**Supplemental Data Tables and Figures for the IDSA-ATS Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines**

## RISK FACTORS FOR ANTIBIOTIC RESISTANCE IN VAP AND HAP

| **Factors which have not been shown to be consistently associated with the development of Ventilator Associated Pneumonia (VAP) caused by Multi-Drug Resistant Pathogens.** |
|---|
| **Factors** |
| • **Re-intubation**<br>• **Immunosuppression**<br>• **Chronic respiratory failure**<br>• **Tracheostomy**<br>• **Diabetes mellitus**<br>• **Recent use of corticosteroids** |

**I. Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**ACCURACY OF SELECTED SAMPLING METHODS AND CULTURE THRESHOLDS TO DIAGNOSE VAP RELATIVE TO HISTOLOGY**

| Study | Pneumonia / Patients | Reference | BBS/TBAS/EA (Any Growth) | | | BBS/TBAS/EA ≥$10^5$ CFU/ml | | | Conventional BAL ≥$10^4$ CFU/ml | | | Protected Specimen Brush ≥$10^3$ CFU/ml | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sens | Spec | PPV | Sens | Spec | PPV | Sens | Spec | PPV | Sens | Spec | PPV |
| **Papazian, 1995** | 18/38 | Histology | 15/18 (83%) | 11/20 (55%) | 15/24 (63%) | 10/18 (56%) | 19/20 (95%) | 10/11 (91%) | 9/18 (50%) | 19/20 (95%) | 9/10 (90%) | 6/18 (33%) | 19/20 (95%) | 6/7 (86%) |
| **Marquette, 1995** | 19/28 | Histology | -- | -- | -- | 12/19 (63%) | 7/9 (78%) | 12/14 (86%) | 9/19 (47%) | 9/9 (100%) | 9/9 (100%) | 11/19 (58%) | 8/9 (89%) | 11/12 (92%) |
| **Torres, 1994[a]** | 18/30 | Histology | 16/18 (89%) | 3/12 (25%) | 16/25 (64%) | 11/18 (61%) | 6/12 (50%) | 11/17 (65%) | 8/18 (44%) | 5/12 (42%) | 8/15 (53%) | 9/18 (50%) | 9/12 (75%) | 9/12 (75%) |
| **Torres, 1994[b]** | 18/30 | Histology | 12/18 (67%) | 4/12 (33%) | 12/20 (60%) | 8/18 (44%) | 7/12 (58%) | 8/13 (62%) | 8/18 (44%) | 6/12 (50%) | 8/14 (57%) | 8/18 (44%) | 10/12 (83%) | 8/10 (80%) |
| **Balthazar 2001** | 20/37 | Histology | -- | -- | -- | -- | -- | -- | 18/20 (90%) | 16/17 (94%) | 17/18 (94%) | -- | -- | -- |
| **Sole-Violan 2006** | 7/9 | Histology | -- | -- | -- | -- | -- | -- | 6/7 (86%) | 1/2 (50%) | 6/7 (86%) | 2/7 (29%) | 2/2 (100%) | 2/2 (100%) |
| **Fabregas 1999** | 13/25 | Histology & Culture | -- | -- | -- | 9/13 (69%) | 11/12 (92%) | 9/10 (90%) | 10/13 (77%) | 7/12 (58%) | 10/15 (67%) | 8/13 (62%) | 9/12 (75%) | 8/11 (73%) |
| **Kirtland 1997** | 14/39 | Histology | -- | -- | -- | -- | -- | -- | 2/14 (14%) | 20/25 (80%) | 2/7 (29%) | 3/14 (21%) | 14/25 (56%) | 3/14 (21%) |
| **Bregeon 2000** | 14/27 | Histology | -- | -- | -- | -- | -- | -- | -- | -- | -- | 8/14 (57%) | 13/13 (100%) | 8/8 (100%) |
| **Chastre 1984** | 6/26 | Histology | -- | -- | -- | -- | -- | -- | -- | -- | -- | 6/6 (100%) | 12/20 (60%) | 6/14 (43%) |

Notes:

1. Torres 1994a/b – Torres 1994a includes all pathogens if growth above the specified threshold whereas Torres 1994b – excludes non-pathogenic organisms (Candida, CNS)
2. Bregeon 2000 – mini-BAL, blind insertion, lavage via catheter within a catheter – excluded from pooled analaysis

Excluded studies:

1. Torres 1996 enrolled 25 patients but reports results relative to 47 lungs. Unable to calculate performance on a per-patient basis.
2. Torres 2000 enrolled 25 patients but reports results relative to 47 lungs. Unable to calculate performance on a per-patient basis.
3. Papazian 1997 only presents accuracy figures for gram stain and intracellular organisms, not for cultures.
4. Tejerina 2010 does not provide accuracy figures for cultures
5. Fabregas 1996 does not provide accuracy figures for cultures by patient (denominator is total biopsies)
6. El Ebiary 1997 only provides accuracy data for cultures positive for Candida
7. Gausssorgues 1989 provides qualitative culture results for BAL and open lung biopsy only, no quantitative data. For the record, though, if one includes Candida as a pathogenic organism then sens 9/9, spec 3/4, ppv, 9/10. If one excludes Candida as a pathogenic organisms then sens 8/9, spec 2/4, ppv 8/10.

| SUMMARY | | | | | | |
|---|---|---|---|---|---|---|
| **Diagnostic Method** | **Sensitivity** | **Specificity** | **Positive Predictive Value** | **Positive Likelihood Ratio** | **Negative Likelihood Ratio** | **Diagnostic Odds Ratio** |
| **BBS/TBAS/EA (Any Growth)** | 75% (58-88%) | 47% (29-65%) | 61% (45-76%) | 1.4 (0.74-2.49) | 0.56 (0.17-1.83) | 2.49 (0.42-15) |
| **BBS/TBAS/EA (≥$10^5$ CFU/ml)** | 57% (45-69%) | 83% (70-92%) | 81% (67-91%) | 3.31 (0.88-11) | 0.53 (0.35-0.81) | 6.65 (1.4-31) |
| **Conventional BAL (≥$10^4$ CFU/ml)** | 57% (47-66%) | 80% (71-88%) | 77% (66-85%) | 2.4 (0.99-5.6) | 0.56 (0.33-0.96) | 5.7 (1.3-25) |
| **Protected Specimen Brush (≥$10^3$ CFU/ml)** | 48% (38-57%) | 72% (63-80%) | 60% (49-71%) | 1.9 (0.98-3.6) | 0.72 (0.51-1.0) | 3.5 (1.1-12) |

**Evidence Extraction Table: Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Type of information (published or unpublished) | published | published | published |
| Journal name | NEJM | Annals of Interna Medicine | Critical Care Medicine |
| Language of publication | English | English | English |
| Funding body | Yes | Yes | Yes |
| Ethics approval | Yes | Yes | Yes |
| Country where study was done | Canada and US | France | Spain |
| **METHODS** | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | |
| Randomization | truly random | truly random | truly random |
| Concealment | no | no | no |
| Not stopped early | not stopped early | not stopped early | not stopped early |
| NOTES: | | | |
| ***if COHORT STUDY*** | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | |
| Selection of the non exposed cohort | | | |
| Ascertainment of exposure | | | |
| Demonstration that outcome of interest was not present at start of study | | | |
| Comparability of cohorts on the basis of the design or analysis | | | |
| Assessment of outcome | | | |
| Was follow-up long enough for outcomes to occur? | | | |

**Evidence Extraction Table: Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Adequacy of follow up of cohorts | | | |
| Co-Interventions similar between groups? | | | |
| NOTES: | | | |
| ***if CASE-CONTROL STUDY*** | | | |
| Is case definition adequate? | | | |
| Representativeness of the cases | | | |
| Selection of controls | | | |
| Definition of controls | | | |
| Comparability of cases and controls | | | |
| Ascertainment of exposure | | | |
| Same method of ascertainment for cases and controls | | | |
| Non-response rate | | | |
| Co-interventions similar between groups? | | | |
| NOTES: | | | |
| **INTERVENTIONS BEING COMPARED** | | | |
| **Intervention 1 (experimental)** | Bronchoscopic BAL with quantitative culture | PSB or BAL with quantitative culture | PSB or BAL with quantitative culture |
| other Tx used (if relevant for interpretation) | | | |
| Tx not allowed (if relevant for interpretation) | | | |
| **Intervention 2 (comparison)** | ETA with nonquantitative culture | ETA with semi-quantitative culture | ETA with semi-quantitative culture |
| other Tx used (if relevant for interpretation) | | | |
| Tx not allowed (if relevant for interpretation) | | | |
| duration of treatment | | | |
| NOTES: | | | |
| **BASELINE CHARACTERISTICS** | | | |
| **Number randomised** | | | |
| Intervention | 365 | 204 | 45 |
| Comparison | 374 | 209 | 43 |
| Total (only if not reported separately) | | | |
| **Age** | | | |
| Intervention (mean or median) | 59.3 | 63 | 50.4 |
| Comparison (mean or median) | 58.7 | 63 | 55.6 |
| Total (mean or median) (only if not reported separately) | | | |
| unit (e.g. mean and SD) | mean (SD) | mean (SD) | mean (SD) |
| Age range (e.g. 22-73) | | | |

**Evidence Extraction Table: Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Age inclusion criterion (e.g. older than 16) | adults | older than 18 | no specified |
| **Male gender** | | | |
| Intervention | 70.10% | 69.10% | 75.50% |
| Comparison | 68.40% | 70.80% | 69.70% |
| Total (only if not reported separately) | | | |
| **Severity of illness** | | | |
| Name of score (e.g. APACHE, SOFA, ...) | Apache II | SAPS | Apache II |
| Intervention group mean score | 20.1 | 44 | 15.8 |
| Comparison group mean score | 19.8 | 42 | 15 |
| | | SAPS II | |
| **Study population** | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical |
| NOTES: | | | |
| **OUTCOMES** | | | |
| **Mortality (all cause)** | | | |
| Are the data available? | Data available | Data available | Data available |
| location or duration of follow-up (choose from the list) | 28 day | 28 day | Hospital |
| Intervention group: # with event | 69 | 63 | 10 |
| Intervention group: Total | 365 | 204 | 45 |
| Comparison group: # with event | 69 | 81 | 9 |
| Comparison group: Total | 374 | 209 | 43 |
| Blinding [patients] (only relevant for RCTs) | no | no | no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | no |
| Blinding [data collectors] (only relevant for RCTs) | no | no | no |
| Blinding [analysts] (only relevant for RCTs) | no | no | no |
| ITT analysis performed (only relevant for RCTs) | yes | yes | probably yes |
| NOTES: | | | |
| **Number of ventilator days (if only ventilator-free days reported, go to next)** | | | |
| Are the data available? | Data available | Not reported | Data available |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | days | | days |
| How data were reported (mean or median and type of variance) | median (IQR) | | mean (SD) |
| Intervention group: (mean or median) | 8.9 | | 19.9 |

**Evidence Extraction Table: Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | 365 | | 45 |
| Comparison group: (mean or median) | 8.8 | | 19.2 |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | 374 | | 43 |
| Blinding [patients] (only relevant for RCTs) | no | | no |
| Blinding [personnel] (only relevant for RCTs) | no | | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no | | no |
| Blinding [data collectors] (only relevant for RCTs) | no | | no |
| Blinding [analysts] (only relevant for RCTs) | no | | no |
| ITT analysis performed (only relevant for RCTs) | yes | | yes |
| NOTES: | | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | |
| Are the data available? | | Data available | |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | days | |
| How data were reported (mean or median and type of variance) | | mean (SD) | |
| Intervention group: (mean or median) | | 7.8 | |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | 204 | |
| Comparison group: (mean or median) | | 7 | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | 209 | |
| Blinding [patients] (only relevant for RCTs) | | no | |
| Blinding [personnel] (only relevant for RCTs) | | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | no | |
| Blinding [data collectors] (only relevant for RCTs) | | no | |
| Blinding [analysts] (only relevant for RCTs) | | no | |
| ITT analysis performed (only relevant for RCTs) | | yes | |
| NOTES: | | | |
| **Length of ICU stay** | | | |
| Are the data available? | Data available | Data available | Data available |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | days | days | days |

**Evidence Extraction Table: Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| How data were reported (mean or median and type of variance) | median (IQR) | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | 12.3 | 19.3 | 23.6 |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | 365 | 204 | 45 |
| Comparison group: (mean or median) | 12.2 | 17.6 | 22.4 |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | 374 | 209 | 43 |
| Blinding [patients] (only relevant for RCTs) | no | no | no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | no |
| Blinding [data collectors] (only relevant for RCTs) | no | no | no |
| Blinding [analysts] (only relevant for RCTs) | no | no | no |
| ITT analysis performed (only relevant for RCTs) | yes | yes | yes |
| NOTES: | | | |
| **Length of hospital stay** | | | |
| Are the data available? | Data available | Data available | Not reported |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | days | days | |
| How data were reported (mean or median and type of variance) | median (IQR) | mean (SD) | |
| Intervention group: (mean or median) | 40.2 | 26.7 | |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | 365 | 204 | |
| Comparison group: (mean or median) | 47.0 | 25.1 | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | 374 | 209 | |
| Blinding [patients] (only relevant for RCTs) | no | no | |
| Blinding [personnel] (only relevant for RCTs) | no | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | |
| Blinding [data collectors] (only relevant for RCTs) | no | no | |
| Blinding [analysts] (only relevant for RCTs) | no | no | |
| ITT analysis performed (only relevant for RCTs) | yes | yes | |
| NOTES: | | | |
| **Clinical cure (as defined by the study authors)** | | | |
| Are the data available? | Not measured | Not measured | Not measured |

**Evidence Extraction Table: Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with semi-quantitative culture results?**

**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Definition (provide details if relevant) | | | |
| Duration of follow-up (time point when outcome was measured) [days] | | | |
| Intervention group: # with event | | | |
| Intervention group: Total | | | |
| Comparison group: # with event | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Recurrent pneumonia** | | | |
| Are the data available? | Not reported | Not measured | Not measured |
| Duration of follow-up [days] | | | |
| Intervention group: # with event | | | |
| Intervention group: Total | | | |
| Comparison group: # with event | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Number of antibiotic days** | | | |
| Are the data available? | Data available | Data available | Not reported |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | days | days | |
| How data were reported (mean or median and type of variance) | mean (SD) | mean (SD) | |
| Intervention group: (mean or median) | 10.4 | 8.7 | |
| Intervention group: (variance) | | | |

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**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Intervention group: total number of patients | 365 | 204 | |
| Comparison group: (mean or median) | 10.6 | 10.9 | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | 374 | 209 | |
| Blinding [patients] (only relevant for RCTs) | no | no | |
| Blinding [personnel] (only relevant for RCTs) | no | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | |
| Blinding [data collectors] (only relevant for RCTs) | no | no | |
| Blinding [analysts] (only relevant for RCTs) | no | no | |
| ITT analysis performed (only relevant for RCTs) | yes | yes | |
| NOTES: | Days alive without antibiotics | At 14 days | |
| **Development of resistance (as defined by the study authors)** | | | |
| Are the data available? | Not measured | Data available | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with event | | 125 | |
| Intervention group: Total | | 204 | |
| Comparison group: # with event | | 125 | |
| Comparison group: Total | | 209 | |
| Blinding [patients] (only relevant for RCTs) | | no | |
| Blinding [personnel] (only relevant for RCTs) | | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | no | |
| Blinding [data collectors] (only relevant for RCTs) | | no | |
| Blinding [analysts] (only relevant for RCTs) | | no | |
| ITT analysis performed (only relevant for RCTs) | | yes | |
| NOTES: | | There was no definition | |
| **Any adverse effect** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with at least one event (if this was reported) | | | |
| Intervention group: # of events per group (if this was reported) | | | |
| Intervention group: Total | | | |
| Comparison group: #with at least one event (if this was reported) | | | |
| Comparison group: # of events per group (if this was reported) | | | |
| Comparison group: Total | | | |

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**INVASIVE QUANTITATIVE CULTURES VS NON-INVASIVE SEMIQUANTITATIVE**

| **Last name of the first author** | **Canadian Critical Care Trials Group** | **Fagon** | **Solé-Violan** |
|---|---|---|---|
| **Year** | **2006** | **2000** | **2000** |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Serious adverse effect** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with at least one event (if this was reported) | | | |
| Intervention group: # of events per group (if this was reported) | | | |
| Intervention group: Total | | | |
| Comparison group: #with at least one event (if this was reported) | | | |
| Comparison group: # of events per group (if this was reported) | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| | | Inappropriate treatment was more frequent in non-invasive group | |

**Author(s):** The Canadian Critical Care Trials Group/ NEJM 2006, Fagon JY/ Ann Intern Med 2000 and Solé-Violan J/ Critical Care Medicine 2000

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | Inconsistency | **Indirectness** | **Imprecision** | **Other considerations** | **Invasive sampling with quantitative cultures** | **Non-invasive sampling with semi-quantitative cultures** | **Relative (95% CI)** | **Absolute** | | |
| **Mortality** | | | | | | | | | | | | |
| CCCTG[1], Fagon [2] Solé-Violan {Sole Violan, 2000 #54 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 142/614 (23.1%) | 159/626 (25.4%) | OR 0.91 (0.75 to 1.11) | 17 fewer per 1000 (from 51 fewer to 20 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |

[1] unblinded randomized trials

| Study | Setting | N | Randomized | Blinded | Inclusion | Invasive | Non-Invasive |
|---|---|---|---|---|---|---|---|
| Sanchez-Nieto 1998[3] | Mixed Med-Surg ICU, Spain | 51 | Yes | No | Clinically suspected VAP in patients on vent >72hrs | PSB ($\geq 10^3$) and BAL ($\geq 10^4$) | QEA ($\geq 10^5$) |
| Ruiz 2000[4] | 3 Respiratory & Surgial ICUs, Spain | 76 | Yes | No | Clinically suspected VAP in patients on vent >48hrs | PSB ($\geq 10^3$) and BAL ($\geq 10^4$) | TBAS ($\geq 10^5$) |

| **Study** | **Antibiotic Changes** | | |
|---|---|---|---|
| | Invasive | Non-Invasive | P |
| Sanchez-Nieto 1998[3] | 10/24 (42%) | 4/27 (16%) | <.05 |
| Ruiz 2000[4] | 10/37 (27%) | 7/39 (18%) | NS |

| **Study** | **Vent Days** | | | **ICU Days** | | | **Mortality** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Invasive | Non-Invasive | P | Invasive | Non-Invasive | P | Invasive | Non-Invasive | P |
| Sanchez-Nieto 1998[3] | 23 ± 12d | 20 ± 17d | NS | 28 ± 17d | 26 ± 18d | NS | 11/24 (46%) | 7/27 (26%) | NS |
| Ruiz 2000[4] | 19 ± 15d | 20 ± 24d | NS | 21 ± 15d | 21 ± 18d | NS | 14/37 (41%) | 18/39 (46%) | NS |

| **Study** | **Antibiotic Days** | | | **Resistance** | | |
|---|---|---|---|---|---|---|
| | Invasive | Non-Invasive | P | Invasive | Non-Invasive | P |
| Sanchez-Nieto 1998[3] | -- | -- | -- | -- | -- | -- |
| Ruiz 2000[4] | 13 ± 4d | 12 ± 4d | NS | See below | See below | NS |

| Ruiz – microbial re-evaluation amongst patients with failure to respond to initial abx | | | |
|---|---|---|---|
| | **Invasive** | **Non-Invasive** | **P** |
| Re-evaluated | 20/37 | 20/39 | NS |
| MRSA | 3/20 | 2/20 | NS |
| *Pseudomonas aeruginosa* | 4/20 | 7/20 | NS |

| **SUMMARY OF FINDINGS- Should patients with suspected VAP be treated based on the results of invasive sampling (i.e., bronchoscopy, blind bronchial sampling) with quantitative culture results, non-invasive sampling (i.e., endotracheal aspiration) with quantitative culture results, or non-invasive sampling with quantitative culture results?** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Design (No of Studies)** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication Bias** | **Summary of Findings** | | | |
| | | | | | **Define Group** Invasive Quantitative | **Define Group** Non-Invasive Quantitative | **RR or MD (CI)** | |
| | | | | | **No. of pts 61** | **No. of pts 66** | | Quality of the Evidence |
| All Cause Mortality **RCT (2)** | Some Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Num/Denom** **25/61** | **Num/Denom** **25/66** | **RR** 1.14 (0.54, 2.41) | Moderate (ΦΦOO) |
| Vent days **RCT (2)** | No Serious Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Mean (SD**) 23 (12) n=24 19 (15) n= 37 | **Mean (SD)** 20 (17) n = 27 20 (24) n = 39 | **Days** 1.48 [-4.15, 7.12] | Moderate (ΦΦOO) |
| Vent free days | | | | | | | | |
| ICU LOS **RCT (2)** | No Serious Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Mean (SD)** 28 (17) n=24 21 (15) n= 37 | **Mean (SD)** 26 (18) n = 27 21 (18) n = 39 | **Days** 0.75 [-5.13, 6.63] | Moderate (ΦΦOO) |
| Hospital LOS | | | | | | | | |
| Clinical Cure | | | | | | | | |
| Treatment Failure **RCT (1)** | NA | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Num/Denom** 15/37 | **Num/Denom** 20/39 | **RR** 0.79 [0.48, 1.30] | Low (ΦOOO) |
| Recurrent Pneumonia | | | | | | | | |
| Antibiotic Days **RCT (1)** | NA | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | 13 (4) n= 37 | 12 (4) n=39 | **Days** 3.20 [-4.45, -1.95] | Low (ΦOOO) |
| Antibiotic Free Days | | | | | | | | |
| Development of Resistance (MRSA) **RCT (1)** | N/A | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Num/Denom** 3/20 | **Num/Denom** 2/20 | **RR** 1.05 [0.69, 1.61] | Low (ΦOOO) |
| Any Adverse event N/A | | | | | | | | |
| Serious adverse event N/A | | | | | | | | |

**II. If invasive quantitative cultures are performed, should patients with suspected VAP whose culture results are below the diagnostic threshold for VAP (protected specimen brush with <$10^3$ colony forming units (CFU)/ml, bronchoalveolar lavage with <$10^4$ CFU/ml) have their antibiotics withheld rather than continued?**

| Description of the VAP diagnosis and definition of VAP "Threshold" in RCTs | | |
|---|---|---|
| **Reference** | VAP Diagnosis | VAP "Threshold" Negative Invasive Sampling |
| **Canadian Critical Care Trials Group (CCCTG), 2006 [1]** | Clinically | BAL <$10^4$<br>BAL<$10^3$ (if prior antibiotics) |
| **Fagon, 2000 [5]** | Clinically | PSB <$10^3$<br>BAL <$10^4$ |
| **Ruiz, 2000 [4]** | Clinically | Blood Cultures or<br>PSB <$10^3$<br>BAL <$10^4$ |
| **Sanchex-Nieto, 1998[3]** | Clinically | PSB <$10^3$<br>BAL <$10^4$ |
| **Sole-Violan, 2000[6]** | Clinically | PSB <$10^3$<br>BAL <$10^4$ |

| Information regarding the intervention of the PICO questions among RCTs. | | | |
|---|---|---|---|
| **Reference** | Antibiotics Withheld | Antibiotics Given | Total |
| **CCCTG, 2006 [1]** | - - | - - | 50/365 (13.7%)[a] |
| **Fagon, 2000 [5]** | 97/114 | 17/114 | 114/204 |
| **Ruiz, 2000 [4]** | - - | - - | - - |
| **Sanchex-Nieto, 1998[3]** | 0/7 | 6/7 | 6/7 |
| **Sole-Violan, 2000[6]** | 0/17 | 17/17 | 17 |

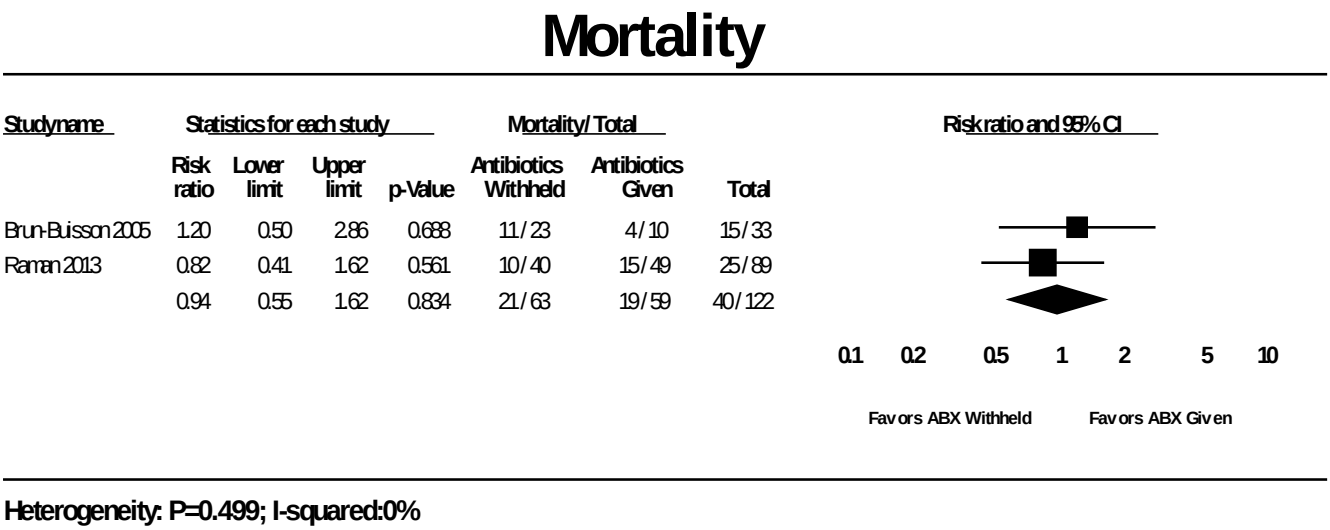
| Information regarding the intervention among observational studies. | | |
|---|---|---|
| **Reference** | Antibiotics Withheld | Antibiotics Given |
| **Fagon. 2000[5]** | 97/114 | 17/114 |
| **Meduri, 1992[7]** | 11/14 | 3/14 |
| **Bonten, 1997[8]** | 17/34 | 17/34 |
| **Marik, 2001[9]** | 36/42 | 6/42 |
| **Bruin-Buisson, 2005*[10]** | 23/33 | 10/33 |
| **Raman, 2013*[11]** | 40/89 | 49/89 |
| **TOTAL** | 224/326 (68.7%) | 102/326(31.3%) |

* Studies reporting outcomes data among patients managed with antibiotics withheld or continued when culture results were available.

| Observational studies regarding negative or below the "threshold" quantitative cultures. | | | |
|---|---|---|---|
| Reference | **Study Type** | **VAP Diagnosis** | **VAP "Threshold" Negative Invasive Sampling** |
| **Meduri, 1992 [7]** | Prospective Observational | Clinically | BAL $<10^4$<br>PSB $<10^3$<br>Or both with appropriate response to antibiotics |
| **Bonten, 1997 [8]** | Prospective Observational | Clinically | PSB $<10^3$<br>BAL$<10^4$ |
| **Marik, 2001 [9]** | Prospective Observational | Clinically | Blinded PSB $\leq 5 \times 10^2$ |
| **Brun-Buisson, 2005 [10]** | Prospective Observational | Clinically | Blinded PTC $< 10^3$<br>BAL $<10^4$<br>EA semiquantitative score <4+ |
| **Raman, 2013 [11]** | Retrospective Observational | Clinically | BAL $<10^4$<br>Mini BAL $<10^4$ |

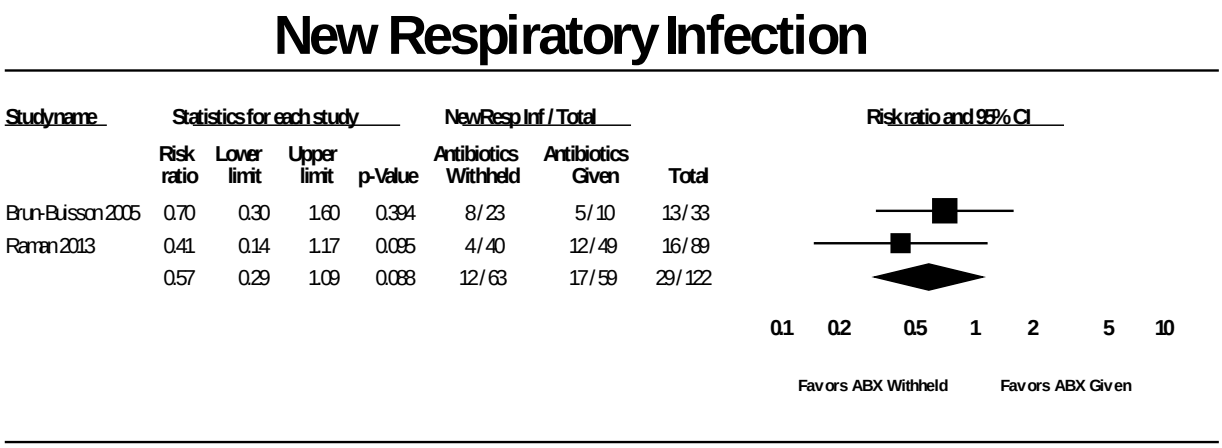
| Randomized Controlled Trials regarding negative or below the "threshold" quantitative cultures. | | | |
|---|---|---|---|
| Reference | **Study Type** | **Intervention** | **Comparison** |
| **Canadian Critical Care Trials Group (CCCTG), 2006 [1]** | RCT | Invasive Quantitative Culture | Non-invasive Qualitative Culture |
| **Fagon, 2000 [5]** | RCT | Invasive Quantitative Culture | Non-invasive Qualitative Culture |
| **Ruiz, 2000 [4]** | RCT | Invasive Quantitative Culture | Non-invasive Quantitative Culture |
| **Sanchez-Nieto, 1998[3]** | RCT | Invasive Quantitative Culture | Non-invasive Quantitative Culture |
| **Sole-Violan, 2000[6]** | RCT | Invasive Quantitative Culture | Non-invasive Qualitative Culture |
| **Berton, 2012[12]** | Meta-analysis of RCTs | Invasive Quantitative Culture | Non-invasive Qualitative Culture |

**Mortality among studies where antibiotics were withheld in VAP patients with negative culture or below the threshold microbiology results.**




**Heterogeneity: P=0.499; I-squared:0%**

**New respiratory infection among studies where antibiotics were withheld in VAP patients with negative culture or below the threshold microbiology results.**




**Heterogeneity: P=0.437; I-squared:0%**

| Duration of Antibiotics, Superinfection and Multidrug resistant rates among studies where antibiotics were withheld in VAP patients with negative culture or below the threshold microbiology results [11] | | | |
|---|---|---|---|
| | Antibiotics Withheld N=63 | Antibiotics Given N=59 | P |
| **Duration of antibiotics** | 4 (3, 4) | 9 (6, 14) | <.001 |
| **Superinfection rate*** | 9/40 (22.5%) | 18/49 (42.9%) | .008 |
| **Multidrug resistant superinfection rate** | 3/40 (7.5%) | 15/49 (35.7%) | .003 |
| ***Median (interquartile range)** | | | |

## III. In patients with suspected HAP (non-VAP), should treatment be guided by the results of microbiologic studies performed on respiratory samples or should treatment be empiric?

| **GRADE EVIDENCE PROFILE** | |
|---|---|
| **Last name of the first author** | **Herer** |
| **Year** | **2009** |
| Type of information (published or unpublished) | published |
| Journal name | Clin Microbiol Infect |
| Language of publication | English |
| Funding body | No noted |
| Ethics approval | Yes |
| Country where study was done | France |
| **METHODS** | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | |
| Randomization | truly random |
| Concealment | probably no |
| Not stopped early | not stopped early |
| NOTES: | |
| ***if COHORT STUDY*** | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | |
| Selection of the non exposed cohort | |
| Ascertainment of exposure | |
| Demonstration that outcome of interest was not present at start of study | |
| Comparability of cohorts on the basis of the design or analysis | |
| Assessment of outcome | |
| Was follow-up long enough for outcomes to occur? | |
| Adequacy of follow up of cohorts | |
| Co-Interventions similar between groups? | |
| NOTES: | |
| ***if CASE-CONTROL STUDY*** | |
| Is case definition adequate? | |
| Representativeness of the cases | |
| Selection of controls | |
| Definition of controls | |
| Comparability of cases and controls | |
| Ascertainment of exposure | |
| Same method of ascertainment for cases and controls | |
| Non-response rate | |
| Co-interventions similar between groups? | |
| **INTERVENTIONS BEING COMAPRED** | |
| **Intervention 1 (experimental)** | Bronchoscopic Dx of HAP w/PSB and immediate GS |
| other Tx used (if relevant for interpretation) | |
| Tx not allowed (if relevant for interpretation) | |
| **Intervention 2 (comparison)** | non-invasive management |
| other Tx used (if relevant for interpretation) | |
| Tx not allowed (if relevant for interpretation) | |
| duration of treatment | |
| NOTES: | |
| **BASELINE CHARACTERISTICS** | |
| **Number randomised** | |
| Intervention | 34 |
| Comparison | 34 |
| Total (only if not reported separately) | |

| GRADE EVIDENCE PROFILE | |
|---|---|
| **Last name of the first author** | **Herer** |
| **Year** | **2009** |
| **Age** | |
| Intervention (mean or median) | 65.9 |
| Comparison (mean or median) | 65.8 |
| Total (mean or median) (only if not reported separately) | |
| unit (e.g. mean and SD) | mean (SD) |
| Age range (e.g. 22-73) | |
| Age inclusion criterion (e.g. older than 16) | not mentioned |
| **Male gender** | |
| Intervention | 73.00% |
| Comparison | 68.00% |
| Total (only if not reported separately) | |
| **Severity of illness** | |
| Name of score (e.g. APACHE, SOFA, ...) | McCabe-Jackson |
| Intervention group mean score | |
| Comparison group mean score | |
| Total (only if not reported separately) | |
| **Study population** | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | |
| NOTES:A28 | cancer and rehab |
| **VAP patients included** | |
| Intervention | 0 |
| Comparator | 0 |
| **Exclusions** | |
| | Immunocompromised, tracheostomy, unstable for bronch |
| **Prior Antibiotics** | |
| Intervention | 10 |
| Comparator | 10 |
| **Number with organism(s) identified** | |
| **Intervention** | 24 |
| **Comparator** | 0 initially, then 9 had subsequent bronch due to poor response to Abx |
| **OUTCOMES** | |
| **Mortality (all cause)** | |
| Are the data available? | Data available |
| location or duration of follow-up (choose from the list) | 28 day |
| Intervention group: # with event | 7 |
| Intervention group: Total | 32 |
| Comparison group: # with event | 3 |
| Comparison group: Total | 30 |
| Blinding [patients] (only relevant for RCTs) | no |
| Blinding [personnel] (only relevant for RCTs) | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no |
| Blinding [data collectors] (only relevant for RCTs) | no |
| Blinding [analysts] (only relevant for RCTs) | no |
| ITT analysis performed (only relevant for RCTs) | yes |
| NOTES: | |
| **Number of ventilator days (if only ventilator-free days reported, go to next)** | |
| Are the data available? | |
| Duration of follow-up [days] | |

| GRADE EVIDENCE PROFILE | |
|---|---|
| **Last name of the first author** | **Herer** |
| **Year** | **2009** |
| unit (days, hours, etc.) | |
| How data were reported (mean or median and type of variance) | |
| Intervention group: (mean or median) | |
| Intervention group: (variance) | |
| Intervention group: total number of patients | |
| Comparison group: (mean or median) | |
| Comparison group: (variance) | |
| Comparison group: total number of patients | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Number of ventilator-free days (if ventilator days not reported)** | |
| Are the data available? | |
| Duration of follow-up [days] | |
| unit (days, hours, etc.) | |
| How data were reported (mean or median and type of variance) | |
| Intervention group: (mean or median) | |
| Intervention group: (variance) | |
| Intervention group: total number of patients | |
| Comparison group: (mean or median) | |
| Comparison group: (variance) | |
| Comparison group: total number of patients | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Length of ICU stay** | |
| Are the data available? | |
| Duration of follow-up [days] | |
| unit (days, hours, etc.) | |
| How data were reported (mean or median and type of variance) | |
| Intervention group: (mean or median) | |
| Intervention group: (variance) | |
| Intervention group: total number of patients | |
| Comparison group: (mean or median) | |
| Comparison group: (variance) | |
| Comparison group: total number of patients | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Length of hospital stay** | |

| GRADE EVIDENCE PROFILE | |
|---|---|
| **Last name of the first author** | **Herer** |
| **Year** | **2009** |
| Are the data available? | Data available |
| Duration of follow-up [days] | days |
| unit (days, hours, etc.) | |
| How data were reported (mean or median and type of variance) | mean (SD) |
| Intervention group: (mean or median) | 33 |
| Intervention group: (variance) | 28 |
| Intervention group: total number of patients | 3 |
| Comparison group: (mean or median) | 35 |
| Comparison group: (variance) | 35 |
| Comparison group: total number of patients | 34 |
| Blinding [patients] (only relevant for RCTs) | no |
| Blinding [personnel] (only relevant for RCTs) | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no |
| Blinding [data collectors] (only relevant for RCTs) | no |
| Blinding [analysts] (only relevant for RCTs) | no |
| ITT analysis performed (only relevant for RCTs) | yes |
| NOTES: | |
| **Clinical cure (as defined by the study authors)** | |
| Are the data available? | Data available |
| Definition (provide details if relevant) | |
| Duration of follow-up (time point when outcome was measured) [days] | 28 |
| Intervention group: # with event | 25 |
| Intervention group: Total | 34 |
| Comparison group: # with event | 27 |
| Comparison group: Total | 34 |
| Blinding [patients] (only relevant for RCTs) | no |
| Blinding [personnel] (only relevant for RCTs) | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no |
| Blinding [data collectors] (only relevant for RCTs) | no |
| Blinding [analysts] (only relevant for RCTs) | no |
| ITT analysis performed (only relevant for RCTs) | yes |
| NOTES: | |
| **Recurrent pneumonia** | |
| Are the data available? | |
| Duration of follow-up [days] | |
| Intervention group: # with event | |
| Intervention group: Total | |
| Comparison group: # with event | |
| Comparison group: Total | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Number of antibiotic days** | Number of patients who received antibiotics |
| Are the data available? | Data available |
| Duration of follow-up [days] | N/A |
| unit (days, hours, etc.) | |
| How data were reported (mean or median and type of variance) | |

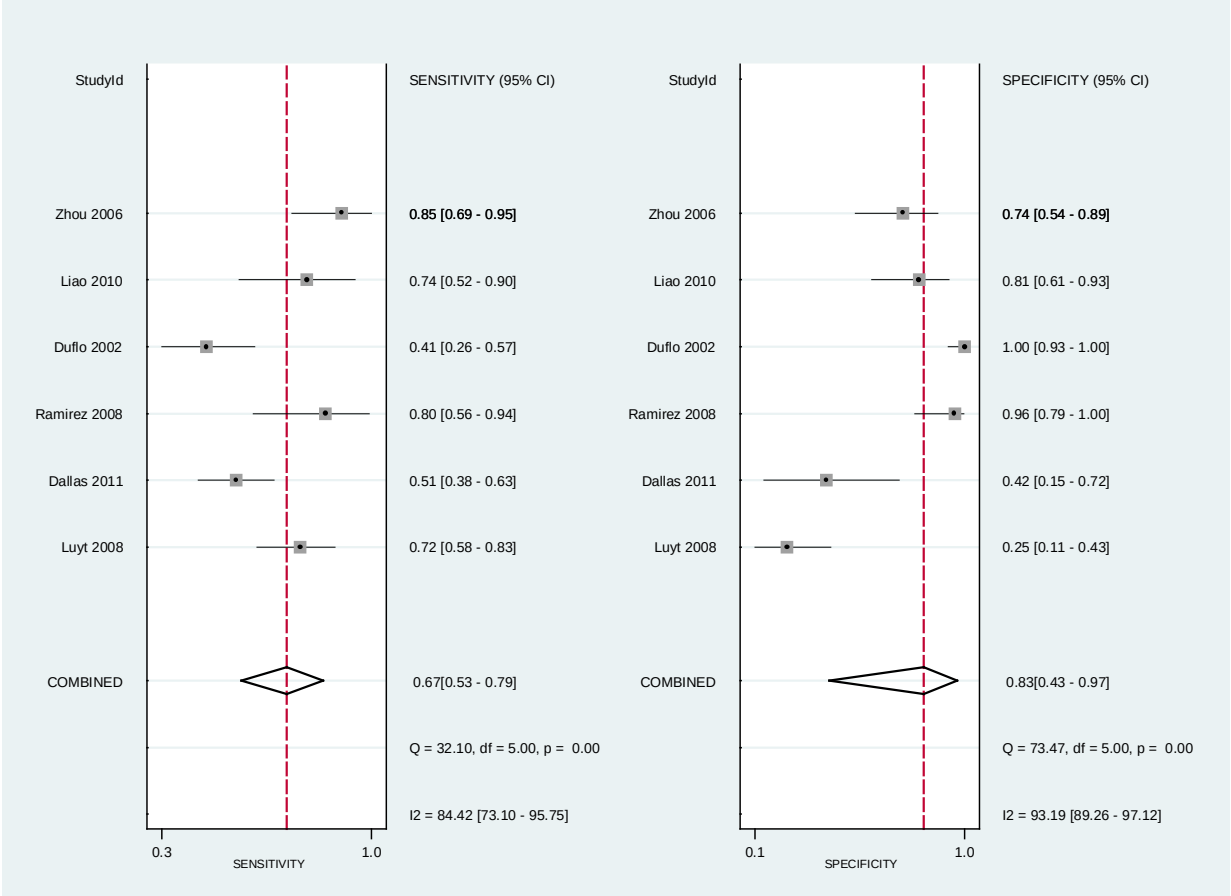
| GRADE EVIDENCE PROFILE | |
|---|---|
| **Last name of the first author** | **Herer** |
| **Year** | **2009** |
| Intervention group: (mean or median) | 26 of 34 |
| Intervention group: (variance) | |
| Intervention group: total number of patients | |
| Comparison group: (mean or median) | 34 of 34 |
| Comparison group: (variance) | |
| Comparison group: total number of patients | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Development of resistance (as defined by the study authors)** | |
| Are the data available? | |
| Duration of follow-up [days] | |
| Intervention group: # with event | |
| Intervention group: Total | |
| Comparison group: # with event | |
| Comparison group: Total | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Any adverse effect** | |
| Are the data available? | |
| Duration of follow-up [days] | |
| Intervention group: # with at least one event (if this was reported) | |
| Intervention group: # od events per group (if this was reported) | |
| Intervention group: Total | |
| Comparison group: #with at least one event (if this was reported) | |
| Comparison group: # od events per group (if this was reported) | |
| Comparison group: Total | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |
| NOTES: | |
| **Serious adverse effect** | |
| Are the data available? | |
| Duration of follow-up [days] | |
| Intervention group: # with at least one event (if this was reported) | |
| Intervention group: # od events per group (if this was reported) | |
| Intervention group: Total | |
| Comparison group: #with at least one event (if this was reported) | |

| GRADE EVIDENCE PROFILE | |
|---|---|
| **Last name of the first author** | **Herer** |
| **Year** | **2009** |
| Comparison group: # od events per group (if this was reported) | |
| Comparison group: Total | |
| Blinding [patients] (only relevant for RCTs) | |
| Blinding [personnel] (only relevant for RCTs) | |
| Blinding [outcome assessors] (only relevant for RCTs) | |
| Blinding [data collectors] (only relevant for RCTs) | |
| Blinding [analysts] (only relevant for RCTs) | |
| ITT analysis performed (only relevant for RCTs) | |

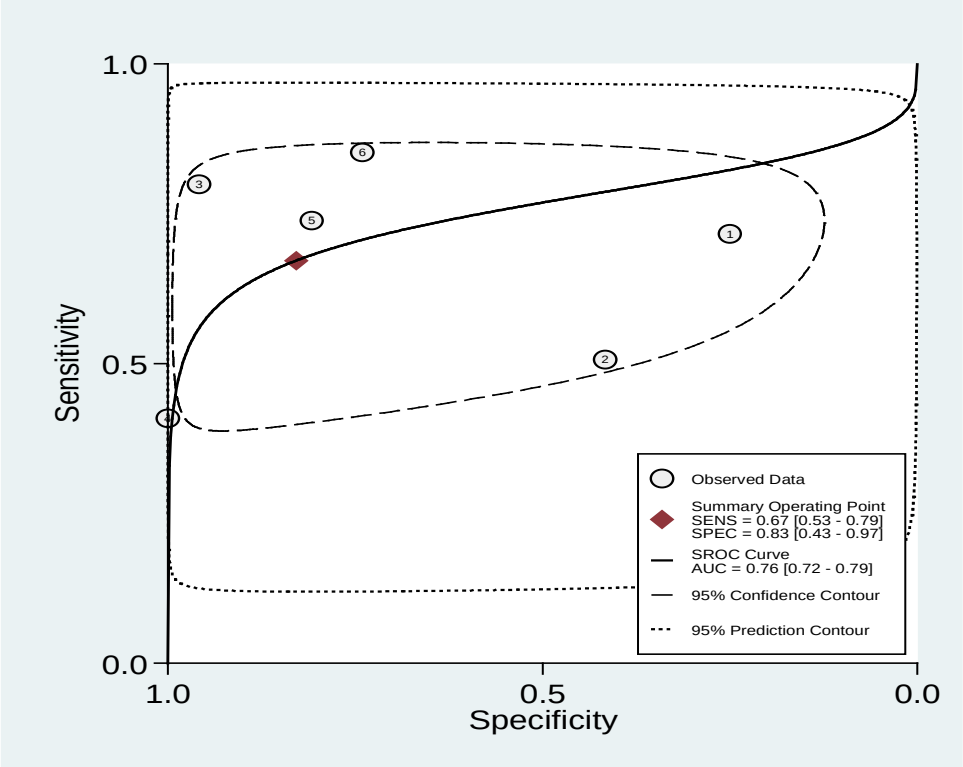
## IV. In patients with suspected HAP/VAP, should procalcitonin plus clinical criteria or clinical criteria alone be used to decide whether or not to initiate antibiotic therapy?

| Study | Groups | test brand | PCT cutoff level (ng/mL) | Sensitivity (%) | Specificity (%) | PPV | NPV | n VAP | n Non-VAP | TP | TN | FP | FN | AUC | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Luyt 2008 | VAP vs. non VAP | time-resolved amplified cryptate emission technology (Brahms) | 0.5 | 72 | 24 | 43 | 53 | 32 | 41 | 38 | 8 | 24 | 15 | 0.51 | |
| Luyt 2008 | VAP vs. non VAP | time-resolved amplified cryptate emission technology (Brahms) | 1 | 53 | 37 | 40 | 50 | 32 | 41 | | | | | | |
| Luyt 2008 | VAP vs. non VAP | time-resolved amplified cryptate emission technology (Brahms) | 2 | 41 | 61 | 45 | 57 | 32 | 41 | | | | | | |
| Dallas 2011 | nosocmial pneumonia (VAP) definitely absent vs. indeterminate vs. definitely present | enzyme-linked fluorescent assay (BRAHMS assay) | 1 | 50 | 40 | 84 | 11 | 67 | 12 | 34 | 5 | 7 | 33 | 0.506 | not only VAP. Data is for all nosocomial pneumonia |
| Ramirez 2008 | VAP nonsuspected vs. nonconfirmed vs. confirmed | time-resolved amplified cryptate emission technology (Brahms) | 2.99 | 78 | 97 | 87.5 | 94 | 20 | 24 | 16 | 23 | 1 | 4 | 0.87 | data for sensitivity/specificity is for suspected VAP vs. nonsuspected VAP |
| Duflo 2002 | VAP vs. non VAP vs. control | immunoluminometric assay (Lumitest; Brahms Diagnostica, | 3.9 | 41 | 100 | | | 44 | 52 | 18 | 52 | 0 | 26 | 0.787 | |
| Liao 2010 | VAP vs. non VAP | | 0.31 | 73.9 | 80.8 | | | 23 | 26 | 17 | 21 | 5 | 6 | | no AUC data in abstract |
| Zhou 2006 | VAP vs. non VAP | semi-solid phase immunoassay | 0.5 | 85.3 | 74.1 | 80.5 | 80 | 34 | 27 | 29 | 20 | 7 | 5 | | no AUC data in absract |
| Linssen 2008 | VAP vs. non VAP | | | | | | | 51 | 66 | | | | | 0.373 | no sensitivity/specificity data |

**Forest plot of the sensitivity and specificity of serum procalcitonin in the diagnosis of HAP/VAP.**



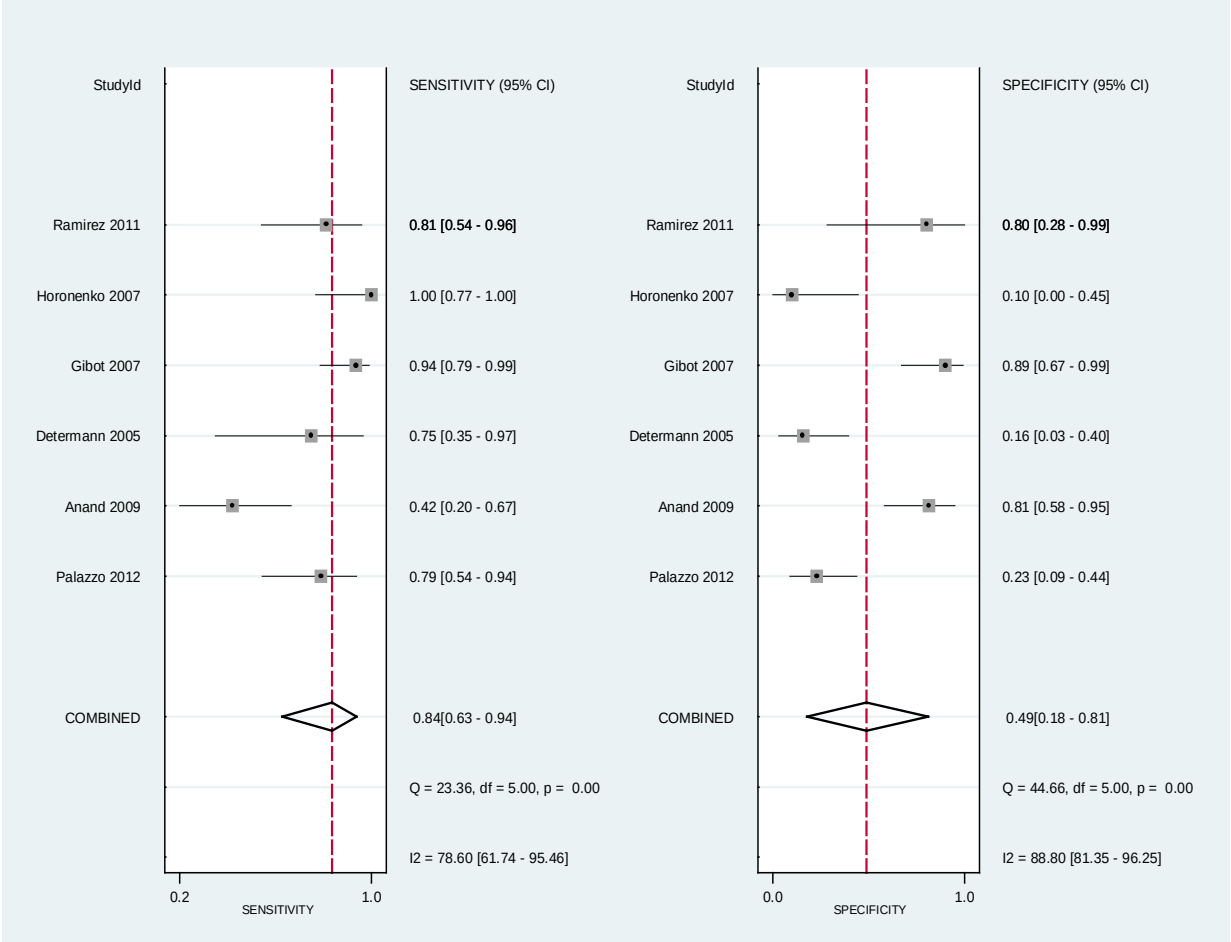
**Summary receiver operating characteristic (SROC) curve for serum procalcitonin in the diagnosis of HAP/VAP.**



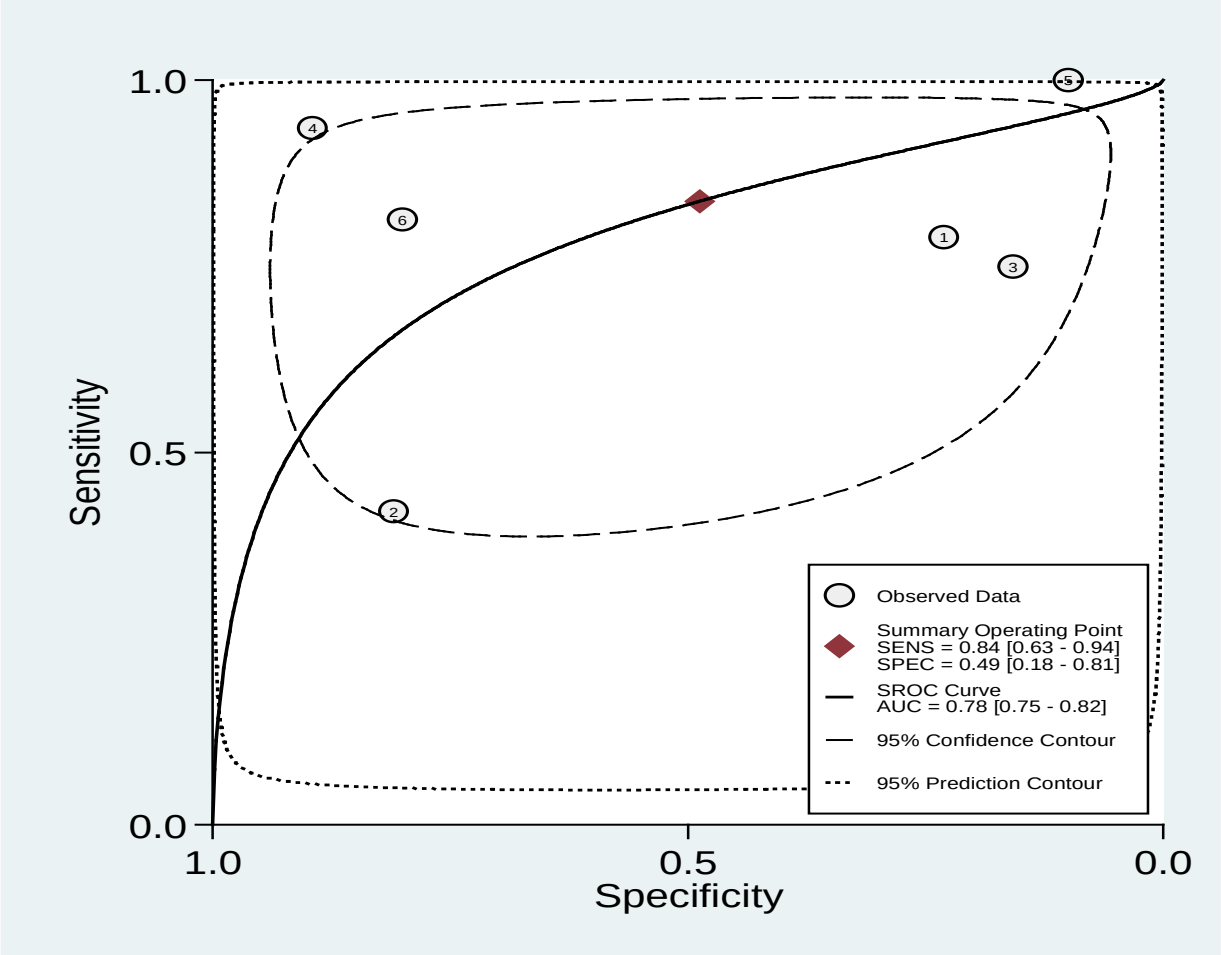
## V. In patients with suspected HAP/VAP, should soluble triggering receptor expressed on myeloid cells (sTREM-1) plus clinical criteria or clinical criteria alone be used to decide whether or not to initiate antibiotic therapy?

