Microbial cause of ICU-acquired pneumonia: hospital-acquired pneumonia versus ventilator-associated pneumonia

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Microbial etiology of ICU-acquired pneumonia: HAP vs VAP

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Purpose of review: Successful treatment of patients with hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) remains a difficult and complex undertaking. Better knowledge of the pathogens involved in that setting may allow reassessment of our current modalities of therapy and definition of better protocols.

Recent findings: Microorganisms responsible for HAP/VAP differ according to geographic areas, ICU patients specific characteristics, durations of hospital and ICU stays before onset of the disease, and risk factors for MDR pathogens. However, a number of studies have shown that gram-negative bacilli (GNB)—particularly *Pseudomonas aeruginosa* and Enterobacteriaceae—cause many of the respiratory infections in this setting, with minimal differences between HAP and VAP, indicating that the etiology depends more on the underlying clinical condition of patients rather than previous intubation.

Summary: When selecting initial antimicrobial therapy in patients with HAP/VAP, more attention should be paid to individual risk factors for MDR pathogens, severity of the clinical situation and the local epidemiology than to the type of pneumonia.

Keywords: ventilator-associated pneumonia, hospital-acquired pneumonia, microbial etiologies.

Introduction

The clinical spectrum of lower respiratory tract infections potentially affecting patients managed in the intensive care unit (ICU) includes different diseases with peculiar epidemiological, clinical and microbiological aspects. The term “HAP” refers to hospital-acquired pneumonia contracted by a patient at least 48–72 hours after being admitted to the hospital and can be divided into non-ventilated HAP and ventilated HAP (when the patient is ventilated as a result of the pneumonia). “VAP” specifically refers to pneumonia that occurs in association with endotracheal intubation after at least 48 hours of mechanical ventilation. With current standard-of-care therapy, clinical success rates for patients admitted to the ICU with HAP/VAP are often less than 60%, related to the many challenges that encompass antibiotic therapy in critically ill patients, including difficulties in identifying microbial etiologies, relative low penetration of most antibiotics into the lung tissue and the frequency of difficult-to-treat or highly resistant pathogens in that setting [1,2]. Obviously, better knowledge of HAP/VAP microbial etiologies might allow better identification of patients at high risk of infection caused by problematic pathogens, such as multidrug-resistant (MDR) nonfermenting gram-negative bacilli (GNB) and extended spectrum betalactamase (ESBL)-producing Enterobacteriaceae (including carbapenemase-producing GNB), and consequently, better selection of initial antibiotics, while avoiding overuse of broad-spectrum antibiotics when the infection is caused by susceptible microorganisms [3–5]. The present review summarizes current data available on these issues for patients admitted to the ICU.

Microbial etiologies of VAP

Microorganisms responsible for VAP differ according to geographic areas, ICU patients specific characteristics, durations of hospital and ICU stays before onset of the disease, and risk factors for MDR pathogens [3,4]. However, a number of studies have shown that gram-

negative bacilli (GNB)—particularly *Pseudomonas aeruginosa* and Enterobacteriaceae—cause many of the respiratory infections in this setting, with relatively minor changes in the distribution of the pathogens during the last decade [2,6–8]. Among a total of 12 851 bacterial isolates that were isolated from patients hospitalized with VAP in US and European medical centers as part of the SENTRY Antimicrobial Surveillance Program from January 2009 to December 2012, the same top 11 organisms were observed in both geographic regions, and Gram-negative organisms represented 61.5/76.1% of strains in US/Europe, respectively [8]. Of the top 11 most frequently isolated organisms, 9 were Gram-negative bacilli in both regions; only *Staphylococcus aureus* among Gram-positive pathogens (number 1 or 2 rank) was commonly isolated, whereas *Streptococcus pneumoniae* was ranked 10th in the USA and 11th in EMR. *P. aeruginosa* was the most frequently isolated GNB in both regions (21% of cases in both regions) and showed reduced susceptibility to most antimicrobials tested, including ceftazidime (79.6/68.7% susceptibility in US/Europe), meropenem (76.3/65.8%) and piperacillin/tazobactam (72.9/63.9%). *Klebsiella* spp. was isolated from 9.7/11.6% of cases and showed extended-spectrum β-lactamase (ESBL) phenotype rates of 19.5/35.1% in US/Europe. *Enterobacter* spp. ranked fourth in the US (5.9%) and sixth in Europe (5.5%), whereas *Escherichia coli* ranked fifth in the US (5.5%) and third in Europe (11.8%). *Acinetobacter* spp. and *Stenotrophomonas maltophilia* combined were isolated from 8.0/10.7% of cases in US/Europe.

