Lack of impact of selective digestive decontamination on Pseudomonas aeruginosa ventilator-associated pneumonia: benchmarking the evidence base

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Background: The selective digestive decontamination (SDD) component antibiotics have activity against Pseudomonas aeruginosa, an important ventilator-associated pneumonia (VAP) isolate. Evaluating the relationship between the anti-pseudomonal activity of SDD towards its VAP prevention effect is complicated by postulated indirect effects of SDD mediated in the concurrent control groups. The objective here is to address these effects through a benchmarking analysis of the evidence base.

Methods: Forty-eight observational studies of VAP incidence and 43 interventional studies of SDD and other methods of VAP prevention were sourced from 10 reviews. The P. aeruginosa isolate proportion (P. aeruginosa-IP) data were summarized by meta-analysis using random effects methods. The mode of VAP diagnosis, proportion of trauma admissions and the intervention method under study were examined in meta-regression models as potential group-level predictors of P. aeruginosa-IP.

Results: The mean P. aeruginosa-IP derived from the observational studies (the benchmark) is 22.3% [95% confidence interval (CI) 19.8%–25.2%] versus 19.6% (95% CI 15.6%–24.4%) and 20.8% (95% CI 14.6%–28.5%) for concurrent control groups and intervention groups of SDD studies, respectively. In the meta-regression models, the proportion of trauma admissions is negatively correlated with P. aeruginosa-IP, whereas membership of neither a concurrent control nor intervention group of an SDD study is negatively correlated.

Conclusions: There is no evidence for either direct or indirect effects of SDD on P. aeruginosa-IP that could account for the profound effects of SDD on VAP incidence.

Keywords: antibiotic prophylaxis, study design, mechanical ventilation, cross-infection, nosocomial infection

Introduction

Approximately 20%–25% of patients receiving prolonged mechanical ventilation (MV) develop ventilator-associated pneumonia (VAP).1–5 Pseudomonas aeruginosa accounts for approximately 20% of VAP isolates3,6,7 and is associated with increased mortality risk.8 Systematic reviews of more than 30 controlled studies of selective digestive decontamination (SDD) provide compelling evidence of reductions in VAP of >50%9,10 versus marginally significant reductions of <20% with non-antibiotic-based methods of prevention such as those based on the management of gastric pH,11 tracheal suction12 or humidification.13 SDD decreases colonization with aerobic Gram-negative bacilli at the oropharynx in concurrent controlled trials.14 Also, SDD formulations usually include polymyxin together with an aminoglycoside, both of which have anti-pseudomonal activity. Indeed, studies prior to 1980 suggested that aerosolized polymyxin alone may be efficacious in reducing colonization15 and subsequent pneumonia16,17 associated with P. aeruginosa. Evaluating the contribution of the anti-pseudomonal activity of SDD towards the overall VAP incidence is complicated because of postulated indirect or contextual effects of SDD mediated in concurrent control groups. The indirect effect of vaccination programmes contributing to herd immunity in a population is a better recognized example of a contextual effect.

That SDD could create these contextual effects within the intensive care unit (ICU) was postulated in the original 1984 study of SDD.18 It was considered that studying SDD using a concurrent control and intervention patients 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.18 (reference 18, page 186). Hence, to avoid these contextual effects, the 1984 study18 and others19 were intentionally non-concurrent in design. Moreover, in an analysis of >150 studies of various VAP prevention methods, concurrency as a study design factor has a profound and unexplained effect on VAP incidence among the SDD studies.20

The aim of this analysis is to test for direct and indirect or contextual effects of SDD on the proportion of P. aeruginosa among the VAP isolates among the component groups of the SDD studies. The analysis requires an external benchmark of P. aeruginosa isolate proportion (P. aeruginosa-IP) derived from observational studies against which the dispersion of P. aeruginosa-IP among groups within the SDD and broader evidence base can be assessed. This analysis also examines the non-concurrent control groups of SDD studies and the component groups of studies of non-antibiotic methods of VAP prevention from the broader VAP prevention evidence base, as these groups would not be expected to exhibit a direct or contextual effect on P. aeruginosa-IP.

Methods

Overview

This is a group-level analysis of ICU patient groups receiving MV as abstracted in 10 published reviews of VAP incidence and specific VAP prevention methods.1-5,9,11-13,21 The objectives here are (i) to derive a benchmark of P. aeruginosa-IP from observational studies in the literature; (ii) to assess the dispersion among the group-specific P. aeruginosa-IP of control groups and intervention groups of interventional studies of SDD and other methods of VAP prevention versus the P. aeruginosa-IP benchmark using caterpillar plots; and (iii) to assess the impact of group-level factors as explanatory variables towards the dispersion among group-specific P. aeruginosa-IP using meta-regression.

