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ORIGINAL

Differences in hospital- and ventilator-associated pneumonia due to *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant) between Europe and Latin America: A comparison of the EUVAP and LATINVAP study cohorts

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KEYWORDS
Methicillin-resistant *Staphylococcus aureus*;
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Abstract
Purpose: A comparison is made of epidemiological variables (demographic and clinical characteristics) and outcomes in patients with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) caused by methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) in the Latin American VAP (LATINVAP) vs. the European Union VAP (EUVAP) cohorts of patients admitted to intensive care units (ICUs).
Methods: The EUVAP project was a prospective, multicenter observational study reporting 827 patients with HAP/VAP in 27 ICUs from 9 European countries. The LATINVAP project was a multicenter prospective observational study, with an identical design, performed in 17 ICUs from 4 Latin American countries involving 99 patients who developed HAP/VAP. Episodes of VAP/HAP caused by *S. aureus*, MSSA, and MRSA were compared in both cohorts.
Results: Forty-five patients had *S. aureus* HAP/VAP in the EUVAP cohort vs. 11 patients in the LATINVAP cohort. More patients had MRSA in the LATINVAP study than in the EUVAP (45% vs. 33%). ICU mortality among patients with MSSA HAP/VAP in EUVAP was 10% vs. 50% for LATINVAP (OR = 9.75, $p = 0.01$). Fifteen patients in the EUVAP cohort developed MRSA HAP/VAP as opposed to 5 in LATINVAP. In the EUVAP study there was an ICU mortality rate of 33.3%. In the LATINVAP cohort, the ICU mortality rate was 60% (OR for death = 3.0; 95%CI 0.24–44.7).

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Conclusion: MRSA pneumonia was associated with poorer outcomes in comparison with MSSA. Our study suggests significant variability among European and Latin American ICU practices that may influence clinical outcomes. Furthermore, patients with pneumonia in Latin America have different outcomes.

PALABRAS CLAVE
SAMR;
NAV;
Infecciones respiratorias;
Staphylococcus aureus;
Neumonía

Diferencias entre la neumonía de origen nosocomial y asociada a la ventilación por *Staphylococcus aureus* (susceptible a la meticilina y resistente a la meticilina) en europa y latinoamérica: comparación de las cohortes de estudio EUVAP y LATINVAP

Resumen
Objetivo: comparar las variables epidemiológicas (características demográficas y clínicas) y los efectos en pacientes con neumonía intrahospitalaria (NIH) o neumonía asociada a la ventilación (NAV) causada por *Staphylococcus aureus* susceptible a la meticilina (SASM) y resistente a la meticilina (SARM) en las cohortes LATINVAP y EUVAP de pacientes admitidos en unidades de cuidados intensivos (UCI).
Métodos: El proyecto EUVAP fue un estudio prospectivo, multicéntrico y observacional sobre 827 pacientes con NIH/NAV de 27 UCI de 9 países europeos. El proyecto LATINVAP fue un estudio pospectivo, multicéntrico y observacional de idéntico diseño que se llevó a cabo en 17 UCI de 4 países latinoamericanos y en el que se evaluaron 99 pacientes que habían desarrollado HAP/VAP. Se compararon entre las cohortes los episodios de VAP/HAP causados por *S. aureus* (SASM y SARM).
Resultados: Cuarenta y cinco pacientes presentaron NIH/NAV por *S. aureus* en la cohorte EUVAP frente a 11 pacientes en la cohorte LATINVAP. El número de pacientes con SARM en el estudio LATINVAP fue superior al del estudio EUVAP (45% frente al 33%). La mortalidad en la UCI entre los pacientes con NIH/NAV por SASM del estudio EUVAP fue del 10% frente al 50% en el caso del estudio LATINVAP (OR = 9,75, p = 0,01). Quince pacientes de la cohorte EUVAP desarrollaron NIH/NAV por SARM frente a 5 de la cohorte LATINVAP. En el estudio EUVAP se registró una tasa de mortalidad del 33,3%. En la cohorte LATINVAP la tasa de mortalidad en la UCI fue del 60% (OR de muerte = 3,0; IC del 95% de 0,24 a 44,7).
Conclusiones: La neumonía por SARM se asoció a unos peores resultados en comparación con la neumonía por SASM. Nuestro estudio sugiere una variabilidad importante entre las prácticas de las UCI europeas y latinoamericanas que podría influir sobre los resultados clínicos. Además, los pacientes con neumonía de Latinoamérica presentaron resultados diferentes.

