Official journal of the Spanish Society of Chemotherapy

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Current treatment of nosocomial pneumonia and ventilator-associated pneumonia

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Revista Española de Quimioterapia
doi:10.37201/req/s03.06.2022

ABSTRACT

Hospital-acquired pneumonia and ventilator-associated pneumonia are severe nosocomial infections leading to high morbidity and mortality. Broad-spectrum antibiotics with coverage against all likely pathogens are recommended by the international guidelines. Inappropriate empirical treatment is one of the most important prognostic factors. Knowledge of local epidemiology and continuous microbiological surveillance is crucial for improving clinical approaches to empirical antimicrobial treatment. The development of protocols and policies for training healthcare professionals on preventive strategies, such as the "Pneumonia Zero" project, and improved implementation of antimicrobial stewardship practices, will aid early de-escalation of antibiotics and prevent resistance.

Keywords: hospital-acquired pneumonia, ventilator-associated pneumonia, multidrug-resistance, antimicrobial stewardship

INTRODUCTION

Hospital-acquired (HAP), hospital-acquired pneumonia requiring mechanical ventilation or ventilated HAP (vHAP), and ventilator-associated pneumonia (VAP) are three conditions associated with a high risk of death and morbidity. The severity of illness and infections caused by multidrug-resistant (MDR) organisms are two factors associated with the worst outcomes. In general, the negative consequences of initial inappropriate antibiotic therapy may be less pronounced in non-ventilated HAP than in VAP, given that HAP patients tend to be less severely ill. MDR pathogens tend to be less common in HAP patients who develop the infection outside of the intensive care unit (ICU), particularly early in the hospitalization course.

Data from the National Surveillance Program of ICU-Acquired Infection in Europe Link for Infection Control through Surveillance (ENVIN-HELICS) [1], elucidated that the likelihood of receiving inadequate empirical treatment for VAP caused by *Pseudomonas aeruginosa* is around 30%, even in patients receiving combination treatment. Antimicrobial stewardship programs are central to minimize the effects associated with the use of antimicrobials (e.g., drug resistance, toxicity), while promoting the use of cost-effective treatments. Local antibiotic resistance is strongly affected by local antibiotic prescription policies.

Herein we propose an approach to the empirical treatment of HAP and VAP, and targeted use of antimicrobials in the context of MDR organisms. Carbapenem-sparing treatments will be reviewed to provide an approach to new therapies.

EMPIRICAL THERAPY: SEEKING FOR RISK FACTORS TO MDR ORGANISMS

The latest international guidelines in Europe and America serve as tools for the management of HAP and VAP [2-4]. The appropriate antimicrobial regimen for HAP depends upon the presence or absence of risk factors for MDR pathogens, knowledge of the predominant pathogens (and susceptibility patterns) within the health care setting (local ecology), and the individual patient's prior microbiology data (surveillance cultures). Still, the appropriateness of empirical therapy may sometimes be challenging, and the risk of developing infections caused by MDR microorganisms during treatment may lead to adverse outcomes and increased mortality. Clinicians should differentiate VAP from vHAP, as clinical implications, prognosis, and approach to treatment may vary [5,6].

