**Article**

**Unusually High Incidences of *Staphylococcus aureus* Infection within Studies of Ventilator Associated Pneumonia Prevention Using Topical Antibiotics: Benchmarking the Evidence Base**

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**Abstract:** Selective digestive decontamination (SDD, topical antibiotic regimens applied to the respiratory tract) appears effective for preventing ventilator associated pneumonia (VAP) in intensive care unit (ICU) patients. However, potential contextual effects of SDD on *Staphylococcus aureus* infections in the ICU remain unclear. The *S. aureus* ventilator associated pneumonia (*S. aureus* VAP), VAP overall and *S. aureus* bacteremia incidences within component (control and intervention) groups within 27 SDD studies were benchmarked against 115 observational groups. Component groups from 66 studies of various interventions other than SDD provided additional points of reference. In 27 SDD study control groups, the mean *S. aureus* VAP incidence is 9.6% (95% CI; 6.9–13.2) versus a benchmark derived from 115 observational groups being 4.8% (95% CI; 4.2–5.6). In nine SDD study control groups the mean *S. aureus* bacteremia incidence is 3.8% (95% CI; 2.1–5.7) versus a benchmark derived from 10 observational groups being 2.1% (95% CI; 1.1–4.1). The incidences of *S. aureus* VAP and *S. aureus* bacteremia within the control groups of SDD studies are each higher than literature derived benchmarks. Paradoxically, within the SDD intervention groups, the incidences of both *S. aureus* VAP and VAP overall are more similar to the benchmarks.

**Keywords:** ventilator associated pneumonia; *Staphylococcus aureus*; antibiotic prophylaxis; study design; intensive care; mechanical ventilation; cross infection; no scomial infection; selective digestive decontamination; antibiotics

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**1. Introduction**

Ventilator associated pneumonia (VAP) in association with *Staphylococcus aureus* has been reported in numerous studies from intensive care units (ICU) worldwide [1–196]. Approximately 20% of ICU patients receiving prolonged mechanical ventilation develop ventilator-associated pneumonia (VAP) and *S. aureus* accounts for approximately 20% of VAP isolates [197].

Selective digestive decontamination (SDD) is a novel intervention using various regimens of topical antibiotics that are applied to the upper airway of patients receiving mechanical ventilation to reduce microbial colonization with the objective of preventing not only pneumonia but also bacteremic infections [198–202]. In contrast to other infection prevention strategies such as topical antiseptics such as chlorhexidine or non-antimicrobial methods, SDD selectively decreases colonization with aerobic gram negative bacilli at the oro-pharynx. However, SDD may increase colonization with gram positive bacteria including staphylococci [203,204].

In numerous studies and systematic reviews, the evidence in support of SDD in preventing ICU acquired infections such as VAP and bacteremia, appears compelling. These studies and systematic
reviews report apparent reductions in the overall incidence of VAP of >50% [198–202] versus other methods of VAP prevention for which the reduction is generally <50% [205–218]. An apparent reduction in the overall incidence of bacteremia of >25% with SDD is also reported [199,200].

The effects of topical antibiotics such as SDD on the incidence of acquired infection with *S. aureus* in the ICU is of interest for two reasons.

Firstly, there is a concern that decontamination regimens might alter the ICU microbiome and the infection risk for those patients concurrent in the ICU not receiving the intervention [219–222]. Where any contextual risk leads to decreases or increases in infections rates it is termed “herd protection” and “herd peril”, respectively [223]. Typically, contextual effects are not apparent within individual studies examined in isolation but become apparent only by comparing the infection incidences observed within the individual studies to incidence benchmarks derived from other studies in the literature.

Second, it is possible that the effect of topical placebo in this context is not neutral in that the proportion of *Staphylococcus aureus* among VAP isolates is higher among studies of SDD that used topical placebo to achieve observer blinding than among studies without any intervention [224]. Clarifying whether these contextual or placebo effects might be present within studies of VAP prevention methods is crucial towards evaluating any apparent effect sizes of SDD [225].

The overall study objectives here are

- to survey and visually compare the incidence of *S. aureus* VAP (and VAP overall) within component (control and intervention) groups decanted from these studies versus an external benchmark.
- to model the effects of various group level factors within these studies on *S. aureus* VAP (and VAP overall) incidence. A key factor is membership of a component group of a study which either did or did not use topical placebo to achieve observer blinding.
- To collate data on the incidence of *S. aureus* bacteremia and methicillin resistant *S. aureus* (MRSA) VAP among those studies for which this data is available.

In all three objectives, a category of observational studies serves to derive external benchmarks for the incidences of *S. aureus* VAP, MRSA-VAP, VAP overall and *S. aureus* bacteremia. Also, studies of interventions other than topical antibiotics, being studies of non-antibiotic methods and studies of methods using topical antiseptics, provide additional points of reference.

2. Materials and Methods

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

2.1. Study Selection and Decant of Groups

The literature search and analytic approach used here (Figure 1) is as described previously [223]. These six steps (Figure 1; 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” up to December 2015. The use of systematic reviews as the starting point for benchmarking *S. aureus* VAP incidence serves two purposes; they provide estimates of the apparent effect size of the interventions of interest and, they provide objective and transparent sources of VAP incidence data.

2. Systematic reviews of studies of patient populations requiring prolonged (>24 h) mechanical ventilation were then streamed into one of three categories; systematic reviews of studies in which there was no intervention (observational studies), systematic reviews of infection prevention studies using topical antibiotics in any formulation [198–202], systematic reviews of studies of
non-antibiotic interventions (non-antibiotic studies) and systematic reviews of studies of topical antiseptics. The studies of non-antibiotic methods of VAP prevention encompass a broad range of methods delivered either via the gastric route [205–208], the airway route [209–216] or via the oral care route [201,202,217,218].

3. The studies within these systematic reviews were screened against the following eligibility criteria. Inclusion criteria; infection prevention studies using concurrent controls and also observational studies for which incidence data for \( S. aureus \) VAP was extractable as an incidence proportion. The denominator for this incidence proportion is the numbers of patients receiving mechanical ventilation with an ICU stay of at least 24 h. Exclusion criteria; studies limited to patients with the acute respiratory distress syndrome. Studies in a language other than English were included where these had been abstracted in an English language systematic review.

4. A hand search was undertaken for additional studies not identified within systematic reviews including studies published since 2015.

5. All eligible studies were then collated and any duplicate studies were removed and streamed into groups of patients from studies without a VAP prevention method (observational groups) or component groups of the studies of antibiotics, studies of anti-septics and studies of non-antibiotic interventions.

6. The component groups were decanted from each study as observational, control or intervention groups.

2.2. Outcomes of Interest

The \( S. aureus \) VAP proportion is derived as follows; the numerator is the number of patients with VAP found to have an \( S. aureus \) isolate and the denominator is the number of patients receiving prolonged mechanical ventilation. In addition, the following were also extracted where available; the proportion of admissions for trauma, the incidence proportion of VAP overall, the incidence proportion of MRSA-VAP’s, and the incidence proportion of \( S. aureus \) bacteremia. Those groups for which the proportion of admissions for trauma was >50% were arbitrarily designated as originating from trauma ICU’s. The bacteremia incidences were expressed as a proportion using the number of patients with prolonged (>24 h) mechanical ventilation in the ICU as the denominator. Other parameters extracted were whether the mode of VAP diagnosis required bronchoscopic sampling, and whether the study originated from either the United States of America or Canada (North America).

2.3. Benchmarking: Visual

Scatter plots were generated to facilitate a visual benchmark of the VAP, \( S. aureus \) VAP and bacteremia incidence rates and these were generated as follows. The data for VAP, \( S. aureus \) VAP, overall bacteremia and \( S. aureus \) bacteremia, were logit transformed as previously [27]. For \( S. aureus \) VAP this transformation proceeds as follows; with the number of mechanically ventilated patients as the denominator (D), the number of patients with \( S. aureus \) VAP as the numerator (N), and R being the \( S. aureus \) VAP proportion (N/D), the logit (\( S. aureus \) VAP) is \( \log(N/(D-N)) \) and its variance is \((1/R)/(1-R)\)). The \( S. aureus \) VAP benchmark is derived using the observational studies and is the mean of the logit (\( S. aureus \) VAP) weighted by the inverse variance. The derived logits were back transformed onto the percentage scale. The overall VAP and \( S. aureus \) bacteremia benchmarks were likewise derived. For each end point, the benchmark is the mean incidence derived from the observational studies. These respective benchmarks were then used as reference lines in the scatterplots of \( S. aureus \) VAP, VAP overall, MRSA-VAP, and bacteremia.
Figure 1. Flow chart of literature search and study and group decant. Search method, screening criteria and resulting classification of eligible studies and subsequent decant of component groups. The six numbered arrows are as follows; (1) An electronic search for systematic reviews containing potentially eligible studies using search terms; “ventilator associated pneumonia”, “mechanical ventilation”, “intensive care unit”, each combined with either “meta-analysis” or “systematic review” up to December 2015; (2) Studies were streamed into one of four categories; studies in which there was no intervention (observational studies), studies of non-antibiotic methods, topical antiseptics or topical antibiotics; (3) The studies were screened against inclusion and exclusion criteria; (4) A hand search was undertaken for additional studies; (5) eligible studies were then collated and any duplicate studies were removed; (6) The component groups were decanted from each study being control (rectangles), intervention (ovals) and observation (diamond) groups. Note; the total numbers do not tally as some systematic reviews provided studies in more than one category and some studies provided groups in more than one category.
2.4. Benchmarking: Meta-Regression

Group level regression models of VAP and *S. aureus* VAP proportions were developed using generalized estimating equation methods (‘xtgee’ command in STATA; release 12.0, STATA Corp., College Station, TX, USA). Generalized estimating equation regression models accommodate any intra-cluster correlation. In these regression models, the predictor variables were the component group membership as follows; type of component group being either a control or intervention and type of intervention under study being a topical antibiotic, a topical antiseptic or a non-antibiotic intervention. Additional predictor variables were; origin from a trauma ICU, origin from a North American ICU, whether the mode of diagnosis of VAP required bronchoscopic sampling and year of study publication. All factors in both models were entered as discrete variables with the category of observational groups acting as the reference (benchmark) category in each model. All factors were entered into the regression models without any pre-selection step.

3. Results

3.1. Characteristics of the Studies

Of the 198 studies identified by the search (Figure 1), 109 were sourced from 19 systematic reviews (Table 1) [198–202,205–218]. The majority of studies were published between 1990 and 2010 and a minority originated from trauma ICU’s. Bronchoscopic methods for VAP sampling and diagnosis were more commonly used among observational studies than other studies. The studies of non-antibiotic based methods were drawn from studies of gastric acid based and airway based interventions for the prevention of ICU acquired infections among patients receiving prolonged mechanical ventilation. The studies of topical antiseptic based methods include various interventions such as chlorhexidine and povidone-iodine as topical antiseptic agents [157–170]. There were 27 studies of topical antibiotics which studied various types of SDD and similar topical antibiotic interventions.

A total of 289 component groups were decanted from these 198 studies. There were 115 groups from observational studies Table S1, see Additional file 1), 93 groups from studies of various non-antibiotic based methods of VAP prevention (Table S2, see Additional file 1), 28 groups from studies of topical anti-septics and 53 groups from studies of topical antibiotics (Table S3, see Additional file 1). Twelve studies had more than one observational, control or intervention group. The majority of groups from studies of topical antibiotics methods had less than 60 patients per group versus more than 70 patients in the majority of all remaining groups.