Introduction

Data from EPIC II study[1] confirmed that *Staphylococcus aureus* is classified among the top three pathogens associated with nosocomial infections in the ICU, particularly Hospital Acquired Pneumonia (HAP) or Ventilator-Associated Pneumonia (VAP). *S. aureus* is associated with high mortality, morbidity and costs.[2–5] The ZEPHyR project (Linezolid in the treatment of subjects with nosocomial pneumonia proven to be due to methicillin-resistant *S. aureus*) was a large multicenter randomized double blind, comparator-controlled, multicenter, phase 4 study control trial that compared linezolid with vancomycin in patients with nosocomial pneumonia.[6,7] A secondary analysis using a multivariate analysis suggested that Latin American sites were independently associated with an increased risk of death (OR >3).[5] It is not clear what kind of impact geographical variations may operate when it comes to clinical outcomes of patients with *S. aureus* pneumonia, particularly when infection occurs with multi-drug resistant strains.

The EUVAP was a large prospective, multicenter, observational study that reported the clinical management of pneumonia in 27 European ICUs from 9 European countries (Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain, and Turkey). 2436 intubated patients were included in the study, of whom 827 presented HAP/VAP.[8] Due to the lack of information in Latin-America, we underwent a similar multicenter project in ICUs from 4 countries in Latin-America.

The objective of this study was to compare epidemiological variables (demographics and clinical characteristics), management strategies and outcomes in patients with hospital acquired pneumonia (HAP) or VAP caused by MSSA and MRSA in LATINVAP vs. EUVAP cohorts of patients admitted to ICUs. The primary endpoint was to compare mortality and the secondary endpoints were outcomes such as duration of mechanical ventilation, time to resolution based on fever, oxygenation ratio and leukocyte count, duration of antibiotics and length of hospital stay.

Patients and methods

The LATINVAP was a multicenter prospective observational study, with an identical design to the EUVAP study, performed in 17 ICUs from 4 Latin American countries (Argentina, Colombia, Peru, and Ecuador) during 2008. Ethical approval according to local legislation was mandatory for study participation and informed consent was waived.

The inclusion and exclusion criteria were identical for the LATINVAP and the EUVAP: All patients requiring ICU admission for a diagnosis of pneumonia or receiving invasive mechanical ventilation for 48 h, irrespective of the admission diagnosis, were included.[8] VAP/HAP was defined as the presence of a new or progressive pulmonary infiltrate and two of the following: temperature >38.3 °C or <36.0 °C, leukocyte count >12,000 mm^{-3} or <4000 mm^{-3}, or purulent tracheal secretions. The diagnosis of VAP/HAP was considered to be microbiologically confirmed if either Broncho-alveolar Lavage (BAL) or Endotracheal Aspirate (ETA) cultures had significant growth in accordance with standard thresholds.[9] The presence or absence of a new or progressive radiographic infiltrate was based on the interpretation of the chest radiograph by board certified radiologists who were blinded to the study. The organism(s) causing pneumonia and their antimicrobial susceptibility testing results were recorded, according with local policies. Quantitative samples were interpreted using classical breakpoints for respiratory specimens.[9] Criteria for clinical stability have been reported elsewhere.[10]

Study cohort of interest included microbiological confirmed HAP/VAP episodes caused by *S. aureus*. The groups were further stratified in MSSA or MRSA according to the susceptibility reports following the laboratory standards of each institution.

