Aus der Klinik für Anästhesiologie der Ludwig-Maximilians-Universität München

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Preventing ventilator-associated pneumonia: what is the evidence?

A systematic review and meta-analysis.

Dissertation
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Index of Abbreviations

CDC	Centers for Desease Control and Prevention
CLRT	continuous lateral rotation therapy
ET	endotracheal
GI	gastrointestinal
HH	heated humidifier
HME	heat and moisture exchanger
HMEF	heat and moisture exchanger filter
ICU	intensive care unit
MeSH	medical subject heading
MRSA	methicillin resistant Staphylococcus aureus
NPPV	noninvasive positive-pressure ventilation
OR	odds ratio
PEEP	positive endexpiratory pressure
RCT	randomized controlled trial
SD	standard deviation
SDD	selective decontamination of the digestive tract
VAP	ventilator-associated pneumonia
WMD	weighted mean difference

1. Introduction

1.1. Background

Ventilator-associated pneumonia (VAP) is the most common infectious complication in ICU patients requiring mechanical ventilation (MV). The reported incidence of VAP rates ranges between 8 and 28%.[56] VAP is known to increase the length of ICU and hospital stay, and it is associated with a high morbidity and mortality.[2, 3, 107, 149, 182, 331, 368] It is well established that VAP is associated with prolonged ventilation, ICU stay and additional hospital costs of greater than $40,000 per patient.[285] However, whether the about 30% higher mortality in patients with VAP is due to VAP itself or due to the more frequent presence of underlying determinants in patients who develop VAP, remains controversial.[56, 266, 285]

Microaspirations of oropharyngeal or gastric secretions are assumed to be the leading cause in the pathogenesis of VAP.[3, 70, 117] Here the cuff of the endotracheal tube (ET-tube) itself plays a decisive role, considering that the natural defense mechanisms to clear the airways from secretions are impaired and leakage around the tube cuff facilitates the descent of pathogens into the lower airways, especially in atelectatic areas. Sedation, the existence of a nasogastric tube, bacterial overgrowth in the stomach and oropharynx and a compromised immune defense due to the underlying disease of critically ill patients are additional contributing factors in the pathogenesis of VAP. Hematogenic spread from other infectious sources can also account for the development of VAP.

VAP is commonly distinguished into early (<96 h after intubation) and late (>96 hours after intubation) onset VAP. Early onset VAP is generally caused by antibiotic sensitive pathogens such as oxacillin-sensitive staphylococcus aureus, hemophilus influenzae and streptococcus pneumonia.[185] Late VAP is generally caused by antibiotic resistant pathogens such as methicillin resistant staphylococcus aureus, pseudomonas aeroginosa and acinetobacter species.[3]

The prevention of VAP has been the subject of investigation for several decades with numerous strategies and techniques aimed at interrupting the oropharyngeal, gastropharyngeal and bloodstream route of infection.

There are a number of systematic reviews that compared the efficacy of various interventions for the prevention of VAP.[11] In addition, the Center for Disease Control, the American Thoracic Society and other additional expert groups have published guidelines for the prevention of VAP.[3, 67, 92, 117, 164, 184, 331, 340] However, this leaves the clinician with an abundant literature that is difficult to interpret, and despite the large number of systematic reviews and guidelines to date

there is currently no comprehensive quantitative systematic review summarizing the efficacy of all published interventions for the prevention of VAP. The vast number of meta-analyses conducted for single interventions as well as the different meta-analytic techniques used, makes it virtually impossible for clinicians to qualify effective VAP prevention.

1.2. Research question

Therefore, we have conducted a comprehensive and up-to-date quantitative systematic review of VAP prevention methods of randomized controlled trials (RCTs). By analyzing all of the results with one statistical technique we have made them comparable with one another, allowing for easier interpretation of successful prevention strategies for clinicians working in ICU wards.

2. Methods

2.1. Search strategy

a) Electronic databases

The search of electronic databases is the foundation of our search strategy. It was performed in two steps.

Step I

To get an overview of the literature and clinical trials of interventions for the prevention of VAP we conducted a preliminary PubMed search for the MeSH Term “Ventilator-associated Pneumonia”, limited to randomized controlled trials:

("pneumonia, ventilator-associated"[MeSH Terms] OR ventilator-associated pneumonia[Text Word]) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]).

Subsequently we limited our search term to meta-analyses and systematic reviews:

("pneumonia, ventilator-associated"[MeSH Terms] OR ventilator-associated pneumonia[Text Word]) AND systematic[sb].

We were aware of the fact that this search would not lead to a highly sensitive outcome, since the MeSH Term “Ventilator Associated Pneumonia” was only introduced to PubMed in 2007. Therefore, we reviewed titles, abstracts and MeSH-Term listings of relevant articles and preventive strategies found by the initial search. We then formed the following thematic groups and subgroups for the development of a more detailed search strategy:

1. Oral care: toothbrushing, chlorhexidine decontamination.
2. Gastrointestinal interventions: antibiotics, selective digestive tract decontamination, early gastrostomy, small-intestinal feeding, metoclopramide, acidification of enteral feeding, sucralfate, intermittent enteral feeding, immunonutrition.
3. Airway management: weaning protocols, early tracheostomy, noninvasive positive-pressure ventilation NPPV, endotracheal suctioning, ventilator circuit changes, heat and moisture exchangers.
4. Endotracheal (ET) tubes: subglottic suctioning, gel lubrication of the tracheal tube cuff, silver-coated endotracheal tube.

5. Positioning: semi-recumbent positioning, kinetic bed therapy, oscillating beds, prone positioning, chest physiotherapy.

Step II

Pubmed

The second step of our search strategy was the development of a more sensitive and exact search string. Hereby we implemented a selection of those previously screened MeSH Terms that would identify as many randomized controlled trials as possible for each of the five intervention groups.

Due to the heterogeneity of the intervention groups we developed a specific search string for each one with the support of a professional librarian. This group-specific search string was then linked to a search string covering the general fields of pneumonia, mechanical ventilation, intensive care unit and randomized controlled trial.

The group-specific search strings were the following:

Oral Care:

("anti-bacterial agents"[MAJR] OR "anti-bacterial agents"[Pharmacological Action] OR Anti-Bacterial Agents[Text Word] OR ("local anti-infective agents"[Text Word] OR "anti-infective agents, local"[MAJR] OR "anti-infective agents, local"[Pharmacological Action] OR Anti-Infective Agents, Local[Text Word]) OR ("chlorhexidine"[MeSH Terms] OR Chlorhexidine[Text Word]) OR ("decontamination"[MeSH Terms] OR Decontamination[Text Word]) OR "antibiotic prophylaxis"[MAJR] OR ("mouthwashes"[TIAB] NOT Medline[SB]) OR "mouthwashes"[MeSH Terms] OR "mouthwashes"[Pharmacological Action] OR (mouthwash[TIAB] OR mouthwash/water[TIAB] OR mouthwash'[TIAB] OR mouthwashes[TIAB] OR mouthwashes/daily[TIAB] OR mouthwasheses[TIAB] OR mouthwashing[TIAB] OR mouthwashings[TIAB]) OR "toothbrushing"[MeSH Terms] OR (toothbrush[TIAB] OR toothbrush/chewing[TIAB] OR toothbrush/dentifrice[TIAB] OR toothbrush/irrigator[TIAB] OR toothbrush/paste[TIAB] OR toothbrush/toothpaste[TIAB] OR toothbrush'[TIAB] OR toothbrush's[TIAB] OR toothbrushed[TIAB] OR toothbrusher[TIAB] OR toothbrushers[TIAB] OR toothbrushes[TIAB] OR toothbrushing[TIAB] OR toothbrushing'[TIAB] OR toothbrushings[TIAB]) OR "dentifrices"[MeSH Terms] OR ("dental plaque"[MeSH Terms] OR Dental Plaque[Text Word]) OR ("gels"[MeSH Terms] OR Gels[Text Word]) OR ("chemoprevention"[MeSH Terms] OR Chemoprevention[Text Word]) OR "Anti-Infective Agents"[MAJR:noexp] OR "Anti-Infective Agents"[Pharmacological Action] OR MOUTHRINSE OR MOUTHRINS*[TIAB]) AND (PC[SH]) AND ((Humans[Mesh]))

Methods

Gastrointestinal Interventions:

(("antacids"[MeSH Terms] OR "antacids"[Pharmacological Action] OR Antacids[Text Word]) OR ("anti-ulcer agents"[MeSH Terms] OR "anti-ulcer agents"[Pharmacological Action] OR Anti-Ulcer Agents[Text Word]) OR "enteral nutrition"[MAJR] OR ("peptic ulcer"[MeSH Terms] OR Peptic Ulcer[Text Word]) OR ("sucralfate"[MeSH Terms] OR Sucralfate[Text Word]) OR ("gastrostomy"[MeSH Terms] OR Gastrostomy[Text Word]) OR DIGESTIVE SYSTEM[MAJR:noexp] OR "DIGESTIVE TRACT"[TI] OR "INTESTINAL TRACT"[TI])

Airway Management:

(("Nebulizers and Vaporizers"[MeSH] OR Nebulizer*[TIAB] OR Vaporizer*[TIAB] OR "Suction"[MeSH] OR "suction*"[Text Word] OR "Filtration"[MeSH] OR "Filtration"[Text Word] OR "Heat"[MeSH] OR "Heat"[Text Word] OR "Humidity"[MeSH] OR "Humidity"[Text Word] OR "Tracheostomy"[MeSH] OR "Tracheostomy"[Text Word] OR "Ventilators, Mechanical"[MH] OR MECHANICAL VENTILATOR*)

ET-Tubes:

Suction[MH] OR Suction* OR Drainage[MH] OR Drainage[Text Word] OR Glottis[MH] OR Silver[MH] OR Tracheostomy[MH] OR Tracheostomy[Text Word] OR Equipment Design[MH] OR Equipment Contamination[MH])

Positioning:

(ROTATION[MH] OR ROTATION*[TIAB] OR PRONE POSITION[MH] OR (PRONE[TIAB] AND POSITION*[TIAB]) OR SUPINE POSITION[MH] OR SUPINE[TIAB] OR POSTURE[MH] OR POSTURE[TIAB] OR POSTURAL[TIAB])

The search string covering the fields of pneumonia, mechanical ventilation, intensive care unit and randomized controlled trial was the following:

(RANDOMIZED CONTROLLED TRIAL OR RANDOMIZED CONTROLLED TRIALS OR (RANDOM*[TIAB] AND TRIAL*[TIAB]) OR RCT[TIAB] OR RCTS[TIAB]) AND ((PNEUMONIA[MH:noexp] OR BRONCHOPNEUMONIA[MH] OR "Pneumonia, Aspiration"[MeSH] OR "Pneumonia, Aspiration"[Text Word] OR "Pneumonia, Bacterial"[MeSH] OR "Pneumonia, Bacterial"[Text Word] OR "Pneumonia, Ventilator-Associated"[MeSH] OR ventilator-associated pneumonia*[Text Word] OR (PNEUMONIA AND VENTILATOR ASSOCIATED) OR (PNEUMONIA[TIAB] AND (MECHANICAL VENTILATORS OR MECHANICAL VENTILATOR OR MECHANICAL VENTILATION OR

ARTIFICIAL RESPIRATION OR MECHANICALLY VENTILATED))) OR ((INTENSIVE CARE UNITS[MH] OR CRITICAL CARE[MH:noexp] OR INTENSIVE CARE[MH:noexp]) AND RESPIRATION, ARTIFICIAL[MH]) OR RESPIRATORY TRACT INFECTIONS/PC[MH:noexp] OR RESPIRATORY SYSTEM/MICROBIOLOGY[MH:noexp] OR OROPHARYNX[MH] OR DIGESTIVE SYSTEM[MH:noexp] OR DIGESTIVE SYSTEM[TIAB])

Embase and Cochrane

Since EMBASE and the Cochrane Library differ from PubMed in their content, we repeated our search strategy in a simplified form in these databases focusing our search on the following keywords:

EMBASE database:

(((('ventilator associated pneumonia'/exp OR 'ventilator associated pneumonia') OR 'ventilator associated pneumonias') OR (('pneumonia'/exp OR 'pneumonia') AND (('ventilator'/exp OR 'ventilator') OR ('mechanical ventilation'/exp OR 'mechanical ventilation') OR 'mechanically ventilated' OR ('artificial respiration'/exp OR 'artificial respiration'))) AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)) OR ((((('ventilator associated pneumonia'/exp OR 'ventilator associated pneumonia') OR 'ventilator associated pneumonias') OR (('pneumonia'/exp OR 'pneumonia') AND (('ventilator'/exp OR 'ventilator') OR ('mechanical ventilation'/exp OR 'mechanical ventilation') OR 'mechanically ventilated' OR ('artificial respiration'/exp OR 'artificial respiration')))) AND ('randomized controlled trial'/exp))

Cochrane database:

(ventilator OR mechanical ventilation OR mechanically ventilated OR artificial respiration):ti,ab,kw and (pneumonia):ti,ab,kw.

Email-alerts

All electronic database searches had an activated e-mail alert that informed us weekly of new references in our search strategy. We finalized our search and the selection of included trials on October 15th 2008, thus potential references after this date are not included in our analysis.

b) Review methods

We screened the titles and abstracts of the identified references and selected potentially relevant randomized controlled trials (RCTs) for retrieval. The screening was done by two of the reviewers (Simona Voegele (SV) and Dr. Serpil Cakmakkaya (SC)). In case there were doubts about the selection of references a consensus was formed within our own research team that included Dr. Oliver Radke (OR) and my mentor Dr. Christian C. Apfel (CCA)).

Once potentially relevant articles were retrieved, a reviewer (SV or SC) was responsible for the data entry of each of the intervention groups. If methodological questions arose, trials were discussed with at least one additional reviewer from our team. Upon completion of the methodological evaluation and data entry, the results of the intervention groups were presented to the group members, discussed and finalized.

c) Hand search of reference lists

All reference lists of retrieved trials were screened to identify and evaluate any potentially relevant RCTs.

d) Institute of Scientific Indexing (ISI)

In order to identify recently published trials, we entered studies that were published after 2001 into the Cited Reference Search of the Science Citation Index. Then we performed a prospective search from the date of publication and identified all publications citing the entered trial.

e) Contacting authors

Authors were contacted for missing data and methodological details of their trials which could not be clarified within our group.

We made at least two attempts to contact an author. Otherwise we tried to contact colleagues that had recently published with them. If these attempts were unsuccessful and essential information for inclusion was missing, their trial was not included.

f) Clinicaltrials.gov

We searched clinicaltrials.gov, a service of the U.S. National Institutes of Health, entering the term “ventilator-associated pneumonia” in order to identify ongoing unpublished studies.

If a trial was potentially useful, the study coordinators were contacted via email for preliminary data to be included into our anaylsis.

g) Language

We placed no language barriers in order to ensure this work is the most comprehensive review to date.

Members of our team analysed the English, German, Spanish, French and Italian articles. All other languages were translated by physicians and other health care workers from our institution.

h) Publication type

Any type of publication, as well as data from unpublished trials, was eligible for our meta-analysis, if there was enough information available to satisfy our inclusion criteria.

2.2. Inclusion and exclusion criteria

a) Methodological criteria

To be included in our meta-analysis, studies had to be randomised, controlled clinical trials.

Blinding was not a mandatory inclusion criterion because it is not possible to blind a majority of the preventive strategies for VAP, such as positioning or airway management.

We utilized allocation concealment as a tool for quality assessment. Allocation concealment is considered to have an even greater impact on the possible introduction of bias to a study than blinding[167, 168] and it is the quality measure applied in the RevMan Program 4.2 of the Cochrane Collaboration. The score we used (A = adequate, B = unclear, C = inadequate, D = not used) was adapted from the RevMan Program 4.2.

We did not rate our studies with a quality score. It has been shown that quality score ratings are very inconsistent in their outcomes when compared to each other.[168] In view of this fact, some authorities consider the evaluation of topic-specific details, such as the definition of pneumonia in our case, to be of more relevance to the quality of a meta-analysis than a quality score.[102] Therfore we outlined relevant details of study quality in our study characteristics tables.

b) Patient population

The study population consisted of critically ill adult patients requiring mechanical ventilation (MV) on an ICU or other special care unit, such as a respiratory care unit.

This systematic review included clinical trials of adults greater than 18 years old; however, trials that contained some patients under 18 years of age were included, if their primary focus was unequivocally on adult patients.

We excluded trials of cardiac surgery patients due to their expected short duration on MV, unless the trial reported abstractable pneumonia data of a subgroup of patients requiring MV for more than 48 hours.

Trials of transplant patients were also excluded since their condition, under immunosuppressive medication, is rather unique and can not be compared to that of other critically ill trauma, medical or surgical patients.

c) Outcomes

To be included pneumonia had to be either a primary or a secondary outcome of a study. If a trial studied a preventive strategy for VAP but only reported on one of our secondary outcomes, it was not selected for our meta-analysis.

d) Mechanical ventilation

If less than 100% of patients were mechanically ventilated, we only included the trial if it was fair to assume that MV was evenly distributed between treatment and control groups. We assumed this to be the case when more than 90% received MV in a study.

For inclusion at least 90% of the study patients in treatment and control groups had to be mechanically ventilated for at least 48 hours. We assumed that intubation was equal to MV, unless noted otherwise.

e) Definition of VAP

Currently there is no “gold standard” criteria basis for the diagnosis of VAP.[56, 283] We therefore accepted a trial if the definition of VAP coincided with international standards, as suggested by the Centers for Disease Control and Prevention (CDC), the American Thoracic Society or other feasible authorities and guidelines.[3, 331, 342]

If there was more than one definition for pneumonia given in a trial, we chose the most frequently used and abstracted the corresponding data.

2.3. Primary and secondary outcomes

The primary outcome of our meta-analysis was the incidence of ventilator-associated pneumonia (VAP).

Even though pneumonia cases were not explicitly described as VAP, we considered them to be ventilator-associated if at least 90% of patients were ventilated for more than 48 hours.

Secondary outcomes were mortality, the duration of MV and length of ICU stay.

All results are outlined in tables and figures of the corresponding paragraph. We did not outline results in figures when only one study was available for a preventive technique.

The secondary outcomes, duration of MV and the length of ICU stay, are outlined in the results tables, but are only explicitly mentioned in the text if their outcomes contribute significantly to the character of a preventive strategy.

2.4. Data abstraction and statistics

We used the review manager program 4.2 (RevMan 4.2) of the Cochrane Collaboration for our statistical analysis.

Overall estimates of dichotomous data are expressed as odds ratios and 95% confidence intervals, overall estimates of continuous data as weighted mean differences and 95% confidence intervals. The fixed effects model was used for analysis if the test for heterogeneity was not significant at the level of p=0.05, the random effects model if it was statistically significant.

The weight we assigned to the studies through the RevMan program was calculated as follows: 1/SD (standard deviation).

We grouped trials of a preventive strategy when possible and calculated summary effect estimates. Subgroups were formed to emphasize a difference in the intervention strategy or when studies were not comparable.

We abstracted dichotomous data of pneumonia and mortality rates, as well as the mean and standard deviation for the continuous outcomes like duration of MV and length of ICU stay. If outcomes were reported differently and data could not be integrated in our analysis, we expressed this by brackets around outcomes in the study characteristics tables.

Since studies reported mortality rates for different time intervals, e.g. ICU mortality, hospital mortality, 60-day mortality, we always abstracted the data of the longest time interval, assuming that the occurrence of death is a constant process over time.

In studies with more than one study group, we divided the control group by the number of study groups such that every study patient was included only once in our analysis. If some of the groups were out of our focus of interest, we only integrated some of the groups to maintain the power of our interest groups.

We controlled for potential confounders, especially if more than one intervention was studied in a trial.

2.5. Adjustments to predefined methods

As mentioned above, included studies had a protocol that expected the patients to be ventilated for at least 48 hours. We also considered studies with an average MV duration of clearly more than 48 hours even if it was not predefined in the study's protocol or if it was appropriate to assume secondary to the critically ill status of the study population. However, if the criterion was not mentioned or it seemed unlikely, that the vast majority of patients were ventilated over 48 hours, these studies had to be excluded.

3. Results

3.1. Search results

Figure 1 illustrates the process of our search and election process over time.

We reviewed the results of our PubMed search for every single intervention group, totalling in 1181 refrences. We discarded trials not in accordance with our inclusion criteria and retrieved 190 potentially relevant articles for closer evaluation. Duplicates that were identified due to similarities in the general part of the group-specific search strings were discarded.

Our EMBASE search led to 403 results, with 84 potentially relevant references. Sixty-four of the 84 were discarded as duplicates. Thus our EMBASE search added 20 potentially relevant articles to our final selection of articles.

The Cochrane search resulted in 364 results, with 109 potentially relevant references. Eighty-seven of the 109 were identified as duplicates and discarded. Twenty-two were added to our final subset of articles.

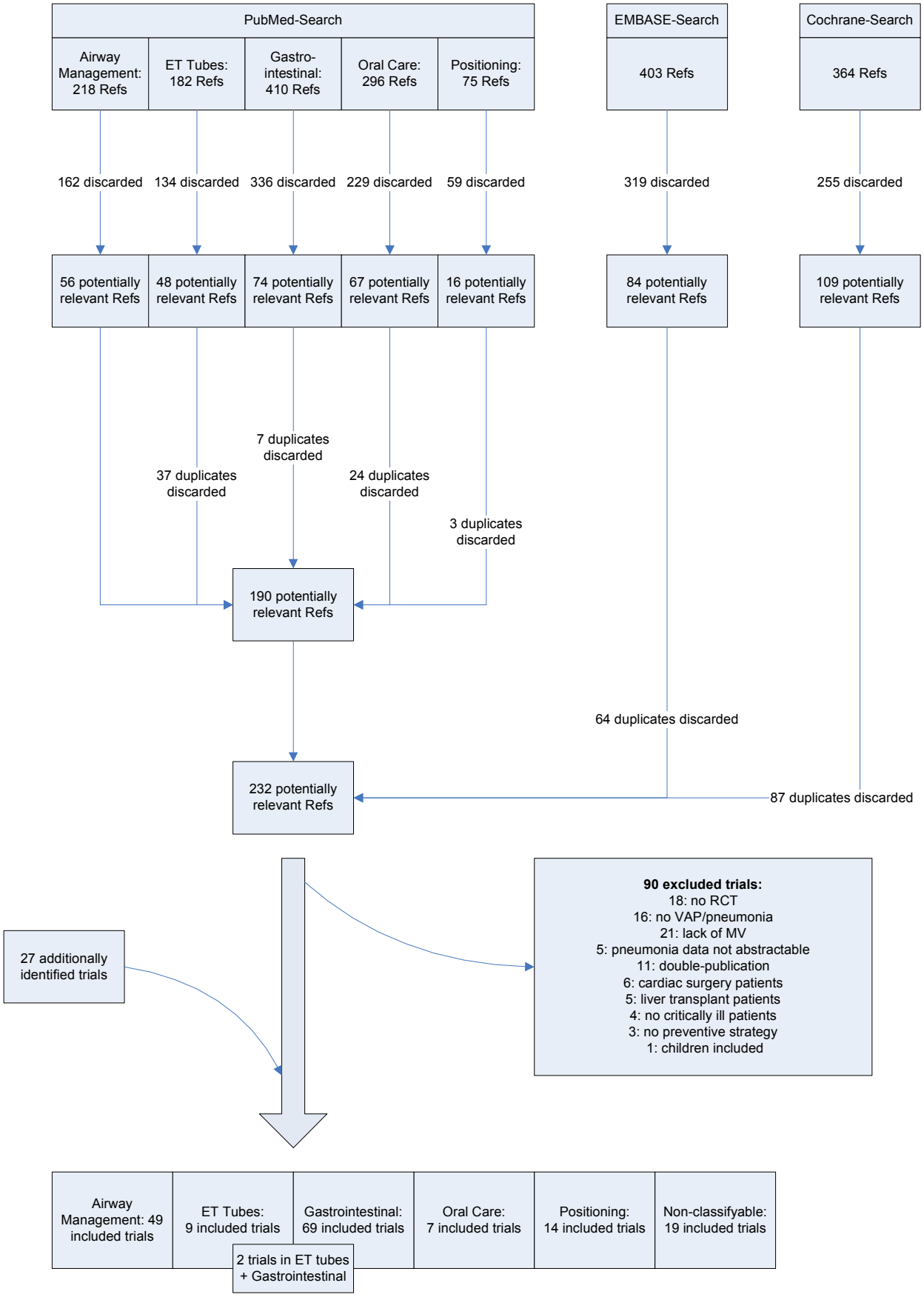
In total, the search of electronic databases identified 1948 references, of which 232 were retrieved for analysis.

At the time of our search, clinicaltrials.gov reported 24 ongoing studies in the patient recruitment phase, of which 9 were chosen for follow up. The corresponding authors were contacted, but none could provide usable data for our analysis.

Twenty-seven trials were additionally identified by the hand search of the reference lists of included articles.

Results

Figure 1: Trial-flow



3.2. Relevant trials

In total, 169 studies met our inclusion criteria and were included in our analysis. Detailed information of the trials are outlined in the study characteristics tables in the appendix. Not all preventative strategies mentioned in our primary intervention groups were studied by RCTs and therefore do not appear in the final analysis. Conversely, additional methods for the prevention of VAP were identified during the search process and were added to the according intervention groups. A sixth group, "Non-classifiable preventive strategies" was created for methods not matching any of the other intervention groups.

3.3. Excluded trials

Ninety trials were excluded from our anaylsis for methodological reasons or if they fulfilled one or more exclusion criteria. The specific reasons for exclusion can be inferred from the flow chart of our search and from the table of excluded trials in the appendix.

3.4. Oral care

a) Antiseptic decontamination

Pneumonia

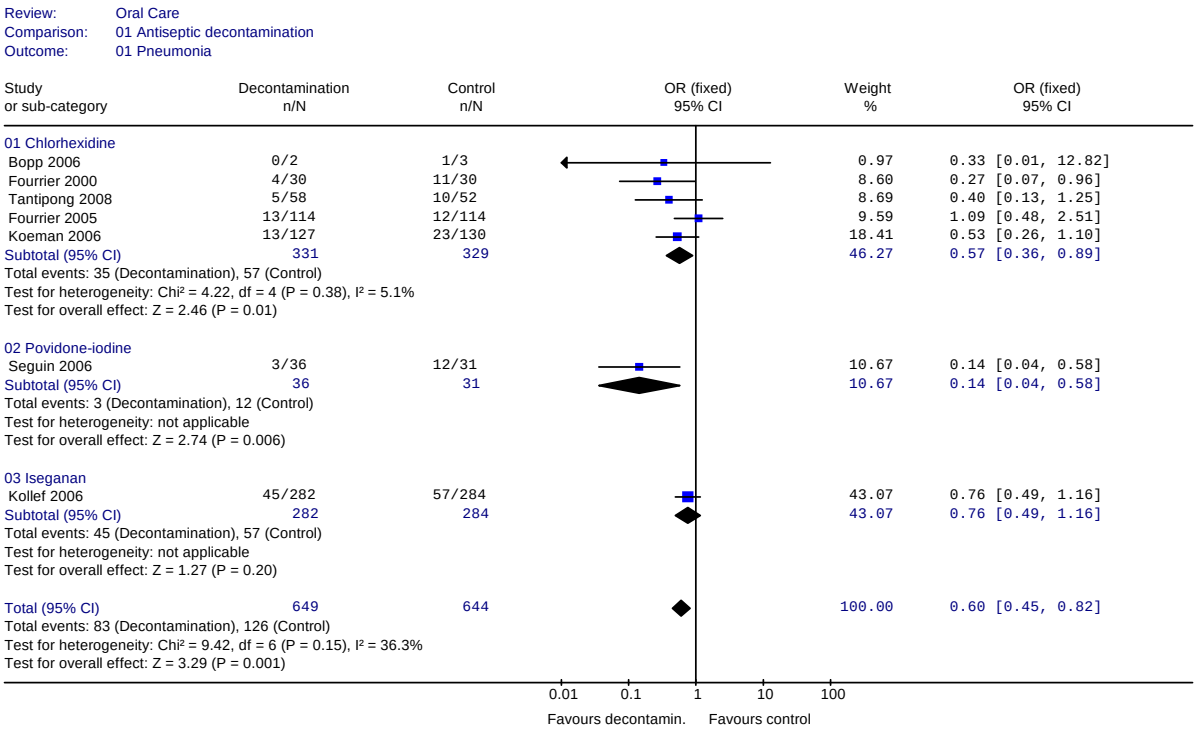
Overall the results for oral care with an antiseptic agent show a statistically significant reduction of pneumonia rates (OR=0.60, 0.45-0.82) (Figure 2) (Table 1).

Five trials administering chlorhexidine to the buccal cavity for decontamination met our inclusion criteria.[44, 118, 119, 179, 333] The overall results show a significant reduction of VAP rates (OR = 0.57, 0.36 – 0.89).

Another trial achieved a significant reduction of the incidence of pneumonia with the administration of povidone-iodine instead of chlorhexidine (OR = 0.14, 0.04 – 0.58).[306]

The results of a decontamination regimen with iseganan in a large study failed to reach statistical significance, although the odds ratio was numerically less than one (OR = 0.76, 0.49 – 1.16).[192]

Figure 2: Oral Care: Antiseptic decontamination, pneumonia outcomes



Mortality

Overall, there was no evidence for an effect of oral care with anitiseptics on mortality rates (OR=1.14, 0.85-1.53) (Figure 3) (Table 1).

This was also true for the results of the subgroups, of which none reached statistical significance.

Figure 3: Oral Care: Antiseptic decontamination, mortality outcomes

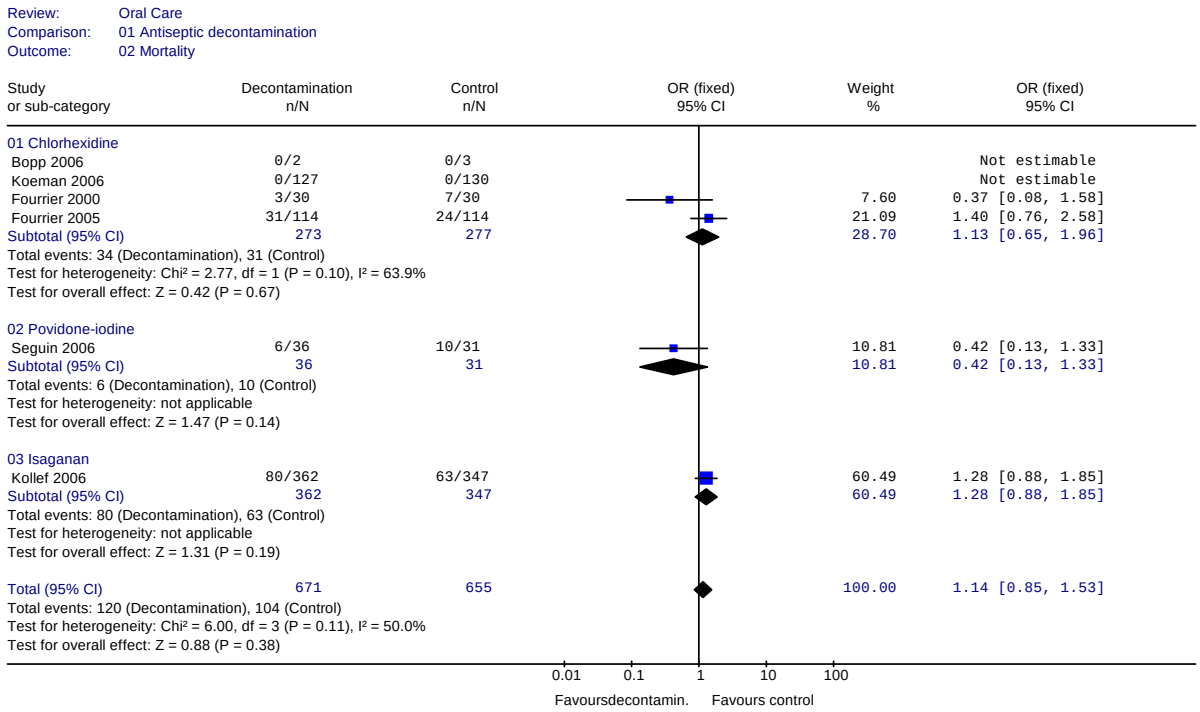


Table 1: Outcomes Oral Care: Antiseptic decontamination

Study ID	***Intervention***	***Study/ Control group***	***Pneumonia OR [95% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Bopp 2006	Chlorhexidine	2/ 3	0.33 [0.01, 12.82]	Not estimable		
Fourrier 2000	Chlorhexidine	30/ 30	0.27 [0.07, 0.96]	0.37 [0.08, 1.58]	-5.00 [-13.35, 3.35]	-6.00 [-14.89, 2.89]
Fourrier 2005	Chlorhexidine	114/ 114	1.09 [0.48, 2.51]	1.40 [0.76, 2.58]	1.10 [-1.16, 3.36]	-0.70 [-2.95, 1.55]
Koeman 2006	Chlorhexidine	127/ 130	0.53 [0.26, 1.10]	Not estimable	2.21 [-0.30, 4.72]	1.32 [-2.38, 5.02]
Tantipong 2008	Chlorhexidine	58/ 52	0.40 [0.13, 1.25]			
Subtotal:			*0.57 [0.36, 0.89] (f)*	*0.13 [0.65, 1.96] (f)*	*1.34 [-0.31, 2.99] (f)*	*-0.42 [-2.29, 1.46] (f)*
Seguin 2006	Povidone-iodine	36/ 31	0.14 [0.04, 0.58]	0.42 [0.13, 1.33]	-1.00 [-4.36, 2.36]	1.00 [-5.23, 7.23]
Kollef 2006	Iseganan	282/ 284	0.76 [0.49, 1.16]	1.28 [0.88, 1.85]		
Totals			**0.60 [0.45, 0.89] (f)**	**1.14 [0.85, 1.53] (f)**	**0.89 [-0.59, 2.37] (f)**	**-0.30 [-2.09, 1.50] (f)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

3.5. Airway management

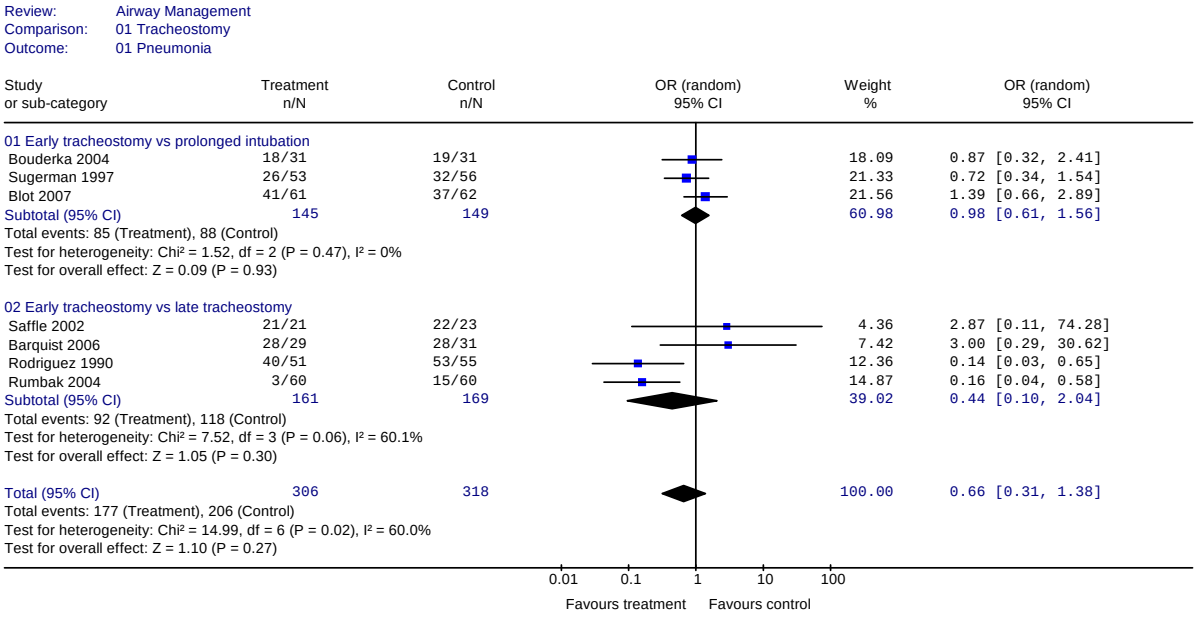
a) Tracheostomy

Pneumonia

Seven trials reported on the incidence of pneumonia in patients with a tracheostomy performed early (days 1-8 of MV) compared to patients undergoing prolonged intubation or late tracheostomy performed after day 8 of MV (Figure 4) (Table 2). [19, 34, 45, 291, 298, 302, 330]

Overall the results do not show a statistically significant reduction of VAP, although the odds ratio is numerically less than one (OR = 0.66, 0.31 - 1.38), which is also true for the early versus late tracheostomy subgroup analysis (OR = 0.44, 0.10 - 2.04).