| | Study | Groups | | sTREM cutoff level (pg/mL) | Sensitivity (%) | Specificity (%) | PPV | NPV | n VAP | n Non-VAP | TP | TN | FP | FN | AUC | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Palazzo 2012[13] | VAP vs. non VAP | ELISA | 204 | 79 | 23 | 43 | 60 | 19 | 26 | 15 | 6 | 20 | 4 | 0.5668 | BAL TREM |
| **6** | Anand 2009[14] | definite absence VAP vs. indeterminate VAP vs. definite VAP vs. alveolar hemorrhage | ELISA | 200 | 42.1 | 90.5 | 80 | 63.3 | 19 | 21 | 8 | 17 | 4 | 11 | | BAL TREM |
| **4** | Determann 2005[15] | VAP vs. non VAP | ELISA | 200 | 75 | 84 | | | 9 | 19 | 6 | 3 | 16 | 2 | 0.83 | BAL TREM |
| **7** | Wu 2011 | VAP culture positive vs. culture negative | | | | | | | | | | | | | 0.544 | sensitivity and specificity data available for APACHE II score and changes in sTREM |
| | Gibot 2007[16] | VAP vs extrapulmonary infection | Immunoblot | 5 | 93.5 | 89.5 | | | 31 | 19 | 29 | 17 | 2 | 2 | | BAL TREM |
| | Horonenko 2007[17] | | ELISA | 184 | 100 | 10 | | | 14 | 10 | 14 | 1 | 9 | 0 | | |
| | Ramirez 2011[18] | | ELISA | 900 | 81.2 | 80 | | | 16 | 5 | 13 | 4 | 1 | 3 | | |

**Forest plot of the sensitivity and specificity of sTREM-1 in the diagnosis of HAP/VAP.**



**Summary receiver operating characteristic (SROC) curve for sTREM-1 in the diagnosis of HAP/VAP.**



## VIII. Should patients with VAT receive antibiotic therapy?

| Evidence Profile- Should patients with VAT receive antibiotic therapy? | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | | Risk difference Quality | | participants | Quality |
| **Mortality VAT vs No VAT** | | | | | | | | | | | | | | |
| Nseir 2002 [19] MICU | prospective observational cohort study | | | | | 478/1490 | 64/165 | 1.21[0.98,1.48] | | | | | 1655 | Low |
| Nseir 2002 [19] SICU | prospective observational cohort | | | | | 20/36 | 111/198 | 0.99[0.72,1.36] | | | | | 234 | Low |
| Nseir 2004 [20] | prospective observational case-control | | | | | 28/81 | 33/81 | 1.18[0.79,1.76] | | | | | 162 | Low |
| Nsier 2008* | prospective multi-site randomized unblinded | | | | | 20/55 | 16/55 | 0.80[0.47,1.37] | | | | | 110 | Moderate |
| *Study stopped early as interim analysis showed mortality differences | | | | | | | | | | | | | | |
| Total | | 0% | | | | 637/1824 | 133/337 | 1.11[0.96,1.30] | | | | | 2161 | |
| **MV Days VAT vs noVAT** | | | | | | | | | | | | | | |
| Nseir 2002 [19] MICU | prospective observational cohort | | | | | 8.8±7.4 | 26±17.1 | 17.2[14.56,19.84] | | | | | 1655 | Low |
| Nseir 2002 [19] SICU | prospective observational cohort | | | | | 27.9±17.1 | 25.1±17.1 | -2.80[-8.87,3.27] | | | | | 234 | Low |
| Nseir 2004 [20] | prospective observational | | | | | 19.1±15.2 | 21.5±12 | 2.40[-1.82,6.62] | | | | | 162 | Low |

| **Evidence Profile- Should patients with VAT receive antibiotic therapy?** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | | Risk difference Quality | | participants | Quality |
| | case-control | | | | | | | | | | | | | |
| Nsier 2008* [21] | prospective multi-site randomized unblinded | | | | | 13.3±13.1 | 21.6±16 | 8.3[2.83,13.77] | | | | | 110 | Moderate |
| *Study stopped early as interim | | | | | | | | | | | | | | |
| analysis showed mortality differences | | | | | | | | | | | | | | |
| Total | | 95% | | | | 1824 | 337 | 6.46[-3.05,15.97] | | | | | 2161 | |
| **ICU LOS VAT vs NoVAT** | | | | | | | | | | | | | | |
| Nseir 2002 [19] MICU | prospective observational cohort | | | | | 12.8±19.1 | 33.4±20.9 | 20.60[17.27,23.93 | | | | | 1655 | Low |
| Nseir 2002 [19] SICU | prospective observational cohort | | | | | 33.9±19.4 | 33.2±21.7 | -.7['-8.29,6.89] | | | | | 234 | Low |
| Nseir 2004 [20] | prospective observational case-control | | | | | 24±20.2 | 27±13.1 | 3.00['-3.05,9.05] | | | | | 162 | Low |
| Nsier 2008* [21] | prospective multi-site randomized unblinded | | | | | 17.6±16.6 | 28±15.7 | 10.4[4.36,16.44] | | | | | 110 | Moderate |
| *Study stopped early as interim | | | | | | | | | | | | | | |
| analysis showed mortality differences | | | | | | | | | | | | | | |
| Total | | 93% | | | | 1798 | 337 | 8.62[-1.81,19.05] | | | | | 2161 | |
| Treatment of VAT Mortality | | | | | | | | | | | | | | |
| Nseir 2002 [19] MICU | prospective observational cohort | | | | | 27/55 | 41/110 | .62[0.32,1.19] | | | | | 165 | Low |

| **Evidence Profile- Should patients with VAT receive antibiotic therapy?** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | Risk difference Quality | participants | Quality |
| Nseir 2002 [19] SICU | prospective observational cohort | | | | | 7/10 | 13/26 | .43[0.09,2.03] | | | 36 | Low |
| Nseir 2004 [20] | prospective observational case-control | | | | | 14/34 | 8/25 | .67[0.23,1.99] | | | 59 | Low |
| Nsier 2005 [22] non COPD | retrospective observational matched | | | | | 11/43 | 5/12 | 2.08[0.55,7.91] | | | 55 | Low |
| Nseir 2008 [21] | prospective multi-site randomized unblinded | | | | | 17/36 | 4/22 | 0.25[0.07,0.88] | | | 58 | Moderate |
| Total | | 26% | | | | 76/178 | 71/195 | .62[0.35,1.10] | | | 373 | |
| Treatment of vVAT MV Days | | | | | | | | | | | | |
| Nseir 2002 [19] MICU | prospective observational cohort | | | | | 37±38.4 | 30.6±28.9 | -6.4[-32.66,19.86] | | | 165 | Low |
| Nseir 2002 [19] SICU | prospective observational cohort | | | | | 27.9±17.1 | 25.1±17.1 | -2.80[-8.33,2.73] | | | 36 | Low |
| Nseir 2004 [20] | prospective observational case-control | | | | | 24.7±11.8 | 17±11.1 | -7.70[-13.88,-1.52] | | | 59 | Low |
| Nsier 200 [22] 5 non COPD | retrospective observational matched | | | | | 22.3±17.2 | 18.8±9.7 | -3.50[-11.02,4.02] | | | 55 | Low |
| Nseir 2008 [21] | prospective multi-site randomized unblinded | | | | | 26±15 | 29±17 | 3.00[-5.63,11.63] | | | 58 | Moderate |
| Total | | 1% | | | | 178 | 195 | 3.53[6.88,.19] | | | 373 | |
| Treatment f VAT ICU LOS | | | | | | 33.9±19.4 | 33.2±21.7 | -0.70[-7.24,5.84] | | | 165 | Low |
| Nseir 2002 [19] MICU | prospective observational cohort | | | | | 46.6±43.5 | 36.2±27.6 | -10.4[-39.37,18.57] | | | 36 | Low |
| Nseir 2002 [19] SICU | prospective observational | | | | | 28.6±12.5 | 21.3±13 | -7.3[-13.90,-0.7] | | | 59 | Low |

| **Evidence Profile- Should patients with VAT receive antibiotic therapy?** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | | Risk difference Quality | | participants | Quality |
| | cohort | | | | | | | | | | | | | |
| Nseir 2004 [20] | prospective observational case-control | | | | | 30.5±16.8 | 24.8±14.5 | -5.7[-15.32,3.92] | | | | | 55 | Low |
| Nsier 2005 [22] non COPD | multi site randomized | | | | | 36±21 | 40±23 | 4.00[-7.81,15.81 | | | | | 58 | Moderate |
| Nseir 2008 [21] | prospective multi-site randomized unblinded | | | | | | | | | | | | | |
| Total | | 0% | | | | 178 | 195 | -3.5[-7.40,0.41] | | | | | 373 | |

## X. What antibiotics are recommended for empiric treatment of clinically suspected VAP?

| Distribution of pathogens and antimicrobial resistance patterns associated with 8,474 cases of ventilator-associated pneumonia reported to the U.S. Centers for Disease Control and Prevention, 2009-2010 [23] | | |
|---|---|---|
| **Pathogen** | **Frequency** | **Antimicrobial Resistance Rates** |
| ***Staphylococcus aureus*** | 24.1% | Methicillin / oxacillin resistant – 48% |
| ***Pseudomonas aeruginosa*** | 16.6% | Ciprofloxacin / levofloxacin resistant – 33%<br>Imipenem / meropenem resistant – 30%<br>Cefepime / ceftazidime resistant – 28%<br>Piperacillin-tazobactam resistant – 19%<br>Aminoglycoside resistant – 11%<br>Resistant to ≥3 of the above classes – 18% |
| ***Klebsiella* species** | 10.1% | Cefepime / ceftazidime / cefotaxime resistant – 24%<br>Imipenem / meropenem resistant – 11%<br>Resistant to ≥3 classes – 13% |
| ***Enterobacter* species** | 8.6% | Cefepime / ceftazidime / ceftriaxone resistant – 30%<br>Imipenem / meropenem resistant – 4%<br>Resistant to ≥3 classes – 1% |
| ***Acinetobacter baumannii*** | 6.6% | Imipenem / meropenem resistant – 61%<br>Resistant to ≥3 classes – 63% |
| ***Escherichia coli*** | 5.9% | Ciprofloxacin / levofloxacin resistant – 35%<br>Cefepime / ceftazidime / ceftriaxone resistant – 16%<br>Imipenem / meropenem resistant – 4%<br>Resistant to ≥3 classes – 3% |

| SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC TREATMENTS FOR VAP - NOTABLE EXCLUSION CRITERIA | | | |
|---|---|---|---|
| **Study** | **Rx A** | **Rx B** | **Summary of exclusion criteria** |
| Alvarez 2001 [24] | Meropenem | Ceftaz-Amikacin | Renal insufficiency, hepatic insufficiency, leukopenia, pregnancy, life expectancy of <1 month, exposure to antibiotics active against the patient's pneumonia pathogens within the preceding 3 days |
| Sieger 1997 [25] | Meropenem | Ceftaz-Tobra | Renal insufficiency, hepatic insufficiency, history of seizures, central nervous system disease, terminal illness, neutropenia, cystic fibrosis, concomitant antibiotics for another focus of infection, pregnancy |
| Brown 1984 [26] | Moxalactam | Carbenicillin-Tobra | Not explicitly stated. |
| Kljucar 1987 [27] | Ceftazidime | Ceftaz-Tobra<br>Azlocillin-Tobra | Fewer than 5 days of intensive care prior to pneumonia onset |
| Chastre 2008 [28] | Doripenem | Imipenem | VAP caused by pathogens resistant to imipenem or meropenem, APACHE score <8 or >29, concurrent infection requiring non-study antibacterials or prolonged antibiotic therapy, structural lung disease, acute respiratory distress syndrome, septic shock, end-stage renal disease, cavitary lung disease, primary of secondary lung cancer, cystic fibrosis, immunocompromising illness, rapidly progressive disease, need for activated protein C |
| Kollef 2012 [28] | Doripenem x7days | Imipenem<br>x 10 days | Known history of MRSA or *Stenotrophomonas maltophila* infection, acute respiratory distress syndrome, congestive heart failure, >24 hours treatment for the current infection, chest trauma with severe lung bruising or loss of stability of the thoracic cage, active seizure disorder within the previous 2 years, burns to >15% of body surface area, cirrhosis, empyema, lung cancer within the previous 2 years, chronic bronchitis with increased disease severity within the previous 30 days, bronchiectasis, tuberculosis, chemical pneumonitis, cystic fibrosis, pregnancy, study drug allergy |
| Hartenauer 1990 [29] | Ceftazidime | Imipenem | Infection with a resistant pathogen, antibiotic treatment before the clinical trial, pregnancy, known allergy to study drugs |
| Torres 2000 [30] | Ciprofloxacin | Imipenem | Changes in systemic antibiotics in the 5 days before enrollment, neutropenia, immunosuppression, exposure to study medication within 30 days prior to enrollment, pregnancy |
| Fink 1994 [31] [32] | Ciprofloxacin | Imipenem | Prior antibiotics for the study infection, neutropenia |
| Shorr 2005 | Levofloxacin | Imipenem | Known resistance to study drugs, receiving additional antibiotic therapy, APACHE score >35, creatinine clearance >35, >15% total body burns, significant 3$^{rd}$ degree burns, immunosuppression, structural lung disease, empyema, concurrent non-bacterial pulmonary infection, pregnancy |
| Réa Neto 2008 [33] | Doripenem | Piperacillin-tazobactam | Known resistance to study drugs, concomitant systemic antimicrobials other than vancomycin or amikacin, >24 hours of systemic antibiotics within the preceding 3 days, APACHE <8 or >25, mechanical ventilation for ≥5 dyas, postobstructive pneumonia, cavitary lung disease, lung cancer or lung metastases, acute respiratory distress syndrome, cystic fibrosis, need for dialysis, rapidly progressive disease, immunosuppression, severe liver disease, neutropenia, thrombocytopenia, study drug allergy |
| Polk 1997 [34] | Vancomycin<br>Aztreonam | Imipenem | Hospitalized for >10 days prior to study entry, Glasgow Coma Scale ≤7, penetrating or blunt trauma to alimentary tract with contamination, need for additional systemic antimicrobials other than study drugs, allergy to study drugs, pregnancy, severe renal dysfunction, dialysis, burn injury to >5% of total body surface area, leukopenia, cystic fibrosis, HIV, previous documented Gram-positive or anaerobic pneumonia within the preceding week |
| Beaucaire 1995 [35] | Isepamicin | Amikacin | Infection resistant to study medications, infection requiring more than 14 days therapy, previous exposure to isepamicin, renal insufficiency, hepatic insufficiency, hearing impairment, high probability of death, meningitis, brain abscess, pregnancy. |
| Ahmed 2007 [36] | Cefepime-levofloxacin | Pip-tazo + Amikacin | Acute or chronic renal insufficiency |
| Beaucaire 1999 [37] | Cefipime/<br>Amikacin | Ceftazidime/<br>Amikacin | Patients allergic to cephalosporins, aminoglycosides, L-arginine or with contra-indication to the prescription of these treatments 6taient excluded. Patients who were neutropenic (secondary to bone marrow disorder or chemotherapy), patients with septic shock and those under dialysis intermittently or continuous were excluded. |
| Croce 2003 | Cefoperazone | Cefoperazone/<br>Gentamicin | Pregnancy, allergy to penicillin, cephalosporin, aminoglycoside, pneumonia at time of admission, concomitant infection or use of other antibiotics, renal insufficiency (cr > 1.5) |

| SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC TREATMENTS FOR VAP - NOTABLE EXCLUSION CRITERIA | | | |
|---|---|---|---|
| **Study** | **Rx A** | **Rx B** | **Summary of exclusion criteria** |
| Croce 2003 | Ceftazidime | Ceftazidime/ Gentamicin | Pregnancy, allergy to penicillin, cephalosporin, aminoglycoside, pneumonia at time of admission, concomitant infection or use of other antibiotics, renal insufficiency (cr > 1.5) |
| Reeves 1989 [38] | Ceftriaxone | Cefotaxime | Known or need for another antibiotic, requirement for antibiotics for extrathoracic chest infection with a gram negative resistant to the study antibiotics, |
| Saginur 1997 [39] | Ceftazidime | Ciprofloxacin | Exclusion criteria were patients at high risk of death within 72 h of study enrolment; a history of allergy or severe adverse reaction to ciprofloxacin, other quinolone derivatives or cephalosporins; pregnancy or lactation; severe renal impairment (serum creatinine more than 265 µmol/L); mild infection not requiring parenteral antibiotics; alternative diagnosis for pulmonary infiltrate (eg, cardiac failure, pulmonary embolus, etc); prior oral or parenteral antibiotics for this infection with the exception of cases of clinical worsening after a course of less than 48 h; concomitant antibiotics for other infection where the antibiotics have a similar spectrum of activity; previous enrolment in this study; or granulocytopenia or known human immunodeficiency virus infection. |
| Alvarez-Lerma 2001 [40] | Pip/Tazo+ Amikacin | Ceftazidime+ Amikacin | Pregnant and breast feeding, documented hypersensitivity to study drugs or beta lactams, renal failure, treatment with antibiotics within 72 hours of study inclusion, need for concomitant administration of antibiotics, treatment with probenicid, granulocytopenia, liver dysfunction, massive aspiration, life expectancy < 1 month and DNR |
| Bruin-Bruisson 1998 [41] | Pip/Tazo+ Amikacin | Ceftazidime+ Amikacin | Patients were not eligible if they were diagnosed as having AIDS, a hematologic malignancy, or severe neutropenia or had a history of documented allergy to b-lactam antibiotics. Likewise, patients were not eligible if death was expected within 7 days of inclusion or a do-not-rescuscitate order had been written or if they had a severity score (simplified acute physiology [SAPS II] score) on inclusion higher than 50 and three or more organ failures or a rapidly fatal underlying disease. In addition, patients with suspected or documented tuberculosis, suspected or documented infection due to MRSA only, or a concomitant infection requiring other antimicrobial therapy (or that had necessitated the recent [ <48 hours previously] introduction of antibiotics were not eligible. |
| Freire 2010 [42] | Tigecycline +/- Ceftazidime | Imipenen +/- Vancomycin | Exclusion criteria included antibacterial drugs administered for N24 h to treat the current episode of suspected HAP unless a repeat respiratory culture showed that a pathogen was resistant to that agent and/or the patient had worsening or no improvement in clinical signs and symptoms of pneumonia, HIV positive, on immunosuppressive therapy, APACHE II score N30, cystic fibrosis, pulmonary malignancy, postobstructive pneumonia, bronchiectasis, sarcoidosis, pulmonary abscess, empyema, active tuberculosis, and infections known to be caused by Legionella, Pneumocystis, or mycobacteria. Additional exclusions included absolute neutrophil count b1 × 109/L, aspartate aminotransferase or alanine aminotransferase N10× upper limit of normal (ULN) or bilirubin or alkaline phosphatase N3× ULN, creatinine clearance (CL) b41 mL/min per 1.73 m2, or hypersensitivity to any of the agents that could be used in the trial. |
| Giamarellos-Bourboulis 2008 [43] | Clarithromycin + usual therapy | Usual therapy | Exclusion criteria were as follows: (1) neutropenia, defined as a neutrophil count !500 cells/mL; (2) HIV infection; (3) oral intake of corticosteroids at a dose _1 mg/kg of equivalent prednisone for a period 11 month; (4) administration of drotrecogin alfa in the previous 5 days; and (5) atrioventricular block of second or third degree. |
| Heyland 2008 [44] | Meropenem | Meropenem-Cipro | Intubation <96 hours, immunocompromised, unable to tolerate bronchoscopy, allergy to any study drug, expected to die within 24 hours, unlikely to be discharged from ICU within 3 weeks of admission to ICU, known to be previously colonized with Pseudomonas or MRSA, exposure to carbapenem or cipro within 7 days prior to enrollment, receipt of any other antibiotic for the current episode of VAP. |
| Thomas 1994 [45] | Ceftriaxone | Cefotaxime | History of hypersensitivity to beta-lactams, treatment with other antibiotics in the three days prior to enrollment unless there was a failure of treatment, Immunosuppression, a critically ill state, neutropenia. Serious hepatic disease, need for other antibacterial agents, requirement for a narrower spectrum antibiotic, previous investigational drug within 2 weeks, pregnancy and lactation |
| Fagon 2000 [5] | Quinupritin/ Dalfopristin | Vancomycin | Patients were excluded if they were pregnant or lactating, had a life expectancy of less than 1 mo, or had pneumonia caused exclusively by organisms other than gram-positive pathogens. Also excluded were patients who had received effective systemic antimicrobial therapy for more than 24 h within 7 d before enrollment, had significant neutropenia (less than 500/mm3), underlying immunocompromising disease (HIV-positive status with a CD4 count, 200/ml, splenectomy) or therapy (patients receiving . 40 mg/d of corticosteroids or other immunosuppressive therapy), |

| SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC TREATMENTS FOR VAP - NOTABLE EXCLUSION CRITERIA | | | |
|---|---|---|---|
| **Study** | **Rx A** | **Rx B** | **Summary of exclusion criteria** |
| | | | or had documented allergy to streptogramin, glycopeptide, or beta-lactam antibiotics. |
| Wunderink 2008 [46] | Linezolid | Vancomycin | Study exclusions were as follows: pregnancy; hypersensitivity to LZD or VAN; concurrent use of another investigational medication; infection due to Gram-positive organisms known to be resistant to either study drug; treatment for _ 48 h prior to study enrollment with any agent with antimicrobial activity against the<br>patient's MRSA isolate (*eg*, VAN, clindamycin, trimethoprim/sulfamethoxazole, rifampin, or LZD); infection primarily due to an organism other than MRSA; the presence of neutropenia, AIDS, lymphoma, or the need for chemotherapy; the presence of anticipated limitations of therapy in the 7 days following study enrollment; contraindication to bronchoscopy; tracheostomy for 60 days; or a history of bone marrow or lung transplantation. |
| Wunderink 2012 [47] | Linezolid | Vancomycin | Patients with treatment with linezolid, vancomycin, or teicoplanin for .48 hours within or before the 72-hour pre-study period (if treatment continued into that period) were excluded. All patients who were considered to have experienced clinical failure for any of these drugs were specifically excluded. Patients previously treated with any other MRSA-active antibiotic (for >48 hours, but within the 72-hour pre-study period only) were also excluded, unless documented as having a treatment failure. In mixed infection, patients were discontinued from the study if the investigator felt that the Gram-negative bacterium was the predominant pathogen. Patients co-infected with Gram-negative bacteria resistant to the empirical antibiotic were also discontinued. Therefore, all patients with mixed infections had adequate Gram-negative antibiotic coverage. |
| Kollef 2004 | Linezolid | Vancomycin | Exclusion criteria included infecting Gram-positive organism resistant to either study medication |

| STUDY CHARACTERISTICS | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Rx A** | **Rx B** | **Blinded** | **N** | **Mech Vent** | **Staph aureus** | **MRSA** | **Pseuds** | **Resist A** | **Resist B** | **Resistant ≥1 study drug** |
| Alvarez 2001 | Meropenem | Ceftaz-Amikacin | No | 140 | 100% | 15/140 (11%) | -- | 27/140 (19%) | -- | -- | 6/140 (4.3%) |
| Sieger 1997 | Meropenem | Ceftaz-Tobra | No | 211 | 70% | -- | -- | -- | -- | -- | -- |
| Brown 1984 | Moxalactam | Carbenicillin-Tobra | No | 48 | 85%[a] | Excluded | -- | 7/34 (21%) | 2/58 (3.4%) | 0/58 (0%) | 18/58 (31%) |
| Kljucar 1987 | Ceftazidime | Ceftaz-Tobra | No | 33 | 100% | 7/33 (21%) | -- | 18/33 (55%) | -- | -- | -- |
| Kljucar 1987 | Ceftazidime | Azlocillin-Tobra | No | 33 | 100% | 7/33 (21%) | -- | 23/33 (70%) | -- | -- | -- |
| Chastre 2008 | Doripenem | Imipenem | No | 531 | 100% | 150/409 (37%) | 57/409 (14%) | 56/409 (14%) | 35/206 (17%) | 39/203 (19%) | 74/409 (18%) |
| Kollef 2012 | Doripenem x7days | Imipenem x 10 days | Yes | 274 | 100% | 52/167 (31%) | 11/167 (6.6%) | 27/167 (16%) | 18/144 (13%) | 18/154 (12%) | 36/298 (12%) |
| Hartenauer 1990 | Ceftazidime | Imipenem | No | 45 | 100% | 12/45 (27%) | -- | 11/45 (24%) | -- | -- | -- |
| Torres 2000 | Ciprofloxacin | Imipenem | No | 149 | 100% | 2/75 (2.7%) | 1/75 (1.3%) | 26/75 (35%) | 1/74 (1.4%) | 2/78 (2.6%) | -- |
| Fink 1994 | Ciprofloxacin | Imipenem | Yes | 405[b] | 79% | 46/359 (13%) | 2/359 (0.6%) | 91/402 (22%) | 9/205 (4.4%) | 10/200 (5.0%) | -- |
| Shorr 2005 | Levofloxacin | Imipenem | No | 222 | 100% | 50/222 (23%) | 13/222 (5.9%) | 34/222 (15%) | -- | -- | -- |
| Réa Neto 2008 | Doripenem | Piperacillin-tazobactam | No | 448 | 22%[c] | 112/285 (39%) | 68/285 (24%) | 54/285 (19%) | 19/225 (8.4%) | 32/223 (14%) | -- |
| Polk 1997 | Vancomycin Aztreonam | Imipenem | No | 122 | 100% | -- | -- | -- | -- | -- | -- |
| Beaucaire 1995 | Isepamicin[d] | Amikacin | No | 113[d] | 100% | -- | -- | 35/130 (27%) | -- | -- | -- |
| Ahmed 2007 | Cefepime-levofloxacin | Pip-tazo + Amikacin | No | 93 | 100% | 25/93 (27%) | -- | 37/93 (40%) | 5/47 (11%) | 3/46 (6.5%) | -- |
| Beaucaire 1999 | Cefipime/ Amikacin | Ceftazidime/ Amikacin | No | 275 | 100% | 19/275 (7%) | -- | 16/275 (6%) | 48/293 (16%) | 68/294 (23%) | -- |
| Croce 2003[e] | Cefoperazone | Ceftazidime | No | 39 | 100% | 11/59 (19%) | -- | 6/59 (10%) | -- | -- | -- |
| Croce 2003[e] | Cefoperazone/ Gentamicin | Ceftazidime/ Gentamicin | No | 70 | 100% | 31/137 (23%) | -- | 13/137 (10%) | -- | -- | -- |
| Reeves 1989 | Ceftriaxone | Cefotaxime | No | 51 | 90% | 5/51 (10%) | 2/51 (4%) | 2/51 (4%) | -- | -- | -- |
| Saginur 1997[f] | Ceftazidime | Ciprofloxacin | No | 149 | 52% | 18/149 | -- | 4/149 | -- | -- | -- |

| STUDY CHARACTERISTICS | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Rx A** | **Rx B** | **Blinded** | **N** | **Mech Vent** | **Staph aureus** | **MRSA** | **Pseuds** | **Resist A** | **Resist B** | **Resistant ≥1 study drug** |
| | | | | | | (12%) | | (3%) | | | |
| Alvarez-Lerma 2001 | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | No | 124 | 85% | 10/124 (8%) | -- | 13/124 (10%) | -- | -- | -- |
| Brun-Buisson 1998 | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | No | 197[g] | 100% | 29/190 (15%) | 7/190 (3.7%) | 42/190 (22%) | 18/152 (12%) | 29/151 (19%) | -- |
| Freire 2010 | Tigecycline +/- Ceftazidime | Imipenen +/- Vancomycin | Yes | 934 | 34% | 25/253 (10%) | 21/253 (8%) | 18/253 (7%) | -- | -- | -- |
| Giamarellos-Bourboulis 2008 | Clarithro + usual therapy | Usual therapy | Yes | 200 | 100% | -- | -- | 29/200 (15%) | -- | -- | -- |
| Thomas 1994 | Ceftriaxone | Cefotaxime | Yes | 142[h] | 100% | 26/93 (28%) | 1/93 (1%) | -- | -- | -- | -- |
| Damas (A) 2006 | Cefipime | Cefipime – Amikacin | No | 39 | 100% | 10/39 (25%) | 1/39 (3%) | 7/39 (18%) | -- | -- | -- |
| Damas (B) 2006 | Cefipime | Cefipime - Levofloxacin | No | 40 | 100% | 11/40 (28%) | 3/40 (8%) | 9/40 (23%) | -- | -- | 1/40 (2.5%) |
| Heyland 2008 | Meropenem | Meropenem - Ciprofloxacin | Yes | 739 | 100% | 127/739 (17%) | 12/739 (2%) | 47/739 (6%) | 46/739 (6.2%) | 59/739 (7.6%) | 38/739 (5.1%) |
| Manhold 1998[e] | Cipro | Ceftazidime - Gentamicin | No | 18[d] | 100% | 5/18 (28%) | 3/18 (17%) | 2/18 (11%) | -- | -- | -- |
| Fagon 2000 | Quinupristin/ Dalfopristin | Vancomycin | Yes | 304 | 74% | 135/304 (44%) | 38/304 (13%) | -- | -- | -- | -- |
| Wunderink 2008 | Linezolid | Vancomycin | No | 149 | 100% | -- | 50/149 (33%) | -- | -- | -- | -- |
| Wunderink 2012 | Linezolid | Vancomycin | Yes | 1125 | 25% | | 176/1125 (16%) | -- | -- | -- | -- |
| Kollef 2004 | Linezolid | Vancomycin | Yes | 544 | 100% | 221/544 (41%) | 91/544 (17%) | -- | -- | -- | -- |

[a] 29/34 evaluable patients had ICU-acquired pneumonia, subset on vents not reported but 31/34 evaluable patients had endobronchial secretion samples
[b] Includes 88 patients (22%) with community-acquired severe pneumonia
[c] Study included because clinical cure rates amongst the clinically evaluable subset of VAP patients reported
[d] Study included two isepamicin arms, isepamicin 7.5mg/kg twice daily and isepamicin 15mg/kg once daily. Only data from the isepamicin once daily arm are included in this summary.
[e] Percentages for bacteria are based on percentages of isolates not number of patients. No of patients with different types of isolates was not available.
[f] Outcome data abstracted for mechanically ventilated patients with the exception of AEs
[g] 197 patients enrolled but only 127 had VAP and the report is on those patients
[h] Data reported only for 93 clinically evaluable patients

| OUTCOMES | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rx A | Rx B | Clinical Response | | | Vent Days | | | Hospital Days | | | Mortality | | |
| | | | A | B | Diff | A | B | Diff | A | B | Diff | A | B | Diff |
| Alvarez 2001 | Meropenem | Ceftaz-Amikacin | 47/69 (68%) | 39/71 (55%) | .04 | 16.5 ±11.4 | 17.0 ±12.4 | NS | 34.3 ±20.3 | 35.9 ±21.3 | NS | 16/69 (23%) | 20/71 (28%) | NS |
| Sieger 1997 | Meropenem | Ceftaz-Tobra | 76/106 (72%) | 62/105 (59%) | .10 | -- | -- | -- | -- | -- | -- | 13/104 (13%) | 23/107 (21%) | .06 |
| Brown 1984 | Moxalactam | Carbenicillin-Tobra | 11/18 (61%)[a] | 7/16 (44%)[a] | NS | -- | -- | -- | 25.3± 19.0[b] | 19.7± 18.1[b] | NS | 11/18 (61%) | 9/16 (56%) | NS |
| Kljucar 1987 | Ceftazidime | Ceftaz-Tobra | 12/16 (75%) | 12/17 (71%) | NS | -- | -- | -- | -- | -- | -- | 0/16 (0%) | 1/17 (5.9%) | NS |
| Kljucar 1987 | Ceftazidime | Azlocillin-Tobra | 12/16 (75%) | 8/17 (47%) | NS | -- | -- | -- | -- | -- | -- | 0/16 (0%) | 2/17 (12%) | NS |
| Chastre 2008 | Doripenem | Imipenem | 147/249 (59%)[c] | 146/252 (58%)[c] | NS | -- | -- | -- | -- | -- | -- | 27/249 (11%) | 24/252 (10%) | NS |
| Kollef 2012 | Doripenem x 7 days | Imipenem x 10 days | 36/79 (46%) | 50/88 (57%) | NS | -- | -- | -- | -- | -- | -- | 26/115 (23%) | 18/112 (16%) | NS |
| Hartenauer 1990 | Ceftazidime | Imipenem | 17/21 (81%)[c] | 16/24 (67%)[c] | NS | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Torres 2000 | Ciprofloxacin | Imipenem | 40/57 (70%)[c] | 34/52 (65%)[c] | NS | -- | -- | -- | -- | -- | -- | 8/41 (20%)[d] | 4/34 (12%)[d] | NS |
| Fink 1994 | Ciprofloxacin | Imipenem | 74/121 (61%)[e] | 71/130 (55%)[e] | NS | -- | -- | -- | -- | -- | -- | 43/202 (21%) | 38/200 (19%) | NS |
| Shorr 2005 | Levofloxacin | Imipenem | 65/111 (59%) | 70/111 (63%) | NS | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Réa Neto 2008 | Doripenem | Piperacillin-tazobactam | 20/29 (69%)[f] | 15/26 (58%)[f] | NS | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Polk 1997 | Vancomycin Aztreonam | Imipenem | "no difference," actual figures not provided | | NS | -- | -- | -- | -- | -- | -- | 10/63 (16%) | 9/59 (15%) | NS |
| Beaucaire 1995 | Isepamicin | Amikacin | 23/44 (52%) | 25/41 (61%) | NS | -- | -- | -- | -- | -- | -- | 17/56 (30%) | 15/57 (26%) | NS |
| Ahmed 2007 | Cefepime-levofloxacin | Pip-tazo + Amikacin | -- | -- | -- | 6.3±1.6 | 8.2±2.1 | <.05 | 16±2.1 | 19±3.4 | <.05 | 13/38 (35%) | 15/38 (40%) | NS |
| Beaucaire 1999 | Cefipime/ Amikacin | Ceftazidime/ Amikacin | 68/141 (48%) | 60/134 (45%) | NS | -- | -- | -- | -- | -- | -- | 29/141 (20%) | 21/134 (16%) | -- |
| Croce 2003 | Cefoperazone | Ceftazidime | 10/19 (53%) | 12/20 (60%) | -- | 19±14 | 18±25 | -- | -- | -- | -- | -- | -- | -- |
| Croce 2003 | Cefoperazone/ Gentamicin | Ceftazidime/ Gentamicin | 10/35 (29%) | 12/35 (34%) | -- | 12±5 | 14±9 | -- | -- | -- | -- | -- | -- | -- |
| Reeves 1989 | Ceftriaxone | Cefotaxime | 12/25 | 19/26 | -- | -- | -- | -- | -- | -- | -- | 2/25 | 4/26 | -- |

| OUTCOMES | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rx A | Rx B | Clinical Response | | | Vent Days | | | Hospital Days | | | Mortality | | |
| | | | A | B | Diff | A | B | Diff | A | B | Diff | A | B | Diff |
| | | | (48%) | (73%) | | | | | | | | (8%) | (15%) | |
| Saginur[h] 1997 | Ceftazidime | Ciprofloxacin | 14/34 (41%) | 17/30 (57%) | -- | -- | -- | -- | -- | -- | -- | 6/77[i] (8%) | 8/62[i] (13%) | -- |
| Alvarez-Lerma 2001 | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | 44/88 (50%) | 16/36 (28%) | -- | -- | -- | -- | -- | -- | -- | 27/88 (31%) | 8/36 (22%) | |
| Bruin-Bruisson 1998 | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | 28/58 (48%) | 23/69 (33%) | -- | 7[j] | 8[j] | -- | -- | -- | -- | 8/51 (15%) | 12/61 (20%) | -- |
| Freire 2010 | Tigecycline +/- Ceftazidime | Imipenen +/- Vancomycin | 59/127 (46%) | 67/116 (58%) | -- | -- | -- | -- | 11.2[k] | 9.2[k] | 0.046 | 25/131 (19%) | 15/122 (12%) | -- |
| Giamarellos-Bourboulis 2008 | Clarithro + usual therapy | Usual therapy | 61/100 (61%) | 54/100 (54%) | -- | 16 (8, >28) | 22.5 (12, >28) | -- | -- | -- | -- | 28/100 (28%) | 31/100 (31%) | NS |
| Thomas 1994 | Ceftriaxone | Cefotaxime | 37/53 (70%) | 26/40 (65%) | NS | -- | -- | -- | -- | -- | -- | 13/53 (25%) | 12/40 (30%) | -- |
| Damas (A) 2006 | Cefepime | Cefepime - Amikacin | -- | -- | -- | -- | -- | -- | -- | -- | -- | 2/20 (10%) | 4/19 (21%) | |
| Damas (B) 2006 | Cefepime | Cefepime - Levofloxacin | -- | -- | -- | -- | -- | -- | -- | -- | -- | 2/20 (10%) | 4/20 (16%) | |
| Heyland 2008 | Meropenem | Meropenem-cipro | 203/369 (55%) | 220/369 (60%) | NS | 10.2 ±7.4 | 10.4 ± 8.1 | NS | -- | -- | -- | 67/370 (18%) | 71/369 (19%) | NS |
| Manhold 1998 | Cipro | Ceftazidime - Gentamicin | -- | -- | | 8.7 (iqr 3.8 - 24.8) | 9.3 (iqr 3.8 – 21.6) | | 45.8 (iqr 24 – 317) | 39.1 (iqr 19.7 – und) | | 67/370 (18%) | 71/369 (19%) | |
| Manhold 1998 | Cipro | Ceftazidime - Gentamicin | 2/10 (20%) | 4/8 (50%) | -- | -- | -- | -- | -- | -- | -- | 8/10 (80%) | 4/8 (50%) | -- |
| Fagon 2000 | Quinupritin/ Dalfopristin | Vancomycin | 65/150 (43%) | 67/148 (45%) | | -- | -- | -- | -- | -- | -- | 38/150 (25%) | 32/148 (22%) | |
| Wunderink[g] 2008 | Linezolid | Vancomycin | 13/23 (56%) | 9/19 (47%) | NS | 10.4±1.6 | 14.3±2.1 | -- | 18.8±1.6 | 20.1±1.4 | | 4/30 (13%) | 6/20 (30%) | 0.15 |
| Wunderink 2012 | Linezolid | Vancomycin | 102/186 (55%) | 92/205 (45%) | | -- | -- | -- | -- | -- | -- | 94/597 (16%) | 100/587 (17%) | -- |
| Kollef 2004 | Linezolid | Vancomycin | 109/241 (45%) | 79/216 (37%) | | -- | -- | -- | -- | -- | -- | 59/282 (21%) | 69/262 (26%) | |

[a] clinical response defined as radiographic clearing
[b] hospital days *after* pneumonia diagnosis
[c] clinically evaluable population
[d] microbiologically confirmed and clinically evaluable population
[e] excludes patients with community acquired pneumonia and those with "indeterminate" clinical responses
[f] clinically evaluable population with confirmed VAP

[g] clinically evaluable patients with MRSA VAP
[h] Response rates are for mechanically ventilated patients
[I] Mortality is for all patients
[J] Median. IQR not reported
[k] variance not reported

| COMPLICATIONS | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rx A | Rx B | Acquired Resistance | | | Superinfection | | | Adverse Events | | |
| | | | A | B | Diff | A | B | Diff | A | B | Diff |
| Alvarez 2001 | Meropenem | Ceftaz-Amikacin | | | | 5/69 (7.2%) | 3/71 (4.2%) | NS | 31/69 (45%) | 35/71 (49%) | NS |
| Sieger 1997 | Meropenem | Ceftaz-Tobra | 3/106 (2.8%) | 7/105 (6.7%) | NS | -- | -- | -- | 23/106 (22%) | 20/105 (19%) | NS |
| Brown 1984 | Moxalactam | Carbenicillin-Tobra | -- | -- | -- | -- | -- | -- | 5/18 (28%) | 3/16 (19%) | NS |
| Kljucar 1987 | Ceftazidime | Ceftaz-Tobra | -- | -- | -- | 0/16 (0%) | 2/17 (12%) | NS | 4/16 (25%) | 1/17 (5.9%) | NS |
| Kljucar 1987 | Ceftazidime | Azlocillin-Tobra | -- | -- | -- | 0/16 (0%) | 0/17 (0%) | NS | 4/16 (25%) | 0/17 (0%) | NS |
| Chastre 2008 | Doripenem | Imipenem | 10/28 (36%)[a] | 10/19 (52%)[a] | NS | 20/249 (8.0%) | 28/252 (11%) | NS | 45/262 (17%) | 46/263 (18%) | NS |
| Kollef 2012 | Doripenem | Imipenem | -- | -- | -- | -- | -- | -- | 106/115 (92%) | 107/112 (96%) | NS |
| Hartenauer 1990 | Ceftazidime | Imipenem | -- | -- | -- | -- | -- | -- | 1/21 (4.8%) | 1/24 (4.2%) | NS |
| Torres 2000 | Ciprofloxacin | Imipenem | 1/14 (7.1%) | 4/12 (33%) | NS | -- | -- | -- | 21/72 (29%) | 14/77 (18%) | NS |
| Fink 1994 | Ciprofloxacin | Imipenem | 20/202 (10%) | 27/200 (14%) | NS | 28/202 (14%) | 41/200 (21%) | .10 | 132/202 (65%) | 148/200 (74%) | NS |
| Shorr 2005 | Levofloxacin | Imipenem | 1/16 (6.3%)[a] | 1/18 (5.6%)[a] | NS | 3/111 (2.7%) | 10/111 (9.0%) | .05 | 34/111 (31%) | 36/111 (32%) | NS |
| Réa Neto 2008 | Doripenem | Piperacillin-tazobactam | -- | -- | -- | -- | -- | -- | 67/223 (30%) | 58/221 (26%) | NS |
| Polk 1997 | Vancomycin Aztreonam | Imipenem | -- | -- | -- | 19/63 (30%) | 11/59 (19%) | NS | -- | -- | -- |
| Beaucaire 1995 | Isepamicin | Amikacin | -- | -- | -- | 3/44 (6.8%) | 2/41 (4.9%) | NS | 6/56 (11%) | 5/57 (9%) | NS |
| Ahmed 2007 | Cefepime-levofloxacin | Pip-tazo + Amikacin | -- | -- | -- | -- | -- | -- | 4/47 (8.5%) | 5/46 (11%) | NS |
| Beaucaire 1999 | Cefepime/ Amikacin | Ceftazidime/ Amikacin | -- | -- | -- | -- | -- | -- | 84/141 (60%) | 73/134 (54%) | |
| Croce 2003 | Cefoperazone | Ceftazidime | -- | -- | -- | 8/19 (42%) | 3/20 (15%) | | -- | -- | -- |
| Croce 2003 | Cefoperazone/ Gentamicin | Ceftazidime/ Gentamicin | -- | -- | -- | 17/35 (49%) | 17/35 (49%) | NS | -- | -- | -- |
| Reeves 1989 | Ceftriaxone | Cefotaxime | 0/25 (0%) | 1/26 (4%) | -- | -- | -- | -- | 0/25 (0%) | 0/26 (0%) | -- |
| Saginur 1997 | Ceftazidime | Ciprofloxacin | -- | -- | -- | -- | -- | -- | 4/77[b] | 7/72[b] | -- |

| COMPLICATIONS | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rx A | Rx B | Acquired Resistance | | | Superinfection | | | Adverse Events | | | |
| | | | A | B | Diff | A | B | Diff | A | B | Diff | |
| | | | | | | | | | (5%) | (10%) | | |
| Alvarez-Lerma 2001 | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | -- | -- | -- | 5/88 (6%) | 3/36 (8%) | -- | 21/88 (24%) | 5/36 (14%) | -- | |
| Bruin-Bruisson 1998 | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | -- | -- | -- | 4/46 (9%) | 12/58 (21%) | -- | 37/98 (38%) | 38/99 (38%) | NS | |
| Freire 2010 | Tigecycline +/- Ceftazidime | Imipenen +/- Vancomycin | -- | -- | -- | -- | -- | -- | 368/467 (79%) | 367/467 (79%) | NS | |
| Giamarellos-Bourboulis 2008 | Clarithro + usual therapy | usual therapy | -- | -- | -- | -- | -- | -- | 3/100 (3%) | 0/100 (0%) | NS | |
| Thomas 1994 | Ceftriaxone | Cefotaxime | -- | -- | -- | 16/53 (30%) | 7/40 (18%) | -- | -- | -- | -- | |
| Damas (A) 2006 | Cefipime | Cefipime - Amikacin | -- | -- | -- | -- | -- | | 1/20 (5%) | 3/19 (16%) | | |
| Damas (B) 2006 | Cefipime | Cefipime - Levofloxacin | -- | -- | -- | -- | -- | | 1/20 (5%) | 3/20 (15%) | | |
| Heyland 2008 | Meropenem | Meropenem -Cipro | 71/370 (19%) | 57/369 (15%) | | -- | -- | | 28/370 (8%) | 20/369 (5%) | | |
| Manhold 1998 | Cipro | Ceftazidime - Gentamicin | -- | -- | -- | 6/10 (60%) | 1/8 (13%) | -- | -- | -- | -- | |
| Fagon 2000 | Quinupritin/ Dalfopristin | Vancomycin | -- | -- | -- | -- | -- | -- | 36/150 (24%) | 29/148 (20%) | -- | |
| Wunderink[g] 2008 | Linezolid | Vancomycin | -- | -- | -- | -- | -- | -- | 19/74 (26%) | 23/72 (32%) | -- | |
| Wunderink 2012 | Linezolid | Vancomycin | -- | -- | -- | -- | -- | -- | 7/597 (1%) | 13/587 (2%) | -- | |
| Kollef 2004 | Linezolid | Vancomycin | -- | -- | -- | -- | -- | -- | -- | -- | -- | |

[a] Analysis limited to patients with susceptible Pseudomonas aeruginosa isolates at baseline
[b] AE for all patients

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Saginur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| **Mortality (all cause)** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | low risk of bias | really cannot tell | really cannot tell | not applicable | low risk of bias | really cannot tell | really cannot tell | really cannot tell | really cannot tell | really cannot tell | really cannot tell | low risk of bias | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | not applicable | really cannot tell | not applicable | really cannot tell | high risk of bias | low risk of bias | really cannot tell | low risk of bias | low risk of bias | not applicable | really cannot tell | low risk of bias | low risk of bias | really cannot tell | low risk of bias |
| Allocation concealment (selection bias) | low risk of bias | really cannot tell | really cannot tell | not applicable | low risk of bias | really cannot tell | really cannot tell | really cannot tell | really cannot tell | really cannot tell | really cannot tell | low risk of bias | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | not applicable | really cannot tell | not applicable | really cannot tell | high risk of bias | really cannot tell | really cannot tell | low risk of bias | low risk of bias | not applicable | really cannot tell | low risk of bias | low risk of bias | really cannot tell | low risk of bias |
| Blinding | probably low risk of bias | probably low risk of bias | probably low risk of bias | not applicable | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | not applicable | low risk of bias | not applicable | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | low risk of bias |
| ITT analysis performed | probably low risk of bias | probably low risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | probably low risk of bias | probably high risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | low risk of bias | low risk of bias | high risk of bias | low risk of bias | low risk of bias | not applicable | probably high risk of bias | not applicable | probably low risk of bias | high risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | not applicable | low risk of bias | probably high risk of bias | probably high risk of bias | probably high risk of bias | low risk of bias |
| Serious loss to follow-up | high risk of bias | probably low risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias |
| Selective outcome reporting | probably low risk of bias | probably low risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | not applicable | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias |
| Study stopped early | low risk of bias | probably low risk of bias | low risk of bias | not applicable | low risk of bias | probably high risk of bias | low risk of bias | probably high risk of bias | low risk of bias | low risk of bias | really cannot tell | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | probably high risk of bias | low risk of bias | really cannot tell | low risk of bias |
| **Number of ventilator days or ventilator-free days** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | really cannot tell | really cannot tell | not applicable | not applicable | not applicable | high risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Allocation concealment (selection bias) | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | really cannot tell | really cannot tell | not applicable | not applicable | not applicable | high risk of bias | really cannot tell | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Blinding | not | not | not | not | not | not | not | not | not | not | not | not | not | not | not | not | not | proba | high | not | not | not | high | low | not | low | high | not | not | not | not | not |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Sagin ur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | applicable | bly high risk of bias | risk of bias | applicable | applicable | applicable | risk of bias | risk of bias | applicable | risk of bias | risk of bias | applicable | applicable | applicable | applicable | applicable |
| ITT analysis performed | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | really cannot tell | low risk of bias | not applicable | low risk of bias | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Serious loss to follow-up | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | really cannot tell | low risk of bias | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Selective outcome reporting | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | probably low risk of bias | not applicable | not applicable | not applicable | really cannot tell | low risk of bias | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Study stopped early | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | really cannot tell | not applicable | not applicable | not applicable | really cannot tell | low risk of bias | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| **Length of ICU stay** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Allocation concealment (selection bias) | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Blinding | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | low risk of bias | not applicable | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| ITT analysis performed | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | low risk of bias | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable |
| Serious loss to follow-up | not applicable | not applicable | not applicable | not applicab | not applica | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applica | low risk of bias | not applicab | low risk of bias | not applica | not applica | not applicable | not applicable | not applic |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Saginur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| | | | | le | ble | | | | | | | | | | | | | | | | | ble | | le | | ble | ble | | | | able |
| Selective outcome reporting | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Study stopped early | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| **Length of hospital stay** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable |
| Allocation concealment (selection bias) | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable |
| Blinding | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | high risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable |
| ITT analysis performed | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable |
| Serious loss to follow-up | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable |
| Selective outcome reporting | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable |
| Study stopped early | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Sagnur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| **Clinical cure (as defined by the study authors)** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | low risk of bias | really cannot tell | really cannot tell | really cannot tell | low risk of bias | really cannot tell | really cannot tell | really cannot tell | really cannot tell | not applicable | really cannot tell | low risk of bias | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | really cannot tell | really cannot tell | really cannot tell | not applicable | not applicable | low risk of bias | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | low risk of bias | low risk of bias | not applicable | low risk of bias |
| Allocation concealment (selection bias) | low risk of bias | really cannot tell | really cannot tell | really cannot tell | low risk of bias | really cannot tell | really cannot tell | really cannot tell | really cannot tell | not applicable | really cannot tell | low risk of bias | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | really cannot tell | really cannot tell | really cannot tell | not applicable | not applicable | really cannot tell | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | low risk of bias | low risk of bias | not applicable | low risk of bias |
| Blinding | high risk of bias | probably high risk of bias | high risk of bias | high risk of bias | low risk of bias | low risk of bias | probably high risk of bias | high risk of bias | probably high risk of bias | not applicable | high risk of bias | high risk of bias | probably low risk of bias | high risk of bias | probably high risk of bias | probably high risk of bias | probably high risk of bias | high risk of bias | low risk of bias | probably high risk of bias | not applicable | not applicable | low risk of bias | probably high risk of bias | low risk of bias | high risk of bias | high risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias |
| ITT analysis performed | high risk of bias | probably low risk of bias | low risk of bias | high risk of bias | high risk of bias | low risk of bias | probably low risk of bias | high risk of bias | low risk of bias | not applicable | probably low risk of bias | high risk of bias | low risk of bias | low risk of bias | high risk of bias | low risk of bias | low risk of bias | high risk of bias | probably high risk of bias | probably high risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | high risk of bias | low risk of bias | probably high risk of bias | probably high risk of bias | not applicable | low risk of bias |
| Serious loss to follow-up | probably high risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias |
| Selective outcome reporting | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | not applicable | low risk of bias |
| Study stopped early | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | low risk of bias | probably low risk of bias | low risk of bias | not applicable | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | low risk of bias | not applicable | low risk of bias |
| **Recurrent pneumonia** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | not applicable | really cannot tell | not applicable | not applicable | not applicable | really cannot tell | really cannot tell | not applicable | not applicable | really cannot tell | really cannot tell | low risk of bias | not applicable | not applicable | not applicable | really cannot tell | really cannot tell | really cannot tell | not applicable | really cannot tell | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Allocation concealment (selection bias) | not applicable | really cannot tell | not applicable | not applicable | not applicable | really cannot tell | really cannot tell | not applicable | not applicable | really cannot tell | really cannot tell | low risk of bias | not applicable | not applicable | not applicable | really cannot tell | really cannot tell | really cannot tell | not applicable | really cannot tell | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Saginur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| Blinding | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | low risk of bias | probably high risk of bias | not applicable | not applicable | probably high risk of bias | high risk of bias | high risk of bias | not applicable | not applicable | not applicable | probably high risk of bias | probably high risk of bias | high risk of bias | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| ITT analysis performed | not applicable | probably low risk of bias | not applicable | not applicable | not applicable | low risk of bias | probably high risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | high risk of bias | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | probably high risk of bias | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Serious loss to follow-up | not applicable | probably low risk of bias | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Selective outcome reporting | not applicable | probably low risk of bias | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | probably high risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Study stopped early | not applicable | probably low risk of bias | not applicable | not applicable | not applicable | probably high risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| **Number of antibiotic days** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Allocation concealment (selection bias) | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Blinding | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| ITT analysis performed | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Serious loss to | high risk of | not applic | not applic | not appl | not app | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not applic | not app | not applic | not appl | not applic | not app | not app | not applic | not applic | not applic | not ap |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Saginur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| follow-up | bias | able | able | icable | licable | able | able | able | able | able | able | able | able | able | able | able | able | able | able | able | able | able | licable | able | icable | able | licable | licable | able | able | able | plicable |
| Selective outcome reporting | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Study stopped early | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| **Development of resistance** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | not applicable | not applicable | really cannot tell | not applicable | low risk of bias | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | low risk of bias | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Allocation concealment (selection bias) | not applicable | not applicable | really cannot tell | not applicable | low risk of bias | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | really cannot tell | not applicable | not applicable | really cannot tell | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Blinding | not applicable | not applicable | high risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | low risk of bias | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| ITT analysis performed | not applicable | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | low risk of bias | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Serious loss to follow-up | not applicable | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Selective outcome reporting | not applicable | not applicable | low risk of bias | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | low risk of bias | probably high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable |
| Study stopped early | not applicable | not applicable | low risk of bias | not applicable | low risk of bia | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicabl |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Sagingur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| | | | | | s | | | | | | | | | | | | | | | | | | | | | | | | | | e |
| **Any adverse effect** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | low risk of bias | really cannot tell | really cannot tell | really cannot tell | low risk of bias | not applicable | really cannot tell | really cannot tell | really cannot tell | not applicable | not applicable | low risk of bias | really cannot tell | low risk of bias | low risk of bias | really cannot tell | really cannot tell | not applicable | not applicable | really cannot tell | really cannot tell | high risk of bias | low risk of bias | really cannot tell | low risk of bias | low risk of bias | low risk of bias | really cannot tell | low risk of bias | low risk of bias | not applicable | low risk of bias |
| Allocation concealment (selection bias) | low risk of bias | really cannot tell | really cannot tell | really cannot tell | low risk of bias | not applicable | really cannot tell | really cannot tell | really cannot tell | not applicable | not applicable | low risk of bias | really cannot tell | low risk of bias | high risk of bias | really cannot tell | really cannot tell | not applicable | not applicable | really cannot tell | really cannot tell | high risk of bias | really cannot tell | really cannot tell | low risk of bias | low risk of bias | low risk of bias | really cannot tell | low risk of bias | low risk of bias | not applicable | low risk of bias |
| Blinding | high risk of bias | probably high risk of bias | high risk of bias | high risk of bias | low risk of bias | not applicable | probably high risk of bias | high risk of bias | probably high risk of bias | not applicable | not applicable | high risk of bias | probably low risk of bias | high risk of bias | high risk of bias | probably high risk of bias | probably high risk of bias | not applicable | not applicable | probably high risk of bias | probably high risk of bias | high risk of bias | low risk of bias | probably high risk of bias | low risk of bias | high risk of bias | high risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias |
| ITT analysis performed | high risk of bias | probably low risk of bias | low risk of bias | high risk of bias | low risk of bias | not applicable | probably high risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | probably high risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | low risk of bias | low risk of bias | probably high risk of bias | probably high risk of bias | not applicable | low risk of bias |
| Serious loss to follow-up | high risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias |
| Selective outcome reporting | probably high risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | probably low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | not applicable | low risk of bias |
| Study stopped early | probably high risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | not applicable | low risk of bias | probably high risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | low risk of bias | | low risk of bias | low risk of bias | not applicable | not applicable | low risk of bias | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | low risk of bias | not applicable | low risk of bias |
| **Serious adverse effect** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Random sequence generation (selection bias) | really cannot tell | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias |
| Allocation concealment (selection bias) | really cannot tell | not applicable | really cannot tell | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | low risk of bias |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Brown 1984** | **Klujcar 1987** | **Reeves 1989** | **Hartenauer 1990** | **Fink 1994** | **Thomas 1994** | **Beaucaire 1995** | **Saginur 1997** | **Sieger 1997** | **Polk 1997** | **Manhold 1998** | **Bruin-Bruisson 1998** | **Beaucaire 1999** | **Fagon 2000** | **Torres 2000** | **Alvarez-Lerma 2001** | **Alvarez 2001** | **Croce 2003** | **Kollef 2004** | **Shorr 2005** | **Damas 2006** | **Ahmed 2007** | **Heyland 2008** | **Chastre 2008** | **Giamarellos 2008** | **Wunderink 2008** | **Rea-Neto 2008** | **Freire 2010** | **Kollef 2012** | **Wunderink 2012** | **Maskin 2002** | **Joshi 2006** |
| Blinding | really cannot tell | not applicable | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | high risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias |
| ITT analysis performed | really cannot tell | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias |
| Serious loss to follow-up | really cannot tell | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias |
| Selective outcome reporting | really cannot tell | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias |
| Study stopped early | really cannot tell | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | not applicable | low risk of bias | not applicable | not applicable | not applicable | not applicable | low risk of bias |

