Prevention of VAP in ICU

DM Seminar

Pawan K. Singh

Contents

1. VAP introduction
2. Oral care
3. ET modifications
4. Suction and humidification
5. Probiotics
6. Stress ulcer prophylaxis
7. Antibiotics and VAT
8. Misc.

VAE: Ventilator related events

- VAC (Ventilator associated conditions): after improvement for 2 days or more increase in PEEP (>3 cm H_2O) or FiO_2 (>20%)
- IVAC (infection related VAC): body temperature (>38° C or <36°C) or TLC (<4,000/µL or > 11,000/µL) with starting of one antibiotic that is continued for 4 days **+ VAC**
- VAP: **IVAC +** positive ETA g/s or culture

NHSN Surveillance Guidelines for Diagnosis of VAE

Name: Description	Dependent Qualification	Definition
VAC: new respiratory deterioration	≥2 calendar days of stable or decreasing daily minimum PEEP or daily minimum F_{IO_2}	Followed by a daily Minimum PEEP of ≥3 cm H_2O OR Minimum F_{IO_2} by >20 points sustained for ≥2 calendar days
iVAC: VAC + clinical signs of infection	Within 2 calendar days before or after onset of a VAC Excludes the first 2 d of mechanical ventilation	Temperature: <36°C or >38°C OR Leukocyte count: ≤4000 or ≥12,000 cells/mm^3 AND One or more new antibiotics continued for ≥4 d
Possible VAP: IVAC + qualitative evidence of pulmonary infection	Within 2 calendar days before or after onset of a VAC Excludes the first 2 d of mechanical ventilation	Gram staining of endotracheal aspirate or BAL showing ≥25 neutrophils and ≤10 epithelial cells per low-power field OR Positive culture from sputum, endotracheal aspirate, BAL, lung tissue

Probable VAP: IVAC + quantitative evidence of pulmonary infection	Within 2 calendar days before or after onset of a VAC Excludes the first 2 d of mechanical ventilation	Positive culture of endotracheal aspirate $\geq 10^5$ CFU/mL, or positive BAL culture with $\geq 10^4$ CFU/mL, or positive culture of protected specimen brush $\geq 10^3$ CFU/mL OR One of the following (without requirement for purulent secretions) Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from indewelling chest tube) Positive lung histopathology Positive diagnostic test for legionella Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

	Klompas et al. 2011* (N=44)	Hayashi et al. 2013 (N=153)	Klein Klouwenberg et al. 2014* (N=81)	Kollef et al. 2014 (N=67)	All Studies Combined* (N=345)
Pneumonia and/or aspiration	10 (23%)	66 (43%)	28 (35%)	21 (31%)	125 (36%)
Pulmonary edema, pleural effusion, and/or heart failure	8 (18%)	40 (26%)	39 (48%)	10 (15%)	97 (28%)
Atelectasis	5 (11%)	25 (16%)	12 (15%)	6 (9.0%)	48 (14%)
Acute respiratory distress syndrome	7 (16%)	10 (6.5%)	-	14 (21%)	31 (9.0%)
Mucous plugging	1 (2%)	-	-	-	1 (0.3%)
Abdominal distension / compartment syndrome	1 (2%)	2 (1.3%)	9 (11%)	-	12 (3.5%)
Pulmonary embolus	1 (2%)	3 (2.0%)	-	-	4 (1.2%)
Pneumothorax	-	-	2 (2.5%)	2 (3.0%)	4 (1.2%)
Radiation pneumonitis	1 (2%)	-	-	-	1 (0.3%)
Sepsis syndrome / extra-pulmonary infection	1 (2%)	-	9 (11%)	3 (4.5%)	13 (3.8%)
Poor pulmonary toilet	1 (2%)	-	-		1 (0.3%)
Acute neurological event	-	-	10 (12%)		10 (2.9%)
Transfusion-associated lung injury	-	-	-	2 (3.0%)	2 (0.6%)
Other	-	-	-	9 (13%)	9 (2.6%)
No apparent pulmonary complication	18 (41%)	17 (11%)	10 (12%)	-	45 (13%)

See et al Infect Control Hosp Epidemiol. 2016 Jul;37(7):818-24

Summarizing

- Majority of VAEs are caused by four conditions:
  - **Pneumonia accounted for about 25-40% of VAEs**
  - Fluid overload for 20-40%
  - Atelectasis for 10-15%
  - ARDS for 10-20%

Incidence and effect

- 38 % of the patients ventilated for more than 48hrs develop VAP
- Incidence of 40.1 VAP /1000 Mechanical ventilation days
- **Duration** of hospital stay doubles after VAP
- **Cost** increases 2.48 times after development of VAP
- *Acinetobacter baumannii* is the most common organism followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*
- VAP increased **mortality** upto 10 to 32%

Mathai et al J Infect Public Health. 2015 Mar-Apr;8(2):127-35

What we know so far?

Table 18: Preventive strategies for VAP

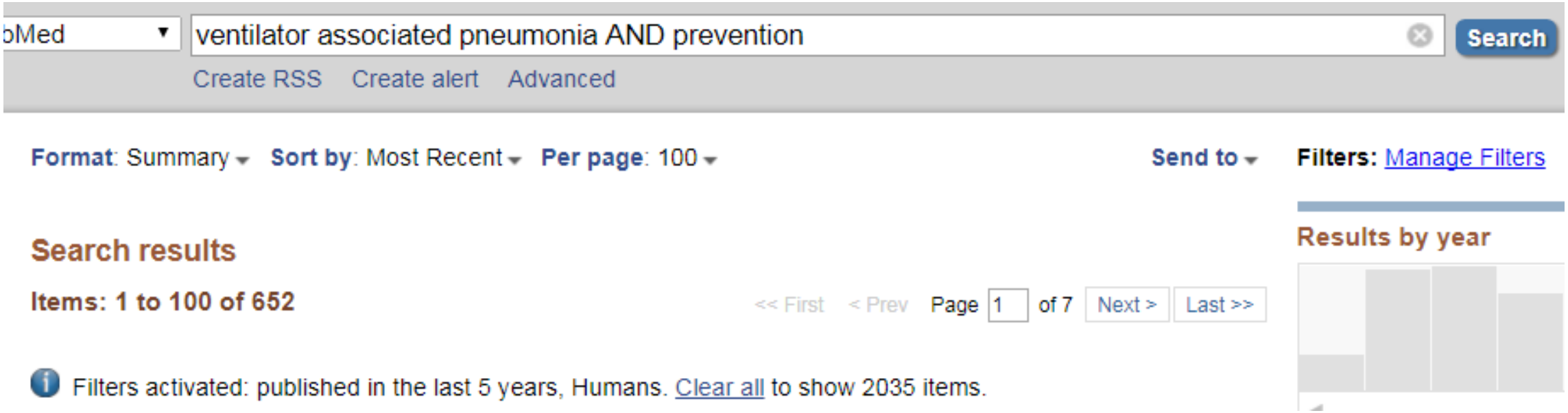
The following strategies are recommended in prevention of VAP:
Oral cavity decontamination with 2% chlorhexidine (1A)[412-415]
Hand hygiene preferably using alcohol-based hand rubs or soap and water (1A)[416]
Use of sedation and weaning protocols (1A)[419,420]
Use of NIV to avoid intubation, where feasible (1A)[264,421]
Subglottic secretion drainage (2A)[422,423]
Heat moisture exchangers in place of heated humidifiers (2A)[424-428]
Closed suction systems (2A)[429-431]
Use of orotracheal intubation as opposed to nasotracheal intubation (2A)[432,433]
Proper and timely disposal of condensates (3A)[434,435]
Maintaining tracheal cuff pressures <25 cm H_2O (2A)[436]
Wipe stethoscopes with alcohol rubs (2A)[437]
Regular postural mobilization to prevent stasis of secretions (2A)
Use of only normal saline for suctioning (3A)
Proper sterilization of nebulizer and other chambers (2A)
Head end elevation to 30°–45° (2A)
The following strategies are not recommended in prevention of VAP:
Antibiotics for prevention of VAP (2A)
Selective digestive tract decontamination (2A)[438]
Routine ventilator circuit changes (2A)[439,440]
Early tracheostomy (2A)

Gupta et al Lung India 2012 Jul-Sep; 29: S27–S62.

At the end of this seminar we should be…

- Aware of the current concepts in VAP prevention
- Look at new novel methods of VAP prevention and evidence behind them
- Substantiate the evidence behind the already established methods of VAP prevention
- Address the controversies regarding VAP prevention
- And Finally able to formulate ***“VAP prevention bundle for RICU”***

Evidence in Last 5 years

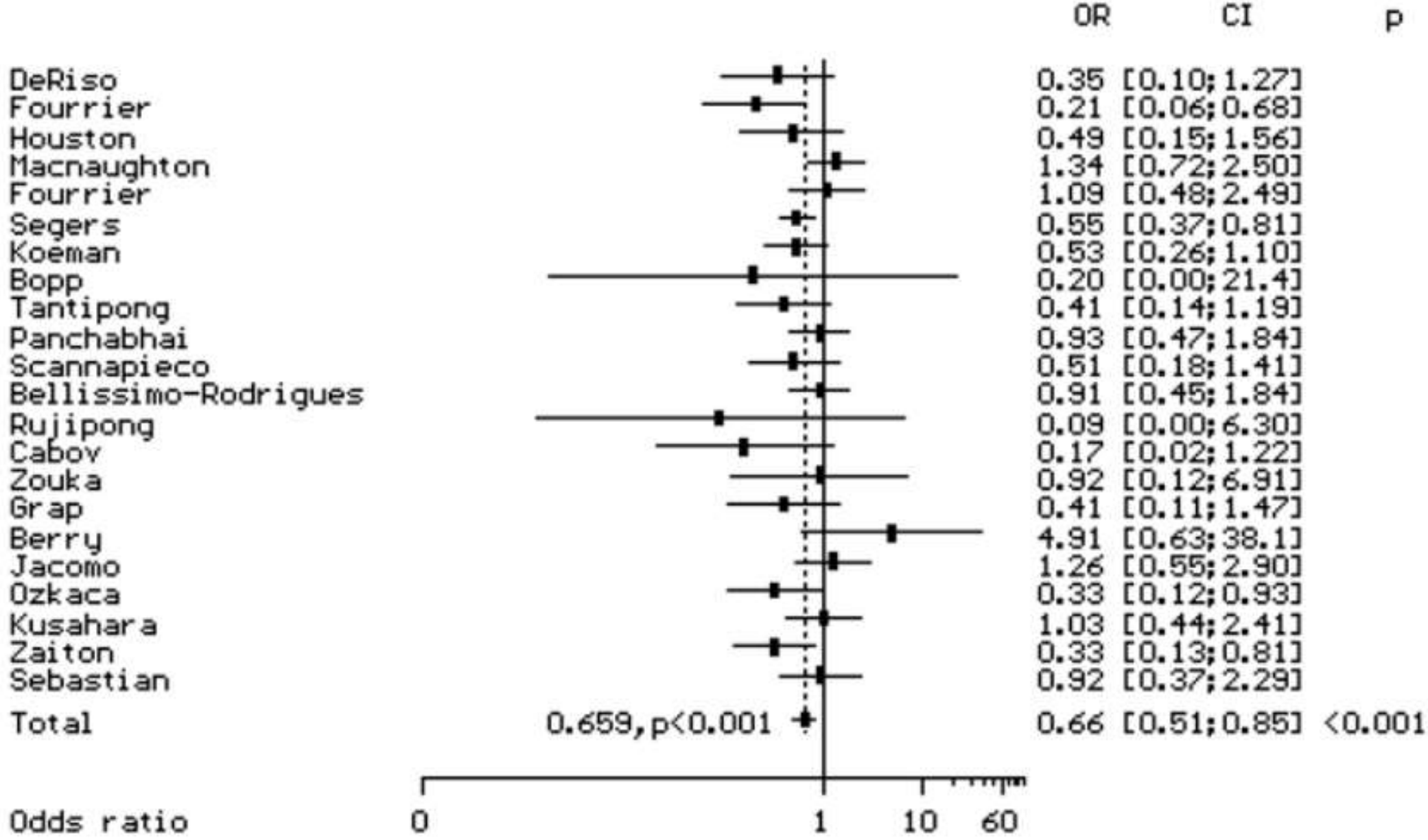


Section 1. Oral Care

Effectiveness of oral CHX: A systematic review

- **Methods**: Twenty-two randomized trials including 4277 patients were identified.
- **Results**: Chlorhexidine significantly reduced the incidence of nosocomial pneumonia (OR 0.66; 95% confidence interval [CI] 0.51-0.85) and ventilator-associated pneumonia (OR 0.68, 95% CI 0.53-0.87).
- No effect on mortality.

Silvestri et al Minerva Anestesiol 2014 Jul;80(7):805-20


OR
CI
p
DeRiso
Fourrier
Houston
Macnaughton
Fourrier
Segers
Koeman
Bopp
Tantipong
Panchabhai
Scannapieco
Bellissimo-Rodrigues
Rujipong
Cabov
Zouka
Grap
Berry
Jacomo
Ozkaca
Kusahara
Zaiton
Sebastian
Total
0.659, p<0.001
0.35 [0.10; 1.27]
0.21 [0.06; 0.68]
0.49 [0.15; 1.56]
1.34 [0.72; 2.50]
1.09 [0.48; 2.49]
0.55 [0.37; 0.81]
0.53 [0.26; 1.10]
0.20 [0.00; 21.4]
0.41 [0.14; 1.19]
0.93 [0.47; 1.84]
0.51 [0.18; 1.41]
0.91 [0.45; 1.84]
0.09 [0.00; 6.30]
0.17 [0.02; 1.22]
0.92 [0.12; 6.91]
0.41 [0.11; 1.47]
4.91 [0.63; 38.1]
1.26 [0.55; 2.90]
0.33 [0.12; 0.93]
1.03 [0.44; 2.41]
0.33 [0.13; 0.81]
0.92 [0.37; 2.29]
0.66 [0.51; 0.85]
<0.001
Odds ratio
0
1
10
60

CHX… ok! but ***Concentration***?- a meta-analysis

- **Methods**: Eighteen RCTs were included and a meta-analysis was used (n= 1918). All studies indicated chlorhexidine could significantly prevent and reduce the incidence of VAP
- **Results**: Nine studies showed 0·12% chlorhexidine had a significant effect [RR = 0·53, 95% CI (0·43-0·67), p < 0·00001]. Three studies proved the adequate effect of the 0.2% chlorhexidine on the prevention of VAP [RR = 0·55, 95% CI (0·37-0·81), p = 0·002].
- **Conclusion**: Concertation of CHX should be equal to greater than 0.12% w/v

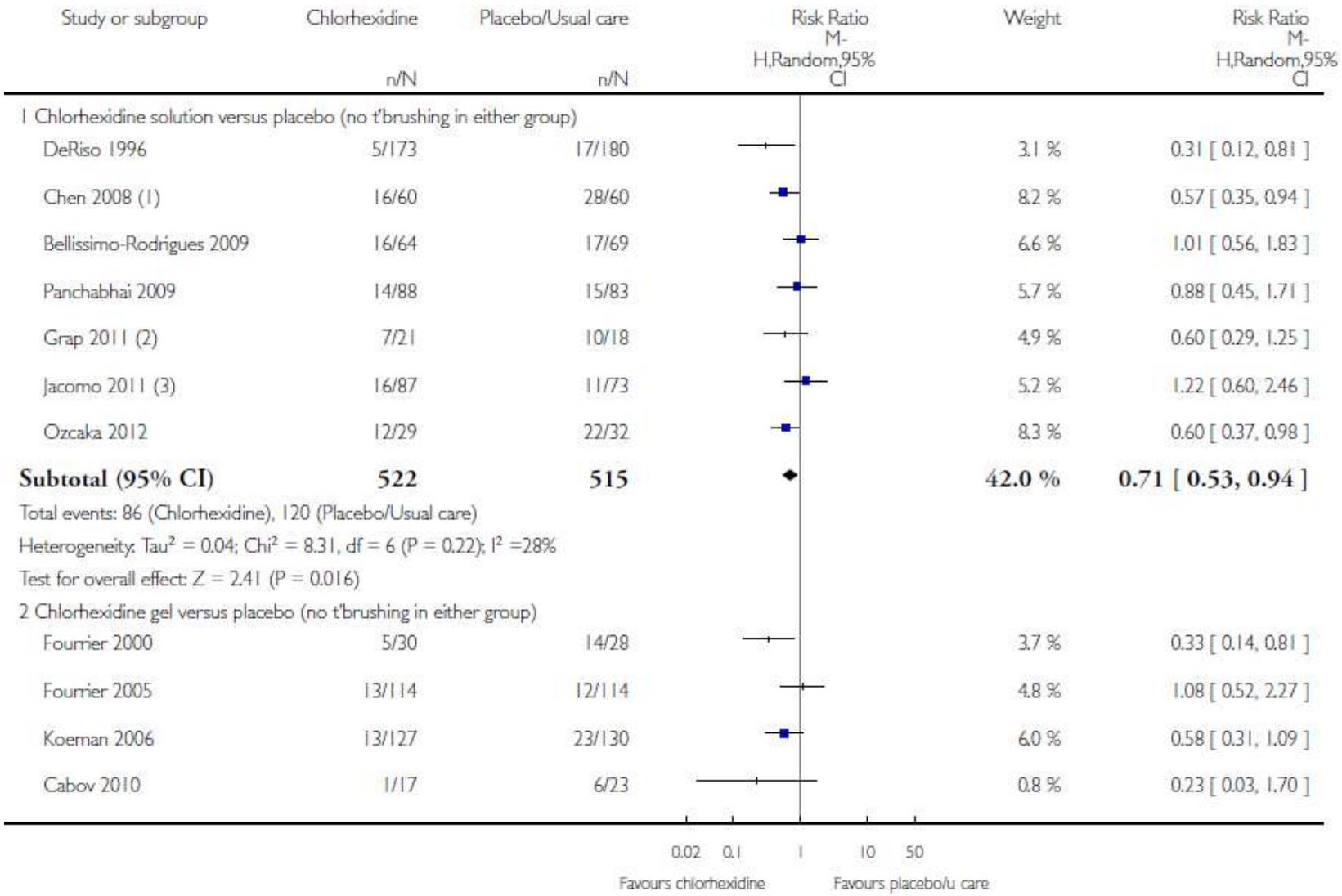
Zhang et al J Clin Nurs. 2014 Jun;23(11-12):1461-75

Oral hygiene care: Components

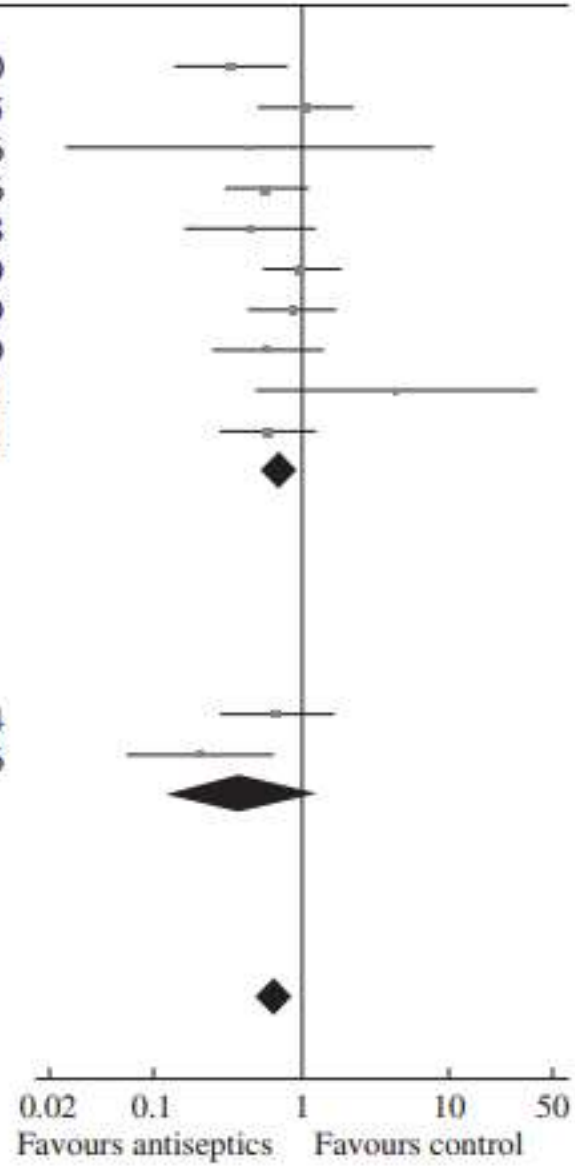
- **Methods:** 38 RCTs (6016 participants). Main comparisons: CHX mouthrinse or gel Vs placebo; toothbrushing Vs no toothbrushing; and comparisons of oral care solutions.
- **Results:** CHX mouthrinse or gel, as part of OHC, reduces the risk of VAP compared to placebo from 25% to about 19% (RR 0.74, 95% CI 0.61 to 0.89, P = 0.002). NNT of 17.
- There is no evidence of a difference in outcomes of mortality, duration of MV or duration of ICU stay
- Effects of toothbrushing on the outcomes of VAP is unknown.
- Povidone iodine is more effective than saline/placebo

Hua et al Cochrane Database Syst Rev. 2016 Oct 25;10:CD008367.

Incidence of VAP



First author or subgroup	Favours experimental		Control		Weight	Risk ratio	Year	Risk ratio
	Events	Total	Events	Total		M-H, random, 95% CI		M-H, random, 95% CI
2.1.1 Chlorhexidine								
Fourrier[26]	5	30	15	30	8.2%	0.33 (0.14, 0.80)	2000	
Fourrier[29]	13	114	12	114	10.5%	1.08 (0.52, 2.27)	2005	
Bopp[30]	0	2	1	3	1.0%	0.44 (0.03, 7.52)	2006	
Koeman[31]	13	127	23	130	12.9%	0.58 (0.31, 1.09)	2006	
Tantipong[34]	5	58	10	52	6.6%	0.45 (0.16, 1.23)	2008	
Bellissimo-Rodrigues[35]	16	64	17	69	14.0%	1.01 (0.56, 1.83)	2009	
Panchabhai[36]	14	88	15	83	12.1%	0.88 (0.45, 1.71)	2009	
Scannapieco[37]	7	58	12	59	8.5%	0.59 (0.25, 1.40)	2009	
Berry[38]	4	71	1	78	1.7%	4.39 (0.50, 38.39)	2011	
Grap[39]	7	21	10	18	10.7%	0.60 (0.29, 1.25)	2011	
Subtotal (95% CI)		**633**		**636**	**86.1%**	**0.71 (0.54, 0.94)**		
Total events	84		116					
Heterogeneity: $tau^2 = 0.03$; $chi^2 = 10.31$, df, = 9 ($P = 0.33$); $I^2 = 13\%$								
Test for overall effect: $Z = 2.40$ ($P = 0.02$)								
2.1.2 Povidone-iodine								
Chua[28]	6	22	8	20	8.3%	0.68 (0.29, 1.62)	2004	
Seguin[33]	3	36	25	62	5.5%	0.21 (0.07, 0.64)	2006	
Subtotal (95% CI)		**58**		**82**	**13.9%**	**0.39 (0.11, 1.36)**		
Total events	9		33					
Heterogeneity: $tau^2 = 0.54$; $chi^2 = 3.05$, df = 1 ($P = 0.08$); $I^2 = 67\%$								
Test for overall effect:								
Total (95% CI)		**691**		**718**	**100**	**0.66 (0.49, 0.88)**		
Total events	93		149					
Heterogeneity: $tau^2 = 0.06$; $chi^2 = 14.81$, df = 11 ($P = 0.19$); $I^2 = 26\%$								
Test for overall effect: $Z = 2.85$ ($P = 0.004$)								
Test for subgroup differences: $chi^2 = 0.82$, df = 1 ($P = 0.36$); $I^2 = 0\%$								



Enhanced oral care? Toothbrush, CHX, Suction

- **Methods:** A historical control study of all 1087 patients, 528 patients before a practice change were compared with 559 patients after a practice change
  - Practice: Oral hygiene measures (teeth brushing, 1% oral chlorhexidine and oropharyngeal suction)
- **Results:** The mean incidence of VAP was 0.09 (8.9%) (95% CI 0.07-0.12) before and was 0.04 (4.1%) (95% CI 0.03-0.06) after practice change. The mean VAPi per 1000 ventilator days was 13.6 (95% CI 13.1-14.0) before and 6.9 (95% CI 6.5-7.1) after.
- There was a £6319 ($10,112, €7518) cost saving on preventing VAP
- Relative risk reduction of 0.53 (95% CI 0.25-0.71) and NNT of 21

Cutler et al Intensive Crit Care Nurs. 2014 Apr;30(2):61-8

Does brushing teeth really help?- a meta-analysis

Alhazzani et al

- Six trials enrolling 1,408 patients,
- Results suggested that toothbrushing significantly reduced VAP (risk ratio, 0.26; 95% CI, 0.10-0.67; p = 0.006).
- Use of CHX antisepsis seems to attenuate the effect of toothbrushing on VAP (p for the interaction = 0.02).
- Toothbrushing did not impact length of ICU stay, or ICU or hospital mortality.

