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ORIGINAL ARTICLE

Retrospective Study

Ventilator-associated pneumonia in patients with cancer: Impact of multidrug resistant bacteria

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Author contributions: Cornejo-Juárez P designed, made the analysis and wrote the paper; González-Oros I and Mota-Catañeda P performed the research; Vilar-Compte D and Volkow-Fernández P supervised the report and made intellectual contributions.

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Abstract

BACKGROUND

Patients with cancer have several risk factors for developing respiratory failure requiring mechanical ventilation (MV). The emergence of multidrug resistant bacteria (MDRB) has become a public health problem, creating a new burden on medical care in hospitals, particularly for patients admitted to the intensive care unit (ICU).

AIM

To describe risk factors for ventilator-acquired pneumonia (VAP) in patients with cancer and to evaluate the impact of MDRB.

METHODS

A retrospective study was performed from January 2016 to December 2018 at a cancer referral center in Mexico City, which included all patients who were admitted to the ICU and required MV ≥ 48 h. They were classified as those who developed VAP versus those who did not; pathogens isolated, including MDRB. Clinical evolution at 60-d was assessed. Descriptive analysis was carried out; comparison was performed between VAP *vs* non-VAP and MDRB *vs* non-MDRB.

RESULTS

Two hundred sixty-three patients were included in the study; mean age was 51.9 years; 52.1% were male; 68.4% had solid tumors. There were 32 episodes of VAP with a rate of 12.2%; 11.5 episodes/1000 ventilation-days. The most frequent bacteria isolated were the following: *Klebsiella* spp. [*n* = 9, four were Extended-Spectrum Beta-Lactamase (ESBL) producers, one was Carbapenem-resistant (CR)]; *Escherichia coli* (*n* = 5, one was ESBL), and *Pseudomonas aeruginosa* (*n* = 8, two were

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CR). One Methicillin-susceptible *Staphylococcus aureus* was identified. In multivariate analysis, the sole risk factor associated for VAP was length of ICU stay (OR = 1.1; 95%CI: 1.03-1.17; *P* = 0.003). Sixty-day mortality was 53% in VAP and 43% without VAP (*P* = 0.342). There was not higher mortality in those patients with MDRB.

CONCLUSION
This study highlights the high percentage of Gram-negative bacteria, which allows the initiation of empiric antibiotic coverage for these pathogens. In this retrospective, single center, observational study, MDRB VAP was not directly linked to increased mortality at 60 days.

Key words: Ventilator-associated pneumonia; Cancer; Multidrug resistance bacteria; Mortality; Intensive care unit; Mechanical ventilation

Core tip: This is a retrospective study to evaluate the risk factors for ventilator-associated pneumoniae (VAP) in patients with cancer who are admitted at an intensive care unit and require mechanical ventilation for > 48 h. We emphasized in microbiology etiology, particularly multidrug resistant bacteria (MDRB). We included 263 patients during 2 year-period; 32 developed VAP, with a rate of 11.5 episodes/1000 ventilation-days. Gram-negative bacteria were isolated in 95% of cases, being the rate of MDRB 24.1%. Sixty-day mortality was 53% in VAP and 43% without VAP. There was not higher mortality in patients with MDRB.

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INTRODUCTION

The prognosis of malignancies has improved during recent decades, with an increase in overall survival[1,2]. However, patients with cancer have elevated risks of infections and potential complications related with treatment, particularly chemotherapy, central lines, extensive surgeries, and other factors that lead to higher morbidity and mortality[2]. Likewise, patients with cancer have several risk factors for developing respiratory failure related to infectious and non-infectious processes, such as pneumonia, lung thrombosis, sepsis, transfusion-related acute lung injury (TRALI), and lung edema[1]. Therefore, these patients sometimes require support with mechanical ventilation (MV) and admission to the intensive care unit (ICU). The development of Ventilator-Associated Pneumonia (VAP) is the most frequent ICU-acquired infection, occurring in 25%-30% of patients intubated for > 48 h, with an incremental proportional risk within the first 14 d of ventilation[3-5]. The estimated incidence of VAP range from 2-16 episodes per 1000 ventilator-days[5]. On the other hand, the emergence of multidrug resistant bacteria (MDRB) has become a public health problem, creating a new burden on medical care in hospitals, particularly for patients admitted to ICU[6].

