# Approccio Diagnostico-terapeutico e Criticità nella Gestione delle VAP

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**Francesco G. De Rosa**
Associate Professor, Infectious Diseases
University of Turin, Italy
*Fellow, Infectious Diseases Society of America*

# Disclosures

## Consultant/advisory board/speaker fees

- Pfizer, MSD, Angelini, Tillots, Menarini
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- BioTest, Nordic Pharma, InfectoPharma
- Gilead Sciences, GSK, Hikma, Advanz, Correvio

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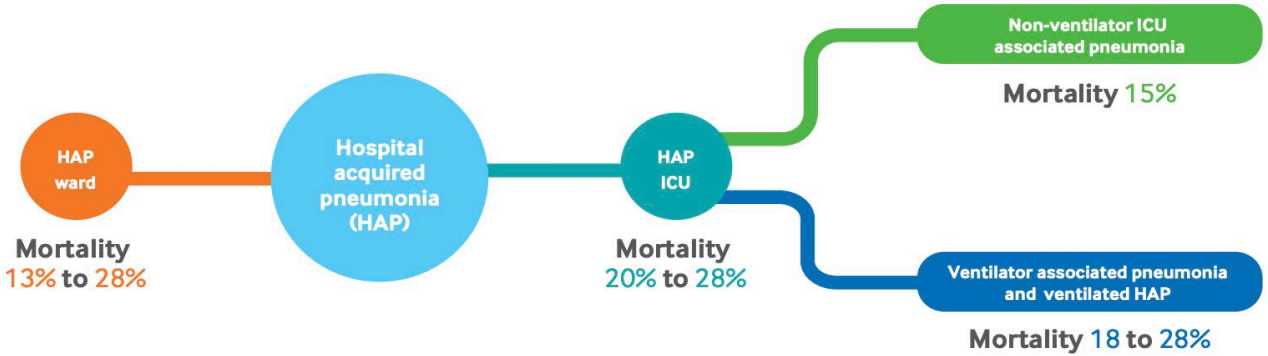
- Pfizer, MSD, Shionogi

# Hospital-acquired Pneumonia




- **Incidence: 5–40%**
- Progressive risk: peak at **5–9 days of MV**
- **Metrics depending on setting and diagnostic algorithm**
- Microbiological confirmation: strongly recommended; method: controversial
- **Prevention:** reduction of modifiable & non-modifiable risk factors
- **Treatment duration:** 7 days, with caveat
- **De-escalation & antibiotic-free** days to be implemented

Cillóniz C *et al. BMJ* 2021;375:e065871; Papazian L *et al. Intensive Care Med* 2020;46:888–906.

# Definitions

- **CDC/NHSH 2008**[1]
- **CDC 2012**
- **ECDC-HELICS 2010**[2] Clinical + imaging + microbiology
- **CDC/NHSH 2013-2021:**[3]
  - *VAE: ventilator-associated events;*
  - *VAC: ventilator-associated condition;*
  - *IVAC: infection-related ventilator-associated complication;*
  - *Possible and probable VAP*

**Ventilator-associated events (VAE):**
This definition is for use in surveillance; it is not a clinical definition algorithm and is not intended for use in the clinical management of patients

1. Horan TC *et al*. *Am J Infect Control* 2008;36:309–32; 2. Plachouras D *et al*. *Intensive Care Med* 2018;44:2216–18; 3.Centres for Disease Control and Prevention (2018) National Healthcare Safety Network (NHSN) Patient Safety Component Manual. CDC, Atlanta. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf (accessed September 2023).

# HAP & VAP
# - “Disease Difficult to Characterize” -

## No Diagnostic gold standard: Diagnostic Methodology

Invasive Vs. Non-invasive

Conventional Vs. fast-track

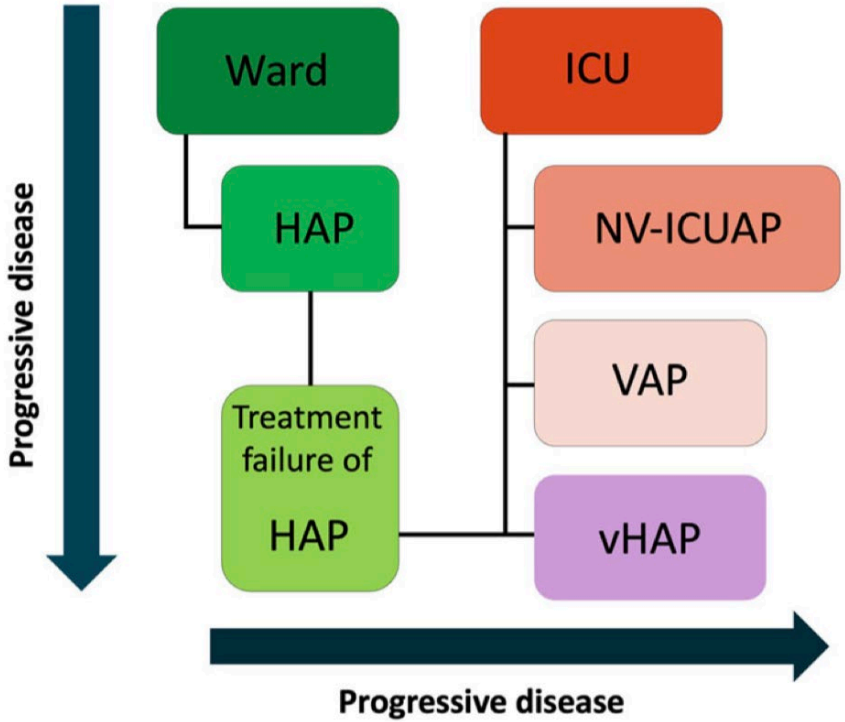
## Algorythms of empiric treatment

MRSA, Enterobacterales (ESBL, KPC, NDM)

*P. aeruginosa*, *A. baumanni*

# Example of "Progressive Disease" in HAP - VAP

## Amani Alnimir Infect Dis Ther 2023



# Risk Factors for HAP & VAP
## European Vs. US Guidelines

**Table 2 | High risk of MDR pathogens in HAP/VAP**

| European guidelines (2017) | US guidelines (2016) |
|---|---|
| Previous antibiotic treatment | Previous antibiotic treatment |
| ≥5 days of hospitalization | ≥5 days of hospitalization |
| Septic shock | Septic shock |
| Hospital settings with high rates of MDR pathogens (>25%) | ARDS before VAP |
| Previous colonization by MDR Pathogens | Acute renal replacement therapy before initiation of VAP |
| Mortality risk >15% | |

VAP=ventilator associated pneumonia; ARDS=acute respiratory distress syndrome; HAP=hospital-acquired pneumonia; MDR=multidrug resistant.[4];[6]

Cillóniz C *et al. BMJ* 2021;375:e065871.