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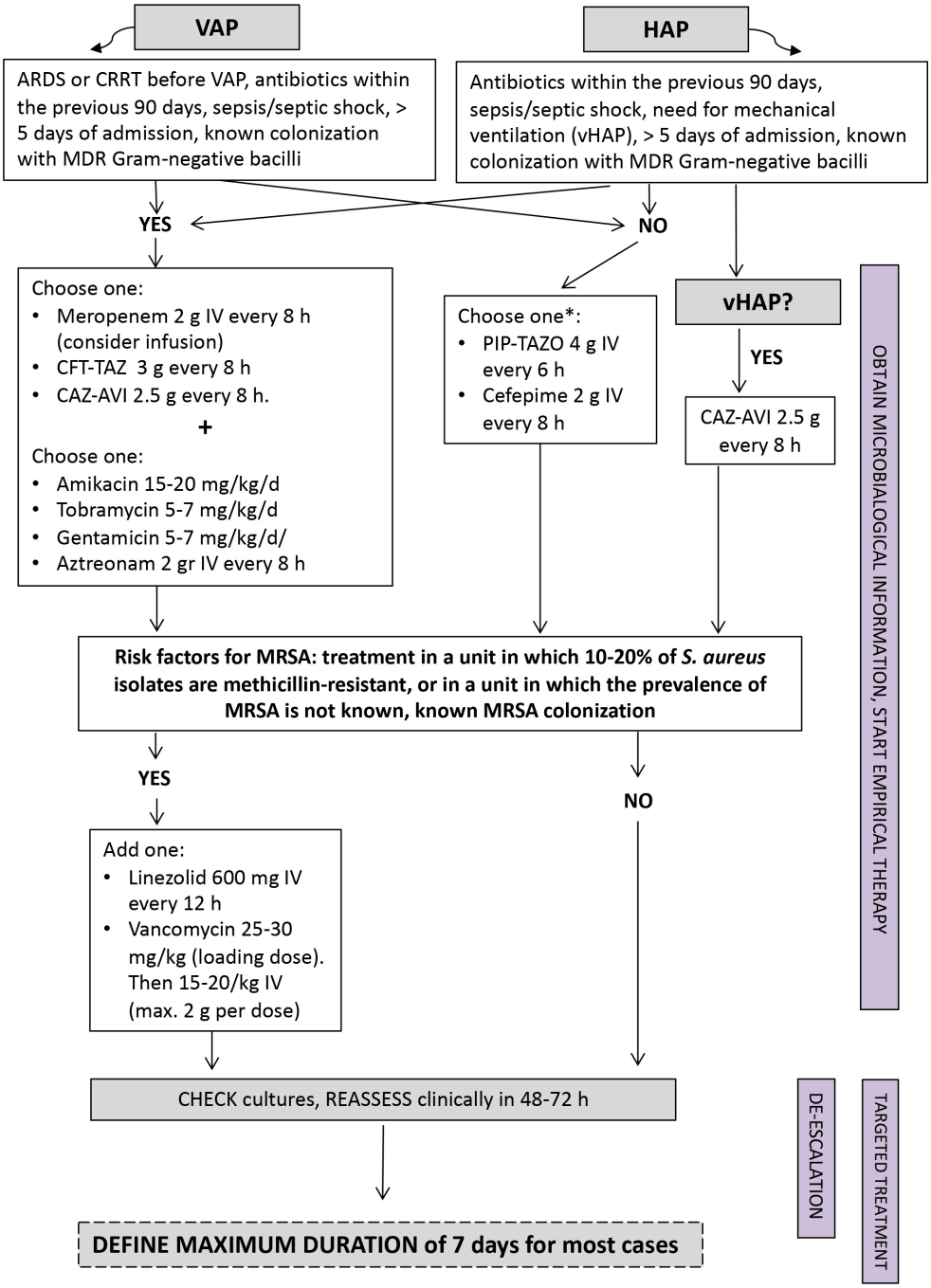

Figure 1 Management of HAP, vHAP and VAP.

Risk factors for MDR gram-negative bacilli: Local prevalence of >10%, unknown local epidemiology, septic shock, acute respiratory distress syndrome prior to VAP, renal replacement therapy, received antibiotics in the last 90 days, ≥ 5 days of hospital stay, known previous colonization (microbiological surveillance).
Risk factors for MRSA: local prevalence >10-20%, unknown prevalence of MRSA, influenza infection.