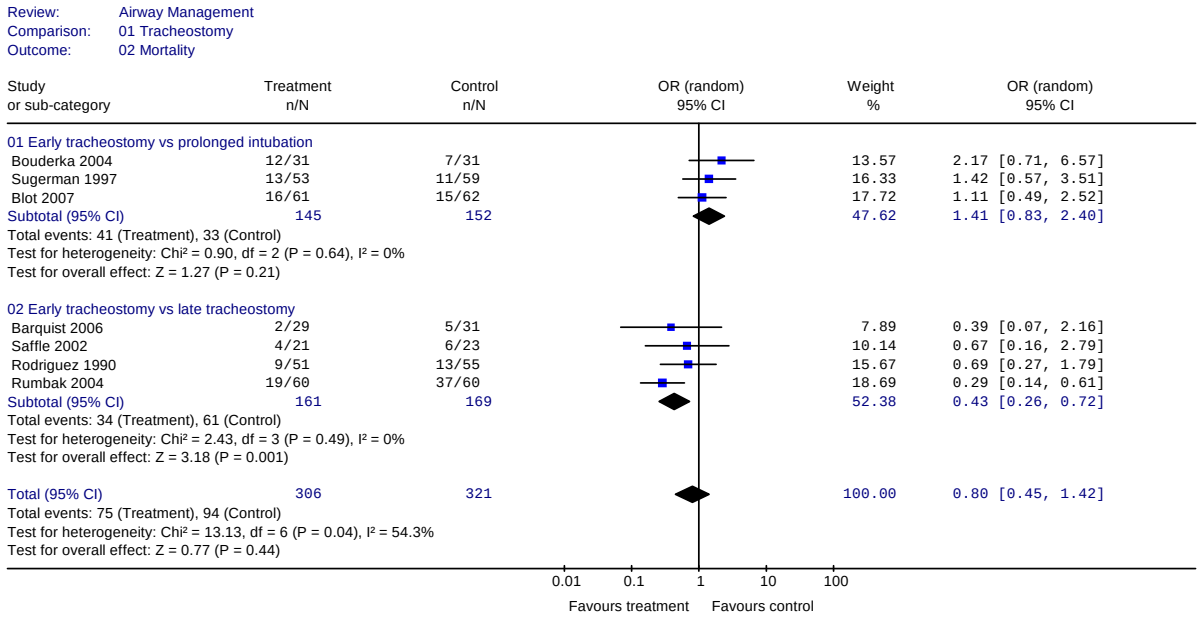
Figure 4: Airway Management: Tracheostomy, pneumonia outcomes.



Mortality

Although the second subgroup analysis, comparing early with late tracheostomy, resulted in a significant reduction of mortality (OR = 0.43, 0.26 - 0.72). This could not be confirmed by the overall assessment (OR = 0.80, 0.45 – 1.42) (Figure 5) (Table 2).

Figure 5: Airway Management: Tracheostomy, mortality outcomes.



Length of ICU stay

The length of ICU stay, reported by four trials, was significantly reduced by early tracheostomy (WMD: -8.96, -17.53 - -0.39) (Table 2).

Table 2: Outcomes Airway Management: Tracheostomy

Study ID	***Intervention***	***Study/ Control group***	***Pneumonia OR [95% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Blot 2007	Early Tracheostomy vs. prolonged intubation	61/ 62	1.39 [0.66, 2.89]	1.11 [0.49, 2.52]		
Bouderka 2004	Early tracheostomy vs. prolonged intubation	31/ 31	0.87 [0.32, 2.41]	2.17 [0.71, 6.57]	-3.00 [-7.53, 1.53]	
Sugerman 1997	Early tracheostomy vs. prolonged intubation	53/ 59	0.72 [0.42, 1.54]	1.42 [0.57, 3.51]		-4.00 [-4.74, -3.26]
Subtotal			*0.98 [0.61, 1.56] (r)*	*1.41 [0.83, 2.40] (r)*		
Saffle 2002	Early tracheostomy vs. late tracheostomy	21/ 23	2.87 [0.11, 74.28]	0.67 [0.16, 2.79]	4.10 [1.23, 6.97]	1.10 [-3.14, 5.34]
Barquist 2006	Early vs. late tracheostomy	29/ 31	3.00 [0.29, 30.62]	0.39 [0.07, 2.16]		
Rodriguez 1990	Early vs. late tracheostomy	51/ 55	0.14 [0.03, 0.65]	0.69 [0.27, 1.79]	-20.00 [-20.84, -19.16]	-21.00 [-22.09, -19.91]
Rumbak 2004	Early vs. late tracheostomy	60/ 60	0.16 [0.04, 0.58]	0.29 [0.14, 0.61]	-9.80 [-11.48, -8.12]	-11.40 [-12.42, -10.38]
Subtotal			*0.44 [0.10, 2.04] (r)*	*0.43 [0.26, 0.72] (r)*	*-8.64 [-20.63, 3.35] (r)*	*-10.71 [-19.43, -1.99] (r)*
Total:			**0.66 [0.31, 1.38] (r)**	**0.80 [0.45, 1.42] (r)**	**-7.27 [-17.70, 3.17] (r)**	**-8.96 [-17.53, -0.39] (r)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

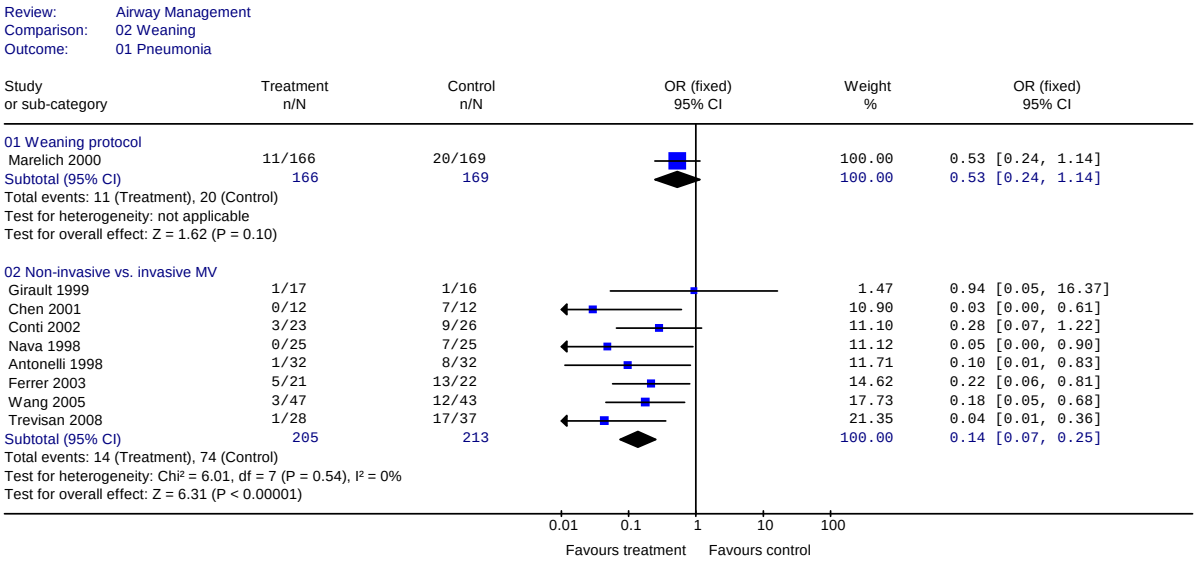
b) Weaning

Pneumonia

Nine trials studied the influence of weaning procedure changes on pneumonia, either by implementing a weaning protocol[232] or by non-invasive instead of invasive MV[13, 58, 69, 110, 128, 253, 345, 373] (Figure 6) (Table 3). Of the trials implementing non-invasive MV, in all trials but two[13, 69], patients received invasive MV before randomization to non-invasive or invasive MV.

In the subgroup implementing a weaning protocol the odds ratio was numerically less than one, but the result did not achieve statistical significance (OR = 0.53, 0.24 – 1.14), whereas non-invasive MV resulted in a significant reduction of VAP rates (OR = 0.14, 0.07 – 0.25).

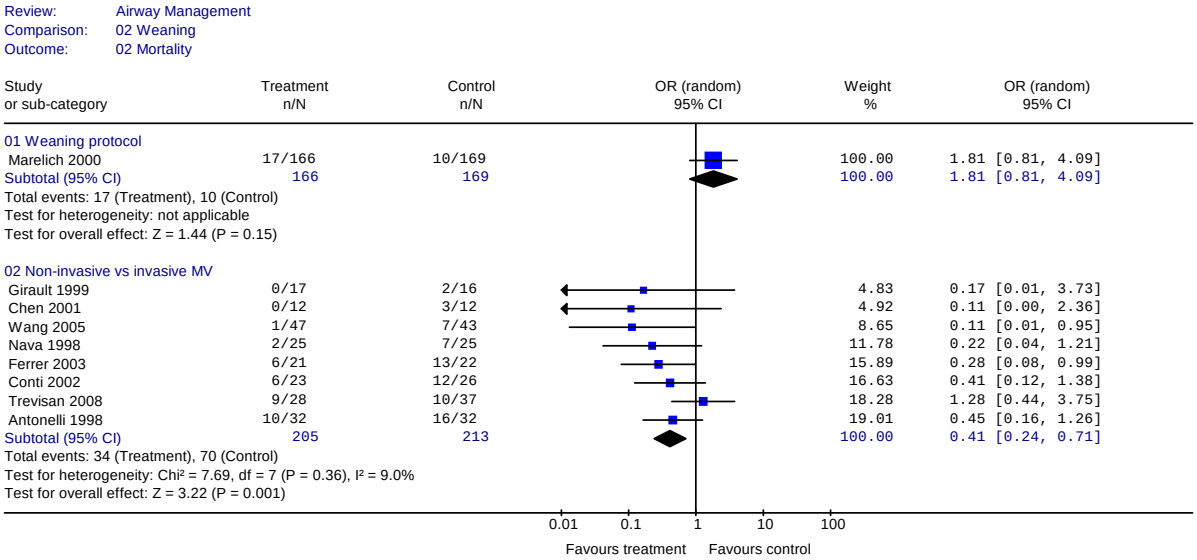
Figure 6: Airway Manangement: Weaning, pneumonia outcomes.



Mortality

Mortality was significantly reduced by non-invasive MV as opposed to invasive MV (OR = 0.41, 0.24 – 0.71) (Table 3). The implementation of a weaning protocol did not lead to a benefit of survival (OR = 1.81, 0.81 – 4.09).

Figure 7: Airway Management: Weaning, mortality outcomes.



Duration of MV/ Length of ICU stay

While the duration of MV was not significantly influenced (WMD = -1.88, -6.33 - 2.56), the length of ICU stay was significantly reduced in the group of patients receiving non-invasive MV (WMD=-4.78, -6.90 - -2.67) (Table 3). It was not assessed by the trial of protocol weaning.

Table 3: Outcomes Airway Management: weaning

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	**Length of ICU stay WMD [95% CI]**
Marelich 2000	Weaning Protocol	166/ 169	0.53 [0.24, 1.14]	1.81 [0.81, 4.09]		
Antonelli 1998	Non-invasive vs. invasive MV	32/ 32	0.10 [0.01, 0.83]	0.45 [0.16, 1.26]	-3.00 [-5.67, -0.33]	-7.00 [-13.37, -0.63]
Chen 2001	Non-invasive vs. invasive MV	12/ 12	0.03 [0.00, 0.61]	0.11 [0.00, 2.36]	-8.00 [-15.22, -2.18]	
Conti 2002	Non-invasive vs. invasive MV	23/ 26	0.28 [0.07, 1.22]	0.41 [0.12, 1.38]	1.00 [-10.20, 12.20]	1.00 [-9.93, 11.93]
Ferrer 2003	Non-invasive vs. invasive MV	21/ 22	0.22 [0.06, 0.81]	0.28 [0.08, 0.99]	-8.70 [-15.22, -2.18]	-10.90 [-17.44, -4.36]
Girault 1999	Non-invasive vs. invasive MV	17/ 16	0.94 [0.05, 16.37]	0.17 [0.01, 3.73]	8.08 [5.49, 10.67]	-1.71 [-6.63, 3.21]
Nava 1998	Non-invasive vs. invasive MV	25/ 25	0.05 [0.00, 0.90]	0.22 [0.04, 1.21]	-6.40 [-11.74, -1.06]	-8.90 [-14.67, -3.13]
Trevisan 2008	Non-invasive vs. invasive MV	28 37	0.04 [0.01, 0.36]	1.28 [0.44, 3.75]	-2.39 [-7.38, 2.60]	-1.90 [-7.36, 3.56]
Wang 2005	Non-invasive vs. invasive MV	47/ 43	0.18 [0.05, 0.68]	0.11 [0.01, 0.95]	2.00 [-0.86, 4.86]	-4.00 [-8.01, 0.01]
Subtotal:			*0.14 [0.07, 0.25] (f)*	*0.41 [0.24, 0.71] (r)*	*-1.88 [-6.33, 2.56](r)*	*-4.78 [-6.90, -2.67] (f)*

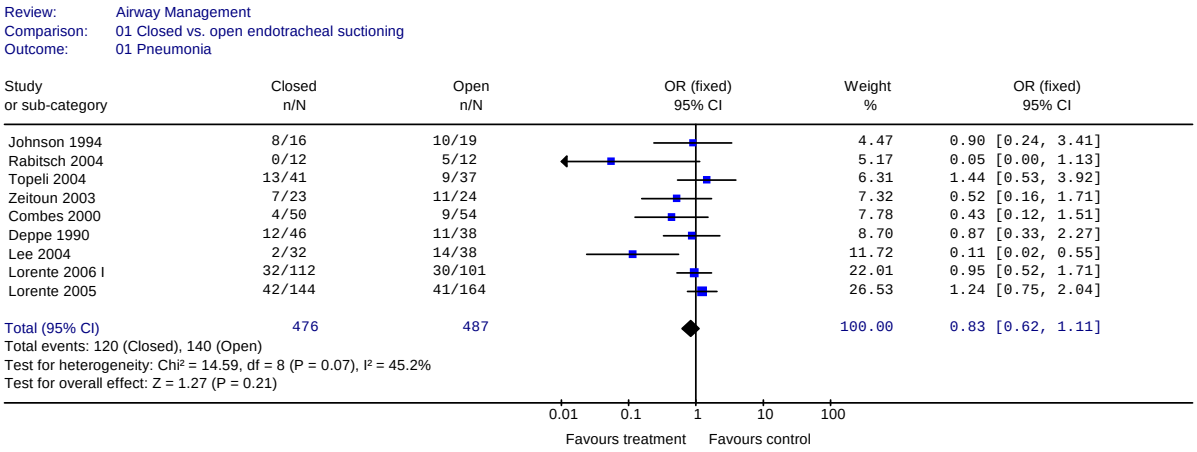
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

c) Closed vs. open endotracheal suctioning

Pneumonia

Nine trials utilizing a closed rather than an open endotracheal suction catheter system met our inclusion criteria.[68, 88, 165, 207, 216, 220, 280, 339, 384] Pneumonia rates were not significantly different, although the odds ratio was numerically less than one (OR = 0.83, 0.62 – 1.11) (Figure 8) (Table 4).

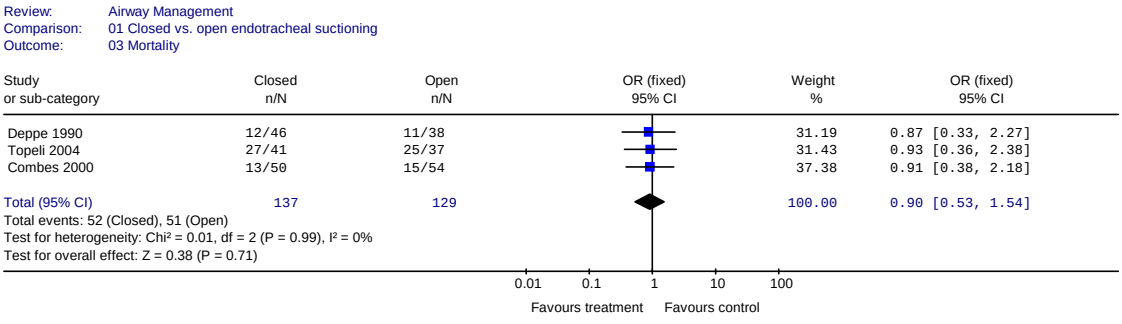
Figure 8: Airway Management: Closed vs. open endotracheal suctioning, pneumonia outcomes.



Mortality

In those studies with abstractable mortality data the choice of the suctioning system did not have an impact on mortality (OR = 0.90, 0.53 – 1.54) (Table 4).

Figure 9: Airway Management: Closed vs. open endotracheal suctioning, mortality outcomes.



Duration of MV/ Length of ICU stay

In the two trials assessing the duration of MV, the time period was significantly increased with the closed suctioning technique (WMD = 0.68, 0.29 – 1.06) (Table 4). Although it should be noted that one of the two studies[339] was weighted with 99.47%, hence resembling a large part of this outcome.

Results for the length of ICU stay were not significant.

Table 4: Outcomes Airway Management: closed vs. open endotracheal suctioning

Study ID	*Intervention*	*Study Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Combes 2000	Closed vs. open endotracheal suctioning	50/ 54	0.43 [0.12, 1.51]	0.91 [0.38, 2.18]	-3.60 [-8.92, 1.72]	-4.30 [-10.10, 1.50]
Deppe 1990	Closed vs. open endotracheal suctioning	46/ 38	0.87 [0.33, 2.27]	0.87 [0.33, 2.27]		
Johnson 1994	Closed vs. open endotracheal suctioning	16/ 19	0.90 [0.24, 3.41]			
Lee 2004	Closed vs. open endotracheal suctioning	32/ 38	0.11 [0.02, 0.55]			-13.10 [-20.41, -5.79]
Lorente 2005	Closed vs. open endotracheal suctioning	144/ 164	1.24 [0.75, 2.04]			
Lorente 2006 I	Closed vs. open endotracheal suctioning	112/ 101	0.95 [0.52, 1.71]			
Rabitsch 2004	Closed vs. open endotracheal suctioning	12/ 12	0.05 [0.00, 1.13]			
Topeli 2004	Closed vs. open endotracheal suctioning	41/ 37	1.44 [0.53, 3.92]	0.93 [0.36, 2.38]	0.70 [0.31, 1.09]	0.80 [0.24, 1.36]
Zeitoun 2003	Closed vs. open endotracheal suctioning	23/ 24	0.52 [0.16, 1.71]			
Total:			**0.83 [0.62, 1.11] (f)**	**0.90 [0.53, 1.54] (f)**	**0.68 [0.29, 1.06] (f)**	**-4.86 [-12.59, 2.87] (r)**

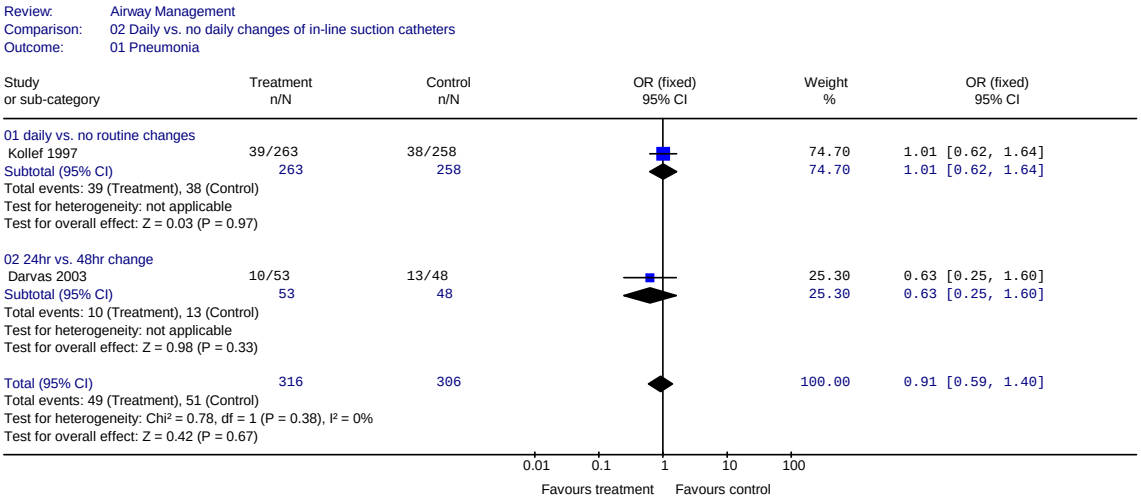
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

d) Daily vs. no daily changes of in-line suction catheters

Pneumonia

Two trials studied the effects of a change of in-line (closed) suction catheters every 24 hours versus every 48 hours[78] and versus no routine changes[187]. VAP rates were not significantly different between the groups (OR = 0.91, 0.59 – 1.40) (Figure 10) (Table 5).

Figure 10: Airway Management: Daily vs. no daily changes of in-line suction catheters.



Results

Mortality

The frequency of catheter changes had no impact on mortality rates (OR=0.94, 0.66-1.26) (Table 5).

Table 5: Outcomes Airway Management: daily vs. no daily changes of in-line suction catheters

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Kollef 1997	Daily vs. no routine change of suction catheters	263/ 258	1.01 [0.62, 1.64]	0.92 [0.62, 1.36]	-0.30 [-1.73, 1.13]	0.10 [-1.43, 1.63]
Darvas 2003	Daily vs. 48-h change of suction catheters	53/ 48	0.63 [0.25, 1.60]	1.04 [0.45, 2.41]	1.28 [-2.09, 4.65]	1.21 [-3.26, 5.68]
Total:			**0.91 [0.59, 1.40] (f)**	**0.94 [0.66, 1.34] (f)**	**-0.06 [-1.38, 1.26] (f)**	**0.22 [-1.23, 1.66] (f)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

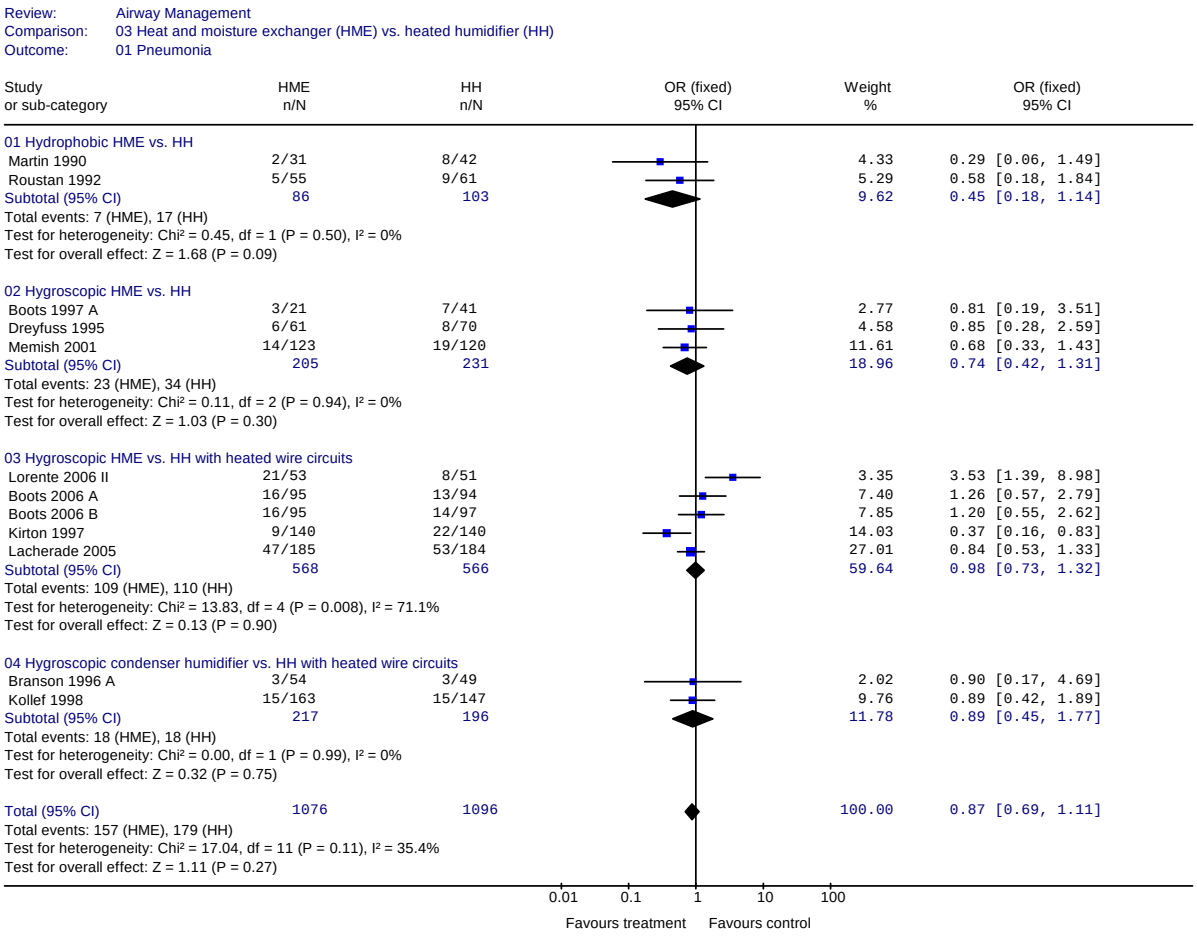
e) Heat and moisture exchanger (HME) vs. heated humidifier (HH)

Pneumonia

Eleven trials assessed the influence of different heat and moisture exchangers (HME) versus heated humidifiers (HH) on the development of pneumonia.[42, 43, 95, 176, 217, 233, 238, 295] Since one trial[42] contributed two comparisons to this group twelve data sets were evaluable.

Neither the overall results, nor the subgroup results, revealed a significant difference in pneumonia rates in patients ventilated with a HME or HH (OR = 0.87, 0.69 – 1.11) (Figure 11) (Table 6).

Figure 11: Airway Management: Heat and moisture exchanger (HME) vs. heated humidifier (HH), pneumonia outcomes.



Mortality

Overall, there was no effect on mortality (OR = 1.03, 0.82 – 1.28). Three of the subgroups had no significant impact on mortality, while the second subgroup which compared a hygroscopic HME with a HH with non-heated wires, showed a significant increase of mortality in the HME group (OR = 1.56, 1.00 – 2.44) (Figure 12) (Table 6).

Figure 12: Airway Management: Heat and moisture exchanger (HME) vs. heated humidifier (HH), mortality outcomes.

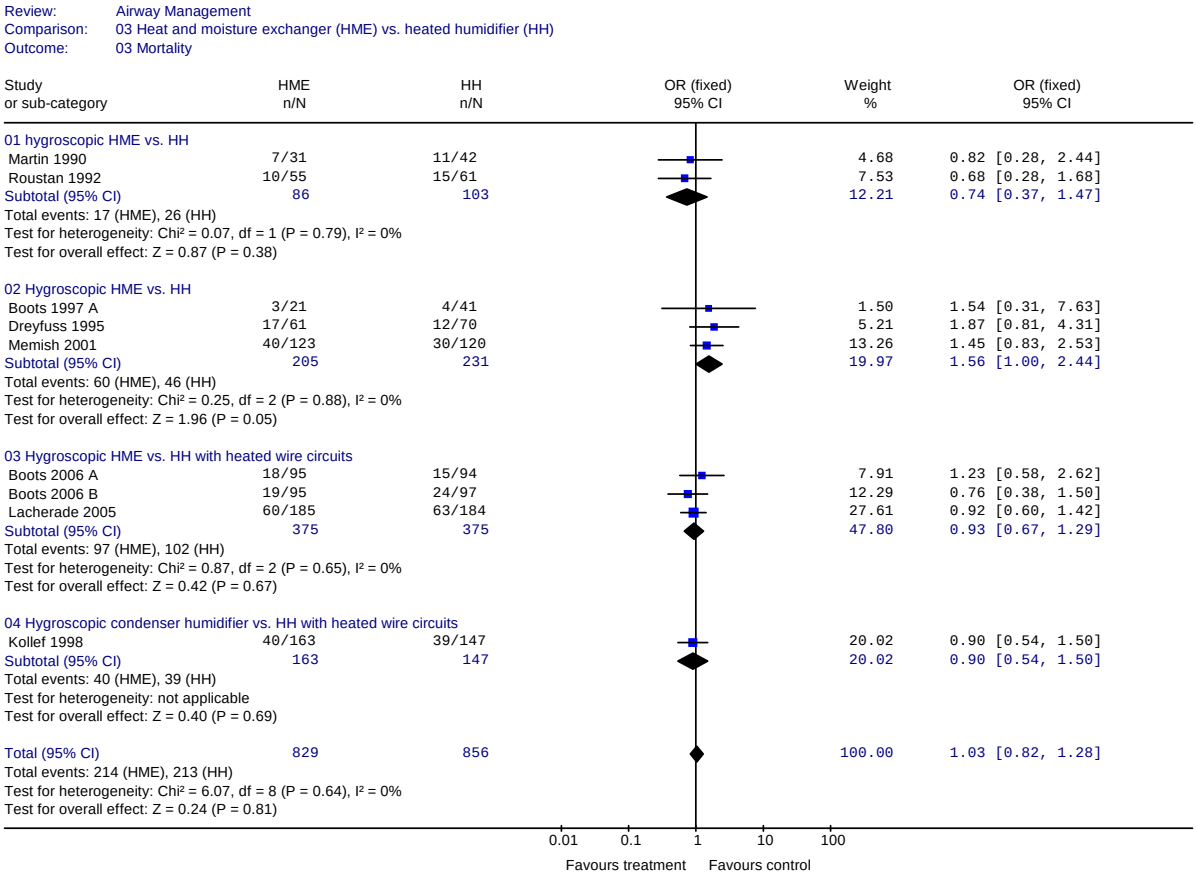


Table 6: Outcomes Airway Management: Heat and moisture exchanger (HME) vs. heated humidifier (HH)

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Martin 1990	Hydrophobic HME vs. HH	31/ 42	0.29 [0.06, 1.49]	0.82 [0.28, 2.44]	-3.80 [-8.44, 0.84]	
Roustan 1992	Hydrophobic HME vs. HH	55/ 61	0.58 [0.18, 1.84]	0.68 [0.28, 1.68]	2.70 [-2.16, 7.56]	4.60 [-0.48, 9.68]
Subtotal:			*0.45 [0.18, 1.14] (f)*	*0.74 [0.37, 1.47] (f)*	*-0.70 [-4.05, 2.66] (f)*	
Boots 1997 A	Hygroscopic HME vs. HH	21/ 41	0.81 [0.19, 3.51]	1.54 [0.31, 7.63]		
Dreyfuss 1995	Hygroscopic HME vs. HH	61/ 70	0.85 [0.28, 2.59]	1.87 [0.81, 4.31]	-2.50 [-6.47, 1.47]	
Memish 2001	Hygroscopic HME vs. HH	123/ 120	0.68 [0.33, 1.42]	1.45 [0.83, 2.53]	-1.60 [-4.09, 0.89]	
Subtotal:			*0.74 [0.42, 1.31] (f)*	*1.56 [1.00, 2.44] (f)*	*-1.85 [-3.97, 0.26] (f)*	
Lorente 2006 II	Hygroscopic HME vs. HH with heated wire circuits	53/ 51	3.53 [1.39, 8.98]		-1.35 [-7.79, 5.09]	
Boots 2006 A	Hygroscopic HME vs. HH with heated wire circuits	95/ 94	1.26 [0.57, 2.79]	1.23 [0.58, 2.62]		
Boots 2006 B	Hygroscopic HME vs. HH with heated wire circuits	95/ 97	1.20 [0.55, 2.62]	0.76 [0.38, 1.50]		
Kirton 1997	Hygroscopic HME vs. HH with heated wire circuits	140/ 140	0.37 [0.16, 0.83]			
Lacherade 2005	Hygroscopic HME vs. HH with heated wire circuits	185/ 184	0.84 [0.53, 1.33]	0.92 [0.60, 1.42]	-1.40 [-4.61, 1.81]	-3.90 [-9.18, 1.38]

Subtotal:			*0.98 [0.73, 1.32] (f)*	*0.93 [0.67, 1.29] (f)*	*-1.39 [-4.26, 1.48]*	
Branson 1996 A	Hygroscopic condenser humidifier vs. HH with heated wire circuits	54/ 49	0.90 [0.17, 4.69]		-0.40 [-1.79, 0.99]	
Kollef 1998	Hygroscopic condenser humidifier vs. HH with heated wire circuits	163/ 147	0.89 [0.42, 1.89]	0.90 [0.54, 1.50]	0.90 [-0.21, 2.01]	0.40 [-0.85, 1.65]
Subtotal:			*0.89 [0.45, 1.77] (f)*		*0.39 [-0.47, 1.26] (f)*	
Total:			**0.87 [0.69, 1.11] (f)**	**1.03 [0.82, 1.28] (f)**	**-0.07 [-0.82, 0.68] (f)**	**0.41 [-0.77, 1.59] (f)**

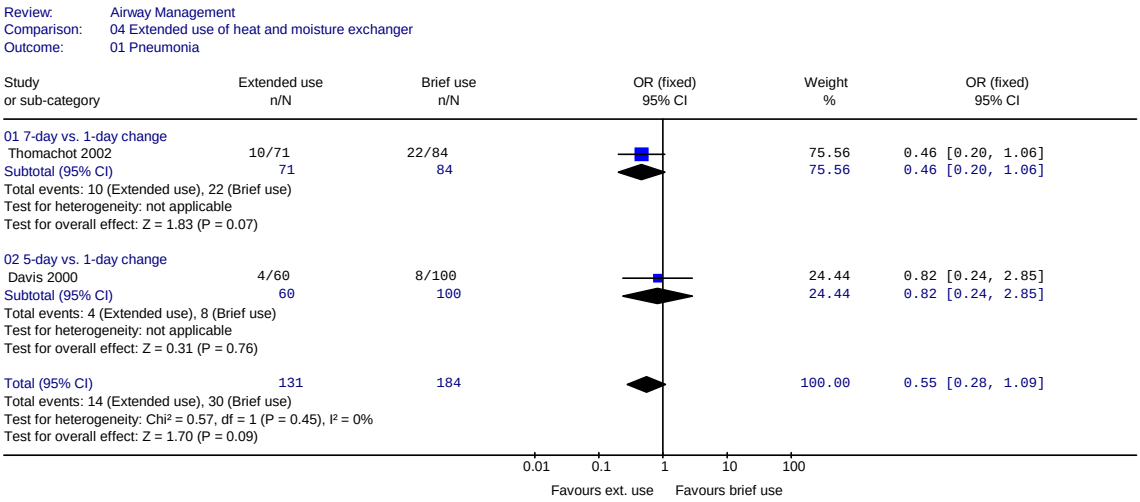
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

f) Extended use of heat and moisture exchanger (HME)

Pneumonia

Two trials assessed the effect of the extended use of HME with a 5- or a 7-day change versus daily changes of HME, on pneumonia rates.[81, 334] None of the results achieved statistical significance; however, the overall odds ratio was numerically less than one (OR = 0.55, 0.28 – 1.09) (Figure 13) (Table 7).

Figure 13: Airway Management: Extended use of heat and moisture exchanger, pneumonia outcomes.



Mortality

Mortality rates were not significantly influenced by an extended use of HME (Table 7).

Table 7: Outcomes Airway Management: Extended use of heat and moisture exchanger

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Davis 2000	5-day vs. 1-day HME change	60/ 100	0.82 [0.24, 2.85]		0.50 [-0.43, 1.43]	
Thomachot 2002	7-day vs. 1-day HME change	71/ 84	0.46 [0.20, 1.06]	1.38 [0.71, 2.68]	-0.90 [-3.38, 1.58]	0.70 [-4.00, 5.40]
Total:			**0.55 [0.28, 1.09] (f)**		**0.33 [-0.55, 1.20] (f)**	

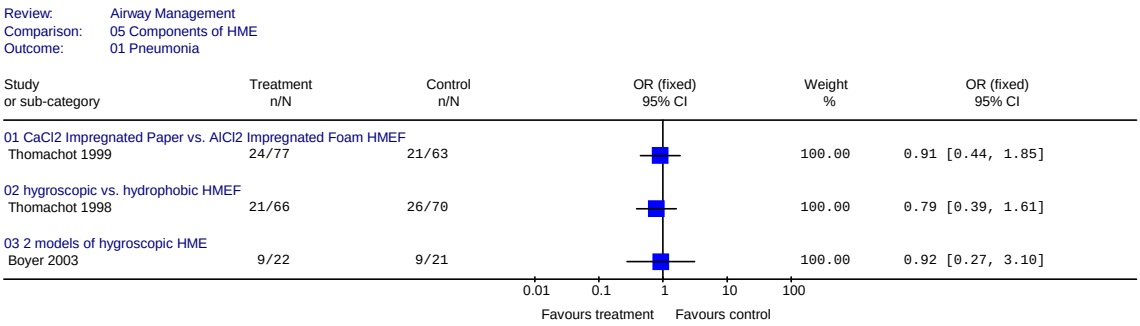
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

g) Components of heat and moisture exchanger (HME)

Pneumonia

Two different models of HME[46] and HMEF[335] and a hydrophobic versus a hygroscopic HMEF[336] were studied, but none of the compared VAP rates were significantly different (Figure 14) (Table 8). Due to the heterogeneity of the components no overall estimate was calculated.

Figure 14: Airway Management: Components of Heat and Moisture Exchanger, pneumonia outcomes.



Mortality/ Duration of MV

When data of mortality rates and the duration of MV was available, no significant impact on these outcomes was evident (Table 8).

Table 8: Outcomes Airway Management: Components of heat and moisture exchanger (HME)

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Boyer 2003	2 models of hygroscopic HME	22/ 21	0.92 [0.27, 3.10]		-2.00 [-15.46, 11.46]	
Thomachot 1998	Hygroscopic vs. hydrophobic HME	66/ 70	0.79 [0.39, 1.61]	0.97 [0.39, 2.37]	-0.50 [-4.37, 3.37]	
Thomachot 1999	$CaCl_2$- vs. $AlCl_2$- filter HME	77/ 63	0.91 [0.44, 1.85]	1.08 [0.44, 2.65]	-1.20 [-3.65, 1.25]	

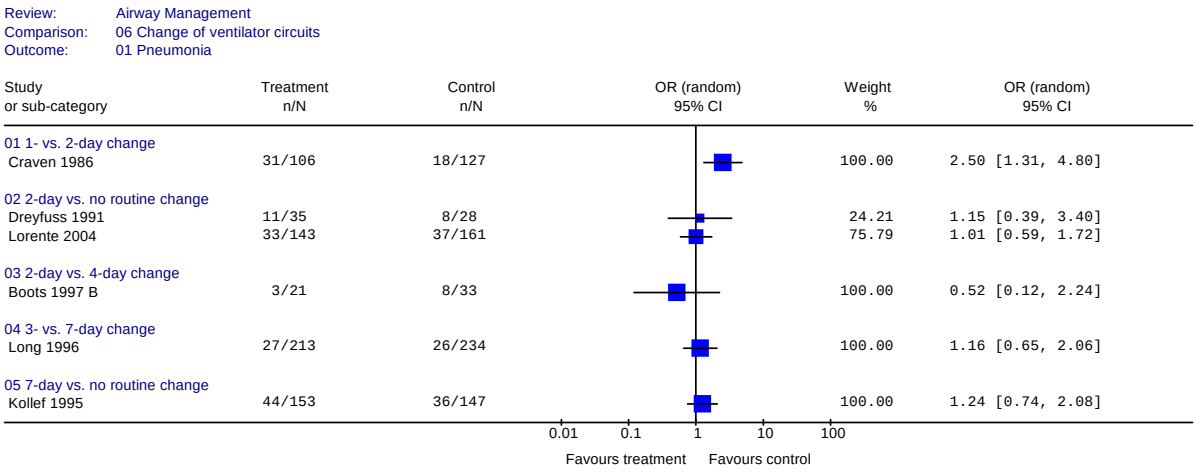
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

h) Change of ventilator circuits

Pneumonia

The impact of different intervals of ventilator circuit changes on VAP rates was studied by six trials.[43, 75, 96, 189, 214, 215] Due to the varying change intervals of the treatment and control groups we could not calculate a summary estimate. In the study comparing one- to two-day circuit changes, VAP rates were significantly lower in the group receiving two-day changes. None of the other compared pneumonia rates were significantly different (Figure 15) (Table 9).

