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Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors

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Abstract *Purpose:* As per 2005 American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) guidelines for managing hospital-acquired pneumonia, patients with early-onset pneumonia and without risk factors do not need to be treated for potentially resistant microorganisms (PRM). *Methods:* This was a secondary analysis of a prospective, observational, cohort, multicentre study conducted in 27 ICUs from nine European countries. *Results:* From a total of 689 patients with nosocomial pneumonia who required mechanical ventilation, 485 patients with confirmed etiology and antibiotic susceptibility were further analysed. Of these patients, 152 (31.3 %) were allocated to group 1 with early-onset pneumonia and no risk factors for PRM acquisition, and 333 (68.7 %) were classified into group 2 with early-onset pneumonia with risk factors for PRM or late-onset pneumonia. Group 2 patients were older and had more chronic renal failure and more severe illness (SAPS II score, 44.6 ± 16.5 vs. 47.4 ± 17.8, $p = 0.04$) than group 1 patients. Trauma patients were more frequent and surgical patients less frequent in group 1 than in group 2 ($p < 0.01$). In group 1, 77 patients (50.7 %) had PRM in spite of the absence of classic risk factors recognised by the current guidelines. A logistic regression analysis identified that presence of severe sepsis/septic shock (OR = 3.7, 95 % CI 1.5–8.9) and pneumonia developed in centres with greater than 25 % prevalence of PRM (OR = 11.3, 95 % CI 2.1–59.3) were independently associated with PRM in group 1 patients. *Conclusions:* In patients admitted to ICUs with a prevalence of PRM greater

than 25 % or with severe sepsis/septic shock, empiric therapy for group 1 nosocomial pneumonia requiring mechanical ventilation should also include agents likely to be effective for PRM pathogens.

Keywords HAP · VAP · Multidrug-resistant organisms · Septic shock · Guidelines · Antibiotic treatment

Introduction

In 2005, the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) published an evidence-based guideline for the management of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and health-care-associated pneumonia (HCAP) [1]. One important factor in the successful treatment of patients with pneumonia was the use of appropriate initial therapy [2–4]. In the EPICII study, potentially resistant microorganisms (PRM) were pathogens that contributed about 50 % of microbiologically confirmed infections in the ICU [5], and the failure to provide therapy for these organisms has been identified as a common reason for inappropriate initial therapy.

Since many patients without risk factors for PRM might develop pneumonia with these pathogens, it is possible that guideline-directed therapy would lead to inappropriate initial treatment and a higher ICU mortality than in patients with PRM and known risk factors. However, there are other factors, including the hospital ecology, presence of shock, or the type of prior antibiotic treatment that would be considered for clinical decision making that might help in selecting the correct treatment option. The main goal of the present study was to assess the accuracy of the 2005 ATS/IDSA guidelines to predict the presence of PRM in a multicentre cohort of ICU patients with HAP/VAP. Our hypothesis was that presence of severe sepsis/septic shock and baseline PRM have to be considered in the decision-making process of therapy.

Materials and methods

A secondary analysis of EU-VAP/CAP Study, a prospective, observational study that was conducted in 27 ICUs from nine European countries (Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain and Turkey). The capacity for the majority of participating units was more than eight beds (26 out of 27 ICUs). Further details can be found elsewhere [6]. Only patients with nosocomial pneumonia who required mechanical ventilation were selected in the present study. Further details from the selected population are detailed in the study profile figure following the strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies [7] (Fig. 1). Patient demographics, primary diagnosis, ICU and hospital length of stay (LOS), the McCabe [8] classification of co-morbidities [likely to survive 5 years or more, 1–5 years (ultimately fatal) or less than 1 year (rapidly fatal)], SAPS II score [9] and outcome (ICU mortality) were recorded for all patients. Each clinical episode of pneumonia was described separately. The data collection of patients with a clinical diagnosis of pneumonia included clinical signs of sepsis which were classified into sepsis, severe sepsis and septic shock [10]. Sepsis-related organ failure scored by SOFA [11] and severity of illness scored by SAPS II were collected at ICU admission for HAP and on the day of clinical suspicion and the previous day of clinical suspicion for VAP patients. Other suspected or concurrent infections, diagnostic procedures including microbiological testing, antibiotic use, the time period between clinical suspicion of pneumonia and the first dose of appropriate antibiotic, clinical response and pneumonia's contribution to death were collected. The participating centres either received ethical approval from their institutions or ethical approval was waived. Informed consent was waived owing to the observational nature of the study.

