Hospital-Acquired Pneumonia: The Lebanese Societies for Pulmonary, Critical Care, and Infectious Diseases and Clinical Microbiology Joint Guidelines

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Research Article

Keywords: antibiotics, guidelines, hospital-acquired pneumonia, intensive care unit, Lebanon, mechanical ventilation, nosocomial pneumonia, ventilator-associated pneumonia

Posted Date: May 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-398183/v1

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Abstract

Background: The Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM), the Lebanese Society of Critical Care Medicine (LSCCM), and the Lebanese

Pulmonary Society (LPS) play a major role in guiding clinicians across Lebanon in prescribing antibiotics for the management of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Members of these societies have tailored the international recommendations for the management of HAP/VAP to local epidemiological and microbiological data. The aims of these local guidelines are to guide clinicians in the prevention of VAP, selection of appropriate empiric and targeted antimicrobial regimens for VAP/HAP and to contribute to improving patient outcomes.

Methods: Recommendations in these guidelines are adapted from international guidelines and are modeled based on locally-derived epidemiological and microbiological data, as well as the availability of antimicrobial agents and other resources.

Results: These guidelines aim to combine both clinical and bacteriological strategies to appropriately diagnose and manage HAP/VAP. They recommend implementing evidence-based preventive measures to lower the rate of VAP and improve patient outcomes. The recommended duration of treatment with antibiotics in general should not exceed 7 days in patients with HAP whereas it should be 7–8 days in patients with VAP. Imunnosuppressed patients with *Pseudomonas aeruginosa* infection might require longer courses. Ceftolozane/tazobactam (CFT/TAZ) and ceftazidime/avibactam (CAZ/AVI) are considered good options in patients with HAP/VAP caused by extended spectrum beta-lactamase-producing Enterobacterales and multidrug-resistant *Pseudomonas aeruginosa*. They also play a key role in the implementation of a carbapenem-sparing strategy in an antimicrobial stewardship program.

Conclusion: These guidelines represent a major step towards establishing Lebanese national guidelines for the management of HAP/VAP. They also emphasize on timeliness and appropriateness of antibiotic therapy for the management of HAP/VAP.

Keywords: antibiotics; guidelines; hospital-acquired pneumonia; intensive care unit; Lebanon; mechanical ventilation; nosocomial pneumonia; ventilator-associated pneumonia

1. Background

Nosocomial pneumonia (NP) is the most common nosocomial infection observed among patients in the intensive care unit (ICU). NP includes hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) which are associated with life-threatening complications and increased morbidity and mortality (1).

Different rates of HAP/VAP have been reported from varying regions around the world. In 2013, the National Healthcare Safety Network (NHSN) reported that the average rate of VAP in the United States of America (USA) was 1–2.5 cases/1000 days of mechanical ventilation (MV) (2). A recent study from the USA revealed a rate of HAP of 1.6% in hospitalized patients (3). The European Center for Disease Prevention and Control (ECDC) described that the rate of VAP was 8.9 episodes/1000 days of MV (4), and the prevalence of HAP was 1.3% (5). In the Middle East, a multicenter study by the Gulf Cooperation Council reported a VAP rate of 4.8 per 1000 ventilator days according to data collected from Oman, Bahrain, and Saudi Arabia (6). Recently, a study from a tertiary care center in Lebanon over a 10-year period reported a VAP rate of 7.9 per 1000 ventilator-days and examined the causative bacterial pathogens (7).

Mortality has been reported to be significantly increased in patients with HAP. Micek et al. (8) reported that patients with HAP have an 8.4-fold increased risk of death, an 8-fold increase in need for MV, and a longer duration of hospitalization compared with patients without HAP. Among

ICU patients, crude mortality of HAP and VAP was the same (9). Recently, an analysis of seven clinical trial datasets showed that ICU patients with ventilated-HAP (vHAP) had the highest all-cause mortality rate at day 28 (27.8%), followed by VAP (18%) and non-ventilated HAP (NV-HAP) (14.5%) (10).

HAP has been associated with serious complications including respiratory failure, pleural effusions, septic shock, renal failure, and empyema (1). In addition, studies estimated that VAP prolongs the length of MV by 7.6 to 11.5 days and hospitalization by 11.5 to 13.1 days compared to similar patients without VAP (11,12). Moreover, HAP/VAP cause an increased cost of care and considerable financial burden where the excess cost was estimated to be approximately $40,000 per patient (3,12).

The NHSN data reports from 2016 showed that *Staphylococcus aureus* (24.7%) was the most prevalent pathogen causing VAP in the USA followed by *Pseudomonas aeruginosa* (16.5%) (13). A study that assessed the microbiological etiologies of HAP/VAP in USA, Europe, and Latin America found that the incidence of pathogens causing HAP/VAP was consistent over more than 10 years with the 6 most prevalent pathogens being *S. aureus* (28%), *P. aeruginosa* (21.8%), *Klebsiella* species (9.8%), *Escherichia coli* (6.9%), *Acinetobacter* species (6.3%), and *Enterobacter* species (6.8%). These pathogens were responsible for around 80% of HAP or VAP episodes; *P. aeruginosa* and *Acinetobacter* species were more common in VAP cases (14).

Data on HAP/VAP epidemiology, microbiology, and susceptibility of causative organisms from the Arab countries in the Middle East are scarce. **Table 1** summarizes the findings of 3 studies from Lebanon. In a 10-year study from Lebanon, *S. aureus, P. aeruginosa, Klebsiella* species, *E. coli, Acinetobacter* species, and *Enterobacter* species were the most common pathogens associated with VAP (7). Despite being comparable to data from western countries, such data

might not be representative on the national level and variation from one institution to another is possible. A recent report proposed a VAP treatment algorithm based on international guidelines and tailored to local hospital microbiology (15).

HAP/VAP are associated with multidrug-resistant organisms (MDROs) leading to poor outcomes. Susceptibility data in pathogens isolated from VAP cases showed extensively and multidrug-resistant (MDR) pathogens, including *Acinetobacter* species and *P. aeruginosa*, to be prevalent (7,16).

Table 1. Distribution of bacteria causing VAP according to local studies

Organism	Kanafani et al. 2003 (16)	Awad et al. 2018 (15)	Kanafani et al. 2019 (7)
Acinetobacter baumannii	-	37.33%	32.6%
Acinetobacter anitratus	24%	-	-
Pseudomonas aeruginosa	17.4%	30.67%	16.5%
Enterobacterales	-	14.67%	-
Klebsiella species	13%	-	8.3% *
Escherichia coli	10.9%	-	12.4%
Enterobacter species	4.3%	-	5%
Stenotrophomonas maltophilia	6.5%	12%	6%
Coagulase-negative *staphylococci*	10.9%	-	-
Staphylococcus aureus	6.5%	4%	4.6%
Others	6.5%	1.33%	3.7%
Serratia marcescens	-	-	3.7%

Proteus mirabilis	-	-	3.7%
Citrobacter species	-	-	2.3%
Burkholderia cepacia	-	-	1.4%

* *Klebsiella pneumoniae*

The extensive and random use of antibiotics, particularly broad-spectrum agents, imposes a substantial financial burden on hospitals and national healthcare systems, and increases the risk of emergence of MDROs. International recommendations for the management of HAP/VAP have to be tailored to local epidemiological and microbiological data. Thus, establishing national guidelines is essential to guide clinicians in the selection of appropriate empiric and targeted antimicrobial regimens. In addition to implementing preventive bundles, these guidelines would contribute to improving patient outcomes. These present guidelines were developed by a panel including presidents and president elects of the 3 societies: the Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM) (6 members), Lebanese Society of Critical Care Medicine (LSCCM) (6 members), and the Lebanese Pulmonary Society (LPS) (5 members).

2. Methods

We reviewed the epidemiology of HAP/VAP worldwide and in Lebanon. Our recommendations are adapted from international guidelines and are modeled based on locally-derived susceptibility data and on the availability of various antimicrobial agents and other resources. These guidelines describe detailed recommendations about diagnosis, prevention, and assessment of these infections, identification of risk factors, and antimicrobial management in adults with HAP/VAP.

Moreover, these guidelines describe the experience of two major Lebanese medical centers with antimicrobial stewardship and the impact of COVID-19 and influenza viruses pandemics on the clinical presentation and management of bacterial pneumonia. The international guidelines reviewed herein are:

- The 2016 clinical practice guidelines of the Infectious Diseases Society of America and the American Thoracic Society for the management of adults with hospital-acquired and ventilator-associated pneumonia (1).
- The 2017 international guidelines of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT) for the management of HAP/VAP (20).
- The ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients (57).
- The clinical practice guidelines of the Association of Medical Microbiology and Infectious Disease Canada and the Canadian Thoracic Society for HAP/VAP in adults (21).
- The joint guidelines of the Indian Chest Society (ICS) and the National College of Chest Physicians (NCCP) of India for diagnosis and management of community-acquired pneumonia (CAP) and HAP in adults (22).
- The guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) for NP (33).

- The guidelines of the American Thoracic Society and Infectious Diseases Society of America for the management of adults with HAP/VAP, and healthcare-associated pneumonia (63).
- The guidelines of the Spanish Society of Chemotherapy for antibiotic selection in the treatment of acute invasive infections by *P. aeruginosa* (79).

3. Results

3.1. Definition of HAP/VAP

HAP is a pneumonia that occurs 48 hours or more after admission which was not incubating at the time of admission and not associated with MV. VAP is a pneumonia that arises after more than 48 hours of MV. vHAP is a pneumonia that occurs 48 hours or more after admission which was not incubating at the time of admission and not associated with MV. It occurs in patients with severe HAP who require MV. ICU HAP is defined as a pneumonia that occurs 48 hours or more after ICU admission. Besides being associated with MDROs, vHAP has the highest mortality rate compared to VAP and non-ventilated HAP, a poor clinical prognosis, and the poorest clinical outcome (17,18). Therefore, optimal antibiotic therapy should be selected and guided by local susceptibility rates and MDROs risk factors.

