International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

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Original publication available at:
https://doi.org/10.1183/13993003.00582-2017

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International ERS/ESCIM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)

Guidelines for the management of HAP/VAP of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESCMID), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latino-americana del Tórax (ALAT).

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ABSTRACT

The most recent European guidelines and task force reports on hospital-acquired (HAP) and ventilator-acquired pneumonia (VAP) were published almost 10 years ago. Since then, further randomized clinical trials of HAP and VAP have been conducted and new information has become available. Studies of epidemiology, diagnosis, empiric treatment, response to treatment, new antibiotics or new forms of antibiotic administration, and disease prevention have changed old paradigms. In addition, important differences between approaches in Europe and the US have become apparent. The European Respiratory Society (ERS) launched a project to develop new international guidelines for HAP and VAP. Other European societies including the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), were invited to participate, and appointed their representatives. The Latin American Society of Thoracic Diseases (ALAT) was also invited.

A total of 15 experts and two methodologists made up the panel. Three experts from the US were also invited (Michael Niederman, Marin Kollef, and Richard Wunderink).

Applying the GRADE methodology, the panel selected seven PICO questions which generated a series of recommendations for HAP/VAP diagnosis, treatment and prevention.
INTRODUCTION

Hospital-acquired pneumonia (HAP) is an infection of the pulmonary parenchyma caused by pathogens that are present in hospital settings (1). Nosocomial pneumonia develops in patients admitted to the hospital for more than 48 hours, and usually the incubation period is at least two days. Among nosocomial pneumonias, ventilator-acquired pneumonia (VAP) develops in intensive care unit (ICU) patients who have been mechanically ventilated for at least 48 hours. Patients with severe nosocomial pneumonia who require mechanical ventilation during their treatment after the onset of infection do not meet the definition of VAP. In contrast, ventilator-acquired tracheobronchitis (VAT) is characterized by signs of respiratory infection without new radiographic infiltrates, in a patient who has been ventilated for at least 48 hours (2).

HAP is the second most common nosocomial infection and the leading cause of death from nosocomial infections in critically ill patients. Its incidence ranges from five to more than 20 cases per 1000 hospital admissions (1), with the highest rates in immune-compromised, surgical and elderly patients. Approximately one-third of nosocomial pneumonia, and the majority are VAP are acquired in the ICU. US epidemiologic studies report an incidence of VAP of between 2 and 16 episodes per 1000 ventilator-days (3,4). Cook et al (5) estimated the risk of VAP to be 3% per day during the first five days on MV, 2% per day from the fifth to the tenth day, and 1% per day for the remaining days. However, with respect to earlier reports (6), VAP seems to be on the decrease, probably due to better implementation of preventive strategies. In trauma and brain injury patients the incidence is still very high (50%) probably related to the depressed level of consciousness and consequently microaspiration at the time of trauma (7).

Hospital-acquired pneumonia, and most prominently VAP, increase duration of hospitalization and healthcare costs; a recent matched case-control study from a large US database demonstrated longer durations of MV, ICU stay and hospitalization in patients with VAP than in those without. Worse outcomes have been consistently reported over the years (6,7,8), and mean hospital charges per VAP patient have increased by approximately 40,000 US$ (7,8) In a systematic review of economic analyses of health-care associated infections the mean attributable cost of VAP was 9969 $ (9).
In UK (10) a conservative estimated cost was 10,000 pounds which is equivalent to 7 extra days of ICU. 350 pounds was the estimated price of any preventive measure to be considered cost-benefit (10). In Turkish University Hospitals (11) the mean cost of ICU patients with VAP was 4 times greater compared to those without VAP.

Healthcare-associated pneumonia (HCAP) develops in non-hospitalized patients (1) who have multiple risks for being colonized by nosocomial multidrug-resistant (MDR) pathogens. Risk factors for developing HCAP are hospitalization for 2 days or more within the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy, chronic dialysis, home wound care, and contact with subjects colonized by MDR pathogens. Studies in the US (12) have reported that HCAP is often caused by MDR microorganisms in critically ill patients; in contrast, European data (13) suggest that the etiology in HCAP patients is similar to that of community-acquired pneumonia, and that these patients are often not critically ill. For this reason, HCAP management is not covered in these guidelines.

The time of onset of nosocomial pneumonia also affects the possible etiology, empirical antimicrobial treatment, and outcomes (14). Previously, VAP was categorized as either early or late onset (15). In an interesting study by Trouillet et al. (16), specific risk factors were strongly associated with infection by MDR pathogens: duration of MV $\geq$ 7 days (odds ratio [OR] = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum drugs (OR = 4.1). More recent reports (17-20) have challenged this classification; indeed, some investigators have found comparable etiologies in patients with early or late onset VAP. This may be related to the worldwide rise in MDR pathogens, and emphasizes that the local ICU ecology is the most important risk factor for acquiring MDR pathogens, irrespective of the length of intubation. The initial HAP or VAP severity (e.g., septic shock) is also a strong risk factor for MDR pathogens, regardless of time of onset.

The crude mortality of nosocomial pneumonia may be as high as 70% (1). Several reports have estimated that a third to a half of all VAP-related deaths are the direct result of the infection, with a higher mortality rate in cases caused by *P. aeruginosa* (21).
and *Acinetobacter* spp. (21,22). Attributable VAP mortality is defined as the percentage of deaths that would not have occurred in the absence of the infection. Recent studies have reappraised the impact of VAP on mortality (23-25). In particular, the risk of VAP is time-dependent, as mentioned above, and this may cause a significant time-dependent bias because mortality and ICU discharge act as competing endpoints. Thus, the most recent studies reported an attributable mortality of 10% (25,26), with surgical patients and those with mid-range illness severity presenting the highest associated risk.

In 2005 the ATS/IDSA published evidence-based guidelines for the management of HAP/VAP (1). A task-force of three European societies – the European Respiratory Society (ERS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Society of Intensive Care Medicine (ESICM) – also published recommendations for HAP and VAP (27). Since those guidelines were published, a great deal of progress has been made in the understanding of HAP/VAP: for example, with regard to the different forms of the disease (specifically ventilator-associated tracheobronchitis (VAT) and VAP), new knowledge about MDR pathogens, new studies for validating guidelines, the bacteriology of HAP in non-intubated patients, new drug development and new trials of aerosolized antibiotics, and new evidence and concepts regarding prevention (e.g., the zero-VAP concept). In addition, regulatory agencies are trying to find surrogate endpoints to replace 28-day mortality and to improve the design of randomized clinical trials in this field of investigation. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) published their latest guidelines in July 2016 (28). These guidelines differ from the previous recommendations published in 2005 in introducing the use of GRADE methodology for the evaluation of all available evidence, in removing the concept of HCAP, in using antibiograms to guide antibiotic treatments, and in administering short-course therapy for most HAP or VAP patients regardless of their microbial etiology, as well as antibiotic de-escalation.

The ERS, ESCMID, ESICM and the ALAT all support new evidence-based guidelines for HAP/VAP and have appointed a panel of experts to develop clinical recommendations. Although IDSA/ATS were also developing new guidelines, the panel
thought that a European perspective was needed in view of the differences between the US and European approaches in several areas, which we list here:

1. Ventilator-associated complications (VAC) (29) is a surrogate measure of VAP which has become very popular in the US in recent years for benchmarking purposes. However, because of its lack of sensitivity and specificity it has not been widely implemented in Europe.
2. There are differences in the definitions of HAP and VAP.
3. Diagnosis of HAP/VAP is still a matter of controversy, particularly with regard to the role of quantitative cultures and bronchoscopic sampling. Different approaches are applied in Europe and the US (1,28).
4. The efficacy of certain antibiotics varies widely in different geographic regions, as does the frequency of MDR pathogens in different European countries (17).
5. Attitudes and beliefs about how to best prevent pneumonia, including the use of selective digestive decontamination (SDD), differ considerably. This is due mainly to the wide variation in VAP incidence between Europe and the US (28,29). In particular, following an extensive implementation of ventilator bundles in the last decade in the US there has been a consistent drop in VAP rates. This is not the case in Europe where incidence remains high in many ICUs, in spite of the consistent use of ventilator bundles (30).
6. Antimicrobial stewardship is an important issue in both Europe and the United States, but the approach to this problem in the two continents differs considerably, particularly in relation to the need for prior authorization of certain antibiotics before their use in the ICU as part of empiric therapy (31). In addition, in some European countries, there is such a strong emphasis on stewardship, that physicians may be reluctant to use broad-spectrum empiric therapy that is intended to target at least 95% of the likely pathogens, an implied goal of the latest IDSA/ATS guidelines.
SCOPE AND PURPOSE

The purpose of this document is to provide guidance on the most effective treatments and management strategies for adult patients with HAP and VAP. The recommendations reported in this guideline may not apply to patients with a secondary immune deficiency (related to HIV infection, treatment, or disease-induced immunosuppression) or primary immune deficiency; in these patients, HAP and VAP can be caused by a broad spectrum of microorganisms and the diagnostic and therapeutic approaches are very different.

These guidelines are intended mainly for specialists in respiratory medicine and critical care managing adults with HAP or VAP. They may also be of interest to general internists, specialists in infectious diseases, pharmacists, microbiologists, and policy makers.

METHODS

These guidelines were developed by a committee of experts from the ERS, ESCIM, ESCMID and ALAT. The committee included specialists in respiratory medicine with expertise in the management of patients with lung infections, intensive care specialists, as well as microbiologists and methodologists with experience in evidence synthesis and guideline development.

The committee’s first face-to-face meeting was held in February 2013, where a total of seven clinical questions were formulated. The guideline process continued with a series of telephone conferences and electronic-based discussions between committee members. A second face-to-face meeting was held in Barcelona (February 2015) to decide on the guideline recommendations.

In collaboration with the methodologists, a search strategy was designed using key terms and keywords for each clinical question. The search was limited to human studies (systematic reviews, randomized clinical trials or observational studies) written in
English. The Pubmed platform was used to search MEDLINE. The Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR) and the National Health Services Economic Evaluation Database (EED) were also searched to find additional studies and economic evaluations. All searches were performed until December 2014 and guideline panel members monitored the literature relevant to their assigned clinical question up to September 2016. The search retrieved 5,560 citations; after the review of title and abstract and full-text when needed, a total of 109 references were included for analysis (figure 1).

Assessment of the level of evidence and grade of recommendations

Evidence levels and recommendation grades used in this guideline followed the GRADE methodology (32,33). The GRADE has four levels of evidence: high, moderate, low and very low. Recommendations are classified as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of the management options compared, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation. Recommendations and their strength were decided by consensus and, if required, by voting. Online Supplement Table 1 provides a suggested interpretation of these recommendations by the targeted stakeholders, who include patients, clinicians and health policy makers.

These guidelines will be considered for revision in 2020, or sooner if relevant new evidence becomes available.
**PICO QUESTIONS AND RECOMMENDATIONS**

In Table 1 all PICO questions and corresponding recommendations are listed.