Figure 15: Airway Management: Change of ventilator circuits, pneumonia outcomes.



Mortality

None of the trials demonstrated a significant difference in mortality rates (Figure 16) (Table 9).

Figure 16: Airway Management: Change of ventilator circuits, mortality outcomes.

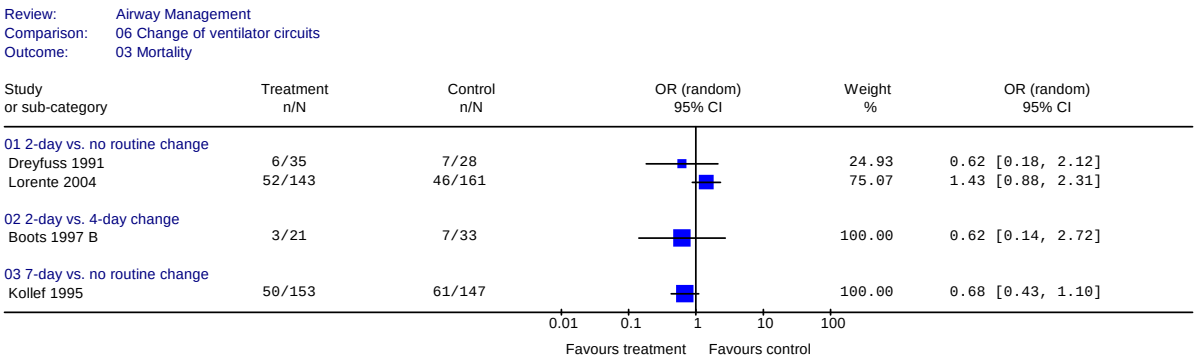


Table 9: Outcomes Airway Management: Change of ventilator circuits

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	**Length of ICU stay WMD [95% CI]**
Craven 1986	1-day vs. no routine change of ventilator circuits	106/ 127	2.5 [1.31, 4.80]			

Dreyfuss 1991	2-day vs. no routine change of ventilator circuits	35/ 28	1.15 [0.39, 3.40]	0.62 [0.18, 2.12]	2.80 [-1.41, 7.01]	
Lorente 2004	2-day vs. no routine change of ventilator circuits	143/ 161	1.01 [0.59, 1.72]	1.43 [0.88, 2.31]	-3.50 [-7.64, 0.64]	
Boots 1997 B	2-day vs. 4-day change	21/ 33	0.52 [0.12, 2.24]	0.62 [0.14, 2.72]		
Long 1996	3-day vs. 7-day change	213/ 234	1.16 [0.65, 2.06]			
Kollef 1995	7-day vs. no routine change	153/ 147	1.24 [0.74, 2.08]	0.68 [0.43, 1.10]	1.60 [-1.46, 4.66]	

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

i) Heated vs. non-heated wire circuits

Pneumonia

Results were not significantly different in a subgroup of a trial, assessing whether the use of heated or non-heated wire circuits had an impact on pneumonia rates (OR = 1.68, 0.51 – 5.55) (Table 10).[47]

Table 10: Outcomes Airway Management: Heated vs. non-heated wire circuits

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Branson 1996 B	Heated vs. non-heated wire circuits	49/ 48	1.68 [0.51, 5.55]		1.90 [-1.28, 5.08]	

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

j) Oro- vs. nasotracheal intubation

Pneumonia/ Mortality

One large trial compared oro- with nasotracheal intubation in order to reduce contamination of tracheal secretions with bacteria from the nares.[158] Results for VAP were not statistically significant, although the odds ratio was numerically less than one (0.49, 0.21 – 1.14) (Table 11).

Differences in mortality rates were not significant, either (OR = 1.19, 0.75 – 1.89).

Table 11: Outcomes Airway Management: Oro- vs. nasotracheal intubation

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Holzapfel 1993	Oro- vs. nasotracheal intubation	151/ 149	0.49 [0.21, 1.14]	1.19 [0.75, 1.89]		-1.50 [-4.48, 1.48]

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

k) Bacterial filter

Pneumonia/ Mortality

In a trial assessing the impact of a bacterial filter in the ventilator circuits neither the incidence of pneumonia nor mortality rates were significantly altered (Table 12).[219]

Table 12: Outcomes Airway Management: Bacterial filter

Study ID	Intervention	Study/ Control group	Pneumonia OR [95% CI]	Mortality OR [95% CI]	Duration of MV WMD [95% CI]	Length of ICU stay WMD [95% CI]
Lorente 2003	Bacterial filter	114/ 116	1.19 [0.64, 2.19]	1.51 [0.85, 2.69]	-1.16 [-5.38, 3.06]	-2.03 [-6.51, 2.45]

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

3.6. Gastrointestinal interventions

a) Selective decontamination of the digestive tract (SDD)

Pneumonia

Twenty-seven trials studying the effects of different regimens of selective decontamination of the digestive tract (SDD) met our inclusion criteria. There are different ways and agents used to implement SDD, represented by the four subgroups of our analysis. Topical antibiotic and antimycotic agents, normally including polymyxin E, tobramycin or amphotericin B, can be applied topically to the oropharynx alone, or additionally to the gastrointestinal (GI) tract. Systemic antibiotics can supplement the topical treatments.

With all of the subgroups showing a significant reduction of pneumonia rates, the overall outcome emphasizes the evidence of that effect of SDD (OR = 0.32, 0.24 – 0.44) (Figure 17) (Table 13).

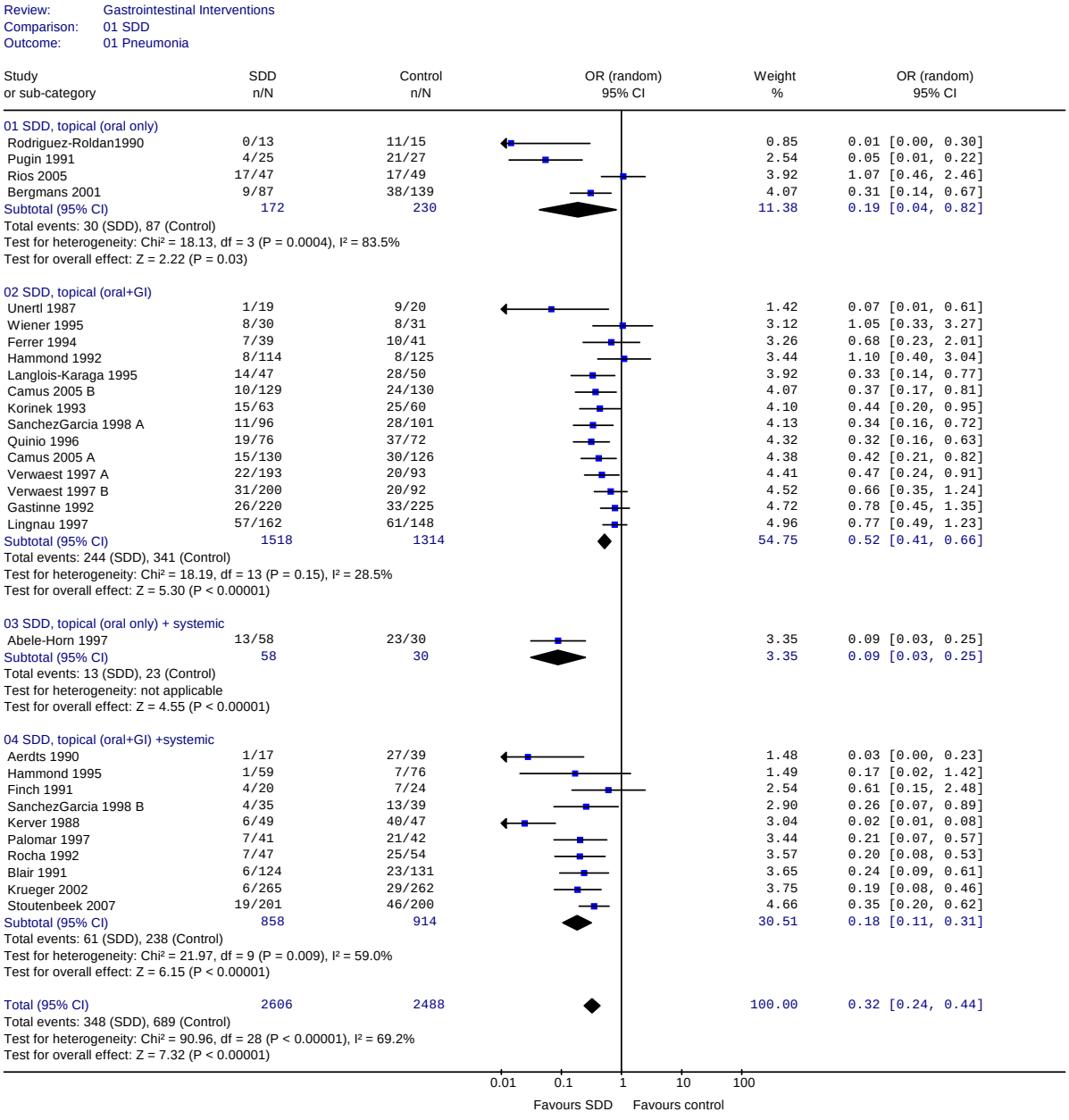
The first subgroup, containing four trials reached a statistically significant effect by administering topical agents to the oropharynx only, without performing systemic prophylaxis (OR=0.19, 0.04-0.82). [27, 277, 288, 290]

The second subgroup, including twelve trials[50, 111, 124, 140, 196, 206, 211, 279, 304, 356, 367, 377], with two trials[50, 367] contributing two comparisons each, applied topical agents to the oropharynx and the GI without adminsitering systemic prophylaxis (OR=0.52, 0.41-0.66).

The SDD-regimen of the trial of the third subgroup consisted of the application of topical agents to the oropharynx only and the administration of systemic antibiotics (OR=0.09, 0.03-0.25).[4]

The nine trials and one subgroup of a trial comprised the fourth subgroup. Their regimen consisted of topical antibiotic and antimycotic agents applied to the oropharynx and the GI tract with the administration of systemic antibiotics (OR=0.18, 011-0.31).[8, 31, 113, 139, 173, 200, 264, 289, 304, 325]

Figure 17: Gastrointestinal Interventions: SDD, pneumonia outcomes



Mortality

From all but two trials mortality data was abstractable (Table 13) (Figure 18).

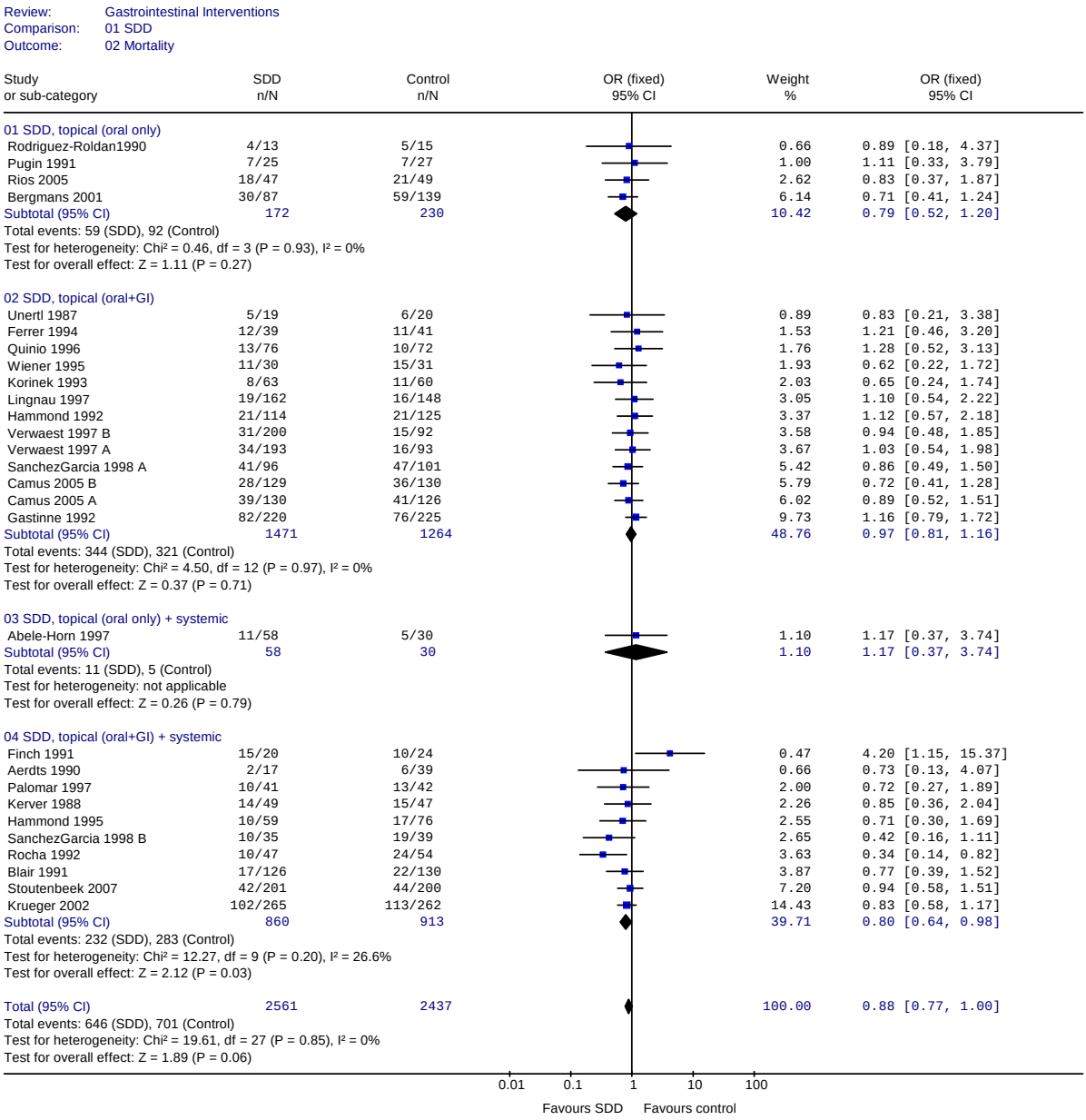
The only subgroup with a significant reduction of mortality rates was the fourth, administering topical agents orally and to the GI plus systemic prophylaxis (OR = 0.80, 0.64 – 0.98).

The result of the first subgroup was not significant, although the odds ratio was numerically less than one (OR = 0.79, 0.52 – 1.20).

With the data available there was no evidence for an effect in the the second and third subgroup (OR = 0.95, 0.80 – 1.14) (OR = 1.17, 0.37 – 3.74).

With p=0.06 the overall outcome failed to reach statistical significance, although the odds ratio was numerically less than one (OR = 0.88, 0.77 – 1.00).

Figure 18: Gastrointestinal Interventions: SDD, mortality outcomes



Duration of MV

Evaluating the results of the eight trials assessing the duration of MV, an adverse effect in terms of an increase of the duration of MV was observed (WMD = 0.46, 0.04 – 0.89) (Table 13).

This is mainly due to the second subgroup (WMD = 0.56, 0.13 – 1.00) where one large trial with an assigned weight of 89.62% had a big impact on this outcome.[211]

The results of subgroups one, three, and four were not significant.

Length of ICU stay

The length of ICU stay, assessed by eleven trials, could be significantly reduced by SDD (WMD = -0.53, -0.89 - -0.16).

However, only the results of the second and the third subgroup complied with this overall estimate, whereas subgroups one and four failed to show an effect (Table 13).

Table 13: Outcomes Gastrointestinal Interventions: Selective decontamination of the digestive tract (SDD)

Study ID	***Intervention***	***Study/ Control group***	***Pneumonia OR [95% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Bergmans 2001	SDD, topical (oral only)	87/ 139	0.31 [0.14, 0.67]	0.71 [0.41, 1.24]		
Pugin 1991	SDD, topical (oral only)	25/ 27	0.05 [0.01, 0.22]	1.11 [0.33, 3.79]	-1.10 [-4.62, 2.42]	-1.90 [-5.87, 2.07]
Rios 2005	SDD, topical (oral only)	47/ 49	1.07 [0.46, 2.46]	0.83 [0.37, 1.87]	-4.00 [-9.94, 1.94]	3.00 [-3.64, 9.64]
Rodriguez-Roldan 1990	SDD, topical (oral only)	13/ 15	0.01 [0.00, 0.30]	0.89 [0.18, 4.37]		
Subtotal:			*0.19 [0.04, 0.82] (r)*	*0.79 [0.52, 1.20] (f)*	*-1.85 [-4.88, 1.17] (f)*	*-0.61 [-4.02, 2.80] (f)*
Camus 2005 A	SDD, topical (oral+GI)	130/ 126	0.42 [0.21, 0.82]	0.89 [0.52, 1.51]		
Camus 2005 B	SDD, topical (oral+GI)	129/ 130	0.37 [0.17, 0.81]	0.72 [0.41, 1.28]		
Ferrer 1994	SDD, topical (oral+GI)	39/ 41	0.68 [0.23, 2.01]	1.21 [0.46, 3.20]	0.90 [-3.41, 2.61]	1.00 [-2.85, 4.85]
Gastinne 1992	SDD, topical (oral+GI)	220/ 225	0.78 [0.45, 1.35]	1.16 [0.79, 1.72]		-1.00 [-4.27, 2.27]
Hammond 1992	SDD, topical (oral+GI)	114/ 125	1.10 [0.40, 3.04]	1.12 [0.57, 2.18]		-0.60 [-4.00, 2.80]
Korinek 1993	SDD, topical (oral+GI)	63/ 60	0.44 [0.20, 0.95]	0.65 [0.24, 1.74]	-0.40 [-3.41, 2.61]	-1.20 [-7.07, 4.67]
Langlois-Karaga 1995	SDD, topical (oral+GI)	47/ 50	0.33 [0.14, 0.77]			
Lingnau 1997	SDD, topical (oral+GI)	162/ 148	0.77 [0.49, 1.23]	1.10 [0.54, 2.22]	0.60 [0.15, 1.05]	-0.50 [-0.88, -0.12]
Quinio 1996	SDD, topical (oral+GI)	76/ 72	0.32 [0.16, 0.63]	1.28 [0.52, 3.13]	-0.30 [-3.07, 2.47]	0.30 [-3.99, 4.59]
Sanchez Garcia 1998 A	SDD, topical (oral+GI)	96/ 101	0.34 [0.16, 0.72]	0.86 [0.49, 1.50]		
Unertl 1987	SDD, topical (oral+GI)	19/ 20	0.07 [0.01, 0.61]	0.83 [0.21, 3.38]		
Verwaest 1997 A	SDD, topical (oral+GI)	193/ 93	0.47 [0.24, 0.91]	1.03 [0.54, 1.98]		
Verwaest 1997 B	SDD, topical (oral+GI)	200/ 92	0.66 [0.35, 1.24]	0.94 [0.48, 1.85]		
Wiener 1995	SDD, topical (oral+GI)	30/ 31	1.05 [0.33, 3.27]	0.62 [0.22, 1.72]		
Subtotal:			*0.52 [0.41, 0.66] (r)*	*0.97 [0.81, 1.16] (f)*	*0.56 [0.13, 1.00] (f)*	*-0.49 [-0.86, -0.12] (f)*
Abele-Horn 1997	SDD, topical (oral only) + systemic	58/ 30	0.09 [0.03, 0.25]	1.17 [0.37, 3.74]	-1.70 [-4.67, 1.27]	-4.00 [-7.73, -0.27]

Aerdts 1990	SDD, topical (oral+GI) + systemic	17/ 39	0.03 [0.00, 0.23]	0.73 [0.13, 4.07]		
Blair 1991	SDD, topical (oral+GI) + systemic	124/ 131	0.24 [0.09, 0.61]	0.77 [0.39, 1.52]		
Finch 1991	SDD, topical (oral+GI) + systemic	20/ 24	0.61 [0.15, 2.48]	4.20 [1.15, 15.37]		
Hammond 1995	SDD, topical (oral+GI) + systemic	59/ 76	0.17 [0.02, 1.42]	0.71 [0.30, 1.69]		-1.30 [-6.34, 3.74]
Kerver 1988	SDD, topical (oral+GI) + systemic	49/ 47	0.02 [0.01, 0.08]	0.85 [0.36, 2.04]		
Krueger 2002	SDD, topical (oral+GI) + systemic	265/ 262	0.19 [0.08, 0.46]	0.94 [0.58, 1.17]		
Palomar 1997	SDD, topical (oral+GI) + systemic	41/ 42	0.21 [0.07, 0.57]	0.72 [0.27, 1.89]		
Rocha 1992	SDD, topical (oral+GI) + systemic	47/ 54	0.20 [0.08, 0.53]	0.34 [0.14, 0.82]	-0.10 [-5.01, 4.81]	1.00 [-5.98, 7.98]
Sanchez Garcia 1998 B	SDD, topical (oral+GI) + systemic	35/ 39	0.26 [0.07, 0.89]	0.42 [0.16, 1.11]		
Stoutenbeek 2007	SDD, topical (oral+GI) + systemic	201/ 200	0.35 [0.20, 0.62]	0.94 [0.58, 1.51]		
Subtotal:			*0.18 [0.11, 0.31] (r)*	*0.80 [0.64, 0.98] (f)*		*-0.51 [-4.60, 3.57]*
Total:			**0.32 [0.24, 0.44] (r)**	**0.88 [0.77, 1.00] (f)**	**0.46 [0.04, 0.89] (f)**	**-0.53 [-0.89, -0.16] (f)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

b) Selective decontamination of the digestive tract (SDD) with additional topical antibiotics

Pneumonia

Three trials compared the application of either topical gentamicin[194, 204] or mupirocin[250] in addition to a SDD regimen, of which only the study adding mupirocin could show a significant reduction of pneumonia rates (OR=0.32, 0.16-0.62) (Table 14).

Mortality

There was no evidence for an effect on mortality rates (Table 14).

Table 14: Outcomes Gastrointestinal Interventions: SDD with additional topical agents

Study ID	*Intervention*	*Treatment/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Konrad 1991	Additional gentamicin vs. SDD: topical (oral+GI) + systemic	20/ 20	1.00 [0.13, 7.89]	1.00 [0.24, 4.18]		
Laggner 1994	Additional gentamicin vs. SDD: topical (oral only)	33/ 34	0.23 [0.02, 2.22]	0.54 [0.19, 1.50]	-4.10 [-17.26, 9.06]	-6.60 [-30.21, 17.01]
Nardi 2001	Additional mupirocin vs. SDD: topical (oral+GI)	119/ 104	0.32 [0.16, 0.62]	0.80 [0.43, 1.49]	-1.80 [-4.67, 1.07]	-1.20 [-4.04, 1.64]

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

c) Interventions to reduce the bacterial reflux load

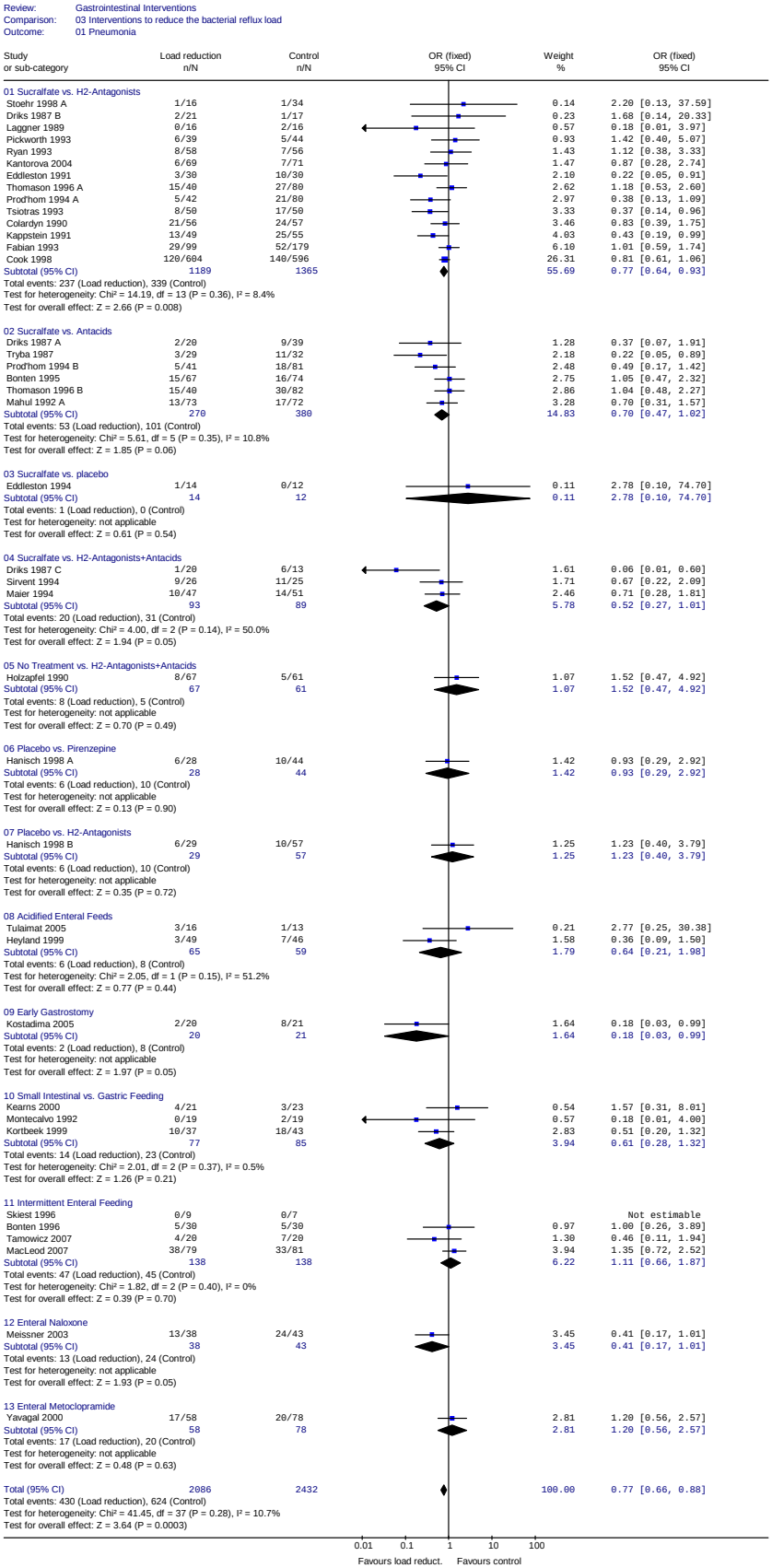
Pneumonia

Sucralfate vs. H2-antagonists

Fourteen trials compared the administration of sucralfate versus H_2-anatgonists for stress ulcer prophylaxis.[66, 71, 99, 101, 106, 169, 170, 203, 270, 276, 299, 323, 337, 352] Herein the objective was to keep stomach pH-levels low with sucralfate thereby reducing the bacterial reflux load of potential aspiration contents.

The incidence of pneumonia could be significantly reduced by administering sucralfate as opposed to H_2-antagonists (OR = 0.77, 0.64 – 0.93) (Figure 19).

Figure 19: Gastrointestinal Interventions: Interventions to reduce the bacterial reflux load, pneumonia outcomes



Results

Sucralfate vs. antacids

The six trials comparing sucralfate versus antacids for stress ulcer prophylaxis failed to show a significant reduction of pneumonia rates, although the odds ratio was numerically less than one (OR = 0.70, 0.47 – 1.02) (Figure 19).[40, 99, 227, 276, 337, 346]

Other interventions

Of the other interventions attempting to reduce the bacterial reflux load by keeping the gastric pH low, only early gastrostomy (OR = 0.18, 0.03 – 0.99) could show a significant reduction in pneumonia rates (Figure 19).[198]

With the confidence interval extending to 1.01 the intervention of sucralfate as opposed to H_2-antagonists in combination with antacids[99, 228, 316] (OR = 0.52, 0.27 – 1.01), and the administration of enteral naloxone[237] in order to fasten emptying of the stomach (OR = 0.41, 0.17 – 1.01) just failed statistical significance.

The remaining interventions, sucralfate vs. placebo[100], no treatment vs. H_2-antagonists plus antacids[159], placebo vs. pirenzepine[141], placebo vs. H_2-antagonists[141], acidification of enteral feeds[151, 353], small intestinal vs. gastric feeding[171, 197, 244], intermittent enteral feeding[41, 224, 317, 332], and enteral metoclopramide[381] also failed to show a significant effect.

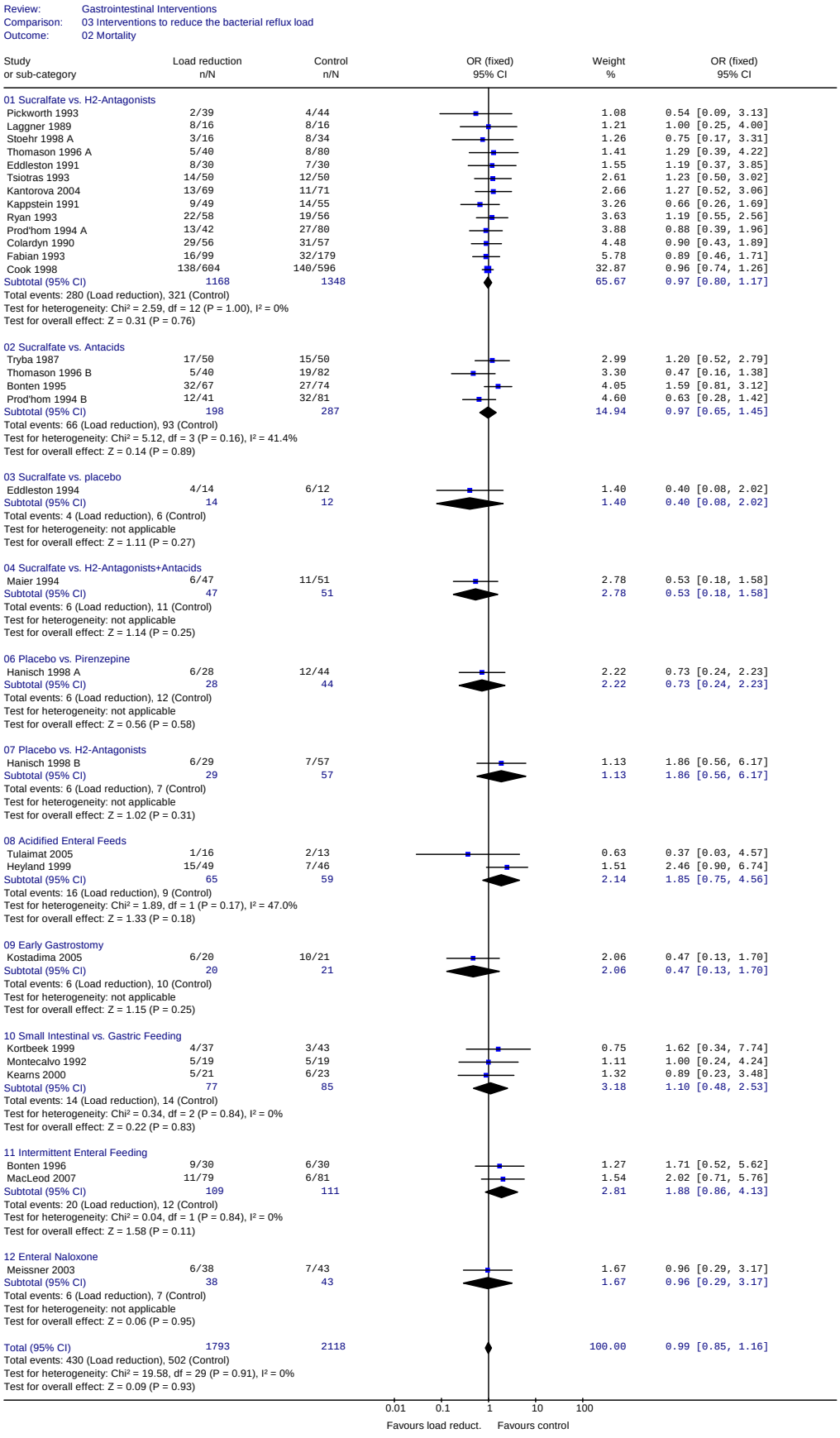
Overall, the attempt to reduce the bacterial reflux load decreased pneumonia-rates significantly (OR = 0.75, 0.65 – 0.87) (Figure 19).

Mortality

Sucralfate vs. H_2-antagonists

There was no effect on mortality rates in this reference group (OR = 0.97, 0.80 – 1.17) (Figure 20).

Figure 20: Gastrointestinal Interventions: Interventions to reduce the bacterial reflux load, mortality outcomes



Results

Sucralfate vs. antacids

Mortality rates were not different between the groups receiving sucralfate and antacids, respectively (OR = 0.97, 0.65 – 1.45).

Other interventions

There was no evidence for an effect on mortality rates in any of the reference groups of the other interventions.

The overall result of the interventions attempting to preserve a low gastric pH was not statistically significant regarding mortality rates (OR = 0.99, 0.85 – 1.16).

Length of ICU stay

The overall result for the length of ICU stay showed no significant change in this outcome (WMD = 0.65, -0.70, 1.99), with discordant significant results of the two subgroups of sucralfate versus H_2-antagonists plus antacids (WMD = -4.50, -8.89, -0.11) and intermittent enteral feeding (WMD = 1.10, 0.52, 1.68) (Table 15). Nevertheless, each of them was only represented by one study with abstractable data for this outcome.