Gu et al

- Four studies with a total of 828 patients
- Toothbrushing did not significantly reduce the incidence of VAP (RR, 0.77; 95% CI, 0.50 to 1.21) and intensive care unit mortality (RR, 0.88; 95% CI, 0.70 to 1.10).

Alhazzani et al Crit Care Med. 2013 Feb;41(2):646-55
Gu et al Crit Care. 2012 Oct 12;16(5):R190

Soft Toothbrush Vs Distilled Water

Nasriani et al

- **Methods:** RCT, 168 intubated patients, Two groups. In the experimental group, the patients' teeth were brushed twice a day and distilled water in addition chlorhexidine.
- **Results:** There was a significant difference in incidence of VAP on day five between the two groups ($P<0.05$) (8.2% vs 6.1%).

Chacko et al

- **Methods**: 230 patients were enrolled in this RCT, Indian ICU
- Tooth-brushing with concurrent suctioning technique was not proved to be superior to mouth-swabbing. (Toothbrushing Vs no Toothbrushing)

Nasiriani et al Tanaffos. 2016; 15(2): 101–107
Chacko et al Br J Nurs. 2017 Jun 8;26(11):594-599

Povidone iodine in place of CHX?

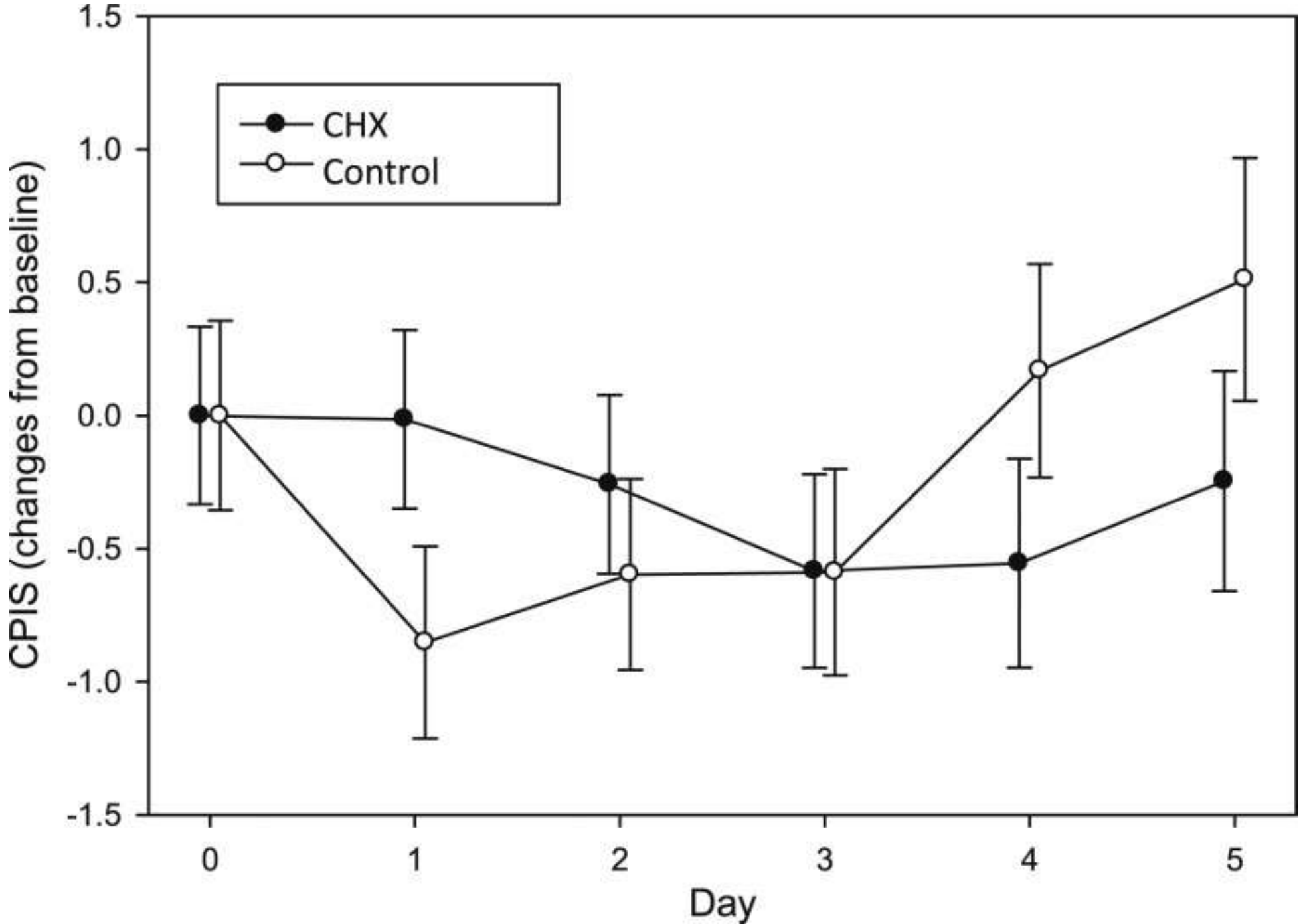
- **Methods:** 179 severely brain-injured patients expected to be mechanically ventilated for more than 24 hrs were randomly assigned to receive oropharyngeal care with povidone-iodine (n = 91) or placebo (n = 88) six times daily
- **Results:** VAP occurred in 24 patients (31%) in the povidone-iodine group and 20 (28%) in the placebo group (relative risk, 1.11 [95% CI, 0.67-1.82]; p = 0.69).
- There was no significant difference between the two groups for VATS

Seguin et al Crit Care Med. 2014 Jan;42(1):1-8

Pre-intubation CHX for VAP prevention (RCT)

- **Methods:** Subjects were randomly assigned to oral application of 5 mL CHX 0.12% solution before intubation (intervention group, n = 157), or to a control group (n = 157).
- All subjects received CHX bid after intubation.
- **Results:** No significant difference was identified between two groups

Munro et al Chest. 2015 Feb; 147(2): 328–334.


CHX
Control
CPIS (changes from baseline)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
1
2
3
4
5
Day

Oral topical decontamination gel/paste?

- **Methods**: Sixteen trials involving 2399 participants were included. Meta-analysis was done
- **Results**: Oral topical antiseptics significantly reduced the incidence of VAP [risk ratio (RR): 0.66; 95% confidence interval (CI): 0.49-0.88]. There was a significant reduction of VAP with antibiotic agents other than iseganan (RR: 0.27; 95% CI: 0.18-0.42).
- Neither antiseptics nor antibiotics affected all-cause mortality, duration of ventilation, or duration of ICU stay.
- Most common used gel was CHX

Li et al J Hosp Infect. 2013 Aug;84(4):283-93

CHX baths?- RCT

- **Methods**: Single center RCT. 2 % CHX body wash every day vs soap and water body scrubs
- **Results**: Of 350 patients randomized. Patients acquired 53 infections. Compared with soap and water bathing, CHX decreased the risk of acquiring infections (hazard ratio = 0.555; 95% CI, 0.309-0.997; p = 0.049). 13 versus 8 for ventilator-associated pneumonia
- Absolute risk reduction for acquiring a hospital-acquired infection was 9.0% (95% CI, 1.5-16.4%; p = 0.019

Swan et al Crit Care Med. 2016 Oct;44(10):1822-32.

Conclusion

- In the background of the use of CHX, toothbrush's significance is not known
- Theoretically it helps to remove plaques and biofilms with added risk of tube displacement
- Current evidence is divided over the same
- But individual RCTs have demonstrated good outcomes with use of Toothbrush
- Can be recommended with a frequency of twice a day

Conclusion

- OHC including chlorhexidine mouthwash or gel reduces the risk of developing ventilator-associated pneumonia in critically ill patients from 25% to about 19%.
- Considering the safety of chlorhexidine, it is recommended for all patients
- Other agents including antibiotics mixtures, Povidone iodine were not helpful

Section 2. Selective Oral Decontamination

Selective digestive tract decontamination-RCT **(Methodology)**

- SDD regimen consists of 4 days of IV cefotaxime and topical application of tobramycin, Colistin, and amphotericin B in the oropharynx and stomach
- Surveillance cultures of ETA and oropharyngeal and rectal swabs were obtained on admission and twice weekly thereafter.
- Antibiotic resistance was monitored with the use of point-prevalence studies on the third Tuesday of each month (Rectal swabs and ETA).

De Smetet al N Engl J Med. 2009 Jan 1;360(1):20-31.

Selective oropharyngeal decontamination

- SOD consisted of oropharyngeal application of the same paste used for SDD but without IV cefotaxime

Results

- These data show an absolute reduction in mortality of 3.5 and 2.9 percentage points (corresponding to relative reductions of 13% and 11%) at day 28 with SDD and SOD.
- Patients were treated with topical components at a cost per day of $1 for SOD and $12 for SDD, without evidence of the emergence of antibiotic-resistant pathogens or increased rates of detection of C. difficile toxin

Table 2. Primary and Secondary End Points.*

End Point	Study Group			Unadjusted Odds Ratio or Hazard Ratio (95% CI)†			Adjusted Odds Ratio or Hazard Ratio (95% CI)†		
	Standard Care (N=1990)	SDD (N=2045)	SOD (N=1904)	Standard Care	SDD	SOD	Standard Care	SDD	SOD
Death — no. (%)									
During the first 28 days	544 (27.5)	546 (26.9)	502 (26.6)	1.00	0.94 (0.82–1.08)	0.95 (0.82–1.10)	1.00	0.83 (0.72–0.97)	0.86 (0.74–0.99)
In the ICU	443 (22.3)	440 (21.5)	416 (21.8)	1.00	0.91 (0.79–1.06)	0.97 (0.83–1.13)	1.00	0.81 (0.69–0.94)	0.87 (0.74–1.02)
In the hospital	632 (31.8)	665 (32.6)	584 (30.7)	1.00	0.99 (0.86–1.13)	0.94 (0.82–1.08)	1.00	0.88 (0.76–1.01)	0.85 (0.74–0.98)
Time to outcome for survivors at day 28 — days									
Cessation of mechanical ventilation				1.00	1.06 (0.96–1.18)	1.01 (0.89–1.15)	1.00	1.10 (0.99–1.22)	1.03 (0.90–1.17)
Median	8	7	8						
Interquartile range	3–17	4–15	4–15						
Discharge from ICU				1.00	1.02 (0.92–1.12)	1.00 (0.89–1.11)	1.00	1.09 (0.99–1.21)	1.06 (0.94–1.19)
Median	9	9	9						
Interquartile range	6–19	6–18	6–17						
Discharge from hospital				1.00	1.04 (0.91–1.19)	1.05 (0.91–1.22)	1.00	1.13 (1.01–1.25)	1.13 (0.96–1.32)
Median	29	28	28						
Interquartile range	16–48	16–45	16–47						

* Ratios for death are odds ratios, and ratios for time to outcome are hazard ratios. All adjusted and duration outcomes exclude the 12 patients who declined to provide permission to use data, and all outcomes for death at 28 days exclude an additional 44 patients for whom data were unavailable. In-hospital mortality data were unavailable for three patients (two in the selective digestive tract decontamination [SDD] group and one in the standard-care group). Other mortality outcomes include all patients assigned to a study regimen. Data on the duration of the hospital stay and the duration of mechanical ventilation were unavailable for three patients (two in the selective oropharyngeal decontamination [SOD] group and one in the SDD group) and eight patients (five in the SOD group and three in the standard-care group), respectively.

† Odds ratios were calculated with the use of random-effects logistic-regression models to account for ICU-level clustering. All models for adjusted outcomes included the Acute Physiology and Chronic Health Evaluation (APACHE II) score (≥20 vs. <20), age (>65 years vs. ≤65 years), intubation status during ICU stay, reason for admission to ICU (surgical vs. medical), and sex. The odds ratios for the outcome of death during the first 28 days were 2.56 (95% CI, 2.26 to 2.92) for an APACHE II score of 20 or more, 1.87 (95% CI, 1.65 to 2.12) for an age greater than 65 years, 1.67 (95% CI, 1.29 to 2.15) for mechanical ventilation during the ICU stay, 0.61 (95% CI, 0.53 to 0.69) for surgical admission, and 1.09 (95% CI, 0.96 to 1.24) for male sex. Corresponding estimates for death in the ICU and in-hospital death were broadly similar. Hazard ratios were calculated from a Cox regression model with censoring at day 28 and with adjustment for ICU-level clustering (hazard ratios >1.00 indicate a tendency toward a shorter duration of mechanical ventilation and a shorter ICU or hospital stay). Models for adjusted outcomes included the same covariates as those in the logistic-regression models except for the duration of the hospital stay, which was stratified according to surgical status because of a departure from the proportional-hazards assumption. Infinite durations were used for patients who died.

Table 4. Detection of Antibiotic-Resistant, Gram-Negative Bacteria in Rectal and Respiratory Tract Samples during Point-Prevalence Surveys.*

Organism	Resistant to Aminoglycosides†			Resistant to Ciprofloxacin			Resistant to Ceftazidime			Multiresistant A‡			Multiresistant B§		
	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD
	percentage of patients														
Rectal samples															
Escherichia coli	4.5¶	4.9¶	1.8	4.9¶	4.5	2.9	3.3¶	2.3	1.3	2.2¶	2.3¶	0.5	1.4	1.0	0.5
Klebsiella pneumoniae	2.6¶	1.4	1.0	3.0¶‖	1.4	0.7	2.2¶	1.1	0.4	0.6	1.0	0.6	1.9¶‖	0.3	0.3
Enterobacter cloacae	1.7¶	1.8¶	0.6	1.3	1.6	0.5	4.7¶	4.2¶	1.7	1.0	1.1	0.5	0.6	1.0	0.2
Pseudomonas aeruginosa	1.2	1.0	0.7	1.6	1.6	0.7	2.6¶	1.8¶	0.7	1.3¶	0.8	0.4	0.4	0.3	0.4
Respiratory tract samples															
E. coli	1.3¶	0.5	0	1.0	0.2	0.4	1.0¶	0.5	0	0.4	0.1	0	0.4	0.2	0
K. pneumoniae	2.0¶‖	0.5	0.2	2.4¶‖	0.4	0.2	1.9¶‖	0.6	0.2	0.1	0.2	0.1	2.0	0.2	0.1
E. cloacae	1.5¶	0.5	0.4	1.1‖	0.2	0.4	3.8¶‖	0.6	1.2	0.6	0.2	0	0.6	0.1	0.
P. aeruginosa	2.6¶	1.8	1.0	3.7¶‖	1.8	0.9	3.5¶‖	1.1	0.4	2.2	1.2	0.4	0.8	0.1	0.

Limitations

- No restriction of other antibiotics for use
- No blinding
- Poor conducted randomization
- No long term follow up
- Definition of VAP

Selective digestive decontamination: *met-analysis*

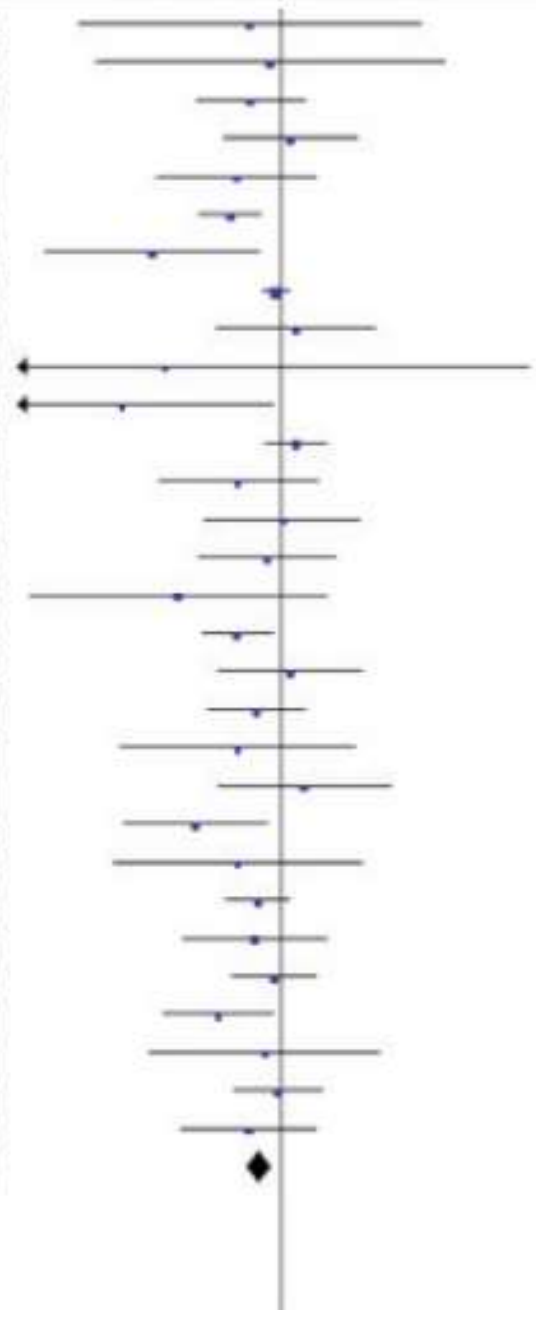
- **Methods**: Data from 29 randomized trials was (n=3715).
- **Results:** The risk ratio (RR) for death was 0.95 (95% CI, 0.92-0.99; p=0.02) in the intervention group.
- In sub-group analysis, only SDD significantly decreased mortality as compared to control (n=1022; RR, 0.84; 95%CI, 0.76-0.92; p=0.0003). The RR for in-ICU death was 0.78 (CI 95%, 0.69-0.89; p=0.0001)
- For SOD (RR 1.00 CI95%, 0.84-1.21; p=0.96; I2 =0%)

Rouilly et al Clin Infect Dis. 2015 Jan 1;60(1):64-75.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Aerdts 1991	2	17	6	39	0.2%	0.76 [0.17, 3.41]
Arnow 1996	3	36	3	33	0.2%	0.92 [0.20, 4.23]
Blair 1991	24	126	32	130	1.9%	0.77 [0.48, 1.24]
Cerra 1992	13	25	10	21	1.3%	1.09 [0.61, 1.96]
Cockerill 1992	11	75	16	75	0.9%	0.69 [0.34, 1.38]
de Jonge 2003	69	466	107	468	4.8%	0.65 [0.49, 0.85]
De La Cal 2005	5	54	15	53	0.5%	0.33 [0.13, 0.84]
De Smet 2009	440	2045	443	1990	13.0%	0.97 [0.86, 1.09]
Ferrer 1994	12	39	11	41	0.9%	1.15 [0.57, 2.29]
Flaherty 1990	0	51	1	56	0.0%	0.37 [0.02, 8.77]
Fox 1991	2	12	8	12	0.3%	0.25 [0.07, 0.94]
Gastine 1992	75	220	67	225	4.9%	1.14 [0.87, 1.50]
Godard 1990	12	97	15	84	0.9%	0.69 [0.34, 1.40]
Hammond 1992	14	114	15	125	1.0%	1.02 [0.52, 2.03]
Kerver 1988	14	49	15	47	1.2%	0.90 [0.49, 1.65]
Korineck 1993	3	63	7	60	0.3%	0.41 [0.11, 1.51]
Krueger 2002	52	265	75	262	4.0%	0.69 [0.50, 0.93]
Lingnau 1997	19	162	16	148	1.1%	1.08 [0.58, 2.03]
Mandelli 1989	48	377	30	193	2.4%	0.82 [0.54, 1.25]
Pneuomkitos 2002	5	31	7	30	0.4%	0.69 [0.25, 1.94]
Quinio 1996	13	76	10	72	0.8%	1.23 [0.58, 2.63]
Rocha 1992	10	47	24	54	1.1%	0.48 [0.26, 0.89]
Rodriguez 1990	4	15	5	13	0.4%	0.69 [0.23, 2.05]
Sanchez Garcia 1998	51	131	66	140	4.8%	0.83 [0.63, 1.09]
Silvestri 2004	12	42	15	42	1.1%	0.80 [0.43, 1.50]
Stoutenbeek 2007	42	201	44	200	2.9%	0.95 [0.65, 1.38]
Ulrich 1989	15	48	28	52	1.8%	0.58 [0.36, 0.95]
Unertl 1987	5	19	6	20	0.5%	0.88 [0.32, 2.40]
Verwaest 1997	65	393	31	185	2.7%	0.99 [0.67, 1.46]
Wierner 1995	11	30	15	31	1.3%	0.76 [0.42, 1.37]
Subtotal (95% CI)		**5326**		**4901**	**57.7%**	**0.84 [0.76, 0.92]**
Total events	1051		1143			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 34.35$, df = 29 (P = 0.23); $I^2 = 16\%$

Test for overall effect: Z = 3.64 (P = 0.0003)

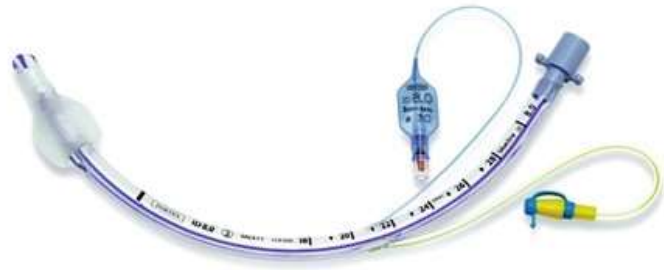


Conclusions.

- SDD with systemic antimicrobial therapy reduced mortality
- But long term consequences of overuse of antibiotics might be grave.
- It will add to the cost of therapy without any significant benefit
- Should not be recommended

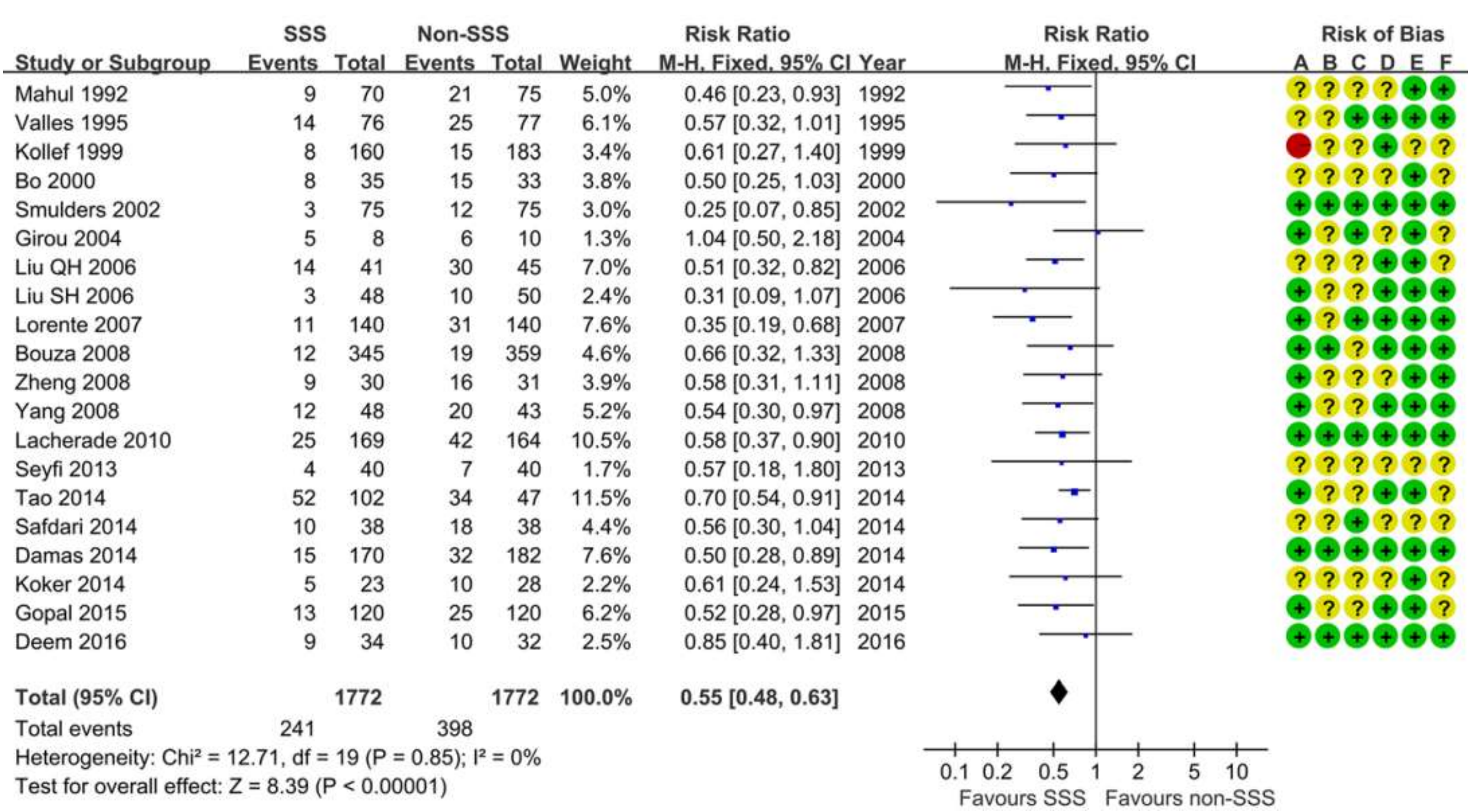
Section 3. Subglottic Suction

Subglottic suction ET tubes for VAP prevention



- Twenty RCTs (N = 3544) were analyzed.
- Subglottic secretion suction was associated with reduction of VAP incidence in all trials (RR = 0.55, 95 % CI 0.48-0.63; $p < 0.00001$).
- GRADE level was high.
- Subglottic secretion suction significantly reduced incidence of early onset VAP, and duration of mechanical ventilation. It delayed the time-to-onset of VAP.
- However, no significant differences in late onset VAP, intensive care unit mortality, hospital mortality, or ICU length of stay were found.