# Risk Factors for HAP & VAP

| MDRO | Risk factors |
|---|---|
| MRSA | ⇒ Age<br>⇒ NP appearance > 6 days after admittance<br>⇒ NP development excluding summers<br>⇒ Respiratory diseases<br>⇒ Multilobar involvement |
| *Pseudomonas aeruginosa* | |
| KPC | ⇒ Admission to ICU, antimicrobial use<br>⇒ Prior carbapenem<br>⇒ Invasive operation<br>⇒ Previous non-KPC-Kp infections<br>⇒ Duration of previous antibiotic therapy before KPC colonization |
| *Enterobacteriaceae* | ⇒ Male sex<br>⇒ Admission from another health care facility<br>⇒ Ventilation at any point before culture during the index hospitalization<br>⇒ Receipt of any carbapenem in the prior 30 days<br>⇒ Receipt of any anti-MRSA agent in the prior 30 days |
| *Acinetobacter baumannii* | ⇒ APACHE II score at admission<br>⇒ Systemic illnesses (chronic respiratory disease and cerebrovascular accident)<br>⇒ Presence of excess non-invasive or invasive devices (mechanical ventilation)<br>⇒ Ever used antibiotics within 28 days (carbapenem and cefepime) |

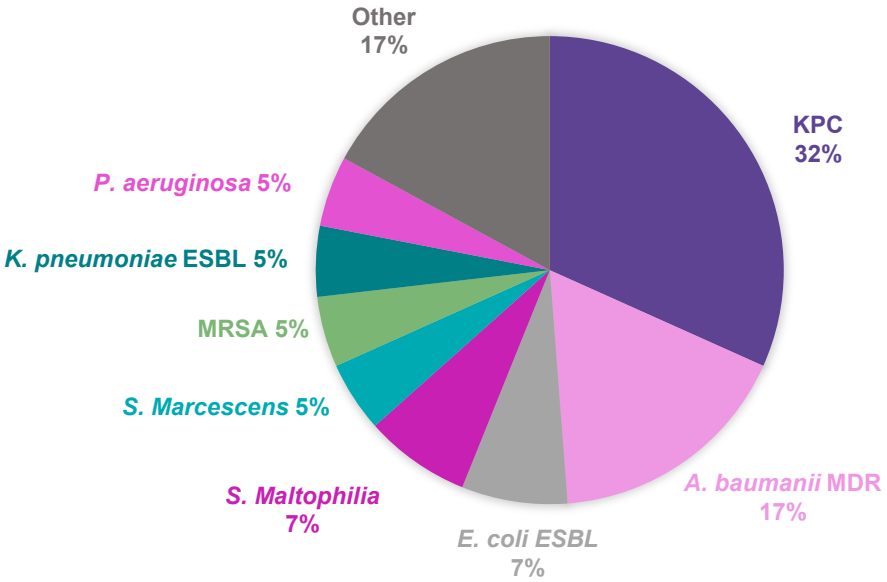
Zaragoza R *et al*. *Crit Care* 2020;24:383.

# Etiology of HAP-VAT-VAP (2010–2019)

| Reference | Type of infection | Microbiology | | | | |
|---|---|---|---|---|---|---|
| Ferrer et al. [30] | HAP | *S. aureus*, 17.7% | *P. aeruginosa*, 17.7% | *E.coli*, 6.5% | *Enterobacter* spp., 4.3% | *K. pneumoniae*, 3.2% |
| Esperatti et al. [22] | VAP | *P. aeruginosa*, 24% | *S. aureus*, 23% | *E. coli*, 7% | *Enterobacter* spp., 6% | *H. influenzae*, 4% |
| Restrepo et al. [31] | VAP | *S. aureus*, 38.7% | *H. influenzae*, 23.4% | *P. aeruginosa*, 14.7% | *k. pneumoniae*, 11.5% | *E. coli*, 11.1% |
| | | MDR, 30% | | | | |
| Quartin et al. [32]* | VAP | *S. aureus*, 60.3% | *P. aeruginosa*, 9.4% | *Acinetobacter* spp., 7.3% | *Klebsiella* spp., 6.8% | *Enterobacter* spp., 5.1% |
| Nseir et al. [33] | VAT | *P. aeruginosa*, 34.4% | *S. aureus*, 20.5% | *A. baumanii*, 11.5% | *K. oxytoca*, 10.6% | *Enterobacter* spp., 9.8% |
| | | MDR, 36.8% | | | | |
| Martín-Loeches et al. [21] | VAT | *P. aeruginosa*, 25% | *S. aureus*, 23% | *Klebsiella* spp., 15% | *E. coli*, 12% | *Enterobacter* spp., 11% |
| | | MDR, 61% | | | | |
| | VAP | *P. aeruginosa*, 24% | *S. aureus*, 24% | *Klebsiella* spp., 14% | *Enterobacter* spp., 12% | *E. coli*, 11% |
| | | MDR, 61% | | | | |
| ECDC [18] | VAP | *P. aeruginosa*, 20.8% | *S. aureus*, 17.8% | *Klebsiella* spp., 16.1% | *E. coli*, 13.3% | *Enterobacter* spp., 10.3% |
| Koulenti et al. [29] | HAP | *Enterobacteriaceae*, 32.9% | *S. aureus*, 24.9% | *P. aeruginosa*, 17.4% | *A. baumanii*, 15.4% | |
| ENVIN-HELICS [3] | VAP | *P. aeruginosa*, 23.8% | *S. aureus*, 13.5% | *Klebsiella* spp., 10.3% | *E. coli*, 9.1% | *Enterobacter* spp., 8.6% |
| | | PIP/TAZ R, 34.1%<br>Carba R, 37.9%<br>Colistin R, 8.6% | MRSA, 12.7% | PIP/TAZ R, 50%<br>Carba R, 23.5%<br>3°G cef R, 37% | PIP/TAZ R, 21.7%<br>Carba R, 0%<br>3°G cef R, 12.5% | |
| Pulido et al. [34] | VAP | *P. aeruginosa*, 21.1% | *A. baumanii*, 17.9% | *K. pneumoniae*, 15.6% | *S. aureus*, 13.3% | *E. coli*, 7.8% |
| Huang et al. [35] | VAP | *A. baumanii*, 33.9% | *K. pneumoniae*, 23.6% | *P. aeruginosa*, 19.8% | *S. aureus*, 7.1% | *S. maltophilia*, 3.8% |
| | | Carba R, 76.4% | Carba R, 44% | Carba R, 59.5% | MRSA, 60% | |
| Cantón-Bulnes et al. [36] | VAT | *P. aeruginosa*, 24.5% | *H. influenzae*, 18.9% | *E. coli*, 9.4% | *S. aureus*, 9.4% | *K. pneumoniae*, 7.5% |
| Ibn Saied et al. [37] | VAP | *P. aeruginosa*, 33.5% | *Enterobacteriaceae*, 32.3% | *S. aureus*, 19% | *S. pneumoniae*, 4.9% | *S. maltophilia*, 4.7% |

Zaragoza R *et al*. *Crit Care* 2020;24:383.

# VAP: Example of Local Epidemiology on Respiratory Isolates




**Further changes expected with NDM Enterobacterales**

Local epidemiology data. City of Health & Sciences, Turin, Italy, 2019.