Table 15: Outcomes Gastrointestinal Interventions: Interventions to reduce the bacterial reflux load

Study ID	***Intervention***	***Study/ Control group***	***Pneumonia OR [95% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WM [95% CI]
Colardyn 1990	Sucralfate vs. H_2-antagonists	56/ 57	0.83 [0.39, 1.75]	0.90 [0.43, 1.89]		
Cook 1998	Sucralfate vs. H_2-antagonists	604/ 596	0.81 [0.61, 1.06]	0.96 [0.74, 1.26]		
Driks 1987 B	Sucralfate vs. H_2-antagonists	21/ 17	1.68 [0.14, 20.33]			
Eddleston 1991	Sucralfate vs. H_2-antagonists	30/ 30	0.22 [0.05, 0.91]	1.19 [0.37, 3.85]	2.20 [1.55, 2.85]	3.00 [2.10, 3.90]
Fabian 1993	Sucralfate vs. H_2-antagonists	99/ 179	1.01 [0.59, 1.74]	0.89 [0.46, 1.71]		
Kantorova 2004	Sucralfate vs. H_2-antagonists	69/ 71	0.87 [0.28, 2.74]	1.27 [0.52, 3.06]	-0.40 [-3.10, 2.30]	-2.20 [-5.36, 0.96]
Kappstein 1991	Sucralfate vs. H_2-antagonists	49/ 55	0.43 [0.19, 0.99]	0.66 [0.26, 1.69]		
Laggner 1989	Sucralfate vs. H_2-antagonists	16/ 16	0.18 [0.01, 3.97]	1.00 [0.25, 4.00]	-0.30 [-2.81, 2.21]	
Pickworth 1993	Sucralfate vs. H_2-antagonists	39/ 44	1.42 [0.40, 5.07]	0.54 [0.09, 3.13]		
Prod'hom 1994 A	Sucralfate vs. H_2-antagonists	42/ 80	0.38 [0.13, 1.09]	0.88 [0.39, 1.96]		
Ryan 1993	Sucralfate vs. H_2-antagonists	58/ 56	1.12 [0.38, 3.33]	1.19 [0.55, 2.56]		

Stoehr 1998 A	Sucralfate vs. H_2-antagonists	16/ 34	2.20 [0.13, 37.59]	0.75 [0.17, 3.31]		
Thomason 1996 A	Sucralfate vs. H_2-antagonists	40/ 80	1.18 [0.53, 2.60]	1.29 [0.39, 4.22]		
Tsiotras 1993	Sucralfate vs. H_2-antagonists	50/ 50	0.37 [0.14, 0.96]	1.23 [0.50, 3.02]	-2.50 [-4.11, -0.89]	
Subtotal:			*0.77 [0.64, 0.93] (f)*	*0.97 [0.80, 1.17] (f)*	*-0.19 [-2.88, 2.50] (r)*	*0.63 [-4.45, 5.71] (r)*
Bonten 1995	Sucralfate vs. antacids	67/ 74	1.05 [0.47, 2.32]	1.59 [0.81, 3.12]		-2.20 [-12.73, 8.33]
Driks 1987 A	Sucralfate vs. antacids	20/ 39	0.37 [0.07, 1.91]			
Mahul 1992 A	Sucralfate vs. antacids	73/ 72	0.70 [0.31, 1.57]			
Prod'hom 1994 B	Sucralfate vs. antacids	41/ 81	0.49 [0.17, 1.42]	0.63 [0.28, 1.42]		
Thomason 1996 B	Sucralfate vs. antacids	40/ 82	1.04 [0.48, 2.27]	0.47 [0.16, 1.38]		
Tryba 1987	Sucralfate vs. antacids	29/ 32	0.22 [0.05, 0.89]	1.20 [0.52, 2.79]		
Subtotal:			*0.70 [0.47, 1.02] (f)*	*0.97 [0.65, 1.45] (f)*		
Eddleston 1994	Sucralfate vs. placebo	14/ 12	2.78 [0.10, 74.70]	0.40 [0.08, 2.02]		
Driks 1987 C	Sucralfate vs. H_2-antagonists + antacids	20/ 13	0.06 [0.01, 0.60]			
Maier 1994	Sucralfate vs. H_2-antagonists + antacids	47/ 51	0.71 [0.28, 1.81]	0.53 [0.18, 1.58]	-4.40 [-8.89, 0.09]	-4.5 [-8.89, -0.11]
Sirvent 1994	Sucralfate vs. H_2-antagonists + antacids	29/ 32	0.67 [0.22, 2.09]			
Subtotal:			0.52 [0.27, 1.01] (f)			
Holzapfel 1990	No treatment vs. H_2-antagonists + antacids	67/ 61	1.52 [0.47, 4.92]			
Hanisch 1998 A	Placebo vs. pirenzepine	28/ 44	1.23 [0.40, 3.79]	0.73 [0.24, 2.23]		
Hanisch 1998 B	Placebo vs. H_2-antagonists	29/ 57	1.23 [0.40, 3.79]	1.86 [0.56, 6.17]		
Heyland 1999	Acidified enteral feeds	49/ 46	0.36 [0.09, 1.50]	2.46 [0.90, 6.74]		
Tulaimat 2005	Acidified enteral feeds	16/ 13	2.77 [0.25, 30.38]	0.37 [0.03, 4.57]		
Subtotal:			*0.64 [0.21, 1.98] (f)*	*1.85 [0.75, 4.56] (f)*		
Kostadima 2005	Early gastrostomy	20/ 21	0.18 [0.03, 0.99]	0.47 [0.13, 1.70]	-0.30 [-8.43, 7.83]	0.00 [-8.46, 8.46]
Kearns 2000	Small intestinal vs. gastric feeding	21/ 23	1.57 [0.31, 8.01]	0.89 [0.23, 3.48]	-4.00 [-10.21, 2.21]	1.00 [-0.18, 2.18]
Kortbeek 1999	Small intestinal vs. gastric feeding	37/ 43	0.51 [0.10, 1.32]	1.62 [0.34, 7.74]		
Montecalvo 1992	Small intestinal vs. gastric feeding	19/ 19	0.18 [0.01, 4.00]	1.00 [0.24, 4.24]	-1.20 [-7.01, 4.61]	-0.60 [-6.70, 5.50]
Subtotal:			*0.61 [0.28, 1.32] (f)*	*1.10 [0.48, 2.53] (f)*	*-2.51 [-6.75, 1.73] (r)*	*0.94 [-0.22, 2.10] (r)*

Bonten 1996	Intermittent enteral feeding	30/ 30	1.00 [0.26, 3.89]	1.71 [0.52, 5.62]		
MacLeod 2007	Intermittent enteral feeding	79/ 81	1.35 [0.73, 2.26]	2.02 [0.71, 5.76]		1.10 [0.52, 1.68]
Skiest 1996	Intermittent enteral feeding	9/ 7	Not estimable			
Tamowicz 2007	Intermittent enteral feeding	20/ 20	0.46 [0.11, 1.94]			
Subtotal:			*1.11 [0.66, 1.87] (f)*	*1.88 [0.86, 4.13] (f)*		
Meissner 2003	Enteral naloxone	38/ 43	0.41 [0.17, 1.01]	0.96 [0.29, 3.17]		
Yavagal 2000	Enteral metoclopramide	58/ 78	1.20 [0.56, 2.57]			
Total:			**0.77 [0.66, 0.88] (f)**	**0.99 [0.85, 1.16] (f)**	**-1.03 [-3.41, 1.35] (r)**	**0.65 [-0.70, 1.99] (r)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

d) H_2-antagonist vs.antacid

Pneumonia

One trial was identified comparing the H_2-receptor antagonist ranitidine and the antacid pirenzepine for stress ulcer prophylaxis.[347] The odds ratio was numerically larger than one (OR = 4.00, 0.95 – 16.92), favoring pirenzepine, but the result failed to reach statistical significance (p = 0.06) (Table 16).

Table 16: Outcomes Gastrointestinal Interventions: Ranitidine vs. pirenzepine

Study ID	***Intervention***	***Study/ Control group***	***Pneumonia OR [95% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Tryba 1988	H_2-antagonist vs. antacid	28/ 33	3.00 [0.95, 16.92]			

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

e) Enriched enteral nutrition

Pneumonia/ Mortality

Summarizing the data of four trials implementing a formula of enriched enteral nutrition does not suggest a significant reduction of pneumonia (OR = 1.38, 0.51 – 3.75) or mortality rates (OR = 0.71, 0. 40 – 1.27) (Table 17).[51, 160, 239, 321]

Table 17: Outcomes Gastrointestinal Interventions: Enriched enteral nutrition

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Caparros 2001	Enriched enteral nutrition	122/ 98	1.62 [0.88, 2.98]	0.70 [0.39, 1.27]		
Houdijk 1998	Enriched enteral nutrition	35/ 37	0.27 [0.09, 0.81]			
Mendez 1997	Enriched enteral nutrition	22/ 21	2.42 [0.68, 8.64]	0.95 [0.06, 16.28]		
Spindler-Vesel 2007	Enriched enteral nutrition	87/ 26	3.53 [1.12, 11.13]			
Total:			**1.38 [0.51, 3.75] (r)**	**0.71 [0.04, 1.27] (f)**		

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

f) Early enteral nutrition

Pneumonia

Two trials met our inclusion criteria, but both of them had discordant significant results, so no evidence for an effect of early enteral nutrition on the incidence of pneumonia could be shown (OR = 0.83, 0.11 – 6.23) (Table 18).[163, 193]

Mortality

The outcome for mortality was not significant (OR = 0.65, 0.31 – 1.37) (Table 18).

Table 18: Outcomes Gastrointestinal Interventions: Early enteral nutrition

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Ibrahim 2002	Early enteral nutrition	75/ 75	2.20 [1.13, 4.29]	0.69 [0.32, 1.47]		3.80 [0.18, 7.42]
Kompan 2004	Early enteral nutrition	27/ 25	0.28 [0.09, 0.88]	0.30 [0.01, 7.63]	-2.70 [-9.71, 4.31]	-4.70 [-12.82, 3.42]
Total:			**0.83 [0.11, 6.23] (r)**	**0.65 [0.31, 1.37] (f)**		**2.39 [-0.92, 5.70] (f)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

g) Enteral vs. parenteral feeding

Pneumonia/ Duration of MV

One trial comparing enteral with parenteral feeding met our inclusion criteria.[201]

Pneumonia rates were significantly reduced in the patient group receiving enteral feeding (OR=0.30, 0.10-0.85), as was the duration of MV (WMD=-0.40, -0.75- -0.05) (Table 19).

Table 19: Outcomes Gastrointestinal Interventions: Enteral vs. parenteral feeding

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Kudsk 1992	Enteral vs. parenteral feeding	51/ 45	0.30 [0.10, 0.85]		-0.40 [-0.75, -0.05]	

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

3.7. Positioning

a) Rotational therapy

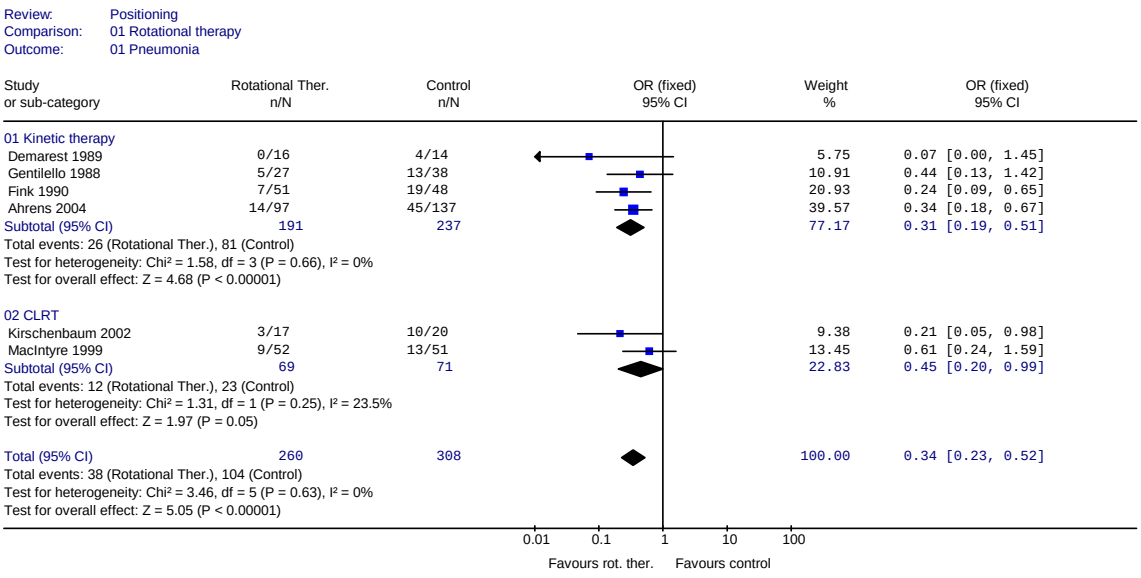
Pneumonia

Six trials studying the effects of rotational therapy met our inclusion criteria. Four[11, 86, 114, 126] implemented a kinetic therapy, an automated turning of the patient in his bed of at least 40 degrees to each side, and two[175, 223] implemented a continuous lateral rotation therapy (CLRT), an automated turning of the patient of up to 40 degrees.

Overall, pneumonia rates were significantly reduced in patients undergoing rotational therapy (OR = 0.34, 0.23 – 0.52).

Both of the subgroups showed a significant reduction of the incidence of pneumonia, with a greater impact in the kinetic therapy group (Figure 21).

Figure 21: Positioning: Rotational therapy, pneumonia outcomes.



Mortality

There was no significant impact on mortality rates in the subgroups or the overall estimate (OR = 1.12, 0.77 – 1.63) (Figure 22).

Figure 22: Positioning: Rotational therapy, mortality outcomes.

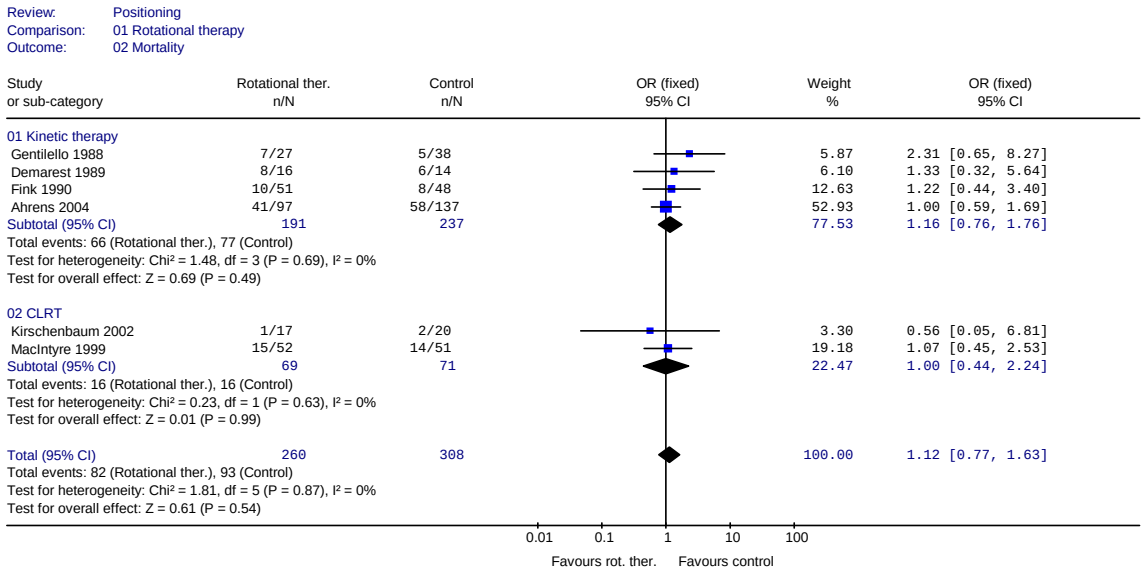


Table 20: Outcomes Positioning: Rotational therapy

Study ID	***Intervention***	***Study/ Control group***	***Pneumonia OR [95% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Ahrens 2004	Kinetic therapy	97/ 137	0.34 [0.18, 0.67]	1.00 [0.59, 1.69]	0.61 [-2.40, 3.62]	-0.18 [-3.42, 3.06]
Demarest 1989	Kinetic therapy	16/ 14	0.07 [0.00, 1.45]	1.33 [0.32, 5.64]		
Fink 1990	Kinetic therapy	51/ 48	0.24 [0.09, 0.65]	1.22 [0.44, 3.40]		
Gentilello 1988	Kinetic therapy	27/ 38	0.44 [0.13, 1.42]	2.31 [0.65, 9.27]	-1.50 [-4.79, 1.79]	1.80 [-5.34, 8.94]
Subtotal:			*0.31 [0.19, 0.51] (f)*	*1.16 [0.76, 1.76] (f)*	*-0.35 [-2.58, 1.87] (f)*	*0.16 [-2.79, 3.11] (f)*
Kirschenbaum 2002	Continous lateral rotation therapy (CLRT)	17/ 20	0.21 [0.05, 0.98]	0.56 [0.05, 6.81]	-3.00 [-7.19, 1.19]	
MacIntyre 1999	Continous lateral rotation therapy (CLRT)	52/ 51	0.61 [0.24, 1.59]	1.07 [0.45, 2.53]		
Subtotal:			*0.45 [0.20, 0.99] (f)*	*1.00 [0.44, 2.24] (f)*		
Total:			**0.34 [0.23, 0.52] (f)**	**1.12 [0.77, 1.63] (f)**	**-0.93 [-2.90, 1.03] (f)**	

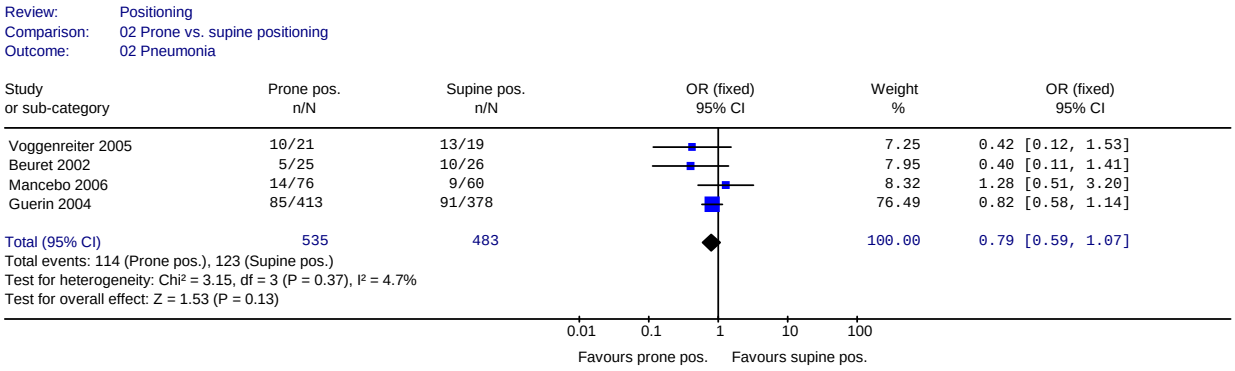
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

b) Prone vs. supine positioning

Pneumonia

Four trials studied prone as opposed to supine positioning in the prevention of pneumonia.[30, 136, 229, 370] Prone sessions ranged from four hours daily[30], to eight hours[136], eight to twenty-three[370] and 20 hours[229]. Overall there was a lack of evidence for a treatment effect, although the odds ratio was numerically less than one (OR = 0.79, 0.59 – 1.07) (Figure 23) (Table 21).

Figure 23: Positioning: Prone vs. Supine positioning, pneumonia outcomes.



Mortality

Results were similar for mortality; although not statistically significant, the odds ratio was numerically less than one (OR = 0.47, 0.20 – 1.13) (Figure 24).

Figure 24: Positioning: Prone vs. supine positioning, mortality outcomes.

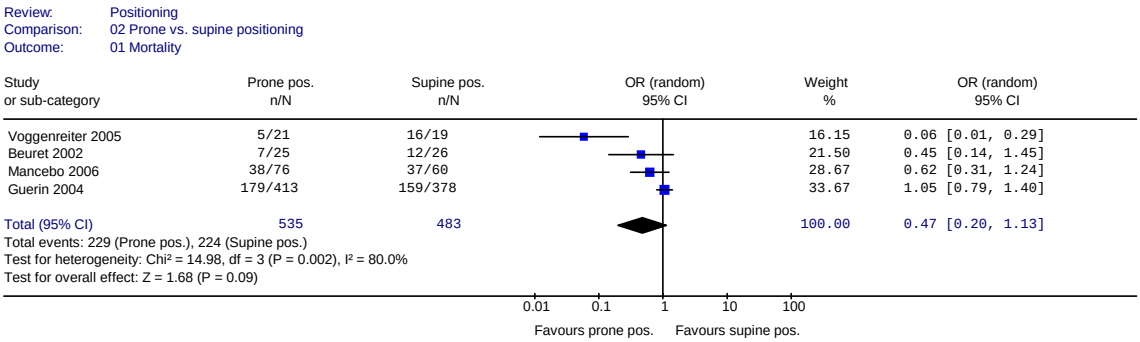


Table 21: Outcomes Gastrointestinal Interventions: Prone vs. supine positioning

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Beuret 2002	Prone vs. supine positioning	25/ 26	0.40 [0.11, 1.41]	0.45 [0.14, 1.45]	-1.90 [-9.75, 5.95]	-2.90 [-13.45, 7.65]
Guerin 2004	Prone vs. supine positioning	413/ 378	0.82 [0.58, 1.14]	1.05 [0.79, 1.40]	-0.40 [-1.55, 0.75]	
Mancebo 2006	Prone vs. supine positioning	76/ 60	1.28 [0.51, 3.20]	0.62 [0.31, 1.24]		1.40 [-5.73, 8.53]
Voggenreiter 2005	Prone vs. supine positioning	21/ 19	0.42 [0.12, 1.53]	0.06 [0.01, 0.29]	-9.00 [-25.21, 7.21]	
Total:			**0.79 [0.59, 1.07] (f)**	**0.47 [0.20, 1.13] (r)**	**-0.47 [-1.61, 0.66] (f)**	**0.05 [-5.86, 5.96] (f)**

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

c) Semirecumbent vs. supine positioning

Pneumonia

Three trials studied the impact of semirecumbent positioning as opposed to supine positioning on pneumonia rates.[94, 172, 364] The result did not achieve significance (p=0.06), although the odds ratio was less than one (OR = 0.40, 0.15 – 1.04) (Figure 25).

A fourth trial, combining semirecumbency with subglottic secretion drainage was integrated in a separate analysis, with the result for pneumonia rates remaining non-significant (p=0.07) (OR=0.47, 0.21-1.06) (Figure 26).[129] Potential confounding due to subglottic secretion drainage is minimal, since results for this intervention proved to be highly significant in our analysis (3.8.a)), and would have led to more positive results than negative ones, as opposed to our case.

Figure 25: Positioning: Semirecumbent vs. supine positioning, pneumonia outcomes, analysis I.

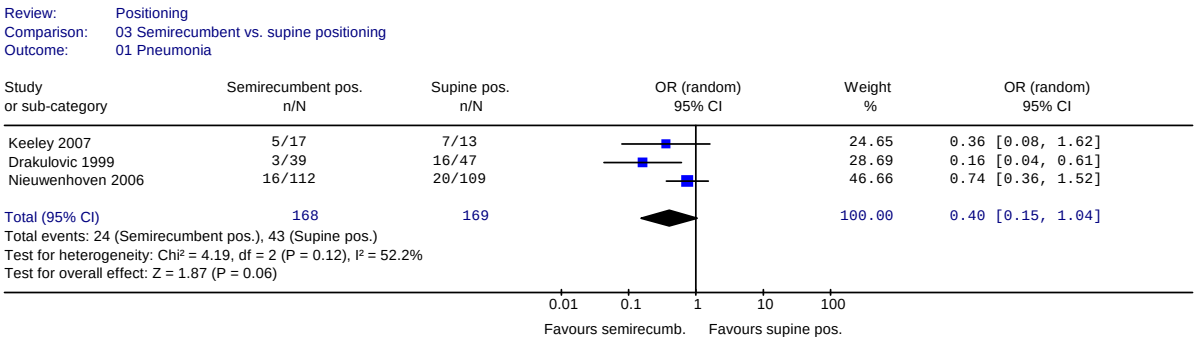
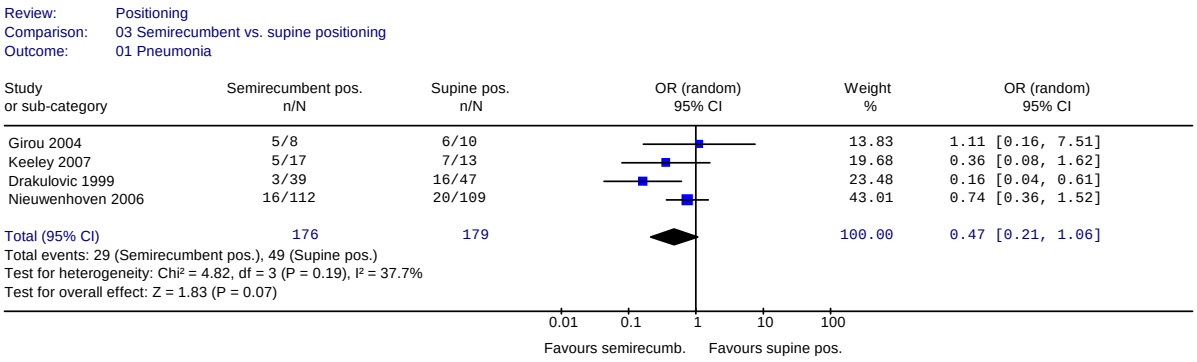


Figure 26: Positioning: Semirecumbent vs. supine positioning, pneumonia outcomes, analysis II.



Mortality

Mortality rates were not influenced by the manner in which patients were positioned (OR = 0.92, 0.54 – 1.56) (Figure 27).

Figure 27: Positioning: Semirecumbent vs. supine positioning, mortality outcomes.

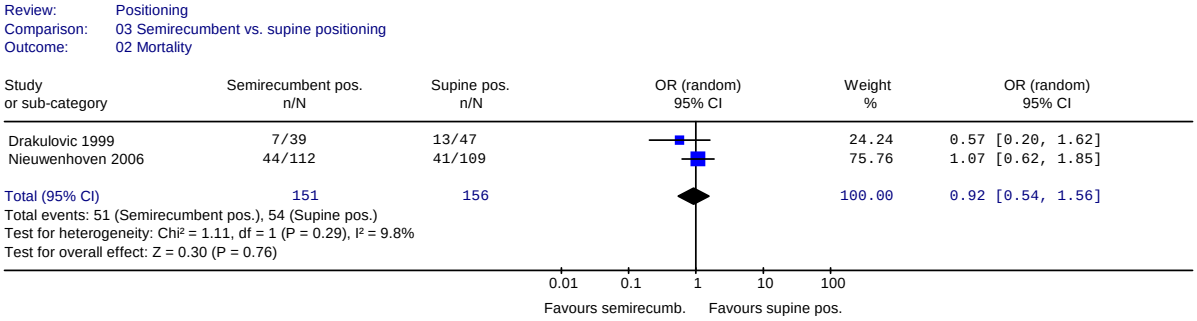


Table 22: Outcomes Positioning: Semirecumbent vs. supine positioning

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	**Length of ICU stay WMD [95% CI]**
Keeley 2007	Semirecumbent vs. supine positioning	17/ 13	0.36 [0.08, 1.62]			
Drakulovic 1999	Semirecumbent vs. supine positioning	39/ 47	0.16 [0.04, 0.61]	0.57 [0.20, 1.62]	-1.10 [-3.89, 1.69]	-0.40 [-3.57, 2.77]
Nieuwenhoven 1999	Semirecumbent vs. supine positioning	112/ 109	0.74 [0.36, 1.52]	1.07 [0.62, 1.85]		
Total analysis I:			**0.40 [0.15, 1.04] (r)**	**0.93 [0.58, 1.51] (f)**		
Girou 2004	Semirecumbency + subglottic secretion drainage	8/ 10	1.11 [0.16, 7.51]			
Total analysis II:			**0.47 [0.47, 0.21, 1.06] (r)**			

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

3.8. ET Tubes

a) Subglottic secretion drainage

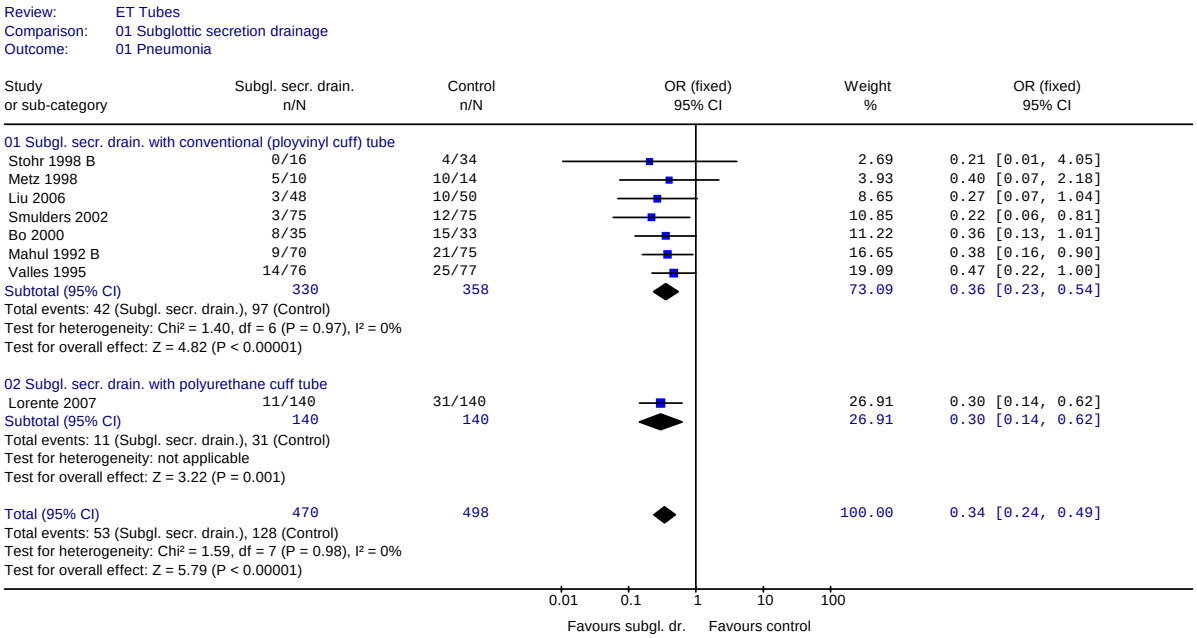
Pneumonia

Eight trials ventilating their patients using a special endotracheal tube that allows subglottic secretion drainage through a lumen above the tube cuff met our inclusion criteria.[36, 212, 218, 227, 241, 319, 323, 359]

Lorente et al. additionally used a newly designed polyurethane cuff tube and this was therefore analyzed in a separate subgroup.[218]

Overall, VAP rates were significantly decreased in patients undergoing subglottic secretion drainage (OR = 0.34, 0.24 – 0.49) (Figure 28), as was also true for both of the subgrous.

Figure 28: ET Tubes: Subglottic secretion drainage, pneumonia outcomes

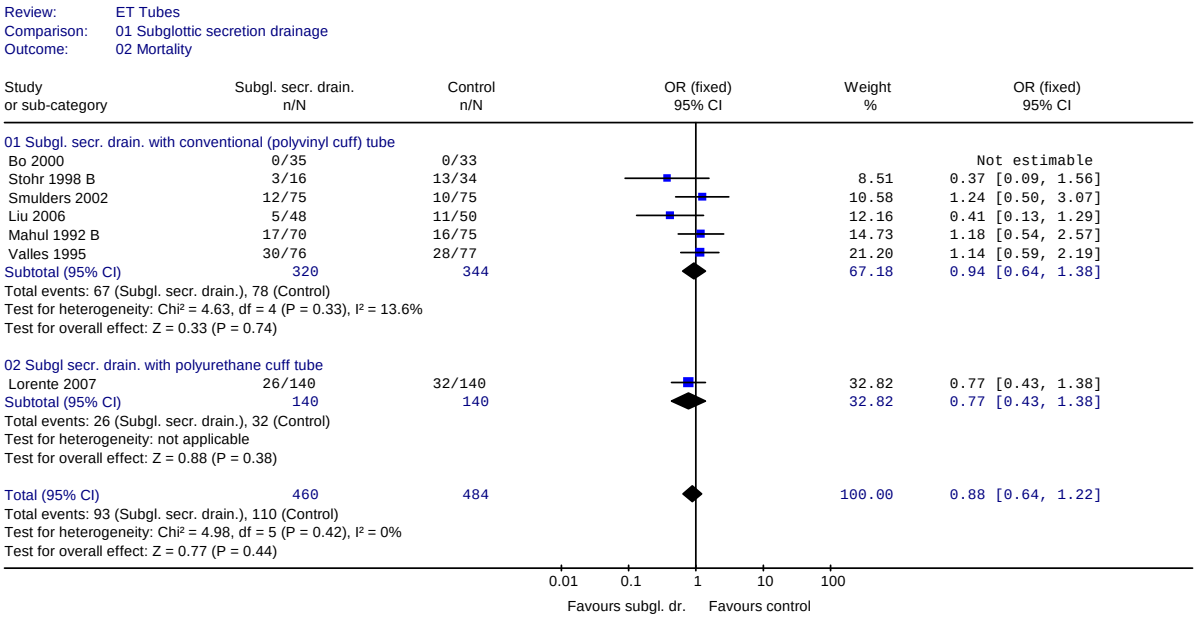


Mortality

Overall, there was no evidence for an effect regarding mortality rates (OR = 0.88, 0.64 – 1.22) (Figure 29).

In the second subgroup, combining subglottic secretion drainage with a polyurethane cuff tube, the OR was numerically less than one, without reaching statistical significance (OR = 0.77, 0.43 – 1.38).

Figure 29: ET Tubes: Subglottic secretion drainage, mortality outcomes



Duration of MV/ Length of ICU stay

With abstractable data of only three trials, no significant difference could be shown in the duration of MV, although the weighted mean difference was numerically less than zero (WMD = -1.10, -2.49 – 0.30) (Table 23).

The length of ICU stay was significantly decreased considering the two trials assessing this outcome (WMD = -2.76, from -4.48 to -1.04) (Table 23).

Table 23: Outcomes ET Tubes: Subglottic secretion drainage

Study ID	***Intervention***	***Treatment/ Control group***	***Pneumonia OR [96% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Stohr 1998	Subglottic secretion drainage	32/ 34	1.06 [0.06, 17.77]	0.37 [0.12, 1.15]		
Metz 1998	Subglottic secretion drainage	10/ 14	0.40 [0.07, 2.18]			
Liu 2006	Subglottic secretion drainage	48/ 50	0.27 [0.07, 1.04]	0.41 [0.13, 1.29]	0.00 [-4.83, 4.83]	
Smulders 2002	Subglottic secretion drainage	75/ 75	0.22 [0.06, 0.81]	1.24 [0.50, 3.07]	-1.30 [-2.88, 0.28]	-3.00 [-4.86, -1.14]
Bo 2000	Subglottic secretion drainage	35/ 33	0.36 [0.13, 1.01]	Not estimable		
Mahul 1992 B	Subglottic secretion drainage	70/ 75	0.38 [0.16, 0.90]	1.18 [0.54, 2.57]		
Valles 1995	Subglottic secretion drainage	76/ 77	0.47 [0.22, 1.00]	1.14 [0.59, 2.19]		
Subtotal			*0.36 [0.23, 0.54]*	*0.94 [0.64, 1.38]*	*-1.18 [-2.67, 0.32]*	
Lorente 2007	Subglottic secretion	140/ 140	0.30 [0.14, 0.62]	0.77 [0.43, 1.38]	-0.60 [-4.33, 3.13]	-1.40 [-5.84, 3.04]

	drainage				
Total:		**0.34 [0.24, 0.49] (f)**	**0.88 [0.64, 1.22] (f)**	**-1.10 [-2.49, 0.30] (f)**	**-2.76 [-4.48, -1.04] (f)**

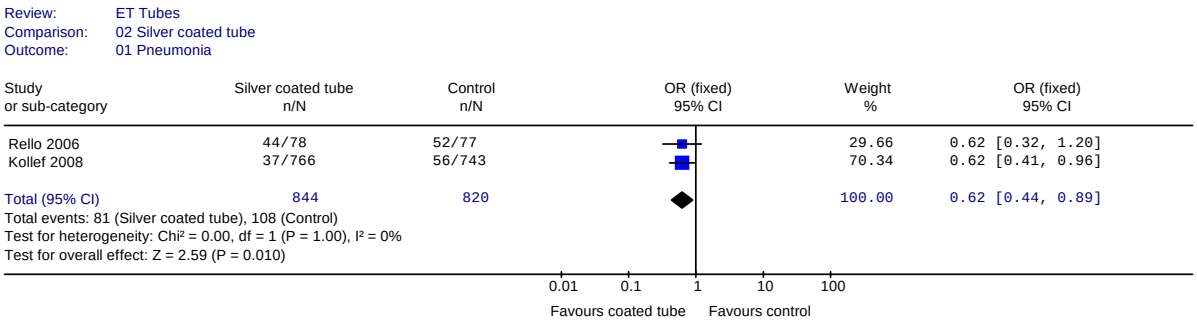
Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

b) Silver-coated tube

Pneumonia

In two recently published trials comprising more than 1600 patients, the influence of a silver coated ET tube on VAP rates was investigated.[186, 284] Overall, pneumonia rates were significantly reduced (OR=0.62, 0.44 – 0.89) (Figure 30) (Table 24).

Figure 30: ET Tubes: Silver coated tube, pneumonia outcomes.



Mortality/ Duration of MV

Data of the two secondary outcomes, mortality and duration of MV, could only be abstracted from the trial of Rello et al. and were not significantly different, although the weighted mean difference for the duration of MV was larger than zero (WMD = 1.80, -0.04 – 3.64) (Table 24).

Table 24: Outcomes ET Tubes: Silver coated endotracheal tube

Study ID	***Intervention***	***Treatment/ Control group***	***Pneumonia OR [96% CI]***	***Mortality OR [95% CI]***	***Duration of MV WMD [95% CI]***	Length of ICU stay WMD [95% CI]
Rello 2006	Silver coated endotracheal tube	78/ 77	0.62 [0.32, 1.20]	1.29 [0.62, 2.69]	1.80 [-0.04, 3.64]	
Kollef 2008	Silver coated endotracheal tube	766/ 743	0.62 [0.41, 0.96]			
Total:			**0.62 [0.44, 0.89]**			

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

c) Automated control of endotracheal tube cuff pressure

Pneumonia/ Mortality

Whether the automated control of the tube cuff pressure had an impact on VAP rates was studied by one recently published trial.[357] An effect on VAP rates could not be significantly proven, although the odds ratio was numerically less than one (OR = 0.69, 0.32 – 1.47) (Table 25).

Although the odds ratio was larger than one, mortality rates were not significantly different (OR = 1.40, 0.70 – 2.77).

Table 25: Outocmes ET Tubes: Automated control of endotracheal tube cuff pressure

Study ID	*Intervention*	*Treatment/ Control group*	*Pneumonia OR [96% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Valencia 2007	Automated control of endotracheal tube cuff pressure	73/ 69	0.69 [0.32, 1.47]	1.40 [0.70, 2.77]		-2.58 [-4.31, -0.85]

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

3.9. Non-classifyable preventive strategies

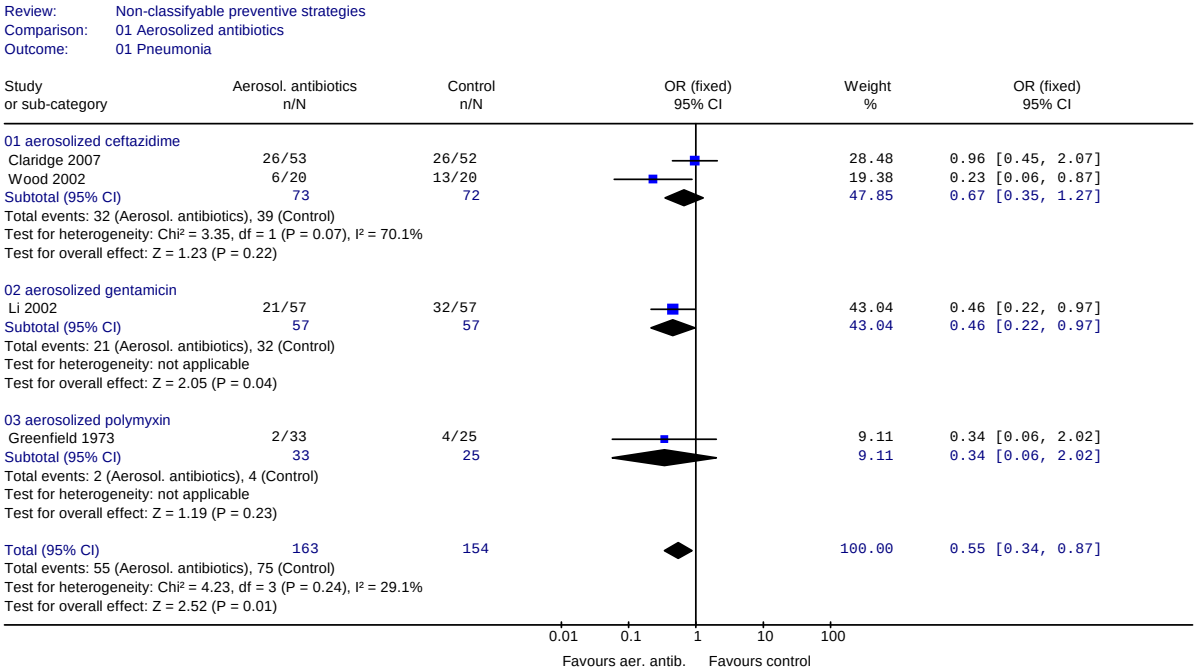
a) Aerosolized antibiotics

Pneumonia

Four trials applying the aerosolized antibiotics ceftazidime[62, 379], gentamicin[209] and polymyxin[134] to the lungs met our inclusion criteria.