Mao et al Crit Care. 2016 Oct 28;20(1):353.


SSS
Non-SSS
Risk Ratio
Risk Ratio
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
A B C D E F
Mahul 1992 9 70 21 75 5.0% 0.46 [0.23, 0.93] 1992
Valles 1995 14 76 25 77 6.1% 0.57 [0.32, 1.01] 1995
Kollef 1999 8 160 15 183 3.4% 0.61 [0.27, 1.40] 1999
Bo 2000 8 35 15 33 3.8% 0.50 [0.25, 1.03] 2000
Smulders 2002 3 75 12 75 3.0% 0.25 [0.07, 0.85] 2002
Girou 2004 5 8 6 10 1.3% 1.04 [0.50, 2.18] 2004
Liu QH 2006 14 41 30 45 7.0% 0.51 [0.32, 0.82] 2006
Liu SH 2006 3 48 10 50 2.4% 0.31 [0.09, 1.07] 2006
Lorente 2007 11 140 31 140 7.6% 0.35 [0.19, 0.68] 2007
Bouza 2008 12 345 19 359 4.6% 0.66 [0.32, 1.33] 2008
Zheng 2008 9 30 16 31 3.9% 0.58 [0.31, 1.11] 2008
Yang 2008 12 48 20 43 5.2% 0.54 [0.30, 0.97] 2008
Lacherade 2010 25 169 42 164 10.5% 0.58 [0.37, 0.90] 2010
Seyfi 2013 4 40 7 40 1.7% 0.57 [0.18, 1.80] 2013
Tao 2014 52 102 34 47 11.5% 0.70 [0.54, 0.91] 2014
Safdari 2014 10 38 18 38 4.4% 0.56 [0.30, 1.04] 2014
Damas 2014 15 170 32 182 7.6% 0.50 [0.28, 0.89] 2014
Koker 2014 5 23 10 28 2.2% 0.61 [0.24, 1.53] 2014
Gopal 2015 13 120 25 120 6.2% 0.52 [0.28, 0.97] 2015
Deem 2016 9 34 10 32 2.5% 0.85 [0.40, 1.81] 2016
Total (95% CI) 1772 1772 100.0% 0.55 [0.48, 0.63]
Total events 241 398
Heterogeneity: Chi² = 12.71, df = 19 (P = 0.85); I² = 0%
Test for overall effect: Z = 8.39 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours SSS
Favours non-SSS

- ARR (0.0953) meant that SSS can reduce 9.53 % of the absolute rate of VAP.
- NNT: 10.49
- Sensitivity analyses found that both **intermittent and continuous suction can prevent VAP**, with no significant difference between subgroups.

Summarizing the results

	RR	P	GOE
VAP incidence	0.55 (0.48, 0.63)	<0.00001	High
VAP intermittent SSS	0.52 (0.43, 0.64)	<0.00001	High
VAP continuous SSS	0.61(0.5, 0.73)	<0.00001	High
ICU mortality	0.98(0.85, 1.13)	0.77	High
Time-to-onset of VAP	3.92 (2.56, 5.27)	<0.00001	mod
Duration of MV	−1.17 (–2.28, –0.06)	0.006	Mod
ICU length of stay	−1.64 (–3.95, 0.66)	0.16	mod

Subglottic suction in tracheostomy tube?

- **Methods**: 18 tracheostomied patients were randomized to get continuous suction from above the inflated cuff
- **Results**: The prevalence of VAP were 56% in the control group and 11% in the suction tracheotomy group (p = 0.02).

Ledgerwood et al Ann Otol Rhinol Laryngol. 2013 Jan;122(1):3-8.

Conclusion

- Sub-glottis suction tube decreases incidence of VAP
- Should be recommended in all settings

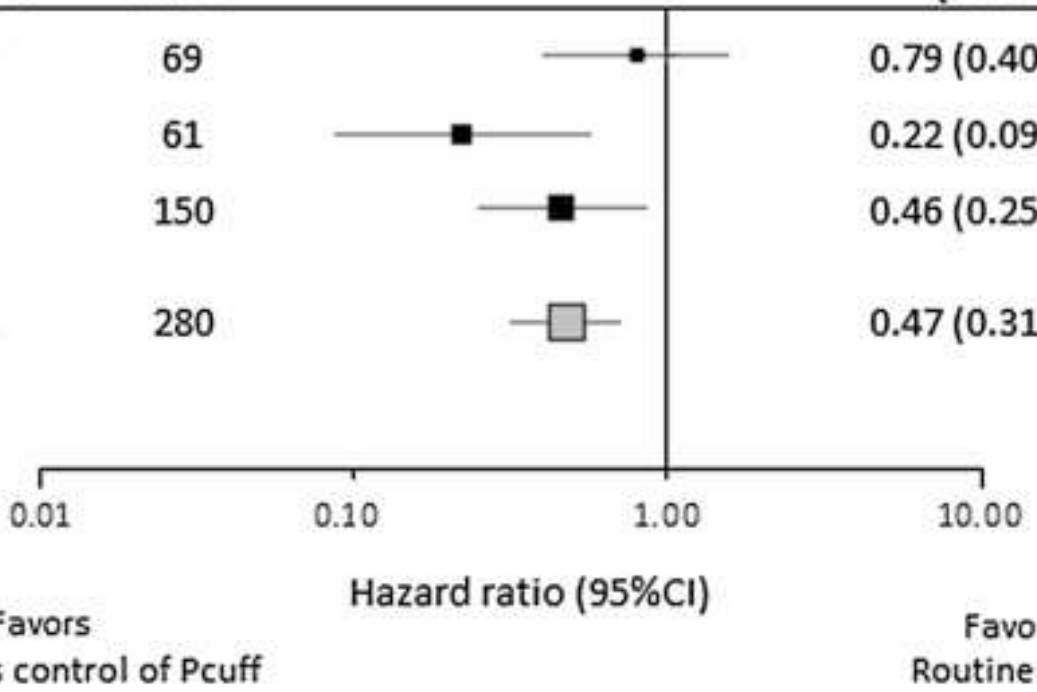
Section 4. ET cuff shape and pressure

Continuous vs intermittent cuff pressure monitoring

- **Methods**: Data from 3 prospective controlled trials which evaluated the impact of continuous control of *Pcuff* on the incidence of VAP, were obtained and pooled together.
- **Results**: 263 (48.4 %) patients received continuous control of *Pcuff,* and 280 (51.5 %) patients received routine control of *Pcuff*. 36 (13.6 %) VAP were diagnosed in continuous control group, and 72 (25.7 %) in routine care group (HR 0.47, 95 % CI 0.31–0.71, $p < 0.001$).
- NNT to prevent one VAP episode was 8.

Nseir et al Ann Intensive Care. 2015; 5: 43.

	Continuous Control of Pcuff		Routine Care		HR	
	Events	Total	Events	Total	(95%CI)	P Value
Valencia, 2007	15	68	20	69	0.79 (0.40-1.56)	0.50
Nseir , 2011	6	61	19	61	0.22 (0.09-0.57)	0.002
Lorente, 2014	15	134	33	150	0.46 (0.25-0.85)	0.013
Overall	36	263	72	280	0.47 (0.31-0.71)	0.0003
Heterogeneity	I^2=58% (P=0.085)					



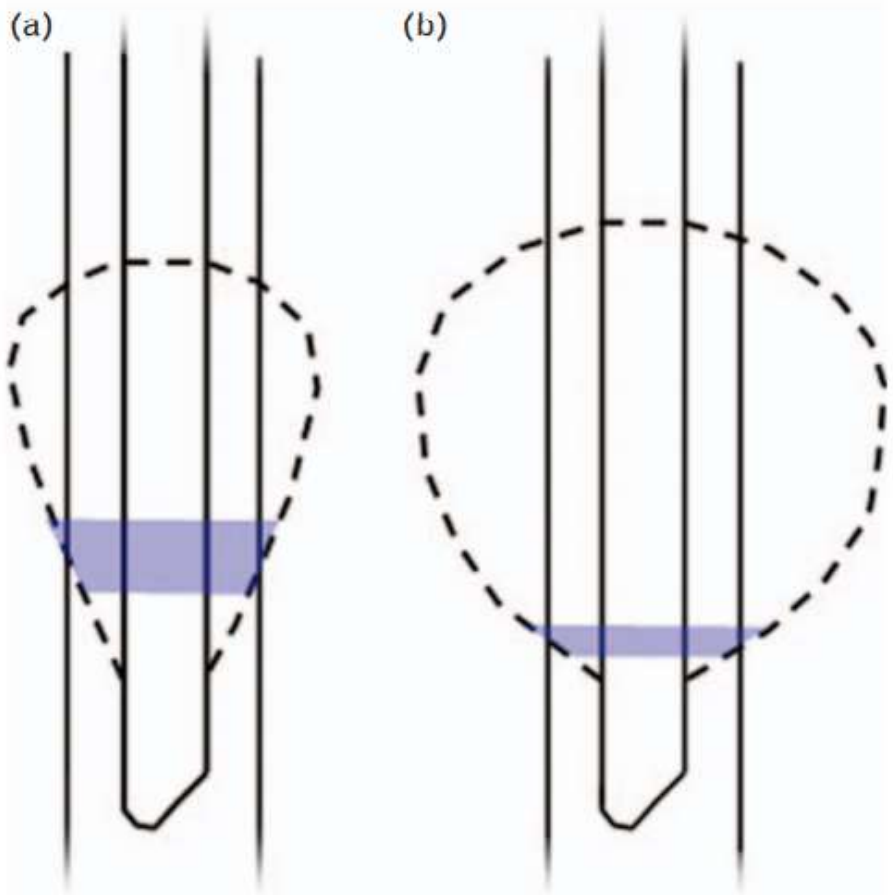
- No significant impact was found on duration of mechanical ventilation, mechanical ventilation-free days, antimicrobial treatment, or ICU mortality.
- Cuff pressure kept was 25 cmH_2O

	Continuous control of P_{cuff}		
	Yes ($n = 263$)	**No ($n = 280$)**	***p* value**
Mean P_{cuff}	25 (24, 26)	22 (21, 24)	<0.001
Underinflation of P_{cuff}	2 (1)	118 (42)	<0.001
% P_{cuff} measurements <20 cmH_2O	0 (0,0)	16 (0, 18)	<0.001
Overinflation of P_{cuff}	8 (3)	82 (29)	<0.001

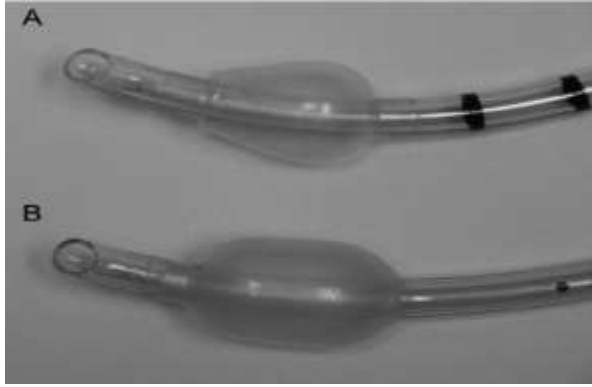
Conclusion

- Continuous monitoring of cuff provides an evidence towards decrease in VAP rates but quality of evidence is still poor
- Can be recommended as it still help to avoid under/over-inflation of cuff

Conical cuffs vs convectional cuffs



Conical cuffs vs convectional cuffs



Philippart et al

- **Methods:** Multicenter, open-label RCT in 4 parallel groups. 621 patients were included at intubation with either a (A) cylindrical polyvinyl chloride (n = 148), (B) cylindrical polyurethane (n = 143), (C) conical polyvinyl chloride (n = 150) or (D) conical polyurethane (n = 162) cuff.
- **Results:** 604 were analyzed (ITT).

Monsel et al

- 109 patients Comparing the tapered-cuff with standard-cuff group in post op period
- Postoperative pneumonia rates were comparable (42 vs. 44%, P = 0.87)

Philippart et al Am J Respir Crit Care Med 191 (6), 637-645
Monsel et al Anesthesiology. 2016 May;124(5):1041-52.

Tracheal colonization on day 2 and VAP occurrence during the ICU stay

Group	PVC, cylindrical	PU, cylindrical	PVC, conical	PU, conical	*p*
Number of patients at day 2	129	123	129	153	
Tracheal colonization at 48 hours					
Over 10^3 cfu/mL	0.66 [0.58-0.74]	0.61 [0.53-0.70]	0.67 [0.60-0.76]	0.62 [0.55-0.70]	*0.55*
Over 10^4 cfu/mL	0.55 [0.47-0.63]	0.50 [0.42-0.58]	0.57 [0.48-0.65]	0.50 [0.42-0.58]	*0.44*
Over 10^5 cfu/mL	0.41 [0.33-0.50]	0.38 [0.31-0.47]	0.50 [0.42-0.58]	0.42 [0.34-0.50]	*0.12*
Over 10^6 cfu/mL	0.23 [0.17-0.31]	0.27 [0.20-0.35]	0.32 [0.25-0.41]	0.29 [0.22-0.37]	*0.56*
Cumulative VAP during the stay, n (%)	14 (10.8)	21 (17.1)	17 (13.2)	25 (16.3)	*0.20*

Philippart et al Am J Respir Crit Care Med 191 (6), 637-645

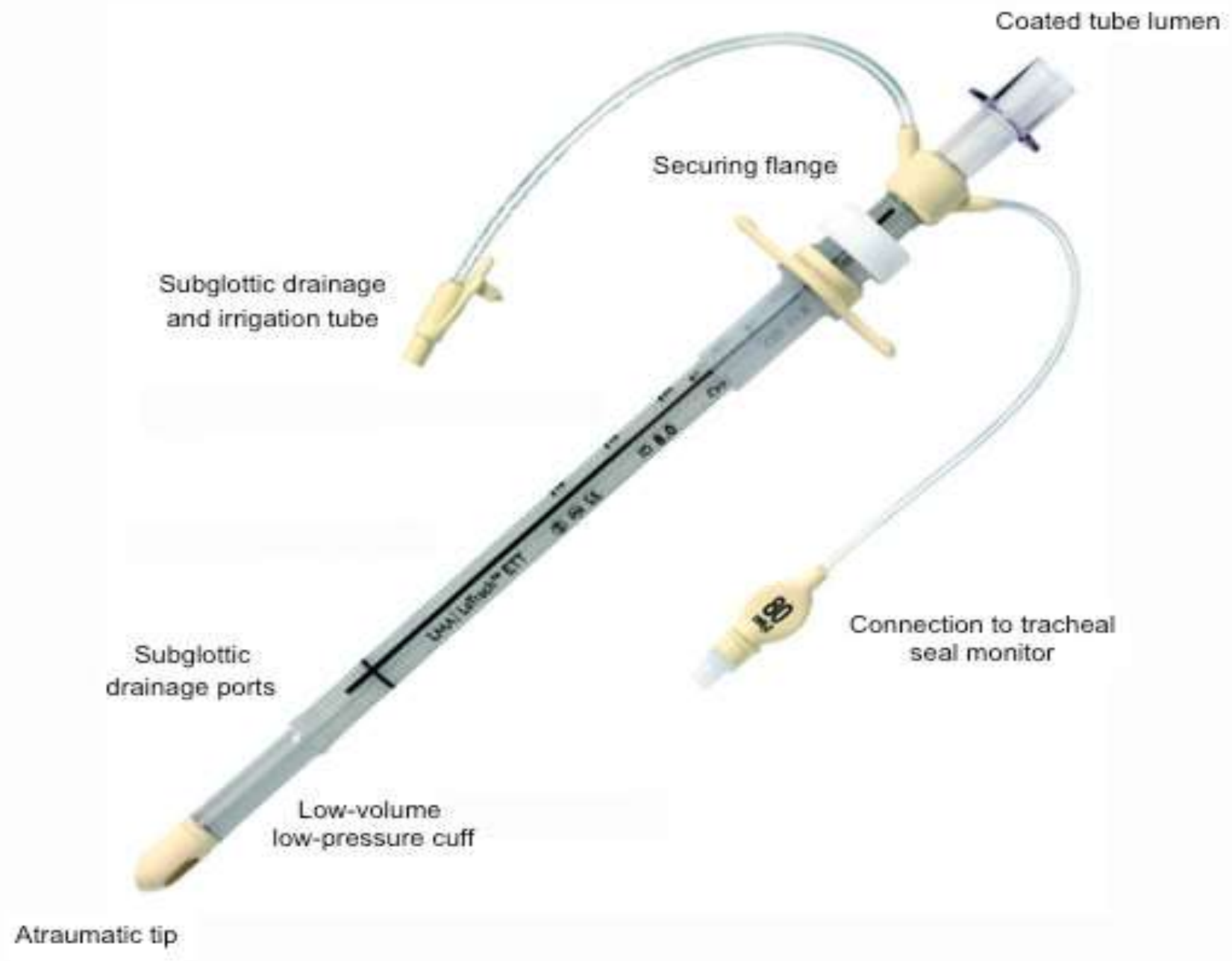
Conclusion

- Conical cuffs/ Polyurethane ET tubes failed to improve VAP incidence

Venner-PneuX endotracheal tube system

- **Device**: It has, sub-glottic suction as well as irrigation ports and continuous cuff-pressure monitoring
- **Methods**: RCT. Group A (VennerPneuX ET tube, n = 120) or Group B (Standard ET tube, n = 120). All were undergoing cardiothoracic surgery
- **Results:** The median intubation times were 14.7 (7.3, 2927.2) h and 13 (2.5, 528.7)Hrs . VAP incidence was significantly lower in the Venner-PneuX ET group, (10.8% Vs 21 p = 0.03). There was no significant difference between the two groups in terms of intensive care unit stay (P = 0.2) and in-hospital mortality (P = 0.2)

Frey et al Eur J Cardiothorac Surg. 2015 Mar;47(3):e92-6


Coated tube lumen
Securing flange
Subglottic drainage
and irrigation tube
Connection to tracheal
seal monitor
Subglottic
drainage ports
Low-volume
low-pressure cuff
Atraumatic tip

Post operative data

	Standard ET tube	Venner-PneuX tube	*P*-value
n	120	120	
CPB time (min)[a]	105 (62)	110 (58)	0.3
Intubation time (h) [b]	13	15	0.5
ICU stay (days)[b]	1.5	2	0.2
Re-exploration, *n* (%)	10 (8%)	17 (14%)	0.2
Survival	99%	98%	0.2
VAP incidence, *n* (%)	25 (21%)	13 (11%)	0.03
VAP incidence density[c]	184	52	<0.01

Frey et al Eur J Cardiothorac Surg 2015 Mar;47(3):e92-6

Low volume-low pressure ET tubes

Effect of PEEP & type of tracheal cuff on the incidence of aspiration

- **Methods**: Forty patients. 20 patients were randomly intubated with Hi-Lo tubes (HL group), 20 subjects were intubated with SealGuard tubes (SG group)
- A 5-cm H_2O positive expiratory pressure was used during the first 5 hrs of stay
- At 1 hr, 5 hrs, and thereafter hourly until 12 hrs, bronchoscopy was used to test the presence of dye on the trachea caudal to the cuff

Lucangelo et al Crit Care Med. 2008 Feb;36(2):409-13.

- **Main Results**:. One hour after PEEP removal, all subjects in group HL exhibited a dyed lower trachea. One patient in group SG presented a leak at the eighth hour, and at the 12th hour three of them were still sealed.
- **Conclusions**: 5 cm H2O positive expiratory pressure was effective in delaying the passage of fluid around the cuffs of tracheal tubes. The SealGuard tube proved to be more resistant to leakage than Hi-Lo

Lucangelo et al Crit Care Med. 2008 Feb;36(2):409-13.

A low-volume, low-pressure tracheal tube cuff reduces pulmonary aspiration

- **Methods:** Prospective, blinded, RCT
- **Interventions:** The LVLP cuff was compared with HVLP cuffs for leakage of dye placed in the subglottic space
- **Main Results**: In the rigid tracheal model, the incidence of leakage was 0% in the LVLP group and 100% in the HVLP group ($p < .01$). Dye leakage in anesthetized patients was 0% before movement and 5% after in the LVLP group and in the HVLP group 22% increasing to 67% after movement ($p < .001$).

Young et al Crit Care Med 2006; 34:632–639

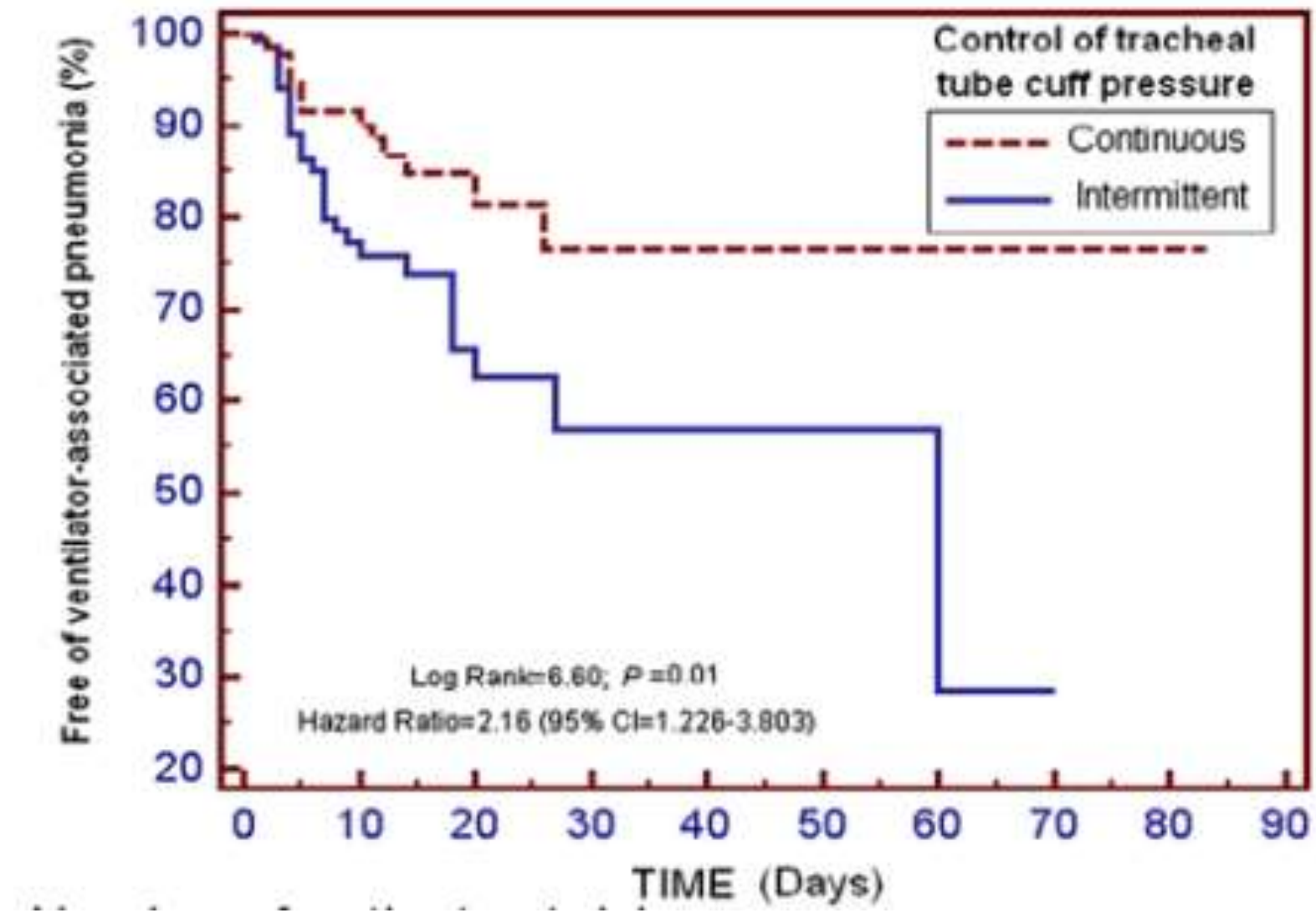
Conclusions

- The LVLP cuffed tracheal and tracheostomy tubes reduced pulmonary aspiration in the benchtop models and in anesthetized patients.
- The availability and standardization might be prohibitive
- Long term risk for tracheal injury have not been assessed yet
- Can be recommended on experimental purposes