The aim of this study was to describe the clinical characteristics, local pathogens included MDRB, risk factors, and outcomes in patients with cancer who develop VAP.

MATERIALS AND METHODS

We conducted a retrospective analysis of all patients admitted to the ICU who required MV for ≥ 48 h at the Instituto Nacional de Cancerología (INCan), a cancer referral center in Mexico City, from January 1st 2016 to December 31st, 2018.

Demographic and clinical data were recorded from the clinical electronic charts of the patients and included the following age; sex; body mass index (BMI); type of neoplasm; current status of cancer (recent diagnosis; complete or partial remission, progression, or relapse); Charlson Comorbidity Index; history of chemotherapy, radiotherapy, biologic drugs, recent hospitalization, or antimicrobials used (during the last 3 mo); Sequential Organ Failure Assessment score (SOFA) and Acute Physiology Age Chronic Health Evaluation (APACHE) II at ICU admission; indication for and days of MV; tracheostomy; bronchial culture or bronchioalveolar lavage; diagnosis of VAP; bacteria isolated that were classified as susceptible, MDRB, or extreme drug-resistant (XDR) bacteria; type and number of days of antimicrobials; length of hospitalization, length of ICU stay, and 60-d outcome.

Pneumonia was clinically suspected on the presence of new and/or progressive pulmonary infiltrates in a chest X-ray, along with two of the following criteria: Hyperthermia (≥ 38 °C) or hypothermia (≤ 36 °C); leukocytosis (≥ 12000/mL) or leucopenia (≤ 4000/mL), and purulent pulmonary secretions[7,8].

VAP was defined as pneumonia in a patient on mechanical ventilation for > 2 calendar days on the day of event, with day of ventilator placement being Day 1 and the ventilator was in place on the date of event of the day before[9]. In those patients who were admitted to the ICU with pre-existing pneumonia, the clinical worsening, and/or the appearance of new clinical data compatible with pneumonia criteria were considered to be redefined as VAP.

Endotracheal aspirate or sputum cultures together with blood cultures were performed on day one the ICU stay and later in the case of clinical deterioration or suspected pneumonia. Bronchial samples were taken by sterile aspiration through the endotracheal tube and inoculated on blood, MacConkey, Sabouraud, and chocolate agar. Bacterial identification was performed by Mass Spectrometry Especially Matrix-Assisted Laser Desorption and Ionization -Time of Flight- Mass Spectrometry (MALDI-TOF-MS; Microflex, United States). Antimicrobial susceptibility testing was performed by means of BD Automated Phoenix™ (United States) and by the Kirby-Bauer disk diffusion technique in the case of resistant strains (Clinical Laboratory Standards Institute. Microbiological data were collected from the patient's electronic clinical chart and from Microbiology Laboratory data including cultures from the lower respiratory tract (sputum, tracheal, bronchial aspirate, or bronchioalveolar lavage). Polymicrobial pneumonia was defined when more than one pathogen was identified. The presence of MDR/XDR pathogens was recorded and defined according to Magiorakos criteria[10].

Primary outcome was VAP development. Secondary outcome was clinical evolution at 60-d.

Statistical analysis

Descriptive analysis was carried out with mean ± SD or median [Interquartile range (IQR)]. The student *t*-test or the Mann-Whitney *U* test were used to compare continuous variables as appropriate. The χ^2 or Fisher exact test was utilized to compare categorical variables. Variables with *P* values of ≤ 0.3 in the univariate analysis were included in the multivariate analysis. A logistic regression model was performed for risk factors associated with VAP and for 60-day mortality. OR with 95%CI were calculated. *P* values of ≤ 0.05 were considered statistically significant. Data was analyzed using STATA (ver. 14) software. The study was approved by the INCan Institutional Review Board (REF/INCAN/CI/0922/2019).

RESULTS

Patient characteristics

During the study period, 736 patients were admitted to the ICU: 345 patients required MV for less than 48 h and 128 did not require intubation; 263 patients were included. Mean age was 51.9 ± 17.8 years; 188 (68.4%) were patients with solid tumors and there were 88 (31.8%) with hematologic malignancies; 123 (46.8%) were in cancer progression or relapse; eight patients had two different neoplasms. Other demographic and clinical data are shown in Table 1.

The main cause for MV was septic shock (*n* = 91, 34.6%), followed by post-surgical procedure (*n* = 42, 16%), pneumonia (*n* = 38, 14.5%), and hypovolemic shock (*n* = 37, 14.1%). The median length of MV was 8 d (IQR 4, 12 d).