In a recent study designed for assessing the potential usefulness of ceftazidime/avibactam in 726 patients with nosocomial pneumonia, including 246 patients with VAP, prominent GNB isolated from respiratory site or blood were *K. pneumonia*e and *P. aeruginosa* [9]. 100 patients (28%) had one or more ceftazidime-non-susceptible Gram-negative pathogen, including 79 with Enterobacteriaceae and 25 with *P. aeruginosa*. *S. aureus* (detected in 58 patients, [16%]) was the only Gram-positive pathogen to be isolated in ten or

more patients. Very similar data were obtained in 2016 in a large French surveillance network that included 5 465 episodes of VAP in which the infection was microbiologically documented by semi- or quantitative cultures, the two most frequently isolated microorganisms being *P. aeruginosa* (19.9%) and *S. aureus* (13.5%) (Surveillance des infections nosocomiales en réanimation adulte, Réseau REA-Raisin, France, résultats 2016. www.invs.santepubliquefrance.fr).

As reported in many longitudinal case series, many episodes of VAP are increasingly caused by pathogens with a reduced susceptibility to current antibiotics, rendering more and more difficult the selection of initial antimicrobial treatment [2,7]. Although VAP typically involves infection with a single pathogen, polymicrobial infection are common (table 1) [10,11]. Interestingly, the clinical outcomes were not influenced by the polymicrobial etiology, when appropriate antibiotic therapy was administered [10].

Until recently, MDR pathogens were isolated more frequently in late-onset VAP cases than in early-onset cases, mostly reflecting prior use of broad-spectrum antibiotics in these patients [4,6,12]. However, several more recent studies found similar rates of etiologies in patients with early- and late-onset VAP (Table 1) [13–17]. In early-onset pneumonia, the initial VAP severity—i.e.; the presence of sepsis or septic shock (odds ratio [OR] = 3.7)—and pneumonia that developed in a center with a prevalence of resistant pathogens greater than 25% were independently associated with the presence of resistant pathogens (OR = 11.3), emphasizing that the local ICU ecology is the most important risk factor for acquiring MDR pathogens, irrespective of the length of intubation [14].

Based on these data, the recent European guidelines for the management of HAP/VAP suggest that the selection of patients with early-onset VAP (within 4 days of hospital admission) to receive empirical treatment with narrow-spectrum antibiotics should be based on the individual risks, the severity of the clinical situation (shock), and the frequency and

type of MDR pathogens detected in the ICU [3]. Because MDR pathogens are more frequently found in immunocompromised patients with VAP, they should be treated accordingly, using broad-spectrum antibiotics [3].

Extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE) are increasingly encountered in patients with hospital acquired infections, including VAP, with additional mortality and cost. They now represent 19 to 61% of the episodes, varying according to species and to countries [8,18]. Several studies suggest that previous colonization and antibiotic therapy are the two most important risk factors associated with ESBL-PE related infection [19,20]. In a study conducted in 587 patients with suspected VAP, 40 patients (6.8%) were colonized with ESBL-PE prior to the development of pneumonia and 20 (3.4%) had VAP caused by this microorganism, of whom 17 were previously colonized with ESBL-PE [21]. Thus, positive and negative predictive values of prior ESBL-PE colonization for predicting ESBL-PE involvement in VAP were 41.5% and 99.4%, respectively, confirming that screening for ESBL-producing GNB digestive colonization by weekly active surveillance cultures could reliably exclude the involvement of such pathogens when rectal and/or tracheal swabs for ESBL-PE are negative.

