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Determinants of prescription and choice of empirical therapy for hospital-acquired and ventilator-associated pneumonia

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ABSTRACT: The objectives of this study were to assess the determinants of empirical antibiotic choice, prescription patterns and outcomes in patients with hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) in Europe.

We performed a prospective, observational cohort study in 27 intensive care units (ICUs) from nine European countries. 100 consecutive patients on mechanical ventilation for HAP, on mechanical ventilation >48 h or with VAP were enrolled per ICU.

Admission category, sickness severity and *Acinetobacter* spp. prevalence >10% in pneumonia episodes determined antibiotic empirical choice. Trauma patients were more often prescribed non-anti-*Pseudomonas* cephalosporins (OR 2.68, 95% CI 1.50–4.78). Surgical patients received less aminoglycosides (OR 0.26, 95% CI 0.14–0.49). A significant correlation ($p<0.01$) was found between Simplified Acute Physiology Score II score and carbapenem prescription. Basal *Acinetobacter* spp. prevalence >10% dramatically increased the prescription of carbapenems (OR 3.5, 95% CI 2.0–6.1) and colistin (OR 115.7, 95% CI 6.9–1,930.9). Appropriate empirical antibiotics decreased ICU length of stay by 6 days (26.3±19.8 days *versus* 32.8±29.4 days; $p=0.04$). The antibiotics that were prescribed most were carbapenems, piperacillin/tazobactam and quinolones. Median (interquartile range) duration of antibiotic therapy was 9 (6–12) days. Anti-methicillin-resistant *Staphylococcus aureus* agents were prescribed in 38.4% of VAP episodes.

Admission category, sickness severity and basal *Acinetobacter* prevalence >10% in pneumonia episodes were the major determinants of antibiotic choice at the bedside. Across Europe, carbapenems were the antibiotic most prescribed for HAP/VAP.

KEYWORDS: Antibiotic policy, appropriate treatment, combination therapy, hospital-acquired pneumonia, ventilator-associated pneumonia

Nosocomial pneumonia is the second most prevalent nosocomial infection in hospital in-patients, with ventilator-associated pneumonia (VAP) being the leading nosocomial infection in the intensive care unit (ICU). It has been estimated that more than 50% of critically ill patients will receive at least one antibiotic during their ICU stay, with pneumonia being the main reason for antibiotic prescription [1–3]. In fact, a recent large, multicentre, point-prevalence study involving 13,796 critically ill patients (EPIC II study) documented that 71% of the patients admitted to the critical care department were receiving antibiotic therapy [4].

Compelling data has shown that delays in the administration of appropriate antibiotic therapy is strongly associated with worse outcomes [5–8] but, paradoxically, when or how to treat a patient with suspicion of an infection remains very controversial. Moreover, despite the well-known importance of optimising empirical antibiotic therapy for improving outcomes in ICU patients [9], little is known about real prescription patterns and, especially, the particular factors that determine antibiotic choice in daily clinical practice. In fact, the decision-making process is complex and influenced by several factors that are not yet definitively characterised. Some factors that have been suggested to influence the antibiotic choice are previous hospitalisation, previous antibiotic exposure and underlying diseases [1, 10, 11]. However, more research on these causes of variability is required.

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In 2006, KOLLEF *et al.* [12] published the results of the Assessment of Local Antimicrobial Resistance Measures (ALARM) study, which was performed in 20 ICUs in the USA. The aim of this study was to evaluate clinical characteristics and treatment patterns among patients with VAP. The authors reported that >100 different antibiotic regimens had been prescribed to the 398 patients with VAP. However, there is no such similar study in the literature focused on European ICUs.

The hypothesis of our study was that factors other than prior antibiotic exposure and length of stay (LOS) would influence prescription decisions. Therefore, the primary aim of this analysis was to prospectively identify the factors that determine empirical antibiotic prescription in nosocomial pneumonia, other than previous hospitalisation and previous antibiotic prescription. Secondary objectives were to describe the patterns of empirical antibiotic treatment (*e.g.* the most used antibiotic agents, combination or monotherapy and previous antibiotic prescription) in hospital-acquired pneumonia (HAP)/VAP to compare different admission categories in terms of management, to record differences between countries and institutions and to describe the outcomes of patients with HAP/VAP in a large cohort of patients from different European ICUs.

MATERIALS AND METHODS

EU-VAP/CAP was a prospective, observational survey conducted in 27 ICUs from nine European countries (Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain and Turkey). The principal investigator contacted one coordinator in each country who selected the participating centres within that country. All patients requiring ICU admission for diagnosed pneumonia or who were on invasive mechanical ventilation (MV) for >48 h, regardless of admission diagnosis, were included. The aim was to collect data on 100 consecutive admissions in each participant ICU. The data collection period ranged from 6 to 12 months during the period 2007–2008.