Table 1 Clinical and demographic characteristics of all patients with mechanical ventilation during the study period (*n* = 263)

Characteristics, *n* (%)	Total (*n* = 263)	VAP (*n* = 32)	Non-VAP (*n* = 231)	*P* value
Age (yr)[1]	51.9 ± 17.8	49 ± 19.7	52.3 ± 17.5	0.329
Gender- Masculine	137 (52.1)	16 (50)	110 (47.6)	0.800
Body mass index[1]	26.2 ± 5.6	24.9 ± 4.5	26.4 ± 5.7	0.188
Solid tumor[2]	188 (68.1)	25 (67.6)	163 (68.2)	0.938
Cervical	21 (7.6)	2 (5.4)	19 (7.9)	0.749
Head and neck	21 (7.6)	3 (8.1)	18 (7.5)	1
Colon-rectum	20 (7.2)	1 (2.7)	19 (7.9)	0.492
Breast	18 (6.5)	2 (5.4)	16 (6.7)	1
Germinal	15 (5.4)	2 (5.4)	13 (5.4)	1
Esophagus-stomach	14 (5.1)	3 (8.1)	11 (4.6)	0.399
Sarcoma	13 (4.7)	2 (5.4)	11 (4.6)	0.688
Ovarian	10 (3.6)	1 (2.7)	9 (3.8)	1
Lung	10 (3.6)	1 (2.7)	9 (3.8)	1
Prostate	9 (3.3)	2 (5.4)	7 (2.9)	0.348
Liver and bile ducts	9 (3.3)	1 (2.7)	8 (3.3)	1
Pancreas	7 (2.5)	1 (2.7)	6 (2.5)	1
Kidney and bladder	5 (1.8)	2 (5.4)	3 (1.3)	0.136
Other	16 (5.8)	2 (5.4)	14 (5.9)	1
Hematological malignancies[2]	88 (31.9)	12 (32.4)	76 (31.8)	0.938
Lymphoblastic leukemia	26 (9.4)	3 (8.1)	23 (9.6)	1
Myeloid leukemia	12 (4.3)	3 (8.1)	9 (3.8)	0.207
Non-Hodgkin lymphoma	25 (9.1)	2 (5.4)	23 (9.6)	0.548
Hodgkin lymphoma	4 (1.5)	1 (2.7)	3 (1.2)	0.439
Multiple myeloma	14 (5.1)	2 (5.4)	12 (5)	1
Other[3]	7 (2.5)	1 (2.7)	6 (2.5)	1
Cancer stage				
Recent diagnosis	117 (44.5)	11(34.4)	105 (45.4)	0.236
Progression	93 (35.4)	16 (50)	78 (33.8)	0.07
Relapse	30 (11.4)	2 (6.2)	28 (12.1)	0.551
Partial remission	21 (8)	2 (6.2)	19 (8.2)	1
Complete remission	2 (0.7)	1 (3.1)	1 (0.4)	0.228
Chemotherapy within 3 mo	99 (37.6)	16 (50)	83 (35.9)	0.123
Radiotherapy during the previous 6 mo	23 (8.7)	3 (94)	20 (8.7)	0.749
Biologic antineoplastic drugs	22 (8.4)	6 (18.8)	16 (6.9)	0.155
Charlson index	3 (2, 5)	3 (2, 5)	3 (2, 5)	1
Hospital admission within 3-mo period	75 (28.5)	5 (15.6)	70 (30.3)	0.09
Days of recent hospitalization[4]	7 (4,12)	5 (4,9)	7 (4,12)	0.544
Recent broad antimicrobials	36 (13.7)	1 (3.1)	35 (15.1)	0.09

[1]Median ± SD.
[2]Percentage was obtained from 276 patients because 13 patients had two different neoplasms (5 in VAP group and 8 in Non-VAP).
[3]Four had myelodysplastic syndrome, three had chronic leukemia.

[4]Median (Interquartile range). VAP: Ventilator-associated pneumonia.

Risk factors for VAP

There were 32 episodes of VAP; the rate was 12.2%, with an incidence of 11.5 episodes/1000 ventilation-days. Mean days of MV until VAP diagnosis was 13.1 ± 8.8. d (Table 2).