3.2. VAP Benchmarking: Visual

There was significant disparity in the summary incidences of both VAP (Figure 2) and *S. aureus* VAP (Figure 3) among the control groups versus the respective benchmarks (Table 1). For VAP and *S. aureus* VAP, the incidences among the control groups in studies of topical antibiotics were each higher by >50% versus the respective benchmarks whereas these incidences for control groups of studies of non-antibiotic based methods were each similar to the corresponding benchmarks. (Table 1). There was no apparent relationship between *S. aureus* VAP and year of publication (Figure 4). Also, there is no impression that the high summary VAP or *S. aureus* VAP incidences was driven by a minority of outlier studies that may have been subject to outbreaks.
Table 1. Characteristics of studies.

| Variable                                              | Observational (No Intervention) | Non-Antibiotic Studies | Topical Antiseptic Studies | Topical Antibiotic Studies |
|-------------------------------------------------------|---------------------------------|------------------------|----------------------------|---------------------------|
| Supplemental material                                  | Table S1                        | Table S2               | Table S3                   | Table S4                  |
| Number of studies                                      | 106                             | 50                     | 14                         | 26                        |
| Publication year (range)                               | 1987–2016                       | 1987–2016              | 2000–2014                  | 1987–2015                 |
| Studies sourced from systematic reviews                 | 45                              | 32                     | 8                          | 24                        |
| Topical placebo used in study                          | NA                              | 8                      | 7                          | 14                        |
| Bronchoscopic sampling for VAP diagnosis (n)           | 58                              | 8                      | 5                          | 8                         |
| Trauma ICU’s (n)                                      | 21                              | 11                     | 3                          | 8                         |
| North American ICU’s (n)                               | 21                              | 13                     | 2                          | 1                         |
| Patients per study group median (IQR)                  | 279                             | 75                     | 114                        | 52                        |
| VAP incidence per 100 patients                         | 20.8                            | 19.0–22.8              | 21.6                       | 19.9–21.8                 |
| Control (mean)                                         | 20.1                            | 19.2–21.4              | 13.6–28.9                  | 26.9–38.9                 |
| n                                                      | 115                             | 14                     | 14                         | 14                        |
| Intervention (mean)                                   | 16.5                            | 13.8                   | 8.6–21.4                   | 12.0–18.1                 |
| n                                                      | 43                              | 14                     | 14                         | 14                        |
| S. aureus VAP incidence per 100 patients               | 4.8                             | 4.2–5.6                | 7.2                        | 5.1–9.6                   |
| Control (mean)                                         | 5.1                             | 2.7–9.3                | 2.7–9.3                    | 6.9–13.2                  |
| n                                                      | 115                             | 14                     | 14                         | 14                        |
| Intervention (mean)                                   | 3.1                             | 3.1                    | 1.6–6.1                    | 4.8–8.3                   |
| n                                                      | 43                              | 14                     | 14                         | 14                        |

* Note, several studies had more than one control and or intervention group. Hence the number of groups does not equal the number of studies; b Studies that were sourced from 19 systematic reviews (200–204, 207–220); c Bronchoscopic versus tracheal sampling for VAP diagnosis; d Trauma ICU arbitrarily defined as an ICU with more than 50% of admissions for trauma; e Number of studies originating from either the United States of America or Canada; f Data is median and inter-quartile range (IQR).

Figure 2. Incidence of ventilator associated pneumonia (VAP) versus benchmark. The component (C = control; I = intervention) groups of studies in which there was no intervention (Ob = observational), studies of non-antibiotic methods, topical antiseptics (AS) or topical antibiotics (SDD). The VAP benchmark is the summary mean (central vertical line) derived from the observation studies. These data are listed in Table S1–S4 (see Additional file 1). Note that the horizontal axis is a logit scale.
The models were repeated with component groups of 14 studies of antiseptic based methods [139–143] repeating the models limited to studies obtained from systematic reviews revealed similar findings. Microorganisms arbitrarily reclassified as belonging to studies of topical antibiotics. In these models, the coefficients for the control groups of this augmented category of topical antibiotics studies remained significant.

Microorganisms

These meta-regression models were each repeated with the following sensitivity tests. Firstly, repeating the models limited to studies obtained from systematic reviews revealed similar findings (Table 2, footnote c and d). Second, as a test for potentially missing studies of topical antibiotics, the models were repeated with component groups of 14 studies of antiseptic based methods [139–143] arbitrarily reclassified as belonging to studies of topical antibiotics. In these models, the coefficients for

Figure 3. Incidence of S. aureus VAP versus benchmark. The component (C = control; I = intervention) groups of studies in which there was no intervention (Ob = observational), studies of non-antibiotic methods, topical antiseptics (AS) or topical antibiotics (SDD). The S. aureus VAP benchmark is the summary mean (central vertical line) derived from the observation studies (These data are listed in Table S1–S4 (see Additional file 1). Note that the horizontal axis is a logit scale. Figure 3a (top) indicates component groups that came studies that were (open triangles) or were not (solid triangles) from studies in which topical placebo was used to achieve observer blinding and Figure 3b (bottom) indicates the mean incidence (and 95% confidence interval) for each category.

Figure 4. S. aureus VAP incidence versus year of publication. Dot plot of S. aureus VAP incidence for all observational and control groups for studies of non-antibiotics based methods (open circle) control groups from studies of topical anti-septics (open blue triangles) and topical antibiotics (SDD) studies (solid red triangles) by year of study publication. Note that the y-axis is a logit scale. The linear regression derived from the observational study groups was non-significant (p = 0.34) and hence a locally weighted regression and smoothing scatterplot (LOWESS) regression line is given.

These meta-regression models were each repeated with the following sensitivity tests. Firstly, repeating the models limited to studies obtained from systematic reviews revealed similar findings (Table 2, footnote c and d). Second, as a test for potentially missing studies of topical antibiotics, the models were repeated with component groups of 14 studies of antiseptic based methods [139–143] arbitrarily reclassified as belonging to studies of topical antibiotics. In these models, the coefficients for
the control groups of this augmented category of topical antibiotics studies remained significant in both the VAP and S. aureus VAP models (Table 2, footnote e).

### 3.3. MRSA-VAP

Of the studies analyzed here, the incidence of MRSA S. aureus VAP was available from only 108 groups. These data are presented in Figure 5.

#### Table 2. Logit regression models

| Factor                              | VAP     | S. aureus VAP |
|-------------------------------------|---------|---------------|
|                                     | Coefficient | 95% CI | p     | Coefficient | 95% CI | p     |
| Groups from observational studies (reference group) | −1.30 | −1.62 to −0.97 | −2.70 | −3.01 to −2.29 |
| Control groups                      |         |         |       |             |         |       |
| Non-antibiotic studies, no placebo  | +0.04   | −0.21 to +0.29 | 0.77  | +0.10       | −0.15 to +0.33 | 0.42 |
| Non-antibiotic studies; with topical placebo | −0.08 | −0.60 to +0.45 | 0.77  | +0.33       | −0.14 to +0.81 | 0.17 |
| Topical antiseptic studies; no placebo | −0.11 | −0.66 to +0.44 | 0.69  | +0.01       | −0.55 to +0.57 | 0.97 |
| Topical antiseptic studies; with topical placebo | −0.20 | −0.81 to +0.41 | 0.53  | +0.07       | −0.48 to +0.62 | 0.81 |
| Topical antibiotic studies; no placebo | +0.50  | +0.05 to +0.95 | 0.03  | +0.31       | +0.08 to +0.69 | 0.12 |
| Topical antibiotic studies; with topical placebo | +0.38  | −0.04 to +0.79 | 0.08  | +0.48       | +0.15 to +0.82 | 0.004 |

| Non-antibiotic studies              | −0.34   | −0.60 to −0.09 | 0.008 | −0.14       | −0.39 to +0.12 | 0.30 |
| Topical antiseptic studies;         | −0.77   | −1.18 to −0.35 | 0.001 | −0.53       | −1.03 to −0.03 | 0.039 |
| Topical antibiotic studies;         | −0.57   | −0.90 to −0.23 | 0.001 | −0.21       | −0.53 to +0.11 | 0.20 |
| Trauma ICU                           | +0.29   | +0.18 to +0.59 | 0.001 | +0.06       | +0.04 to +0.18 | 0.001 |
| Mode of diagnosis                    | −0.03   | −0.21 to +0.14 | 0.73  | +0.08       | −0.11 to +0.28 | 0.41 |
| North American study                | −0.31   | −0.56 to −0.06 | 0.01  | −0.28       | −0.54 to −0.02 | 0.04 |
| Year of publication                 | +0.01   | −0.01 to +0.01 | 0.88  | −0.01       | −0.03 to +0.001 | 0.08 |

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*Abbreviations; ICU, Intensive care unit; VAP, ventilator associated pneumonia; 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 −1.4 equates to a proportion of 20%; a logit equal to −3 equates to a proportion of 4.8%). The other coefficients represent the difference in logits for groups positive for that factor versus the reference group; The VAP logit regression model was repeated limited to studies that had been cited in one of the systematic reviews. In this model the coefficients were +0.47; +0.01 to +0.93, p = 0.045 (without topical placebo use) and +0.37; −0.07 to +0.81, p = 0.097 (with topical placebo use); The S. aureus VAP logit regression model was repeated limited to studies that had been cited in one of the systematic reviews. In this model the coefficients were +0.45; −0.10 to +1.00, p = 0.11 (without topical placebo use) and +0.59; +0.08 to +1.09, p = 0.023 (with topical placebo use); The S. aureus VAP logit regression model was repeated with component groups of Topical antiseptic studies arbitrarily reclassified as belonging to studies of topical antibiotics. In this collapsed model the coefficients were +0.28; −0.11 to +0.67, p = 0.16 (without topical placebo use) and +0.45; +0.06 to +0.84, p = 0.02 (with topical placebo use); Trauma ICU arbitrarily defined as an ICU for which >50% of admissions were for trauma; Diagnosis of VAP using bronchoscopic versus tracheal based sampling; Originating from an ICU in The United States of America or Canada; Year of study publication with the coefficient representing the increment for each year post 1985.*
3.4. Overall and S. aureus bacteremia

The incidence of *S. aureus* bacteremia (Table 3) was available from only 38 groups from 21 studies. The *S. aureus* bacteremia incidence was less than 4% for 15 of 18 groups from either observational studies or studies of anti-septic methods. By contrast, the *S. aureus* bacteremia incidence was less than 4% for only 9 of 20 groups from studies of SDD (Figure 6; *p* = 0.014, Chi-square, 1 d.f.).

![Figure 5](image1.png)

**Figure 5.** Incidence of methicillin resistant *S. aureus* (MRSA) *S. aureus* VAP. The component (C = control; I = intervention) groups of studies in which there was no intervention (Ob = observational), studies of non-antibiotic methods, topical antiseptics (AS) or topical antibiotics (SDD). (These data are listed in Table S1–S4 (see Additional file 1). The symbol sizes are proportional to the inverse of the study variance. Note that the horizontal axis is a logit scale.

![Figure 6](image2.png)

**Figure 6.** Incidence of *S. aureus* bacteremia. The component (C = control; I = intervention) groups of studies in which there was no intervention (Ob = observational) or studies of non-antibiotic based methods, topical antiseptics (AS) or topical antibiotics (SDD). The *S. aureus* bacteremia benchmark is the summary mean (central vertical line) derived from the observation studies (These data are listed in Table S4 (see Additional file 1). Symbols indicates component groups that came studies that were (open triangles) or were not (solid triangles) from studies in which topical placebo was used to achieve observer blinding. The symbol sizes are proportional to the inverse of the study variance. Note that the horizontal axis is a logit scale.
Table 3. *S. aureus* bacteremia data.

| Factor                                            | *S. aureus* bacteremia Incidence | 95% CI     | Number of Groups |
|---------------------------------------------------|----------------------------------|------------|-----------------|
| Groups from observational studies                 | 2.1                              | 1.1–4.1    | 10              |
| Non-antibiotic studies                            | 1.8                              | 0.6–5.1    | 3               |
| Control and Intervention groups                   | 1.2                              | 0.4–3.1    | 5               |
| Topical antiseptic studies; Control and Intervention groups | 3.8                              | 2.1–5.7    | 9               |
| Intervention groups                               | 4.2                              | 2.9–5.9    | 11              |

4. Discussion

This is an analysis of the incidences of *S. aureus* VAP and related infections within studies of SDD among a broad range of studies of VAP prevention methods. This analysis is informed by data from other studies in this patient group; *S. aureus* VAP and VAP benchmarks are derived from observational studies without an intervention and studies of non-antibiotic and anti-septic intervention methods provide additional points of reference.

The mean incidence of VAP overall within the control groups of SDD studies is higher than literature derived benchmarks whereas paradoxically the mean incidence in the SDD intervention groups is more similar to the benchmarks. This specific finding is entirely consistent with the apparent >50% reduction in VAP incidence by the SDD intervention as noted in multiple systematic reviews [198–202]. Furthermore, the mean incidence of *S. aureus* VAP and *S. aureus* bacteremia within the control groups of SDD studies are higher than literature derived benchmarks.

There are four key limitations to this analysis, the first being that the studies have been published over a period of three decades. Although there was no apparent trend in *S. aureus* VAP over this time (Figure 4), there was considerable heterogeneity in the interventions, populations, prevalence of antibiotic resistance, and study designs among the studies here. Moreover, the inclusion criteria for all intervention studies here have been intentionally broadly specified. Note that the literature search and analysis has been undertaken by a single author and the analysis is not intended to be a systematic review. The data from each of the studies is displayed in tables and figures to facilitate verification.

The second limitation is that VAP, and consequently *S. aureus* VAP, is a somewhat subjective end point. Moreover, only a limited number of key group level factors were entered into the regression models and there was no ability to adjust for the underlying patient level risk within the analysis. Hence, the nature of the contextual factor remains unidentified. However, as a counter to these limitations, the findings of a sensitivity analysis limited to studies that used topical placebo to achieve observer blinding gave similar VAP and *S. aureus* VAP incidence estimates.