**Table 1. PICO Questions and Recommendations**

<table>
<thead>
<tr>
<th>Title</th>
<th>Recommendations</th>
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| **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 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)**. |
| **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 recommendation, very low quality of evidence)**.  
Remarks:  
The risk of C.dificile infections is increased with third Generation cephalosporins compared to penicillins or quinolones. 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. However, the presence of other clinical conditions may make individuals unsuitable for this recommendation. The rate of resistant pathogens is highly variable across different countries, settings and hospitals. A prevalence of resistant pathogens in local microbiologic data above 25% is considered a high background rate (the rate of resistance in the ICU caring for the patient (not the hospital as a whole) is the relevant factor to consider). |
**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).*

Remarks:

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 for potentially resistant microorganisms:

- Hospital settings with high rates of MDR pathogens.
- Previous antibiotic use
- Recent prolonged hospital stay (>5 days of hospitalization)
- Previous colonization with MDR pathogens

The rate of resistant pathogens varies widely across different countries, settings and hospitals. However, a prevalence of resistant pathogens in local microbiologic data above 25% represents a high risk situation (including Gram-negative bacteria and MRSA).

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...
<table>
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<tr>
<th>Question 4</th>
<th>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?</th>
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<td></td>
<td>We suggest using a 7- to 8-day course of antibiotic therapy in patients with ventilator-associated pneumonia (VAP) without immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation or necrotizing pneumonia, and with a good clinical response to therapy (Weak recommendation, moderate quality of evidence). Remarks: This recommendation also includes patients with non-fermenting Gram-negatives, <em>Acinetobacter</em> and MRSA with a good clinical response. Longer courses of antibiotics may be needed in patients with inappropriate initial empiric therapy and should be individualized to the patient's clinical response, specific bacteriologic findings (such as pan drug resistance, MRSA or bacteremia), and the serial measurement of biomarkers when indicated (See PICO 6 and Table 3). The panel believes that applying the rationale and recommendations used for VAP in non-ventilated patients with hospital acquired pneumonia represents good practice (Good practice statement). 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).</td>
</tr>
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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).

The panel find it reasonable to consider selected patients at low risk for MDR pathogens (see PICO 2) and some patients at high risk for MDR pathogens for initial empiric monotherapy, if there is a single antibiotic therapy that is effective against >90% of Gram-negative bacteria according to the local antibiogram. However, other clinical conditions, particularly severe illness or septic shock, may make individuals unsuitable for this recommendation.
<table>
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<tr>
<th>Question 5</th>
<th>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 72-96h?</th>
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<tr>
<td>Remarks:</td>
<td>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.</td>
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<tr>
<td>Question 5</td>
<td>The panel believes that performing routine bedside clinical assessment in patients receiving antibiotic treatment for VAP or HAP represents good practice (Good practice statement).</td>
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<tr>
<td>Remarks:</td>
<td>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 (PaO2/FiO2), and calculation of one or more scores such as CPIS, ODIN, SOFA, SAPSII and APACHEII.</td>
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<tr>
<td></td>
<td>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).</td>
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<tr>
<td>Remarks:</td>
<td>Biomarker determinations may include C-reactive protein (CRP), procalcitonin (PCT), copeptin, and mid-regional pro-atrial natriuretic peptide (MR-proANP). Clinicians should take into consideration the availability, feasibility and costs of each biomarker before routine testing.</td>
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<tr>
<th>Question 6</th>
<th>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?</th>
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<td>Remarks:</td>
<td>We do not recommend the routine measurement of serial serum procalcitonin (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).</td>
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The panel believes that the measurement of serial serum procalcitonin levels together with clinical assessment in specific clinical circumstances (see table 3) with the aim of reducing antibiotic treatment duration represents good practice (Good practice statement).

<table>
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<tr>
<th>Question 7</th>
<th>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? (Standard care being treatment dispensed in the intensive care unit (ICU) by the medical team in their usual manner.)</th>
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<tr>
<td>The guideline panel decided not to issue a recommendation on the use of chlorhexidine to perform selective oral decontamination in patients requiring mechanical ventilation until more safety data become available, due to the unclear balance between a potential reduction in pneumonia rate and a potential increase in mortality (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 (Weak recommendation, low quality of evidence). Remarks: Although establishing a cut-off value for low and high resistance settings is a dilemma, the committee felt that a 5% threshold was reasonable.</td>
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</table>
**Question #1: In intubated patients suspected of having VAP, should distal quantitative samples be obtained instead of proximal quantitative samples?**

**RECOMMENDATIONS**

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 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).

**Benefits and harms**

Invasive techniques require the participation of qualified clinicians, may compromise gas exchange during the procedure, and may be associated with higher direct costs (34-37). However, a pooled analysis of five RCTs (34) did not show any difference in overall mortality between VAP patients diagnosed through invasive or non-invasive techniques (see online supplement, profile 2). No RCTs have compared qualitative and quantitative cultures of the same bacteriological sample. 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. However, antibiotic therapy for a current episode of HAP/VAP can alter and modify the results from quantitative cultures when samples are obtained within 48 hours of starting a new antibiotic regimen.

Three RCTs have compared the effectiveness of invasive methods using quantitative cultures versus non-invasive methods using qualitative cultures (34,35,37). A pooled analysis did not show any significant influence of the approach used on the change of the initial antibiotic regimen (34). The studies were not blinded and the results varied widely. The fact that some investigators may be reluctant to withhold therapy until quantitative results are available may explain these findings.
The number of antibiotic free-days was assessed in two RCTs although the results were not pooled (34,35). In one study with 413 patients, the invasive distal quantitative strategy was combined with an algorithm for treatment de-escalation and led to a significant increase in the day-14 antibiotic free-days ($5.0 \pm 5.1$ vs. $2.2 \pm 3.5$) and day-28 antibiotic free-days ($11.5 \pm 9.0$ vs. $7.5 \pm 7.6$), in comparison to non-invasive methods using qualitative cultures. The difference was statistically significant for all antibiotic classes except carbapenems (37). In that study, all microorganisms recovered from qualitative culture including potentially non-pathogenic organisms, such as coagulase-negative *Staphylococci*, were treated and antibiotics may have been overused in the qualitative proximal culture arm (37). In the Canadian Critical Care Trial Group study, the day-28 antibiotic-free days were similar between groups (34). In that study, there were no clear recommendations on antimicrobial de-escalation and the research protocol may have facilitated appropriate discontinuation of antibiotics or targeted therapy in the two groups, thus minimizing the differences between them (34).

Overall mortality, ICU length of stay and duration of mechanical ventilation did not show differences between the two interventions in a pooled analysis (34). The potential downsides of narrowing antimicrobial therapy in response to the results of quantitative cultures have also been evaluated in cohort studies, in which this diagnostic strategy was not associated with an increase in mortality or length of stay (37,38) (see online supplement, profile 1).

Non-invasive diagnostic methods (e.g., endotracheal aspirate collection) led to an over-identification of bacteria by initial direct examination of samples. In one clinical trial, bacterial identification was achieved by endotracheal qualitative aspirates in 86% of the patients, but in only 43% with the use of bronchoscopic distal quantitative methods (35). This important difference in bacterial identification may explain the reduction in antibiotic-free days and overall antibiotic exposure between the two approaches seen in previous trials. The link between antibiotic use and antibiotic resistance both inside a unit and at an individual level on the infecting flora and on the gut microbiota has been clearly identified (39). Moreover, a recent observational study in 89 patients with
clinically suspected VAP and a negative (<$10^4$ colony forming units/mL) quantitative bronchoalveolar lavage compared patients with early (within one day) and late antibiotic discontinuation. Despite similar severity scores, there were no differences in mortality between patients with early (25.0%) and late discontinuation (30.6%). There were significantly fewer superinfections (22.5% vs. 43%), respiratory superinfections (10.0% vs. 29.0%), and multidrug resistant superinfections (7.5% vs. 36%), in the early than in the late discontinuation group (40).

Nevertheless, 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 (35,37,41,42). This may not be feasible in all situations. In practice, when antimicrobials have recently been modified, both qualitative and quantitative samples lose their sensitivity and specificity (43-47). A negative finding indicates either that the patient has been successfully treated for pneumonia and that the bacteria were eradicated (but de-escalation may not always be possible), or that the lung infection was not present to begin with (leading to an active search for other diseases and withdrawal or adjustment of antimicrobial therapy). To cope with this problem, if bacteriological analyses are not available immediately, processing of a bacteriologic specimen collected after refrigeration can offer good reliability (48).

The guideline panel noted that invasive techniques using quantitative cultures are widely available and feasible at most of the specialized centers that care for patients with VAP. Panel members felt that the overall benefits in terms of antibiotic exposure probably outweigh the harms in comparison to non-invasive methods using qualitative cultures, particularly if samples are collected before new antibiotics are started. 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.
Relative importance of the outcomes

The panel placed greater value on the potential benefits of reducing antibiotic exposure (and its impact on antibiotic resistance) than on the potential complications of invasive techniques. However, there is some concern that if the procedure is performed shortly after a recent change in antibiotics, or at a center without technical expertise, a false negative result may mean that patients are not treated in an efficient and timely manner.

Resource use

No appropriate cost-effectiveness studies have been identified. 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.
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?

RECOMMENDATIONS

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 recommendation, very low quality of evidence)

Remarks:
The risk of C. difficile infections is increased with third generation cephalosporins compared to penicillins or quinolones.

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. However, the presence of other clinical conditions may make individuals unsuitable for this recommendation. The rate of resistant pathogens is highly variable across different countries, settings and hospitals. A prevalence of resistant pathogens in local microbiologic data above 25% is considered a high background rate (the rate of resistance in the ICU caring for the patient (not the hospital as a whole) is the relevant factor to consider).

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 PICO 3) (Strong recommendation, low quality of evidence)
The panel believes that tailoring antibiotic therapy to the susceptibility data of the etiologic pathogen once microbiologic and clinical response data become available (day 3) represents good practice (Good practice statement)
**Benefits and Harms**

The efforts to define a population of nosocomial pneumonia patients who can receive appropriate narrow-spectrum empiric antibiotic therapy rather than broad-spectrum multidrug therapy may help to prevent the overuse of our most effective antibiotics and thus avoid future resistance. In addition, the use of a focused, narrower spectrum regimen may forestall some of the side effects associated with the use of multiple, broad-spectrum antibiotics.

Our search did not find any randomized controlled trials comparing the effectiveness of broad-spectrum and narrow-spectrum empiric antibiotic use in patients with anticipated low risk MDR pathogens. Available RCTs comparing mono versus dual empirical antibiotic therapy in patients with VAP/HAP have specifically excluded patients with high disease severity. Even in this population, all patients received broad-spectrum antibiotics.

Time of onset of pneumonia has been extensively described in the literature as an important risk factor for specific pathogens, mainly MDR pathogens. Early-onset HAP and VAP, defined as occurring within the first 4 days of hospitalization, 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 hospitalization) are more likely to be caused by MDR pathogens, and are associated with increased patient mortality and morbidity (17). However, even with early onset HAP/VAP, the presence of other classic risk factors for resistance narrows the population that might potentially benefit from less broad spectrum therapy (1,18). These risk factors have been identified as: previous antimicrobial therapy or hospitalization (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 (1,18).