The participating centres either received ethical approval from their institutions or ethical approval was waived. Informed consent was waived due to the observational nature of the study.

Definitions

Nosocomial pneumonia wass defined as pulmonary infection not incubating at the time of admission and that occurred >48 h after hospital admission.

HAP was defined as pulmonary infection in patients without MV, not incubating at the time of admission and that occurred ⩾48 h after admission [1].

VAP was defined as pulmonary infection arising ⩾48 h after intubation with no evidence of pneumonia at the time of intubation, or the diagnosis of a new pulmonary infection if the initial ICU admission was for pneumonia [1]. Early-onset VAP was defined as VAP with onset >48 h but <5 days after intubation [1]. Late-onset VAP was defined as VAP with onset ⩾5 days after intubation [1].

Admission category was classified as medical, surgical or trauma. Comorbidity definitions are detailed in the supplementary data. Peri-operative antibiotic prophylaxis or antibiotics for <48 h were not considered as previous antibiotic therapy.

Statistical analysis

Statistical analysis was conducted using SPSS v11.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as mean±SD, median (interquartile range) and proportions where appropriate. Unpaired t-tests were used to compare normally distributed continuous variables, Mann–Whitney test for non-normally distributed variables and Chi-squared test and Fisher's exact test for categorical variables. Independent variables were selected taking into account American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines (LOS and prior antibiotic use), diagnostic algorithms [3, 13], and Latin-America guidelines. Variables analysed were antibiotic class prescriptions, duration of antibiotic therapy, prior antibiotic treatment, appropriateness of therapy depending on posterior cultures, patient outcomes and several other factors likely to be associated with prescription patterns, such as basal prevalence of certain pathogens (methicillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter baumannii*) in pneumonia episodes, prior intubation and admission diagnosis. A multivariate logistic regression model was used to identify independent variables associated with the use of specific antimicrobial agents. The variables were included in the multivariate analysis if they were significant in the univariate analysis ($p<0.05$), had a p-value $\leqslant 0.20$, were hypothesised by the authors or were clinically significant. The contribution of each variable in each step of the model was assessed by the log-likelihood ratio test.

The logistic regression models were assessed for goodness of fit using the method of HOSMER and LEMESHOW [14]. Values of the Hosmer and Lemeshow tests for each model are reported in table 1. We introduced a robust estimation of the variance to our logistic multivariate models to control the possible correlation among different observations belonging to the same centre. We used STATA v11.0 (StataCorp, College Station, TX, USA) to introduce this robust estimation of the centre effect. The significance level for all the analyses was defined as $p<0.05$.

RESULTS

224 eligible patients with HAP and 465 patients with VAP were enrolled during the study period. Mean age was 58.9±18.1 yrs and 69.1% were male. Table 2 summarises the demographics and clinical characteristics of the patient population. The most frequent ICU admission diagnoses included medical condition (n=470, 68.2%), general post-operative care (n=118, 17.1%) and trauma (n=101, 14.7%). The mean Simplified Acute Physiology Score (SAPS) II score at baseline was 46.6±19.9. For VAP patients, mean duration of MV prior to VAP diagnosis was 7.7±7.9 days (median 5 days). Details of the demographic characteristics of the whole study population, as well as diagnostic procedures, have been reported previously [15]. In patients that did not have positive cultures, ICU LOS was 16 (10–30.5) days and hospital LOS was 30 (16–54) days.

For the whole patient group, prior antibiotic treatment was prescribed to 91 (13.2%) patients, without statistical differences between HAP, early-onset VAP or late-onset VAP. The most

TABLE 1 Variables associated with different therapy decisions in intubated patients with hospital-acquired pneumonia/ventilator-associated pneumonia

