Update in Main Infectious Syndromes

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Empirical treatment of adults with hospital-acquired pneumonia: lights and shadows of the 2016 Clinical Practice ATS/IDSA Guidelines

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ABSTRACT

Hospital-acquired pneumonia (HAP) is a common cause of nosocomial infection associated with significant morbidity and mortality. New clinical practice guidelines for the management of adults with hospital-acquired pneumonia have been published in 2016 by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS). This review focuses on the recent recommendations and their limitations. We also focus on new therapeutic options that might improve the treatment and outcomes of these patients.

Tratamiento empírico de la neumonía nosocomial en adultos: luces y sombras de las guías de práctica clínica de la ATS/IDSA de 2016

RESUMEN

La neumonía nosocomial es una causa frecuente de infección intrahospitalaria y tiene una elevada morbilidad y mortalidad. En el año 2016 se ha publicado una nueva guía de práctica clínica para el manejo de la neumonía nosocomial en adultos, elaborada por la Infectious Diseases Society of America (IDSA) y la American Thoracic Society (ATS). Esta revisión comenta nuestra opinión sobre las nuevas recomendaciones y sus limitaciones, así como en las nuevas opciones terapéuticas disponibles que podrían mejorar el tratamiento y pronóstico de estos pacientes.

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Hospital acquired pneumonia (HAP) is defined as an inflammatory process in lung tissue caused by infectious pathogens that is not present at the time of hospital admission and occurring 48 hours or more post admission[1].

It represents the second most prevalent hospital-acquired infection[2], and is an important concern for national public health system due to its high morbidity and mortality as well as the huge amount of health resources that consumes. It is important to note the differences between HAP and ventilator-associated pneumonia (VAP). VAP is defined as the pneumonia that arises more than 48 to 72 hours after endotracheal intubation. Despite this infection is also a nosocomial pneumonia, in the next lines we will refer to HAP exclusively in patients without intubation.

There are different challenges for physicians in the treatment of HAP. There is very little current information regarding the aetiology of HAP. Most data concerning the aetiology of nosocomial pneumonia refer especially to VAP population. A recent review published by our group describes that up to 60% of the cases of HAP are caused by gram-negative bacilli. *Pseudomonas aeruginosa* (24%) and *Klebsiella* spp. (11%) were the most frequently microorganisms isolated. The most frequent gram-positive pathogen associated with HAP was *Staphylococcus aureus,* accounting for 30% of the cases[1]. Remarkably, the risk factors for multidrug resistant HAP are not well defined. Antibiotic resistance is a global health problem worldwide, especially in those infections caused by gram-negative bacilli. The infections caused by these multidrug resistant strains receive often inappropriate antimicrobial therapy and it might negatively impact on outcomes.

New clinical practice guidelines for the management of adults with hospital-acquired pneumonia have been published in 2016 by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS)[3]. In these guidelines, the distinction between "early onset" pneumonia (occurs in the first 96 hours of hospital admission) and "late onset" pneumonia

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(appears after >96 hours) has been removed. This division was based on the fact that within the first days of hospital admission, gram-positive cocci still predominate on the flora of the respiratory system. After 5-7 days of illness, oropharynx fibronectin disappears and some receptors that allow the gram-negative rods colonization are exposed. Antibiotic pressure selects multiresistant strains and *P. aeruginosa* colonization[4]. Recent studies have questioned the relationship between the timing of nosocomial pneumonia and the risk of multidrug-resistant (MDR) pathogens. However, most of these researches were focused on VAP[5,6].

The 2016 guidelines on HAP[3] remark two factors to decide the empirical antibiotic therapy for patients with HAP: risk of MDR infection and severity of disease. After the review of several articles, the authors identify the use of prior intravenous antibiotic treatment within 90 days as the only risk factor for MDR HAP. Other factors such as the existence of comorbidity, recent hospital admission, the use of prior oral antibiotics, current hospitalization in an area of high prevalence of multi-drug resistances or previous colonization by multi-drug resistant microorganisms were not taken into account. Those patients who require mechanical ventilation or present shock at the time of diagnosis were categorized as patients who had high risk of mortality. Some measures such as empirical double