Several studies showed that the percentage of MDR pathogens among patients with early-onset VAP varied from as low as 10% to as high as 51%. In general, if the overall incidence of MDR pathogen VAP is > 25%, the frequency of MDR pathogens in early
onset pneumonia is similar to the overall frequency of MDR pathogens causing nosocomial pneumonia (Table 2 and online supplement, profile 3).

One prospective observational cohort study of 689 mechanically ventilated patients with nosocomial pneumonia showed that 152 out of 485 patients with a confirmed microbiologic diagnosis had early onset (< 5 days of MV) pneumonia with no classic risk factors for MDR pathogens. Seventy-seven of these 152 patients (51%) were infected with potentially resistant microorganisms, and these organisms were associated with the presence of severe sepsis or septic shock (OR 3.7) and the development of pneumonia in centers with a prevalence of MDR pathogens of above 25% (OR 11.3) (18) (see online supplement, profile 3).

One further prospective observational study in 276 patients with ICU-acquired pneumonia (146 with VAP) classified patients into early-onset without risk factors for MDR pathogens (38 patients) and late-onset or with risk factors for MDR pathogens (238 patients) according to the 2005 ATS/IDSA guideline (1,19). The incidence of MDR pathogens did not differ between the two groups (26% and 29%, respectively). However, there were some patients with early onset pneumonia who did not have classic risk factors for MDR pathogens; 46% had current or former alcohol abuse, 37% recent surgery, 34% chronic heart disease, 24% chronic lung disease, 24% diabetes mellitus and 18% had previous use of corticosteroids. Only 18% of the patients with early-onset and no risk factors for MDR pathogens underwent therapy that complied with the recommendations of the 2005 ATS/IDSA guideline regarding the use of limited spectrum antibiotic therapy and from those 43% presented initial non-response to therapy (19) (see online supplement, profile 4).

In another prospective cohort study assessing the risk factors for the isolation of pathogens that are potentially resistant to multiple drugs in ICU-acquired pneumonia, the strongest predictors for infection with MDR pathogens were older age and prior antibiotics either as prophylaxis (OR 4.6) or as therapy (OR 8.2) 95% In that study, an early-onset HAP was defined as occurring in less than 5 days of admission, and 52% of this population had MDR pathogens. The risk of infection with either *Pseudomonas*
*aeruginosa* or ESBL-producing organisms rose in parallel with time in the ICU, occurring in only 10% of infections that began less than 4 days after the admission, but in 34% of infections beginning between days 6 and 9 after admission (49) (see online supplement, profile 3).

In an observational prospective cohort study including 124 patients with bacteriologically confirmed HAP and an overall incidence of MDR pathogens of 30%, the multivariate analysis identified certain factors associated with a lower risk of MDR pathogens. The combination of these factors in a cohort of 26 patients allowed the validation of an algorithm that identified all patients with antimicrobial susceptible HAP. The absence of prior antimicrobial treatment, the presence of prior antimicrobial treatment with neurologic disturbances on ICU admission and early-onset pneumonia, and the presence of prior antimicrobial treatment without neurologic disturbances but with aspiration on ICU admission were always associated with antimicrobial-susceptible HAP (50).

The major concern when using empiric narrow-spectrum therapy, even in selected patients, is that not all the etiologic pathogens will be treated if the patient is actually infected with an MDR pathogen. A prospective observational study conducted to define the impact of bronchoalveolar lavage (BAL) data on the selection of antibiotics and the outcomes of patients with ventilator-associated pneumonia (VAP) concluded that when adequate antibiotic therapy was initiated early in patients with a strong clinical suspicion of VAP, the mortality rate (38%) was lower in comparison with inadequate therapy (91%) or no therapy (60%). Even when patients were switched to an adequate therapy when BAL data became available, mortality was comparable to those who continued to receive inadequate therapy (51).

In addition, a prospective cohort study carried out to assess the rate of appropriateness of empirical antimicrobial therapy in 115 VAP patients showed that the mortality rate was significantly higher in the patients with inappropriate empirical therapy than in those with appropriate treatment (47% and 20%, respectively). A limited-spectrum therapy was used in 79 patients (69%) according to the criteria of early-onset VAP (<5 days)
without recent prior hospitalization or prior antibiotic treatment. In 21 patients out of 79 (27.%) treatment was escalated by either adding another antibiotic, using broader spectrum therapy, or both (52) (see online supplement, profile 4).

A group of observational retrospective or cohort studies including mixed populations has suggested the presence of other additional factors related to either an increase or a decrease of MDR pathogen incidence. Age over 65 years was associated with a higher risk of MRSA infection (53); gastric acid suppressive therapy, tube feeding, chronic dialysis and congestive heart failure may increase the incidence of MDR pathogens in either hospital or community acquired pneumonia (54). Surgery can be a surrogate marker of prior antibiotic therapy as a prophylaxis which was associated with a high incidence of Gram-negative bacteria or staphylococcal early onset pneumonias (51). Acute renal failure was associated with a higher risk of community acquired pneumonia (CAP) due to \textit{P. aeruginosa}, ESBL-producing Enterobacteriaceae, and MRSA (52). Early aspiration in patients who have been resuscitated from cardiac arrest has been associated with a relatively low frequency of MDR pathogens (57).

**Relative Importance of the Outcomes**

The direct consequences of narrow or broad-spectrum empiric antibiotic therapy in patients with a low probability of MDR pathogens have not been assessed. The guideline panel considered that the appropriateness of treatment is an adequate surrogate outcome for the important direct consequences of empiric treatment. 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.

**Resource Use**

There are no cost effectiveness studies comparing the use of using narrow or broad-spectrum empiric therapy in HAP or VAP.
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, it still remains to be determined whether the use of a narrow spectrum agent in appropriate patients will lead to a cost benefit.

In contrast, 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.

Some data point to a higher utilization of resources when MDR pathogens are present. In a large European study, patients with potentially resistant microorganism HAP had fewer ventilator free days, longer ICU stay, longer hospital stay and more use of combination antibiotic therapy (17). Similarly, a study of 200 VAP patients found that patients with MDR infection had longer ICU stay and mechanical ventilation than patients without these pathogens (53).

**Balance between desirable effects and undesirable effects**

The percentage of potentially MDR pathogens is significant even in early-onset HAP/VAP, and several studies have also identified risk factors for MDR pathogens in patients with either nosocomial or healthcare-associated pneumonia (HCAP), regardless of the time of infection onset (20). In consequence, if certain factors (other than the classic MDR risk factors) are present, this might lead to the presence of MDR pathogens in a patient with early-onset VAP, and the use of narrow spectrum therapy would not be an appropriate choice.

At the present time, the number of patients with early onset HAP who can safely receive empiric narrow spectrum therapy is limited. Selection 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. Inappropriate therapy may increase non-response to
therapy, which can in turn prolong the duration of mechanical ventilation, antibiotic use, and ICU length of stay, and may also increase inpatient mortality.

Even though there are doubts about the effectiveness of using broad-spectrum empiric antibiotic therapies in most patients with suspected HAP/VAP, the guideline panel considers that the potential benefits outweigh the risks.

If the use of a narrow spectrum agent as empiric therapy is possible in a selected group of patients, this may reduce the emergence of antibiotic-resistant organisms in intubated ICU patients, since antibiotic use is known to promote subsequent resistance in both individual patients and in the ICU in general. In addition, avoidance of multiple, broad spectrum drugs may avoid drug-related toxicities including drug-induced renal insufficiency (e.g., with the use of nephrotoxic agents such as aminoglycosides and vancomycin) (58).

In the future, as rapid diagnostic tests (particularly polymerase chain reaction, PCR) become available (59), it may be possible to rely on the high sensitivity (i.e., the ability to detect both colonizing and infecting pathogens) of these methods and to select a narrow spectrum empiric therapy if no MDR pathogens are identified from a deep respiratory tract sample (endotracheal aspirate or bronchoalveolar lavage).
Table 2: Relationship between the frequency of multi-drug-resistant pathogens in early onset nosocomial pneumonia vs. the overall frequency of multi-drug-resistant pathogens causing hospital-acquired pneumonia

<table>
<thead>
<tr>
<th>Study – Year (ref)</th>
<th>% MDR in EOP</th>
<th>% MDR in HAP Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montravers – 2002 (ref 55)</td>
<td>similar to overall</td>
<td>34%</td>
</tr>
<tr>
<td>Leroy – 2003 (ref 50)</td>
<td>19%</td>
<td>30%</td>
</tr>
<tr>
<td>Ferrer – 2010 (ref 19)</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>Perbet – 2011 (ref 57)</td>
<td></td>
<td>similar to overall</td>
</tr>
<tr>
<td>Restrepo – 2013 (ref 20)</td>
<td>27.8%</td>
<td>30%</td>
</tr>
<tr>
<td>Martin-Loeches – 2013 (ref 18)</td>
<td>51%</td>
<td>57%</td>
</tr>
<tr>
<td>Arvanitis – 2014 (ref 53)</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>Verhamme – 2007 (ref 49)</td>
<td>52%*</td>
<td>--</td>
</tr>
</tbody>
</table>

Early-onset pneumonia was defined as occurring ≤5 days of admission

MDR: multidrug resistant; EOP: early onset pneumonia; HAP: hospital acquired pneumonia
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?

RECOMMENDATIONS

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)

Remarks:

The panel finds it reasonable to consider as “high risk HAP/VAP” patients who present HAP/VAP and either septic shock and/or the following risk factors for potentially resistant microorganisms:
- Hospital settings with high rates of MDR* pathogens.
- Previous antibiotic use
- Recent prolonged hospital stay (>5 days of hospitalization)
- Previous colonization with MDR* pathogens

The rate of resistant pathogens varies widely across different countries, settings and hospitals. However, a prevalence of resistant pathogens in local microbiologic data above 25% represents a high risk situation (including Gram-negative bacteria and MRSA).

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 XDR/PDR* non-fermenting Gram-negative bacteria and CRE (carbapenem-resistant Enterobacteriaceae) isolates (Weak recommendation, low quality of evidence).
*MDR: Multidrug resistant microorganism; A pathogen not susceptible to at least one agent from 3 or more classes of antibiotics
*XDR: Extensive resistant microorganism. A pathogen susceptible to only one or two classes of antibiotics
*PDR: Pan drug resistant microorganism. A pathogen not susceptible to all antibiotics

**Remarks:**

The panel find it reasonable to consider selected patients at low risk for MDR pathogens (see PICO 2) and some patients at high risk for MDR pathogens for initial empiric monotherapy, if there is a single antibiotic therapy that is effective against >90% of Gram-negative bacteria according to the local antibiogram. However, other clinical conditions, particularly severe illness or septic shock, may make individuals unsuitable for this recommendation.