Definitions

Hospital-acquired pneumonia (HAP) was defined as a pulmonary infection that was not incubating at the time of admission and occurred 48 h or more after hospital admission. Ventilator-associated pneumonia (VAP) was defined as a pulmonary infection arising more than 48 h after tracheal intubation with no evidence of pneumonia at the time of intubation or the diagnosis of a new pulmonary infection if the initial admission to ICU was due to pneumonia [1].

We reassessed the probability of pneumonia of the enrolled patients after collecting clinical and microbiologic data and included in the analysis only those patients with an established definitive microbiologic diagnosis of pneumonia and antibiotic susceptibility: 1. Definite microbiological isolate and histological demonstration of pneumonia; or 2. (a) definite microbiological isolate, and (b) new or progressive pulmonary infiltrate on chest X-ray or cavitation or consolidation and (c) new fever evidenced by a rise in core body temperature (>1 and >38.3 °C)

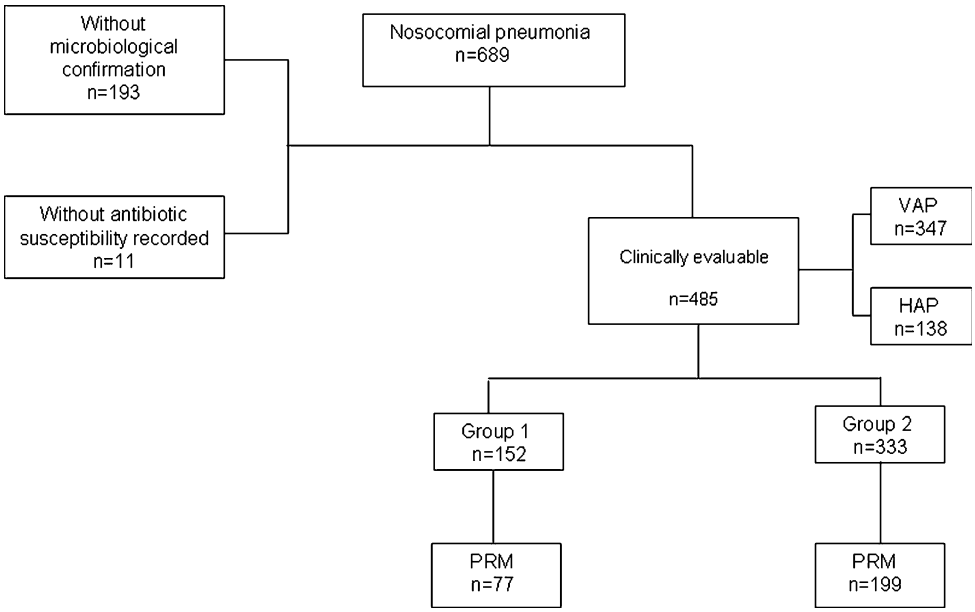

Fig. 1 Study profile

compared with the previous 24-h period or hypothermia below 36.5 °C, and (d) new leucocytosis evidenced by a greater than 25 % increase in circulating leucocytes compared with the previous 24-h period, or a left shift of at least 10 %, or a neutrophil count below 1×10^9/l, and (e) purulent tracheal aspirate, and (f) worsening gas exchange [12].