Whether current decision-making algorithms for empiric antibiotic treatment can be improved and thus avoid initially inappropriate treatment or unnecessary carbapenem use is unknown and would depend of the local prevalence of infections caused by ESBL-PE [4,22,23]. In a retrospective nested case-control study performed in eight Dutch hospitals, a scoring system that consisted of 9 clinical predictors available at the onset of infection identified hospital-onset infection caused by 3rd generation cephalosporin-resistant GNB with an acceptable sensitivity (81.5%) and yet, reduced the proportion of patients classified as at risk (i.e.; eligible for empiric carbapenem therapy) by 49%, compared to a basic model

incorporating only prior ESBL-PE colonization and exposure to cephalosporins and/or fluoroquinolones [24].

The emergence of infections caused by carbapenem-resistant Enterobacteriaceae (CRE) worldwide represents an alarming problem, although the prevalence of such infections is highly variable across different countries [25–27]. No studies specifically addressing the role of CRE in HAP and VAP are available so far. However, prior use of a carbapenems and prior hospitalization in a country where CRE is highly prevalent have been reported as independent risk factors for the acquisition of KPC- *Klebsiella pneumoniae* and other CRE [28,29].

Oropharyngeal or tracheal colonization with *P. aeruginosa* increases with increased length of hospitalization, prior antibiotic use, and severity of illness, and is an important risk factor for VAP caused by this microorganism. In an international observational study that included 1873 ventilated patients in 11 countries across four regions, including the United States, Europe, Latin America, and Asia Pacific, corresponding *P. aeruginosa* VAP prevalences were 4.1%, 3.4%, 4.8%, 4.6%, and 3.2%, respectively ($p = 0.49$) [30]. Although none of the predefined risk factors were predictive of *P. aeruginosa* VAP in multivariate regression analysis, high proportion of resistance in the community or hospital unit was significant for prior *P. aeruginosa* colonization, which was in turn predictive of *P. aeruginosa* VAP: the odds of developing *P. aeruginosa* VAP were eight times higher in patients with prior *P. aeruginosa* colonization than in non-colonized patients [30]. In a study that enrolled 3,837 patients with VAP, including 959 episodes caused by *P. aeruginosa*, risk factors for *P. aeruginosa* VAP were older age, transfer from medical ICU or medical unit, length of MV, antimicrobial use, and admission to a ward with high incidence of *P. aeruginosa* infections, confirming the importance of local epidemiology when assessing the risk of developing an infection caused by MDR pathogens [31].

Acinetobacter baumannii is a common cause of ICU-acquired infection, accounting for 8 to 14% of VAP in the United States and Europe, but much higher rates (19% to >50%) in Asia, Latin America, and some Middle Eastern countries [32–36]. In a cohort of 827 cases of VAP in 27 ICUs in Europe, *A. baumannii* was globally implicated in 11% of early-onset and 26.5% of late-onset VAP, but it was the most common cause of VAP in Greece and Turkey [37]. A prospective study in 10 Asian countries from 2008 to 2009 of HAP/VAP in adults (n=2,554) implicated *Acinetobacter* spp. in 36.5% of cases. Importantly, many isolates are now resistant to all antimicrobials except colistin (polymyxin E) and tigecycline, and some infections are untreatable with existing antimicrobial agents [32,33,38]. Global spread of MDR-*A. baumannii* strains reflects dissemination of a few clones between hospitals, geographic regions, and continents; while excessive use of antibiotics amplifies this spread.