# Diagnosis of VAP in Critically Ill Adult Patients: A Systematic Review & Meta-analysis

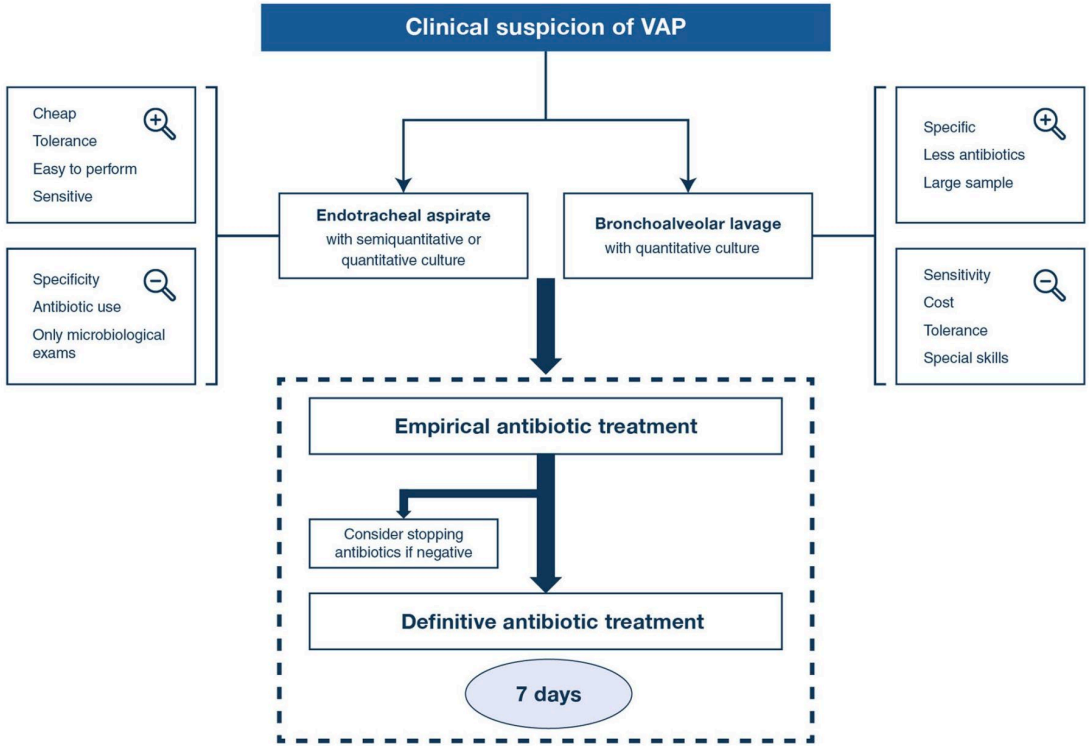
Estimates of the performance of physical examination, chest radiography, laboratory values, and CPIS for the diagnosis of ventilator-associated pneumonia, relative to **reference standard of histopathology from lung biopsy**

| | No. of cohorts (patients) | Sensitivity, % (95% CI) | Specificity, % (95% CI) | Diagnostic odds ratio (95% CI) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) | GRADE |
|---|---|---|---|---|---|---|---|
| *Histopathology reference standard* | | | | | | | |
| Fever | 5 (142) | 66.4 (40.7–85) | 53.9 (34.5–72.2) | 2.31 (0.98–5.43) | 1.44 (1.01–2.05) | 0.62 (0.36–1.09) | Low |
| Purulent secretions | 4 (336) | 77 (64.7–85.9) | 39 (25.8–54) | 2.13 (1.34–3.41) | 1.26 (1.06–1.5) | 0.59 (0.42–0.83) | Moderate |
| Infiltrate on chest radiography | 7 (238) | 88.9 (73.9–95.8) | 26.1 (15.1–41.4) | 2.83 (1.18–6.82) | 1.2 (1.03–1.4) | 0.42 (0.2–0.92) | Low |
| Leukocytosis | 3 (88) | 64.2 (46.9–78.4) | 59.2 (45–72) | 2.6 (1.05–6.45) | 1.57 (1.03 to 2.4) | 0.61 (0.36–1.01) | Low |
| Sputum from endotracheal aspirate ($>10^5$ CFU/mL) | 3 (75) | 75.7 (51.5–90.1) | 67.9 (40.5–86.8) | 6.59 (2.17–20.04) | 2.36 (1.19–4.66) | 0.36 (0.18–0.73) | Very Low |
| Protected specimen brush ($>10^3$ CFU/mL) | 7 (201) | 61.4 (43.7–76.5) | 76.5 (64.2–85.6) | 5.19 (2.31–11.65) | 2.62 (1.63–4.19) | 0.5 (0.33–0.77) | Low |
| Bronchoalveolar lavage ($>10^4$ CFU/mL) | 10 (307) | 71.1 (49.9–85.9) | 79.6 (66.2–88.6) | 9.57 (4.04–22.71) | 3.48 (2.13–5.7) | 0.36 (0.2–0.66) | Low |
| CPIS > 6 | 4 (343) | 73.8 (50.6–88.5) | 66.4 (43.9–83.3) | 5.56 (1.30–23.84) | 2.2 (1.09–4.43) | 0.4 (0.17–0.92) | Low |

CFU = colony-forming units; CI = confidence interval; CPIS = Clinical Pulmonary Infection Score; GRADE = Grading of Recommendations, Assessments, Development and Evaluation

Fernando SM *et al*. *Intens Care Med* 2020;46:1170–9.

# VAP: Clinical & Microbiological Strategies




Papazian L *et al. Intensive Care Med* 2020;46:888–906.

# “Invasive Microbiology”

| 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society [34] | 2017 International ERS/ESICM/ESCMID/ALAT guidelines [38] |
|---|---|
| *Should patients with suspected VAP be treated based on the results of invasive sampling (BAL, PSB, blind mini-BAL) with quantitative culture results, noninvasive sampling (endotracheal aspiration) with quantitative culture results, or noninvasive sampling with semiquantitative culture results?*<br>**Recommendation**<br>We suggest noninvasive sampling with semiquantitative cultures to diagnose VAP, rather than invasive sampling with quantitative cultures and rather than noninvasive sampling with quantitative cultures (weak recommendation, low-quality evidence) | *In intubated patients suspected of having VAP, should distal quantitative samples be obtained instead of proximal quantitative samples?*<br>**Recommendation**<br>We suggest obtaining distal quantitative samples (prior to any antibiotic treatment) in order to reduce antibiotic exposure in stable patients with suspected VAP and to improve the accuracy of the results. (weak recommendation, low quality of evidence) |
| *If invasive quantitative cultures are performed, should patients with suspected VAP whose culture results are below the diagnostic threshold for VAP (PSB with $< 10^3$ CFU/mL, BAL with $< 10^4$ CFU/mL) have their antibiotics withheld rather than continued?*<br>**Recommendation**<br>Noninvasive sampling with semiquantitative cultures is the preferred methodology to diagnose VAP; however, the panel recognizes that invasive quantitative cultures will occasionally be performed by some clinicians. For patients with suspected VAP whose invasive quantitative culture results are below the diagnostic threshold for VAP, we suggest that antibiotics be withheld rather than continued (weak recommendation, very low-quality evidence) | We recommend obtaining a lower respiratory tract sample (distal quantitative or proximal quantitative or qualitative culture) to focus and narrow the initial empiric antibiotic therapy. (strong recommendation, low quality of evidence) |

*BAL* Bronchoalveolar lavage, *PSB* protected specimen brush, *CFU* colony-forming units

Papazian L *et al*. *Intens Care Med* 2020;46:888–906.