The overall outcome indicates a significant reduction of VAP rates in patients receiving aerosolized antibiotics (OR = 0.55, 0.34 – 0.87) (Figure 31).

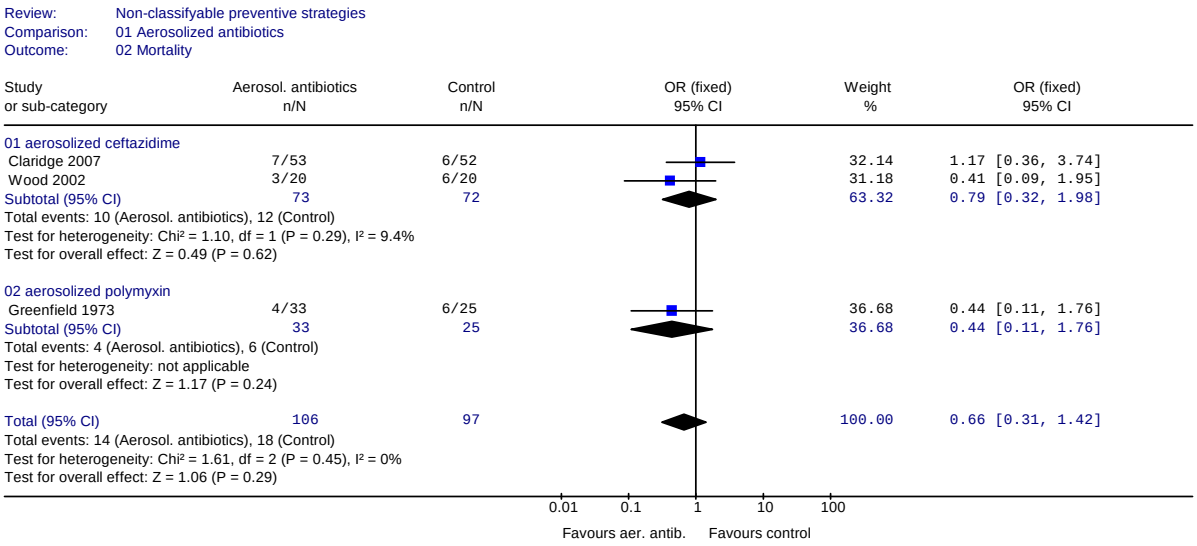
Figure 31: Non-classifyable preventive strategies: Aerosolized antibiotics, pneumonia outcomes



Mortality

The effect of aerosolized antibiotics on mortality rates failed to reach statistical significance, although the odds ratio was numerically less than one (OR = 0.66, 0.31 – 1.42) (Figure 32).

Figure 32: Non-classifyable preventive strategies: Aerosolized antibiotics, mortality outcomes

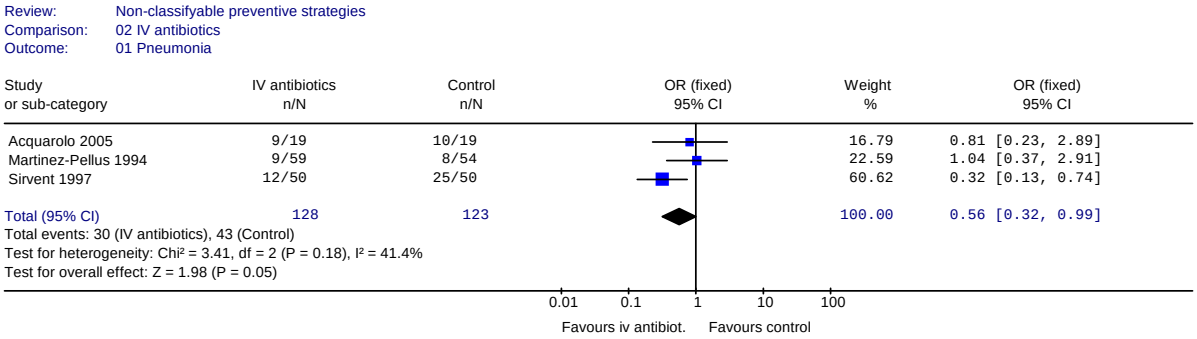


b) IV antibiotics

Pneumonia

Data about the influence of systemic antibiotic prophylaxis on VAP rates was available from three trials whose antibiotic regimens consisted of a three-day application of ampicillin-sulbactam[6], four-day administration of cefotaxime[235], and two doses of cefuroxime[315]. There was evidence for a significant treatment effect of systemic antibiotic prophylaxis (OR = 0.56, 0.32 – 0.99) (Figure 33).

Figure 33: Non-classifyable preventive strategies: IV antibiotics, pneumonia outcomes



Mortality/ Duration of MV

There was no significant difference in mortality rates (OR = 1.14, 0.59 – 2.18) (Table 26). The duration of MV was significantly increased in the group receiving systemic antibiotic prophylaxis (WMD = 1.70, -0.04 – 3.44).

c) Pharyngeal vs. tracheal decontamination

Pneumonia/ Mortality/ Duration of MV/ Length of ICU stay

Whether a decontamination regimen was administered to the pharynx or directly into the trachea had no significant impact on pneumonia (OR = 1.93, 0.32 – 11.43) (Table 26).[236]

There was no effect on mortality rates (OR = 0.72, 0.21 – 2.48). Neither the results for the duration of MV (WMD = 3.00, -0.32 – 6.32) nor the length of ICU stay (WMD = 2.00, -1.83 – 5.83) were statistically significant, although the weighted mean differences for both of the outcomes were larger than zero.

d) Systemic search for maxillary sinusitis

Pneumonia/ Mortality

Whether the search for maxillary sinusitis in nasotracheally intubated patients, in order to reduce cross infection, had an impact on the occurrence of VAP was studied by one large randomized controlled trial.[157] Using a log-rank test the authors were able to describe a significant reduction in the rate of VAP (relative risk 0.61, p=0.02 log rank test) and in the morality rate (relative risk 0.71, p=0.03 logrank test). However, this meta-analysis was using a binary approach that does not take the time course into consideration and therefore the odds ratio for the VAP rate (0.67, 0.41 – 1.08) and mortality rates (OR = 0.68, 0.46 – 1.02) failed statistical signficance (Table 26).

e) Chest physiotherapy

Pneumonia/ Mortality

A study of chest physiotherapy demonstrated a significant reduction of VAP (OR = 0.14, 0.03 – 0.70); however, there was no evidence of a treatment effect regarding mortality rates (OR = 1.20, 0.33 – 4.42) (Table 26).[258]

f) Manual lung hyperinflation and postural drainage

Pneumonia/ Mortality

A trial studying the effects of manual lung hyperinflation and postural drainage showed neither a significant effect on VAP rates (OR=0.79, 0.16-4.00) nor on mortality rates (0.20, 0.01-4.40) (Table 26).[257]

g) Granulocyte colony-stimulating factor

Pneumonia

A study administering two different doses of a granulocyte-stimulating factor failed to show a significant effect on the incidence of pneumonia (OR = 2.15, 0.38 – 12.06) (Table 26).[143]

h) Decontamination of the subglottic area

Pneumonia/ Mortality/ Length of ICU stay

Decontamination of the subglottic area with nonabsorbable antibiotics led to a significant reduction of pneumonia rates in the trial implementing this regimen (OR = 0.17, 0.05 – 0.56) (Table 26).[273]

Whereas the results for mortality rates were statistically not significant, the length of ICU stay in the study group was significantly reduced (WMD = -7.00, -10.78 - -3.22) (Table 26).

i) Early PEEP

Pneumonia/ Mortality

The administration of early PEEP, studied by two trials, demonstrated significantly decreased VAP rates (OR = 0.41, 0.18 – 0.91), but had no impact on mortality rates (OR = 0.96, 0.54 – 1.71) (Table 26).[231, 269]

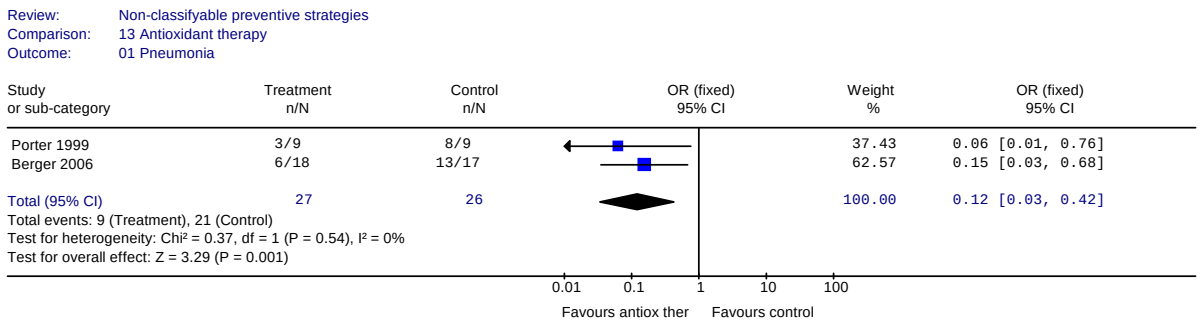
j) Antioxidant therapy

Pneumonia/ Mortality/ Length of ICU stay

Two small trials demonstrated a significant reduction of pneumonia rates by administering two different regimen of antioxidant therapy (OR = 0.12, 0.03 – 0.42) (Figure 34) (Table 26).[24, 274]

In the trial where data on mortality and the length of ICU stay was abstractable, no deaths occurred. The length of ICU stay was significantly reduced (WMD = -13.80, -21.52 - -6.09) (Table 26).

Figure 34: Non-claasifyable preventive strategies: Antioxidant therapy, pneumonia outcomes.



k) Endonasal mupirocin

Pneumonia

The effect of the administration of endonasal mupirocin on MRSA pneumonia was not significant (OR = 0.54, 0.11 – 2.58) (Table 26).[91]

Table 26: Outcomes non-classifyable preventive strategies

Study ID	*Intervention*	*Study/ Control group*	*Pneumonia OR [95% CI]*	*Mortality OR [95% CI]*	*Duration of MV WMD [95% CI]*	Length of ICU stay WMD [95% CI]
Claridge 2007	Aerosolized ceftazidime	53/ 52	0.96 [0.45, 2.07]	1.17 [0.36, 3.74]		
Greenfield 1973	Aerosolized polymyxin	33/ 25	0.34 [0.22, 0.97]	0.44 [0.11, 1.76]		
Li 2002	Aerosolized gentamicin	57/ 57	0.46 [0.22, 0.97]			
Wood 2002	Aerosolized ceftazidime	20/ 20	0.23 [0.06, 0.87]	0.41 [0.09, 1.95]	-2.00 [-9.46, 5.46]	-2.00 [-9.13, 5.13]
Total:			**0.55 [0.34, 0.87] (f)**	**0.66 [0.31, 1.42] (f)**		
Acquarolo 2005	Iv antibiotics	19/ 19	0.07 [0.00, 1.32]	0.80 [0.22, 2.95]	-0.70 [-5.94, 4.54]	0.20 [-5.66, 6.06]
Martinez-Pellus 1994	Iv antibiotics	59/ 54	1.04 [0.37, 2.91]	1.05 [0.35, 3.13]	2.00 [0.15, 3.85]	1.00 [-2.87, 4.87]
Sirvent 1997	Iv antibiotics	50/ 50	0.32 [0.13, 0.74]	1.54 [0.53, 4.42]		-3.00 [-6.77, 0.77]
Total:			**0.44 [0.24, 0.80] (f)**	**1.14 [0.59, 2.18] (f)**	**1.70 [-0.04, 3.44] (f)**	**-0.83 [-3.29, 1.62] (f)**
Martinez-Pellus 1996	Pharyngeal vs. tracheal decontamination	31/ 28	1.93 [0.32, 11.43]	0.72 [0.21, 2.48]	3.00 [-0.32, 6.32]	2.00 [-1.83, 5.83]
Holzapfel 1999	Systemic search for maxillary sinusitis	199/ 200	0.67 [0.41, 1.08]	0.68 [0.46, 1.02]	1.50 [-1.32, 4.32]	1.90 [-0.95, 4.75]
Ntoumenopoulos 2002	Chest physiotherapy	24/ 36	0.14 [0.03, 0.70]	1.20 [0.33, 4.42]		
Ntoumenopoulos 1998	Manual lung hyperinflation and postural drainage	22/ 24	0.79 [0.16, 4.00]	0.20 [0.01, 4.40]	0.90 [-1.76, 3.56]	0.60 [-2.41, 3.61]
Heard 1998 A	Granulocyte colony-stimulating factor	13/ 8	1.27 [0.10, 16.81]			
Heard 1998 B	Granulocyte colony-stimulating factor	14/ 9	3.2 [0.30, 34.59]			
Total:			**2.15 [0.38, 12.06] (f)**			
Pneumatikos 2002	Decontamination of subglottic area	31/ 30	0.17 [0.05, 0.56]	0.63 [0.18, 2.27]	-1.00 [-3.06, 1.06]	-7.00 [-10.78, -3.22]
Manzano 2008	Early PEEP	64/ 63	0.30 [0.11, 0.84	1.24 [0.57, 2.71]		
Pepe 1984	Early PEEP	44/ 48	0.70 [0.18, 2.67]	0.70 [0.29, 1.67]		
Porter 1999	Antioxidant therapy	9/ 9	0.06 [0.01, 0.76]			-13.80 [-21.52, -6.09]
Berger 2006	Antioxidant therapy	18/ 17	0.15 [0.03, 0.68]			

Total:		**27/ 26**	**0.12 [0.03, 0.42] (f)**
Di Filippo 1999	Endonasal mupirocin	24/ 24	0.54 [0.11, 2.58]

Abbreviations: OR: odds ratio, CI: confidence interval, WMD: weighted mean difference, (f): fixed effects model, (r): random effects model.

4. Discussion

The results of this meta-anylsis and systematic review suggest that it is possible to reduce the rate of VAP by certain mechanical, chemical and antibiotic strategies.

Of the five intervention groups, the interventions that were statistically significant and were supported by more than one study are non-invasive ventilation, the aspiration of subglottic secretions, the administration of antibiotics, either in form of selective decontamination of the digestive tract (SDD), administered as an aerosol to the lungs or administered intravenously. The same is true for oral care with antiseptics, positioning of the patient with rotational therapy, sucralfate (instead of H_2-antagonists) and antioxidant therapy.

Various interventions proved to be effective, but were represented by only one study. These included antioxidant therapy, chest physiotherapy, trace element supplementation, subglottic decontamination, early gastrostomy and enteral (instead of parenteral) nutrition.

The results and their clinical relevance are discussed below. All interventions are evaluated in regard to earlier recommendations for its usage by the current VAP prevention guidelines of different expert groups. The exact guideline recommendations are listed in the appendix of this document (Table 54). The quoted guidelines are the current CDC guidelines for the prevention of health-care associated pneumonia[331], the guidelines published by the American Thoracic Society[3], the original and updated version by a Canadian expert group[92, 248], of a European expert group[340] and of an American expert group[67].

4.1. Oral Care

a) Antiseptic decontamination

Our results show a significant reduction of pneumonia rates in long-term ventilated patients receiving oral decontamination with antiseptics, including chlorhexidine, iseganan and povidone-iodine. There was no evidence for an effect on mortality rates.

In their central guidelines for the prevention of VAP and nosocomial pneumonia, the CDC and the American Thoracic Society recommend chlorhexidine use for cardiac surgery only.[3, 331] According to their statement there is no evidence for a benefit in the general ICU population, what is in contrast to our results. Their recommendations are mainly based on two randomised controlled trials showing a positive effect on VAP rates in cardiac surgery patients.[89, 161], whereas other trials identified by our search remain unmentioned. Nevertheless, in the latest guideline on

VAP prevention of the Canadian expert group, the authors state that the use of chlorhexidine and povidone-iodine should be considered, whereas they do not recommend the use of iseganan.[248]

Of the three agents, chlorhexidine is the most intensively studied, being a promising antiseptic agent, with resistance rates of pathogens that are lower than those developing with antibiotic decontamination.[32, 318, 322] Recently, three metaanalyses were published and also showed a significant reduction of pneumonia rates by chlorhexidine application.[54, 59, 181] As opposed to our anaylsis though, cardiac surgery patients were included in their calculations. This may have led to an overinterpretation of their results, since VAP per definition derives from long-term ventilation, which is not the case in most of cardiac surgery patients.

Iseganan and povidone-iodine have each been studied by one recently published trial.

In a large multicenter study, Kollef et al. did not show a significant reduction of pneumonia or mortality rates by applying a solution of iseganan to the buccal cavity.[192] Although low resistance rates make iseganan an attractive agent[247], taking the results of this high quality and well powered trial into account, currently there is no evidence for a reduction of VAP rates with iseganan use.

The application of a povidone-iodine solution to the nares and pharynx in a study by Seguin et al. led to a highly significant reduction of pneumonia rates in a population of head injury patients.[306] Due to the small sample size and the limited patient population of this study, these results should be reproduced in a large randomized controlled trial in order to evaluate the effect in a general ICU population. If results are positive, povidone-iodine could be considered a powerful oral antiseptic agent in the prevention of VAP.

Even though our inclusion criteria were strict, some limitations to our results have to be mentioned.

First, studies were rather heterogeneous in their designs, applying chlorhexidine in varying concentrations, intervals and application manners. The study of Koeman et al. was the only study with a significant reduction of pneumonia rates in our statistical model.[179] At the same time, it was one of two studies with the highest concentrations and the highest frequency of chlorhexidine application, including the buccal cavity and not teeth and gingiva alone, as in other studies.

Secondly, there were two studies that were included in other meta-analyses and would have met our inclusion criteria.[133, 225] However, in the original publications important data on VAP rates was missing, and the data reported in those meta-analyses was inconsistent.[54, 59, 181] Thus, we

made several attempts for clarification from the primary authors of the studies but did not get verification that allowed us to included any data from these two studies.

Overall, oral decontamination with antiseptics, especially chlorhexidine, seems to be an effective and safe strategy for the prevention of VAP.

4.2. Airway Management

a) Tracheostomy

Thus far no clear recommendations have been formulated regarding the timing of tracheostomy in ventilated patients, by various reviews and the VAP prevention guideline of the Canadian expert group.[92, 135, 144, 222, 248] This is mainly due to the lack of good quality data and prospectively designed studies. In their evidence-based guidelines on weaning and discontinuing ventilatory support, MacIntyre et al. therefore recommend early tracheostomy only if there is a benefit for the patient, as there is less sedation, lower respiratory resistance, a psychological benefit and enhanced mobility.[222]

Although more recently conducted RCTs included in our meta-analysis have not been considered by these guidelines, the question of when to perform a tracheostomy can not be completely clarified with the evidence available.[19, 34, 45, 298, 302] The data seems to show a trend towards a reduction of pneumonia rates in early tracheostomized patients. Nevertheless, the differing time points for early and late tracheostomy or prolonged intubation between the studies as a potential confounder have to be considered. Also, whereas most of the studies were nonsignificant in their results regarding VAP, two studies did show a significant reduction of pneumonia rates.[291, 298] Hence it could be possible, that the sample size is too small to demonstrate a significant overall treatment effect of early tracheostomy.

Early tracheostomy is considered superior to prolonged intubation because mortality rates were significantly reduced in the subgroup of early versus late tracheostomy. The length of ICU stay was significantly reduced in both of the studied subgroups.

At this point there is no clear evidence for a clinically relevant effect of early tracheostomy on VAP. Nevertheless, early tracheostomy performed on days 1-8 seems to be favourable considering a trend in the reduction of pneumonia and mortality rates, the duration of MV and the length of ICU stay.

b) Weaning

Our data demonstrated a significant reduction of pneumonia and mortality rates in patients that were extubated early and then ventilated with non-invasive pressure ventilation. This is in accordance with the fact that the ET tube is considered to be one of the greatest risk factors for VAP by the authorities and experts in the field; therefore, it should be removed as soon as possible.[92, 135, 144, 222, 248] By removing the tube, natural defense mechanisms and clearing of the airway is made possible, and the collection of contaminated secretions above the tube cuff and its microleakage are prevented. A European expert group has proposed to further invastigate the benefit of non-invasive ventilation for VAP prevention in 2001[340] and the CDC and the American Thoracic Society have recommended its implementation as soon as possible.[3, 331]

Even though two of the included trials strictly speaking did not perform weaning, since they randomized their patients to either non-invasive or invasive MV from the beginning, without having performed invasive MV with an endotracheal tube before, we included them in this group due to the equivalence of the performed intervention in critically ill patients.[13, 69] The fact that by performing a sensitivity analysis excluding these trials, results for weaning with non-invasive MV regarding VAP rates remain highly significant ($p<0.001$) proves that no bias was introduced by the inclusion of these two trials.

The implementation of a weaning protocol in the study of Marelich et al. failed to reach statistical significance in reducing pneumonia rates in comparison with physician directed weaning.[232] Still, it seems reasonable to implement weaning protocols in ICUs due to the advantages that have been shown in earlier trials and the advantages stated by clinical practice guidelines.[103, 104, 190, 222] The American Thoracic Society also recommends the implementation of weaning protocols in their prevention guidelines.[3]

Considering our results and the advantages explained above, non-invasive MV should be implemented in the weaning process whenever possible.

c) Closed vs. open endotracheal suctioning

According to our data, whether patients were suctioned by a closed or open method had no significant impact on VAP. Our results agree with those of three recently published meta-analyses on this issue and the CDC-guidelines and those of the European expert group, that do not recommend one method or the other for preventing VAP.[166, 307, 328, 331, 340, 372] Nevertheless, a Canadian expert group has recommended closed suctioning in their original and updated guidelines.[92, 248] Although we identified one additional RCT in our analysis which showed a

significant reduction of pneumonia rates by closed suctioning, it did not lead to a change of the overall outcome and was a trial of limited quality.[207] The results for the duration of MV, which was significantly increased by the closed suctioning technique, could also have limited validity, since it is basically resembled by one small study with a weight of 99.47%.[339]

The advantage of the closed suctioning catheter system is an unchanged lung volume, alveolar recruitment, oxygenation and lower levels of environmental contamination[52, 64, 226] , but on the other hand there is evidence for an increased microbial colonization of the catheter surface and the lower respiratory tract.[88, 121, 339] The closed system seems to be more expensive than the open system, although there are arguments for the contrary if the catheter changes are limited to the clinically necessary.[92, 216, 220]

Taking into account our results and the literature reports, closed suctioning does not appear to be superior to the open suctioning technique in the prevention of VAP.

d) Daily vs. no daily changes of in-line suction catheters

Our results gave no reason to assume that extended use of suction catheters increases pneumonia rates. The CDC and the European expert group give no recommendation regarding this issue, and in a recently published VAP prevention guideline, changes with every new patient have been recommended.[248, 331, 340] As mentioned above, there are studies reporting a contamination of in-line suction catheters[88, 120, 339] but the effect of changing suction catheters daily or at longer intervals doesn't seem to have an effect on pneumonia rates. To change suction catheters less frequently in order to save costs therefore seems feasible and safe.

e) Heat and moisture exchanger (HME) vs. heated humidifier (HH)

When comparing HMEs and HHs in VAP prevention various metaanalyses and guidelines now recommend the use of HMEs[70, 92, 180]. In contrast, most authors don't recommend one humidification device or the other.[3, 67, 248, 255, 308, 331, 340] One argument in favour of HMEs is to keep away contaminated condensation of the wire circuits that could otherwise reach the patient's trachea and provoke infection[233]. However, this has been alleviated by newer HH devices with heated wire circuits that reduce the condensate to a considerable degree. And since it is normally the patient's bacteria that contaminates the circuits and not environmental germs, it is not clear whether the contaminated condensate plays a role in the development of VAP.[95, 146]

None of the subgroups showed a significant reduction of VAP rates with any of the devices. Only two single studies reached statistical significance, one using a HME, the other using a HH:

Kirton et al. demonstrated a significant reduction of pneumonia rates in patients ventilated with a HME, even though they were using heated wire circuits in their HH system.[176] In the latest published study, Lorente et al. used an auto-feed chamber in addition to heated wire circuits to further reduce bacterial contamination, leading to a highly significant reduction of pneumonia rates compared to the group ventilated with a HME.[217] Whether this auto-feed chamber is a new device with the ability to significantly reduce contamination and pneumonia rates should be further evaluated in another RCT.

HMEs can persuade with less care provider time and cost savings[176, 188], and since at this point none of the humidification systems seem to lead to a better outcome in VAP rates the choice should be made by individual considerations.

f) Extended use of heat and moisture exchangers (HME)

An extended use of HME for up to one week can save costs and seems to be a feasible and safe option according to our data. This is in accordance with recommendations of the current prevention guidelines.[67, 92, 248, 331] Our results show a trend towards less VAP rates by less changes of the HME, while there was no significant impact on the secondary outcomes.

In a study by Boisson et al. contamination rates and performance of a 48 hour versus a daily change of HME as recommended by the manufacturers were compared. A contamination of the ventilator's side of the HME after 48 hours of use could not be found and a change in the HME's performance after 48 hours was not witnessed, either.[37] If these results are also true for a use of up to 7 days needs to be proven, but seems to be likely due to our results.

g) Components of heat and moisture exchanger (HME)

There have been attempts to improve the performance of HME by changing some of the filter components, an aspect that has not been evaluated by the guidelines so far. According to the lack of effect obvious from our results, at this point there is no evidence for superiority of one component over others.

h) Change of ventilator circuits

In addition to RCTs considered by earlier guidelines and reviews[3, 67, 92, 248, 331, 340], we have identified new evidence[43, 75, 215] that strengthens earlier recommendations to only change ventilator circuits when they are malfunctioning or visibly soiled.

Our data shows that in a study by Craven et al., patients receiving circuit changes at a two day interval instead of daily had a significantly lower VAP rate. [75] It was therefore questioned, whether by changing the circuits, the airway could be contaminated with environmental bacteria.

Even though in none of the other studies a less frequent change of the circuits, with change-intervals of up to seven days, led to a significant reduction of pneumonia or mortality rates, not changing circuits frequently seemed to have no negative impact on the development of VAP. Furthermore, by changing circuits less frequently costs and workload can be reduced.[147, 199]

i) Heated vs. non-heated wire circuits

Even though we mentioned earlier that heated wire circuits are believed to reduce VAP rates by partially hindering the formation of contaminated condensation in the circuits, there was no evidence for a reduction of pneumonia rates in the study of Branson et al.[47] Whether there is a true lack of effect or if this was due to the small sample size of this study, needs to be proven by larger trials. As mentioned above, it might also be that the pathogenic role of the condensates are overestimated.[95, 146] None of the guidelines has evaluated this detail in the airway management strategy and its role for VAP prevention so far.

j) Oro- vs. nasotracheal intubation

Based on the only study from Holzapfel et al. no clear statement can be made as to whether oro- or nasotracheal intubation leads to lower VAP rates.[158] Although this trial is the only one on this issue, orotracheal intubation has widely been recommended by current guidelines as the preferable way of intubation.[3, 92, 248, 331, 340] This is due to the evidence that although airway complications might occur more often in orally intubated patients, maxillary sinusitis is a frequent complication in nasotracheally intubated patients, and should therefore be considered a reason to choose the oral route of intubation.[16, 242, 294, 303]

k) Bacterial filter

According to the nonsignificant results of Lorente et al. a recommendation for the use of bacterial filters to prevent VAP does not seem accurate. [219] Of the current guidelines, the CDC gives no recommendation, and another expert group does not recommend its usage.[248, 331]

4.3. Gastrointestinal Interventions

Although there is an ongoing debate about the relevance of the colonization of the upper intestinal tract for the development of VAP[3, 39, 341], various GI interventions, most importantly the selective decontamination of the digestive tract (SDD) and strategies to reduce the bacterial reflux load, are subject of VAP research.

a) Selective decontamination of the digestive tract (SDD)

Considering the highly significant result ($p < 0.001$) of our analysis there is no doubt about the effectiveness of SDD in reducing VAP rates. All of the slightly varying methods of SDD show a significant effect, with the application of topical agents to the buccal cavity and the GI tract with or without adding systemic antibiotics having the most significant treatment effect. Mortality rates could only be reduced significantly by combining topical application with systemic antibiotics.

Since Stoutenbeek et al. first published the concept of SDD in 1984[326], there have been more than fifty trials investigating its effects on infection rates and mortality in ICU patients. Eleven meta-analyses concerning SDD have been published in the last two decades , all reporting a significant reduction in pneumonia or other infections, and all but three reporting significant reductions of mortality rates, with two emphasizing the efficacy of topical and systemic antibiotics combined.[1, 77, 150, 162, 183, 210, 251, 301, 309, 310, 366] Our analysis is the first exclusively taking into account its effectiveness in mechanically ventilated ICU patients. Although there is as much evidence for a benefit as in the other fields of preventive strategies, the fear of provoking multiresistant bacterial strains keeps authorities and guidelines from recommending this strategy for routine use in ICU patients.[3, 67, 92, 248, 331, 340] There is an ongoing debate as to what extent resistance can develop and in which patients it should still be implemented. Also there are expert groups negating the risk to enforce resistancies.[311] Of the twenty-seven trials included in our analysis eight reported an increase in resistant bacteria strains, endorsing the concerns regarding SDD.[140, 204, 206, 279, 289, 304, 367, 377]

SDD is effective in preventing VAP, but it is in everyone’s interest to prevent the emergence of resistant bacterial strains, especially in ICUs, where the repercussions are severe. Therefore individual factors of the patient’s health status and resistance patterns in ICUs should decide whether the benefit for the patient outweighs the risk of potentiating resistance.

b) Selective decontamination of the digestive tract (SDD) with additional topical antibiotics

By adding mupirocin to the classic topical SDD regimen of tobramycin, polymyxin E and amphotericin B, Nardi et al. showed a significant decrease of pneumonia rates.[250] Their aim was to increase the effect of SDD due to the high rates of MRSA (60%) in Italian ICUs. Two other studies did find an alternative SDD regimen to be superior over the conventional one.

Since resistance patterns of bacterial strains differ from country to country, adding new substances to the traditional components might be a way to improve the effect of SDD, but the efficacy and safety has to be evaluated in detail for each of the new approaches.

c) Interventions to reduce the bacterial reflux load

Various interventions to decrease VAP rates by reducing the bacterial reflux load have been studied and were included in our analysis.

Among these, the type of stress ulcer prophylaxis is a central issue that has been evaluated by several reviews and meta-analyses with somewhat discordant results and recommendations for implementation.[3, 67, 72-74, 92, 331, 340, 348-350]

According to our data, sucralfate significantly decreased VAP-rates compared to H_2-antagonists. Results just failed to reach significance when sucralfate was compared with H_2-antagonists combined with antacids ($p=0.05$) and when compared with antacids alone ($p=0.06$), but a trend in the effectiveness can be assumed. Mortality rates were not influenced by the type of stress ulcer prophylaxis used.

The most adduced reason for concerns with preferring sucralfate over H_2-antagonists or antacids is the possible risk of a higher incidence of bleeding in patients treated with sucralfate. Of the trials included in our analysis, Cook et al. reported a significantly higher incidence of bleeding in the patient group receiving sucralfate compared to those receiving H_2-antagonists.[71] Since this large trial provides about half of the patient population in this comparator group, a higher incidence of bleeding has to be taken into account when clinicians decide to administer sucralfate for stress ulcer prophylaxis for prevention of VAP. Nevertheless, it has to be emphasized that none of the other trials reported an increase of bleeding in patients treated with sucralfate.

Of the other attempts to reduce the bacterial burden of the stomach only the performance of early gastrostomy in patients requiring enteral feeding in a study of Kostadima et al. showed

significant results in reducing VAP rates.[198] There was no significant effect on mortality, and so far, none of the current guidelines have evaluated early gastrostomy as a prevention strategy. When interpreting these results, the small sample size of only 41 patients has to be taken into account. Furthermore, gastrostomy as an invasive method is neither easy nor cheap to implement on a broad ICU population. Therefore, more data and an evaluation of risks and benefits is needed before it can be considered as a preventative strategy for VAP.

The application of enteral naloxone in patients under opioid analgesia in a trial of Meissner et al. just failed to reach statistical significance with p=0.05 and the confidence interval extending to 1.01.[237] Naloxone has been shown to increase gastric emptying, and given enterally it has a local but a limited systemic opioid-antagonistic effect due to a high hepatic first-pass metabolism.[115, 243] Meissner et al. showed that with enteral naloxone the suppressive effects of opioids on GI motility could be antagonized successfully and that the gastric tube reflux and pneumonia rates were significantly reduced.

So far, this is the only RCT of naloxone administered for antagonism of opioid effects in the GI tract and it has not been mentioned by any of the guidelines thus far. The mechanism of action of naloxone and its possible value for the prevention of VAP in patients under opioid analgesia sound very promising and more data of large RCTs would be helpful to evaluate its effects more reliably.

With the enteral administration of metoclopramide, Yavagal et al. hypothesized reduced pneumonia rates due to the antagonistic effect it has on dopaminergic D2 receptors of the upper GI tract.[142, 381] Even though by this interaction the pressure of the esophageal sphincter and gastric contractility is increased and therefore the gastroesophageal reflux supposedly declines, the authors could not demonstrate an effect neither on VAP rates in the subgroup included in our analysis, nor on pneumonia rates in a more general ICU population. Metoclopramide was mentioned, but not recommended by one guideline only.[67]

Of the other interventions intented to reduce the bacterial reflux load, none showed significant results in the reduction of VAP or mortality rates.

Intermittent as opposed to continuous enteral feeding, with the aim to decrease the gastric pH by not feeding the patient continuously, had no effect on the patient's pneumonia or mortality rates. Even though we did identify new evidence[224, 332], these results are in accordance with two of the guidelines evaluating intermittent feeding, giving no recommendation for its usage.[67, 331]

In regard to small intestinal versus gastric feeding and the acidification of enteral feeds there was no evidence for a treatment effect, although there was a trend in the results towards a reduction

of pneumonia rates. There was no recommendation for both of these strategies by two of the VAP prevention guidelines.[67, 331] Further research with sufficiently powered RCTs revealing a possible positive effect are needed.

Overall, the reduction of the bacterial reflux load with interventions that lower the gastric pH levels proved to be clinically relevant, and seem to be an essential part in the prevention of VAP. Nevertheless, not all interventions studied showed a significant treatment effect, partly due to a lack of appropriately powered RCTs.

d) H_2-antagonist vs. antacid

So far, a superiority of H_2-anatagonists over antacids regarding the prevention of VAP has not been proven, and no recommendation for the use of one of the two agents has been made by the current VAP prevention guidelines.

Comparing the antacid pirenzepine with the H_2-antagonist ranitidine, Tryba et al. could not prove a significant difference in the treatment effects of these agents, although there was a trend towards a better outcome with pirenzepine ($p=0.06$).[347] In another trial, Thomason et al. did not find a difference in the pneumonia rates of patients receiving antacids or ranitidine.[337] This study does not appear in the analysis of this comparator group for methodological reasons. Being a study with three intervention groups, it was already considered in the comparator group sucralfate vs. antacids and patients would have been included twice in the analysis.

Neither antacids nor H_2-antagonists were superior with regard of the prevention of VAP.

e) Enriched enteral nutrition

Although some of the studies administering enriched enteral nutrition had significant effects of both, de- and increased, VAP rates, the overall effect of our analysis was not significant. Due to the variable feeding formulas of the four trials summarized in this group the results need to be interpreted with caution.

Our results are in accordance with an earlier meta-analysis of immunonutrition of Heyland et al., who did not find a difference in infection and mortality rates in patients receiving enriched enteral nutrition.[154] Nevertheless, another meta-analysis of immunonutrition in critically ill patients, published by Montejo et al. reported a significantly lower rate of nosocomial pneumonia, taking eleven studies into account.[245] Discrepancies to our results can be explained by the different patient population, since patients in this meta-analysis did not have to be

mechanically ventilated, whereas our inclusion criteria were restricted to RCTs evaluating the outcome VAP.

Of the VAP prevention guidelines only Collard et al. made a statement regarding glutamine nutritional support, giving no recommendation for its administration.[67]

At this point there is not enough data, or data of too discrepant feeding formulas, to discard an effect of enriched enteral nutrition on VAP rates. If the beneficial effects of immunonutrition on various infectious outcomes in a population of critically ill patients reported by Montejo et al. can also be reached in the subgroup of mechanically ventilated patients, needs to be proven by sufficiently powered RCTs.

f) Early enteral nutrition

Our results of early enteral nutrition are difficult to interpret due to the diverging methods of implementation between the two trials. While Kompan et al.[193] compare early enteral feeding at admission to feeding after 24 hours, Ibrahim et al.[163] compare full caloric goals at day one or day five after admission. While in the study of Kompan et al. pneumonia rates were statistically significantly decreased, the opposite was the case in the study of Ibrahim et al.

