ERS pocket guidelines

Management of hospital-acquired pneumonia and ventilator-associated pneumonia: an ERS/ESICM/ESCMID/ALAT guideline

From the Task Force for the Management of Hospital-acquired Pneumonia (HAP)/Ventilator-associated Pneumonia (VAP)

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It was prepared by Ignacio Martin-Loeches and Daire Nicholas Kelly under the supervision of the ERS Methodologist Dr. David Rigau.

Question 1: In intubated patients suspected of having VAP should distal quantitative samples be obtained instead of proximal-quantitative samples?

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**
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**

<u>Evidence on benefits and harms</u>

- No RCTs have compared qualitative and quantitative cultures of the same bacteriological sample.
- Non-invasive diagnostic methods lead to an over-identification of bacteria by initial direct examination of the samples.
- Quantitative cultures help to guide initial antibiotic therapy for VAP; when available, they allow the precise identification of the causative organisms and susceptibility patterns, thus providing invaluable information for optimal antibiotic selection.
- The collection of a bacteriologic sample before any change in antimicrobial therapy allows the immediate withdrawal of the antibiotic following a negative finding and a subsequent de-escalation according to the micro-organisms grown from bacteriologic culture.

Rationale of recommendation

The guideline panel noted that invasive techniques using quantitative cultures are widely available and feasible at most of the specialised centres that care for patients with VAP. Panel members felt that the overall benefits in terms of antibiotic exposure probably outweigh the potential harms associated with invasive techniques, particularly if samples are collected before new antibiotics are started. The panel took into consideration the potentially high costs due to the future of emerging antibiotic resistance with the routine use of broad-spectrum, and prolonged courses of antibiotics, and the reduced direct costs related to a short course of antibiotics

Implementation considerations

In critically ill VAP patients, the benefits of invasive techniques are less clear, due to the potential deleterious impact of bronchoscopy on gas exchange, especially in patients with severe acute respiratory distress syndrome (ARDS) and profound (unstable) septic shock. Mini-BAL can partially overcome these deleterious effects.

Of note, if the procedure is performed shortly after a recent change in antibiotics, or at a centre without technical expertise, a false negative result may mean that patients are not treated in an efficient and timely manner.

If bacteriological analyses are not immediately available, processing of a bacteriological specimen collected after refrigeration can offer good reliability.

Question 2: Can patients suspected of having nosocomial pneumonia (HAP and VAP), who have early onset infection and none of the classic risk factors for MDR pathogens, be treated appropriately if they receive a different, and narrower spectrum empiric therapy than patients with late onset infection and/or the presence of MDR risk factors?

We suggest using narrow spectrum antibiotics (ertapenem,ceftriaxone, cefotaxime, moxifloxacin, levofloxacin) in patients with suspected low risk of resistance and early onset HAP/VAP	• Weak recommend-ation • Very low quality of evidence
We recommend broad-spectrum empiric antibiotic therapy targeting *Pseudomonas aeruginosa* and ESBL-producing organisms, and, in settings with high prevalence of *Acinetobacter* spp., in patients with suspected early onset HAP/VAP who are in septic shock, in patients who are in hospitals with a high background rate of resistant pathogens present in local microbiologic data, and in patients with other (non-classic) risk factors for MDR pathogens (see question 3)	• Strong recommendation • Low quality of evidence

Evidence on benefits and harms

- There are no RCTs comparing the effectiveness of broad- and narrow-spectrum empiric antibiotic use in patients with anticipated low-risk MDR pathogens.
- Early onset HAP and VAP, defined as occurring within the first 4 days of hospitalisation, usually carry a better prognosis, and are more likely to be caused by antibiotic-sensitive bacteria than other types of pneumonia.
- Late-onset HAP and VAP (5 days or more of hospitalisation) are more likely to be caused by MDR pathogens, and are associated with increased patient mortality and morbidity.
- Risk factors for antibiotic resistance have been identified as: previous antimicrobial therapy or hospitalisation (2 or more days) in the preceding 90 days, and more recently the non-classic risk of having a high frequency of antibiotic resistance in the community or in the specific hospital unit.