3.2. Assessment and Diagnosis

The clinical criteria for the diagnosis of VAP have a high sensitivity but a low specificity; critically ill ventilated patients can develop complications such as atelectasis, pulmonary edema, pulmonary

embolism, and pulmonary trauma that may closely resemble VAP (19) and that need to be considered in the differential diagnosis.

In addition to the clinical signs of respiratory infections (cough, sputum production, chest pain, fever), the assessment of the patient should include:

- Radiological tests,
- Respiratory sample cultures,
- Analytical determinations,
- Scores from various rating scales such as the Clinical Pulmonary Infection Scale (CPIS) (20).

3.2.1 Clinical assessment

The diagnosis is usually made when a patient develops symptoms including fever, purulent tracheobronchial secretions, and a new or changing pulmonary infiltrate or a new onset of leukocytosis (21). Patients with a strong suspicion of VAP/HAP but insufficient evidence for infection must be re-evaluated periodically (22). Risk stratification regarding the acquisition of MDROs should be assessed to guide decisions on empiric antibiotic treatment (22).

A good practice in patients receiving antibiotherapy for VAP/HAP consists of doing a routine bedside clinical assessment (20). This assessment consists of measuring body temperature, performing a culture of the tracheobronchial secretion and assessing its purulence and volume, evaluating the resolution of the chest radiograph infiltrate, evaluating white blood cell count and arterial oxygen pressure/inspiratory oxygen fraction (PaO_2/FiO_2), and calculating at least 1 of the following scores: Acute Physiology and Chronic Health Evaluation II (APACHE II), CPIS, Organ

Dysfunction and Infection System (ODIN), Simplified Acute Physiological Score II (SAPS II), and Sequential Organ Failure Assessment (SOFA) (20).

Treatment is considered successful or the bacteria are eradicated in case of negative findings. Negative findings can also suggest that the lung infection was not present initially, so antimicrobial therapy should be adjusted or discontinued.

Several clinical factors of pneumonia can be evaluated semi-objectively using the CPIS (**Table 2**). The clinical course of VAP can be described using serial CPIS measurements which allows the identification of patients with a good therapeutic response 3 days after the diagnosis (23). A CPIS of 0 to 6 is a low predictor of pneumonia whereas diagnosis is more certain when the score ranges from 7 to 12. SOFA score is also used to assess HAP/VAP patients, wherein a decreased SOFA score is associated with a decreased survival (24).

Table 2. Clinical Pulmonary Infection Scale

CPIS	**0**	**1**	**2**
Tracheal secretions	Rare	Abundant	Abundant and purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (˚C)	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 and ≤ 36
Leukocytes count (/mm3)	≥ 4,000 and ≤ 11,000	< 4,000 and > 11,000	< 4,000 and > 11,000 and band forms ≥ 500
PaO2/FiO2 (mmHg)	≥ 240 or ARDS		≤ 240 and no evidence of ARDS

Microbiology	Negative		Positive

ARDS: acute respiratory distress syndrome; PaO_2/FiO_2: arterial oxygen pressure/inspiratory oxygen fraction. Adapted from Fartoukh M, et al., 2003 (25).

3.2.2 Microbiological assessment

In stable patients with suspected VAP/HAP, one or more lower respiratory tract samples should be sent for Gram stain and culture before the initiation of antibiotics (22,26), and a blood sample should be sent for culture as well. A good quality sputum should be sent to the microbiology laboratory in all patients suspected of having HAP (> 25 leucocytes and < 10 squamous cells per low-power field). Semi-quantitative cultures of lower respiratory tract secretions can be performed instead of qualitative cultures. They can be easier to interpret and equally discriminatory for the presence of pneumonia as compared to quantitative cultures (22). In unstable patients, the appropriate management should not be delayed to perform diagnostic sampling (22).

Lower respiratory tract samples (distal quantitative, proximal quantitative, qualitative) are obtained to de-escalate and narrow the initial empiric antibiotic therapy (20).

3.2.3 Radiological assessment

Chest X-rays are done routinely but are neither sensitive nor specific. CT scan should not be routinely obtained for diagnosing HAP/VAP.

3.2.4 Biological assessment

No ideal biomarker for evaluating the therapeutic response is yet available. Theoretically, the main characteristics of the ideal biomarker are affordability, easy access, timely manner results, and contribution to decreasing the consumption of antibiotics (19).

The mid-regional pro-atrial natriuretic peptide, procalcitonin (PCT), C-reactive protein (CRP), and copeptin have been suggested as biomarkers for NP (19,20). However, treatment outcomes have not yet been compared in HAP/VAP patients managed based on either the clinical assessment or biomarker measurement (20).

PCT and CRP can help in monitoring and assessing prognosis where the measurement of PCT and CRP at the beginning of VAP infection and on day 3-4 can predict mortality, and the decrease in either one of these markers is a predictor of survival (24). The value of PCT particularly on day 3 highly predicts mortality risks (27).

An elevated level of PCT was found to be associated with an increased risk of mortality in critically ill patients (28). The same meta-analysis showed that the prognostic performance of this biomarker was almost the same in patients with VAP and those with CAP (28). Whether patients are to be admitted to the ICU or treated as outpatients, the decision can be based on the additional information provided by PCT for risk scores (28). Conversely, PCT has a limited role in cases of hemodialysis, renal failure, and resuscitated cardiac arrest (29). The diagnosis of HAP/VAP (22), or the decision to initiate or reduce the duration of treatment with antibiotics (30) cannot be made based on PCT and CRP alone.

Since serial measurements of PCT levels have a marginal impact on shortening the duration of antibiotic treatment in patients with a good response to initial treatment (20), relying on clinical criteria is recommended to decide whether or not to initiate antibiotic treatment or follow-up

(1,20). The duration of antibiotic treatment can be shortened based on both the serial serum PCT levels and clinical assessment in specific clinical circumstances. However, this practice is not endorsed for decision-making upon initiation of treatment (20).

Bacterial HAP/VAP can be differentiated from other non-infective etiologies, and deciding whether antibiotic treatment can be stopped are possible in case of a serum PCT levels < 0.5 ng/mL (22).

3.2.5 Microbiological diagnosis

It may not be always feasible to collect a bacteriological sample and modify the antibiotic therapy accordingly. In addition , the yield of cultures from respiratory samples is not very high. In practice, both qualitative and quantitative samples lose their sensitivity and specificity when antibiotics have recently been started or modified (26). So, both clinical and bacteriological assessments have to be combined to appropriately diagnose and manage HAP/VAP (22).

Definite Diagnosis:

The criteria for a definite diagnosis are:

- Positive blood culture in the absence of extrapulmonary infections,
- Positive pleural fluid culture, transthoracic biopsy, tracheobronchial aspirates (TBAS $\geq 10^5$ CFU/ml), protected specimen brushing (PSB) ($\geq 10^3$ CFU/ml), or bronchoalveolar lavage (BAL) ($\geq 10^4$ CFU/ml),
- Seroconversion (4-fold increase of immunoglobulin G titer) for *Chlamydia pneumoniae* or *Legionella pneumophila* > 1:128, *Coxiella burnetii* > 1:80, and respiratory viruses (influenza virus A and B, parainfluenza virus 1–3, respiratory syncytial virus, adenovirus).

- Positive reverse transcription polymerase chain reaction (RT-PCR) for respiratory viruses (influenza viruses A and B, parainfluenza virus 1-3, respiratory syncytial virus, adenovirus).

Presumptive Diagnosis:

Predominant microorganism in a sputum sample compatible with Gram stain result.

3.2.6 Lower respiratory tract sampling techniques

To identify the causative agent of NP in intubated patients, it is recommended to perform a qualitative or quantitative or semi-quantitative (preferred) analysis of the respiratory secretions taking into consideration the quality of the respiratory samples (20). The European guidelines recommend to obtain the distal quantitative samples before antibiotic treatment, since negative results may be observed if samples are obtained within 48 hours of starting antibiotic therapy (20). Using distal quantitative cultures may reduce antibiotic overuse and consequently decrease the risk of bacterial resistance and reduce health expenditure (20).

Samples of respiratory secretions can be obtained using non-invasive or invasive techniques (**Table 3;** 20). Also, the diagnosis of HAP/VAP is established using various sampling techniques like bronchoscopic or non-bronchoscopic BAL, endotracheal aspirate (ETA), and PSB (22). If a diagnosis of VAP is suspected, individual preferences, local expertise, and cost will guide the choice of the preferred method for lower respiratory tract sample collection (bronchoscopic or non-bronchoscopic, blind or targeted); nevertheless, blind ETA sampling is the easiest and is equally useful (22). Routine ETA culture is not recommended. Whenever feasible, an antibiogram should be requested (**Figure 1;** 22).