Based on 2005 ATS/IDSA guidelines for managing HAP, an episode of pneumonia was considered to be caused by PRM if methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa, Acinetobacter baumannii* or *Stenotrophomonas maltophilia* were identified [1]. Polymicrobial pneumonia was defined as identification of more than one potentially pathogenic microorganism as causative agents. Each clinical episode of pneumonia was described separately. For patients with a clinical diagnosis of pneumonia, data collection included clinical signs of sepsis to classify into sepsis, severe sepsis and septic shock. To qualify as severe sepsis, new/worsening organ dysfunction (OD) other than the lung must be present and related to the episode of pneumonia [13]. Clinical response and pneumonia's contribution to death were recorded. Further details can be found elsewhere [6]. The initial empirical antimicrobial treatment was administered in accordance with local adaptation of the ATS/IDSA guidelines [1] and was subsequently revised according with the microbiologic results. Appropriateness of antibiotic therapy was defined when the causative organism was susceptible to one or more of the prescribed anti-infectives with in vitro testing.

According to the 2005 ATS/IDSA guidelines for HAP, VAP and HCAP [1], we aggregated patients into two groups: group 1, early-onset pneumonia without risk factors for PRM infection; and group 2, early-onset pneumonia with risk factors for PRM infection (who have received prior antibiotics or who have had prior hospitalization within the past 90 days and immunosuppressive disease and/or therapy) or late-onset pneumonia. Risk factors for PRM acquisition included those for HCAP, as has been defined by the 2005 ATS/IDSA guidelines [1]. Time of onset of pneumonia was defined on the basis of 2005 ATS/IDSA guidelines as follows: early-onset HAP, defined as occurring within the first 4 days of hospitalization and late-onset HAP as occurring 5 days or more after hospitalization; early-onset VAP, defined as occurring within the first 4 days of intubation and late-onset VAP as occurring 5 days or more after intubation. Patients with community-acquired pneumonia or HCAP were not included in the present analysis. We assessed the adequacy of the guidelines to predict the isolated pathogens according to each patient's category. When the isolated pathogen corresponded to the expected one, the microbial prediction of the guidelines was considered as adequate microbial prediction. Centres participating were divided into quartiles depending on the prevalence of PRM. Centres with a prevalence of PRM greater than 25 % were considered high risk for PRM acquisition, because this represents more than one isolate in an 8-bed ICU. The prevalence of the PRM was based from data extracted from the study database.

Statistical analysis

Discrete variables were expressed as counts (%) and continuous variables as mean and standard deviation (SD), unless stated otherwise; all statistical tests were two-sided. Differences in categorical variables were

calculated using two-sided likelihood ratio Chi-square test or Fisher exact test and the Mann–Whitney *U* test or Kruskal–Wallis test was used for continuous variables, when appropriate. A logistic regression analysis was used to assess the risk factors for PRM acquisition. In order to avoid spurious associations, variables entered in the regression models were those with a relationship in univariate analysis ($p < 0.10$) or a plausible relationship with the dependent variable. The variables included were age, sex, severity-of-illness by SAPS II score, centres with PRM greater than 25 %, presence of VAP and severe sepsis/septic shock. Data analysis was performed using SPSS for Windows 20.0 (SPSS, Chicago, IL, USA).

Results

Six hundred and eighty-nine patients with nosocomial pneumonia who required mechanical ventilation were prospectively enrolled. Two hundred and four (29.6 %) patients were excluded from the database (Fig. 1), because they did not have microbiologically documented pneumonia ($n = 193$) or antibiotic susceptibility recorded ($n = 11$). Subsequently, 485 patients with confirmed organisms and antibiotic susceptibility were further analysed. Mean age was 58.5 ± 18.0 years, 339 (69.9 %) patients were male, and SAPS II score on admission was 46.5 ± 17.6 points.

One hundred and fifty-two (31.3 %) patients were allocated to group 1 with early-onset pneumonia and no risk factors for PRM acquisition, whereas 333 (68.7 %) were classified into group 2 with early-onset pneumonia with risk factors for PRM or late-onset pneumonia (Table 1). Group 2 patients were older and had more chronic renal failure and more severe illness (SAPS II score, 44.6 ± 16.5 vs. 47.4 ± 17.8, $p = 0.04$) than group 1 patients. Trauma patients were more frequent (and surgical patients less frequent) in group 1 than in group 2 ($p < 0.01$). Further details are listed in Table 1.