Study selection and component group designations

The inclusion criteria for this analysis were a study of ICU patients receiving MV as abstracted in any of the 10 reviews1-5,9,11-13,21 and for which P. aeruginosa-IP and denominator data (numbers of VAP isolates) were available. The exclusion criteria that were specified by Liberati et al.9 were applied to achieve harmonization across studies sourced from all 10 systematic reviews. Specifically, studies of specific pre-selected types of patients (patients undergoing elective oesophageal resection, cardiac or gastric surgery, liver transplant or suffering from acute liver failure), studies of non-ICU populations, populations for which the proportion receiving MV for >24 h was <50% and studies for which VAP data were not available. Also, paediatric studies and studies published before 1984 do not appear among the studies abstracted in the review of Liberati et al.,9 and these study types are also excluded.

Categories of benchmark and component groups

The observational study (benchmark) groups from which the benchmark is derived (Table S1, available as Supplementary data at JAC Online) are abstracted in one of six reviews of VAP incidence.1-5,21 The component groups of the interventional studies of VAP prevention methods were sourced from four systematic reviews of studies of non-antibiotic methods.5,11-13 together with additional control groups from studies of these methods as abstracted in Safdar et al.7 (Table S2, available as Supplementary data at JAC Online) or the systematic review of SDD5 (Table S3, available as Supplementary data at JAC Online).

There are five types of component groups among the interventional studies of VAP prevention methods: the control and intervention groups from studies of non-antibiotic methods as abstracted in any of four systematic reviews;5,11-13 the control and intervention groups from concurrent control design studies of SDD regimen as abstracted in Liberati et al.21 and the non-concurrent control groups that were additional to the concurrent control and intervention study arms of three-arm SDD studies abstracted in Liberati et al.9

Data extraction

The P. aeruginosa-IP is the proportion of P. aeruginosa among the VAP isolates. This calculation allows for patients with multiple isolates. Also, the mode of VAP diagnosis, the group average duration of MV and the proportion of trauma admissions were abstracted directly from the original publication.

Statistical analysis

The P. aeruginosa-IP data were converted into logits for analysis as follows: if D represents the denominator, N represents the numerator and R represents the P. aeruginosa-IP (R = N/D), the logit (P. aeruginosa-IP) is log(N/(D – N)) and its variance is 1/(D×R×(1 − R)) 22,23 This variance formula was used to calculate the group-specific 95% confidence intervals (CIs). Using these calculated logits and using the inverse variance as the group weight, the metan command24 in STATA (version 11.0, STATA Corp., College Station, TX, USA) generates summary logits by a random effects method together with the standard errors (SEs) and r2, which are measures of within- and between-group variances, respectively, and the associated 95% CIs. The metan command also generates the caterpillar plots of the group-specific logits and 95% CIs.

The P. aeruginosa-IP benchmark was derived from the observational study (benchmark) groups as mean logit P. aeruginosa-IP. The associated 95% CI and 95% prediction interval (PI) were calculated on the logit scale using the metan command as mean±1.96×(SE2+r2)0.5 24

Comparisons of medians were made using either the Kruskal–Wallis test and comparisons of VAP incidence means were made using the two-sample t-test.

Caterpillar plots

Because of the logit scale, caterpillar plots were used in this analysis to display the deviation from the benchmark and the associated 95% PI. A caterpillar plot is a forest plot-like display of group-specific odds and 95% CIs with the studies listed in rank order of increasing event rate. This display reveals both the overall symmetry of the individual group results and their deviation from the summary value, with the larger groups, having greater precision, expected to deviate less.

Meta-regression

The calculated logits and logit variances were used with the metareg command25 in STATA (version 11.0, STATA Corp., College Station, TX, USA) to perform meta-regression models that incorporate group-level factors as predictors. There are four meta-regression models of logit P. aeruginosa-IP, including the observational study (benchmark) groups with either the control (models 1 and 2) or the intervention (models 3 and 4) groups of the prevention studies. Models 1 and 3 include group
membership (observational studies, SDD study or non-antimicrobial method study groups) as the only predictors. Models 2 and 4 include six additional group-level properties as predictor variables: whether the mode of diagnosis of VAP required bronchoscopic sampling, whether <90% of patients had received >24 h of MV, year of publication, number of patients in the group (group size), origin from a European ICU and the proportion of trauma admissions to the ICU. Coefficients were compared using the lincom (linear combination) post-estimation command in STATA.