Optimal treatment of VAP implies that the selection of initial antimicrobial agents could be done based on an accurate prediction of the responsible pathogens and of their susceptibility patterns, in order to avoid both ineffective therapy when the pathogen is highly resistant to antibiotics and excessive antibiotic use when it can be covered by a narrow-spectrum agent [3,4]. Unfortunately, although major risk factors for MDR pathogens include prolonged hospitalization before onset of VAP, prior antibiotic use, high frequency of antibiotic resistance in the specific hospital unit, immunosuppressive disease and/or therapy, and patient's severity, the exact weight of each of these factors is mostly unknown and no accurate algorithm to manage patients with VAP is thus readily available. Interestingly, in a single-center prospective study conducted in Spain that included 316 patients with clinical and microbiological diagnosis of ICU-acquired pneumonia, 289 (91%) had at least one risk factor for MDR microorganisms causing pneumonia, but MDR caused pneumonia in only 107 [34%] patients, reflecting the poor performance of all risk factors when taken individually for avoiding overuse of broad-spectrum antibiotics in this setting, with always higher-sensitivity

values compared with specificity [39]. The highest negative predictive values were for intravenous antibiotic use (79%) and 5 or more days of hospitalization before pneumonia (80%).

Microbial etiologies of HAP

HAP incidence ranges from 5 to more than 20 cases per 1000 hospital admissions, with the highest rates in immunocompromised, post-surgery and elderly patients [3,40–43]. However, in contrast to VAP patients in whom it is relatively easy to collect distal respiratory secretions through the endotracheal tube as soon as the infection is suspected and before the introduction of any new antibiotics, obtaining reliable specimens from the lower respiratory tract for microbiological cultures in patients developing HAP is difficult and thus most of them are receiving new antibiotics before specimens can be obtained. As a consequence, microbial etiologies remain poorly documented in a large fraction of patients with HAP (Table 2) [37,44–46]. Among 421 episodes of ICU-acquired suspected bacterial pneumonia prospectively collected in Barcelona, Spain, 248 patients (59%) had VAP, 69 patients (16%) had non-ventilated HAP, and 104 patients (25%) had ventilated HAP (The FNIH HABP/VABP Project. https://fnih.org/what-we-do/biomarkers-consortium/programs/ventilator-acquired-bacterial-pneumonia). Not surprisingly, patients with non-ventilated HAP had a lower percentage of positive microbiology results (54.8%) compared to ventilated HAP and VAP.

The study by Esperatti et al. analyzed 315 episodes of ICU-acquired pneumonia and found that microbial etiology between VAP and non-ventilated HAP were similar, with the only exception that they observed a higher proportion of *S. pneumoniae* in non-ventilated HAP cases [47]. Using data from 27 ICUs in Europe that participated to the EU-VAP/CAP project, the most frequent microorganisms reported in patients with HAP were

Enterobacteriaceae, *S. aureus, P. aeruginosa* and *A. baumannii* , but the dominant isolates differed between countries. *S. aureus* was the dominant microorganism in Spain, France, Belgium and Ireland, whereas for Italy and Portugal it was *P. aeruginosa* , for Greece and Turkey *Acinetobacter* spp., and for Germany *E. coli* (Table 2) [37].

Very similar findings were reported in the SENTRY Antimicrobial Surveillance Program (1997–2008): the 6 top pathogens causing 80% of HAP cases were: *S. aureus, P. aeruginosa, Klebsiella* spp., *E. coli, Acinetobacter* spp., and *Enterobacter* spp. [44]. Secondary analysis of the data obtained in 485 intubated patients with HAP who were part of this project and in whom confirmed etiology and antibiotic susceptibility patterns were available identified that presence of severe sepsis/septic shock (OR = 3.7, 95 % CI 1.5–8.9) and pneumonia developed in centers with greater than 25 % prevalence of MDR pathogens (OR = 11.3, 95 % CI 2.1–59.3) were independently associated with MDR, even in patients with early onset pneumonia and no other risk factors [14].

