Decreasing incidence and mortality among hospitalized patients suffering a ventilator-associated pneumonia

Analysis of the Spanish national hospital discharge database from 2010 to 2014

Javier de Miguel-Díez, MD, PhD, Ana López-de-Andrés, PharmD, PhD, Valentín Hernández-Barrera, MSc, Isabel Jiménez-Trujillo, PhD, Manuel Méndez-Bailón, MD, PhD, José M. de Miguel-Yanes, MD, PhD, Benito del Río-López, MD, PhD, Rodrigo Jiménez-García, MD, PhD.

Abstract
The aim of this study was to describe trends in the incidence and outcomes of ventilator-associated pneumonia (VAP) among hospitalized patients in Spain (2010–2014).

This is a retrospective study using the Spanish national hospital discharge database from year 2010 to 2014. We selected all hospital admissions that had an ICD-9-CM code: 997.31 for VAP in any diagnosis position. We analyzed incidence, sociodemographic and clinical characteristics, procedures, pathogen isolations, and hospital outcomes.

We identified 9336 admissions with patients suffering a VAP. Incidence rates of VAP decreased significantly over time (from 41.7 cases/100,000 inhabitants in 2010 to 40.55 in 2014). The mean Charlson comorbidity index (CCI) was 1.08 ± 0.98 and it did not change significantly during the study period. The most frequent causative agent was Pseudomonas and there were not significant differences in the isolation of this microorganism over time. Time trend analyses showed a significant decrease in in-hospital mortality (IHM), from 35.74% in 2010 to 32.81% in 2014. Factor associated with higher IHM included male sex, older age, higher CCI, vein or artery occlusion, pulmonary disease, cancer, undergone surgery, emergency room admission, and readmission.

This study shows that the incidence of VAP among hospitalized patients has decreased in Spain from 2010 to 2014. The IHM has also decreased over the study period. Further investigations are needed to improve the prevention and control of VAP.

Abbreviations: AIDS = acquired immunodeficiency syndrome, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, ICD-9-CM = International Classification of Diseases-Ninth Revision, Clinical Modification, IHM = in-hospital mortality, LOHS = length of hospital stay, PA = Pseudomonas aeruginosa, SNHDD = Spanish National Hospital Discharge Database, SOFA = Sequential Organ Failure Assessment, VAP = ventilator-associated pneumonia.

Keywords: administrative database, burden of VAP, incidence rate, mortality, ventilator-associated pneumonia

1. Introduction
Ventilator-associated pneumonia (VAP) is a type of nosocomial pneumonia that occurs in patients who receive more than 48 hours of mechanical ventilation. It is associated with mortality. Over the last years, much improvement has been achieved in understanding the underlying causes and control methods for VAP; however, these infections are still a very frequent health care associated complication.

Even if several reports have shown that the incidence of VAP may be decreasing, other studies do not reach this conclusion indicating that the rate is stable over time. The evidence shows that VAP results in a significant increment in resource consumption and in patients requiring excess days of hospitalization. Thus, occurrence of VAP increases health system costs.

Mortality associated with VAP has been reported to range from 33% to 50%. This rate is variable and relies heavily on the underlying medical illness. However, the attributable risk of death has decreased over time, and recently, it has been estimated at 9% to 13%. In any case, the incidence, outcomes, and mortality of VAP could vary due to several factors, including the study population, time of onset, etiologic organisms, and adequacy of antibiotic therapy.
Despite the significant impact of this disease, studies conducted on the trends of epidemiology of VAP are scarce.\(^{12-15}\) Unfortunately, the impact of VAP has not been previously determined for the Spanish health care system. Administrative data could be used as primary case-finding methods for this condition.\(^{16}\) A better understanding of the burden of VAP may help in reducing the incidence and improving patients’ outcomes.

Our objectives were to analyze trends in the incidence, clinical characteristics, and outcomes of VAP in Spain from 2010 to 2014 using the Spanish National Hospital Discharge Database (SNHDD).

2. Methods

We conducted an observational retrospective study using the SNHDD.\(^{17}\) The SNHDD includes information on the sex, age, dates of admission and discharge, up to 14 discharge diagnoses, and up to 20 procedures performed during the hospitalization. The study was conducted with all data included in the SNHDD from January 1, 2010, to December 31, 2014 (5 complete years).

The criteria for diseases and procedures were defined according to the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM), which is used in the Spanish SNHDD. We selected admissions for patients with a diagnosis of VAP (ICD-9-CM code: 997.31) in any position.

The Charlson comorbidity index (CCI) was used to assess the clinical characteristics of the patients.\(^{18}\) We divided patients into 3 categories: low index, which corresponds to patients with no previously recorded disease; medium index, patients with 1 disease category; and high index, patients with 2 or more disease categories.

Irrespective of the position at the diagnoses coding list, we retrieved data about comorbid specific conditions such as acute myocardial infarction, congestive heart failure, vascular disease, cerebrovascular disease, hemiplegia or paraplegia, dementia, chronic obstructive pulmonary disease (COPD), rheumatoid disease, peptic ulcer, liver disease, renal disease, diabetes, any type of malignancy, metastatic cancer, and acquired immunodeficiency syndrome (AIDS) using the enhanced ICD-9-CM. Furthermore, we identified the following as primary diagnosis: cranial hemorrhage, heart disease, vein or artery occlusion, cranial or spine fracture, pulmonary disease, or nonspecified pneumonia and cancer using the specific ICD-9 codes. We analyzed organ failures, procedures, and pneumonia pathogens documented during hospitalizations for VAP using the same source (see Table 1, Supplemental Content, http://links.lww.com/MD/B815).\(^{19}\) According to the SNHDD methodology, only those pathogens that are laboratory confirmed can be included in the discharge report.\(^{17}\) For study purpose, we grouped all species associated with rising IHM in a new variable named “All species that increased IHM.” Hospital outcome variables included emergency room admission, readmission (if the patient had been discharged in the previous 30 days), and the in-hospital mortality (IHIM).