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314 **Table 3. Advantages and disadvantages of invasive and non-invasive sampling techniques**
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	Advantages	Disadvantages
Non-invasive qualitative cultures	• Detect the presence or absence of pathogens (31) • Simple and non-invasive techniques (32)	• Samples are often contaminated by the flora colonizing the upper tracts and are therefore less specific (32) • May overestimate the presence of bacteria in the initial examination of the samples, which can lead to excessive antibiotic use (20)
Invasive quantitative cultures	• Differentiate between infection and colonization (31) • Achieve reliable identification of the causative pathogen (32) • Can guide antimicrobial treatment (20)	• Need qualified personnel • There is potential associated risks on the patient, in addition to the associated costs (20,33)

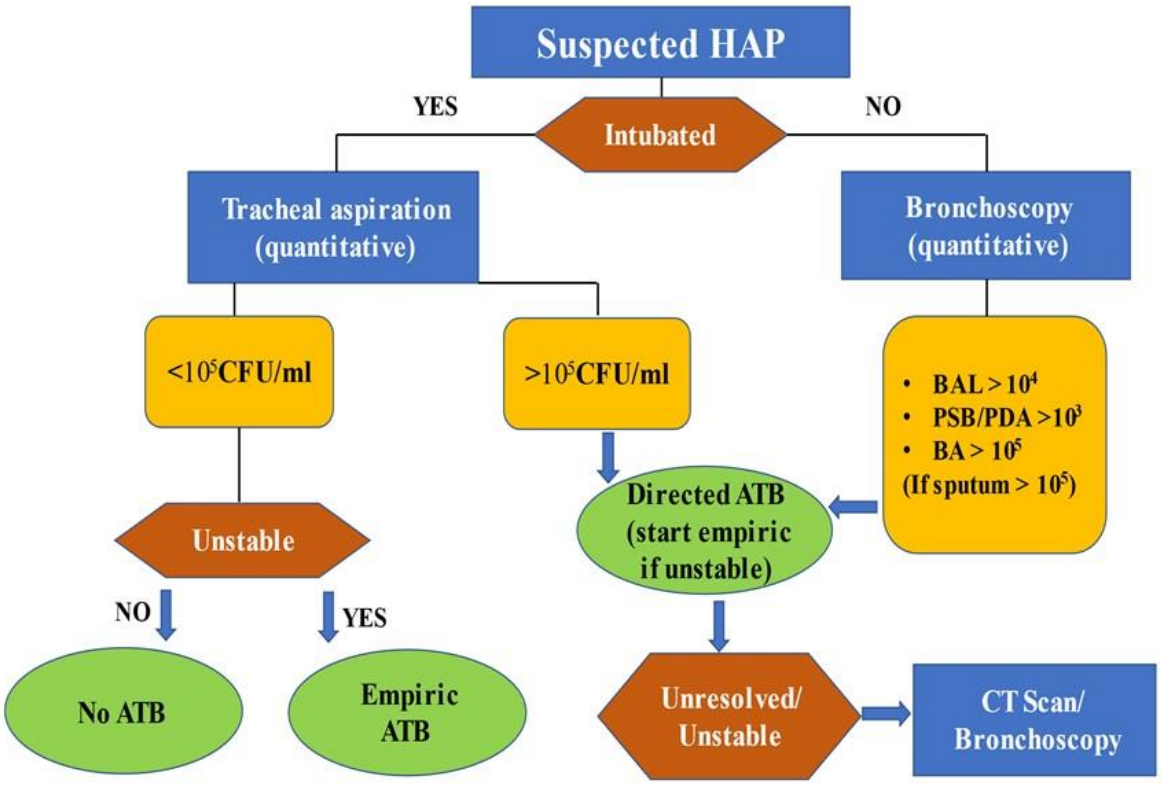

Figure 1. Algorithm for managing suspected HAP

ATB: antibiotic; BA: bronchial aspirate; BAL: bronchoalveolar lavage; CFU: colony-forming unit; CT: computer tomography; HAP: hospital-acquired pneumonia; PDA: protective distal aspirate; PSB: protected specimen brushing.

Recommendations

- We recommend assessing patients clinically through temperature charting, tracheobronchial secretion culture and volume and purulence assessment, evaluation for chest radiograph abnormality resolution, determination of white blood cell count and PaO_2 /FiO_2, and calculation of a relevant score.

- We suggest performing a routine bedside clinical assessment in patients receiving antibiotic treatment for VAP/HAP.
- We recommend performing a qualitative or quantitative (preferred) or semi-quantitative analysis of the respiratory secretions to identify the causative agent of NP in intubated patients.
- In a patient suspected of having VAP, the preferred method for lower respiratory tract sample collection (blind or targeted, bronchoscopic or non-bronchoscopic) depends upon individual preferences, local expertise, and associated cost.
- We recommend obtaining lower respiratory tract samples (distal quantitative, proximal quantitative, qualitative) to de-escalate and narrow the initial empiric antibiotic therapy.
- We do not recommend using PCT and CRP alone to diagnose HAP/VAP, or to initiate or reduce the duration of antimicrobial therapy.
- We suggest combining both clinical and bacteriological strategies to appropriately diagnose and manage HAP/VAP.

3.3. MDROs Risk Factors

MDR *P. aeruginosa*, extended spectrum beta-lactamase-producing Enterobacterales (ESBL-E), methicillin-resistant *S. aureus* (MRSA), *Acinetobacter baumannii* and carbapenem-resistant Enterobacterales (CRE) are the MDROs most commonly involved in NP (**Table 4**). Knowledge of the local epidemiology is essential since there are significant differences in the local prevalence of each MDRO (34). MDR *Pseudomonas* is defined as a pathogen which is resistant to at least one agent in three or more antibiotic classes (35).

3.4. VAP Prevention (level of evidence)

Various organizations have proposed recommendations for VAP prevention. The ones established by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) are evidence-based and include the following (based on level of evidence) (36):

1. **Basic practices** to decrease average duration of MV, length of stay, morality and/or costs:
    a. Use non-invasive positive pressure ventilation in selected populations (high)
    b. Manage patients without sedation whenever possible (moderate)
    c. Interrupt sedation daily (high)
    d. Assess readiness to extubate daily (high)
    e. Perform spontaneous breathing trials with sedatives turned off (high)
    f. Facilitate early mobility (moderate)
    g. Utilize endotracheal tubes with subglottic secretion drainage ports for patients expected to require greater than 48 or 72 hours of MV (moderate)
    h. Change the ventilator circuit only if visibly soiled or malfunctioning (high)
    i. Elevate the head of the bed to 30 to 45° (low, but low cost and simple)

2. **Special approaches**
    a. Improve outcomes but not enough evidence on possible risks:
        i. Selective oral or digestive decontamination (high, but insufficient data on long-term impact on antimicrobial resistance)

b. May lower VAP but insufficient data on impact on MV duration, length of stay or mortality:
    i. Regular oral care with chlorhexidine (moderate)
    ii. Prophylactic probiotics (moderate)
    iii. Ultrathin polyurethane endotracheal tube cuffs (low)
    iv. Automated control of endotracheal tube cuff pressure (low)
    v. Saline instillation before tracheal suctioning (low)
    vi. Mechanical tooth brushing (low)

In addition, the Institute for Healthcare Improvement (IHI) has proposed a bundle which hypothetically provides synergy between different components including (37,38): elevation of the head of the bed, daily sedation interruption and assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, and daily oral care with chlorhexidine. Other organizations have proposed recommendations that are summarized in **Table 5**.

Since *Acinetobacter* is of concern in the Levant region (7), the ESCMID recommendations to reduce the transmission of MDR-*A. baumannii* include (39):

a. Hand hygiene
b. Contact precautions for all colonized patients
c. Alert code for previously colonized patients and pre-emptive contact precautions
d. Education on MDR-*A. baumannii*
e. Environmental cleaning
f. Antimicrobial stewardship
g. Active surveillance as an additional measure, but bathing with chlorhexidine was not supported.

Recommendations

- We prefer to implement evidence-based preventive measures to lower the rate of VAP and improve patient outcomes.

3.5. Treatment of HAP/VAP

Inappropriate antibiotic treatment is an important modifiable prognostic factor that may increase mortality in severe infections (40,41). Timeliness and appropriateness of antibiotic therapy is an important consideration in NP.

3.5.1 HAP risk factors

The risk factors of HAP are (8,42–46):

1. **Patient-related factors:** acute or chronic severe disease, coma, hypotension, malnutrition, prolonged hospitalization, metabolic acidosis, smoking and comorbidities (such as disorders of the central nervous system, chronic obstructive pulmonary disease (COPD), respiratory insufficiency diabetes mellitus, alcoholism, and chronic renal failure).
2. **Management-related factors:** extended/inappropriate antibiotic treatment, administration of sedatives, gastric acid suppressive therapy, corticosteroids and other immunosuppressants, and prolonged surgical procedures (especially at the thoracic or abdominal levels).
3. **Infection prevention-related factors:** hand hygiene compliance failure or inappropriate care of respiratory support equipment.

3.5.2 Treatment options and duration

The selection of appropriate antibiotic regimen and treatment duration are key elements to avoid the emergence of bacterial resistance and achieve the best outcomes. While the duration of therapy for MDROs is not clearly defined, the European guidelines recommend a duration of antibiotic treatment for HAP of maximum 7 days. To avoid multidrug resistance, antibiotic treatment is recommended for 7–8 days in patients with VAP without other respiratory comorbidities (such as lung abscess, lung cavitation, pulmonary empyema, or necrotizing pneumonia), and who present a good therapeutic response. Patients with inappropriate initial empiric therapy may need longer courses of treatment which should be individualized to the patient's clinical response and microbiological findings (20). In patients with *P. aeruginosa* pneumonia who have no significant comorbidities, who defervesce and improve clinically within the first week of therapy, and who have infection with a susceptible *P. aeruginosa* isolate can be treated with regimens of 7 to 10 days. However, based on expert opinion, longer treatment durations (e.g., from 10 to 21 days) may be warranted for patients with serious underlying conditions (e.g., neutropenia), concurrent bloodstream infection, a poor or slow response to therapy, and/or a partially susceptible or multidrug-resistant strain (47). Short duration of treatment could lead to decreased antibiotic exposure during hospitalization in the ICU and increased risk of MDROs. Empirical antimicrobial therapy is selected based on risk factors, previous colonization, and local microbiology. Then, de-escalation is done depending on the type of isolated pathogens and the possible advantages of one antimicrobial over others.

Clinical scores, such as CPIS or CarbaSCORE (48), and non-specific biomarkers, such as PCT and CRP, are tools that can guide therapy and clinical decision-making to appropriately begin or stop antibiotic treatment (49).

New treatment options are currently available in Lebanon with the approval of two beta-lactam/beta-lactamase inhibitor antibiotics namely CFT/TAZ and CAZ/AVI for patients with suspected MDRO infection. These agents demonstrated an appropriate activity and clinical efficacy against ESBL-Enterobacterales and MDR *P. aeruginosa* in clinical trials (50,51) with less risk for emergence of resistance. They are considered good options in the armamentarium particularly for carbapenem-sparing strategies in an antimicrobial stewardship policy (52,53).