Conclusion:

Most of the currently available studies on nosocomial pneumonia in the ICU have shown that a majority of these infections are caused by GNB often highly resistant to antibiotics, rendering difficult the selection of the initial antimicrobial treatment. Although microbial etiologies are frequently poorly documented in HAP cases, the agents responsible for the infection are mostly identical to those observed in VAP, regardless whether pneumonia is acquired during ventilation or not (Table 2). Therefore, when selecting initial antimicrobial therapy in patients with HAP/VAP, more attention should be paid to individual risk factors for MDR pathogens, severity of the clinical situation and the local epidemiology than to the type of pneumonia. In the future, molecular assays directly applicable to respiratory specimen testing might allow to rapidly determine which pathogen is responsible for infection and thus

greatly facilitate the selection of the initial regimen, while avoiding using broad-spectrum antibiotics if no MDR pathogens are identified from a deep respiratory tract sample (endotracheal aspirate or BAL) [3,48].

Key points:

- Better knowledge of the pathogens involved in HAP/VAP may allow reassessment of our current modalities of therapy and definition of better protocols, avoiding initially inappropriate antimicrobial therapy as well as excessive use of broad-spectrum antibiotics.
- HAP/VAP are frequently caused by highly resistant GNB, including *P. aeruginosa* and ESBL-producing Enterobacteriaceae, with minimal differences between these two entities (Tables 1 and 2).
- When selecting initial antimicrobial therapy in patients with HAP/VAP, more attention should be paid to the durations of hospital and ICU stays before onset of the disease, the individual risk factors for MDR pathogens, the severity of the clinical situation and the local epidemiology than to the type of pneumonia.

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Table 1. Most common etiological pathogens isolated from patients with VAP, as documented in a prospective observational study that enrolled patients from 27 ICUs in nine European countries (By courtesy of Dr. Koulenti, Ref. 37).

Causative pathogen	VAP* (n=465)	
	Early-VAP (<5 days) (n=193)	Late-VAP (≥ 5 days) (n=272)
Unknown, n (%)	48 (24.9)	61 (22.4)
Other, n (%)	43 (22.3)	26 (9.6)
Staphylococcus aureus, n (%)	58 (62.4)	58 (21.3)
MRSA, n (%)	18 (9.3)	34 (12.5)
MSSA, n (%)	40 (20.7)	24 (8.8)
P. aeruginosa, n (%)	26 (13.5)	55 (20.2)
Acinetobacter spp., n (%)	16 (8.3)	56 (20.6)
Enterobacteriaceae, n (%)	61(31.6)	92 (33.8)
Polymicrobial infection, n (%)	50 (25.9)	64 (23.5)

*VAP was defined as pneumonia arising 48 hours or more after endotracheal intubation with no evidence of pneumonia at the time of intubation. All 465 episodes of VAP were first episodes.

Table 2. Most common etiological pathogens grouped by type of pneumonia, as documented in a prospective observational study that enrolled patients from 27 ICUs in nine European countries (By courtesy of Dr. Koulenti, Ref. 37).

Causative pathogen	Very early-VAP* (n=138)	VAP** (n=465)	HAP† (n=224)
Unknown, n (%)	59 (42.8)	109 (23.4)	84 (37.5)
Other, n (%)	31 (22.5)	69 (14.8)	20 (8.9)
Staphylococcus aureus, n (%)	26 (18.8)	116 (24.9)	44 (19.6)
MRSA, n (%)	10 (7.2)	52 (11.2)	30 (13.4)
MSSA, n (%)	16 (11.6)	64 (13.8)	14 (6.3)
P. aeruginosa, n (%)	16 (11.6)	81 (12.5)	36 (16.1)
Acinetobacter spp., n (%)	8 (5.8)	72 (15.5)	30 (13.4)
Enterobacteriaceae, n (%)	29 (21)	153 (32.9)	70 (31.3)
Polymicrobial infection, n (%)	25 (18.1)	114 (24.5)	46 (20.5)

*Very early VAP was defined as pneumonia developing within 48 hours after intubation.
**VAP was defined as pneumonia arising 48 hours or more after endotracheal intubation with no evidence of pneumonia at the time of intubation. All 465 episodes of VAP were first episodes.
†HAP was defined as a lung infection presenting in nonintubated patients 48 hours or more after hospital admission, which was not already incubating at the time of such hospital admission.