Variable	Carbapenem	Piperacillin/tazobactam	Quinolones	Colistin	Aminoglycosides	Non-AP cephalosporin	AP cephalosporin	AP agents	Anti-MRSA[#]	Combination
LOS >5 days	1.01	1.14	1.17	**5.25**	1.43	0.60	1.55	1.34	**1.43**	1.20
	(0.65–1.57)	(0.80–1.61)	(0.78–1.75)	**(2.30–11.95)**	(0.97–2.11)	(0.32–1.12)	(0.90–2.67)	(0.96–1.87)	**(1.01–2.03)**	(0.89–1.61)
Previous antibiotics	1.33	**0.39**	**0.37**	0.55	**2.05**	0.28	0.75	0.62	1.35	0.89
	(0.85–2.08)	**(0.22–0.71)**	**(0.17–0.84)**	(0.10–3.08)	**(1.14–3.69)**	(0.08–1.02)	(0.32–1.78)	(0.36–1.06)	(0.79–2.29)	(0.50–1.57)
Trauma	1.28	0.70	0.62	1.59	1.09	**2.68**	0.96	1.06	0.79	1.21
	(0.87–1.86)	(0.35–1.40)	(0.35–1.11)	(0.52–2.29)	(0.52–2.29)	**(1.50–4.78)**	(0.48–1.94)	(0.52–2.16)	(0.38–1.62)	(0.63–2.30)
Surgery	0.76	1.47	0.84	0.16	**0.26**	0.61	0.66	1.01	1.38	0.71
	(0.50–1.16)	(0.92–2.37)	(0.47–1.48)	(0.01–2.18)	**(0.14–0.49)**	(0.26–1.40)	(0.31–1.43)	(0.61–1.67)	(0.86–2.20)	(0.37–1.34)
Basal MRSA prevalence >10%[¶]	1.21	0.77	0.90	0.22	1.38	0.66	1.39	1.13	1.53	1.04
	(0.71–2.06)	(0.31–1.90)	(0.52–1.53)	(0.02–2.14)	(0.63–3.02)	(0.21–2.04)	(0.62–3.15)	(0.69–1.84)	(0.90–2.60)	(0.53–2.04)
Basal *Acinetobacter* prevalence >10%[¶]	**3.50**	0.73	0.77	**115.71**	1.49	**0.13**	0.55	**2.42**	**2.10**	1.54
	(2.0–6.1)	(0.31–1.69)	(0.44–1.34)	**(6.93–1930.94)**	(0.68–3.23)	**(0.04–0.36)**	(0.26–1.17)	**(1.51–3.84)**	**(1.16–3.81)**	(0.73–3.29)
Previous intubation	0.90	**0.67**	0.86	0.70	0.85	1.09	0.97	**0.55**	0.81	**0.64**
	(0.56–1.43)	**(0.45–0.99)**	(0.59–1.23)	(0.29–1.66)	(0.40–1.80)	(0.57–2.06)	(0.61–1.55)	**(0.38–0.78)**	(0.57–1.14)	**(0.42–0.96)**
Goodness of fit p-value	0.784	0.158	0.928	0.954	0.768	0.956	0.730	0.145	0.023	0.148

Data are presented as median (interquartile range). Goodness of fit was assessed using the method of HOSMER and LEMESHOW [14]. AP: anti-pseudomonal; MRSA: methicillin-resistant *Staphylococcus aureus*; LOS: length of stay. Bold signifies significance. [#]: includes vancomycin, teicoplanin and linezolid; [¶]: prevalence in pneumonia episodes.

TABLE 2 Demographics and clinical characteristics of the patient population

	HAP	VAP
Subjects n	224	465
Age yrs	66 (55–74)	60 (42–72)
Male/female %	71.4/28.6	68/32
SAPS II admission	48.5 (36–64)	43 (33–54)
COPD	43 (19.2)	61 (13.1)
Diabetes mellitus	45 (20.1)	66 (14.2)
Cirrhosis	13 (5.8)	18 (3.9)
Chronic renal failure	34 (15.2)	38 (8.2)
Immunosuppression	42 (18.8)	10 (2.2)
Prior antibiotic exposure	27 (12.1)	64 (13.8)
Days of MV prior to VAP	NA	5 (3–9)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; SAPS: Simplified Acute Physiology Score; COPD: chronic obstructive pulmonary disease; MV: mechanical ventilation; NA: not applicable.

prescribed agents were carbapenems (34%), piperacillin/tazobactam (21.9%) and glycopeptides (17.5%). Prior antibiotics were administered in combination in 49.4% of prescriptions. Table 3 details antibiotic choices according to prior antibiotic prescription. Mean duration of initial antibiotic treatment was 9.6±5.2 days after diagnosis. Median duration of initial antibiotic therapy by class is detailed in the supplementary data. The most common aetiological agents for HAP and VAP are summarised in figure 1.

Determinants of empirical antibiotic choice

Table 1 reports the results of the multivariate analysis for factors that determine empirical antibiotic choice. It is worth noting that empirical choice was strongly influenced by factors other than those described previously in the literature (*i.e.* previous hospitalisation or previous antibiotic prescription). First, admission category was a heavy determinant of antibiotic choice. Trauma patients were prescribed non-anti-*Pseudomonas* spp. cephalosporins (OR 2.68, 95% CI 1.50–4.78) more often, while surgical patients were less likely to receive aminoglycosides (OR 0.26, 95% CI 0.14–0.49). In surgical patients, a trend to choose anti-MRSA agents was also observed (OR 1.53, 95% CI 0.90–2.60).