2.1. Statistical analysis

In order to assess time trends, the incidence rates of hospitalizations with VAP were calculated per 100,000 inhabitants. The denominators were the population, reported on December 31 of each year, according to the Spanish National Institute of Statistics.\(^{20}\)

We estimated the proportion of VAP among mechanically ventilated patients dividing the number of VAP by the total number of hospitalized patient who received invasive mechanical ventilation (ICD MD codes 96.7x in any procedure field) each year.

Variables are described as means with standard deviations or as proportions. Bivariate comparisons were done with Student t test, Kruskall–Wallis test, analysis of variance (ANOVA), and x² test.

Multivariable methods include Poisson regression (incidence) or logistic regression (IHIM). The detailed description of the methods can be found elsewhere.\(^{19}\)

The software used for bivariate and multivariable analysis was Stata (Stata, College Station, TX). Statistical significance was set at P < .05 (2-tailed).

2.2. Ethical aspects

Approval by an ethics committee was not necessary according to the Spanish law. To warranty patient anonymity, the database was provided to us by the Ministry of Health after all patient identifiers were deleted. In accordance with the Spanish legislation, informed consent was not necessary.

3. Results

From 2010 to 2014, we identified a total of 9336 admissions with patients suffering a VAP in Spain. Table 1 summarizes the sociodemographic and clinical characteristics of patients included in the study. The mean age was 58.3 ± 18.31 years and there were a predominance of males, without significant changes in age or sex over time. Incidence decreased significantly, from 41.7 cases per 100,000 inhabitants in 2004 to 40.55 in 2014.

As can be seen in Table 1, the proportion of VAP among mechanically ventilated patients remained stable along the study period with figures around 4%.

The mean CCI index was 1.05 ± 0.98 and it did not change significantly during the study period. The most frequent comorbidities were as follows: cerebrovascular disease (21.09%), congestive heart failure (13.7%), COPD (12.14%), and diabetes (10.59%).

The most common primary diagnosis was cranial hemorrhage (15.19%), followed by heart disease (11.51%), cranial or spine fracture (7.18%), cancer (5.81%), and pulmonary disease or pneumonia (5.21%). We did not find significant variations in the prevalence of these conditions over time.

Procedures, hospital outcomes, acute organ failures, and pathogen isolations of patients hospitalized with VAP are summarized in Table 2. We found an increase in the use of bronchoscopies over time, from 12.74% in 2010 to 16.69% in 2014 (P < .05). However, the use of other procedures, such as the thoracentesis or the pleural drainage tube, did not change significantly during the study period.

We observed a significant decrease in the percentage of patients who had undergone surgery, from 77.17% in 2010 to 73.62% in 2014. However, we did not detect significant differences in the prevalence of pressure ulcers, septic shock, emergency room admissions, and readmissions (Table 2).

The mean number of acute organ failures significantly increased during the study period, from 1.24 ± 1.17 in 2010 to 1.37 ± 1.21 in 2014. In particular, we observed an increase in the prevalence of cardiovascular failure (from 27.23% in 2010 to 28.92% in 2014), respiratory failure (from 32.24% in 2010 to 37.49% in 2014), renal failure (from 24.18% in 2010 to 30.33% in 2014), and hepatic failure (from 3.16% in 2010 to 4.11% in 2014).
Table 1
Sociodemographic and clinical characteristics of patients hospitalized who suffered a ventilator-associated pneumonia (VAP) in Spain from 2010 to 2014.

| Age groups, y | 2010 | 2011 | 2012 | 2013 | 2014 | Total | P |
|--------------|------|------|------|------|------|-------|---|
| <25          | 91 (5.13) | 121 (5.86) | 110 (5.94) | 112 (5.99) | 107 (6.03) | 541 (5.79) | .336 |
| 25–34        | 112 (6.31) | 118 (6.71) | 97 (5.24) | 79 (4.22) | 83 (4.68) | 489 (5.24) | .524 |
| 35–44        | 155 (8.74) | 187 (10.06) | 154 (8.32) | 148 (7.91) | 160 (9.02) | 831 (9.06) | .336 |
| 45–54        | 272 (15.33) | 307 (17.43) | 290 (15.66) | 327 (17.48) | 292 (16.46) | 1488 (15.94) | .387 |
| 55–64        | 358 (20.18) | 395 (21.93) | 392 (21.17) | 386 (20.63) | 360 (20.29) | 1891 (20.25) | .113 |
| 65–74        | 428 (24.13) | 509 (26.07) | 441 (23.81) | 467 (24.96) | 433 (21.41) | 2278 (24.4) | .725 |
| 75–84        | 330 (18.6) | 397 (21.93) | 331 (17.87) | 318 (17.1) | 321 (18.07) | 1699 (18.18) | .153 |
| ≥85          | 28 (1.58) | 31 (1.7) | 37 (2.0) | 34 (1.82) | 34 (1.82) | 148 (1.59) | .734 |