Rationale of recommendation

Use of narrow-spectrum therapy may be associated with lower direct costs due to reduced drug acquisition and drug-related toxicity costs, and may potentially reduce the emergence of MDR pathogens, which in turn are very costly to contain and manage. However, if narrow-spectrum empiric antibiotic therapy leads to inappropriate therapy, it may be associated with higher costs due to prolonged mechanical ventilation and length of stay. Due to the large number of patients at risk for MDR pathogens, the guideline panel placed higher value on appropriateness of treatment than on the emergence of resistance or adverse events.

Implementation considerations (figure 1)

The selection of patients with early onset HAP who can safely receive empiric narrow spectrum therapy should be based on an assessment of individual risk factors, severity of illness, and the local frequency of MDR pathogens in the ICU in question. The panel found it reasonable to consider as “low risk” patients without septic shock, with no other risk factors for multiple drug-resistant pathogens and those who are not in hospitals with a high background rate of resistant pathogens.

A prevalence of resistant pathogens in local microbiologic data above 25% (in the ICU caring for the patient, not the hospital as a whole) is considered a high background rate.

When considering antimicrobial treatment, it should be noted that the risk of *C. dificile* infections is increased with third generation cephalosporins compared to penicillins or quinolones.

The panel believes that tailoring antibiotic therapy to the susceptibility data of the aetiological pathogen once microbiologic and clinical response data become available (day 3) represents good practice.

Question 3: When using initial broad spectrum empiric therapy for HAP/VAP, should it always be with two drugs, or can it be with one drug and, if starting with two drugs, do both need to be continued after cultures are available?

We recommend initial empiric combination therapy for high risk HAP/VAP patients to cover Gram-negative bacteria and include antibiotic coverage for MRSA in those patients at risk	• **Strong recommendation** • **Moderate quality of evidence**
If initial combination therapy is started, we suggest continuing with a single agent based on culture results and only consider maintaining definitive combination treatment based on sensitivities in patients with extensive resistant or pan resistant non-fermenting Gram-negative bacteria and CRE (carbapenem-resistant Enterobacteriaceae) isolates	• **Weak recommendation** • **Low quality of evidence**

<u>Evidence on benefits and harms</u>

Combination therapy in comparison to monotherapy showed:

- Reduction in mortality in patients with shock or critically ill due to high-risk life-threatening infections and multidrug-resistant (MDR) bacteria.
- No differences in mortality in patients with low-risk HAP or VAP.
- No differences in treatment failure/cure in patients with low-risk HAP or VAP.
- No differences in super-infections* in patients with VAP.
- No differences in serious adverse events in patients with VAP.

Lower mortality has been reported with combination antimicrobial therapy compared to monotherapy in HAP/VAP patients due to XDR/PDR gram negative bacteria and CRE.

**New, persistent, or worsening signs of infection associated with the isolation of a new pathogen or similar pathogen with a different antibiotic susceptibility profile or site of infection.*

Rationale of recommendation

The panel valued above all the benefits in mortality seen in patients with shock or critically ill due to life-threatening infections and MDR bacteria. Also taken into consideration were the reduced direct costs related to avoiding the overuse of dual broad-spectrum antibiotics and the potentially high costs related to the anticipated drug adverse events and emergence of antibiotic resistance.

Implementation considerations

The first consideration in choosing an empiric therapy is whether the patient is at a high or low risk for both MDR pathogen infection and mortality.

The panel find it reasonable to consider as "high risk HAP/VAP" patients who present HAP/VAP and either septic shock and/or the following risk factors:

- Hospital settings with high rates of MDR pathogens (e.g. above 25%).
- Previous antibiotic use
- Recent prolonged hospital stay (>5 days of hospitalisation)
- Previous colonisation with MDR pathogens

If low risk, recommended empiric therapy is a narrow spectrum agent with activity against non-resistant Gram-negatives and methicillin sensitive *S. aureus* (MSSA). These include ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin.