Secondly, baseline prevalence of *A. baumannii* >10% in pneumonia episodes also influenced the empirical antibiotic choice for the treatment of HAP/VAP in each ICU. In sites where *Acinetobacter* spp. baseline prevalence in pneumonia episodes was >10%, the prescription of carbapenems and colistin for empirical treatment of VAP was dramatically increased (OR 3.50, 95% CI 2.49–4.91 and OR 115.71, 95% CI 6.93–1,930.94, respectively), while lower spectrum antibiotics such as non-anti-*Pseudomonas* spp. cephalosporins were much less likely to be chosen (OR 0.13, 95% CI 0.04–0.36).

Finally, LOS >5 days was significantly associated with the empirical choice of drugs active against less susceptible bacteria, such as colistin (OR 5.25, 95% CI 2.30–11.95) and

TABLE 3 Comparison between previous antibiotic use and empirical choice for antibiotic therapy in patients with nosocomial pneumonia

	Subjects n	CBP#	Pip/tazo	CFP/CFZ	CFX/CRO	Glycopeptides	Linezolid	A/C	FQ	Colistin	Combination
Prior exposure to ATB											
No	598	212 (181)	186 (138)	66 (60)	97 (68)	117 (110)	57 (51)	50 (21)	138 (131)	37 (35)	421
Yes	91	40 (30)	13 (11)	8 (7)	4 (4)	23 (21)	13 (11)	2 (2)	9 (7)	4 (3)	62
Previous ATB class											
CBP	31	6 (5)	2 (2)	4 (3)	0 (0)	11 (9)	6 (5)	0 (0)	3 (3)	2 (1)	18
Pip/tazo	20	13 (10)	0 (0)	2 (2)	1 (1)	6 (6)	2 (2)	1 (1)	2 (1)	15	1 (1)
Glycopeptides	16	8 (5)	0 (0)	2 (2)	1	4 (4)	0 (0)	0 (0)	1 (1)	2 (1)	9
Aminoglycosides	13	7 (7)	2 (2)	1 (1)	0 (0)	5 (5)	1 (1)	0 (0)	1 (0)	1 (1)	11
A/C	12	3 (3)	5 (4)	1 (1)	0 (0)	3 (3)	0 (0)	1 (1)	0 (0)	9	0 (0)
CFP/CFZ	8	5 (5)	1 (1)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	1 (1)	0 (0)	6
CFX/CRO	8	6 (4)	2 (1)	1 (1)	1 (1)	0 (0)	2 (2)	0 (0)	1 (1)	1 (1)	6
FQ	5	3 (2)	5 (0)	0 (0)	1 (1)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)	5
Combination	45	24 (22)	3 (3)	4 (4)	2 (2)	14 (14)	6 (5)	1 (1)	3 (2)	35	4 (3)

Data are presented as total number of patients prescribed each antibiotic (number of times each antibiotic was given in combination with another), unless otherwise stated. The sums of the numbers do not correspond to the number of patients because a patient could receive more than one agent. CBP: carbapenem; Pip/tazo: piperacillin-tazobactam; CFP/CFZ: cefepime/ceftazidime; CFX/CRO: cefotaxime/ceftriaxone; A/C: amoxicillin-clavulanate; FQ: fluoroquinolones; ATB: antibiotic. #: imipenem, n=120; meropenem, n=164.

anti-MRSA agents (OR 1.43, 95% CI 1.01–2.03) in detriment of lower spectrum antibiotics such as non-anti-*Pseudomonas* spp. cephalosporins (OR 0.60, 95% CI 0.32–1.12).

Antibiotic prescription patterns in HAP/VAP

VAP

We identified more than 30 different antibiotic regimens prescribed as initial therapy for VAP. 64 (13.8%) of the patients also received antibiotic therapy >48 h prior to diagnosis of VAP for 9.4±4.9 days. For initial treatment, 150 (32.2%) patients were prescribed one antibiotic, 171 (36.8%) patients were prescribed two antibiotics and 144 (30.9%) patients were prescribed three or more antibiotics. The most prescribed agents were anti-*Pseudomonas* spp. carbapenems (18.5%), piperacillin/tazobactam (13.1%) and fluoroquinolones (9.9%). Antibiotic prescription by admission categories is presented in table 4.