**Benefits and harms**

Most published observational data suggest that survival of ICU patients with severe bacterial infections, including HAP/VAP, depends on early initiation of effective antimicrobial treatment: i.e., the etiologic microbe is sensitive to the therapeutic agent, and the dose administration route and infusion duration are optimal (60,61). However, several studies in critically ill patients also suggest that combination broad-spectrum therapy may be associated with greater toxicity and is a risk factor for the later emergence of multi-resistant organisms and increased rates of superinfection (16,58,62-64).

We identified one systematic review (65) and one meta-analysis (66) which included 11 randomized controlled trials comparing combination with monotherapy therapy for the empirical treatment of VAP. Of the 1,805 patients enrolled in these trials, 85% were ventilated and 14% were infected with Pseudomonas spp. Only two studies included late-onset VAP, and most excluded patients with septic shock and/or those with severe disease, as assessed by APACHE II score or other scoring systems. Monotherapy consisted of a broad spectrum beta-lactam with anti-pseudomonal activity in all studies.
except one, in which levofloxacin was used. Combination therapy consisted of a regimen combining a beta-lactam and a fluoroquinolone (two RCTs) or an aminoglycoside (9 RCTs). Rates of mortality and treatment failure for combination therapy compared with monotherapy were similar in the two treatment options (8 RCT). These results did not change in the sensitivity analyses of high-quality trials, trials enrolling only ventilated patients, and trials including patients with clinically suspected pneumonia or microbiologically proven pneumonia. There were no significant differences in rates of superinfection or serious adverse events. Similar results were obtained in four RCTs comparing dual versus single antibiotic therapy for HAP/VAP (67-70) (see online supplement, profile 5 and 6).

Interestingly, these results corroborate those of other RCTs conducted in ICU patients with severe sepsis or bloodstream infection (71) and other meta-analyses which have compared dual-antibiotic therapy versus monotherapy in settings other than the ICU and in different subsets of patients with other types of infection (72).

However, a substantial fraction of HAP/VAP episodes are associated with septic shock or severe disease or are now caused by MDR Gram-negative pathogens (GNB), including XDR and PDR (18,73,74). In these patients, a regimen initially combining two antibiotics targeting GNB may increase the proportion of appropriately treated patients, and may increase the rate of bacterial killing. Indeed, several observational studies have shown that the use of a regimen which initially combines a broad-spectrum beta-lactam with an aminoglycoside increases the proportion of patients appropriately treated compared to monotherapy or to a regimen combining a beta-lactam with a fluoroquinolone, particularly when the infection is due to a MDR GNB, such as extended-spectrum β-lactamase–producing Enterobacteriaceae, Pseudomonas aeruginosa, or Acinetobacter (75-79).

In addition, a systematic review and meta-analysis of randomized and observational studies concluded that combination antibiotic therapy decreased deaths related to high-risk life-threatening infections (particularly those associated with septic shock, and including those with HAP/VAP) (80,81). Data were only calculated for monotherapy with
a beta-lactam and/or fluoroquinolone (as the primary treatment) and for combination treatment with these same primary agents. While the pooled analysis did not show differences in infection-related mortality between combination and monotherapy, the individual study estimates varied widely. In patients with shock/critical illness, combination therapy was associated with a significantly lower risk of death compared with monotherapy (12 studies; OR 0.51,) (see online supplement, profile 7). A reduction in 28-day mortality was also seen in a recent retrospective cohort study in 4662 cases of culture-positive bacterial infection with septic shock treated with appropriate combination vs. appropriate monotherapy (1 study, 2446 patients; HR 0.77) (81). The beneficial impact of combination therapy was restricted to patients treated with beta-lactams in combination with aminoglycosides, fluoroquinolones, or macrolides/clindamycin.

Available RCTs comparing dual and mono antibiotic therapy in patients with VAP/HAP have specifically excluded patients with high disease severity. However, observational data suggest that combination antibiotic therapy (mainly with a broad-spectrum beta-lactam combined with an aminoglycoside) may reduce mortality in comparison to single therapy. The guideline panel considered that the reduction in mortality and other potential benefits outweigh the potential harms of combination antibiotic therapy in this subset of patients.

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. 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 (figure 2). For those at low risk, the recommended empiric therapy is a narrow spectrum agent with activity against non-resistant Gram-negatives and methicillin-sensitive S. aureus (MSSA). recommended choices are ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin. The use of third generation cephalosporins increases the risk of C. difficile infections and MDR spread compared to penicillins or quinolones.
For the high risk population, at risk for MDR pathogens, initial empiric therapy is determined by whether the patient is has septic shock or not. For those who are not in septic shock, and who are treated in an ICU where a single broad-spectrum agent is active against > 90% of the likely Gram-negative pathogens, based on a local antibiogram, a single agent can be used against Gram-negatives. This should be chosen from agents that are active against \textit{P. aeruginosa}, including: imipenem, meropenem, cefepime, piperacillin/tazobactam, levofloxacin or ceftazidime. If there is no risk for MRSA present in these patients, then any of the monotherapy agents that are active against Pseudomonas would be an effective choice, with the exception of aztreonam, which has no Gram-positive activity and should have another agent added to cover MSSA.

For high risk patients who are not in septic shock, but who are treated in an ICU where > 25% of the \textit{S. aureus} respiratory isolates in their ICU are MRSA, an agent with coverage for this pathogen should be added to initial empiric therapy. As discussed above, this involves choosing between vancomycin and linezolid.

For the high risk patient, who is severely ill or in septic shock, initial empiric therapy should be with a dual Pseudomonal regimen plus MRSA coverage, the latter if the ICU has > 25% of \textit{S. aureus} respiratory isolates as MRSA. The dual Pseudomonal regimen should also be chosen to provide coverage for \textit{Acinetobacter} spp and ESBL-producing \textit{Enterobacteriaceae}, if these pathogens are prevalent in the ICU where the patient is being treated. The Gram-negative regimen should include an anti-Pseudomonal beta-lactam plus a second agent such as an aminoglycoside or an anti-Pseudomonal quinolone (ciprofloxacin or levofloxacin). However, in some ICUs, particularly if \textit{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.

**Continuation of antibiotic therapy**

Clinical trials and observational studies have assessed initial empiric administration of single antibiotic treatment or combination of antibiotics, but few have addressed the continuation of combination therapy. The two most relevant reasons for prescribing combined antibiotics for the entire treatment duration are to enhance treatment efficacy and prevent resistant-strain emergence. However, such regimens did not prevent antimicrobial-resistance emergence during therapy, and were associated with significantly higher nephrotoxicity (72).

In most situations treatment can be safely switched to monotherapy after 3–5 days, provided that the initial therapy was appropriate, the clinical evolution is favorable, and microbiological data do not indicate the presence of very difficult-to-treat microorganisms such as XDR/PDR GNB and carbapenem-resistant Enterobacteriaceae. For these latter situations, multiple observational studies have reported lower mortality with combination antimicrobial therapy than with monotherapy (82-84). The outcomes appear to be especially favorable when patients receive treatment with a carbapenem and a second agent such as colistin, tigecycline, and gentamicin for the duration of treatment, but the best approach is yet to be defined (83,84).

The guideline panel considered that continuing a regimen combining two effective antibiotics for the entire duration of treatment of therapy probably has more undesirable than beneficial effects, except in patients with infection caused by an XDR/PDR pathogen.
Relative importance of the outcomes

The panel valued above all the benefits in mortality and placed equal value on the avoidance of drug adverse events and emerging antibiotic resistance.

Resource use

No appropriate cost-effectiveness studies were identified. The panel took into consideration 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 the emergence of antibiotic resistance with the routine prolonged use of dual broad spectrum antibiotics.
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?

RECOMMENDATIONS

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 necrotizing pneumonia, and with a good clinical response to therapy (Weak recommendation, moderate quality of evidence).

Remarks:
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 individualized to the patient's clinical response, specific bacteriologic findings (such as pan drug resistance, MRSA or bacteremia), and the serial measurement of biomarkers when indicated (See PICO 6 and Table 3).

The panel believes that applying the rationale and recommendations used for VAP in non-ventilated patients with HAP represents good practice (Good practice statement).

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).

Remarks:
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.
Benefits and harms

We identified two recent systematic reviews (85,86) which included six RCT’s comparing short (7-8 days) with long (10-15 days) durations of antibiotic therapy in mixed early and late onset VAP populations. Two French studies (87,88) compared 8 to 15 day antibiotic regimens, three others (89-91) compared 7 to 10 days and one study compared 8 to 12 days. One study (92) discontinued the antibiotic at day 3 if the CPIS score was <7 while others continued the treatment at the discretion of the treating physician. Most studies excluded patients with immunosuppression, cystic fibrosis and patients with lung abscess or empyema. Immunosuppression was defined as leukocytes < 1000/µl, neutrophils < 500/µl, acquired or congenital immunodeficiency syndrome or use of immunosuppressants or long-term corticosteroids (≥0.5 mg/kg/day). Although one study required the presence of organ failure and sepsis, the others included mainly patients with non-severe disease.

There was no difference between short and long courses of antibiotics with regard to mortality (up to 28 days), duration of mechanical ventilation or length of ICU stay. Nor were there differences in mortality in the subset of patients with non-fermenting Gram-negative bacteria, although the number of events was limited (see online supplement, profile 8).

There were no significant differences in relapse rate between short and long courses, although there was a strong trend towards lower relapse in the long-course treatment, clearly driven by data from Chastre et al (87). Most of the patients with relapse in that study had VAP due to non-fermenting Gram negative bacilli; there were no differences in relapse rate in patients with VAP due to other pathogens.

Antibiotic free-days were significantly higher in the short course treatment and the incidence of secondary infections, namely VAP, due to MDR bacteria (86) was lower with the short course than with the long course regimen (43% vs. 58%), although the difference was not statistically significant. However, this difference reached statistical significance when a study published only in abstract form (91) was considered together.
with Chastre’s study (87). Adverse events were reported differently across studies. Treatment discontinuation due to adverse events may be similar with the two treatment options and shorter treatment duration is expected to be associated with better tolerability (see online supplement, profile 8).

There is no evidence relating to patients with a high probability of HAP (who were not mechanically ventilated). However, one study found that in patients with possible HAP and low a CPIS score (low clinical suspicion), a three-day course of antibiotic therapy was associated with a significantly lower risk of superinfection and emergence of antimicrobial resistance than with a long therapy course (92).

Relative importance of the outcomes

The panel considered not only survival and avoidance of relapse as critical endpoint-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.

Resource use

No appropriate cost-effectiveness studies were identified. 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.

Balance between desirable effects and undesirable effects

The trade-off between beneficial and undesirable effects favored short courses of antibiotics in immunocompetent patients with early or late-onset VAP, without cystic fibrosis, empyema, lung abscess, cavitation or necrotizing pneumonia. In patients with VAP due to non-fermenting GNB, a routine 14-day course of antibiotics probably has
more undesirable than beneficial effects, at least in patients with signs of quick
response to treatment.