Participant ICUs were requested to provide follow-up until ICU discharge. Each country had a country coordinator who helped with center recruitment, communication and local ethical requirements. EUVAP and LATINVAP studies were endorsed by the ECCRN Committee of the European Society of Intensive Care Medicine.

Each participating site provided information using a web based data entry form. Data were routinely checked for consistency and for completeness at the coordinating center. Where data could not be confirmed or remained questionable, an investigator (TL) made a final adjudication.

Statistical analysis

All analyzed continuous variables were expressed as mean and standard deviation, all of them and their subgroups presented normal distribution just as Kolmogorov–Smirnov test proved. Comparisons between groups are performed with two-tailed unpaired Student's *t*-test and one-way ANOVA according to data distribution. Estimated mortality was calculated based on severity-of scores at ICU admission. In all analysis two-sided *p*-values less than 0.05 were deemed to represent statistical significance.

Results

Out of 926 patients, 56 had *S. aureus* HAP/VAP: 45/827 (5.4%) from the EUVAP and 11/99 (11.1%) from the LATINVAP cohorts, respectively. Demographics, clinical characteristics, diagnostic methods and clinical outcomes are compared in Table 1.

For MSSA patients, the main underlying disease in EUVAP was neurological (46.6%, $p < 0.05$), being multiple trauma (50%) in LATINVAP. No significant difference was observed in MSSA patients between EUVAP and LATINVAP for the following variables: age and duration of antibiotics. When comparing MRSA patients among the EUVAP and the LATINVAP cohort, the most common underlying disease in EUVAP was sepsis (46.6%) vs. neurological (60%) in LATINVAP.

Three patients had positive blood cultures in LATINVAP (two MRSA) and only one in EUVAP (MSSA). In the LATINVAP, only one MSSA was confirmed by bronchoalveolar lavage; all the remaining respiratory specimens were tracheal aspirates. In the EUVAP, above 50% of *S. aureus* episodes were documented in bronchoscopic samples. More patients had MRSA in the LATINVAP that in the EUVAP (45% vs. 33%, $p < 0.05$). MRSA vs. MSSA pneumonia patients among the EUVAP cohort were more likely to have longer duration of antibiotic days, days on mechanical ventilation and mortality. Time to clinical stability was only available in the EUVAP cohort and data are presented in Table 2. In addition, MRSA vs. MSSA pneumonia patients among the LATINVAP cohort were more likely to have higher ICU mortality, but appear to be spending more time on antibiotics.

In EUVAP, 53.3% of MRSA episodes were treated with linezolid (median of 13 days) in contrast to LATINVAP, where only 20% of MRSA episodes received linezolid (median of 11 days). The overall ICU mortality was 33.3% in EUVAP and 60% in LATINVAP (OR for death = 3.0; 95%CI 0.24-44.7) Three deaths (all in LATINVAP) were estimated to be attributable to pneumonia. Ratios of observed vs. estimated mortality were 0.76 and 0.83 for the risk of death for LATINVAP and EUVAP, respectively, in MRSA infected patients. In survivors the mean duration of MV was 30.3 ± 16.3 days in EUVAP and 11 ± 9 days in LATINVAP ($p = 0.02$).

As shown in Table 1, the ICU mortality for patients with MSSA HAP/VAP in EUVAP was 10% vs. 50% for LATINVAP. The estimated hospital mortality (based on severity-of-illness scores) was 14% in EUVAP and 74% in LATINVAP. Three deaths (2 in LATINVAP) were attributable to pneumonia. Ratios of observed vs. estimated mortality were 0.67 and 0.95 for LATINVAP and EUVAP, respectively, for MSSA cases. In survivors, mean duration of mechanical ventilation in EUVAP was 16.4 ± 19.0 days and 20.6 ± 7.2 days for LATINVAP ($p > 0.20$).