There was a statistically significant difference between median length of ICU stay in patients with VAP (18 d; IQR 9, 27) *vs* those without VAP (8 d; IQR 5, 12; $P < 0.001$). Also, there was a difference in median length of hospitalization (32 d for VAP; IQR 22, 57 d *vs* 21 d for non-VAP; IQR 14, 32; $P < 0.001$). Mean duration of MV was significantly longer in those who developed VAP (16 d; IQR 9, 27) *vs* those who did not (7 d; IQR 4, 11; $P < 0.001$). Data is shown in Table 2.

There were no differences between age, gender, solid or hematological neoplasm, recent chemotherapy, progression or relapse in those who developed VAP *vs* those who did not. The uni- and multivariate analysis is point in Table 3.

Pathogens

There were 42 bacteria identified in patients with VAP. In 16 (50%), only one pathogen was isolated, 11 were polymicrobial (seven cultures with two different pathogens, four with three), and five cultures were negative. The most frequent bacteria isolated were as follows: *Klebsiella* spp. ($n = 9$, 21.4%), four (44.4%) were Extended-Spectrum Beta-Lactamases (ESBL) producers, and one (11.1%) was Carbapenem-resistant (CR); *Escherichia coli* ($n = 5$, 11.9%), one (25%) was ESBL producer; Pse*udomonas aeruginosa* ($n = 8$, 19%), two (25%) were CR; and *Enterobacter* spp. ($n = 6$, 14.3%), among which none was resistant. There were two Gram-positive bacteria identified: one *Enterococcus faecalis* and one Methicillin-susceptible *Staphylococcus aureus* (MSSA) (Figure 1). The rate of MDRB was 24%. There were no differences when comparing MDRB *vs* susceptible, length of hospitalization, previous antibiotics, or days of MV. Patients with MDRB had a longer stay at the ICU (14.1 ± 11 d) *vs* patients with susceptible bacteria (10.1 ± 7.8 d; $P = 0.02$).

Patients who developed VAP more frequently received cephalosporins, carbapenems, Tazobactam/Piperacillin, Vancomycin, and fluoroquinolones; furthermore, the period of administration of carbapenems was longer (Table 4).

Risk factors for VAP

Univariate analysis comparing patients with VAP *vs* non-VAP revealed that tracheostomy and re-intubation were more frequent in VAP (27.9% *vs* 6.6%; $P < 0.001$, and 28% *vs* 10.6%; $P = 0.03$, respectively). Median length of hospitalization was longer for VAP *vs* non-VAP (32 d; IQR 21, 57 d *vs* 21 d *vs* IQR 14, 32; $P < 0.001$), in addition, the median length of ICU stay was 18 d (IQR 9, 27 *vs* 8 d *vs* IQR 5, 12; $P < 0.001$), and median days of MV was VAP 16 d (IQR 9, 27 *vs* non-VAP 7 d; IQR 4, 11; $P < 0.001$). In multivariate analysis, only length of ICU stay was found statistically significant (OR = 1.11; 95%CI: 1.06-1.17; $P < 0.001$)(Table 3).

Risk factors for mortality

One hundred sixteen patients (44.1%) died during the first 60 d: 17 (53%) with VAP *vs* 99 (43%) without VAP ($P = 0.342$). No differences were found between hematologic patients ($n = 42$, 47.7%), *vs* those with solid tumors ($n = 74$, 42.3%; $P = 0.401$). There was no difference in outcome in patients with MDRB ($P = 1$). Univariate and multivariate analysis demonstrated that a recent history of chemotherapy (OR = 2.16; 95%CI: 1.24-3.76) and tracheostomy (OR = 2.52; 95%CI: 1.24-5.13) were predictive risk factors for 60-d mortality (Table 5).

DISCUSSION

This study sought to describe the characteristics of patients with cancer admitted to the ICU who required MV and developed VAP, analyzing risk factors for 60-d mortality.