Any VAP or HAP in patients with cavitation or abscess formation or with necrotizing
radiological characteristics, MRSA pneumonia, secondary bacteremia or concomitant
endocarditis should be excluded from short course therapy.
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 72-96h?

RECOMMENDATIONS

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

Remarks:
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 (PaO2/FiO2), and calculation of one or more scores such as CPIS, ODIN, SOFA, SAPSII and APACHEII.

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)

Remarks:
Biomarker determinations may include C-reactive protein (CRP), procalcitonin (PCT), copeptin, and mid-regional pro-atrial natriuretic peptide (MR-proANP). Clinicians should take into consideration the availability, feasibility and costs of each biomarker before routine testing.
**Benefits and Harms**

There are no randomized controlled trials assessing treatment outcomes of patients with HAP/VAP managed according to clinical evaluation or according to serial biomarker measurements.

Clinical evaluation includes bedside assessment, checking for improvement or worsening of temperature, tracheobronchial secretion volume, culture and purulence, chest radiograph, white blood cell count, \( \text{PaO}_2/\text{FiO}_2 \) ratio, CPIS (93) and ODIN, SOFA, and APACHEII scores. Some studies have demonstrated a benefit of serial CPIS assessments in predicting outcomes as early as days 3 (94,95). With measurement of SOFA (96-98), SAPSII and APACHEII scores at the onset of VAP and serially, prognosis can be predicted; increasing SOFA, lack of improvement of the \( \text{PaO}_2/\text{FiO}_2 \) ratio (98), during the days following the onset of VAP have been associated with non-survival.

**Biomarkers:**
Several prospective observational studies were conducted to assess the value of serum biomarker concentration and kinetics for predicting the outcome in HAP and/or VAP including CRP, PCT, copeptin and MR-proANP.

**CRP.**
Three studies in HAP/VAP patients assessed serial CRP measured at least 3 times a week after antibiotic prescription. In one study using a time-dependent analysis of the relative CRP concentration, CRP levels were significantly higher as early as day 4 in VAP patients with poor outcome than in those with a good outcome. In addition, the authors described different patterns of CRP response to antibiotics which were useful to predict the individual clinical course (99). In another study, CRP concentrations fell between days 1 and 7 in all VAP patients, but were significantly higher in patients with unfavorable outcomes (95). In the third study, CRP was measured in patients with HAP and VAP, and CRP ratios were calculated from HAP/VAP onset until day 10. Patients were classified according to the CRP ratios as ‘good’ responders (CRP ratios lower than
Mortality rates were 53% in the poor response group (n = 34) and 20% in the good response group (n = 30) (p = 0.01).

**PCT.**
Some studies investigated the value of PCT as a prognostic marker during VAP. One study demonstrated that PCT was elevated at the onset of VAP in non-survivors (95). 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 unfavorable outcome, and predicted a poor outcome in the multivariate analysis (9095). One observational study of 45 patients who developed VAP assessed their PCT and CRP levels from the day of VAP diagnosis to day 7 (100). The authors found that PCT levels at days 3 and 7 were significantly higher in non-survivors than in survivors, and that PCT levels at day 3 were the strongest predictor of mortality. PCT levels fell significantly from day 0 to day 7 in the survivor group, but CRP levels did not.

**Copetin.**
Two prospective studies showed that copeptin levels at VAP onset were significantly elevated in non-survivors (96), and were lower in eventual survivors than in eventual non-survivors (97).

**MR-proANP.**
In one study, on day 0, MR-proANP concentration had the highest positive likelihood ratio (2.71) as a predictor of outcome in VAP (97). In the study by Boeck et al, MR-proANP was higher at the onset of VAP in non-survivors than in survivors, and in a logistic regression model it was identified as the best predictor of survival (96).

**Comparison of clinical and biomarker evaluations:**
Two studies compared CRP and CRP ratios with clinical parameters in different groups of HAP/VAP-treated patients. In the study by Moreno et al, at day 0, the poor responders had significantly higher SOFA and APACHE II scores and lower PaO₂/FiO₂ ratio than those with good response, while other clinical parameters did not differ, and
CRP ratios showed significant differences between the two groups were found later, at day 4 (101). Povoa, et al. studied 47 patients with bacteriologically confirmed VAP, at day 0, CRP. Body temperature and WBC count of survivors and non-survivors did not differ, while in the multivariate analysis only day 4 CRP ratio (0.1 increase), age and day 0 SOFA score were independent predictors of death (99). Two other studies compared clinical assessment with PCT and CRP levels. In the first, multivariate analyses retained serum PCT levels and PaO2/FiO2 ratio on days 1, 3, and 7 as strong predictors of unfavorable outcome (95). The other study was performed to determine the prognostic value of PCT and CRP kinetics in critically ill patients who developed VAP. In a multivariate logistic regression model, only decreasing ΔPCT (PCT day 4 – PCT day 0) and decreasing ΔCRP (CRP day 4 – CRP day 0) were significantly lower in survivors (98).

The predictive value of copeptin and clinical assessment including PaO2/FiO2 ratio and SOFA, ODIN and CPIS scores were investigated (102). The SOFA score and the copeptin levels at VAP onset were significantly elevated in non-survivors. The predictive value of serial-measured SOFA significantly exceeded that of single SOFA and copeptin measurements. Regarding the effect of appropriate therapy one study in patients with sepsis showed that PCT kinetics within the first days was associated with the appropriateness of antibiotic therapy and the overall survival (103); and other study in patients with VAP found that CRP was a surrogate of bacterial burden and that the follow-up measurement of CRP anticipates the appropriateness of antibiotic therapy (104).

There are some circumstances such as renal impairment (105), hemodyalisis (106), hemofiltration (107) and after resuscitated cardiac arrest (108) in wich PCT has not value or the accepted thresholds have to be modified.

**Relative importance of the outcomes**

The panel valued above all the benefits in mortality, and secondarily the benefits in other unfavorable outcomes such as VAP recurrence or extrapulmonary infection
requiring antibiotics before day 28, particularly in patients receiving adequate antimicrobial therapy.

Resource use

No appropriate cost-effectiveness studies have been identified comparing the use of bedside clinical assessment with the detection of serial biomarkers to predict adverse outcomes/clinical response at 72-96h. The panel took into consideration the potentially high costs associated with the detection of serial biomarkers in relation to their limited prognosis capacity.
**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?

**RECOMMENDATIONS**

We do not recommend the routine measurement of serial serum procalcitonin (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**).

The panel believes that the measurement of serial serum procalcitonin levels together with clinical assessment in specific clinical circumstances (see table 3) with the aim of reducing antibiotic treatment duration represents good practice (**Good practice statement**).

**Benefits and harms**

Three RCTs including a total of 308 patients compared the discontinuation of antibiotic therapy according to serum PCT levels with the standard duration of antibiotics in patients with HAP or VAP as defined by clinical assessment (109,110). More recently a large RCT (112) in critically ill patients due to different causes provided data for HAP/VAP patients. In these studies, however, the standard duration of antibiotic therapy was substantially longer than 7 to 8 days; in one study, more than 50% of the standard duration population were on antibiotics for more than 14 days (109), while in the most recent study the median duration of antibiotic treatment was 7 days (112). In addition, for the most part these studies excluded patients with initially inappropriate antibiotic therapy and patients with severely compromised immunity.
Routine determination of serum PCT reduces the duration of the antibiotic therapy by 3.2 days and is associated with a significant reduction in 28-day mortality (4 RCTs, 748 patients, OR 0.67) but no differences in in-hospital mortality although data on this latter outcome are limited (110). The number of patients with failure of pneumonia resolution, overall recurrence, duration of ICU stay and duration of mechanical ventilation were similar in the PCT-guided discontinuation strategy and standard antibiotic duration groups (see online supplement, profile 10). However, intentional short duration therapy (7-8 days) was not routinely used in the standard duration group. One systematic review (113) including 5 RCTs and two additional recent studies (111,114) evaluated antibiotic discontinuation according to serum PCT levels in comparison with the standard antibiotic duration in critically ill patients with different pathologies. Pooled estimates showed similar trends, with a mean reduction of antibiotic duration of two days (5 RCTs, 1.96 days Mortality at 28 days was reduced in those patients managed according to PCT levels (4 RCTs, 2,347 patients RR 0.84)), but no differences in hospital mortality were detected.

The guideline panel considers that an equivalent reduction in the antibiotic duration can be achieved by compliance with the 7-8 day treatment period suggested for patients with nosocomial pneumonia and without risk factors necessitating longer duration (Table 3). In this population, the anticipated benefit of routine serum PCT measurement will be minimal or zero and will add costs in the majority of cases.

In patients with severely compromised immunity, inappropriate initial antibiotic therapy and infection with *Pseudomonas* and other non-fermenters, the evidence for the safety of routine 7 to 8 day antibiotic duration is less clear. Given the difficulties in assessing successful antibiotic treatment with clinical parameters or CPIS alone (115), the guideline panel felt that serial PCT measurements may provide additional objective data to supplement clinical criteria in patients for whom the safety of 7-8 days of appropriate therapy has not been demonstrated (Table 3). In all these circumstances shown in Table 3 where short duration therapy is not well studied (just as they are exclusions for PCT studies and they are generally exclusions for short duration studies) and that in these circumstances, we recommend an individualized duration of therapy, and serial
PCT measurements are one factor to be considered. Since these patients are typically treated with longer courses of antibiotics, discontinuation of treatment based on PCT may result in cost savings and less selection for superinfection.

Initially inappropriate antibiotic therapy may result in a delay in clinical response (94,113). Serial PCT levels may therefore assist in planning the duration of therapy in these patients, but have not been validated to decide on antibiotic therapy initiation. The shortest duration of appropriate antibiotic treatment in patients with severely compromised immunity is unknown, since these patients were also excluded from RCTs of antibiotic duration for HAP/VAP and severe sepsis PCT trials.

The most problematic issue facing the attempts to shorten the duration of antibiotic courses is the higher recurrence rate recorded with 7-8 days than with 15 days, particularly for *Pseudomonas* and other non-fermenters (87). However, 59% of patients with VAP due to non-fermenters did not present recurrence after 8 days of treatment. Serial PCT may be valuable to identify these patients. By extension, treatment of other highly resistant bacteria causing HAP/VAP with suboptimal antibiotics, such as carbapenem-resistant Enterobacteriaceae or *Acinetobacter* sp. with second line agents such as colistin or tigecycline, may be optimized by monitoring serial PCT levels.

Other biomarkers such as C-reactive protein may be useful but are more prone to persistent elevation due to the non-infectious inflammatory disorders common in the ICU population. Availability of testing is the primary consideration for using an alternative to PCT.

**Relative importance of the outcomes**

The panel prioritized an easy-to-perform and inexpensive measure like the reduction of antibiotic duration in low risk patients over a routine laboratory measurement, given the uncertainty of the benefits of laboratory values in patients who are already receiving a short course of antibiotic treatment.
Resource use

A cost-effectiveness study performed in Canada showed that 6 days of routine procalcitonin measurement costs seemed to be balanced by a 2-day reduction in antibiotic treatment duration (i.e., the cost of testing equaled the cost of antibiotics saved) (111).

