI	*p*	Coef	95% CI	*p*
Groups from observational studies (reference group)	–2.5	–2.8 to –2.1	.001	–5.7	–6.8 to –4.6	.001
Control groups						
Nonpolymyxin studies	+0.42	–0.69 to +1.53	.46	–0.65	–1.60 to +0.29	.18
Topical polymyxin studies[c,d]	+0.61	+0.26 to +0.95	.001	+1.29	+0.64 to +1.94	.001
Intervention groups						
Nonpolymyxin studies	+0.23	–0.72 to +1.21	.62	+0.64	–0.20 to +1.47	.13
Topical polymyxin studies[c,d]	+0.36	–0.16 to +0.88	.17	+1.22	+0.22 to +2.22	.016
LOS > 5 d[e]	+0.33	–0.01 to +0.68	.06	+0.70	0.01 to +1.39	.05
MVP < 90[f]	–0.03	–0.44 to +0.39	.89	+0.44	–0.29 to +1.17	.24
PPAP[g]	–0.35	–0.45 to –0.25	.001	–0.13	–0.26 to –0.01	.05
Year of publication[h]	–0.03	–0.06 to +0.01	.06	–0.05	–0.09 to –0.01	.01

Abbreviations: CI, confidence interval; LOS; length of intensive care unit stay; MVP, percentage of patients receiving >48 hours of MV; PPAP, protocolized parenteral antibiotic prophylaxis.

[a]These models were derived using generalized estimating equation methods. The findings derived using random effects methods were similar and are not shown.

[b]Interpretation: For each model, the reference group is the observational study (benchmark) groups, and this coefficient equals the difference in logits from 0 (a logit equal to 0 equates to a proportion of 50%; a logit equal to –2.2 equates to a proportion of 10%; a logit equal to –4.6 equates to a proportion of 1%), and the other coefficients represent the difference in logits for groups positive for that factor vs the reference group.

[c]The metaregression model was repeated with the third group from a 3-arm study (Verweast et al [26]), which received topical and parenteral ofloxacin, variously classified as either a control or intervention group. Regardless of how it was classified, the coefficients in the overall and *Pseudomonas* bacteremia models were not materially altered by the inclusion of this group (data not shown).

[d]As a sensitivity test for missing polymyxin studies, the metaregression model was repeated with component groups of all 5 nonpolymyxin studies arbitrarily reclassified as belonging to topical polymyxin studies. In this augmented model, the coefficients the overall and *Pseudomonas* bacteremia models were not materially altered (data not shown).

[e]The reference category is for LOS between 7 and 14 days.

[f]The coefficient representing the increment for groups for which less than 90% of patients received mechanical ventilation.

[g]The coefficient representing the increment for groups which received protocolized parenteral antibiotic prophylaxis.

[h]Year of study publication with the coefficient representing the increment for each year post-1990.

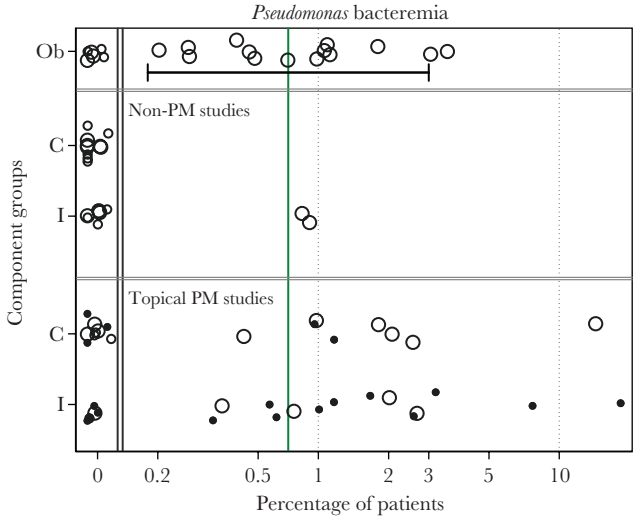

Figure 3. Incidence of *Pseudomonas* bacteremia vs benchmark. The figure displays the *Pseudomonas* bacteremia incidence for the component (C, control; I, intervention) groups of studies of either nonpolymyxin (non-PM)- or topical PM–based methods vs the respective benchmark being the summary mean (solid central vertical line) derived from the observation studies (Ob, observational) and associated 95% prediction limits (horizontal error bar). Incidences from groups that received PPAP are displayed as solid circles, and all other incidences are displayed as open circles. These data are displayed in more detail as caterpillar plots in Supplementary Figures 6–8.

These studies targeted ICU patients, the majority of whom received >24 hours of MV. This analysis is informed by data from other studies of comparable ICU patients receiving >24 hours of MV, including studies without an intervention, from which the benchmarks are derived, and studies of non-PM interventions. Of note, the summary effect sizes here for each of the 2 broad categories of prevention method, non-PM- and PM-based methods, against overall bacteremia incidence are similar to estimates within several systematic reviews and meta-analyses [1–4, 6, 7].

Pseudomonas bacteremias are associated with a doubling of the mortality risk [22]. The *Pseudomonas* bacteremia benchmark derived here is 0.7% (Table 1). Note that this benchmark incidence, being derived from groups within studies in which the majority of patients received >24 hours of MV, is higher than the incidences within the general ICU patient population (Supplementary Table 4).