Table 1 **Most recommended treatment options for HAP, vHAP and VAP.**

Antimicrobial	Characteristics	Use
Piperacillin-tazobactam	In patients with a low-risk for MDR gram-negative bacilli (e.g., ESBL-E, MDR P. aeruginosa, MDR *Acinetobacter* spp.)	Appropriate treatment for early-onset HAP and VAP, in patients with no risk factors for ESBL-E
Meropenem	Coverage to many pathogens, including ESBL-E and P. aeruginosa.	In patients at high-risk for MDR Gram-negative bacilli, is a good option. The recommended standard dose for VAP is 2 gr every 8 h. Prolonged infusions of meropenem can be considered for ventilated HAP and VAP
Ceftolozane/tazobactam (CFT/TAZ)	Various experts recommend this agent to treat *P. aeruginosa* infections	The ASPECT-NP trial demonstrated the non-inferiority of CFT/TAZ when compared with meropenem 1 g every 8 hours. The recommended dose for VAP is 3 g by intravenous infusion within 3 hours every 8 h [12]. The APEKS-NP trial demonstrated cefiderocol was non-inferior to high-dose (2 g), extended-infusion meropenem in terms of all-cause mortality on day 14 in patients with Gram-negative nosocomial pneumonia [17]
Ceftazidime/avibactam (CAZ/AVI)	Third-generation cephalosporin with activity against serin-carbapenemase-producing *P. aeruginosa*, class A, C, and D (OXA-48) beta-lactamases. CAZ/AVI does not have activity against metallo-b-lactamases.	Treatment of infections caused by CPK-like carbapenemase-producing *Enterobacteriaceae*
Cefiderocol	This antibiotic was recently approved by the FDA to treat urinary tract infections. Coverage to metallo-β-lactamases.	VAP: The CREDIBLE-CR trial found that the clinical and microbiological efficacy of cefiderocol was similar to the best available treatments in patients with infections caused by carbapenem-resistant Gram-negative bacteria, including hospital-acquired pneumonia and VAP [13]
Adjunctive aerosolized antibiotics	Controversial, the best available evidence does not support their use. Intravenous colistin is not recommended	-VAP: IASIS and the INHALE trials, did not achieve their primary endpoints [14,15]. The MAGIC-BULLET trial was unable to demonstrate the non-inferiority of colistin compared to meropenem, both in combination with levofloxacin [11]. -VAP caused by MDR *A. baumannii*: aerosolized colistin may be an option as rescue therapy when other systemic treatments fail [16]
Linezolid	For patients admitted in units with a prevalence of MRSA of > 10-20%, or with known colonization by MRSA. Some studies show superior efficacy of linezolid than vancomycin, better lung tissue penetration, and lower incidence of nephrotoxicity	For HAP and VAP cases with known colonization with MRSA, MRSA prevalence > 20% or unknown.

VAP: ventilator-associated pneumonia, HAP: hospital-acquired pneumonia, vHAP: ventilated hospital-acquired pneumonia, ESBL-E : Extended spectrum beta-lactamase *Enterobacteriaceae*, MDR: multidrug-resistant, MRSA: methicillin-resistant *S. aureus*.

Different characteristics predispose individuals to acquired MDR microorganisms, such as the recent use of broad-spectrum antimicrobials, sepsis or shock, known unfavorable local ecology, known colonization with MDR organisms, a recent or current hospitalization for > 5 days [7]. However, there are significant differences in the local prevalence of MDR organisms among centers [8]. Each institution should analyze their local epidemiological data and not rely on national or regional data. In Spain, the 2019 ENVIN-HELICS report quantifies the antibiotic resistance of the most important microorganisms. The report describes all data related to the expected resistance rates in the different ICUs [1].

The MDR organisms most commonly involved in VAP are MDR *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E), *Acinetobacter baumannii*, and carbapenemase-producing *Enterobacteriaceae* (CPE). Once a patient is known to be colonized by an MDR organism, empiric antimicrobial treatment should target such pathogen only if previously described as a potential cause of the suspected infection. The location of colonization is also important.

PRESCRIPTION OF EMPIRICAL THERAPY

Current treatment recommendations for HAP, vHAP and VAP are summarized in Figure 1 [9-12]. New-generation drugs have been clinically validated for the treatment of increasingly common MDR organisms, such as MDR *P. aeruginosa*, ESBL-E, and CPE. Some drugs are useful for improving carbapenem-sparing policies. The Table 1 summarizes the most recommended treatment options for nosocomial pneumonia, including treatments for patients with risk factors for MDR organisms [10,11,13-17]. Also, antimicrobial coverage against MRSA can be added to empirical regimens [18-20].

ANTIMICROBIAL STEWARDSHIP IN NOSOCOMIAL PNEUMONIA

The indiscriminate use of antibiotic combinations can induce the emergence of highly resistant strains. The reassessment of an individual's clinical status at 48-72 hours of initiation of treatment and the use of procalcitonin kinetics when there is clinical uncertainty, could be useful to guide de-escalation and prevent the development of resistance. Advances in developing tools for the rapid diagnosis of nosocomial pneumonia and improved implementation of antimicrobial stewardship programs will reduce the exposure to unnecessary antibiotics.

A 7-day course of antimicrobial therapy is widely recommended by the American and European guidelines, as prolonged courses of antibiotics promote the emergence of resistance. However, the optimal duration of therapy for MDR organisms has not been clearly defined.

CONCLUSIONS

Nosocomial pneumonia is a health-care related infection with significant consequences for the patient and the healthcare system. Appropriate empirical treatment and early de-escalation should be implemented to increase the chance of survival.

Identifying risk factors for MDR organisms, local policies to improve antimicrobial stewardship, and knowledge of local ecology and previous colonization, are of outstanding importance. Healthcare workers should be trained to implement recommended preventive measures, such as adequate hand hygiene and respiratory devices management.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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