# French Multicenter Study: Clinical Vs. Br-BAL/PSB

## Fagon & Chastre, Ann Intern Med 2000; 132: 621

**Multicentric RCT of VAP outcomes; 413 pts in 31 ICUs**

**Clinical Dx (n=204) Vs. Br-PSB/BAL (n=209)**

**Br-BAL/PSB used to adjust or stop Rx**

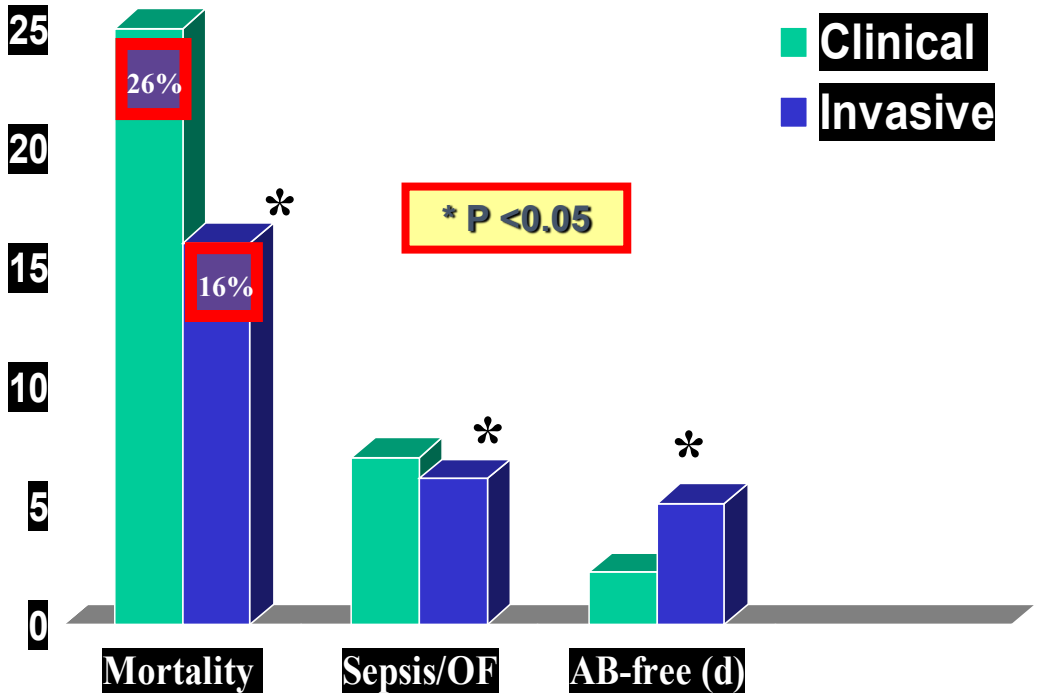
# Microbiological Methodology & Analysis
## Fagon & Chastre, Ann Intern Med 2000; 132: 621

- **Clinical group: Endotracheal Aspirate**
  - Sterile collection by a suction catheter, vortexed for 1 minute
    → Gram staining and culture

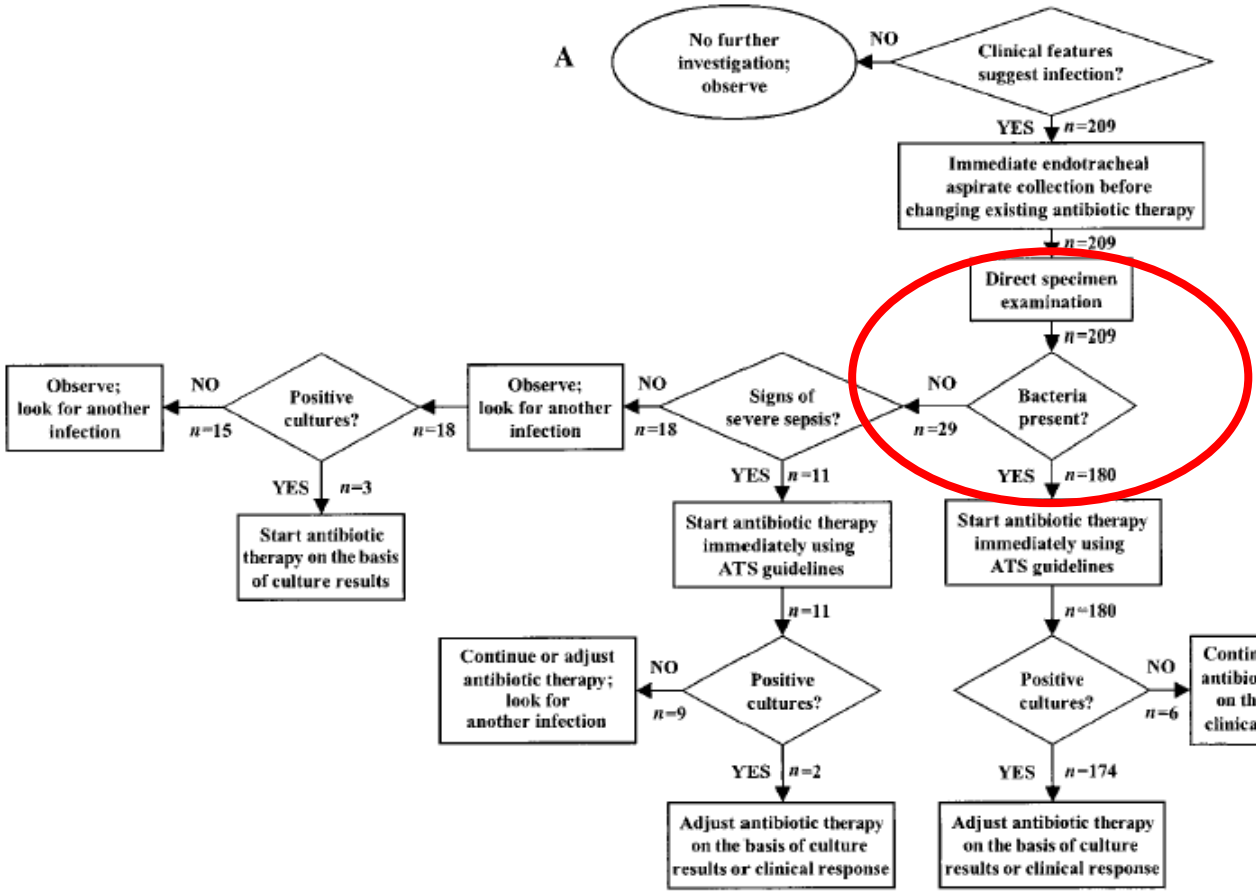
- **Invasive group**
  - **PSB or BAL**
  - **One sample:**
    Gram staining of cytocentrifuge preparations
    → % of cells containing intracellular bacteria
  - **One sample:**
    Quantitative cultures