**SUMMARY OF META-ANALYSES COMPARING DIFFERENT CLASSES OF GRAM-NEGATIVE AGENTS FOR EMPIRIC TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA**

| Comparison | Mortality<br><br>Risk Ratio (95% CI) | Clinical Response<br><br>Risk Ratio (95% CI) | Acquired Resistance<br><br>Risk Ratio (95% CI) | Adverse Events<br><br>Risk Ratio (95% CI) |
|---|---|---|---|---|
| **Combination versus monotherapy[24-27, 44, 48, 49]** | 1.11 (0.90, 1.38) | 0.89 (0.75, 1.07) | 1.13 (0.42, 3.00) | 0.90 (0.69, 1.18) |
| **Cephalosporin versus non-cephalosporin regimens[25, 27, 36, 39-41, 49]** | 0.97 (0.74, 1.27) | 0.92 (0.78, 1.09) | 2.36 (0.63, 8.86) | 1.01 (0.82, 1.25) |
| **Quinolone versus non-quinolone regimens [30-32, 36, 39, 44, 48, 49]** | 1.13 (0.92, 1.39) | 1.05 (0.91, 1.20) | 0.77 (0.59, 1.01) | 0.88 (0.78, 0.99) |
| **Anti-Pseudomonal penicillin versus non-anti-Pseudomonal penicillin regimens [33, 36, 40, 41]** | 1.12 (0.76, 1.66) | 1.10 (0.80, 1.52) | Not Reported | 0.96 (0.77, 1.20) |
| **Aminoglycoside versus non-aminoglycoside regimens[24-27, 36, 48, 49]** | 1.15 (0.88, 1.50) | 0.82 (0.71, 0.95) | Not Reported | 0.96 (0.70, 1.33) |
| **Carbapenem versus non-carbapenem regimens [24, 25, 30-32, 34, 42, 50, 51]** | 0.78 (0.65, 0.94) | 1.02 (0.93, 1.12) | 1.16 (0.53, 2.55) | 1.08 (0.90, 1.28) |

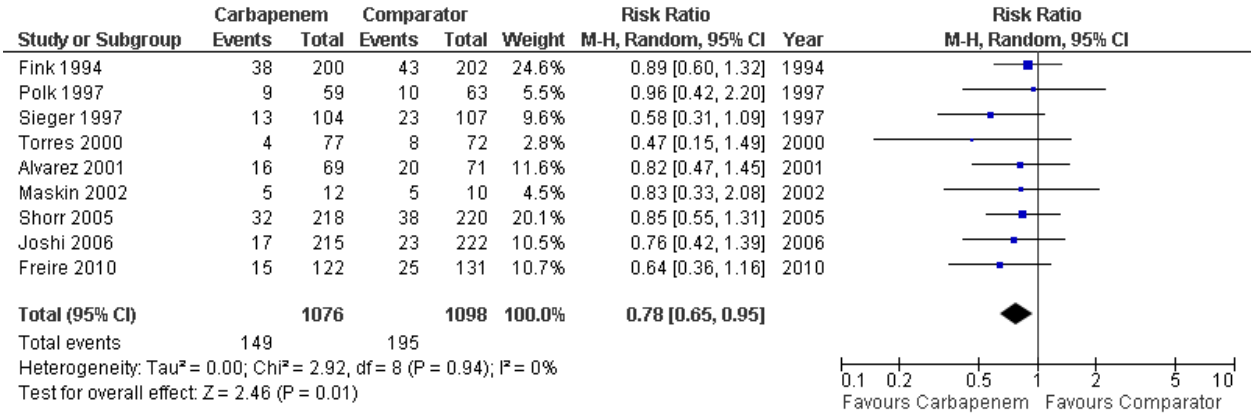
| COMPARISON OF MONOTHERAPY VS COMBINATION THERAPY FOR THE TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP) - OUTCOME: All-cause mortality | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Monotherapy $n_1$** | **Monotherapy N** | **Combination $n_1$** | **Combination N** | **Relative Risk (RR)** | **Standard Error of RR** | **RR 95% CI (lower bound)** | **RR 95% CI (upper bound)** | **Statistical Significance** |
| Brown 1984 | 11 | 18 | 9 | 16 | 1.086 | 0.2898 | 0.616 | 1.917 | Not significant |
| Kljucar 1987 | 0.33 | 16 | 1 | 17 | 0.351 | 1.9771 | 0.007 | 16.896 | Not significant |
| Cometta 1994 | 13 | 91 | 12 | 86 | 1.024 | 0.3710 | 0.495 | 2.118 | Not significant |
| Sieger 1997 | 10 | 104 | 17 | 107 | 0.605 | 0.3740 | 0.291 | 1.260 | Not significant |
| Manhold 1998 | 13 | 28 | 6 | 23 | 1.780 | 0.4055 | 0.804 | 3.940 | Not significant |
| Alvarez-Lerma 2001 | 16 | 69 | 20 | 71 | 0.823 | 0.2897 | 0.467 | 1.452 | Not significant |
| Heyland 2005 | 67 | 370 | 71 | 369 | 0.941 | 0.1536 | 0.696 | 1.272 | Not significant |
| Damas 2006 | 2 | 24 | 9 | 50 | 0.463 | 0.7412 | 0.108 | 1.979 | Not significant |
| **TOTAL** | **132.33** | **720** | **145** | **739** | **0.937** | **0.1082** | **0.758** | **1.158** | **Not significant** |
| **Study** | **Monotherapy Risk** | **Combination Risk** | **Risk Difference (RD)** | | | | | | |
| Brown 1984 | 0.611 | 0.563 | 0.049 | | 49 | more | | | |
| Kljucar 1987 | 0.021 | 0.059 | -0.038 | | -38 | fewer | | | |
| Cometta 1994 | 0.143 | 0.140 | 0.003 | | 3 | more | | | |
| Sieger 1997 | 0.096 | 0.159 | -0.063 | | -63 | fewer | | | |
| Manhold 1998 | 0.464 | 0.261 | 0.203 | which are | 203 | more | monotherapy subjects per 1,000 at risk | | |
| Alvarez-Lerma 2001 | 0.232 | 0.282 | -0.050 | | -50 | fewer | | | |
| Heyland 2005 | 0.181 | 0.192 | -0.011 | | -11 | fewer | | | |
| Damas 2006 | 0.083 | 0.180 | -0.097 | | -97 | fewer | | | |
| **MEDIAN** | **0.162** | **0.186** | **-0.025** | | **-25** | **fewer** | | | |
| **Combination ("control/standard") risk:** | **0.186** | **which is** | **186** | **per 1,000** | | | | | |
| **with RD of** | **25** | **fewer monotherapy subjects per 1,000 at risk** | | | | | | | |
| | this is not-significant (based on RR 95% CI; specific RD 95% CI provided below, FYI) | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy $n_2$** | **Monotherapy N** | **Combination $n_1$** | **Combination $n_2$** | **Combination N** | | | |
| Brown 1984 | 11 | 7 | 18 | 9 | 7 | 16 | | | |
| Kljucar 1987 | 0.33 | 15.67 | 16 | 1 | 16 | 17 | | | |
| Cometta 1994 | 13 | 78 | 91 | 12 | 74 | 86 | | | |
| Sieger 1997 | 10 | 94 | 104 | 17 | 90 | 107 | | | |
| Manhold 1998 | 13 | 15 | 28 | 6 | 17 | 23 | | | |
| Alvarez-Lerma 2001 | 16 | 53 | 69 | 20 | 51 | 71 | | | |
| Heyland 2005 | 67 | 303 | 370 | 71 | 298 | 369 | | | |
| Damas 2006 | 2 | 22 | 24 | 9 | 41 | 50 | | | |

| COMPARISON OF MONOTHERAPY VS COMBINATION THERAPY FOR THE TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP) - OUTCOME: All-cause mortality | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **TOTAL** | **132.33** | **587.67** | **720** | **145** | **594** | **739** | | | |
| **Study** | **Standard Error of RD** | **RD 95% CI (lower bound)** | **RD 95% CI (upper bound)** | | | | | | |
| Brown 1984 | 0.169 | -0.283 | 0.380 | | -283 | | 380 | | |
| Kljucar 1987 | 0.067 | -0.170 | 0.094 | | -170 | | 94 | | |
| Cometta 1994 | 0.052 | -0.099 | 0.106 | | -99 | | 106 | | |
| Sieger 1997 | 0.046 | -0.152 | 0.027 | | -152 | | 27 | | |
| Manhold 1998 | 0.131 | -0.054 | 0.461 | which are | -54 | to | 461 | 95% CI per 1,000 subjects | |
| Alvarez-Lerma 2001 | 0.074 | -0.194 | 0.095 | | -194 | | 95 | | |
| Heyland 2005 | 0.029 | -0.068 | 0.045 | | -68 | | 45 | | |
| Damas 2006 | 0.078 | -0.250 | 0.057 | | -250 | | 57 | | |
| **TOTAL** | **0.021** | **-0.065** | **0.103** | | **-65** | | **103** | | |

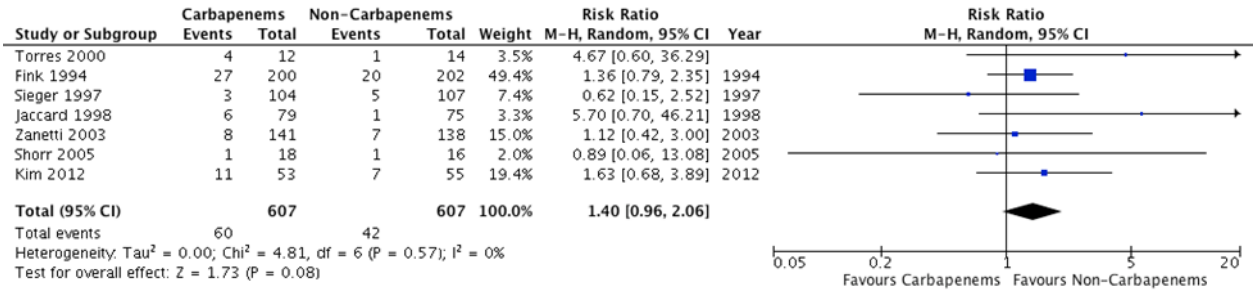
| COMPARISON OF MONOTHERAPY VS COMBINATION THERAPY FOR THE TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP) - OUTCOME: Treatment Failure | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Monotherapy $n_1$** | **Monotherapy N** | **Combination $n_1$** | **Combination N** | **Relative Risk (RR)** | **Standard Error of RR** | **RR 95% CI (lower bound)** | **RR 95% CI (upper bound)** | **Statistical Significance** |
| Rapp 1984 | 2 | 17 | 3 | 18 | 0.706 | 0.8479 | 0.134 | 3.720 | Not significant |
| Kijucar 1987 | 4 | 16 | 4 | 16 | 1.000 | 0.6124 | 0.301 | 3.321 | Not significant |
| Cometta 1994 | 16 | 91 | 14 | 86 | 1.080 | 0.3336 | 0.562 | 2.077 | Not significant |
| Rubinstein 1995 | 43 | 159 | 48 | 138 | 0.778 | 0.1748 | 0.552 | 1.095 | Not significant |
| Sieger 1997 | 30 | 106 | 43 | 105 | 0.691 | 0.1940 | 0.473 | 1.011 | Not significant |
| Alvarez-Lerma M-2001 | 22 | 69 | 32 | 71 | 0.707 | 0.2194 | 0.460 | 1.087 | Not significant |
| Heyland 2005 | 155 | 370 | 140 | 369 | 1.104 | 0.0905 | 0.925 | 1.318 | Not significant |
| **TOTAL** | **272** | **828** | **284** | **803** | **0.929** | **0.0689** | **0.812** | **1.063** | **Not significant** |
| | | | | | | | | | |
| **Study** | **Monotherapy Risk** | **Combination Risk** | **Risk Difference (RD)** | | | | | | |
| Rapp 1984 | 0.118 | 0.167 | -0.049 | | -49 | fewer | | | |
| Kijucar 1987 | 0.250 | 0.250 | 0.000 | | 0 | no difference | | | |
| Cometta 1994 | 0.176 | 0.163 | 0.013 | | 13 | more | | | |
| Rubinstein 1995 | 0.270 | 0.348 | -0.077 | | -77 | fewer | | | |
| Sieger 1997 | 0.283 | 0.410 | -0.127 | which are | -127 | fewer | monotherapy subjects per 1,000 at risk | | |
| Alvarez-Lerma M-2001 | 0.319 | 0.451 | -0.132 | | -132 | fewer | | | |
| Heyland 2005 | 0.419 | 0.379 | 0.040 | | 40 | more | | | |
| **MEDIAN** | **0.270** | **0.348** | **-0.049** | | **-49** | **fewer** | | | |
| | | | | | | | | | |

| COMPARISON OF MONOTHERAPY VS COMBINATION THERAPY FOR THE TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP) - OUTCOME: Treatment Failure | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Combination ("control/standard") risk:** | **0.348** | **which is** | **348** | **per 1,000** | | | | | |
| | | | | | | | | | |
| **with RD of** | **49** | **fewer monotherapy subjects per 1,000 at risk** | | | | | | | |
| | this is not-significant (based on RR 95% CI; specific RD 95% CI provided below, FYI) | | | | | | | | |
| | | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy $n_2$** | **Monotherapy N** | **Combination $n_1$** | **Combination $n_2$** | **Combination N** | | | |
| Rapp 1984 | 2 | 15 | 17 | 3 | 15 | 18 | | | |
| Kijucar 1987 | 4 | 12 | 16 | 4 | 12 | 16 | | | |
| Cometta 1994 | 16 | 75 | 91 | 14 | 72 | 86 | | | |
| Rubinstein 1995 | 43 | 116 | 159 | 48 | 90 | 138 | | | |
| Sieger 1997 | 30 | 76 | 106 | 43 | 62 | 105 | | | |
| Alvarez-Lerma M-2001 | 22 | 47 | 69 | 32 | 39 | 71 | | | |
| Heyland 2005 | 155 | 215 | 370 | 140 | 229 | 369 | | | |
| **TOTAL** | **272** | **556** | **828** | **284** | **519** | **803** | | | |
| | | | | | | | | | |
| **Study** | **Standard Error of RD** | **RD 95% CI (lower bound)** | **RD 95% CI (upper bound)** | | | | | | |
| Brown 1984 | 0.118 | -0.279 | 0.181 | | -279 | | 181 | | |
| Kljucar 1987 | 0.153 | -0.300 | 0.300 | | -300 | | 300 | | |
| Cometta 1994 | 0.056 | -0.097 | 0.124 | | -97 | | 124 | | |
| Sieger 1997 | 0.054 | -0.183 | 0.028 | | -183 | | 28 | | |
| Manhold 1998 | 0.065 | -0.254 | 0.001 | which are | -254 | to | 1 | 95% CI per 1,000 subjects | |
| Alvarez-Lerma 2001 | 0.081 | -0.292 | 0.028 | | -292 | | 28 | | |
| Heyland 2005 | 0.036 | -0.031 | 0.110 | | -31 | | 110 | | |
| **TOTAL** | **0.023** | **-0.095** | **0.137** | | **-95** | | **137** | | |

**Meta-analysis of mortality in trials studying carbapenem vs. non-carbapenem regimens for the treatment of VAP [52].**




**Meta-analysis of carbapenem resistance development with the use of carbapenem vs. non-carbapenem regimens for VAP/HAP.**




| Probability of developing carbapenem resistance with the use of carbapenems vs. non-carbapenems |
|---|
| |
| Carbapenem vs. Other (7 studies: N=1,214 patients) |
| Outcome: Acquired Resistance |
| Relative Risk (RR) = 1.40 (0.95, 2.06); P = 0.083; N = 1,214 |
| Number Needed to Harm (NNH) = 50 |
| Real-life Application for the NNH: |
| # NNT adjusted according the patient's expected event rate (PEER) or baseline risk. |
| If acquired resistance rate in your hospital is 2%: NNH = 125 |
| If acquired resistance rate in your hospital is 3%: NNH = 83 |
| If acquired resistance rate in your hospital is 5%: NNH = 50 |
| If acquired resistance rate in your hospital is 7%: NNH = 36 |
| If acquired resistance rate in your hospital is 10%: NNH = 25 |
| Real-life Application for the Relative Risk Increase (RRI): |
| # Bayesian posterior probability that carbapenems increase acquired resistance by a specific clinical threshold (RRI). |
| RRI>0%: 96% |
| RRI>2.5%: 94% |
| RRI>5%: 93.0% |
| RRI>7.5%: 91.0% |
| RRI>10%: 89.0% |

## XII. What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)?

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Type of information (published or unpublished) | published | published | published | published | published | published | published | published | published | published |
| Journal name | Infection | Diagnost Microbiol Infect Dis | Respiratory Medicine | Infection | Eur J Clin Micro Inf Dis | Can J Infect Dis | Infection | Curr Med Res Op | Clin Infect Dis | Critical Care |
| Language of publication | English | English | English | English | English | English | English | English | English | English |
| Funding body | Not mentioned, probably industry | Wyeth | Probably Wyeth, but not stated | Unknown | Probably Merck | Bayer | Wyeth | Johnson & Johnson | Astellas | Not reported |
| Ethics approval | Not mentioned | Yes | yes | Not mentioned | Yes | Yes | Yes | Yes | Yes | Yes |
| Country where study was done | Europe, Austral, Israel, Mex, Turk | 31 countries | US/Canada | Spain,Others | USA, Russia, others | Canada | Germany, Czech Republic, Hungary | Argentina, Belarus, Brazil,Canada, Chile,Georgia, Russia, South Africa, Ukaine, USA | Multinational | Korea |
| Years study done | 2000-2002 | 2004-2006 | 1997-2001 | 1988-1989 | Not known | | | | | |
| **METHODS** | | | | | | | | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | | | | | | | | |
| Randomization | stated as random but no description | stated as random but no description | truly random | truly random | truly random | truly random | stated as random but no description | stated as random but no description | truly random | truly random |
| Concealment | no | probably yes | yes | no | probably yes | no | yes | no | yes | yes |
| Not stopped early | stopped for low accrual | not stopped early | not stopped early | not stopped early | not stopped early | stopped for low accrual | stopped for low accrual | not stopped early | not stopped early | not stopped early |
| NOTES: | | | | block randomization | | | | | | |
| ***if COHORT STUDY*** | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | | | | representative of such patients in reality | representative of such patients in reality | | | representative of such patients in reality |
| Selection of the non exposed cohort | | | | | | same sample as exposed | same sample as exposed | | | same sample as exposed |
| Ascertainment of exposure | | | | | | secure record (e.g. hospital) | secure record (e.g. hospital) | | | secure record (e.g. hospital) |
| Demonstration that outcome of interest was not present at start of study | | | | | | secure record (e.g. hospital) | secure record (e.g. hospital) | | | secure record (e.g. hospital) |
| Comparability of cohorts on the basis of the design or analysis | | | | | | does not control for any factor | does not control for any factor | | | does not control for any factor |
| Assessment of outcome | | | | | | record linkage (e.g. hospital) | record linkage (e.g. hospital) | | | record linkage (e.g. hospital) |
| Was follow-up long enough for outcomes to occur? | | | | | | yes | yes | | | yes |
| Adequacy of follow up of cohorts | | | | | | at least 80% followed-up | at least 80% followed-up | | | at least 80% followed-up |
| Co-Interventions similar between groups? | | | | | | probably yes | probably yes | | | probably yes |
| NOTES: | | | | | | | | | | |
| ***if CASE-CONTROL STUDY*** | | | | | | | | | | |
| Is case definition adequate? | | | | | | | | | | |
| Representativeness of the cases | | | | | | | | | | |
| Selection of controls | | | | | | | | | | |
| Definition of controls | | | | | | | | | | |
| Comparability of cases and controls | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Ascertainment of exposure | | | | | | | | | | |
| Same method of ascertainment for cases and controls | | | | | | | | | | |
| Non-response rate | | | | | | | | | | |
| Co-interventions similar between groups? | | | | | | | | | | |
| NOTES: | | | | | | | | | | |
| | | | | | | | | | | |
| **INTERVENTIONS BEING COMAPRED** | | | | | | | | | | |
| **Intervention 1 (experimental)** | Moxiflox 400 IV qd | tigecycline 100 followed by 50 q12 | Piperacillin-tazobactam 1g q6h | cefotaxime starting 2 q 8, when improved-2 q 12 | ertapenem 1 gm qd | Cipro 300mg IV q12 | piperacillin-tazobactam 4.5g q8h | doripenem 500mg q8 | Telavancin 10mg/kg/24h | Imipenem and vanco with de-escalation |
| other Tx used (if relevant for interpretation) | switch to oral moxi | optional ceftaz/aminoglycoside/vanco | tobra until pathogen IDed | none | vanco for suspected MRSA | step down to oral cipro (750 q12) by clinical response | | Then PO levofloxacin 750 qd | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | | |
| **Intervention 2 (comparison)** | ceftriaxone 2 gm IV qd | imipenem 500-1000 q8 | Imipenem 500mg q6 | various combination therapy | Cefipime 2 gm q 12 | Ceftazidime 2g IV q8 | Imipenem-cilastatin 1g q8 | piperacillin-tazobactam 4.5g q6h | Vancomycin 1g q12h | Standard without de-escalation |
| other Tx used (if relevant for interpretation) | switch to oral cefuroxime | optional ceftaz/aminoglycoside/vanco | tobra until pathogen IDed | | Flagyl if anaerobes suspected, vanco prn | never oral | | Then PO levofloxacin 750 qd | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | | |
| duration of treatment | 7-14, switch at discretion p | 7-14 days | 5-21 days | at least 3 days | at least 3 days | 12.1d for cipro | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| | day 3 | | | after clinical remission | of IV rx | and 9.8d for ceftazidime | | | | |
| NOTES: | | | | | | | | | | |
| **BASELINE CHARACTERISTICS** | | most reported for VAP and HAP combined, thus unavailable | most reported for VAP and HAP combined | | | | | | | |
| **Number randomised** | | | | | | | | | | |
| Intervention | 78 | 313 | 222 | 280 | 153 | 72 | 110 | 225 | 767 | 54 |
| Comparison | 83 | 313 | 215 | 308 | 150 | 77 | 111 | 223 | 765 | 55 |
| Total (only if not reported separately) | | | | | | | | | | |
| **Age** | | | | | | | | | | |
| Intervention (mean or median) | 67 | | 52.2 | 67 | 68 | 60.9 | 68.4 | 57.5 | 62 | 66 |
| Comparison (mean or median) | 65 | | 52.4 | 65 | 66 | 62.26 | 65.7 | 59.3 | 63 | 62 |
| Total (mean or median) (only if not reported separately) | | | | | | | | | | |
| unit (e.g. mean and SD) | mean (SD) | | | median (IQR) | mean (SD) | mean (SE) | mean (SD) | mean (SD) | mean (SD) | median (IQR) |
| Age range (e.g. 22-73) | | | | 18-96 | | | | | | |
| Age inclusion criterion (e.g. older than 16) | >17 | | | not specified | 18 or above | >17 | >17 | >17 | | |
| **Male gender** | | | | | | | | | | |
| Intervention | 49.00% | | 80.00% | 69.00% | 50.00% | 34.72% | 70.00% | 73.10% | 65.00% | 79.60% |
| Comparison | 57.00% | | 60.00% | 70.00% | 47.10% | 65.28% | 57.66% | 62.20% | 62.00% | 81.80% |
| Total (only if not reported separately) | | | | | | | | | | |
| **Severity of illness** | | | | | | | | | | |
| Name of score (e.g. APACHE, SOFA, ...) | Apache II | | Apache II | | Apache II>15 | nr | Apache II | Apache II | Apache II | Apache II |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Intervention group mean score | 11.5 | | | | 44 | nr | 13.5 | <15 | 15 | 23.3 |
| Comparison group mean score | 10.2 | | 14 | | 44 | nr | 13.3 | <15 | 16 | 22.8 |
| Total (only if not reported separately) | | | 13 | | | | | | | |
| **Study population** | | | | | | | | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Not defined | Not Defined | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | Medical | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | |
| NOTES:A28 | | | | | | | | | | |
| **VAP patients included** | | | | | | | | | | |
| Intervention | 8 | | 71% | 0 | 0 | 38 | 28 | 29 | 216 | 4 |
| Comparator | 6 | | 67% | 0 | 0 | 39 | 19 | 26 | 211 | 5 |
| **Exclusions** | Severe HAP (Apache > 20, shock), | | | | | mild infection not requiring antibiotics | Shock | Resistance to meropenem | Antibiotics >24h in the 72h prior study | antibiotics for more than 48h, and previous diagnosis of pneumonia |
| | risks for non-fermenters (dialysis, | prior Abx>24 for current episode, immunosuppressed, Apache II>30, structural lung disease except COPD, known non bacterial infxn, LFT issues | Previous antibiotics | | Immunocomp, vent, ICU, CA, others | high risk of death in 72h | APACHE II <8 or >25 | APACHE II <8 or >25 | Neutropenia < 500 | |
| | vent>5 days, immunosuppression) | | | | | prior use of antibiotics | prior use of antibiotics last 24h | Antibiotics >24h in the 72h prior study | | |
| **Prior Antibiotics** | | | | | | | | | | |
| Intervention | 40 | | | 0 | | excluded | excluded | excluded | excluded | excluded |
| Comparator | 42 | | | 0 | | excluded | excluded | excluded | excluded | excluded |
| **Organisms Cultured** | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Are the data available? | Partial | yes | yes | no | | | | | | |
| **Intervention (n)** | 77 | 194 | 160 | | | 2 | nr | 22 | 34 | 29 |
| No organisms cultured | | unknown | | | | 9 | nr | 32 | 136 | 25 |
| Non-fermenters/ESBL/Other potentially MDR GNR | 2 | 22 | 22 | | | | | | | 4 |
| MRSA | | 17 | 24 | | | | | | | 8 |
| Other | | 123 | | | | | | 32 | 22 | |
| **Comparator (n)** | 82 | 189 | 137 | | | 2 | nr | 36 | 154 | 25 |
| No organisms cultured | | unknown | | | | 9 | nr | | | 30 |
| Non-fermenters/ESBL/Other potentially MDR GNR | 2 | 31 | 20 | | | | | | | 5 |
| MRSA | | 19 | 23 | | | | | | | 4 |
| Other | | 100 | | | | | | | | |
| **OUTCOMES** | | | | | | Data available | | | Data available | |
| | | | | | | Hospital | Hospital | Hospital | Hospital | Hospital |
| **Mortality (all cause)** | | | | | | 8 | 17 | 30 | 150 | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | 72 | 107 | 217 | 751 | Data available |
| location or duration of follow-up (choose from the list) | 21-31 days after completion of Rx | 10-21 days after completion of Rx | | Short term, but exact time/location not known | 14 days after completion of Tx | 6 | 11 | 31 | 140 | Hospital |
| Intervention group: # with event | 8 | 41 | 23 | 36 | 21 | 77 | 110 | 212 | 752 | 23 |
| Intervention group: Total | 77 | 336 | 222 | 275 | 148 | no | yes | no | yes | 53 |
| Comparison group: # with event | 11 | 43 | 17 | 52 | 20 | no | yes | no | probably yes | 18 |
| Comparison group: Total | 82 | 34 | 215 | 273 | 150 | no | probably yes | yes | probably yes | 55 |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Blinding [patients] (only relevant for RCTs) | no | yes | yes | probably no | yes | no | probably yes | probably yes | probably yes | no |
| Blinding [personnel] (only relevant for RCTs) | no | yes | yes | no | yes | no | probably yes | probably no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no | yes | yes | no | yes | probably yes | yes | no | no | no |
| Blinding [data collectors] (only relevant for RCTs) | no | yes | yes | no | yes | | | | | |
| Blinding [analysts] (only relevant for RCTs) | no | probably no | probably yes | probably no | probably yes | | | | | |
| ITT analysis performed (only relevant for RCTs) | yes | yes | yes | yes | yes | Not reported | Not reported | Not reported | Not reported | no |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not measured | | | | | | |
| Duration of follow-up [days] | | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Comparison group: (variance) | | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Not reported | Not reported | Not reported | Not reported | |
| NOTES: | | | | | | | | | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not measured | | | | | | |
| Duration of follow-up [days] | | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Intervention group: total number of patients | | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Not reported | Not reported | Not reported | Not reported | |
| NOTES: | | | | | | | | | | |
| **Length of ICU stay** | | | | | | | | | | |
| Are the data available? | Not reported | Data available | | Not measured | | | | | | Data available |
| Duration of follow-up [days] | | same | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | | |
| Intervention group: | | | | | | | | | | 21.1 |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| (mean or median) | | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | | 14.1 |
| Comparison group: (variance) | | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Not reported | Not reported | Not reported | Not reported | no |
| NOTES: | | reported only as difference NS | | | | | | | | |
| **Length of hospital stay** | | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Not measured | Not measured | Not reported | | | | | |
| Duration of follow-up [days] | | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| How data were reported (mean or median and type of variance) | | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Data available | Data available | Data available | Data available | |
| NOTES: | | | | | | End of Therapy | Second follow up at 14+-4 days | Test of cure visit 6-20 days | Follow up/Test of cure | |
| **Clinical cure (as** | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| **defined by the study authors)** | | | | | | | | | | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | 17 | 66 | 109 | 441 | |
| Definition (provide details if relevant) | resolution/indeterm./failure | | | MD determination | MD Assessment | 34 | 110 | 134 | 749 | |
| Duration of follow-up (time point when outcome was measured) [days] | 4-15 days after completion of Rx | same | 7-21 days after last Rx | not given | 7-14 days after Rx done | 23 | 74 | 95 | 449 | |
| Intervention group: # with resolution | 56 | 217 | 40 | 217 | 109 | 38 | 111 | 119 | 754 | |
| Intervention group: Total | 77 | 313 | 65 | 275 | 146 | no | probably yes | no | probably yes | |
| Comparison group: # with resolution | 58 | 223 | 43 | 193 | 101 | no | probably yes | probably no | probably yes | |
| Comparison group: Total | 82 | 313 | 72 | 273 | 144 | no | probably yes | probably yes | probably yes | |
| Blinding [patients] (only relevant for RCTs) | no | yes | yes | probably no | yes | no | probably yes | probably no | probably yes | |
| Blinding [personnel] (only relevant for RCTs) | no | yes | yes | no | yes | no | probably yes | probably no | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | yes | yes | no | yes | probably yes | probably yes | probably no | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | yes | yes | no | yes | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | probably no | probably no | probably no | probably yes | | | | | |
| ITT analysis performed (only relevant for RCTs) | yes | yes | yes | yes | yes | Data available | Data available | Data available | Data available | |
| NOTES: | | | | | | | | | | |
| **Recurrent pneumonia** | | | | | | 0 | 5 | 4 | 10 | |
| Are the data available? | Not reported | Not reported | Not reported | | Not reported | 72 | 107 | 134 | 749 | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Duration of follow-up [days] | | | | | | 1 | 5 | 5 | 16 | |
| Intervention group: # with event | | | | | | 77 | 110 | 119 | 754 | |
| Intervention group: Total | | | | | | no | probably yes | probably no | probably no | |
| Comparison group: # with event | | | | | | no | probably yes | probably no | probably no | |
| Comparison group: Total | | | | | | no | probably yes | probably no | probably no | |
| Blinding [patients] (only relevant for RCTs) | | | | | | no | probably yes | no | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | no | probably yes | probably no | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Not reported | Data available | Data available | Not reported | |
| NOTES: | | | | | | | | | | |
| **Number of antibiotic days** | | | | | | | | | | |
| Are the data available? | Not reported | Not reported | | | Not reported | | | | mean (SD) | |
| Duration of follow-up [days] | | | | | | | 8.7 | 10 | | |
| unit (days, hours, etc.) | | | | | | | 3.1 | | | |
| How data were reported (mean or median and type of variance) | | | | | | | 107 | 134 | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Intervention group: (mean or median) | | | | | | | 9 | 9 | 12.5 | |
| Intervention group: (variance) | | | | | | | 3.1 | | | |
| Intervention group: total number of patients | | | | | | | 110 | 119 | 14.1 | |
| Comparison group: (mean or median) | | | | | | | probably yes | no | yes | |
| Comparison group: (variance) | | | | | | | probably yes | no | yes | |
| Comparison group: total number of patients | | | | | | | probably yes | no | yes | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | probably yes | no | no | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | probably yes | no | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | no | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Not reported | Not reported | Not reported | Not reported | |
| NOTES: | | | | | | | | | | |
| **Development of resistance (as defined by the study authors)** | | | | | | | | | | |
| Are the data available? | Not reported | Not reported | | | Not reported | | | | | Data available |
| Duration of follow-up [days] | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Intervention group: # with event | | | | | | | | | | 37.90% |
| Intervention group: Total | | | | | | | | | | |
| Comparison group: # with event | | | | | | | | | | 16.70% |
| Comparison group: Total | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | no |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | no |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | no |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | Data available | Data available | Not reported | | |
| NOTES: | | | | | | | | | | |
| **Any adverse effect** | | | | | drug related only | 7 | 82 | | 616 | |
| Are the data available? | | Not reported | | Not reported | Data available | 72 | 110 | | | |
| Duration of follow-up [days] | | | | | 14 days after Tx done | 4 | 72 | | 751 | |
| Intervention group: # with at least one event (if this was reported) | | | | | | 77 | 111 | | 613 | |
| Intervention group: # of events per group (if this was reported) | 88 | | | | 39 | | | | | |
| Intervention group: Total | 77 | | | | 148 | | | | 752 | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Comparison group: #with at least one event (if this was reported) | | | | | | no | probably yes | | probably yes | |
| Comparison group: # of events per group (if this was reported) | 99 | | | | 29 | no | probably yes | | probably yes | |
| Comparison group: Total | 82 | | | | 150 | no | probably no | | probably no | |
| Blinding [patients] (only relevant for RCTs) | no | | | | yes | no | probably no | | probably no | |
| Blinding [personnel] (only relevant for RCTs) | no | | | | yes | no | probably no | | probably no | |
| Blinding [outcome assessors] (only relevant for RCTs) | no | | | | yes | probably yes | probably yes | | yes | |
| Blinding [data collectors] (only relevant for RCTs) | no | | | | yes | | | | | |
| Blinding [analysts] (only relevant for RCTs) | no | | | | probably yes | | | | | |
| ITT analysis performed (only relevant for RCTs) | yes | | | | yes | Not reported | Data available | Data available | Data available | |
| NOTES: | | | | | | | | | | |
| **Serious adverse effect** | | | | | drug related only | | 25 | 67 | 234 | |
| Are the data available? | Data available | Not reported | | | Data available | | | | | Not reported |
| Duration of follow-up [days] | same | | | | same | | 110 | 223 | 751 | |
| Intervention group: # with at least one event (if this was reported) | 25 | | 83 | | 1 | | 21 | 58 | 197 | |
| Intervention group: # of events per group (if this was reported) | | | | | | | | | | |

| EVIDENCE EXTRACTION TABLE FOR RANDOMIZED CONTROLLED TRIALS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Hoffken | Freire | Joshi | Fernandez Guerrero | yakovlev | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Kim |
| Year | 2007 | 2010 | 2006 | 1991 | 2006 | 1997 | 2006 | 2007 | 2011 | 2012 |
| Intervention group: Total | 77 | | | | 148 | | 111 | 221 | 752 | |
| Comparison group: #with at least one event (if this was reported) | 23 | | 41 | | 0 | | | | yes | |
| Comparison group: # of events per group (if this was reported) | | | | | | | | | probably yes | |
| Comparison group: Total | 82 | | | | 150 | | | | probably no | |
| Blinding [patients] (only relevant for RCTs) | no | | | | yes | | | | no | |
| Blinding [personnel] (only relevant for RCTs) | no | | | | yes | | | | probably no | |
| Blinding [outcome assessors] (only relevant for RCTs) | no | | | | yes | | | | yes | |
| Blinding [data collectors] (only relevant for RCTs) | no | | | | yes | | | | | |
| Blinding [analysts] (only relevant for RCTs) | no | | | | probably yes | | | | | |
| ITT analysis performed (only relevant for RCTs) | yes | | | | yes | | | | | |
| NOTES: | | | | | about 1/4 of patients were NH or rehab | | | | | |

| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| | Random sequence generation (selection bias) | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias |
| | Allocation concealment (selection bias) | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | low risk of bias |
| | Blinding | high risk of bias | probably low risk of bias | low risk of bias | high risk of bias | high risk of bias | low risk of bias | high risk of bias | probably low risk of bias | low risk of bias | high risk of bias |
| | ITT analysis performed | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | ITT analysis performed |
| | Serious loss to follow-up | probably low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias |
| | Selective outcome reporting | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias |
| | Study stopped early | high risk of bias | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably high risk of bias | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias |
| **Number of ventilator days or ventilator-free days** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | | | | | | | | | | |

| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| | Allocation concealment (selection bias) | | | | | | | | | | |
| | Blinding | | | | | | | | | | |
| | ITT analysis performed | | | | | | | | | | |
| | Serious loss to follow-up | | | | | | | | | | |
| | Selective outcome reporting | | | | | | | | | | |
| | Study stopped early | | | | | | | | | | |
| **Length of ICU stay** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | | probably low risk of bias | | | | | | | | |
| | Allocation concealment (selection bias) | | probably low risk of bias | | | | | | | | |
| | Blinding | | probably low risk of bias | | | | | | | | |
| | ITT analysis performed | | low risk of bias | | | | | | | | |
| | Serious loss to follow-up | | low risk of bias | | | | | | | | |
| | Selective outcome reporting | | low risk of bias | | | | | | | | |
| | Study stopped early | | low risk of bias | | | | | | | | |
| **Length of hospital stay** | NOTES: | | | | | | | | | | |

| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | | | | | | | | | | |
| | Allocation concealment (selection bias) | | | | | | | | | | |
| | Blinding | | | | | | | | | | |
| | ITT analysis performed | | | | | | | | | | |
| | Serious loss to follow-up | | | | | | | | | | |
| | Selective outcome reporting | | | | | | | | | | |
| | Study stopped early | | | | | | | | | | |
| **Clinical cure (as defined by the study authors)** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | Random sequence generation (selection bias) |
| | Allocation concealment (selection bias) | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | Allocation concealment (selection bias) |
| | Blinding | high risk of bias | probably risk of bias | low risk of bias | high risk of bias | probably high risk of bias | low risk of bias | probably high risk of bias | probably low risk of bias | low risk of bias | Blinding |

| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| | ITT analysis performed | low risk of bias | low risk of bias | low risk of bias | probably high risk of bias | probably high risk of bias | low risk of bias | probably high risk of bias | probably low risk of bias | low risk of bias | ITT analysis performed |
| | Serious loss to follow-up | probably high risk of bias | low risk of bias | low risk of bias | probably low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | Serious loss to follow-up |
| | Selective outcome reporting | low risk of bias | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | probably low risk of bias | Selective outcome reporting |
| | Study stopped early | high risk of bias | low risk of bias | low risk of bias | probably low risk of bias | probably high risk of bias | probably high risk of bias | low risk of bias | low risk of bias | low risk of bias | Study stopped early |
| **Recurrent pneumonia** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | | | | | | | | | | |
| | Allocation concealment (selection bias) | | | | | | | | | | |
| | Blinding | | | | | | | | | | |
| | ITT analysis performed | | | | | | | | | | |
| | Serious loss to follow-up | | | | | | | | | | |
| | Selective outcome reporting | | | | | | | | | | |
| | Study stopped early | | | | | | | | | | |
| **Number of** | NOTES: | | | | | | | | | | |

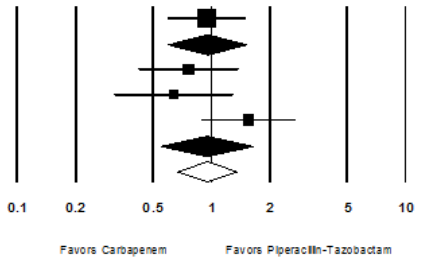
| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| **antibiotic days** | | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | | | | | | | | | | |
| | Allocation concealment (selection bias) | | | | | | | | | | |
| | Blinding | | | | | | | | | | |
| | ITT analysis performed | | | | | | | | | | |
| | Serious loss to follow-up | | | | | | | | | | |
| | Selective outcome reporting | | | | | | | | | | |
| | Study stopped early | | | | | | | | | | |
| **Development of resistance** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | | | | | | | | | | |
| | Allocation concealment (selection bias) | | | | | | | | | | |
| | Blinding | | | | | | | | | | |
| | ITT analysis performed | | | | | | | | | | |
| | Serious loss to follow-up | | | | | | | | | | |
| | Selective outcome | | | | | | | | | | |

| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| | reporting | | | | | | | | | | |
| | Study stopped early | | | | | | | | | | |
| **Any adverse effect** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation (selection bias) | probably low risk of bias | | | | low risk of bias | low risk of bias | | low risk of bias | probably low risk of bias | Random sequence generation (selection bias) |
| | Allocation concealment (selection bias) | probably low risk of bias | | | | probably low risk of bias | probably low risk of bias | | low risk of bias | probably low risk of bias | Allocation concealment (selection bias) |
| | Blinding | high risk of bias | | | | probably high risk of bias | low risk of bias | | probably low risk of bias | low risk of bias | Blinding |
| | ITT analysis performed | low risk of bias | | | | low risk of bias | low risk of bias | | low risk of bias | low risk of bias | ITT analysis performed |
| | Serious loss to follow-up | probably low risk of bias | | | | low risk of bias | low risk of bias | | probably low risk of bias | probably low risk of bias | Serious loss to follow-up |
| | Selective outcome reporting | low risk of bias | | | | probably low risk of bias | probably low risk of bias | | probably low risk of bias | really cannot tell | Selective outcome reporting |
| | Study stopped early | high risk of bias | | | | probably high risk of bias | probably high risk of bias | | low risk of bias | low risk of bias | Study stopped early |
| **Serious adverse effect** | NOTES: | | | | | | | | | | |
| | | | | | | Study | Study | Study | Study | Study | Study |
| | Random sequence generation | probably low risk of bias | | | | | low risk of bias | low risk of bias | low risk of bias | probably low risk of bias | |

| RISK OF BIAS | What antibiotics are recommended for empiric treatment of clinically suspected HAP (non-ventilator associated)? | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality (all cause)** | | Hoffken | Freire | Joshi | Fernandez Guerrero | Saginur R | Scmitt DV | Rea-Neto A | Rubinstein E | Yakovlev | Kim |
| | (selection bias) | | | | | | | | | | |
| | Allocation concealment (selection bias) | probably low risk of bias | | | | | probably low risk of bias | probably low risk of bias | low risk of bias | probably low risk of bias | |
| | Blinding | high risk of bias | | | | | low risk of bias | probably high risk of bias | probably low risk of bias | low risk of bias | |
| | ITT analysis performed | low risk of bias | | | | | low risk of bias | low risk of bias | low risk of bias | low risk of bias | |
| | Serious loss to follow-up | probably low risk of bias | | | | | low risk of bias | low risk of bias | probably low risk of bias | probably low risk of bias | |
| | Selective outcome reporting | low risk of bias | | | | | probably low risk of bias | probably low risk of bias | probably low risk of bias | really cannot tell | |
| | Study stopped early | high risk of bias | | | | | probably high risk of bias | probably low risk of bias | low risk of bias | low risk of bias | |

## HAP: Carbapenem vs. Piperacillin-Tazobactam: 28-day Mortality

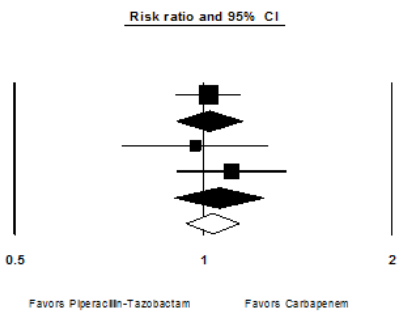
| Group by Carbapenem Type | Study name | Risk ratio | Lower limit | Upper limit | p-Value | Carbapenem | Pip-Tazo | Total |
|---|---|---|---|---|---|---|---|---|
| Doripenem | Rea-Neto 2007 | 0.945 | 0.594 | 1.505 | 0.813 | 30 / 217 | 31 / 212 | 61 / 429 |
| Doripenem | | 0.945 | 0.594 | 1.505 | 0.813 | 30 / 217 | 31 / 212 | 61 / 429 |
| Imipenem | Joshi 2006 | 0.763 | 0.420 | 1.388 | 0.376 | 17 / 215 | 23 / 222 | 40 / 437 |
| Imipenem | Schmitt 2006 | 0.641 | 0.315 | 1.306 | 0.221 | 11 / 111 | 17 / 110 | 28 / 221 |
| Imipenem | Kim 2012 | 1.557 | 0.888 | 2.728 | 0.122 | 21 / 53 | 14 / 55 | 35 / 108 |
| Imipenem | | 0.939 | 0.544 | 1.620 | 0.820 | 49 / 379 | 54 / 387 | 103 / 766 |
| Overall | | 0.943 | 0.662 | 1.343 | 0.743 | 79 / 596 | 85 / 599 | 164 / 1195 |




**Heterogeneity: Tau2=0.047; Q=4.65; df=3; P=0.199; I2=36%**

## HAP: Carbapenem vs. Piperacillin-Tazobactam: Clinical Cure at Test-of-Cure Visit

| Group by Carbapenem Type | Study name | Risk ratio | Lower limit | Upper limit | p-Value | Carbapenem | Pip-Tazo | Total |
|---|---|---|---|---|---|---|---|---|
| Doripenem | Rea-Neto 2007 | 1.019 | 0.902 | 1.150 | 0.762 | 109 / 134 | 95 / 119 | 204 / 253 |
| Doripenem | | 1.019 | 0.902 | 1.150 | 0.762 | 109 / 134 | 95 / 119 | 204 / 253 |
| Imipenem | Joshi 2006 | 0.970 | 0.741 | 1.271 | 0.828 | 43 / 72 | 40 / 65 | 83 / 137 |
| Imipenem | Schmitt 2006 | 1.110 | 0.904 | 1.361 | 0.319 | 73 / 110 | 64 / 107 | 137 / 217 |
| Imipenem | | 1.057 | 0.898 | 1.244 | 0.507 | 116 / 182 | 104 / 172 | 220 / 354 |
| Overall | | 1.032 | 0.936 | 1.138 | 0.523 | 225 / 316 | 199 / 291 | 424 / 607 |




**Heterogeneity: Tau2=0; Q=0.723; df=2; P=0.697; I2=0%**

| **HAP-organism/ prevalence studies** | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Alsuraikh | Avci | Edis | Espejo | Herer | Herer | Kollef | Gianella | Piskin | Esperati | Sopena | Maruyama | Barreiro-Lop. | takano | chung | Jones | Jones | Schussler | watanabe | Rea-Neto | Friere | Weber | Kim | yakovlev | kohlenberg |
| Year | 2008 | 2010 | 2009 | 2011 | 2009 | 2001 | 2005 | 2011 | 2012 | 2010 | 2005 | 2008 | 2005 | 2002 | 2011 | 2010 | 2010 | 2006 | 2008 | 2008 | 2010 | 2007 | 2012 | 2006 | 2010 |
| Journal name | Kuwait Medical Journal | Turkish J Med Sci | Respiration | Clin Microbiol Infect | Clin Microbiol Infect | Eur respir J | Chest | Clin Micr Inf | BMC Inf Dis | AJRCCM | Chest | Resp Med | Enferm Infec Micro Clin | | AJRCCM | CID | CID | AJRCCM | Int Med | curr med resh opin | Diag Micro Infect Dis | Infect Cont Hosp Ep | Critical Care | Eur J Clin Micro Inf Dis | Intensive Care Med |
| Language of publication | English | English | English | English | English | English | English | English | English | English | English | English | spanish | English | English | English | English | English | English | English | Eng | English | English | Eng | Eng |
| Country where study was done | Kuwait | Turkey | Turkey | Spain | France | France | USA | Spain | Turkey | Spain | Spain | Japan | Spain | Japan | Asia | World | USA | France | Japan | NA, SA, Eur | 31 countries | USA | Korea | Many | Germany |
| Years study done | 2005 | 2006-2007 | 2005-2006 | 1984-2009 | 2002-2004 | ? | 2002-3 | 2010 | 2005-08 | unknown | 1999-2000 | 2004-05 | 1997-1999 | 1996-98 | 2008-09 | 2004-08 | 2004-08 | 2001 | 2002-2004 | ? | 2004-06 | 2000-2003 | 204-2006 | Not known | 2005-2007 |
| **METHODS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| ***if COHORT STUDY*** | | | | | | | | | | | | | | | | | | | 7% VAP | 22% VAP | | | 8% VAP | 33% HCAP | 0 VAP |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | representative of such patients in reality | representative of such patients in reality | representative of such patients in reality | | selected non-representative population | selected non-representative population | | representative of such patients in reality | representative of such patients in reality | selected non-representative population | representative of such patients in reality | representative of such patients in reality | | representative of such patients in reality | representative of such patients in reality | insufficiently reported | insufficiently reported | representative of such patients in reality | representative of such patients in reality | selected non-representative population | representative of such patients in reality | representative of such patients in reality | selected non-representative population | selected non-representative population | selected non-representative population |
| Inclusion of non-ventilated ICU patients? (Yes/no) | No | No | no | no | no | no | yes | no | no | only ICU | no | yes | no | no | yes | yes | yes | yes | prob a few | probably | yes | yes | See Bottom | No | All ICU |

| **HAP-organism/ prevalence studies** | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Alsuraikh | Avci | Edis | Espejo | Herer | Herer | Kollef | Gianella | Piskin | Esperati | Sopena | Maruyama | Barreiro-Lop. | takano | chung | Jones | Jones | Schussler | watanabe | Rea-Neto | Friere | Weber | Kim | yakovlev | kohlenberg |
| Year | 2008 | 2010 | 2009 | 2011 | 2009 | 2001 | 2005 | 2011 | 2012 | 2010 | 2005 | 2008 | 2005 | 2002 | 2011 | 2010 | 2010 | 2006 | 2008 | 2008 | 2010 | 2007 | 2012 | 2006 | 2010 |
| Specific ward/specialty | Medical | Med/Surg | all non-ICU wards | no | rehab hospital | rehab hosp. | no | Int Med | no | ICU | no | no | no | med/surg | no | ? | ? | thoracic surg | pulm/med | no | no | no | Medical ICU | no | Any ICU |
| Immunosuppressed excluded? | no | No | yes | no | no | no | no | no | no | yes | no | no | no | no | no | no | no | no | no | yes | yes | no | no | yes | no |
| **ORGANISM SPECIFIC RESULTS (n)** | | Percents given," n" calculated | | | | | calculated from %s | | | | | | | | | PERCENTS | PERCENTS | | | | | | | | |
| Total Episodes (n) | 132 | 106 | 154 | 90 | 34 | | 835 | 105 | 218 | 151 | 165 | 33 | 67 | 80 | 1553 | ? | ? | 42 | 816 | 274 | ? | 226 | 108 | 303 | 898 |
| Streptococcus sp. | 0 | 1 | 3 | 24 | 10 | | 142 | 3 | 11 | 6 | 16 | 4 | 6 | 3 | 36 | Unknown | Unknown | 6 | 41 | | | 15 | 2 | 39 | 21 |
| Staphylococcus aureus **(only use this cell if MSSA/ MRSA not specified)** | | | | 5 | 10 | | | | 19 | | | 9 | 1 | | 245 | 27 | 37 | 1 | | | | | | | |
| MSSA | 5 | 6 | 5 | | | | 191 | 2 | | 9 | 3 | | | 4 | | | | | 35 | 68 | 75 | 36 | 5 | 17 | 83 |
| MRSA | 1 | 14 | 6 | | | | 217 | 2 | | 12 | 1 | | | 13 | | | | | 141 | 33 | 36 | 55 | 31 | 18 | 49 |
| Non-fermenters **(only use this cell if individual non-fermenters not provided)** | | | | | | | | | | | | | | | | | | | | | | | | | |