It is important to note that almost two thirds of the patients had a solid tumor and one third had received chemotherapy within the last 3 mo. It is relevant to highlight that 46.8% of patients were on cancer relapse or progression, because policies in our

Table 2 Clinical data related with current hospitalization and mechanical ventilation (*n* = 263)

Characteristic – *n* (%)	Total (*n* = 263)	VAP (*n* = 32)	Non-VAP (*n* = 231)	*P* value
Length of hospitalization (d)[1]	22 (14, 34)	32 (22, 57)	21 (14, 32)	0.0001
Length of ICU stay (d)[1]	8 (5, 13)	18 (9, 27)	8 (5, 12)	< 0.0001
Causes for MV				
Septic shock	91 (34.6)	10 (31.3)	81 (35)	0.843
Post-surgical procedure	42 (16)	8 (25)	34 (14.7)	0.193
Respiratory failure secondary to pneumonia	37 (14)	3 (9.4)	34 (14.7)	0.589
Hypovolemic shock	37 (14)	8 (25)	29 (12.5)	0.09
Neurologic cause	13 (4.9)	0	13 (5.6)	N/A
Lung tumor activity	7 (2.7)	1 (3.1)	6 (2.6)	0.601
Post-CPR	7 (2.7)	1 (3.1)	6 (2.6)	0.601
Acute pulmonary edema	6 (2.3)	0	6 (2.6)	N/A
Malignant central airway obstruction	5 (1.9)	0	5 (2.2)	N/A
Cardiac failure	3 (1.1)	1 (3.1)	2 (0.8)	0.323
Bronchospasm	2 (0.8)	0	2 (0.8)	N/A
Pulmonary embolism	2 (0.8)	0	2 (0.8)	N/A
TRALI	1 (0.4)	0	1 (0.4)	N/A
Other causes	10 (3.8)	0	10 (4.3)	N/A
SOFA at ICU admission[2]	8.3 ± 3.4	8.7 ± 2.8	8.3 ± 3.4	0.477
Days of mechanical ventilation[1]	8 (4, 12)	16 (9, 27)	7 (4, 11)	< 0.0001
Tracheostomy	68 (25.9)	19 (59.4)	49 (21.2)	< 0.0001
Re-intubation	27 (10.3)	7 (21.9)	20 (8.7)	0.03
Mortality at 60 d	116 (44.1)	9 (28.1)	72 (31.7)	0.839

[1]Median (Interquartile range).
[2]mean ± SD. CPR: Cardiopulmonary resuscitation; N/A: Not applicable; TRALI: Transfusion-related acute lung injury; ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment score; MV: Mechanical ventilation; VAP: Ventilator-associated pneumonia.

hospital include the admission at the ICU of patients who have an expectation of survival more than 3 mo, an adequate functional state, and if they are receiving the first or second line of neoplastic treatment even if they are not in remission. Regarding the risk factors analyzed in relation to cancer such as solid tumor *vs* hematological, clinical stage of cancer, or recent chemotherapy, there was no relationship with the development of VAP. The median of Charlson Comorbidity Index was 3 for the whole group, that corresponds to one-year mortality rate of 52%. SOFA index was less than 10 in all patients, without differences between VAP *vs* non-VAP, that indicates between one or two organ failures, and a mortality percentage between 10% and 25%.

The incidence of VAP varies among different series, the latter related to the characteristics of ICU and type of hospitals, and ranges between 2.1 and 24.5 cases/1000 ventilator-days[4,11]. Specifically, a study performed in patients with cancer, VAP was reported in 42/1000 ventilator-days[11]. The incidence we found in this study was 12.2% and 11.5 cases/1000 ventilator-days, lower than those reported in these previous studies[4,11].

VAP is associated with longer hospital and ICU stays, higher hospital-related costs, and greater in-hospital mortality[4]. We also described longer ICU and hospital stays and more days of MV in patients with VAP, more often requiring tracheostomy and re-intubation. These findings would be explained by effect-cause bias, because patients with VAP are patients who are more difficult to extubate, they require a tracheostomy more frequently, more days of antibiotics, and this leads to more days of hospitalization. An important finding in this study was that patients with VAP more frequently received broad-spectrum antibiotics (particularly cephalosporins,

Table 3 Univariate and multivariate analysis for ventilator-associated pneumonia in patients with mechanical ventilation (*n* = 263)