A beneficial effect of enteral feeding regarding infectious complications, especially compared with parenteral nutrition can not be discarded, and could be the reason for the result of Kompan et al.[246, 272] Nevertheless, bacterial overgrowth and gastroesophageal reflux due to enteral nutrition should be taken into account, and could explain the outcome of Ibrahim et al. Of the guidelines only the European expert group makes early enteral nutrition a subject of discussion emphasizing the controversity in the possible benefits but also disadvantages.[340] Whether early or late enteral nutrition plays a role in preventing VAP remains unclear and if the diverging results are due to the different feeding protocols needs to be investigated in future trials.

g) Enteral vs. parenteral feeding

Kudsk et al. showed a significant reduction of VAP rates and ventilator days in patients receiving enteral nutrition support as opposed to those with total parenteral feeding.[201] This is in accordance with a recently published guideline of nutrition support in mechanically ventilated critically ill patients by Heyland et al., that emphasized the superiority of enteral vs. parenteral feeding regarding infectious complications by their strong recommendation.[152] In an earlier meta-analysis, Moore et al. showed a reduction of septic complications in high risk surgical

patients fed enterally.[246] Of the VAP prevention guidelines only the American Thoracic Society addresses this issue, recommending enteral feeding over parenteral.[3]

Due to our inclusion criteria of at least 90% of MV some of the studies included by Heyland et al., which were clearly below this margin, were not included in our analysis. Still it is reasonable to assume, that a certain regimen that brings a benefit to critically ill patients in general is also of advantage for ventilated patients. Only the fact that enteral feeding can produce bacterial overgrowth in the stomach, especially when the bowel is malfunctioning and not processing the food, could lead to the assumption that there could be an adverse effect on VAP, which might therefore be more frequent in these patients. On the other hand, the protective features of enteral feeding like improved wound healing, decreased catabolic response to injury, GI functioning, and improvement of clinical outcomes, as reported by Heyland et al. , seem to outweigh the risks of enteral feeding.[148]

Even though the statistically significant result of enteral versus parenteral feeding is supported by only one study, taking additional evidence of the literature into account, it is fair to assume a clinically relevant effect of enteral over parenteral feeding.

4.4. Positioning

a) Rotational therapy

Rotational therapy is one of various positioning strategies that are implemented in the care of ICU patients in order to improve oxygenation and prevent the development of VAP.

Overall, results for rotational bed therapy and the reduction of VAP rates were statistically significant ($p<0.01$), with both of the subgroups, kinetic therapy (automated turning of the patient in his bed of at least 40 degrees to each side), and continuous lateral rotation therapy (CLRT, automated turning of the patient in his bed of up to 40 degrees to each side), being significant. There was no clinically relevant difference in mortality rates or the length of MV and ICU stay between treatment and control groups however.

Three recently published meta-analysis evaluating rotational therapy techniques reported comparable results, even though these were papers of a broader patient population, not solely on mechanically ventilated patients.[70, 85, 130]

Despite this, the CDC provides no recommendations for rotational therapy as a preventive strategy in their guidelines for the prevention of health-care associated pneumonia.[331] One reason for this discrepancy might be that the CDC has also considered trials of a more general ICU

population, not only mechanically ventilated patients, e.g. a trial of liver transplant patients. It is possible, that mechanically ventilated patients might specifically benefit from rotational therapy. Furthermore, the CDC did not consider all of the studies included in this systematic review; in addition no overall estimates were calculated in their recommendations.

Other guidelines claim that clinicians should keep their implementation in mind. Again, some of these guidelines did not include the latest publications which are included in this meta-analysis, or considered interventions that failed to demonstrate efficacy according to our analysis.[67, 92, 248]

In a recently published national survey of positioning therapy in German ICUs, Bein et al. reported that approximately 30% of ICUs in Germany frequently implement either CLRT or kinetic therapy.[21] High costs for special beds and patient intolerance are the most frequent reasons why kinetic therapy is not utilized.

Study quality of some of the included trials was not always optimal, nevertheless rotational therapy seems to be an effective method for the prevention of VAP. However, the high costs will probably always limit its usage on a broad ICU patient population.

b) Prone vs. supine positioning

RCTs considering prone positioning as a preventive strategy for VAP have been published only recently. They have shown that oxygenation can be improved by prone positioning, but complications like pressure sores, tube obstruction and selective extubation have also been reported.[48, 125, 136, 205, 271, 287, 371] Two of the current VAP prevention guidelines and one recently published meta-analysis on prone positioning have evaluated prone positioning as a preventive strategy for VAP[5, 12, 92, 248, 338], without recommending its usage for VAP prevention apart from one of the meta-analysis[329] that included two trials not meeting our inclusion criteria. Results of our analysis are statistically not significant, although with p=0.13 and p=0.09 for pneumonia and mortality rates, respectively, one can note a trend towards a treatment effect. Prone sessions differed slightly between groups, which might have introduced bias to the interpretation of the results. In contrast to the recently published meta-analyses, we distracted the number of patients with pneumonia at study entry for data analysis of the trial of Voggenreiter et al.[370]

Clinicians in Germany seem to consider prone positioning as advantageous, since according to the survey of Bein et al. mentioned above, prone positioning is preferred over rotational therapy of 39% of German ICUs.[21]

A benefit regarding VAP could not be confirmed by our analysis, although we do not discard its beneficial effect in lung oxygenation, which might be proven by future studies.

c) Semirecumbent vs. supine positioning

Semirecumbent positioning is widely accepted in ICUs and has been recommended as a preventive strategy for nosocomial pneumonia in all of the recently published guidelines. [3, 67, 92, 248, 331, 340] These recommendations are mainly based on the results of Drakulowic et al. and two other studies, published by Orozco-Levi et al. and Torres et al., revealing that in the semirecumbent position the reflux of radioactively labelled gastric contents into the airways was significantly lower than in the supine position.[94, 262, 343] The trial of Draculovic had no intention-to-treat analysis and excluded patients not maintained at 45° for more than 45 minutes.

In 2006 Nieuwenhoven et al. demonstrated in an intention-to-treat analysis that the targeted 45° could not be reached, measuring backrest elevation with a computer-based pendulum system.[364] The mean head-of-bed elevation achieved in their study was about 30°, and compared to their ICU standard of 10° head of bed elevation, the reduction of VAP rates was not significant.

The third study of our analysis of Keeley et al. which compares 45° to 25° head-of-bed elevation, statistically significant results in this small study of thirty patients were not achieved.[172]

In a second analysis we integrated a study of Girou et al. who combined semirecumbency of 30° with subglottic secretion drainage.[129] Since subglottic secretion drainage has been proven to be highly significant in reducing pneumonia rates, we would have expected an overinterpretation of the treatment effect of semirecumbent positioning by integrating the results of this trial. But considering the results were negative, we assumed the influence on the outcome by subglottic secretion drainage was minimal in this case, and added this trial to the analysis of this group.

Results of our analysis did not reach statistical significance, not for pneumonia or mortality rates. Still, the effect on pneumonia just failed to reach statistical significance in both of the analyses ($p=0.06$, $p=0.07$). Due to the heterogeneity in the angles applied in the treatment and control groups, we applied the random effects model for analysis; however the test for heterogeneity was not significant.

Draculovic and Keeley were the only authors who claimed to have reached the 45° degrees of head-of-bed elevation, with a significant reduction of VAP rates in the Draculovic-study, and a possible trend in the reduction of pneumonia rates in the study of Keeley et al. Nevertheless, Nieuwenhoven et al. have demonstrated in a high quality trial that it is unclear that 45° head–of-bed elevation in ICUs can be achieved, even when it is specifically attempted for the concerns of a study. Reasons might have been health-care worker related or due to patient discomfort. The achieved 30° of backrest elevation compared to 10° did not lead to a statistically significant reduction of VAP rates. How Draculovic and Keeley reached a head of bed elevation of 45°

while other authors failed to do so is an interesting discrepancy. Nieuwenhoven et al. argue that elevating the patient head of bed too much, microleakage around the tracheal tube cuff enhanced by gravity could actually provoke nosocomial pneumonia. Also, according to the authors, changing the patient's position for medical or nursing care could facilitate microleakage. Furthermore, they state that it might be more reasonable to compare 45° to an elevation of 10°, and not 0° as it was done by Drakulovic, Torres and Orozco-Levi, because a position of 0° does not resemble real life conditions, especially if patients are fed enterally.

There is evidence suggesting that backrest elevation of 45° significantly reduces VAP rates. Nevertheless, we have to question the relevance of this preventive strategy in reality, since the targeted 45° are hardly achieved. Also, whether or not microleakage is enhanced by backrest elevation due to gravity, needs to be investigated further.

4.5. ET Tubes

a) Subglottic secretion drainage

Our anaylsis showed a highly significant reduction of VAP rates in patients undergoing drainage of subglottic secretions through a lumen above the tube cuff ($p<0.01$), while there was no evidence for a reduction of mortality rates. No serious adverse events were reported. These findings are in accordance with previous results and recommendations of meta-analyses and guidelines, with the difference that we were able to identify new evidence underlining the effectiveness of this strategy. [3, 90, 92, 248, 331] Controversies regarding subglottic suctioning reported by the guideline of the European expert group, which is the least recent of the guidelines, should be clarified by the new evidence published after the communication of these guidelines.[340]

In contrast to the other studies, Lorente et al. utilized newly developed tubes with a polyurethane cuff.[218] Polyurethane used in tube cuffs promises an important reduction of microleakage, although RCTs comparing conventional material with polyurethane are still pending. Therefore, the authors partly explain their positive results with this new cuff material.

Trial quality was good in most cases, although allocation concealment was unclear in six of the seven trials. Also, in the two Chinese studies the suctioning intervals were unclear.[36, 212]

The study of Mahul et al. was conducted in a two by two factorial design, and was the only study in our analysis where patients were included twice, in the stress ulcer prophylaxis group and the subglottic suctioning group.[227] Since the authors have proven the absence of interaction between the two factors, the chance of having introduced bias to our results by doing so can be discarded.

The reported additional costs of about 25% for the special tubes needed for subglottic secretion drainage should be taken into account with regard to the positive treatment effect of this strategy.[227]

Overall, subglottic secretion drainage has proven to be an essential strategy for the prevention of VAP, even though mortality rates could not be positively influenced.

b) Silver-coated tube

VAP rates could be significantly reduced with a newly designed silver-coated tube without provoking adverse events associated with this device. Rello et al. did not reach a significant reduction of pneumonia rates in a trial of 155 patients, but did show a reduction of the bacterial burden of the airways.[284] Kollef et al. conducted a multicenter trial with 54 participating centers including 1509 patients and demonstrated a significant reduction of VAP rates. The authors found the effect of the silver coated tube to be greatest within the first ten days of intubation. The antimicrobial effect of silver and the reduction of biofilm formation and bacterial adhesion on catheters has been described in the literature,[10, 28, 122] however the current guidelines have not addressed this issue so far.

Overall, there seems to be sufficient evidence to consider silver coated tubes efficient and safe devices for VAP prevention.

c) Automated control of endotracheal tube cuff pressure

Valencia et al., who recently developed a device for pressure control, hypothesized a reduction in leakage and subsequent pneumonia rates if cuff pressures are constantly maintained at 20mmHg.[109, 357] Although the device functions reliably, there was no significant effect on VAP rates by automated control of the tube cuff pressure. Whether or not the little power was the reason for the nonsigificant effect is difficult to tell at this point. Also, no statement can be made for other devices used for tube cuff pressure control, since this was a study of a device developed by the authors previously. Whether or not an automated control of the tube cuff pressure has an impact on VAP rates has not been evaluated by the guidelines so far.

4.6. Non-classifyable preventive strategies

a) Aerosolized antibiotics

Our results showed a significant reduction of pneumonia rates by application of aerosolized antibiotics, with no effect on mortality rates.

One aspect should be considered when these results are interpreted, though. The study of Li et al. and Greenfield et al. were not blinded or placebo-controlled.[134, 209] Neither blinding nor placebo-control were inclusion criteria for our meta-analysis, because for some of the preventive strategies for VAP they are not reasonably practicable. This is not true for the application of aerosolized antibiotics, though, which could have been easily implemented in the study protocols of these trials.

The latest published guideline on VAP prevention by Muscedere et al. includes aerosolized antibiotics in their considerations, giving no recommendation for its implementation as a preventive strategy.[248]

Since a probable facilitation of resistance always has to be taken into account when administering antibiotics prophylactically and there are some methodological limitations to the studies of this analysis, the application of aerosolized antibiotics should be considered as a preventive strategy for VAP with caution.

b) IV antibiotics

In patients receiving systemic antibiotic prophylaxis, VAP rates were significantly reduced while mortality rates were unchanged. This was mainly due to the results of Sirvent et al. who showed a 50% reduction of pneumonia rates by administering a twofold dose of cefuroxime at intubation and twelve hours later.[315] The reason for a significant increase in the duration of MV is unclear to us at this point and should not be overinterpreted without further investigation given the small sample size.

So far, the administration of systemic antibiotics for prevention of VAP has not been recommended for general use by nearly all of the current guidelines.[3, 92, 248, 331, 340] As mentioned above, administering antibiotics prophylactically, given the fear of creating resistance is reasonable, and it is up to the clinician to evaluate the pros and cons for their patient.

c) Pharyngeal vs. tracheal decontamination

In the study of Martinez-Pellus et al. there was no evidence demonstrating that pharyngeal decontamination was superior to tracheal in reducing VAP rates, which is an issue that has not been addressed by the guidelines thus far.[236] Compared with a historical control group, which was not included in our analysis due to lack of randomization, pneumonia rates were significantly reduced by either one of the decontamination strategies. This is in accordance with the significant effect of other decontamination strategies outlined above, whereas, given the available data, tracheal decontamination does not seem to be superior to pharyngeal decontamination.

d) Systemic search for maxillary sinusitis

Even though not confirmed by our analysis (we used the chi-square test) Holzapfel et al. were able to demonstrate a significant reduction of VAP rates by systematically searching for maxillary sinusitis via CT scan.[157] In addition, the authors were able to demonstrate a reduction in mortality but have cautiously recommended that such results need to be repeated. However, since this intervention explicitly aims at patients intubated by the nasotracheal route, it is unclear whether orally intubated patients would benefit from systematically conducted CT scans to detect sinusitis. This may be one of the reasons why only two of the current guidelines include systemic search for maxillary sinusitis but don't recommend its implementation.[92, 248]

e) Chest physiotherapy

In a small study, Ntoumenopoulos et al. showed a significant reduction of pneumonia rates by chest physiotherapy, consisting of gravity-assisted drainage, chest wall vibrations and airway suctioning twice daily.[258] According to these results chest physiotherapy seems to be an appropriate method to assist in the clearance of the lungs from secretions which are impaired by the endotracheal tube and MV. Nevertheless, some aspects of the physiotherapy treatment require a cautious interpretation of these results.

First, airway suctioning as a determined part of the physiotherapy protocol alone might have contributed to the positive outcome. The nursing staff also implemented airway suctioning in the control group, but only if considered necessary. In another study by the same author, which is discussed below, postural drainage and manual lung hyperinflation did not have significant treatment effects on VAP rates.[257] In that study, airway suctioning was part of the standard nursing care and applied to both patient groups in the same manner.

Second, the randomization according to the date of admission and the small patient population could have limited the validity of these results. Dodek et al. were the only that integrated chest physiotherapy into their guidelines without recommending its usage.[92] In the updated version of this guideline, this prevention strategy remains unmentioned.[248]

More data with a sufficiently powered randomised controlled trial is needed to evealute the effect of this physiotherapy protocol.

f) Manual lung hyperinflation and postural drainage

As mentioned above, Ntoumeopoulos et al. did not show a reduction of pneumonia rates with a physiotherapy protocol, implementing manual lung hyperinflation and postural drainage.[257] The effects of manual lung hyperinflation, as there is re-expansion of the atelectatic lungs, improvement of the lung compliance and oxygenation as well as sputum clearance have been reported in the literature.[155, 221, 268, 293, 314] Nevertheless, the applied pressure of 40mmHg in this trial could also have damaged the lung tissue and therefore a treatment effect could have been concealed. None of the current guidelines have approached this prevention strategy so far.

Whether a treatment effect on VAP was not proven due to the little power of this study or due to a lack of effect or even adverse effect of the intervention, needs to be examined in a large randomized controlled trial.

g) Granulocyte colony-stimulating factor

The effect of a granulocyte colony-stimulating factor is supposed to help the body in critically ill patients to fight pathogens and infections by promoting the differentiation and proliferation of neutrophil precursor cells, prolonging the survival of neutrophils and acting as a chemotactic trigger for granulocytes and TNF-alpha suppression.[20, 131, 320, 374]

In a level II trial implementing two different doses of the granulocyte colony-stimulating factor filgrastim, Heard et al. could not show a significant treatment effect regarding VAP rates and of the current guidelines only the CDC refers to granulocyte colony-stimulating factors as a preventive strategy but gives no recommendation for its usage.[143, 331] The authors argue that this could be due to the late onset of filgrastim or due to the small sample size of this study. They also state that it might be due to the fact that filgrastim enhances lung tissue damage and potential for ARDS due to the neutrophilia it provokes and the neutrophil products that are dispensed during migration to the lungs. These hypotheses should be explored by further

investigations, therefore at this stage the role of granulocyte-stimulating factors as a preventive strategy for VAP remains unclear.

h) Decontamination of the subglottic area

Pneumatikos et al. conducted a study of an antibiotic decontamination regimen of polymyxin E, tobramycin and amphotericin B. This was continuously administered to the subglottic area and suctioned at least once hourly through a dorsal lumen of the ET- tube.[273] They added the antibiotic regimen used for SDD, to the prevention strategy of subglottic secretion drainage. The reduction of VAP rates was highly significant (p=0.03), but there was no influence on mortality rates. Tracheal colonization and the length of stay were significantly lower in the treatment group.

The small sample size and some methodologic features, like the nondescribed randomization technique and the little concretized diagnosis of pneumonia, limit the quality of this trial. Nevertheless, the antibiotic decontamination of a crucial area for the development of VAP, the subglottic area above the tube cuff, combined with subglottic secretion drainage may add up the effects of two preventive techniques that have already proven to be significant on their own. As with the SDD regimen, resistance has to be taken into account, even though the area the antibiotics are applied to is small. So far, the guidelines have not mentioned decontamination of the subglottic area as a preventive strategy, and more data should be gathered to strengthen the evidence available at this point.

i) Early PEEP

In the study by Pepe et al. pneumonia rates could not be reduced by applying an early PEEP of 8cmH_2O for 72 hours in addition to intermittent positive pressure ventilation.[269] The same is true for the main outcome, ARDS, and mortality rates. In a recently published trial by Manzano et al.[231], applying PEEP of 5-8cmH_2O to nonhypoxemic patients could significantly reduce VAP rates, and the overall outcome of our analysis for the reduction of VAP rates of early PEEP was statistically significant. A protective effect of PEEP regarding lung edema and ventilator-induced lung injury has been described in the literature[97, 358], but so far, it has not been discussed by the current guidelines.

Manzano et al. emphasize that their positive results are only applicable to nonhypoxemic patients and therefore the application of PEEP can not be recommended for general use as a prevention strategy. Nevertheless a positive treatment effect was evident from this trial and further

investigation should strengthen this evidence and could clarify whether the application of early PEEP is protective for a general ICU population.

j) Antioxidant therapy

In severly ill patients, oxidative stress is high and the possibility to support antioxidant biochemical pathways by supplementation of trace elements and vitamins, has been widely described in the literature.[23, 267, 275, 282, 375] In a recently published meta-analysis of Heyland et al., a possible survival benefit for ICU patients treated with antioxidant therapy containing selenium was described, whereas this preventive strategy remains unmentioned by the guidelines.[153]

Two studies met our inclusion criteria and significantly reduced VAP rates in a population of burn and trauma patients, applying two different regimens of a parenteral antioxidant therapy.

Berger et al. applied a regimen containing zinc, selenium and copper through a central line catheter during eight, fourteen or twenty-one days, in severly burned patients.[24]

The regimen applied to trauma patients by Porter et al. for seven days, consisted of N-acetylcysteine, selenium and vitamins C and E.[274]

The small patient populations of the studies could limit the validity of these results. Furthermore, the publication of Berger et al. aggregates data of two conducted randomized controlled trials. Even though they were of almost identical design, there might be methodological limitations. The first study was published in detail in 1998.[25] The second study was published as a poster but did not give detailed information on the clinical outcomes we were interested in, and we could not include it in our analysis.[26] Since the study protocols were almost identical, apart from the slightly different time interval of study drug administration (eight vs. fourteen and twenty-one days), we considered the risk of introducing bias by integrating the aggregated data as being small.

Antioxidant therapy appears to be effective in reducing VAP rates in trauma and burn patients. Whether this is true for a general and larger ICU population needs to be demonstrated with more RCTs of this prevention strategy.

k) Endonasal mupirocin

In a study aimed at reducing MRSA pneumonia by applying nasal mupirocin versus placebo three times a day for three days, Di Filippo et al. could not show a significant effect of this prevention method.[91] However, colonization rates of the nares with MRSA in the treatment group, was significantly lower. Only one of the VAP guidelines mentions mupirocin

decontamination, without giving a recommendation concearning its usage.[248] A larger, sufficiently powered RCT would be needed to detect a significant treatment effect.

4.7. Limitations

Even though our inclusion criteria were strict, some limitations of this meta-analysis have to be mentioned.

First, the quality of some of the trials included in our analysis was not always optimal, and the trial quality was given no weight in our statistical calculations by the program we used (RevMan 4.2).

Also, since we wanted our results to be valid for a broad ICU population, we did not differenciate between the subgroups of patients with different underlying conditions, e.g. burn patients, trauma patients, medical patients, etc. We can not rule out that this was a source of bias for our results.

Furthermore, even though our search strategy was profound, there might be evidence that was not captured by our search strategy, even though the chance for this is negligible.

5. Conclusion

From the results of this meta-analysis, various methods and techniques for the prevention of VAP were demonstrated as being effective and clinically relevant and allow for conclusions regarding the pathogenesis of VAP.

The endotracheal tube itself, impairs natural defenses and allows micro-leakage of contaminated secretions, and seems to be the most important factor in the development of VAP; therefore, this type of pneumonia could even be regarded as intubation-associated rather than ventilator-associated. Non-invasive, as opposed to invasive MV (OR=0.14, 0.07-0.25), subglottic secretion drainage (OR=0.34, 0.24-0.49) and the usage of a silver-coated tube (OR=0.62, 0.44-0.89) appears to significantly reduce VAP rates.

Another decisive factor in the prevention of VAP seems to be the reduction of the bacterial load, and various strategies with statisctically significant results aimed at different origins and sites of potential contamination. Oral decontamination with antiseptics (OR=0.60, 0.45-0.82) and subglottic decontamination (OR=0.17, 0.05-0.56) target the buccal cavity. Selective decontamination of the digestive tract (OR=0.32, 0.24-0.43), sucralfate versus H_2-antagonists (OR=0.77, 0.64-0.93) early gastrostomy (OR=0.18, 0.03-0.99) and enteral versus parenteral nutrition (OR=0.30, 0.10-0.85) appeal to the digestive tract. The lung itself is the target of the application of aerosolized antibiotics (OR=0.55, 0.34-0.87). Systemic approaches for the reduction of infectious complications include administration of systemic antibiotics (OR=0.56, 0.32-0.99) and antioxidant therapy (OR=0.12, 0.03-0.42).

Preventative strategies aimed at better ventilation of all lung areas and clearance of secretions, which proved to be statistically significant, are rotational therapy (OR=0.34, 0.23-0.52) and chest physiotherapy (OR=0.14, 0.03-0.70).

An intervention which proved to be statistically significant but was restricted to nonhypoxemic patients was the application of early PEEP (OR=0.41, 0.18-0.91).

Why other interventions, which are believed to be effective or have been described as effective in the literature, did not reach statistical significance in this meta-analysis, was either due to new evidence or insufficient power due to small sample sizes and should be subject to further research. In particular, the effects of semirecumbent positioning and early tracheostomy should be reconsidered.

When implementing a prevention strategy, various factors determine whether it is feasible and safe, and this dictates its usage. With the pharmacologic strategies, resistance rates can be

facilitated, and even though various decontamination regimen proved to be highly significant, it is up to the treating physician to decide whether a potential benefit for the patient regarding VAP rates outweighs the risk of introducing resistance. This is especially true for antibiotic decontamination regimens, unlike decontamination with antiseptics which has a lower risk for resistance.

Costs are another key factor determining whether a strategy is implemented in ICUs, and if it should be taken into account when future research is done. Even though there are strategies like rotational therapy that have shown to be clinically effective, they can be very unpopular among physicians due to the high costs, and might not be within the budget of ICUs.

On the other hand, promising new developments in tube devices, like new polyurethane cuffs or silver coating of the inner surface of the tubes, seem to be effective and affordable and continues to be advanced by the industry and researchers.

Even though a strategy proved to be statistically significant in reducing VAP rates, in most cases the secondary outcomes including mortality, the duration of mechanical ventilation and the length of ICU stay, remained unchanged. In part, this might be due to the fact that there was not enough power to demonstrate a treatment effect, especially regarding mortality rates. Nevertheless, an effect of VAP on mortality has not been clearly proven so far.

Future research should focus on prevention strategies that are feasible and safe to implement and that are in accordance with the available budget and human recources in ICUs. To reduce microleakage of contaminated secretions of the tube cuff is the crucial factor for reducing VAP rates.

6. Summary

In this quantitative systematic review, we summarized and compared the efficacy of all interventions that have been studied for the prevention of VAP and compared them to current recommendations and guidelines. By applying a consistent statistical method for analysis to all prevention strategies, results are comparable between one another. This gives clinicians an overview of all the available evidence and its effectiveness.

We searched Pubmed, Embase, the Cochrane-library, Scientific Indexing and clinicaltrials.gov for relevant randomised controlled trials and complemented it with a hand search of the reference lists of relevant articles.

A total of 1948 citations were screened of which 169 met our pre-defined inclusion criteria. The overall results, including odds ratios (OR), confidence intervals (CI), numbers of studies and patients are displayed in a forest plot in Figure 35.

The following interventions, ordered according to their effect sizes, were statistically significant and were represented by more than one study: non-invasive as opposed to invasive MV (OR=0.14, 0.07-0.25), selective decontamination of the digestive tract (OR=0.32, 0.24-0.43), subglottic secretion drainage (OR=0.34, 0.24-0.49), rotational therapy (OR=0.34, 0.23-0.52), aerosolized antibiotics (OR=0.55, 0.34-0.87), systemic antibiotics (OR=0.56, 0.32-0.99), oral decontamination with antiseptics (OR=0.60, 0.45-0.82), silver coated tubes (OR=0.62, 0.44-0.89) and sucralfate versus H_2-antagonists (OR=0.77, 0.64-0.93). Antioxidant therapy with trace elements was statistically significant and studied by more than one trial, but in a small number of patients only (OR=0.12, 0.03-0.42).

In addition, the following interventions were statistically significant, but were represented by only one study: chest physiotherapy (OR=0.14, 0.03-0.70), subglottic decontamination (OR=0.17, 0.05-0.56), early gastrostomy (OR=0.18, 0.03-0.99) and enteral vs. parenteral nutrition (OR=0.30, 0.10-0.85).

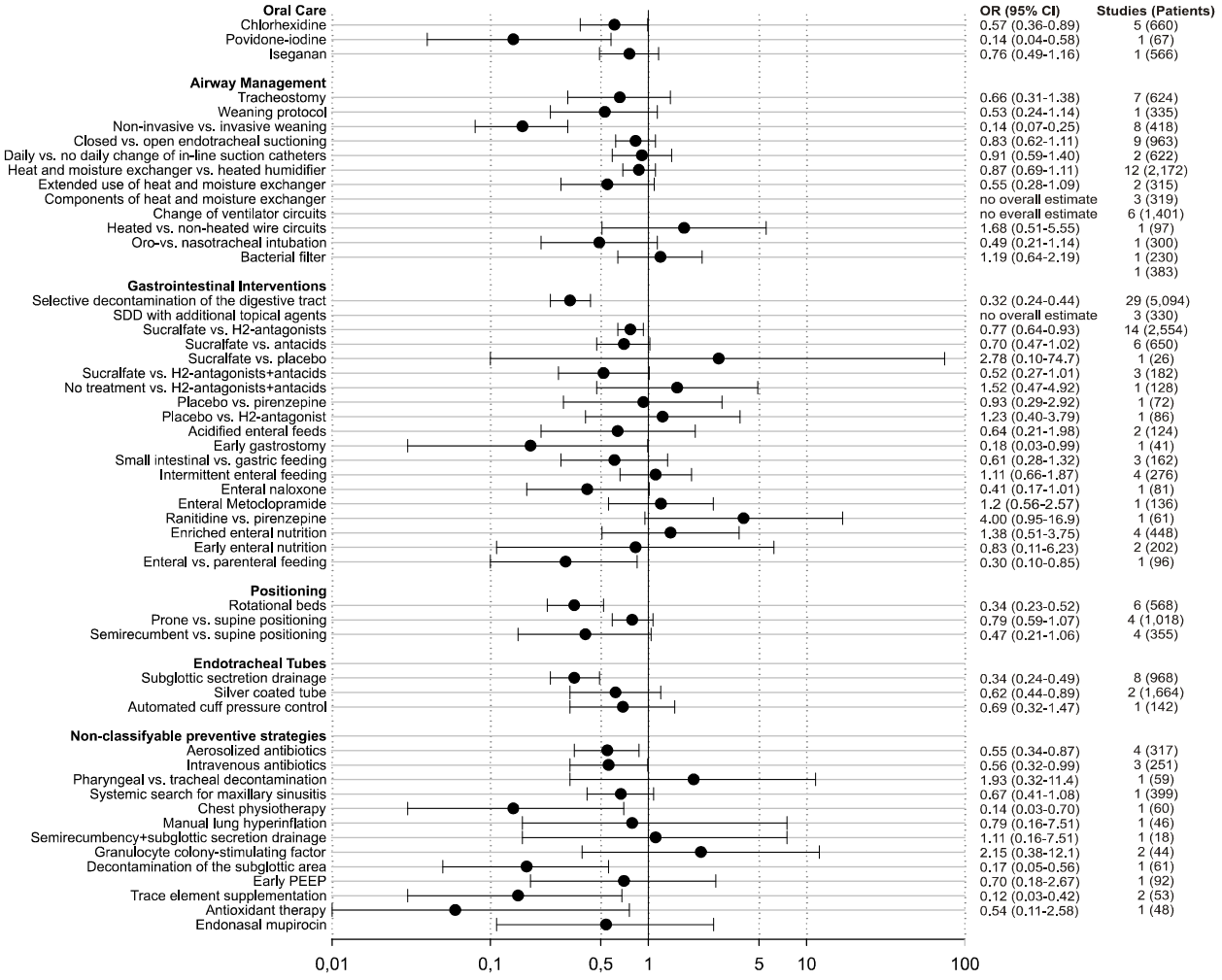
Statistically significant, but applicable only to a subgroup of nonhypoxemic patients, was the early application of PEEP (OR=0.41, 0.18-0.91).

All other interventions, e.g. the type of humidifier or filter, suction technique or changes of breathing circuits failed to reach statistical significance. This was also true for semirecumbent positioning (OR=0.40, 0.15-1.04), early tracheostomy (OR=0.66, 0.31-1.38) and prone positioning (OR=0.79, 0.59-1.07).

Summary

The incidence of VAP can be reduced by a number of mechanical, chemical and antibiotic interventions, all of which most likely work through a reduction of the microaspiration-related bacterial load of the lower airways. Current reviews or guidelines are not always supported by the current available evidence. To understand the reasons why interventions with limited efficacy get implemented into clinical practice while other well documented and with superior efficacy do not, could be invaluable for health care policy initiatives.

Figure 35: Forest plot of overall results



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8. So far publicated aspects of this work

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Deutscher Anästhesiekongress, 26.-29.April 2008, Nürnberg (Poster und Kurzvortrag)

Apfel CC, Voegele S, Cakmakkaya OS, Radke OC, Wiener-Kronish JP, Zwissler B.

Preventing ventilator-associated pneumonia. What is the evidence?

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10. Appendix

10.1. Deutsche Zusammenfassung

In diesem quantitativen systematischen Review haben wir die Effektivität aller Interventionen zusammengefasst und verglichen, die als Strategien zur Prävention von beatmungsassoziierter Pneumonie (ventilator-associated pneumonia, VAP) in Studien untersucht wurden, und sie außerdem mit den aktuellen Empfehlungen und Leitlinien verglichen. Indem wir zur Analyse der Präventionsstrategien eine einheitliche statistische Methode angewandt haben, sind die Ergebnisse miteinander vergleichbar. Dies gibt Klinikern einen Überblick über die gesamte vorhandene Evidenz und ihre Wirksamkeit.

Wir durchsuchten Pubmed, Embase, die Cochrane-library, Scientific Indexing und clinicaltrials.gov nach relevanten randomisierten kontrollierten Studien und vervollständigten die Suche mit einer Durchsicht der Referenzlisten relevanter Artikel.

Insgesamt wurden 1948 Zitate überprüft, von denen 169 unseren vordefinierten Einschlusskriterien entsprachen. Die Ergebnisse sind in ihrer Gesamtheit als „Forest Plot“, inklusive der Odds Ratios (OR), Konfidenzintervalle (CI) und der Anzahl der Studien und Patienten in der unten stehenden Abbildung dargestellt.

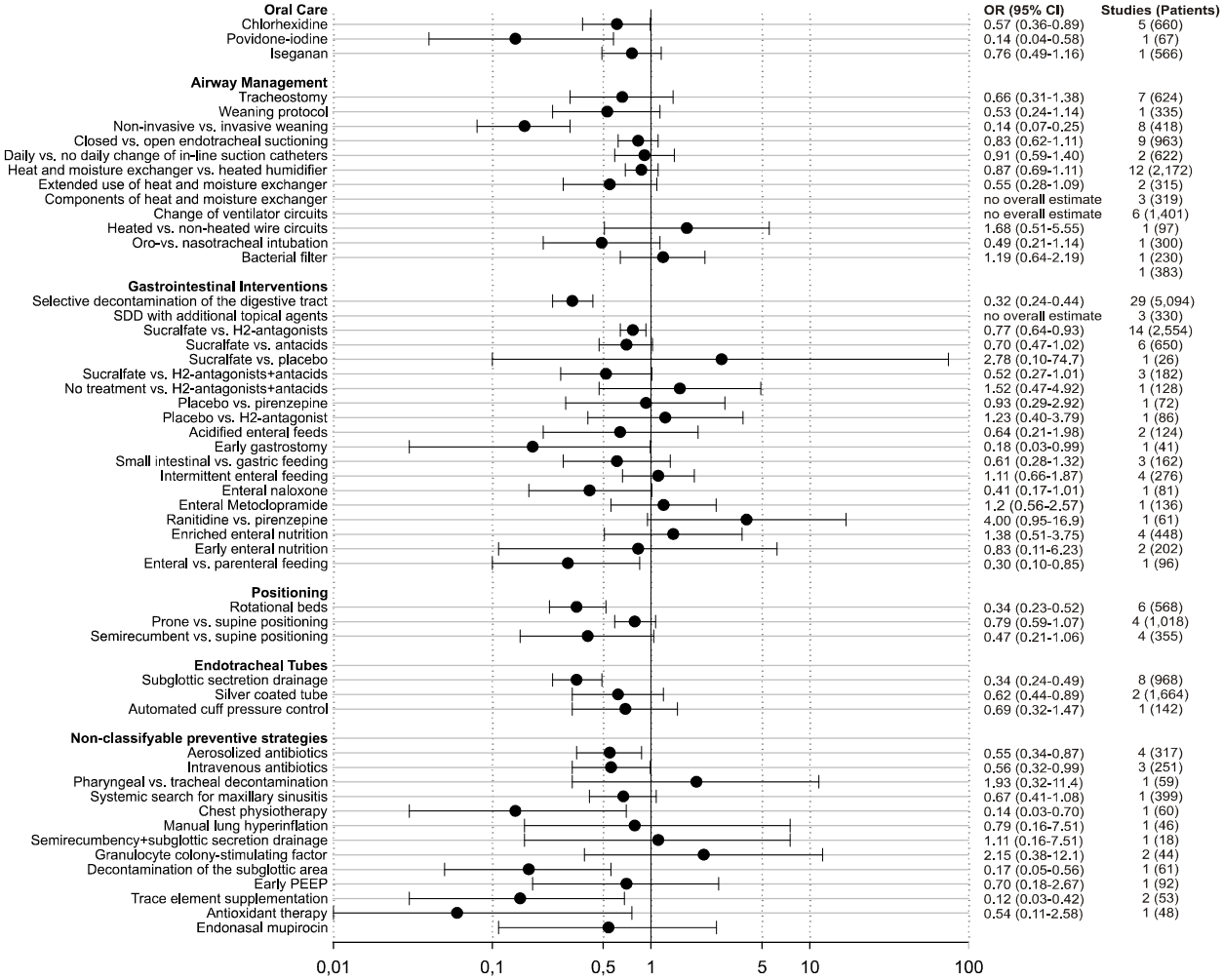
Die folgenden Interventionen, angeordnet entsprechend ihrer Effektgröße, waren statistisch signifikant und wurden von mehr als einer Studie untersucht: nicht-invasive im Gegensatz zu invasiver mechanischer Beatmung (OR=0.14, 0.07-0.25), selektive Darmdekontamination (OR=0.32, 0.24-0.43), subglottische Absaugung (OR=0.34, 0.24-0.49), Rotationsbetten (OR=0.34, 0.23-0.52), als Aerosol verabreichte Antibiotika (OR=0.55, 0.34-0.87), systemisch verabreichte Antibiotika (OR=0.56, 0.32-0.99), orale Dekontamination mit Antiseptika (OR=0.60, 0.45-0.82), mit Silber beschichtete Endotrachealtuben (OR=0.62, 0.44-0.89) und Sukralfat versus H2-Antagonisten (OR=0.77, 0.64-0.93). Antioxidative Therapie durch Zufuhr von Spurenelementen wurde zwar von mehreren Studien, jedoch in nur kleinen Patientengruppen untersucht (OR=0.12, 0.03-0.42).