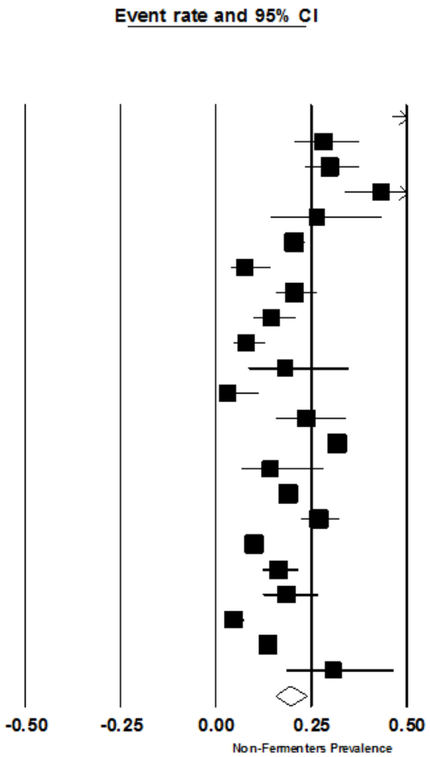
| **HAP-organism/ prevalence studies** | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Alsuraikh | Avci | Edis | Espejo | Herer | Herer | Kollef | Gianella | Piskin | Esperati | Sopena | Maruyama | Barreiro-Lop. | takano | chung | Jones | Jones | Schussler | watanabe | Rea-Neto | Friere | Weber | Kim | yakovlev | kohlenberg |
| Year | 2008 | 2010 | 2009 | 2011 | 2009 | 2001 | 2005 | 2011 | 2012 | 2010 | 2005 | 2008 | 2005 | 2002 | 2011 | 2010 | 2010 | 2006 | 2008 | 2008 | 2010 | 2007 | 2012 | 2006 | 2010 |
| Pseudomonas sp | 61 | 13 | 8 | 39 | 9 | | 154 | 6 | 24 | 19 | 7 | 4 | 2 | 19 | 242 | 22 | 19 | 6 | 149 | 54 | 24 | 25 | 13 | 11 | 86 |
| Acinetobacter sp | 11 | 12 | 36 | 0 | 0 | | 17 | 2 | 21 | 0 | 5 | 2 | 0 | | 209 | 8 | 4 | 0 | 6 | 23 | 27 | 9 | 6 | 3 | 12 |
| Stenotrophomonas | 0 | 5 | 2 | 0 | 0 | | ? | 0 | 0 | 3 | 1 | 0 | 0 | | 43 | 0 | 0 | 0 | | | 2 | 3 | 1 | ? | 25 |
| Hemophilus | 0 | 0 | 6 | 4 | 3 | | 47 | 0 | 0 | 2 | 2 | 1 | 0 | 1 | 32 | | 0 | 10 | 3 | 22 | 13 | 8 | 0 | ? | 21 |
| Enterobacteriaceae | 43 | 55 | 20 | 12 | 6 | | 134 | 5 | 17 | 19 | 8 | 7 | 4 | 13 | 375 | 22 | 22 | 5 | 7 | 98 | 117 | 44 | 12 | 59 | 240 |
| No organisms detected | ??? | ??? | 66 | 0 | ? | | 0 | 84 | 115 | 87 | 106 | 7 | 54 | 28 | ? | 0 | 0 | 18 | | | ? | 26 | 54 | ? | ? |
| Others | | At least 28 of enterics ---- ESBL | | | 1 | | 99 | 1 | 11 | 8 | 10 | 21 | 0 | 23 | 32 | 20 | 20 | 0 | | | 18 | 75 | 0 | ? | ? |
| Legionella | | Immunosuppressed included, but | | | | x | x | 0 | 0 | 0 | 7 | 0 | 0 | | 0 | | | 0 | | | | 0 | 0 | ? | ? |
| **In study 18, "others" and "No organism" grouped together** | | "similar organisms" | | Bacteremic only | | | | | | | | | | | | | | | 262 | | Included only microbiologically evaluable only | | | | |
| | | | | Other 6 not provided | | | | | | | | | | | | | | | | | | | | | |

| **HAP-organism/ prevalence studies** | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Alsuraikh | Avci | Edis | Espejo | Herer | Herer | Kollef | Gianella | Piskin | Esperati | Sopena | Maruyama | Barreiro-Lop. | takano | chung | Jones | Jones | Schussler | watanabe | Rea-Neto | Friere | Weber | Kim | yakovlev | kohlenberg |
| Year | 2008 | 2010 | 2009 | 2011 | 2009 | 2001 | 2005 | 2011 | 2012 | 2010 | 2005 | 2008 | 2005 | 2002 | 2011 | 2010 | 2010 | 2006 | 2008 | 2008 | 2010 | 2007 | 2012 | 2006 | 2010 |
| Hospital type (teaching/non-teaching | ? | Teaching | teaching | teaching | intermediate care/convalesc | intermediate care/convalesc | Multiple | Multiple | tertiary | multiple | multiple | teaching | ? | teaching | Many tertiary | many | many | ? | Many | Many | many | | tertiary | many | many |
| **RESISTANCE PATTERN SPECIFIC RESULTS Rarely availabl e** | | | | | | | | | | | | | | | | | | | | More than one bug could be in the same patients | | | | | |
| | | | | | | | | | | | | | | | | | | | | 11 SA not tested, deleted from "Total episodes" | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | this is number opf pathogens, not number of patients, | | | |
| | | | | | | | | | | | | | | | | | | | | | | | All patients were admitted to ICU, but may have developed HAP either in ICU or on | | |

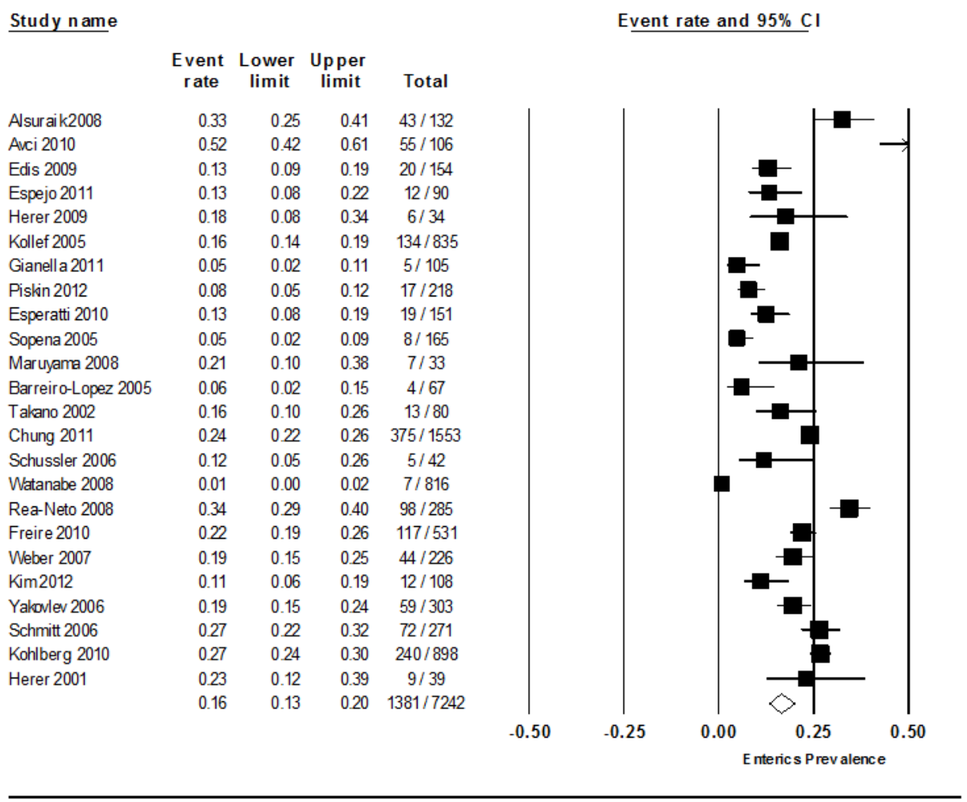
| **HAP-organism/ prevalence studies** | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Alsuraikh | Avci | Edis | Espejo | Herer | Herer | Kollef | Gianella | Piskin | Esperati | Sopena | Maruyama | Barreiro-Lop. | takano | chung | Jones | Jones | Schussler | watanabe | Rea-Neto | Friere | Weber | Kim | yakovlev | kohlenberg |
| Year | 2008 | 2010 | 2009 | 2011 | 2009 | 2001 | 2005 | 2011 | 2012 | 2010 | 2005 | 2008 | 2005 | 2002 | 2011 | 2010 | 2010 | 2006 | 2008 | 2008 | 2010 | 2007 | 2012 | 2006 | 2010 |
| | | | | | | | | | | | | | | | | | | | | | | | floor | | |
| | | | | | | | | | | | | | | | | | | | | | | | Number of pathogens cultured, not number of patients with a positive culture | | |
| | | | | | | | | | | | | | | | | | | | | | | | | Some polymicrobial, so we don't have exact patient level data | |
| | | | | | | | | | | | | | | | | | | | | | | | | | many poly microbial, not patient specific |

## HAP: Non-Fermenters Prevalence

| Study name | Event rate | Lower limit | Upper limit | Total |
|---|---|---|---|---|
| Alsuraik 2008 | 0.55 | 0.46 | 0.63 | 72 / 132 |
| Avci 2010 | 0.28 | 0.21 | 0.38 | 30 / 106 |
| Edis 2009 | 0.30 | 0.23 | 0.38 | 46 / 154 |
| Espejo 2011 | 0.43 | 0.34 | 0.54 | 39 / 90 |
| Herer 2009 | 0.26 | 0.14 | 0.44 | 9 / 34 |
| Kollef 2005 | 0.20 | 0.18 | 0.23 | 171 / 835 |
| Gianella 2011 | 0.08 | 0.04 | 0.15 | 8 / 105 |
| Piskin 2012 | 0.21 | 0.16 | 0.27 | 45 / 218 |
| Esperatti 2010 | 0.15 | 0.10 | 0.21 | 22 / 151 |
| Sopena 2005 | 0.08 | 0.05 | 0.13 | 13 / 165 |
| Maruyama 2008 | 0.18 | 0.08 | 0.35 | 6 / 33 |
| Barreiro-Lopez 2005 | 0.03 | 0.01 | 0.11 | 2 / 67 |
| Takano 2002 | 0.24 | 0.16 | 0.34 | 19 / 80 |
| Chung 2011 | 0.32 | 0.30 | 0.34 | 494 / 1553 |
| Schussler 2006 | 0.14 | 0.07 | 0.28 | 6 / 42 |
| Watanabe 2008 | 0.19 | 0.16 | 0.22 | 155 / 816 |
| Rea-Neto 2008 | 0.27 | 0.22 | 0.32 | 77 / 285 |
| Freire 2010 | 0.10 | 0.08 | 0.13 | 53 / 531 |
| Weber 2007 | 0.16 | 0.12 | 0.22 | 37 / 226 |
| Kim2012 | 0.19 | 0.12 | 0.27 | 20 / 108 |
| Yakovlev 2006 | 0.05 | 0.03 | 0.08 | 14 / 303 |
| Kohlenberg 2010 | 0.14 | 0.12 | 0.16 | 123 / 898 |
| Herer 2001 | 0.31 | 0.18 | 0.47 | 12 / 39 |
| | 0.19 | 0.15 | 0.24 | 1473 / 6971 |

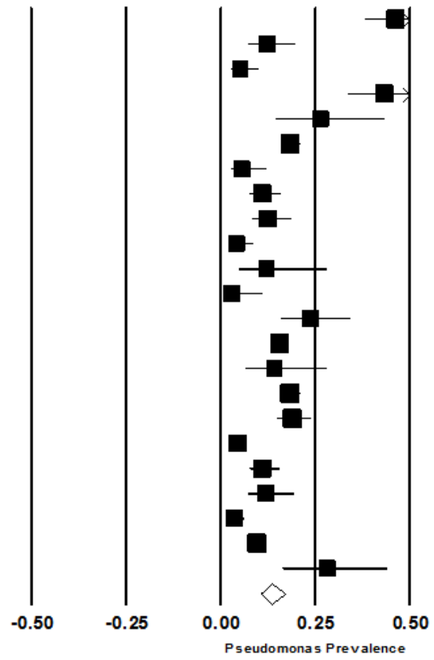


## HAP: Enterics Prevalence

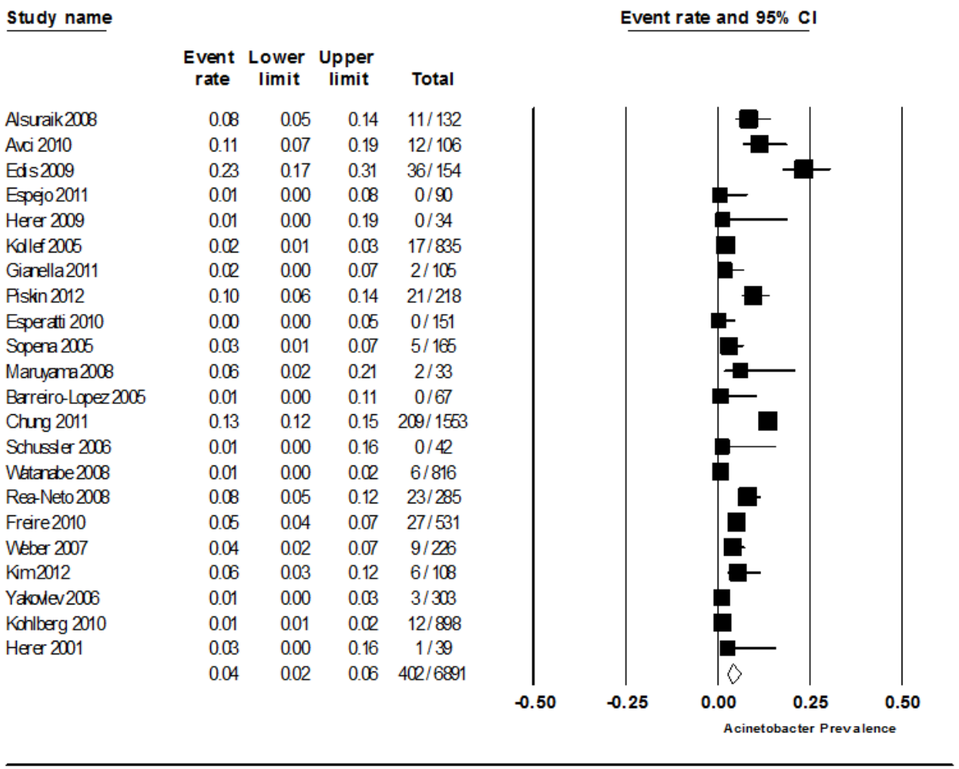


## HAP: Pseudomonas Prevalence

| Study name | Event rate | Lower limit | Upper limit | Total |
|---|---|---|---|---|
| Alsuraik 2008 | 0.46 | 0.38 | 0.55 | 61 / 132 |
| Avci 2010 | 0.12 | 0.07 | 0.20 | 13 / 106 |
| Edis 2009 | 0.05 | 0.03 | 0.10 | 8 / 154 |
| Espejo 2011 | 0.43 | 0.34 | 0.54 | 39 / 90 |
| Herer 2009 | 0.26 | 0.14 | 0.44 | 9 / 34 |
| Kollef 2005 | 0.18 | 0.16 | 0.21 | 154 / 835 |
| Gianella 2011 | 0.06 | 0.03 | 0.12 | 6 / 105 |
| Fiskin 2012 | 0.11 | 0.07 | 0.16 | 24 / 218 |
| Esperatti 2010 | 0.13 | 0.08 | 0.19 | 19 / 151 |
| Sopena 2005 | 0.04 | 0.02 | 0.09 | 7 / 165 |
| Maruyama 2008 | 0.12 | 0.05 | 0.28 | 4 / 33 |
| Barreiro-Lopez 2005 | 0.03 | 0.01 | 0.11 | 2 / 67 |
| Takano 2002 | 0.24 | 0.16 | 0.34 | 19 / 80 |
| Chung 2011 | 0.16 | 0.14 | 0.17 | 242 / 1553 |
| Schussler 2006 | 0.14 | 0.07 | 0.28 | 6 / 42 |
| Watanabe 2008 | 0.18 | 0.16 | 0.21 | 149 / 816 |
| Rea-Neto 2008 | 0.19 | 0.15 | 0.24 | 54 / 285 |
| Freire 2010 | 0.05 | 0.03 | 0.07 | 24 / 531 |
| Weber 2007 | 0.11 | 0.08 | 0.16 | 25 / 226 |
| Kim 2012 | 0.12 | 0.07 | 0.20 | 13 / 108 |
| Yalovlev 2006 | 0.04 | 0.02 | 0.06 | 11 / 303 |
| Kohlenberg 2010 | 0.10 | 0.08 | 0.12 | 86 / 898 |
| Herer 2001 | 0.28 | 0.16 | 0.44 | 11 / 39 |
| | 0.13 | 0.10 | 0.17 | 986 / 6971 |

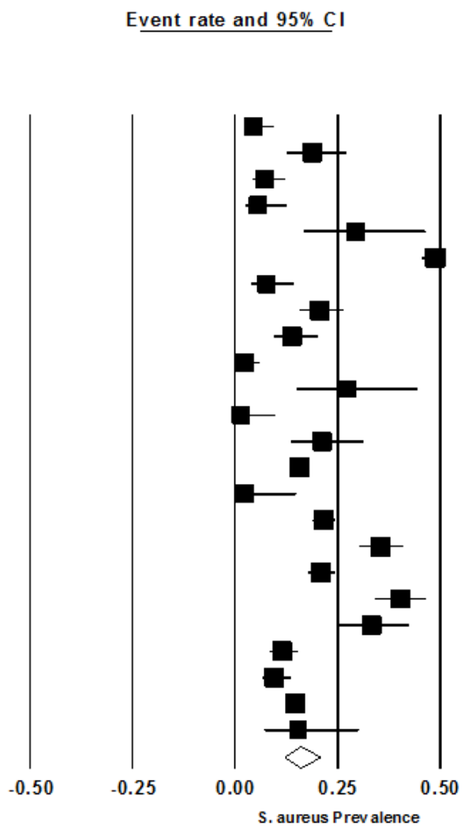


## HAP: Acinetobacter spp. Prevalence



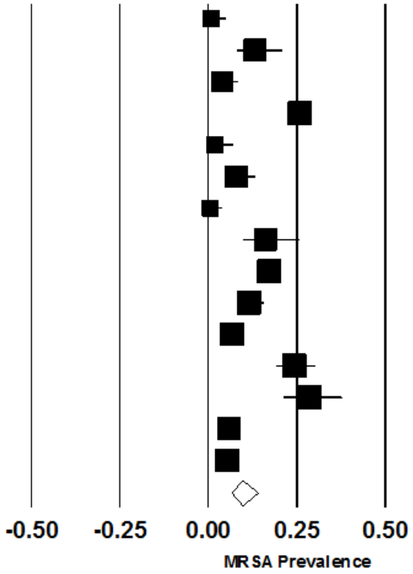
## HAP: S. aureus Prevalence

| Study name | Event rate | Lower limit | Upper limit | Total |
|---|---|---|---|---|
| Alsuraik2008 | 0.05 | 0.02 | 0.10 | 6 / 132 |
| Avci 2010 | 0.19 | 0.13 | 0.27 | 20 / 106 |
| Edis 2009 | 0.07 | 0.04 | 0.12 | 11 / 154 |
| Espejo 2011 | 0.06 | 0.02 | 0.13 | 5 / 90 |
| Herer 2009 | 0.29 | 0.17 | 0.47 | 10 / 34 |
| Kollef 2005 | 0.49 | 0.45 | 0.52 | 408 / 835 |
| Gianella 2011 | 0.08 | 0.04 | 0.15 | 8 / 105 |
| Piskin 2012 | 0.21 | 0.16 | 0.27 | 45 / 218 |
| Esperatti 2010 | 0.14 | 0.09 | 0.20 | 21 / 151 |
| Sopena 2005 | 0.02 | 0.01 | 0.06 | 4 / 165 |
| Maruyama 2008 | 0.27 | 0.15 | 0.45 | 9 / 33 |
| Barreiro-Lopez 2005 | 0.01 | 0.00 | 0.10 | 1 / 67 |
| Takano 2002 | 0.21 | 0.14 | 0.32 | 17 / 80 |
| Chung 2011 | 0.16 | 0.14 | 0.18 | 245 / 1553 |
| Schussler 2006 | 0.02 | 0.00 | 0.15 | 1 / 42 |
| Watanabe 2008 | 0.22 | 0.19 | 0.25 | 176 / 816 |
| Rea-Neto 2008 | 0.35 | 0.30 | 0.41 | 101 / 285 |
| Freire 2010 | 0.21 | 0.18 | 0.25 | 111 / 531 |
| Weber 2007 | 0.40 | 0.34 | 0.47 | 91 / 226 |
| Kim 2012 | 0.33 | 0.25 | 0.43 | 36 / 108 |
| Yakovlev 2006 | 0.12 | 0.08 | 0.16 | 35 / 303 |
| Schmitt 2006 | 0.10 | 0.07 | 0.14 | 26 / 271 |
| Kohlenberg 2010 | 0.15 | 0.13 | 0.17 | 132 / 898 |
| Herer 2001 | 0.15 | 0.07 | 0.30 | 6 / 39 |
| | 0.16 | 0.12 | 0.21 | 1525 / 7242 |



**HAP: MRSA Prevalence**

| Study name | Event rate | Lower limit | Upper limit | Total |
|---|---|---|---|---|
| Alsuraik 2008 | 0.01 | 0.00 | 0.05 | 1 / 132 |
| Avci 2010 | 0.13 | 0.08 | 0.21 | 14 / 106 |
| Edis 2009 | 0.04 | 0.02 | 0.08 | 6 / 154 |
| Kollef 2005 | 0.26 | 0.23 | 0.29 | 217 / 835 |
| Gianella 2011 | 0.02 | 0.00 | 0.07 | 2 / 105 |
| Esperatti 2010 | 0.08 | 0.05 | 0.13 | 12 / 151 |
| Sopena 2005 | 0.01 | 0.00 | 0.04 | 1 / 165 |
| Takano 2002 | 0.16 | 0.10 | 0.26 | 13 / 80 |
| Watanabe 2008 | 0.17 | 0.15 | 0.20 | 141 / 816 |
| Rea-Neto 2008 | 0.12 | 0.08 | 0.16 | 33 / 285 |
| Freire 2010 | 0.07 | 0.05 | 0.09 | 36 / 531 |
| Weber 2007 | 0.24 | 0.19 | 0.30 | 55 / 226 |
| Kim 2012 | 0.29 | 0.21 | 0.38 | 31 / 108 |
| Yakovlev 2006 | 0.06 | 0.04 | 0.09 | 18 / 303 |
| Kohlenberg 2010 | 0.05 | 0.04 | 0.07 | 49 / 898 |
| | 0.10 | 0.06 | 0.14 | 629 / 4895 |



## XIII. Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP?

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| Source of information | 43(3):623 (retrospective analysis) | 29(11):2433-39 (retrospective analysis) | 33:464-8 (retrospective analysis) | 43(13):925-42 (retrospective analysis) | 4(1):584-9 (prospective pkpd study) | 17:497-504; prospective randomised study | 51(9):3304-10 | 34:394-400 | 44:99-108 | 189:1590-1597 | 30:162-168 | 130:947-955 | 39:38-43 | 179:436-440 | 56:1065-1072 | 43:623-629 | 33:464-468 | 39:153-158 | 29:1107-1115 |
| Journal name | Antimicrob. Agents Chemother | Clin Ther | Int J Antimicrob Agents | Clin Pharmacokinet | Int J Pharm Pharm Sci | Int J Antimicrob Agents | Antimicrob Agents Chemother | Eur Respir J | J Antimicrob Chemother | J. Inf. Dis. | Int. J. Antimicrob. Agents | Chest | Scan. J. Infect. Dis. | Am. J. Surg | Antimicrob. Agents Chemother. | Antimicrob. Agents Chemother. | Int. J. Antimicrob. Agents | Int. J. Antimicrob. Agents | Clin Therapeutics |
| Language | English | English | English | English | English | English | English | English | English | English | English | English | English | English | English | English | English | English | English |
| Funding body | Abbott Diagnostics | Nil | Nil | Nil | research grant from THE 90TH ANNIVERSARY OF CHULAL | Glaxo Wellcome | MSD | Italian Ministry fo Health | Nil declared | Ortho-McNeil Pharmaceutical | Departmental | Not known | Not known | GlaxoWellcome | Pfizer (Wyeth) | Abbott | Hospital support | Not known | University funded |

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| | | | | | ONGKORN UNIVERSITY FUND (Ratchadaphiseksomphot Endowment Fund) | | | | | | | | | | | | | | |
| ETHICS approval | Not stated - retrospective chart review | IRB - yes (retrospective chart review) | IRB - yes (retrospective chart review) | Not stated - retrospective chart review | Yes | IRB - yes | Yes | yes | yes | Yes | Yes | Yes | Yes | Yes | Yes | Not Stated | Yes | Yes | Yes |
| COUNTRY where study was done | USA | Spain | Spain | USA | Thailand | USA | Germany | Italy | Multi-national | United States and Canada | Hungary | United States-St Louis MO | Greece | United States, Memphis TN | United States | United States (New York) | Spain | Poland | United States-St. Louis |
| | Tobramycin/ Gentamycin | ceftazidime | piperacillin/tazobactam | Vancomycin | Cefoperazone/sulbactam | Ceftazidime (lower dose | Imipenem-cilastatin | Amikacin; ciprofloxacin; levof | Isepamicin | Levofloxacin | Levofloxacin (500 mg dose) | Vancomycin PK indices and mortality associated | Assessment of high dose vs lose dose Amp/Sulin | Comparison of intermittent and continuous | Pharmacological and patient specific factors; HAP treated with tigecycline | PK/PD factors of aminoglycoside antibioti | Comparison of the treatment of VAP | Assess the efficacy of PTZ continuous infusion during the | Determine if aggressive dosing of vancomy |

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| | | | | | | mean 3g infusion vs 6g bolus) | | loxacin; ceftazidime; cefotaxime | | | | with HCAP | treatment of A. baumanii VAP | ceftazidime PK in HAP and comparison to healthy volunteers | | cs (tobramycin, gentamycin) against gram negative pneumonia | with either continuous or intermittent infusion of PTZ | first days of VAP therapy usng therpeutic drug monitoring for real time dose adjustment | cin associated with greater risk of renal toxicity with HCAP attributed to MRSA. |
| METHODS | | | | | | | | | | | Open label | | | | | | | | |
| *if RANDOMIZED TRIAL* (or non-randomized experimental study) | | open label | open label | | | | | | | | | | | | | | | | |
| Randomization | | | No | No | No | Yes | Yes | No | yes | No | | | Yes | Yes | Original published trial randomized; this study assessing PK/PD of tigcycline. Original study comparing tigecycline and imipenem. | | | | |

| **Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| Concealment | | | | | | No | No | | no | | | | | | | | | | |
| Not stopped early | | No | No | | | No | No | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | | | | | | | | |
| *if COHORT STUDY* | | | | | | | | | | | | | | | | | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | Good (only gram neg pneumonia with gram pos and fungal pneumonia excluded) | Good (only culture pos gram neg pneumonia) | Good (only culture pos gram neg pneumonia) | Good (only S. aeurus LRTI) | Good | Good | Good | | | Good | Good | Good | Good | Good | Good | Good | Good | Good | |
| Selection of the non exposed cohort | No comparator group | Good | Good | No comparator group | No comparator group | Good | Good | | | No comparator group | No comparator group | Mortality study; survivors vs non survivors; MRSA only | Clinical, bacteriological, mortality associated with low dose/high dose | Gram negative HAP >48 hours following admission. | Acute HAP; ≥ 48 hours after admission | No comparator group | Both int and cont infusion groups the same | No comparator group | |

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| | | | | | | | | | | | | | amp/sul vs A. baumanii VAP | | | | | | |
| Ascertainment of exposure | Infection parameters reasonable | VAP (radiograph, sputum, WCC, fever and quantitative culture) | VAP (radiograph, sputum, WCC, fever and quantitative culture) | clinical, radiographic and micro evidence of LRTI | | clinical, radiographic and micro evidence of LRTI | clinical, radiographic and micro evidence of LRTI | | | HAP (Radiographic evicence, abnormal body temperature, abnormal peripheral white blood cell count, microbiological evidence) | VAP; Clinical Pulmonary Infection Score (CPIS) ≥6, microbiological evidence | Definition of HCAP; > 2 days after hospital admission, Positive BAL culture, fever, leukocytosis, purulent tracheal aspirate | VAP defined by Quantitative BAL (1 x 10^4), abnormal temp, leukocytosis or leukopenia, purulent sputum, radiographic | Temp >100.4, WBC ≥10,000 mm3, radiographic, ≥10^5 CFU BAL culture | Radiographic, Fevor or leukocytosis, in the absence of resp failure requiring vent., the presence of two of the following: cough, dyspnea or tacypnea, auscultatory finds of rales of pulmonary consolidation, hypoexemia, or purulent sputum. | Definition of pneumonia; radiograph, microbiology, leukocytosis or fever | Radiography, purulent sputum, fever, leukopenia, >10^6 CFU/ml BAL culture | VAP (ATS/IDSA guidelines); radiography, fever, purulent secretions, leukocytosis or leukopenia. BAL >10^4 CFU/ml | |
| Demonstration that outcome of interest was not presen | Presence of infection parameters | Presence of infection parameters | Presence of infection parameters | Presence of infection parameters | HAP per ATS definition | Presence of infection parameters | Presence of infection param | | | No acute inflammation was present on admission; | Not mentioned | Yes | Yes, A. baumanii strains resistant to Amp/sul excluded as if other organisms | Yes | Yes | Yes | Yes | Yes | Yes |

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| t at start of study | | | | | | | eters | | | hospitalized for > 72 hrs. | | | ≥10^4. | | | | | | |
| Comparability of cohorts on the basis of the design or analysis | No comparator group | Good | Good | No comparator group | No comparator group | Good | Good | | | No comparator group | No comparator group | Good | Good | Good | Good | No comparator group | Good | No comparator group | |
| Assessment of outcome | Decreased infection symptoms (WCC, fever, sputum load) | Cure (complete resolution of signs and symptoms of infection) | Cure (complete resolution of signs and symptoms of infection) | Decreased infection symptoms (WCC, fever, sputum load) | | Cure, Improved or failure | Cure, Improved or failure | | | Clinical outcome (success vs failure of treatment and microbiological outcome (eradication vs persistence) | Target AUC/MIC of 100-125 for both Gram (-) and (+), Clinical outcome (cure, improvement, failure per CPIS score), and Microbiological (eradication, failure, superinfection) | Mortality; PK parameters for vancomycin in survivors vs non survivors | Bacteriological, clinical cure, mortality, adverse effects comparing low dose (18g/9g) vs high dose (24 g/12 g) | HAP clinical outcome between intermittent and continuous ceftazidime (cure, improvement, failure, indeterminate) | Both clinical and microbiological | clinical response through leukocytosis and temperature resolution | Clinical cure and failure | Clinical and microbiological cure/failure | |
| Was | Unclea | Uncl | Uncl | Uncle | Unclear | Yes | Yes | | | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| follow-up long enough for outcomes to occur? | r | ear | ear | ar | | | | | | | | | | | | | | | |
| Adequacy of follow up of cohorts | Appears appropriate | Appears appropriate | Appears appropriate | Appears appropriate | Appears appropriate | Appears appropriate | Appears appropriate | | | Adequate | Adequate | Adequate | Adequate | Adequate | Adequate | Adequate | Adequate | Adequate | |
| Co-Interventions similar between groups? | No comparator group | Yes | Yes | No comparator group | No comparator group | Yes | Yes | | | No comparator group | No comparator group | Yes | Yes | Yes | | No comparator group | Yes | No comparator group | |
| *if CASE-CONTROL STUDY* | | | | | | | | | | | | | | | | | | | |
| Is case definition adequate? | | | | | | | | yes | | | | | | | | | | | |
| Representativ | | | | | | | | good | | | | | | | | | | | |

| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| e of the cases | | | | | | | | | | | | | | | | | | | |
| Selection of controls | | | | | | | | random | | | | | | | | | | | |
| Definition of controls | | | | | | | | non-PK/PD dose adjustment | | | | | | | | | | | |
| Comparability | | | | | | | | appropriate | | | | | | | | | | | |
| Ascertainment of exposure | | | | | | | | PK/PD and clinical outcome | | | | | | | | | | | |
| Same method of ascertainment for cases and control | | | | | | | | Yes | | | | | | | | | | | |

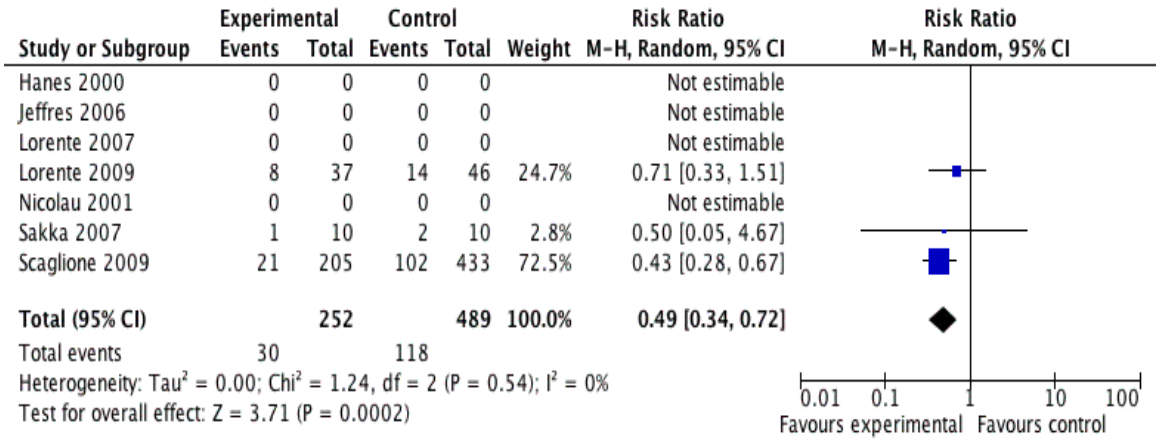
| Data Extraction Table - Should antibiotic dosing be determined by PK/PD data or the manufacturer's prescribing information in patients with HAP/VAP | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Kashuba, | Lorente | Lorente | Moise-Broder | NARAWADEENIAMHUN | Nicolau | Sakka | Scaglione | Tod | Drusano, G.L. | Benko, R | Jeffres, M.N. | Betrosian, A.P. | Hanes, S.D. | Bhavnani, S.M. | Kashuba, A.D.M. | Lorente, L. | Duszynska, W. | Jeffres, M.N. |
| Year | 1999 | 2007 | 2009 | 2004 | 2012 | 2001 | 2007 | 2009 | 1999 | 2004 | 2007 | 2006 | 2007 | 2000 | 2012 | 1999 | 2009 | 2012 | 2007 |
| s | | | | | | | | | | | | | | | | | | | |
| Non-response rate | | | | | | | | Measured | | | | | | | | | | | |
| Co-interventions similar between groups? | | | | | | | | Yes | | | | | | | | | | | |

**STUDIES DESCRIBING PK/PD TARGETS ASSOCIATED WITH IMPROVED PATIENT OUTCOMES WITH SUGGESTED DOSING REGIMENS FOR PATIENTS WITHOUT RENAL OR HEPATIC DYSFUNCTION**

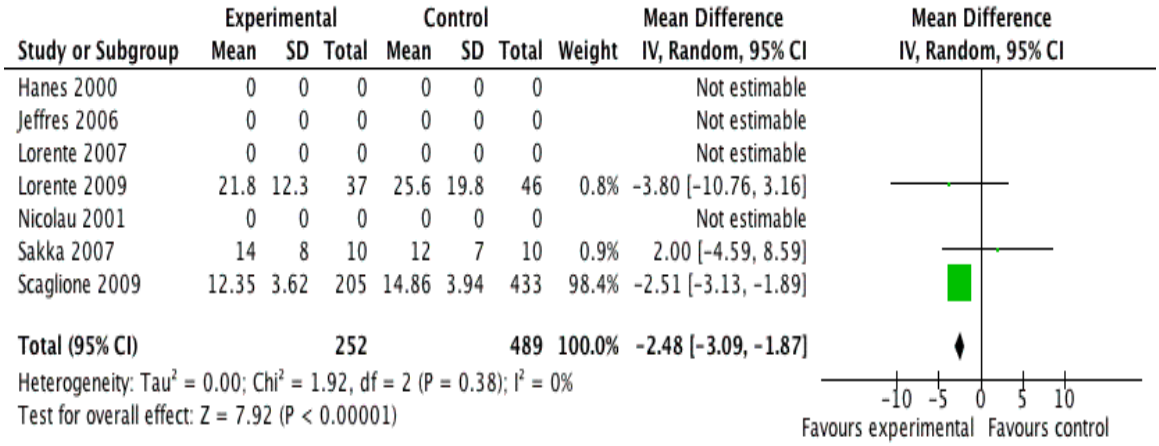
| Drug | PK/PD target associated with improved outcome of HAP/VAP | Reference | Suggested dosing for patients without renal or hepatic dysfunction |
|---|---|---|---|
| Aminoglycosides | Cmax/MIC 8-10<br>AUC/MIC 100 | [53, 54] | Gentamicin and Tobramycin 7mg/kg and Amikacin 30mg/kg 24-hourly [55] |
| Levofloxacin | AUC/MIC > 87 | [56] | 750mg daily or 500mg 12-hourly [57, 58] |
| Vancomycin | AUC/MIC > 400 | [59] | 30mg/kg loading dose followed by dose based on CrCL [60] |
| Tigecycline (not approved for HAP/VAP) | AUC/MIC > 0.9 | [61] | 200mg loading dose followed by 50-100mg 12-hourly [61] |
| Cefoperazone (Discontinued in the US, EU, and Australia) | 50% T>MIC | [62] | 2g 8-hourly using a 4-hour infusion [62] |
| Ceftazidime | 45% T>MIC | [63] | 2g 8-hourly using a 4-hour infusion [64] |
| Ceftazidime and Cefepime | 100% T>MIC | [65] | 2g 8-hourly using a 4-hour infusion [66] |
| Meropenem | 54% T>MIC for microbiological response<br>$C_{min}$:MIC > 5 for clinical response | [67] | 1g 8-hourly using a 3-hour infusion [68] |
| Meropenem | 75% T>MIC | [69] | 1g 8-hourly using a 3-hour infusion [68] |

*PK/PD – pharmacokinetic/pharmacodynamic; Cmax – maximum concentration in a dosing interval; MIC – minimum inhibitory concentration; AUC – area under the concentration-time curve; T>MIC – time for which the antibiotic concentration is maintained above the MIC (expressed as a percentage of dosing interval); Cmin – minimum concentration in a dosing interval; CrCL – creatinine clearance
**Recommended doses are based on cited articles andexpert opinion. Extended infusions of beta-lactams are suggested based on PK/PD simulation analyses

**Forest plot of studies reporting the effect of a PK/PD intervention on mortality. In these studies, the PK/PD intervention was either dosing guided by therapeutic drug monitoring or beta-lactam antibiotic administration by continuous infusion**




**Forest plot of studies reporting the effect of a PK/PD intervention on length of ICU stay. In these studies, the PK/PD intervention was either dosing guided by therapeutic drug monitoring or beta-lactam antibiotic administration by continuous infusion**

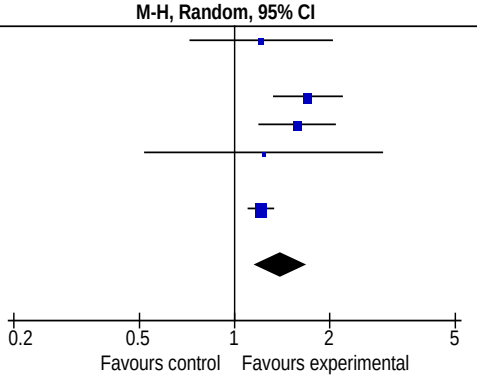


**Forest plot of studies reporting the effect of a PK/PD intervention on clinical cure as defined by the study authors. In these studies, the PK/PD intervention was either dosing guided by therapeutic drug monitoring or beta-lactam antibiotic administration by continuous infusion.**

| | Experimental | | Control | | | Risk Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI |
| Hanes 2000 (1) | 10 | 14 | 10 | 17 | 10.2% | 1.21 [0.72, 2.04] |
| Jeffres 2006 | 0 | 0 | 0 | 0 | | Not estimable |
| Lorente 2007 | 50 | 56 | 34 | 65 | 24.5% | 1.71 [1.33, 2.19] |
| Lorente 2009 | 33 | 37 | 26 | 46 | 22.3% | 1.58 [1.20, 2.08] |
| Nicolau 2001 (2) | 7 | 17 | 6 | 18 | 4.3% | 1.24 [0.52, 2.94] |
| Sakka 2007 | 0 | 0 | 0 | 0 | | Not estimable |
| Scaglione 2009 | 168 | 205 | 293 | 433 | 38.6% | 1.21 [1.11, 1.33] |
| **Total (95% CI)** | | **329** | | **579** | **100.0%** | **1.40 [1.16, 1.69]** |
| Total events | 268 | | 369 | | | |

Heterogeneity: Tau² = 0.02; Chi² = 8.92, df = 4 (P = 0.06); I² = 55%

Test for overall effect: Z = 3.47 (P = 0.0005)




Footnotes

(1) # of events estimated based on percentage reported in the study

(2) # of events estimated based on percentage reported in the study

## XIV. Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone?

| INCLUSION CRITERIA: CLINICAL AND MICROBIOLOGICAL | | | | |
|---|---|---|---|---|
| Study | **Setting** | **Indication** | **Bacterial species treated** | **Antibiotic susceptibility** |
| **Brown[70]** | ICU's at 16 sites in United States and Canada | VAP Clinical diagnosis | *Pseudomonas aeruginosa* in 41%, other non-fermenting Gram negatives 10%, multiple pathogens, *Klebsiella, Enterobacter, Serratia, Citrobacter* species, 15% | Susceptible to tobramycin |
| **LeConte[71]** | ICU-single site France | | Gram-negative or gram-positives | Susceptible to tobramycin |
| **Hallal[72]** | Surgical and Trauma ICUs single site, United States | VAP Clinical criteria + > $10^4$CFU/ml | *Pseudomonas aeruginosa* or *Acinetobacter* species sensitive to tobramycin | Susceptible to tobramycin |
| **Palmer[73]** | MICU and SICU Single site United States | VAP Clinical Diagnosis | Gram-negatives or Gram positives, most were MDR | No exclusions |
| **Kofteridis[74]** | ICU-single site in Greece | VAP BAL with >$10^4$ CFU/ml | *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumanii* | Susceptible only to colistin |
| **Korbilia[75]** | ICU-single site in Greece | Clinical diagnosis of pneumonia and quantitative cultures | Gram-negative susceptible to colistin and no more than two other antibiotics *Pseudomona aeruginosa, Acintetobacter baumanni,* and *Klebsiella baumannil* | Susceptible to colistin and no more than two other antibiotics |
| **Rattanaumpawan[76]** | ICU | VAP-clinical diagnosis and Gram negative on endotracheal aspirate | *Pseudomonas aeruginosa Acinetobacter* | Susceptible to colistin (could also be sensitive to other antibiotic classes) |
| **Doshi [77]** | ICUs Three sites United States | VAP + BAL or tracheal aspirate | Primarily *Pseudomona aeruginosa* and *Acinetobacter spp* | Susceptible only to colistin |
| **Tumbarello [78]** | ICU-single site in Italy | VAP clinical diagnosis and BAL showing single organism | *Acinetobacter baumanni, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* | Susceptible only to colistin |

| DOSING AND DELIVERY OF AEROSOLIZED ANTIBIOTICS | | | | | |
|---|---|---|---|---|---|
| Reference | **Antibiotic** | **Dose** | **Device** | **MMAD*** | **Deposition data[††]** |
| **Brown[70]** | Tobramycin | 40mg/5mL normal saline q 8 hours | Instilled in endotracheal tube | – | None |
| **Le Conte[71]** | Tobramycin | 6mg/kg/day | Pneumatic nebulizer ATOMECA Nantes, France | 2 µm | Central |
| **Hallal[72]** | Tobramycin TOBI** | 300mg Q12 hours | Jet nebulizer PARI* | No data in ventilated patients | No data in ventilated patients |
| **Palmer[73]** | Gentamicin | 80mg/2mL normal saline Q 8 hours | Jet nebulizer AeroTech II nebulizer [CIS-US, Bedford, 132 MA] | 2 µm | Central |
| **Kofteridis[74]** | Colistin | 2 million IU Q 12 hours | Not described | Not determined | Not determined |
| **Korbilia[75]** | Colistin | 2.1±0.9 International untis [IU] Q12 h hours | Not described | Not determined | Not determined |
| **Rattanaumpa-wan[76]** | Colistimethate sodium† | 75mg /4mL [NS] equivalent to 2.2 IU Q 12 hours | Jet or ultrasonic | Not determined | Not determined |
| **Doshi[77]** | Colistin | 75-150mg Q 12hours | Jet, ultrasonic or vibrating mesh | 1-5 µm | Not determined |
| **Tumbarello[78]** | Colistimethate sodium | 1 million IU Q 8 hours | Jet or ultrasonic | Not determined | Not determined |

* MMAD= mass median aerodynamic diameter
** Tobi delivered with PARI was FDA approved for spontaneously breathing patients
†One milligram of colistin base is contained in 2.4 mg of colistimethate sodium.
Colistimethate sodium has a potency of 12,500 IU per mg
Pure colistin base has been assigned a potency of 30,000 IU per mg
†† Central deposition refers to deposition in the trachea and major bronchi; peripheral deposition is desirable for effe