Continuous ET cuff pressure control system

- **Methods:** Prospective observational study of patients undergoing mechanical ventilation using either continuous or intermittent endotracheal tube cuff pressure control.
- **Results:** Lower incidence of VAP with the continuous (n = 150) than with the intermittent (n = 134) pressure control system (22.0% versus 11.2%; p = 0.02)
- Subglottic suction was also found to be significantly associated with protection towards VAP development

Lorente et al Crit Care. 2014 Apr 21;18(2):R77


Free of ventilator-associated pneumonia (%)
100
90
80
70
60
50
40
30
20
0
10
20
30
40
50
60
70
80
90
TIME (Days)
Control of tracheal tube cuff pressure
Continuous
Intermittent
Log Rank=6.60; P =0.01
Hazard Ratio=2.16 (95% CI=1.226-3.803)

Conclusion

- Continuous cuff pressure monitoring has a protective role against VAP occurrence
- Can be recommended for regular use
- Incorporated in new generation ventilators

Section 5. Other ET modifications

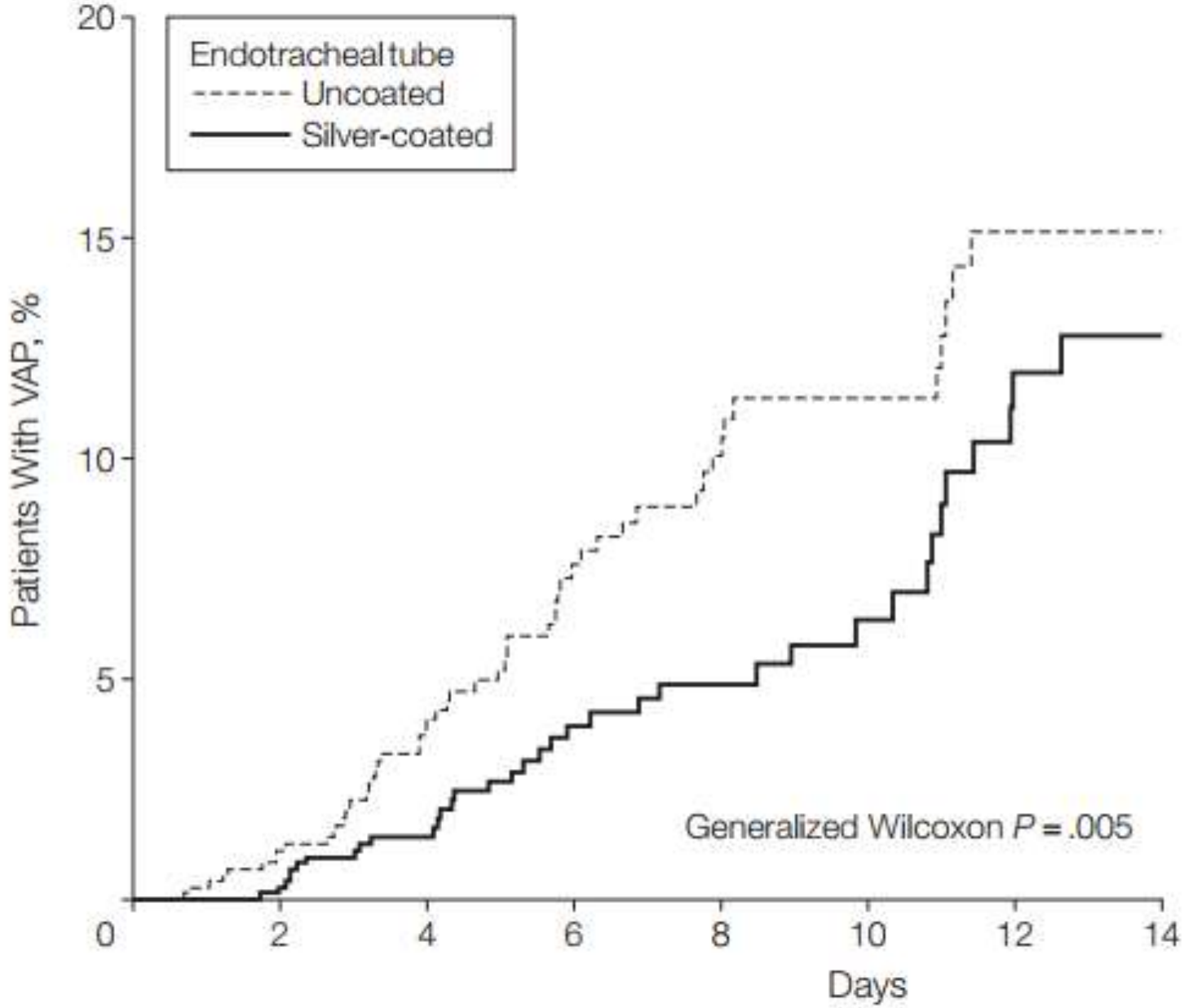
Silver-coated endotracheal tubes

- FDA approved
- The silver coating is on the outer tube surface, including the cuff surface and on the interior surface of the airway lumen
- Agento® I.C. Silver-Coated Endotracheal Tubes
- Ionic silver reacts strongly with the thiol groups of vital enzymes, proteins and DNA in the bacteria

The NASCENT trial

- **Methods**: Prospective, randomized, controlled study conducted in 54 centers in North America. A total of were randomized.
- **Results**: VAP rates were 4.8% in the group receiving the silver-coated tube and 7.5% (P=.03) in the control group, with a relative risk reduction of 35.9%. (P=.005).
- No significant differences were observed in durations of intubation, intensive care unit stay, and hospital stay, mortality
- **Conclusion**: Patients receiving a silver-coated endotracheal tube had a statistically significant reduction in the incidence of VAP

Kollef et al *JAMA.* 2008;300(7):805-813.


Endotracheal tube
Uncoated
Silver-coated
Patients With VAP, %
20
15
10
5
0
2
4
6
8
10
12
14
Days
Generalized Wilcoxon P = .005

Cochrane review: Silver coated ET tubes for VAP prevention

- 3 Eligible studies were reviewed, total of 2801 patients
- The mean duration of intubation was between 3.2 and 7.7 days
- Number needed to treat for an additional beneficial outcome (NNTB) = 37
- The risk of VAP within 10 days of intubation was significantly lower with the silver-coated ETTs compared with non-coated ETTs (NNTB = 32; low-quality evidence).
- There were no statistically significant differences between groups in hospital mortality; device-related adverse events; duration of intubation; and length of hospital

Tokmaji et al Cochrane Database Syst Rev. 2015 Aug 12;(8):CD009201.

Conclusion

- Silver coated ET tubes decreases the risk of VAP
- Quality of evidence is low
- No mortality benefit
- Added cost and issue of availability
- Long term adverse effect of mucosal exposure to silver is not studied
- Cannot be recommended as of now

Section 6. Suction & Humidification

Closed suction vs Open ET suction

- **Methods:** Prospective randomized study, in 100 patients in surgical Intensive Care Unit requiring mechanical ventilation for more than 48hrs.
- Patients randomly allocated into two groups (50 patients each): CTSS group and OTSS group.

Hamishekar et al Anesth Pain Med. 2014 Dec; 4(5): e21649.

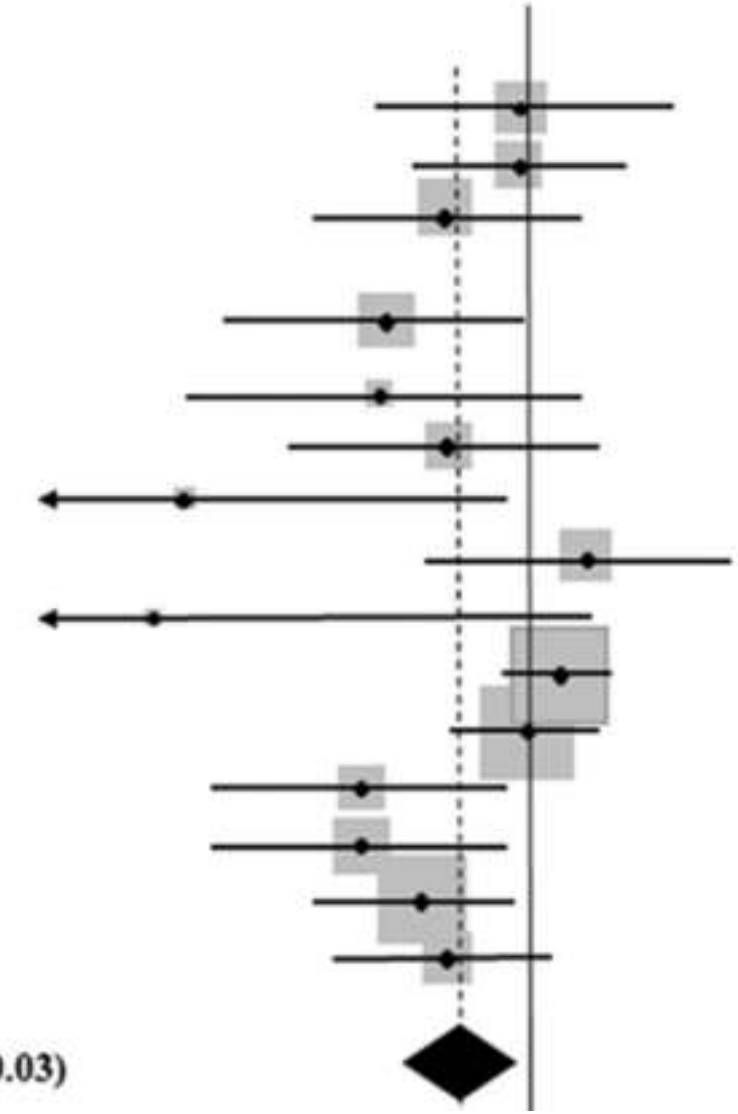
Results:

- Among the patients in OTSS and CTSS groups, 20% and 12% developed VAP, respectively.
- Use of CTSS compared with OTSS did not show statistically significant effect on VAP incidence in multivariate analysis

Closed suction vs Open suction: Meta-analysis

- **Methods:** Sixteen trials with 1,929 participants were included.
- **Results:** Compared with OTSS, CTSS was associated with a reduced incidence of VAP (RR 0.69; 95 % CI 0.54–0.87).
- Compared with OTSS, CTSS was not associated with reduction of mortality or reduced length of mechanical ventilation

Kuriyama et al Intensive Care Med. 2015 Mar;41(3):402-11



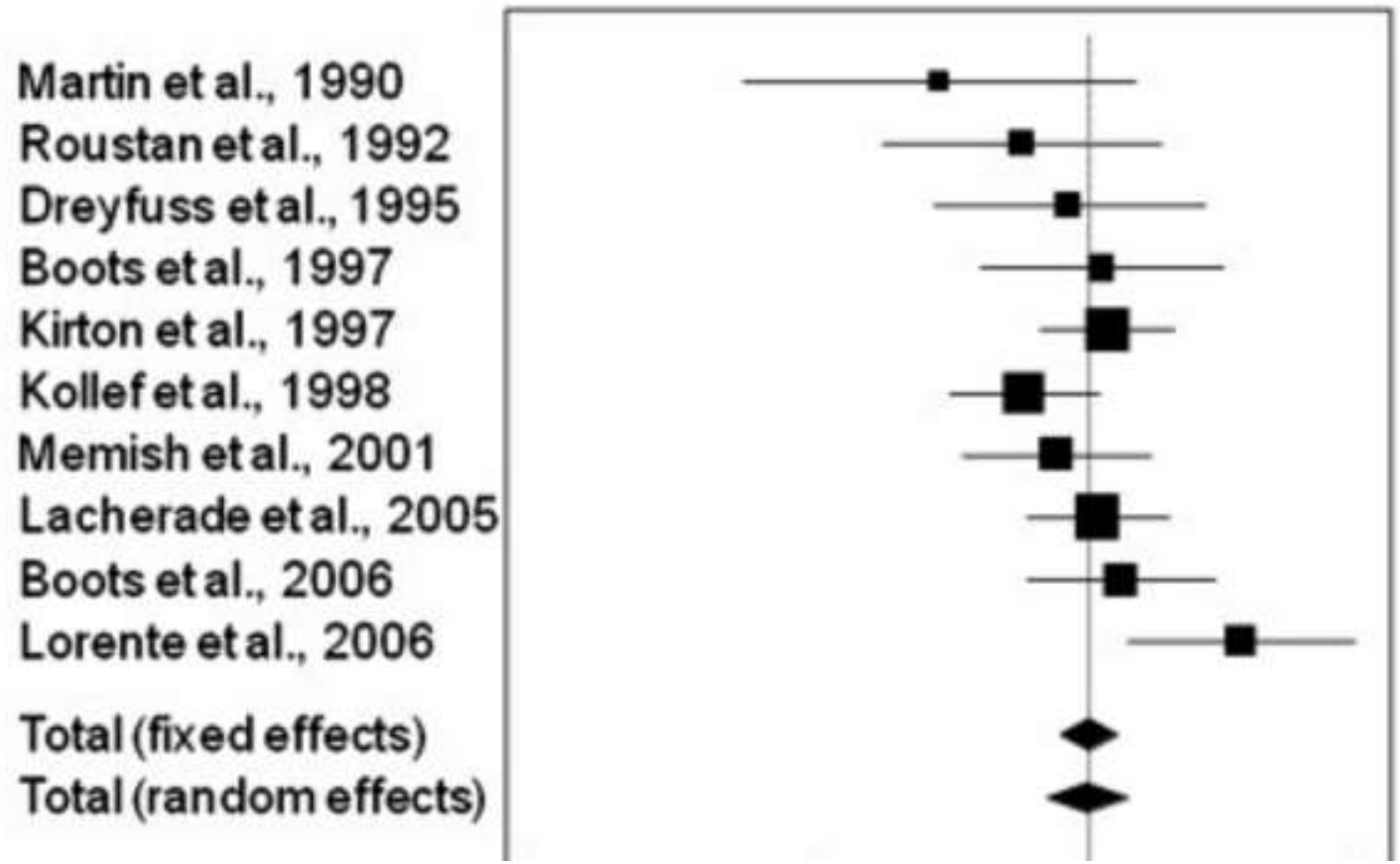
Trial (Year)	Favors CTSS	Favors OTSS	RR (95% CI)	CTSS event/ total	OTSS event/ total	Weight
Conrad (1989)			0.94 (0.39, 2.27)	6/ 16	6/ 15	5.05
Deppe (1990)			0.95 (0.50, 1.82)	12/ 46	11/ 38	6.84
Johnson (1994)			0.63 (0.31, 1.29)	8/ 16	10/ 19	7.39
Adams (1997)			Not estimable			
Welte (1997)			0.52 (0.28, 0.96)	9/ 27	16/ 25	7.96
Combes (2000)			0.41 (0.14, 1.25)	4/ 54	9/ 50	3.62
Zeitoun (2003)			0.66 (0.31, 1.41)	7/ 23	11/ 24	6.21
Lee (2004)			0.17 (0.04, 0.71)	2/ 32	14/ 39	2.48
Topeli (2004)			1.30 (0.63, 2.69)	9/ 37	13/ 41	6.53
Rabistch (2004)			0.09 (0.01, 1.48)	0/ 12	5/ 12	0.71
Lorente (2005)			1.14 (0.78, 1.66)	43/ 210	42/ 233	11.41
Lorente (2006)			1.00 (0.63, 1.57)	33/ 236	31/ 221	10.19
Wang (2006)			0.41 (0.21, 0.82)	9/ 42	13/ 25	6.90
Li (2007)			0.43 (0.22, 0.82)	9/ 40	21/ 40	7.43
Fakhar (2010)			0.58 (0.38, 0.88)	23/ 82	36/ 74	10.93
David (2010)			0.56 (0.27, 1.14)	10/ 100	18/ 100	6.56
Total (I^2=38.6%, p=0.03)			**0.69 (0.54, 0.88)**	**184/ 973**	**256/ 956**	**100.00**

Role of HME in VAP prevention

- **Methods:** Data from ten studies was extracted and analyzed. Total sample of 1077 and 953 patients in the HME and HH groups
- **Results:** Comparison between the use of HME and HH did not reveal any differences in terms of VAP occurrence (OR = 0.998; 95% CI: 0.778–1.281).
- The use of HME and HH did not afford different results in terms of mortality (OR = 1.09; 95% CI: 0.864–1.376).

Meneguetti et al BMC Anesthesiol. 2014 Dec 13;14:115.

Effect of HME in preventing VAP: a meta-analysis.



Meneguetti et al BMC Anesthesiol. 2014 Dec 13;14:115.

Study	HME	HH	Odds ratio	95% CI	P	Weight
Martin et al. 1990	2/31	8/42	0.29	0.05 to 1.49		1.45
Roustan et al. 1992	5/55	10/61	0.51	0.16 to 1.59		2.85
Dreyfuss et al. 1995	6/61	8/70	0.84	0.27 to 2.58		3.07
Boots et al. 1997	14/75	7/41	1.11	0.41 to 3.02		3.84
Kirton et al. 1997	35/140	31/140	1.17	0.67 to 2.03		12.57
Kollef et al. 1998	20/163	27/147	0.62	0.33 to 1.16		9.89
Memish et al. 2001	13/123	16/120	0.76	0.35 to 1.67		6.32
Lacherade et al. 2005	27/186	25/184	1.08	0.60 to 1.94		11.16
Boots et al. 2006	25/190	10/97	1.31	0.60 to 2.87		6.35
Lorente et al. 2006	21/53	8/51	3.52	1.38 to 8.97		4.40
Total (fixed effects)	168/1077	150/953	1.00	0.78 to 1.27	0.99	

HME vs HH?

- **Methods**: Retrospective study, before and after use of a heat and moisture exchanger (HME) filter. 314 were admitted to the ICU, 168 of whom were included in group HH (heated humidifier) and 146 in group HME.
- **Results**: The frequency of VAP per 1000 ventilator-days was similar for both the HH and HME groups (18.7 vs 17.4, respectively; P = 0.97).

Martins et al Braz J Med Biol Res. 2012 Dec;45(12):1295-300

Saline instillation before tracheal suctioning

- **Methods:** One hundred thirty patients were assigned to the saline group and 132 to the control group.
- **Results:** The incidence of microbiological proven VAP was significantly lower in the saline group (23.5% vs 10.8%; p = 0.008).
- The relative risk reduction of VAP in the saline instillation group was 54% (95% CI, 18%-74%) and the number needed to treat was eight (95% CI, 5-27).

Caruso et al Crit Care Med. 2009 Jan;37(1):32-8

	Total	Saline	Control	*p*
Number of patients (%)	262	130 (49.6)	132 (50.4)	
Clinically suspected VAP events (%)	74 (28.2)	32 (24.6)	42 (31.8)	0.22
Microbiological proven VAP (%)	45 (17.2)	14 (10.8)	31 (23.5)	0.008
Incidence density/1.000 MV days	15.44	9.62	21.22	0.011
Early-onset VAP (2–5 days of MV) (%)	13 (5.0)	4 (3.1)	9 (6.8)	0.98
VAP between 5 and 10 days of MV) (%)	16 (6.1)	7 (5.4)	9 (6.8)	0.17
VAP after 10 days of MV (%)	16 (6.1)	3 (2.3)	13 (9.8)	0.31
Patients using antibiotics at intensive unit care admission (%)	188 (72.0)	98 (76.0)	90 (68.2)	0.17
Patients using antibiotics at the day of clinically suspected VAP (%)	74 (28.2)	31 (23.8)	38 (28.8)	0.38
Patients that used antibiotics during intensive unit care stay (%)	258 (98.5)	130 (100)	128 (97)	0.12

Conclusion

- HME was not superior to heated humidification
- Saline instillation before suction does improve VAP incidence, given its easy to implement tech- Saline instillation before suction can be recommended as a routine practice.
- Closed Suction vs open Suction. Though the level of evidence is low but there is a trend towards increased VAP in open suction techniques.
- Closed suction can be recommended in all patients

Section 7. Probiotics

Probiotics for VAP prevention

- **Methods:** Randomized, controlled multicenter trial, 235 critically ill adult patients who were expected to receive mechanical ventilation for ≥48 h.
- The patients were randomized to receive (1) a probiotics capsule containing live Bacillus subtilis and Enterococcus faecalis (Medilac-S) 0.5 g three times daily or (2) standard preventive strategies alone, for a maximum of 14 days.

Zeng et al Intensive Care Med. 2016 Jun;42(6):1018-28.

- **Results:** The incidence of microbiologically confirmed VAP in the probiotics group was significantly lower than that in the control patients (36.4 vs. 50.4 %, respectively; P = 0.031).
- The mean time to develop VAP was significantly longer in the probiotics group than in the control group (10.4 vs. 7.5 days; P = 0.022).
- The administration of probiotics did not result in any improvement in the incidence of duration of mechanical ventilation, mortality and length of hospital stay.

Primary outcome	Probiotics group	Control group	*P* value
Incidence of clinically diagnosed VAP	48/118 (40.7 %)	62/117 (53.0 %)	0.059
Incidence of microbiologically confirmed VAP	43/118 (36.4 %)	59/117 (50.4 %)	0.031
Patients with Gram-negative VAP	27/43 (62.8 %)	35/59 (59.3 %)	0.866
Patients with Gram-positive VAP	7/43 (16.3 %)	13/59 (22.0 %)	0.603
Patients with *Candida* VAP	1/43 (2.3 %)	2/59 (3.4 %)	
Patients with polymicrobial VAP	8/43 (18.6 %)	9/59 (15.3 %)	
Patients with late-onset VAP	36/43 (83.7 %)	47/59 (79.7 %)	
Number of pathogens isolated			
Total number of pathogens isolated	56	67	0.637
Pseudomonas aeruginosa	13	19	
Acinetobacter baumannii	10	14	
Enterobacteriaceae	3	3	
Klebiella pneumonia	6	7	
Stenotrophomonas maltophilia	4	1	
Staphylococcus aureus	12	16	
Streptococcus species	2	4	
Candida species	2	4	
Other	4	1	
Time to occurrence of VAP (days)	10.4 ± 2.95	7.5 ± 2.9	0.022
Recurrent episode(s) of VAP during study period	1	0	NS

Probiotics for preventing VAP: a systematic review

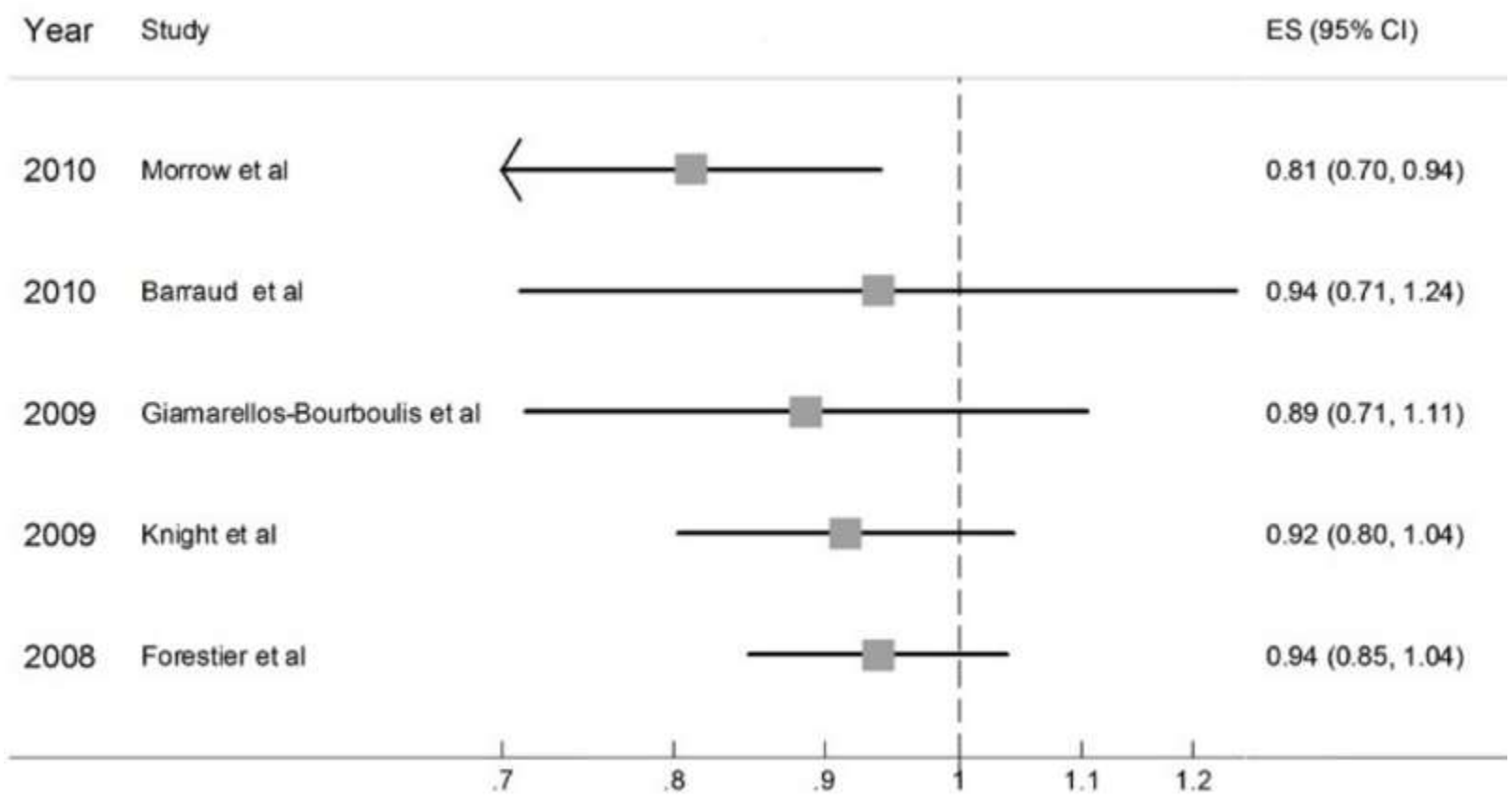
Wang et al

- Data of 844 patients from 5 trials were subjected to meta-analysis.
- Probiotics did not significantly decrease the incidence of VAP (RR 0.94, 95%CI 0.85-1.04, p=0.22), however, the administration of probiotics reduced the risk of VAP caused by Pseudomonas aeruginosa (P. aeruginosa) (RR 0.30, 95%CI 0.11-0.91, P=0.03).