Characteristics	Univariate			Multivariate	
	NAV (*n* = 32)	No-NAV (*n* = 231)	*P* value	OR	*P* value
Female	16 (50)	121 (52.4)	0.8	-	
Male	16 (50)	110 (47.6)			
Age < 60 yr	21 (65.6)	134 (58)	0.411	-	
Age ≥ 60 yr	11 (34.4)	97 (42)			
Solid tumor	12 (37.5)	76 (32.9)	0.605	-	
Hematologic malignancy	20 (62.5)	155 (67.1)			
Recent diagnosis, complete or partial remission	14 (43.8)	125 (54.1)	0.271	1	0.541
Progression or relapse	18 (56.2)	106 (45.9)		1.3 (0.55 - 3.03)	
Non-recent chemotherapy	16 (50)	148 (64.1)	0.123	1	0.727
Recent chemotherapy	16 (50)	83 (35.9)		1.16 (0.49-2.76)	
SOFA at ICU admission	8.71 ± 2.79	8.26 ± 3.42	0.477	-	
Days of hospitalization length[1]	32 (22, 57)	21 (14, 32)	0.0001	1	0.301
				1 (0.99- 1.01)	
Days of ICU length[1]	18 (9, 27)	8 (5, 12)	< 0.0001	1	< 0.0001
				1.11 (1.06-1.17)	
Alive	10 (31.2)	122 (52.8)	0.02	1	0.125
Death	22 (68.8)	109 (47.2)		2.04 (0.82-5.12)	

[1]Median (Interquartile range). ICU: Intensive care unit.

Tazobactam/Piperacillin, carbapenems, and Vancomycin). It is noteworthy that frequent causes for ICU admission were septic shock and respiratory failure secondary to pneumonia; thus, broad-spectrum antibiotics are usually initiated empirically in these patients.

Some studies have described Gram-negative bacilli as the most common group of VAP-associated pathogens, accounting for over 50% of cases; *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, in addition to *S. aureus*[4,12]. We found that 95% of Gram-negative bacteria in this series were *Klebsiella* spp., *P. aeruginosa*, *Enterobacter* spp., and *E. coli* the most common pathogens. It is important to emphasize that there were only two Gram-positive bacteria identified. Additionally, we found that 34.3% of the infections were polymicrobial, similar to 40% reported in other studies[3].

Likewise, an increase has been described in the isolation of Gram-negative MDRB strains in patients with VAP[13]. Nevertheless, we identified only 21.4% of MDRB strains as follows: ESBL-*Klebsiella* spp. in 44.4%; ESBL-*E. coli* in 25%; *P. aeruginosa* CR in 25%, and *Klebsiella* spp. in 11.1%. The rate of MDRB described in this study was similar to that which we have previously reported in health care-associated infections in the same ICU during 2013 and 2014 (24%)[14]. The National Healthcare Surveillance Network in the United States in 2014 found the following higher rates of MDR in patients with VAP: 37% of Methicillin-resistant *S. aureus* (MRSA); 31.1% CR-*P. aeruginosa*, and 14% CR-*Klebsiella pneumoniae*. A study performed to assess the microbiological profile and MDR Gram-negative bacteria in the ICU during 2010-2011, showed *Citrobacter* and K. pneumoniae as the most common isolated pathogens, with a high prevalence of carbapenemase- producing bacteria (48%)[15], considerably higher than the results found in our study.

MDRB strains have been related with widespread use of antimicrobials, prolonged use of MV, longer length of hospitalization, and prior antibiotic therapy[12]. In this study, only longer ICU stay was more frequent in patients with these bacteria (*P* = 0.02).

Sixty-day mortality was reported in 44.1% (48.8% in hematological and 43.4% in patients with solid tumors; *P* = 0.457). In a previous study performed in the same ICU, the mortality rate for patients with MV was 34.4% (73% for hematological patients and

Table 4 Use of antimicrobials in patients with ventilator-associated pneumonia *vs* those who did not develop the latter