The third limitation is that only those studies with data available were able to be included in this analysis. Several studies that included ICU patients not limited to those receiving prolonged mechanical ventilation were not included in the analysis here. For example, in one large Dutch study of SDD [226] only 45 of 10,993 (0.45%) patients had *S. aureus* bacteremia of which only 2 were MRSA. A second is a large American controlled trial of chlorhexidine bathing [227] in which 31 of 9340 patients had *S. aureus* bacteremia (0.3%). A third is a large American controlled trial of targeted chlorhexidine decontamination [228] in which 2007 of 122,646 patients had *S. aureus* bacteremia (1.6%). All three
of these studies lack *S. aureus* VAP data, and the proportion of patients that received mechanical ventilation is either 50% or not stated.

The fourth limitation is that the analysis here is inherently observational. Inferences for what may account for the disparate observations can only be speculative. In this regard, a major related limitation is that a contextual effect is difficult to measure reliably. The analysis here has merely identified a high incidence of *S. aureus* VAP and *S. aureus* bacteraemia among the control groups of topical antibiotics studies that remains without an explanation. It remains possible that a high *S. aureus* VAP, VAP or *S. aureus* bacteraemia incidence, served as a prompt to undertake a study of a topical antibiotics regimen. However, this was not explicitly stated in any of the studies analyzed here nor is there any impression of high incidence studies that were outlier as a consequence of having been subject to outbreaks of *S. aureus* VAP.

The *S. aureus* bacteremia benchmark is derived from only 55 *S. aureus* bacteremia events among 3057 patients among ten observational studies with available data. However, this incidence is comparable with estimates reported in the literature. For example, 45 and 94 *S. aureus* bacteremia events were observed among 4473 and 4913 ICU patients giving incidences of 1.0% [229] and 1.9% [230], respectively.

The *S. aureus* VAP benchmark and the MRSA-VAP benchmark, being 4.8% (95% CI: 4.2–5.6) and 2.2% (95% CI: 1.7–2.7), respectively, are somewhat more secure and each are also comparable to incidence estimates reported in the literature. Among 1873 mechanical ventilation patients of 56 ICUs of a survey across four multinational regions, there were 65 *S. aureus* VAP (27 MRSA) events observed for an incidence of 3.5% (and 1.5% for MRSA) [54].

Are the findings here robust to possible publication bias and undiscovered data? As a counter to this limitation, the findings of a sensitivity analysis using the 14 studies of antiseptic based methods to augment the category of studies of topical antibiotics failed to annul the statistical significance of membership of a control group receiving topical placebo within this augmented category of studies of topical antibiotics. Hence, within the category of the studies of topical antibiotics, there would need to be more that 14 studies with control group incidences of *S. aureus* VAP similar to those among the studies of antiseptic based methods to have been overlooked or unpublished to account for these findings within the meta-regression.

The disparity in the incidence of *S. aureus* VAP among studies of topical antibiotics versus the respective benchmarks recapitulates similar observations for various endpoints among studies of SDD versus externally derived benchmarks from populations of patients receiving prolonged mechanical ventilation. For example, with respect to *Candida* as a respiratory tract isolate [221], candidemia [222], and overall bacteraemia [220] in each case, the incidence of these end points are higher among control groups of studies of SDD versus the respective literature derived benchmarks. The first study of SDD asked whether the traditional randomized controlled trial format is an appropriate study design for the assessment of decontamination within the context of an ICU [231]. Without the ability to measure and control for the contextual effects resulting from a decontamination intervention, the attribution of any apparent effect to control or to intervention groups will be ambiguous in any single study. Moreover, the use of topical placebo to achieve observer blinding in this context might act as a pernicious confounder [224]. The contextual effects of using topical antibiotics in an attempt to prevent infections in mechanically ventilated patients is a hazard that warrants careful consideration.

5. Conclusions

There is an excess in the incidence of *S. aureus* VAP in the studies of topical antibiotics versus benchmarks derived from the observational groups and also versus both the studies of non-antibiotic based methods and the studies of anti-septic methods. This excess is inapparent in any single study of topical antibiotics examined in isolation and is apparent only on reference to an external benchmark incidence. This excess cannot be readily accounted for. It likely represents herd peril resulting from
the use of SDD. This together with the excess of *S. aureus* bacteremias, and VAP overall implies a profound contextual effect within the topical antibiotics studies.

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**References**

1. A’Court, C.H.; Garrard, C.S.; Crook, D.; Bowler, I.; Conlon, C.; Peto, T.; Anderson, E. Microbiological lung surveillance in mechanically ventilated patients, using non-directed bronchial lavage and quantitative culture. *Q. J. Med.* 1993, 86, 635–648. [CrossRef] [PubMed]
2. Alvarez-Lerma, F. ICU-acquired Pneumonia Study Group. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. *Intensive Care Med.* 1996, 22, 387–394. [CrossRef] [PubMed]
3. Antonelli, M.; Moro, M.L.; Capelli, O.; De Blasi, R.A.; D’Errico, R.R.; Conti, G.; Buci, M.; Gasparetto, A. Risk factors for early onset pneumonia in trauma patients. *Chest* 1994, 105, 224–228. [CrossRef] [PubMed]
4. Apostolopoulos, E.; Bakakos, P.; Katostaras, T.; Gregorakos, L. Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. *Respir. Care* 2003, 48, 681–688. [PubMed]
5. Baker, A.M.; Meredith, J.W.; Haponik, E.F. Pneumonia in intubated trauma patients. *Microbiology and outcomes. Am. J. Respir. Crit. Care Med.* 1996, 153, 343–349. [CrossRef] [PubMed]
6. Bekaert, M.; Timsit, J.F.; Vansteelandt, S.; Depuydt, P.; Vézin, A.; Garrouste-Orgeas, M.; Decruyenaere, J.; Clec’h, C.; Azoulay, E.; Benoit, D. Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. *Am. J. Respir. Crit. Care Med.* 2011, 184, 1133–1139. [CrossRef] [PubMed]
7. Bercault, N.; Boulain, T. Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: A prospective case-control study. *Crit. Care Med.* 2001, 29, 2303–2309. [CrossRef] [PubMed]
8. Berrouane, Y.; Daudenthun, I.; Riegel, B.; Emery, M.N.; Martin, G.; Krivosic, R.; Grandbastien, B. Early onset pneumonia in neurosurgical intensive care unit patients. *J. Hosp. Infect.* 1998, 40, 275–280. [CrossRef] [PubMed]
9. Bochicchio, G.V.; Joshi, M.; Bochicchio, K.; Tracy, K.; Scalea, T.M. A time-dependent analysis of intensive care unit pneumonia in trauma patients. *J. Trauma* 2004, 56, 296–301. [CrossRef] [PubMed]
10. Bonten, M.J.; Gaillard, C.A.; van Tiel, F.H.; Smeets, H.G.; van der Geest, S.; Stobberingh, E.E. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. *Chest* 1994, 105, 878–884. [CrossRef] [PubMed]
11. Boots, R.J.; Phillips, G.E.; George, N.; Foaagali, J.L. Surveillance culture utility and safety using low-volume blind bronchoalveolar lavage in the diagnosis of ventilator-associated pneumonia. *Respirology* 2008, 13, 87–96. [CrossRef] [PubMed]
12. Bornstain, C.; Azoulay, E.; De Lassence, A.; Cohen, Y.; Costa, M.A.; Mourvillier, B.; Descorps-Declere, A.; Garrouste-Orgeas, M.; Thuong, M.; Schlemmer, B.; et al. Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clin. Infect. Dis.* 2004, 38, 1401–1408. [CrossRef] [PubMed]
13. Braun, S.R.; Levin, A.B.; Clark, K.L. Role of corticosteroids in the development of pneumonia in mechanically ventilated head-trauma victims. *Crit. Care Med.* 1986, 14, 198–201. [CrossRef] [PubMed]
14. Bregenon, F.; Papazian, L.; Visconti, A.; Gregoire, R.; Thirion, X.; Gouin, F. Relationship of microbiologic diagnostic criteria to morbidity and mortality in patients with ventilator-associated pneumonia. *JAMA* 1997, 277, 655–662. [CrossRef] [PubMed]
15. Bronchard, R.; Albaladejo, P.; Brezac, G.; Geffroy, A.; Seince, P.F.; Morris, W.; Branger, C.; Marty, J. Early onset pneumonia: Risk factors and consequences in head trauma patients. *Anesthesiology* 2004, 100, 234–239. [CrossRef] [PubMed]
16. Cade, J.F.; McOwat, E.; Siganporia, R.; Keighley, C.; Presneill, J.; Sinickas, V. Uncertain relevance of gastric colonization in the seriously ill. *Intensive Care Med.* 1992, 18, 210–217. [CrossRef] [PubMed]
17. Cavalcanti, M.; Ferrer, M.; Ferrer, R.; Morforte, R.; Garnacho, A.; Torres, A. Risk and prognostic factors of ventilator-associated pneumonia in trauma patients. Crit. Care Med. 2006, 34, 1067–1072. [CrossRef] [PubMed]
18. Cendrero, J.A.; Solé-Violán, J.; Benítez, A.B.; Catalán, J.N.; Fernández, J.A.; Santana, P.S.; de Castro, F.R. Role of different routes of tracheal colonization in the development of pneumonia in patients receiving mechanical ventilation. Chest 1999, 116, 462–470. [CrossRef]
19. Chaari, A.; El Habib, M.; Ghdhoun, H.; Algia, N.B.; Chtara, K.; Hamida, C.B.; Chelly, H.; Bahloul, M.; Bouaziz, M. Does low-dose hydrocortisone therapy prevent ventilator-associated pneumonia in trauma patients? Am. J. Ther. 2015, 22, 22–28. [CrossRef] [PubMed]
20. Chastre, J.; Trouillet, J.L.; Vuagnat, A.; Joly-Guillou, M.L.; Clavier, H.; Dombret, M.C.; Gibert, C. Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med. 1998, 157, 1165–1172. [CrossRef] [PubMed]
21. Chevret, S.; Hemmer, M.; Carlet, J. Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. Intensive Care Med. 1993, 19, 256–264. [CrossRef] [PubMed]
22. Cook, A.; Norwood, S.; Berne, J. Ventilator-associated pneumonia is more common and of less consequence in trauma patients compared with other critically ill patients. J. Trauma Acute Care Surg. 2010, 69, 1083–1091. [CrossRef] [PubMed]
23. Craven, D.E.; Kunches, L.M.; Lichtenberg, D.A.; Kollisch, N.R.; Barry, M.A.; Heeren, T.C. McCabe WR Nosocomial infection and fatality in medical and surgical intensive care unit patients. Arch. Intern. Med. 1988, 148, 1161–1168. [CrossRef] [PubMed]
24. Daschner, F.; Kappstein, I.; Schuster, F.; Scholz, R.; Bauer, E.; Jooßens, D.; Just, H. Influence of disposable (‘Conchapak’) and reusable humidifying systems on the incidence of ventilation pneumonia. J. Hosp. Infect. 1988, 11, 161–168. [CrossRef]
25. De Latorre, F.J.; Pont, T.; Ferrer, A.; Rossello, J.; Palomar, M.; Planas, M. Pattern of tracheal colonization during mechanical ventilation. Am. J. Respir. Crit. Care Med. 1995, 152, 1028–1033. [CrossRef] [PubMed]
26. Ertugrul, B.M.; Yildirim, A.; Ay, P.; Oncu, S.; Cagatay, A.; Cakar, N.; Ertekim, C.; Ozsut, H.; Eraksoy, H.; Calangu, S. Ventilator-associated pneumonia in surgical emergency intensive care unit. Saudi Med. J. 2006, 27, 52–57. [PubMed]
27. Evans, H.L.; Zonies, D.H.; Warner, K.J.; Bulger, E.M.; Sharar, S.R.; Maier, R.V.; Cuschieri, J. Timing of intubation and ventilator-associated pneumonia following injury. Arch. Surg. 2010, 145, 1041–1046. [CrossRef] [PubMed]
28. Ewig, S.; Torres, A.; El-Ebiary, M.; Fábregas, N.; Hernandez, C.; Gonzalez, J.; Nicolas, J.M.; Soto, L. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. 1999, 159, 188–198. [CrossRef] [PubMed]
29. Fagon, J.Y.; Chastre, J.; Domart, Y.; Trouillet, J.L.; Pierre, J.; Darne, C.; Gibert, C. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am. Rev. Respir. Dis. 1989, 139, 877–884. [CrossRef] [PubMed]
30. Gacouin, A.; Barbarot, N.; Camus, C.; Salomon, S.; Isslame, S.; Marque, S.; Lavoué, S.; Donnio, P.Y.; Thomas, R.; Le Tulzo, Y. Late-onset ventilator-associated pneumonia in nontrauma intensive care unit patients. Anesth. Analg. 2009, 109, 1584–1590. [CrossRef] [PubMed]
31. Garrouste-Orgeas, M.; Chevret, S.; Arlet, G.; Marie, O.; Rouveau, M.; Popoff, N.; Schlemmer, B. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. Am. J. Respir. Crit. Care Med. 1997, 156, 1647–1656. [CrossRef] [PubMed]
32. George, D.L.; Falk, P.S.; Wunderink, R.G.; Leeper, K.V., Jr.; Meduri, G.U.; Steere, E.L.; Glen Mayhall, C. Epidemiology of ventilator-acquired pneumonia based on protected bronchoscopic sampling. Am. J. Respir. Crit. Care Med. 1998, 158, 1839–1847. [CrossRef] [PubMed]
33. Georges, H.; Leroy, O.; Guery, B.; Alfandari, S.; Beaucaire, G. Predisposing factors for nosocomial pneumonia in patients receiving mechanical ventilation and requiring tracheotomy. Chest 2000, 118, 767–774. [CrossRef] [PubMed]
Giard, M.; Lepape, A.; Allouchiche, B.; Guerin, C.; Lehot, J.J.; Robert, M.O.; Vanhems, P. Early-and late-onset ventilator-associated pneumonia acquired in the intensive care unit: Comparison of risk factors. *J. Crit. Care* **2008**, *23*, 27–33. [CrossRef] [PubMed]