There are 2 unexpected observations here. The summary overall and *Pseudomonas* bacteremia incidences derived from the control groups of studies of topical PM methods are higher vs the respective benchmarks and also vs the same incidences derived from the groups of non-PM-based methods. By contrast, the same incidences derived from the intervention groups of the PM-based methods are in each case more similar to the respective benchmarks than are the incidences derived from the control groups of these studies. That the *Pseudomonas* bacteremia incidences among the intervention groups of the topical PM studies are generally higher than for the respective incidences among the control and intervention groups of the non-PM studies is indeed surprising.

Metaregression models were developed using several group-level predictors of overall and *Pseudomonas* bacteremia incidences in an effort to account for these disparate observations. However, membership to neither type of intervention group was negatively associated with overall or *Pseudomonas* bacteremias within these models. By contrast and in each case, membership of a control group of a topical PM study remained a significant predictor of a higher incidence for each type of bacteremia, with the size of these associations exceeding the magnitudes of the associations with the group-wide use of PPAP. The association between group-wide use of PPAP and the incidence of overall bacteremia within the control and intervention groups of the SDD studies has previously been demonstrated among a larger collection of studies [13].

There are 4 key limitations to this analysis, the first being that the studies were published over a period of 3 decades. Hence, there was considerable heterogeneity in the interventions, populations, and study designs among the studies here. Moreover, the inclusion criteria for both the non-PM and topical PM interventions have been intentionally broadly specified. Hence, the summary effect sizes derived here, as displayed in Supplementary Figures 1 and 2, are indicative and intended for internal reference only.

The second limitation is that the analysis is inherently observational. A limited number of key group-level factors was entered into the metaregression models, and there was no ability to adjust for the underlying patient-level risk within the analysis. Hence, neither the nature of the contextual factor nor the exact source of the bacteremias can be identified.

The third limitation is that only those studies for which data were available were able to be included in this analysis. There were only 5 studies of non-PM interventions found for inclusion in the analysis.

Finally, another limitation is that this analysis is constrained by how the data were presented in the primary publications. The measure of bacteremia available from these publications for use in the analysis here, being an incidence proportion, is not ideal. A better measure would have been the incidence density being the number of infection episodes per 1000 days in mechanical ventilation. However, this measure was not available in the primary publications.

Are the findings robust to possible publication bias and undiscovered data? There are at least another ~1000 control group patients from ~20 known concurrent design studies of SDD/SOD in the literature for which *Pseudomonas* bacteremia data were not available. Assuming an incidence equivalent to the benchmark of 0.7% would give an additional 7 *Pseudomonas* bacteremias among this hypothetical 1000. Tallying these hypothetical and known bacteremias among 13 control groups as noted here would give 23 *Pseudomonas* bacteremias among

2000 control group patients, for an overall hypothetical incidence of 1.2%, which does not quench the excess.

However, at an expected incidence of <1% among patients receiving MV, *Pseudomonas* is a rare event. The majority of the SDD/SOD randomized controlled trials (RCTs) even among studies not included here had <70 patients per study arm. This relatively small group size would have been a limiting factor in whether *Pseudomonas* bacteremias were observed. A strength of this analysis is that, with the continuity correction, these 0 event studies are retained in the analysis. Also, the 95% CIs are displayed on the logit scale in the caterpillar plots with the group-specific *Pseudomonas* bacteremia incidence estimate. In this way, the relative precision associated with each estimate can be visualized even for 0 event studies on the logit scale (Supplementary Figures 6–8).

The disparity in the incidence of *Pseudomonas* bacteremia within studies of topical PM vs the respective benchmarks recapitulates similar observations for various end points among RCTs of SDD/SOD vs externally derived benchmarks from populations of patients receiving prolonged MV, for example, with respect to *Staphylococcus aureus* as a VAP isolate [27], *Acinetobacter* as a VAP isolate [28], *Candida* as a respiratory tract isolate [29], candidemia incidence [30], and *Pseudomonas* as a VAP isolate [14]. For each of these end points, the incidence is higher among control groups of randomized controlled trials of SDD/SOD vs the respective benchmarks.

CONCLUSIONS

Despite an apparent significant effect size of topical PM–based methods against overall bacteremia, there is a paradoxical excess of overall and *Pseudomonas* bacteremias in the studies of topical PM vs the benchmarks derived from the observational groups and also vs the non-PM studies. This excess is inapparent in any single topical PM study examined in isolation. The excess in *Pseudomonas* bacteremias cannot be readily accounted for in metaregression models.

Reconciling the apparent significant effect size against bacteremia overall with the higher incidence of overall and *Pseudomonas* bacteremias in the control groups vs the benchmark incidences and also vs the intervention group incidences implicates a contextual effect within the topical PM studies. This contextual effect presumably results from an altered microbiome consequent on the topical PM [31] and paradoxically causes an increase in both overall and *Pseudomonas* bacteremias in the studies of topical PM. The inference that topical PM–based interventions prevent *Pseudomonas* bacteremias is spurious and unsafe, with the higher incidences within the component groups of the topical PM–based studies otherwise unexplained.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the corresponding author.

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Author contributions. As sole author, J.H. designed the study, performed the statistical analysis, and wrote the manuscript. J.H. read and approved the final manuscript and is the guarantor of the paper.

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