If high-risk, not in septic shock and being treated in an ICU where a single broad-spectrum agent covers >90% of the likely Gram-negative pathogens, based on a local antibiogram, a single agent can be used against Gram-negatives. If >25% of the *S. aureus* isolates in their ICU are MRSA, an agent with coverage for this should be added to initial empiric therapy (vancomycin or teicoplanin).

If high-risk and severely ill or in septic shock, initial empiric therapy should be with a dual Pseudomonal regimen plus MRSA coverage if their ICU has >25% of *S. aureus* isolates as MRSA. However, if *Acinetobacter* is a possible pathogen, the second agent will need to be colistin. The anti-Pseudomonal beta-lactams include: imipenem, meropenem, cefepime, piperacillin/tazobactam, ceftazidime and aztreonam. If an aminoglycoside is added (an agent that adds additional Gram-negative coverage) it should be chosen from gentamicin, tobramycin and amikacin, but in many ICUs, amikacin is the most active agent in this setting. For ESBL-producing organisms, a third-generation cephalosporin is not reliable, and preferred therapy is with a carbapenem, but there may be some role for cefepime and piperacillin/tazobactam, depending on local susceptibilities.

Question 4: In patients with HAP/VAP can duration of antimicrobial therapy be shortened to 7–10 days for certain populations, as compared to 14 days, without increasing rates of relapsing infections or decreasing clinical cure?

We suggest using a 7- to 8-day course of antibiotic therapy in patients with VAP without immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation or necrotising pneumonia, and with a good clinical response to therapy	• **Weak recommendation** • **Moderate quality of evidence**
We suggest against routine treatment with antibiotics for longer than 3 days in patients with low probability of HAP and no clinical deterioration within 72 hours of symptom onset	• **Weak recommendation** • **Low quality of evidence**

Evidence on benefits and harms

Short course antibiotic therapy in comparison to longer courses showed:

- No differences in overall 28-day mortality (all patients or the subgroup of non-fermenting Gram-negative bacteria).
- No differences in duration of mechanical ventilation.
- No differences in length of ICU stay.
- No significant trend towards more relapses.
- No differences in emergence of resistances (assessed by secondary infections to resistant bacteria).
- More antibiotic-free days.

In patients with suspected HAP but low scores on the CPIS, a 3-day course of antibiotics was associated with a reduced risk of superinfection or resistance compared to the standard duration of treatment.

Rationale of recommendation

The panel considered not only survival and avoidance of relapse as critical end-point variables, but also avoidance of individual (adverse events) and collective (emergence of antimicrobial resistance) collateral damage. All these factors were considered to be more critical than potential therapeutic failure. The panel took into consideration the potentially high costs related to the future emergence of antibiotic resistance with the routine use of a prolonged course of antibiotics and the reduced direct costs related to a short course of antibiotics.

Implementation considerations

This recommendation also includes patients with non-fermenting Gram-negatives, *Acinetobacter* and MRSA with a good clinical response.

Longer courses of antibiotics may be needed in patients with inappropriate initial empiric therapy and should be individualised to the patient's clinical response, specific bacteriologic findings (such as pan drug resistance, MRSA or bacteraemia), and the serial measurement of biomarkers when indicated (See question 6).

The term “low probability HAP” refers to patients with low Clinical Pulmonary Infection Scores (CPIS), or a clinical presentation not highly suggestive of pneumonia (e.g. 6 or lower) at symptom onset and continuing up to 72 hours.

Immunosuppression was defined as leukocytes <1000 μL^{-1}, neutrophils <500 μL^{-1}, acquired or congenital immunodeficiency syndrome, or use of immunosuppressants or long-term corticosteroids ($\geq$0.5 $mg \cdot kg^{-1} \cdot day^{-1}$).