Gruson, D.; Hilbert, G.; Vargas, F.; Valentino, R.; Bebear, C.; Allery, A.; Bebear, C.; Gbikpi-Benissan, G.E.; Cardinaud, J.P. Rotation and restricted use of antibiotics in a medical intensive care unit: Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 837–843. [CrossRef] [PubMed]

Gruson, D.; Hilbert, G.; Vargas, F.; Valentino, R.; Bui, N.; Pereyre, S.; Bebear, C.; Bebear, C.M.; Gbikpi-Benissan, G. Strategy of antibiotic rotation: Long-term effect on incidence and susceptibilities of Gram-negative bacilli responsible for ventilator-associated pneumonia. *Crit. Care Med.* **2003**, *31*, 1908–1914. [CrossRef] [PubMed]

Guimaraes, M.M.; Rocco, J.R. Prevalence of ventilator-associated pneumonia in a university hospital and prognosis for the patients affected. *J. Bras. Pneumol.* **2006**, *32*, 339–346. [CrossRef] [PubMed]

Gursel, G.; Aydogdu, M.; Nadir Ozis, T.; Tasyurek, S. Comparison of the value of initial and serial endotracheal aspirate surveillance cultures in predicting the causative pathogen of ventilator-associated pneumonia. *Scand. J. Infect. Dis.* **2010**, *42*, 341–346. [CrossRef] [PubMed]

Heyland, D.K.; Cook, D.J.; Schoenfeld, P.S.; Frietag, A.; Varon, J.; Wood, G. The effect of acidified enteral feeds as aspiration in mechanically ventilated patients using small-bore nasogastric tubes. *J. Parenter. Enter. Nutr.* **2000**, *24*, 103–106. [CrossRef] [PubMed]

Hugonnier, S.; Uçkay, I.; Pittet, D. Staffing level: A determinant of late-onset ventilator-associated pneumonia. *Crit. Care Med.* **2007**, *35*, R80. [CrossRef] [PubMed]

Hyllienmark, P.; Gardlund, B.; Persson, J.O.; Ekdahl, K. Nosocomial pneumonia in the ICU: A prospective cohort study. *Scand. J. Infect. Dis.* **2007**, *39*, 676–682. [CrossRef] [PubMed]

Ibáñez, J.; Peñañuelas, A.; Marsé, P.; Jordá, R.; Raurich, J.M.; Mata, F. Incidence of gastroesophageal reflux and aspiration in mechanically ventilated patients using small-bore nasogastric tubes. *J. Parenter. Enter. Nutr.* **2000**, *24*, 103–106. [CrossRef] [PubMed]

Ibrahim, E.H.; Ward, S.; Sherman, G.; Kollef, M.H. A comparative analysis of patients with early-onset vs. late-onset nosocomial pneumonia in the ICU setting. *Chest* **2000**, *117*, 1434–1442. [CrossRef] [PubMed]

Jacobs, S.; Chang, R.W.; Lee, B.; Bartlett, F.W. Continuous enteral feeding: A major cause of pneumonia among ventilated intensive care unit patients. *J. Parenter. Enter. Nutr.* **1999**, *14*, 353–356. [CrossRef] [PubMed]

Jaillette, E.; Nseir, S. Relationship between inhaled β2-agonists and ventilator-associated pneumonia: A cohort study. *Crit. Care Med.* **2011**, *39*, 725–730. [CrossRef] [PubMed]

Jaimes, F.; De La Rosa, G.; Gómez, E.; Múnera, P.; Ramírez, J.; Castrillón, S. Incidence and risk factors for ventilator-associated pneumonia in a developing country Where is the difference? *Respir. Med.* **2007**, *101*, 762–767. [CrossRef] [PubMed]

Jiménez, P.; Torres, A.; Rodríguez-Roisín, R.; de la Bellacasa, J.P.; Aznar, R.; Gatell, J.M.; Agustí-Vidal, A. Incidence and etiology of pneumonia acquired during mechanical ventilation. *Crit. Care Med.* **1989**, *17*, 882–885. [CrossRef] [PubMed]

Kallel, H.; Chelly, H.; Bahloul, M.; Ksibi, H.; Dammak, H.; Chaari, A.; Hamida, C.B.; Rekik, N.; Bouazizi, M. The effect of ventilator-associated pneumonia on the prognosis of head trauma patients. *J. Trauma Acute Care Surg.* **2005**, *59*, 705–710.

Kanafani, Z.A.; Kara, L.; Hayek, S.; Kanj, S.S. Ventilator-associated pneumonia at a tertiary-care center in a developing country: Incidence, microbiology, and susceptibility patterns of isolated microorganisms. *Infect. Control Hosp. Epidemiol.* **2003**, *24*, 864–869. [CrossRef] [PubMed]

Kollef, M.H. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* **1993**, *270*, 1965–1970. [CrossRef] [PubMed]

Kollef, M.H.; Silver, P.; Murphy, D.M.; Trovillion, E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. *Chest* **1995**, *108*, 1655–1662. [CrossRef] [PubMed]
53. Kollef, M.H.; Von Harz, B.; Prentice, D.; Shapiro, S.D.; Silver, P.; John, R.S.; Trovillion, E. Patient transport from intensive care increases the risk of developing ventilator-associated pneumonia. *Chest* **1997**, *112*, 765–773. [CrossRef] [PubMed]

54. Kollef, M.H.; Chastre, J.; Fagon, J.Y.; Francois, B.; Niederman, M.S.; Rello, J.; Torres, A.; Vincent, J.L.; Wunderink, R.G.; Go, K.W.; Rehm, C.; et al. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to Pseudomonas aeruginosa. *Crit. Care Med.* **2014**, *42*, 2178–2187. [CrossRef] [PubMed]

55. Koss, W.G.; Khalili, T.M.; Lemus, J.F.; Margulies, D.R.; Shabot, M.M. Nosocomial pneumonia is not prevented by protective contact isolation in the surgical intensive care unit. *Am. Surg.* **2001**, *67*, 1140–1144. [PubMed]

56. Kunac, A.; Sifri, Z.C.; Mohr, A.M.; Horng, H.; Lavery, R.F.; Livingston, D.H. Bacteremia and Ventilator-Associated Pneumonia: A Marker for Contemporaneous Extra-Pulmonic Infection. *Surg. Infect.* **2014**, *15*, 77–83. [CrossRef] [PubMed]

57. Lepelletier, D.; Roquilly, A.; Mahe, P.J.; Loutrel, O.; Champin, P.; Corvec, S.; Naux, E.; Pinaud, M.; Lejs, C.; Asehnoune, K. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. *J. Neurosurg. Anesthesiol.* **2010**, *22*, 32–37. [CrossRef] [PubMed]

58. Luna, C.M.; Blanzaco, D.; Niederman, M.S.; Matarucco, W.; Baredes, N.C.; Desmery, P.; Palizas, F.; Menga, G.; Rios, F.; Apezetegua, C. Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early prediction tool. *Crit. Care Med.* **2003**, *31*, 676–682. [CrossRef] [PubMed]

59. Luyt, C.E.; Guérin, V.; Combes, A.; Trouillet, J.L.; Ayed, S.B.; Bernard, M.; Gibert, C.; Chastre, J. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 48–53. [CrossRef] [PubMed]

60. Magnason, S.; Kristinsson, K.G.; Stefansson, T.; Erlendsdottir, H.; Jonsdottir, K.; Kristjansson, M.; Gudmundsson, S. Risk factors and outcome in ICU-acquired infections. *Acta Anaesthesiol. Scand.* **2008**, *52*, 1238–1245. [CrossRef] [PubMed]

61. Magret, M.; Amaya-Villar, R.; Garnacho, J.; Lisboa, T.; Diaz, E.; DeWaele, J.; Deja, M.; Manno, E.; Rello, J. EU-VAP/CAP Study Group: Ventilator-associated pneumonia in trauma patients is associated with lower mortality: Results from EU-VAP study. *J. Trauma Acute Care Surg.* **2010**, *69*, 849–854. [CrossRef] [PubMed]

62. Mahul, P.; Auboyer, C.; Jospe, R.; Ros, A.; Guerin, C.; el Khouri, Z.; Galliez, M.; Dumont, A.; Gaudin, O. Prevention of nosocomial pneumonia in intubated patients respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med.* **1992**, *18*, 20–25. [CrossRef] [PubMed]

63. Makris, D.; Manoulakas, E.; Komnios, A.; Papakrivou, E.; Tzavaras, N.; Hovas, A.; Zintzaras, E.; Zakynthinos, E. Effect of pravastatin on the frequency of ventilator-associated pneumonia and on intensive care unit mortality: Open-label, randomized study. *Crit. Care Med.* **2011**, *39*, 2440–2446. [CrossRef] [PubMed]

64. Markowicz, P.; Wolff, M.; Djedaini, K.; Cohen, Y.; Chastre, J.; Delclaux, C. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. *Am. J. Respir. Crit. Care Med.* **2000**, *161*, 1942–1948. [CrossRef] [PubMed]

65. Memish, Z.A.; Cunningham, G.; Oni, G.A.; Djazmati, W. The incidence and risk factors of ventilator-associated pneumonia in a Riyadh hospital. *Infect. Control Hosp. Epidemiol.* **2000**, *21*, 271–273. [CrossRef] [PubMed]

66. Michel, F.; Franceschini, B.; Berger, P.; Arnal, J.M.; Gainnier, M.; Sainty, J.M.; Papazian, L. Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: A role for routine endotracheal aspirate cultures. *Chest* **2005**, *127*, 589–597. [CrossRef] [PubMed]

67. Moine, P.; Timsit, J.F.; De Lassence, A.; Troché, G.; Fosse, J.P.; Alberti, C.; Cohen, Y. Mortality associated with late-onset pneumonia in the intensive care unit: Results of a multi-center cohort study. *Intensive Care Med.* **2002**, *28*, 154–163. [CrossRef] [PubMed]

68. Myny, D.; Depuydt, P.; Colardyn, F.; Blot, S. Ventilator-associated pneumonia in a tertiary care ICU analysis of risk factors for acquisition and mortality. *Acta Clin. Belg.* **2005**, *60*, 114–121. [CrossRef] [PubMed]
69. Nguile-Makao, M.; Zahar, J.R.; François, A.; Tabah, A.; Garrouste-Orgeas, M.; Allaouchiche, B.; Goldgran-Toledano, D.; Azoulay, E.; Adrie, C.; et al. Attributable mortality of ventilator-associated pneumonia: Respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive Care Med. 2010, 36, 781–789. [CrossRef] [PubMed]

70. Nielsen, S.L.; Røder, B.; Magnusson, P.; Engquist, A.; Frimodt-møller, N. Nosocomial pneumonia in an intensive care unit in a Danish university hospital: Incidence, mortality and etiology. Scand. J. Infect. Dis. 1992, 24, 65–70. [CrossRef] [PubMed]

71. Noor, A.; Hussain, S.F. Risk factors associated with development of ventilator associated pneumonia. J. Coll. Physicians Surg. Pak. 2005, 15, 92–95. [PubMed]

72. Nseir, S.; Di Pompeo, C.; Soubrier, S.; Cavestri, B.; Jozefowicz, E.; Saunier, F.; Durocher, A. Impact of ventilator-associated pneumonia on outcome in patients with COPD. Chest 2005, 128, 1650–1656. [CrossRef] [PubMed]