Table 1	Recommended initial empiric antibiotic therapy for hospital–acquired pneumonia (non-ventilator-associated pneumonia) (adapted from reference 3)		
Not at high risk of mortality and no factors increasing the likelihood of MRSA	Not at high risk of mortality but with factors increasing the likelihood of MRSA	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacilin-tazobactam 4.5 g IV q6h	Piperacilin-tazobactam 4.5 g IV q6h	Piperacilin-tazobactam 4.5 g IV q6h
OR	OR	OR
Cefepime 2 g IV q8h	Cefepime or ceftazidime 2 g IV q8h	Cefepime or ceftazidime 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem 500 mg IV q6h	Imipenem 500 mg IV q6h	Imipenem 500 mg IV q6h
Meropenem 1 g IV q8h	Meropenem 1 g IV q8h	Meropenem 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15-20 mg/kg IV daily
		Gentamicin 5-7 mg/kg IV daily
		Tobramycin 5-7 mg/kg IV daily
		OR
		Aztreonam 2 g IV q8h
	Plus:	Plus:
	Vancomycin 15 mg/kg IV q8-12h with goal to target 15-20 mg/mL trough level (consider a loading dose of 25-30 mg/kg x 1 for severe illness	Vancomycin 15 mg/kg IV q8-12h with goal to target 15-20 mg/mL trough level (consider a loading dose of 25-30 mg/kg x 1 for severe illness
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA.
		Options include:
		Piperacilin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam-based antibiotic, include coverage for MSSA.		

coverage treatment for gram-negative bacilli are recommended only for these patients.

Empirical antibiotic treatments recommended by new guidelines for the different patient subgroups with HAP are shown in the table 1.

We have some concerns about these recommendations. Firstly, some of the empirical antibiotic treatments proposed are not optimal to treat aspiration pneumonia. We would like to point out that this aetiology is important to consider in older patients, in those with cerebrovascular diseases and/or impaired consciousness at presentation and/or in those patients with swallowing difficulties. Secondly, we think that an initial empirical treatment with levofloxacin o ciprofloxacin as a unique therapy to treat gram-negative bacilli might be inappropriate in most countries due to the high prevalence of resistant strains to these drugs[7]. It is also important to point out that not all drugs combinations used for gram-negative bacilli are synergistic and/or appropriate. Thirdly, the empirical use of vancomycin might be severely compromised, given the profile of patients who are currently admitted to the hospital (elderly and with high comorbidity) because of its toxicity. This fact is particularly relevant for patients receiving concomitant treatment with aminoglycosides.

Finally, the 2016 guidelines on HAP suggest that antibiotic therapy should be adjusted according to the results of antibiogram. However, we would like to emphasize that not all antibiotics have the same bactericidal power, side effects and ability of generating resistances. All these factors should be taken into account when definitive treatment is selected.

Five new antibiotics have been approved recently. They are not included in the new guidelines and may be useful in patients with HAP. Ceftolozane-tazobactam is a beta-lactam antibiotic with a similar chemical structure to ceftazidime. Ceftolozane is larger than ceftazidime, so it cannot be removed by efflux pumps. This antibiotic has also full activity against OprD mutant strains. Moreover, the addition of tazobactam provides activity to many class A beta-lactamases. For all these reasons, ceftolozane-tazobactam offers an excellent coverage against *P. aeruginosa*, even for the multi-drug resistant strains. In a total of 2,968 isolates of *P. aeruginosa* consecutively collected from patients hospitalized with pneumonia in 59 medical centres in the USA and 15 European countries, ceftolozane-tazobactam demonstrated a greater *in vitro* activity than currently available cephalosporins, carbapenems and piperacillin-tazobactam[8].

Avibactam is a new beta-lactamases inhibitor, molecularly very different from existing ones. This inhibitor has an intrinsic antibacterial action and a peculiar structure that protects it from hydrolyzation by several beta-lactamases. Ceftazidime-avibactam is a novel cephalosporin/beta-lactamase inhibitor that inhibits the activities of ambler class A and C beta-lactamases and some ambler class D enzymes. This drug offers coverage for most carbapenemase producing-Enterobacteriaceae in Spain.

Ceftaroline is a new cephalosporin that has a great action against gram-positive pathogens. It binds to different PBP, including PBP2a, making it active against methicillin-resistant *S. aureus* (MRSA). It is one of the antibiotics with greater bactericidal effect against gram-positive and has an inmunomodulatory activity by inhibiting some toxins. As most beta-lactams, it does not have major side effects.

Tedizolid is an oxazolidinone with a long half-life and few significant side effects. A double-blind randomized clinical trial is currently underway to compare tedizolid versus linezolid in patients with HAP[9].

Finally, dalbavancin is a recently approved glycopeptide used to treat infections caused by *S. aureus* and MRSA. Its main advantage is its dosage (once a week) and its few side effects[10]. Further information is needed to recommend this drug in patients with HAP.

In conclusion, HAP is a serious and difficult to treat illness. Some new therapeutic options that might improve the treatment and prognosis of patients who develop this infection have recently appeared. Further studies are needed to define high risk patients for MDR-HAP and to check if new antibiotics have any impact to improve outcomes.

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