For infections with MDR *Acinetobacter*, inhaled colistin has been found to be of benefit. In one study, a response rate of 80% was observed when using inhaled colistin as adjunctive therapy to intravenous antibiotics for VAP caused by drug-resistant Gram-negative bacilli, predominantly *A. baumannii* (54). Unless other options are available, it is preferred to use inhaled colistin for patients with severe pneumonia due to *A. baumannii* that is resistant to beta-lactams and carbapenems (i.e., sensitive to colistin only) since lung concentration attained intravenously is low. Other studies have showed that tigecycline was associated with a good response rate when used in patients with VAP due to MDR *A. baumannii* (55,56).

Ceftobiprole, a fifth-generation broad-spectrum cephalosporin, showed a limited activity against *A. baumannii* (57–59).

Studies have shown that CFT/TAZ is a good choice to treat *P. aeruginosa* (60,61) infections, and ESBL-producing Enterobacterales infections (62). CFT/TAZ presents potent *in-vitro* activity against *P. aeruginosa* including the MDR strains, with less resistance than the current anti-pseudomonal agents (63). CFT/TAZ also exhibits the lowest mutant prevention concentration (MPC) against *P. aeruginosa*, as well as colistin and quinolones (2 mg/L) (61). The ASPECT-NP clinical trial demonstrated that CFT/TAZ was non-inferior to meropenem regarding 28-day all-cause mortality, showed a trend toward reduced mortality in the subset of patients with HAP who

463 required invasive MV (mortality at 28 days, 24.2% vs 37%) and in patients who failed their initial
464 antibiotic treatment (mortality at 28 days, 22.6% vs 45%), and achieved higher levels of
465 microbiological cure in pneumonia caused by *P. aeruginosa* (51).
466 A retrospective study evaluated real-world clinical experiences with CFT/TAZ to treat severe
467 ESBL-producing Enterobacterales infections. Around 84% of total cases and 78% of patients with
468 HAP showed a successful clinical outcome. Interestingly, no clinical failure was reported among
469 patients with CFT/TAZ administered as an empiric therapy compared to patients who had received
470 CFT/TAZ as a targeted or rescue therapy (64).
471 A study assessing the antimicrobial susceptibility of Gram-negative respiratory isolates from ICU
472 patients in hospitals in USA and Europe (SMART 2018) showed that co-resistance existed in
473 commonly prescribed first-line beta-lactam antibiotics; a pathogen that was non-susceptible to one
474 agent had a susceptibility rate of < 35% to other beta-lactams. For instance, when the *Pseudomonas*
475 isolates were non-susceptible to ceftazidime, susceptibility rate to piperacillin/tazobactam or
476 meropenem was very low, 7% and 27.2% respectively (65). These data can guide empiric therapy
477 in patients who fail initial antibiotic therapy.
478 CAZ/AVI is a good choice for patients with bacteremia who required rescue treatment in infections
479 caused by KPC-producing Enterobacterales (66), and infections caused by a CAZ/AVI-susceptible
480 OXA-48 strains (67), as well as infections caused by metallo-β-lactamase-producing
481 Enterobacterales when combined with aztreonam (68). It is associated with improved survival rates
482 in case of infections caused by KPC-producing Enterobacterales (66). The panel recommends the
483 following algorithm for the management of HAP/VAP based on risks for MDROs (**Figure 2**).
484

Recommendations

- We recommend antibiotic treatment for no longer than 7 days in patients with HAP.
- We recommend a duration of antibiotic treatment of 7–8 days in patients with VAP (except in those caused by *P. aeruginosa* where, as discussed above, treatment can be prolonged in certain cases).
- CFT/TAZ and CAZ/AVI are considered good options in patients with HAP/VAP caused by ESBL-Enterobacterales and MDR *P. aeruginosa.*
- CFT/TAZ and CAZ/AVI are considered good options in the implementation of a carbapenem-sparing strategy in an antibiotic stewardship program.
- We suggest using inhaled colistin for patients with severe pneumonia due to *A. baumannii* that is resistant to beta-lactams and carbapenems.

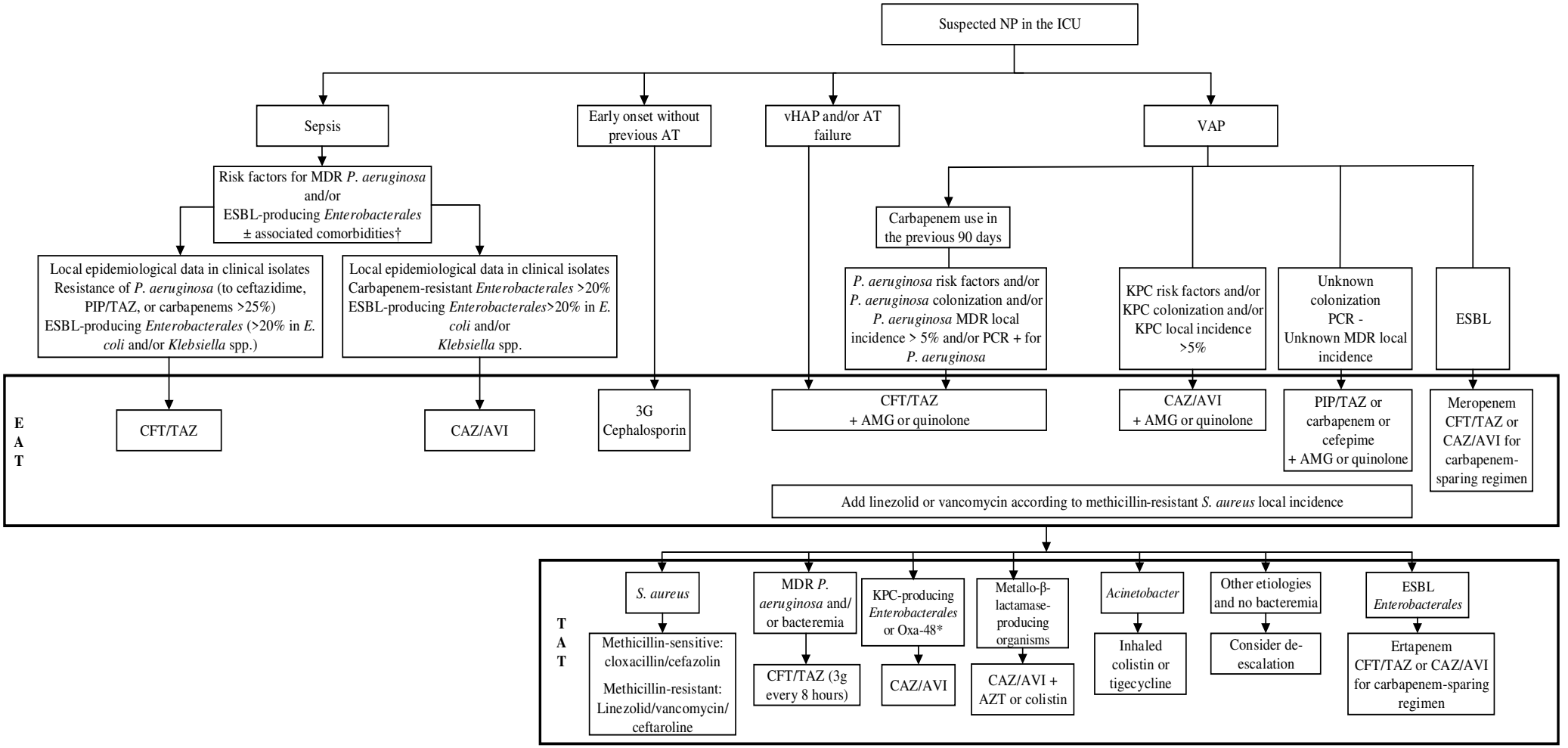

Figure 2. Treatment algorithm for VAP/HAP in ICU

AMG: aminoglycoside; AT: antimicrobial therapy; AZT: aztreonam; CAZ/AVI: ceftazidime/avibactam; CFT/TAZ: ceftolozane/tazobactam; EAT: empirical antimicrobial treatment; KPC: Klebsiella pneumoniae carbapenemase; MDR: multidrug-

*resistant; NP: nosocomial pneumonia; OXA-48: OXA-48 carbapenemase; PCR: polymerase chain reaction; PIP/TAZ, piperacillin/tazobactam; R: resistance; spp.: species plural; TAT: targeted antimicrobial treatment; VAP: ventilator-associated pneumonia; vHAP: ventilated hospital-acquired pneumonia. †Diabetes, COPD, moderate/severe renal/liver disease, immunosuppression/neutropenia, elderly patients, solid tumor, structural lung disease, organ transplantation, hemodialysis *If Oxa-48 susceptible to CAZ/AVI. Adapted from Montravers P. et al, 2018 (17) and Zaragoza R et al., 2020* (17,53).

3.6. Antimicrobial Stewardship: Experience from Two Hospitals in Lebanon

An antimicrobial stewardship strategy for carbapenems did not impair clinical outcomes, and it was associated with a lower rate of adverse drug reactions, lower incidence of carbapenem-resistant *A. baumannii* infections, and a lower incidence of *Clostridium difficile*-associated diarrhea (69). Considering the aforementioned results, implementing a carbapenem-sparing strategy through an AMS program would be beneficial in terms of clinical outcomes and bacterial resistance.

Experience from the Saint George Hospital University Medical Center (70) and the American University of Beirut Medical Center (Infection Control and Prevention Program [ICPP], two major hospitals in Lebanon, has shown that carbapenem-sparing strategies in managing ICU infections were successful in improving carbapenem consumption and eliminating MDROs including *A. baumannii.*

3.7. COVID-19 and Influenza Virus Pandemics

Secondary bacterial pneumonia is a complication of coronavirus disease 2019 (COVID-19) which can be associated with worse outcomes (71). A meta-analysis showed that around 7% of COVID-19 patients had a bacterial infection, out of which 14.3% were secondary infections (72). Bacterial co-infection in patients with influenza virus infections was significantly associated with higher morbidity and mortality (73).