Antimicrobial treatment	Total (*n* = 263)	Non-VAP (*n* = 233)	VAP (*n* = 30)	*P* value
Antibacterial treatment				
Cephalosporins	58 (22)	47 (20.2)	11 (36.7)	0.03
Days of cephalosporins[12]	6 (4, 9)	6 (4, 9)	4 (4, 10)	0.856
TZP	86 (32.6)	69 (29.6)	17 (56.7)	0.002
Days of TZP[2]	6 (4, 9)	7 (4, 9)	6 (5, 7)	0.895
Aminoglycosides	18 (6.8)	14 (6)	4 (13.3)	0.134
Days of aminoglycosides[2]	4 (3, 6)	3 (3, 5)	5 (4, 7)	0.469
Carbapenem	228 (86.7)	198 (85)	30 (100)	0.02
Days of Carbapenem[2]	11 (7, 17)	10 (6, 16)	13 (10, 22)	0.003
Fluoroquinolones	31 (11.8)	23 (9.9)	8 (26.7)	0.006
Days of fluoroquinolones[2]	10 (7, 14)	11 (7, 14)	9 (5, 15)	0.586
Vancomycin	153 (58.2)	130 (55.8)	24 (80)	0.01
Days of vancomycin[2]	7 (4, 10)	7 (4, 10)	7 (4, 10)	0.684
Linezolid	47 (17.8)	39 (16.7)	8 (26.7)	0.205
Days of linezolid[2]	9 (5, 12)	8 (4, 11)	14 (8, 21)	0.05
Clarithromycin	68 (25.8)	59 (25.3)	9 (30)	0.657
Days of clarithromycin[2]	8 (7, 10)	8 (6, 10)	8 (8,10)	0.505
SMX/TMP	68 (25.8)	56 (24)	12 (40)	0.06
Days of SMX/TMP[2]	8 (5, 13)	12 (7, 21)	12 (8, 14)	0.577
Colistin	11 (4.2)	7 (3)	4 (13.3)	0.02
Days of colistin[2]	10 (4, 11)	8 (3, 11)	11 (8, 12)	0.341

[1]Third-generation.
[2]Median (Interquartile range). TZP: Piperacillin/tazobactam; VAP: Ventilator-associated pneumonia.

34.3% for patients with solid tumors)[16], this lower mortality can be related because, in the last study, we included all patients with MV, regardless of ventilation time.

Bundle implementation reduces the rate of VAP; this is the most efficacious measure when compliance rates are high, and includes education and training, hand hygiene, head positioning (> 30º), cuff- pressure maintenance, avoidance of elective changes of circuits, humidifiers, and endotracheal tubes, oral chlorhexidine gluconate, aspiration of subglottic secretions, selective decontamination of the oropharynx tract, and a short course of systemic antibiotics during the intubation of patients with previous decreased consciousness[17,18]. In our hospital, the previous measures, except for the last two, are performed routinely; adherence to prevention bundles is monitored by a nurse from the Infection Control Department who is assigned to the ICU. In addition to the latter prevention measures, enhancing antimicrobial stewardship programs is a simple and cost-effective way to improve clinical outcomes, maintaining quality of care and contributing to the decrease of VAP episodes[19].

There are some imitations of this study. First, it was retrospective, and second was conducted at only one center, it could have the bias inherent to this type of design. However, the hospital is one of the biggest in the region, and the number of patients treated each year is also large. Third, the number of episodes of VAP were not many, which could have influenced not to find significant differences in some of the risk factors studied. On the other hand, the study's main strength is the example of how a study such as the one we present, contributes to reinforcing policies of antimicrobial stewardship within a hospital tailored by the results.

In conclusion, the rate of VAP was similar to that reported in other studies conducted in immunosuppressed patients. However, it is important to highlight the elevated percentage of Gram-negative bacteria as a cause of pneumonia, which permits beginning empiric antibiotic coverage for these pathogens, without the need to

Table 5 Univariate and multivariate analysis for 60-d mortality in patients with mechanical ventilation (*n* = 263)

Characteristics	Univariate			Multivariate	
	Alive (*n* = 147)	Death (*n* = 116)	*P* value	OR	*P* value
Female	79 (53.7)	58 (50)	0.546	-	
Male	68 (46.3)	58 (50)			
Age < 60 yr	83 (56.5)	72 (62.1)	0.358	-	
Age ≥ 60 yr	64 (43.5)	44 (37.9)			
Solid tumor	101 (68.7)	74 (63.8)	0.401	-	
Hematologic malignancy	46 (31.3)	42 (36.2)			
Recent diagnosis, complete or partial remission	85 (57.8)	54 (46.6)	0.069	1	0.237
Progression or relapse	62 (42.2)	62 (53.4)		1.38 (0.81-2.37)	
Non-recent chemotherapy	103 (70.1)	61 (52.6)	0.003	1	0.006
Recent chemotherapy	44 (29.9)	55 (47.4)		2.16 (1.24-3.76)	
SOFA at ICU admission	8.45 ± 3.45	8.15 ± 3.2	0.471	-	
Non-tracheostomy	115 (78.2)	80 (69)	0.088	1	0.01
Required tracheostomy	32 (21.8)	36 (31)		2.52 (1.24-5.13)	
Days of ICU length	8 (6, 13)	8 (5, 15)	0.457	-	
Days of mechanical ventilation	7 (4, 11)	9 (5, 14)	0.029	1	0.15
				1.04 (1.008-1.07)	
Non-VAP	132 (89.8)	99 (85.3)	0.342	-	
VAP	15 (10.2)	17 (14.7)			

ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment score; VAP: Ventilator-acquired pneumonia.