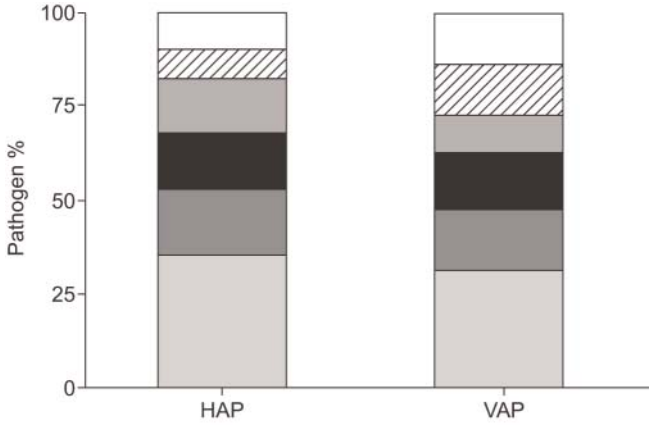

FIGURE 1. Most common aetiological pathogens found in hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) episodes. ▒: Enterobacteriaceae; ■: *Pseudomonas aeruginosa*; ■: *Acinetobacter baumanni*; ■: methicillin-resistant *Staphylococcus aureus*; ▨: methicillin-sensitive *S. aureus*; □: other.

The top three antibiotic prescriptions by country are summarised in table 5. The mean (range) percentage of patients who were initially prescribed carbapenems was 36.1% (0–71.4%). For other antibiotic classes mean use was: ureidopenicillins/monobactam 25.8% (7.9–71.4%), fluoroquinolones 20% (0–44.8%), non-anti-*Pseudomonas* spp. cephalosporins 15.7% (0–49.2%) and cefepime/ceftazidime 10.8% (0–18.9%).

Most of the patients (mean (range) 67.7% (40–85.7%)) received combination therapy. Nonsignificant differences between early- and late-onset VAP were found in terms of monotherapy *versus* combination (early-onset VAP 64.2% *versus* late-onset VAP 70.2%). 23.2% of the combination regimens included aminoglycosides (14% amikacin). Fluoroquinolone-based therapy represented 26.7% of the empirical regimens. Anti-*Pseudomonas* spp. agents were prescribed in 52.5% and 63.6% of patients with early- and late-onset VAP, respectively. Anti-MRSA agents were vancomycin 17.5%, linezolid 12.7% and teicoplanin 8.2%. Finally, 3.2% of episodes received antifungal agents (2.5% azoles and 0.6% echinocandins).

A correlation was found between mean SAPS II score and spectrum of the empirical antibiotic therapy prescribed, ranging from 36.4±13.1 among patients in the lowest therapy spectrum category to 45.1±17.5 in patients prescribed with carbapenems ($p<0.01$; Spearman correlation coefficient 0.22; ANOVA p-value <0.01).

HAP

27 (12.1%) patients received antibiotic therapy prior to HAP, with a mean duration of antibiotic treatment of 9.9±6.0 days. Regarding differences in previous antibiotic prescription between HAP and VAP, 64 (12.1%) patients with VAP *versus*

TABLE 4 Antibiotic prescription for ventilator-associated pneumonia (VAP) according to admission category

	Subjects n	Imip/ merop	Pip/ tazo	CFP/ CFZ	CFX/ CRO	A/C A/S	Amino- glycosides	Quinolones	Glyco- protein	Linezolid	Colistin	Others
Medical VAP												
Early onset	206	15.5	13.6	3.9	10.7	9.7	8.3	10.2	9.7	3.4	0.5	14.5
Late onset	296	20.3	12.8	6.4	4.7	3	12.2	11.5	10.1	5.4	4.7	8.8
Overall	502	18.3	13.1	5.4	7.2	5.8	10.6	11.0	10.0	4.6	3.0	11.0
Surgical VAP												
Early onset	54	13.0	22.2	5.6	3.7	3.7	1.9	11.1	7.4	3.7	0	27.7
Late onset	96	13.5	16.7	6.3	4.2	3.1	3.1	12.5	15.6	9.4	1.0	14.5
Overall	150	13.3	18.7	6	4	3.3	2.7	12.0	12.7	7.3	0.7	19.3
Trauma VAP												
Early onset	107	18.7	13.1	4.7	17.8	5.6	8.4	5.6	7.5	0.9	2.8	14.9
Late onset	158	24.0	7.0	5.1	7.6	1.9	8.9	7.6	6.3	7.6	9.5	14.5
Overall	265	21.9	9.4	4.9	11.7	3.4	8.7	6.8	6.8	4.9	6.8	14.7

Data are presented as %, unless otherwise stated. Imip/merop: imipenem/meropenem; Pip/tazo: piperacillin-tazobactam; CFP/CFZ: cefepime/ceftazidime; CFX/CRO: cefotaxime/ceftriaxone; A/C: amoxicillin-clavulanate; A/S: ampicillin-sulbactam.