Table 3 summarizes some of these selected groups where serial PCT measurement may be of some value. The evidence is only indirect, because to a large extent these patients have been excluded from clinical trials and thus the anticipated benefits of procalcitonin detection are very uncertain.
Table 3. Patients in whom short duration of therapy may not be possible and in whom duration of therapy should be individualized

- Initially inappropriate antibiotic therapy
- Severely immunocompromised patients (such as neutropenia or stem cell transplant)
- Highly antibiotic-resistant pathogens
  a. *Pseudomonas aeruginosa*
  b. Carbapenem-resistant *Acinetobacter* sp.
  c. Carbapenem-resistant Enterobacteriaceae
- Second line antibiotic therapy e.g. colistin, 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? (Standard care being treatment dispensed in ICU by the medical team in their usual manner.)

RECOMMENDATIONS

The guideline panel decided not to issue a recommendation on the use of chlorhexidine to perform selective oral decontamination in patients requiring mechanical ventilation until more safety data become available, due to the unclear balance between a potential reduction in pneumonia rate and a potential increase in mortality (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* (Weak recommendation, low quality of evidence).

Remarks: Although establishing a cut-off value for low and high resistance settings is a dilemma, the committee felt that a 5% threshold was reasonable.

*Low antibiotic consumption in the ICU is <1000 DD/1000 admission days
Benefits and harms

A) Oral decontamination with chlorhexidine

We identified several recent systematic reviews (116-120) and one network meta-analysis (110) that compared the use of oral chlorhexidine to usual care.

In 16 RCTs including 3,630 patients (116), the use of chlorhexidine was associated with a significant reduction of lower respiratory tract infections, including HAP and VAP (RR 0.73), but a non-significant increase in mortality (RR 1.13). There were no significant differences in mean duration of mechanical ventilation or ICU length of stay. Data on hospital length of stay and antibiotic prescriptions were limited. In patients undergoing cardiac surgery, chlorhexidine showed a similar effect, compared to usual care, in the reduction of lower respiratory tract infections including HAP and VAP (RR 0.56). Data about mortality were very limited and did not show a clear effect in this subgroup. Mean duration of mechanical ventilation or ICU length of stay were similar for the chlorhexidine and the usual care groups. The analysis of non-cardiac surgery studies showed that chlorhexidine was associated with a decreased prevalence of VAP (RR 0.78), but excess deaths (RR 1.13.; 45 more per 1,000 patients), though neither reached statistical significance (see online supplement, profile 11).

In 17 RCTS with a total of 2,402 patients (117), excluding patients undergoing cardiac surgery due to short term duration of mechanical ventilation, chlorhexidine was associated with a significant reduction in VAP incidence and a non-significant increase in mortality. Similarly, there was no evidence that duration of mechanical ventilation or duration of ICU stay had any impact on outcomes.

The effects attributed to chlorhexidine were similar to those described in previous systematic reviews (118-120) although none of these included the same studies due to slight differences in the inclusion and exclusion criteria. The association of chlorhexidine use with possible excess mortality was also seen in a recent network meta-analysis (121). One explanation for this may be lung injury associated with aspiration of small
amounts of chlorhexidine (122), but no clear relationship with dose and regimen can be established.

Possible explanations for the inconsistency of the effects observed in these studies may include differences in patient populations and differences in the outcomes assessed. The duration of mechanical ventilation in cardiac surgery patients is typically shorter than in non–cardiac surgery patients. Studies of cardiac surgery patients typically assessed lower respiratory tract infection, not just VAP, and were excluded from the Cochrane systematic review (117). Preventing VAP in persistently intubated patients is probably more difficult than preventing postoperative infections in extubated patients.

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.

Relative importance of the outcomes

There was a wide discrepancy in the panel’s views regarding the benefits of chlorhexidine in reducing nosocomial pneumonia and the potential risks associated with its use. As a result, no recommendation could be made.

Resource use

Although we did not identify any cost-effectiveness analyses for chlorhexidine use, any increase in death risk would have a heavy impact on healthcare costs.

B) Selective oropharyngeal decontamination (SOD) and selective digestive decontamination (SDD)

To reduce the incidence of infectious complications in patients requiring mechanical ventilation, two main antibiotic prophylaxis approaches have been proposed: SDD and
SOD. SDD consists of oropharyngeal (applied as a paste) and gastric administration (through a nasogastric tube) of non-absorbable antibiotics along with intravenous antibiotics. In SOD, the topical antibiotic paste is applied to the oropharynx alone.

We identified several recent systematic reviews (118,120,124) and one network meta-analysis (119) that assessed the effectiveness of either SOD or SDD.

**Selective oropharyngeal decontamination (SOD)**

Three RCTs with a limited sample size (281 patients) compared the use of SOD with topical non-absorbable antibiotics to usual care (118). These studies showed a marked reduction in the incidence of VAP (RR 0.27) and no significant differences in mortality, duration of mechanical ventilation or duration of ICU stay.

In contrast, SOD was associated with a significant reduction in mortality in four RCTs (4,266 patients) in comparison to usual care, and in the one network meta-analysis (OR 0.85) (121). This systematic review includes the results of a large cluster randomized trial (121) (see online supplement, profile 12).

**Selective digestive decontamination (SDD)**

The effectiveness of SDD with topical non-absorbable antibiotics applied in the oropharyngeal and digestive tracts, along with intravenous antibiotics, was assessed in 17 RCTs and 4,045 patients (125). SDD with topical and systemic antibiotics was associated with a significant reduction in mortality (RR 0.75), even though some of the clinical trials included patients not receiving mechanical ventilation.

The reduction in mortality was confirmed in a network meta-analysis of 15 RCTs (7,839 patients) in comparison to usual care (OR 0.73), (110). This systematic review includes the results of a large cluster randomized trial (126). The effect of SOD, SDD or usual care on mortality and antibiotic resistance was assessed in a large cluster randomized
crossover trial in the Netherlands (126). The study included 5,939 patients with an expected duration of intubation of more than 48 hours or an expected ICU stay of more than 72 hours. SDD consisted of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SOD consisted of oropharyngeal application only of the same antibiotics. The adjusted odds ratio of 28 day mortality was 0.83) for SDD (35 deaths less per 1000 patients treated) and 0.86 for SOD (29 deaths less per 1000 patients treated), with usual care being the reference group. Both interventions also reduced the number of patients with at least one episode of ICU bacteremia or candidemia, mainly due to *Staphylococcus aureus*, and glucose-non-fermenting Gram-negative species (126). A recent retraction of the data of this meta-analysis (127) reported changes in secondary outcomes in favor of SDD compared with SOD lower mortality, reduced length of stay, lower rates of ICU-acquired bacteremia and candidemia, and lower prevalence of rectal carriage of antibiotic Gram-negative bacteria, but a more pronounced gradual increase in aminoglycoside-resistant Gram negative bacteria.

**Emergence of resistance: SOD and SDD**

The emergence of antimicrobial resistance has been assessed in both randomized and observational studies of SDD and SOD in ICUs (124). In the study by Daneman et al (124), compared to control groups (which received no intervention), SDD or SOD were not associated with a significant difference in the prevalence of colonization or infection with Gram-positive antimicrobial-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (OR 1.46) or vancomycin-resistant enterococci (OR 0.63).

Prevalence of GNB resistant to selected antibiotics showed a trend toward a reduction for different antibiotics tested with the use of SDD. For polymyxin E or B and third-generation cephalosporins the reduction in resistant bacilli was significant. That review included randomized clinical trials in addition to large cluster randomized trials and non-randomized trials, and so a selection bias cannot be excluded (see online supplement, profile 13).
Recent metagenomic approaches and a recent trial comparing SDD to SOD have reported an increase in the number of antibiotic resistance genes, and especially of genes conferring resistance to aminoglycosides, in the gut flora from patients receiving SDD (128). However, it has not yet been established whether this was directly related to the use of SDD or SOD.

In an earlier analysis, Oostdijk and co-investigators looked at the ecological impact of SDD on all patients in their ICUs, rather than simply the resistance rates in patients randomized to SDD or SOD (129). This clinical trial was a cluster randomized crossover study with each unit using SDD, SOD, or standard care for 6 months (with a 1-month wash-out/wash-in period between) in random order. The critically important aspect of this study is that the authors obtained prevalence colonization cultures from all patients in the ICU, not just those enrolled in the clinical trial. Approximately 70% of patients admitted during the study periods were expected to stay in the ICU less than 48 hours and were therefore excluded. These patients represent a previously unstudied population whose colonization patterns may be affected by SDD. To look at rectal colonization, Oostdijk and colleagues (130) combined SOD and standard care periods and found that its prevalence with ceftazidime-resistant bacteria significantly increased from 5-6% before and during SDD to 15% after the SDD period. *Enterobacter* sp. appeared to exert the greatest selection pressure. Prevalence of respiratory tract colonization with ceftazidime-resistant isolates also gradually increased during SOD and SDD. In another study (131) fecal and gut flora was importantly modified or significantly suppressed (Enterobacteriaceae) as a consequence of SDD compared to SOD or to standard of care. In a follow-up study De smet et al. (132) found trends for higher rates of hospital acquired infections in patients discharged from ICU’s that had received either SDD or SOD.

**Benefits and harms**

Most of the studies were performed in countries and settings with low levels of antibiotic resistance and the study conclusions are primarily applicable to these contexts.
Effectiveness of SOD or SDD in settings with high levels of antibiotic resistance has not been assessed.

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. Considering the clinical benefits of these two strategies 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.

The guideline panel recognizes that establishing a cut-off value for low and high resistance settings is a dilemma, but a 5% threshold seems reasonable.

**Relative importance of the outcomes**

The panel placed similar value on the prevention of mortality, nosocomial pneumonia, and the emergence of resistance.

**Resource use**

A recent cost-effectiveness analysis showed that both SOD and SDD are cost-saving and are more effective than usual care, based on a post-hoc analysis of 5,920 patients from a crossover study using cluster randomization in 13 intensive care units (ICUs), all in the Netherlands (133).
SUMMARY

In these International Guidelines, a panel of experts appointed by ERS, ESICM, ECMID and ALAT provide recommendations for seven PICO questions regarding diagnosis, empirical and definitive antibiotic therapy, and prevention of hospital-acquired and ventilator-acquired pneumonia following a GRADE approach.

AKNOWLEDGEMENTS

We want to thanks Thomy Tonia for her valuable methodologic advice and to Elisabeth Sancho for her administrative and secretarial tasks.
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2000;162(5):505-11


GLOSSARY

ALAT: Asociación Latinoamericano de Tórax
ARDS: Acute respiratory distress syndrome
ATS/IDSA: American Thoracic Society / Infectious diseases society of America
BAL: Bronchoalveolar lavage
CAP: Community-acquired pneumonia
CPIS: Clinical pulmonary infection score
CRP: C-reactive protein
ERS: European Respiratory Society
ESBL: Extended-spectrum Beta-lactamase
ESCMID: European Society of Clinical Microbiology and Infectious Diseases.
ESICM: European Society of Intensive Care Medicine
GNB: Gram negative bacteria
GRADE: Grading of recommendations assessment development and evaluation
HAP: Hospital-acquired pneumonia
HCAP: Health-care associated-pneumonia
ICU: Intensive Care Unite
MDR: Multidrug resistance microorganism
MR-proANP: Mid regional pro atrial natriuretic peptide
MRSA: Methicilin resistance staphylococcus aureus
MSSA: Methicilin sensible staphylococcus aureus
MV: Mechanical ventilation
PCR: Polimerase chain reaction
PCT: Procalcitonin
PICO: Population-intervention-comparison-outcome
RCT: Randomized clinical trial
SDD: Selective digestive decontamination
SOD: Selective oropharyngeal decontamination
VAC: Ventilator-associated complications
VAP: Ventilator associated-pneumonia
VAT: Ventilator-associated tracheobronquitis
XDR/PDR: Extensively drug-resistant/Pandrug resistant microorganism
Records identified through database searching (n = 5543)

Records identified through other sources (n = 17)

Records screened (n = 5560)

Records excluded by title-abstract and duplicates (n = 5407)

Full-text articles excluded (n = 44)
(6) Not in English
(38) Not eligible by population, intervention or design

Full-text articles assessed for eligibility (n = 153)

Studies included in quantitative synthesis (n = 109)
PICO 1: 16
PICO 2: 16
PICO 3: 34
PICO 4: 8
PICO 5: 10
PICO 6: 10
PICO 7: 15
Fig 2: Empiric Antibiotic Treatment Algorithm for HAP/VAP

Empiric Antibiotics for HAP/VAP 2017

HAP/VAP: ASSESS RISK FOR MORTALITY AND MDR PATHOGENS

- LOW MDR and LOW MORTALITY RISK
  - Antibiotic Monotherapy: ertapenem, ceftriaxone, cefotaxime, levofloxacin, moxifloxacin

- HIGH MDR(b) RISK and/or >15% MORTALITY RISK
  - No Septic Shock
    - Single Gram-negative agent (if active for > 90% GNB in the ICU) +/- MRSA therapy
  - Septic Shock
    - Dual Gram-Pseudomonal coverage +/- MRSA therapy

---

(a) 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. Kumar A, Safdar N, Kethireddy S, et al. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study. Crit Care Med 2010;38:1651-1664.

(b) Multidrug resistant pathogens
### Online Supplement

#### Summary of Findings table profiles

<table>
<thead>
<tr>
<th>Question</th>
<th>Profile #</th>
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<tbody>
<tr>
<td>#1: In intubated patients suspected of having VAP should distal quantitative samples be obtained instead of proximal-quantitative samples?</td>
<td>1 and 2</td>
</tr>
<tr>
<td>#2: Can patients suspected of having nosocomial pneumonia (HAP and VAP), who have early onset infection and no 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?</td>
<td>3 and 4</td>
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<td>#3: In patients with initial broad spectrum empiric therapy for HAP/VAP does an initial regimen combining two antibiotics targeting Gram-negative bacteria improve outcomes and when culture data are available, does combination therapy need to be continued as definitive therapy, compared to single antimicrobial agent therapy?</td>
<td>5, 6 and 7</td>
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<tr>
<td>#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?</td>
<td>8 and 9</td>
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<tr>
<td>#5: In patients receiving AB treatment for VAP or HAP, is bedside clinical assessment equivalent to the detection of serial biomarkers to predict adverse outcomes / clinical response at 72-96h?</td>
<td>10 and 11</td>
</tr>
<tr>
<td>#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?</td>
<td>12</td>
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<tr>
<td>#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?</td>
<td>13, 14 and 15</td>
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</table>
Profile #1 Quantitative in comparison to qualitative samples in patients suspected of having VAP

**Bibliography:** Berton DC, Kalil AC, Teixeira PJZ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD006482

<table>
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<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<td><strong>Mortality - 28 days</strong></td>
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<tr>
<td>142/614 (23.1%)</td>
<td>RR 0.91 (0.75 to 1.11)</td>
<td>23 fewer per 1.000 (from 28 more to 63 fewer)</td>
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<td>159/626 (25.4%)</td>
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<td><strong>Antibiotic change</strong></td>
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<td>286/410 (69.8%)</td>
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<td>284/417 (68.1%)</td>
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<td><strong>Duration on mechanical ventilation (days)</strong></td>
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<td>410</td>
<td>MD 0.58 more (0.51 fewer to 1.68 more)</td>
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<td>417</td>
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<td><strong>ICU stay (days)</strong></td>
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<td>614</td>
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<td>626</td>
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<tr>
<td><strong>Number of antibiotic-free days</strong></td>
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<td>Fagon 2000: Invasive distal quantitative strategy vs. qualitative non-invasive methods: significant increase in the day-14 antibiotic free-days (5.0 ± 5.1 vs. 2.2 ± 3.5) and day-28 antibiotic free-days (11.5 ± 9.0 vs. 7.5 ± 7.6)</td>
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<td>CCTG 2006: no differences between groups in the day-28 antibiotic free-days</td>
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

2. Even though 2/3 studies were not blinded, it is unlikely that this affect this outcome. One study had incomplete outcome data but analysis was according to intention to treat population
3. 95% IC of the absolute values result in a appreciable benefit or appreciable harm
4. CCTG 2006 and Sole Violan 2000
5. One or more study(ies) was/were not blinded, review authors believe that this did affected subjective outcomes
7. One study used a guideline for antibiotic deescalation whereas the other did not.
Profile #2 Invasive in comparison to non-invasive samples in patients suspected of having VAP

**Bibliography:** Berton DC, Kalil AC, Teixeira PJZ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD006482

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<td>Imprecision</td>
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<td>№ of patients</td>
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<td>184/692 (26.6%)</td>
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

1. Even though some studies were not blinded, it is unlikely that this affect this outcome
2. 95%CI included appreciable benefit or harm
Profile #3 Prognostic factors of multi-drug resistant pathogens in ICU patients with pneumonia and frequency of MDR pathogens in early-onset VAP

Bibliography:
- Arvanitis M1, Anagnostou T1, Kourkoumpetis TK2, Zikas PD3, Desalermos A2, Mylonakis E. The impact of antimicrobial resistance and aging in VAP outcomes: experience from a large tertiary care center. PLOS One 2014; 9:e89984

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CI: Confidence interval; OR: Odds ratio

1. Martin-Löeches 2013
2. Not directly answering the question about the use of broad or narrow spectrum antibiotic use
3. Verhamme 2007
5. Estimates varied broadly
Profile #4 Narrow spectrum antibiotics in patients without risk factors for multi-drug resistant pathogens

**Bibliography:**


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**CI:** Confidence interval

1. Ferrer 2010
2. Non-comparative results between narrow spectrum and broad spectrum in non-risk factors
3. Leone 2007
Profile #5 Combination of two antibiotics compared to single antimicrobial agent therapy for patients suspected VAP (ventilator associated pneumonia)


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CI: Confidence interval; RR: Risk ratio; n.s: not specified

1. Although not all patients were under mechanical ventilation (85% approximately)
2. 95% CI includes appreciable benefit or harm.
3. Most studies not blinded, that would have affected this subjective outcome. Some with no ITT analysis
**Profile #6** Combination of two antibiotics compared to single antimicrobial agent therapy for patients suspected HAP (hospital-acquired pneumonia)

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CI: Confidence interval; RR: Risk ratio

2. Even though one study was not blinded, this may not affect the results of this objective outcome
3. Low number of events. 95% CI includes appreciable harm or benefit
5. Single study
6. Only 60% of the combination therapy arm included a cephalosporin plus aminoglycoside
7. Awad 2014
9. Two of four studies with serious limitations
11. One study non-blinded, results from subgroup analysis in one study
13. Post-hoc subgroup analysis, unblinded, large number of patients were lost of follow-up
14. Not pooled
15. Adverse events under different categories
16. Not pooled but probably not a problem

**Profile #7** Combination of two antibiotics compared to single antimicrobial agent therapy for patients with high-risk life-threatening infections and MDR bacteria


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CI: Confidence interval; RR: Risk ratio; n.s: not specified

1. Studies including patients with different conditions (not all HAP or VAP). Data were only calculated for monotherapy treatment with beta-lactam and/or fluoroquinolones
2. Data not provided
3. Data only for one type of microorganism
**Profile #8:** Short (fixed)-course antibiotic therapy compared to prolonged-course antibiotic therapy for HAP in HAP (hospital-acquired pneumonia)


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CI: Confidence interval; OR: Odds ratio; MD: Mean difference

1. Overall of good quality. Some RCT open label
2. 95%CI includes large benefit or harm. Low number of events
3. Large heterogeneity
4. Two studies with open design, possible bias for a subjective outcome
5. Not pooled
6. Adverse events assessed using very different definitions
**Profile #9**: Short (fixed)-course antibiotic therapy compared to prolonged-course antibiotic therapy for HAP in HAP (hospital-acquired pneumonia)

**Bibliography:**


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CPIS equal or greater than 6 at day 3 (increased likelihood of bacterial pneumonia)
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CI: Confidence interval; OR: Odds ratio; MD: Mean difference

1. Single study
2. Low number of events
3. Study terminated early (46% of the sample)
4. Study with open design, possible bias for a subjective outcome
Profile #10: Relationship of different biomarkers and clinical scores on 28 days mortality


### Quality assessment

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<td>OR 4.43 (1.08–18.18) for any increase D0 to D4 OR 22.6 for levels &gt;1 ng/mL on D3 Significant greater levels at D4 in non-survivors Sens/spec: 0.90 / 0.74; for Day 4 values &gt;0.47 ng/mL Sens/spec: 0.74 / 0.84; for Day 3 values &gt;1.5 ng/mL</td>
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### Clinical scores

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**SOFA:**
- OR 2.25 (0.48–10.46) for any decrease of scores at Day 0 to Day 4
- Significant greater levels at D4 in non-survivors
- Sens/spec: 0.57 / 0.82; for Day 4 SOFA score >6
- D0 SOFA score (1-point increment); OR 1.469 (1.014–2.127)
- D0 SOFA score (1-point increment); OR 1.28 (1.10-1.49)

**SOFA components:**
- Age: two studies with significant relationship and two studies with non-significant relationship
- White Blood Cell counts: two studies with significant relationship and one study with non-significant relationship
- Temperature: one study with significant relationship and two studies with non-significant relationship
- Lack of improvement of PaO2/FiO2 values: with significant relationship with mortality in three studies

**APACHE II score:**
- No significant relationship with mortality in multivariate regression analysis

**CPIS:**
- Non-significant differences in levels at D4 between survivors and non-survivors.
- Significant decrease of CPIS scores from onset to Day 3, 5, and 7

### Combination of biomarkers and clinical scores

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Combination of SAPS II, SOFA, ODIN, PCT, MR-proANP serum levels has better diagnostic performance in comparison to single assessment.

| CI: Confidence interval; OR: Odds ratio; MD: Mean difference |
|---|---|---|
| 1. No serious inconsistency between studies |
| 2. Pooled results not obtained, most probably results are imprecise for decision making |
Profile #11: Relationship of different biomarkers and adequacy of antibiotic therapy


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Clinical scores

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<td>not serious 1</td>
<td>not serious</td>
<td>serious 2</td>
<td>not serious</td>
<td>CPIS: Significant improvement in patients receiving adequate AB therapy and worsening in those patients with inadequate AB therapy at Day 3</td>
<td>⬤⬤⬤◯</td>
<td>CRITICAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SOFA components: PaO2/FiO2: Significant improvement in patients receiving adequate AB therapy and worsening in those patients with inadequate AB therapy at Day 3</td>
<td>⬤⬤⬤◯</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

CI: Confidence interval; OR: Odds ratio; MD: Mean difference

1. Single study
2. Low number of patients and events
Profile #12 Discontinuation of antibiotic therapy according to serum procalcitonin level compared to not guided discontinuation in HAP / VAP patients


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discontinuation according to procalcitonin</strong></td>
<td></td>
<td></td>
<td>HIGH</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Not guided</strong></td>
<td></td>
<td></td>
<td>69 fewer per 1.000 (from 8 fewer to 115 fewer)</td>
<td></td>
</tr>
<tr>
<td><strong>Relative (95% CI)</strong></td>
<td>OR 0.67 (0.48 to 0.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Absolute (95% CI)</strong></td>
<td>71/735 (18.9%)</td>
<td>96/373 (25.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>28-day mortality</strong></td>
<td>4</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Duration of antibiotic therapy</strong></td>
<td></td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td>1</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Intensive Care Unit mortality</strong></td>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Recurrence of pneumonia</strong></td>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>28-day antibiotic-free days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality assessment</td>
<td>№ of patients</td>
<td>Effect</td>
<td>Quality</td>
<td>Importance</td>
</tr>
<tr>
<td>--------------------</td>
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<tr>
<td><strong>Quality assessment</strong></td>
<td><strong>№ of patients</strong></td>
<td><strong>Effect</strong></td>
<td><strong>Quality</strong></td>
<td><strong>Importance</strong></td>
</tr>
<tr>
<td><strong>№ of studies</strong></td>
<td><strong>Study design</strong></td>
<td><strong>Risk of bias</strong></td>
<td><strong>Inconsistency</strong></td>
<td><strong>Indirectness</strong></td>
</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Non-resolution of pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Recurrence due to resistant organism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Intensive Care Unit duration of stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Duration of hospital stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Duration of mechanical ventilation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

1. 95%CI includes large benefit or harm. Low number of events
2. Most studies not blinded assessing subjective outcome
3. Single study
4. Potential source of bias as this is a per-protocol analysis; exclusion of 9 patients with low PCT measurements in the PCT group may exclude a higher proportion of relatively well patients compared with the control group
5. Non blinded study assessing a subjective outcome, which excluded patients with low PCT values
6. 95% CI ranging from futility to large benefit

95% CI ranging from appreciate benefit or harm
1.

**Profile #13** Topical application of chlorhexidine in comparison to usual care or placebo in patients requiring mechanical ventilation.


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td># of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Lower respiratory tract infections (HAP and VAP)</td>
<td>16</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Lower respiratory tract infections - Cardiac surgery</td>
<td>3</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Lower respiratory tract infections - NON cardiac surgery</td>
<td>13</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Mortality</td>
<td>12</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Mortality - cardiac surgery</td>
<td>3</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Mortality - NON cardiac surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nr of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>--------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>9</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious ²</td>
</tr>
<tr>
<td>6</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>1</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>5</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>6</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>1</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>5</td>
<td>randomised trials not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

1. 95%CI include appreciable benefit and harm
2. 95%CI include appreciable harm or benefit
3. Very low number of events
4. Single study

**Profile #14: Selective oropharyngeal decontamination (SOD) compared to placebo or standard care in patients requiring mechanical ventilation**

**Bibliography:**
- Price R, MacLennan G, Glen J; SuDDICU Collaboration. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ. 2014 Mar 31;348:g2197

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SOD standard care</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.27 (0.18 to 0.42)</td>
<td>344 fewer per 1.000 (from 273 fewer to 387 fewer)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.85 (0.50 to 1.46)</td>
<td>45 fewer per 1.000 (from 138 more to 150 fewer)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR 0.85 (0.74 to 0.97)</td>
<td></td>
<td>CRITICAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MD 1.7 more (4.67 fewer to 1.27 more)</td>
<td></td>
<td>IMPORTANT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MD 4 fewer (7.73 fewer to 0.27 fewer)</td>
<td></td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; MD: Mean difference; n.s.: not specified
1. SOD definition varied widely across studies and reviews included different studies under same concept
2. Low number of events and patients.
3. No explanation was provided
4. Low number of events and patients. 95%CI includes benefit or harm
5. Biggest study (deSmet) was a cluster trial and thus did not randomized patients with a potential for selection bias
6. Single study
Profile #15: Selective oropharyngeal decontamination (SOD) and selective digestive decontamination (SDD) compared to placebo or standard care in patients requiring mechanical ventilation

Bibliography:

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>17 randomised trials, not serious, not serious, not serious, none</td>
<td>496/2025 (24.5%), 614/2050 (30.0%)</td>
<td>OR 0.75 (0.65 to 0.87)</td>
<td>57 fewer per 1.000 (from 28 fewer to 82 fewer)</td>
</tr>
<tr>
<td>Overall mortality (including cluster clinical trials)</td>
<td>15 randomised trials, serious, not serious, serious, not serious, none</td>
<td>n.s., n.s.</td>
<td>OR 0.73 (0.64 to 0.84)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>Methicillin-resistant staphylococcus aureus infection or colonisation</td>
<td>9 randomised trials, serious, not serious, not serious, serious, none</td>
<td>110/2780 (4.0%), 61/1753 (3.5%)</td>
<td>OR 1.46 (0.90 to 2.37)</td>
<td>15 more per 1.000 (from 3 fewer to 44 more)</td>
</tr>
<tr>
<td>Vancomycin-resistant enterococci infection or colonisation</td>
<td>5 randomised trials, serious, not serious, not serious, serious, none</td>
<td>31/2014 (1.5%), 139/2837 (4.9%)</td>
<td>OR 0.63 (0.39 to 1.02)</td>
<td>18 fewer per 1.000 (from 1 more to 29 fewer)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; OR: Odds ratio; n.s.: not specified

1. SOD / SDD with topical AND systemic antibiotics
2. Most studies open and 7/17 with inadequate allocation concealment, but sensitivity analysis did not change the results
3. Included patients in ICU, some not under mechanical ventilation
4. Biggest study (deSmet) was a cluster trial and thus did not randomized patients with a potential for selection bias
5. SOD / SDD with topical OR systemic antibiotics
6. Overall, most randomized and observational studies had adequate quality. It cannot be ruled out a selective outcome reporting
7. 95% CI includes no effect or appreciable harm
8. 95% CI includes appreciable benefit or no effect
### Online Supplement Table: Future research ideas

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>IDEAS</th>
</tr>
</thead>
</table>
| Diagnosis                                  | 1. Assessment of the impact of qualitative proximal versus qualitative distal sampling on prognosis and broad-spectrum antibiotic-free survival in VAP  
2. The study should involve equal proportions of ICUs that routinely use one or the other method and should follow careful guidelines for initiating treatment and de-escalation. Treatment of CNS should be discouraged in both groups. Appropriate therapy in both groups should be chosen by an external physician.  
3. Assessment of the impact of new molecular techniques for microbiological diagnosis of VAP, early adequate therapy and antimicrobial stewardship  
4. When new diagnostic methods become available, should the samples tested be tracheal aspirates or BAL? Can these types of method help us to reduce antibiotic use, or should they only be used with a negative intent, i.e. to narrow the choice if a pathogen is absent, but not always to broaden it if a pathogen is present? |
| Empirical and targeted antibiotic treatments | 1. In patients with HAP/VAP should PK/PD-optimized therapy be used to improve bacterial killing and outcomes?  
2. Should we use aerosolized antibiotics as an adjunctive therapy to systemic antibiotics for treating patients infected with very difficult-to-treat microorganisms, such as XDR/PDR Gram-negative bacteria and carbapenem-resistant Enterobacteriaceae?  
3. Should we use a regimen combining at least two antibiotics throughout the duration of treatment (and not for only 3-5 days) to treat patients infected with very difficult-to-treat microorganisms, such as XDR/PDR Gram-negative bacteria and carbapenem-resistant Enterobacteriaceae?  
4. In patients with HAP/VAP, should antimicrobial therapy be de-escalated once culture results are available in order to avoid the emergence of drug-resistant microorganisms?  
5. In patients with HAP/VAP infected with ESBL-producing Enterobacteriaceae, should we systematically use a carbapenem throughout the entire duration of treatment?  
6. Is a 4-5 day antibiotic regimen used according to PK/PD characteristics as effective as a 7-8 days regimen in terms of VAP outcome (response, mortality, recurrence)? Does it reduce superinfection and the emergence of MDR microorganisms (VAP caused by Pseudomonas and Acinetobacter would be excluded)?  
7. Is a 7-8 day antibiotic regimen non-inferior to a 10-14 days antibiotic regimen for Pseudomonas and Acinetobacter VAP that shows signs of quick response? |
|   | 8. Does a fall in procalcitonin at day 7-8 of therapy for MDR/XDR pathogens predict the safety of discontinuing antibiotics? Is a falling PCT level superior to serial clinical exam or scores such as CPIS for determining the safety of antibiotic discontinuation at 7-8 days for MDR/XDR pathogens?  
9. Is 7-8 days of appropriate antibiotic therapy sufficient for MDR/XDR pneumonia in immunocompromised patients? Can falling PCT levels predict which immunocompromised patients with MDR/XDR pneumonia can be treated with 7-8 days of therapy?  
10. If PCT is not falling at 72-96 hours, how frequently will repeated lower respiratory cultures detect persistence of the original infection and the development of antibiotic-resistant infection?  
|   | Prevention  
|   | 1. What is the most cost-effective antibiotic approach for the prevention of VAP? Is it SOD, SDD, aerosolized antibiotics, or short-course parenteral therapy?  
2. Can the short-term administration of aerosolized antibiotics to high-risk ventilated patients reduce the occurrence of VAP and other complications?  
3. What is the role of non-traditional agents such as the use of monoclonal antibodies, vaccines, antimicrobial peptides and immunomodulators for the prevention of VAP and other ICU-acquired infections?  
4. The clinical effectiveness of SOD and SDD in settings with high rates of antibiotic-resistant bacteria should be established.  
5. The potential effect of chlorhexidine use on mortality and its determinants should be studied.  
6. The benefits of chlorhexidine use in relation to dose, regimes and formulations should be established. |