# Outcomes

## Fagon & Chastre, Ann Intern Med 2000; 132: 621

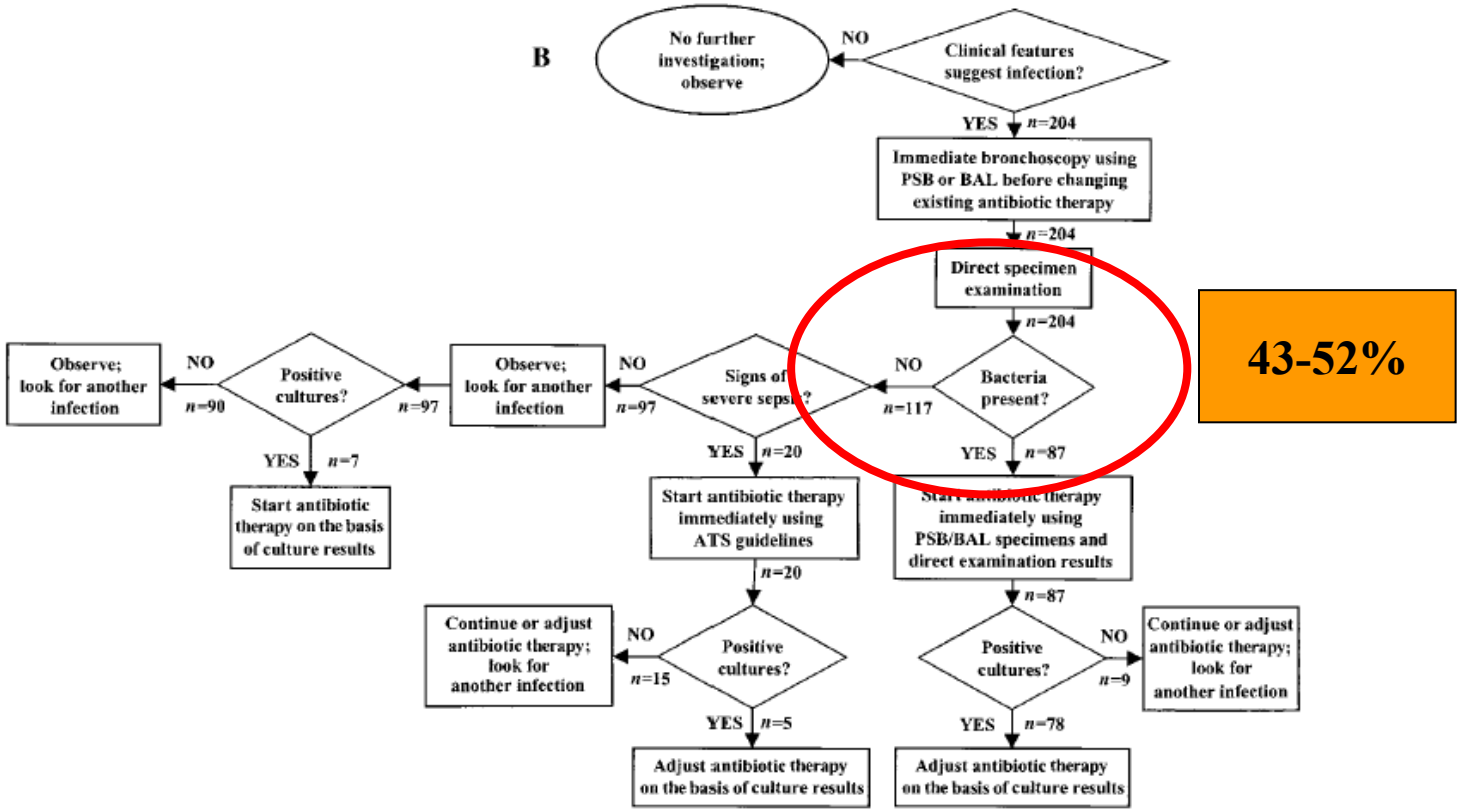


# Clinical Group



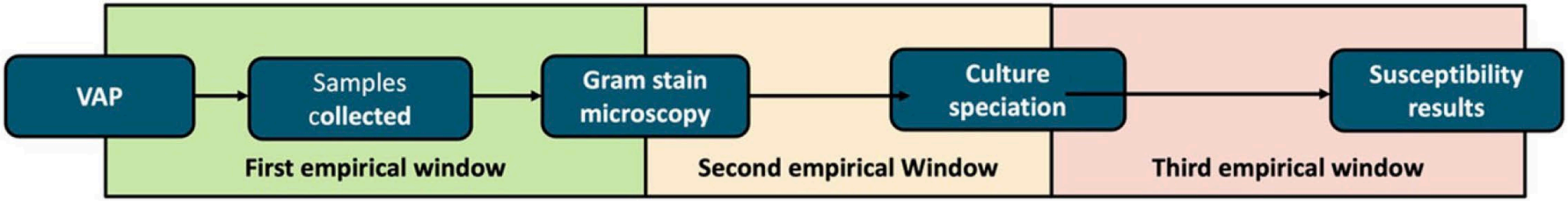

**86-91%**

# Invasive Group



# Empiric Therapeutic Window in VAP

## Amani Alnimir Infect Dis Ther 2023



*Review*

# Nosocomial Pneumonia in the Era of Multidrug-Resistance: Updates in Diagnosis and Management

**Elena Xu [1], David Pérez-Torres [2,†], Paraskevi C. Fragkou [3,†], Jean-Ralph Zahar [4,†] and Despoina Koulenti [1,5,*]**

**Table 2.** Advantages and disadvantages of multiplex PCR panels.

| Advantages | Disadvantages |
|---|---|
| Exceptionally faster time to results for pathogen and resistance profiles: major utility for prompt treatment modification and effective patient management | Over-detection of microbial and viral genome: problem in results interpretation: pathogen or coloniser? (may be partially solved with semi-quantification of bacterial targets) |
| Multiple targets detection at the same and Detection of viral and atypical pathogens as well | The presence of a resistance gene marker may not be linked to the detected microorganism, but to other co-existent organisms either undetectable or below the detection limit, thus making culture-based techniques still necessary in many cases |
| Detection of pathogens even when antimicrobial treatment has been initiated | Initial cost to buy the equipment |
| Potential for better antibiotic utilisation and positive impact on:<br>-nosocomial pneumonia management, shortening hospital stay and decreasing healthcare costs,<br>-antibiotic stewardship programs | Not widely available among different institutions yet |
| Early identification of MDR pathogens should facilitate enhanced infection control practices and reduce spread | Further validation versus traditional diagnostic techniques needed and determination of the effect on antimicrobial prescribing, patient outcomes and resistance is needed |

# Quantitative Agreement: Bacterial Targets Between PN Panel And SOC

**TABLE 3** Quantitative agreement of bacterial targets

| PN panel result (copies/ml) | No. of samples[a] with SOC culture result (CFU/ml) | | | |
|---|---|---|---|---|
| | Not detected | $10^3$ | $10^4$ | $\geq 10^5$ |
| Not detected | 3,734 | 3 | 0 | 0 |
| $10^4$ | 24 (8) | 6 | 4 | 0 |
| $10^5$ | 27 (17) | 3 | 4 | 1 |
| $10^6$ | 9 (4) | 2 | 12 | 3 |
| $\geq 10^7$ | 13 (7) | 2 | 15 | 23 |
| % concordant[b] | 98.1 (3,734/3,807) | 18.8 (3/16) | 11.4 (4/35) | 100 (27/27) |

[a]Numbers in parentheses are the numbers of culture-negative results obtained for specimens from patients who received antibiotics with potential activity against the given bacterial target detected within 72 h preceding specimen collection. One laboratory reported bacterial culture quantitation (11 isolates) as "few," "moderate," or "many"; these were categorized as $10^3$, $10^4$, and $\geq 10^5$ CFU/ml, respectively. Shading indicates concordance between the BioFire PN panel and routine culture quantitation.

[b]Concordance between the PN panel and culture quantitation among all positive cultures was 43.6% (34/78).

**In positive cultures, concordance = 43.6% (34/78)**

- Concordance **poorest** with low bacteria
- **Strong bias toward higher semiquantitative values**, when PN panel is compared to culture
- In case of **discordant quantification**, the **PN panel result was higher than that of culture**, with **72.2%** (34/44) of the results **exceeding culture quantification by >1 log**

- **Targets quantified as $10^4$ copies/ml by the PN panel may frequently be quantified as $10^3$ CFU/ml by routine culture,** ie the culture-based limit of detection
- Their clinical significance is largely unreported
- Interpretation should be done in the context of other clinical & laboratory results (e.g., additional pathogens present at high concentrations in the same specimen)
- **All bacterial targets reported as $10^5$ CFU/ml in culture were reported as $10^5$ genomic copies/ml by the PN panel**

Buchan et al., J Clin Microbiol 58:e00135-20. https://doi.org/ 10.1128/JCM.00135-20

# Early Use of PN Panel → Early Adaptation of Therapy & Reduction of Unnecessary Antimicrobial Exposure & in Adult Patients with Pneumonia

Retrospective multicenter study in 4 French University Hospitals.