Acute myocardial infarction, n (%) 135 (7.61) 132 (6.59) 150 (8.1) 143 (7.64) 104 (5.86) 644 (7.1) .040
Congestive heart failure, n (%) 224 (13.63) 235 (19.38) 265 (14.31) 293 (15.66) 263 (14.83) 1280 (13.71) .001
Peripheral vascular disease, n (%) 109 (6.14) 112 (5.42) 104 (5.62) 103 (5.61) 111 (6.26) 537 (5.77) .734
Cerebrovascular disease, n (%) 354 (19.95) 456 (22.08) 368 (19.87) 397 (22.38) 397 (22.38) 1690 (18.19) .017
Hemiplegia or paraplegia, n (%) 165 (9.3) 196 (9.49) 170 (9.18) 163 (8.78) 177 (9.18) 891 (9.54) .922
Dementia, n (%) 4 (0.23) 12 (0.65) 7 (0.39) 8 (0.43) 5 (0.28) 36 (0.39) .430
Chronic obstructive pulmonary disease, n (%) 205 (11.56) 235 (11.38) 226 (12.2) 229 (12.9) 239 (13.47) 1133 (12.18) .325
Rheumatoid disease, n (%) 15 (0.85) 18 (0.87) 15 (0.81) 12 (0.64) 18 (0.87) 78 (0.78) .841
Peptic ulcer, n (%) 39 (2.2) 34 (1.65) 34 (1.84) 40 (2.14) 26 (1.41) 173 (1.85) .353
Mild liver disease, n (%) 124 (6.99) 137 (6.63) 138 (7.45) 124 (6.63) 133 (7.5) 656 (7.03) .725
Moderate/severe liver disease, n (%) 23 (1.3) 40 (2.08) 45 (2.3) 39 (2.08) 24 (1.3) 133 (1.39) .430
Renal disease, n (%) 77 (4.34) 100 (4.84) 89 (4.81) 104 (5.56) 84 (4.74) 454 (4.86) .544
Diabetes, n (%) 204 (11.5) 226 (10.84) 204 (11.02) 181 (10.21) 164 (9.24) 890 (9.58) .210
Diabetes with complications, n (%) 22 (1.24) 31 (1.51) 30 (1.62) 39 (2.08) 25 (1.41) 119 (1.89) .490
Cancer, n (%) 104 (5.86) 156 (7.57) 131 (7.07) 117 (6.25) 103 (5.81) 611 (6.54) .113
Metastatic cancer, n (%) 45 (2.54) 59 (2.86) 47 (2.54) 45 (2.41) 34 (1.92) 230 (2.46) .456
Acquired immunodeficiency syndrome, n (%) 12 (0.68) 22 (0.17) 17 (0.92) 16 (0.86) 8 (0.45) 75 (0.8) .261
CCI index, mean (SD) 1.05 (0.98) 1.07 (0.98) 1.1 (0.99) 1.1 (0.98) 1.08 (1) 1.08 (0.98) .318
PD: Cranial hemorrhage, n (%) 261 (14.71) 342 (16.56) 255 (13.77) 274 (14.64) 286 (16.12) 1418 (15.19) .097
PD: Heart disease, n (%) 224 (12.63) 219 (10.61) 233 (12.58) 219 (11.7) 180 (10.15) 1075 (11.5) .056
PD: Vein or artery occlusion, n (%) 99 (5.58) 128 (6.2) 108 (5.63) 147 (7.86) 139 (7.84) 621 (6.65) .006
PD: Cranial or spine fracture, n (%) 137 (7.72) 158 (7.65) 139 (7.51) 129 (6.89) 107 (6.03) 670 (7.18) .239
PD: Pulmonary disease or pneumonia, n (%) 101 (5.69) 120 (5.81) 105 (5.45) 90 (4.28) 84 (4.47) 486 (5.21) .153
PD: Cancer, n (%) 97 (5.47) 132 (6.59) 121 (6.53) 109 (6.38) 83 (4.68) 542 (5.81) .108

P value for time trend using Poisson or logistic regression adjusted by age and sex when appropriate.
CCI = Charlson comorbidity index, PD = primary diagnosis.
*Incidence calculated overall number of hospitalizations in Spain that year.
We can see the results of the multivariate analysis of factors independently associated with IHM among hospitalized patients who suffered VAP in Spain from 2010 to 2014 in Table 5. IHM was significantly higher in males, in older subjects, in patients with comorbidities, in those undergoing surgery, and in patients with one of the following primary diagnosis: vein or artery occlusion, pulmonary disease or pneumonia, and cancer. Mortality was also significantly higher in patients with emergency room admissions and those who were readmitted. By contrast, IHM was significantly lower in patients in which primary diagnosis was cranial hemorrhage and cranial or spine fracture.

Time-trend analysis showed a significant decrease in IHM in patients admitted with VAP in Spain from 2010 to 2014.

4. Discussion

Our results show that the rate of hospitalization for VAP has decreased significantly from 2010 to 2014 in Spain. Other authors have reported similar trends.\[^{15,21}\] These results might reflect efficiency of preventive measures and critical care practices. In fact, VAP prevention bundle is one of the major strategies used for reducing the incidence of this condition.\[^{14,22}\]

It includes the following components: medical education, use of subglottic suction endotracheal tubes, semi-recumbent position, sedation protocols for rapid weaning, and oral care with chlorhexidine.\[^{12,24}\] Despite all, it has been demonstrated that there is a wide variability in compliance with VAP-preventive measures across intensive care units in Europe.\[^{25}\] Apart from compliance with VAP prevention bundles, the rising part of noninvasive ventilation support (noninvasive mechanical ventilation and high flow oxygen therapy) might also explain the decreasing incidence of VAP.