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| Type of information (published or unpublished) | published | published | published | published | published | published | published | published | published |
| Journal name | Antimicro Agents and chemo | CID | Surgical Infections | J Antimicrob Chemo | Presse Med | CMI | Crit Care | BMC Anesthesiology | Chest |
| Language of publication | English | English | English | English | french | English | English | English | English |
| Funding body | Grant Lilly Research | None mentioned | None reported | Faculty of Medicine Siriraj Hospital | | No sources of funding | Nektar Therapeutics | None | Universita Cattolica del Sacro Cuore |
| Ethics approval | Yes | retrospective- not reqired | Yes | Yes | yes | Retrospective | informed consent | IRB approved | Not required, retrospective chart review |
| Country where study was done | US | Greece | US | Thailand | France | Greece | US | US | US |
| **METHODS** | | | | | | | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | | | | | | | |
| Randomization | truly random | | truly random | truly random | stated as random but no description | | truly random | | |
| Concealment | yes | | yes | yes | probably yes | | yes | | |
| Not stopped early | not stopped early | | not stopped early | not stopped early | not stopped early | | not stopped early | | |
| NOTES: | | | | | | | | | |
| ***if COHORT STUDY*** | | | | | | | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | | | | representative of such patients in reality | | Yes | |
| Selection of the non exposed cohort | | | | | | same sample as exposed | | chart review | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| Ascertainment of exposure | | | | | | secure record (e.g. hospital) | | chart review | |
| Demonstration that outcome of interest was not present at start of study | | | | | | secure record (e.g. hospital) | | Yes | |
| Comparability of cohorts on the basis of the design or analysis | | | | | | controls for ≥2 important factors | | Equivalent groups | |
| Assessment of outcome | | | | | | record linkage (e.g. hospital) | | Resolution of signs and symptoms of infections | |
| Was follow-up long enough for outcomes to occur? | | | | | | yes | | Yes | |
| Adequacy of follow up of cohorts | | | | | | at least 80% followed-up | | Yes | |
| Co-Interventions similar between groups? | | | | | | yes | | Yes | |
| NOTES: | | | | | | | | | |
| ***if CASE-CONTROL STUDY*** | | | | | | | | | |
| Is case definition adequate? | | yes. ≥2 people/processes to extract information | | | | | | | yes. ≥2 people/processes to extract information |
| Representativeness of the cases | | yes. consequtive or random sample of cases with outcome of interest | | | | | | | yes. consequtive or random sample of cases with outcome of interest |
| Selection of controls | | same population (hospital | | | | | | | same population (hospital |
| Definition of controls | | | | | | | | | explicitly stated |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| | | | | | | | | | that controls had no history of an outcome |
| Comparability of cases and controls | | controls for ≥2 important factors | | | | | | | controls for ≥2 important factors |
| Ascertainment of exposure | | secure record (e.g. hospital) | | | | | | | secure record (e.g. hospital) |
| Same method of ascertainment for cases and controls | | yes | | | | | | | yes |
| Non-response rate | | | | | | | | | different response rate for both groups |
| Co-interventions similar between groups? | | probably yes | | | | | | | yes |
| **INTERVENTIONS BEING COMAPRED** | | | | | | | | | |
| **Intervention 1 (experimental)** | instilled aminoglycoside(tobramycin) | aerosolized colistin | aerosolized aminoglycoside(tobramycin) | aerosolized colistin | aerosolized tobramycin | aerosolize colistin | aerosolized aminoglycoside or vancomycin | aerosolized colistin | aerosolized colistin |
| other Tx used (if relevant for interpretation) | IV tobramycin and cefazolin or piperac | intravenous colistin | IV placebo and Pip Taz or imipenem/cilastatin | systemic antibioitic | IV betalactam and tobramycin | iv colistin | IV antibioitics | IV colistin | IV colistin |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | |
| **Intervention 2 (comparison)** | instill placebo normal saline | intravenous colistin | aerosolized placebo normal salin | aerosolizzed normal saline | aerosolized normal saline | iv colistin | aerosolized normal saline(placebo) | IV colistin | IV colistin |
| other Tx used (if relevant for interpretation) | IV tobramycin and cefazolin or piperac | | IV tobramycin and Pip Taz or imipenem/cilastatin | systemic antibioitic | IV betalactam and tobramycin | | IV antibioitics | | |
| Tx not allowed (if relevant for | | | | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| interpretation) | | | | | | | | | |
| duration of treatment | minimum of 4 days | 10-13 days | 14 days | 9.5±4.6 | 5 days of aerosol | | 14 days or until extubated | | |
| NOTES: | | | | systemic antibioitics chosen by responsible physician | | | systemic antibioitics chosen by responsible physician | Both groups had equivalent amount sof additional antibioitics | |
| **BASELINE CHARACTERISTICS** | | | | | | | | | |
| **Number randomised** | 85 | | 10 | | | | | | |
| Intervention | 45 | | 5 | 51 | 21 | 78 | 19 | 44 | 104 |
| Comparison | 40 | | 5 | 49 | 17 | 43 | 24 | 51 | 104 |
| Total (only if not reported separately) | | | | | | | | | |
| **Age** | | | | | | | | | |
| Intervention (mean or median) | 57 | 62 | 52.6 | 70.2±18.5 | NA | 59.2±19.2 | 62.3 ± 20.4 | 60.9±15.3 | 64 |
| Comparison (mean or median) | 58.4 | 62 | 53.6 | 66.2±15.8 | NA | 60.9±15.7 | 62.7 ± 20.1 | 57.3±15.6 | 66 |
| Total (mean or median) (only if not reported separately) | | | | | | | | | |
| unit (e.g. mean and SD) | | | mean (SD) | mean (SD) | | mean (SD) | mean (SD) | mean±SD | median (IQR) |
| Age range (e.g. 22-73) | 19-85 | | 23-72 | | | | | | 49-77 |
| Age inclusion criterion (e.g. older than 16) | over 18 | | all patients older than 23 | | | | | | Older than 18 |
| **Male gender** | | 58 | 6 | | | | | | |
| Intervention | 72.00% | 69.00% | 80.00% | 60.80% | NA | 78.20% | 73.70% | 50.00% | 71.10% |
| Comparison | 88.00% | 65.00% | 40.00% | 67.30% | NA | 72.10% | 58.30% | 65% | 55.80% |
| Total (only if not reported separately) | | | | | | | | | |
| **Severity of illness** | | | | | | | | | |
| Name of score (e.g. | If other please specify | Apache II | Apache II | Apache II | NA | Apache II | Apache II | Apache II | SOFA |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| APACHE, SOFA, ...) | | | | | | | | | |
| Intervention group mean score | NA | 16.9 | 17 | 19.1±5.8 | NA | 17.4±6 | 22.1±5.4 | 22.4±7.1 | 7 |
| Comparison group mean score | NA | 17.7 | 15 | 18.5±4.7 | | 19.2±7 | 21.7±6.4 | 24±6.9 | 8 |
| Total (only if not reported separately) | | | | | | | | | |
| **Study population** | | | | | | | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Mixed Medical-Surgical | Mixed Medical-Surgical | Trauma | Mixed Medical-Surgical | Multi-center | Mixed Medical-Surgical | Mixed Medical-Surgical | Medical and Surgical ICU | Mixed Medical-Surgical |
| NOTES: | | | | | Await full text | | | | Plus Trauma ICU |
| **OUTCOMES** | | | | | | | | | |
| **Mortality (all cause)** | | | | | | | | | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | Data available | Data available | Data available | Data available |
| location or duration of follow-up (choose from the list) | 2 weeks post end of treatment | ICU | | 28 day | during study | ICU | 28 day | hosptial mortaility | ICU |
| Intervention group: # with event | 13 | 10 | 0 | 21 | 2 | 31 | 4 | 15 | 45 |
| Intervention group: Total | 45 | 43 | 5 | 51 | 21 | 78 | 19 | 44 | 104 |
| Comparison group: # with event | 7 | 18 | 0 | 20 | 4 | 19 | 4 | 27 | 48 |
| Comparison group: Total | 40 | 42 | 5 | 49 | 17 | 43 | 24 | 51 | 104 |
| Blinding [patients] (only relevant for RCTs) | yes | | | probably yes | probably yes | | yes | | |
| Blinding [personnel] (only relevant for RCTs) | yes | | | probably yes | probably yes | | yes | | |
| Blinding [outcome assessors] (only | yes | | | probably yes | probably yes | | yes | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | yes | | | probably yes | probably yes | | yes | | |
| Blinding [analysts] (only relevant for RCTs) | yes | | | probably yes | probably yes | | yes | | |
| ITT analysis performed (only relevant for RCTs) | yes | | | yes | probably yes | | yes | | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | | | | | | | |
| Are the data available? | Not measured | Not reported | Not reported | Not reported | Not reported | Not reported | Data available | Data available | Data available |
| Duration of follow-up [days] | | | | 28 | | | From onset of treatment to extubaion | From onset of treatment until extubatn | From onset of treatment until extubation |
| unit (days, hours, etc.) | | | | | | | days | days | days |
| How data were reported (mean or median and type of variance) | | | | | | | mean (SD) | median and range | median (IQR) |
| Intervention group: (mean or median) | | | | | | | 12.9 | 21.65 | 8 |
| Intervention group: (variance) | | | | | | | 2.1 | 11.75-35 | 6-14.5 |
| Intervention group: total number of patients | | | | | | | 24 | 44 | 104 |
| Comparison group: (mean or median) | | | | | | | 13.5 | 21.5 | 12 |
| Comparison group: (variance) | | | | | | | 2.1 | 8.36-40.5 | 21-Aug |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| Comparison group: total number of patients | | | | | | | 18 | 51 | 104 |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | yes | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | yes | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | yes | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | yes | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | no | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Data available | Not reported | Not reported | Not reported | Data available | Not reported | Not reported |
| Duration of follow-up [days] | | | 28 | | | | from initiation of treatment to EOT | | |
| unit (days, hours, etc.) | | | days | | | | days | | |
| How data were reported (mean or median and type of variance) | | | mean (SD) | | | | median (range) | | |
| Intervention group: | | | 24±3 | | | | 10 | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| (mean or median) | | | | | | | | | |
| Intervention group: (variance) | | | | | | | 26 | | |
| Intervention group: total number of patients | | | | | | | 19 | | |
| Comparison group: (mean or median) | | | 14±13 | | | | 0 | | |
| Comparison group: (variance) | | | | | | | 27 | | |
| Comparison group: total number of patients | | | | | | | 24 | | |
| Blinding [patients] (only relevant for RCTs) | | | yes | | | | yes | | |
| Blinding [personnel] (only relevant for RCTs) | | | yes | | | | yes | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | yes | | | | yes | | |
| Blinding [data collectors] (only relevant for RCTs) | | | yes | | | | yes | | |
| Blinding [analysts] (only relevant for RCTs) | | | yes | | | | yes | | |
| ITT analysis performed (only relevant for RCTs) | | | no | | | | yes | | |
| **Length of ICU stay** | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Data available | Data available |
| Duration of follow-up [days] | | | 28 | | | | | Total time in ICU after treatment | Total time in ICU from start of treatment |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| unit (days, hours, etc.) | | | days | | | | | days | days |
| How data were reported (mean or median and type of variance) | | | | | | | | median and range | median (IQR) |
| Intervention group: (mean or median) | | | | | | | | 24.5 | 12 |
| Intervention group: (variance) | | | | | | | | 15.25-49 | 23-Jul |
| Intervention group: total number of patients | | | | | | | | 44 | 104 |
| Comparison group: (mean or median) | | | | | | | | 23 | 14 |
| Comparison group: (variance) | | | | | | | | Nine to fifty one | 22-Aug |
| Comparison group: total number of patients | | | | | | | | 51 | 104 |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only | | | | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| relevant for RCTs) | | | | | | | | | |
| **Length of hospital stay** | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Data available | Not reported |
| Duration of follow-up [days] | | | | | | | | From treatment Until discharge from hospital | |
| unit (days, hours, etc.) | | | | | | | | days | |
| How data were reported (mean or median and type of variance) | | | | | | | | median and range | |
| Intervention group: (mean or median) | | | | | | | | 33 | |
| Intervention group: (variance) | | | | | | | | 20.99-54.75 | |
| Intervention group: total number of patients | | | | | | | | 44 | |
| Comparison group: (mean or median) | | | | | | | | 40 | |
| Comparison group: (variance) | | | | | | | | 17-61.4 | |
| Comparison group: total number of patients | | | | | | | | 51 | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| **Clinical cure (as defined by the study authors)** | | | | | | | | | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | Data available | Data available | Data available | Data available |
| Definition (provide details if relevant) | resolution of signs and symptoms | resolution of signs and symptoms | if they were extubate, * | Complete resoultion of all signs and symptoms of VAP | Success defined as extubation | Resolution of signs and symptoms | Resolutin of signs and symptoms | Resolution of signs and symptoms | Resolution of signs and symptoms |
| Duration of follow-up (time point when outcome was measured) [days] | | end of treatment | 28 | 28 | during study | variable-retrospective | 14 days or until extubatin | Not clear | At end of treatment |
| Intervention group: # with event | 24 | 23 | 5 | 26 | 7 | 62 | 8 | 24 | 72 |
| Intervention group: Total | 45 | 42 | 5 | 51 | 21 | 78 | 14 | 44 | 104 |
| Comparison group: # with event | 18 | 14 | 3 | 26 | 3 | 26 | 4 | 20 | 57 |
| Comparison group: Total | 40 | 23 | 5 | 51 | 17 | 43 | 18 | 51 | 104 |
| Blinding [patients] (only relevant for RCTs) | yes | | yes | yes | yes | | yes | | |
| Blinding [personnel] (only relevant for RCTs) | yes | | yes | yes | yes | | yes | | |
| Blinding [outcome | yes | | yes | yes | yes | | yes | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | yes | | yes | probably yes | yes | | yes | | |
| Blinding [analysts] (only relevant for RCTs) | yes | | yes | probably yes | yes | | yes | | |
| ITT analysis performed (only relevant for RCTs) | probably yes | | probably no | yes | probably yes | | no | | |
| NOTES: | | | *or if their MODS score improved, fever resolved, CXR and other physical signs improved | | | | | | |
| **Recurrent pneumonia** | | | | | | | | | |
| Are the data available? | | Data available | Data available | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | ICU stay | 28 | | | | | | |
| Intervention group: # with event | 8 | 5 | 0 | | | | | | |
| Intervention group: Total | 25 | 43 | 5 | | | | | | |
| Comparison group: # with event | 11 | 2 | 0 | | | | | | |
| Comparison group: Total | 16 | 43 | 5 | | | | | | |
| Blinding [patients] (only relevant for RCTs) | yes | | yes | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | yes | | yes | | | | | | |
| Blinding [outcome assessors] (only | yes | | yes | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | yes | | yes | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | yes | | yes | | | | | | |
| ITT analysis performed (only relevant for RCTs) | no | | no | | | | | | |
| NOTES: | | | One of intravenous ts group had | | | | | | |
| **Number of antibiotic days** | | | persistant pneumonia,not recurrent | | | | | | |
| Are the data available? | Not measured | Not reported | Not reported | Not reported | Not reported | Data available | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | | | during treatment | | | |
| unit (days, hours, etc.) | | | | | | days | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | |
| Comparison group: total number of | | | | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| patients | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | Data is reported by individual antibioitc so calculation cannot e made by patient | | | |
| **Development of resistance (as defined by the study authors)** | | | | | | | | | |
| Are the data available? | Data available | Not reported | Not reported | Not reported | Not reported | Not reported | Data available | Not reported | Not reported |
| Duration of follow-up [days] | two weeks post end of treatment | | | | | | Through treatment period | | |
| Intervention group: # with event | 1 | | | | | | 0 | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| Intervention group: Total | 25 | | | | | | 19 | | |
| Comparison group: # with event | 0 | | | | | | 8 | | |
| Comparison group: Total | 16 | | | | | | 24 | | |
| Blinding [patients] (only relevant for RCTs) | yes | | | | | | yes | | |
| Blinding [personnel] (only relevant for RCTs) | yes | | | | | | yes | | |
| Blinding [outcome assessors] (only relevant for RCTs) | yes | | | | | | yes | | |
| Blinding [data collectors] (only relevant for RCTs) | yes | | | | | | yes | | |
| Blinding [analysts] (only relevant for RCTs) | yes | | | | | | yes | | |
| ITT analysis performed (only relevant for RCTs) | no | | | | | | yes | | |
| NOTES: | | | | | | | No AA patients developed resistant to aerosolized drug. | | |
| **Any adverse effect** | | | | | | | | | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | Not reported | Not reported | Not reported | Data available |
| Duration of follow-up [days] | 2 weeks post end of treatment | | 14 | 28 | during study | | | | during treatment |
| Intervention group: # with at lest one event (if this was | 5 | 8 | 0 | 13 | 0 | | | | 26 |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| reported) | | | | | | | | | |
| Intervention group: # od events per group (if this was reported) | | | | | 21 | | | | |
| Intervention group: Total | 45 | 43 | 5 | 51 | 0 | | | | 104 |
| Comparison group: #with at lest one event (if this was reported) | 4 | 8 | 2 | 10 | 17 | | | | 23 |
| Comparison group: # od events per group (if this was reported) | | | | | | | | | |
| Comparison group: Total | 40 | 43 | 5 | 49 | | | | | 104 |
| Blinding [patients] (only relevant for RCTs) | yes | | yes | no | | | | | |
| Blinding [personnel] (only relevant for RCTs) | yes | | yes | no | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | yes | | yes | no | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | yes | | yes | no | | | | | |
| Blinding [analysts] (only relevant for RCTs) | yes | | yes | no | | | | | |
| ITT analysis performed (only relevant for RCTs) | yes | | no | yes | | | | | |
| NOTES: | These numbere represent worsened renal function | renal failure | renal failure | Renal impairment was AE | renal failure | | | | Advesre event reported in nephrotoxicity |
| **Serious adverse** | | | | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| **effect** | | | | | | | | | |
| Are the data available? | Not reported | Not reported | Data available | Not reported | Not reported | Not reported | Not reported | None reported | Not reported |
| Duration of follow-up [days] | | | 28 | | | | | | |
| Intervention group: # with at lest one event (if this was reported) | | 0 | 0 | | | | | | |
| Intervention group: # od events per group (if this was reported) | | | | | | | | | |
| Intervention group: Total | | | 5 | | | | | | |
| Comparison group: #with at lest one event (if this was reported) | | | 1 | | | | | | |
| Comparison group: # od events per group (if this was reported) | | | | | | | | | |
| Comparison group: Total | | | 5 | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | yes | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | yes | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | yes | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | yes | | | | | | |
| Blinding [analysts] (only relevant for | | | yes | | | | | | |

| Data Extraction Table- Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Last name of the first author** | **Brown** | **Kofteridis** | **Hallal** | **Rattanaumpawan** | **Le Conte** | **Korbilia** | **Palmer** | **Doshi** | **Tumbarello** |
| **Year** | **1990** | **2010** | **2007** | **2010** | **2000** | **2010** | **2008** | **2013** | **2013** |
| RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | no | | | | | | |
| NOTES: | | | sepsis and acute renal failure | | | | | | |

| **Evidence Profile-Should patients with VAP due to gram-negative bacilli be treated with a combination of inhaled and systemic antibiotics, or systemic antibiotics alone?** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | Risk difference Quality |
| **Mortality** | | | | | | | | | | |
| Brown 1990 | Of 88 enrolled 45 were assessable | | No | | No | 7/40 | 13/45 | 1.65(.73-3.73) | | Moderate |
| Hallal | Single site RCT | | No | Not estimable | No | 0/5 | 0/5 | | | Moderate |
| Koftederis | retrospective case-control | | No | | No | 18/42 | 10/23 | 1(.96-1.05 | | Low |
| Korbilia | comparative cohort study | | No | | No | 19/43 | 31/78 | .9(.58-1.39) | | moderate |
| LeConte | multi center RCT | | No | | No | 4/17 | 2/21 | .4(.8-1.95 | | high |
| Palmer | single cite RCT | | No | | Industry funded | 4/24 | 4/19 | 1.26(.36,4.40 | | moderate |
| Rattapaunamaun | Single cite RCT | | No | | No | 20/49 | 22/51 | 1.06(.67,1.68) | | moderate |
| Total | | 0% | | | | | 216 | 1(.96, 1.05) | | |
| **Clinical outcome** | | | | | | | | | | |
| Brown 1990 | | | No | | | 18/40 | 24/25 | 1.19[0.76,1.84] | | Moderate |
| Hallal | | | No | | | 3/5 | 5/5 | 1.57[.77,3.22] | | Moderate |
| Koftederis | | | No | | | 14/43 | 23/43 | 1.64[.98,2.74] | | Low |
| Korbilia | | | No | | | 26/43 | 62/78 | 1.31[1.01,1.72] | | moderate |
| LeConte | | | No | | | 3/17 | 7/21 | 1.89[0.57,6.22] | | high |
| Palmer | | | No | | | 4/18 | 8/14 | 2.57[0.97, 6.82] | | moderate |
| Rattapaunamaun | | | No | | | 26/49 | 26/51 | .96[0.66, 1.40] | | moderate |
| Total | | 0% | | | | 215 | 257 | 1.29[1.09,1.53] | | |
| **Nephrotoxicity** | | | | | | | | | | |
| Brown 1990 | | | No | | | 4/40 | 5/45 | 1.11[0.32, 3.85 | | Moderate |
| Hallal | | | No | | | 2/5 | 0/5 | .2[0.01,3.35] | | Moderate |
| Koftederis | | | No | | | 8/43 | 8/43 | 1.00[0.41, 2.42] | | Low |
| Korbilia | | | No | | | NA | NA | NA | | NA |
| LeConte | | | No | | | NA | NA | NA | | NA |
| Palmer | | | No | | | NA | NA | NA | | Na |
| Rattapaunamaun | | | No | | | 11/49 | 13/51 | 1.14[0.56, 2.29] | | moderate |
| Total | | 0% | | | | 137 | 144 | 1.03[0.63, 1.69] | | |

## XV. What antibiotics should be used for the treatment for MRSA HAP/VAP?

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Type of information (published or unpublished) | published | published | published | published | published | published | published |
| Journal name | Am J Resp Crit Care | Journal of Antimicrob Chemo | crit care med | J o fAntimicro Chem | Clinical Infectious Diseases | Chest | Clinical Infectious Diseases |
| Language of publication | English | English | English | English | English | English | English |
| Funding body | Rhone-Poulenc Rorer Pharaceuticals | Unrestricted grant from Pharmacia | GrantKorea Healthcare Technology R and D | Pfizer | jointly by Theravance, Inc. and Astellas Pharma Global Development, Inc. | Pfizer Inc. | Pfizer Inc. |
| Ethics approval | Yes | Yes | Yes | yes | institutional review board at each sie approved the protocol | Institutional Review Board or Ethics Committee approval was obtained | by institutional review board or ethics committee at each in- vestigational site |
| Country where study was done | Europe and US | England | Korea | Japan | 38 countries | 36 sites in USA and Puerto Rico | USA, "Europe, Asia, South America, Other" |
| REVIEWED BY | PALMER | PALMER | PALMER | PALMER | SWEENEY | SWEENEY | SWEENEY |
| **METHODS** | | | | | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | | | | | |
| Randomization | truly random | truly random | truly random | truly random | truly random | truly random | truly random |
| Concealment | no | yes | no | no | yes | no | yes |
| Not stopped early | not stopped early | not stopped early | not stopped early | not stopped early | not stopped early | not stopped early | not stopped early |
| NOTES: | | | | | | | |
| ***if COHORT STUDY*** | | | | | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | | | | | |
| Selection of the non exposed cohort | | | | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Ascertainment of exposure | | | | | | | |
| Demonstration that outcome of interest was not present at start of study | | | | | | | |
| Comparability of cohorts on the basis of the design or analysis | | | | | | | |
| Assessment of outcome | | | | | | | |
| Was follow-up long enough for outcomes to occur? | | | | | | | |
| Adequacy of follow up of cohorts | | | | | | | |
| Co-Interventions similar between groups? | | | | | | | |
| NOTES: | | | | | | | |
| ***if CASE-CONTROL STUDY*** | | | | | | | |
| Is case definition adequate? | | | | | | | |
| Representativeness of the cases | | | | | | | |
| Selection of controls | | | | | | | |
| Definition of controls | | | | | | | |
| Comparability of cases and controls | | | | | | | |
| Ascertainment of exposure | | | | | | | |
| Same method of ascertainment for cases and controls | | | | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Non-response rate | | | | | | | |
| Co-interventions similar between groups? | | | | | | | |
| NOTES: | | | | | | | |
| | | | | | | | |
| **INTERVENTIONS BEING COMAPRED** | | | | | | | |
| **Intervention 1 (experimental)** | intravenous quinopristin/dalfopristin | iv linezolid | vancomycin and rifampicin | linezolid | telavancin 10mg/kg IV q 24h | Linezolid 600mg q 12 | linezolid 600 mg IV q 12 h |
| other Tx used (if relevant for interpretation) | aztreonam or tobramycin if GNR also | dummy teichoplanin | | GNR coverage if needed | | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | |
| **Intervention 2 (comparison)** | vancomycin | iv teichoplanin | vancomycin | vancomycin | | | vancomycin 15 mg/kg IV q 12 hours) |
| other Tx used (if relevant for interpretation) | aztreonam or tobramycin if GNR also | dummy linezolid | | GNR coverage if needed | vancomycin 1g IV q 12; adjusted according to institutional policy at each site | vancomycin 1 g iv q 12 | |
| Tx not allowed (if relevant for interpretation) | | | | | | | |
| duration of treatment | 5-14 days | | 14 days | 7-21 days | 7-21 days | 7-14 days | 7-14 days (21d if bacteremic) |
| NOTES: | | multiple sites in addition to lung | | | | | authors make the point that prior investigators may have underdosed vancomycin; dosing in this trial was as per guidelines |
| **BASELINE CHARACTERISTICS** | | | | | | | |
| **Number randomised** | 171 | | 83 | 151 | | 149 | 1225 |
| Intervention | 87 | 100 | 41 | 100 | 767 | 74 (30 mITT) | 618 |
| Comparison | 84 | 102 | 42 | 51 | 765 | 72 (20 mITT) | 607 |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Total (only if not reported separately) | | | | | 1532 | mITT were the patients who met inclusion criterion of baseline mrsa concentration of >= 10^4;3 patients never received study meds after being randomized hence the diff between the two groups and the number randomized | however, primary analysis was performed on pp patients (172 and 176), secondary on mitt (224 and 224) |
| **Age** | | | | | | | |
| Intervention (mean or median) | | 59.2 ±17.2 | 66 | 68.4 median | 62 (18.5) | 55.7 (20.5) | 60.7 (18.0) |
| Comparison (mean or median) | 56.6(mean) | 57.3 ±17.6 | 71 | 67.5 | 63(17.7) | 54.9 (19.2) | 61.6 (17.7) |
| Total (mean or median) (only if not reported separately) | | | | | | | |
| unit (e.g. mean and SD) | mean (SD) | mean (SD) | median (range) | median (range) | mean (SD) | mean (SD) | mean (SD) |
| Age range (e.g. 22-73) | | | 28-98 | 22-96 | | | |
| Age inclusion criterion (e.g. older than 16) | 18 or older | | 18 or older | 20 or older | > or = 18 | > or = 18 | > or = 18 |
| **Male gender** | | | | | | | |
| Intervention | not described | 67.00% | 85.00% | 70.00% | 487(65%) | 22(73%) | 116 (67.4%) |
| Comparison | not described | 68.00% | 83.00% | 70.00% | 469(62%) | 16(80%) | 112 (63.6%) |
| Total (only if not reported separately) | | | | | | | |
| **Severity of illness** | | | | | | | |
| Name of score (e.g. APACHE, SOFA, ...) | Apache II | SOFA | Apache II | If other please specify | Apache II | Apache II | Apache II |
| Intervention group mean score | 15.2 | | 24 | | 15(6.1) | 22.1 (1.1) | 17.2 (6.4) |
| Comparison group mean score | 14.9 | | 24 | | 16(6.2) | 20.0 (1.3) | 17.4 (6.0) |
| Total (only if not | | | | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| reported separately) | | | | | | | |
| **Study population** | | | | | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Mixed Medical-Surgical | If other please specify | Medical | Mixed Medical-Surgical | pna after 48h in hospital or chronic care facility or developed within 7 days after being discharged | mechanically ventilated | "hospitalized" |
| NOTES: | | Noted as ICU's | 73% in each group were ventilated | No severity of illness | characteristics of all treated pop which includes patients with other gram positive infections | modified ITT patient baseline characteristics | all baseline characteristics pp patients only |
| | | | | 51% in each group were vented | | | |
| **OUTCOMES** | | | | | | | |
| | | | | | | | |
| **Mortality (all cause)** | | | | | | | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | Data available | Data available |
| location or duration of follow-up (choose from the list) | 30 day | If other please specify up EOT | If other please specify-up to 60 days | 7-14 days after EOT | within 28 days of end of treatment | 28 day | all cause ITT and mITT mortality at 60 days |
| Intervention group: # with event | 38 | 18 | 11 | 14 | 150 | 4 | 97 (15.7%) and 63 ( 28.1%) |
| Intervention group: Total | 87 | 100 | 41 | 100 | 751 | 30 | 618 and 224 |
| Comparison group: # with event | 32 | 25 | 21 | 7 | 140 | 6 | 35 (17.0%) and 59 (26.3%) |
| Comparison group: Total | 84 | 104 | 42 | 51 | 752 | 20 | 207 and 224 |
| Blinding [patients] (only relevant for RCTs) | no | yes | no | no | probably yes | probably no | yes |
| Blinding [personnel] (only relevant for RCTs) | no | yes | no | no | probably yes | probably no | yes |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Blinding [outcome assessors] (only relevant for RCTs) | no | yes | probably no | no | probably yes | probably no | yes |
| Blinding [data collectors] (only relevant for RCTs) | no | yes | probably no | no | probably yes | probably no | yes |
| Blinding [analysts] (only relevant for RCTs) | no | yes | probably yes | probably yes | probably yes | probably no | yes |
| ITT analysis performed (only relevant for RCTs) | no | yes | yes | yes | | no | yes |
| NOTES: | 63 patients removed from study for inadequat data or prohibited antibioitic use | | modified ITT | | | "More patients were alive [in the mITT pop] at the end of the study (day 28 mortality) in the LZD-treated group than in the VAN-treated group (86.7% vs 70.0%, respectively), but the difference did not reach statis tical significance (p=0.149)." | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | | | | | |
| Are the data available? | Not reported | Not reported | Data available | Not reported | Not measured | Data available | Not measured |
| Duration of follow-up [days] | | | hospitalization | | | 28 day | |
| unit (days, hours, etc.) | | | days | | | days | |
| How data were reported (mean or median and type of variance) | | | median (range) | | | mean (SE) | |
| Intervention group: (mean or median) | | | 28 | | | 10.4 (1.6) | |
| Intervention group: | | | 0-470 | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| (variance) | | | | | | | |
| Intervention group: total number of patients | | | 22 | | | 30 | |
| Comparison group: (mean or median) | | | 20 | | | 14.3(2.1) | |
| Comparison group: (variance) | | | 0-181 | | | | |
| Comparison group: total number of patients | | | 25 | | | 20 | |
| Blinding [patients] (only relevant for RCTs) | | | no | | | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | | no | | | probably no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | probably no | | | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | | probably no | | | probably no | |
| Blinding [analysts] (only relevant for RCTs) | | | probably yes | | | probably no | |
| ITT analysis performed (only relevant for RCTs) | | | probably yes | | | no | |
| NOTES: | | | modified MTT | | | once again modified ITT population | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported | Not measured | Data available | Not measured |

| Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP? | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Duration of follow-up [days] | | | | | | 28 day | |
| unit (days, hours, etc.) | | | | | | days | |
| How data were reported (mean or median and type of variance) | | | | | | mean (SE) | |
| Intervention group: (mean or median) | | | | | | 15.5 (1.8) | |
| Intervention group: (variance) | | | | | | | |
| Intervention group: total number of patients | | | | | | 30 | |
| Comparison group: (mean or median) | | | | | | 11.1 (2.4) | |
| Comparison group: (variance) | | | | | | | |
| Comparison group: total number of patients | | | | | | 20 | |
| Blinding [patients] (only relevant for RCTs) | | | | | | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | probably no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | probably no | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | probably no | |

| Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP? | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| ITT analysis performed (only relevant for RCTs) | | | | | | no | |
| NOTES: | | | | | | once again modified ITT population | modified ITT |
| **Length of ICU stay** | | | | | | | |
| Are the data available? | Not reported | Data available | Data available | Not reported | Not measured | Data available | Not measured |
| Duration of follow-up [days] | | days in ICU after trial entry | until dicharged to floor or dead | | | 28 day | |
| unit (days, hours, etc.) | | days | days | | | days | |
| How data were reported (mean or median and type of variance) | | | median (range) | | | mean (SE) | |
| Intervention group: (mean or median) | | 9 | 28 | | | 12.2 (1.4) | |
| Intervention group: (variance) | | 0-54 | 9-424 | | | | |
| Intervention group: total number of patients | | 100 | 41 | | | 30 | |
| Comparison group: (mean or median) | | 9 | 23 | | | 16.2 (1.9) | |
| Comparison group: (variance) | | 0-105 | 7-151 | | | | |
| Comparison group: total number of patients | | 104 | 42 | | | 20 | |
| Blinding [patients] (only relevant for RCTs) | | yes | probably no | | | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | yes | probably no | | | probably no | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Blinding [outcome assessors] (only relevant for RCTs) | | yes | probably no | | | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | yes | probably no | | | probably no | |
| Blinding [analysts] (only relevant for RCTs) | | yes | probably yes | | | probably no | |
| ITT analysis performed (only relevant for RCTs) | | yes | probably yes | | | no | |
| NOTES: | | | modified ITT | | | once again modified ITT population | |
| **Length of hospital stay** | | | | | | | |
| Are the data available? | Not reported | Not reported | Data available | Not reported | Not measured | Data available | Not measured |
| Duration of follow-up [days] | | | until discharge | | | 28 day | |
| unit (days, hours, etc.) | | | days | | | days | |
| How data were reported (mean or median and type of variance) | | | median (range) | | | mean (SE) | |
| Intervention group: (mean or median) | | | 50 | | | 18.8 (1.6) | |
| Intervention group: (variance) | | | 10-477 | | | | |
| Intervention group: total number of patients | | | 41 | | | 30 | |
| Comparison group: (mean or median) | | | 42 | | | 20.1 (1.4) | |
| Comparison group: (variance) | | | 12-249 | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Comparison group: total number of patients | | | 42 | | | 20 | |
| Blinding [patients] (only relevant for RCTs) | | | no | | | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | | probably no | | | probably no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | no | | | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | | no | | | probably no | |
| Blinding [analysts] (only relevant for RCTs) | | | probably yes | | | probably no | |
| ITT analysis performed (only relevant for RCTs) | | | yes | | | no | |
| NOTES: | | | modified ITT | | | once again modified ITT population | |
| **Clinical cure (as defined by the study authors)** | | | | | | | |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | Data available | Data available |
| Definition (provide details if relevant) | Resolution of signs and symptoms | resolution of signs and symptoms | resolution of signs and symptoms | resolution of signs and symptoms | | | primary outcome with clinical outcome at end of study in per protocol patients; resolution of clinical signs and symptoms of pneumonia compared with baseline, improvement or lack of progression in chest imaging, and no requirement for additional antibacterial treatment |

| Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP? | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Duration of follow-up (time point when outcome was measured) [days] | 7-13 days after end of treatment | up to 21 days after EOT | 14 days | EOT and 7-14 days later | 7-14 days after end of therapy | 28 day | within 5 days of EOT (7-14d, 21d if bacteremic) |
| Intervention group: # with event | 46 | 71 | 22 | 15 | 72/88(81.8%) | 66.70% | 95 ( or 57.6% per protocol patients) |
| Intervention group: Total | 87 | 90 | 41 | 62 | 88 | 30? | 165 (Per protocol patients) |
| Comparison group: # with event | 44 | 67 | 13 | 6 | 86/116(74.1%) | 52.90% | 81 (or 46.6% of per protocol patients) |
| Comparison group: Total | 84 | 92 | 42 | 30 | 116 | 20? | 174(per protocol pts) |
| Blinding [patients] (only relevant for RCTs) | no | yes | no | no | probably yes | probably no | yes |
| Blinding [personnel] (only relevant for RCTs) | no | yes | no | no | probably yes | probably no | yes |
| Blinding [outcome assessors] (only relevant for RCTs) | no | yes | no | no | probably yes | probably no | yes |
| Blinding [data collectors] (only relevant for RCTs) | no | yes | no | no | probably yes | probably no | yes |
| Blinding [analysts] (only relevant for RCTs) | no | yes | probably yes | probably yes | probably yes | probably no | yes |
| ITT analysis performed (only relevant for RCTs) | no | yes | yes | yes | no | no | no |
| NOTES: | | clinical cure could not be defined in 10 in each group | | | microbiologically evaluable pop--monomicrobial mrsa cases only | results given as % ? Presumably from mITT population? | data for clinical cure shown above is for the primary endpoint--clinical outcome at end of study (EOS defined as 7–30 days after EOT) in evaluable per-protocol (PP) patients. Secondary outcomes included: clinical response |

| Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP? | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| | | | | | | | mITT patients at EOS (linezolid group 102/186, 54.8%; vanco group 92/205, 44.9%)and clinical response for pp (linezolid group 150/180,83.3%; vanco group 130/186, 69.9%) and mITT pts (linezolid group 161/201, 80.1%; vanco group 145/214,67.8%) both at end of treatment (EOT). Of note "Clinical outcome was primarily assessed by the investigator within 5 days of EOT and at EOS, with occasional override by the sponsor based on the criteria of Appendix 1. All revisions were made before unblinding" |
| **Recurrent pneumonia** | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | | | | |
| Intervention group: # with event | | | | | | | |
| Intervention group: Total | | | | | | | |
| Comparison group: # with event | | | | | | | |
| Comparison group: Total | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | |
| NOTES: | | | | | | | |
| **Number of antibiotic days** | | | | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | | | | |
| unit (days, hours, etc.) | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | |
| Intervention group: (mean or median) | | | | | | | |
| Intervention group: (variance) | | | | | | | |
| Intervention group: total number of patients | | | | | | | |
| Comparison group: (mean or median) | | | | | | | |
| Comparison group: (variance) | | | | | | | |
| Comparison group: total number of patients | | | | | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Blinding [patients] (only relevant for RCTs) | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | |
| NOTES: | | | | | | | by design patients received either linezolid or vancomycin for 7–14 consecutive days (21 days if bacteremia was documented) |
| **Development of resistance (as defined by the study authors)** | | | | | | | |
| Are the data available? | Not reported | Not reported | Data available | Data available | Not reported | Not reported | Not measured |
| Duration of follow-up [days] | | | 14 | up to 16 days post treatment | | | |
| Intervention group: # with event | | | 14 | 0 | | | |
| Intervention group: Total | | | 41 | 62 | | | |
| Comparison group: # with event | | | 0 | 0 | | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Comparison group: Total | | | 42 | 30 | | | |
| Blinding [patients] (only relevant for RCTs) | | | no | no | | | |
| Blinding [personnel] (only relevant for RCTs) | | | no | no | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | no | no | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | no | no | | | |
| Blinding [analysts] (only relevant for RCTs) | | | probably yes | probably yes | | | |
| ITT analysis performed (only relevant for RCTs) | | | yes | | | | |
| NOTES: | | | resistant to rifampicin reported | | | | |
| **Any adverse effect** | | | | | anemia(hematocrit<30% male, <28% female)/thrombocytopenia(<75k) | anemia (>20% hb decrease)/thrombocytopenia (>20% platelet decrease) | anemia(hb<or=10 g/dL or 0.2g/dL decrease during study period)/thrombocytopenia(<150K if nl at baseline or 50% decrease if low at baseline) |
| Are the data available? | Data available | Data available | Data available | Data available | Data available | Data available | |
| Duration of follow-up [days] | 30 | up to 21 days after EOT | 14 | up to 16 days post treatment | "laboratory assessments were performed …up to the EOT[7-21 days]" | up to 30 days after last antibiotic dose | until 28 days after the last dose of study treatment |
| Intervention group: # with at lest one event (if this was reported) | 181 | | 11 | 55 | 28/6 | "9/2" | 30/8 |

| Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP? | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| Intervention group: # od events per group (if this was reported) | | 250 | | 156 | | | |
| Intervention group: Total | | 250 | 41 | 156 | 196/370 | 73 | 597 |
| Comparison group: #with at lest one event (if this was reported) | 167 | | 6 | 22 | 33/10 | "7/6" | 42/13 |
| Comparison group: # od events per group (if this was reported) | | 276 | | 40 | | | |
| Comparison group: Total | | 276 | 42 | 40 | 199/403 | 72 | 587 |
| Blinding [patients] (only relevant for RCTs) | | | no | no | probably yes | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | | no | no | probably yes | probably no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | no | no | probably yes | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | | no | no | probably yes | probably no | |
| Blinding [analysts] (only relevant for RCTs) | | | probably yes | probably yes | probably yes | probably no | |
| ITT analysis performed (only relevant for RCTs) | | | yes | | | | |
| NOTES: | | | modified ITT | | lab abnormalities in pts with normal values at baseline for the pooled studies safety population; ? In the caseof cratinine, abnl baseline values | | |

| **Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP?** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| | | | | | included | | |
| **Serious adverse effect** | | | | | nephrotoxicity (>50% increase from aseline and with a max value of >1.5mg/dL regardless of initial value | I'm limiting to nephrotoxicity | nephrotoxicity defined as 0.5 mm/ml increase in serum creatinine level if ormal at baseline or 50% increase if abl at baseline) |
| Are the data available? | Data available | Not reported | Data available | Data available | Data available | Data available | Data available |
| Duration of follow-up [days] | 30 | | unclear | up to 16 days post tx | | up to 30 days after last antibiotic dose | until 28 days after the last dose of study treatment |
| Intervention group: # with at lest one event (if this was reported) | 18 | | 1 | 9 | "111" | 0 | 22 |
| Intervention group: # od events per group (if this was reported) | | | | 10 | | | |
| Intervention group: Total | 18 | | 1 | 10 | 716 | 75 | 597 |
| Comparison group: #with at lest one event (if this was reported) | 19 | | 3 | 2 | "69" | 1 | 43 |
| Comparison group: # od events per group (if this was reported) | | | | 3 | | | |
| Comparison group: Total | 19 | | 3 | 3 | 723 | 74 | 587 |
| Blinding [patients] (only relevant for RCTs) | | | no | no | probably yes | probably no | yes |
| Blinding [personnel] (only relevant for RCTs) | | | no | no | probably yes | probably no | yes |
| Blinding [outcome assessors] (only relevant for RCTs) | | | no | no | probably yes | probably no | yes |
| Blinding [data | | | no | no | probably yes | probably no | yes |

| Evidence Extraction Table – What Antibiotics should be used for the treatment of MRSA HAP/VAP? | | | | | | | |
|---|---|---|---|---|---|---|---|
| Last name of the first author | Fagon | Cepeda | Jung | Kohno | Rubinstein | Wunderink | Wunderink |
| Year | 2000 | 2004 | 2010 | 2007 | 2011 | 2008 | 2012 |
| collectors] (only relevant for RCTs) | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | probably yes | probably yes | probably yes | probably no | yes |
| ITT analysis performed (only relevant for RCTs) | | | yes | probably yes | | | yes |
| NOTES: | | | | | | most of the above outcomes are stated to be measured at 28 days; in reality Mortality, ventilator use, and clinical response evaluations were performed at the EOT and FU visits. end of treatment (EOT) □day 14□ and at the end of the study visit (ie, FU), which occurred a mean (□ SD) duration of 14 □ 2 days after the EOT; also this study focused on Microbiological cure ( defined as a repeat BBAL specimen containing □ 102 cfu/mL MRSA)f which our extraction form does not measure | in ITT patients! nephrotoxicity (defined as 0.5-mg/mL increase in serum creatinine level if normal at baseline or 50% increase if abnormal at baseline); Renal toxicity was roughly equivalent in patients with baseline glo- merular filtration rate <50 mL/min (16.2% vancomycin vs 13.8% linezolid) but was higher in vancomycin-treated patients with glomerular filtration rate >50 mL/min at baseline (18.8% vs 5.6% for linezolid). |

| **Evidence Profile-What antibiotics should be used for the treatment for MRSA HAP/VAP?** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Quality Assessment[ǂ] | | | | | | | Summary of Findings | | | | |
| | | | | | | | Number of patients | | Relative risk (CI) | Risk diff (CI) | Quality |
| Outcome | Study | Limitations (=risk of bias) | Inconsistency ($I^2$ shown if >30%) | Indirectness | Imprecision | Pub bias | Linezolid | Vanco | | | |
| Mortality ITT | Wunderink 2008 | | | | | | | | | | |
| | Wunderink 2012* | | | | | | | | | | |
| | Total | | | | | | 102/693 | 111/681 | 0.91 (0.71,1.16) | -0.02(-0.06,0.02) | moderate |
| Mortality mITT | Wunderink 2008 | | | | | | | | | | |
| | Wunderink 2012 | | | | | | | | | | |
| | Total | | $I^2$ = 57% | | | | 67/254 | 63/224 | .83 (.36,1.90) | -.04 (-.22,.14) | moderate |
| Clinical Cure ITT | Kohno 2007 | | | | | | | | | | |
| | Stevens 2002 | | | | | | | | | | |
| | Total | | | | | | 65/132 | 31/81 | 1.27 (.83,1.95) | .12 (-.04,.27) | moderate |
| Clinical Cure mITT | Kohno 2007 | Open label, Industry sponsored | | | | | | | | | |
| | Stevens 2002 | Open label, Industry sponsored | | | | | | | | | |
| | Wunderink 2008 | Open label, Industry sponsored | | | | | | | | | |
| | Wunderink 2012 | Industry sponsored | | 16% of per protocol pts (348) were healthcare associated pneumonia. | | | | | | | |
| | Total | | | | | | 145/273 | 123/270 | 1.18 (1.00,1.40) p=.05 | .08 (0,.17) | moderate |
| | Total minus | | | | | | 43/87 | 31/65 | 1.09 | .04 | moderate |

| **Evidence Profile-What antibiotics should be used for the treatment for MRSA HAP/VAP?** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Quality Assessment[‡] | | | | | | | Summary of Findings | | | | |
| | | | | | | | Number of patients | | Relative risk (CI) | Risk diff (CI) | Quality |
| Outcome | Study | Limitations (=risk of bias) | Inconsistency ($I^2$ shown if >30%) | Indirectness | Imprecision | Pub bias | Linezolid | Vanco | | | |
| | Wunderink2012 | | | | | | | | (.79,1.5) | (-.12,.19) | |
| Nephro-toxicity | Kohno 2007 | | | | | | | | | | |
| | Stevens 2002 | | | | | | | | | | |
| | Wunderink 2008 | | | | | | | | | | |
| | Wunderink 2012 | | | | | | | | | | |
| | Total | | $I^2$ = 79% | Multiple definitions of nephrotoxicty | | | 25/1010 | 52/930 | .46 (.29,.74) p=.001 | -.03 (-.06,.01) | moderate |
| | Total minus wunderink 2012 | | | | | | 3/413 | 9/343 | .26 (.07,.98) p=.05 | -.02 (-.07,.02) | moderate |
| Thrombo-cytopenia | Kohno 2007 | | | | | | | | | | |
| | Stevens 2002 | | | | | | | | | | |
| | Wunderink 2008 | | | | | | | | | | |
| | Wunderink 2012 | | | | | | | | | | |
| | Total | | $I^2$ = 91% | | | | 52/1000 | 26/920 | 1.49 (.38,5.8) | .04 (-.04,.12) | moderate |
| Serious adverse | Kohno 2007 | | | | | | | | | | |
| | Stevens 2002 | | | | | | | | | | |
| | Wunderink 2008 | | | | | | | | | | |
| | Wunderink 2012 | | | | | | | | | | |
| | total | | | | | | 311/1032 | 296/950 | .99 (.86,1.13) | 0 (-.04,.04) | |
| Tx discont 2/2 adverse event | Kohno 2007 | | | | | | | | | | |
| | Stevens 2002 | | | | | | | | | | |
| | Wunderink 2008 | | | | | | | | | | |

| **Evidence Profile-What antibiotics should be used for the treatment for MRSA HAP/VAP?** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Quality Assessment[ǂ] | | | | | | | Summary of Findings | | | | |
| | | | | | | | Number of patients | | Relative risk (CI) | Risk diff (CI) | Quality |
| Outcome | Study | Limitations (=risk of bias) | Inconsistency ($I^2$ shown if >30%) | Indirectness | Imprecision | Pub bias | Linezolid | Vanco | | | |
| | Wunderink 2012 | | | | | | | | | | |
| | total | | | | | | 40/1032 | 29/949 | .98 (.61,1.56) | -.01 (-.02,0) | |
| | Jung 2010 | Open label | | | | | Vanco+ rifampin | vanco | | | |
| Clinical cure mitt | | | | | | | 22/41 54% | 13/42 31% | 1.7 | .23 | Moderate |
| 30d mort | | | | | | | 9/41 22% | 16/42 38% | .58 | -.16 | |
| 60d mort | | | | | | | 11/41 27% | 21/42 50% | .54 | -.23 | |

*Wunderink 2012: incomplete accounting--missing data--mTT was 224 patients per arm, yet the clinical response is reported for 186 patients receiving linezolid and 205 patients treated with vancomycin; clinical outcome was primarily assessed by the investigator within 5 days of EOT and EOS, with occasional override by the sponsor…all revisions were made before unblinding; indirectness--16% of per protocol pts (348) were healthcare associated pneumonia.

α nephrotoxicity definitions used: "judgment of the investigator" (2007);" 0.5-mg/mL increase in serum creatinine level if normal at baseline or 50% increase if abnormal at baseline" (2012); "progression of acute renal failure" (2008) ; not defined (2002)

[ǂ]An assessment of quality of for each endpoint was performed; empty cells denote the fact that no deficiency was noted.

**Limitations = risk of bias**

1.lack of allocation concealment Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (major problem in ''pseudo'' or ''quasi'' randomized trials with allocation by day of week, birth date, chart number, etc)

2. Lack of blinding Patient, care givers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or themedication currently being received in a crossover trial)

3. Incomplete accounting of patients and outcome events Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available

4. Selective outcome reporting bias Incomplete or absent reporting of some outcomes and not others on the basis of the results

5. Other limitations Stopping early for benefit Use of unvalidated outcome measures (e.g., patient-reported outcomes) Carryover effects in crossover trial Recruitment bias in cluster-randomized trials

**Inconsistency** $I^2$ test for heterogeneity?

**Indirectness—**four types. occurs when the population, intervention, or outcomes differ from those in which we are interested or when the two interventions are not compared head-to-head

**Imprecision—**CI and relative or absolute risk

**Publication bias—**funnel plot

| SUMMARY OF FINDINGS: TREATMENT OF MRSA HAP/VAP - LINEZOLID COMPARED WITH VANCOMYCIN OR RIFAMPIN+VANCOMYCIN COMPARED WITH VANCOMYCIN FOR THE TREATMENT OF MRSA HAP/VAP IN ADULTS | | | | | | | |
|---|---|---|---|---|---|---|---|
| Patient or population: adults with MRSA HAP/VAP; Setting: high and middle income countries; Intervention: linezolid or the addition of rifampin; Comparison: vancomycin | | | | | | | |
| | | | | | | | |
| Outcomes | Intervention | Comparison | Relative risk (CI) | Risk diff (CI) | Number of participants (studies) | Quality | Comment |
| Mortality ITT | 102/693 | 111/681 | 0.91 (0.71,1.16) | -0.02 (-0.06, 0.02) | 1374 (2) | Moderate | |
| Mortality mITT | 67/254 | 63/224 | .83 (.36,1.90) | -.04 (-.22,.14) | 478 (2) | Moderate | |
| Clinical Cure ITT | 65/132 | 31/81 | 1.27 (.83,1.95) | .12 (-.04,.27) | 213 (2) | Moderate | |
| Clinical Cure mITT | 145/273 | 123/270 | 1.18 (1.00,1.40) p=.05 | .08 (0,.17) | 543 (4) | Moderate | |
| Clinical Cure mITT minus Wunderink 2012* | 43/87 | 31/65 | 1.09 (.79,1.5) | .04 (-.12,.19) | 152 (3) | Moderate | |
| Nephrotoxicity$\alpha$ | 25/1010 | 52/930 | .46(.29,.74) p=.001 | -.03(-.06,.01) | 1940 (4) | Moderate | See above |
| Nephrotoxicity minus Wunderink 2012 | 3/413 | 9/343 | .26(.07,.98) p=.05 | ..02(-.07,.02) | 756 (3) | Moderate | |
| Thrombocytopenia | 52/100 | 26/920 | 1.49(.38,5.8) | .04(-.04,.12) | 1920(4) | Moderate | |
| Serious adverse | 311/1032 | 296/950 | .99(.86,1.13) | 0(-.04,.04) | 1982(4) | Moderate | |
| Tx discont 2/2 adverse event | 40/1032 | 29/949 | .98(.61,1.56) | -.01(-.02,0) | 1981(4) | Moderate | |
| | Vanco+rif | Vanco | | | | | |
| Clinical cure | 22/41 | 13/42 | 1.73(1.02,2.96) | .23(.02,.44) | 83(1) | Moderate | |
| 30d Mortality | 9/41 | 16/42 | .58(.29.1.15) | -.16(-.36,.03) | 83(1) | Moderate | |
| 60d Mortality | 11/41 | 21/42 | .54(.30,97) | -.23(-.43,-.03) | 83(1) | Moderate | |
| *Wunderink 2012: Serious concerns for bias in one study (industry sponsored, incomplete accounting, “occasional override by the sponsor [regarding clinical outcome];all revisions were made before unblinding” $\alpha$ nephrotoxicity definitions used: ”judgment of the investigator” (2007);” 0.5-mg/mL increase in serum creatinine level if normal at baseline or 50% increase if abnormal at baseline” (2012); “progression of acute renal failure” (2008) ; not defined (2002) | | | | | | | |

Note: Dr. Andre Kalil recused himself from all deliberations regarding the quality of evidence and strength of recommendation for this PICO recommendation.