159 adult patients with a suspicion of CAP, HAP and **VAP**, with appropriate samples (mainly ETA) available. 30 pts not ICU located

**Assess the impact of PN+ on early adaptation of empirical AB therapy in adult pneumonia patients;**

A group of experts (ICU, ID, Lab) examines clinical data and PN+ result to recommend an AB treatment without knowing the culture results for these patients. **-> simulates the real-life situation of having PN+ results BEFORE culture**

**Table 4** Impact of the rm-PCR results on antibiotic prescription, according to the multidisciplinary committee ($n = 159$)

| | Overall, $n = 159$ | CAP, $n = 54$ | HAP, $n = 68$ | VAP, $n = 37$ |
|---|---|---|---|---|
| Antibiotic modification | 123 (77) | 37 (69) | 54 (79) | 32 (87) |
| De-escalation | 63 (40) | 20 (37) | 25 (37) | 18 (49) |
| Escalation | 35 (22) | 8 (15) | 18 (27) | 9 (24) |
| Undetermined | 25 (16) | 9 (17) | 11 (16) | 5 (14) |
| No change | 36 (23) | 17 (32) | 14 (21) | 5 (14) |

Results are presented as *n* (%)
*CAP* community-acquired pneumonia, *HAP* hospital-acquired pneumonia, *VAP* ventilator-associated pneumonia

**ATB treatment would have been changed in 77% of the cases on average (VAP: 87%);**

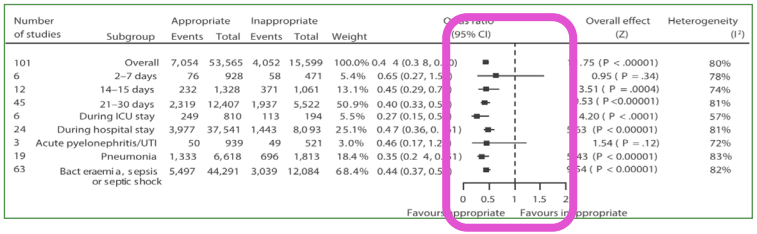
**De-escalation of empiric AB therapy would be the predominant treatment change;**

**Adoption of PN+ would have decreased useof β-lactams from 92% to 82% ('main treatment') and β-lactam companion therapies from 50% to 31%.**

Monard C, et al. *Crit Care*. 2020;24(1):434. doi:10.1186/s13054-020-03114-y

# *Appropriate* Vs. *Inappropriate* Antimicrobial Therapy: Mortality, Cost-effectiveness & Health-economic Outcomes

## Mortality

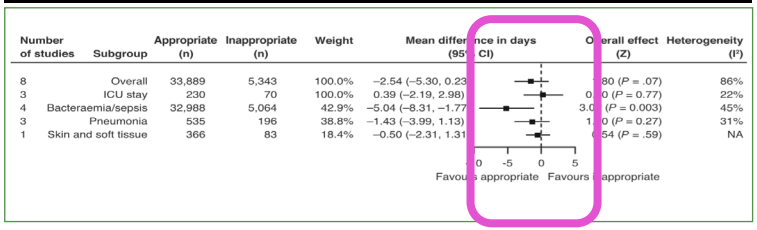


| Number of studies | Subgroup | Appropriate Events | Appropriate Total | Inappropriate Events | Inappropriate Total | Weight | Odds ratio (95% CI) | Overall effect (Z) | Heterogeneity ($I^2$) |
|---|---|---|---|---|---|---|---|---|---|
| 101 | Overall | 7,054 | 53,565 | 4,052 | 15,599 | 100.0% | 0.4 4 (0.3 8, 0.[illegible]0) | [illegible].75 (P < .00001) | 80% |
| 6 | 2–7 days | 76 | 928 | 58 | 471 | 5.4% | 0.65 (0.27, 1.5[illegible]) | 0.95 ( P = .34) | 78% |
| 12 | 14–15 days | 232 | 1,328 | 371 | 1,061 | 13.1% | 0.45 (0.29, 0.7[illegible]) | 3.51 ( P = .0004) | 74% |
| 45 | 21–30 days | 2,319 | 12,407 | 1,937 | 5,522 | 50.9% | 0.40 (0.33, 0.5[illegible]) | [illegible].53 ( P <0.00001) | 81% |
| 6 | During ICU stay | 249 | 810 | 113 | 194 | 5.5% | 0.27 (0.15, 0.5[illegible]) | 4.20 ( P < .0001) | 57% |
| 24 | During hospital stay | 3,977 | 37, 541 | 1,443 | 8,093 | 25.1% | 0.47 (0.36, 0. [illegible].1) | [illegible]53 (P < 0.00001) | 81% |
| 3 | Acute pyelonephritis/UTI | 50 | 939 | 49 | 521 | 3.0% | 0.46 (0.17, 1.2[illegible]) | 1.54 ( P = .12) | 72% |
| 19 | Pneumonia | 1,333 | 6,618 | 696 | 1,813 | 18.4 % | 0.35 (0.2 4, 0.[illegible].1) | [illegible]43 (P < 0.00001) | 83% |
| 63 | Bact eraemi a , sepsis or septic shock | 5,497 | 44,291 | 3,039 | 12,084 | 68.4% | 0.44 (0.37, 0.5[illegible]) | [illegible]54 ( P < 0.00001) | 82% |

0 0.5 1 1.5 2

Favours appropriate Favours inappropriate

## Length of Hospital Stay

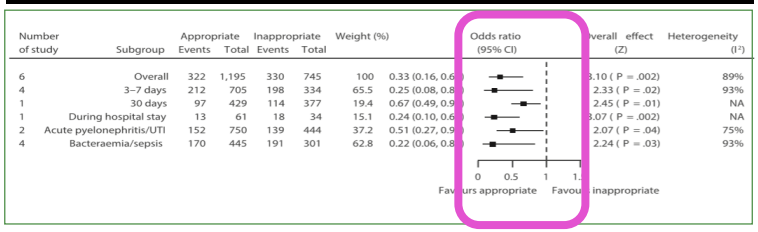


| Number of studies | Subgroup | Appropriate (n) | Inappropriate (n) | Weight | Mean difference in days (95% CI) | Overall effect (Z) | Heterogeneity ($I^2$) |
|---|---|---|---|---|---|---|---|
| 8 | Overall | 33,889 | 5,343 | 100.0% | −2.54 (−5.30, 0.23 | [illegible]80 (P = .07) | 86% |
| 3 | ICU stay | 230 | 70 | 100.0% | 0.39 (−2.19, 2.98) | 0.[illegible]0 (P = 0.77) | 22% |
| 4 | Bacteraemia/sepsis | 32,988 | 5,064 | 42.9% | −5.04 (−8.31, −1.77 | 3.0[illegible] (P = 0.003) | 45% |
| 3 | Pneumonia | 535 | 196 | 38.8% | −1.43 (−3.99, 1.13) | 1.[illegible]0 (P = 0.27) | 31% |
| 1 | Skin and soft tissue | 366 | 83 | 18.4% | −0.50 (−2.31, 1.31 | [illegible].54 (P = .59) | NA |

[illegible].0 -5 0 5

Favou[illegible]s appropriate Favours [illegible]appropriate

## Treatment Failure

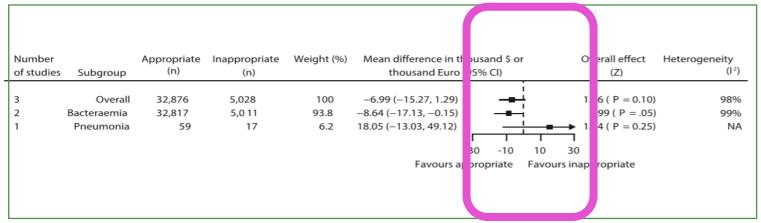


| Number of study | Subgroup | Appropriate Events | Appropriate Total | Inappropriate Events | Inappropriate Total | Weight (%) | Odds ratio (95% CI) | Overall effect (Z) | Heterogeneity ($I^2$) |
|---|---|---|---|---|---|---|---|---|---|
| 6 | Overall | 322 | 1,195 | 330 | 745 | 100 | 0.33 (0.16, 0.6[illegible]) | 3.10 ( P = .002) | 89% |
| 4 | 3–7 days | 212 | 705 | 198 | 334 | 65.5 | 0.25 (0.08, 0.8[illegible]) | 2.33 ( P = .02) | 93% |
| 1 | 30 days | 97 | 429 | 114 | 377 | 19.4 | 0.67 (0.49, 0.9[illegible]) | 2.45 ( P = .01) | NA |
| 1 | During hospital stay | 13 | 61 | 18 | 34 | 15.1 | 0.24 (0.10, 0.6[illegible]) | 3.07 ( P = .002) | NA |
| 2 | Acute pyelonephritis/UTI | 152 | 750 | 139 | 444 | 37.2 | 0.51 (0.27, 0.9[illegible]) | 2.07 ( P = .04) | 75% |
| 4 | Bacteraemia/sepsis | 170 | 445 | 191 | 301 | 62.8 | 0.22 (0.06, 0.8[illegible]) | 2.24 ( P = .03) | 93% |