In agreement with other reports, our study showed a male predominance.\[^{16-24}\] Male sex is one of the nonmodifiable patient-related risk factors for the development of VAP along with others such as preexisting pulmonary disease, AIDS, coma, head trauma, and multiple-organ system failure.\[^{29}\]

The rising use of bronchoscopies in our study is remarkable, whereas the best ways to get microbiological diagnosis in VAP are still discussed. Moreover, it is not clear why the use of bronchoscopy is associated with mortality. It is possible that this procedure is performed more frequently in patients with a worse clinical course, in order to optimize antibiotic treatment.

We also found an increase in the number of organ failures over time. Specifically, we showed an increased failure of vascular, respiratory, hepatic, and renal organs during the study period. It has been found that multiple organ dysfunction, along with a possible immunosuppression and other underlying diseases, increases the risk of opportunistic infections.\[^{10}\]

According to our results, Gram-negative bacteria were the most frequently isolated pathogens with *Pseudomonas* showing the highest prevalence (5.68%). Furthermore, its dominance did not change over time. Other authors have also found that *Pseudomonas aeruginosa* (PA) is one of the most common bacteria causing VAP,\[^{31,32}\] with a prevalence of approximately 30%.
Table 3
Sociodemographic and clinical characteristics of patient hospitalized who suffered a ventilator-associated pneumonia according to hospitalization survival in Spain, 2010–2014.

|                         | Live, n  | Died, n  | IHM 100 | P    |
|-------------------------|----------|----------|---------|------|
| **Total**               | 6080     | 3256     | 34.88   | NA   |
| **Sex**                 |          |          |         |      |
| Male                    | 4217     | 2310     | 35.39   | .002 |
| Female                  | 1863     | 946      | 33.68   |      |
| **Age groups, y**       |          |          |         |      |
| <25                     | 474      | 67       | 12.38   | .001 |
| 25–34                   | 417      | 72       | 14.72   |      |
| 35–44                   | 647      | 157      | 19.53   |      |
| 45–54                   | 1111     | 377      | 25.34   |      |
| 55–64                   | 1232     | 659      | 34.85   |      |
| 65–74                   | 1322     | 956      | 41.97   |      |
| 75–84                   | 799      | 898      | 52.92   |      |
| 85+                     | 78       | 70       | 47.3    |      |
| **Acute myocardial infarction** |          |          |         |      |
| No                      | 5673     | 2999     | 34.58   | .755 |
| Yes                     | 407      | 257      | 38.7    |      |
| **Congestive heart failure** |          |          |         |      |
| No                      | 5355     | 2701     | 33.53   | .011 |
| Yes                     | 725      | 555      | 43.36   |      |
| **Peripheral vascular disease** |          |          |         |      |
| No                      | 5756     | 3041     | 34.57   | .801 |
| Yes                     | 324      | 215      | 39.89   |      |
| **Cerebrovascular disease** |          |          |         |      |
| No                      | 4755     | 2612     | 35.46   | .025 |
| Yes                     | 1325     | 644      | 32.71   |      |
| **Hemiplegia or paraplegia** |          |          |         |      |
| No                      | 5357     | 3088     | 36.57   | .001 |
| Yes                     | 725      | 168      | 19.86   |      |
| **Dementia**            |          |          |         |      |
| No                      | 6068     | 3232     | 34.75   | .051 |
| Yes                     | 12       | 24       | 66.67   |      |
| **Chronic obstructive pulmonary disease** |          |          |         |      |
| No                      | 5418     | 2785     | 33.95   | .048 |
| Yes                     | 662      | 471      | 41.57   |      |
| **Rheumatoid disease**  |          |          |         |      |
| No                      | 6040     | 3218     | 34.76   | .042 |
| Yes                     | 40       | 38       | 48.72   |      |
| **Peptic ulcer**        |          |          |         |      |
| No                      | 5986     | 3177     | 34.67   | .045 |
| Yes                     | 94       | 79       | 45.66   |      |
| **Mild liver disease**  |          |          |         |      |
| No                      | 5745     | 2935     | 33.81   | .001 |
| Yes                     | 335      | 321      | 48.93   |      |
| **Moderate/severe liver disease** |          |          |         |      |
| No                      | 6017     | 3144     | 34.32   | .001 |
| Yes                     | 63       | 112      | 44.6    |      |
| **Renal disease**       |          |          |         |      |
| No                      | 5869     | 3013     | 33.92   | .001 |
| Yes                     | 211      | 243      | 53.22   |      |
| **Diabetes**            |          |          |         |      |
| No                      | 5483     | 2864     | 34.31   | .317 |
| Yes                     | 597      | 392      | 39.64   |      |
| **Diabetes with complications** |          |          |         |      |
| No                      | 6011     | 3186     | 34.64   | .016 |
| Yes                     | 69       | 70       | 50.36   |      |
| **Cancer**              |          |          |         |      |
| No                      | 5777     | 2948     | 33.79   | .001 |
| Yes                     | 303      | 308      | 50.41   |      |
| **Metastatic cancer**   |          |          |         |      |
| No                      | 5968     | 3198     | 34.46   | .001 |
| Yes                     | 112      | 118      | 51.3    |      |
| **Acquired immunodeficiency syndrome, n (%)** |          |          |         |      |
| No                      | 6038     | 3223     | 34.8    | .001 |
| Yes                     | 42       | 33       | 44      |      |
| **PD: Cranial hemorrhage** |          |          |         |      |
| No                      | 5076     | 2842     | 35.89   | .001 |
| Yes                     | 1004     | 414      | 29.2    |      |
| **PD: Heart disease**   |          |          |         |      |
| No                      | 5417     | 2844     | 34.43   | .265 |
| Yes                     | 663      | 412      | 38.53   |      |
| **PD: Vein or artery occlusion** |          |          |         |      |
| No                      | 5743     | 2972     | 34.1    | .001 |
| Yes                     | 337      | 284      | 45.73   |      |
| **PD: Cranial or spine fracture** |          |          |         |      |
| No                      | 5527     | 3139     | 36.22   | .001 |
| Yes                     | 553      | 117      | 17.46   |      |
| **PD: Pulmonary disease or pneumonia** |          |          |         |      |
| No                      | 5841     | 3009     | 34      | .001 |
| Yes                     | 239      | 247      | 50.82   |      |
| **PD: Cancer**          |          |          |         |      |
| No                      | 5791     | 3003     | 34.15   | .001 |
| Yes                     | 289      | 253      | 46.68   |      |