73. Papazian, L.; Bregeon, F.; Thirion, X.; Gregoire, R.; Saux, P.; Denis, J.P.; Perin, G.; Charrel, J.; Dumon, J.F.; Affray, J.P.; Gouin, F. Effect of ventilator-associated pneumonia on mortality and morbidity. Am. J. Respir. Crit. Care Med. 1996, 154, 91–97. [CrossRef] [PubMed]

74. Potgieter, P.D.; Linton, D.M.; Oliver, S.; Forder, A. A Nosocomial infections in a respiratory intensive care unit. Crit. Care Med. 1987, 15, 495–498. [CrossRef] [PubMed]

75. Raineri, E.; Crema, L.; Dal Zoppo, S.; Acquarolo, A.; Pan, A.; Carnevale, G.; Albertario, F.; Candiani, A. Rotation of antimicrobial therapy in the intensive care unit. Impact on incidence of ventilator-associated pneumonia caused by antibiotic-resistant Gram-negative bacteria. Eur. J. Clin. Microbiol. Infect. Dis. 2010, 29, 1015–1024. [CrossRef] [PubMed]

76. Ramirez, P.; Lopez-Ferraz, C.; Gordon, M.; Gimeno, A.; Villarreal, E.; Ruiz, J.; Menendez, R.; Torres, A. From starting mechanical ventilation to ventilator-associated pneumonia, choosing the right moment to start antibiotic treatment. Crit. Care 2016, 20, 169. [CrossRef] [PubMed]

77. Rello, J.; Quintana, E.; Ausina, V.; Castella, J.; Luquin, M.; Net, A.; Prats, G. Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. Chest 1991, 100, 439–444. [CrossRef] [PubMed]

78. Rello, J.; Ausina, V.; Ricart, M.; Puso, C.; Net, A.; Prats, G. Nosocomial pneumonia in critically ill comatose patients: Need for a differential therapeutic approach. Eur. Respir. J. 1992, 5, 1249–1253. [PubMed]

79. Rello, J.; Sonora, R.; Jubert, P.; Artigas, A.; Rué, M.; Vallés, J. Pneumonia in intubated patients: Role of respiratory airway care. Am. J. Respir. Crit. Care Med. 1996, 154, 111–115. [CrossRef] [PubMed]

80. Rello, J.; Ollendorf, D.A.; Oster, G.; Vera-Llonch, M.; Bellm, L.; Redman, R.; Kollef, M.H.; VAP Outcomes Scientific Advisory Group. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002, 122, 2115–2121. [CrossRef] [PubMed]

81. Rello, J.; Lorente, C.; Diaz, E.; Bodi, M.; Boque, C.; Sandiumenge, A.; Santamaria, J.M. Incidence, etiology, and outcome of nosocomial pneumonia in ICU patients requiring percutaneous tracheotomy for mechanical ventilation. Chest 2003, 124, 2239–2243. [CrossRef] [PubMed]

82. Resende, M.M.; Monteiro, S.G.; Callegari, B.; Figueiredo, P.M.; Monteiro, C.R.; Monteiro-Neto, V. Epidemiology and outcomes of ventilator-associated pneumonia in northern Brazil: An analytical descriptive prospective cohort study. BMC Infect. Dis. 2013, 13, 119. [CrossRef] [PubMed]

83. Reusser, P.; Zimmerli, W.; Scheidegger, D.; Marbet, G.A.; Buser, M.; Gyr, K. Role of gastric colonization in nosocomial infections and endotoxemia: A prospective study in neurosurgical patients on mechanical ventilation. J. Infect. Dis. 1989, 160, 414–421. [CrossRef] [PubMed]

84. Rezai, M.S.; Bagheri-Nesami, M.; Nikkhah, A.; Bayg, A.H. Incidence, risk factors, and outcome of ventilator-associated Pneumonia in 18 hospitals of Iran. Running title: Ventilator-associated pneumonia in Iran. Int. J. Adv. Biotechnol. Res. 2016, 7, 936–946. [CrossRef] [PubMed]

85. Rincón-Ferrari, M.D.; Flores-Cordero, J.M.; Leal-Naval, S.R.; Murillo-Cabezas, E.; Cayuelas, A.; Muñoz-Sánchez, M.A.; Sánchez-Olmedo, J.I. Impact of ventilator-associated pneumonia in patients with severe head injury. J. Trauma Acute Care Surg. 2004, 57, 1234–1240. [CrossRef] [PubMed]

86. Rodrigues, P.M.; Neto, C.; Santos, L.R.; Knibel, M.F. Ventilator-associated pneumonia: Epidemiology and impact on the clinical evolution of ICU patients. J. Bras. Pneumol. 2009, 35, 1084–1091. [CrossRef] [PubMed]

87. Rodriguez, J.L.; Gibbons, K.J.; Bitzer, L.G.; Deichert, R.E.; Steinberg, S.M.; Flint, L.M. Pneumonia: Incidence, risk factors, and outcome in injured patients. J. Trauma 1991, 31, 907–912. [CrossRef] [PubMed]
88. Ruiz-Santana, S.; García Jimenez, A.; Esteban, A.; Guerra, L.; Alvarez, B.; Corcia, S.; Gudin, J.; Martínez, A.; Quintana, E.; Armengol, S.; et al. ICU pneumonias: A multi-institutional study. Crit. Care Med. 1987, 15, 930–932. [CrossRef] [PubMed]

89. Salahuddin, N.; Zafar, A.; Sukhyan, L.; Rahim, S.; Noor, M.F.; Hussain, K.; Siddiqui, S.; Islam, M.; Husain, S.J. Reducing ventilator-associated pneumonia rates through a staff education programme. J. Hosp. Infect. 2004, 57, 223–227. [CrossRef] [PubMed]

90. Salata, R.A.; Lederman, M.M.; Shlaes, D.M.; Jacobs, M.R.; Eckstein, E.; Tweardy, D.; Toossi, Z.; Chmielewski, R.; Marino, J. King CH Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. Am. Rev. Respir. Dis. 1987, 135, 426–432. [PubMed]

91. Shahin, J.; Bielinski, M.; Guichon, C.; Flemming, C.; Kristof, A.S. Suspected ventilator-associated respiratory infection in severely ill patients: A prospective observational study. Crit. Care 2013, 17, R251. [CrossRef] [PubMed]

92. Sofianou, D.C.; Constandinidis, T.C.; Yannacou, M.; Anastasiou, H.; Sofianos, E. Analysis of risk factors for ventilator-associated pneumonia in a multidisciplinary intensive care unit. Eur. J. Clin. Microbiol. Infect. Dis. 2000, 19, 460–463. [CrossRef] [PubMed]

93. Stéphan, F.; Mabrouk, N.; Decailliot, F.; Delclaux, C.; Legrand, P. Ventilator-associated pneumonia leading to acute lung injury after trauma: Importance of Haemophilus influenzae. Anesthesiology 2006, 104, 235–241. [CrossRef] [PubMed]

94. Tan, X.; Zhu, S.; Yan, D.; Chen, W.; Chen, R.; Zou, J.; Yan, J.; Zhang, X.; Farmakiotis, D.; Mylonakis, E. Candida spp. airway colonization: A potential risk factor for Acinetobacter baumannii ventilator-associated pneumonia. Med. Mycol. 2016, 54, 557–566. [CrossRef] [PubMed]

95. Tejada Artigas, A.T.; Dronda, S.B.; Vallés, E.C.; Marco, J.M.; Usón, M.C.; Figueras, P.; Suarez, F.J.; Hernandez, A. Risk factors for nosocomial pneumonia in critically ill trauma patients. Crit. Care Med. 2001, 29, 304–349. [CrossRef] [PubMed]

96. Timsit, J.F.; Chevret, S.; Valcke, J.; Misset, B.; Renaud, B.; Goldstein, F.W.; Vaury, P.; Carlet, J. Mortality of nosocomial pneumonia in ventilated patients: Influence of diagnostic tools. Am. J. Respir. Crit. Care Med. 1996, 154, 116–123. [CrossRef] [PubMed]

97. Torres, A.; Aznar, R.; Gatell, J.M.; Jiménez, P.; González, J.; Ferrer, A.; Celis, R.; Rodríguez-Roisin, R. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am. Rev. Respir. Dis. 1990, 142, 523–528. [CrossRef] [PubMed]

98. Trouillet, J.L.; Chastre, J.; Vuagnat, A.; Joly-Guillou, M.L.; Combaux, D.; Dombret, M.C.; Gibert, C. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am. J. Respir. Crit. Care Med. 1998, 157, 531–539. [CrossRef] [PubMed]

99. Urti, T.; Perone, G.; Acquarolo, A.; Zappa, S.; Antonini, B.; Ciani, A. Surveillance of infections acquired in intensive care: Usefulness in clinical practice. J. Hosp. Infect. 2002, 52, 130–135. [CrossRef] [PubMed]

100. Valles, J.; Pobo, A.; García-Esquiero, O.; Mariscal, D.; Reol, J.; Fernández, R. Excess ICU mortality attributable to ventilator-associated pneumonia: The role of early vs. late onset. Intensive Care Med. 2007, 33, 1363–1368. [CrossRef] [PubMed]

101. Vanhems, P.; Bénét, T.; Voirin, N.; Januel, J.M.; Lepape, A.; Allaouchiche, B.; Argaud, L.; Chassard, D.; Guérin, C. Early-onset ventilator-associated pneumonia incidence in intensive care units: A surveillance-based study. BMC Infect. Dis. 2011, 11, 236. [CrossRef] [PubMed]

102. Verhamme, K.M.; De Coster, W.; De Roo, L.; De Beenhouwer, H.; Nollet, G.; Verbeke, J.; Demeyer, L.; Jordens, P. Pathogens in early-onset and late-onset intensive care unit–acquired pneumonia. Infect. Control Hosp. Epidemiol. 2007, 28, 389–397. [CrossRef] [PubMed]

103. Violan, J.S.; Sanchez-Ramírez, C.; Mujica, A.P.; Cendrero, J.C.; Fernandez, J.A.; de Castro, F.R. Impact of nosocomial pneumonia on the outcome of mechanically-ventilated patients. Crit. Care 1998, 2, 19–23. [CrossRef] [PubMed]

104. Woske, H.J.; Röding, T.; Schulz, I.; Lode, H. Ventilator-associated pneumonia in a surgical intensive care unit Epidemiology, etiology and comparison of three bronchoscopic methods for microbiological specimen sampling. Crit. Care 2001, 5, 167–173. [CrossRef] [PubMed]

105. Xie, D.S.; Xiong, W.; Lai, R.P.; Liu, L.; Gan, X.M.; Wang, X.H.; Wang, M.; Lou, Y.X.; Fu, X.Y.; Wang, H.F.; Xiang, H. Ventilator-associated pneumonia in intensive care units in Hubei Province, China: A multicentre prospective cohort survey. J. Hosp. Infect. 2011, 78, 284–288. [CrossRef] [PubMed]
106. Zahar, J.R.; Nguile-Makao, M.; François, A.; Schwebel, C.; Garrouste-Orgeas, M.; Goldgran-Toledano, D.; Azoulay, E.; Thuong, M.; Jamali, S.; et al. Predicting the risk of documented ventilator-associated pneumonia for benchmarking: Construction and validation of a score. *Crit. Care Med.* 2009, 37, 2545–2551. [CrossRef] [PubMed]

107. Acosta-Escribano, J.; Fernández-Vivas, M.; Carmona, T.G.; Caturia-Such, J.; García-Martínez, M.; Menéndez-Mainer, A.; Sanchez-Paya, J. Gastric versus transpyloric feeding in severe traumatic brain injury: A prospective, randomized trial. *Intensive Care Med.* 2010, 36, 1532–1539. [CrossRef] [PubMed]

108. Bonten, M.J.; Gaillard, C.A.; Van der Geest, S.; Van Tiel, F.H.; Beyens, A.J.; Smeets, H.G.; Stobberingh, E.E. The role of intragastric acidity and stress ulcer prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified, randomized, double-blind study of sucralfate versus antacids. *Am. J. Respir. Crit. Care Med.* 1995, 152, 1825–1834. [CrossRef] [PubMed]

109. Combes, P.; Fauvage, B.; Oleyer, C. Nosocomial pneumonia in mechanically ventilated patients, a prospective randomised evaluation of the SteriCath closed suctioning system. *Intensive Care Med.* 2000, 26, 878–882. [CrossRef] [PubMed]

110. Cook, D.; Guyatt, G.; Marshall, J.; Leasa, D.; Fuller, H.; Hall, R.; Peters, S.; Rutledge, F.; Griffith, L.; McLellan, A.; et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N. Engl. J. Med.* 1998, 338, 791–797. [CrossRef] [PubMed]

111. Daumal, F.; Colpart, E.; Manoury, B.; Mariani, M.; Daumal, M. Changing heat and moisture exchangers every 48 hours does not increase the incidence of nosocomial pneumonia. *Infect. Control Hosp. Epidemiol.* 1999, 20, 347–349. [CrossRef] [PubMed]