## XVI. Which antibiotic should be used to treat patients with HAP/VAP due to *P. aeruginosa*?

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC | Jenkins SG, Fisher AC, Peterson JA, Nicholson SC, Kaniga K. | Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. | Rea-Neto A, Niederman M, et al, Friedland I | Chastre J, Wunderink R, et al, Friedland I. | Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC | Magnotti LJ, et al, Fabian TC, Croce MA. | Alvarez-Lerma F, et al; Spanish Collaborative Group for the Study of Severe Infections. | Brun-Buisson C, Sollet JP, Schweich H, Brière S, Petit C for VAP Study Group. | Alvarez Lerma F; Serious Infections Study Group. | Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R. | Kollef MH, Nathwani D, Merchant S, Gast C, Quintana A, Ketter N. |
| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| Source of information | published | published | published | published | published | published | published | published | published | published | published | published |
| Journal name | Crit Care Med 2008; 36:108–117 | Curr Med Res Opin 2009 Dec;25(12:3029-36 | BMC Pulm Med. 2010 Aug 26;10:45. | Curr Med Res Opin. 2008 Jul;24(7):2113-26. | Crit Care Med. 2008 Apr;36(4):1089-96. | Crit Care Med. 2008 Jan;36(1):108-17. | J Trauma. 2009 Apr;66(4):1052-8; discussion 1058-9. | Intensive Care Med. 2001 Mar;27(3):493-502. | Clin Infect Dis. 1998 Feb;26(2):346-54. | J Chemother. 2001 Feb;13(1):70-81. Antibiot Khimioter. 2001;46(12):42-52. | Crit Care. 2012 Nov 13;16(6):R218 | Crit Care. 2010;14(3):R84 |
| Language | English | English | English | English | English | English | English | English | English | Russian and English | English | English |
| Funding body | | | | Industry | Industry | None | None | Industry | Industry | Industry | Industry | |
| ETHICS approval | | | | Yes | Yes | | Yes | Yes | Yes | Yes | Yes | |
| COUNTRY where study was done | N/A | N/A | N/A | Multicenter | North America, Europe, other | USA | USA | Spain | France | 14 Spanich ICUs | Western Europe, North America, Australia; Central and South America; or Eastern | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | | | | | | | | | Europe and Asia | |
| Study population enrollment | N/A | N/A | N/A | | | | January 2004 to December 2006 | Not stated | Not stated | Not stated | April 2008 through June 2011 | |
| Title | Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials | Meta-analysis of doripenem vs comparators in patients with pseudomonas infections enrolled in four phase III efficacy and safety clinical trials. | Systematic review of RCTs of imipenem treatment for pneumonia published in English between 1993 and 2008. | Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. | Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. | Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. | Efficacy of Monotherapy in the Treatment of Pseudomonas Ventilator-Associated Pneumonia in Patients With Trauma | Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. | Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. VAP Study Group. | Efficacy of monotherapy by meropenem in ventilator-associated pneumonia | A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia | Medical resource utilization among patients with ventilator-associated pneumonia: pooled analysis of randomized studies of doripenem versus comparators. |
| | | From abstract, pdf NA, Co-authors from | | From abstract, pdf NA | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Last name of the first author | Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC | Jenkins SG, Fisher AC, Peterson JA, Nicholson SC, Kaniga K. | Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. | Rea-Neto A, Niederman M, et al, Friedland I | Chastre J, Wunderink R, et al, Friedland I. | Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC | Magnotti LJ, et al, Fabian TC, Croce MA. | Alvarez-Lerma F, et al; Spanish Collaborative Group for the Study of Severe Infections. | Brun-Buisson C, Sollet JP, Schweich H, Brière S, Petit C for VAP Study Group. | Alvarez Lerma F; Serious Infections Study Group. | Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R. | Kollef MH, Nathwani D, Merchant S, Gast C, Quintana A, Ketter N. |
| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | Ortho-McNeil/Johnson&Johnson | | | | | | | | | | |
| **METHODS** | | | | | Prospective, multicenter, parallel randomized, active-controlled, open-label study. | Meta-analysis; We included randomized controlled trials that evaluated empirical parenteral antibiotic regimens for adult patients with clinically suspected VAP. | Retrospective review | Open label, prospective, multicenter, randomized phase III clinical trial | Open, multicenter, Randomized trial | Prospective, open label, randomized study in intensive care unit patients with ventilator-associated pneumonia (VAP) | prospective, double-blinded, randomized trial | To assess medical resource utilization in patients with VAP, we conducted a pooled analysis of two prospective, randomized, open-label, multicenter, phase III studies, which also showed that doripenem was clinically noninferior to comparators. |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Last name of the first author | Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC | Jenkins SG, Fisher AC, Peterson JA, Nicholson SC, Kaniga K. | Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. | Rea-Neto A, Niederman M, et al, Friedland I | Chastre J, Wunderink R, et al, Friedland I. | Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC | Magnotti LJ, et al, Fabian TC, Croce MA. | Alvarez-Lerma F, et al; Spanish Collaborative Group for the Study of Severe Infections. | Brun-Buisson C, Sollet JP, Schweich H, Brière S, Petit C for VAP Study Group. | Alvarez Lerma F; Serious Infections Study Group. | Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R. | Kollef MH, Nathwani D, Merchant S, Gast C, Quintana A, Ketter N. |
| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | Meta-analysis on the subset of subjects enrolled in four | We conducted a systematic literature review of randomized controlled trials (RCT) of imipenem treatment for | | | We identified 41 trials randomizing 7,015 patients and comparing 29 unique regimens. Methodological quality was low, reflecting low rates of complete follow-up (43.9%), use of a double-blinded interventional strategy (14.6%), and randomization concealment (48.6%). Overall mortality was 20.3%; treatment failure occurred in 37.4% of patients who could be evaluated microbiologically. No mortality differences were observed between any of the regimens compared. Only one of three pooled comparisons yielded a | One hundred ninety-six patients were identified with late gram-negative VAP. There were 84 patients with Pseudomonas VAP. Monotherapy achieved microbiological resolution in 79 patients (94.1%) with zero recurrence. Thirty-six isolates were completely eradicated at repeat BAL. Five patients (5.9%) required combination therapy to achieve resolution. CONCLUSIONS: | | | | We assessed durations of mechanical ventilation, intensive care unit (ICU) stay, and hospitalization in patients with VAP who |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Last name of the first author | Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC | Jenkins SG, Fisher AC, Peterson JA, Nicholson SC, Kaniga K. | Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. | Rea-Neto A, Niederman M, et al, Friedland I | Chastre J, Wunderink R, et al, Friedland I. | Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC | Magnotti LJ, et al, Fabian TC, Croce MA. | Alvarez-Lerma F, et al; Spanish Collaborative Group for the Study of Severe Infections. | Brun-Buisson C, Sollet JP, Schweich H, Brière S, Petit C for VAP Study Group. | Alvarez Lerma F; Serious Infections Study Group. | Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R. | Kollef MH, Nathwani D, Merchant S, Gast C, Quintana A, Ketter N. |
| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| Randomization | | | | stated as random | truly random | | non-random | truly random | truly random | truly random | truly random | truly random |
| Concealment | | | | yes | yes | | | no | | | | |
| Not stopped early | | | | no | no | | | no | no | no | for harm | no |
| NOTES: | Identified 41 trials randomizing 7,015 patients and comparing 29 unique antibiotic regimens. Methodological quality was low, reflecting low rates of complete follow-up (43.9%), use of a double-blinded interventional strategy (14.6%), and randomization concealment (48.6%). | Four (4) randomized phase III clinical trials of doripenem in subjects with complicated intra-abdominal infections (cIAI) and nosocomial pneumonia/ventilator-associated pneumonia (NP/VAP) due to P. aeruginosa. | Of the 46 studies identified, 20 (N = 4,310) included patients with pneumonia (imipenem 1,667, PA 251; comparator 1,661, PA 270). Seven were double blind, and 7 included US data. Comparator arms included a β-lactam (17, [penicillin 6, carbapenem | | | | | Randomized into blocks of 6 patients - 4 in study group, 2 in control group | | | The study was stopped prematurely at the recommendation of the Independent Data Monitoring Committee that was blinded to treatment arm assignment and performed a scheduled review of data which showed | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | 4, cephalosporin 7, monobactam 1]), aminoglycoside 2, vancomycin 1, and a fluoroquinolone 5; 5 employed double coverage. Thirteen focused exclusively on pneumonia and 7 included pneumonia and other diagnoses. | | | | | | | | signals that were close to the pre-specified stopping limits. | |
| ***if COHORT STUDY*** | | | | | | | | | | | | |
| ***if CASE-CONTROL STUDY*** | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | | | | | | | | | | |
| **INTERVENTIONS BEING COMPARED** | | | | | | | | | | | | |
| **Intervention 1 (experimental)** | | | | Doripenem | doripenem | | | pip/tazo-amikacin | pip/tazo-amikacin | meropenem monotherapy | doripenem | doripenem |
| other Tx used (if relevant for interpretation) | | | | | | | | | | | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | | | | |
| **Intervention 2 (comparison)** | | | | Piperacillin/tazobactam | imipenem | | | ceftazidime-amikacin | ceftazidime-amikacin | ceftazidime plus amikacin | imipenem | pip/tazo and imipenem (2 studies pooled analysis) |
| other Tx used (if relevant for interpretation) | | | | | | | | | | | | |
| Tx not | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| allowed (if relevant for interpretation) | | | | | | | | | | | | |
| duration of treatment | | | | 7-14 days | 7-14 days | | | Amikacin was administered for at least 10 days in patients with confirmed P. aeruginosa infection; and for 3-4 days until microbiologic cultures confirmed absence of P. aeruginosa in all other patients. | The Beta-lactam drug was expected to be administered for 15 days, or up to 21 days for patients with difficult-to-treat organisms. Amikacin dosage was adapted to renal function according to nomograms and trough serum levels. Amikacin was expected to be given for at least 10 days to patients with infection | For inclusion in the analysis of evaluable patients, treatment duration had to exceed 72 hours and be less than 28 days. Amikacin was administered for 10 days in patients with P. aeruginosa infections and at least 3 days in the remaining cases. | comparing a fixed 7-day course of doripenem 1 gram as a 4-hour infusion every 8 hours with a fixed 10-day course of imipenem-cilastatin 1 gram as a 1-hour infusion every 8 hours | |

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| | | | | | | | | | involving P. aeruginosa and for at least 5 days to other patients. | | | |
| NOTES: | | | | | | | | | 204 randomized, 197 received at least 1 dose of study drug, 127 (64.5%) had micro-confirmed VAP (58 TAZ, 69 CAZ), 115 patients patients (51 | 140 VAP patients randomized into two groups | | |

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| | | | | | | | | | TAZ and 64 CAZ) with confirmed VAP and per-protocol | | | |
| **BASELINE CHARACTERISTICS** | | | | | | | | | | | | |
| **Number randomised** | | | | 253 | 531 | | | 124 | 127 | 140 | 274 randomized patients | 625 |
| Intervention | | | | | 264 | | | 88 | 58 | Meropenem 69 | Doripenem 115 | Doripenem 312 |
| Comparison | | | | | 267 | | | 36 | 69 | Ceftaz/Amikacin 71 | Imipenem 112 | Pip/tazo + Imipenem 313 |
| Total (only if separate not reported) | | | | | Clinically evaluable 248 (126 dori, 122 imi) | | | | | | | |
| **Age** | | | | | | | | | | | | |
| Intervention (mean or median) | | | | | 50.7 (19.6) | | | 57.1 (17) | 52.3 ± 2.3 | 61.5 ± 13.7 | 57.5 (16.53) | 51.3 (19.8) |

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| Comparison (mean or median) | | | | | 50.3 (19.0) | | | 60.5 (20) | 57.8 ± 2.1 | 62.3 ± 15.7 | 54.6 (18.46) | 52.2 (19.0) |
| Total (mean or median) (only if separate not reported) | | | | | | | | | | | | |
| unit (e.g. mean and SD) | | | | | Mean (SD) | | | mean (SD) | mean (SD) | mean (SD) | mean (SD) | mean (SD) |
| Age range (e.g. 22-73) | | | | | 18-86 | | | | | | 18;89 | |
| Age inclusion criterion (e.g. older than 16) | | | | | >/= 18 years old | | | | | | | |
| **Male gender** | | | | | | | | | | | | |
| Intervention | | | | | 102 (81.0%) | | | | | 47 (68.1%) | 72 (62.6%) | 237 (76.0) |
| Comparison | | | | | 91 (74.6%) | | | | | 56 (78.9%) | 75 (67.0%) | 238 (76.0) |
| Total (only if separate not reported) | | | | | | | | | | | | |

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| **APACHE 2 score** | | | | | | | | | SAPS-2 score | This was a seriously ill population with an APACHE score of 16.6 at the time of diagnosis with pneumonia; 65.7% were receiving inotropic drugs and 68.6% underwent surgery during the period spent in hospital. | | |
| Intervention | | | | | </= 15 is 59 (46.8%) | | | 16.5 (6.6) | 37 ± 1.4 | 16.5 ± 5.7 | ≤ 15: 48 (41.7%); 16-19: 30 (26.1%); ≥ 20: 37 (32.2%) | APACHE II < 15 = 152 (48.7) |
| Comparison | | | | | </= 15 is 61 (50.0%) | | | 16.9 (6.5) | 37.5 ± 1.6 | 16.6 ± 6.0 | ≤ 15: 49 (43.8%); 16-19: 34 (30.4%); ≥ | APACHE II < 15 = 152 (48.6) |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | | | | | | | | | 20: 29 (25.9%) | |
| Total (only if separate not reported) | | | | | | | | | | | | |
| **Characteristic 1** | | | | | Bacteremia at baseline | | | VAP | | | Pseudomonas | Pseudomonas |
| Intervention | | | | | 13 (10.3%) | | | 75 (85.2%) | | | Pseud 17 (21.5%) | Pseudomonas 36 (11.5%) |
| Comparison | | | | | 11 (9.0%) | | | 31 (86.1%) | | | Pseud 10 (11.4%) | Pseudomonas 37 (11.8%) |
| Total (only if separate not reported) | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| **Characteristic 2** | | | | | # Pseudomonas isolates | | | A total of 94 bacterial organisms were isolated among which gram-negative bacilli predominated, Pseudomonas aeruginosa being the most frequent (14/64 vs. 7/29). | | No significant differences were observed between the patients in the study group and those in the control group with regard to demographic data, concomitant illnesses and presentation of infection, although the control group contained more trauma patients (23.9% versus 11.6%) and there were more surgical patients in the study group (33.3% versus 21.1%). | Pseudomonas aeruginosa bacterial isolates confirmed in 17 (21.5%) of doripenem patients vs. 10 (11.4%) of imipenem patients, and total 27 (16.2%) of patients. | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| Intervention | | | | | 30 | | | | | | | |
| Comparison | | | | | 26 | | | | | | | |
| Total (only if separate not reported) | | | | | | | | | | | | |
| **Characteristic 3** | | | | | | | | | | | | |
| Intervention | | | | | | | | | | | | |
| Comparison | | | | | | | | | | | | |
| Total (only if separate not reported) | | | | | | | | | | | | |
| **Characteristic 4** | | | | | | | | | | | | |
| Intervention | | | | | | | | | | | | |
| Comparison | | | | | | | | | | | | |
| Total (only if separate not reported) | | | | | | | | | | | | |
| **Characteristic 5** | | | | | | | | | | | | |
| Intervention | | | | | | | | | | | | |
| Comparison | | | | | | | | | | | | |
| Total (only if separate not reported) | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| **Characteristic 6** | | | | | | | | | | | | |
| Intervention | | | | | | | | | | | | |
| Comparison | | | | | | | | | | | | |
| Total (only if separate not reported) | | | | | | | | | | | | |
| **Characteristic 7** | | | | | | | | | | | | |
| Intervention | | | | | | | | | | | | |
| Comparison | | | | | | | | | | | | |
| Total (only if separate not reported) | | | | | | | | | | | | |
| NOTES: | | | | Baseline resistance of Klebsiella pneumoniae and Pseudomonas aeruginosa to piperacillin/tazobactam was 44% and 26.9%, respectively; a doripenem minimum inhibitory | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| | | | | concentration (MIC) >8 mug/mL occurred in 0% and 7.7%, respectively. | | | | | | | | |
| | | | | Study limitations included the open-label design, the low rate of monotherapy (adjunctive use of aminoglycoside was required when P. aeruginosa was suspected), and the exclusion of the most critically ill and immunocompro | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | | mized patients. | | | | | | | | |
| **OUTCOMES** | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| **Mortality (all cause)** | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| follow-up | Overall mortality was 20.3%; treatment failure occurred in 37.4% of patients who could be evaluated microbiologically. No mortality differences were observed between any of the regimens compared. Only one of three pooled comparisons yielded a significant difference for treatment failure: The combination of ceftazidime/aminoglycoside was inferior to meropenem (two trials, relative risk 0.70, 95% confidence interval | Fourteen doripenem and 14 comparator subjects died during the study. | | | 28-day all cause mortality; Kaplan-Meier analysis found no difference in cumulative mortality rates between 2 treatment arms. | | | 28-day; crude mortality 30.7% vs. 22.2%; attributed mortality 6.8% vs. 11.1%, NS | 28-day morality rates 16% (TAZ) vs. 20% (CAZ); 30-day-post-therapy mortality 18.4% (18 of 98) in the TAZ group and 22.2% (22 of 99) in the CAZ group (P = .55) | Overall 28-day mortality 16 (23.2%) vs. 20 (28.2%); attributed mortality reported as 10% in each group. | All cause 28-day mortality in the MITT group was numerically greater for patients in the doripenem arm compared to the imipenem-cilastatin arm (21.5% versus 14.8%; 95% CI -5.0 to 18.5) and for patients with Pseudomonas aeruginosa VAP (35.3% vs. 0.0%; 95% CI, 12.6 to | All-cause, overall mortality rates were similar (51/312 [16%] versus 47/313 [15%]; P = 0.648). |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | 0.53– 0.93). Rates of mortality and treatment failure for monotherapy compared with combination therapy were similar (11 trials, relative risk for mortality of monotherapy 0.94, confidence interval 0.76 –1.16; and relative risk of treatment failure for mono therapy 0.88, confidence interval 0.72– 1.07). **CONCLUSION:** Monotherapy is not inferior to combination therapy in the empirical treatment of VAP. Available data neither identify a superior empirical | | | | | | | | | | 58.0). | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | regimen nor conclusively conclude that available regimens result in equivalent outcomes. Larger and more rigorous trials evaluating the choice of, and even need for, empirical therapy for VAP are needed. | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| INT # with event | | | | | 10.8% in the cMITT population | | | | | 16 (23.2%) | 21.50% | 16% |
| INT Total | | | | | | | | | | | | |
| COM # with event | | | | | 9.50% | | | | | 20 (28.2%) | 14.80% | 15% |
| COM Total | | | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | no | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | no | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | yes | | | | | | | |
| Blinding [data collectors] (only relevant for | | | | | no | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | yes | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | yes | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| NOTES: | | | | | Although this was an open-label study, several measures were followed to ensure that the sponsor assessed the data objectively posthoc. These included restricted access to any information regarding treatment assignments or duration of infusion of study drug until after the | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | | | database lock, and blinding of both the statisticians and the medical team supervising the study and determining the evaluability of each patient. | | | | | | | |
| **Number of ventilator days** | | | | | | | | | | | | |
| Are the data available? | | | | | | | | Not measured | Not measured | Not reported | Not measured | Data available |
| follow-up | | | | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | | | | |
| Type of | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| variance | | | | | | | | | | | | |
| INT (central tendency) | | | | | | | | | | | | |
| INT (variance) | | | | | | | | | | | | |
| INT total | | | | | | | | | | | | |
| COM (central tendency) | | | | | | | | | | | | |
| COM (variance) | | | | | | | | | | | | |
| COM total | | | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | Median duration of mechanical ventilation (7 versus 10 days; P = 0.008) was shorter for doripenem than comparators; |
| **Number of ventilator-free days** | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| Are the data available? | | | | | | | | Not measured | Not measured | Not measured | Not measured | Not reported |
| follow-up | | | | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | | | | |
| Type of variance | | | | | | | | | | | | |
| INT (central tendency) | | | | | | | | | | | | |
| INT (variance) | | | | | | | | | | | | |
| INT total | | | | | | | | | | | | |
| COM (central tendency) | | | | | | | | | | | | |
| COM (variance) | | | | | | | | | | | | |
| COM total | | | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| **Length of ICU stay** | | | | | | | | | | | | |
| Are the data available? | | | | | | | | Not measured | Not measured | Data available | Not measured | Data available |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| follow-up | | | | | | | | | | The mean duration of stay in hospital for all patients admitted to the study was 35.1 days, with 24.9 days spent in the ICU. | | Mean duration of ICU stays were 12 and 13 days (P = 0.065). |
| unit (days, hours, etc.) | | | | | | | | | | | | |
| Type of variance | | | | | | | | | | | | |
| INT (central tendency) | | | | | | | | | | | | |
| INT (variance) | | | | | | | | | | | | |
| INT total | | | | | | | | | | 24.2 ± 14.9 | | |
| COM (central tendency) | | | | | | | | | | | | |
| COM (variance) | | | | | | | | | | | | |
| COM total | | | | | | | | | | 25.5 ± 17.5 | | |
| Blinding [patients] | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| RCTs) | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| **Length of hospital stay** | | | | | | | | | | | | |
| Are the data available? | | | | | | | | Not measured | Not measured | Data available | Not measured | |
| follow-up | | | | | | | | | | The mean duration of stay in hospital for all patients admitted to the study was 35.1 days, with 24.9 days spent in the ICU. | | Medjan duration of hospitalization (22 versus 26 days; P = 0.010) was shorter for doripenem than comparators; |
| unit (days, hours, etc.) | | | | | | | | | | | | |
| Type of variance | | | | | | | | | | | | |
| INT (central tendency) | | | | | | | | | | | | |
| INT (variance) | | | | | | | | | | | | |
| INT total | | | | | | | | | | 34.3 ± 20.3 | | |
| COM | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| (central tendency) | | | | | | | | | | | | |
| COM (variance) | | | | | | | | | | | | |
| COM total | | | | | | | | | | 35.9 ± 21.3 | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| [analysts] (only relevant for RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| **Clinical cure (as defined by the study authors)** | | | | | | | | | | | | |
| Are the data available? | | | | Data available | Data available | | | Data available | Data available | Data available | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | Clinical success rates for modified intent-to-treat (mITT) subjects with P. aeruginosa in the cIAI and NP/VAP groups were 78.7% (37/47) and 59.6% (31/52), respectively, following treatment with doripenem versus 74.3% (26/35) and 32.8% (19/58), respectively, for subjects in the comparator groups ($p < 0.05$ for difference in success rates across infection types). Microbiologic eradication rates also favored doripenem, although the differences did | Initial resistance was present in 14.6% (range 4.2-24.0%) of PA isolates in imipenem and 2.5% (range 0.0-7.4%) in comparator groups. Pooled clinical success rates for PA were 45.2% (range 0.0-72.0%) for | Clinical cure rates in clinically evaluable patients (n=253) were 81.3% in the doripenem arm and 79.8% | Clinical responses were classified as | | | | Of 204 patients suspected of having VAP and randomized to a treatment arm of the study, 127 (64%) had bacteriologically confirmed infections, of which 37% were polymicrobial and 32% involved | Satisfactory clinical responses (cure or improvement) were achieved at the end of treatment in 68.1% of meropenem-treated patients and 54.9% in the ceftazidime/amikacin treated group (relative risk 1.25; 95% confidence interval > 1.00, 1.55). When non- | The clinical cure rate at the end of therapy (EOT) in the microbiological intent-to-treat (MITT) population was numerically lower for patients in the doripenem arm compared to the imipenem-cilastatin | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| INT # with event | | | | | 86/126 (68.3%) | | | 44 (50%) ITT, 43 (51.8%) clinically evaluable | | | | |
| INT Total | | | | | | | | | 51% | 68.10% | 41.20% | |
| COM # with event | | | | | 79/122 (64.8%) | | | 16 (44%) ITT, 14 (53.8%) clinically evaluable | | | | |
| COM Total | | | | | | | | | 36% | 54.90% | 60.00% | |
| Blinding [patients] (only relevant for RCTs) | | | | no | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | no | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | no | | | | | | | | |
| Blinding [data | | | | no | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | no | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| NOTES: | CONCLUSION: Monotherapy is not inferior to combination therapy in the empirical treatment of VAP. Available data neither identify a superior empirical regimen nor conclusively conclude that available regimens result in equivalent outcomes. Larger and more rigorous trials evaluating the choice of, and even need for, empirical therapy for VAP are needed. | CONCLUSION: The weighted difference in clinical success rates for subjects with cIAI and NP/VAP infections caused by P. aeruginosa was in favor of doripenem, with the relative benefit of doripenem compared with the comparator agents similar across the two infections. | CONCLUSION: In the 15 years of RCTs of imipenem for pneumonia, PA imipenem resistance rates are high, and PA clinical success and microbiologic eradication rates are directionally lower for imipenem than for comparators. Conversely, initial and treatment-emergent resistance is more likely with the imipenem than the | | Clinical cure rates: cMITT 59.0 vs. 57.8%; CE 68.3 vs. 64.8%; mMITT 57.9 vs. 58.7%; ME 69.0 vs. 64.5%. For Pseudomonas aeruginosa, clinical cure rates dori 16/20 (80%), imi 6/14 (42.9%); Micro cure rates dori 13/20 (65%), imi 5/14 (35.7%). | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| | | | comparator regimens. | | | | | | | | | |
| **Development of resistance (as defined by the study authors)** | | | | | | | | | | | | |
| Are the data available? | | | | | | | | | Not measured | | | |
| follow-up | | | | | | | | | | | | |
| INT # with event | | | | | | | | | | | | |
| INT Total | | | | | | | | | | | | |
| COM # with | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| event | | | | | | | | | | | | |
| COM Total | | | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| **Any adverse effect** | | | | | | | | | | | | |
| Are the data available? | Not reported | Data available | | | | | | Data available | Data available | Data available | Data available | Not reported |
| follow-up | | The proportion of subjects reporting one or more treatment-emergent adverse events or serious adverse events was similar for doripenem and the comparator agents. | | | | | | | | Adverse events judged to be possible or probably related to treatment were reported by seven (10.1%) patients in the meropenem group and by eight patients (11.3%) in the ceftazidime/amikacin group | No difference in adverse events. SAEs not specified. | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| INT # with at least one event (if this was reported) | | | | | | | | 21 (23.9%) | Adverse events were recorded in 37 of 98 TAZ recipients (49 events) | 7 (10.1%) | 106 (92.2%) | |
| INT # of events per group (if this was reported) | | | | | | | | | | | | |
| INT Total | | | | | | | | | | | | |
| COM #with at least one event (if this was reported) | | | | | | | | 5 (13.9%) | 38 of 99 CAZ recipients (46 events) | 8 (11.3%) | 107 (95.5%) | |
| COM # of events per group (if this was reported) | | | | | | | | | | | | |
| COM Total | | | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| [personnel] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| **Serious** | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| **adverse effect** | | | | | | | | | | | | |
| Are the data available? | | | | Data available | Data available | | | Not reported | Data available | Not measured | Not reported | Not reported |
| follow-up | | | | | | | | | | | | |
| INT # with at least one event (if this was reported) | | | | Both study drugs were generally well tolerated, as only 16.1% and 17.6% of patients receiving doripenem and piperacillin/tazobactam, respectively, had a drug-related adverse event. | Dori 70 (27%) | | | | SAE in 24 TAZ recipients | | | |
| INT # of events per group (if this was reported) | | | | | | | | | | | | |
| INT Total | | | | | | | | | | | | |
| COM #with at least one | | | | | Imi 72 (27%) | | | | SAE in 17 CAZ recipients | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| event (if this was reported) | | | | | | | | | | | | |
| COM # of events per group (if this was reported) | | | | | | | | | | | | |
| COM Total | | | | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [data collectors] | | | | | | | | | | | | |

| **Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa?** | | | | | | | | | | | | |
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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| (only relevant for RCTs) | | | | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | | | | |
| ***Additional dichotomous outcome*** | | | | | | | | | | | | |

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| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| NOTES: | | | | | | | | Eradication rates for Pseudomonas aeruginosa infection: 8/14 (57.1%) for TAZ/Amikacin compared to 5/7 (71.4%) for CAZ/Amikacin. | | Bacterial eradication rates for Pseudomonas aeruginosa infection were 8/14 (57.1%) in the Meropenem group vs. 7/13 (53.8%) in the CAZ/Amikacin group | | P. aeruginosa was eradicated from 16/24 (67%) doripenem recipients and 10/24 (42%) comparator recipients (P = 0.147). In patients with P. aeruginosa at baseline, median durations of mechanical ventilation (7 versus 13 days; P = 0.031) and ICU stay (13 versus 21 days; P = 0.027) were shorter for doripenem; corresponding hospital stays were 24 and 35 days (P = 0.129). |
| ***Additional*** | | | | | | | | | | | | |

| Data Extraction Data- Which antibiotic should be used to treat patients with HAP/VAP due to P. aeruginosa? | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC | Jenkins SG, Fisher AC, Peterson JA, Nicholson SC, Kaniga K. | Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. | Rea-Neto A, Niederman M, et al, Friedland I | Chastre J, Wunderink R, et al, Friedland I. | Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC | Magnotti LJ, et al, Fabian TC, Croce MA. | Alvarez-Lerma F, et al; Spanish Collaborative Group for the Study of Severe Infections. | Brun-Buisson C, Sollet JP, Schweich H, Brière S, Petit C for VAP Study Group. | Alvarez Lerma F; Serious Infections Study Group. | Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R. | Kollef MH, Nathwani D, Merchant S, Gast C, Quintana A, Ketter N. |
| Year | 2008 | 2009 | 2010 | 2008 | 2008 | 2008 | 2009 | 2001 | 1998 | 2001 | 2012 | 2010 |
| ***dichotomous outcome*** | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| ***Additional continuous outcome*** | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| ***Additional continuous outcome*** | | | | | | | | | | | | |
| NOTES: | | | | | | | | | | | | |

| SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC ANTIBIOTIC TREATMENTS FOR HAP AND VAP WITH PSEUDOMONAS COHORT | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rx A | Rx B | N | Mech Vent | Pseudomonas patients | All Patient and Pseudomonas (PA) Clinical Response | | | Pseudomonas Patient Mortality | | | All-patient Mortality | | |
| | | | | | | A | B | Diff | A | B | Diff | A | B | Diff |
| Alvarez-Lerma 2001 [24] | Meropenem | Ceftaz-Amikacin | 140 | 100% | 27/140 (19%) | 47/69 (68%) | 39/71 (55%) | .04 | NR | -- | -- | 16/69 (23%) | 20/71 (28%) | NS |
| Sieger 1997 [25] | Meropenem | Ceftaz-Tobra | 211 | 70% | 12/211 (6%) | 76/106 (72%) | 62/105 (59%) | .10 | NR | -- | -- | 13/104 (13%) | 23/107 (21%) | .06 |
| Brown 1984 [26] | Moxalactam | Carbenicillin-Tobra | 48 | 85%[a] | 7/34 (21%) | 11/18 (61%)[a] | 7/16 (44%)[a] | NS | NR | | -- | 11/18 (61%) | 9/16 (56%) | NS |
| Kljucar 1987 [27] | Ceftazidime | Ceftaz-Tobra | 33 | 100% | 18/33 (55%) | 12/16 (75%) | 12/17 (71%) | NS | NR | -- | -- | 0/16 (0%) | 1/17 (5.9%) | NS |
| Kljucar 1987 [27] | Ceftazidime | Azlocillin-Tobra | 33 | 100% | 23/33 (70%) | 12/16 (75%) | 8/17 (47%) | NS | NR | -- | -- | 0/16 (0%) | 2/17 (12%) | NS |
| Chastre 2008 [28] | Doripenem | Imipenem | 531 | 100% | 56/409 (14%) | 147/249 (59%)[c] PA 16/20 (80%) | 146/252 (58%)[c] PA 6/14 (43%) | NS | 7/20 (35%) | 6/14 (43%) | NS | 27/249 (11%) | 24/252 (10%) | NS |
| Kollef 2012 [79] | Doripenem x 7 days | Imipenem x 10 days | 274 | 100% | 27/167 (16%) | 36/79 (46%) PA (41%) | 50/88 (57%) PA (60%) | NS | 6/17 (35.3%) | 0/10 (0%) | 95% CI 12.6-58 | 26/115 (23%) | 18/112 (16%) | NS |
| Hartenauer 1990 [29] | Ceftazidime | Imipenem | 45 | 100% | 7/45 (16%) | 17/21 (81%)[c] | 16/24 (67%)[c] | NS | NR | -- | -- | -- | -- | -- |
| Torres 2000 [30] | Ciprofloxacin | Imipenem | 149 | 100% | 26/75 (35%) | 40/57 (70%)[c] | 34/52 (65%)[c] | NS | NR | -- | -- | 8/41 (20%)[d] | 4/34 (12%)[d] | NS |
| Fink 1994 [31] | Ciprofloxacin | Imipenem | 405[b] | 79% | 91/402 (22%) | 74/121 (61%)[e] | 71/130 (55%)[e] | NS | NR | -- | -- | 43/202 (21%) | 38/200 (19%) | NS |
| Shorr 2005 [32] | Levofloxacin | Imipenem | 222 | 100% | 34/222 (15%) | 65/111 (59%) | 70/111 (63%) | NS | NR | -- | -- | -- | -- | -- |
| Réa Neto 2008 [33] | Doripenem (+ Aminoglycoside if Pseudomonas) | Piperacillin-tazobactam (+ Aminoglycoside if Pseudomonas) | 448 | 22%[c] | 54/285 (19%) | 20/29 (69%)[f] | 15/26 (58%)[f] | NS | 6/32 (19%) | 8/44 (18%) | NS | 30/217 (14%) | 31/212 (15%) | NS |
| Beaucaire 1995 [35] | Isepamicin | Amikacin | 113[d] | 100% | 35/130 (27%) | 23/44 (52%) | 25/41 (61%) | NS | NR | -- | -- | 17/56 (30%) | 15/57 (26%) | NS |
| Ahmed 2007 [36] | Cefepime-levofloxacin | Pip-tazo + Amikacin | 93 | 100% | 37/93 (40%) | -- | -- | -- | -- | -- | -- | 13/38 (35%) | 15/38 (40%) | NS |
| Beaucaire 1999 [37] | Cefipime/ Amikacin | Ceftazidime/ Amikacin | 275 | 100% | 16/275 (6%) | 68/141 (48%) | 60/134 (45%) | NS | NR | | | 29/141 (20%) | 21/134 (16%) | -- |

| SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC ANTIBIOTIC TREATMENTS FOR HAP AND VAP WITH PSEUDOMONAS COHORT | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rx A | Rx B | N | Mech Vent | Pseudomonas patients | All Patient and Pseudomonas (PA) Clinical Response | | | Pseudomonas Patient Mortality | | | All-patient Mortality | | |
| | | | | | | A | B | Diff | A | B | Diff | A | B | Diff |
| Croce 1993 [80] | Cefoperazone | Ceftazidime | 39 | 100% | 6/59 (10%) | 10/19 (53%) | 12/20 (60%) | -- | NR | -- | -- | -- | -- | -- |
| Croce 1993 [80] | Cefoperazone/ Gentamicin | Ceftazidime/ Gentamicin | 70 | 100% | 13/137 (10%) | 10/35 (29%) | 12/35 (34%) | -- | NR | -- | -- | -- | -- | -- |
| Reeves 1989 [38] | Ceftriaxone | Cefotaxime | 51 | 90% | 2/51 (4%) | 12/25 (48%) | 19/26 (73%) | -- | NR | -- | -- | 2/25 (8%) | 4/26 (15%) | -- |
| Saginur[h] 1997 [39] | Ceftazidime | Ciprofloxacin | 149 | 52% | 4/149 (3%) | 14/34 (41%) | 17/30 (57%) | -- | NR | -- | -- | 6/77[i] (8%) | 8/62[i] (13%) | -- |
| Alvarez-Lerma 2001[40] | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | 124 | 85% | 13/124 (10%) | 44/88 (50%) | 16/36 (28%) | -- | NR | -- | -- | 27/88 (31%) | 8/36 (22%) | |
| Bruin-Bruisson 1998[41] | Pip/Tazo + Amikacin | Ceftazidime + Amikacin | 197 | 100% | 42/190 (22%) | 28/58 (48%) | 23/69 (33%) | -- | NR | -- | -- | 8/51 (15%) | 12/61 (20%) | -- |
| Freire 2010 [42] | Tigecycline +/- Ceftazidime | Imipenen +/- Vancomycin | 934 | 34% | 18/253 VAP (7%)<br><br>24/626 Non-VAP (4%) | 59/127 (46%) VAP<br>217/313 (69%) Non-VAP<br>PA 7/11 (63.6%) Non-VAP<br>PA 3/11 (27.3%) VAP | 67/116 (58%) VAP<br>223/313 (71%) Non-VAP<br>PA 8/13 (69.2%) Non-VAP<br>PA 6/7 (85.7%) VAP | -- | NR | -- | -- | Overall 66/467 (14.1%)<br><br>25/131 (19%) VAP<br><br>41/336 (12.2%) Non-VAP | Overall 57/467 (12.2%)<br><br>15/122 (12%) VAP<br><br>43/345 (12.5%) Non-VAP | NS |
| Giamarellos-Bourboulis 2008 [43] | Clarithro + usual therapy | Usual therapy | 200 | 100% | 29/200 (15%) | 61/100 (61%) | 54/100 (54%) | -- | NR | -- | -- | 28/100 (28%) | 31/100 (31%) | NS |
| Damas (A) 2006 [48] | Cefepime | Cefepime - Amikacin | 39 | 100% | 7/39 (18%) | 37/53 (70%) | 26/40 (65%) | NS | NR | -- | -- | 2/20 (10%) | 4/19 (21%) | |
| Damas (B) 2006 [48] | Cefepime | Cefepime - Levofloxacin | 40 | 100% | 9/40 (23%) | -- | -- | -- | NR | -- | -- | 2/20 (10%) | 4/20 (16%) | |
| Heyland 2008 [44] | Meropenem | Meropenem-cipro | 739 | 100% | 47/739 (6%) | 203/369 (55%) | 220/369 (60%) | NS | NR | -- | -- | 67/370 (18%) | 71/369 (19%) | NS |
| Manhold 1998 [49] | Cipro | Ceftazidime - Gentamicin | 18[d] | 100% | 2/18 (11%) | 2/10 (20%) | 4/8 (50%) | -- | NR | -- | -- | 8/10 (80%) | 4/8 (50%) | -- |
| Awad SS 2014 [81] | Ceftobiprole | Ceftazidime-Linezolid | 781 | 38% | 101/781 (13%) | 195/391 (49.9%) | 206/390 (52.8%) | NS | NR | | | HAP 16.7% | HAP 18.0% | NS |

| SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC ANTIBIOTIC TREATMENTS FOR HAP AND VAP WITH PSEUDOMONAS COHORT | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Rx A** | **Rx B** | **N** | **Mech Vent** | **Pseudomonas patients** | **All Patient and Pseudomonas (PA) Clinical Response** | | | **Pseudomonas Patient Mortality** | | | **All-patient Mortality** | | |
| | | | | | | A | B | Diff | A | B | Diff | A | B | Diff |
| (HAP, including 210 VAP) | | | | | | HAP 171/287 (59.6%) VAP 24/104 (23.1%) PA 17/27 (63%) | HAP 167/284 (58.8%) VAP 19/70 (27.1%) PA 24/34 (71%) | | | | | VAP 26.9% | VAP 19.8% | |
| Kim 2012 [82] (HAP) | Imipenem + Vancomycin with De-escalation | Non-carbapenem + Non-vancomycin, No de-escalation | 109 | 50% | 13/108 (12%) | NR | NR | | NR | -- | -- | 21/53 (39.6%) | 14/55 (25.9%) | NS |
| Joshi 2006 [50](NP) | Pip/Tazo + Tobramycin | Imipenem + Tobramycin | 437 | 69% | 35/437 (8%) | 121/222 (54.5%) | 111/215 (51.6%) | NS | NR | -- | -- | 23/222 (10%) | 17/215 (8%) | NS |
| West 2003 [83] (NP) | Levofloxacin (+ Ceftazidime for Pseudomonas) | Imipenem + Amikacin or other AG for Pseudomonas) | 438 | 71% | 34/438 (8%) | 135/204 (66.2%) PA 11/17 (64.7%) | 143/206 (69.4%) PA 7/17 (41.2%) | NS | NR | -- | -- | 38/220 (17.3%) | 32/218 (14.7%) | NS |
| Zanetti 2003 [84] (NP) | Cefipime | Imipenem | 281 | 66% | 59/148 (40%) | 76/108 (70%) PA 23/27 (75%) | 75/101 (74%) PA 23/32 (72%) | NS | NR | -- | -- | 28/108 (26%) | 19/101 (19%) | NS |
| Jaccard 1998 [85] (NP or peritonitis) | Imipenem | Pip/Tazo | 154 NP | | 45/154 (29%) | 23/79 (29%) PA 12/24 (50%) [g] | 13/75 (17%) PA19/21 (90%) [g] | | NR | | | 6/79 (8%) | 7/75 (9%) | NS |
| Thomas 1994 [45] | Cefotaxime | Ceftriaxone | 93 | -- | -- | -- | -- | -- | -- | -- | -- | 12/40 (30%) | 13/53 (25%) | NS |
| Cometta 1994 [86] | Imipenem | Imipenem + netilmicin | 177 [h] | 55% | 34/177 (19%) | 16/91 (17.6%) | 14/86 (16.3%) | | NR | -- | -- | 13/91 (14%) | 12/86 (14%) | NS |
| Giamarellou 1990 [87] | Pefloxacin | Imipenem | 71 | 72% | 25 of 88 pathogens | 23/35 (65.7%) | 19/35 (52.8%) | | NR | | | 1/25 (4%) | 4/29 (14%) | NS |

**NR = Not Reported; NP = Nosocomial pneumonia; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia**

[a] clinical response defined as radiographic clearing

[b] hospital days *after* pneumonia diagnosis

[c] clinically evaluable population

[d] microbiologically confirmed and clinically evaluable population

[e] excludes patients with community acquired pneumonia and those with "indeterminate" clinical responses

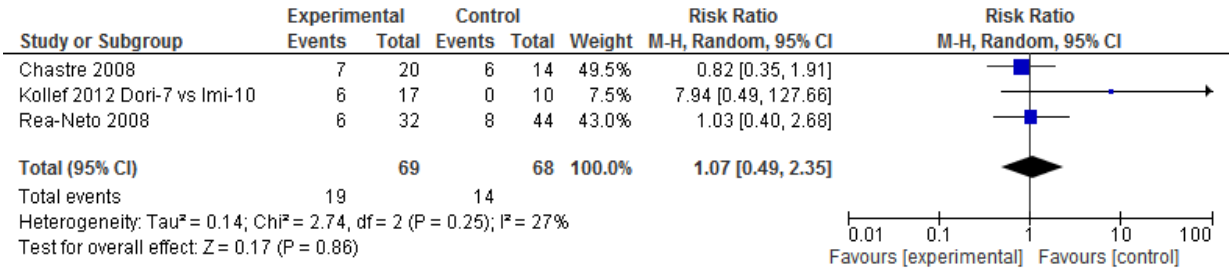
[f] clinically evaluable population with confirmed VAP

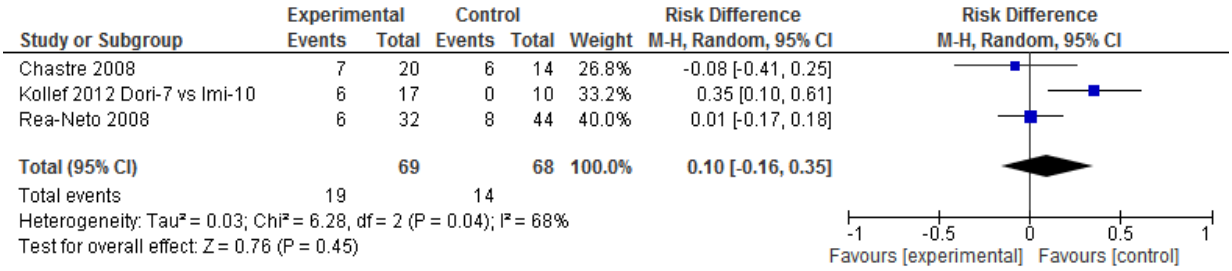
[g] P=0.004 for PA group

[h] Subgroup with nosocomial pneumonia

**Mortality, doripenem vs. comparator for P. aeruginosa HAP/VAP:**

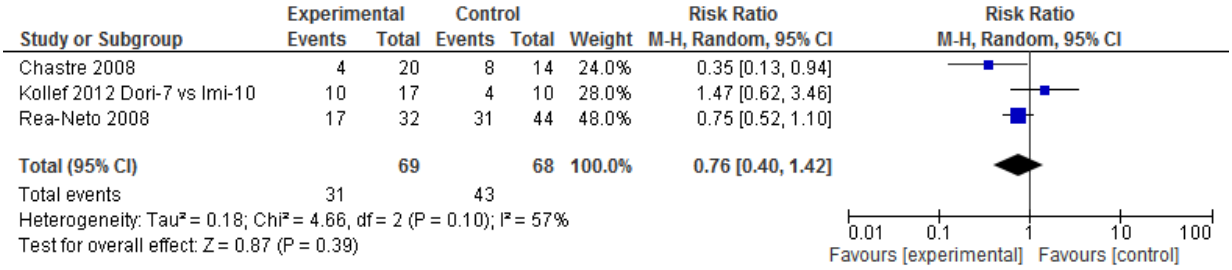
Chastre 2008 [28]: Doripenem vs. Imipenem
Rea-Neto 2008 [33]: Doripenem vs. Piperacillin/tazobactam
Kollef 2012 [79]: Doripenem 7 days vs. Imipenem 10 days

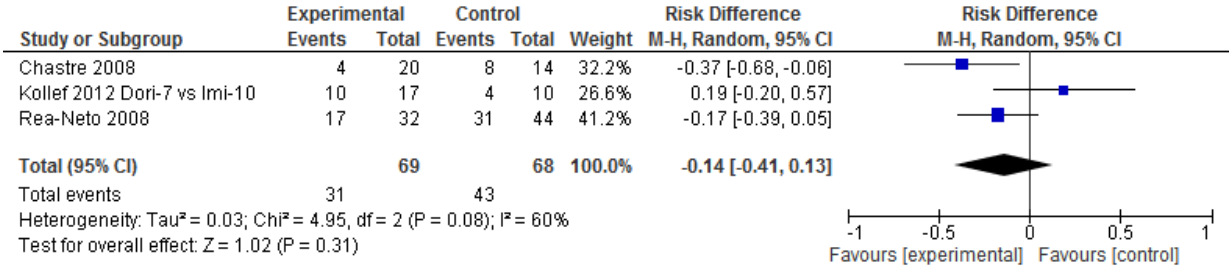



**Treatment Failure, doripenem vs. comparator for P. aeruginosa HAP/VAP:**

Chastre 2008 [28]: Doripenem vs. Imipenem
Rea-Neto 2008 [33]: Doripenem vs. Piperacillin/tazobactam
Kollef 2012 [79]: Doripenem 7 days vs. Imipenem 10 days



## XVII. Should monotherapy or combination therapy be used to treat patients with HAP/VAP due to *P. aeruginosa*?

| **Comparison of monotherapy vs combination therapy for the treatment of ventilator-associated pneumonia (VAP)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **OUTCOME: All-cause mortality** | | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy N** | **Combination $n_1$** | **Combination N** | **Relative Risk (RR)** | **Standard Error of RR** | **RR 95% CI (lower bound)** | **RR 95% CI (upper bound)** | **Statistical Significance** |
| Brown 1984 | 11 | 18 | 9 | 16 | 1.086 | 0.2898 | 0.616 | 1.917 | Not significant |
| Kljucar 1987 | 0.33 | 16 | 1 | 17 | 0.351 | 1.9771 | 0.007 | 16.896 | Not significant |
| Cometta 1994 | 13 | 91 | 12 | 86 | 1.024 | 0.3710 | 0.495 | 2.118 | Not significant |
| Sieger 1997 | 10 | 104 | 17 | 107 | 0.605 | 0.3740 | 0.291 | 1.260 | Not significant |
| Manhold 1998 | 13 | 28 | 6 | 23 | 1.780 | 0.4055 | 0.804 | 3.940 | Not significant |
| Alvarez-Lerma 2001 | 16 | 69 | 20 | 71 | 0.823 | 0.2897 | 0.467 | 1.452 | Not significant |
| Heyland 2005 | 67 | 370 | 71 | 369 | 0.941 | 0.1536 | 0.696 | 1.272 | Not significant |
| Damas 2006 | 2 | 24 | 9 | 50 | 0.463 | 0.7412 | 0.108 | 1.979 | Not significant |
| **TOTAL** | **132.33** | **720** | **145** | **739** | **0.937** | **0.1082** | **0.758** | **1.158** | **Not significant** |
| | | | | | | | | | |
| **Study** | **Monotherapy Risk** | **Combination Risk** | **Risk Difference (RD)** | | | | | | |
| Brown 1984 | 0.611 | 0.563 | 0.049 | | 49 | more | | | |
| Kljucar 1987 | 0.021 | 0.059 | -0.038 | | -38 | fewer | | | |
| Cometta 1994 | 0.143 | 0.140 | 0.003 | | 3 | more | | | |
| Sieger 1997 | 0.096 | 0.159 | -0.063 | | -63 | fewer | | | |
| Manhold 1998 | 0.464 | 0.261 | 0.203 | which are | 203 | more | monotherapy subjects per 1,000 at risk | | |
| Alvarez-Lerma 2001 | 0.232 | 0.282 | -0.050 | | -50 | fewer | | | |
| Heyland 2005 | 0.181 | 0.192 | -0.011 | | -11 | fewer | | | |
| Damas 2006 | 0.083 | 0.180 | -0.097 | | -97 | fewer | | | |
| **MEDIAN** | **0.162** | **0.186** | **-0.025** | | **-25** | **fewer** | | | |
| | | | | | | | | | |
| **Combination ("control/standard") risk:** | **0.186** | **which is** | **186** | **per 1,000** | | | | | |
| | | | | | | | | | |
| **with RD of** | **25** | **fewer monotherapy subjects per 1,000 at risk** | | | | | | | |
| | this is not-significant (based on RR 95% CI; specific RD 95% CI provided below, FYI) | | | | | | | | |
| | | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy $n_2$** | **Monotherapy N** | **Combination $n_1$** | **Combination $n_2$** | **Combination N** | | | |
| Brown 1984 | 11 | 7 | 18 | 9 | 7 | 16 | | | |
| Kljucar 1987 | 0.33 | 15.67 | 16 | 1 | 16 | 17 | | | |

| **Comparison of monotherapy vs combination therapy for the treatment of ventilator-associated pneumonia (VAP)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **OUTCOME: All-cause mortality** | | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy N** | **Combination $n_1$** | **Combination N** | **Relative Risk (RR)** | **Standard Error of RR** | **RR 95% CI (lower bound)** | **RR 95% CI (upper bound)** | **Statistical Significance** |
| Cometta 1994 | 13 | 78 | 91 | 12 | 74 | 86 | | | |
| Sieger 1997 | 10 | 94 | 104 | 17 | 90 | 107 | | | |
| Manhold 1998 | 13 | 15 | 28 | 6 | 17 | 23 | | | |
| Alvarez-Lerma 2001 | 16 | 53 | 69 | 20 | 51 | 71 | | | |
| Heyland 2005 | 67 | 303 | 370 | 71 | 298 | 369 | | | |
| Damas 2006 | 2 | 22 | 24 | 9 | 41 | 50 | | | |
| **TOTAL** | **132.33** | **587.67** | **720** | **145** | **594** | **739** | | | |
| | | | | | | | | | |
| **Study** | **Standard Error of RD** | **RD 95% CI (lower bound)** | **RD 95% CI (upper bound)** | | | | | | |
| Brown 1984 | 0.169 | -0.283 | 0.380 | | -283 | | 380 | | |
| Kljucar 1987 | 0.067 | -0.170 | 0.094 | | -170 | | 94 | | |
| Cometta 1994 | 0.052 | -0.099 | 0.106 | | -99 | | 106 | | |
| Sieger 1997 | 0.046 | -0.152 | 0.027 | | -152 | | 27 | | |
| Manhold 1998 | 0.131 | -0.054 | 0.461 | which are | -54 | to | 461 | 95% CI per 1,000 subjects | |
| Alvarez-Lerma 2001 | 0.074 | -0.194 | 0.095 | | -194 | | 95 | | |
| Heyland 2005 | 0.029 | -0.068 | 0.045 | | -68 | | 45 | | |
| Damas 2006 | 0.078 | -0.250 | 0.057 | | -250 | | 57 | | |
| **TOTAL** | **0.021** | **-0.065** | **0.103** | | **-65** | | **103** | | |

| **Comparison of monotherapy vs combination therapy for the treatment of ventilator-associated pneumonia (VAP)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **OUTCOME: Treatment Failure** | | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy N** | **Combination $n_1$** | **Combination N** | **Relative Risk (RR)** | **Standard Error of RR** | **RR 95% CI (lower bound)** | **RR 95% CI (upper bound)** | **Statistical Significance** |
| Rapp 1984 | 2 | 17 | 3 | 18 | 0.706 | 0.8479 | 0.134 | 3.720 | Not significant |
| Kijucar 1987 | 4 | 16 | 4 | 16 | 1.000 | 0.6124 | 0.301 | 3.321 | Not significant |
| Cometta 1994 | 16 | 91 | 14 | 86 | 1.080 | 0.3336 | 0.562 | 2.077 | Not significant |
| Rubinstein 1995 | 43 | 159 | 48 | 138 | 0.778 | 0.1748 | 0.552 | 1.095 | Not significant |
| Sieger 1997 | 30 | 106 | 43 | 105 | 0.691 | 0.1940 | 0.473 | 1.011 | Not significant |
| Alvarez-Lerma M-2001 | 22 | 69 | 32 | 71 | 0.707 | 0.2194 | 0.460 | 1.087 | Not significant |
| Heyland 2005 | 155 | 370 | 140 | 369 | 1.104 | 0.0905 | 0.925 | 1.318 | Not significant |
| **TOTAL** | **272** | **828** | **284** | **803** | **0.929** | **0.0689** | **0.812** | **1.063** | **Not significant** |
| | | | | | | | | | |
| **Study** | **Monotherapy Risk** | **Combination Risk** | **Risk Difference (RD)** | | | | | | |
| Rapp 1984 | 0.118 | 0.167 | -0.049 | | -49 | fewer | | | |
| Kijucar 1987 | 0.250 | 0.250 | 0.000 | | 0 | no difference | | | |
| Cometta 1994 | 0.176 | 0.163 | 0.013 | | 13 | more | | | |
| Rubinstein 1995 | 0.270 | 0.348 | -0.077 | | -77 | fewer | | | |
| Sieger 1997 | 0.283 | 0.410 | -0.127 | which are | -127 | fewer | monotherapy subjects per 1,000 at risk | | |
| Alvarez-Lerma M-2001 | 0.319 | 0.451 | -0.132 | | -132 | fewer | | | |
| Heyland 2005 | 0.419 | 0.379 | 0.040 | | 40 | more | | | |
| **MEDIAN** | **0.270** | **0.348** | **-0.049** | | **-49** | **fewer** | | | |
| | | | | | | | | | |
| **Combination ("control/standard") risk:** | **0.348** | **which is** | **348** | **per 1,000** | | | | | |
| | | | | | | | | | |
| **with RD of** | **49** | **fewer monotherapy subjects per 1,000 at risk** | | | | | | | |
| | this is not-significant (based on RR 95% CI; specific RD 95% CI provided below, FYI) | | | | | | | | |
| | | | | | | | | | |
| **Study** | **Monotherapy $n_1$** | **Monotherapy $n_2$** | **Monotherapy N** | **Combination $n_1$** | **Combination $n_2$** | **Combination N** | | | |
| Rapp 1984 | 2 | 15 | 17 | 3 | 15 | 18 | | | |
| Kijucar 1987 | 4 | 12 | 16 | 4 | 12 | 16 | | | |
| Cometta 1994 | 16 | 75 | 91 | 14 | 72 | 86 | | | |
| Rubinstein 1995 | 43 | 116 | 159 | 48 | 90 | 138 | | | |
| Sieger 1997 | 30 | 76 | 106 | 43 | 62 | 105 | | | |
| Alvarez-Lerma M-2001 | 22 | 47 | 69 | 32 | 39 | 71 | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Comparison of monotherapy vs combination therapy for the treatment of ventilator-associated pneumonia (VAP)** | | | | | | | | | |
| **OUTCOME: Treatment Failure** | | | | | | | | | |
| Heyland 2005 | 155 | 215 | 370 | 140 | 229 | 369 | | | |
| **TOTAL** | **272** | **556** | **828** | **284** | **519** | **803** | | | |
| | | | | | | | | | |
| **Study** | **Standard Error of RD** | **RD 95% CI (lower bound)** | **RD 95% CI (upper bound)** | | | | | | |
| Brown 1984 | 0.118 | -0.279 | 0.181 | | -279 | | 181 | | |
| Kljucar 1987 | 0.153 | -0.300 | 0.300 | | -300 | | 300 | | |
| Cometta 1994 | 0.056 | -0.097 | 0.124 | | -97 | | 124 | | |
| Sieger 1997 | 0.054 | -0.183 | 0.028 | | -183 | | 28 | | |
| Manhold 1998 | 0.065 | -0.254 | 0.001 | which are | -254 | to | 1 | 95% CI per 1,000 subjects | |
| Alvarez-Lerma 2001 | 0.081 | -0.292 | 0.028 | | -292 | | 28 | | |
| Heyland 2005 | 0.036 | -0.031 | 0.110 | | -31 | | 110 | | |
| **TOTAL** | **0.023** | **-0.095** | **0.137** | | **-95** | | **137** | | |

| SUBGROUP ANALYSES BY STUDY DESIGN AND THERAPY TYPE | | | | |
|---|---|---|---|---|
| | No. of studies | Pooled OR (95% CI) | P-value for difference | P-value for heterogeneity; $I^2$ (%) |
| Study design | | | | |
| Prospective study | 2 | 0.64 (0.27-1.48) | 0.291 | 0.099;69.3 |
| Retrospective study | 8 | 1.0 (0.59-1.69) | 0.991 | 0.032;54.4 |
| Therapy type | | | | |
| Definitive therapy | 8 | 0.90 (0.53-1.54) | 0.704 | 0.027;55.6 |
| Appropriate empirical therapy | 2 | 0.80 (0.22-2.89) | 0.734 | 0.023;80.6 |
| OR, odds ratio; CI, confidence interval | | | | |

| MORTALITY OUTCOMES | | | | | |
|---|---|---|---|---|---|
| | | Mortality Rate by Therapy n of Deaths/Total n of Patients (%) | | | |
| | Sample Size, n | Monotherapy | Combination Rx | Odds Ratio (95% Confidence Interval) | *P* |
| Intensive care unit mortality | 2446 | 437/1223 (35.7%) | 352/1223 (28.8%) | 0.75 (0.63-0.88) | .0006 |
| Hospital mortality | 2446 | 584/1223 (47.8%) | 457/1223 (37.4%) | 0.69 (0.59-0.81) | <.0001 |
| Death from: | | | | | |
| Refractory shock | 2446 | 311/1223 (25.4%) | 258/1223 (21.1%) | 0.78 (0.65-0.95) | .01 |
| Sepsis-related organ failure | 2446 | 184/1223 (15%) | 137/1223 (11.2%) | 0.71 (0.56-0.90) | .005 |
| Nonsepsis-related organ failure | 2446 | 89/1223 (7.3%) | 62/1223 (5.1%) | 0.68 (0.49-0.95) | .02 |