TABLE 5 Top three antibiotic prescriptions per country for countries with more than one investigation site

	HAP	VAP	Early-onset VAP	Late-onset VAP
Spain				
First	Piperacillin-tazobactam	Carbapenem	Cefotaxime/ceftriaxone	Carbapenem
Second	Glycopeptides	Piperacillin-tazobactam	Carbapenem	Piperacillin-tazobactam
Third	Quinolones	Quinolones	Piperacillin-tazobactam	Quinolones
Greece				
First	Carbapenem	Carbapenem	Carbapenem	Carbapenem
Second	Piperacillin-tazobactam	Colistin	Glycopeptides	Colistin
Third	Quinolones	Glycopeptides	Piperacillin-tazobactam	Linezolid
Germany				
First	Piperacillin-tazobactam	Piperacillin-tazobactam	Piperacillin-tazobactam	Piperacillin-tazobactam
Second	Quinolones	Quinolones	Quinolones	Quinolones
Third	Cefotaxime/ceftriaxone	Carbapenem	Carbapenem	Glycopeptides
France				
First	Aminoglycosides	Cefotaxime/ceftriaxone	Cefotaxime/ceftriaxone	Cefotaxime/ceftriaxone
Second	Piperacillin-tazobactam	Aminoglycosides	Carbapenem	Aminoglycosides
Third	Carbapenem	Carbapenem	Aminoglycosides	Piperacillin-tazobactam
Belgium				
First	Carbapenem	Piperacillin-tazobactam	Piperacillin-tazobactam	Piperacillin-tazobactam
Second	Piperacillin-tazobactam	Amoxicillin-clavulanate/ampicillin-sulbactam	Carbapenem	Amoxicillin-clavulanate/ampicillin-sulbactam
Third	Amoxicillin-clavulanate/ampicillin-sulbactam	Carbapenem	Quinolones	Quinolones
Italy				
First	Glycopeptides	Carbapenem	Carbapenem	Carbapenem
Second	Carbapenem	Glycopeptides	Glycopeptides	Linezolid
Third	Quinolones	Linezolid	Amoxicillin-clavulanate/ampicillin-sulbactam	Glycopeptides
Turkey				
First	Carbapenem	Carbapenem	Carbapenem	Carbapenem
Second	Glycopeptides	Aminoglycosides	Aminoglycosides	Aminoglycosides
Third	Aminoglycosides	Glycopeptides	Piperacillin-tazobactam	Glycopeptides

HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia.

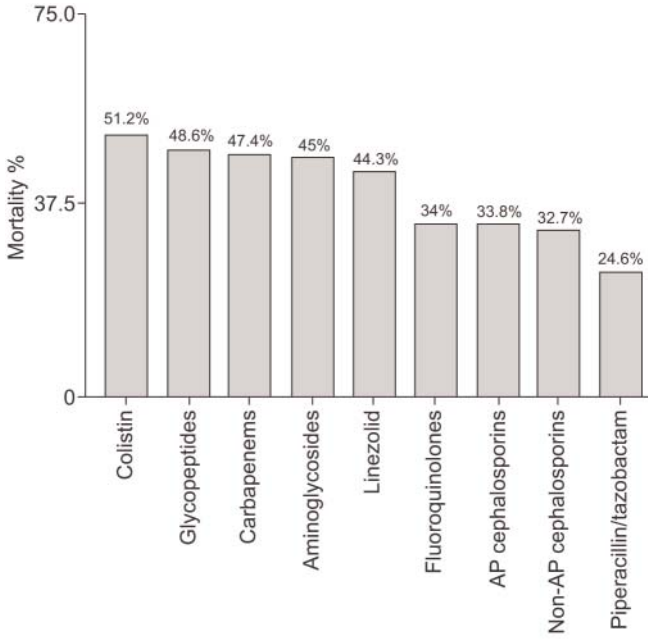

FIGURE 2. Mortality rates according to antibiotic class. Patients could receive more than one antibiotic. AP: anti-pseudomonal.