Among the 152 patients from group 1, 77 patients (50.7 %) had PRM despite being early-onset pneumonia episodes, without risk factors for PRM acquisition (Table 2). Risk factors for PRM in the overall population, i.e. group 1 and group 2, are displayed in Table 3. The analysis was restricted to group 1 (early-onset pneumonia without risk factors for PRM infection) and a logistic regression analysis identified that the presence of severe sepsis/septic shock (OR = 3.7, 95 % CI 1.5–8.9, $p < 0.01$) and pneumonia developed in centres with more than a 25 % prevalence of PRM (OR = 11.3, 95 % CI 2.1–59.3, $p < 0.01$) were independently associated with PRM causing pneumonia. In the whole cohort, similar associations were found for severe sepsis/septic shock (OR = 1.8, 95 % CI 1.1–2.8) and therapy in centres with more than a 25 % prevalence of PRM (OR = 6.8, 95 % CI 3.1–15.6).

Two hundred and twenty-five (46.4 %) of the patients in this study received guideline-concordant antibiotics. Significant differences were observed in terms of guideline-concordant appropriateness between group 1 and group 2 patients (93.4 vs. 24.9 %, $p < 0.01$). One hundred and ninety-one patients (39.4 %) died. Patients from group 2 presented a higher ICU mortality than

Table 1 Comparison of demographic and clinical characteristics among patients with nosocomial pneumonia according to the 2005 ATS/IDSA guidelines group and confirmed etiology

	Group 1 ($n = 152$)	Group 2 ($n = 333$)	*p* value
Age, mean years (SD)	55.96 (19.97)	60.22 (17.10)	0.004
Male gender, *n* (%)	105 (69.1)	234 (70.3)	0.8
Mean SAPS II score (SD)	43.9 (16.6)	47.5 (17.7)	0.03
Diagnostic category at admission, *n* (%)			
Medical	92 (61.3)	205 (61.9)	0.001
Surgery	13 (8.7)	69 (20.8)	
Trauma	45 (30)	57 (17.2)	
Length of ICU stay, days (SD)[a]	24.32 (23.7)	28.03 (20.21)	0.04
Length of hospital stay, days (SD)[a]	45.36 (36.2)	53.40 (35.8)	0.004
Pre-existing comorbid conditions, *n* (%)			
COPD	22 (14.5)	50 (15.0)	0.9
Diabetes	21 (13.8)	59 (17.7)	0.3
Chronic heart failure	31 (20.4)	71 (21.3)	0.9
Cirrhosis	5 (3.3)	12 (3.6)	0.9
Chronic renal failure	0 (0)	19 (5.7)	<0.001
Alcohol abuse	18 (11.8)	28 (8.4)	0.2
Current hospitalization of ≥5 days	0	285 (85.6)	<0.001
Antimicrobial therapy in preceding 90 days	0	74 (22.2)	<0.001
Prevalence of PRM >25 %	136 (34.1)	263 (65.9)	<0.001

SAPS simplified acute physiology score, *ICU* intensive care unit, *COPD* chronic obstructive pulmonary disease

[a] In survivors

Table 2 Etiologic diagnosis of pneumonia among patients with nosocomial pneumonia according to the 2005 ATS/IDSA guidelines group

	Group 1 ($n = 152$)	Group 2 ($n = 333$)	Overall ($n = 485$)	p value
Polymicrobial, n (%)	51 (23.5)	109 (23.1)	160 (23.2)	0.9
Patients with potentially resistant microorganisms, n (%)	77 (50.7)	199 (59.8)	276 (56.9)	0.07
Potentially resistant microorganisms, n (%)				
Pseudomonas aeruginosa	33 (21.7)	82 (24.6)	115 (23.7)	0.5
Stenotrophomonas maltophilia	2 (1.3)	14 (4.2)	16 (3.3)	0.1
Methicillin-resistant *Staphylococcus aureus*	24 (15.8)	58 (17.4)	82 (16.9)	0.6
Acinetobacter baumannii	24 (15.8)	77 (23.1)	101 (20.8)	0.07
Non-potentially resistant microorganisms, n (%)				
Methicillin-sensitive *Staphylococcus aureus*	36 (23.7)	41 (12.3)	77 (15.9)	0.002
Escherichia coli	20 (13.2)	56 (16.8)	76 (15.7)	0.3
Klebsiella pneumoniae	17 (11.2)	40 (12.0)	57 (11.8)	0.8
Streptococcus pneumoniae	11 (7.2)	10 (3.0)	21 (4.3)	0.05
Serratia marcescens	7 (4.6)	10 (3.0)	17 (3.5)	0.4
Haemophilus influenzae and *Moraxella catharralis*	16 (10.5)	16 (4.8)	32 (6.6)	0.02
Citrobacter	3 (2.0)	4 (1.2)	7 (1.4)	0.6
Morganella		2 (0.6)	2 (0.4)	0.9
Enterobacter sp.	11 (7.2)	29 (8.7)	40 (8.2)	0.7
Proteus	5 (3.3)	13 (3.9)	18 (3.7)	0.9