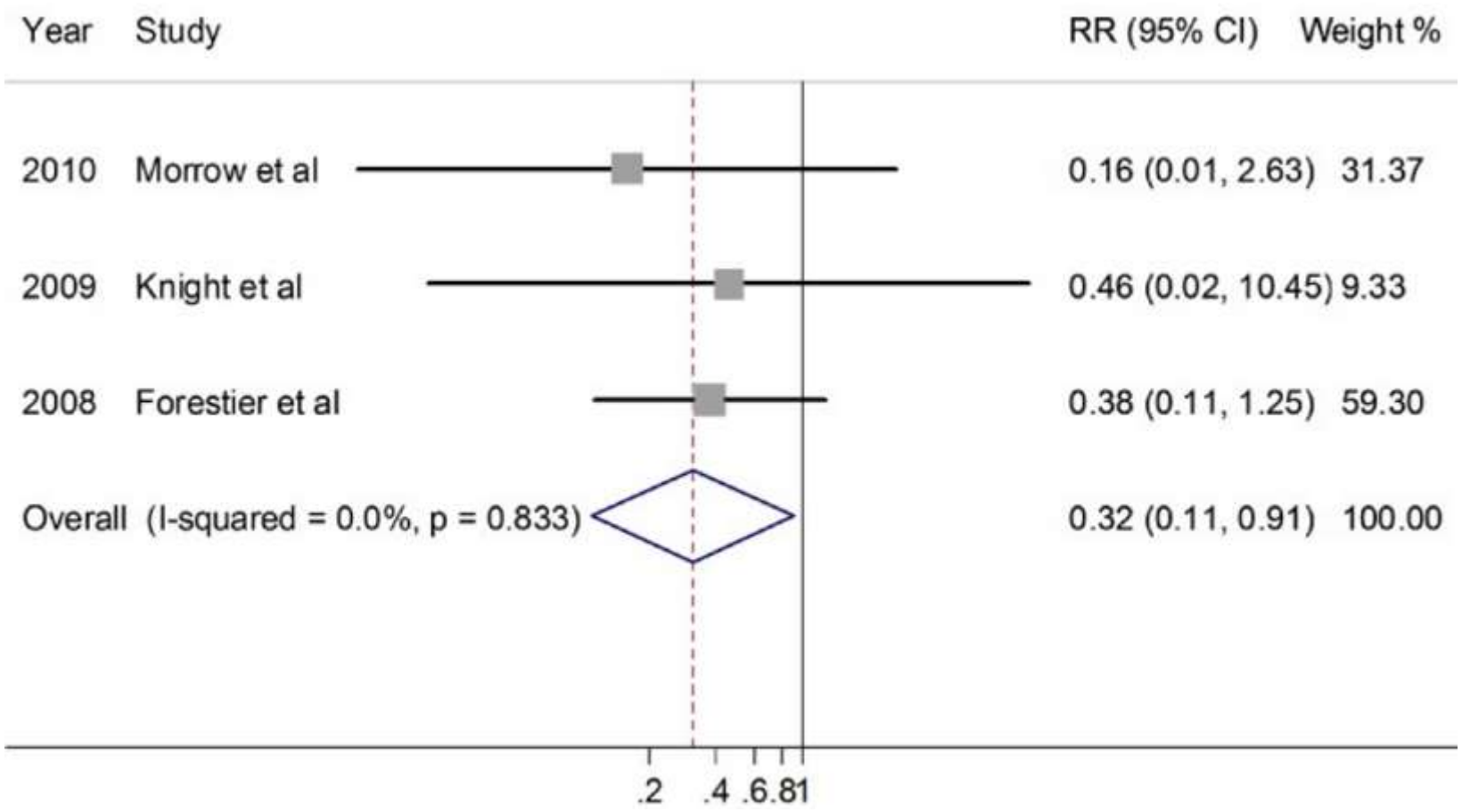
Gu et al

- A total of 1,142 patients from seven trials were subjected to meta-analysis.
- Probiotics did not significantly decrease the incidence of VAP (OR, 0.82; 95% CI, 0.55-1.24; P 5 .35), with low heterogeneity among the studies (I^2 5 36.5%, P 5 .15).

Wang et al PLoS One. 2013 Dec 18;8(12):e83934.
Gu et al Chest. 2012 Oct;142(4):859-868


Year
Study
ES (95% CI)
2010
Morrow et al
0.81 (0.70, 0.94)
2010
Barraud et al
0.94 (0.71, 1.24)
2009
Giamarellos-Bourboulis et al
0.89 (0.71, 1.11)
2009
Knight et al
0.92 (0.80, 1.04)
2008
Forestier et al
0.94 (0.85, 1.04)
.7
.8
.9
1
1.1
1.2

Relative risk for VAP caused by P. aeruginosa



Probiotic therapy in critical illness: a meta-analysis

- **Methods:** Thirty trials that enrolled 2972 patients were analyzed. Most of the patients received probiotics for 2 weeks.
- **Results:** Probiotics were associated with a significant reduction in infections (RR 0.80, 95 % CI 0.68, 0.95, P = 0.009) including VAP (RR 0.74, 95 % CI 0.61, 0. 90, P = 0.002).
- No effect on mortality, LOS or diarrhea was observed.

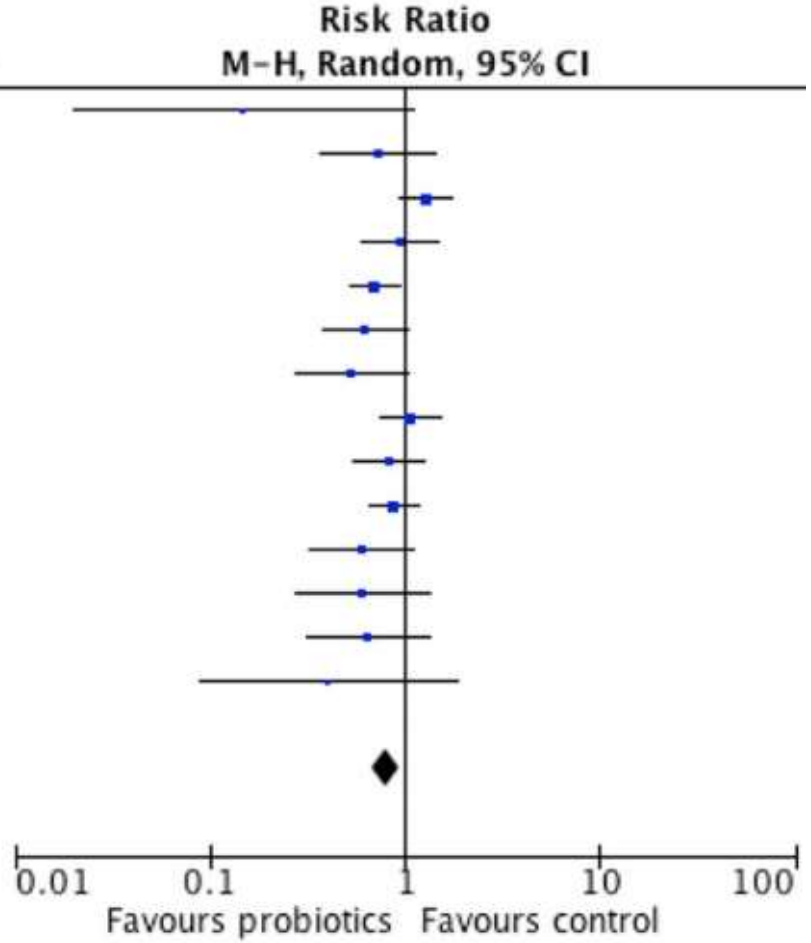
Manzanares et al Crit Care. 2016 Aug 19;19:262.

Effect of probiotics on overall infections

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kecskes 2003	1	22	7	23	0.7%	0.15 [0.02, 1.12]	2003
Lu 2004	8	20	11	20	4.8%	0.73 [0.37, 1.42]	2004
Jain 2004	33	45	26	45	12.8%	1.27 [0.93, 1.72]	2004
McNaught 2005	21	52	22	51	8.3%	0.94 [0.59, 1.48]	2005
Kotzampassi 2006	22	35	27	30	13.7%	0.70 [0.53, 0.93]	2006
Li 2007	8	14	10	11	7.6%	0.63 [0.38, 1.03]	2007
Olah 2007	9	33	15	29	4.9%	0.53 [0.27, 1.02]	2007
Besselink 2008	46	152	41	144	11.1%	1.06 [0.75, 1.51]	2008
Barraud 2010	26	87	29	80	8.9%	0.82 [0.53, 1.27]	2010
Ferrie 2011	14	18	16	18	13.1%	0.88 [0.65, 1.18]	2011
Tan 2011	9	26	15	26	5.4%	0.60 [0.32, 1.12]	2011
Wang 2013	8	62	13	61	3.5%	0.61 [0.27, 1.36]	2013
Lopez de Toro 2014	9	46	13	43	4.1%	0.65 [0.31, 1.36]	2014
Sanaie 2014	2	20	5	20	1.1%	0.40 [0.09, 1.83]	2014
Total (95% CI)		**632**		**601**	**100.0%**	**0.80 [0.68, 0.95]**	
Total events	216		250				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 20.22$, df = 13 (P = 0.09); $I^2 = 36\%$

Test for overall effect: Z = 2.61 (P = 0.009)

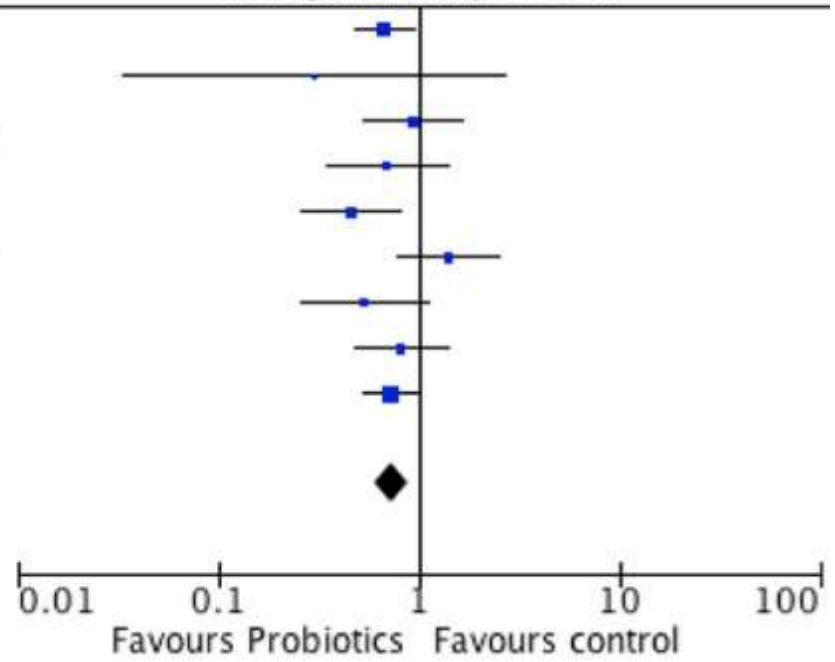


Effects of probiotics on the incidence of VAP

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kotzampassi 2006	19	35	24	30	20.4%	0.68 [0.48, 0.97]	2006
Klarin 2008	1	23	3	21	0.8%	0.30 [0.03, 2.70]	2008
Forestier 2008	19	102	21	106	10.2%	0.94 [0.54, 1.64]	2008
Knight 2009	12	130	17	129	6.9%	0.70 [0.35, 1.41]	2009
Morrow 2010	13	73	28	73	9.8%	0.46 [0.26, 0.82]	2010
Barraud 2010	23	87	15	80	9.7%	1.41 [0.79, 2.51]	2010
Tan 2011	7	26	13	26	6.2%	0.54 [0.26, 1.13]	2011
Rongrungruang 2015	18	75	22	75	10.9%	0.82 [0.48, 1.40]	2015
Zeng 2016	43	118	59	117	25.1%	0.72 [0.54, 0.97]	2016
Total (95% CI)		**669**		**657**	**100.0%**	**0.74 [0.61, 0.90]**	
Total events	155		202				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.86$, df = 8 (P = 0.27); $I^2 = 19\%$

Test for overall effect: Z = 3.04 (P = 0.002)

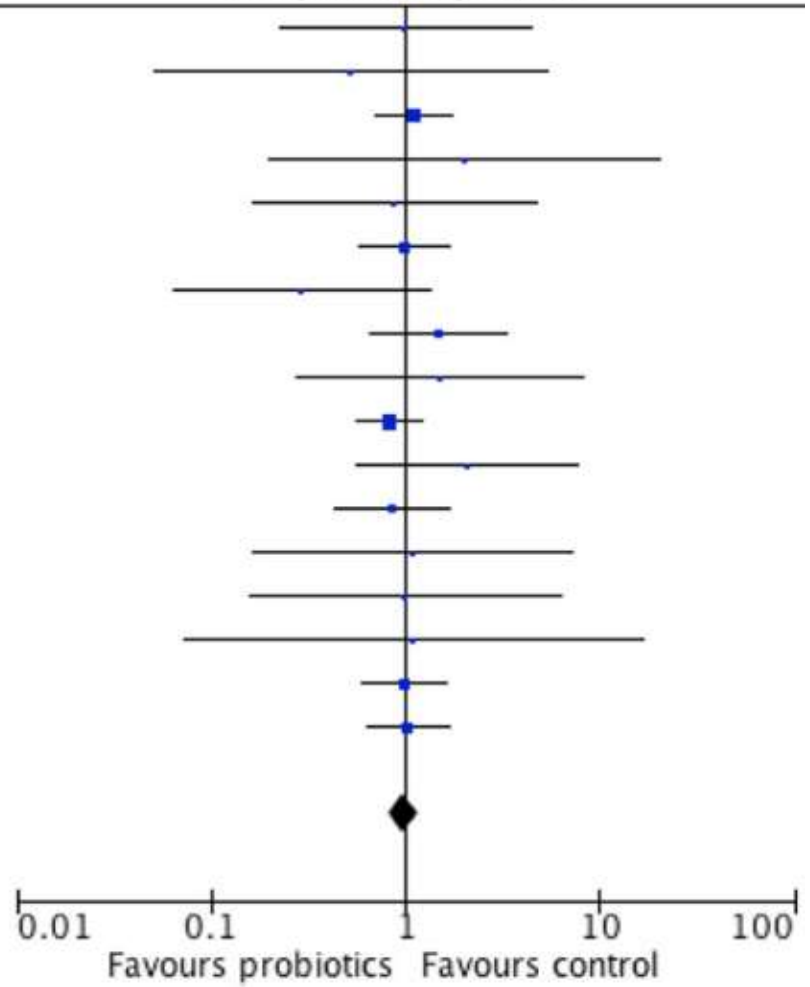


Effect on hospital mortality.

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tempe 1983	3	20	3	20	1.5%	1.00 [0.23, 4.37]	1983
Kecskes 2003	1	22	2	23	0.6%	0.52 [0.05, 5.36]	2003
Jain 2004	22	45	20	45	16.4%	1.10 [0.71, 1.71]	2004
Lu 2004	2	20	1	20	0.6%	2.00 [0.20, 20.33]	2004
Klarin 2005	2	8	2	7	1.1%	0.88 [0.16, 4.68]	2005
McNaught 2005	18	52	18	51	11.6%	0.98 [0.58, 1.66]	2005
Olah 2007	2	33	6	29	1.4%	0.29 [0.06, 1.34]	2007
Besselink 2008	14	152	9	144	5.0%	1.47 [0.66, 3.30]	2008
Klarin 2008	3	22	2	22	1.1%	1.50 [0.28, 8.12]	2008
Knight 2009	35	130	42	129	22.7%	0.83 [0.57, 1.21]	2009
Frohmader 2010	5	20	3	25	1.9%	2.08 [0.56, 7.68]	2010
Morrow 2010	12	68	15	73	6.9%	0.86 [0.43, 1.70]	2010
Sharma 2011	2	24	2	26	0.9%	1.08 [0.17, 7.10]	2011
Ferrie 2011	2	18	2	18	0.9%	1.00 [0.16, 6.35]	2011
Cui 2013	1	23	1	25	0.4%	1.09 [0.07, 16.39]	2013
Lopez de Toro 2014	19	46	18	43	13.3%	0.99 [0.60, 1.61]	2014
Zeng 2016	26	118	25	117	13.6%	1.03 [0.63, 1.68]	2016
Total (95% CI)		**821**		**817**	**100.0%**	**0.98 [0.82, 1.18]**	
Total events	169		171				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.84$, $df = 16$ ($P = 0.98$); $I^2 = 0\%$

Test for overall effect: $Z = 0.19$ ($P = 0.85$)



Conclusion

- Probiotics have an protective effect against on all hospital acquired infections
- There has been no documentation of adverse effects related to them
- But data is divided over the exact impact
- Currently cannot be recommended in all patients

Section 8. Positioning

VAP and endotracheal tube repositioning

- **Methods:** Single center observational study, took 4 controls for one VAP patients to study the risk factors for VAP
- **Results:** 263 eligible patients identified, and 47 cases of VAP were documented in the study period,

Independent risk factors for the development of ventilator-acquired pneumonia (logistic regression)

Risk factor	Adjusted OR	95% CI	*P* value
ETT repositioning*	3.11	1.03-9.42	.04
Diabetes	0.42	0.17-1.00	.05
Antibiotics on day 1 of ICU admission	0.45	0.23-0.88	.02

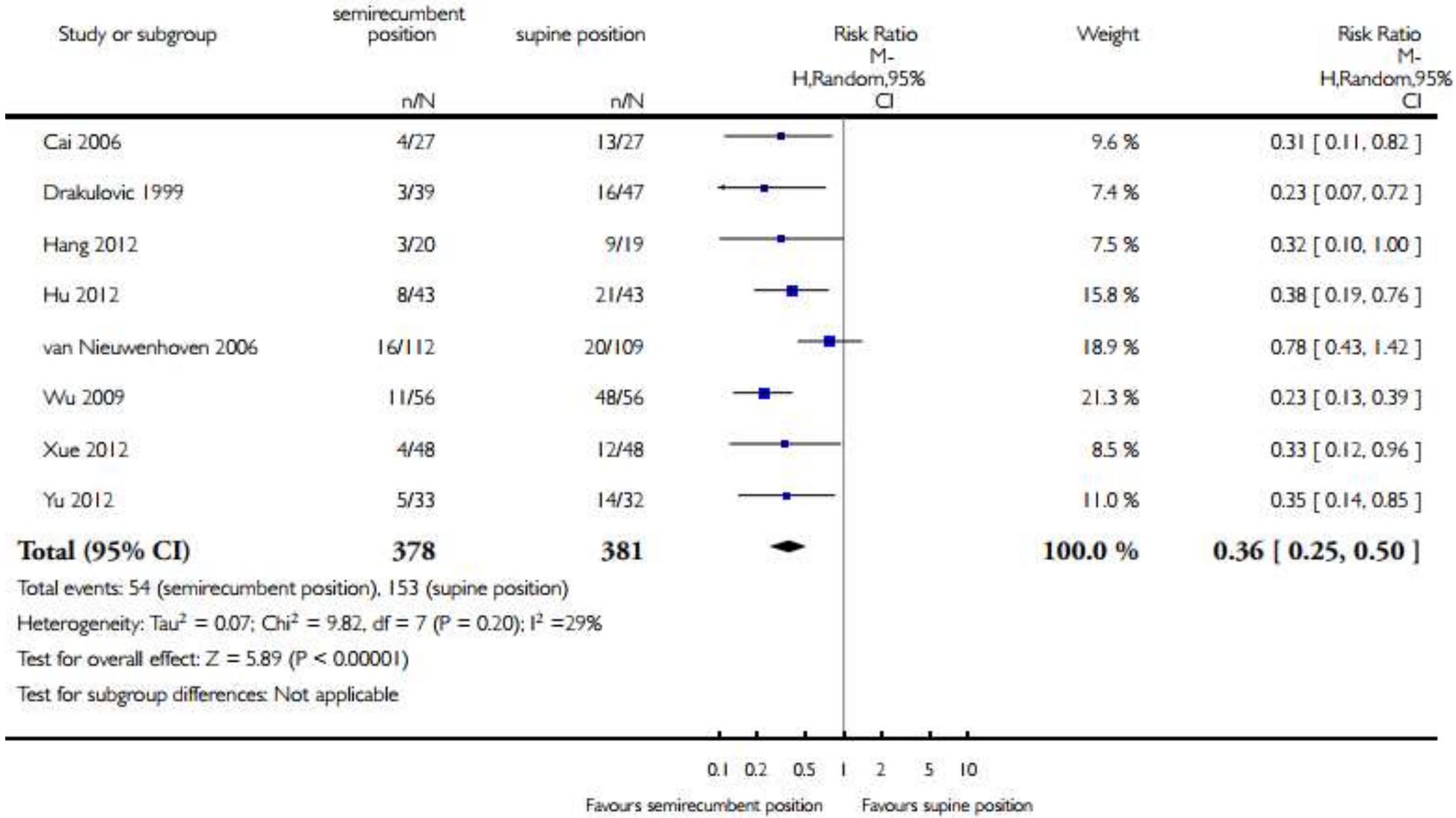
Murphy et al American Journal of Infection Control 42 (2014) 1328-30

Semi-recumbent position versus supine position

- **Methods:** 10 trials involving 878 participants. Semi-recumbent position (30º to 60º) versus supine position (0° to 10°) VAP rates were compared.
- **Results:** A semi-recumbent position significantly reduced the risk of VAP compared to supine position (14.3% versus 40.2%, RR 0.36; 95% CI 0.25 to 0.50).
- No significant difference in ICU mortality, hospital mortality, length of ICU stay, duration of ventilation, antibiotic use and **pressure ulcers**

Wang et al Cochrane Database Syst Rev. 2016 Jan 8;(1):CD009946

Outcome: 1 Clinically suspected pneumonia



Conclusions

- A semi-recumbent position (≧ 30º) may reduce clinically suspected VAP compared to a 0° to 10° supine position.
- However, the evidence is seriously limited with a high risk of bias.
- But given its harmless and easily done nature, this intervention should be used in all patients
- ET repositioning should be avoided and its **requirement** should be reduced.

Section 9. Inhaled Antibiotics

Why use at all?

- Direct delivery to the site of infection
- Concentrations in the lung that would not be tolerated if given intravenously
- May shorten the duration of systemic antibiotics

Inhaled Antibiotics for VAP.

- **Methods:** An aerosol of polymyxin B was administered to the upper airways of 292 patients.
- **Results:** Although only one of the patients studied acquired pneumonia due to Ps. aeruginosa, 10 others acquired pneumonia caused by a polymysinx-resistant organism. The mortality rate for acquired pneumonia in this study, 64 per cent, was greater than that in previous studies.
- Continuous use of polymyxin B aerosol appears to be a dangerous form of therapy.


ORIGINAL ARTICLE ARCHIVE

Aerosol Polymyxin and Pneumonia in Seriously Ill Patients

T. W. Feeley, M.D., G. C. du Moulin, M.S., J. Hedley-Whyte, M.D., L. S. Bushnell, M.D., J. P. Gilbert, Ph.D., and D. S. Feingold, M.D.