Discussion

To the best of our knowledge, this is the first multinational study specifically designed to enrol consecutive intubated patients to assess the development of HAP/VAP in Latin-American ICUs. MRSA was associated with prolonged clinical resolution, duration of mechanical ventilation and ICU mortality in comparison with MSSA, consistent with other reports.[10,11] Our results suggest that HAP/VAP patients enrolled in a Latin-American cohort were more likely to die compared to cohort from Europe when MRSA and MSSA were confirmed microbiologically. In addition, patients with MRSA

Table 1 Clinical characteristics of HAP/VAP patients with *S. aureus* (MSSA and MRSA) from the EUVAP and LATINVAP cohorts.

	EUVAP			LATINVAP		
	S. aureus ($n=45$)	MSSA ($n=30$)	MRSA ($n=15$)	*S. aureus* ($n=11$)	MSSA ($n=6$)	MRSA ($n=5$)
Age (years ± SD)	52.7 ± 19.1	50.8 ± 21.8	54.7 ± 16.4	52.6 ± 17.3	57.1 ± 22.9	48.2 ± 11.7
Source of infection %						
Neurological	42.2	46.6*	33.3*	36.3	16.6*	60*
Sepsis	15.5	0	46.6	27.2	16.6	40
Trauma	20	26.6	6.6	27.2	50.1	0
Cardiovascular	15.5	20	6.6	0	0	0
Gastrointestinal	6.6*	6.6*	6.6	9.1*	16.6*	0
Severity of illness						
APACHE	18.6	15.2	22	N.A.	N.A.	N.A.
SAPS II	N.A.	N.A.	N.A.	64.9	63.8	66
Clinical parameters at baseline						
Fever income (°C)	38.6	38.7	38.5	38.8	38.8	38.8
Leukocyte entry (cells/mm^3)	13,981	11,916	16,047	14,766	14,566	14,966
PaO_2/FiO_2 (units)	237	250	225	197	194	200
Diagnostic confirmation method, %						
BAL	6.6*	0	20	9.1*	16.6	0
BAS	51.1	56.6	40	0	0	0
PBS	40	40.1	40	0	0	0
Blood cultures	2.3	3.3	0	18.1	16.6	20
Endotracheal aspirate	0	0	0	72.7	66.6	80
Clinical outcomes, n (%)						
ICU mortality (%)	21.6	10	33.3	55	50	60
Duration of mechanical ventilation, mean days ± SD	15.9 ± 17.8	16.4 ± 19.4	30.3 ± 16.3*	15.8 ± 8.5	20.6 ± 7.2	11 ± 9.8*
Duration of antibiotics, mean days ± SD	13.1 ± 5.1*	10.9 ± 4.8*	15.4 ± 5.4*	9.7 ± 3.3*	7.8 ± 3.1*	11.6 ± 3.1*

MSSA: methicillin susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; BAL: broncho-alveolar lavage; BAS: bronchial aspirate; PBS: protected brush specimen.

* *p*-Value <0.05, when comparing EUVAP vs. LATINVAP cohorts, for *S. aureus*, MRSA and MSSA.

Table 2 Time to clinical stability for HAP/VAP EUVAP cohort.

Clinical variables	Time to clinical stability (mean days ± SD)			
	S. aureus ($n = 45$)	MSSA ($n = 30$)	MRSA (n = 15)	p value*
Fever (°C)	5.6 ± 2.3	2.8 ± 0.8	8.4 ± 3.8	<0.05
PaO_2/FiO_2 (mmHg)	5.3 ± 3.6	2.7 ± 2.6	8.06 ± 4.7	<0.05
Leukocytes ($\times 10^9\ L^{-1}$)	7.0 ± 4.8	6.03 ± 4.2	8.01 ± 5.5	<0.05

MSSA: methicillin susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.
* p-Value for comparison between MSSA with MRSA patients.

HAP/VAP have worse clinical outcomes compared to MSSA in both cohorts.