112. Djedaini, K.; Billiard, M.; Mier, L.; Le Bourdelles, G.; Brun, P.; Markowicz, P.; Estagnasie, P.; Coste, F.; Boussougant, Y; Dreyfuss, D. Changing heat and moisture exchangers every 48 h rather than 24 h does not affect their efficacy and the incidence of nosocomial pneumonia. *Am. J. Respir. Crit. Care Med.* 1995, 152, 1562–1569. [CrossRef] [PubMed]

113. Drakulovic, M.B.; Torres, A.; Bauer, T.T.; Nicolas, J.M.; Nogué, S.; Fèrier, M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet* 1999, 354, 1851–1858. [CrossRef]

114. Dreyfuss, D.; Djedaini, K.; Weber, P.; Brun, P.; Lanore, J.J.; Rahmani, J.; Coste, F. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 h versus no change. *Am. Rev. Respir. Dis.* 1991, 143 Pt 1, 738–743. [CrossRef] [PubMed]

115. Dreyfuss, D.; Djedaini, K.; Gros, I.; Mier, L.; Le Bourdelles, G.; Cohen, Y.; Estagnasie, P.; Coste, F.; Boussougant, Y. Mechanical ventilation with heated humidifiers or heat and moisture exchangers: Effects on patient colonization and incidence of nosocomial pneumonia. *Am. J. Respir. Crit. Care Med.* 1995, 151, 986–992. [PubMed]

116. Driks, M.R.; Craven, D.E.; Celli, B.R.; Manning, M.; Burke, R.A.; Garvin, G.M.; Kunches, L.M.; Farber, H.W.; Wedel, S.A.; McCabe, W.R. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. *N. Engl. J. Med.* 1987, 317, 1376–1382. [CrossRef] [PubMed]

117. Fabian, T.C.; Boucher, B.A.; Croce, M.A.; Kuhl, D.A.; Janning, S.W.; Coffey, B.C.; Kudsk, K.A. Pneumonia and stress ulceration in severely injured patients: A prospective evaluation of the effects of stress ulcer prophylaxis. *Arch. Surg.* 1993, 128, 185–192. [CrossRef] [PubMed]

118. Forestier, C.; Guelon, D.; Cluytens, V.; Guillart, T.; Sirot, J.; De Champs, C. Oral probiotic and prevention of *Pseudomonas aeruginosa* infections: A randomized, double-blind, placebo-controlled pilot study in intensive care unit patients. *Crit. Care* 2008, 12, R69. [CrossRef] [PubMed]

119. Holzapfel, L.; Chevret, S.; Madinier, G.; Olen, F.; Demengeon, G.; Couprie, A. Chaudet M Influence of long-term oro- or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: Results of a prospective, randomized, clinical trial. *Crit. Care Med.* 1993, 21, 1132–1138. [CrossRef] [PubMed]

120. Holzapfel, L.; Chastang, C.; Demengeon, G.; Bohe, J.; Piralla, B.; Couprie, A. A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 1999, 159, 695–701. [CrossRef] [PubMed]
121. Kappstein, I.; Schulgen, G.; Friedrich, T.; Hellinger, P.; Benzing, A.; Geiger, K.; Daschner, F.D. Incidence of pneumonia in mechanically ventilated patients treated with sucralfate or cimetidine as prophylaxis for stress bleeding: Bacterial colonization of the stomach. *Am. J. Med.* 1991, 91, S125–S131. [CrossRef]

122. Kirschenbaum, L.; Azzi, E.; Steir, T.; Tietjen, P.; Astiz, M. Effect of continuous lateral rotational therapy on the prevalence of ventilator-associated pneumonia in patients requiring long-term ventilatory care. *Crit. Care Med.* 2002, 30, 1983–1986. [CrossRef] [PubMed]

123. Kirton, O.C.; DeHaven, B.; Morgan, J.; Civetta, J. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: Rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest* 1997, 112, 1055–1059. [PubMed]

124. Knight, D.J.; Gardiner, D.; Banks, A.; Snape, S.E.; Weston, V.C.; Bengmark, S.; Girling, K.J. Effect of symbiotic therapy on the incidence of ventilator associated pneumonia in critically ill patients: A randomised, double-blind, placebo-controlled trial. *Intensive Care Med.* 2009, 35, 854–861. [CrossRef] [PubMed]

125. Kollef, M.H.; Shapiro, S.D.; Fraser, V.J.; Silver, P.; Murphy, D.M.; Trovillion, E.; Hearns, M.L.; Richards, R.D.; Cracchiolo, L.; Hossin, L. Mechanical ventilation with or without 7-day circuit changes. A randomized controlled trial. *Ann. Intern. Med.* 1995, 123, 168–174. [CrossRef] [PubMed]

126. Kollef, M.H.; Prentice, D.; Shapiro, S.D.; Fraser, V.J.; Silver, P.; Trovillion, E.; Weilitz, P.; Von Harz, B.E.; St. John, R.O. Mechanical ventilation with or without daily changes of in-line suction catheters. *Am. J. Respir. Crit. Care Med.* 1997, 156, 466–472. [CrossRef] [PubMed]

127. Kortbeek, J.B.; Haigh, P.I.; Doig, C. Duodenal versus gastric feeding in ventilated blunt trauma patients: A randomized controlled trial. *J. Trauma* 2019, 86, 992–998. [CrossRef] [PubMed]

128. Kostadima, E.; Kaditis, A.G.; Alexopoulos, E.I.; Zakythinos, E.; Sfyras, D. Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients. *Eur. Respir. J.* 2005, 26, 106–111. [CrossRef] [PubMed]

129. Lacherade, J.C.; Auburtin, M.; Cerf, C.; Van de Louw, A.; Soufir, L.; Rebufat, Y.; Rezaiguia, S.; Ricard, J.D.; Launey, Y.; Nesseler, N.; Le Cousin, A.; Feuillet, F.; Garlantezec, R.; Mallédant, Y.; Seguin, P. Effect of a fever control protocol-based strategy on ventilator-associated pneumonia in severely brain-injured patients. *Crit. Care* 2014, 18, 1. [CrossRef] [PubMed]

130. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S.; Kortbeek, J.B.; Haigh, P.I.; Doig, C. Duodenal versus gastric feeding in ventilated blunt trauma patients: A randomized controlled trial. *Crit. Care Med.* 2002, 30, 1983–1986. [CrossRef] [PubMed]

131. Lacherade, J.C.; Auburtin, M.; Cerf, C.; Van de Louw, A.; Soufir, L.; Rebufat, Y.; Rezaiguia, S.; Ricard, J.D.; Launey, Y.; Nesseler, N.; Le Cousin, A.; Feuillet, F.; Garlantezec, R.; Mallédant, Y.; Seguin, P. Effect of a fever control protocol-based strategy on ventilator-associated pneumonia in severely brain-injured patients. *Crit. Care* 2014, 18, 1. [CrossRef] [PubMed]

132. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S. Intermittent subglottic secretion drainage and ventilator-associated pneumonia A multicenter trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 910–917. [CrossRef] [PubMed]

133. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S. Intermittent subglottic secretion drainage and ventilator-associated pneumonia A multicenter trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 910–917. [CrossRef] [PubMed]

134. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S. Intermittent subglottic secretion drainage and ventilator-associated pneumonia A multicenter trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 910–917. [CrossRef] [PubMed]

135. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S. Intermittent subglottic secretion drainage and ventilator-associated pneumonia A multicenter trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 910–917. [CrossRef] [PubMed]

136. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S. Intermittent subglottic secretion drainage and ventilator-associated pneumonia A multicenter trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 910–917. [CrossRef] [PubMed]

137. Lacherade, J.C.; De Jonghe, B.; Guezennec, P.; Debbat, K.; Hayon, J.; Monsel, A.; Bastuji-Garin, S. Intermittent subglottic secretion drainage and ventilator-associated pneumonia A multicenter trial. *Am. J. Respir. Crit. Care Med.* 2010, 182, 910–917. [CrossRef] [PubMed]

138. Lorente, L.; Lecuona, M.; Jiménez, A.; Mora, M.L.; Sierra, A. Bacterial filters in respiratory circuits: An unnecessary cost? *Crit. Care Med.* 2003, 31, 2126–2130. [CrossRef] [PubMed]

139. Lorente, L.; Lecuona, M.; Galván, R.; Ramos, M.J.; Mora, M.L.; Sierra, A. Periodically changing ventilator circuits is not necessary to prevent ventilator-associated pneumonia when a heat and moisture exchanger is used. *Infect. Control Hosp. Epidemiol.* 2004, 25, 1077–1082. [CrossRef] [PubMed]

140. Lorente, L.; Lecuona, M.; Galván, R.; Ramos, M.J.; Mora, M.L.; Sierra, A. Periodically changing ventilator circuits is not necessary to prevent ventilator-associated pneumonia when a heat and moisture exchanger is used. *Infect. Control Hosp. Epidemiol.* 2004, 25, 1077–1082. [CrossRef] [PubMed]

141. Lorente, L.; Lecuona, M.; Martín, M.M.; García, C.; Mora, M.L.; Sierra, A. Ventilator-associated pneumonia using a closed versus an open tracheal suction system. *Crit. Care Med.* 2005, 33, 115–119. [CrossRef] [PubMed]

142. Lorente, L.; Lecuona, M.; Jiménez, A.; Mora, M.L.; Sierra, A. Tracheal suction by closed system without daily change versus open system. *Intensive Care Med.* 2006, 32, 538–544. [CrossRef] [PubMed]

143. Lorente, L.; Lecuona, M.; Jimenez, A.; Mora, M.L.; Sierra, A. Ventilator-associated pneumonia using a heated humidifier or a heat and moisture exchanger: A randomized controlled trial [ISRCTN88724583]. *Crit. Care* 2006, 10, R116. [CrossRef] [PubMed]

144. Lorente, L.; Lecuona, M.; Jimenez, A.; Mora, M.L. Sierra: Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. *Am. J. Respir. Crit. Care Med.* 2007, 176, 1079–1083. [CrossRef] [PubMed]

145. Lorente, L.; Lecuona, M.; Jiménez, A.; Lorenzo, L.; Roca, I.; Cabrera, J.; Llanos, C.; Mora, M.L. Continuous endotracheal tube cuff pressure control system protects against ventilator-associated pneumonia. *Crit. Care* 2014, 18, 1. [CrossRef] [PubMed]
139. Manzano, F.; Fernandez-Mondejar, E.; Colmenero, M.; Poyatos, M.E.; Rivera, R.; Machado, J.; Catalan, I.; Artigas, A. Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit. Care Med. 2008, 36, 2225–2231. [CrossRef] [PubMed]

140. Martin, C.; Ferrin, G.; Gevaudan, M.J.; Saux, P.; Gouin, F. Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. Chest 1990, 97, 144–149. [CrossRef] [PubMed]

141. Morrow, L.E.; Kollef, M.H.; Casale, T.B.; Collepardi, M.; Mitro, R.; Levison, M.; Cho, S.K.; Beggs, J.M. Probiotic prophylaxis of ventilator-associated pneumonia: A blinded, randomized, controlled trial. Am. J. Respir. Crit. Care Med. 2000, 161, 1844–1849. [CrossRef] [PubMed]

142. Martin, C.; Perrin, G.; Gevaudan, M.J.; Saux, P.; Gouin, F. Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. Chest 1990, 97, 144–149. [CrossRef] [PubMed]

143. Pneumatikos, I.; Konstantonis, D.; Tsalakis, I.; Theodorou, V.; Vretzakis, G.; Danielides, V.; Bouros, D. Prevention of nosocomial maxillary sinusitis in the ICU: The effects of topically applied alpha-adrenergic agonists and corticosteroids. Intensive Care Med. 2006, 32, 532–537. [CrossRef] [PubMed]

144. Prod’hom, G.; Leuenberger, P.; Koerfer, J.; Blum, A.; Chiolero, R.; Schaller, M.D.; Perret, C.; Spinnler, O.; Blondel, J.; Siegrist, H.; et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. Ann. Intern. Med. 1994, 120, 653–662. [CrossRef] [PubMed]

145. Pneumatikos, I.; Konstantonis, D.; Tsalakis, I.; Theodorou, V.; Vretzakis, G.; Danielides, V.; Bouros, D. Prevention of nosocomial maxillary sinusitis in the ICU: The effects of topically applied alpha-adrenergic agonists and corticosteroids. Intensive Care Med. 2006, 32, 532–537. [CrossRef] [PubMed]

146. Ryan, P.; Dawson, J.; Teres, D.; Celoria, G.; Navab, F. Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. Arch. Surg. 1993, 128, 1353–1357. [CrossRef] [PubMed]

147. Reingruber, J.; Mercier, E.; Le Gouge, A.; Boulain, T.; Desachy, A.; Bellec, F.; Lascarrou, J.B. Effect of Not Monitoring Residual Gastric Volume on Risk of Ventilator-Associated Pneumonia in Adults Receiving Mechanical Ventilation and Early Enteral Feeding. A Randomized Controlled Trial. JAMA 2013, 309, 249–256. [CrossRef] [PubMed]

148. Rumbak, M.J.; Truncale, T.; Newton, M.N.; Adams, B.; Hazard, P. A Prospective, Randomized Study Comparing Early Versus Delayed Percutaneous Tracheostomy In Critically Ill Medical Patients Requiring Prolonged Mechanical Ventilation. Chest 2000, 118, 97S–98S.