N Engl J Med 1975; 293:471-475 | September 4, 1975 | DOI: 10.1056/NEJM197509042931003

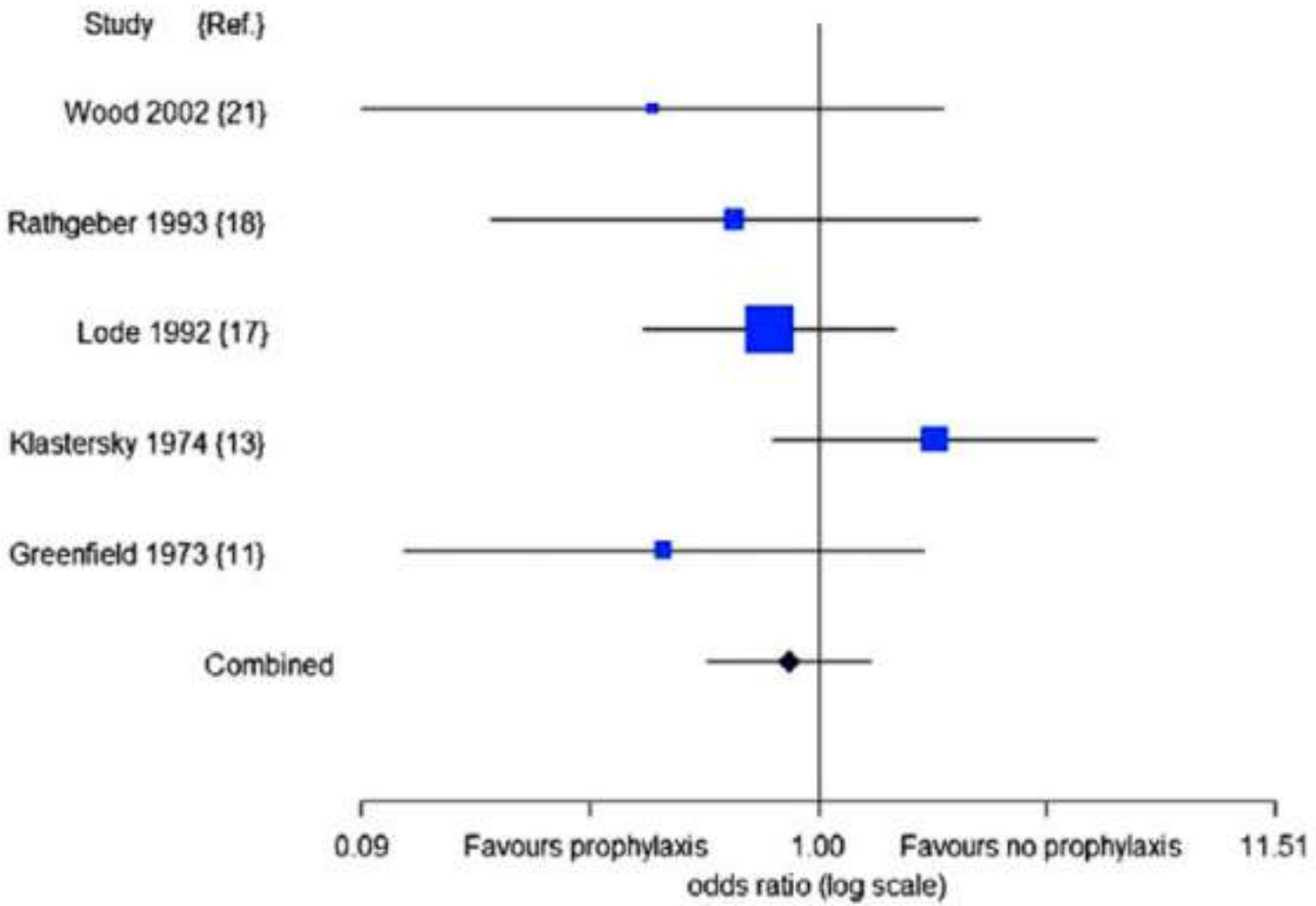
Feeley et al N Engl J Med. 1975 Sep 4;293(10):471-5.

Administration of antibiotics via the respiratory tract for the prevention of VAP: a meta-analysis.

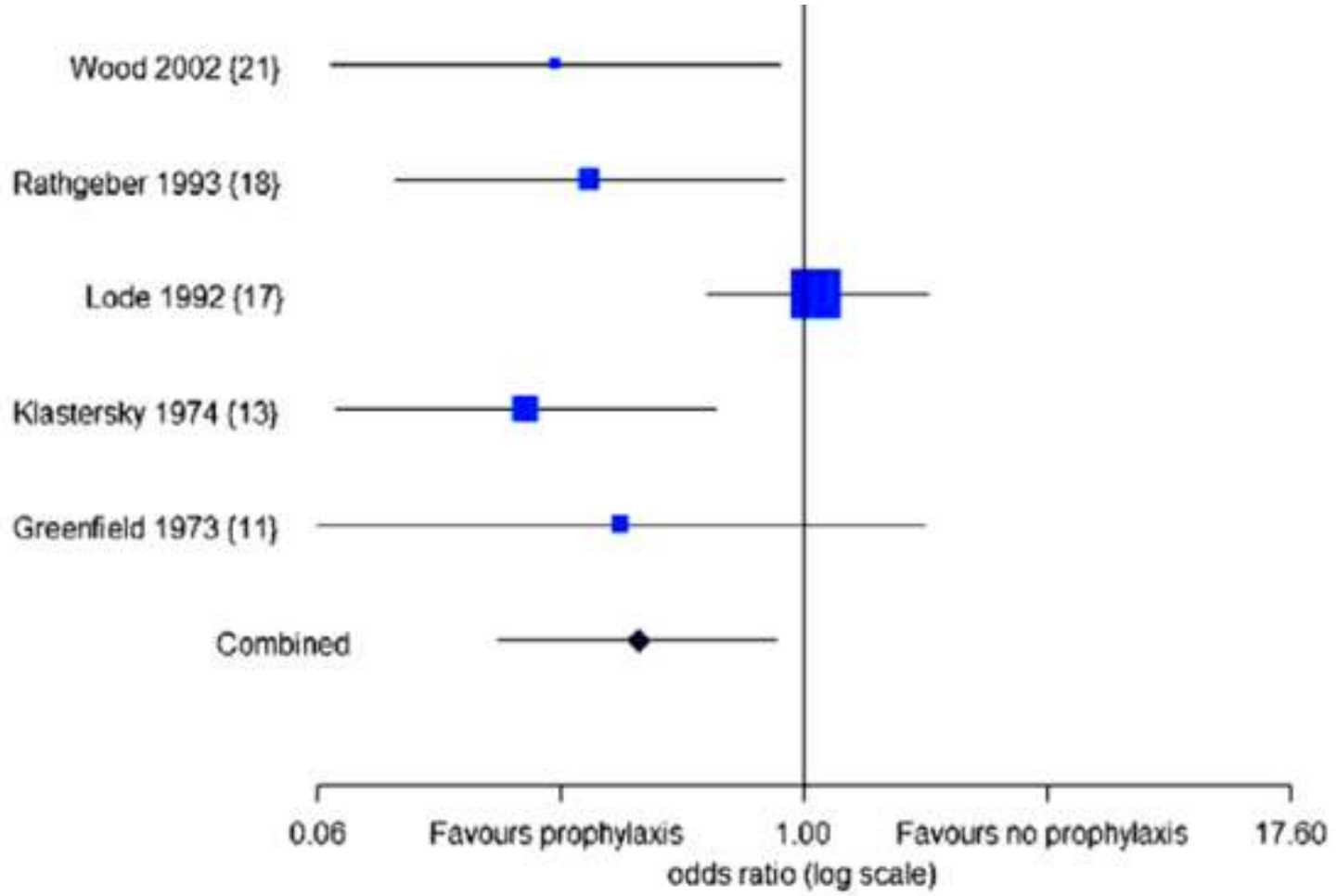
- **Methods:** 8 comparative trials (5 RCTs and 3 non-randomized trials). 1,877 patients were included
- **Results:** ICU-acquired pneumonia was less common in the group of patients that received the antibiotic prophylaxis (OR = 0.49, 95% CI 0.32-0.76). No difference in mortality was found between the compared groups (OR = 0.86, 95% CI 0.55-1.32).

Falagas et al Crit Care. 2006;10(4):R123.

Odds ratio for mortality



Odds ratios of intensive care unit-acquired pneumonia



Drug Adverse Events

- Bronchial Constriction Renal toxicity, Tinnitus, vestibular Toxicity, hoarseness

Nebulized Colistin for VAP prevention

- **Methods:** single-centre, RCT, prophylaxis with 500 000 U colistin (Col group) or normal saline (NS group), thrice daily, for the first 10 ICU days or until extubation
- **Results:** In total, 168 patients entered the study. VAP incidence was not different between Col and NS group patients (14 (16.7%) versus 25 (29.8%), respectively, p=0.07.
- **Conclusion:** Neb Colistin had no impact on reducing VAP rates
- No increase in resistance

Karvouniaris et all Eur Respir J 2015 Dec;46(6):1732-9.

	Overall n=168	Col group n=84	NS group n=84	p
Primary outcome				
VAP	39 (23.2)	14 (16.7)	25 (29.8)	0.07
Secondary outcomes				
VAP IDR	18	11.4	25.6	<0.01
GNB-VAP	30 (17.9)	9 (10.7)	21 (25)	0.03
MDR-VAP	22 (13.1)	6 (7.1)	16 (19)	0.04
VAP due to *Acinetobacter baumannii*	13 (7.7)	2 (2.8)	11 (13.1)	0.02
VAP due to *Staphylococcus* species	9 (5.4)	5 (6)	4 (4.8)	1.0
VAP during the 10-day prophylaxis	28 (16.7)	9 (10.7)	19 (22.6)	0.06
VAP post 10-day prophylaxis	11 (6.5)	5 (6)	6 (7.1)	1.0
VAP following VAT	6 (3.6)	4 (4.8)	2 (2.4)	0.68
VAT IDR	5.3	4.1	6.6	<0.01
VAT	11 (6.5)	5 (6)	6 (7.1)	1.0
GNB-VAT	11 (6.5)	5 (6)	6 (7.1)	1.0
MDR-VAT	9 (5.4)	4 (4.8)	5 (6)	1.0
VAT due to *Acinetobacter baumannii*	5 (3)	2 (2.4)	3 (3.6)	1.0
VAT during the 10-day prophylaxis	7 (4.2)	2 (2.4)	5 (6)	0.44
Airway colonisation	34 (20.2)	16 (19)	18 (21.4)	0.85
During the 10-day prophylaxis	22 (13.1)	6 (7.1)	16 (19)	<0.01
After the 10-day prophylaxis	12 (7.1)	10 (11.9)	2 (2.4)	<0.01
Due to GNB	33 (19.6)	15 (17.9)	18 (21.4)	0.70
Due to MDR	28 (16.7)	13 (15.5)	15 (17.9)	0.84
ICU mortality	54 (32.1)	25 (29.8)	29 (34.5)	0.62
ICU stay days	13.5 (7–28)	16.5 (7–29.7)	13 (6.25–24.7)	0.31
Hospital mortality	60 (35.7)	29 (34.5)	31 (36.9)	0.87
Hospital stay days	20 (12–30)	23 (12–30)	19 (12.2–30)	0.38
MV days[¶]	12 (5–21)	13.5 (5–24.5)	9 (5–18.7)	0.26
MV days before first episode of VAI	7 (4–12.2)	10 (7–15)	6 (4–10)	0.01
MV days before first episode of VAP	6 (4–12)	10 (5.5–16.5)	4 (3.5–10.5)	0.07
MV-free days	1 (0–3)	1 (0–3)	1 (0–3)	0.90
Days without systemic antibiotic exposure	1 (0–5)	2.5 (0–5)	0.5 (0–3)	0.06
Tracheostomy	76 (45.2)	43 (51.2)	33 (39.3)	0.16

Topical antibiotics

- Several antibiotics like metronidazole, tobramycin, nystatin, polymyxin have been used in topical manner for preventing VAP
- But their efficacy is less than chlorhexidine solution

Inhaled antibiotics beyond AG, Polymyxin and Vancomycin

- **Methods**: A systematic review was done and data was extracted from 34 studies (heterogenous methodology) for efficacy and safety of inhaled antibiotics
- **Results**: Subgroup analysis where inhaled antibiotics were used for *prevention of VAP* did not show any significant difference to favor the use of inhaled antibiotics
- Increase in Resistant organisms
- Ceftazidime and Vancomycin when used for treatment of *pseudomonas VAP* & *Gram positive VAP* did show significant difference

Falagas et al Int J Antimicrob Agents. 2015 Mar;45(3):221-33

Single shot of antibiotics?

- **Methods:** A prospective cohort of comatose patients who were administered with a single-dose of antibiotic within 4 h of intubation was compared with control group (71 in the prophylaxis group & 58 as control)
- **Results:** Incidence of VAP was lower in the prophylaxis group: 10.8 vs 28.4 episodes/1,000 days on MV (P = .015).
- No differences in mortality/late onset VAP was found
- The propensity-score regression analysis confirmed that a single dose of antibiotic prophylaxis was independently associated with lower incidence of EO-VAP (OR, 0.11; 95% CI, 0.02-0.58; P = .009).

Valles et al Chest. 2013 May;143(5):1219-1225

Conclusion

- Inhaled antibiotics of *ANY group* should not be used for prevention of VAP
- This modality might have a role in treatment of VAP

Section 10. Stress ulcer prophylaxis

PPI versus histamine 2 receptor antagonists for stress ulcer prophylaxis: a meta-analysis

- **Methods:** 14 trials enrolling a total of 1,720 patients were included.
- **Results:** PPI were more effective than H2R antagonists at reducing clinically important upper gastrointestinal bleeding (RR 0.36; 95% CI 0.19-0.68; $p = 0.002$) and overt upper gastrointestinal bleeding (RR 0.35; 95% CI 0.21-0.59; $p < 0.0001$)
- There were no differences between proton pump inhibitors and histamine 2 receptor antagonists in the **risk of nosocomial pneumonia**, ICU mortality or ICU length of stay

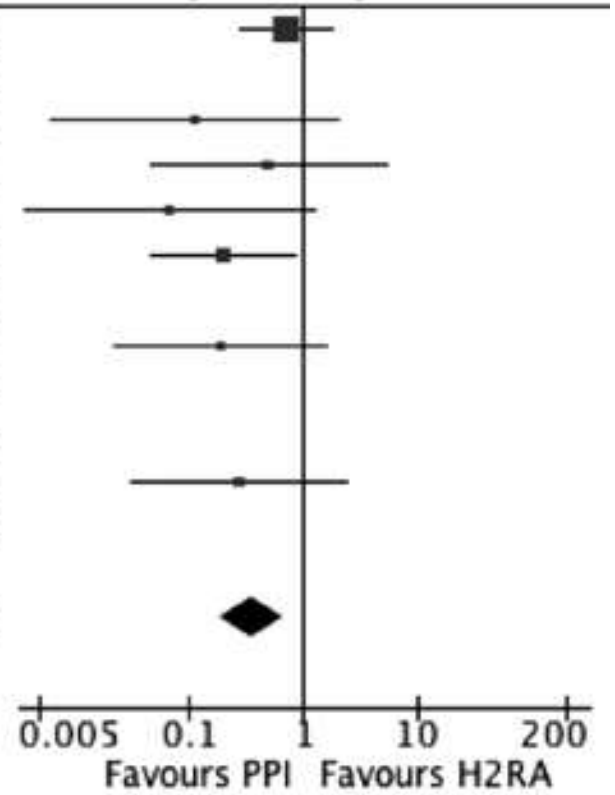
Alhazzani et al Crit Care Med. 2013 Mar;41(3):693-705

Forrest plot for clinically important gastrointestinal bleeding outcome.

Study or Subgroup	Favours PPI Events	Total	H2RA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	7	178	10	181	45.7%	0.71 [0.28, 1.83]
Fink 2003	0	158	0	31		Not estimable
Hata 2005	0	70	4	70	4.8%	0.11 [0.01, 2.03]
Kantorova 2004	1	72	2	71	7.2%	0.49 [0.05, 5.32]
Kotlyanskaya 2007	0	45	3	21	4.8%	0.07 [0.00, 1.27]
Levy 1996	2	32	11	35	19.9%	0.20 [0.05, 0.83]
Morris 2002	0	169	0	33		Not estimable
Phillips 1998	1	33	4	25	9.0%	0.19 [0.02, 1.59]
Powell 1993	0	20	0	11		Not estimable
Rosaliti 1993	0	14	0	14		Not estimable
Solouki 2009	1	61	4	68	8.7%	0.28 [0.03, 2.43]
Somberg 2008	0	167	0	35		Not estimable
Total (95% CI)		**1019**		**595**	**100.0%**	**0.36 [0.19, 0.68]**
Total events	12		38			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.13$, df = 6 (P = 0.53); $I^2 = 0\%$

Test for overall effect: Z = 3.14 (P = 0.002)

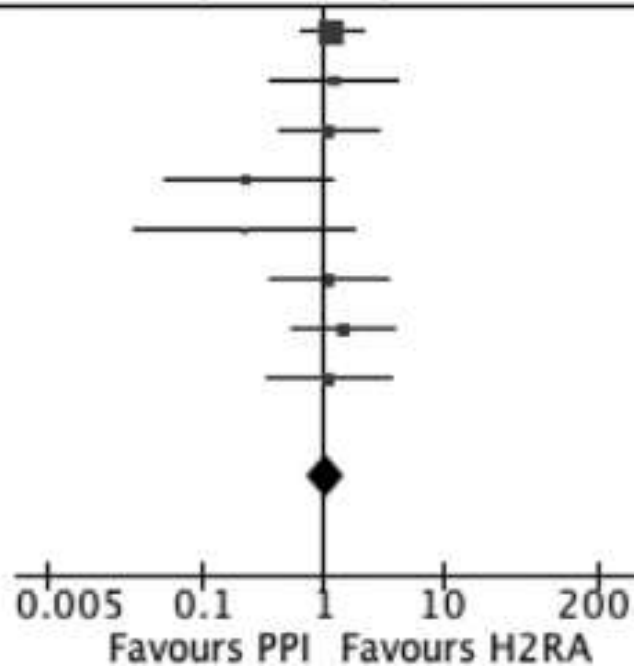


Forrest plot for nosocomial pneumonia outcome

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	20	178	17	181	35.6%	1.20 [0.65, 2.21]
De Azevedo 2000	5	38	4	38	8.7%	1.25 [0.36, 4.30]
Kantorova 2004	8	72	7	71	14.5%	1.13 [0.43, 2.94]
Kotlyanskaya 2007	2	45	4	21	5.1%	0.23 [0.05, 1.17]
Levy 1996	1	32	5	35	3.0%	0.22 [0.03, 1.77]
Phillips 1998	6	33	4	25	10.0%	1.14 [0.36, 3.60]
Solouki 2009	8	61	6	68	13.3%	1.49 [0.55, 4.04]
Somberg 2008	16	167	3	35	9.6%	1.12 [0.34, 3.63]
Total (95% CI)		**626**		**474**	**100.0%**	**1.06 [0.73, 1.52]**
Total events	66		50			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.28$, $df = 7$ ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: $Z = 0.30$ ($P = 0.76$)



Sucralfate versus PPI and/or $Hist_2$ R blockers.

- **Materials:** This is a single-center retrospective cohort analysis of all intubated, adult surgical patients
- **Results:** There were 45 instances of VAP in the 504 study patients, 33 in the PPI/H2 group, and 12 in the S group ($P < 0.01$). VAP per 1000 ventilator days were 10.2 for PPI/H2 and 3.7 for S ($P < 0.01$).
- Culprit bacteria were mostly Pseudomonas, gram-negative bacilli, and methicillin-resistant Staphylococcus aureus in PPI/H2 patients (n = 29) compared with oropharyngeal flora in S patients (n = 6; $P < 0.001$).

Grindlinger et al J Surg Res. 2016 Dec;206(2):398-404.

Clinical comparison of the 45 VAP patients

Variable	Sucralfate	PPI/H2	P value
n	12	33	<0.01
Age	56.4 ± 22.7	61.0 ± 14.7	ns
Male sex	7	24	ns
Trauma (*n*)	10	20	ns
Nontrauma	2	13	ns
APACHE II	17.9 ± 8.1	18.5 ± 6.1	ns
ISS (trauma)	32.8 ± 12.4	35.3 ± 15.8	ns
Ventilator days	17.4 ± 11.0	19.5 ± 15.2	ns
VAP onset postintubation (d)	11.2 ± 7.6	11.9 ± 8.7	ns
# VAP/1000 ventilator days	3.7	10.2	<0.002
ICU LOS	25.2 ± 16.9	27.9 ± 16.8	ns
C. *difficile* colitis: confirmed (toxin +)	0	1	ns
C. *difficile* colitis: suspected (toxin –)	4	16	ns

VAP Bacteriology

BAL bacteria	Sucralfate ($n = 12$)	PPI/H2 ($n = 33$)	P value
Group B, G S. *pyogenes*	1	0	
S. *aureus*	2	0	
MRSA	1	5	
H. *influenza*	4	4	
P. *aeruginosa*	0	12	
S. *maltophilia*	1	2	
A. *baumannii*	1	0	
S. *marcescens*	1	2	
Other gnb	2	10	
Combined nosocomial flora	6	29	<0.001

Effects of sucralfate and acid-suppressive drugs on preventing VAP: a meta-analysis

- **Methods:** A total of 15 RCTs involving 1315 patients in the sucralfate group and 1568 patients in the acid-suppressive drug group were included and analzyed.
- **Results:** The incidence of VAP was significantly reduced in the sucralfate group (RR =0.81,95% CI 0.7-0.95,P =0.008), while no difference was found between the two groups in the incidence of stress-related gastrointestinal bleeding (RR =0.96,95% CI 0.59-1.58,P =0.88).
- No statistical difference was found in the days on ventilator, duration of ICU stay and ICU mortality in the two groups.

Hongli et al Chin J Intern Med, 2014,53(01): 48-54.

Stress ulcer prophylaxis: Is it really indicated?

- A total of 57 studies were included in the review. The literature on SUP in the ICU includes limited trial data and methodological weak studies.
- The reported incidence of GI bleed varies considerably. Data on the incidence and severity of GI bleeding in general medical ICUs is lacking.
- In essence, it is unresolved if ICU patients benefit overall from SUP.
- This met-analysis highlighted the fact that exact incidence of stress ulcers and GI bleed due to them is lacking
- Most the recommending authorities in favor of SUP have derived their conclusion from poorly conducted observational studies or expert opinions

Krag et al Acta Anaesthesiol Scand. 2013 Aug;57(7):835-47

Can we just stop using PPI?- RCT

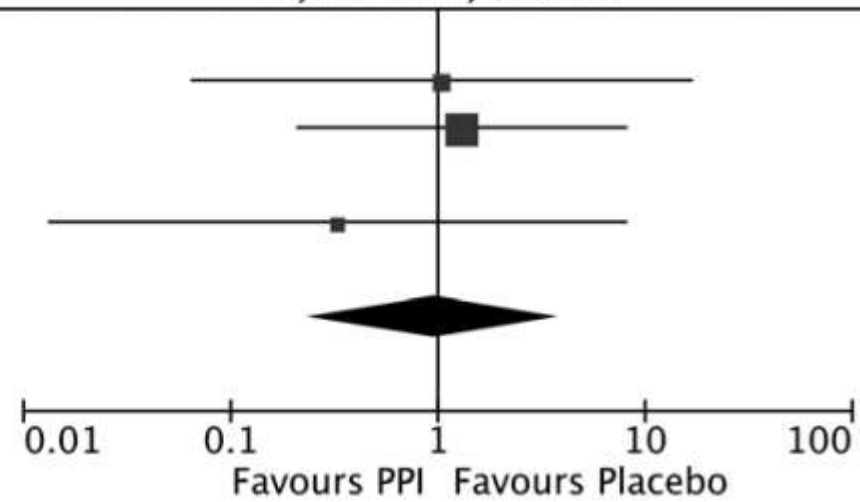
- **Methods**: In 10 ICUs, patients were randomized to receive 40 mg of IV pantoprazole daily or placebo.
- **Results**: UGI bleed developed in 6.1% of patients in the pantoprazole group and 4.8% in the placebo group (p = 1.0).
- VAP developed in 20.4% of patients in the pantoprazole group and 14.3% in the placebo group (p = 0.58). C. difficile was identified in 4.1% pantoprazole patients and in 2.4% placebo patients (p = 1.0).
- Meta-analyzed five trials (n= 604) of PPI versus placebo; there was no statistically significant difference in the risk of UGI bleed, or mortality.