Results

P. aeruginosa-IP data were available for 121 groups (Tables S1–S3), including 48 groups from observational (benchmark) studies abstracted in four non-systematic and three systematic reviews1–5,21 and 73 component groups from 43 interventional studies of SDD and non-antibiotic methods of VAP prevention abstracted in five systematic reviews (Table 1).5,9,11–13 The groups of the prevention studies had fewer patients (P=0.0001) and a higher proportion of admissions for trauma (P=0.03). Most studies were published in the 1990s. One of the studies had a duplex design, that is all control group patients routinely received 4 days of parenteral antibiotics as part of the study protocol.

The mean VAP incidence was >60% lower in the intervention groups versus the concurrent control groups of the SDD studies (P=0.005). However, in comparing the mean VAP incidences among component groups of the SDD studies versus the benchmark groups (Table 1), the concurrent control groups display greater disparity from the benchmark groups (15 percentage points, P=0.005) than is the case for the SDD intervention groups (10 percentage points, P=0.004) or the non-concurrent control groups (8 percentage points, P=0.2), as previously noted.20,26

The mean P. aeruginosa-IP derived from observational studies (which is the P. aeruginosa-IP benchmark) was 22.3%, the median was 22.7% and the 95% CI and 95% PI were 19.8%–25.2% and 11%–40%, respectively (Figure 1 and Table 2). The equivalence in the mean and median indicate a symmetrical distribution (Figure 1). The replicate derivations of mean P. aeruginosa-IP derived from various sources of observational studies were all within 5 percentage points of the P. aeruginosa-IP benchmark (Table 2 and Figure 2). The mean P. aeruginosa-IP derived from the control groups and the

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Observational studies</th>
<th>non-antibiotic</th>
<th>SDD, non-concurrent</th>
<th>SDD, concurrent</th>
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<td>Sourcesabc</td>
<td>Table S1–S25,11–13</td>
<td>Table S39</td>
<td>Table S39</td>
<td>Table S39</td>
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<tr>
<td>Number of studies</td>
<td>48</td>
<td>23</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Bronchoscopic samplingd</td>
<td>23</td>
<td>10</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Group characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients per group, median (IQR)f,g</td>
<td>255 (103–518)</td>
<td>78 (51–183)</td>
<td>86 (61–124)</td>
<td>57 (36–94)</td>
</tr>
<tr>
<td>Days of ventilation, median (IQR)fh</td>
<td>11 (7.9–13.0)</td>
<td>11.3 (6.6–14.9)</td>
<td>8.2 (7.3–9.0)</td>
<td>10.5 (8.5–14.0)</td>
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<td>Percentage of trauma patients, median (IQR)i,l</td>
<td>9 (3–29)</td>
<td>12 (10–36)</td>
<td>18 (2–23)</td>
<td>38 (20–67)</td>
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<tr>
<td>Number of VAP isolates per group, median (IQR)k,g</td>
<td>66 (37–99)</td>
<td>25 (13–47)</td>
<td>24 (11–79)</td>
<td>31 (19–38)</td>
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<tr>
<td>VAP incidence per 100 patients</td>
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<tr>
<td>cohort, mean (95% CI)</td>
<td>24% (20%–29%)jk,l</td>
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<tr>
<td>control, mean (95% CI)</td>
<td>NA</td>
<td>22% (11%–33%)km</td>
<td>16% (9%–24%)</td>
<td>39% (29%–49%) km</td>
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<td>intervention, mean (95% CI)</td>
<td>NA</td>
<td>18% (10%–27%)kj</td>
<td>NA</td>
<td>14% (10%–18%)</td>
</tr>
</tbody>
</table>

aThe following systematic reviews were the sources for these studies: George1 (Table 1), Cook and Kollef2 (Table 1), Chastre and Fagon3 (Table 1), Bergmans and Bonten4 (Table 2.5), Safdar et al.5 (Table 1) and Melsen et al.21 (Table 2).

bThe following systematic reviews were the source for these studies: Messori et al1 (Table 1), Cook and Kollef2 (Table 1), Chastre and Fagon3 (Table 1), Safdar et al.5 (Table 2).

cLiberati et al.9 (Analysis 1.5 and 2.5) was the source for these studies.

dBronchoscopic versus tracheal sampling for VAP diagnosis.

eData are earliest to most recent year of publication.

fData are median and interquartile range (IQR).

gData are median and IQR.