149. Ryan, P.; Dawson, J.; Teres, D.; Celoria, G.; Navab, F. Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. Arch. Surg. 1993, 128, 1353–1357. [CrossRef] [PubMed]

150. Smulders, K.; van der Hoeven, H.; Weers-Pothoff, I.; Vandenbroucke-Grauls, C. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. Chest 2002, 121, 858–862. [CrossRef] [PubMed]

151. Staudinger, T.; Blondel, J.; Siegrist, H.; et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. Ann. Intern. Med. 1994, 120, 653–662. [CrossRef] [PubMed]

152. Thomachot, L.; Leone, M.; Razzouk, K.; Antonini, F.; Viallet, R.; Martin, C. Do the components of heat and moisture exchangers, one hydrophobic and one hygroscopic, on humidifying efficacy and the incidence of nosocomial pneumonia? Crit. Care Med. 1999, 27, 923–928. [CrossRef] [PubMed]

153. Thomachot, L.; LeGouge, A.; Boulain, T.; Desachy, A.; Bellec, F.; Lascarrou, J.B. Effect of Not Monitoring Residual Gastric Volume on Risk of Ventilator-Associated Pneumonia in Adults Receiving Mechanical Ventilation and Early Enteral Feeding. A Randomized Controlled Trial. JAMA 2013, 309, 249–256. [CrossRef] [PubMed]

154. Thomachot, L.; Leone, M.; Razzouk, K.; Antonini, F.; Vialet, R.; Martin, C. Randomized Clinical Trial of Extended Use of a Hydrophobic Condenser Humidifier: 1 vs. 7 Days. Crit. Care Med. 2002, 30, 232–237. [CrossRef] [PubMed]

155. Zeng, J.; Wang, C.T.; Zhang, F.S.; Qi, F.; Wang, S.F.; Ma, S.; Wu, T.J.; Tian, H.; Tian, Z.T.; Zhang, S.L.; et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: A randomized controlled multicenter trial. Intensive Care Med. 2016, 42, 1018–1028. [CrossRef] [PubMed]

156. Kantorova, I.; Svoboda, P.; Scheer, P.; Doubek, J.; Rehorkova, D.; Bosakova, H.; Ochmann, J. Stress ulcer prophylaxis in critically ill patients: A randomized controlled trial. Hepatogastroenterology 2004, 51, 757–761. [PubMed]
157. Ćabov, T.; Macan, D.; Husedžinović, I.; Škrin-Šubić, J.; Bošnjak, D.; Šestan-Crnec, S.; Perić, B.; Kovač, Z.; Golubović, V. The impact of oral health and 0.2% chlorhexidine oral gel on the prevalence of nosocomial infections in surgical intensive-care patients: A randomized placebo-controlled study. *Wien. Klin. Wochenschr.* 2010, 122, 397–404. [CrossRef] [PubMed]

158. Caruso, P.; Denari, S.; Ruiz, S.A.; Demarzo, S.E.; Deheinzelin, D. Saline instillation before tracheal suctioning decreases the incidence of ventilator-associated pneumonia. *Crit. Care Med.* 2009, 37, 32–38. [CrossRef] [PubMed]

159. Fourrier, F.E.; Cau-Pottier, H.; Boutigny, M.; Roussel-Delvallez, M.; Jourdain; Chopin, C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. *Intensive Care Med.* 2000, 26, 1239–1247. [CrossRef] [PubMed]

160. Fourrier, F.; Dubois, D.; Pommier, P.; Herbecq, P.; Leroy, O.; Desmettre, T.; Roussel-Delvallez, M. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit a double-blind placebo-controlled multicenter study. *Crit. Care Med.* 2005, 33, 1728–1735. [CrossRef] [PubMed]

161. Genuit, T.; Bochicchio, G.; Napolitano, L.M.; McCarter, R.J.; Roghman, M.C. Prophylactic chlorhexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. *Surg. Infect.* 2001, 2, 5–18. [CrossRef] [PubMed]

162. Koeman, M.; van der Ven, A.J.; Hak, E.; Joore, H.C.; Kaasjager, K.; de Smet, A.G.; Ramsay, G.; Dormans, T.P.; Aarts, L.P.; de Bel, E.E.; et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 2006, 173, 1348–1355. [CrossRef] [PubMed]

163. Kollef, M.H.; Afessa, B.; Anzueto, A.; Veremakis, C.; Kerr, K.M.; Margolis, B.D.; Schinner, R. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: The NASCENT randomized trial. *JAMA* 2008, 300, 805–813. [CrossRef] [PubMed]

164. Lorente, L.; Lecuona, M.; Jiménez, A.; Palmero, S.; Pastor, E.; Lafuente, N.; Ramos, M.J.; Mora, M.L.; Sierra, A. Ventilator-associated pneumonia with or without toothbrushing a randomized controlled trial. *Eur. J. Clin. Microbiol. Infect. Dis.* 2012, 31, 1–9. [CrossRef] [PubMed]

165. Mori, H.; Hirasawa, H.; Oda, S.; Shiga, H.; Matsuda, K.; Nakamura, M. Oral care reduces incidence of ventilator-associated pneumonia in ICU populations. *Intensive Care Med.* 2006, 32, 230–236. [CrossRef] [PubMed]

166. Panchabhai, T.S.; Dangayach, N.S.; Krishnan, A.; Kothari, V.M.; Karnad, D.R. Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: An open-label randomized trial with 0.01% potassium permanganate as control. *Chest* 2009, 135, 1150–1156. [CrossRef] [PubMed]

167. Seguin, P.; Tanguy, M.; Laviolle, B.; Tirel, O.; Malledant, Y. Effect of oropharyngeal decontamination by povidone-iodine on ventilator-associated pneumonia in patients with head trauma. *Crit. Care Med.* 2006, 34, 1514–1519. [CrossRef] [PubMed]

168. Seguin, P.; Laviolle, B.; Dahyot-Fizelier, C.; Dumont, R.; Veber, B.; Gergaud, S.; Asehnoune, K.; Mimoz, O.; Donnio, P.Y.; Bellissant, E.; et al. Effect of oropharyngeal povidone-iodine preventive oral care on ventilator-associated pneumonia in severely brain-injured or cerebral hemorrhage patients: A multicenter, randomized controlled trial. *Crit. Care Med.* 2014, 42, 1–8. [CrossRef] [PubMed]

169. Tantipong, H.; Morkchareonpong, C.; Jaityindee, S.; Thamlikitkul, V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. *Infect. Control Hosp. Epidemiol.* 2008, 29, 131–136. [CrossRef] [PubMed]

170. Pobo, A.; Lisboa, T.; Rodriguez, A.; Sole, R.; Magret, M.; Treffler, S.; Gómez, F.; Rello, J. A randomized trial of dental brushing for preventing ventilator-associated pneumonia. *Chest* 2009, 136, 433–439. [CrossRef] [PubMed]

171. Abele-Horn, M.; Dauber, A.; Bauernfeind, A.; Russwurm, W.; Seyfarth-Metzger, I.; Gleich, P.; Ruckdeschel, G. Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD). *Intensive Care Med.* 1997, 23, 187–195. [CrossRef] [PubMed]

172. Aerds, S.J.; van Dalen, R.; Clasener, H.A.; Festen, J.; van Lier, H.J.; Vollaard, E.J. Antibiotic prophylaxis of respiratory tract infection in mechanically ventilated patients. A prospective, blinded, randomized trial of the effect of a novel regimen. *Chest* 1991, 100, 783–791. [CrossRef] [PubMed]
173. Bergmans, D.C.; Bonten, M.J.; Gaillard, C.A.; Paling, J.C.; van der Geest, S.; van Tiel, F.H.; Beysens, A.J.; De Leeuw, P.W.; Stobberingh, E.E. Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. Am. J. Respir. Crit. Care Med. 2001, 164, 382–388. [CrossRef] [PubMed]

174. Hammond, J.M.; Potgieter, P.D.; Saunders, L.G. Selective decontamination of the digestive tract in multiple trauma patients-Is there a role? Results of a prospective, double-blind, randomized trial. Crit. Care Med. 1994, 22, 33–39. [CrossRef] [PubMed]

175. Blair, P.; Rowlands, B.J.; Lowry, K.; Webb, H.; Armstrong, P.; Smilie, J. Selective decontamination of the digestive tract: A stratified, randomized, prospective study in a mixed intensive care unit. Surgery 1991, 110, 303–309. [PubMed]

176. Ferrer, M.; Torres, A.; Gonzalez, J.; Puig de la Bellacasa, J.; El-Ebiary, M.; Roca, M.; Gatell, J.M.; Rodriguez-Roisin, R. Utility of selective digestive decontamination in mechanically ventilated patients. Ann. Intern. Med. 1994, 120, 389–395. [CrossRef] [PubMed]

177. Korinek, A.M.; Laisne, M.J.; Nicolas, M.H.; Raskine, L.; Deroin, V.; Sanson-lepors, M.J. Selective decontamination of the digestive tract: A stratified, randomized, prospective study in a mixed intensive care unit. Intensive Care Med. 1990, 16, 307–311. [CrossRef] [PubMed]

178. Bonten, M.J.; Gaillard, C.A.; Johanson, W.G., Jr.; Van Tiel, F.H.; Smeets, H.G.; Van Der Geest, S.; Stobberingh, E.E. Colonization in patients receiving and not receiving topical antimicrobial prophylaxis. Am. J. Respir. Crit. Care Med. 1994, 150, 1332–1340. [CrossRef] [PubMed]

179. Georges, B.; Mazerolles, M.; Decun, J.-F.; Rouge, P.; Pomies, S.; Cougot, P.; Andrieu, P.; Virenque, C. Décontamination digestive sélective résultats d’une étude chez le polytraumatisé. Réanim. Urgence 1994, 3, 621–627. [CrossRef]

180. Jacobs, S.; Foweraker, J.E.; Roberts, S.E. Effectiveness of selective decontamination of the digestive tract (SDD) in an ICU with a policy encouraging a low gastric pH. Clin. Intensive Med. 1992, 3, 52–58.

181. Palomar, M.; Alvarez-Lerma, F.; Jorda, R.; Bermejo, B.; Catalan Study Group of Nosocomial Pneumonia Prevention. Prevention of nosocomial infection in mechanically ventilated patients: Selective digestive decontamination versus sucralfate. Clin. Intensive Care 1997, 8, 228–235. [CrossRef]

182. Langlois-Karaga, A.; Bues-Charbit, M.; Davignon, A.; Albanese, J.; Durbec, O.; Martin, C.; Morati, N.; Balansard, G.Selective digestive decontamination in multiple trauma patients: Cost and efficacy. Pharm. World Sci. 1995, 17, 12–16. [CrossRef] [PubMed]

183. Korinek, A.M.; Laisne, M.J.; Nicolas, M.H.; Raskine, L.; Deroin, V.; Sanson-lepors, M.J. Selective decontamination of the digestive tract in neurosurgical intensive care unit patients: A double-blind, randomized, placebo-controlled study. Crit. Care Med. 1993, 21, 1466–1473. [CrossRef]

184. Laggner, A.N.; Tryba, M.; Georgopoulos, A.; Johannsen, K.; Grimm, G.; Graninger, W.; Schneeweiss, B.; Druml, W. Oropharyngeal decontamination with gentamicin for long-term ventilated patients on stress ulcer prophylaxis with sucralfate? Wien. Klin. Wochenschr. 1994, 106, 15–19. [PubMed]

185. Quinio, B.; Albanese, J.; Bues-Charbit, M.; Viviand, X.; Martin, C. Selective decontamination of the digestive tract versus sucralfate. Ann. Pharmacother. 1994, 28, 582–586. [CrossRef]

186. Rolando, N.; Gimson, A.; Wade, J.; Philpott-Howard, J.; Casewell, M.; Williams, R. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology 1993, 17, 196–201. [CrossRef] [PubMed]