Alhazzani et al Crit Care Med. 2017 Jul;45(7):1121-1129

Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Powell 1993	0	20	0	10		Not estimable	1993
Kantorova 2004	1	72	1	75	24.7%	1.04 [0.06, 16.98]	2004
Alhazzani 2016	3	49	2	42	56.8%	1.30 [0.21, 8.20]	2016
Selvanderan 2016	0	106	0	108		Not estimable	2016
Lin 2016	0	60	1	60	18.5%	0.33 [0.01, 8.21]	2016
Total (95% CI)		**307**		**295**	**100.0%**	**0.96 [0.24, 3.82]**	
Total events	4		4				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.54$, df = 2 (P = 0.76); $I^2 = 0\%$

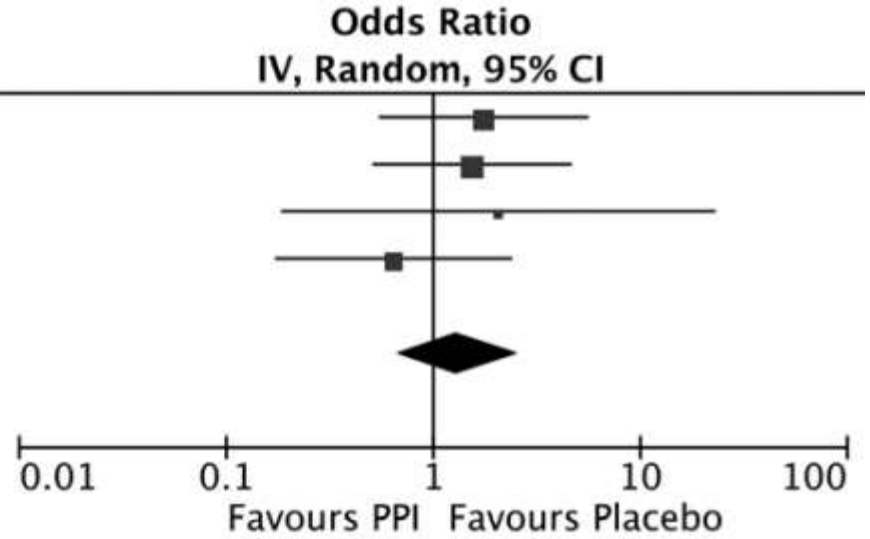
Test for overall effect: Z = 0.06 (P = 0.95)



Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Kantorova 2004	8	72	5	75	32.0%	1.75 [0.54, 5.63]	2004
Alhazzani 2016	10	49	6	42	35.5%	1.54 [0.51, 4.66]	2016
Selvanderan 2016	2	106	1	108	7.5%	2.06 [0.18, 23.04]	2016
Lin 2016	4	60	6	60	25.1%	0.64 [0.17, 2.40]	2016
Total (95% CI)		**287**		**285**	**100.0%**	**1.32 [0.68, 2.55]**	
Total events	24		18				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.57$, df = 3 (P = 0.67); $I^2 = 0\%$

Test for overall effect: Z = 0.82 (P = 0.41)



Does PPI cause harm?

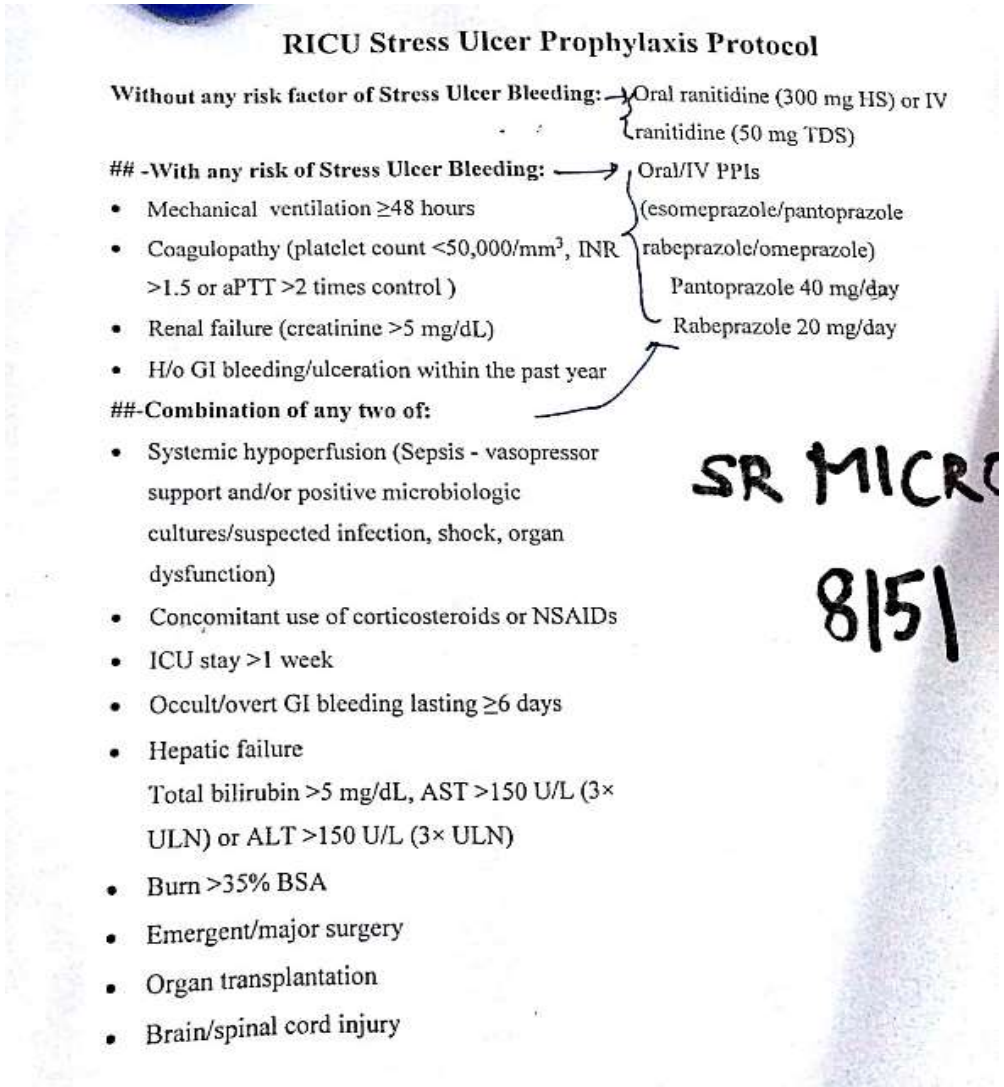
- **Methods**: Randomized double blind RCT of Pantoprazole Vs Placebo in critically ill patients
- **Results:** None of the 214 patients randomized had an episode of clinically significant gastrointestinal bleeding, 3 patients had VAP (placebo: 1 vs pantoprazole: 2), and one patient was diagnosed with Clostridium difficile infection (0 vs 1).
- Administration of pantoprazole was not associated with any difference in rates of overt bleeding (6 vs 3; p = 0.50) or daily hemoglobin concentrations. Mortality was similar between groups

Selavderan et al Crit Care Med. 2016 Oct;44(10):1842-50.

Conclusion

- VAP was less in patients treated with Sucralfate rather than PPI/H2R.
- Unless precluded by active GI hemorrhage, previous gastrectomy or NSAID/dual anti platelet therapy, or otherwise contraindicated, Sucralfate should be preferred for SUP in intubated patients.
- Stress ulcer prophylaxis is a controversial subject with initial recommendation coming without any strong evidence behind them
- But their harmful effect to increase VAP/HAI incidence cannot be disregarded and alternative modalities must be tried

What change can me make to our existing protocol?



RICU Stress Ulcer Prophylaxis Protocol

Without any risk factor of Stress Ulcer Bleeding: → Oral ranitidine (300 mg HS) or IV ranitidine (50 mg TDS)

-With any risk of Stress Ulcer Bleeding: → Oral/IV PPIs (esomeprazole/pantoprazole rabeprazole/omeprazole)

- Mechanical ventilation ≥48 hours
- Coagulopathy (platelet count <50,000/mm^3, INR >1.5 or aPTT >2 times control)
- Renal failure (creatinine >5 mg/dL)
- H/o GI bleeding/ulceration within the past year

Pantoprazole 40 mg/day

Rabeprazole 20 mg/day

##-Combination of any two of:

- Systemic hypoperfusion (Sepsis - vasopressor support and/or positive microbiologic cultures/suspected infection, shock, organ dysfunction)
- Concomitant use of corticosteroids or NSAIDs
- ICU stay >1 week
- Occult/overt GI bleeding lasting ≥6 days
- Hepatic failure
  Total bilirubin >5 mg/dL, AST >150 U/L (3× ULN) or ALT >150 U/L (3× ULN)
- Burn >35% BSA
- Emergent/major surgery
- Organ transplantation
- Brain/spinal cord injury

SR MICR

8151

- Duration of mechanical ventilation does not determine choice of SUP
- Duration of ICU stay, hepatic failure, and sepsis are not related to benefits with SUP
- First line SUP can be Sucralfate rather than Ranitidine/PPI

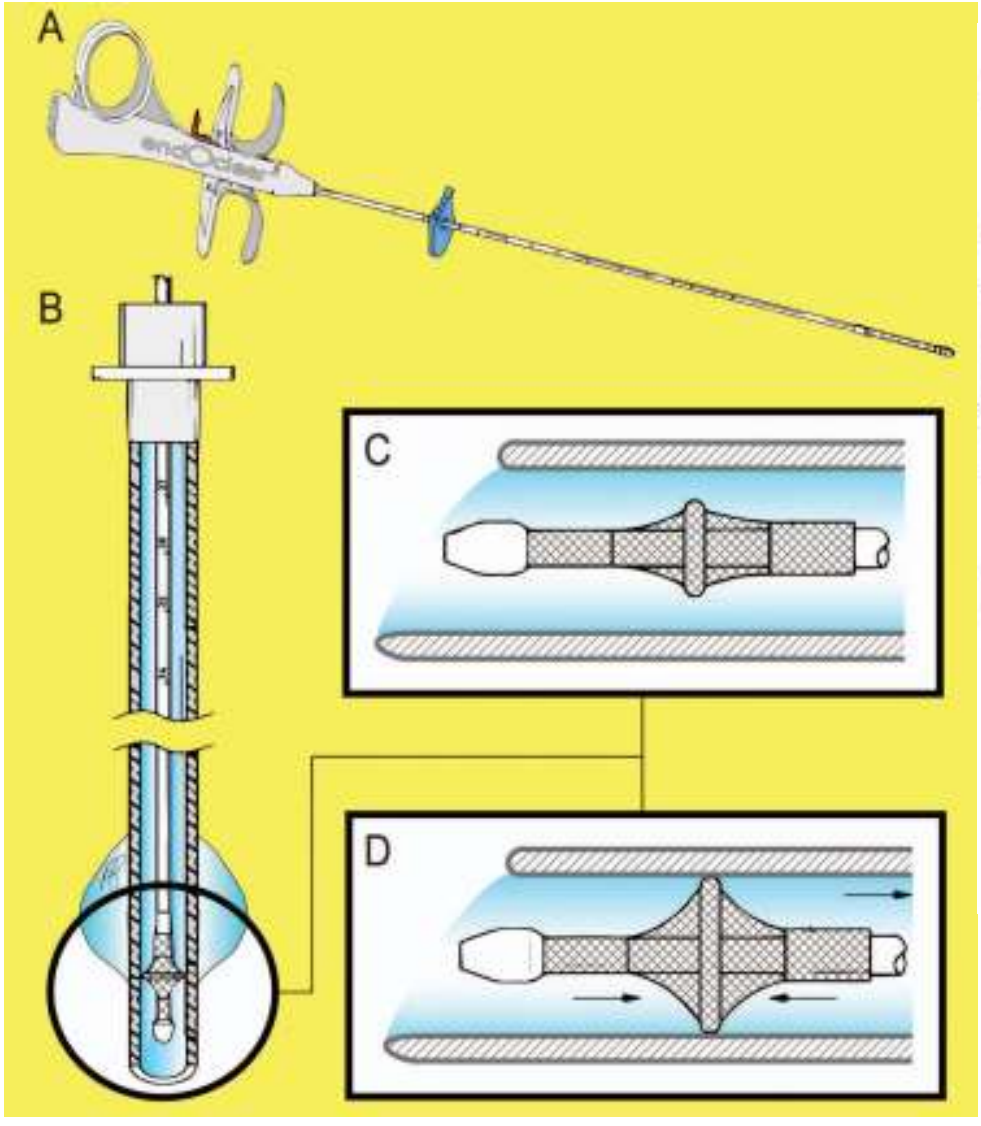
Section 11. *Cleaning* The ET

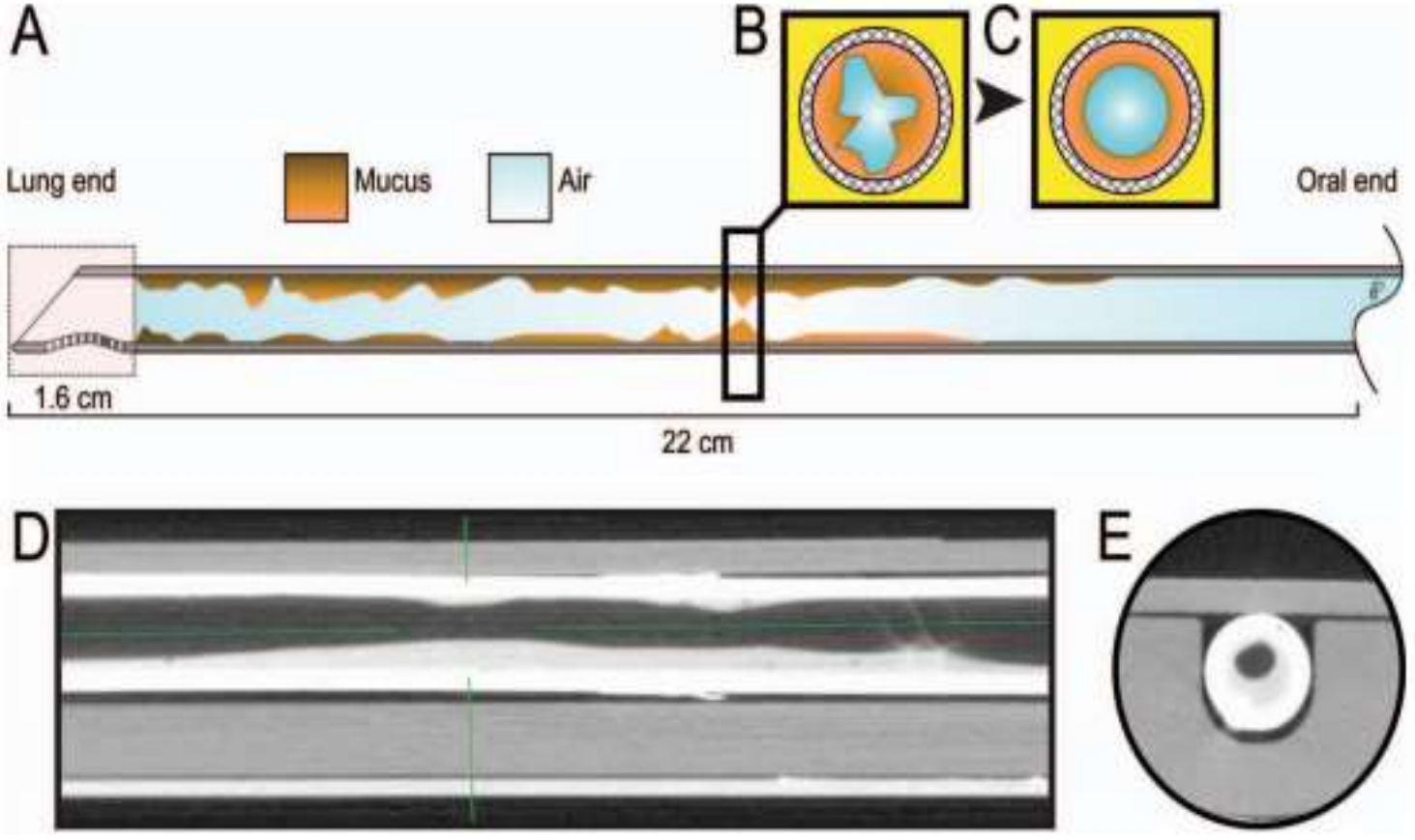
Cleaning ET with Foley?

- **Methods:** Forty-five children were randomized in equal numbers to endotracheal tube cleaning group for three times a day (group A), twice daily (group B), or to a control group with no endotracheal tube cleaning (group C).
- **Results**: Study mentions decrease in bacterial load, biofilms but has given no data on VAP prevention

Liu et al Pediatr Crit Care Med. 2013 Sep;14(7):e338-43

ET Cleaned With a Novel Method





Pinciroli et al Respir Care. 2016 Nov;61(11):1431-1439.

ET cleaning by novel (endOclear) method: RCT

- **Methods:** Subjects were randomized to either the use of the device every 8 h, or the institutional standard of care only. ETTs were collected at extubation and analyzed with HRCT for quantification of mucus volume.
- **Results**: 74 subjects were enrolled (77 ETTs, 37 treatment vs 40 controls). Treated tubes showed reduced mucus accumulation (0.12 vs 0.71; p .004) and reduced occlusion (1.7 vs 8.9; p .039).

Pinciroli et al Respir Care. 2016 Nov;61(11):1431-1439.

- Data on microbial colonization did not show any significant difference
- No adverse events were reported.
- The endOclear is a safe and effective device. It prevents luminal occlusion, thereby better preserving ETT nominal function

Table 3. Colonization of Collected ETTs by Bacterial and *Candida* Species

	Control no. ETTs (%)	Treatment no. ETTs (%)	Frequency, breaths/min (95% CI)	*P*
No growth	1 (3)	6 (16)	6.49 (0.81–51.36)	.07
Pathogens*	21 (53)	14 (38)	0.72 (0.43–1.2)	.2
VAP causatives†	15 (38)	7 (19)	0.50 (0.23–1.1)	.08
MDR	10 (25)	8 (22)	0.86 (0.38–1.95)	.72
Candida spp.	21 (53)	16 (43)	0.82 (0.51–1.32)	.4

Conclusion

- Small studies
- Not significant benefit
- Additional cost
- Cannot be recommended

Section 12. Treating VAT

VATS as predecessor of VAP?

- VAT is defined using all the following criteria:
  - fever (>38°C)
  - purulent sputum production
  - positive (≥10^5 cfu/mL) endotracheal aspirate culture
  - no radiographic signs of new pneumonia

Treating VAT?

- **Methods**: Prospective observational study. All VAT patients were treated and followed (n= 122)
- **Results**: Seventy-four (60%) patients received antimicrobial treatment. Appropriate antibiotic treatment was the only factor independently associated with reduced risk for transition from VAT to VAP (OR [95% CI] 0.12[0.02-0.59], P = 0.009).
- NNT to prevent one episode of VAP was 5

Nseir et al Crit Care. 2014 Jun 23;18(3):R129.

Aerosolized antibiotics and VAT in the ICU

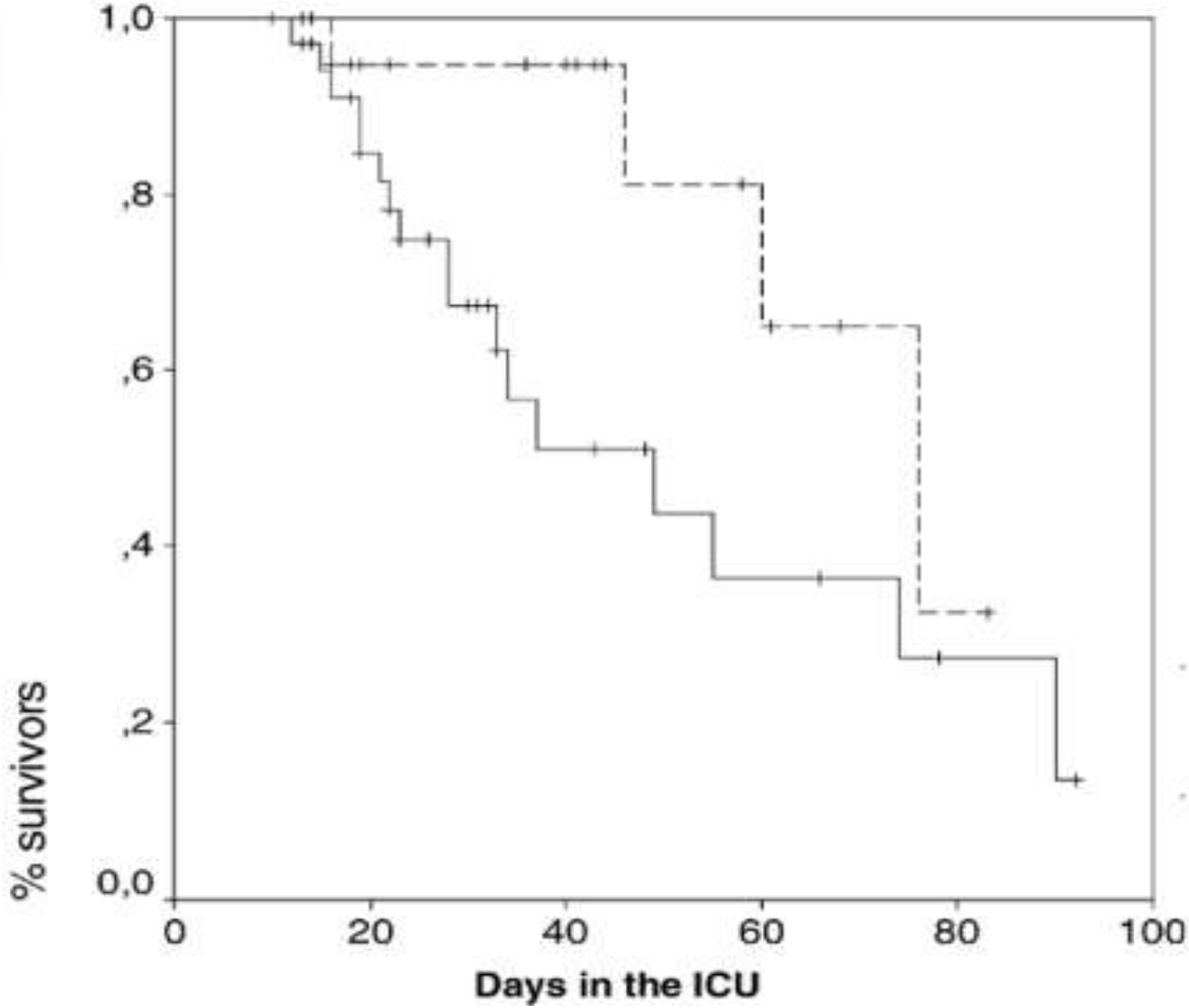
- **Methods**: 43 patients of VAT were randomized (double blinded) to either receive organism specific aerosolized antibiotic of placebo for 14 days
- **Results**: 5 patients developed VAP in treatment group and 11 patients developed VAP in control group.
- No difference in mortality or hospital stay

Palmer et al Crit Care Med. 2008 Jul;36(7):2008-13

IV antibiotics for VAT

- **Methods:** Prospective, RCT study. Patients were randomly assigned (1:1) to receive or not receive intravenous antibiotics for 8 days. Fifty-eight patients were randomly assigned.
- **Results:** No difference was found in mechanical ventilation duration and length of ICU stay
- Subsequent VAP (13% versus 47%, P = 0.011, [OR] 0.17, 95% CI 0.04 to 0.70) and ICU mortality (18% versus 47%, P = 0.047, OR 0.24, 95% CI 0.07 to 0.88) rates were significantly lower in the antibiotic group

Nseir et al Crit Care. 2008;12(3):R62.


1,0
,8
,6
,4
,2
0,0
% survivors
0
20
40
60
80
100
Days in the ICU

Conclusion

- Idea of treating VAT with antibiotics defeats the purpose and objective of **antibiotics stewardship**
- Prime focus should be on prevention of VAT/VAP/HAI rather than treating it
- Mortality difference with good quality evidence of well conducted RCT favoring treatment of VAT does not exist
- VAT treatment cannot be recommended

Section 13. *Feed* Modifications

Acidified enteral feeds in critically ill patients

- **Methods:** 120 MV patients were enrolled. Vital High Nitrogen was used as the standard feeding formula for the control group (pH = 6.5). Hydrochloric acid was added to achieve a pH of 3.5 in the experimental group.
- **Results:** The main outcome measure was gastric colonization. Secondary outcomes included gastric pH, pneumonia, and mortality. There was no difference in the incidence of pneumonia (6.1% in the acid feeds group vs. 15% in the control group; p = .19)

Heyland et al Crit Care Med. 1999 Nov;27(11):2399-406.

Gastric feed Vs small bowel feed: a meta-analysis

- **Methods:** Data from ten RCTs including 830 patients were retrieved and subjected to analysis
- **RESULTS:** As compared with gastric feeding, small bowel feeding significantly reduced the incidence of HAP [RR 0.67, 95%CI(0.51-0.89), P = 0.005; I(2) = 0%)], but did not reduce the mortality or ICU stay.
- Subgroup analysis indicated that small bowel nutrition reduced the incidence of VAP [RR 0.64, 95%CI(0.46-0.90), P = 0.01; I(2) = 9%)] as well

Xie et al Zhonghua Yi Xue Za Zhi. 2013 Sep 17;93(35):2786-9.