Table 3 Comparison of demographic and clinical characteristics among patients with nosocomial pneumonia according to the 2005 ATS/IDSA guidelines group

	Group 1 ($n = 152$)			Group 2 ($n = 333$)			Overall ($n = 485$)		
	No PRM ($n = 75$)	PRM ($n = 77$)	p value	No PRM ($n = 134$)	PRM ($n = 199$)	p value	No PRM ($n = 209$)	PRM ($n = 276$)	p value
Age, mean years (SD)	50.7 (20.3)	59.1 (18.2)	0.09	63.4 (15.9)	58.5 (17.2)	0.09	58.8 (18.6)	58.7 (17.5)	0.8
Male gender, n (%)	50 (66.7)	55 (71.4)	0.6	97 (72.4)	137 (68.8)	0.5	147 (70.3)	192 (69.6)	0.9
Mean SAPS II score (SD)	40.9 (15.5)	46.8 (17.3)	0.02	46.5 (16.3)	48.1 (18.7)	0.4	44.5 (16.2)	47.8 (18.3)	0.04
Diagnostic category at admission, n (%)									
Medical	41 (55.4)	51 (67.1)	0.2	83 (62.4)	122 (61.6)	0.2	124 (59.9)	173 (63.1)	0.7
Surgery	6 (8.1)	7 (9.2)		32 (24.1)	37 (18.7)		38 (18.4)	44 (16.1)	
Trauma	27 (36.5)	18 (23.7)		18 (13.5)	39 (19.7)		45 (21.7)	57 (20.8)	
Pre-existing comorbid conditions, n (%)									
COPD	8 (10.7)	14 (18.2)	0.2	21 (15.7)	29 (14.6)	0.8	29 (13.9)	43 (15.6)	0.7
Diabetes	7 (9.3)	14 (18.2)	0.2	24 (17.9)	35 (17.6)	0.9	31 (14.8)	49 (17.8)	0.4
Chronic heart failure	13 (17.3)	18 (23.4)	0.4	42 (31.3)	29 (14.6)	<0.01	55 (26.3)	47 (17.0)	0.01
Cirrhosis	1 (1.3)	4 (5.2)	0.7	3 (2.2)	9 (4.5)	0.3	4 (1.9)	13 (4.7)	0.1
Chronic renal failure	3 (4.0)	5 (6.5)	0.7	15 (11.2)	28 (14.1)	0.5	18 (8.6)	33 (12.0)	0.2
Alcohol abuse	10 (13.3)	8 (10.4)	0.6	10 (7.5)	18 (9.0)	0.6	20 (9.6)	26 (9.4)	0.9
Current hospitalization of ≥5 days				120 (89.6)	165 (82.9)	0.1	120 (57.4)	165 (59.8)	0.6
Antimicrobial therapy in preceding 90 days				10 (7.5)	18 (9.0)	0.01	20 (9.6)	26 (9.4)	<0.001
Prevalence of PRM >25 %	64 (47.1)	72 (52.9)	0.1	80 (30.4)	183 (69.6)	<0.01	144 (36.1)	255 (63.9)	<0.01
VAP	59 (78.7)	40 (51.9)	<0.01	99 (73.9)	149 (74.9)	0.8	158 (75.6)	189 (68.5)	0.1
Severe sepsis and septic shock	44 (60.3)	64 (86.5)	<0.01	99 (73.9)	149 (74.9)	0.8	131 (65.8)	210 (78.9)	<0.01