The panel believes that applying the rationale and recommendations used for VAP in non-ventilated patients with hospital acquired pneumonia represents good practice.

Question 5: In patients receiving antibiotic treatment for VAP or HAP, is bedside clinical assessment equivalent to the detection of serial biomarkers to predict adverse outcomes/clinical response at 72–96 h?

We do not recommend routinely performing biomarker determinations in addition to bedside clinical assessment in patients receiving antibiotic treatment for VAP or HAP to predict adverse outcomes and clinical response at 72–96 hours

- **Strong recommendation**
- **Moderate quality of evidence**

Evidence on benefits and harms

- Studies have demonstrated a benefit of serial clinical assessments such as CPIS or SOFA in predicting outcomes as early as day 3 in patients with HAP/VAP.
- Some observational studies have shown a relationship between day 1 to 7 biomarker levels (CRP, PCT, copeptin and MR-proANP) and 28-day mortality or adequacy of antibiotic therapy. Due to the lack of clinical trials, the effectiveness or related costs of a therapy guided by these biomarkers are not known.

Rationale of recommendation

There are no RCTs assessing treatment outcomes of patients with HAP/VAP managed according to clinical evaluation. The panel took into consideration the potentially high costs associated with the detection of serial biomarkers in relation to their limited prognosis capacity.

Implementation considerations

The panel believes that performing routine bedside clinical assessment in patients receiving antibiotic treatment for VAP or HAP represents good practice.

Clinical evaluation usually involves measurement of temperature, tracheobronchial secretion volume, culture and purulence assessment of tracheobronchial secretions, evaluation for chest radiograph resolution, white blood cell count, arterial partial pressure of oxygen/inspiratory fraction of oxygen ratio (PaO_2/FiO_2), and calculation of one or more scores such as CPIS, ODIN, SOFA, SAPSII and APACHEII.

Question 6: In patients with HAP with severe sepsis or VAP, can serum procalcitonin be used to reduce the duration of antibiotic therapy, compared to care that is not guided by serial biomarker measurements?

We do not recommend the routine measurement of serial serum PCT levels to reduce duration of the antibiotic course in patients with HAP or VAP when the anticipated duration is 7 to 8 days

- **Strong recommendation**
- **Moderate quality of evidence**

Evidence on benefits and harms

- In studies of PCT kinetics, although the levels of this biomarker decreased during the clinical course of all VAPs, they were significantly higher on days 1, 3 and 7 in patients with an unfavourable outcome, and predicted a poor outcome in the multivariate analysis.
- Routine determination of serum PCT reduces the duration of antibiotic treatment and 28-day mortality when compared to standard antibiotic therapy, but no differences were seen in in-hospital mortality, failure of pneumonia resolution, overall recurrence, duration of ICU stay and duration of mechanical ventilation.

However, in the studies analysed, intentional short duration therapy (7–8 days) was not routinely used in the standard duration group.

Rationale of recommendation

The panel considered that an equivalent reduction in the antibiotic duration to that seen in the PCT measurement groups in the above-mentioned studies can be achieved by the 7–8 day treatment period suggested for patients with nosocomial pneumonia and without risk factors necessitating longer duration.

Implementation considerations

The panel believes that the measurement of serial serum procalcitonin levels together with clinical assessment in specific clinical circumstances with the aim of reducing antibiotic treatment duration represents good practice. These situations include initially inappropriate antibiotic therapy, severely immunocompromised patients, highly antibiotic resistant-pathogens and second-line antibiotic therapy (*e.g*. colisitin, tigecycline).

Question 7: In patients requiring mechanical ventilation for greater than 48 hours, does topical application of non-absorbable antimicrobials (antibiotics or chlorhexidine) in the oropharynx (SOD) or in the oropharynx and intestinal tract along with intravenous antibiotics (SDD) reduce the risk of VAP occurrence and/or improve patient outcome compared to standard care?