Außerdem waren die folgenden Interventionen statistisch signifikant, wurden jedoch nur von einer Studie untersucht: Physiotherapie des Thorax (OR=0.14, 0.03-0.70), subglottische Dekontamination (OR=0.17, 0.05-0.56), frühzeitige Gastrostomie (OR=0.18, 0.03-0.99) und enterale versus parenterale Ernährung (OR=0.30, 0.10-0.85).

Statistisch signifikant war außerdem die frühzeitige Anwendung von PEEP (OR=0.41, 0.18-0.91), jedoch nur in einer Untergruppe von nicht hypoxämischen Patienten.

Alle anderen Interventionen, beispielsweise die Art der Atemwegsbefeuchter oder –filter, Absaugetechniken und –vorrichtungen und Wechseln der Beatmungsschläuche waren statistisch nicht signifikant. Dies galt auch für die Oberkörperhochlagerung (OR=0.40, 0.15-1.04), frühzeitige Tracheostomie (OR=0.66, 0.31-1.38) und Bauchlagerung (OR=0.79, 0.59-1.07).

Die Inzidenz von VAP kann durch eine Anzahl an mechanischen, chemischen und antibiotischen Interventionen, die wahrscheinlich über eine Reduktion der durch Mikroaspiration bedingten Keimbelastung wirken, gesenkt werden. Diese Daten bestätigen jedoch nicht immer Schlussfolgerungen von Reviews oder Leitlinien. Die Hintergründe zu verstehen, warum Interventionen mit begrenzter Effektivität im klinischen Alltag eingesetzt werden andere mit gut dokumentierter und besserer Wirksamkeit nicht, könnte für gesundheitspolitische Initiativen von unschätzbarem Wert sein.



10.2. Curriculum Vitae

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10.3. Tables

a) Study characteristics of included trials

Table 27: Study characetristics Oral Care

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Bopp 2006[44]	RCT	5 pts., mixed	Suctioning toothbrush using 0.12% chlorhexidine solution (cheeks, teeth, ET-tube) twice daily vs. standard oral care	P, M, (MV), (LOS)	A	Unclear	Unclear	- Various intents to contact authors regarding pneumonia definition were unsuccessful
Fourrier 2000[118]	RCT, single-blind	60 pts., medico-surgical	0.2% chlorhexidine gel (oral cavity) thrice daily vs. standard oral care (bicarbonate serum + aspiration)	P, M, MV, LOS	B	a) fever or hypothermia b) CXR c) leukocytosis or leucopenia d) pos. tracheal aspirate or BAL culture	Unclear	
Fourrier 2005[119]	RCT, double-blind, placebo-controlled, multicenter	228 pts., mixed	0.2% chlorhexidine gel (gingival and dental plaque) thrice daily vs. placebo gel	P, M, MV, LOS	A	a) fever or hypothermia b) CXR c) leukocytosis or leucopenia d) pos. tracheal aspirate or BAL culture	Unclear	
Koeman 2006[179]	RCT, double-blind, placebo-controlled, multicenter	157 pts, mixed, surgical	2 % chlorhexidine gel (buccal cavity) four times daily vs. placebo gel	P, M, MV, LOS	B	CXR plus at least three of the following: a) fever or hypothermia b) leukocytosis and/or left shift or leucopenia c) purulent tracheal aspirate d) pos. culture from tracheal aspirates (>48h of MV)	48 h	- Chlorhexidine/ colistin decontamination group excluded
Tantipong 2008[333]	RCT	110 pts., mixed	2% chlorhexidine rinse (toothbrushing and mucosa of oral cavitiy) four times daily vs. saline rinse	P, (MV)	D	CXR plus at least three of the following: a) fever or hypothermia b) leukocytosis or leukopenia c) purulent tracheal aspirate d) pos. tracheal culture	48 h	- Subgroup data of pts. mechanically ventilated for more than 48 h abstracted
Kollef 2006.[192]	RCT, double-blind, placebo controlled	709 pts., mixed	Isaganan oral rinse (9mg) six times daily vs. placebo rinse	P, M	A	CXR, pos. BAL culture plus at least two of the following: a) fever or hypothermia b) leukocytosis or leucopenia c) purulent sputum or tracheal secretions	48 h	
Seguin 2006[306]	RCT	67 pts., surgical with severe head trauma	10 % povidone-iodine rinse (oro- and nasopharynx) vs. saline rinse	P, M, MV, LOS	A	CXR plus two of the following a) fever or hypothermia b) purulent endotracheal aspirate c) leukocytosis or leucopenia (all symptoms for >48 h)	48 h	- Standard care group (no instillation but aspiration of secretions) excluded

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 28 Study characteristics Airway Management: Tracheostomy

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Blot 2007[34]	RCT, multicenter	123 pts., medical, surgical	Early (<4d) tracheostomy vs. prolonged endotracheal intubation	P, M, (MV), (LOS)	A	a) CXR b) fever c) leukocytosis d) purulent tracheal secretions or gas exchange alterations e) pos. pos. BAL, PSB, catheter or tracheal aspirate cultures	7 d	- Unpublished data - Author contacted for methodological details
Bouderka 2004[45]	RCT	63 pts, head trauma	Early (<5d) tracheostomy vs. prolonged endotracheal intubation	P, M, MV	B	CDC-criteria[123]	5 d	
Sugerman 1997[330]	RCT	112 pts., trauma, non-trauma	Early (3-5d) tracheostomy vs. prolonged endotracheal intubation until day 14	P, M, LOS	A	a) leukocytosis or left shift b) fever c) CXR d) pos. sputum culture	3 d	- Only early randomization group included
Saffle 2002[302]	RCT	44 pts., burn center	Early (3-4d) vs. late (14d) tracheostomy	P, M, MV, LOS	A	CDC-criteria[123]	48 h	
Barquist 2006[19]	RCT	60 pts., trauma	Early (<8d) vs. late (>28d) tracheostomy	P, M, (MV), (LOS)	A	CDC-criteria[123]	3 d	
Rodriguez 1990[291]	RCT	106 pts., surgical	Early (<8d) vs. late (>8d) tracheostomy	P, M, MV, LOS	D	a) fever b) leukocytosis c) pos. Gram stain d) pos. sputum culture e) CXR	24 h	
Rumbak 2004[298]	RCT	120 pts., medical	Early (<2d) vs. late (14-16d) tracheostomy	P, M, MV, LOS	A	a) clinical criteria b) pos. PSB or BAL culture	14 d	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 29: Study characteristics Airway Management: Weaning

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Marelich 2000[232]	RCT	335 pts., medical, trauma	Weaning protocol vs. physician-directed weaning	P, M, (MV)	A	Clinical suspition of pneumonia plus two of the following: a) pos. endotracheal aspirate or bronchoscopy cultures b) fever or leukocytosis c) CXR	48 h	
Antonelli 1998[13]	RCT	64 pts., mixed	Noninvasive vs. invasive MV	P, M, MV, LOS	B	a) CXR b) fever or hypothermia c) purulent tracheobronchial secretions d) leukocytosis e) worsening of gas exchange f) pos. BAL culture	Unclear	
Chen 2001[57]	RCT	24 pts., respiratory (COPD)	Noninvasive vs. invasive MV after 3d of invasive MV	P, M, MV	B	CXR plus at least 2 of the following: a) fever b) leukocytosis c) purulent tracheal secretions	3 d	- Article translated from Chinese
Conti 2002[69]	RCT	49 pts., respiratory (COPD)	Noninvasive vs. invasive MV	P, M, MV, LOS	A	CXR plus at least two of the following: a) leucocytosis b) fever c) purulent aspirations d) pos. BAL culture	Unclear	- Author provided pneumonia definition - Patients with persistent weaning failure
Ferrer 2003[110]	RCT	43 pts., mixed	Noninvasive vs. invasive MV after 3d of weaning failure from invasive MV with T-piece	P, M, MV, LOS	B	CXR plus at least two of the following: a) fever or hypothermia b) leukopenia or leukocytosis c) purulent tracheal secretions	Unclear	
Girault 1999[128]	RCT	33 pts., medical	Noninvasive vs. invasive MV after 2h of weaning failure from invasive MV with T-piece	P, M, MV, LOS	B	CXR plus at least two of the following: a) fever b) leukocytosis c) pos. endotracheal secretion cultures	48 h	- Author provided pneumonia definition
Nava 1998[253]	RCT	50 pts., respiratory (COPD)	Noninvasive vs. invasive MV after weaning failure from invasive MV with T-piece	P, M, MV, LOS	A	CXR plus at least two of the following: a) fever b) leukocytosis c) pos. Gram stain of suctioning material from the lower respiratory tract	36 h	
Trevisan 2008[345]	RCT	65 pts., mixed	Noninvasive vs. invasive MV after weaning failure from invasive MV after 30 min	P, M, MV, LOS	A	CPIS ≥ 7[278] or: Clinical findings or pos. CXR plus at least one of the following: a) purulent tracheal secretions b) fever	48 h	

						c) leukocytosis	
Wang 2005[373]	RCT, multicenter	90 pts., respiratory, medical (COPD)	Noninvasive vs. invasive MV after invasive MV	P, M, MV, LOS	B	a) >48h of MV b) CXR c) physical examination d) plus at least one of the following: - leukocytosis or leucopenia ± left shift - fever - purulent airway secretion - pos. culture of bronchial secretions	Unclear

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 30: Study characteristics Airway Management: Closed vs. open endotracheal suctioning

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Combes 2000[68]	RCT	104 pts., neurosurgical	Closed vs. open endotracheal suctioning	P, M, MV, LOS	B	a) CXR b) purulent secretions with a positive sputum culture c) leukocytosis or leukopenia d) fever (>48h of MV)	48 h	
Deppe 1990[88]	RCT	84 pts., surgical	Closed vs. open endotracheal suctioning	P, M	B	a) purulent sputum (Gram stain) and sputum culture b) fever or hypothermia c) CXR d) leukocytosis or leucopenia e) in hospital ≥48h	48 h	
Johnson 1994[165]	RCT	35 pts., surgical, trauma	Closed vs. open endotracheal suctioning	P	D	CXR plus two the following: a) purulent sputum (Gram stain) b) fever c) leukocytosis	Unclear	- Patients ≥ 17 years
Lee 2004[207]	RCT	70 pts., mixed	Closed vs. open endotracheal suctioning	P, (MV), LOS	D	CDC-criteria[123]	Unclear	- Article translated from Korean
Lorente 2005[220]	RCT	308 pts., medical-surgical	Closed vs. open endotracheal suctioning	P, (M), (MV)	B	a) purulent sputum b) fever or hypothermia c) leukocytosis or leukopenia d) CXR e) pos. culture of respir. secretions or blood	48 h	- Patients with MV <48h excluded from analysis
Lorente 2006 I[216]	RCT	213 pts., medical-surgical	Closed vs. open endotracheal suctioning	P, (M), (MV)	B	a) purulent sputum b) fever or hypothermia	Unclear	- Patients with MV <48h excluded from analysis

						c) leukocytosis or leukopenia d) CXR e) pos. culture of respir. secretions or blood		
Rabitsch 2004[280]	RCT	24 pts., medical	Closed vs. open endotracheal suctioning	P	A	American College of Chest Physicians: CXR plus one of the following: a) radiographic evidence of cavitation b) histological evidence c) positive blood culture d) purulent tracheal aspirate e) pos. pleural fluid culture with two of the following: - fever - leukopenia or leukocytosis	72 h	
Topeli 2004[339]	RCT	78 pts., medical	Closed vs. open endotracheal suctioning	P, M, MV, LOS	B	CXR plus two of the following: a) fever or hypothermia c) leukocytosis or leukopenia d) purulent tracheobronchial secretions or pos. Gram stain	48 h	
Zeitoun 2003[384]	RCT	47 pts., medical-surgical	Closed vs. open endotracheal suctioning	P	B	a) fever b) CXR c) leukocytosis d) purulent tracheobronchial secretions	48 h	- Patients ≥ 13 years

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 31: Study characteristics Airway Management: Daily vs. no daily changes of in-line suction catheters

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Kollef 1997[187]	RCT	521 pts., mixed	Daily vs. no routine changes of in-line suction catheters	P, M, MV, LOS	A	CXR (>48h of MV) plus one of the following: a) radiographic evidence of pulmonary abscess formation b) histologic evidence c) pos. blood or pleural fluid culture d) two of the following: - fever - leukocytosis - purulent tracheal aspirate	12 h	
Darvas 2003[78]	RCT	101 pts., medical-surgical	Daily vs. 48 hr-change of closed suctioning catheter	P, M, MV, LOS	A	CXR plus one of the following: a) pos. pleural fluid or blood cultures for	48 h	- Patients >16 years

						same organism as in tracheal aspirate b) radiographic cavitation c) histopathologic evidence d) two of the following: - fever - leukocytosis - purulent tracheal aspirate		

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 32: Study characteristics Airway Management: Heat and moisture exchanger (HME) vs. heated humidifier (HH)

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Martin 1990[233]	RCT	73 pts., mixed	Hydrophobic HME vs. HH	P, M, MV	B	a) purulent sputum b) pos. respiratory cultures c) CXR	24 h	
Roustan 1992[295]	RCT	116 pts., mixed	Hydrophobic HME vs. HH	P, M, MV, LOS	B	a) CXR b) fever c) leukocytosis d) purulent tracheobronchial secretions	Unclear	
Boots 1997 A[43]	RCT	62 pts., general	Hygroscopic HME vs. HH	P, M, (MV)	B	a) CXR b) fever or hypothermia c) leukocytosis or leucopenia d) pos. culture of tracheal aspirate e) purulent sputum f) $\downarrow PaO_2/FiO_2$	48 h	- HME group with 2-day changes divided and integrated in both comparisons
Dreyfuss 1995[95]	RCT	164 pts., mixed	Hygroscopic HME vs. HH	P, M, MV	B	a) CXR b) purulent tracheal aspirates c) pos. PSB or catheter culture or pos. blood culture with same organism isolated from blood and sputum specimens d) 48h of MV	48 h	
Memish 2001[238]	RCT	243 pts., medical-surgical	Hygroscopic HME vs. HH	P, M, MV	D	CDC-criteria[123] plus at least one of the following: a) purulent sputum b) pos. blood culture c) pos. transtracheal aspirate culture d) virus or viral antigen in respiratory secretions e) antibody titer f) histopathologic evidence	48 h	

Lorente 2006 II[217]	RCT	104 pts., medical-surgical	HME vs. HH with double-heated wire circuits	P, MV	B	a) purulent sputum b) fever or hypothermia c) leukocytosis or leukopenia d) CXR e) pos. culture of respir. Secretions f) >48h of MV	5 d	
Boots 2006 A[42]	RCT	189 pts., general	HME vs. HH with single-heated wire circuits	P, M, (MV), (LOS)	B	Onset of a new clinical syndrome (>48h of MV) consistent with pneumonia as determined by the treating consultant and on the basis of a CPIS ≥6[278]	48 h	- HME group divided and integrated in both comparisons
Boots 2006 B[42]	RCT	192 pts., general	HME vs. HH with double-heated wire circuits	P, M, (MV), (LOS)	B	Onset of a new clinical syndrome (>48h of MV) consistent with pneumonia as determined by the treating consultant and on the basis of a CPIS ≥6[278]	48 h	- HME group divided and integrated in both comparisons
Kirton 1997[176]	RCT	280 pts., trauma	HME vs. HH with heated wire circuits	P	B	CDC criteria[123]	3 d	- Patients ≥ 15 years
Lacherade 2005[202]	RCT, multicenter	369 pts., surgical-medical	Hygroscopic HME vs. HH with heated wire circuits	P, M, MV, LOS	A	CXR, >48h of MV, pos. culture of protected telescoping catheter or BAL plus two of the following: a) fever or hypothermia b) leukocytosis or leukopenia c) purulent tracheal secretions	48 h	
Branson 1996 A[47]	RCT	103 pts., medical-surgical	Hygroscopic condenser humidifier vs. HH with heated wire cicuits	P, MV	D	a) purulent sputum b) pos. respiratory cultures c) fever d) CXR	24 h	- Study divided for 2 comparisons
Kollef 1998[188]	RCT	310 pts., medical-surgical	Hygroscopic condenser humidifier vs. HH with heated wire circuits	P, M, MV, LOS	A	American College of Chest Physicians: CXR (>48h of MV) plus one of the following: a) radiographic evidence of pulmonary abscess b) histologic evidence c) pos. blood or pleural fluid culture d) two of the following: - fever - leukocytosis - purulent tracheal aspirate	Unclear	

Abbreviations: RCT: randomized controlled trial; pts: patients; HH: heated humidifier; HME: heat and moisture exchanger; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush, CPIS: Clinical Pulmonary Infection Score;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 33: Study characteristics Airway management: Extended use of heat and moisture exchanger

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Davis 2000[81]	RCT	160 pts., surgical	24-hr vs. 120-hr. change of a hygroscopic HME	P, MV	B	CDC-criteria[123]	48 h	- Hydrophobic HME group (120-hr change) excluded since no control group
Thomachot 2002[334]	RCT	155 pts., trauma, medical, postoperative	1- vs. 7-day change of a hydrophobic HME	P, M, MV, LOS	B	a) purulent tracheal aspirates b) deterioration of arterial PaO_2 c) CXR d) pos. PSB or BAL culture	48 h	

Abbreviations: RCT: randomized controlled trial; pts: patients; HME: heat and moisture exchanger; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 34: Study characteristics Airway Management: Components of heat and moisture exchanger

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Boyer 2003[46]	RCT	43 pts., medical	2 models of hygroscopic HME (Hygrolife and EdithFlex)	P, MV	B	a) CXR b) purulent tracheal aspirate c) pos. PSB or BAL culture	48 h	
Thomachot 1998[336]	RCT	136 pts., head trauma, medical, postoperative	Hygroscopic vs. hydrophobic HMEF	P, M, MV	B	a) purulent tracheal aspirates b) deterioration of arterial PaO_2 c) CXR d) pos. PSB or BAL culture	24 h	
Thomachot 1999[335]	RCT	140 pts., head trauma, medical, postoperative	2 different hygroscopic HMEF ($CaCl_2$ vs. $AlCl_2$ impregnated)	P, M, MV	B	a) purulent tracheal aspirates b) deterioration of arterial PaO_2 c) CXR d) pos. PSB or BAL culture	24 h	

Abbreviations: RCT: randomized controlled trial; pts: patients; HME: heat and moisture exchanger; HMEF: heat and moisture exchange filter; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 35: Study characteristics Airway Management: Change of ventilator circuits

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition for Pneumonia	Min. duration of MV	Notes
Craven 1986[75]	RCT	233 pts., medical, surgical, cardiac	24hr- vs. 48hr-change of ventilator circuits	P, (M), (MV)	D	a) purulent sputum b) pos. sputum culture c) leukocytosis d) fever e) CXR	48 h	
Dreyfuss 1991[96]	RCT	73 pts., mixed	48hr- vs. no change of ventilator circuits	P, M, MV	D	a) CXR b) purulent tracheal aspirates a) pos. PSB culture	48 h	
Lorente 2004[215]	RCT	304 pts., medical-surgical	48hr- vs. no change of ventilator circuits	P, M, MV	B	a) purulent sputum b) fever or hypothermia c) leukocytosis or leukopenia d) CXR e) pos. culture of respir. secretions or blood	72 h	
Boots 1997 B[43]	RCT	54 pts., general	HME with 2-day vs. 4-day circuit change	P, M, (MV)	B	a) CXR b) fever or hypothermia c) leukocytosis or leucopenia d) pos. culture of tracheal aspirate e) purulent sputum f) ↓PaO2/FiO2	48 h	- HME group with 2-day changes divided and integrated in both comparisons
Long 1996[214]	RCT	447 pts., medical, neurosciences	Change of ventilator circuits once vs. thrice weekly	P	D	CXR, consolidation, cavitation, or pleural effusion plus one of the following: a) purulent sputum b) pos. blood culture c) pos. culture of bronchial washing, brushing, or biopsy d) isolation of virus or detection of viral antigen e) diagnostic antibody titer f) histopathologic evidence	Unclear	
Kollef 1995[189]	RCT	300 pts., mixed	7-day vs. no routine change of ventilator circuits	P, M, MV	A	CXR plus one of the following: a) pos. pleural or blood cultures b) roentgenographic cavitation c) histopathologic evidence d) two of the following: - fever - leukocytosis - purulent tracheal aspirate	5 d	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 36: Study characteristics Airway Management: Heated vs. non-heated wire circuits

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Branson 1996 B[47]	RCT	97 pts., medical-surgical	HH with heated- vs. non-heated wire circuits	P, MV	D	a) purulent sputum b) pos. respiratory cultures c) fever d) CXR	24 h	- Study divided for 2 comparisons

Abbreviations: RCT: randomized controlled trial; pts: patients; HH: heated humidifier; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 37: Study characteristics Airway Management: Oro- vs. nasotracheal intubation

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Holzapfel 1993[158]	RCT	300 pts., general	Oro- vs. nasotracheal intubtion	P, M, (MV), LOS	B	a) CXR b) fever or hypothermia c) leukocytosis or leukopenia and/or purulent tracheobronchial secretions d) pos. PSB culture	7 d	- Patients >15 years

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 38: Study characteristics Airway Management: Bacterial filter

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Lorente 2003[219]	RCT	171 pts., medical-surgical	Bacterial filter	P, M, MV, LOS	B	a) purulent sputum b) fever or hypothermia	24 h	- Subgroup of patients with MV >48 h evaluated

						c) leukocytosis or leucopenia d) CXR e) pos. culture of respiratory secretions or blood		

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 39: Study characteristics Gastrointestinal Interventions: Selective decontamination of the digestive tract (SDD)

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Bergmans 2001[27]	RCT, placebo-controlled, double-blind	226 pts, medical, surgical, trauma, neurologic	SDD: topical (oral only)	P, M, (MV), (LOS)	A	a) CXR b) at least three of the following: - fever or hypothermia - leukocytosis ± left shift or leucopenia - pos. Gram stain - pos. tracheal aspirate culture c) pos. BAL, PSB, blood or pleural fluid culture	48 h	- Two control groups combined (treatment and control patients in same ICU or separarted). - Patients ≥ 16 years.
Pugin 1991[277]	RCT, double-blind, placebo-controlled	52 pts., surgical	SDD: topical (oral only)	P, M, MV, LOS	A	CPIS ≥7during the course of intubation that remained elevated (≥7) for ≥3 d[276]	48 h	
Rios 2005[288]	RCT, double-blind, placebo-controlled	96 pts., surgical, medical, trauma	SDD: topical (oral only)	P, M, MV, LOS	A	a) CXR b) pos. tracheal aspirate or blood culture b) two of the following - fever or hypothermia - leukocytosis or leucopenia - purulent tracheal aspirate	96 h	- Patients ≥16 years
Rodriguez-Roldan 1990[290]	RCT, double-blind, placebo-controlled	28 pts., mixed	SDD: topical (oral only)	P, M, (MV)	B	At least one of each of the following criteria: a) clinical criteria: fever, purulent bronchorrhea, leukocytosis, ↓PaO_2/FiO_2 b) radiologic criteria c) bacteriologic criteria: pos. culture of tracheal aspirate	Unclear	
Camus 2005 A[50]	RCT, placebo-controlled, multicenter	256 pts., mixed	SDD: topical (oral+GI) (control group: no regimen)	P, M, (MV), (LOS)	B	CDC-criteria[123]	48 h	- Study group received polymyxin plus tobramycin; control group received no regimen
Camus 2005 B[50]	RCT, placebo-controlled, multicenter	259 pts., mixed	SDD: topical (oral+GI) (control group: mupirocin/chlorhexidine)	P, M, (MV), (LOS)	B	CDC-criteria[123]	48 h	- Study group received polymyxin, tobramycin, nasal mupirocin and chlorhexidine wash; control group received

								nasal mupirocin and chlorhexidine wash only.
Ferrer 1994[111]	RCT, placebo-controlled, double-blind	80 pts., respiratory	SDD: topical (oral +GI)	P, M, MV, LOS	B	a) CXR b) purulent tracheal secretions c) fever d) leukocytosis or leukopenia	72 h	- All patients received iv-prophylaxis, - Data and definition of clinically suspected pneumonia abstracted
Gastinne 1992[124]	RCT, placebo-controlled, double-blind, multicenter	445 pts., medical, trauma, postoperative	SDD: topical (oral + GI)	P, M, (MV), LOS	B	a) CXR b) purulent tracheal aspirate c) fever d) leukocytosis e) >48h after admission	24 h	- Patients > 15 years
Hammond 1992[140]	RCT, double-blind, placebo-controlled	239 pts., medical, surgical and trauma	SDD: topical (oral +GI)	P, M, LOS	B	a) CXR (>48 h after admission) b) purulent bronchial secretions c) fever d) leukocytosis or left shift e) pos. Gram stain f) pos. tracheal aspirate culture g) $\downarrow PaO_2/FiO_2$	48 h	- All patients received IV-prophylaxis
Korinek 1993[196]	RCT, placebo-controlled, double-blind	123 pts., neurosurgical	SDD: topical (oral+GI)	P, M, MV, LOS	A	a) fever b) leukocytosis c) purulent sputum d) CXR e) pos. PSB or plugged telescoping catheter culture	5 d	
Langlois-Karaga 1995[206]	RCT, double-blind, placebo-controlled	97 pts., multiple-trauma	SDD: topical (oral+GI)	P, (MV)	A	a) purulent bronchial secretions b) fever c) leukocytosis d) CXR e) $\downarrow PaO_2/FiO_2$	48 h	- Patients ≥ 15 years
Lingnau 1997[211]	RCT, double-blind, placebo-controlled	310 pts., trauma	SDD: topical (oral+GI)	P, M, MV, LOS	A	a) purulent sputum b) pos. culture of bronchial secretions c) deterioration of lung function	48 h	- All patients received iv-prophylaxis - PTA group (polymyxin E, tobramycin, amphotericin B) and PCA group (polymyxin E, ciprofloxacin, amphotericin B) combined
Quinio 1996[279]	RCT, double-blind, placebo-controlled	148 pts., multiple trauma	SDD: topical (oral+GI)	P, M, MV, LOS	A	a) purulent tracheal aspirate b) fever c) leukocytosis d) CXR	Unclear	- Patients ≥16 years
Sanchez Garcia 1998 A[304]	RCT, placebo-controlled, double-blind	197 pts., medical, surgical	SDD: topical (oral+GI)	P, M, (MV), (LOS)	A	CXR plus at least three of the following: a) fever b) leukocytosis or leukopenia c) purulent tracheal aspirate d) pos. culture of lower airway secretions	48 h	- Patients ≥ 16 years - Sucralfate vs. antacids as possible confounding factor
Unertl 1986[356]	RCT	39 pts.,	SDD:	P, M, (LOS)	A	a) CXR	6 d	

		anesthesiologic, neurological, neurosurgical	topical (oral+GI)			b) purulent tracheobronchial secretions c) at least two of the following: - fever - leukocytosis or leukopenia - ↓PaO_2/FiO_2		
Verwaest 1997 A[367]	RCT, placebo-controlled	286 pts., mixed	SDD: topical (oral+GI) (ofloxacin-amphotericin B)	P, M, (LOS)	A	a) purulent tracheal aspirate (Gram stain) b) pos. tracheal aspirate culture c) fever d) leukocytosis e) CXR	48 h	- All patients received systemic iv ofloxacin prophylaxis
Verwaest 1997 B[367]	RCT, placebo-controlled	292 pts., mixed	SDD: topical (oral+GI) (polymyxin E-tobramycin-amphotericin B)	P, M, (LOS)	A	a) purulent tracheal aspirate (Gram stain) b) pos. culture from tracheal aspirate c) fever d) leukocytosis e) CXR	48 h	- All patients received systemic iv cefotaxime prophylaxis
Wiener 1995[377]	RCT, placebo-controlled, double-blind	61 pts., medical, surgical	SDD: topical (oral+GI)	P, M, (MV), (LOS)	B	a) CXR b) fever and/or leukocytosis c) pos. culture of lower respiratory tract secretions	48 h	
Abele-Horn 1997[4]	RCT	88 pts., mixed	SDD: topical (oral only) + systemic	P, M, MV, LOS	D	CPIS >7 for ≥3d[278]	4 d	
Aerdts 1990[8]	RCT	56 pts., mixed	SDD: topical (oral + GI) + systemic	P, M, (MV), (LOS)	D	Pos. culture and Gram stain of tracheal aspirate, plus at least two of the following: a) purulent tracheal aspirate b) leukocytosis c) fever	5 d	- Two control groups, receiving antibiotics effecting the colonizing resistance or not in case of infection, were grouped. - Patients ≥ 16 years; - Outcome: 'lower respiratory tract infection', not explicitly pneumonia
Blair 1991[31]	RCT	256 pts., mixed	SDD: topical (oral+GI) + systemic	P, M, (LOS)	B	a) fever b) leukocytosis or leucopenia c) CXR d) purulent sputum	Unclear	- 93% of patients intubated - Data of secondary infection (>48h in ICU) abstracted - Outcome 'respiratory infection', not explicitly pneumonia
Finch 1991[113]	RCT	44 pts., mixed	SDD: topical (oral + GI) + systemic	P, M	A	a) CXR b) systemic signs of sepsis c) evaluation of sputum obtained by tracheal aspiration or bronchoscopy	Unclear	- Unpublished data - Author contacted for methodological details, results extracted from review of D'amico et al. [77]
Hammond 1995[139]	RCT, placebo-controlled, double-blind	135 pts., mixed	SDD: topical (oral + GI) + systemic	P, M, LOS	B	a) CXR (>48 h after admission) b) purulent bronchial secretions c) fever d) leukocytosis or left shift e) pos. Gram stain f) pos. tracheal aspirate culture	48 h	- Patients with primary or secondary infection at study entry

						g) ↓PaO_2/FiO_2		
Kerver 1988[173]	RCT	96 pts., surgical	SDD: topical (oral +GI) + systemic	P, M, (LOS)	B	CXR plus at least three of the following: a) fever b) leukocytosis or leukopenia c) left shift d) decrease in platelet count	Unclear	- All patients also received chlorhexidine rinse - Outcome 'lower respiratory tract infection', not explicitly pneumonia
Krueger 2002[200]	RCT, double-blind, placebo-controlled, multicenter	546 pts., surgical, trauma	SDD: topical (oral+GI) + systemic	P, M, (MV), (LOS)	A	a) CXR or ↓PaO_2/FiO_2 b) purulent tracheobronchial secretions (Gram stain) c) at least one of the following: - fever - leukocytosis - leukopenia - left shift	Unclear	- Intubation rate: 93% (treatment group) vs. 92% (control group)
Palomar 1997[264]	RCT, multicenter	129 pts., medical, surgical	SDD: topical (oral+GI) + systemic	P, M	B	CDC-criteria[123]	4 d	- Third study group (sucralfate + iv–antibiotics) excluded
Rocha 1992[289]	RCT, placebo-controlled, double-blind	101 pts., mixed	SDD: topical (oral+GI) + systemic	P, M, MV, LOS	A	a) purulent pulmonary secretions b) CXR c) one of the following: - fever or hypothermia - leukocytosis or leukopenia - physical examination - ↓PaO_2/FiO_2	3 d	- Outcome 'lower respiratory tract infection', not pneumonia
Sanchez Garcia 1998 B[304]	RCT, placebo-controlled, double-blind	74 pts., medical, surgical	SDD: topical (oral+GI), systemic	P, M, (MV), (LOS)	A	CXR plus at least three of the following: a) fever b) leukocytosis or leukopenia c) purulent tracheal aspirate d) pos. culture of lower airway secretions	48 h	- Patients ≥ 16 years - Sucralfate vs. antacids as possible confounding factor
Stoutenbeek 2007[325]	RCT, multicenter	401 pts., trauma	SDD: topical (oral+GI) + systemic	P, M, (MV), (LOS)	A	a) CXR (>48 h) b) purulent tracheal aspirate c) fever d) leukocytosis or leukopenia	Unclear	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 40: Study characteristics Gastrointestinal Interventions: SDD with additional topical agents

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Konrad 1991[194]	RCT	40 pts., surgical	SDD: nasal gentamicin in addition to SDD: topical (oral+GI) + systemic	P, M	B	a) CXR b) purulent tracheal secretions with pos. Gram stain c) pos. bacterial culture d) one of the following: - fever - leukocytosis - pos. auscultation	4 d	
Laggner 1994[204]	RCT, double-blind, placebo-controlled	67 pts., mixed	SDD: orally administered gentamicin in addition to standardized amphotericin B	P, M, MV, LOS	A	a) CXR b) tracheal colonization c) fever d) leukocytosis or leukopenia	5 d	- All patients received sucralfate, amphotericin B and oral disinfectants
Nardi 2001[250]	RCT, double-blind	223 pts., mixed	Nasal mupirocin decontamination in addition to SDD: topical (oral+GI)	P, M, MV, LOS	A	a) CXR b) purulent tracheal secretions c) fever d) leukocytosis or leukopenia e) hypoxemia	48 h	- Data and definition of clinically suspected pneumonia abstracted

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 41: Study characteristics Gastrointestinal Interventions: Interventions to reduce the bacterial reflux load

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Colardyn 1990[66]	RCT	113 pts., medical	Sucralfate vs. H_2-antagonists (cimetidine)	P, M	B	Clinical and radiological criteria	Unclear	- Abstract
Cook 1998[71]	RCT, double-blind, placebo-controlled	1200 pts., mixed	Sucralfate vs. H_2-antagonists (ranitidine)	P, M, (LOS)	A	CDC-criteria[123]	48 h	- Data of CDC definition of pneumonia abstracted
Driks 1987 B[99]	RCT	38 pts., surgical, medical, coronary	Sucralfate vs. H_2-antagonists (cimetidine or ranitidine)	P, (M), (MV)	B	CXR plus at least three of the following: a) purulent sputum (Gram stain) b) pos. tracheal aspirate culture c) leukocytosis d) fever	24 h	- Control group divided through numbers of comparisons (three)

Eddleston 1991[101]	RCT	60 pts., mixed	Sucralfate vs. H_2-antagonists (ranitidine)	P, M, MV, LOS	B	a) CXR b) ↓PaO_2/FiO_2 c) pos. culture from tracheal aspirate d) fever or leukocytosis e) organism colonized in ascending order the stomach, oropharynx and trachea	4 d	- Patients ≥ 15 years
Fabian 1993[106]	RCT	278 pts., trauma	Sucralfate vs. H_2-antagonists (bolus or continuous cimetidine)	P, M, (LOS)	B	a) CXR b) purulent tracheal aspirate c) pos. culture d) fever e) leukocytosis	Unclear	- Cimetidine groups (bolus+continuous) combined
Kantorova 2004[169]	RCT, placebo-controlled	140 pts., trauma	Sucralfate vs. H_2-antagonists (famotidine)	P, M, MV, LOS	A	CXR plus at least 3 of the following: a) purulent tracheal aspirate b) leukocytosis or left shift c) fever d) pos. BAL, PSB or tracheal aspirate culture e) pos. blood or pleural fluid culture	48 h	- Placebo and proton pump inhibitor group excluded
Kappstein 1991[170]	RCT	104 pts., anesthesiologic	Sucralfate vs. H_2-antagonists (cimetidine)	P, M, (MV)	D	CXR plus at least three of the following: a) purulent tracheal secretions b) pos. culture of tracheal secretions c) leukocytosis d) fever	24 h	
Laggner 1989[203]	RCT	32 pts., mixed	Sucralfate vs. H_2-antagonists (ranitidine)	P, M, MV	B	a) CXR b) bronchial colonization c) leukocytosis d) fever	48 h	
Pickworth 1993[270]	RCT	92 pts., trauma	Sucralfate vs. H_2- antagonists (ranitidine)	P, M, (MV), (LOS)	B	CXR plus three of the following: a) fever b) leukocytosis c) pos. sputum culture d) pos. Gram stain	Unclear	- Patients ≥15 years
Prod'hom 1994 A[276]	RCT	122 pts., medical, surgical	Sucralfate vs. H_2- antagonists (ranitidine)	P, M	A	CXR plus at least one of the following: a) one of the following: -pos. pleural fluid or blood culture with same pathogen as isolated in tracheal aspirate - radiographic cavitation - histopathologic evidence b) At least two of the following: - pos. Gram stain - leukocytosis - fever	24 h	- Sucralfate group divided for comparison with the antacid and ranitidine group
Ryan 1993[299]	RCT	114 pts., medical, surgical	Sucralfate vs. H_2-antagonists (cimetidine)	P, M, (MV)	B	CDC-criteria[123]	48 h	- Patients >16 years
Stoehr 1998 A[323]	RCT	50 pts., surgical	Sucralfate vs. H_2-antaginists (ranitidine)	P, M	B	Unclear (conference report)	3 d	- All patients received subglottic lavage and suctioning