P-value to assess differences in IHM using logistic regression adjusted by age and sex when appropriate.

IHM = in-hospital mortality, PD = primary diagnosis.
| Procedure                        | Live No  | Died No  | IHM 100 | P  |
|----------------------------------|----------|----------|---------|----|
| Thoracentesis                    | 5698     | 3138     | 34.73   | .176 |
| Pleural drainage tube            | 5409     | 2901     | 34.91   | .243 |
| Bronchoscopy                     | 5191     | 2737     | 34.52   | .019 |
| Transfusion                      | 4565     | 2177     | 32.29   | <.001 |
| Dialysis                         | 5646     | 2611     | 31.62   | <.001 |
| Tracheostomy                     | 3236     | 1757     | 35.19   | <.001 |
| Pressure ulcers                  | 5638     | 3078     | 35.31   | <.001 |
| Undergone surgery                | 1419     | 843      | 37.27   | <.001 |
| Emergency room admission         | 1099     | 615      | 35.88   | .560 |
| Readmission                      | 5684     | 2916     | 33.91   | <.001 |
| Septic shock                     | 5324     | 2191     | 29.16   | <.001 |
| Vascular organ failure           | 4815     | 1808     | 27.3    | <.001 |
| Respiratory organ failure        | 4305     | 1780     | 29.25   | <.001 |
| Neurological organ failure       | 1775     | 1476     | 45.4    | .01 |
| Hematologic organ failure        | 5763     | 2867     | 33.22   | <.001 |
| Hepatic organ failure            | 5947     | 3025     | 33.72   | <.001 |
| Renal organ failure              | 4915     | 1826     | 27.09   | <.001 |
| Pseudomonas                      | 5767     | 3049     | 34.62   | .159 |
| Other gram-negatives bacteria    | 5797     | 3079     | 34.69   | .160 |
| Klebsiella pneumoniae            | 5911     | 3155     | 34.8    | .270 |
| Staphylococcus aureus sensible to methicillin | 5985 | 3174 | 35 | .827 |
| Staphylococcus aureus resistant to methicillin | 185 | 30.71 | .905 |
| Candidiasis                      | 5934     | 3162     | 34.76   | .371 |
| Streptococcus pneumoniae         | 5935     | 3184     | 34.92   | .678 |
| Escherichia coli                 | 5971     | 3194     | 34.85   | .960 |
| Haemophilus influenzae           | 5960     | 3214     | 35.03   | .029 |
| Aspergilosis                     | 6042     | 3203     | 34.65   | <.001 |
| Non specified Streptococcus      | 6030     | 3240     | 34.95   | .151 |
| All species that increased IHM   | 5096     | 2622     | 33.97   | .004 |

P value to assess differences in IHM using logistic regression adjusted by age and sex.
IHM = in-hospital mortality.
*All pathogens exception made of Staphylococcus aureus sensible to methicillin, Streptococcus pneumoniae, Haemophilus influenzae, and nonspecified Streptococcus.
The relatively low part of methicillin-resistant \textit{Staphylococcus aureus} has to be pointed out as an element of European epidemiology during the last years that may be different elsewhere.

The low percentage of cases is surprising in which there is an isolated microorganism. It may be because the techniques used to obtain microbiologic specimens, such as bronchoscopy examinations, are not routinely performed in clinical practice, as it has been found in other studies.\cite{13}

IHM decreased over time among patients with a diagnosis of VAP in our study, despite the significant increase in mean number of acute organ failures during this period, which could be due to an improvement in the management of these patients over time. These data corroborate to previous studies. In a population-based cohort, the hospital mortality decreased significantly during a 7-year study period.\cite{13} Rosenberger et al\cite{35} also showed that mortality following an episode of VAP decreased over time and attributed this to advancements in pulmonary and general critical care rather than any specific interventions.

We found a higher mortality in males, in the elderly subgroups, in patients undergoing surgery, and in those with underlying diseases. In fact, CCI was independently associated with an increased risk of IHM in our study. Tseng et al\cite{36} also showed that high CCI, as well as high Sequential Organ Failure Assessment (SOFA) score, significantly affect hospital mortality in patients with VAP. The isolation of Aspergillus was also associated with increased IHM.

In our study of VAP patients, IHM was higher when principal diagnosis was occlusion of a vessel, pulmonary disease, or cancer. Malignancy has also been reported as a prognostic indicator of hospital mortality in a recent study.\cite{37} Patients with cancer are at a high risk of infections and subsequent complications. Identified risk factors for VAP in cancer patients include age (≥65 years), surgery, and tracheostomy.\cite{38} On the contrary, IHM was lower when principal diagnosis was cranial hemorrhage or cranial or spinal fracture. Cinotti et al\cite{39} found that among patients suffering from subarachnoid hemorrhage, longer ICU stay and time with mechanical ventilation increased the risk of VAP, but not of mortality.