## XVIII. Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?

| **Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?** | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Type of information (published or unpublished) | published | published | published | published |
| Journal name | Journal Antimicrob Chemo | J Antimicrob Chemother | Antimicrob Agents Chemother | Antimicrob Agents Chemother |
| Language of publication | English | English | English | English |
| Funding body | | | | |
| Ethics approval | Yes | Yes | Yes | Yes |
| Country where study was done | Italy | England | Spain, Switzerland, Russia, Israel, Poland | Worldwide |
| **METHODS** | | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | | |
| Randomization | | | stated as random but no description | stated as random but no description |
| Concealment | | | probably yes | probably yes |
| Not stopped early | | | not stopped early | not stopped early |
| NOTES: | | | | Pools data from 6 RCTs |
| ***if COHORT STUDY*** | | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | representative of such patients in reality | representative of such patients in reality | | |
| Selection of the non exposed cohort | NO control group (case series) | NO control group (case series) | | |
| Ascertainment of exposure | secure record (e.g. hospital) | secure record (e.g. hospital) | | |
| Demonstration that outcome of interest was not present at start of study | secure record (e.g. hospital) | secure record (e.g. hospital) | | |
| Comparability of cohorts on the basis of the design or analysis | | | | |
| Assessment of outcome | | | | |
| Was follow-up long enough for outcomes to occur? | yes | yes | | |
| Adequacy of follow up of cohorts | at least 80% followed-up | at least 80% followed-up | | |
| Co-Interventions similar between groups? | | | | |
| NOTES: | | | | |
| ***if CASE-CONTROL STUDY*** | | | | |
| Is case definition adequate? | | | | |
| Representativeness of the cases | | | | |
| Selection of controls | | | | |
| Definition of controls | | | | |

| **Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?** | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Comparability of cases and controls | | | | |
| Ascertainment of exposure | | | | |
| Same method of ascertainment for cases and controls | | | | |
| Non-response rate | | | | |
| Co-interventions similar between groups? | | | | |
| **INTERVENTIONS BEING COMAPRED** | | | | |
| **Intervention 1 (experimental)** | Ertapenem | Temocillin | Cefepime | Doripenem |
| other Tx used (if relevant for interpretation) | | | | |
| Tx not allowed (if relevant for interpretation) | | | | |
| **Intervention 2 (comparison)** | | | Imipenem-Cilastatin | Piperacillin-Tazobactam or Imipenem-cilastatin |
| other Tx used (if relevant for interpretation) | | | | |
| Tx not allowed (if relevant for interpretation) | | | | |
| duration of treatment | | | | |
| NOTES: | | | | |
| **BASELINE CHARACTERISTICS** | | | | |
| **Number randomised** | | | 23 | 29 |
| Intervention | 20 | 2 | 13 | 10 |
| Comparison | 0 | | 10 | 19 |
| Total (only if not reported separately) | | | | |
| **Age** | | | | |
| Intervention (mean or median) | 67 | | 55(18) | |
| Comparison (mean or median) | | | 53(18) | |
| Total (mean or median) (only if not reported separately) | | | | |
| unit (e.g. mean and SD) | mean (SD) | | mean (SD) | |
| Age range (e.g. 22-73) | | | not stated | |
| Age inclusion criterion (e.g. older than 16) | 18 years or older | | 16 years or older | |
| **Male gender** | | | | |
| Intervention | 12 (60%) | | 72 (67%) | |
| Comparison | 74.60% | | 67 (66%) | |
| Total (only if not reported separately) | | | | |
| **Severity of illness** | | | | |
| Name of score (e.g. APACHE, SOFA, ...) | Apache II | | Apache II | |
| Intervention group mean score | 23.2 | | 15.6 (6.6) | |
| Comparison group mean score | | | 14.8 (6.3) | |

| Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli? | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| **Study population** | | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Mixed Medical-Surgical | | Mixed Medical-Surgical | |
| NOTES: | | | ESBL were 23 cases in a RCT of 209 patients | Paper says 40 ESBL nosocomial pneumonias but data only on 29 |
| | | | Demographics not reported seperately for ESBL | |
| **OUTCOMES** | | | | |
| **Mortality (all cause)** | | | | |
| Are the data available? | Data available | Not reported | Data available | Not reported |
| location or duration of follow-up (choose from the list) | | | | |
| Intervention group: # with event | 3 | | 1 | |
| Intervention group: Total | | | 13 | |
| Comparison group: # with event | | | 0 | |
| Comparison group: Total | | | 10 | |
| Blinding [patients] (only relevant for RCTs) | | | yes | |
| Blinding [personnel] (only relevant for RCTs) | | | probably yes | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | yes | |
| Blinding [data collectors] (only relevant for RCTs) | | | yes | |
| Blinding [analysts] (only relevant for RCTs) | | | yes | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | | | No separate data for ESBL | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | |
| unit (days, hours, etc.) | | | | |
| How data were reported (mean or median and type of variance) | | | | |
| Intervention group: (mean or median) | | | | |
| Intervention group: (variance) | | | | |
| Intervention group: total number of patients | | | | |
| Comparison group: (mean or median) | | | | |
| Comparison group: (variance) | | | | |

| **Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?** | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Comparison group: total number of patients | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | | | No data | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | |
| unit (days, hours, etc.) | | | | |
| How data were reported (mean or median and type of variance) | | | | |
| Intervention group: (mean or median) | | | | |
| Intervention group: (variance) | | | | |
| Intervention group: total number of patients | | | | |
| Comparison group: (mean or median) | | | | |
| Comparison group: (variance) | | | | |
| Comparison group: total number of patients | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| **Length of ICU stay** | | | | |
| Are the data available? | Not reported | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | |
| unit (days, hours, etc.) | | | | |
| How data were reported (mean or median and type of variance) | | | | |

| Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli? | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Intervention group: (mean or median) | | | | |
| Intervention group: (variance) | | | | |
| Intervention group: total number of patients | | | | |
| Comparison group: (mean or median) | | | | |
| Comparison group: (variance) | | | | |
| Comparison group: total number of patients | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| **Length of hospital stay** | | | | |
| Are the data available? | Data available | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | 13.2 | | | |
| unit (days, hours, etc.) | days | | | |
| How data were reported (mean or median and type of variance) | mean (SD) | | | |
| Intervention group: (mean or median) | | | | |
| Intervention group: (variance) | | | | |
| Intervention group: total number of patients | | | | |
| Comparison group: (mean or median) | | | | |
| Comparison group: (variance) | | | | |
| Comparison group: total number of patients | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| **Clinical cure (as defined by the study authors)** | | | | |
| Are the data available? | Data available | Data available | Data available | Data available |
| Definition (provide details if relevant) | Not reported | Not reported | Not reported | Not reported |

| Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli? | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Duration of follow-up (time point when outcome was measured) [days] | At discharge from hospital | Not reported | 30-days | 30 days |
| Intervention group: # with event | 16 (80%) | 2 (100%) | 9 (69%) | 8 |
| Intervention group: Total | | | 13 | 10 |
| Comparison group: # with event | | | 10 (100%) | 15 |
| Comparison group: Total | | | 10 | 19 |
| Blinding [patients] (only relevant for RCTs) | | | yes | yes |
| Blinding [personnel] (only relevant for RCTs) | | | probably yes | yes |
| Blinding [outcome assessors] (only relevant for RCTs) | | | yes | yes |
| Blinding [data collectors] (only relevant for RCTs) | | | yes | yes |
| Blinding [analysts] (only relevant for RCTs) | | | yes | yes |
| ITT analysis performed (only relevant for RCTs) | | | no | yes |
| **Recurrent pneumonia** | | | | |
| Are the data available? | Data available | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | Not reported | | | |
| Intervention group: # with event | 3 | | | |
| Intervention group: Total | | | | |
| Comparison group: # with event | | | | |
| Comparison group: Total | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | 2 Pseudomonas, 1 Erta resistant Kleb | | | |
| **Number of antibiotic days** | | | | |
| Are the data available? | Data available | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | | |
| unit (days, hours, etc.) | | | | |
| How data were reported (mean or median and type of variance) | mean (SE) | | | |
| Intervention group: (mean or median) | 13.2 | | | |

| **Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?** | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Intervention group: (variance) | | | | |
| Intervention group: total number of patients | | | | |
| Comparison group: (mean or median) | | | | |
| Comparison group: (variance) | | | | |
| Comparison group: total number of patients | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | | | | |
| **Development of resistance (as defined by the study authors)** | | | | |
| Are the data available? | Data available | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | not reported | | | |
| Intervention group: # with event | 1 | | | |
| Intervention group: Total | | | | |
| Comparison group: # with event | | | | |
| Comparison group: Total | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | One erta resistant Kleb | | | |
| **Any adverse effect** | | | | |
| Are the data available? | Data available | Data available | Not reported | Not reported |
| Duration of follow-up [days] | | | | |
| Intervention group: # with at least one event (if this was reported) | 1 | | | |
| Intervention group: # of events per group (if | | | | |

| **Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?** | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| this was reported) | | | | |
| Intervention group: Total | | | | |
| Comparison group: #with at least one event (if this was reported) | | | | |
| Comparison group: # of events per group (if this was reported) | | | | |
| Comparison group: Total | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | One case of mild elevation of LFTs | In overall cohort of patients with ESBL (most Bloodstream or UTI 2 out of 30 cases got C.diff in stool | Not reported seperatley for ESBL | |
| **Serious adverse effect** | | | | |
| Are the data available? | | | Not reported | Not reported |
| Duration of follow-up [days] | | | | |
| Intervention group: # with at least one event (if this was reported) | | | | |
| Intervention group: # of events per group (if this was reported) | | | | |
| Intervention group: Total | | | | |
| Comparison group: #with at least one event (if this was reported) | | | | |
| Comparison group: # of events per group (if this was reported) | | | | |
| Comparison group: Total | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | |

| **Data Extraction Table- Which antibiotic should be used to treat patients with HAP/VAP due to extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli?** | | | | |
|---|---|---|---|---|
| Last name of the first author | Basetti | Balakrishnan | Zanetti | Kaniga |
| Year | 2007 | 2011 | 2003 | 2010 |
| Blinding [analysts] (only relevant for RCTs) | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | |
| NOTES: | | | Not reported seperately for ESBL | |
| | Only included Ertapenem sensivite ESBL | Only 2 cases of HAP in a series of 30 cases | This is retrieving the data on ESBL from the paper which was HAP all comers | The paper summarises the ESBL data from 6 RCTs, 2 of which were in pneumonia |
| | Kleb pneumo 14 | | | |
| | Enterobacter cloacae 2 | | | |
| | Proteus mirabalis 1 | | | |
| | Citrobacter freundii 2 | | | |
| | Kleb micro success 12/14 | | | |
| | Enterobacter 2/2 | | | |
| | Proteus 1/2 | | | |
| | Citrobacter 0/2 | | | |

## XIX. Which antibiotic should be used to treat patients with HAP/VAP due to *Acinetobacter* species?

| **Data Extraction Table-Which antibiotic should be used to treat patients with HAP/VAP due to Acinetobacter species?** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Wood | Betrosian | Betrosian | Garnacho-Montero | Durante-Mangoni | Kofteridis | Korbila | Rattanaunpawan | Aydemar |
| Year | 2002 | 2007 | 2008 | 2003 | 2013 | 2010 | 2010 | 2010 | 2013 |
| Type of information (published or unpublished) | published | published | published | published | published | published | published | published | published |
| Journal name | Clin Infect Dis | Scand J Infect Dis | J Infect | Clin Infect Dis | Clin Infect Dis | Clin Infect Dis | Clin Microbiol Infect | J Antimicrob Chemother | Epidemiol Infect |
| Language of publication | English | English | English | English | English | English | English | English | English |
| Funding body | | | | | Yes | | | Yes | No |
| Ethics approval | Not reported | Yes | Yes | Not reported | Yes | Not reported | Yes | Yes | Yes |
| Country where study was done | US | Greece | Greece | Spain | Italy | Greece | Greece | Thailand | Turkey |
| **METHODS** | | | | | | | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | | | | | | | |
| ***if COHORT STUDY*** | | | | | | | | | |
| ***if CASE-CONTROL STUDY*** | | | | | | | | | |
| | | | | | | | | | |
| **INTERVENTIONS BEING COMPARED** | | | | | | | | | |
| **Intervention 1 (experimental)** | ampicillin/sulbactam | Ampicillin/sulbactam 18 g/ 9 g every 8 h | Ampicillin/sulbactam 18 g/ 9 g every 8 h | imipenem-cilastatin 2-3 g per day | Colistin 2 MU every 8 hours intravenously plus rifampicin 600 mg every 12 hours intravenously | Aerosolized plus iv colistin | aerosolized colistin (mean 2.1 MIU) plus iv colistin (mean 7 MIU day) | Nebulized colistimethate sodium (equivalent to 75 mg colistin base) | Colistin IV plus Rifampicin |
| other Tx used (if relevant for interpretation) | | | | | | | | | |

| **Data Extraction Table-Which antibiotic should be used to treat patients with HAP/VAP due to Acinetobacter species?** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Wood | Betrosian | Betrosian | Garnacho-Montero | Durante-Mangoni | Kofteridis | Korbila | Rattanaunpawan | Aydemar |
| Year | 2002 | 2007 | 2008 | 2003 | 2013 | 2010 | 2010 | 2010 | 2013 |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | |
| **Intervention 2 (comparison)** | imipenem/cilastatin | Ampicilin/sulbactam 24 g/ 12 g every 8 h | Colistin 3 MIU every 8 h | colistin (adjusted for renal function) | Colistin 2 MU every 8 hours intravenously | iv colistin | iv colistin (mean 6.4 MIU day) | Placebo (nebulized sterile normal saline) | Colistin IV |
| other Tx used (if relevant for interpretation) | | | | | | | | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | |
| duration of treatment | | 7 / 10 days | 8-10 days | Physician in charge decided on the duration of therapy | At least 10 days and up to a maxim of 21 days | Physician in charge decided on the duration of therapy | Physician in charge decided on the duration of therapy. At least three days or more. | | Physician decided the duration of the treatment |
| NOTES: | 77 VAP episodes in 75 patients | | | | | | Patients were included in aerosolized colistin group if duration of treatment was 50% or more of iv colistin treatment duration | | |
| **BASELINE CHARACTERISTICS** | | | | | | | | | |
| **Number randomised** | | 27 (MDR ABAU VAP) | 28 (MDR ABAU VAP) | | 210 | | | 102 | |
| Intervention | 14 | 14 | 13 | 14 (ABAU imipenem susceptible) | 105 | 43 | 78 | 51 | 21 |

| Data Extraction Table-Which antibiotic should be used to treat patients with HAP/VAP due to Acinetobacter species? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Wood | Betrosian | Betrosian | Garnacho-Montero | Durante-Mangoni | Kofteridis | Korbila | Rattanaunpawan | Aydemar |
| Year | 2002 | 2007 | 2008 | 2003 | 2013 | 2010 | 2010 | 2010 | 2013 |
| Comparison | 63 | 13 | 15 | 21 (ABAU susceptible exclusively to colistin) | 105 | 43 | 43 | 49 | 22 |
| Total (only if not reported separately) | | | | | | | | | |
| **Age** | | | | | | | | | |
| Intervention (mean or median) | 42 | 67 (4.5) | 72 (5) | 64,5 (11) | 62 (15.1) | 62 (15.1) | 59,2 (19,2) | 70,2 (18,5) | 58 |
| Comparison (mean or median) | 43 | 72 (2.8) | 67 (9) | 56,9 (13.1) | 61 (15.7) | 62.35 (14.92) | 60,9 (15,7) | 66,2 (15,8) | 63 |
| Total (mean or median) (only if not reported separately) | | | | | | | | | |
| unit (e.g. mean and SD) | mean (SD) | mean (SD) | mean (SD) | mean (SD) | mean (SD) | mean (SE) | mean (SD) | mean (SD) | mean (SD) |
| Age range (e.g. 22-73) | | | | not stated | | | | | |
| Age inclusion criterion (e.g. older than 16) | | | | | older than 18 years | | | older than 17 | alder than 17 |
| **Male gender** | | | | | | | | | |
| Intervention | 12 (85,7%) | 7 (50%) | 7 (53,8) | 12 (85,7) | 67 (64.4%) | 28 (65%) | 61 (78,2%) | 31 (60,8%) | 67.70% |
| Comparison | 50 (79%) | 8 (61.5%) | 7 (46,6) | 14 (66,6) | 70 (66.7%) | 30 (69%) | 31 (72,1%) | 33 (67,3%) | 72.70% |
| Total (only if not reported separately) | | | | | | | | | |
| **Severity of illness** | | | | | | | | | |
| Name of score (e.g. APACHE, SOFA, ...) | Apache II | Apache II | Apache II | Apache II | SAPS | Apache II | Apache II | Apache II | 19.1 |
| Intervention group mean score | 15 | 15 | 14 | 20.5 | 40.8 | 16.95 | 17.4 | 19.1 | 20.1 |
| Comparison group mean score | 17 | 15 | 14 | 19.6 | 39.0 | 17.74 | 19.2 | 18.5 | 18.0 |
| | | | | | SAPS II | | | | |
| **Study population** | | | | | | | | | |

| Data Extraction Table-Which antibiotic should be used to treat patients with HAP/VAP due to Acinetobacter species? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Wood | Betrosian | Betrosian | Garnacho-Montero | Durante-Mangoni | Kofteridis | Korbila | Rattanaunpawan | Aydemar |
| Year | 2002 | 2007 | 2008 | 2003 | 2013 | 2010 | 2010 | 2010 | 2013 |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Trauma | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | Mixed Medical-Surgical | If other please specify |
| NOTES: | Acinetobacter VAP | | | | Extensively drug-resistant ABAU. Patients with VAP 144 (69.8%) and patients with HAP 18 (8.6%) | Patients with MDR VAP due to gram-negative bacteria (66 cases were ABAU, 8 K. pneumoniae, 12 P. aeruginosa) | 57/78 had VAP caused by ABAU; 35/43 had VAP caused by ABAU | GNB VAP | Critical ill patients |
| **OUTCOMES** | | | | | | | | | |
| **Mortality (all cause)** | | | | | | | | | |
| NOTES: | | | | No separate data for ESBL | | All cause mortality | All cause in-hospital mortality | | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Length of ICU stay** | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Length of hospital stay** | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Clinical cure (as defined by the study authors)** | | | | | | | | | |
| NOTES: | | | | | | | | | |

| Data Extraction Table-Which antibiotic should be used to treat patients with HAP/VAP due to Acinetobacter species? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Wood | Betrosian | Betrosian | Garnacho-Montero | Durante-Mangoni | Kofteridis | Korbila | Rattanaunpawan | Aydemar |
| Year | 2002 | 2007 | 2008 | 2003 | 2013 | 2010 | 2010 | 2010 | 2013 |
| **Recurrent pneumonia** | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Number of antibiotic days** | | | | | | | | | |
| NOTES: | | Overall, the duration of therapy was 8 (2) days | | | | | | | |
| **Development of resistance (as defined by the study authors)** | | | | | | | | | |
| NOTES: | | | | | Data are for rifampicin resistance. No patient developed colistin | | | | |
| **Any adverse effect** | | | | | | | | | |
| NOTES: | | One case of mild elevation of LFTs | | Nephrotoxicity | | Nephrotoxicity | | | |
| **Serious adverse effect** | | | | | | | | | |

| Data Extraction Table-Which antibiotic should be used to treat patients with HAP/VAP due to Acinetobacter species? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the first author | Wood | Betrosian | Betrosian | Garnacho-Montero | Durante-Mangoni | Kofteridis | Korbila | Rattanaunpawan | Aydemar |
| Year | 2002 | 2007 | 2008 | 2003 | 2013 | 2010 | 2010 | 2010 | 2013 |
| | | The diagnosis of VAP was stablished when the BAL grew at least 10000 cfu/ml | The diagnosis of VAP was stablished when the BAL grew at least 10000 cfu/ml | | Significant increase of microbiological eradication was observed in the colistin plus rifampicin group (P=.03) | Addition of aerosolized colistin to iv colistin did not provide additional therapeutic benefit to patients with MDR VAP due to gram-negative bacteria | Limitations: retrospective analysis. Nevertheles the number of patients with VAP caused by ABAU is relatively large, and the used of inhaled colistin was independently associated with clinical cure of VAP in a multivariate analysis. | ABAU 69.6% (intervention group) vs. 61.2% (comparison group). Favourable microbiological outcome was greater in the intervention group. | Ten (23%) patients developed nephrotoxicity during colistin treatment |

| GRADE EVIDENCE PROFILE: ADJUVANT INHALED ANTIBIOTIC TREATMENT | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | Risk difference Quality | participants | Quality |
| **Mortality** | | | | | | | | | | | | |
| Brown 1990 | Of 88 enrolled 45 were assessable | | No | | No | 7/40 | 13/45 | 1.65(.73-3.73) | | Moderate | 95 | Moderate |
| Hallal | Single site RCT | | No | Not estimable | No | 0/5 | 0/5 | | | Moderate | | Low |
| Koftederis | retrospective case-control | | No | | No | 18/42 | 10/23 | 1(.96-1.05 | | Low | | |
| Korbilia | comparative cohort study | | No | | No | 19/43 | 31/78 | .9(.58-1.39) | | moderate | | |
| LeConte | multi center RCT | | No | | No | 4/17 | 2/21 | .4(.8-1.95 | | high | | |
| Palmer | single cite RCT | | No | | Industry funded | 4/24 | 4/19 | 1.26(.36,4.40 | | moderate | | |
| Rattapaunamaun | Single cite RCT | | No | | No | 20/49 | 22/51 | 1.06(.67,1.68) | | moderate | | |
| Total | | 0% | | | | | 216 | 1(.96, 1.05) | | | | |
| **Clinical outcome** | | | | | | | | | | | | |
| Brown 1990 | | | No | | | 18/40 | 24/25 | 1.19[0.76,1.84 ] | | Moderate | | |
| Hallal | | | No | | | 3/5 | 5/5 | 1.57[.77,3.22] | | Moderate | | |
| Koftederis | | | No | | | 14/43 | 23/43 | 1.64[.98,2.74] | | Low | | |
| Korbilia | | | No | | | 26/43 | 62/78 | 1.31[1.01,1.72 ] | | moderate | | |
| LeConte | | | No | | | 3/17 | 7/21 | 1.89[0.57,6.22 ] | | high | | |
| Palmer | | | No | | | 4/18 | 8/14 | 2.57[0.97, 6.82] | | moderate | | |
| Rattapaunamaun | | | No | | | 26/49 | 26/51 | .96[0.66, 1.40] | | moderate | | |
| Total | | 0% | | | | 215 | 257 | 1.29[1.09,1.53 ] | | | | |
| **Nephrotoxicity** | | | | | | | | | | | | |
| Brown 1990 | | | No | | | 4/40 | 5/45 | 1.11[0.32, 3.85 | | Moderate | | |
| Hallal | | | No | | | 2/5 | 0/5 | .2[0.01,3.35] | | Moderate | | |
| Koftederis | | | No | | | 8/43 | 8/43 | 1.00[0.41, 2.42] | | Low | | |
| Korbilia | | | No | | | NA | NA | NA | | NA | | |

| GRADE EVIDENCE PROFILE: ADJUVANT INHALED ANTIBIOTIC TREATMENT | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies for each outcome | Limitations -risk of bias | Inconsistency=I2 | Indirectness | Imprecision | Publication bias | Control | Experimental | Relative Risk | Absolute risk control | Risk difference Quality | participants | Quality |
| LeConte | | | No | | | NA | NA | NA | | NA | | |
| Palmer | | | No | | | NA | NA | NA | | Na | | |
| Rattapaunamaun | | | No | | | 11/49 | 13/51 | 1.14[0.56, 2.29] | | moderate | | |
| Total | | 0% | | | | 137 | 144 | 1.03[0.63, 1.69] | | | | |

## XX. Which antibiotic should be used to treat patients with HAP/VAP due to carbapenem-resistant pathogens?

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Type of information (published or unpublished) | published | published | published | published | | published | | published | published |
| Journal name | Journal of Antimicrobial Chemotherapy | Journal of Intensive Care Medicine | Journal of Infection | Surgical Infections | Intensive Care Medicine | Respiraoty Medicine | Journal of Antimicrobial Chemotherapy | BMC Anesthesiology | Chemotherapy |
| Language of publication | English | English | | | | English | | English | |
| Funding body | No specific funding | no financial support | | | | | | | |
| Ethics approval | Yes | institutional review board reviewed and approved | | | | | | | |
| Country where study was done | Italy | USA | | | | | | | |
| REVIEWED BY | SWEENEY | SWEENEY | SWEENEY | SWEENEY | SWEENEY | SWEENEY | SWEENEY | SWEENEY | |
| **METHODS** | case series: prospective unconrolled carbapenem resistant acinetobacter bacteremia (10) and pna (19) all tx with colistin and rif | case series 55 pts carbapenem resistant acinetobacter pna | case series: 33 pts with carbapenem resistant Acinetobacter spp. infections and received tigecycline alone or in combination | | | | pilot study; all 10 pts (only 4 with vap) with carb res treated with imi/rif | could not determine how many patients had carbapenem resistant infections; emailed corresponding author--no response | no separate analysis for VAP pts; pts on vanco+colistin were on vanco not for acinetobacter but for either empiric or directed gram + coverage |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Randomization | | | | | | | | | |
| Concealment | | | | | | | | | |
| Not stopped early | | | | | | | | | |
| NOTES: | | | | 10 patients, cannot determin if any patients had carbapenem resistant infections | carbapenem SENSITIVE infections | no control group; Cannot identify pts with carbapenem resistant infections | | | |
| ***if COHORT STUDY*** | | | | | | | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | | | | | | | |
| Selection of the non exposed cohort | | | | | | | | | |
| Ascertainment of exposure | | | | | | | | | |
| Demonstration that outcome of interest was not present at start of study | | | | | | | | | |
| Comparability of cohorts on the basis of the design or analysis | | | | | | | | | |
| Assessment of outcome | | | | | | | | | |
| Was follow-up long enough for outcomes to | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| occur? | | | | | | | | | |
| Adequacy of follow up of cohorts | | | | | | | | | |
| Co-Interventions similar between groups? | | | | | | | | | |
| NOTES: | | | | | | | | | |
| ***if CASE-CONTROL STUDY*** | | | | | | | | | |
| Is case definition adequate? | | | | | | | | | |
| Representativeness of the cases | | | | | | | | | |
| Selection of controls | | | | | | | | | |
| Definition of controls | | | | | | | | | |
| Comparability of cases and controls | | | | | | | | | |
| Ascertainment of exposure | | | | | | | | | |
| Same method of ascertainment for cases and controls | | | | | | | | | |
| Non-response rate | | | | | | | | | |
| Co-interventions similar between groups? | | | | | | | | | |
| NOTES: | | | | | | | | | |
| | | | | | | | | | |
| **INTERVENTIONS BEING COMAPRED** | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| **Intervention 1 (experimental)** | colistin sulphomethate sodium (6million units or approx 100,000U/kg divided in 3 doses) and rifampicin 10mg/kg q 12h) | 22 on monotherapy (minocycline/doxy, amp/sulbactam, AG, colistin, Tige) and 33 on various combo | | | | all 60 pts received inhaled colistin; no control arm | | | colistin+vanco |
| other Tx used (if relevant for interpretation) | | | | | | | | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | |
| **Intervention 2 (comparison)** | | | | | | | | | Colistin |
| other Tx used (if relevant for interpretation) | | | | | | | | | |
| Tx not allowed (if relevant for interpretation) | | | | | | | | | |
| duration of treatment | | | | | | | | | |
| NOTES: | | | no comparison made, cannot separate vap cases | | | | | | |
| **BASELINE CHARACTERISTICS** | | | | | | | | | |
| **Number randomised** | | | | | | | | | |
| Intervention | 19 | 55 | | | | | | | |
| Comparison | | | | | | | | | |
| Total (only if not reported separately) | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| **Age** | | | | | | | | | |
| Intervention (mean or median) | | | | | | | | | |
| Comparison (mean or median) | | | | | | | | | |
| Total (mean or median) (only if not reported separately) | | | | | | | | | |
| unit (e.g. mean and SD) | | | | | | | | | |
| Age range (e.g. 22-73) | | | | | | | | | |
| Age inclusion criterion (e.g. older than 16) | | | | | | | | | |
| **Male gender** | | | | | | | | | |
| Intervention | | | | | | | | | |
| Comparison | | | | | | | | | |
| Total (only if not reported separately) | | | | | | | | | |
| **Severity of illness** | | | | | | | | | |
| Name of score (e.g. APACHE, SOFA, ...) | | | | | | | | | |
| Intervention group mean score | | | | | | | | | |
| Comparison group mean score | | | | | | | | | |
| Total (only if not reported separately) | | | | | | | | | |
| **Study population** | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| | | | | | | | | | |
| **OUTCOMES** | | | | | | | | | |
| | | | | | | | | | |
| **Mortality (all cause)** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| location or duration of follow-up (choose from the list) | | | | | | | | | |
| Intervention group: # with event | | | | | | | | | |
| Intervention group: Total | | | | | | | | | |
| Comparison group: # with event | | | | | | | | | |
| Comparison group: Total | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Comparison group: (mean or median) | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| follow-up [days] | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Length of ICU stay** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | |
| Comparison group: total | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| number of patients | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Length of hospital stay** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Intervention group: (variance) | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | |
| Comparison group: (variance) | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Clinical cure (as defined by the** | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| **study authors)** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Definition (provide details if relevant) | | | | | | | | | |
| Duration of follow-up (time point when outcome was measured) [days] | | | | | | | | | |
| Intervention group: # with event | | | | | | | | | |
| Intervention group: Total | | | | | | | | | |
| Comparison group: # with event | | | | | | | | | |
| Comparison group: Total | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Recurrent pneumonia** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| Intervention group: # with event | 22/29 (including bacteremic patients had a favorable outcome) | Clinical responses were achievedin 60.0% of sulbactam-based, 66.7% of polymyxin-based, 77.8% of aminoglycoside-based, 80.6% of minocycline-based, and 90.0% of tigecycline-based regimens | | | | | | | |
| Intervention group: Total | | | | | | | | | |
| Comparison group: # with event | | | | | | | | | |
| Comparison group: Total | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Number of antibiotic days** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| unit (days, hours, etc.) | | | | | | | | | |
| How data were reported (mean or median and type of variance) | | | | | | | | | |
| Intervention group: (mean or median) | | | | | | | | | |
| Intervention group: (variance) | | | | | | | | | |
| Intervention group: total number of patients | | | | | | | | | |
| Comparison group: (mean or median) | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Comparison group: (variance) | | | | | | | | | |
| Comparison group: total number of patients | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Development of resistance (as defined by the study authors)** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| Intervention group: # with event | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Intervention group: Total | | | | | | | | | |
| Comparison group: # with event | | | | | | | | | |
| Comparison group: Total | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Any adverse effect** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| Intervention group: # with at lest one event (if this was reported) | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| Intervention group: # od events per group (if this was reported) | | | | | | | | | |
| Intervention group: Total | | | | | | | | | |
| Comparison group: #with at lest one event (if this was reported) | | | | | | | | | |
| Comparison group: # od events per group (if this was reported) | | | | | | | | | |
| Comparison group: Total | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |
| **Serious adverse** | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| **effect** | | | | | | | | | |
| Are the data available? | | | | | | | | | |
| Duration of follow-up [days] | | | | | | | | | |
| Intervention group: # with at lest one event (if this was reported) | | | | | | | | | |
| Intervention group: # od events per group (if this was reported) | | | | | | | | | |
| Intervention group: Total | | | | | | | | | |
| Comparison group: #with at lest one event (if this was reported) | | | | | | | | | |
| Comparison group: # od events per group (if this was reported) | | | | | | | | | |
| Comparison group: Total | | | | | | | | | |
| Blinding [patients] (only relevant for RCTs) | | | | | | | | | |
| Blinding [personnel] (only relevant for RCTs) | | | | | | | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | | | | | | | |
| Blinding [data collectors] (only | | | | | | | | | |

| **Evidence Extraction Table** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Last name of the fist author | Bassetti | Chan | Guner | Hallal | Kallel | Michalopoulos | Saballs | Doshi | Garnacho-montero |
| Year | 2008 | 2010 | 2011 | 2007 | 2007 | 2008 | 2006 | 2013 | 2013 |
| relevant for RCTs) | | | | | | | | | |
| Blinding [analysts] (only relevant for RCTs) | | | | | | | | | |
| ITT analysis performed (only relevant for RCTs) | | | | | | | | | |
| NOTES: | | | | | | | | | |

| **EVIDENCE PROFILE-Which antibiotic should be used to treat patients with HAP/VAP due to carbapenem-resistant pathogens?** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Quality Assessment[‡] | | | | | | | Summary of Findings | | | | |
| | | | | | | | Event/# of patients | | Relative risk (CI) | Risk diff (CI) | Quality |
| Outcome | Study | Limitations (=risk of bias) | Inconsistency ($I^2$ shown if >30%) | Indirectness | Imprecision | Pub bias | Experimental | Colistin | | | |
| Mortality | Betrosian 2008 | Likely open label | | | | | | | | | moderate |
| | Korbila 2010* | Observational | | * | | | | | | | Very Low |
| | Kofteridis 2010 | Observational | | | | | | | | | Low |
| | Aydemir 2013 | open label | | | | | | | | | moderate |
| | Durante-Mangoni 2013 | open label | | | | | | | | | moderate |
| | Tumbarello 2013 | Observational | | | | | | | | | Low |
| | Kalin 2014 | Observational | | | | | | | | | Low |
| | Total | | $I^2$ = 0% | | | | 174/400 | 178/384 | 1.03 (.85,1.25) | 0.02 [-0.06, 0.11] | low |
| Clinical Cure | Betrosian 2008 | Likely open label | | | | | | | | | Moderate |
| | Korbila 2010* | Observational | | * | | | | | | | Very low |
| | Kofteridis 2010 | Observational | | | | | | | | | low |
| | Gedik 2012 | Observational | | | | | | | | | low |
| | Aydemir 2013 | Open label | | | | | | | | | moderate |
| | Tumbarello 2013 | Observational | | | | | | | | | |
| | Kalin 2014 | Observational | | | | | | | | | moderate |
| | Total | | $I^2$ = 0% | | | | 200/317 | 136/294 | **1.29 [1.12, 1.49] favors experimental** | 0.14 [0.07, 0.22] | low |
| | Total minus Korbilla* | | $I^2$ = 0% | | | | 138/239 | 110/251 | **1.28 [1.08, 1.51] favors experimental** | 0.13 [0.05, 0.22] | low |
| Nephro-toxicity | Betrosian 2008 | Likely open label | | | | | | | | | moderate |
| | Kofteridis 2010 | Observational | | | | | | | | | low |
| | Tumbarello 2013 | Observational | | | | | | | | | Low |
| | Total | | | | | | 36/160 | 36/162 | 0.98 [0.65, 1.47] | -0.00 [ -0.09, 0.09] | Low |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Inhaled+IV colistin | IV colistin | | | |
| Mortality | Korbila 2010 | Observational | | * | | | | | | | Very Low |
| | Kofteridis 2010 | Observational | | | | | | | | | Low |
| | Rattanaumpawan 2010α | Open label | | | | | | | | | moderate |
| | Tumbarello 2013 | Observational | | | | | | | | | Low |
| | Total | | | | | | 96/255 | 99/224 | 0.86 [0.69,1.07] | -0.07 [-0.16, 0.02] | Low |
| Clinical Cure | Korbila 2010 | Observational | | * | | | | | | | Very Low |
| | Kofteridis 2010 | Observational | | | | | | | | | Low |
| | Rattanaumpawan 2010α | Open label | | | | | | | | | moderate |
| | Tumbarello 2013 | Observational | | | | | | | | | Low |
| | Total | | | | | | 173/259 | 110/220 | 1.29[1.11, 1.51] favors inhaled | 0.15 [0.07, 0.24] | low |
| | Total minus Korbilla | | | | | | 111/181 | 84/177 | 1.28[1.07, 1.55] | 0.14 [0.04, 0.24] | Low |
| | | | | | | | Rifampin+ colistin | colistin | | | |
| Clinical cure | | | | | | | | | | | |
| | Aydemir 2013 | open label | | | | | | | | | Moderate |
| | Durante-Mangoni 2013 | open label | | | | | | | | | moderate |
| | Total | | | | | | 58/125 | 61/127 | 0.95 [0.74, 1.22] Trend favors rifampin | -0.02 [-0.14, 0.10] | moderate |

* Korbilla issues: approximately 50% of patients may have had carbapenem sensitive infections AND the distribution of Carbapenem infections are not equally distributed between the two tx groups
α Inhaled Colistin plus systemic antibiotics according as per attending physicians
∓ An assessment of quality of for each endpoint was performed; empty cells denote the fact that no deficiency was noted.

**Limitations = risk of bias**
1.lack of allocation concealment Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (major problem in‘‘pseudo’’ or ‘‘quasi’’ randomized trials with allocation by day of week, birth date, chart number, etc)
2. Lack of blinding Patient, care givers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or themedication currently being received in a crossover trial)
3. Incomplete accounting of patients and outcome events Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available

4. Selective outcome reporting bias Incomplete or absent reporting of some outcomes and not others on the basis of the results
5. Other limitations Stopping early for benefit Use of unvalidated outcome measures (e.g., patient-reported outcomes) Carryover effects in crossover trial Recruitment bias in cluster-randomized trials

**Inconsistency** $I^2$ test for heterogeneity?
**Indirectness—**four types. occurs when the population, intervention, or outcomes differ from those in which we are interested or when the two interventions are not compared head-to-head
**Imprecision—**CI and relative or absolute risk?
**Publication bias—**funnel plot

**SUMMARY OF FINDINGS: XX. Which antibiotic should be used to treat patients with HAP/VAP due to carbapenem-resistant pathogens?**

EXPERIMENTAL COMPARED WITH COLISTIN IV OR COLISTIN INHALED +IV COMPARED WITH COLISTIN IV OR RIFAMPIN+COLISTIN IV COMPARED WITH COLISTIN IV FOR THE TREATMENT OF CARBAPENEM RESISTANT HAP/VAP

Patient or population: adults with MRSA HAP/VAP; Setting: high and middle income countries; Intervention: Experimental or the addition of inhaled colistin or the addition of rifampin; Comparison: Colisitin IV

| Outcomes | Intervention | Comparison | Relative risk (CI) | Risk diff (CI) | Number of participants (studies) | Quality | Comment |
|---|---|---|---|---|---|---|---|
| | Experimental | Colisitin IV | | | | | |
| Mortality | 174/400 | 178/384 | 1.03 (.85,1.25) | 0.02 [-0.06, 0.11] | 784 (7) | Low | |
| Clinical Cure | 200/317 | 136/294 | 1.29 [1.12, 1.49] | 0.14 [0.07, 0.22] | 611 (7) | Low | |
| Clinical Cure minus Korbila | 111/181 | 84/177 | 1.28[1.07, 1.55] | 0.14 [0.04, 0.24] | 358( 6) | Low | |
| Nephrotoxicity | 36/160 | 36/162 | 0.98 [0.65, 1.47] | -0.00 [-0.09,0.09] | 322 (3) | Low | |
| | Inhaled+IV colistin | IV colistin | | | | | |
| Mortality | 96/255 | 99/224 | 0.86 [0.69,1.07] | -0.07 [-0.16, 0.02] | 479 (4) | | |
| Clinical Cure | 173/259 | 110/220 | 1.29[1.11, 1.51] | 0.15 [0.07, 0.24] | 479(4) | Low | |
| Clinical Cure minus Korbila | 111/181 | 84/177 | 1.28[1.07, 1.55] | 0.14 [0.04, 0.24] | 358 (3) | Low | |
| | Rifampin+ colistin | colistin | | | | | |
| Clinical cure | 58/125 | 61/127 | 0.95 [0.74, 1.22] Trend favors rifampin | -0.02 [-0.14, 0.10] | 252(2) | Moderate | |

* Includes: ampicillin/sulbactam, colistin IV+inhaled, colistin+ either carbapenem, tigecycline,

$\alpha$ nephrotoxicity definitions used: ”judgment of the investigator” (2007);” 0.5-mg/mL increase in serum creatinine level if normal at baseline or 50% increase if abnormal at baseline” (2012); “progression of acute renal failure” (2008) ; not defined (2002)

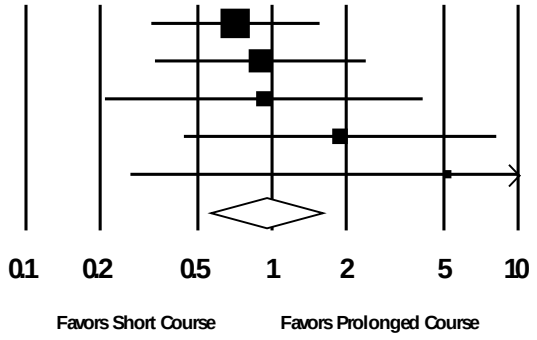
## XXI. Should patients with VAP receive 7 days or 8-15 days of antibiotic therapy?

| Quality assessment | | | | | | | Summary of findings | | | | | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Short course | Long course | Relative (95% CI) | Absolute | | |
| **Mortality all organisms (follow-up 21-28 days)** | | | | | | | | | | | | |
| 5 Chastre, Medina, Fekih-Hassen, Capellier, Kollef | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 80/446 (17.9%) | 74/454 (16.3%)<br>0% | OR 1.12 (.79 to 1.59) | 20 more per 1000 (from 96 more to 12714 more)<br>0 more per 1000 (from 0 more to 0 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Mortality NGF-GN (follow-up mean 28 days)** | | | | | | | | | | | | |
| 5 Chastre, Medina, Fekih-Hassen, Capellier, Kollef | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 43/191 (22.5%) | 39/157 (24.8%)<br>0% | OR 0.94 (0.56 to 1.59) | 11 fewer per 1000 (from 92 fewer to 96 more)<br>0 fewer per 1000 (from 0 fewer to 0 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Clinical Cure VAP all organisms (follow-up 10-28 days)** | | | | | | | | | | | | |
| 3 Chastre, Capellier, Kollef | randomised trials | serious | no serious inconsistency | no serious indirectness | no serious imprecision | none | 135/392 (61%) | 257/401 (64.6%)<br>0% | OR 0.88 (0.66 to 1.7) | 30 fewer per 1000 (from 100 fewer to 110 more)<br>0 fewer per 1000 (from 0 fewer to 0 more) | ⨁⨁⨁◯ MODERATE | |
| **Clinical Cure VAP NGF-GN (follow-up 10-28 days)** | | | | | | | | | | | | |
| 2 Chastre, Kollef | randomised trials | serious | no serious inconsistency | no serious indirectness | no serious imprecision | none | 40/96 (41.7%) | 43/83 (51.8%)<br>0%<br>0% | OR 0.66 (0.37 to 1.2) | 518 fewer per 1000 (from 234 fewer to 45 more)<br>0 fewer per 1000 (from 0 fewer to 0 more)<br>0 fewer per 1000 (from 0 fewer to 0 more) | ⨁⨁⨁◯ MODERATE | |
| **Recurrence VAP all organisms** | | | | | | | | | | | | |
| 4 Chastre, Medina, Fekih-Hasssen, Capellier | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 90/367 (24.5%) | 73/366 (19.9%)<br>0% | OR 1.30 (0.92 to 1.85) | 45 more per 1000 (from 13 fewer to 116 more)<br>0 more per 1000 (from 0 fewer to 0 more) | ⨁⨁⨁◯ MODERATE | |
| **Recurrence VAP NGF-GN** | | | | | | | | | | | | |
| 4 Chastre, Medina, Fekih-Hassen; | randomised trials | serious | no serious inconsistency | no serious indirectness | no serious imprecision | none | 53/147 (36.1%) | 31/118 (26.3%) | OR 1.42 (0.66 to 3.04) | 73 more per 1000 (from 72 more to 257 more) | ⨁⨁⨁◯ MODER | |

| Quality assessment | | | | | | | Summary of findings | | | | | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Short course | Long course | Relative (95% CI) | Absolute | | |
| Capellier | | | | | | | | 0% | | 0 more per 1000 (from 0 more to 0 more) | ATE | |
| | | | | | | | | 0% | | 0 more per 1000 (from 0 more to 0 more) | | |

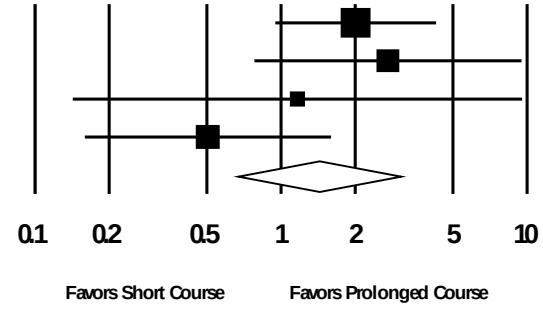
## All-Cause Mortality: NF-GNR Only/VAP and Randomized Studies: Short vs. Prolonged Course

| Studyname | Odds ratio | Lower limit | Upper limit | p-Value | Death / Total: Short Fixed Course | Death / Total: Prolonged Course | Death / Total: Total |
|---|---|---|---|---|---|---|---|
| Chastre 2003 | 0.71 | 0.32 | 1.56 | 0.39 | 15 / 64 | 19 / 63 | 34 / 127 |
| Medina 2007 | 0.90 | 0.33 | 2.41 | 0.83 | 11 / 40 | 11 / 37 | 22 / 77 |
| Fekih-Hassen 2009 | 0.93 | 0.21 | 4.11 | 0.92 | 5 / 14 | 6 / 16 | 11 / 30 |
| Kollef 2012 | 1.89 | 0.44 | 8.18 | 0.39 | 8 / 32 | 3 / 20 | 11 / 52 |
| Capellier 2012 | 5.16 | 0.26 | 100.52 | 0.28 | 4 / 41 | 0 / 21 | 4 / 62 |
| | 0.94 | 0.56 | 1.59 | 0.83 | 43 / 191 | 39 / 157 | 82 / 348 |




## Pneumonia Recurrence: NF-GNR Only/VAP and Randomized Studies: Short vs. Prolonged Course

| Studyname | Odds ratio | Lower limit | Upper limit | p-Value | Recurrence / Total: Short Fixed Course | Recurrence / Total: Prolonged Course | Recurrence / Total: Total |
|---|---|---|---|---|---|---|---|
| Chastre 2003 (France) | 2.01 | 0.94 | 4.28 | 0.07 | 26 / 64 | 16 / 63 | 42 / 127 |
| Medina 2007 (Uruguay) | 2.72 | 0.78 | 9.52 | 0.12 | 12 / 27 | 5 / 22 | 17 / 49 |
| Fekih-Hassen 2009 (Tunisia) | 1.17 | 0.14 | 9.59 | 0.89 | 2 / 14 | 2 / 16 | 4 / 30 |
| Capellier 2012 (France) | 0.50 | 0.16 | 1.60 | 0.25 | 13 / 42 | 8 / 17 | 21 / 59 |
| | 1.42 | 0.66 | 3.04 | 0.37 | 53 / 147 | 31 / 118 | 84 / 265 |



## XXIII. Should antibiotic therapy be de-escalated or fixed in patients with HAP/VAP?

**De-escalation compared to fixed regimen for VAP**

**Patient or population:** patients with VAP
**Settings:** hosptital (ICU mostly)
**Intervention:** De-escalation
**Comparison:** fixed regimen

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk **fixed regimen** | Corresponding risk **De-escalation** | | | |
| **Mortality** Follow-up: mean 30 days | **226 per 1000** | **197 per 1000** (157 to 243) | **OR 0.84** (0.64 to 1.1) | 1218 (6 studies) | ⨁⊖⊖⊖ **very low**[1,2] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Significant variation of design and method of de-escalation
[2] No explanation was provided

| **Evidence Profile** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **No of Studies (6)** | Inconsistency | **Indirectness** | Imprecision | **Publication Bias** | **Summary of Findings** | | | | |
| | | | | | **De-escalation** | **No De-escalation** | | | |
| **Kim et al. Crit Care 2012 Prospective; Randomized for Initial Rx (Imipenem+Vanc vs Other) AND protocol driven de-escalation based on Cult.** | | Single ICU, Korea, only 50% VAP, more patients in DE group had adequate initial Rx | | Open-label | **No. of pts=53** | **No of pts=55** | | | Quality of the Evidence |
| All Cause Mortality | | | | | **21/53 (39.6%)** | **14/55 (25.9%)** | | | Low; ? effect of initial therapy |
| Vent days | | | | | **etc** | **etc** | | | |
| Vent free days | | | | | | | | | |
| ICU LOS | | | | | 21.1 | 14.1 (p=0.464) | | | " |
| Hospital LOS | | | | | | | | | |
| Clinical Cure | | | | | | | | | |
| Recurrent Pneumonia | | | | | | | | | |
| Antibiotic Days | | | | | | | | | |
| Development of Resistance | | | | | 37.9% (mostly MRSA; no diff for GNR) | 16.7% | | | " |
| Any Adverse event | | | | | | | | | |
| Serious adverse event | | | | | | | | | |
| **Alvarez-Lerma et al. Crit Care 2006 Prospective, observational, Initial ABX-imipenem +/- aminogly +/- glycopeptides; De-escalate based on microb (no guidance for such)** | | 24 Spanish ICUs, Nosoc PNA; Mech Vent ≈ 90%, Different groups identified (for this eval included patients with suscept organisms for DE vs NDE) | | Open-label | **No. of pts=56 (pts with susceptible organisms whose Rx was modified)** | **No of pts=38 (pts with susceptible organisms whose RX not modified)** | | | Quality of the Evidence |
| **All cause mortality** | | | | | **14.8%** | **25%** | | | |
| Vent days | | | | | | | | | |
| Vent free days | | | | | | | | | |
| ICU LOS | | | | | 23.7% | 36.7% | | | |
| Hospital LOS | | | | | | | | | |

| **Evidence Profile** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **No of Studies (6)** | Inconsistency | **Indirectness** | Imprecision | **Publication Bias** | **Summary of Findings** | | | | |
| | | | | | **De-escalation** | **No De-escalation** | | | |
| Clinical Cure (mod ITT pop) | | | | | 50% | 44.7% | | | |
| Recurrent Pneumonia | | | | | | | | | |
| Antibiotic Days | | | | | 18 | 16 (p>0.05) | | | |
| Development of Resistance | | | | | | | | | |
| Any Adverse event | | | | | | | | | |
| Serious adverse event | | | | | | | | | |
| **Joung et al. Crit Care 2011 Retrospective, observational, Initial ABX-non protocolized; De-escalate based on microb (no guidance for such)** | | 24 surg ICU, Korea; Nosoc PNA; Mech Vent ≈ 90%, | | Open-label | **No. of pts=44** | **No of pts=93** | | | Quality of the Evidence |
| **All cause mortality** | | | | | **"lower" raw data not presented, but indicated at p=0.01** | | | | |
| **PNA-related mortality 30d** | | | | | **1/44; 2.3% (p=0.03)** | **13/93; 14%** | | | |
| Vent days | | | | | | | | | |
| Vent free days | | | | | | | | | |
| ICU LOS | | | | | | | | | |
| Hospital LOS | | | | | | | | | |
| Clinical Cure | | | | | | | | | |
| Recurrent Pneumonia | | | | | | | | | |
| Antibiotic Days | | | | | | | | | |
| Development of Resistance | | | | | | | | | |
| Any Adverse event | | | | | | | | | |
| Serious adverse event | | | | | | | | | |
| **Joffe et al. J Crit Care 2008 2nd analysis of VAP Randomized to bronch or endotrach cultures, Initial ABX-imipenem vs imipenem + cipro; De-escalate based on microb ("urged" to do so)** | | 28 ICUs, Canada; This Eval based on patients with positive cultures at enrollment | | Open-label | **No. of pts=320** | **No of pts=92** | | | Quality of the Evidence |

| **Evidence Profile** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **No of Studies (6)** | Inconsistency | **Indirectness** | Imprecision | **Publication Bias** | **Summary of Findings** | | | | |
| | | | | | **De-escalation** | **No De-escalation** | | | |
| **All cause mortality** | | | | | **55/320 (17.2%)** | **13/92 (14.1%)** | | | |
| Vent days | | | | | **9.8** | **14.7 (p=0.03)** | | | |
| Vent free days | | | | | | | | | |
| ICU LOS | | | | | | | | | |
| Hospital LOS | | | | | | | | | " |
| Clinical Cure | | | | | | | | | |
| Recurrent Pneumonia | | | | | 3.8% | 2.2% | | | |
| Antibiotic Days | | | | | | | | | |
| Development of Resistance | | | | | "no difference" | | | | |
| Any Adverse event | | | | | | | | | " |
| Serious adverse event | | | | | | | | | |
| **Kollef et al. Chest 2006 Prospective, observational. VAP, No protocolized initial ABX or guidance for de-escalation** | | 20 ICUs, US; This Eval based on De-escalation vs no change | | Open-label | **No. of pts=88** | **No of pts=245** | | | Quality of the Evidence |
| **All cause mortality** | | | | | **15/88 (17%)** | **58/245 (23.7%)** | | | |
| Vent days | | | | | | | | | |
| Vent free days | | | | | | | | | |
| ICU LOS | | | | | | | | | |
| Hospital LOS | | | | | | | | | " |
| Clinical Cure | | | | | | | | | |
| Recurrent Pneumonia | | | | | | | | | |
| Antibiotic Days | | | | | | | | | |
| Development of Resistance | | | | | | | | | |
| Any Adverse event | | | | | | | | | " |
| Serious adverse event | | | | | | | | | |
| **Eachempati et al. J Trauma 2009 Retrospective, observational. VAP, protocolized initial ABX and guidance for de-escalation** | | Single surgical ICU in NY 20 ICUs, | | Open-label | **No. of pts=77** | **No of pts=57** | | | Quality of the Evidence |

| **Evidence Profile** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **No of Studies (6)** | Inconsistency | **Indirectness** | Imprecision | **Publication Bias** | **Summary of Findings** | | | | |
| | | | | | **De-escalation** | **No De-escalation** | | | |
| **All cause mortality** | | | | | **26/77 (33.8%)** | **24/57 (42.1%)** | | | |
| Vent days | | | | | | | | | |
| Vent free days | | | | | | | | | |
| ICU LOS | | | | | | | | | |
| Hospital LOS | | | | | | | | | " |
| Clinical Cure | | | | | | | | | |
| Recurrent Pneumonia | | | | | 21/77 (27.3%) | 20/57 (35.1%) | | | |
| Antibiotic Days | | | | | | | | | |
| Development of Resistance | | | | | | | | | |
| Any Adverse event | | | | | | | | | " |
| Serious adverse event | | | | | | | | | |

## XXIV. Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Type of information (published or unpublished) | published | published | unpublished |
| Journal name | Lancet | Eur Resp J | ATS abstract, unpublished data from author published in Cochrane Review |
| Language of publication | English | English | English |
| Funding body | Assistance Publique-Hopitaux de Paris, France, and Brahms, Germany | Swiss National Foundation, Margarete unde Walter Liechtenstein Foundation, Feiwillige Akademische Gesellschaft, Will Rogers Foundation, University Hospital Basel, Brahms AG. | ? Awaiting study text |
| Ethics approval | Ethics committee of the Saint-Louis University Hospital | | ? Awaiting study text |
| Country where study was done | France | USA and Switzerland | Uruguay |
| | | | |
| **METHODS** | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | |
| Randomization | truly random | truly random | truly random |
| Concealment | yes | yes | yes |
| Not stopped early | not stopped early | not stopped early | not stopped early |
| NOTES: | | | |
| ***if COHORT STUDY*** | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | |
| Selection of the non exposed cohort | | | |
| Ascertainment of exposure | | | |
| Demonstration that outcome of interest was not present at start of study | | | |
| Comparability of cohorts on the basis of the design or analysis | | | |
| Assessment of outcome | | | |
| Was follow-up long enough for outcomes to occur? | | | |