hP=0.0001, x² = 26.3; degrees of freedom = 3, Kruskal–Wallis test.

iP=0.99, x² = 0.13; degrees of freedom = 3, Kruskal–Wallis test.

jP=0.03, x² = 8.7; degrees of freedom = 3, Kruskal–Wallis test.

kComparison of VAP incidence of concurrent control groups of SDD versus benchmark groups, P=0.005, two-sample t-test.

lComparison of VAP incidence of intervention groups of non-antibiotic versus benchmark groups, P=0.17, two-sample t-test.

mComparison of VAP incidence of intervention groups of concurrent SDD studies versus benchmark groups, P=0.004, two-sample t-test.

nComparison of VAP incidence of concurrent control groups of concurrent SDD versus control groups of non-antibiotic studies, P=0.03, two-sample t-test.
Figure 1. A caterpillar plot of the study-specific (small diamonds) *P. aeruginosa*-IP and 95% CIs from observational (benchmark) studies together with the summary *P. aeruginosa*-IP (broken line) and 95% CI (large open diamond) and 95% PI (solid horizontal line). The summary is the *P. aeruginosa*-IP benchmark. Note that the x-axis is a logit scale. The logit values equivalent to percentage values of 3%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70% and 80% are 2.35, 2.29, 2.22, 1.4, 0.85, −0.41, 0.0, 0.41, 0.85 and 1.4, respectively. The *P. aeruginosa*-IP data are derived from observational studies abstracted in six reviews.1–5,21
intervention groups of both the non-antibiotic methods of VAP prevention and from the intervention groups and the various control groups of the SDD studies are also each within 5 percentage points of the benchmark (Table 2). The SE and $\tau^2$ were similar for each mean $P. aeruginosa$–IP derived from the various sources of observational and interventional study groups (Table 2).

### Meta-regression models

The proportion of trauma admissions was a significant negative predictor of $P. aeruginosa$–IP in all models (Table 3). The coefficients for trauma in the regression model equate to a difference of approximately 12% between groups, with 100% versus 0% of admissions for trauma. There were no other significant predictors. In particular, in all models neither the effect of membership of a control nor membership of an intervention group of a VAP prevention study of whichever type were significant predictors (Table 3).

### Discussion

The present analysis found that the mean $P. aeruginosa$–IPs among control and intervention groups of SDD studies were similar. Moreover, the dispersion around the benchmark was similar for control and for intervention groups from studies of SDD despite large (>10 percentage point) disparities in mean VAP incidence between the benchmark groups versus both the concurrent control and intervention groups of these studies (Table 1). In the meta-regression models, the proportion of trauma admissions had a significant negative correlation with $P. aeruginosa$–IP, whereas membership of neither a control nor an intervention group in an SDD study did. The findings here add to a number of paradoxical observations among the SDD studies.26

All observational studies used in deriving the benchmark and in the meta-regression modelling were sourced exclusively from studies abstracted in 10 reviews.1–5,9,11–13,21 A new literature search was not undertaken and the analysis was specifically limited to studies identified in 10 published reviews and to the use of those studies exclusively. This narrowed focus allows scrutiny of the component groups that form an entire evidence base. The four systematic reviews5,11–13 of non-antibiotic methods of VAP prevention were chosen because they were the largest available. The benchmark derived here is within 5 percentage points of the $P. aeruginosa$–IP reported in large French,6 US7 and literature-derived2 multicentre databases.

This analysis was conducted at a group level rather than a patient level and is not adjusted for underlying patient risk. Adjusting for patient risk is an important consideration in profiling patient level and is not adjusted for underlying patient risk. Hence the analysis required a method to accommodate the heterogeneity (over-dispersion) in event rates arising from different patient populations in different centres among studies published over three decades with a considerable range of interventions under study.

A more recent development in relation to managing heterogeneity is the use of random effects methods to measure the separate contributions of the variance arising from between groups (heterogeneity, $\tau^2$) versus that from within groups (sampling, SE) towards the overall dispersion of study results around the mean results.28 This approach is particularly applicable where there is a substantial range in study sizes within the analysis.29

In the meta-regression models, the proportion of trauma admissions was a significant negative group-level predictor of $P. aeruginosa$–IP (Table 3). Admission for trauma has not previously been recognized as a significant patient-level predictor of $P. aeruginosa$–IP. However, in a 42 month database from a single multidisciplinary ICU, Agbaht et al.30 noted that $P. aeruginosa$ accounted for 18.5% and 9.5% of VAP isolates among patients admitted for non-trauma conditions versus trauma, respectively. The size of the difference found in the study by Agbaht et al.,30 9 percentage points, is similar to the approximately 12 percentage point difference between the predictions obtained in meta-regression model 1 here for hypothetical groups with 0% and 100% trauma admissions.