The hallmark of the clinical presentation in patients with secondary bacterial pneumonia is the exacerbation of fever and respiratory symptoms after initial improvement in the symptoms of acute viral infection. Fever may abate for one or more days of viral infection, but instead of continuing

to improve, the patient with secondary bacterial pneumonia relapses with higher fever, cough, production of purulent sputum, and radiographic evidence of new pulmonary infiltrates. The most common bacterial pathogens found in bacterial superinfections after influenza virus pneumonia are Gram-positive bacteria such as *Streptococcus pneumonia* and *S. aureus* including MRSA (73). Conversely, bacterial superinfections after COVID-19 infection are mostly caused by Gram-negative bacteria such as *A. baumannii*, *P. aeruginosa*, and *Klebsiella pneumonia*, and fungi such as *Aspergillus* (74). A recent study showed that patients with COVID-19 who required MV were significantly more likely to develop VAP than patients who required MV for other reasons with an incidence density of 28/1000 ventilator days versus 13/1000 (p value=0,009) respectively and the mortality rate for COVID-19 VAP was higher than for VAP in non COVID-19 infected patients (75).

In the context of reduced routine invasive microbiological investigation (bronchoscopy), the extensive use of broad-spectrum empirical antibiotics should be avoided.

4. Conclusion

These guidelines represent a major step towards establishing Lebanese national guidelines for the management of HAP/VAP. They also emphasize on implementing evidence-based preventive measures to lower the rate of VAP and improve patient outcomes, and on timeliness and appropriateness of antibiotic therapy for the management of HAP/VAP.

5. List of Abbreviations

ALAT: Asociación Latinoamericana del Tórax

AMG: aminoglycoside

AMS: antimicrobial stewardship

APACHE II: Acute Physiology and Chronic Health Evaluation II

ARDS: acute respiratory distress syndrome

AT: antimicrobial therapy

ATB: antibiotic

AUBMC: American University of Beirut Medical Center

AVI: avibactam

AZT: aztreonam

BA: bronchial aspirate

BAL: bronchoalveolar lavage

CAP: community-acquired pneumonia

CAZ: ceftazidime

CFT: ceftolozane

CFU: colony-forming unit

CPE: carbapenemase-producing Enterobacterales

CPIS: Clinical Pulmonary Infection Scale

CRP: C-reactive protein

CT: computer tomography

EAT: empirical antimicrobial treatment

ECDC: European Center for Disease Prevention and Control

ERS: European Respiratory Society

ESBL-E: extended spectrum beta-lactamase-*producing* Enterobacterales

ESCMID: European Society of Clinical Microbiology and Infectious Diseases

ESICM: European Society of Intensive Care Medicine

ETA: endotracheal aspirate

FiO_2: inspiratory oxygen fraction

HAP: hospital-acquired pneumonia

ICPP: Infection Control and Prevention Program

ICS: Indian Chest Society

ICU: intensive care unit

IHI: Institute for Healthcare Improvement

KPC: Klebsiella pneumoniae carbapenemase

LPS: Lebanese Pulmonary Society

LSCCM: Lebanese Society of Critical Care Medicine

LSIDCM: Lebanese Society of Infectious Diseases and Clinical Microbiology

MDR: multidrug-resistant

MDROs: multidrug-resistant organisms

MRSA: methicillin-resistant *Staphylococcus aureus*

MV: mechanical ventilation

NCCP: National College of Chest Physicians

NHSN: National Healthcare Safety Network

NP: nosocomial pneumonia

ODIN: Organ Dysfunction and Infection System

OXA-48: OXA-48 carbapenemase

PaO_2: arterial oxygen pressure

PCR: polymerase chain reaction

PCT: procalcitonin

PDA: protective distal aspirate

PIP: piperacillin

PSB: protected specimen brushing

R: resistance

RT-PCR: reverse transcription polymerase chain reaction

SAPS II: Simplified Acute Physiological Score II

SEPAR: Spanish Society of Pulmonology and Thoracic Surgery

SOFA: Sequential Organ Failure Assessment

Spp.: species plural

TAT: targeted antimicrobial treatment

TAZ: tazobactam

TBAS: tracheobronchial aspirates

USA: United States of America

VAP: ventilator-associated pneumonia

vHAP: ventilated-HAP

6. Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

Moussa Riachy, Claude Afif, Jacques Choucair, Patricia Yazbeck, Madonna J. Matar, Zeina Aoun-Bacha, Wajdy Abi Saleh, Georges S. Juvelekian, Nadine Yared, Pierre Bou Khalil, Viviane Chalhoub, Ralph Nehme, Youssef Haddad, Salah Zeineddine, and Souha S. Kanj declare that they have no competing interests.

Aline El Zakhem has received personal fees for consultancies and lectures from MSD and Pfizer.

Rani Abu Khuzam has received personal fees for clinical studies from Novartis.

Funding

Editorial and medical writing assistance was provided by Mohammad Yassine, BPharm, MSc (major contribution) and Racha Aaraj, Pharm D, MSc, MPH from Phoenix Clinical Research, Lebanon. Medical writing support was funded by MSD Lebanon.

Authors' contributions

Dr. Souha Kanj and Dr. Moussa Riachi provided expert insight and guidance on the development of this manuscript. All authors provided expert input at each round of review of the paper. They all contributed to the development of the manuscript and approved the final version.

Acknowledgements

Editorial and medical writing assistance was provided by Mohammad Yassine, BPharm, MSc (major contribution) and Racha Aaraj, Pharm D, MSc, MPH from Phoenix Clinical Research, Lebanon. Medical writing support was funded by MSD Lebanon. The views and opinions expressed are those of the authors only.

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7. References

1. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice

Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–111.

2. Dudeck MA, Weiner LM, Allen-Bridson K, Malpiedi PJ, Peterson KD, Pollock DA, et al. National Healthcare Safety Network (NHSN) Report, Data Summary for 2012, Device-associated Module. Am J Infect Control. 2013;41(12):1148–66.

3. Giuliano KK, Baker D, Quinn B. The epidemiology of nonventilator hospital-acquired pneumonia in the United States. American Journal of Infection Control. 2018;46(3):322–7.

4. Healthcare-associated infections in intensive care units - Annual Epidemiological Report for 2016 [Internet]. European Centre for Disease Prevention and Control. 2018 [cited 2020 Dec 12]. Available from: https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-intensive-care-units-annual-epidemiological-0

5. Walter J, Haller S, Quinten C, Kärki T, Zacher B, Eckmanns T, et al. Healthcare-associated pneumonia in acute care hospitals in European Union/European Economic Area countries: an analysis of data from a point prevalence survey, 2011 to 2012. Euro Surveill. 2018;23(32).

6. El-Saed A, Al-Jardani A, Althaqafi A, Alansari H, Alsalman J, Al Maskari Z, et al. Ventilator-associated pneumonia rates in critical care units in 3 Arabian Gulf countries: A 6-year surveillance study. Am J Infect Control. 2016;44(7):794–8.

7. Kanafani ZA, El Zakhem A, Zahreddine N, Ahmadieh R, Kanj SS. Ten-year surveillance study of ventilator-associated pneumonia at a tertiary care center in Lebanon. J Infect Public Health. 2019;12(4):492–5.

8. Micek ST, Chew B, Hampton N, Kollef MH. A Case-Control Study Assessing the Impact of Nonventilated Hospital-Acquired Pneumonia on Patient Outcomes. Chest. 2016;150(5):1008–14.

9. Kohlenberg A, Schwab F, Behnke M, Geffers C, Gastmeier P. Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database. Intensive Care Med. 2010;36(6):971–8.

10. Talbot GH, Das A, Cush S, Dane A, Wible M, Echols R, et al. Evidence-Based Study Design for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia. The Journal of Infectious Diseases. 2019;219(10):1536–44.

11. Muscedere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S120-125.

12. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol. 2012;33(3):250–6.

13. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol. 2016;37(11):1288–301.

14. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S81-87.

15. Awad LS, Abdallah DI, Mugharbil AM, Jisr TH, Droubi NS, El-Rajab NA, et al. An antibiotic stewardship exercise in the ICU: building a treatment algorithm for the management of ventilator-associated pneumonia based on local epidemiology and the 2016 Infectious Diseases Society of America/American Thoracic Society guidelines. Infect Drug Resist. 2018;11:17–28.

16. Kanafani ZA, Kara L, Hayek S, Kanj SS. Ventilator-associated pneumonia at a tertiary-care center in a developing country: incidence, microbiology, and susceptibility patterns of isolated microorganisms. Infect Control Hosp Epidemiol. 2003;24(11):864–9.

17. Zaragoza R, Vidal-Cortés P, Aguilar G, Borges M, Diaz E, Ferrer R, et al. Update of the treatment of nosocomial pneumonia in the ICU. Crit Care. 2020;24(1):383.

18. Vallecoccia MS, Dominedò C, Cutuli SL, Martin-Loeches I, Torres A, De Pascale G. Is ventilated hospital-acquired pneumonia a worse entity than ventilator-associated pneumonia? Eur Respir Rev. 2020;29(157).

19. Salluh JIF, Souza-Dantas VC, Póvoa P. The current status of biomarkers for the diagnosis of nosocomial pneumonias. Curr Opin Crit Care. 2017;23(5):391–7.

20. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-

acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J. 2017;50(3).

21. Rotstein C, Evans G, Born A, Grossman R, Light RB, Magder S, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. Can J Infect Dis Med Microbiol. 2008;19(1):19–53.

22. Gupta D, Agarwal R, Aggarwal AN, Singh N, Mishra N, Khilnani GC, et al. Guidelines for diagnosis and management of community- and hospital-acquired pneumonia in adults: Joint ICS/NCCP(I) recommendations. Lung India. 2012;29(Suppl 2):S27-62.