								- Various attempts to contact authors regarding pneumonia definition failed
Thomason 1996 A[337]	RCT	120 pts., trauma, surgical, neurosurgical	Sucralfate vs. H_2-antagonists (ranitidine)	P, M, (MV)	B	CXR plus three of the following: a) leukocytosis b) pos. tracheal or blood culture c) pos. Gram stain d) fever	24 h	
Tsiotras 1993[352]	RCT	100 pts., head trauma	Sucralfate vs. H_2-antagonists (ranitidine)	P, M, MV	B	a) CXR b) fever c) leukocytosis d) purulent tracheal secretions	48 h	
Bonten 1995[40]	RCT, double-blind	141 pts., mixed	Sucralfate vs. antacids	P, M, LOS	A	CXR, pos. BAL, PSB, blood or pleural fluid culture plus at least one of the following: a) fever or hypothermia b) leukocytosis and/or left shift or leucopenia c) pos. Gram stain	3 d	- Patients ≥ 15 years
Driks 1987 A[99]	RCT	59 pts., surgical, medical, coronary	Sucralfate vs. antacids	P, (M), (MV)	B	CXR plus at least three of the following: a) purulent sputum (Gram stain) b) pos. tracheal aspirate culture c) leukocytosis d) fever	24 h	- Control group divided through numbers of comparisons (three)
Mahul 1992 A[227]	RCT	145 pts., medical, surgical	Sucralfate vs. antacids	P, (M), (LOS)	B	a) CXR (after 48h of intubation) b) pos. BAL culture	3d	- No interactions between SDD and subglottic suctioning proven by statistical testing
Prod'hom 1994 B[276]	RCT	122 pts., medical, surgical	Sucralfate vs. antacids	P, M	A	CXR plus at least one of the following: a) one of the following: -pos. pleural fluid or blood culture with same pathogen as isolated in tracheal aspirate - radiographic cavitation - histopathologic evidence b) At least two of the following: - pos. Gram stain - leukocytosis - fever	24 h	- Sucralfate group divided for comparison with the antacid and ranitidine group
Thomason 1996 B[337]	RCT	122 pts., trauma, surgical, neurosurgical	Sucralfate vs. antacids	P, M, (MV)	B	CXR plus three of the following: a) leukocytosis b) pos. tracheal or blood culture c) pos. Gram stain d) fever	24 h	
Tryba 1987[346]	RCT	100 pts., surgical	Sucralfate vs. antacids	P, M, (MV)	B	CXR plus three of the following: a) fever b) leukocytosis c) bacteria in the tracheal smear	24 h	

						d) suggestive changes in the arterial blood gases		
Eddleston 1994[100]	RCT, placebo-controlled	26 pts., mixed	Sucralfate vs. placebo	P, M	B	a) CXR b) ↓PaO_2/FiO_2 c) pos. culture from tracheal aspirate d) fever or leukocytosis e) organism colonized in ascending order the stomach, oropharynx and trachea	Unclear	- Data of 'retrograde pneumonia' (see pneumonia definition (e)
Driks 1987 C[99]	RCT	33 pts., surgical, medical, coronary	Sucralfate vs. antacids + H_2-antagonists (cimetidine or ranitidine)	P, (M), (MV)	B	CXR plus at least three of the following: a) purulent sputum (Gram stain) b) pos. tracheal aspirate culture c) leukocytosis d) fever	24 h	- Control group divided through numbers of comparisons (three)
Maier 1994[228]	RCT	98 pts., trauma	Sucralfate vs. H_2-antagonists (ranitidine) + antacids	P, M, MV, LOS	B	CDC-criteria[123]	72 h	
Sirvent 1994[316]	RCT	51 pts., mixed	Sucralfate vs. H_2-antagonists (ranitidine) + antacids	P	B	a) fever b) leukocytosis c) purulent sputum d) CXR e) pos. bronchial brushing culture	5 d	- Article translated from Spanish.
Holzapfel 1990[159]	RCT	128 pts., mixed	H_2-antagonists (cimetidine) + antacids vs. no treatment	P	B	a) classical criteria b) pos. PSB culture	Unclear	- Abstract
Hanisch 1998 A[141]	RCT, placebo-controlled	72 pts., surgical	Pirenzepine vs. placebo	P, M, (MV), (LOS)	A	a) CXR b) purulent tracheal secretions or pos. tracheal aspirate culture c) fever d) leukocytosis	48 h	- Placebo group divided for comparison with ranitidine and pirenzepine - Comparison ranitidine vs. pirenzepine excluded
Hanisch 1998 B[141]	RCT, placebo-controlled	86 pts., surgical	H_2-antagonists (ranitidine) vs. placebo	P, M, (MV), (LOS)	A	a) CXR b) purulent tracheal secretion or pos. tracheal aspirate culture c) fever d) leukocytosis	48 h	- Placebo group divided for comparison with ranitidine and pirenzepine - Comparison ranitidine vs. pirenzepine excluded
Heyland 1999[151]	RCT, double-blind, placebo controlled	95 pts., mixed	Acidified enteral feeds vs. control feeds	P, M, (MV), (LOS)	A	Clinical evaluation plus at least one of the following: a) pos. pleural fluid culture b) rapid cavitation of lung infiltrate (CT) c) histopathologic evidence	48h	- Authors describe different pneumonia definitions and corresponding data
Tulaimat 2005[353]	RCT, double-blind, placebo-controlled	29 pts., respiratory	Acidified feeds (potassium sorbate) vs. standard feeding formula	P, M	A	CXR plus at least two of the following: a) fever or hypothermia c) leukocytosis or leukopenia d) purulent sputum e) pos. blood or pleural fluid culture for the same organism isolated from sputum or BAL fluid f) radiographic cavitation	Unclear	- Patients ≥16 years
Kostadima 2005[198]	RCT	41 pts., stroke or head injury	Early gastrostomy (within 24h of intubation) vs. nasogastric tube feeding	frequency of VAP, length of ICU stay, duration of MV,	B	American Thoracic Society: CXR plus at least two of the following: a) fever	Unclear	

				ICU mortality, mortality attributed to VAP		b) leukocytosis or leukopenia c) purulent tracheal aspirates		
Kearns 2000[171]	RCT	44 pts., medical	Small intestinal vs. gastric feeding	P, M, MV, LOS	A	CXR plus two of the following: a) leukocytosis b) fever c) pos. glucose test or blue discoloration in the endotracheal secretions	24 h	
Kortbeek 1999[197]	RCT	80 pts., trauma	Small intestinal (duodenum) vs. gastric feeding	P, M, (MV), (LOS)	A	CDC-criteria[123]	48 h	
Montecalvo 1992[244]	RCT	38 pts., medical and surgical	Small intestinal (jejunal) vs. gastric tube feeding	P, M, MV, LOS	B	CXR (>5 d) plus three of the following: a) purulent sputum (pos. Gram stain) b) pos sputum culture c) fever d) leukocytosis	Unclear	- Author confirmed MV rate of 100%
Bonten 1996[41]	RCT	60 pts., mixed, cardiosurgical	Intermittent enteral feeding (20 h continuous with a 4 h fast)	P, M	A	CXR, pos. BAL, blood or pleural fluid culture plus at least three of the following: a) fever or hypothermia b) leukocytosis and/or left shift or leukopenia c) pos. Gram stain d) pos. tracheal aspirate culture	3 d	- Patients ≥ 15 years
MacLeod 2007[224]	RCT	164 pts., trauma	Intermittent (every 4 h) vs. continuous enteral feeding	P, M, LOS	A	CDC-criteria[123]	48 h	
Skiest 1996[317]	RCT	16 pts., medical, surgical	Intermittent (16 h continuous with a 8 h fast) vs. continuous enteral feeding	P	B	a) CXR b) purulent tracheal secretions c) pos. tracheal secretion, pleural fluid or bronchoscopy culture d) leukocytosis or fever	4 d	
Tamowicz 2007[332]	RCT	40 pts., mixed	Intermittent (18h continuous with a 6h fast) vs. continuous enteral feeding	P	B	a) >48h of MV b) fever c) leukocytosis or leukopenia d) CXR e) physical examination f) ↓PaO_2/FiO_2 g) pos. PSB, endotracheal aspirate and blood culture	6 d	
Meisner 2003[237]	RCT, double-blind, placebo-controlled	84 pts., mixed	Enteral naloxone	P, M, (MV), (LOS)	A	CXR plus at least one of the following: a) leukocytosis or leukopenia b) fever or hypothermia	7 d	
Yavagal 2000[381]	RCT, double-blind, placebo-controlled	136 pts., mixed	Enteral metoclopramide (10mg every 8h)	P, (M)	B	a) CXR b) pos. tracheal or sputum culture c) fever d) leukocytosis or leukopenia	Unclear	- Subgroup data of mechanically ventilated patients abstracted

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 42: Study characteristics Gastrointestinal Interventions: H_2-antagonist vs. antacid

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Tryba 1988[347]	RCT	61 pts., surgical, anesthesiological	H_2-antagonist vs. antacid	P	B	a) CXR b) fever c) leukocytosis d) bacteria in tracheal swab e) major alterations in blood gases	unclear	- Subgroup of patients receiving MV

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 43: Study characteristics Gastrointestinal Interventions: Enriched enteral nutrition

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Caparros 2001[51]	RCT, single-blind, multicenter	220 pts., medical, surgical , trauma	High-protein diet enriched with arginine, fiber, and antioxidants	P, M, (MV), (LOS)	A	CXR, plus at least two of the following: a) fever or hypothermia b) leukocytosis or leukopenia c) pos. sputum, bronchial aspirates or bronchial brushing culture d) pos. blood culture e) antibody titer	5d	- MV rate: 96,7% (study group) vs. 98% (control group)
Houdijk 1998[160]	RCT	72 pts., multiple-trauma	Glutamine-enriched enteral nutrition	P, (MV)	A	CXR plus one of the following: a) leukocytosis b) fever c) pos. Gram stain d) pos. sputum culture	Unclear	
Mendez 1997[239]	RCT, placebo-controlled, double-blind	43 pts., trauma	Immune-enhancing diet (supplemental arginine, trace elements, increased omega-3 acids)	P, M, (MV), (LOS)	A	a) CXR b) fever c) leukocytosis d) pos. Gram stain and sputum culture	Unclear	- Author confirmed MV rate of 100%
Spindler-Vesel 2007[321]	RCT, double-blind, placebo controlled	113 pts., surgical	Enriched enteral nutrition (glutamine, fiber, peptide) vs. standard feeding	P, (MV), (LOS)	A	CDC-criteria and consensus conferences on VAP[123, 286]	Unclear	- Treatment groups A-C combined for comparison with control group D - Author confirmed MV rate of 100%

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 44: Study characteristics Gastrointestinal Interventions: Early enteral nutrition

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Ibrahim 2002[163]	RCT	150 pts., medical	High- vs. low-caloric early enteral feeding	P, M, (MV), LOS	B	American College of Chest Physicians: CXR: a) plus one of the following: - pos. pleural/blood cultures for the same organism cultured from tracheal aspirate or sputum - radiographic cavitation - histopathologic evidence b) or plus two of the following: - fever - leukocytosis - purulent tracheal aspirate	24 h	
Kompan 2004[193]	RCT	52 pts., trauma	Early enteral feeding (0 vs. 24h after admission)	P, M, MV, LOS	A	CXR plus at least two of the following: a) purulent tracheal aspirate b) fever c) leukocytosis	Unclear	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 45: Study characteristics Gastrointestinal Interventions: Enteral vs. parenteral feeding

Study ID	Methods	Participants, ICU type	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Kudsk 1992[201]	RCT	98 pts., trauma	Enteral vs. parenteral feeding	P, MV	B	a) fever b) leukocytosis c) pos. sputum/ BAL culture or purulent sputum d) CXR	Unclear	- Author confirmed MV rate of 100%

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 46: Study characteristics Positioning: Rotational Therapy

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Ahrens 2004[11]	RCT, multicenter	234 pts., medical, surgical, trauma	Kinetic therapy (arc of ≥80˚ for ≥18h per day) vs. manual turning every 2h	P, M, MV, LOS	D	American College of Chest Physicians: CXR (>48h of MV) plus one of the following: a) radiographic evidence of pulmonary abscess formation b) histologic evidence c) pos. blood or pleural fluid culture d) two of the following: - fever - leukocytosis - purulent tracheal aspirate	Unclear	
Demarest 1989[86]	RCT	30 pts., trauma	Kinetic therapy (arc of ≤120˚, continuously) vs. manual turning every 2h	P, M	A	a) purulent sputum b) CXR c) fever	Unclear	
Fink 1990[114]	RCT	99 pts., trauma	Kinetic therapy (arc of 80˚ for 10-16h per day) vs. manual turning every 2h	P, M, (MV), (LOS)	A	a) fever b) purulent sputum (Gram stain) c) pos. sputum culture d) CXR	Unclear	- MV-rate: 100% (control group) vs. 92.2% (treatment group)
Gentilello 1988[126]	RCT	65 pts., surgical	Kinetic therapy (arc of 124˚, continuously) vs. manual turning every 2h	P, M, MV, LOS	B	a) purulent tracheal aspirate and pos. Gram stain b) pos. bacterial cultures c) CXR d) leukocytosis or leukopenia or left shift e) fever	Unclear	- MV-rate of 100% confirmed by author
Kirschenbaum 2002[175]	RCT	37 pts., chronic ventilator unit	Continuous Lateral Rotation Therapy (CLRT) (arc of 60˚, 18h per day, plus percussion every 2h) vs. manual turning every 2 h	P, M, MV	D	a) fever b) CXR c) pos. BAL or deep tracheal aspirate culture	Unclear	- Only tracheostomized patients
MacIntyre 1999[223]	RCT, multicenter	104 pts., mixed	Continuous Lateral Rotation Therapy (CLRT) (arc of 60˚, continuously) vs. manual turning according to ICU standard	P, M	B	CXR (>24h after initiation of therapy) or pos. PSB culture plus at least two of the following: a) fever b) leukocytosis c) purulent sputum	24 h	- Outcome: ‘lower respiratory tract infection’, not explicitly pneumonia

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 47: Study characteristics Positioning: Prone vs. supine positioning

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Beuret 2002[29]	RCT	51 pts., comatose	Prone (4h per day) vs. supine positioning	P, M, MV, LOS	B	a) CXR b) purulent tracheal secretions c) pos. PSB culture	Unclear	
Guerin 2004[136]	RCT	781 pts., mixed	Prone (8h per day) vs. supine positioning	P, M, MV	A	CXR (>48h of MV), pos. BAL or Wimberley brush culture, plus at least one of the following: a) fever or hypothermia b) purulent tracheal aspirates c) leukocytosis or leukopenia	48 h	
Mancebo 2006[229]	RCT, multicenter	136 pts., mixed (with severe ARDS)	Prone vs. supine positioning (targeted daily 20-h prone sessions)	P, M, LOS	A	No standardized criteria. Every center applied own criteria	Unclear	- Author contacted for pneumonia criteria
Voggenreiter 2005[370]	RCT	40 pts., trauma	Prone vs. supine positiong (daily 8- to 23-h prone sessions)	P, M, MV	A	a) fever b) CXR c) pos. BAL culture	Unclear	- MV-rate of 100% confirmed by author

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 48: Study characteristics Positioning: Semirecumbent vs. supine positioning

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Keeley 2007[172]	RCT	30 pts., mixed	Semirecumbent positioning vs. 25° head of bed elevation	P	A	CXR plus at least two of the following: a) fever b) leucopenia or leukocytosis c) purulent tracheal secretions	24 h	- Data of clinically suspected pneumina abstracted
Drakulovic 1999[94]	RCT	86 pts., respiratory, medical	Semirecumbent vs. supine positioning	P, M, MV, LOS	A	CXR plus at least two of the following: a) fever	Unclear	- Data of clinically suspected pneumonia

						b) leucopenia or leukocytosis c) purulent tracheal secretions		abstracted
Nieuwenhoven 2006[364]	RCT, multicenter	221 pts., mixed	Semirecumbent vs. supine positioning	P, M, (MV), (LOS)	A	CDC-criteria[123]	48 h	- Data of clinically suspected pneumonia abstracted
Girou 2004[129]	RCT	18 pts., medical	Semirecumbent positioning (30°) and continuous subglottic secretion drainage vs. supine positioning	P, (MV)	B	a) fever b) leukocytosis c) purulent tracheal secretions d) CXR e) pos. PSB culture and/or pos. direct examination of BAL fluid	5d	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 49: Study characteristics ET tubes: Subglottic secretion drainage

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Bo 2000 [36]	RCT	68 pts., surgical	Subglottic secretion drainage	P, M	B	Modified CPIS >6[278]	72 h	- Article translated from Chinese - Suctioning intervals unclear
Liu 2006 [212]	RCT	108 pts., respiratory	Subglottic secretion drainage	P, M, MV	B	CXR plus at least two of the following: a) fever b) leukocytosis or leukopenia c) purulent secretions d) pos. sputum culture	48 h	- Article translated from Chinese - Suctioning intervals unclear
Mahul 1992 B [227]	RCT	145 pts., medical, surgical	Subglottic secretion drainage (1h intervals)	P, M	B	a) CXR (>48h of intubation) b) pos. BAL culture	3 d	- Stress ulcer prophylaxis and subglottic suctioning were tested for interaction
Metz 1998 [241]	RCT	24 pts., trauma, surgical	Subglottic lavage and secretion drainage (3h intervals)	P	B	a) fever b) leucocytosis or leucopenia c) CXR d) purulent tracheal secretions e) pos. BAL or tracheal secretions culture	3 d	We dropped the pharyngeal lavage group
Smulders 2002[319]	RCT	150 pts., general	Subglottic secretion drainage (20sec intervals) vs. standard endotracheal tube	P, M, MV, LOS	A	American College of Chest Physicians: CXR infiltrate plus: a) radiographic evidence for cavitation or histologic evidence or pos. blood culture b) pos. pleural fluid culture c) two of the following: - fever	72 h	

						- leukocytosis or leukopenia, - purulent tracheal aspirate		
Stohr 1998 B [323]	RCT	50 pts., surgical	Subglottic lavage and secretion drainage (4 h intervals) vs. standard endotracheal tube	P, M	B	Unclear (conference report)	Unclear	-Various attempts to contact authors regarding pneumonia definition failed
Valles 1995 [359]	RCT	152 pts., medical, surgical	Subglottic secretion drainage (continuous) vs. no drainage	P, M, (MV), (LOS)	B	a) fever b) leukocytosis or leucopenia c) purulent secretions d) CXR e) pos. PSB or BAL culture	72 h	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush; CPIS: Clinical Pulmonary Infection Score;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 50: Study characteristics ET Tubes: Silver coated endotracheal tube

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Rello 2006 [284]	RCT, single-blind, multicenter	121 pts., mixed	Silver coated tube vs. standard endotracheal tube	P, M, MV	B	Modified CPIS >6[278]	24 h	- CPIS>6 score was infection threshold, not explicitly 'pneumonia threshold'
Kollef 2008[186]	RCT, single-blind, multicenter	1509 pts., mixed	Silver coated tube vs. standard endotracheal tube	P, (M), (MV), (LOS)	A	Quantitative BAL fluid cultures obtained at suspicion of VAP or positive CXR plus 2 clinical signs (fever/hypothermia, leukocytosis/leukopenia, purulent tracheal aspirate)	24.h	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush; CPIS: Clinical Pulmonary Infection Score;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 51: Study characteristics ET Tubes: Automated control of endotracheal tube cuff pressure

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumonia	Min. duration of MV	Notes
Valencia 2007 [357]	RCT	142 pts., respiratory, general	Automated control of endotracheal tube cuff pressure vs. conventional management of the tube cuff pressure	P, M, LOS	A	CXR plus at least two of the following: a) fever or hypothermia b) leukocytosis or leucopenia c) purulent respiratory secretions.	48 h	

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used;

Table 52: Study characteristics Non-calssifyable Interventions

Study ID	Methods	Participants	Interventions	Outcomes	AC	Definition of pneumoniaeumonia	Min. duration of MV	Notes
Claridge 2007 [62]	RCT, double-blind, placebo-controlled	105 pts., trauma	Aerosolized ceftazidime	P, M, (MV), (LOS)	A	Pos. quantitative BAL cultures plus at least three of the following: a) leukocytosis or leukopenia b) fever or hypothermia c) CXR d) purulent secretions	Unclear	
Greenfield 1973 [134]	RCT	58 pts., respiratory-surgical	Aerosolized polymyxin	P, M, (MV), (LOS)	B	a) CXR b) pos. Gram stain of sputum c) pos. sputum culture d) evaluation of temp. course and white blood cell count	24 h	
Li 2002 [209]	RCT	114 pts., mixed	Aerosolized gentamicin	P	B	At least two of the following for >48h: a) fever or increase of at least 1˚C/day b) leukocytosis or leukopenia c) purulent sputum and pos. sputum culture d) CXR	4 d	- Article translated from Chinese
Wood 2002 [379]	RCT, placebo-controlled, double-blind	40 pts., trauma	Aerosolized ceftazidime	P, M, MV, LOS	A	Pos. BAL culture plus American College of Chest Physicians criteria for the systemic inflammatory response syndrome	7 d	- Patients ≥ 16 years
Acquarolo 2005 [6]	RCT	38 pts., general-neurological (brain injury)	Intravenous ampicillin-sulbactam (3-day regimen)	P, M, MV, LOS	A	a) CXR, b) pos. BAL or mini-BAL culture c) one of the following:	48 h	- Data of late-onset pneumonia abstracted

						- fever or hypothermia - leukocytosis or leucopenia		
Martinez-Pellus 1994 [235]	RCT	113 pts., trauma	Intravenous cefotaxime (4-day regimen) in addition to pharyngeal decontamination	P, M, MV, LOS	B	CDC-criteria:[123]	72 h	- Article translated from Spanish
Sirvent 1997[315]	RCT	100 pts., head injury or stroke	Intravenous cefuroxime (twofold high dose at intubation)	P, M, LOS	B	CXR, pos. BAL culture plus two of the following: a) fever b) leukocytosis c) purulent tracheal secretions d) ↓PaO2/FiO2 e) CPIS >6[278]	72 h	
Martinez-Pellus 1996 [236]	RCT	59 pts., trauma	Topical pharyngeal decontamination vs. topical tracheal decontamination	P, M, MV, LOS	B	CXR (>48h in ICU) plus at least one of the following a) fever b) leukocytosis c) ↓PaO_2/FiO_2	72 h	- Historical control group excluded - Article translated from Spanish
Holzapfel 1999 [157]	RCT	399 pts., mixed	Systemic search for maxillary sinusitis	P, M, MV, LOS	A	a) CXR b) fever or hypothermia c) leukocytosis or leucopenia and /or purulent tracheobronchial secretions d) pos. PSB culture	7 d	- Patients > 15 years
Ntoumenopoulos 2002 [258]	RCT, partly blinded	60 pts., medical, surgical, trauma	Chest physiotherapy twice daily	P, M, (MV), (LOS)	D	Clinical diagnosis and CPIS[278] of same calendar day	48 h	- ICU staff excluding physiotherapists were blinded to physiotherapy, physiotherapists were blinded to diagnosis of VAP
Ntoumenopoulos 1998 [257]	RCT	46 pts., trauma	Manual lung hyperinflation and postural drainage twice daily	P, M, MV, LOS	A	CXR plus at least three of the following: a) fever b) leukocytosis c) purulent sputum with bacteria on Gram stain d) pos. culture	24 h	- Data of confirmed pneumonia abstracted, since criteria for clinically suspected pneumonia insufficient
Heard 1998 A [143]	RCT, placebo-controlled, double-blind, multicenter	21 pts., traumatic head injury or intracerebral hemorrhage	Daily subcutaneous injection of recombinant human granulocyte colony-stimulating factor (filgrastim, 75µg)	P, (MV), (LOS)	B	a) CXR b) pos. quantitative culture of secretions from the lower respiratory tract If no bronchoscopy possible a) plus clinical criteria	72 h	- Control group divided for both comparisons
Heard 1998 B [143]	RCT, placebo-controlled, double-blind, multicenter	23 pts., traumatic head injury or intracerebral hemorrhage	Daily subcutaneous injection of recombinant human granulocyte colony-stimulating factor (filgrastim, 300µg)	P, (MV), (LOS)	B	a) CXR b) pos. quantitative culture of secretions from the lower respiratory tract If no bronchoscopy possible a) plus clinical criteria	72 h	- Control group divided for both comparisons
Pneumatikos 2002 [273]	RCT	79 pts., trauma	Selective decontamination of the subglottic area vs. placebo followed by	P, M, MV, LOS	B	Clinical and laboratory data plus pos. PSB culture	5 d	

			subglottic secretion drainage					
Manzano 2008[231]	RCT	127 pts., general, trauma	Early application of PEEP in nonhypoxemic pts.	P, M, (MV), (LOS)	A	CDC-criteria[123]	48 h	
Pepe 1984 [269]	RCT	92 pts., mixed	Early vs. late application of PEEP	P, M	B	a) pos. culture from endotracheal aspirate b) fever c) leukocytosis d) CHR, congestive heart failure or extensive atelectasis	Unclear	
Porter 1999 [274]	RCT	18 pts., trauma	Antioxidant therapy (selenium, vitamin E, vitamin C, N-acetycysteine) vs. no treatment	P, LOS	A	a) fever b) leukocytosis c) CXR d) change in sputum quality or quantity e) pos. sputum Gram stain f) pos. PSB or BAL culture	unclear	- Patients ≥15 years - Author confirmed MV-rate of 100%
Berger 2006 [24]	RCT, placebo-controlled, double-blind	35 pts., burn center	Antioxidant therapy (selenium, copper and zinc) vs. placebo	P, (M), (MV), (LOS)	B	a) SIRS (fever, tachycardia, leukocytosis) b) CXR c) hypoxemia d) purulent sputum or tracheal secretion e) pos. BAL or mini-BAL culture f) >48h of MV	24h	- Two trials combined - Only patients with MV >24h included
Di Filippo 1999 [91]	RCT, double-blind	48 pts., mixed	Endonasal mupirocin (3× for 3d) vs. placebo	P	B	a) at least one of classic sepsis criteria (tachycardia, hypocapnia or hyperventilation, fever or leukocytosis) b) purulent sputum ± CXR c) pos. PSB culture	48h	- Article translated from Italian - Outcome: MRSA pneumonia

Abbreviations: RCT: randomized controlled trial; pts: patients; CXR: chest X-ray; BAL: bronchoalveolar lavage; PSB: protected specimen brush; CPIS: Clinical Pulmonary Infection Score;

Outcomes: P: pneumonia, M: mortality, MV: duration of mechanical ventilation, LOS: length of stay, Outcome in brackets: data reported but not abstractable;

AC: allcocation concealment: A=adequate, B=unclear, C=inadequate, D=not used

b) Study characteristics of excluded trials

Table 53: Excluded trials with reason for exclusion

Study ID	Reason for exclusion	Intervention Group
Adams 1997 [7]	Liver transplant patients	AM
Aerdts 1991 [9]	Double publication (see Aerdts 1990, J Antimicrob Chemother)	GI
Apte 1992 [14]	31% (study group) vs. 22% (control group) mechanically ventilated	GI
Armstrong 1992 [15]	No pneumonia data, no % of MV	GI
Badger 1991 [17]	Liver transplant patients	GI
Barker 2002 [18]	No pneumonia/VAP as an outcome	NC
Ben-Menachem 1994 [22]	65% (control), 72% (sucralfate) and 76% (cimetidine) mechanically ventilated	GI
Beuret 2002 [29]	Double-publication (see Beuret 2002, Intensive Care Med)	P
Blot 2003 [33]	Study protocol, no trial	AM
Blunt 2001 [35]	No pneumonia as an outcome	ET
Boldt 1999 [38]	No RCT, no VAP	NC
Brook 1999 [49]	No pneumonia as an outcome	NC
Cerra 1992 [53]	Pneumonia data not abstractable since not number of patients but number of episodes reported	GI
Chastre 2005 [55]	Abstract of Kollef 2006	OC
Chen 2006 [58]	No abstractable pneumonia data	GI
Choi 2005 [60]	No RCT	AM
Cioffi 1994 [61]	60% (antacids+cimetidine-group) vs. 58% (sucralfate-group) of patients intubated	GI
Clini 2006 [63]	Patients not MV	NC
Cockerill 1992 [65]	89% vs.80% intubated	GI
Croton 1981 [76]	No ICU patients, postop. patients	NC
Daschner 1988 [79]	Randomization? No response from author	AM
Davis 2000 [80]	Abstract of Davis 2000 Crit Care Med	AM
De Jonge 2003 [82]	No outcome VAP or Pneumonia treatment group: 83.7% intubated control group: 86.9% intubated	GI
De La Cal 2005 [83]	74% (treatment group) vs. 80% (control group) intubated	GI
deBoisblanc 1993 [84]	86% (study group) vs. 84% (control group) mechanically ventilated	P
Demetriou 1993 [87]	No RCT, comment on original publication (Montecalvo 1992)	GI
DeRiso 1996 [89]	Heart surgery patients	OC
Douzinas 2006 [93]	Patients all already had VAP; gastro-esophageal reflux, not VAP is outcome of this trial	GI
Dries 2004 [98]	Retrospective study, no RCT	AM
Ephgrave 1998 [105]	No report on % of ventilated patients, author contacted: most patients were intubated over night, but only 25-35% for >48h	GI
Fagon 2000 [108]	No preventive strategy	AM
Ferrer 2006 [112]	Control group not MV	AM
Flaherty 1990 [116]	Open heart surgery patients, mean duration of mech. vent. 1.8 days	GI
Freytag 2003 [120]	No pneumonia/VAP as outcome	AM
Geroulanos 1986 [127]	Cardiac surgery patients	NC
Gosney 2006 [132]	None of the patients required mech. vent.	GI
Grap 2004 [133]	No incidence of VAP reported. Author contacted but no response.	OC
Hammarqvist 1999 [137]	Double-publication: same contents as original Houdijk-publication (Lancet 1998)	GI
Hammond 1993 [138]	Subgroup analysis of patients included in study published by Hammond in the Lancet 1992	GI
Heslet 2002 [145]	No RCT	
Hoffer 1999 [156]	No VAP as outcome, no % of mechanically ventilated patients, not the intervention and study population we are looking at	GI
Houston 2002 [161]	Cardiovascular patients	OC
Kindgen Milles 2002 [174]	Excluded patients requiring mech. vent. for >48h	AM
Kirton 1997 [177]	Patients included in Kirton 1997 in Chest	AM
Klastersky 1974 [178]	25.5% (study group) vs. 21.4% (control group) MV	NC
Kollef 1999 [191]	Cardiac Surgery Patients	ET
Konrad 1995 [195]	No pneumonia/VAP as an outcome	NC
Leur 2003[361]	Pneumonia episodes, not cases reported; no preventive strategy for VAP	AM
Levy 1997 [208]	72% (ranitidine group) vs. 50% (omeprazole group) mechanically ventilated	GI
Lode 1992 [213]	No RCT	NC
Mandelli 1989 [230]	48.1% (cefoxitin group) vs. 44.9% (penicillin group) vs. 47.7% (control group) intubated at admission	GI
Martin 1993[234]	Not clear how many % of patients intubated; attempt to contact author considering the definitions for study entry it is unlikely	GI
Metz 1993[240]	93% (study group) vs. 80% (placebo group) mechanically ventilated	GI
Mustafa 1995[249]	Letter, no RCT	GI
Nathens 2002[252]	Only about 80% MV (author contacted)	NC
Nelson 1992[254]	No abstractable pneumonia/VAP data, only “pulmonary process complications”	P
Normand 2005[256]	No pneumonia/VAP as outcome	OC

Ogata 2004[259]	No pneumonia/VAP as outcome	OC
Okuda 2003[260]	No pneumonia/VAP as an outcome, not our study population	OC
Ong 2004[261]	No abstractable pneumonia data	NC
Ortiz 1998[263]	No VAP/pneumonia as outcome	GI
Palomar 1992[265]	Double publication; patients included in publication of Palomar 1997	GI
Rathgeber 1993[281]	Children included	NC
Rossi 2004[292]	No ICU or critically ill patients	NC
Ruiz 1998[296]	No preventive strategy, diagnostic strategy	NC
Ruiz 1998[297]	No preventive strategy, diagnostic strategy	NC
Sacks 2003[300]	No RCT	NC
Segers 2006[305]	Cardiac surgery patients	OC
Siempos 2007[309]	No RCT	OC
Silvestri 2007[312]	No RCT	GI
Simms 1991[313]	No report on % of intubated patients at admission; at diagnosis of pneumonia 78% intubated	GI
Stoller 2003[324]	Not randomized, no RCT	AM
Strong 1992[327]	Not our study population, "malnoutrished, hospitalized patients"; unclear, how many % of patients intubated	GI
Traver 1995[344]	89.8% vs. 88.7% mechanically ventilated	P
Tryba 1988[351]	Double publication (J Clin Anesth 1988)	GI
Tulli 1986[354]	Post-op patients, not our study population	GI
Ulrich 1989[355]	77% (treatment group) vs. 83% (control group) mechanically ventilated	GI
Valles 1991[360]	Preliminary data of Valles 1995, Ann Int Med	ET
Van Enckevort 2001[362]	Liver transplant patients; no VAP as outcome	GI
Van Nieuwenhoven 2004[363]	No RCT, no VAP/pneumonia as outcome	GI
Van Saene 2006[365]	No RCT	GI
Vogel 1981[369]	No RCT	NC
Whiteman 1995[376]	Liver transplant patients	P
Winter 1992[378]	Control group partly retrospectively studied, 85% mechanically ventilated (author contacted)	GI
Wood 2007[380]	No RCT, review	NC
Young 1999[382]	No pneumonia/VAP as an outcome	ET
Young 2006[383]	No pneumonia/VAP as an outcome	ET
Zeitoun 2001[385]	Abstract of Zeitoun 2003-J Clin Nurs	AM
Zhang 2004[386]	No VAP as outcome	P
Zwaveling 2002[387]	Liver transplant patients	GI

Abbreviations: AM: Airway Management, ET: Endotracheal Tube, GI: Gastrointestinal Inetrventions, NC: Not Classifyable, OC: Oral Care, P: Positioning,

c) Table of guideline recommendations

Table 54: Table of guideline recommendations

	Torres 2001[340]	Collard 2003[67]	Tablan 2004 (CDC-guideline)[331]	Dodek 2004[92]	Am. Thor. Soc. Guidelines 2005[3]	Muscedere 2008[248]	Metaanayltic results and recommendations
Oral Care							
Antiseptic Decontamination							
Chlorhexidine			no recommendation for routine use		no recommendation for routine use	should be considered	++
Povidone-Iodine						should be considered	++
Iseganan						not recommended	+/-
Airway Management							
Tracheostomy				no recommendation		no recommendation	+/-
Weaning							
Weaning protocol					recommended		(+)
Non-invasive MV	probably beneficial but should be investigated		recommended		recommended		++
Closed vs. open endotr. suct.	still controversial		no recommendation	closed suctioning system recommended		closed suctioning system recommended	+/-
Daily vs. no daily change of in-line suction catheters	still controversial		no recommendation			change for every new patient recommended	+/-
Heat and moisture exchanger vs. heated humidifier	still controversial	no recommendation	no recommendation	heat and moisture exchangers recommended	no recommendation	no recommendation	+/-
Extended use of heat and moisture exchanger		less changes recommended	not routine change more frequently than every 48 h	weekly changes		extended use of 5-7 days	(+)
Components os heat and moisture exchanger							+/-
Change of ventilator circuits (less frequent)	weekly changes	less changes recommended	no routine changes	no routine changes		no scheduled changes	(+)
Heated vs. non-heated wire circuits							+/-
Oro- vs. nasotracheal intubation	orotracheal intubation recommended		orotracheal intubation recommended	orotracheal intubation recommended	orotracheal intubation recommended	orotracheal intubation recommended	(+)
Bacterial filter			no recommendation			not recommended	+/-

	Torres 2001[340]	Collard 2003[67]	Tablan 2004 (CDC-guideline)[331]	Dodek 2004[92]	Am. Thor. Soc. Guidelines 2005[3]	Muscedere 2008[248]	Metaanayltic results and recommendations
Gastrointestinal Interventions							
Selective Decontamination of the digestive tract (SDD)	recommendation for subgroups of patients	no recommendation	no recommendation for routine use	no recommendation	no recommendation for routine use	no recommendation	++
SDD with additional topical antibiotics							+/-
Interventions to reduce the bacterial reflux load							
Sucralfate vs. H2-antagonists	still controversial	recommendation for sucralfate	no recommendation		recommendation for sucralfate and H2-antagonists		++
Sucralfate vs. Antacids	still controversial	recommendation for sucralfate	no recommendation				(+)
Sucralfate vs. Placebo	still controversial		no recommendation	no recommendation			+/-
Sucralfate vs. H2-antagonists + antacids	still controversial		no recommendation				(+)
No treatment vs. H2-antagonists +antacids	still controversial	recommendation for sucralfate	no recommendation				+/-
Placebo vs. Pirenzepine							+/-
Placebo vs- H2-antagonist							+/-
Acidified enteral feeds		no recommendation	no recommendation				+/-
Early gastrostomy							(+)
Small intestinal vs. Gastric feeding		no recommendation	no recommendation				+/-
Intermittent enteral feeding		no recommendation	no recommendation				+/-
Enteral naloxone							(+)
Enteral metoclopramide		not recommended					+/-
H2-antagonist vs. Antacid							+/-
Enriched enteral nutrition		no recommendation (glutamine)					+/-
Early enteral nutrition	still controversial						+/-
Enteral vs. Parenteral feeding					enteral feeding recommended		++

Appendix

	Torres 2001[340]	Collard 2003[67]	Tablan 2004 (CDC-guideline)[331]	Dodek 2004[92]	Am. Thor. Soc. Guidelines 2005[3]	Muscedere 2008[248]	Metaanayltic results and recommendations
Positioning							
Rotational therapy		consideration in select patient populations (surgical, neurological)	no recommendation	should be considered		should be considered	++
Prone vs. Supine positioning				no recommendation		no recommendation	(+)
Semirecumbent vs. Supine positioning	recommended	recommended	recommended	recommended	recommended	recommende	(+)
Endotracheal tubes							
Subglottic secretion drainage	still controversial	no recommendation for general use	Recommended	Recommended	Recommended	recomended in pts. ventilated 72h	++
Silver coated tube							++
Automated cuff presure control							+/-
Non-classifyable preventive strategies							
Aerosolized antibiotics						no recommendation	++
Intravenous antibiotics	still controversial		no recommendation	no recommendation	no recommendation for routine use	no recommendation	++
Pharyngeal vs. tracheal decontamination							+/-
Systemic search for maxillary sinusitis				no recommendation		no recommendation	(-)
Chest physiotherapy				no recommendation			++
Manual lung hyperinflation							+/-
Granulocyte colony-stimulating factor			no recommendation				+/-
Decontamination of the subglottic area							++
Early PEEP							+/-
Antioxidant therapy							++
Endonasal mupirocin						no recommendation	+/-

Abbreviations: ++ recommended or statistically significant, (+) probably beneficial but non-significant, +/- equivocal or no recommendation, (-) possibly harmful and therefore not recommended, -- should be avoided because harmful