Incidence of MRSA in Latin America was higher when compared with incidence in Europe. Similar epidemiological reports[1,12] confirm the fact that MRSA is a problem of higher importance in Latin-America than in Europe. Therefore, active surveillance for MRSA and standard infection control preventive measures,[13] which are important everywhere, should be particularly encouraged in this high-risk patients group.

In a systematic review, Falagas and collaborators[14,15] confirmed that both in-hospital and ICU mortality of patients with VAP due to *S. aureus* had higher rate of methicillin-resistant strains (MRSA). Moreover, the EPIC II study confirmed these findings in a sub-analysis of MRSA episodes.[16] Interestingly, MRSA pneumonia was associated with significantly higher ICU mortality in the LATINVAP, confirming data from multivariate analysis reported in the ZEPHyR study.[6] Overall, in MRSA pneumonia, treatment failure rates as high as 40% have been reported and attributed to inadequate duration of therapy,[17] emphasizing the value of ''right first time''.[18] MRSA VAP is a difficult-to-treat infection with longer times to clinical resolution (Table 2) and duration of mechanical ventilation when compared with other pathogens, even if appropriate therapy is delivered.[19] Therefore, duration of therapy should be based on individualized follow-up for resolution of signs and symptoms of infection.[20,21] Patients with advanced age, immunosuppressors, acute kidney injury, nephrotoxic agents or severe sepsis/septic shock should avoid glycopeptides.[22,23] Paradoxically, benefit of vancomycin may be higher in patients with low glomerular filtration rate, due to drug accumulation.[7]

In addition to survival, this study demonstrates the impact of MRSA pneumonia in costs associated with increased use of health care resources by increase on length of stay.[5,24] Managing increasingly limited resources is one of the key challenges. However, effect modification due to varying levels of diagnostic tests and types of empirical treatment could have influenced our results. Our findings reinforce the critical nature of bacterial illnesses in ICU hospitalized patients and the importance of delivering rapid diagnostics and effective antimicrobial therapy early in the illness.[25–27]

This study has different limitations. One of them is the unavailability of time to clinical stability in the LATINVAP cohort. Also, participating ICUs were not representative of each country and only 4 countries participated. Some patients had an important severity-of-illness, which was associated with extremely high risk of death. As a consequence, results of this study should be broadly generalized with caution. However, this is inherent to all epidemiological studies in which participation is voluntary. Second, study data were entered by investigators at each site raising the possibility of inconsistencies; we attempted to minimize this risk through use of standardized definitions, direct web-base server data entry and revision of each included case for inconsistencies. Third, estimated mortality is based on data not customized to Latin-America and scores validation should be performed in different countries. Moreover, scores estimating mortality were different in the EUVAP and LATINVAP. However, mortality adjustment for severity using these scores is better than none. Finally, each participating site performed laboratory testing according to their own local protocols and did not have isolates referred to a central laboratory for standardized testing of susceptibilities. Similarly, therapy was not standardized and was decided but each attending, allowing comparisons due to variability in medical practice.

In summary, our study suggests that MRSA HAP/VAP is associated with worse clinical outcomes compared to MSSA HAP/VAP patients in the ICU setting. In addition, there are important differences among MRSA HAP/VAP enrolled in the LATINVAP cohort compared to the EUVAP cohort. Our study also suggests that there is significant variability among European and Latin-American ICU practices related to case-mixes, diagnostic tests, use of antimicrobials and management that may influence clinical outcomes. Further studies should focus on strategies that may standardize care in order to survival and reduce the use of expensive health care resources.

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Conflicts of interest

Jordi Rello serves as member of the Advisory Boards and Speaking Bureaus of Pfizer and Astellas. Jordi Rello has received research grant support from Pfizer. Dr. Marcos I. Restrepo participated in advisory boards for Theravance, Forest Laboratories, Johnson & Johnson, Trius and Novartis. Consultant for Theravance, Trius and Pfizer (Wyeth).

The remaining authors declared no conflict of interest.

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Appendix A.

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