23. Luna CM, Blanzaco D, Niederman MS, Matarucco W, Baredes NC, Desmery P, et al. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med. 2003;31(3):676–82.

24. Seligman R, Meisner M, Lisboa TC, Hertz FT, Filippin TB, Fachel JMG, et al. Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. Crit Care. 2006;10(5):R125.

25. Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar J-R, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003;168(2):173–9.

26. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. Summary of the international clinical guidelines for the management of hospital-acquired and ventilator-acquired pneumonia. ERJ Open Res. 2018;4(2).

27. Seligman R, Seligman BGS, Teixeira PJZ. Comparing the accuracy of predictors of mortality in ventilator-associated pneumonia. J Bras Pneumol. 2011;37(4):495–503.

28. Liu D, Su L, Guan W, Xiao K, Xie L. Prognostic value of procalcitonin in pneumonia: A systematic review and meta-analysis. Respirology. 2016;21(2):280–8.

747 29. Amour J, Birenbaum A, Langeron O, Le Manach Y, Bertrand M, Coriat P, et al. Influence of renal
748 dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after
749 vascular surgery. Crit Care Med. 2008;36(4):1147–54.

750 30. Nora D, Salluh J, Martin-Loeches I, Póvoa P. Biomarker-guided antibiotic therapy-strengths and
751 limitations. Ann Transl Med. 2017;5(10):208.

752 31. Berton DC, Kalil AC, Teixeira PJZ. Quantitative versus qualitative cultures of respiratory secretions
753 for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database Syst
754 Rev. 2014;(10):CD006482.

755 32. Díaz E, Martín-Loeches I, Vallés J. [Nosocomial pneumonia]. Enferm Infecc Microbiol Clin.
756 2013;31(10):692–8.

757 33. Blanquer J, Aspa J, Anzueto A, Ferrer M, Gallego M, Rajas O, et al. SEPAR Guidelines for
758 Nosocomial Pneumonia. Arch Bronconeumol. 2011;47(10):510–20.

759 34. Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local
760 microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired
761 pneumonia. Chest. 2006;130(3):787–93.

762 35. Abrahamian FM, Deblieux PM, Emerman CL, Kollef MH, Kupersmith E, Leeper KV, et al. Health
763 care-associated pneumonia: identification and initial management in the ED. Am J Emerg Med.
764 2008;26(6 Suppl):1–11.

765 36. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent
766 ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp
767 Epidemiol. 2014;35(8):915–36.

768 37. Al-Thaqafy MS, El-Saed A, Arabi YM, Balkhy HH. Association of compliance of ventilator bundle
769 with incidence of ventilator-associated pneumonia and ventilator utilization among critical patients
770 over 4 years. Ann Thorac Med. 2014;9(4):221–6.

771 38. Evans B. Best-practice protocols: VAP prevention. Nurs Manage. 2005;36(12):10, 12, 14 passim.

772 39. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines
773 for the management of the infection control measures to reduce transmission of multidrug-resistant
774 Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014;20 Suppl 1:1–55.

775 40. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance,
776 inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic
777 shock: a retrospective cohort study. Crit Care. 2014;18(6):596.

778 41. Kollef MH. Treatment of ventilator-associated pneumonia: get it right from the start. Crit Care Med.
779 2003;31(3):969–70.

780 42. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management
781 of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J
782 Respir Crit Care Med. 2005;171(4):388–416.

783 43. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial
784 therapy, and preventive strategies. A consensus statement, American Thoracic Society, November
785 1995. Am J Respir Crit Care Med. 1996;153(5):1711–25.

786 44. Sopena N, Heras E, Casas I, Bechini J, Guasch I, Pedro-Botet ML, et al. Risk factors for hospital-
787 acquired pneumonia outside the intensive care unit: a case-control study. Am J Infect Control.
788 2014;42(1):38–42.

789 45. Di Pasquale M, Aliberti S, Mantero M, Bianchini S, Blasi F. Non-Intensive Care Unit Acquired
790 Pneumonia: A New Clinical Entity? Int J Mol Sci. 2016;17(3):287.

791 46. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk
792 for hospital-acquired pneumonia. JAMA. 2009;301(20):2120–8.

793 47. Kanj SS, Sexton DJ. Pseudomonas aeruginosa pneumonia - UpToDate [Internet]. [cited 2021 Mar
794 9]. Available from: https://www.uptodate.com/contents/pseudomonas-aeruginosa-pneumonia

795 48. Teysseyre L, Ferdynus C, Miltgen G, Lair T, Aujoulat T, Lugagne N, et al. Derivation and validation
796 of a simple score to predict the presence of bacteria requiring carbapenem treatment in ICU-acquired
797 bloodstream infection and pneumonia: CarbaSCORE. Antimicrob Resist Infect Control. 2019;8:78.

798 49. Millot G, Voisin B, Loiez C, Wallet F, Nseir S. The next generation of rapid point-of-care testing
799 identification tools for ventilator-associated pneumonia. Ann Transl Med. 2017;5(22):451.

800 50. Torres A, Zhong N, Pachl J, Timsit J-F, Kollef M, Chen Z, et al. Ceftazidime-avibactam versus
801 meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a
802 randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis. 2018;18(3):285–95.

51. Kollef MH, Nováček M, Kivistik Ü, Réa-Neto Á, Shime N, Martin-Loeches I, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2019;19(12):1299–311.

52. Bassetti M, Righi E, Vena A, Graziano E, Russo A, Peghin M. Risk stratification and treatment of ICU-acquired pneumonia caused by multidrug- resistant/extensively drug-resistant/pandrug-resistant bacteria. Curr Opin Crit Care. 2018;24(5):385–93.

53. Montravers P, Bassetti M. The ideal patient profile for new beta-lactam/beta-lactamase inhibitors. Curr Opin Infect Dis. 2018;31(6):587–93.

54. Qureshi ZA, Hittle LE, O'Hara JA, Rivera JI, Syed A, Shields RK, et al. Colistin-resistant Acinetobacter baumannii: beyond carbapenem resistance. Clin Infect Dis. 2015;60(9):1295–303.

55. Curcio D, Fernández F, Vergara J, Vazquez W, Luna CM. Late onset ventilator-associated pneumonia due to multidrug-resistant Acinetobacter spp.: experience with tigecycline. J Chemother. 2009;21(1):58–62.

56. Metan G, Alp E, Yildiz O, Percin D, Aygen B, Sumerkan B. Clinical experience with tigecycline in the treatment of carbapenem-resistant Acinetobacter infections. J Chemother. 2010;22(2):110–4.

57. Awad SS, Rodriguez AH, Chuang Y-C, Marjanek Z, Pareigis AJ, Reis G, et al. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis. 2014;59(1):51–61.

58. Scheeren TWL. Ceftobiprole medocaril in the treatment of hospital-acquired pneumonia. Future Microbiol. 2015;10(12):1913–28.

59. Syed YY. Ceftobiprole medocaril: a review of its use in patients with hospital- or community-acquired pneumonia. Drugs. 2014;74(13):1523–42.

60. Mensa J, Barberán J, Soriano A, Llinares P, Marco F, Cantón R, et al. Antibiotic selection in the treatment of acute invasive infections by Pseudomonas aeruginosa: Guidelines by the Spanish Society of Chemotherapy. Rev Esp Quimioter. 2018;31(1):78–100.

61. Bassetti M, Vena A, Russo A, Croxatto A, Calandra T, Guery B. Rational approach in the management of Pseudomonas aeruginosa infections. Curr Opin Infect Dis. 2018;31(6):578–86.

831 62. Bassetti M, Righi E, Carnelutti A, Graziano E, Russo A. Multidrug-resistant Klebsiella pneumoniae:
832 challenges for treatment, prevention and infection control. Expert Rev Anti Infect Ther.
833 2018;16(10):749–61.

834 63. Goodlet KJ, Nicolau DP, Nailor MD. In Vitro Comparison of Ceftolozane-Tazobactam to
835 Traditional Beta-Lactams and Ceftolozane-Tazobactam as an Alternative to Combination
836 Antimicrobial Therapy for Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2017;61(12).

837 64. Bassetti M, Vena A, Giacobbe DR, Falcone M, Tiseo G, Giannella M, et al. Ceftolozane/Tazobactam
838 for Treatment of Severe ESBL-Producing Enterobacterales Infections: A Multicenter Nationwide
839 Clinical Experience (CEFTABUSE II Study). Open Forum Infect Dis. 2020;7(5):ofaa139.

840 65. 40th International Symposium on Intensive Care & Emergency Medicine. Critical Care.
841 2020;24(1):87.

842 66. Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C, et al. Efficacy of
843 Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by Klebsiella
844 pneumoniae Carbapenemase-producing K. pneumoniae. Clin Infect Dis. 2019;68(3):355–64.

845 67. Alraddadi BM, Saeedi M, Qutub M, Alshukairi A, Hassanien A, Wali G. Efficacy of ceftazidime-
846 avibactam in the treatment of infections due to Carbapenem-resistant Enterobacteriaceae. BMC
847 Infectious Diseases. 2019;19(1):772.

848 68. Marshall S, Hujer AM, Rojas LJ, Papp-Wallace KM, Humphries RM, Spellberg B, et al. Can
849 Ceftazidime-Avibactam and Aztreonam Overcome β-Lactam Resistance Conferred by Metallo-β-
850 Lactamases in Enterobacteriaceae? Antimicrob Agents Chemother. 2017;61(4).

851 69. Lew KY, Ng TM, Tan M, Tan SH, Lew EL, Ling LM, et al. Safety and clinical outcomes of
852 carbapenem de-escalation as part of an antimicrobial stewardship programme in an ESBL-endemic
853 setting. J Antimicrob Chemother. 2015;70(4):1219–25.

854 70. Chamieh A, Nawfal TD, Ballouz T, Afif C, Juvelekian G, Hlais S, et al. Control and Elimination of
855 Extensively Drug-Resistant Acinetobacter baumanii in an Intensive Care Unit. Emerg Infect Dis.
856 2019;25(10):1928–31.