0 0.5 1 1.[illegible]

Fav[illegible]urs appropriate Favou[illegible] inappropriate

## Costs



| Number of studies | Subgroup | Appropriate (n) | Inappropriate (n) | Weight (%) | Mean difference in t[illegible]ousand $ or thousand Euro [illegible]5% CI) | Overall effect (Z) | Heterogeneity ($I^2$) |
|---|---|---|---|---|---|---|---|
| 3 | Overall | 32,876 | 5,028 | 100 | −6.99 (−15.27, 1.29) | 1.[illegible]6 ( P = 0.10) | 98% |
| 2 | Bacteraemia | 32,817 | 5,0 11 | 93.8 | −8.64 (−17.13, −0.15) | [illegible]99 ( P = .05) | 99% |
| 1 | Pneumonia | 59 | 17 | 6.2 | 18.05 (−13.03, 49.12) | 1.[illegible]4 ( P = 0.25) | NA |

[illegible]0 -10 10 30

Favours a[illegible]ppropriate Favours inap[illegible]propriate

***Rapid diagnostics for early identification of etiology ensure appropriate initial antimicrobial therapy***

Bassetti et al., 2020.. Intern. J. of Antimicrobial Agents 56 106184.

# VAP: Initial Antibiotic Treatment

**MDR Risk Factors**

- Antibiotics: previous 90 days
- Hospital stay >5 days
- Septic shock at VAP onset
- ARDS prior to VAP onset
- RRT prior to VAP onset
- Previous MDR colonization

| Situation | Therapeutic class | Agent |
|---|---|---|
| Early VAP (< 5 days), without MDR bacteria risk factor* | Non-antipseudomonal β-lactam | Amoxicillin/clavulanic acid<br>OR<br>Third generation cephalosporin |
| Late VAP (≥ 5 days),<br>OR<br>Risk factors for MDR bacteria | β-lactam active against *Pseudomonas aeruginosa*<br>AND<br>Non β-lactam antipseudomonal agent | Cefepime 2 g q 8 h<br>OR<br>Ceftazidime 2 g q 8 h<br>OR<br>Piperacillin–tazobactam 4 g q 6 h<br>OR<br>Meropenem 2 g q 8 h<br>Amikacin 25 mg/kg/day<br>OR<br>Ciprofloxacin 1200 mg/day |
| Known MRSA colonization, or high (> 20%) MRSA prevalence in the unit | Agent active against MRSA | Vancomycin 30–45 mg/kg/day<br>OR<br>Linezolid 600 mg/12 h |
| Known colonization with carbapenem-resistant Enterobacteriaceae or Pseudomonas aeruginosa susceptible only to new beta-lactam agents | New β-lactam agent | Ceftolozane–tazobactam 3 g q 8 h‡<br>OR<br>Ceftazidime–avibactam 2.5 g q 8 h‡<br>OR<br>Meropenem–vaborbactam 4 g q 8 h‡<br>OR<br>Imipenem–relebactam 1.5 g q 6 h‡ |

*This situation and the corresponding antimicrobial agents are not mentioned in IDSA/ATS guidelines

‡The empirical use should be restricted to patients colonized by specific pathogens (carbapenem-resistant *Enterobacteriaceae* or extensively drug-resistant *P. aeruginosa*), according to previous susceptibility testing

Papazian L *et al. Intensive Care Med* 2020;46:888–906.

# US & European Guidelines: Choice of Empiric Treatment

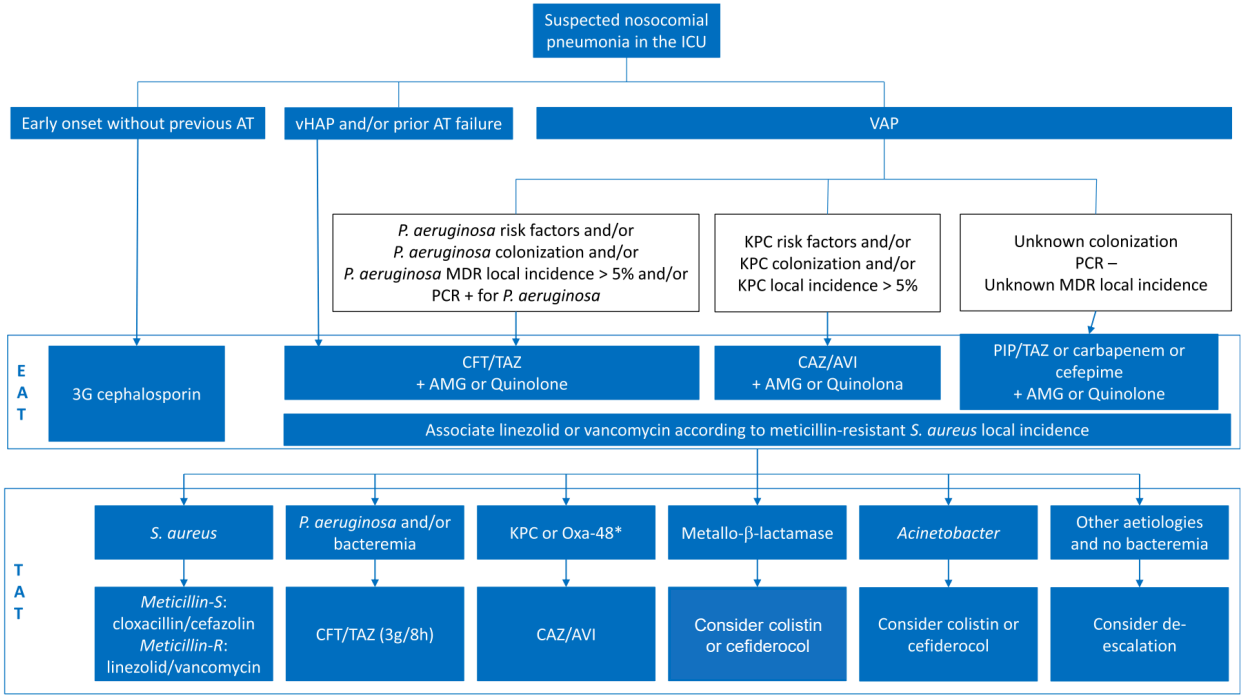
**Table 1 | Empiric treatment according to US And European guidelines**

| Risk for MDR pathogens | US guidelines | European guidelines |
|---|---|---|
| Low | | **(≤15% mortality risk, low MDR risk)**<br>Narrow spectrum antimicrobial with activity for meticillin susceptible *S aureus* and non-resistant Gram negatives: ertapenem, ceftriaxone, cefotaxime, moxifloxacin, levofloxacin |
| High | | **(>15% mortality risk and/or high MDR risk)**<br>No septic shock: monotherapy with broad spectrum agent active against >90% of likely Gram negative pathogens +/- MRSA (if > 25% of *S aureus* isolates are MRSA)<br>Septic shock: combination therapy with anti-pseudomonal regimen +/- MRSA (if > 25% of *S aureus* isolates are MRSA) |

Both guidelines agree on stratifying patients according to individual and local community risk factors for MDR pathogens.[6]

Cillóniz C *et al. BMJ* 2021;375:e065871.