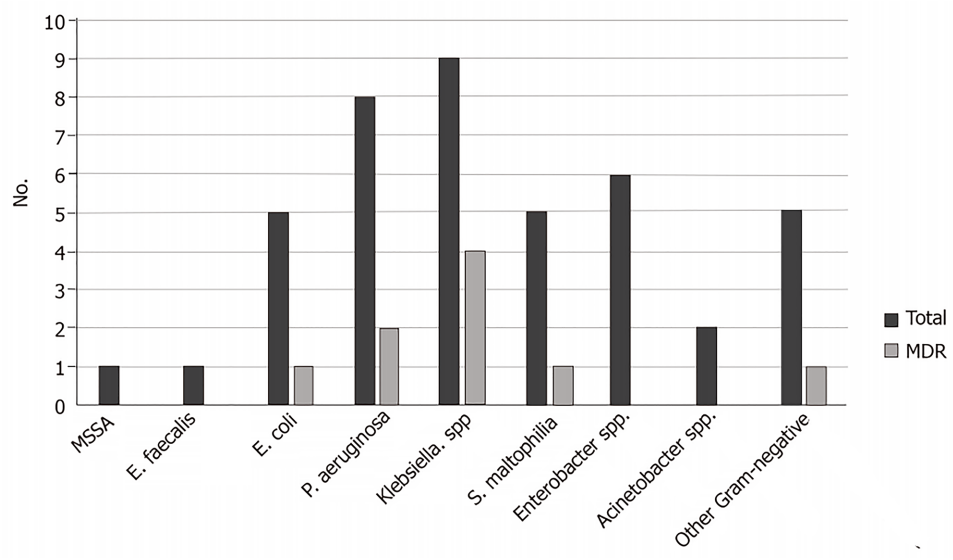

Figure 1 Pathogens isolated from patients with ventilator-acquired pneumonia in patients with cancer including multidrug resistant bacteria. MDR: Multidrug resistant.

cover Gram-positive bacteria, particularly Vancomycin for Methicillin-resistant *S. aureus*. In this retrospective, single center, observational study, MDRB VAP was not directly linked to increased mortality at 60 d.

ARTICLE HIGHLIGHTS

Research background

Patients with cancer have several risk factors for developing respiratory failure requiring mechanical ventilation (MV). The emergence of multidrug resistant bacteria (MDRB) has become a public health problem, creating a new burden on medical care in hospitals, particularly for patients admitted to the intensive care unit (ICU).

Research motivation

To establish and/or modify guidelines for the initiation of empirical antimicrobial treatment in cancer patients who develop VAP.

Research objectives

To describe in the patient with cancer which are the risk factors for developing ventilator-acquired pneumonia, and if there is a higher incidence of episodes secondary to multidrug-resistant bacteria.

Research methods

A retrospective study carried out over a two-year period, that included all patients with mechanical ventilation who were admitted to the ICU, and we analyzed those who developed an episode of VAP and the bacteria involved.

Research results

Two hundred sixty-three patients were included; two thirds with a solid tumor. There were 32 episodes of VAP; 11.5 episodes/1000 ventilation-days. Gram-negative bacteria were involved in 95%of cases, 24% were MDRB. There were no differences in mortality between those patients with VAP *vs* non-VAP, neither when MDRB *vs* non-MDRB were compared. Length of ICU was documented as risk factor for VAP. Recent chemotherapy and tracheostomy were predictive risk factors for 60-d mortality.

Research conclusions

The rate of VAP was similar to that reported in other studies. We described an elevated percentage of Gram-negative bacteria as a cause of pneumonia, which permits beginning empiric antibiotic coverage for these pathogens. MDRB were found in a quarter of the episodes, and were not linked to increased mortality at 60 d.

Research perspectives

To perform a monitoring for a longer period of time will allow evaluating the evolution of bacterial resistance, and establishing whether, with a greater number of cases, it can impact the mortality of these patients.

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