Other factor independently associated with IHM mortality among patients hospitalized with VAP in the present study was emergency room admission. Prior reports that have examined the effect of boarding on intensive care unit outcomes, including VAP, have found an association between increased emergency department LOHS with poor outcome.\cite{40,41} Thus, for example, it has been demonstrated that in blunt trauma patients who are emergently intubated, increased emergency department length of stay is an independent risk factor for pneumonia. VAP interventions, successful in the intensive care unit, should be implemented early in the hospital course, and efforts should be made to minimize hospital crowding and emergency department length of stay.\cite{40}

Readmission increases the risk of IHM after VAP in our population. In a retrospective case–control study, patients in the VAP group had a greater number of readmissions than the control group patients.\cite{42}

This study examines the impact of VAP across the Spanish health care system rather than at an institutional level. The strengths of our findings lie in the large sample size, the 5-year follow-up period, and the standardized methodology, which has been used to investigate VAP and its complications.\cite{7,42} Nevertheless, our study has some limitations. Our data source was the SNHDD, an administrative database that uses information the physician has included in the discharge report. Administrative data can be inaccurate for detection of hospital-acquired infections, including VAP. A systematic review by Goto et al\cite{16} included 2 studies for VAP and both reported low to moderate sensitivity (42%–72%) and moderate to high specificity (82%–92%). It is unclear how this may affect the results of the study. Regardless, as the methodology has remained stable, the results of this study may still provide valuable insights.

% of 4,138 patients.\cite{17} In addition, VAP caused by PA has been associated with higher case fatality rates than that by other bacteria.\cite{14}

The relatively low part of methicillin-resistant \textit{Staphylococcus aureus} has to be pointed out as an element of European epidemiology during the last years that may be different elsewhere.

The low percentage of cases is surprising in which there is an isolated microorganism. It may be because the techniques used to obtain microbiologic specimens, such as bronchoscopy examinations, are not routinely performed in clinical practice, as it has been found in other studies.\cite{13}

IHM decreased over time among patients with a diagnosis of VAP in our study, despite the significant increase in mean number of acute organ failures during this period, which could be due to an improvement in the management of these patients over time. These data corroborate to previous studies. In a population-based cohort, the hospital mortality decreased significantly during a 7-year study period.\cite{13} Rosenberger et al\cite{35} also showed that mortality following an episode of VAP decreased over time and attributed this to advancements in pulmonary and general critical care rather than any specific interventions.

We found a higher mortality in males, in the elderly subgroups, in patients undergoing surgery, and in those with underlying diseases. In fact, CCI was independently associated with an increased risk of IHM in our study. Tseng et al\cite{36} also showed that high CCI, as well as high Sequential Organ Failure Assessment (SOFA) score, significantly affect hospital mortality in patients with VAP. The isolation of Aspergillus was also associated with increased IHM.

In our study of VAP patients, IHM was higher when principal diagnosis was occlusion of a vessel, pulmonary disease, or cancer. Malignancy has also been reported as a prognostic indicator of hospital mortality in a recent study.\cite{37} Patients with cancer are at a high risk of infections and subsequent complications. Identified risk factors for VAP in cancer patients include age (≥65 years), surgery, and tracheostomy.\cite{38} On the contrary, IHM was lower when principal diagnosis was cranial hemorrhage or cranial or spinal fracture. Cinotti et al\cite{39} found that among patients suffering from subarachnoid hemorrhage, longer ICU stay and time with mechanical ventilation increased the risk of VAP, but not of mortality.

Other factor independently associated with IHM mortality among patients hospitalized with VAP in the present study was emergency room admission. Prior reports that have examined the effect of boarding on intensive care unit outcomes, including VAP, have found an association between increased emergency department LOHS with poor outcome.\cite{40,41} Thus, for example, it has been demonstrated that in blunt trauma patients who are emergently intubated, increased emergency department length of stay is an independent risk factor for pneumonia. VAP interventions, successful in the intensive care unit, should be implemented early in the hospital course, and efforts should be made to minimize hospital crowding and emergency department length of stay.\cite{40}

Readmission increases the risk of IHM after VAP in our population. In a retrospective case–control study, patients in the VAP group had a greater number of readmissions than the control group patients.\cite{42}

This study examines the impact of VAP across the Spanish health care system rather than at an institutional level. The strengths of our findings lie in the large sample size, the 5-year follow-up period, and the standardized methodology, which has been used to investigate VAP and its complications.\cite{7,42} Nevertheless, our study has some limitations. Our data source was the SNHDD, an administrative database that uses information the physician has included in the discharge report. Administrative data can be inaccurate for detection of hospital-acquired infections, including VAP. A systematic review by Goto et al\cite{16} included 2 studies for VAP and both reported low to moderate sensitivity (42%–72%) and moderate to high specificity (82%–92%). It is unclear how this may affect the results of the study. Regardless, as the methodology has remained stable, the results of this study may still provide valuable insights.