857 71. Vaillancourt M, Jorth P. The Unrecognized Threat of Secondary Bacterial Infections with COVID-
858 19. mBio. 2020;11(4):e01806-20.

72. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26(12):1622–9.

73. Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller RR, et al. Critical Illness from 2009 Pandemic Influenza A (H1N1) Virus and Bacterial Co-Infection in the United States. Crit Care Med. 2012;40(5):1487–98.

74. Clancy CJ, Nguyen MH. COVID-19, superinfections and antimicrobial development: What can we expect? Clin Infect Dis. 2020;.

75. Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Critical Care. 2021;25(1):25.

76. Torre-Cisneros J, Natera C, Mesa F, Trikic M, Rodríguez-Baño J. Clinical predictors of methicillin-resistant Staphylococcus aureus in nosocomial and healthcare-associated pneumonia: a multicenter, matched case-control study. Eur J Clin Microbiol Infect Dis. 2018;37(1):51–6.

77. Torre-Cisneros J, Tejero García R, Natera Kindelán C, Font Ugalde P, Franco Álvarez de Luna F, Castón Osorio JJ, et al. [Risk factors of nosocomial pneumonia caused by methicillin-resistant Staphylococcus aureus]. Med Clin (Barc). 2012;138(3):99–106.

78. Metersky ML, Frei CR, Mortensen EM. Predictors of Pseudomonas and methicillin-resistant Staphylococcus aureus in hospitalized patients with healthcare-associated pneumonia. Respirology. 2016;21(1):157–63.

79. Buhl M, Peter S, Willmann M. Prevalence and risk factors associated with colonization and infection of extensively drug-resistant Pseudomonas aeruginosa: a systematic review. Expert Rev Anti Infect Ther. 2015;13(9):1159–70.

80. Fernández-Barat L, Ferrer M, De Rosa F, Gabarrús A, Esperatti M, Terraneo S, et al. Intensive care unit-acquired pneumonia due to Pseudomonas aeruginosa with and without multidrug resistance. J Infect. 2017;74(2):142–52.

81. Venier AG, Gruson D, Lavigne T, Jarno P, L'hériteau F, Coignard B, et al. Identifying new risk factors for Pseudomonas aeruginosa pneumonia in intensive care units: experience of the French national surveillance, REA-RAISIN. J Hosp Infect. 2011;79(1):44–8.

82. Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant Pseudomonas aeruginosa: risk factors and clinical impact. Antimicrob Agents Chemother. 2006;50(1):43–8.

83. Nakamura A, Miyake K, Misawa S, Kuno Y, Horii T, Kondo S, et al. Meropenem as predictive risk factor for isolation of multidrug-resistant Pseudomonas aeruginosa. J Hosp Infect. 2013;83(2):153–5.

84. Tartof SY, Kuntz JL, Chen LH, Wei R, Puzniak L, Tian Y, et al. Development and Assessment of Risk Scores for Carbapenem and Extensive β-Lactam Resistance Among Adult Hospitalized Patients With Pseudomonas aeruginosa Infection. JAMA Netw Open. 2018;1(6):e183927.

85. Gao B, Li X, Yang F, Chen W, Zhao Y, Bai G, et al. Molecular Epidemiology and Risk Factors of Ventilator-Associated Pneumonia Infection Caused by Carbapenem-Resistant Enterobacteriaceae. Front Pharmacol. 2019;10:262.

86. Sbrana F, Malacarne P, Bassetti M, Tascini C, Vegnuti L, Della Siega P, et al. Risk factors for ventilator associated pneumonia due to carbapenemase-producing Klebsiella pneumoniae in mechanically ventilated patients with tracheal and rectal colonization. Minerva Anestesiol. 2016;82(6):635–40.

87. Peralta G, Sánchez MB, Garrido JC, De Benito I, Cano ME, Martínez-Martínez L, et al. Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with Escherichia coli bacteraemia. J Antimicrob Chemother. 2007;60(4):855–63.

88. Aydemir H, Tuz HI, Piskin N, Celebi G, Kulah C, Kokturk F. Risk factors and clinical responses of pneumonia patients with colistin-resistant Acinetobacter baumannii-calcoaceticus. World J Clin Cases. 2019;7(10):1111–21.

89. Zheng Y, Wan Y, Zhou L, Ye M, Liu S, Xu C, et al. Risk factors and mortality of patients with nosocomial carbapenem-resistant Acinetobacter baumannii pneumonia. Am J Infect Control. 2013;41(7):e59-63.

90. Cordes LG, Brink EW, Checko PJ, Lentnek A, Lyons RW, Hayes PS, et al. A cluster of Acinetobacter Pneumonia in foundry workers. Ann Intern Med. 1981;95(6):688–93.

914 91. Centers for Disease Control and Prevention (CDC). Acinetobacter baumannii infections among
915 patients at military medical facilities treating injured U.S. service members, 2002-2004. MMWR
916 Morb Mortal Wkly Rep. 2004;53(45):1063–6.

917 92. Scott P, Deye G, Srinivasan A, Murray C, Moran K, Hulten E, et al. An outbreak of multidrug-
918 resistant Acinetobacter baumannii-calcoaceticus complex infection in the US military health care
919 system associated with military operations in Iraq. Clin Infect Dis. 2007;44(12):1577–84.

920 93. Álvarez-Lerma F, Palomar-Martínez M, Sánchez-García M, Martínez-Alonso M, Álvarez-
921 Rodríguez J, Lorente L, et al. Prevention of Ventilator-Associated Pneumonia: The Multimodal
922 Approach of the Spanish ICU "Pneumonia Zero" Program. Crit Care Med. 2018;46(2):181–8.

923 94. Bouadma L, Deslandes E, Lolom I, Le Corre B, Mourvillier B, Regnier B, et al. Long-term impact
924 of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care
925 unit. Clin Infect Dis. 2010;51(10):1115–22.

926 95. Berenholtz SM, Pham JC, Thompson DA, Needham DM, Lubomski LH, Hyzy RC, et al.
927 Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the
928 intensive care unit. Infect Control Hosp Epidemiol. 2011;32(4):305–14.

929 8. Tables

930 **Table 4. Risk factors of MDRO causing NP**

MDRO	Risk factors
MRSA (76–78)	○ Age ○ NP appearance > 6 days after admission ○ NP development excluding summers ○ Respiratory diseases ○ Multilobe involvement ○ Respiratory infection/colonization caused by MRSA in the previous year ○ Hospitalization in the previous 90 days ○ Recent nursing home or hospital stay

MDRO	Risk factors
	○ Recent exposure to fluoroquinolones or antibiotics treating Gram-positive organisms
Pseudomonas aeruginosa (79–84)	○ Increased age ○ Length of MV ○ Antibiotics at admission ○ Transfer from a medical unit or ICU ○ Admission in a ward with higher incidence of patients with *P. aeruginosa* infections ○ ICU stay ○ Bedridden status ○ Presence of invasive devices ○ Prior use of certain antibiotics (broad-spectrum cephalosporins, aminoglycosides, carbapenems, fluoroquinolones) ○ Diabetes mellitus ○ Surgery
Enterobacterales (producing ESBL, CRE) (85–87)	○ Admission to ICU and antimicrobial use ○ Invasive operation ○ Duration of previous antibiotic therapy ○ Male gender ○ Admission from another healthcare facility ○ Ventilation at any point before culture during the index hospitalization ○ Receipt of any carbapenem in the prior 30 days

MDRO	Risk factors
Acinetobacter baumannii (52,88–92)	○ Prior colonization with MRSA ○ Prior beta-lactam use, particularly carbapenems ○ Prior fluoroquinolone use ○ Bedridden status ○ Debilitated status of patients in ICU ○ Current or prior intensive care unit admission ○ Presence of a central venous catheter ○ Recent surgery ○ MV ○ Hemodialysis ○ Malignancy

CRE: carbapenem-resistant Enterobacterales; ESBL: extended spectrum beta-lactamase; ICU: intensive care unit; MDRO: multidrug-resistant organism; MRSA: methicillin-resistant Staphylococcus aureus; MV: mechanical ventilation; NP: nosocomial pneumonia.

Table 5. Different VAP prevention bundles

	Intervention	SHEA/IDSA (36)	IHI bundle (37,38)	Spanish bundle (93)	French bundle (94)	Johns Hopkins bundle (95)	Level of recommendation (SHEA/IDSA)
1	Head of bed elevation	B	X	X	X	X	Low

	Intervention	SHEA/IDSA (36)	IHI bundle (37,38)	Spanish bundle (93)	French bundle (94)	Johns Hopkins bundle (95)	Level of recommendation (SHEA/IDSA)
2	Non-invasive positive pressure ventilation in selected populations	B					High
3	Minimize sedation or manage without sedation whenever possible	B		X		X	Moderate
4	Daily sedation interruption	B	X				High
5	Daily assessment of readiness to extubate	B	X			X	High
6	Perform spontaneous breathing trials with sedatives turned off	B					High
7	Facilitate early mobility	B					Moderate
8	Utilize endotracheal tubes with subglottic	B					Moderate

	Intervention	SHEA/IDSA (36)	IHI bundle (37,38)	Spanish bundle (93)	French bundle (94)	Johns Hopkins bundle (95)	Level of recommendation (SHEA/IDSA)
	secretion drainage ports for patients expected to require > 48 or 72 hours of MV						
9	Avoiding elective changes of ventilator circuits, humidifiers, and endotracheal tubes (only when visibly soiled)	B		X			High
10	Daily oral care with chlorhexidine	S	X	X	X		Moderate
11	Selective oral or digestive decontamination	S					High*
12	Prophylactic probiotics	S					Moderate