# Treatment Algorithm: Example




**Wide Window for the new BL/BLI, including Cefiderocol**

vHAP, ventilated hospital-acquired pneumonia

Zaragoza *et al*. *Crit Care* 2020;24:383.

# Duration of Antibiotic Therapy in Gram-negative Infections with a Particular Focus on MDR pathogens

## Ongoing studies on shorter <8 days treatment of VAP

## REGARD-VAP trial

- Multinational multicentre study, 460 patients enrolled (November 22, 2023)
- Aims: clinical non-inferiority and superiority of SAT (up to 7 days) vs long antibiotic treatment (LAT)
- NCT03382548: https://clinicaltrials.gov/ct2/show/NCT03382548

## DATE trial (Duration of Antibiotic Treatment for Early VAP)

- Completed in early 2022 with pending results: 22 patients enrolled
- 4- vs 8-day treatment for early VAP
- NCT01994980: https://clinicaltrials.gov/ct2/show/NCT01994980

Haddad SF *et al. Curr Opin Infect Dis* 2022;35:614–620.

# Discontinuation of Therapy: IDSA Guidelines

**Recommendation**:

1. For patients with HAP/VAP, w criteria to guide the discontinuation of antibiotic th *(weak recommendation, low-quality evidence)*

De-escalation
Highly recommended
- IDSA & ERS Guidelines -

Remarks:
It is not known if the benefits of using PCT levels to determine whether or not to discontinue antibiotic therapy exist in settings where standard antimicrobial therapy for VAP is already 7 days or less

1. Kahil AC *et al. Clin Infect Dis* 2016:63:e61–111; 2. Torres A *et al. Eur Respir J* 2017;50:1700582.

# Respiratory Viruses in Nosocomial Pneumonia: An Evolving Paradigm

## Nosocomial spread of common respiratory viruses

## Common cause of nosocomial pneumonia

- Influenza, respiratory syncytial virus, adenovirus, and rhinovirus
- Especially among immunosuppressed and pediatric patients

## Difficult differential between bacterial & viral infections

## Crude mortality in viral HAP and VAP

Rival or exceed those in bacterial NP

## Current medical needs

- Rigorous prospective, multicenter trials
- Studies of novel therapeutics for these viral infections

Zilberbeg MD *et al. Viruses* 2023;15:1676.

# Metagenomics for Microbiological Diagnosis of HAP & VAP

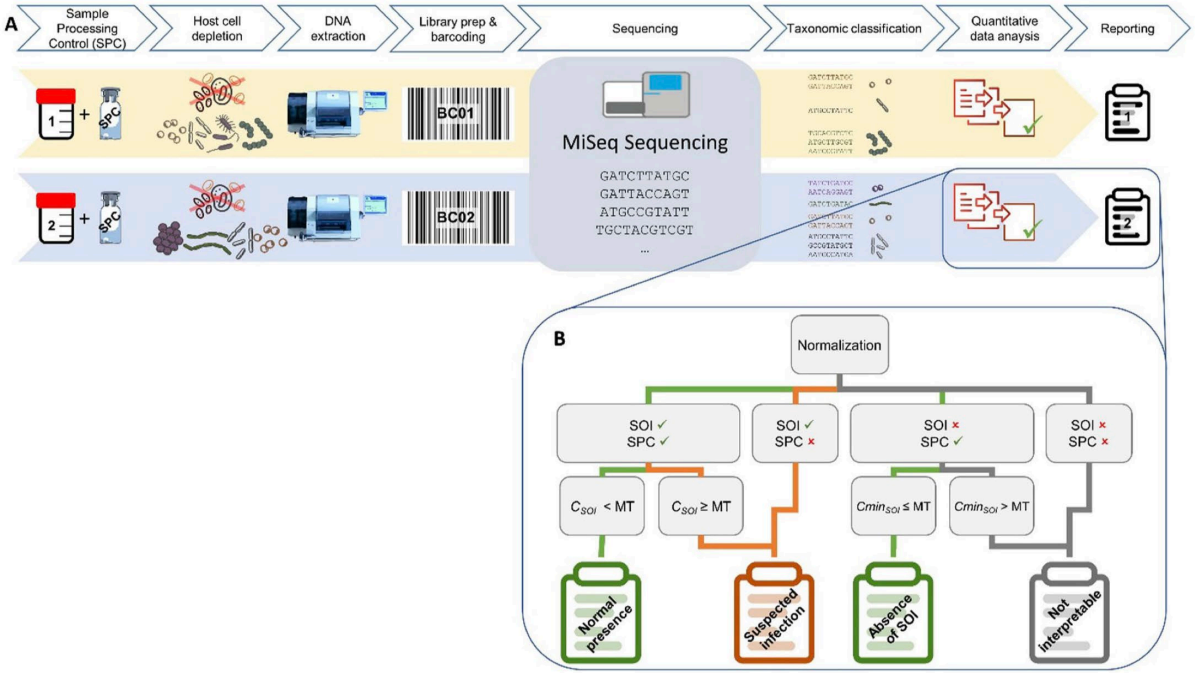



**Fig. 1** Complete workflow for clinical metagenomic analysis of BAL samples. **A** is the experimental workflow in which two independent samples are analyzed in the same sequencing run. **B** represents the rule of interpretation applied independently to each SOI to determine whether it is involved in patient infection or presence at normal concentration or absence in the sample or the inability to interpret the result. *SOI* species of interest, *SPC* sample processing control, *MT* metagenomic threshold

Heitz M et al. Resp Research 2023

# Metagenomics for Microbiological Diagnosis of HAP & VAP
## Heitz M et al. Resp Research 2023

**Table 1** Microorganisms of the mNGS pneumonia panel (n = 19)

| |
|---|
| *Acinetobacter baumannii* |
| *Citrobacter freundii*<br>*Citrobacter koseri* |
| *Enterobacter aerogenes* |
| *Escherichia coli* |
| *Haemophilus influenzae* |
| *Hafnia alvei* |
| *Klebsiella oxytoca* |
| *Klebsiella pneumoniae* |
| *Legionella pneumophila* |
| *Morganella morganii* |
| *Proteus mirabilis*<br>*Proteus vulgaris* |
| *Providencia stuartii*<br>*Pseudomonas aeruginosa* |
| *Serratia marcescens* |
| *Staphylococcus aureus* |
| *Stenotrophomonas maltophilia* |
| *Streptococcus pneumoniae* |

# (Early) Sensitivity Vs. (Delayed) Specificity

**A. Esame microscopico diretto / (Fast track) / colturale**

**B. Decidere su quali casi usare Fast-track Microbiology**

- Criteri diagnostico-terapeutici
- Protocollo condiviso con microbiologi, intensivisti e pneumologi

**C. Fast-track**

- Escalation (myne)– de-escalation

**D. Definite de-escalation "composita" con colturali (CIII?)**

**E. Integrare uso biomarkers**

**F. Antibiotic free-days importante misura in ICU**

# Conclusions

- **Choice of clinical / invasive strategy**
- **Fast microbiological testing for VAP**
  - Potential results in real time to tailor therapy on pathogens and MDR determinants
  - Support clinical data
- **Local ICU ecology of utmost importance**
- **Mathematical models and scoring systems**
  - Still not sufficiently developed for operational application
- **Areas for priority research studies in VAP**
  - Clinical utility & implementation of rapid diagnostics
  - Validation of prediction scores in making clinical decisions