\begin{table}
\centering
\caption{Factors independently associated with in-hospital mortality among patient hospitalized who suffered a ventilator-associated pneumonia in Spain, 2010–2014.}
\begin{tabular}{lll}
\hline
 & Odds ratio (OR) & 95\% CI \\
\hline
Sex & & \\
Female & 1 & \\
Male & 1.16 & (1.05–1.28) \\
Age group, y & & \\
<25 & 1 & \\
25–34 & 1.15 & (0.80–1.65) \\
35–44 & 1.51 & (1.10–2.07) \\
45–54 & 2.02 & (1.51–2.70) \\
55–64 & 3.11 & (2.35–4.13) \\
65–74 & 4.12 & (3.12–5.44) \\
75–84 & 6.14 & (4.64–8.14) \\
≥85 & 3.82 & (2.50–5.84) \\
Charlson comorbidity index & & \\
1 & 1.00 & (1.04–1.15) \\
2 & 0.80 & (0.69–0.91) \\
3 & 1.48 & (1.24–1.77) \\
4 & 0.57 & (0.46–0.77) \\
5 & 1.81 & (1.49–2.21) \\
6 & 1.52 & (1.24–1.86) \\
Undergone surgery & 1.14 & (1.02–1.28) \\
Emergency room admission & 1.15 & (1.03–1.31) \\
Readmission & 1.45 & (1.23–1.71) \\
Year & 0.95 & (0.92–0.98) \\
\hline
\end{tabular}
\end{table}

OR obtained using logistic regression adjusted by all study variables significantly in the bivariable analysis. Only those with significant ORs are shown. 95\% CI = 95\% confidence interval, PD = primary diagnosis.
constant throughout the study, we consider that changes detected over time are valuable. Furthermore, as the database does not include dates for diagnosis or procedures, it fails to establish a temporal relationship between the procedures, surgeries, septic shock, and pressure ulcers in the patients with VAP. Also, it is not possible to determine whether comorbidities were already present when the patient was admitted or may have appeared during the hospital stay. However, it is logical to think that chronic conditions (i.e., diabetes, COPD, etc.) were present by the time of admission. Finally, our findings are limited by the lack of data, including, among others, severity of illness, antimicrobial therapy, specimen quality, and length of stay in the intensive care unit. These and other factors that may influence in VAP outcomes could not be analyzed.

In addition, we cannot identify whether changes in the use of strategies to prevent VAP during the study period may have had an influence on the results.

The study is limited by the fact that if a patient was admitted in the same year twice or more times, this event could not be detected; this is a consequence of the anonymity of the database. Furthermore, if a patient is transferred from one to another hospital, it would also be counted as 2 different admissions. However, the SNHDD has proved to be useful for epidemiological investigation, covers over 98% of hospital admission in Spain, and the Ministry of Health conducts periodical audits to warrant its validity.\(^{[17,43]}\) The code for VAP was first used in the SNHDD in 2010, so some underreporting in the first years could be expected.

In conclusion, this study shows that the incidence of VAP among hospitalized patients has decreased in Spain from 2010 to 2014. The IHM has also decreased over the study period. These results indicate that both prevention and management of VAP have probably got better in Spain during the study period.

Acknowledgment

We would like to thank the Spanish Ministry of Health and Social Policy for providing the records of the SNHDD.