The guideline panel decided not to issue a recommendation on the use of chlorhexidine to perform selective oral decontamination in patients requiring mechanical ventilation	• **No formal recommendation**
We suggest the use of SOD, but not SDD, in settings with low rates of antibiotic-resistant bacteria and low antibiotic consumption	• **Strong recommendation** • **Moderate quality of evidence**

Evidence on benefits and harms

- The use of chlorhexidine was associated with a significant reduction of lower respiratory tract infections, including HAP and VAP, but a non-significant increase in mortality.
- There were no significant differences in mean duration of mechanical ventilation or ICU length of stay.
- In settings with low levels of antibiotic resistance, SOD (with topical non-absorbable antibiotics) and SDD (with oropharyngeal and digestive tube administration of topical non-absorbable antibiotics and intravenous antibiotics) may be associated with reductions in nosocomial pneumonia and death. The potential effects of antibiotic use on antimicrobial resistance are uncertain.

Rationale of recommendation

The absence of a clear payoff between clinical benefits and the potential increase in mortality associated with chlorhexidine and uncertainties regarding the appropriate dose, regimens and formulations prevented the guideline panel from developing recommendations until further evidence becomes available about its effectiveness.

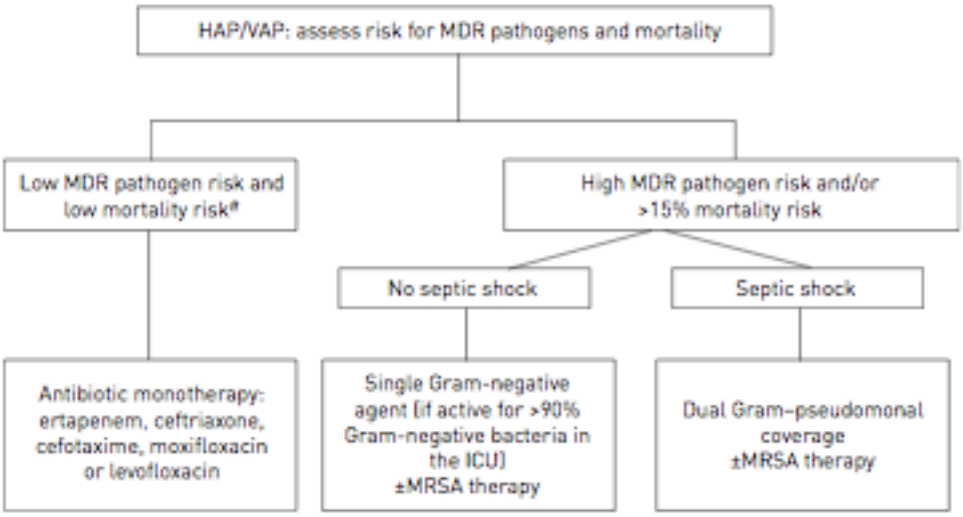
Considering the clinical benefits of SOD vs. SDD to be similar, the guideline panel advocated the use of SOD and avoiding supplementary intravenous antibiotics as in SDD. It should be stressed that all these studies were performed at a time when VAP bundles were not routinely applied and the incremental benefit of SOD and SDD to a VAP bundle is largely unknown. Both SOD and SDD might be cost-saving strategies

Implementation considerations

The potential effect of chlorhexidine use on mortality and its determinants should be studied and the benefits of its use in relation to dose, regimes and formulations should be established

When establishing the cut-off value for low and high resistance settings in determining whether the use of SOD is appropriate, the panel felt that a 5% threshold was reasonable.

Figure 1. Empiric antibiotic algorithm for HAP/VAP



Empiric antibiotic treatment algorithm for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP). MDR: multidrug-resistant; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*. #: low risk for mortality is defined as a ≤15% chance of dying, a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection.