Korean Guidelines for the Management and Antibiotic Therapy in Adult Patients with Hospital-Acquired Pneumonia

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Abstract

Background: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are correlated with high morbidity and mortality rates. Guidelines that consider local epidemiologic data are fundamental for identifying optimal treatment strategies. However, Korea has no HAP/VAP guidelines.

Methods: This study was conducted by a committee of nine experts from the Korean Academy of Tuberculosis and Respiratory Diseases Respiratory Infection Study Group using the results of Korean HAP/VAP epidemiologic studies. Eleven key questions for HAP/VAP diagnosis and treatment were addressed. The Convergence of Opinion on Suggestions and Evidence (CORE) process was used to derive suggestions, and evidence levels and recommendation grades were in accordance with the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology.

Results: Suggestions were made for the 11 key questions pertinent to diagnosis, biomarkers, antibiotics, and treatment strategies for adult patients with HAP/VAP.

Conclusion: Using the CORE process and GRADE methodology, the committee generated a series of recommendations for HAP/VAP diagnosis and treatment in the Korean context.

Keywords: pneumonia; hospital-acquired pneumonia; ventilator-associated pneumonia; guideline; Korea

Background

Hospital-acquired pneumonia (HAP) is a type of pneumonia that develops in patients admitted to the hospital for >48 hours. Ventilator-associated pneumonia (VAP) is a type of pneumonia that develops in patients receiving mechanical ventilation for at least 48 hours in the intensive care unit. HAP is the second most common nosocomial infection and is the leading cause of mortality from nosocomial infections in patients with critical illness.[1] Consequently, several HAP guidelines have been published by international respiratory and infectious disease societies.[1-5]

International guidelines can be good reference for HAP management. However, developing local guidelines that consider epidemiologic data and recommend initial treatment with antibiotics accordingly is also fundamental. Epidemiologic data on HAP should include causative pathogens, antibiotic resistance patterns, and antibiotic treatment status. Therefore, epidemiologic studies on Korean patients with HAP were conducted.[6-10] The current study aimed to evaluate the most effective management and treatment strategies for adult patients with HAP in the Korean context using epidemiologic data.

Methods

HAP guidelines were developed by a committee of nine experts from the Korean Academy of Tuberculosis and Respiratory Diseases (KATRD) Respiratory Infection Study Group. The committee included respiratory medicine specialists with expertise in managing patients with pulmonary infections and intensive care specialists. All committee meetings were conducted via virtual web conferences.

The Convergence of Opinion on Suggestions and Evidence (CORE) process, a

consensus-based approach for making clinical suggestions, was used to derive suggestions (**Figure 1**). It yields recommendations that are highly in accordance with those that were developed using the Institute of Medicine-adherent methodology for clinical practice guidelines.[11-13] In addition, the evidence levels and recommendation grades used in these guidelines were based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology.[14,15] Google Surveys were used to create multiple-choice surveys, which were administered among the members of the KATRD Respiratory Infection Study Group. Each survey question comprised five parts, which were as follows: 1) a key question in the modified Patient, Intervention, Comparator, and Outcomes (PICO) format, 2) a summary of evidence pertinent to the key questions, 3) multiple choices, including a strong or weak suggestion for or against a course of action, or no suggestion, 4) multiple choices for opinions on the level of evidence, including high, moderate, low, and very low quality, and 5) a free-text box for comments. The survey was initially administered on August 12–19, 2022. Invitations were sent to 62 clinicians, and 54 (87.1%) participated in the first survey. The second survey, which was identical to the first one, except that it included the results obtained from the first round, was then conducted. The following were the details added in the second survey: 1) the proportion of participants who selected each multiple-choice option and 2) the representative comments from the participants. The second survey was re-administered on September 2–9, 2022. Invitations were sent to 54 clinicians who participated in the first survey, and 51 (94.4%) completed it.

Agreement among the participants on directionality was tabulated for each multiple-choice question, and the results were reported as a suggestion for, no suggestion, and suggestion against a course of action. An agreement of at least 70% was required to establish a consensus suggestion for or against a course of action. This threshold optimizes the concordance between

CORE-derived consensus recommendations and the suggestions in the Institute of Medicine-adherent methodology for clinical practice guidelines.[11,13,16] **Supplementary Table 1** shows the results of the two surveys. After tabulating the results, the guidelines were written and finalized after further input from the KATRD, Korean Society of Infectious Diseases, Korean Society of Critical Care Medicine, and Korean Society for Antimicrobial Therapy.

Results

Table 1 presents all key questions and corresponding recommendations. In addition, in the subsections of each key question, summaries of evidence were provided. Moreover, our suggestions for HAP and VAP were compared with those of the 2016 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA)[3] and the 2017 European Respiratory Society (ERS)/European Society of Intensive Care Medicine (ESICM)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/Latin American Thoracic Association (ALAT).[4]

Key question 1.

Should quantitative cultures using invasive sampling be performed for pathogen identification in patients with suspected VAP?

PICO

Population	Patients with suspected VAP

Intervention	Quantitative culture using invasive sampling
Comparator	Qualitative culture using tracheal aspirate
Outcome	Mortality, length of intensive care unit (ICU) stays, and ventilator-free days

Recommendation

We **suggest against** routine quantitative cultures using invasive sampling (e.g., bronchoalveolar lavage [BAL] and protected specimen brush [PSB]) for pathogen identification in patients with suspected VAP (conditional recommendation, moderate-quality evidence).

Summary of evidence

There were five randomized control trials (RCTs) for this key question (**Table 2**). In all studies, except one, the mortality rate, length of ICU stay, and duration of ventilator days did not differ between patients with VAP who underwent quantitative culture using invasive sampling and those who underwent qualitative culture using tracheal aspirate for identifying.[17-21] In addition, a meta-analysis including five RCTs and other observational studies showed no difference in terms of length of ICU stay and duration of ventilator days between patients who underwent invasive sampling and those who underwent qualitative culture using tracheal aspirate. However, invasive sampling was more likely to be associated with reduced mortality compared with qualitative culture using tracheal aspirate (odds ratio [OR]: 0.91, 95% confidence interval [CI]: 0.75–1.11).[22] Therefore, the 2016 ATS/IDSA guidelines for HAP/VAP recommend qualitative culture using tracheal aspirate rather than quantitative culture using invasive sampling for pathogen identification in patients with VAP.[3] However, qualitative culture using

tracheal aspirates may increase the proportion of drug-resistant pathogens due to the overuse of antibiotics caused by failure to discriminate between pathogens and colonizers.[20] Therefore, quantitative culture using invasive sampling could reduce the duration of antibiotic treatment, the proportion of drug-resistant pathogens, and the incidence of co-infection due to early antibiotic discontinuation if pathogens are not identified.[23-26] In this regard, the 2017 ERS/ESICM/ESCMID/ALAT guidelines for HAP/VAP recommend obtaining a distal quantitative sample (before any antibiotic treatment) to reduce antibiotic exposure in stable patients with suspected VAP and to improve result accuracy.[4] However, other outcomes (e.g., mortality, length of ICU stay, and duration of ventilator days), except for antibiotic use, were similar between patients who underwent quantitative culture and those who underwent qualitative culture. No other RCTs have been performed since 2006, and patients may develop complications caused by procedures (e.g., bronchoscopy). Therefore, we **suggest against** routine quantitative cultures using invasive sampling (e.g., BAL and PSB) for pathogen identification in patients with suspected VAP.

Comparison of the current recommendations with those of other clinical practice guidelines

There was no difference in terms of mortality, length of ICU stay, and duration of ventilator days between quantitative culture using invasive sampling and qualitative culture using tracheal aspirate (weak recommendation, low-quality evidence).Thus, the 2016 ATS/IDSA guidelines recommend qualitative culture using tracheal aspirate rather than quantitative culture using invasive sampling for pathogen identification in patients with VAP.[3] Regarding the evidence of this recommendation, one RCT showed that quantitative culture is more useful than qualitative culture in distinguishing pathogens from colonizers. However, qualitative cultures can be performed more rapidly, are associated with fewer complications, and require

less equipment than quantitative cultures using invasive sampling. Therefore, qualitative culture using tracheal aspirates for pathogen detection is recommended.[3]

The 2017 ERS/ESICM/ESCMID/ALAT guidelines recommend obtaining a distal quantitative sample before any antibiotic treatment to reduce antibiotic exposure in stable patients with suspected VAP and to improve result accuracy (weak recommendation, low-quality evidence).[4] However, the 2017 ERS/ESICM/ESCMID/ALAT guidelines also recommend qualitative culture using tracheal aspirate for pathogen detection in patients with acute respiratory distress syndrome or severe septic shock because of the unclear benefit of invasive procedures and the risk of complications in quantitative culture using invasive sampling (e.g., hypoxia).[4]

Key question 2.

Should treatment decisions be made based on procalcitonin plus clinical criteria in patients with suspected HAP/VAP?

PICO

Population	Patients with suspected HAP/VAP
Intervention	Clinical criteria plus procalcitonin
Comparator	Clinical criteria only
Outcome	Diagnostic accuracy

Recommendation

We **suggest against** treatment decisions based on procalcitonin plus clinical criteria for patients

with suspected HAP/VAP (conditional recommendation, moderate-quality evidence).

Summary of evidence

The efficacy of procalcitonin in HAP/VAP diagnosis is unclear as the number of observational studies is only limited (**Table 3**). In addition, procalcitonin can exhibit false positives in patients who underwent surgery and those with trauma, burns, cardiogenic shock, severe pancreatitis, autoimmune disease, severe renal failure, or severe liver failure. Further, it can exhibit false negatives in patients with local infection without signs of systemic infection and early bacterial infection within 6 hours.[27] The accuracy of procalcitonin for diagnosing VAP in a prospective observational study was poor (area under the curve: 0.62, 95% CI: 0.50–0.73).[28] Moreover, the results of other small observational studies were similar to those of previous studies.[29-31] According to a meta-analysis of the 2016 ATS/IDSA guidelines, the sensitivity and specificity of procalcitonin for HAP/VAP diagnosis were 67% and 83%, respectively.[3] As studies on this issue were limited and heterogeneous and the study outcomes were poor, we disagreed that treatment decisions based on procalcitonin and clinical criteria were more effective than those based on clinical criteria alone in patients with HAP/VAP.

Comparison of the current recommendations with those of other clinical practice guidelines

To decide whether or not to initiate antibiotic therapy in patients with suspected HAP/VAP, the 2016 ATS/IDSA guidelines recommended using clinical criteria alone rather than procalcitonin plus clinical criteria (strong recommendation, moderate-quality evidence).[3] The 2017 ERS/ESICM/ESCMID/ALAT guidelines do not include a clinical question about the diagnostic usefulness of procalcitonin for determining whether to initiate antibiotic therapy in patients

with HAP/VAP.[4]

Key question 3.

Should polymerase chain reaction (PCR) tests for atypical pathogens be performed on patients with HAP/VAP?

PICO

Population	Patients with HAP/VAP
Intervention	PCR test for atypical pathogen
Comparator	No PCR test for atypical pathogen
Outcome	Prevalence of atypical pathogen in patients with HAP/VAP

Recommendation

We **suggest against** PCR tests for atypical pathogens in patients with HAP/VAP (conditional recommendation, moderate-quality evidence).

Summary of evidence

Traditionally, atypical pneumonia has been defined as pneumonia caused by pathogens such as *Mycoplasma*, *Chlamydia*, and *Legionella* bacterium. In addition to these bacterial infections, viruses and fungi can also cause atypical pneumonia. Viruses generally cause pneumonia in immunocompromised patients. However, viruses are not infrequently detected as pathogens in patients with HAP/VAP who are immunocompetent.[32,33] In a Korean single-center study, viruses were identified in approximately 22.5% of patients with severe HAP/VAP requiring

ICU admission and 11% of immunocompetent patients.[32] In a study of patients with relatively mild HAP who did not require mechanical ventilation, viruses were detected in approximately 22.7% of patients.[33] Regarding bacterial pathogens, *Mycoplasma* and *Chlamydia* species are rarely reported in patients with HAP/VAP. *Legionella* was once a common cause of HAP, accounting for approximately 10% of nosocomial infections in the 1990s.[34] However, since 2010, with proper hospital plumbing and water quality management, only 10–15 cases per 100,000 people have been reported worldwide.[35] In a Korean multicenter retrospective study of patients with HAP/VAP published in 2021, approximately 17.5% were tested for atypical pneumonia pathogens. However, all results were negative.[36] Therefore, we agreed not to recommend PCR testing for identifying atypical pathogens in patients with HAP/VAP.

Comparison of the current recommendations with those of other clinical practice guidelines

There are no clinical questions or recommendations regarding PCR testing for atypical pathogens in patients with HAP/VAP in the 2016 ATS/IDSA and 2017 ERS/ESICM/ESCMID/ALAT guidelines.[3,4]

Key question 4.

Is empiric piperacillin/tazobactam, compared with cefepime, effective in decreasing mortality in patients with HAP/VAP?

PICO

Population	Patients with HAP/VAP

Intervention	Empiric piperacillin/tazobactam
Comparator	Empiric cefepime
Outcome	Mortality

Recommendation

We make **no suggestion** for using specific antibiotics (piperacillin/tazobactam or cefepime) for the empiric treatment of patients with HAP/VAP (inconclusive, low-quality evidence).

Summary of evidence

The single agents currently recommended for empirical HAP/VAP treatment include piperacillin/tazobactam and cefepime, which have anti-methicillin-sensitive *Staphylococcus aureus* and antipseudomonal effects. In a multicenter HAP/VAP study published in 2021, piperacillin/tazobactam (59.3%) and cefepime (6.7%) were the most frequently prescribed empirical antibiotics in Korea.[36] **Table 4** shows the results of the two antimicrobial agents evaluated in febrile patients with sepsis and neutropenia. Retrospective studies of septic shock showed that the cefepime group had a higher mortality rate than the piperacillin/tazobactam group. However, the interpretation of results is limited as confounding factors have not been adjusted.[37,38] In a meta-analysis of febrile neutropenic patients, the cefepime group had a high mortality rate.[39] In addition, in a Korean retrospective study of 43 patients with severe community-acquired pneumonia, the mortality rate did not significantly differ between the two agents (both groups used drugs combined with ciprofloxacin).[40]

No study has directly compared the clinical effects of piperacillin/tazobactam and cefepime in patients with HAP/VAP. However, previous studies comparing the pharmacodynamic/pharmacokinetic effects, antibiotic sensitivity, and drug toxicity of the two

drugs may be used as a reference for drug selection. In evaluating lung penetration of antimicrobial agents using the lung epithelial fluid/plasma concentration, the lung permeability of piperacillin/tazobactam was 0.568/0.913, and the permeability of cefepime was higher at 0.99–1.12.[41] If the time exceeding the minimum inhibitory concentration for gram-negative bacteria was measured, the probability of achieving the bacteriostatic/bactericidal goal of cefepime against gram-negative bacteria was higher than that of piperacillin/tazobactam (88%/81% vs 79%/71%). Therefore, the previous study suggested cefepime as a preferred empiric antibiotic for gram-negative pulmonary infections.[42]

Piperacillin/tazobactam may have a higher risk of acute kidney injury than cefepime combined with vancomycin.[43-48] However, the causal association and the mechanism of kidney injury are not completely identified. It is mainly related to the inhibition of creatinine secretion, and the clinical significance of the patient's prognosis is not significant.[49] By contrast, cefepime easily crosses the blood–brain barrier, which causes neurotoxicity that is characterized by symptoms such as decreased consciousness, aphasia, myoclonic myoclonus, seizures, and coma through concentration-dependent γ-aminobutyric acid antagonism.[50] In most cases, symptoms improve if the drug is discontinued. However, caution is required as no improvement is observed in some cases. Thus, clinical data on the difference in terms of mortality rates between cefepime and piperacillin/tazobactam in HAP/VAP is not sufficient to recommend the use of one agent. We agreed to make no recommendation for a preferred agent between piperacillin/tazobactam and cefepime for HAP/VAP.

Comparison of the current recommendations with those of other clinical practice guidelines

There are no clinical questions or recommendations regarding a preference between piperacillin/tazobactam and cefepime for HAP/VAP treatment in the 2016 ATS/IDSA and 2017

ERS/ESICM/ESCMID/ALAT guidelines.[3,4]

Key question 5.

Is empiric fluoroquinolone combination therapy compared with β-lactam monotherapy effective in decreasing mortality in patients with HAP/VAP who are at high risk of multidrug resistance and mortality?

PICO

Population	Patients with HAP/VAP who are at high risk of multidrug resistance and mortality
Intervention	Empiric combination therapy with fluoroquinolone
Comparator	Empiric beta-lactam monotherapy
Outcome	Mortality

Recommendation

We **suggest** empiric β-lactam plus fluoroquinolone combination therapy for patients with HAP/VAP who are at high risk of multidrug resistance and mortality (conditional recommendation, low-quality evidence).

Summary of evidence

In the 2016 ATS/IDSA guidelines, combination therapy with β-lactam and other classes of antipseudomonal antibiotics, which increases the appropriateness and clinical response of empiric treatment against multidrug-resistant gram-negative bacteria, was weakly

recommended for patients with HAP/VAP who are at high risk of multidrug resistance and mortality.[3] There was no difference in terms of mortality, clinical response, side effects, or incidence of resistance between monotherapy and combination therapy (**Table 5**).[51,52] Nevertheless, the applicability of these results may be limited since many of these studies excluded patients with comorbidities or colonization of resistant strains and allowed additional empiric treatment for *Pseudomonas aeruginosa* until the actual pathogen was identified. The 2017 ERS/ESICM/ESCMID/ALAT guidelines also strongly recommend combination therapy for high-risk patients with HAP/VAP, including those with septic shock and multidrug resistance. The target strains included methicillin-resistant *Staphylococcus aureus* and gram-negative bacteria.[4] However, no subsequent clinical trials have been conducted to support these recommendations. A Korean HAP/VAP multicenter study showed that 47.3% of initial empirical antibiotics were combination therapy. The most commonly used combination antibiotics were piperacillin/tazobactam (59.3%) and respiratory fluoroquinolone (32.1%).[6] In another Korean study that only analyzed patients from general wards in the same cohort, 70.8% of all combination therapies were β-lactam plus fluoroquinolones. However, combination therapy was not associated with a reduced mortality rate.[8] Therefore, we agreed that empirical combination therapy is unnecessary for patients with HAP/VAP who are at low risk of multidrug resistance and mortality. However, considering the current frequency of combination therapy in Korea with a high multidrug resistance rate and the fact that there are no data on the side effects and costs of combination therapy, we agree that combination therapy with β-lactam plus fluoroquinolone could be an empiric treatment for patients with HAP/VAP who are at high risk of mortality, such as those with septic shock. In addition, after empiric combination therapy, a gradual reduction should be followed. In particular, one or more antibiotics should be discontinued according to microbiological test results, and the antibiotic treatment duration

should be decreased if there are improvements in clinical signs.[53]

Comparison of the current recommendations with those of other clinical practice guidelines

The 2016 ATS/IDSA guidelines made a weak recommendation with low-quality evidence for empiric combination therapy of two antipseudomonal antibiotics, including β-lactams and other classes for patients with VAP who exhibit risk factors for multidrug resistance (history of intravenous antibiotic administration within 90 days, septic shock, acute respiratory distress syndrome, hospitalization for >5 days, and renal replacement therapy during VAP onset), patients admitted to units in which ≥10% of gram-negative bacteria are resistant to a single treatment, or patients admitted to units where local antibiogram data are not available.[3] In addition, empiric combination therapy of two antipseudomonal antibiotics with β-lactams and other classes is weakly recommended for patients with HAP only if there is a risk of mortality or multidrug resistance, such as those with a history of intravenous antibiotic treatment within 90 days (weak recommendation, very low-quality evidence).[3]

In the 2017 ERS/ESICM/ESCMID/ALAT guidelines, combination therapy is strongly recommended with moderate-quality evidence only for patients with high-risk HAP/VAP, including those with septic shock or risk factors for multidrug resistance (hospital environment with a high multidrug resistance rate, previous history of antibiotic use, long-term hospitalization of >5 days, and colonization of previous multidrug-resistant bacteria). In addition, the target strains included methicillin-resistant *Staphylococcus aureus* and gram-negative bacteria.[4]

Key question 6.

Should anaerobic coverage be considered in empiric antibiotic selection when treating HAP/VAP?

PICO

Population	Patients with HAP/VAP
Intervention	Considering anaerobic coverage
Comparator	Not considering anaerobic coverage
Outcome	Clinical response

Recommendation

We **suggest against** considering anaerobic coverage when selecting empiric antibiotics in patients with HAP/VAP (conditional recommendation, moderate-quality evidence).

Summary of evidence

The aging society is associated with an increasing rate of risk factors for aspiration, including chronic neurological disorders and tube feeding, among patients with HAP/VAP.[54-56] This key question was discussed because the limitations in identifying anaerobes may cause an underestimation of the potential role of anaerobes in patients with HAP/VAP.[57] Anaerobes were considered as major pathogens of aspiration pneumonia. In fact, 60%–90% of pathogens in aspiration pneumonia were anaerobes based on studies published until the late 1990.[57] However, according to more recent studies published after 2000, community-acquired pneumonia or HAP/VAP caused by aspiration had similar causative pathogens compared with the usual community-acquired pneumonia or HAP/VAP and revealed a low rate of anaerobes (1%–2%).[56,58] Moreover, an RCT comparing the efficacy and safety of moxifloxacin and

ampicillin/sulbactam in patients with aspiration pneumonia or lung abscess showed no significant intergroup differences in terms of main outcomes between the two agents.[59] Considering the results of a previous study and the notion that a subset of empirical HAP/VAP antibiotics is effective against anaerobes, we suggest against considering anaerobic coverage when selecting empiric antibiotics in patients with HAP/VAP.

Comparison of the current recommendations with those of other clinical practice guidelines

The 2016 ATS/IDSA and 2017 ERS/ESICM/ESCMID/ALAT guidelines do not have recommendations for anaerobic coverage in empiric antibiotic selection for patients with HAP/VAP.[3,4]

Key question 7.

Should combination therapy be used to treat patients with HAP/VAP caused by Pseudomonas infection?

PICO

Population	Patients with pseudomonas-related HAP/VAP
Intervention	Combination therapy
Comparator	Monotherapy
Outcome	Mortality

Recommendation

We **suggest against** combination antibiotics for patients with HAP/VAP caused by

Pseudomonas infection (conditional recommendation, moderate-quality evidence).

Evidence summary

If *P. aeruginosa* was identified as the causative strain in patients with HAP/VAP, combination therapy did not have any benefits.[60] There was also no difference in terms of mortality between monotherapy and combination therapy in pneumonia accompanied by *P. aeruginosa* bacteremia.[61] Accordingly, the 2016 ATS/IDSA guidelines recommend monotherapy if the risk of septic shock or mortality is not high in HAP/VAP caused by *P. aeruginosa.*[3] In a Korean retrospective observational study, combination therapy showed a trend toward reduced mortality in *P. aeruginosa* bacteremia.[62] However, in a recent meta-analysis involving pneumonia and bacteremia caused by *P. aeruginosa*, there was no evident association between combination therapy and mortality reduction (**Table 6**).[63] In multidrug-resistant *P. aeruginosa* pneumonia, the benefit of colistin-based combination therapy has been reported in severe pneumonia cases.[64,65] However, comparative clinical trials and meta-analyses that have been performed since then have not confirmed the benefits of combination therapy.[66-68] Ceftolozane/tazobactam, a recently approved multidrug-resistant *P. aeruginosa* therapy, has a higher cure rate and fewer side effects than colistin-based combination therapy. Previous studies have shown that monotherapy is recommended for multidrug-resistant *P. aeruginosa.*[67,69,70] Based on this notion, we recommend a single susceptible antibiotic treatment for HAP/VAP, in which *P. aeruginosa* has been identified as the causative strain. We agreed not to recommend combination therapy for HAP/VAP caused by *P. aeruginosa*.

Comparison of the current recommendations with those of other clinical practice guidelines

The 2016 ATS/IDSA guidelines recommend monotherapy for *P. aeruginosa*-induced HAP/VAP in cases where the risk of septic shock or mortality is not high (strong recommendation, low-quality evidence). However, combination therapy was recommended in cases with a high risk of mortality (weak recommendation, very low-quality evidence).[3] However, the 2017 ERS/ESICM/ESCMID/ALAT guidelines do not have relevant clinical questions or recommendations.[4]

In addition, the 2021 IDSA guidelines on the use of antibiotics related to multidrug-resistant pathogens do not recommend combination therapy for managing difficult-to-treat *P. aeruginosa*. If ceftolozane/tazobactam or other effective antimicrobials can be used, monotherapy is recommended.[69] The 2022 ESCMID guidelines for treating infections caused by multidrug-resistant gram-negative bacilli also recommend monotherapy for mild infections.[70]

Key question 8.

Should inhaled colistin be added to systemic colistin therapy for VAP caused by carbapenem-resistant gram-negative bacteria (CRGNB)?

PICO

Population	Patients with VAP caused by CRGNB
Intervention	Systemic plus inhaled colistin therapy (adjunctive therapy)
Comparator	Systemic colistin therapy alone
Outcome	Mortality, clinical resolution, bacterial eradication, and

nephrotoxicity

Recommendation

We **suggest** systemic plus inhaled colistin therapy (adjunctive therapy) for patients with VAP caused by CRGNB (conditional recommendation, low-quality evidence).

Summary of evidence

Whether colistin is an appropriate VAP treatment was not clear due to its low pulmonary tissue penetration rate when administered intravenously.[71] To overcome this, systemic plus inhaled colistin therapy (adjunctive therapy) has been proposed based on studies showing that inhaled colistin treatment could have a higher concentration in the lung tissue and lung epithelial lining fluid than intravenous colistin.[72,73] Retrospective studies have reported the use of adjunctive therapy in patients with VAP caused by multidrug-resistant *Acinetobacter baumannii* or *P. aeruginosa*. However, there was no significant difference in terms of mortality between patients with VAP patients with adjunctive therapy and those without.[74-79] However, adjunctive therapy was associated with a higher clinical cure rate (69.2% vs 54.8%, $P = 0.03$) and shorter mechanical ventilation time (8 vs 12 days, $P = 0.001$).[79] In addition, in an RCT on this issue, there was no difference in terms of clinical response (51% vs 53%, $P = 0.84$). However, regarding microbiological response, adjunctive therapy was superior to intravenous colistin monotherapy (60.9% vs 38.2%, $P = 0.03$).[80] Meanwhile, there was no significant difference in terms of side effects, such as renal toxicity and bronchoconstriction related to drug inhalation, between the two groups. In a meta-analysis comparing intravenous colistin monotherapy and adjunctive therapy for patients with VAP, no significant difference was observed in terms of mortality between the two groups. However, adjunctive therapy was superior to intravenous

monotherapy in terms of clinical response, microbiological eradication, and infection-related mortality. Further, there was no difference in terms of nephrotoxicity between the two groups.[81] Based on this, the 2016 ATS/IDSA guidelines recommend adjunctive therapy rather than intravenous monotherapy if the drug is the only sensitive antibiotic for patients with VAP caused by gram-negative rod bacilli.[3] In a Korean retrospective observational study of VAP caused by CRGNB, adjunctive therapy had a higher microbiological eradication rate and a lower overall mortality rate than intravenous monotherapy.[82] In a Taiwanese multicenter observational study, adjunctive therapy had a lower treatment failure rate than intravenous monotherapy.[83] Based on these results (**Table 7**), we agreed that inhaled colistin therapy can be added to systemic therapy for treating VAP caused by CRGNB.

Comparison of the current recommendations with those of other clinical practice guidelines

The 2016 ATS/IDSA guideline recommends adjunctive therapy if colistin is the only susceptible antibiotic (weak recommendation, very low-quality evidence).[3] There are no relevant clinical questions or recommendations in the 2017 ERS/ESICM/ESCMID/ALAT guidelines.[4]

However, the 2022 ESCMID guidelines for treating infections caused by multidrug-resistant gram-negative bacilli recommended avoiding inhaled therapy because there is no sufficient evidence showing that adjunctive therapy have clear clinical benefits. Further, safety, particularly the prevention of respiratory side effects, is challenging to ensure (weak recommendation, very low-quality evidence).[70] In addition, the recently published IDSA guidelines for treating carbapenem-resistant *A. baumanii* infection do not recommend the use of inhaled colistin as adjunctive therapy as it lacks clinical benefit and there are concerns regarding unequal distribution in the infected lungs and respiratory complications such as

bronchoconstriction in 10%–20% of patients receiving inhaled antibiotics.[86]

Key question 9.

Should the duration of antimicrobial therapy for HAP/VAP be shortened to 7–8 days (short-course therapy), compared with 10–15 days (long-course therapy), without increasing the rate of relapsing infections?

PICO

Population	Patients with HAP/VAP
Intervention	Antimicrobial therapy for 7–8 days
Comparator	Antimicrobial therapy for 10–15 days
Outcome	HAP/VAP relapse

Recommendation

We **suggest** shortening the duration of antimicrobial therapy to 7–8 days in patients with HAP/VAP who exhibit a good clinical response to antimicrobial therapy (conditional recommendation, moderate-quality evidence).

Summary of evidence

In a previous study, the ATS guidelines recommended that HAP/VAP should be treated for at least 14–21 days.[87] However, the recommendations differed based on the severity of diseases, time to clinical response, and the causative organisms. Moreover, short-term treatment (7–10 days) had been recommended for HAP/VAP caused by methicillin-sensitive *S. aureus* or *H.*

influenza.[87] Subsequent comparative clinical studies revealed that short-term treatment did not differ with traditional long-term treatment in terms of clinical results[88,89] based on the 2005 revised ATS/IDSA guidelines that exerted efforts to shorten the treatment period from 14–21 to 7 days.[1] However, pneumonia caused by non-glucose fermenting gram-negative bacillus (GNB) was more likely to have a higher recurrence rate in patients receiving short-term treatment.[89] Thus, short-term treatment was recommended only if the causative organism was not *P. aeruginosa* and if the patient had a good clinical response.[1] Moreover, the 2016 ATS/IDSA guidelines also confirmed no significant difference in terms of mortality, cure, and recurrence rates between patients receiving short-term treatment (7–8 days) and those receiving long-term treatment (10–15 days).[3] Previous meta-analyses of VAP caused by non-glucose-fermenting GNBs, mostly containing *Pseudomonas* and *Acinetobacter*, showed that patients receiving short-term were at higher risk of recurrence.[90,91] however, the updated meta-analysis of the 2016 ATS/IDSA guidelines did not show difference in terms of recurrence and mortality.[3] In a recent clinical trial of the non-inferiority for pneumonia recurrence between patients who received short-term antibiotic treatment (8 days) and long-term antibiotic therapy (15 days) in patients with VAP caused by *P. aeruginosa*, the recurrence of pneumonia differed by 7.9% (9.2% in the 15-day group and 17% in the 8-day group). Moreover, there was an increasing trend in the length of ICU stay and mortality rate in the 8-day group.[92] However, the results should be cautiously interpreted because the study was terminated early due to difficulties in registering the participants. Based on the recent data, we agreed that short-course antibiotic therapy requires attention in patients with VAP caused by non-glucose-fermenting GNB, in light of the recent evidence indicating that the risk of recurrence may increase in patients with VAP caused by non-glucose-fermenting GNB who receive short-course therapies (**Table 8**).

Comparison of the current recommendations with those of other clinical practice guidelines

The 2016 ATS/IDSA guidelines recommend 7-day antimicrobial therapy rather than a longer-course treatment (strong recommendation, moderate-quality evidence).[3] Based on existing evidence showing that the risk of recurrence may increase in patients receiving short-course antibiotic therapy, separate recommendations were considered for patients with VAP caused by glucose non-fermenting GNB. However, no other recommendations were made as a slight increase in recurrence rates did not affect mortality and clinical cure rates. The 2017 ERS/ESICM/ESCMID/ALAT guidelines suggest the use of 7–8-day antibiotic therapy in patients with HAP/VAP patients without immunodeficiency, cystic fibrosis, empyema, lung abscess, or cavitation or necrotizing pneumonia and with a good clinical response to therapy (weak recommendation, moderate-quality evidence.[4] In addition, the guidelines recommend that patients who have received inadequate initial empirical treatment may require a longer antibiotic treatment and that the treatment must be individualized according to the patient's clinical response, specific bacterial findings, and serial biomarker measurements.[4]

Key question 10.

Should antimicrobial therapy be de-escalated in patients with HAP/VAP?

PICO

Population	Patients with HAP/VAP
Intervention	Antimicrobial de-escalation
Comparator	No antimicrobial de-escalation

Outcome	Clinical outcomes (mortality, length of stay, and recurrent infection), superinfection, duration of antimicrobial therapy, treatment cost, and the emergence of a resistant pathogen

Recommendation

We **suggest** antimicrobial de-escalation via one or more of the following in patients with HAP/VAP (conditional recommendation, moderate-quality evidence):

1. Narrowing the spectrum of an antimicrobial based on the results of microbiology studies
2. Discontinuation of treatment with one or more antimicrobials based on the results of microbiology studies
3. Shortening the therapy if the patient shows signs of clinical improvement

Summary of evidence

In 2001, antimicrobial de-escalation in patients with HAP/VAP was publicized for the first time at the Consensus Conference on the Diagnosis and Treatment of VAP.[95] Subsequently, the ATS, Task Force of Three European Societies, ERS, ESCMID, and ESICM recommended the de-escalation of antibiotics in HAP/VAP treatment.[1,2] Two randomized clinical studies and five observational studies were analyzed in the 2016 ATS/IDSA guidelines.[3] They recommend antimicrobial de-escalation in HAP/VAP treatment based on expert opinions that they are beneficial because of reduced antibiotic side effects, resistance, and low antibiotic costs. According to a meta-analysis of antimicrobial de-escalation in patients with pneumonia who are admitted to the ICU that was published later, antimicrobial de-escalation is advantageous over fixed treatment in terms of 15-day mortality, length of hospital stay, and antibiotic cost. However, most evaluation parameters were not significant.[96] Subsequent observational studies

have not identified consistent advantages in evaluation parameters other than cost reduction due to antimicrobial de-escalation.[97-99] However, only a few studies have evaluated antibiotic de-escalation in patients with HAP/VAP patients, and most of them are observational studies. Hence, there is a possibility of selection bias. Further, there are few studies on the development of resistance due to the de-escalation therapy are accepted as limitations. Therefore, the results of related studies cannot be accepted as they are. The recently announced definition of antimicrobial de-escalation is narrowing the spectrum of antibiotics based on microbiological test results, causing the discontinuation of one or more antibiotics based on microbiological test results, and shortening the duration of antibiotic treatment if clinical signs improve.[53] Based on the recently published definition of antimicrobial de-escalation, we agreed on the need for antimicrobial de-escalation, with consideration of the benefits of reducing the length of hospital stay and antibiotic cost and the antibiotic stewardship program (**Table 9**).

Comparison of the current recommendations with those of other guidelines

In the 2016 ATS/IDSA guidelines, two RCTs and five observational studies were analyzed.[3] Antimicrobial de-escalation was not associated with a significant difference in mortality rate and length of ICU stay compared with fixed treatment. The results on recurrence of pneumonia, duration of antibiotic use, presence of superinfection, and development of resistant strain were conflicting. Nevertheless, antimicrobial de-escalation was recommended, and this reflects the experts' opinion that antimicrobial de-escalation has advantages in terms of reducing antibiotic costs and reducing side effects and resistance caused by antibiotic use (weak recommendation, very low-quality recommendation). The 2017 ERS/ESICM/ESCMID/ALAT guidelines had no relevant clinical key questions or recommendations.[4]

Key question 11.

Should antibiotics be discontinued according to procalcitonin plus clinical criteria for patients with HAP/VAP whose duration of therapy should be individualized (e.g., resistant pathogens, initially inappropriate antibiotics, or immunocompromised hosts)?

PICO

Population	Patients with HAP/VAP requiring antibiotic treatment with individualized durations
Intervention	Procalcitonin plus clinical criteria
Comparator	Clinical criteria alone
Outcome	Antibiotic duration and treatment outcomes (mortality rate, mechanical ventilation duration, and length of stay)

Recommendation

We **suggest** discontinuing antibiotic therapy according to procalcitonin plus clinical criteria in patients with HAP/VAP whose therapy duration should be individualized (e.g., resistant pathogens, initially inappropriate antibiotics, and immunocompromised hosts) (conditional recommendation, moderate-quality evidence).

Summary of evidence

In a meta-analysis including 14 studies with 4,221 patients with acute respiratory infections, discontinuing antibiotic therapy according to procalcitonin level plus clinical criteria reduced the therapy duration for approximately 3.5 days compared with discontinuing antibiotic therapy

based on clinical criteria alone. In addition, there were no intergroup differences in terms of mortality and treatment failure rates.[100] Previous meta-analysis evaluating acute respiratory infections in patients with HAP/VAP has limitations. Thus, the 2016 ATS/IDSA guidelines performed a meta-analysis, including three RCTs of 308 patients with VAP.[3] Other studies also revealed that the procalcitonin group had a significantly shorter duration of antibiotic therapy than the control group (9.1 vs 12.1 days, $P < 0.001$). Further, there were no intergroup differences in terms of mortality rate, days of mechanical ventilation, and length of ICU and hospital stay.[3,101-103] In a succeeding RCT evaluating approximately 1,600 patients with critical illness, the procalcitonin group also had a shorter antibiotic duration by 2.7 days than the control group (95% CI: 1.26–4.12 days, $P < 0.001$).[104] However, previous studies have shown that the duration of antibiotic therapy has decreased in the control groups who discontinued antibiotic treatment without considering procalcitonin levels (from approximately 15 to 9.3 days in a study published in 2009 and 2016) (**Table 10**). Considering the decreasing tendency in antibiotic duration, the role of procalcitonin in decreasing the duration of antibiotic therapy in patients with HAP/VAP who can be treated with a short (7–8 days) course of antibiotics may be extremely limited. Thus, we suggest discontinuing antibiotics according to procalcitonin plus clinical criteria in patients with HAP/VAP whose therapy duration should be individualized, which included those with HAP/VAP caused by non-glucose fermenting gram-negative bacilli (*Pseudomonas* and *Acinetobacter*),[89] those with HAP/VAP caused by other resistant pathogens, including carbapenem-resistant Enterobacteriaceae and methicillin-resistant *Staphylococcus aureus*, and a subset of patients with HAP/VAP who were excluded from previous RCTs (i.e., inappropriate antibiotics used as initial agents and immunocompromised hosts).

Comparison with the current recommendations with those of other guidelines

The 2016 ATS/IDSA guidelines recommend considering both procalcitonin level and clinical criteria when discontinuing antibiotic treatment in patients with HAP/VAP (weak recommendation, low-quality evidence).[3] It was weakly recommended as the benefits of using procalcitonin levels, which are used to determine whether or not to discontinue antibiotic therapy in cases where standard antibiotic therapy for HAP/VAP is already 7 days or less, have not been identified.[3] The 2017 ERS/ESICM/ESCMID/ALAT guidelines do not recommend the routine measurement of serial procalcitonin levels for reducing the duration of antibiotic therapy in patients with HAP/VAP patients if the anticipated duration is 7–8 days (strong recommendation, moderate-quality evidence).[4] However, the guidelines recommend the measurement of serial serum procalcitonin levels along with clinical assessment in specific clinical circumstances (i.e., HAP/VAP caused by non-glucose fermenting gram-negative bacilli or other resistant pathogens or immunocompromised hosts [good practice statement]).

Conclusion

Several international guidelines for the diagnosis and treatment of adult patients with HAP/VAP have been published. However, the treatment for nosocomial infections should reflect local epidemiology, microbial resistance, and healthcare utilization patterns. This notion provided momentum for the development of the first Korean guidelines for HAP/VAP, which aims to apply the most updated evidence to this document and optimize it for HAP/VAP practice in Korea. These guidelines contain 11 key questions and recommendations, along with relevant evidence.

Notes

Authors' contributions

Conceptualization: Jeon K. Methodology: all authors. Formal analysis: all authors. Software: all authors. Validation: all authors. Investigation: all authors. Writing – original draft preparation: Choi H, Min KH, Lee YS, Chang Y, Oh JY, Baek AR, Lee J, and Jeon K. Writing – review and editing: all authors. Approval of the final manuscript: all authors.

Conflicts of interest

The authors declare no potential conflict of interest related to this article.

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Table 1. Key questions and recommendations

Key questions	Recommendations
Question 1: Should quantitative cultures using invasive sampling be performed for pathogen identification in patients with suspected VAP?	We **suggest against** routine quantitative cultures using invasive sampling for pathogen identification in patients with suspected VAP (conditional recommendation, moderate-quality evidence).
Question 2: Should treatment decisions be made based on procalcitonin plus clinical criteria in patients with suspected HAP/VAP?	We **suggest against** treatment decisions based on procalcitonin plus clinical criteria for patients with suspected HAP/VAP (conditional recommendation, moderate-quality evidence).
Question 3: Should PCR tests be performed to assess for atypical pathogens in patients with HAP/VAP?	We **suggest against** PCR test for atypical pathogens in patients with HAP/VAP (conditional recommendation, moderate-quality evidence).
Question 4: Is empiric piperacillin/tazobactam, compared with cefepime, effective in decreasing mortality rates in patients with HAP/VAP?	We make **no suggestion** for using specific antibiotics (piperacillin/tazobactam or cefepime) in the empiric treatment for patients with HAP/VAP (inconclusive, low-quality evidence).
Question 5: Is empiric fluoroquinolone combination therapy, compared with β-lactam monotherapy, effective in decreasing mortality in patients with HAP/VAP who are at high risk for multidrug resistance and mortality?	We **suggest** empiric β-lactam plus fluoroquinolone combination therapy in patients with HAP/VAP who are at high risk of multidrug resistance and mortality (conditional recommendation, low-quality evidence).
Question 6: Should anaerobic coverage be considered in selecting empiric antibiotics when treating patients with HAP/VAP?	We **suggest against** considering anaerobic coverage when selecting empiric antibiotics in patients with HAP/VAP (conditional recommendation, moderate-quality evidence).
Question 7: Should combination therapy be used to treat patients with HAP/VAP caused by Pseudomonas infection?	We **suggest against** combination antibiotics for patients with HAP/VAP caused by Pseudomonas infection (conditional recommendation, moderate-quality evidence).
Question 8: Should inhaled colistin be added to systemic colistin therapy for VAP caused by carbapenem-resistant gram-negative bacteria?	We **suggest** systemic plus inhaled colistin therapy (adjunctive therapy) in patients with VAP caused by carbapenem-resistant gram-negative bacteria (conditional recommendation, low-quality evidence).
Question 9: Should the duration of antimicrobial therapy for HAP/VAP be	We **suggest** shortening the duration of antimicrobial therapy to 7–8 days in patients

shortened to 7–8 days (short course therapy), compared with 10–15 days (long course therapy), without increasing the rate of relapsing infections?	with HAP/VAP who have good clinical response to antimicrobial therapy.
Question 10: Should antimicrobial therapy be de-escalated in patients with HAP/VAP?	We **suggest** antimicrobial de-escalation via one or more of the following in patients with HAP/VAP (conditional recommendation, moderate-quality evidence): 1. Narrowing the spectrum of an antimicrobial based on the results of the microbiology studies 2. Discontinuation of one or more antimicrobials based on the results of the microbiology studies 3. Shortening the therapy if the patient shows signs of clinical improvement
Question 11: Should antibiotic treatment be discontinued according to procalcitonin plus clinical criteria in patients with HAP/VAP whose therapy duration should be individualized (including those with resistant pathogens, those who initially received inappropriate antibiotics, and those with immunocompromised hosts)?	We **suggest** discontinuing antibiotics according to procalcitonin plus clinical criteria in patients with HAP/VAP whose therapy duration should be individualized (e.g., resistant pathogens, initially inappropriate antibiotics, and immunocompromised hosts) (conditional recommendation, moderate-quality evidence).

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; PCR, polymerase chain reaction

Table 2. Comparison of mortality in patients with VAP treated based on quantitative culture results using invasive procedures and those treated according to qualitative culture results using trans-tracheal aspiration.

Study	No. of Patients	Mortality		
		Quantitative cultures using invasive sampling	Qualitative cultures using trans-tracheal aspirate	
Heyland D et al. 2006[17]	740	18.9%	18.4%	28-Day mortality (P = 0.94)
Fagon JY et. al., 2000[18]	413	16.2%	25.8%	14-Day mortality (P = 0.022)
Ruiz M et al. 2000[19]	76	38%	46%	30-Day mortality (P = 0.46)
Violán JS et al. 2000[20]	91	22.2%	20.9%	Overall mortality (P = NS)
Sanchez-nieto JM et al. 1998[21]	51	46%	26%	Crude mortality (P = NS)

NS, not significant

Table 3. Performance characteristics of serum procalcitonin for HAP/VAP diagnosis

Study	Year	No. of Patients	Category	Cutoff value	Sensitivity	Specificity
Duflo F et al.[31]	2002	96	VAP	3.9 ng/mL	41%	100%
Luyt CE et al.[28]	2008	41	VAP	0.5 ng/mL	72%	24%
Ramirez P et al.[29]	2008	44	VAP	2.99 ng/mL	78%	97%
Dallas J et al.[30]	2011	104	HAP/VAP	1 ng/mL	50%	49%

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia

Table 4. Comparison of mortality rates between the piperacillin/tazobactam and cefepime groups in different studies with various designs and populations.

Study	Study design and population	Mortality rate		P-value or 95% CI
		piperacillin/tazobactam	cefepime	
Ross et al., 2021[37]	A retrospective cohort study of patients with septic shock (n = 120)	ICU: 37.5% 30-day: 52.5%	55.8% 65.8%	P < 0.01 P = 0.049
Smith et al., 2020[38]	A retrospective cohort study of patients with septic shock (n = 400)	ICU: 39.8% 30-day: 50.8%	52.8% 65.3%	P < 0.05 P < 0.05
Lee, 2018[40]	A retrospective cohort study of patients with severe community-acquired pneumonia who were admitted to the ICU (n = 43)	18%	14%	NS
Yahav et al., 2007[39]	A systematic review and meta-analysis with febrile neutropenia (n=814)	15/416	30/398	2.14 (1.17–3.89)

ICU, intensive care unit; CI, confidence interval; NS, not significant

Table 5. Comparison of the mortality rates of patients with HAP/VAP between the beta-lactam monotherapy group and the fluoroquinolone combination therapy group

Study	Study population and design	Mortality		Effect size (P-value or 95% CI)
		Monotherapy	Fluoroquinolone Combination therapy	
Damas et al., 2006[51]	RCT of patients with VAP	Cefepime (n = 20)	Cefepime + levofloxacin (n = 20) Cefepime + amikacin (n = 19)	No difference (P = 0.74)
Heyland et al., 2008[52]	RCT of patients with late VAP	Meropenem 25.6% (10/39)	Meropenem + levofloxacin 29.4% (5/17)	RR: 1.05 (95% CI: 0.78–1.42, P = 0.74)

RCT, randomized controlled trial; RR, relative risk; CI, confidence interval.

Table 6. Comparison of mortality rate between monotherapy and combination therapy for pseudomonas infection in various studies with different designs and populations.

Study	Study design	Mortality		P-value
		Monotherapy	Combination	
Garnacho-Montero et al., 2007[60]	Observational, multicenter study	12/34 (35.3%)	60/144 (41.7%)	0.69
Peña et al., 2013[61]	Post hoc analysis of a prospective cohort	70/339 (20.6%)	13/71 (18.3%)	0.97
Park et al., 2012[62]	Retrospective cohort study	17/32 (53.1%)	10/33 (30.3%)	0.01
Onorato et al., 2022[63]	Meta-analysis of 19 studies	537/2563 (20.9%)	283/1244 (22.7%)	0.658

Table 7. Comparison of patients with VAP who presented with carbapenem-resistant gram-negative bacilli treated with colistin systemic therapy alone versus systemic plus inhaled colistin therapy (adjunctive therapy)

Study	Study design /number of patients (systemic therapy + inhaled therapy vs systemic therapy alone)	Pathogens	Outcome measures (systemic plus inhaled therapy vs systemic therapy alone)		
			Clinical response, %	Mortality, %	Nephrotoxicity, %
Rattanaumpawan et al., 2010[80]	Randomized controlled trial (51 vs 49)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	51 vs 53	39 vs 45	22 vs 27
Korbila et al., 2010[74]	Retrospective cohort study (78 vs 43)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	79 vs 60	40 vs 44	-
Kofteridis et al., 2010[75]	Case-control study (43 vs 43)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	74 vs 60	23 vs 42	19 vs 19
Naesens et al., 2011[76]	Retrospective cohort study (9 vs 5)	*P. aeruginosa*	78 vs 40	67 vs 100	11 vs 60
Kalin et al., 2012[77]	Retrospective cohort study (29 vs 15)	*A. baumanii*	14 vs 40	55 vs 47	41 vs 20
Doshi et al., 2013[78]	Retrospective cohort study (44 vs 51)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	100 vs 100	36 vs 53	-
Tumbarello et al., 2013[79]	Case-control study (104 vs 104)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	69 vs 55	43 vs 46	25 vs 22
Demirdal et al., 2016[84]	Matched case-control study (43 vs 80)	*A. baumanii*	40 vs 56	53 vs 48	49 vs 54
Choe et al., 2019[82]	Retrospective cohort study (35 vs 86)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	49 vs 42	23 vs 49	59 vs 38
Feng et al., 2021[83]	Retrospective cohort study (181 vs 326)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	59 vs 54	31 vs 33	-
Bao et al., 2022[85]	Propensity score- matched	*Multidrug-resistant gram-*	68 vs 32	32 vs 45	16 vs 10

	case-control study (31 vs 31)	*negative bacteria*			

Table 8. Comparison of relapse rates in patients with VAP caused by non-glucose fermenting gram-negative bacilli between the short- and long-course treatment groups from the randomized controlled trials

Study	Pathogens	Relapse		Follow-up period
		Short-course treatment	Long-course treatment	
Chastre et al., 2003[89]	*P. aeruginosa*, *A. baumanii*, *S. maltophilia*	40.6% (26/64)	25.4% (16/63)	28 days
Medina et al., 2007[93]	*P. aeruginosa*, *A. baumanii*	44.4% (12/27)	22.7% (5/22)	NA
Fekih Hassen et al., 2009[94]	*P. aeruginosa*, *A. baumanii*	14.3% (2/14)	12.5% (2/16)	ICU stays
Bouglé et al., 2022[92]	*P. aeruginosa* only	17.0% (15/88)	9.2% (9/98)	90 days

NA, not applicable; ICU, intensive care unit

Table 9. Summary of the treatment outcomes of antibiotic de-escalation versus non-de-escalation in patients with HAP/VAP.

Antibiotic de-escalation in patients with HAP/VAP (vs. non-de-escalation)		
Mortality		Similar
Length of hospital stay	ICU	Similar (decrease?)
	Hospital	Decrease
Recurrent infection		Controversial, similar?
Superinfection		Controversial
Antibiotic duration		Controversial, decrease?
Emergence of resistant pathogens		Increase?
Cost (antibiotics, hospitalization)		Decrease

ICU, intensive care unit

Table 10. Comparison of the duration of antibiotic treatment between procalcitonin level plus clinical criteria and clinical criteria alone in patients with HAP/VAP

Study	Duration of antibiotic therapy, days		Other outcomes
	Procalcitonin group	Control group	
Stolz et al., 2009[101]	10	15	No intergroup differences in the number of MV-free days, ICU-free days, LOS in the hospital, and 28-day mortality rate
Bouadma et al., 2010[102]	10.3	13.3	The mortality rate of the PCT group was not inferior to that of the control group at days 28 and 60
De Jong et al., 2016[104]	7.5	9.3	The mortality rate of the PCT group decreased compared with that of the control group

MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay; PCT, procalcitonin.

Figure legend

Figure 1. The Convergence of Opinion on Suggestions and Evidence process. PICO: Patient, Intervention, Comparator, Outcome