Flaw of the studies

- Most of them were surgical patients
- Nutrition was supplemented with TPN/PPN
- Other patients underwent UGIE only for tube placement

Conclusion

- Inspite of results it cannot be recommended due to lack of quality evidence and requirement of **doing an endoscopic procedure** in a critically ill mechanically ventilated patients

Section 14. Bundle & Audit approach

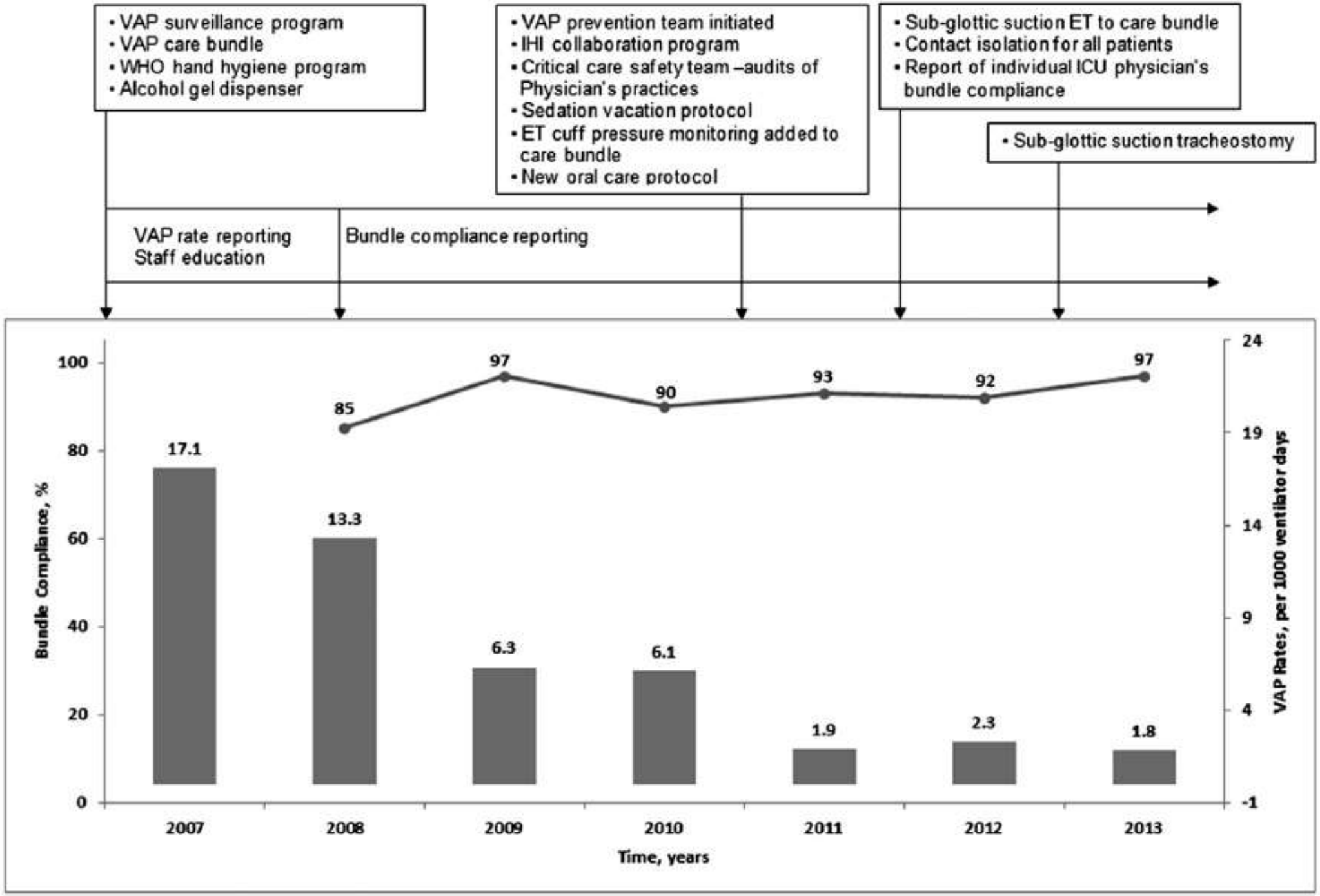
Role of Bundle approach

- **Methods:** All mechanically ventilated patients were prospectively followed for VAP development. In 2011, a 7-element care bundle was implemented.
- **Results:** 3665 patients received MV, with 9445 monitored observations for bundle compliance. The total bundle compliance before and after initiation of the VAP team was 90.7% and 94.2%, ($P < .001$). The number of VAP episodes decreased from 144 during 2008-2010 to only 14 during 2011-2013 ($P < .0001$). The rate of VAP decreased from 8.6 per 1000 ventilator-days to 2.0 per 1000 ventilator-days ($P < .0001$)

Khan et al Am J Infect Control. 2016 Mar 1;44(3):320-6

VAP prevention bundle

Bundle element	How compliance was monitored
HOB elevation 30° to 45°	Direct observation of angle of HOB
Daily "sedation vacation" and daily assessment of readiness for extubation	Documentation: ICU flow sheet and RT notes
PUD prophylaxis	Documentation on MAR
DVT prophylaxis	Documentation on MAR
Oral care with chlorhexidine solution	Documentation and direct oral inspection
Adequate endotracheal tube cuff pressure (20-25 cmH_2O)	Documentation: RT notes
In-line suction system and endotracheal tube with and subglottic suctioning	Documentation: ICU flow sheet and RT notes


• VAP surveillance program
• VAP care bundle
• WHO hand hygiene program
• Alcohol gel dispenser
• VAP prevention team initiated
• IHI collaboration program
• Critical care safety team –audits of Physician's practices
• Sedation vacation protocol
• ET cuff pressure monitoring added to care bundle
• New oral care protocol
• Sub-glottic suction ET to care bundle
• Contact isolation for all patients
• Report of individual ICU physician's bundle compliance
• Sub-glottic suction tracheostomy
VAP rate reporting
Staff education
Bundle compliance reporting
Bundle Compliance, %
VAP Rates, per 1000 ventilator days
Time, years
2007
2008
2009
2010
2011
2012
2013
85
97
90
93
92
97
17.1
13.3
6.3
6.1
1.9
2.3
1.8

Ass. Between Bundle Components & Outcomes

- **Methods:** Retrospective study included 5539 patients from January 1, 2009, to December 31, 2013, at Brigham and Women's Hospital.
- **Results:** Sedative infusion interruptions were associated with less time to extubation (HR, 1.81; 95% CI, 1.54-2.12; P < .001) and a lower hazard for VAP (HR, 0.51, 95% CI, 0.38-0.68; P < .001).
- Similar associations were found for spontaneous breathing trials (HR for extubation, 2.48; 95% CI 2.23-2.76; P < .001; HR for mortality, 0.28; 95% CI, 0.20-0.38; P = .001).

Klompas et al JAMA Intern Med 2016 Sep 1;176(9):1277-83.

Results… but

- Spontaneous breathing trials were also associated with lower hazards for VAE (HR, 0.55; 95% CI, 0.40-0.76; P < .001).
- Associations with less time to extubation were found for head-of-bed elevation (HR, 1.38, 95% CI, 1.14-1.68; P = .001) and thromboembolism prophylaxis (HR, 2.57; 95% CI, 1.80-3.66; P < .001) but not ventilator mortality.
- Oral care with CHX was associated with an **increased risk** for ventilator mortality (HR, 1.63; 95% CI, 1.15-2.31; P = .006), and stress ulcer prophylaxis was associated with an increased risk for ventilator-associated pneumonia (HR, 7.69; 95% CI, 1.44-41.10; P = .02).

Process of Care	HR (95% CI) VAEs	*P* Value	IVACs	*P* Value	Possible VAP	*P* Value
Head-of-bed elevation	1.33 (0.84-2.11)	.23	1.16 (0.59-2.28)	.66	1.60 (0.53-4.88)	.41
Sedative infusion interruptions	0.95 (0.67-1.35)	.76	1.04 (0.61-1.78)	.88	0.82 (0.37-1.82)	.63
Spontaneous breathing trials	0.55 (0.40-0.76)	<.001	0.60 (0.37-1.00)	.05	0.79 (0.39-1.60)	.52
Prophylaxis						
Thromboembolism	0.78 (0.38-1.62)	.51	0.96 (0.26-3.56)	.96	1.13 (0.16-7.78)	.90
Stress ulcer	1.34 (0.87-2.07)	.19	1.62 (0.78-3.35)	.20	7.69 (1.44-41.10)	.02
Oral care with chlorhexidine	0.87 (0.61-1.23)	.42	0.60 (0.36-1.00)	.05	0.55 (0.27-1.14)	.11

Process of Care	Outcome, HR (95% CI)							
	Time to Extubation Alive	*P* Value	Ventilator Mortality	*P* Value	Time to Hospital Discharge Alive[a]	*P* Value	Hospital Mortality[a]	*P* Value
Head-of-bed elevation	1.38 (1.14-1.68)	.001	0.86 (0.59-1.25)	.42	1.01 (0.96-1.05)	.80	0.98 (0.93-1.03)	.36
Sedative infusion interruptions	1.81 (1.54-2.12)	<.001	0.51 (0.38-0.68)	<.001	1.09 (1.05-1.14)	<.001	0.92 (0.88-0.96)	<.001
Spontaneous breathing trials	2.48 (2.23-2.76)	<.001	0.28 (0.20-0.38)	<.001	1.00 (0.98-1.02)	.92	0.99 (0.96-1.02)	.46
Prophylaxis								
Thromboembolism	2.57 (1.80-3.66)	<.001	1.39 (0.82-2.37)	.23	1.02 (0.97-1.07)	.41	0.97 (0.92-1.02)	.26
Stress ulcer	1.12 (0.95-1.32)	.17	0.91 (0.64-1.31)	.62	1.00 (0.98-1.03)	.89	1.00 (0.96-1.04)	.90
Oral care with chlorhexidine	0.92 (0.80-1.04)	.18	1.63 (1.15-2.31)	.006	0.99 (0.98-1.01)	.26	1.01 (0.98-1.05)	.44

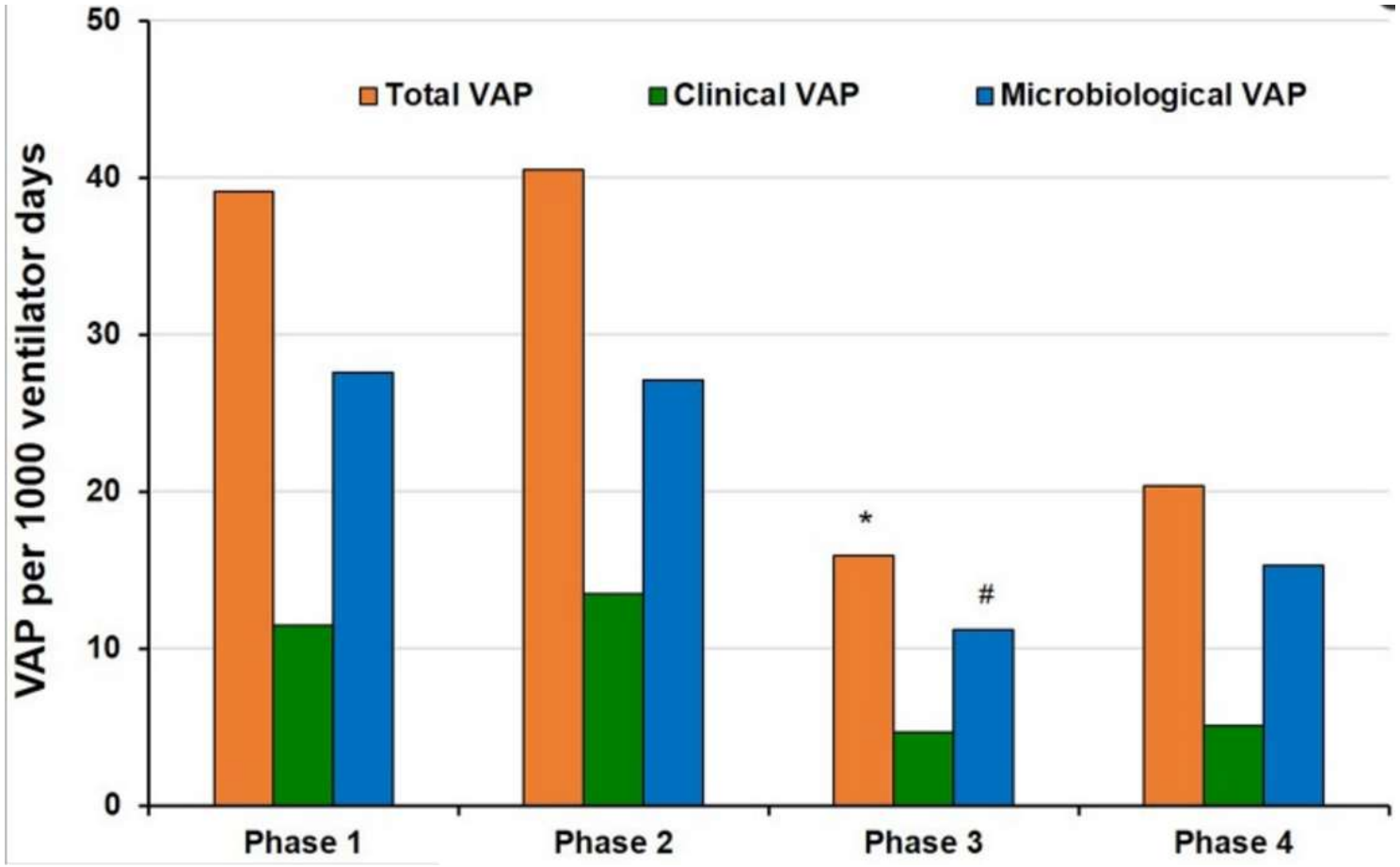
Role of external audit?

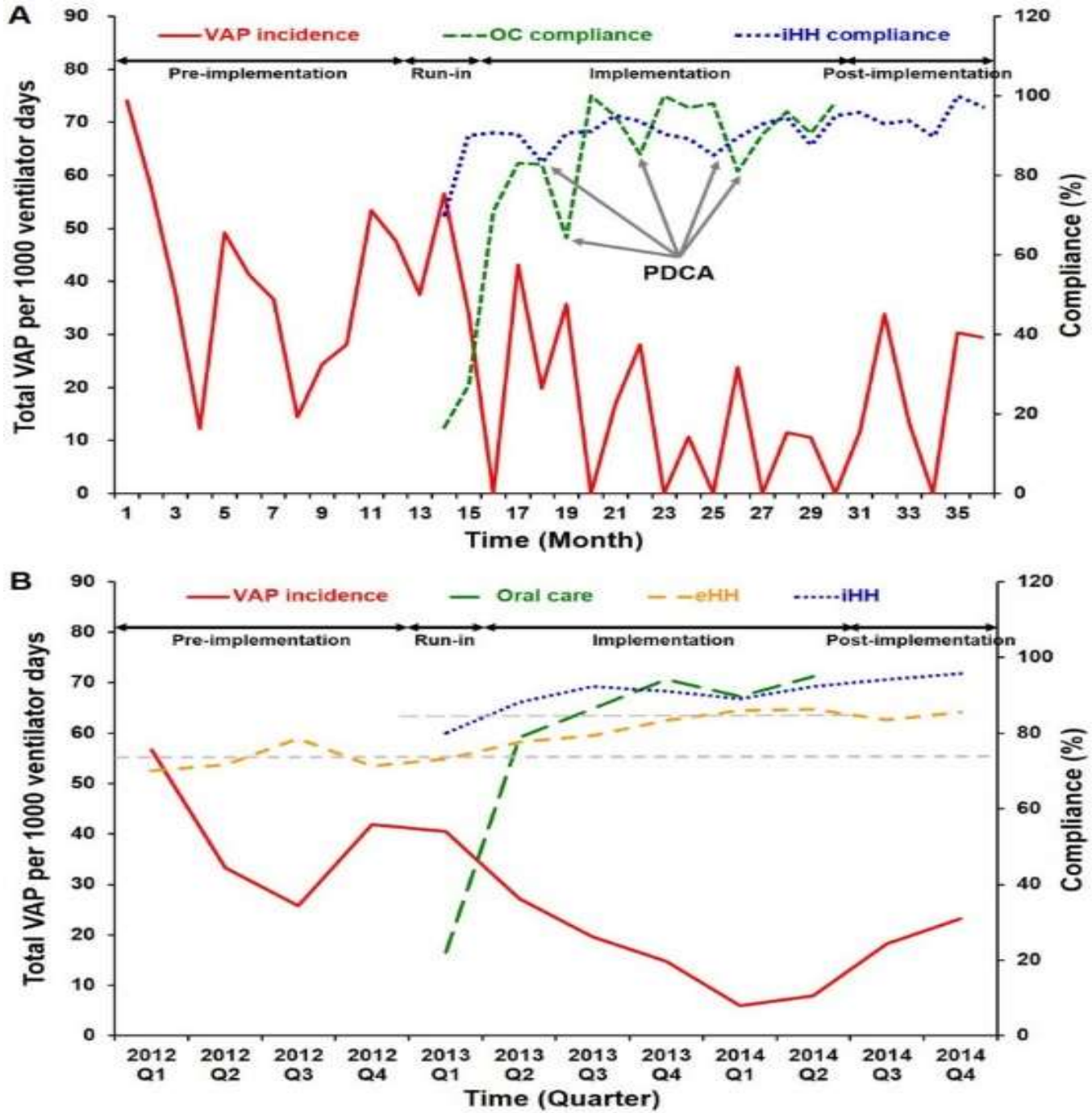
- **Methods:** This 3-year, study with interrupted time-series analysis. External HH audit (eHH) performed by non-unit-based observers was a done before and after bundle implementation. 3-component bundle included: **an education program**, **an internal HH audit** (iHH), and a standardized oral care (OC) protocol. The study periods comprised 4 phases:
  - 12-month pre-implementation phase 1 (eHH+/education-/iHH-/OC-)
  - 3-month run-in phase 2 (eHH+/education+/iHH+/OC+)
  - 15-month implementation phase 3 (eHH+/education+/iHH+/OC+)
  - 6-month post-implementation phase 4 (eHH+/education-/iHH+/OC-)

Su et al PLoS One. 2017 Aug 2;12(8):e0182252

Results:

- A total of 2553 ventilator-days were observed.
- VAP incidences in phase 1-4 were 39.1, 40.5, 15.9, and 20.4, respectively.
- VAP was significantly reduced by 59% in phase 3 but rebounded in phase 4.
- VAP incidence was inversely correlated to compliance of OC ($r2 = 0.531$, $P = 0.001$) and eHH ($r2 = 0.878$, $P < 0.001$),
- Compared to eHH, iHH provided more efficient and faster improvements for standard HH practice.
- The minimal compliances required for significant VAP reduction were 85% and 75% for OC and eHH (both $P < 0.05$, IRR 0.28 and 0.42, respectively).


50
40
30
20
10
0
VAP per 1000 ventilator days
Total VAP
Clinical VAP
Microbiological VAP
*
#
Phase 1
Phase 2
Phase 3
Phase 4


A
VAP incidence
OC compliance
iHH compliance
Pre-implementation
Run-in
Implementation
Post-implementation
PDCA
Total VAP per 1000 ventilator days
Compliance (%)
Time (Month)
B
VAP incidence
Oral care
eHH
iHH
Pre-implementation
Run-in
Implementation
Post-implementation
Total VAP per 1000 ventilator days
Compliance (%)
2012 Q1
2012 Q2
2012 Q3
2012 Q4
2013 Q1
2013 Q2
2013 Q3
2013 Q4
2014 Q1
2014 Q2
2014 Q3
2014 Q4
Time (Quarter)

Section 15. Miscellaneous

Is inhaled prophylactic heparin useful for prevention VAP?

- **Methods:** A phase 2, double-blind, RCT. were randomized to usual care, nebulization of UFH (5000 U in 2 mL), or nebulization with 0.9% sodium chloride (2 mL) 4 times daily
- **Results:** A total of 214 patients were enrolled (72 usual care, 71 inhaled sodium heparin, 71 inhaled sodium chloride). There were no differences between treatment groups in terms of the development of VAP

IPHIVAP J Crit Care. 2016 Oct;35:231-239

Early tracheostomy Vs late tracheostomy: a meta-analysis

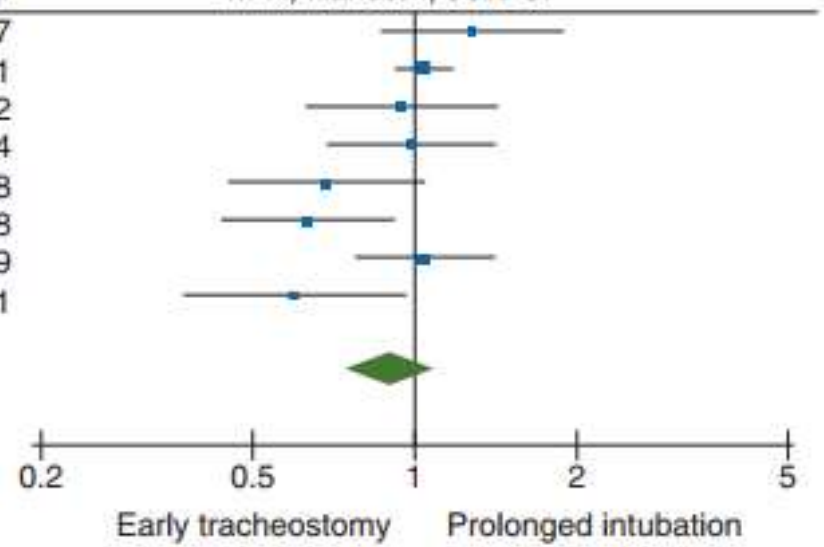
- **Methods:** Systematic review was done and data from 14 trials was identified for comparison between the outcomes of Trach. Within 10 days Vs Trach after 10 days (n= 2406)
- **Results:** Trach within 10 days was not associated with any difference in mortality [RR: 0.93 (0.83–1.05)], or duration of mechanical ventilation [20.19 days (21.13–0.75)], intensive care stay [20.83 days (22.05–0.40)], or incidence of VAP.
- However, duration of sedation was reduced in the early tracheostomy groups [22.78 days (23.68 to 21.88)]

Szakmany et al Br J Anaesth. 2015 Mar;114(3):396-405

Study or Subgroup	Early tracheostomy Events	Total	Prolonged intubation Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Sugerman 1997	25	53	34	92	11.2%	1.28 (0.86, 1.89)	1997
Saffle et al 2002	21	21	22	23	20.5%	1.04 (0.92, 1.18)	2001
Bouderka et al 2004	18	31	19	31	10.7%	0.95 (0.63, 1.43)	2002
Blot et al 2008	30	61	31	62	12.2%	0.98 (0.69, 1.40)	2004
Terragni et al 2010	30	209	44	210	10.3%	0.69 (0.45, 1.05)	2008
Saboori, 2009	12	20	19	20	11.8%	0.63 (0.44, 0.92)	2008
Trouillet 2011	50	109	47	107	14.3%	1.04 (0.78, 1.40)	2009
Zheng et al 2012	17	58	30	61	9.0%	0.60 (0.37, 0.96)	2011
Total (95% CI)		562		606	100.0%	0.90 (0.75, 1.08)	
Total events	203		246				

Heterogeneity. $Tau^2 = 0.04$; $Chi^2 = 18.20$, $df = 7$ ($P = 0.01$); $I^2 = 62\%$

Test for overall effect: $Z = 1.12$ ($P = 0.26$)



Conclusion

- Early tracheostomy (within 10 days) has no impact on most of the ICU related outcomes.
- Cannot be recommended

Duration of intubation before reaching ICU?

- **Methods:** Single-center retrospective cohort study of all intubated adult patients with trauma (n=860).
- **Results:** Thirty-five patients (6.4%) were diagnosed as having early VAP. Using multivariable logistic regression the duration of intubation prior to hospital admission was not associated with subsequent diagnosis of VAP (OR 0.90; 95% CI, 0.70-1.15).
- Location of intubation was similarly not associated with VAP

Mohr et al J Crit Care. 2014 Aug;29(4):539-44.

Conclusion

- Delaying intubation in Emergency/Ward is not justified with intent to prevent VAP

Other Novel methods

- Coating ET tube with copper: No significant difference found [1]
- Low dose Hydrocortisone: No significant difference [2]
- Listerine®/Soda Bicarb oral rinse: No significant benefit [3]
- Monitoring residual gastric volume: No association with VAP [4]
- Continuous oral suction: study only on 6 patients [5]
- Hydrogen peroxide for oral rinse: better than placebo (no comparison with CHX [6]
- Thymosin alpha-1 for VAP prevention: Chinese study in 52 patients [7]
- Hydroxyethyl methacrylate (HEMA) coated ET tubes: Phase I/II study [8]

Ref…

- 1. Rivero et al Rev Chilena Infectol. 2014 Jun;31(3):274-9.
- 2. Chaari et al Am J Ther. 2015 Jan-Feb;22(1):22-8
- 3. Berry et al Intensive Crit Care Nurs. 2013 Oct;29(5):275-81
- 4. Reigneir et al JAMA. 2013 Jan 16;309(3):249-56.
- 5. Chow et al Int J Nurs Stud. 2012 Nov;49(11):1333-41.
- 6. Nobahar et al Braz J Infect Dis. 2016 Sep-Oct;20(5):444-50
- 7. Zhang et al Sichuan Da Xue Bao Yi Xue Ban. 2015 Nov;46(6):957-9.
- 8. Jones et al Mol Pharm. 2015 Aug 3;12(8):2928-36

Take Home Message

Helps In VAP prevention

- Subglottic Suction ET Tubes
- Silver Coated ET tubes
- Positioning of patients
- Oral Care with CHX
- Sedation vacation
- Early weaning
- Hand hygiene
- Cuff pressure monitoring

Does not help in VAP prevention

- Tooth brush
- Closed suction
- Antibiotics
- Avoiding SUP
- Probiotics