	Intervention	SHEA/IDSA (36)	IHI bundle (37,38)	Spanish bundle (93)	French bundle (94)	Johns Hopkins bundle (95)	Level of recommendation (SHEA/IDSA)
13	Ultrathin polyurethane endotracheal tube cuffs	S					Low
14	Automated control of endotracheal tube cuffs	S					Low
15	Saline instillation before tracheal suctioning	S					Low
16	Mechanical toothbrushing	S					Low
17	Peptic ulcer disease prophylaxis	NR	X			X	Moderate
18	Deep venous thrombosis prophylaxis		X			X	N/A
19	Education and training in airway management			X			N/A

	Intervention	SHEA/IDSA (36)	IHI bundle (37,38)	Spanish bundle (93)	French bundle (94)	Johns Hopkins bundle (95)	Level of recommendation (SHEA/IDSA)
20	Strict hand hygiene before airway management and glove and gown compliance			X	X		N/A
21	Control and maintenance of cuff pressure (French: > 20 cm H_2O)			X	X		N/A
22	Orogastric rather than nasogastric feeding tubes				X		N/A
23	Avoiding gastric overdistention				X		N/A
24	Eliminating non-essential tracheal suctioning				X		N/A

936 *B: basic practices; IDSA: Infectious Diseases Society of America; MV: mechanical ventilation;*
937 *N/A: not available; NR: not recommended; S: special approaches; SHEA: Society for Healthcare*
938 *Epidemiology of America. *Improves outcomes but not enough evidence on possible risks*
939 *(insufficient data on long-term impact on antimicrobial resistance).*
940

Figures

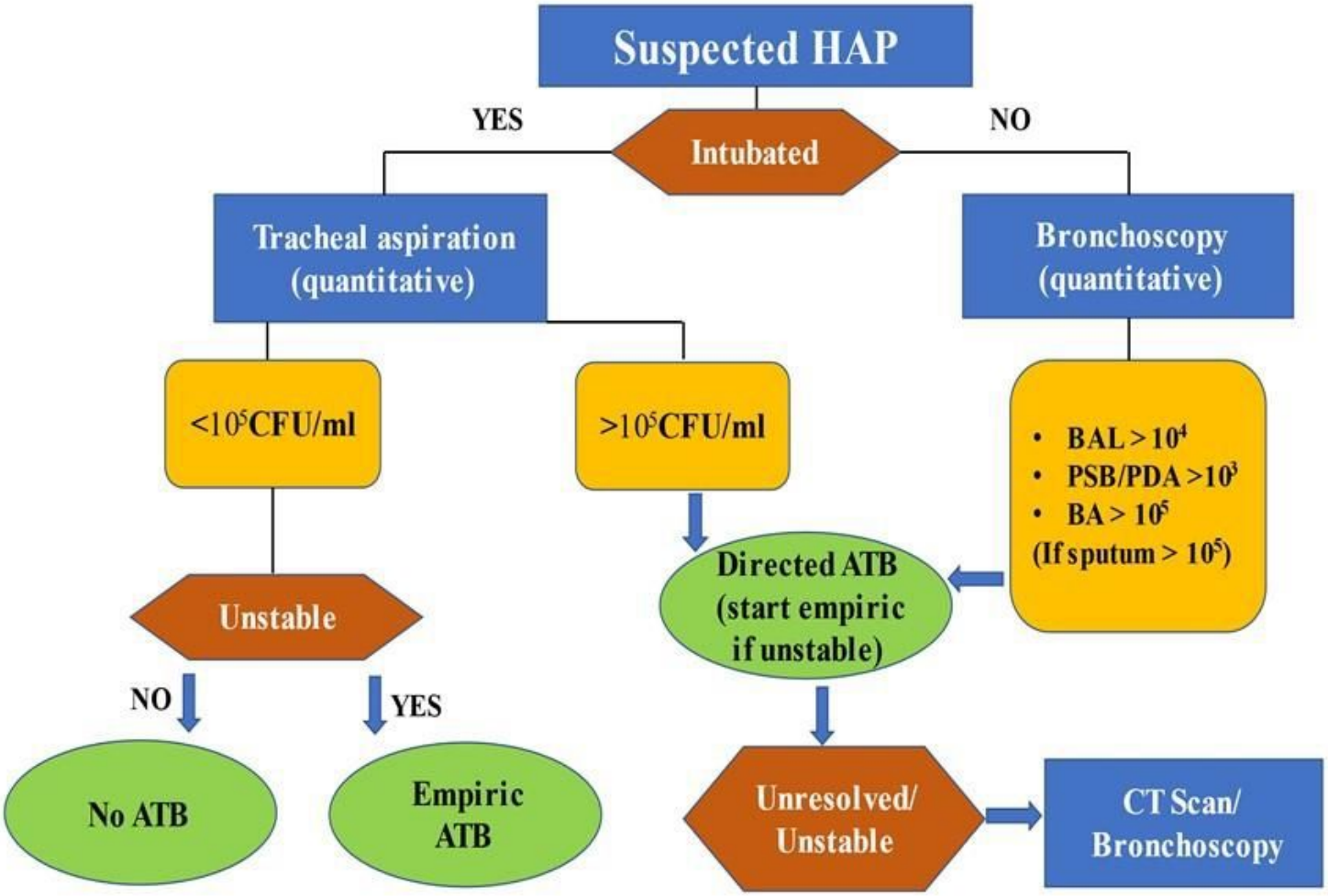

Figure 1

Algorithm for managing suspected HAP ATB: antibiotic; BA: bronchial aspirate; BAL: bronchoalveolar lavage; CFU: colony-forming unit; CT: computer tomography; HAP: hospital-acquired pneumonia; PDA: protective distal aspirate; PSB: protected specimen brushing.

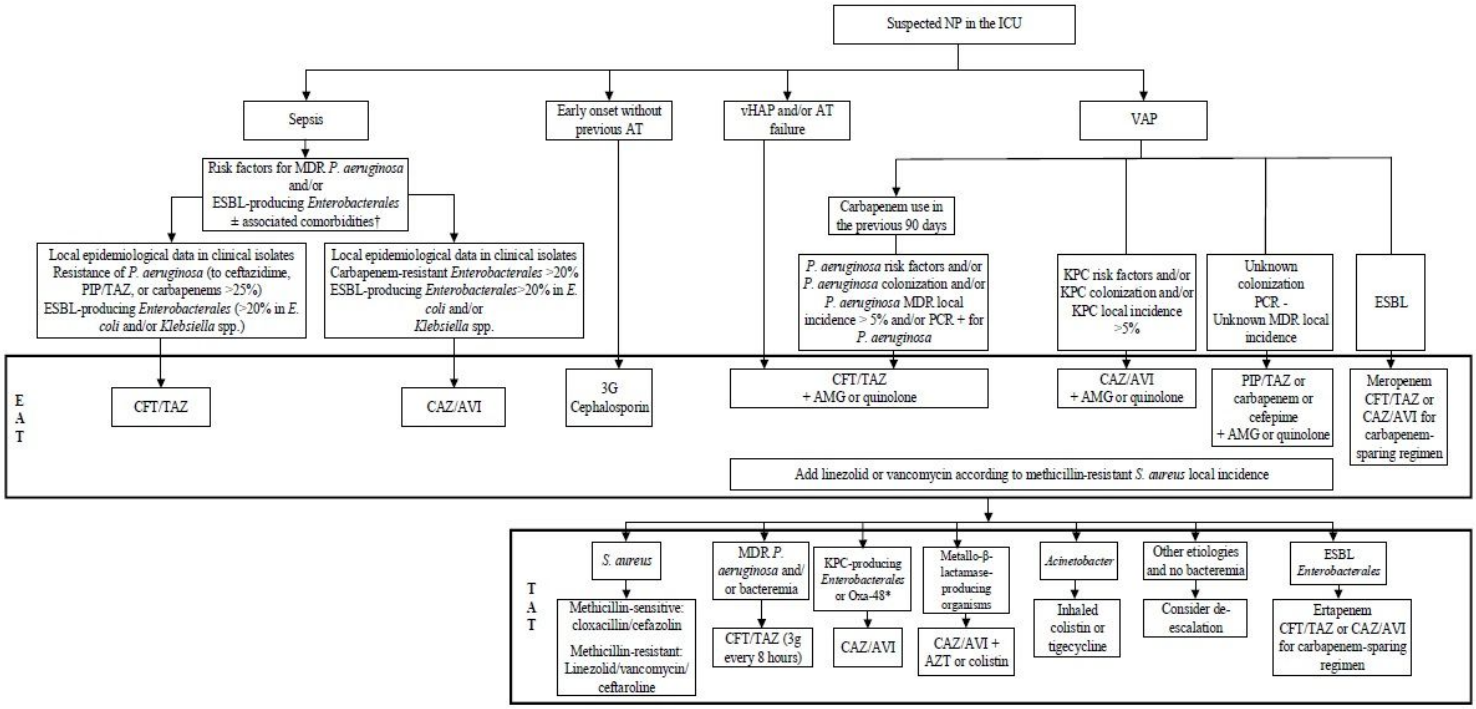

Figure 2

Treatment algorithm for VAP/HAP in ICU. AMG: aminoglycoside; AT: antimicrobial therapy; AZT: aztreonam; CAZ/AVI: ceftazidime/avibactam; CFT/TAZ: ceftolozane/tazobactam; EAT: empirical antimicrobial treatment; KPC: Klebsiella pneumoniae carbapenemase; MDR: multidrug-resistant; NP: nosocomial pneumonia; OXA-48: OXA-48 carbapenemase; PCR: polymerase chain reaction; PIP/TAZ, piperacillin/tazobactam; R: resistance; spp.: species plural; TAT: targeted antimicrobial treatment; VAP: ventilator-associated pneumonia; vHAP: ventilated hospital-acquired pneumonia. †Diabetes, COPD, moderate/severe renal/liver disease, immunosuppression/neutropenia, elderly patients, solid tumor, structural lung disease, organ transplantation, hemodialysis *If Oxa-48 susceptible to CAZ/AVI. Adapted from Montravers P. et al, 2018 (17) and Zaragoza R et al., 2020 (17,53).