There are several limitations of this analysis. There was no exploration beyond simple linear relationships between the group-level predictors and the logit $P. aeruginosa$–IP. Also, it was not possible to explore the impact of, and possible confounding from, other patient-level risk factors for $P. aeruginosa$–associated VAP using the aggregated data examined here. In particular, it remains possible that the group-level effect of proportion of trauma admissions noted here is mediated by patient-level risk factors that cannot be addressed in a group-level analysis.31

There were nine SDD studies abstracted in Liberati et al.9 that were not to be included in the analysis here, as either VAP or
Figure 2. A caterpillar plot of the study-specific (small diamonds) and summary P. aeruginosa-IP and 95% CIs from non-concurrent control (top) and concurrent control (middle) and intervention (bottom) groups of SDD studies together with the P. aeruginosa-IP benchmark and 95% PI (solid vertical and horizontal lines; from Figure 1). Note that the x-axis is a logit scale. The P. aeruginosa-IP data are derived from component groups of SDD studies abstracted in Liberati et al.9 The control group of the Ferrer study (indicated with an asterisk) is a duplex control group, as all control group patients routinely received 4 days of cefotaxime.
<table>
<thead>
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<th>Factor</th>
<th>Observational studies and control groups from interventional studies</th>
<th>Observational studies and intervention groups from interventional studies</th>
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<tr>
<td></td>
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<td>coefficient</td>
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<td>(reference group)</td>
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<td>SDD and non-concurrent &lt;90% MVb</td>
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<td>European ICUc</td>
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<td>Group size &gt;75 patients</td>
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<tr>
<td>Mode of diagnosisa</td>
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<tr>
<td>Proportion of trauma admissionsa</td>
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<td>Year of publicationf</td>
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</table>

aInterpretation. The observational study (benchmark) groups in each model form the reference group and the size of this coefficient equals the difference in logits from 0 (a logit equal to 0 equates to a proportion of 50%; a logit equal to -1.24 equates to a proportion of 22%). The other coefficients in each model represent the additional difference in logits for groups positive for that factor versus the reference group.

bFor studies for which <90% of patients received >24 h of MV.

cOriginating from a member state of the European Union as of 2010 or Switzerland or Norway.

dDiagnosis of VAP using bronchoscopic versus tracheal-based sampling.

ePer 100% of admissions for trauma.

fPer year, with year of publication centred at 1995 = 0.
P. aeruginosa-IP data were not available. However, the studies included in the analysis here account for >60% of the statistical weight in the summary estimate of SDD effect on VAP. Also, the 3-fold difference between VAP incidence in control and intervention groups noted here (Table 1) corresponds approximately to the effect size estimated by Liberati et al.9

The epidemiology of colonization with P. aeruginosa and other Gram-negative bacteria within the ICU is complex and the potential for a contextual effect of SDD mediated via cross-transmission is conjectural. MV increases the risk of acquisition of P. aeruginosa carriage for patients within the ICU by nearly 3-fold.32 However, SDD may only partially reduce P. aeruginosa colonization and appears not to interrupt cross-transmission to and from non-SDD-treated patients.33 Moreover, Dutch ICUs that used SDD for periods of 6 months experienced marked effects on the bacterial ecology of multiresistant Gram-negative bacteria, including P. aeruginosa, with a considerable rebound effect during the 3 months after the discontinuation of SDD use.34

The findings presented here are in striking contrast to findings from the analysis of VAP incidence among >150 studies of VAP prevention methods in which unusually high VAP incidences20 and unusual patterns15 in the VAP isolates suggested that apparent outbreaks had occurred in as many as 15 of 51 studies (29%) that had used antibiotic-based methods of VAP prevention versus only 2 of 110 studies (2%) that had used antibiotic-based methods of VAP prevention.

Conclusions

Among the studies of patients receiving MV derived from 10 reviews, there is wide variation in VAP incidence. Among these studies, the proportion of trauma admissions as a group-level factor has a significant negative association with P. aeruginosa-IP, whereas membership of an intervention or control group of an SDD study does not. There is no evidence of any direct or indirect effects of SDD on P. aeruginosa-IP among the intervention or control groups that could account for the profound effects of SDD on VAP incidence.

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Transparency declarations

None to declare.

Supplementary data

Tables S1, S2 and S3 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