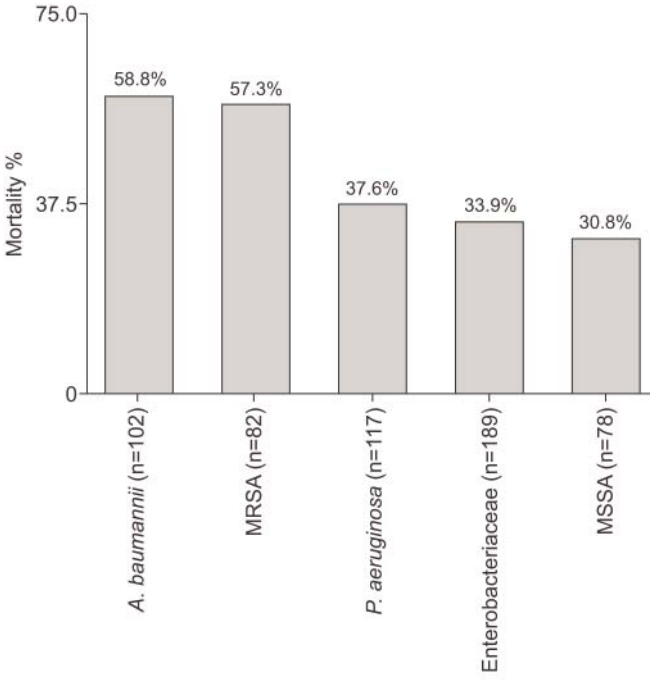

FIGURE 3. Mortality rates according to aetiological agent. Patients could be infected by more than one pathogen. *A. baumannii*: *Acinetobacter baumannii*; MRSA: methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa: Pseudomonas aeruginosa*; Enterobacteriaceae: *Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Proteus mirabilis, Serratia* spp., *Citrobacter* spp., and other Enterobacteriaceae; MSSA: methicillin-sensitive *S. aureus*.

27 (13.8%) patients with HAP received previous antibiotics for >48 h (OR 1.16, 95% CI 0.72–1.88). Nonsignificant differences were identified between admission categories: 13 (9.9%) trauma patients, 17 (13.9%) surgery patients and 61 (14.3%) medical patients received previous antibiotics >48 h (p=0.45).

More than 30 different antibiotic regimens were identified as initial therapy. Patients were prescribed one (n=66, 29.5%), two (n=68, 30.4%) or three or more (n=90, 40.2%) different antibiotics. The top three antibiotic prescriptions by country are summarised in table 5. The median (interquartile) proportion of patients per country initially prescribed carbapenems was 37% (0–70%). For the following most prescribed classes, median values were: piperacillin/tazobactam 35.3% (5.3–66.7%), non-pseudomonal cephalosporins 12.5% (0–23.2%) and cefepime/ceftazidime 10.7% (0–25.0%).

Combination therapy was prescribed to 70.6% of patients (22.2–87.5%). 54 (34.2%) combination regimens comprised fluoroquinolones while 21.5% included aminoglycosides (13 (8.2%) amikacin). Anti-MRSA agents were administered as follows: vancomycin (20.2%), linezolid (13.9%) and teicoplanin (11.4%). Antifungal agents were prescribed in 7.5% of episodes (6.6% azoles and 0.9% echinocandins). Regarding the use of three antibiotics as empirical therapy, it was equally common in patients with positive cultures (25.5%) as in the overall population (28%; p>0.25), but was significantly higher (OR 1.9, 95% CI 1.12–3.37) in patients with HAP and positive cultures (70.8%) compared to patients with HAP without positive cultures (29.7%).

Outcomes

Overall mortality was 35.7% and was not significantly different between HAP and VAP (38.3% *versus* 34.2%; p>0.2). In patients without positive cultures, mortality was 30.1%. We recorded pathogens and susceptibilities in 484 cases. Patients with initial appropriate antibiotic therapy had lower mortality rates than patients with inappropriate therapy (35.1% *versus* 48.1%; p=0.01). 300 (70%) patients survived and were discharged from the ICU. Figure 2 represents mortality according to antibiotic class and figure 3 shows the percentage of patients infected by each microorganism and mortality.

Regarding days of MV, survivors and nonsurvivors differed in 5 days in accordance to appropriateness (19.7±18.7 days *versus* 25.1±28.7 days; p=0.08). Moreover, patients with appropriate empirical therapy had lower LOS in the ICU (26.3±19.8 *versus* 32.8±29.4 days; p<0.05).

DISCUSSION

This is the first study that identifies variables associated with empirical antibiotic choice for nosocomial pneumonia, rather than focusing on risk factors for specific pathogens. Moreover, it is the largest European study that defines the real antibiotic prescription patterns and the outcomes of therapy in a cohort of critically ill patients with HAP/VAP. Duration of antibiotic therapy was <10 days. Our findings suggest that baseline prevalence of *A. baumannii* >10% in pneumonia episodes, severity of sickness and admission category are major determinants of antibiotic choice at the bedside.

This study is comparable to the ALARM study, performed in a cohort of US ICUs [12], with some remarkable differences. First, the EU-VAP/HAP study included twice as many patients as the ALARM study (827 *versus* 398 patients). Another difference is that this study is European, while the

ALARM study is American, and large differences exist regarding prescription patterns between the two continents. In the EU-VAP/HAP study most of the patients (68.7%) received combination therapy as empirical therapy, a proportion similar to that observed in the ALARM study (68.8%) [12]. However, in the US study, cefepime (30.4%), piperacillin/tazobactam (27.9%), carbapenems (11.3%) and quinolones (11.3%) were the leading empirical antibiotics for VAP, while in Europe prescriptions were led by carbapenems (36.1%), ureidopenicillin/monobactam (25.8%), fluoroquinonoles (20%) and non-anti-*Pseudomonas* spp. cephalosporins (15.7%). There were also significant differences in the prescription of antibiotics prior to VAP/HAP onset. In our study, the rates of previous antibiotic prescription (12.1% in HAP and 13.8% in VAP) were significantly lower than in the ALARM study (40.7%), but closer to other European studies (28%) [16].