187. Camus, C.; Salomon, S.; Bouchigny, C.; Gacouin, A.; Lavoué, S.; Donnio, P.Y.; Bellissant, E. Short-Term Decline in All-Cause Acquired Infections With the Routine Use of a Decontamination Regimen Combining Topical Polymyxin, Tobramycin, and Amphotericin B With Mupirocin and Chlorhexidine in the ICU: A Single-Center Experience. Crit. Care Med. 2014, 42, 1121–1130. [CrossRef] [PubMed]

188. Bonten, M.J.; Gaillard, C.A.; Johanson, W.G., Jr.; Van Tiel, F.H.; Smeets, H.G.; Van Der Geest, S.; Stobberingh, E.E. Colonization in patients receiving and not receiving topical antimicrobial prophylaxis. Am. J. Respir. Crit. Care Med. 1994, 150, 1332–1340. [CrossRef] [PubMed]

189. De Leeuw, P.W.; Stobberingh, E.E. Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. Am. J. Respir. Crit. Care Med. 2001, 164, 382–388. [CrossRef] [PubMed]

190. Laggner, A.N.; Tryba, M.; Georgopoulos, A.; Johannsen, K.; Grimm, G.; Graninger, W.; Schneeweiss, B.; Druml, W. Oropharyngeal decontamination with gentamicin for long-term ventilated patients on stress ulcer prophylaxis with sucralfate? Wien. Klin. Wochenschr. 1994, 106, 15–19. [PubMed]

191. Langlois-Karaga, A.; Bues-Charbit, M.; Davignon, A.; Albanese, J.; Durbec, O.; Martin, C.; Morati, N.; Balansard, G. Selective digestive decontamination in multiple trauma patients: Cost and efficacy. Pharm. World Sci. 1995, 17, 12–16. [CrossRef] [PubMed]
205. Messori, A.; Trippoli, S.; Vaiani, M.; Gorini, M.; Corrado, A. Bleeding and pneumonia in intensive care

201. Pileggi, C.; Bianco, A.; Flotta, D.; Nobile, C.G.; Pavia, M. Prevention of ventilator-associated pneumonia,

206. Huang, J.; Cao, Y.; Liao, C.; Wu, L.; Gao, F. Effect of histamine-2-receptor antagonists versus sucralfate on

204. Nardi, G.; Valentinis, U.; Proietti, A.; De Monte, A.; Di Silvestre, A.; Muzzi, R.; Giordano, F. Epidemiological

203. Saunders, G.L.; Hammond, J.M.; Potgieter, P.D.; Plumb, H.A.; Forder, A.A. Microbiological surveillance

202. Chan, E.Y.; Ruest, A.; Meade, M.O.; Cook, D.J. Oral decontamination for prevention of pneumonia in

199. Prophylaxis with enteral antibiotics in ventilated patients: Selective decontamination or selective

198. Antibiotic prophylaxis to reduce

197. Ventilator-associated pneumonia. [CrossRef] [PubMed]

196. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of

195. A randomized, double-blind, placebo-controlled multicenter trial. Am. J. Respir. Crit. Care Med. 1998, 158,

194. Trivert, J.; Fagon, J.Y. Ventilator-associated pneumonia. [CrossRef] [PubMed]

193. Ulrich, C.; Harinck-deWeerd, J.E.; Bakker, N.C.; Jacz, K.; Doornbos, L.; De Ridder, V.A. Selective

debacterialization of the digestive tract with norfloxacin in the prevention of ICU-acquired infections:

192. Wiener, J.; Itokazu, G.; Nathan, C.; Kabins, S.A.; Weinstein, R.A. A randomized, double-blind, placebo-controlled

191. Stoutenbeek, C.P.; van Saene, H.K.F.; Little, R.A.; Whitehead, A. The effect of selective decontamination

190. Sanchez-Garcia, M.; Cambronero, J.A.; Lopez-Diaz, J.; Cerdá Cerdá, E.; Rubio Blasco, J.; Gómez

199. Hurley, J.C. Prophylaxis with enteral antibiotics in ventilated patients: Selective decontamination or selective

198. Liberati, A.; D’Amico, R.; Pifferi, S.; Torri, V.; Brazzi, L.; Parmelli, E. Antibiotic prophylaxis to reduce

197. Chastre, J.; Fagon, J.Y. Ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. 2002, 165, 867–903.

196. Verwaest, C.; Verhaegen, J.; Ferdinande, P.; Schetz, M.; Van den Berghe, G.; Verbist, L.; Lauwers, P.

195. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients

194. Ventilation-associated pneumonia: A prospective randomized study. Intensive Care Med. 1989, 15, 424–431. [CrossRef] [PubMed]

193. Chastre, J.; Fagon, J.Y. Ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. 2002, 165, 867–903.

192. Unertl, K.; Ruckdeschel, G.; Selbmann, H.K.; Jensen, U.; Forst, H.; LenhartK, F.P. Peter Prevention of

191. Unertl, K.; Ruckdeschel, G.; Selbmann, H.K.; Jensen, U.; Forst, H.; LenhartK, F.P. Peter Prevention of

190. Sanchez-Garcia, M.; Cambronero, J.A.; Lopez-Diaz, J.; Cerdá Cerdá, E.; Rubio Blasco, J.; Gómez

189. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of

188. Chastre, J.; Fagon, J.Y. Ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. 2002, 165, 867–903.

187. Liberati, A.; D’Amico, R.; Pifferi, S.; Torri, V.; Brazzi, L.; Parmelli, E. Antibiotic prophylaxis to reduce

186. Respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst. Rev.

185. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of

184. Selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. J. Antimicrob. Chemother. 1992, 30, 73–87. [CrossRef] [PubMed]

183. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections:

182. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients

181. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of

180. The effect of prolonged systematic use of topical SDD on bacterial colonization of the tracheobronchial tree and

179. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of

178. Randomized, controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. Clin. Infect. Dis. 1995, 20, 861–867. [CrossRef] [PubMed]

177. Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients:

176. Antibiotic resistance. A three year study. J. Antimicrob. Chemother. 1997, 49, 63–71. [CrossRef] [PubMed]

175. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of

174. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients

173. Selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. J. Antimicrob. Chemother. 1992, 30, 73–87. [CrossRef] [PubMed]

172. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections:

171. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients

170. Winter, R.; Humphreys, H.; Pick, A.; MacGowan, A.P.; Willatts, S.M.; Speller, D.C. A controlled trial of
207. Alhazzani, W.; Almasoud, A.; Jaeschke, R.; Lo, B.W.; Sindi, A.; Altayyar, S.; Fox-Robichaud, A. Small bowel feeding and risk of pneumonia in adult critically ill patients: A systematic review and meta-analysis of randomized trials. Crit. Care 2013, 17, R127. [CrossRef] [PubMed]

208. Melsen, W.G.; Rovers, M.M.; Bonten, M.J.M. Ventilator-associated pneumonia and mortality: A systematic review of observational studies. Crit. Care Med. 2009, 37, 2709–2718. [PubMed]

209. Safdar, N.; Dezfulian, C.; Collard, H.R.; Saint, S. Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. Crit. Care Med. 2005, 33, 2184–2193. [CrossRef] [PubMed]

210. Han, J.; Liu, Y. Effect of ventilator circuit changes on ventilator-associated pneumonia: A systematic review and meta-analysis. Respir. Care 2010, 55, 467–474. [PubMed]

211. Subirana, M.; Solá, I.; Benito, S. Closed tracheal suction systems versus open tracheal suction systems for mechanically ventilated adult patients. Cochrane Database Syst. Rev. 2007, 4, CD004581. [CrossRef]

212. Siempos, I.I.; Vardakas, K.Z.; Kopterides, P.; Falagas, M.E. Impact of passive humidification on clinical outcomes of mechanically ventilated patients: A meta-analysis of randomized controlled trials. Crit. Care Med. 2007, 35, 2843–2851. [PubMed]

213. Muscedere, J.; Rewa, O.; McKechnie, K.; Jiang, X.; Laporta, D.; Heyland, D.K. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis. Crit. Care Med. 2011, 39, 1985–1991. [CrossRef] [PubMed]

214. Delaney, A.; Gray, H.; Laupland, K.B.; Zuege, D.J. Kinetic bed therapy to prevent nosocomial pneumonia in mechanically ventilated patients: A systematic review and meta-analysis. Crit. Care 2006, 10, R70. [CrossRef] [PubMed]

215. Sud, S.; Friedrich, J.O.; Taccone, P.; Polli, F.; Adhikari, N.K.; Latini, R.; Gattinoni, L. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. Intensive Care Med. 2010, 36, 585–599. [CrossRef] [PubMed]

216. Siempos, I.I.; Vardakas, K.Z.; Falagas, M.E. Closed tracheal suction systems for prevention of ventilator-associated pneumonia. Br. J. Anaesth. 2008, 100, 299–306. [CrossRef] [PubMed]

217. Silvestri, L.; Weir, I.; Gregori, D.; Taylor, D.; Van Saene, J.; Van Saene, H. Effectiveness of oral chlorhexidine on nosocomial pneumonia, causative microorganisms and mortality in critically ill patients: A systematic review and meta-analysis. Minerva Anestesiol. 2014, 80, 805–820. [PubMed]

218. Labeau, S.O.; Van de Vyver, K.; Brusselaers, N.; Vogelaers, D.; Blot, S.I. Prevention of ventilator-associated pneumonia with oral antiseptics: A systematic review and meta-analysis. Lancet Infect. Dis. 2011, 11, 845–854. [CrossRef]

219. Hurley, J.C. Profound effect of study design factors on ventilator-associated pneumonia incidence of prevention studies: Benchmarking the literature experience. J. Antimicrob. Chemother. 2008, 61, 1154–1161. [CrossRef] [PubMed]

220. Hurley, J.C. Topical antibiotics as a major contextual hazard toward bacteremia within selective digestive decontamination studies: A meta-analysis. BMC Infect. Dis. 2014, 14, 1. [CrossRef] [PubMed]

221. Hurley, J.C. Impact of selective digestive decontamination on respiratory tract Candida among patients with suspected ventilator-associated pneumonia. A meta-analysis. Eur. J. Clin. Microbiol. Infect. Dis. 2016, 35, 1121–1135. [CrossRef] [PubMed]

222. Hurley, J.C. ICU-acquired candidemia within selective digestive decontamination studies: A meta-analysis. Intensive Care Med. 2015, 41, 1877–1885. [CrossRef] [PubMed]

223. Hurley, J.C. Ventilator Associated Pneumonia prevention methods using topical antibiotics: Herd protection or herd peril? Chest 2014, 146, 890–898. [CrossRef] [PubMed]

224. Hurley, J.C. The perfidious effect of topical placebo: A calibration of Staphylococcus aureus Ventilator Associated Pneumonia incidence within Selective Digestive Decontamination (SDD) studies versus the broader evidence base. Antimicrob Agents Chemother. Antimicrob. Agents Chemother. 2013, 57, 4524–4531. [CrossRef] [PubMed]

225. Hróbjartsson, A.; Gøtzsche, P.C. Placebo interventions for all clinical conditions. Cochrane Database Syst. Rev. 2010, CD003974. [CrossRef]

226. Oostdijk, E.A.N.; Kesecioglu, J.; Schultz, M.J.; Visser, C.E.; de Jonge, E.; van Essen, E.H.R.; Bernards, A.T.; Purmer, I.; Brimicombe, R.; Bergmans, D.; van Tiel, F.; et al. Notice of Retraction and Replacement: Oostdijk et al. Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs: A Randomized Clinical Trial. JAMA 2014, 312, 1429–1437, JAMA 2017, 317, 1583–1584. [CrossRef] [PubMed]
227. Noto, M.J.; Domenico, H.J.; Byrne, D.W.; Talbot, T.; Rice, T.W.; Bernard, G.R.; Wheeler, A.P. Chlorhexidine bathing and health care–associated infections: A randomized clinical trial. JAMA 2015, 313, 369–378. [CrossRef] [PubMed]

228. Huang, S.S.; Septimus, E.; Kleinman, K.; Moody, J.; Hickok, J.; Avery, T.R.; Lankiewicz, J.; Gombosev, A.; Terpstra, L.; Hartford, F.; et al. Targeted versus universal decolonization to prevent ICU infection. N. Engl. J. Med. 2013, 368, 2255–2265. [CrossRef] [PubMed]

229. Laupland, K.B.; Kirkpatrick, A.W.; Church, D.L.; Ross, T.; Gregson, D.B. Intensive-care-unit-acquired bloodstream infections in a regional critically ill population. J. Hosp. Infect. 2004, 58, 137–145. [CrossRef] [PubMed]

230. Ibrahim, E.H.; Sherman, G.; Ward, S.; Fraser, V.J.; Kollef, M.H. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000, 118, 146–155. [CrossRef] [PubMed]

231. Stoutenbeek, C.P.; van Saene, H.K.; Miranda, D.R.; Zandstra, D.F. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med. 1984, 10, 185–192. [CrossRef] [PubMed]

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