References

[1] Shirpit P, Meirson M, Mendelson G, et al. Intervention to reduce ventilator-associated pneumonia in individuals on long-term ventilation by introducing a customized bundle. J Am Geriatr Soc 2013;61:2089–93.
[2] Kilic AC, Meteysky ML, Kompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:375–82.
[3] Dudek MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network report, data summary for 2011, device-associated module. Am J Infect Control 2013;41:286–300.
[4] Dudek MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. Am J Infect Control 2011;39:798–816.
[5] Wang Y, Eldfudge N, Meteysky ML, et al. National trends in patient safety for four common conditions, 2005-2011. N Engl J Med 2014;370:341–51.
[6] Muscedere JG, Day A, Heyland DK, et al. Attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis 2010;51 (Suppl 1):SI20–5.
[7] Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol 2012;33:250–6.
[8] American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171:388–416.
[9] Melsen WG, Rovers MM, Koeman M, et al. Estimating the attributable mortality of ventilator-associated pneumonia from randomised prevention studies. Curr Care Med 2011;39:2736–42.
[10] Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013;13:665–71.
[11] Chittawatanarak K, Jaapakdee W, Chotirosniramit N, et al. Microbiological, resistance patterns, and risk factors of mortality in ventilator-associated bacterial pneumonia in a Northern Thai tertiary-care university hospital based general surgical intensive care unit. Infect Drug Resist 2014;7:203–10.
[12] Zuschneid I, Schwab F, Geffers C, et al. Trends in ventilator-associated pneumonia rates within the German nosocomial infection surveillance system (KISS). Infect Control Hosp Epidemiol 2007;28:314–8.
[13] Ding S, Kikikaya O, Senkal S, et al. Temporal trends of ventilator-associated pneumonia incidence and the effect of implementing health-care bundles in a suburban community. Chest 2013;144:1461–8.
[14] Aggazzotti G, Ferrari E, Giovannazi C, et al. Trends in ventilator-associated pneumonia: impact of a ventilator care bundle in an Italian tertiary care hospital intensive care unit. Am J Infect Control 2014;42:1312–6.
[15] Choi JY, Kwak YG, Yoo H, et al. Trends in the incidence rate of device-associated infections in intensive care units after the establishment of the Korean Nosocomial Infections Surveillance System. J Hosp Infect 2015;91:28–34.
[16] Goto M, Ohl ME, Schweizer ML, et al. Accuracy of administrative code data for the surveillance of healthcare-associated infections: a systematic review and meta-analysis. Clin Infect Dis 2014;58:688–96.
[17] Instituto Nacional de Gestión Sanitaria, Ministerio de Sanidad, Servicios Sociales e Igualdad. Spanish National Hospital Discharge Database. Conjunto Mínimo Básico de Datos, Hospitales del INSALUD. Available at: http://www.ingesa.msc.es/estadEstudios/dokuPublica/CMBD2001. htm. Accessed September 6, 2016.
[18] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[19] Jiménez Trujillo J, Jiménez-Garza R, de Miguel-Díez J, et al. Incidence, characteristic and outcomes of ventilator-associated pneumonia among type 2 diabetes patients: an observational population-based study in Spain. Eur J Intern Med 2017;40:72–8.
[20] Instituto Nacional de Estadística. Population Estimates 2010. Available at: www.ine.es. Accessed September 6, 2016.
[21] El-Saed A, Al-Jardani A, Althaqaaf A, et al. Ventilator-associated pneumonia rates in critical care units in 3 Arabian Gulf countries: a 6-year surveillance study. Am J Infect Control 2016;44:794–8.
[22] Ali Thaqaty MS, El-Saed A, Arabi YM, et al. Association of compliance of ventilator bundle with incidence of ventilator-associated pneumonia and ventilator utilization among critical patients over 4 years. Ann Thorac Med 2014;9:221–6.
[23] Pérez-Granda MJ, Muñoz P, Heras C, et al. Prevention of ventilator-associated pneumonia: can knowledge and clinical practice be simply assessed in a large institution? Respir Care 2013;58:1213–9.
[24] Ah HS, Khan FY, George S, et al. Epidemiology and outcome of ventilator-associated pneumonia in a heterogenous ICU population in Qatar. Biomed Res Int 2016;2016:8231787.
[25] Kaier K, Lambert ML, Frank UK, et al. Impact of availability of guidelines and active surveillance in reducing the incidence of ventilator-associated pneumonia in Europe and worldwide. BMC Infect Dis 2014;14:199.
[26] Rello J, Olleンドorff DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002;122:2115–21.
[27] Jaism F, De La Rosa G, Gómez E, et al. Incidence and risk factors for ventilator-associated pneumonia in a developing country: where is the difference? Respir Med 2007;101:762–7.
[28] Resende MM, Monteiro SG, Callegari B, et al. Epidemiology and outcomes of ventilator-associated pneumonia in northern Brazil: an analytical descriptive prospective cohort study. BMC Infect Dis 2013;13:119.
[29] Bonten MJ, Kollef MH, Hall JB. Risk factors for ventilator-associated pneumonia: from epidemiology to patient management. Clin Infect Dis 2004;38:1141–9.
[30] Heredia-Rodríguez M, Peláez MT, Fierro J, et al. Impact of ventilator-associated pneumonia on mortality and epidemiological features of patients with secondary peritonitis. Ann Intensive Care 2016;6:34.
[31] Tumbarello M, De Pascale G, Trecaichem EM, et al. Clinical outcomes of Pseudomonas aeruginosa pneumonia in intensive care unit patients. Intensive Care Med 2013;39:682–92.
[32] Micek S, Johnson MT, Reichley R, et al. An institutional perspective on the impact of recent antibiotic exposure on length of stay and hospital costs for patients with gram-negative sepsis. BMC Infect Dis 2012;12:56.
[33] Kollef MH, Chastre J, Fagon JY, et al. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to Pseudomonas aeruginosa. Crit Care Med 2014;42:2378–87.
[34] Tsay TB, Jiang YZ, Hsu CM, et al. Pseudomonas aeruginosa colonization enhances ventilator-associated pneumonia-induced lung injury. Respir Res 2016;17:101.
[35] Rosenberger LH, Hranjec T, McLeod MD, et al. Improvements in pulmonary and general critical care reduces mortality following ventilator-associated pneumonia. J Trauma Acute Care Surg 2013;74:568–74.
[36] Tseng CC, Liu SF, Wang CC, et al. Impact of clinical severity index, infective pathogens, and initial empiric antibiotic use on hospital mortality in patients with ventilator-associated pneumonia. Am J Infect Control 2012;40:648–52.
[37] Inchai J, Pothirat C, Liwsrisakun C, et al. Ventilator-associated pneumonia: epidemiology and prognostic indicators of 30-day mortality. Jpn J Infect Dis 2015;68:181–6.
[38] Park SA, Cho SS, Kwak GJ. Factors influencing ventilator-associated pneumonia in cancer patients. Asian Pac J Cancer Prev 2014;15:5787–91.
[39] Cinotti R, Dordonnat-Moynard A, Feuillet F, et al. Risk factors and pathogens involved in early ventilator-acquired pneumonia in patients with severe subarachnoid hemorrhage. Eur J Clin Microbiol Infect Dis 2014;33:823–30.
[40] Carr BG, Kaye AJ, Wiebe DJ, et al. Emergency department length of stay: a major risk factor for pneumonia in intubated blunt trauma patients. J Trauma 2007;63:9–12.
[41] Chalfin DB, Trzeciak S, Likourezos A, et al. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. Crit Care Med 2007;35:1477–83.
[42] Yang CC, Shih NC, Chang WC, et al. Long-term medical utilization following ventilator-associated pneumonia in acute stroke and traumatic brain injury patients: a case-control study. BMC Health Serv Res 2011;11:289.
[43] Ribera A, Marsal JR, Freire-González I, et al. Predicting in-hospital mortality with coronary bypass surgery using hospital discharge data: comparison with a prospective observational study. Rev Esp Cardiol 2008;61:843–52.