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Adequacy of follow up of cohorts | | | |
| Co-Interventions similar between groups? | | | |
| NOTES: | | | |
| ***if CASE-CONTROL STUDY*** | | | |
| Is case definition adequate? | | | |
| Representativeness of the cases | | | |
| Selection of controls | | | |
| Definition of controls | | | |
| Comparability of cases and controls | | | |
| Ascertainment of exposure | | | |
| Same method of ascertainment for cases and controls | | | |
| Non-response rate | | | |
| Co-interventions similar between groups? | | | |
| NOTES: | | | |
| | | | |
| **INTERVENTIONS BEING COMAPRED** | | | |
| **Intervention 1 (experimental)** | Procalcitonin measuresments and algorithm on using PCT to guide initiation and discontinuation of abx | Daily PCT measures used to guide stopping abx (PCT<0.5 or decrease by ≥80%) | PCT measure day 7 used to inform stopping abx |
| other Tx used (if relevant for interpretation) | | | |
| Tx not allowed (if relevant for interpretation) | | | |
| **Intervention 2 (comparison)** | Physician discretion starting and stopping abx, access to a summary of recommendations for duration of abx for different infections | Physician discretion (education campaign regarding ATS guidelines for antibiotic discontinuation) | Routine clinical practice (ICU guideline for duration of Rx) |
| other Tx used (if relevant for interpretation) | | | |
| Tx not allowed (if relevant for interpretation) | | | |
| duration of treatment | | | |
| NOTES: | | | |

| Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| **BASELINE CHARACTERISTICS** | | | |
| **Number randomised** | 630 | 101 | 81 |
| Intervention | 311 | 51 | |
| Comparison | 319 | 50 | |
| Total (only if not reported separately) | | | |
| **Age** | | | |
| Intervention (mean or median) | 61 (15.2) | 59 (18-83) | |
| Comparison (mean or median) | 62.1 (15.0) | 53 (21-88) | |
| Total (mean or median) (only if not reported separately) | | | |
| unit (e.g. mean and SD) | mean (SD) | mean (range) | |
| Age range (e.g. 22-73) | | 18-88 | |
| Age inclusion criterion (e.g. older than 16) | age ≥18 | | |
| **Male gender** | | | |
| Intervention | 67.00% | 74.00% | |
| Comparison | 65.00% | 75.00% | |
| Total (only if not reported separately) | | | |
| **Severity of illness** | | | |
| Name of score (e.g. APACHE, SOFA, ...) | SOFA | SOFA | |
| Intervention group mean score | 8.0 (4.7) | 8.2 (3.4) | |
| Comparison group mean score | 7.7 (4.6) | 7.3 (3.4) | |
| Total (only if not reported separately) | | | |
| **Study population** | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Mixed Medical-Surgical | Mixed Medical-Surgical | |
| NOTES: | Baseline traits for the full study population (outcomes for VAP patients only) | | |
| | | | |
| **OUTCOMES** | | | |
| | | | |

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| **Mortality (all cause)** | | | |
| Are the data available? | Data available | Data available | Data available |
| location or duration of follow-up (choose from the list) | 28 day | 28 day | 28 day |
| Intervention group: # with event | 14 | 8 | 8 |
| Intervention group: Total | 75 | 51 | 31 |
| Comparison group: # with event | 17 | 12 | 11 |
| Comparison group: Total | 66 | 50 | 35 |
| Blinding [patients] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [analysts] (only relevant for RCTs) | probably no | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | probably yes | yes | no |
| NOTES: | outomes data are for the subset of patients with HAP/VAP from the larger sepsis trial, subset data comes from a Cochrane review that includes unpublished data gathered from the authors | | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | |
| Are the data available? | Not reported | Data available | Data available |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | | |
| How data were reported (mean or median and type of variance) | | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | | 9.4 (8.7) | 16.5 (16.2) |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | 51 | 31 |

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Comparison group: (mean or median) | | 9.8 (7.6) | 16.6 (11.8) |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | 50 | 35 |
| Blinding [patients] (only relevant for RCTs) | | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [analysts] (only relevant for RCTs) | | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | | yes | no |
| NOTES: | | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | |
| Are the data available? | | | |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | | |
| How data were reported (mean or median and type of variance) | | | |
| Intervention group: (mean or median) | | | |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | | |
| Comparison group: (mean or median) | | | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |

| Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Length of ICU stay** | | | |
| Are the data available? | Not reported | Data available | Data available |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | | |
| How data were reported (mean or median and type of variance) | | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | | 14.7 (8.2) | 17.2 (7.4) |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | 51 | 31 |
| Comparison group: (mean or median) | | 17.3 (12.9) | 20 (14.4) |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | 50 | 35 |
| Blinding [patients] (only relevant for RCTs) | | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [analysts] (only relevant for RCTs) | | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | | yes | no |
| NOTES: | | | |

| Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| **Length of hospital stay** | | | |
| Are the data available? | Not reported | Data available | Not reported |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | | |
| How data were reported (mean or median and type of variance) | | mean (SD) | |
| Intervention group: (mean or median) | | 17.1 (9.2) | |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | 51 | |
| Comparison group: (mean or median) | | 19.5 (11.2) | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | 50 | |
| Blinding [patients] (only relevant for RCTs) | | probably no | |
| Blinding [personnel] (only relevant for RCTs) | | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | | probably no | |
| Blinding [data collectors] (only relevant for RCTs) | | probably no | |
| Blinding [analysts] (only relevant for RCTs) | | probably no | |
| ITT analysis performed (only relevant for RCTs) | | yes | |
| NOTES: | | | |
| **Clinical cure (as defined by the study authors)** | | | |
| Are the data available? | Not reported | Not reported | Data available |
| Definition (provide details if relevant) | | | |
| Duration of follow-up (time point when outcome was measured) [days] | | | |
| Intervention group: # with event | | | |

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Intervention group: Total | | | |
| Comparison group: # with event | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | reports clinical failure rather than cure |
| **Recurrent pneumonia** | | | |
| Are the data available? | Not reported | Not reported | Data available |
| Duration of follow-up [days] | | | |
| Intervention group: # with event | | | 14 |
| Intervention group: Total | | | 31 |
| Comparison group: # with event | | | 10 |
| Comparison group: Total | | | 35 |
| Blinding [patients] (only relevant for RCTs) | | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [analysts] (only relevant for RCTs) | | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | | yes | no |
| NOTES: | | | |

| Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| **Number of antibiotic days** | | | |
| Are the data available? | Data available | Data available | Data available |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | | |
| How data were reported (mean or median and type of variance) | mean (SD) | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | 7.3 (5.3) | 12.5 (7.8) | 7.9 (2.4) |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | 75 | 51 | 31 |
| Comparison group: (mean or median) | 9.4 (5.7) | 15.7 (7.6) | 11.9 (3.6) |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | 66 | 50 | 35 |
| Blinding [patients] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [analysts] (only relevant for RCTs) | probably no | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | probably yes | yes | no |
| NOTES: | | | |
| **Number of antibiotic free days** | | | |
| Are the data available? | Data available | Data available | Data available |
| Duration of follow-up [days] | 28 day | 28 day | 28 day |
| unit (days, hours, etc.) | days | days | days |
| How data were reported (mean or median and type of variance) | mean | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | 12.8 | 12.7 (8.5) | 13.3 (2.8) |

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | 75 | 51 | 31 |
| Comparison group: (mean or median) | 9.7 | 9.5 (7.7) | 10.6 (3.7) |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | 66 | 50 | 35 |
| Blinding [patients] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [analysts] (only relevant for RCTs) | probably no | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | probably yes | yes | no |
| NOTES: | | | |
| **Development of resistance (as defined by the study authors)** | | | |
| Are the data available? | Not reported | Not reported | Data available |
| Duration of follow-up [days] | | | |
| Intervention group: # with event | | | 7 |
| Intervention group: Total | | | 31 |
| Comparison group: # with event | | | 5 |
| Comparison group: Total | | | 35 |
| Blinding [patients] (only relevant for RCTs) | | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | probably no | probably no |
| Blinding [data collectors] (only relevant for RCTs) | | probably no | probably no |

| Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Blinding [analysts] (only relevant for RCTs) | | probably no | probably no |
| ITT analysis performed (only relevant for RCTs) | | yes | no |
| NOTES: | | | |
| **Any adverse effect** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with at least one event (if this was reported) | | | |
| Intervention group: # of events per group (if this was reported) | | | |
| Intervention group: Total | | | |
| Comparison group: #with at least one event (if this was reported) | | | |
| Comparison group: # of events per group (if this was reported) | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Serious adverse effect** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with at least one event (if this was reported) | | | |

| **Data Extraction Table-Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP?** | | | |
|---|---|---|---|
| Last name of the first author | Bouadma | Stolz | Pontet |
| Year | 2010 | 2009 | 2007 |
| Intervention group: # of events per group (if this was reported) | | | |
| Intervention group: Total | | | |
| Comparison group: #with at least one event (if this was reported) | | | |
| Comparison group: # of events per group (if this was reported) | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |

| Risk of bias assessment- Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | | |
|---|---|---|---|---|
| | | Pontet 2007 | Stolz 2009 | Bouadma 2010 |
| **Pontet scored mainly from Cochrane review since it is only in abstract form** | | | | |
| **Mortality (all cause)** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | low risk of bias | low risk of bias |
| | Allocation concealment (selection bias) | low risk of bias | low risk of bias | low risk of bias |
| | Blinding | probably low risk of bias | probably low risk of bias | probably low risk of bias |
| | ITT analysis performed | low risk of bias | low risk of bias | low risk of bias |
| | Serious loss to follow-up | really cannot tell | low risk of bias | low risk of bias |
| | Selective outcome reporting | really cannot tell | low risk of bias | low risk of bias |
| | Study stopped early | low risk of bias | low risk of bias | low risk of bias |
| | NOTES: | Although studies were not blind score low prob of bias because of objective nature of mortality | | |
| **Number of ventilator days or ventilator-free days** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Allocation concealment (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Blinding | probably high risk of bias | probably high risk of bias | not applicable |
| | ITT analysis performed | low risk of bias | low risk of bias | not applicable |
| | Serious loss to follow-up | really cannot tell | low risk of bias | not applicable |
| | Selective outcome reporting | really cannot tell | low risk of bias | not applicable |
| | Study stopped early | low risk of bias | low risk of bias | not applicable |
| | NOTES: | | | Not available for VAP population |
| **Length of ICU stay** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Allocation concealment (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Blinding | probably high risk of bias | probably high risk of bias | not applicable |
| | ITT analysis performed | low risk of bias | low risk of bias | not applicable |
| | Serious loss to follow-up | really cannot tell | low risk of bias | not applicable |
| | Selective outcome reporting | really cannot tell | low risk of bias | not applicable |
| | Study stopped early | low risk of bias | low risk of bias | not applicable |
| | NOTES: | | | Not available for VAP population |
| **Length of hospital stay** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Allocation concealment (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Blinding | probably high risk of bias | probably high risk of bias | not applicable |
| | ITT analysis performed | low risk of bias | low risk of bias | not applicable |
| | Serious loss to follow-up | really cannot tell | low risk of bias | not applicable |

| Risk of bias assessment- Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | | |
|---|---|---|---|---|
| | | Pontet 2007 | Stolz 2009 | Bouadma 2010 |
| | Selective outcome reporting | really cannot tell | low risk of bias | not applicable |
| | Study stopped early | low risk of bias | low risk of bias | not applicable |
| | NOTES: | | | Not available for VAP population |
| **Clinical cure (as defined by the study authors)** | | Study | Study | Study |
| | Random sequence generation (selection bias) | not applicable | not applicable | not applicable |
| | Allocation concealment (selection bias) | not applicable | not applicable | not applicable |
| | Blinding | not applicable | not applicable | not applicable |
| | ITT analysis performed | not applicable | not applicable | not applicable |
| | Serious loss to follow-up | not applicable | not applicable | not applicable |
| | Selective outcome reporting | not applicable | not applicable | not applicable |
| | Study stopped early | not applicable | not applicable | not applicable |
| | NOTES: | Data not reported | Data not reported | Data not reported |
| **Recurrent pneumonia** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | not applicable | not applicable |
| | Allocation concealment (selection bias) | low risk of bias | not applicable | not applicable |
| | Blinding | probably high risk of bias | not applicable | not applicable |
| | ITT analysis performed | low risk of bias | not applicable | not applicable |
| | Serious loss to follow-up | really cannot tell | not applicable | not applicable |
| | Selective outcome reporting | really cannot tell | not applicable | not applicable |
| | Study stopped early | low risk of bias | not applicable | not applicable |
| | NOTES: | | Data not reported | Data not reported |
| **Number of antibiotic days** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | low risk of bias | low risk of bias |
| | Allocation concealment (selection bias) | low risk of bias | low risk of bias | low risk of bias |
| | Blinding | probably high risk of bias | probably high risk of bias | probably high risk of bias |
| | ITT analysis performed | low risk of bias | low risk of bias | low risk of bias |
| | Serious loss to follow-up | really cannot tell | low risk of bias | low risk of bias |
| | Selective outcome reporting | really cannot tell | low risk of bias | low risk of bias |
| | Study stopped early | low risk of bias | low risk of bias | low risk of bias |
| | NOTES: | | | |
| **Development of resistance** | | Study | Study | Study |
| | Random sequence generation (selection bias) | low risk of bias | not applicable | not applicable |
| | Allocation concealment (selection bias) | low risk of bias | not applicable | not applicable |
| | Blinding | probably high risk of bias | not applicable | not applicable |

| Risk of bias assessment- Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | | |
|---|---|---|---|---|
| | | Pontet 2007 | Stolz 2009 | Bouadma 2010 |
| | ITT analysis performed | low risk of bias | not applicable | not applicable |
| | Serious loss to follow-up | really cannot tell | not applicable | not applicable |
| | Selective outcome reporting | really cannot tell | not applicable | not applicable |
| | Study stopped early | low risk of bias | not applicable | not applicable |
| | NOTES: | | Data not reported | Data not reported |
| **Any adverse effect** | | Study | Study | Study |
| | Random sequence generation (selection bias) | not applicable | not applicable | not applicable |
| | Allocation concealment (selection bias) | not applicable | not applicable | not applicable |
| | Blinding | not applicable | not applicable | not applicable |
| | ITT analysis performed | not applicable | not applicable | not applicable |
| | Serious loss to follow-up | not applicable | not applicable | not applicable |
| | Selective outcome reporting | not applicable | not applicable | not applicable |
| | Study stopped early | not applicable | not applicable | not applicable |
| | NOTES: | Data not reported | Data not reported | Data not reported |
| **Serious adverse effect** | | Study | Study | Study |
| | Random sequence generation (selection bias) | not applicable | not applicable | not applicable |
| | Allocation concealment (selection bias) | not applicable | not applicable | not applicable |
| | Blinding | not applicable | not applicable | not applicable |
| | ITT analysis performed | not applicable | not applicable | not applicable |
| | Serious loss to follow-up | not applicable | not applicable | not applicable |
| | Selective outcome reporting | not applicable | not applicable | not applicable |
| | Study stopped early | not applicable | not applicable | not applicable |
| | NOTES: | Data not reported | Data not reported | Data not reported |

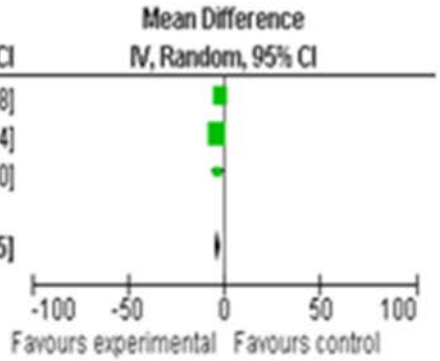
# PCT- Forest plots

## Antibiotic Duration

| Study or Subgroup | PCT Mean | PCT SD | PCT Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bouadma | 7.3 | 5.3 | 75 | 9.4 | 5.7 | 66 | 35.6% | -2.10 [-3.92, -0.28] |
| Pontet | 7.9 | 2.4 | 31 | 11.9 | 3.6 | 35 | 48.9% | -4.00 [-5.46, -2.54] |
| Stolz | 12.5 | 7.8 | 51 | 15.7 | 7.6 | 50 | 15.5% | -3.20 [-6.20, -0.20] |
| **Total (95% CI)** | | | **157** | | | **151** | **100.0%** | **-3.20 [-4.45, -1.95]** |

Heterogeneity: Tau² = 0.27; Chi² = 2.54, df = 2 (P = 0.28); I² = 21%

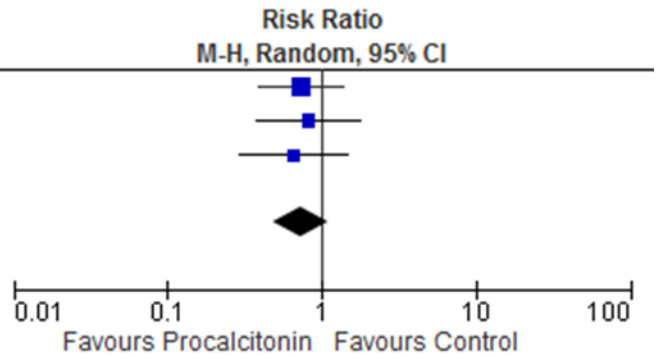
Test for overall effect: Z = 5.02 (P < 0.00001)



## Mortality

| Study or Subgroup | PCT Events | PCT Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bouadma 2010 | 14 | 75 | 17 | 66 | 44.3% | 0.72 [0.39, 1.35] |
| Pontet | 8 | 31 | 11 | 35 | 29.0% | 0.82 [0.38, 1.78] |
| Stolz 2009 | 8 | 51 | 12 | 50 | 26.7% | 0.65 [0.29, 1.46] |
| **Total (95% CI)** | | **157** | | **151** | **100.0%** | **0.73 [0.48, 1.11]** |
| Total events | 30 | | 40 | | | |

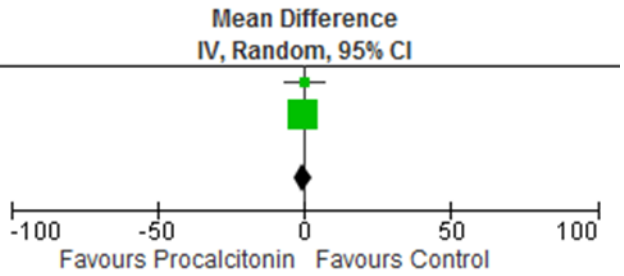
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)




## Duration of Mechanical Ventilation

| Study or Subgroup | Procalcitonin Mean | Procalcitonin SD | Procalcitonin Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Pontet | 16.5 | 16.2 | 31 | 16.6 | 11.8 | 35 | 17.5% | -0.10 [-7.01, 6.81] |
| Stolz 2009 | 9.4 | 8.7 | 51 | 9.8 | 7.6 | 50 | 82.5% | -0.40 [-3.58, 2.78] |
| **Total (95% CI)** | | | **82** | | | **85** | **100.0%** | **-0.35 [-3.24, 2.54]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



| SUMMARY OF FINDINGS - Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Design (No of Studies)** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication Bias** | **Summary of Findings** | | | |
| | | | | | **Define Group** PCT guided | **Define Group** Clinical Criteria | **RR or MD (CI)** | |
| | | | | | **No. of pts 157** | **No of pts 151** | | **Quality of the Evidence** |
| All Cause Mortality **RCT (3)** | No Serious Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI crossing 1) | None Or Not Known | **Numerator/denom** **30/157** | **Numerator/denom** **40/151** | 0.73 (0.48, 1.11) | Moderate (ΦΦΦO) |
| Vent days **RCT (2)** | No Serious Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | 16.5 (16.2) n=31<br>9.4 (8.7) n= 51 | 16.6 (11.8) n = 35<br>9.8 (7.6) n = 50 | days -0.35 [-3.24, 2.54] | Moderate (ΦΦOO) |
| Vent free days **RCT (2)** | No Serious Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | 17.2 (7.4) n=31<br>14.7 (8.2) n=51 | 20 (14.4) n=35<br>17.3 (12.9) n=50 | days minus 2.8 (-8.24, 2.64) | Moderate (ΦΦOO) |
| ICU LOS **RCT (2)** | No Serious Inconsistency | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | 17.2(7.4) n=31<br>14.7 (8.2) n= 51 | 20(14.4) n = 35<br>17.3 (12.9) n = 50 | -2.68 [-6.01, 0.66] | Moderate (ΦΦOO) |
| Hospital LOS **RCT (1)** | N/A | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | 17.1 (9.2) n=51 | 19.5 (1.2) n=50 | Days minus 2.4 (-6.40, 1.60) | Low (ΦOOO) |
| Clinical Cure **N/A** | | | | | | | | |
| Treatment Failure **RCT (1)** | N/A | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Numerator/denom** 8/31 | **Numerator/denom** 8/35 | 1.17 (0.38, 3.62) | Low (ΦOOO) |
| Recurrent Pneumonia **RCT (1)** | N/A | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Numerator/denom** 14/31 | **Numerator/denom** 10/35 | 2.06 (0.74, 5.70) | Low (ΦOOO) |
| Antibiotic Days **RCT (3)** | No Serious Inconsistency | No Serious Indirectness | No Serious Imprecision | None Or Not Known | 7.9 (2.4) n= 31<br>12.5 (7.8) n= 51<br>7.3 (5.3) n=75 | 11.9 (3.6) n=35<br>15.7 (7.6) n=50<br>9.4 (5.7) n= 66 | Days -3.20 [-4.45, -1.95] | High (ΦΦΦΦ) |
| Antibiotic Free Days **RCT (2)** | No Serious Inconsistency | No Serious Indirectness | No Serious Imprecision | None Or Not Known | 13.3 (2.8) n= 31<br>12.7 (8.5) n= 51 | 10.6 (3.7) n= 35<br>10.6 (3.7) n= 50 | Days 2.53 [1.20, 3.87] | High (ΦΦΦΦ) |
| Development of Resistance **RCT (1** | N/A | No Serious Indirectness | Serious imprecision (Wide CI) | None Or Not Known | **Numerator/denom** 7/31 | **Numerator/denom** 5/35 | 1.6 (0.6,4.5) | Low (ΦOOO) |

| SUMMARY OF FINDINGS - Should discontinuation of antibiotic therapy be based upon procalcitonin (PCT) levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP? | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Design (No of Studies)** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication Bias** | **Summary of Findings** | | | |
| | | | | | **Define Group** PCT guided | **Define Group** Clinical Criteria | **RR or MD (CI)** | |
| | | | | | **No. of pts 157** | **No of pts 151** | | **Quality of the Evidence** |
| Any Adverse event N/A | | | | | | | | |
| Serious adverse event N/A | | | | | | | | |

## XXV. Should discontinuation of antibiotic therapy be based upon the CPIS plus clinical criteria or clinical criteria alone in patients with suspected HAP/VAP?

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Type of information (published or unpublished) | published | published | published |
| Journal name | AMJRCCM | chest | CCM |
| Language of publication | English | English | English |
| Funding body | Bayer | Elan pharma and hospital foundat | CDC, Bayer, Merck |
| Ethics approval | Yes | yes | yes |
| Country where study was done | US | US | US |
| Years study done | unknown | 2002-2003 | 1999-2000 |
| **METHODS** | | | |
| ***if RANDOMIZED TRIAL* (or non-randomized experimental study)** | | | |
| Randomization | truly random | stated as random but no description | |
| Concealment | no | probably no | |
| Not stopped early | stopped for benefit | not stopped early | |
| NOTES: | | | |
| ***if COHORT STUDY*** | | | |
| Representativeness of the exposed cohort (i.e. similarity to such patients in real life) | | | representative of such patients in reality |
| Selection of the non exposed cohort | | | Pre-Post, quasi-experimental |
| Ascertainment of exposure | | | secure record (e.g. hospital) |
| Demonstration that outcome of interest was not present at start of study | | | secure record (e.g. hospital) |
| Comparability of cohorts on the basis of the design or analysis | | | does not control for any factor |
| Assessment of outcome | | | record linkage (e.g. hospital) |
| Was follow-up long enough for outcomes to occur? | | | yes |
| Adequacy of follow up of cohorts | | | at least 80% followed-up |
| Co-Interventions similar between groups? | | | probably yes |
| ***if CASE-CONTROL STUDY*** | | | |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Is case definition adequate? | | | |
| Representativeness of the cases | | | |
| Selection of controls | | | |
| Definition of controls | | | |
| Comparability of cases and controls | | | |
| Ascertainment of exposure | | | |
| Same method of ascertainment for cases and controls | | | |
| Non-response rate | | | |
| Co-interventions similar between groups? | | | |
| NOTES: | | | |
| | | | |
| **INTERVENTIONS BEING COMPARED** | | | |
| **Intervention 1 (experimental)** | D/C Abx day 3 if CPIS<=6 | recommendation to stop Abx* | recommendation to stop Abx* |
| other Tx used (if relevant for interpretation) | Cipro until Day 3 | | |
| Tx not allowed (if relevant for interpretation) | | | |
| **Intervention 2 (comparison)** | Abx per MD choice | standard care | standard care |
| other Tx used (if relevant for interpretation) | | | |
| Tx not allowed (if relevant for interpretation) | | | |
| duration of treatment | | | |
| NOTES: | Only patients with CPIS<=6 at onset were randomized | | |
| **BASELINE CHARACTERISTICS** | | | |
| **Number randomised** | | | |
| Intervention | 39 | 154 | 52 |
| Comparison | 42 | 148 | 50 |
| Total (only if not reported separately) | | | |
| **Age** | | | |
| Intervention (mean or median) | 69 | 60 | 56 |
| Comparison (mean or median) | 65 | 60 | 63 |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Total (mean or median) (only if not reported separately) | | | |
| unit (e.g. mean and SD) | | mean (SD) | mean (SD) |
| Age range (e.g. 22-73) | | | |
| Age inclusion criterion (e.g. older than 16) | | >18 | >18 |
| **Male gender** | | | |
| Intervention | almost all (VA) | 45.00% | 44.00% |
| Comparison | almost all (VA) | 55.00% | 54.00% |
| Total (only if not reported separately) | | | |
| **Severity of illness** | | | |
| Name of score (e.g. APACHE, SOFA, ...) | APACHE III | Apache II | Apache II |
| Intervention group mean score | 42.7 | 23.00% | 25 |
| Comparison group mean score | 41 | 23 | 26 |
| Total (only if not reported separately) | | | |
| **Study population** | | | |
| Please choose type of patients from the list (e.g. medical, surgical, ...) | Mixed Medical-Surgical-79% surgical | Medical | Medical |
| NOTES:A28 | | | |
| **VAP patients included** | | | |
| Intervention | 23 | 154 | 52 |
| Comparator | 24 | 148 | 50 |
| **Exclusions** | | | |
| | CPIS>6 on day 3 | non-medical patients | BACTEREMIA |
| | | | |
| **Prior Antibiotics** | | | |
| Intervention | | not relevant | not relevant |
| Comparator | | | |
| **Organisms Cultured** | | | |
| Are the data available? | no | yes, not relevant | yes, not relevant |
| **Intervention (n)** | | | |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| No organisms cultured | | | |
| Non-fermenters/ESBL/Other potentially MDR GNR | | | |
| MRSA | | | |
| Other | | | |
| **Comparator (n)** | | | |
| No organisms cultured | | | |
| Non-fermenters/ESBL/Other potentially MDR GNR | | | |
| MRSA | | | |
| Other | | | |
| **OUTCOMES** | | | |
| | | | |
| **Mortality (all cause)** | | | |
| Are the data available? | Data available | Data available | Data available |
| location or duration of follow-up (choose from the list) | 30 day | Hospital | Hospital |
| Intervention group: # with event | 5 | 48 | 27 |
| Intervention group: Total | 39 | 150 | 52 |
| Comparison group: # with event | 13 | 52 | 21 |
| Comparison group: Total | 42 | 140 | 50 |
| Blinding [patients] (only relevant for RCTs) | probably no | probably no | probably no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | no |
| Blinding [data collectors] (only relevant for RCTs) | no | no | no |
| Blinding [analysts] (only relevant for RCTs) | no | no | no |
| ITT analysis performed (only relevant for RCTs) | yes | yes | yes |
| NOTES: | | | |
| **Number of ventilator days (if only ventilator-free days repored, go to next)** | | | |
| Are the data available? | Not reported | Data available | Not reported |
| Duration of follow-up [days] | | Hospital | |
| unit (days, hours, etc.) | | | |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| How data were reported (mean or median and type of variance) | | | |
| Intervention group: (mean or median) | | | |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | | |
| Comparison group: (mean or median) | | | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Number of ventilator-free days (if ventilator days not reported)** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| unit (days, hours, etc.) | | | |
| How data were reported (mean or median and type of variance) | | | |
| Intervention group: (mean or median) | | | |
| Intervention group: (variance) | | | |
| Intervention group: total number of patients | | | |
| Comparison group: (mean or median) | | | |
| Comparison group: (variance) | | | |
| Comparison group: total number of patients | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Length of ICU stay** | | | |
| Are the data available? | Data available | Data available | Data available |
| Duration of follow-up [days] | hospital stay | same | same |
| unit (days, hours, etc.) | days | days | days |
| How data were reported (mean or median and type of variance) | other (please specify)mean/median/range | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | 9.4/4 | 6.8 | 21.7 |
| Intervention group: (variance) | (1-47) range | 6.1 | 12.9 |
| Intervention group: total number of patients | 39 | 150 | 52 |
| Comparison group: (mean or median) | 14.7/9 | 7 | 23.1 |
| Comparison group: (variance) | (1-91) | 7.3 | 17.4 |
| Comparison group: total number of patients | 42 | 140 | 50 |
| Blinding [patients] (only relevant for RCTs) | probably no | probably no | |
| Blinding [personnel] (only relevant for RCTs) | no | no | |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | |
| Blinding [data collectors] (only relevant for RCTs) | no | no | |
| Blinding [analysts] (only relevant for RCTs) | no | no | |
| ITT analysis performed (only relevant for RCTs) | yes | yes | |
| NOTES: | | reported only as difference NS | |
| **Length of hospital stay** | | | |
| Are the data available? | Not reported | Data available | Data available |
| Duration of follow-up [days] | | hospital stay | hospital stay |
| unit (days, hours, etc.) | | days | days |
| How data were reported (mean or median and type of variance) | | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | | 15.7 | 34.2 |
| Intervention group: (variance) | | 18.2 | 26.2 |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Intervention group: total number of patients | | 150 | 52 |
| Comparison group: (mean or median) | | 15.4 | 39.3 |
| Comparison group: (variance) | | 15.9 | 33.1 |
| Comparison group: total number of patients | | 140 | 50 |
| Blinding [patients] (only relevant for RCTs) | | probably no | no |
| Blinding [personnel] (only relevant for RCTs) | | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | no | no |
| Blinding [data collectors] (only relevant for RCTs) | | no | no |
| Blinding [analysts] (only relevant for RCTs) | | no | no |
| ITT analysis performed (only relevant for RCTs) | | yes | yes |
| NOTES: | | | |
| **Clinical cure (as defined by the study authors)** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Definition (provide details if relevant) | | | |
| Duration of follow-up (time point when outcome was measured) [days] | | | |
| Intervention group: # with resolution | | | |
| Intervention group: Total | | | |
| Comparison group: # with resolution | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Recurrent pneumonia** | | | |
| Are the data available? | Not reported | Data available | Data available |
| Duration of follow-up [days] | | hospital stay | hospital stay |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Intervention group: # with event | | 26 | 4 |
| Intervention group: Total | | 150 | 52 |
| Comparison group: # with event | | 27 | 12 |
| Comparison group: Total | | 140 | 50 |
| Blinding [patients] (only relevant for RCTs) | | probably no | no |
| Blinding [personnel] (only relevant for RCTs) | | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | | no | no |
| Blinding [data collectors] (only relevant for RCTs) | | no | no |
| Blinding [analysts] (only relevant for RCTs) | | no | no |
| ITT analysis performed (only relevant for RCTs) | | yes | no |
| NOTES: | | | |
| **Number of antibiotic days** | includes only those w/o extra pulm infxn | | |
| Are the data available? | Data available | Data available | Data available |
| Duration of follow-up [days] | hospital stay | hospital stay, doesn't include recurrent VAP days | hospital stay, doesn't include recurrent VAP days |
| unit (days, hours, etc.) | days | days | days |
| How data were reported (mean or median and type of variance) | mean/range | mean (SD) | mean (SD) |
| Intervention group: (mean or median) | 3 | 6 | 8.6 |
| Intervention group: (variance) | range-3 | 4.9 | 5.1 |
| Intervention group: total number of patients | 39 | 150 | 52 |
| Comparison group: (mean or median) | 9.4 | 8 | 14.8 |
| Comparison group: (variance) | range 4-20 | 5.6 | 8.1 |
| Comparison group: total number of patients | 39 | 140 | 50 |
| Blinding [patients] (only relevant for RCTs) | probably no | probably no | no |
| Blinding [personnel] (only relevant for RCTs) | no | no | no |
| Blinding [outcome assessors] (only relevant for RCTs) | no | no | no |
| Blinding [data collectors] (only relevant for RCTs) | no | no | no |
| Blinding [analysts] (only relevant for RCTs) | no | no | no |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| ITT analysis performed (only relevant for RCTs) | **no** | yes | no |
| NOTES: | | | |
| **Development of resistance (as defined by the study authors)** | ***resistance OR superinfection*** | | |
| Are the data available? | Data available | Not reported | Not reported |
| Duration of follow-up [days] | hospital stay | | |
| Intervention group: # with event | 5 | | |
| Intervention group: Total | 39 | | |
| Comparison group: # with event | 14 | | |
| Comparison group: Total | 42 | | |
| Blinding [patients] (only relevant for RCTs) | probably no | | |
| Blinding [personnel] (only relevant for RCTs) | no | | |
| Blinding [outcome assessors] (only relevant for RCTs) | no | | |
| Blinding [data collectors] (only relevant for RCTs) | no | | |
| Blinding [analysts] (only relevant for RCTs) | no | | |
| ITT analysis performed (only relevant for RCTs) | yes | | |
| NOTES: | | | |
| **Any adverse effect** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with at lest one event (if this was reported) | | | |
| Intervention group: # od events per group (if this was reported) | | | |
| Intervention group: Total | | | |
| Comparison group: #with at lest one event (if this was reported) | | | |
| Comparison group: # od events per group (if this was reported) | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |

| **Last name of the first author** | **Singh** | **Micek** | **Ibrahim** |
|---|---|---|---|
| **Year** | **2000** | **2004** | **2001** |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **Serious adverse effect** | | | |
| Are the data available? | Not reported | Not reported | Not reported |
| Duration of follow-up [days] | | | |
| Intervention group: # with at lest one event (if this was reported) | | | |
| Intervention group: # od events per group (if this was reported) | | | |
| Intervention group: Total | | | |
| Comparison group: #with at lest one event (if this was reported) | | | |
| Comparison group: # od events per group (if this was reported) | | | |
| Comparison group: Total | | | |
| Blinding [patients] (only relevant for RCTs) | | | |
| Blinding [personnel] (only relevant for RCTs) | | | |
| Blinding [outcome assessors] (only relevant for RCTs) | | | |
| Blinding [data collectors] (only relevant for RCTs) | | | |
| Blinding [analysts] (only relevant for RCTs) | | | |
| ITT analysis performed (only relevant for RCTs) | | | |
| NOTES: | | | |
| **END** | ITT anlaysis of % with Abx days > 3 | *not truly CPIS but criteria maps to CPIS <=4 | Not truly CPIS, but maps about to CPIS<= |
| | CPIS-11/39 | We don't know how many patients there were in whom Abx were continued despite the low CPIS, docs could have chosen to ignore the recommendation if there were other factors that worried them. We don't know at what day the recommendation to stop Abx was made for the cohort. | |
| | standard -38/39 | | bacteremia excluded |
| | | | |
| | only about 60% VAP | | |
| | | | |
| | | | |
| | | | |
| | | | |

| Last name of the first author | Singh | Micek | Ibrahim |
|---|---|---|---|
| Year | 2000 | 2004 | 2001 |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | We don't know how many patients there were in whom Abx were continued despite the low CPIS, docs could have chosen to ignore the recommendation if there were other factors that worried them. We don't know at what day the recommendation to stop Abx was made for the cohort. |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | |
|---|---|---|---|---|
| | | Singh* | Micek | Ibrahim |
| **Mortality (all cause)** | Random sequence generation (selection bias) | low risk of bias | low risk of bias | not applicable |
| | Allocation concealment (selection bias) | probably high risk of bias | really cannot tell | not applicable |
| | Blinding | high risk of bias | high risk of bias | high risk of bias |
| | ITT analysis performed | low risk of bias | low risk of bias | low risk of bias |
| | Serious loss to follow-up | low risk of bias | low risk of bias | low risk of bias |
| | Selective outcome reporting | low risk of bias | low risk of bias | low risk of bias |
| | Study stopped early | low risk of bias | low risk of bias | low risk of bias |
| | NOTES: | Regarding allocation concealment: Randomization was conducted in groups of four, with no more than 2 in a row assigned to one group | | |
| **Number of ventilator days or ventilator-free days** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | | same as above | |
| **Length of ICU stay** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | Same as above | same as above | |
| **Length of hospital stay** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |

| Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies | | | | |
|---|---|---|---|---|
| | | Singh* | Micek | Ibrahim |
| | NOTES: | | same as above | |
| **Clinical cure (as defined by the study authors)** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | | | |
| **Recurrent pneumonia** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | | same as above | |
| **Number of antibiotic days** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | probably low risk of bias | |
| | Study stopped early | | | |
| | NOTES: | Same as above | Only Abx days in initial pneumonia reported, but similar risk of recurrent pneumonia in each group, so limited potential for bias | |
| **Development of resistance** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |

| **Risk of bias assessment for RANDOMIZED trials or non-randomized experimental studies** | | | | |
|---|---|---|---|---|
| | | Singh* | Micek | Ibrahim |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | Same as above | | |
| **Any adverse effect** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | | | |
| **Serious adverse effect** | | Study | Study | Study |
| | Random sequence generation (selection bias) | | | |
| | Allocation concealment (selection bias) | | | |
| | Blinding | | | |
| | ITT analysis performed | | | |
| | Serious loss to follow-up | | | |
| | Selective outcome reporting | | | |
| | Study stopped early | | | |
| | NOTES: | | | |

**SEARCH STRINGS**

| **VAP (Medline)** |
|---|
| 1. pneumonia/ |
| 2. bronchopneumonia/ |
| 3. pleuropneumonia/ |
| 4. pneumonia, aspiration/ |
| 5. pneumonia, bacterial/ |
| 6. pneumonia, mycoplasma/ |
| 7. pneumonia, pneumococcal/ |
| 8. pneumonia, staphylococcal/ |
| 9. (pneumoni$ or pleuropneumo$ or bronchopneumo$).tw. |
| 10. or/1-9 |
| 11. ventilators, mechanical/ |
| 12. respiration, artificial/ |
| 13. ((endotrach$ or intratrach$ or trach$ or orthotrach$) adj intubat$).tw. |
| 14. ((ventilat$ or respirator or respirators) adj2 (associat$ or acquire$ or induce$)).tw. |
| 15. vap.tw. |
| 16. or/11-15 |
| 17. 10 and 16 |
| 18. ventilator associated pneumonia/ |
| 19. 17 or 18 |
| 20. limit 19 to English |
| 21. limit 19 to abstracts |
| 22. 20 or 21 |
| 23. limit 22 to "all adult (19 plus years)" |
| 24. limit 22 to "all child (0 to 18 years)" |
| 25. 22 not 23 not 24 |
| 26. 23 or 25 |
| 27. limit 26 to humans |
| 28. limit 26 to animal |
| 29. 26 not 27 not 28 |
| 30. 27 or 29 |
| **HAP (Medline)** |
| 1. pneumonia/ or bronchopneumonia/ or pleuropneumonia/ or pneumonia, aspiration/ or pneumonia, bacterial/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/ |
| 2. (pneumoni$ or pleuropneumo$ or bronchopneumo$).tw. |
| 3. 1 or 2 |
| 4. (hap or (hospital$ adj2 (associat$ or acquire$))).tw. |
| 5. cross infection/ |
| 6. iatrogenic disease/ |
| 7. infectious disease transmission, professional-to-patient/ |
| 8. infectious disease transmission, patient-to-professional/ |
| 9. (nosocomial or iatrogenic or (cross adj infect$)).tw. |
| 10. or/4-9 |
| 11. 3 and 10 |
| 12. hospital units/ or intensive care units/ or burn units/ or coronary care units/ or respiratory care units/ or hospitals/ |
| 13. 3 and 12 |
| 14. ((pneumoni$ or pleuropneumo$ or bronchopneumo$) adj3 (post-operat$ or postoperat$ or hospital or hospitals or hospitaliz$ or (intensive adj care))).tw. |
| 15. 11 or 13 or 14 |
| 16. limit 15 to English |
| 17. limit 15 to abstracts |
| 18. 16 or 17 |

| |
|---|
| 19. limit 18 to "all adult (19 plus years)" |
| 20. limit 18 to "all child (0 to 18 years)" |
| 21. 18 not 19 not 20 |
| 22. 19 or 21 |
| 23. limit 22 to humans |
| 24. limit 22 to animal |
| 25. 22 not 23 not 24 |
| 26. 23 or 25 |
| **VAT (Medline)** |
| 1. Ventilators, Mechanical/ or Respiration, Artificial/ |
| 2. bronchitis/ or bronchiolitis/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchiolitis, viral/ or bronchitis, chronic/ |
| 3. Tracheitis/ |
| 4. 2 or 3 |
| 5. 1 and 4 |
| 6. ((ventilat$ or respirator or respirators or intubat$) adj7 (bronchiti$ or tracheiti$ or tracheobronchiti$ or bronchotracheiti$ or rhinotracheiti$ or laryngotracheobronchiti$)).tw. |
| 7. (vat and (vap or ventilat$ or vari)).tw. |
| 8. (ventilatory anaerobic threshold$ or ventricular arrhythmi$ threshold$).tw. |
| 9. 7 not 8 |
| 10. 6 or 9 |
| 11. (tracheiti$ or tracheobronchiti$ or bronchotracheiti$ or rhinotracheiti$ or laryngotracheobronchiti$).tw. |
| 12. 1 and 11 |
| 13. 5 or 10 or 12 |
| 14. limit 13 to english |
| 15. limit 13 to abstracts |
| 16. 14 or 15 |
| 17. limit 16 to "all adult (19 plus years)" |
| 18. limit 16 to "all child (0 to 18 years)" |
| 19. 16 not 17 not 18 |
| 20. 17 or 19 |
| 21. limit 20 to humans |
| 22. limit 20 to animal |
| 23. 20 not 21 not 22 |
| 24. 21 or 23 |
| **Treatment (Medline)**[1] |
| 1. drug resistance, multiple/ or drug resistance, multiple, bacterial/ |
| 2. (multiple adj drug$ adj2 resistan$).tw. |
| 3. mdr.tw. |
| 4. ((multi-drug$ adj resistan$) or (multidrug$ adj resistan$)).tw. |
| 5. or/1-4 |
| 6. infection risk/ |
| 7. (risk or risks).mp. |
| 8. risk/ or logistic models/ or risk assessment/ or risk factors/ |
| 9. causa$.ti,ab. |
| 10. etiol$.ti,ab. |
| 11. aetiol$.ti,ab. |
| 12. or/6-11 |
| 13. prevalence/ |
| 14. probability/ |
| 15. incidence/ |
| 16. odds ratio/ |

[1] Treatment strategies incorporate the sensitive therapy hedge from McMaster University's Health Information Research Unit (HIRU).

| |
|---|
| 17. comparative study/ |
| 18. exp cohort studies/ |
| 19. exp case control studies/ |
| 20. cross-sectional studies/ |
| 21. (cohort adj (stud$ or survey$)).ti,ab. |
| 22. (case control adj (stud$ or survey$)).ti,ab. |
| 23. (comparative adj (stud$ or survey$)).ti,ab. |
| 24. or/13-23 |
| 25. 12 or 24 |
| 26. 5 and 25 |
| **Diagnosis (Medline)**[2] |
| 1. exp "sensitivity and specificity"/ |
| 2. (sensitiv$ or specificit$).tw. |
| 3. diagnosis/ |
| 4. diagnos$.mp. |
| 5. diagnostic$.hw. |
| 6. diagnosis, differential/ |
| 7. di.fs. |
| 8. ((post-test or posttest) adj probabilit$).tw. |
| 9. ((pre-test or pretest) adj probabilit$).tw. |
| 10. predictive value$.tw. |
| 11. likelihood ratio$.tw. |
| 12. or/1-11 |
| **Multi-drug Resistance Risk (Medline)**[3] |
| 1. drug resistance, multiple/ or drug resistance, multiple, bacterial/ |
| 2. (multiple adj drug$ adj2 resistan$).tw. |
| 3. mdr.tw. |
| 4. ((multi-drug$ adj resistan$) or (multidrug$ adj resistan$)).tw. |
| 5. or/1-4 |
| 6. infection risk/ |
| 7. (risk or risks).mp. |
| 8. risk/ or logistic models/ or risk assessment/ or risk factors/ |
| 9. causa$.ti,ab. |
| 10. etiol$.ti,ab. |
| 11. aetiol$.ti,ab. |
| 12. or/6-11 |
| 13. prevalence/ |
| 14. probability/ |
| 15. incidence/ |
| 16. odds ratio/ |
| 17. comparative study/ |
| 18. exp cohort studies/ |
| 19. exp case control studies/ |
| 20. cross-sectional studies/ |
| 21. (cohort adj (stud$ or survey$)).ti,ab. |
| 22. (case control adj (stud$ or survey$)).ti,ab. |
| 23. (comparative adj (stud$ or survey$)).ti,ab. |
| 24. or/13-23 |
| 25. 12 or 24 |

[2] Diagnosis strategies drew on a combination of HIRU's sensitive diagnosis hedge with additional terms from the Scottish Intercollegiate Guideline Network.

[3] Drug resistance terminology combined with a 'risk' hedge adapted primarily from HIRU's Etiology hedge with additional terms and subject headings to capture study types recommended by the panel

| |
|---|
| 26. 5 and 25 |
| **Methicillin Resistant Staphyloccocus aureus (Medline)** |
| 1. methicillin-resistant staphylococcus aureus/ |
| 2. ((methicillin resistan$ or penicillin$ resistan$ or oxacillin$ resistan$ or ampicillin$ resistan$) adj (staph$ or s) adj aureus).mp. |
| 3. Methicillin Resistance/ and (staph$ adj aureus).mp. |
| 4. (methicillin adj resistan$).mp. and Staphylococcus Aureus/ |
| 5. (mrsa or orsa).tw. |
| 6. or/1-5 |
| **Pseudomonas aeruginosa (Medline)** |
| 1. Pseudomonas aeruginosa/ |
| 2. Pseudomonas Infections/ and (aeruginosa or pyocyanea).tw. |
| 3. ((pseudomonas or p) adj (aeruginosa or pyocyanea)).ti. |
| 4. or/1-3 |
| **Pharmacokinetic/pharmacodynamic Factors** |
| 1. pharmacokinetics/ |
| 2. pharmacokine$.mp. |
| 3. pharmacodynamic$.mp. |
| 4. (drug$ adj2 (kinetic$ or kineses)).mp. |
| 5. toxicokine$.mp. |
| 6. (ADME or ADMET).mp. |
| 7. (pd or pk).fs. |
| 8. (absorption or absorb$ or distribut$ or localiz$ or biotransform$ or excret$ or biochemical$ or half-life).tw. |
| 9. ((serum or plasma or drug$ or antibiotic$ or blood or urine or stool) adj2 (level$ or sampl$ or cultur$ or assay$ or concentrat$)).tw. |
| 10. or/1-9 |
| **Antibiotics (Medline)** |
| 1. beta-lactams/ or carbapenems/ or thienamycins/ or imipenem/ or cephalosporins/ or cefamandole/ or cefoperazone/ or cefazolin/ or cefonicid/ or cefsulodin/ or cephacetrile/ or cefotaxime/ or cefixime/ or cefmenoxime/ or cefotiam/ or ceftizoxime/ or ceftriaxone/ or cefuroxime/ or cephalothin/ or cephapirin/ or cephalexin/ or cefaclor/ or cefadroxil/ or cefatrizine/ or cephaloglycin/ or cephradine/ or cephaloridine/ or ceftazidime/ or cephamycins/ or cefmetazole/ or cefotetan/ or cefoxitin/ or clavulanic acids/ or clavulanic acid/ or amoxicillin-potassium clavulanate combination/ or monobactams/ or aztreonam/ or moxalactam/ or penicillins/ or amdinocillin/ or amdinocillin pivoxil/ or cyclacillin/ or methicillin/ or nafcillin/ or oxacillin/ or cloxacillin/ or dicloxacillin/ or floxacillin/ or penicillanic acid/ or penicillin g/ or ampicillin/ or amoxicillin/ or azlocillin/ or mezlocillin/ or piperacillin/ or pivampicillin/ or talampicillin/ or carbenicillin/ or carfecillin/ or penicillin g benzathine/ or penicillin g procaine/ or sulbenicillin/ or penicillin v/ or sulbactam/ or ticarcillin/ [BETA LACTAMS MESH] |
| 2. (beta-lactam$ or carbapenem$ or thienamycin$ or imipenem$ or cephalosporin$ or cefamandole$ or cefoperazone$ or cefazolin$ or cefonicid$ or cefsulodin$ or cephacetrile$ or cefotaxime$ or cefixime$ or cefmenoxime$ or cefotiam$ or ceftizoxime$ or ceftriaxone$ or cefuroxime$ or cephalothin$ or cephapirin$ or cephalexin$ or cefaclor$ or cefadroxil$ or cefatrizine$ or cephaloglycin$ or cephradine$ or cephaloridine$ or ceftazidime$ or cephamycins$ or cefmetazole$ or cefotetan$ or cefoxitin$ or clavulanic acid$ or (amoxicillin adj potassium adj clavulanate$) or monobactam$ or aztreonam$ or moxalactam$ or penicillin$ or amdinocillin$ or amdinocillin pivoxil$ or cyclacillin$ or methicillin$ or nafcillin$ or oxacillin$ or cloxacillin$ or dicloxacillin$ or floxacillin$ or penicillanic acid$ or ampicillin$ or amoxicillin$ or azlocillin$ or mezlocillin$ or piperacillin$ or pivampicillin$ or talampicillin$ or carbenicillin$ or carfecillin$ or sulbenicillin$ or sulbactam$ or ticarcillin$).tw. [beta lactams] |
| 3. fluoroquinolones/ or ciprofloxacin/ or fleroxacin/ or enoxacin/ or norfloxacin/ or ofloxacin/ or pefloxacin/ [fluoroquinolones] |
| 4. (fluoroquinolone$ or ciprofloxacin$ or fleroxacin$ or enoxacin$ or norfloxacin$ or ofloxacin$ or pefloxacin$).tw. [fluoroquinolones] |
| 5. (linezolid$ or zyvox$ or u100766 or pnu100766 or u 100766 or pnu 100766 or linox).af. or 165800-03-3.rn. [linezolid] |
| 6. aminoglycosides/ or anthracyclines/ or aclarubicin/ or daunorubicin/ or carubicin/ or doxorubicin/ or epirubicin/ or |

| | |
|---|---|
| | idarubicin/ or nogalamycin/ or menogaril/ or plicamycin/ or butirosin sulfate/ or gentamicins/ or sisomicin/ or netilmicin/ or hygromycin b/ or kanamycin/ or amikacin/ or dibekacin/ or nebramycin/ or tobramycin/ or metrizamide/ or neomycin/ or framycetin/ or paromomycin/ or ribostamycin/ or puromycin/ or puromycin aminonucleoside/ or spectinomycin/ or streptomycin/ or dihydrostreptomycin sulfate/ or streptothricins/ or streptozocin/ [aminoglycosides] |
| 7. | (aminoglycoside$ or anthracycline$ or aclarubicin$ or daunorubicin$ or carubicin$ or doxorubicin$ or epirubicin$ or idarubicin$ or nogalamycin$ or menogaril$ or plicamycin$ or butirosin sulfate$ or gentamicin$ or sisomicin$ or netilmicin$ or hygromycin b or kanamycin$ or amikacin$ or dibekacin$ or nebramycin$ or tobramycin$ or metrizamide$ or neomycin$ or framycetin$ or paromomycin$ or ribostamycin$ or puromycin$ or puromycin aminonucleoside$ or spectinomycin$ or streptomycin$ or dihydrostreptomycin sulfate$ or streptothricins$ or streptozocin$).tw. [aminoglycosides] |
| 8. | glycopeptides/ or bleomycin/ or peplomycin/ or phleomycins/ or peptidoglycan/ or ristocetin/ or teicoplanin/ or vancomycin/ [glycopeptides] |
| 9. | (glycopeptide$ or bleomycin$ or peplomycin$ or phleomycin$ or peptidoglycan$ or ristocetin$ or teicoplanin$ or vancomycin$).tw. [glycopeptides] |
| 10. | triazoles/ or amitrole/ or fluconazole/ or guanazole/ or itraconazole/ or trapidil/ [triazoles] |
| 11. | (triazole$ or amitrole$ or fluconazole$ or guanazole$ or itraconazole$ or trapidil$).tw. [triazoles] |
| 12. | or/1-11 |
| **Time Factors (Medline)** | |
| 1. | Time Factors/ |
| 2. | "Drug Administration Schedule"/ |
| 3. | treatment duration/ |
| 4. | ((length or duration) adj2 (therap$ or treatment$)).tw. |
| 5. | or/1-4 |
| **Enteric Bacteria (Medline)** | |
| 1. | exp Enterobacteriaceae/ |
| 2. | exp Enterobacteriaceae Infections/ |
| 3. | (enterobacteri$ or (enteric adj3 (bacteri$ or patho$))).tw. |
| 4. | (calymmatobacterium or cronobacter or citrobacter or edwardsiella or enterobacter or erwinia or escherichia or hafnia or klebsiella or kluyvera or morganella or pantoea or pectobacterium or photorhabdus or plesiomonas or proteus or providencia or salmonella or serratia or shigella or wigglesworthia or xenorhabdus or Yersinia).tw. |
| 5. | or/1-4 |
| **Acinetobacter (Medline)** | |
| 1. | Acinetobacter Infections/ |
| 2. | exp acinetobacter/ or acinetobacter baumannii/ or acinetobacter calcoaceticus/ or acinetobacter junii/ or acinetobacter lwoffii/ |
| 3. | acinetobacter$.mp. |
| 4. | or/1-3 |
| **Antibiograms (Medline)** | |
| 1. | exp Microbial Sensitivity Tests/ or ((microb$ or viral or bacteria$ or fung$ drug$ or vir$ drug$) adj sensitiv$ test$).tw. |
| 2. | antibiogram$.tw. |
| 3. | minimum inhibit$ concentrat$.tw. |
| 4. | ((antibacter$ or antimicrob$) adj susceptib$).tw. |
| 5. | or/1-5 |
| **Cell Cultures (Medline)** | |
| 1. | ((cell$ or sputum$ or respirat$ or bronchoalveol$ or endotrach$ or trach$ or serial$ or surveillan$ or aspirate$) adj5 (culture$ or test$ or screen$ or lavag$)).tw. |
| 2. | Cell Culture Techniques/ or Primary Cell Culture/ or Batch Cell Culture Techniques/ or Tissue Culture Techniques/ |
| 3. | 1 or 2 |

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