SAPS simplified acute physiology score, *COPD* chronic obstructive pulmonary disease, *VAP* ventilator-associated pneumonia, *PRM* potentially resistant microorganisms

patients from group 1 (42.6 vs. 32.2 %, $p = 0.03$). ICU mortality was also higher in patients with PRM (47.5 vs. 28.7 %, $p < 0.01$) and received more inappropriate antimicrobial therapy (29.6 vs. 11.5 %, $p < 0.01$) than patients without PRM acquisition. Patients with initial appropriate antibiotic therapy had lower mortality rates than patients with inappropriate therapy (35.4 vs. 48.1 %, $p = 0.01$).

Discussion

The main finding of the present study was that many patients who develop pneumonia in the ICU are infected with PRM in spite of the absence of risk factors listed in the 2005 ATS/IDSA guidelines. Institutions with a prevalence of PRM greater than 25 % were associated with a higher risk of HAP/VAP caused by these pathogens. Therefore, patients admitted to centres with a high prevalence of PRM or those affected by severe sepsis and septic shock should be considered at risk for PRM when they develop HAP/VAP and receive empirical treatment, even in the absence of other risk known factors that were included in the 2005 ATS/IDSA guidelines.

Our study does not cover HCAP and focusses on HAP/VAP episodes that required endotracheal intubation [14]. The 2005 ATS/IDSA guidelines for HAP/VAP have been validated previously [15]. Whereas we reported 50.7 % of PRM in group 1, Ferrer et al. [15] found 26 %, despite the absence of risk factors for these microorganisms according to the guidelines in the overall population; it increased to 42 % if only patients with etiologic diagnosis were considered, as in the present study. Pneumonia with *A. baumannii* in our European multicentre population was more than tenfold higher in both groups (Table 2) than in some prior studies published elsewhere [6]. Indeed, Ferrer et al. [15] reported similar rates of appropriate initial treatment and clinical response in patients with and without risk factors for PRM, showing a trend to lower mortality in early-onset pneumonia patients without risk factors for PRM (group 1). The difference between the adopted definitions of appropriate treatment is that for Ferrer et al. [15] two antibiotics to which the microorganism was susceptible were needed to consider therapy appropriate for *P. aeruginosa* HAP/VAP, whereas one susceptible agent was enough for our study. This might have improved the outcome for "inappropriate treatment" in Ferrer et al's study because, for example, patients with carbapenem-susceptible, but aminoglycoside-resistant, *P. aeruginosa* could be defined as receiving inappropriate therapy, yet still receive one effective agent. Following the results from a randomized trial of combination versus monotherapy for the empiric treatment of late-onset VAP in patients at low risk for difficult-to-treat gram-negative bacteria, monotherapy was associated with similar outcomes compared with combination therapy and the adequacy of initial antibiotics and microbiological eradication of high risk of difficult-to-treat gram-negative bacteria (i.e. *Pseudomonas* sp., *Acinetobacter* sp. and multidrug-resistant gram-negative bacilli) infecting organisms was higher in the combination group compared with the monotherapy group, but there were no differences in clinical outcomes [16].