Finally, the EU-VAP/HAP study included admission category as a variable, which was not considered in the ALARM study, but did not record de-escalations and escalations of therapy.

The ATS/IDSA guidelines recommend the selection of empirical treatment for HAP/VAP according to several factors, mainly risk factors for multidrug-resistant bacteria (LOS, underlying diseases and previous antibiotic prescription) and local susceptibilities [1]. However, our study introduces a new factor with important weight that determines empirical antibiotic choice for HAP/VAP: admission category. In our study, differences were found in daily practice between trauma and non-trauma patients. For instance, trauma patients were treated with non-anti-*Pseudomonas* spp. cephalosporins more than twice as often as patients without trauma. Moreover, despite carbapenems being the most prescribed antibiotics in the overall population, in surgical patients the most prescribed agent was piperacillin-tazobactam in both early- and late-onset VAP.

An expert committee participated in a VAP diagnosis and therapy consensus conference in 2001 [11]. Peers were asked which antibiotic they would choose for early- or late-onset VAP depending on admission category. For trauma patients, non-anti-*Pseudomonas* spp. agents were first choice, but for medical and surgical patients anti-*Pseudomonas* spp. agents were the most common choice. Indeed, trauma patients with VAP are more likely to be infected with endogenous flora such as methicillin-sensitive *Staphylococcus aureus* [17]. Despite this, admission category or SAPS II score were not mentioned in a recently reported summary of European guidelines on HAP/VAP [18]. Our findings show that empirical antibiotic treatment required for the optimal management of pneumonia differs depending on admission category, and must be considered when prescribing antibiotics at the bedside.

This is the first study that identifies the variables associated with decision of therapy in intubated patients. The association between prevalence of *A. baumannii* >10% in pneumonia episodes and specific antimicrobial agents is new and endorses the importance of local surveillance practices to identify the local flora in each ICU, facilitating appropriate antibiotic prescription in individual patients. The hypothesis that a basal prevalence of a pathogen in pneumonia episodes >10% may drive antibiotic choice is new, and we have adapted it from a previous definition of colonisation by BONTEN *et al.* [19]. Knowledge on prevalence of certain pathogens in pneumonia (and other nosocomial infections) episodes influences patterns of prescription and helps to reduce risk of inappropriate empirical therapy. In our cohort of patients, inappropriateness of initial therapy was also significantly associated with higher mortalities [5, 7–9, 17, 20] and increased the ICU stay by 6 days. The reduction in the LOS represents an important contribution in the understanding of the impact of appropriate antibiotic therapy in resource utilisation.

This study was performed in 27 sites from nine different European countries that were not randomly selected, therefore, it could be argued that these sites may not be representative enough of the practices in Europe. In addition, the study has a predominance of central or southern European countries, and the epidemiology and clinical practice in these areas may be somewhat different to more northern and eastern European practices. Certainly, further and more extensive work throughout Europe on this subject is strongly recommended. However, 689 critically ill patients with HAP/VAP were finally enrolled which, to the best of our knowledge, makes this the largest multinational European cohort. In addition, a major factor influencing antibiotic choice is the presence of endemic situations with some microorganisms. It is believed that the higher the MRSA prevalence rate, the higher the anti-MRSA prescription rate. Certainly, the presence of different environments influenced prescription patterns. Rather than a limitation, this variability in the scenarios is one of the most important features of the study. A real limitation might be the fact that the availability of different antimicrobial agents depends on the country, which obviously can affect the absolute prescription rates of certain antibiotics. Also, empirical choice might have been influenced by factors other than the ones captured.

In summary, our study identified that >10% basal prevalence in pneumonia episodes by *A. baumannii*, SAPS II score and admission category are strong determinants of antibiotic choices. These new observations are important and should be considered in further updates of guidelines for the treatment of HAP/VAP. Moreover, our results confirm the importance of appropriate initial therapy in the use of healthcare resources, evidenced by prolongation of ICU stay by 6 days. Furthermore, this large multicentre study evidences the broad variability in antibiotic prescription across Europe, with carbapenems being the most prescribed antibiotic class for HAP/VAP.

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STATEMENT OF INTEREST

A statement of interest for J. Rello can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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