In the logistic regression analysis, only severe sepsis/septic shock and therapy in a centre with a PRM prevalence above 25 % were independent variables associated with pneumonia caused by PRM. The fact that centres with a high rate of PRM predicts the isolation of PRM seems obvious, because an event predicts the same event in the future. The presence of centres with above 25 % isolation of PRM was an independent risk factor for PRM acquisition when combining other factors that reflected severity of illness such as severe sepsis or septic shock. The risk factors that are traditionally associated with HAP due to PRM are duration of hospitalization [12], prior antibiotic exposure [17] and host risk factors, such as the presence of particular comorbid conditions (COPD) [18] or coma [19]. Interestingly, the information extracted from the present manuscript considers that the environment should be taken into account in addition to the host–pathogen interaction. Nseir et al. [20] recently reported that if the prior occupant of a patient's room in the ICU had harboured gram-negative bacilli, this was an independent risk factor for subsequent acquisition of *P. aeruginosa* (OR 2.3, 95 % CI 1.2–4.3) or *A. baumannii* (OR 4.2, 95 % CI 2.0–8.8). Use of highly discriminating genetic typing to identify the transmission has shown in prospective studies that transmission accounts for about 15 % of ICU-acquired infections [21]. Consideration of the particularities of each ICU ecology can provide a more rational basis for selecting initial therapy for HAP/VAP. In fact, the findings in our study reinforce the idea that organisms might differ among different institutions [22] and, moreover, among different ICUs in the same hospital [23]. The observed differences in pathogen etiology across institutions might reflect differences in patterns of antibiotic use as has been previously reported [24].

PRM pathogens have been recognized to contribute to unfavourable clinical outcome and increased resource utilization [25, 26]. Higher hospital mortality has been attributed to increased risk of inadequate initial antibiotic treatment due to the presence of antibiotic resistance. Whereas Damas et al. [27] found that the type of bacteria was not a risk factor for occurrence of septic shock and mortality, our group [26] found that severity of sickness was one of the important major determinants of antibiotic choice for HAP/VAP and therefore improved outcome when appropriate therapy is provided. Kumar et al. [28], in a recent metanalysis that included patients with serious bacterial infections (not specifically related to HAP/VAP but to all kinds of sources of sepsis), suggested that combination antibiotic therapy improves survival and clinical response of high-risk, life-threatening infections, particularly those associated with septic shock. Along the same lines, Kollef et al. [29] found that inappropriate initial antibiotic therapy of VAP attributed to potentially antibiotic-resistant gram-negative bacteria was associated with greater 30-day mortality.

The clinical presentation of HAP might vary widely, from a relatively benign illness to a devastating illness

resulting in septic shock. Information of the incidence of septic shock among VAP patients remains scarce. Lisboa et al. [30] reported that septic shock was an independent variable associated with ICU mortality (OR 4.40, 95 % CI 2.71–7.15). Kumar et al. [31] conducted a cohort study and reported that effective antimicrobial administration within the first hour of documented hypotension was associated with 79.9 % survival to hospital discharge.

The present study has several potential limitations. First, patients included in the present study were based on a voluntary, self-selected (by institution) basis and not randomized; therefore the possibility of unforeseen and unmeasured biases that could affect the results are possible. Secondly, there is a high predominance of central and southern European countries. These regions might present a different ecology than other northern European regions; however, the key message is that the antibiotic therapy provided for HAP/VAP should be targeted at PRM considered in those patients admitted to sites with a high prevalence of these organisms and the findings might be generalized. Third, the present manuscript represents a secondary analysis that focussed on the spectrum of practice in the diagnosis of HAP/VAP in ICUs; owing to the observational nature of the study, a potential bias caused by control selection in secondary data analysis can be minimized. In addition, the definition of PRM indicated by the authors of the ATS/IDSA guidelines was used in the present manuscript; however, extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE) and vancomycin-resistant enterococci (VRE) were not specifically recorded. Finally, we were unable to validate former ATS/IDSA guidelines because of a lack of information in the database.

In summary, the present study shows that a high prevalence of PRM in the ICU and the presence of severe sepsis/septic shock in patients with HAP/VAP with no other risk factors for PRM according to the 2005 ATS/IDSA guidelines were independent risk factors for PRM as the causative pathogen and in these patients empiric therapy should include agents likely to be effective for those organisms, thereby reducing inappropriate therapy and improving outcome. Therefore, it is also important to define correct antibiotic stewardship strategies in order to avoid a vicious cycle of higher antibiotic consumption and higher prevalence of PRM that is neither helpful nor desirable. De-escalation helps to avoid overtreatment and leads to a shorter duration of antibiotic exposure.

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Conflicts of interest The authors declare no conflict of interest regarding the present manuscript.

Appendix: EU-VAP/CAP Study

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