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The impact of hospital-acquired infections with multidrug-resistant bacteria in an oncology intensive care unit

P. Cornejo-Juárez [a,*], D. Vilar-Compte [a], C. Pérez-Jiménez [a], S.A. Ñamendys-Silva [b], S. Sandoval-Hernández [a], P. Volkow-Fernández [a]

[a] Department of Infectious Disease, Instituto Nacional de Cancerología, Av. San Fernando No. 22, Col. Sección XVI, Tlalpan, 14080 México, D.F., Mexico
[b] Department of Critical Care Medicine, Instituto Nacional de Cancerología, Mexico City, Mexico

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SUMMARY

Objective: To describe overall site-specific hospital-acquired infection (HAI) rates and to describe the microbiological and antibiotic resistance profiles of infecting pathogens, together with their impact on multidrug-resistant (MDR) bacteria-associated mortality.
Methods: We conducted a 5-year retrospective descriptive study of HAI in patients in the intensive care unit (ICU) of a cancer center in Mexico from January 2007 to December 2011. The following information was collected: patient characteristics and comorbidities, data related to the neoplasm and its treatment, microbiology, and the resistance pattern of all isolates.
Results: During the study period, 1418 patients were admitted to the ICU; 134 of them developed 159 infections, with an incidence of 11.2/100 hospitalized patients and 32.2/per 1000 patient-days. Two hundred sixty-six microorganisms were isolated. The overall prevalence of MDR-HAI was 39.5%. The most frequent organisms were as follows: 54 (20%) *Escherichia coli* (94.4% of these were extended-spectrum beta-lactamase producers), 32 (12%) *Staphylococcus aureus* (90.6% of these were methicillin-resistant), 32 (12%) *Enterococcus faecium* (18.7% of these were vancomycin-resistant), and 20 (6%) *Acinetobacter baumannii* (all were MDR). Among patients admitted to the ICU, 252 (17.8%) died. Death was related to the HAI in 58 (23%) of these patients ($p < 0.001$) and 51 (88%) had a MDR organism isolated ($p = 0.05$).
Conclusions: The emergence of MDR bacteria poses a difficult task for physicians, who have limited therapeutic options. Critically ill cancer patients admitted to the ICU are at major risk of a bacterial MDR-HAI that will impact adversely on mortality.

1. Introduction

Hospital-acquired infections (HAI) have been recognized for over a century as a critical problem affecting the quality of healthcare, and they constitute a major source of adverse healthcare outcomes.[1,2] 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 intensive care units (ICU).[1] In critical care units, there is extensive antimicrobial use, which imposes a selection pressure and promotes the emergence of MDRB.[1] In addition to this, ICU patients have an increased risk of infection due to their underlying diseases or conditions, impaired immunity, and exposure to multiple invasive devices (mechanical ventilation, central venous catheters (CVC), and urinary tract catheters).[1,3,4] The incidence of ICU-HAI is 5–10-times higher than HAI rates in general wards.[5] HAI in the ICU has been associated with increased morbidity, mortality, and costs.[1,6,7]

The aim of this study was to describe the incidence of HAI in an oncology ICU and to describe the microbiological and antibiotic resistance profiles of infecting pathogens, together with their impact on MDRB-associated mortality.

2. Methods

The National Cancer Institute of Mexico (INCan), located in Mexico City, is a 135-bed referral and teaching hospital for adult patients with cancer, with an average 170 000 medical visits per

* Corresponding author.
E-mail address: patcornejo@yahoo.com (P. Cornejo-Juárez).

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year. Each year 7500 hospital discharges, 1400 long-term indwelling CVC placements, 34 000 chemotherapy infusion sessions, and >3500 major surgery procedures are carried out. Efforts have been made to improve the outcome of cancer patients admitted to the six-bed medical and surgical ICU,[8] including better selection of patients and standardized care. Nonetheless, mortality trends have increased over the past years, in parallel with an increase in MDRB-HAI (Table 1).

We conducted a 5-year retrospective descriptive study of HAI in patients in the ICU, from January 2007 to December 2011. Data were obtained from ICU daily reports, infection control surveillance forms, microbiology laboratory reports, and patient medical charts. The following information was collected: patient characteristics and comorbidities, data related to the neoplasm and its treatment, microbiology, and the resistance pattern of all isolates. The Sequential Organ Failure Assessment (SOFA) score[9] at ICU admission and at detection of the infection, length of ICU stay, number of ventilator days, days of CVC placement, and urinary tract catheter days were also reviewed. HAI was defined using the Centers for Disease Control and Prevention criteria (CDC, 2008).[10]

Cultures were obtained from blood, urine, tracheo-bronchial secretions, and from any other site with a clinical suspicion of infection. Bacteria were cultured using standard microbiological methods. Antimicrobial susceptibility testing was performed using the automated BD Phoenix system (USA) and the Kirby–Bauer disk diffusion technique (Clinical Laboratory Standards Institute, CLSI).[11] Antimicrobial treatment was considered appropriate when the patient received an antibiotic to which the isolated bacteria were susceptible, during the first 24 h of clinical infection, and if the patient received this for ≥72 h.[12]

Infections occurring at more than one site in the same patient were reported as separate infection events, unless the same bacterium was isolated at the same time. The clinical outcome was assessed until hospital discharge or death. For the purposes of this investigation, death was classified as attributed to the HAI or as non-HAI infection-related according to the medical professional who certified the death, along with a clinical chart review by at least two of the authors of the current article.

MDRB included the following: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), and extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella spp*. *Pseudomonas aeruginosa*, *Acinetobacter spp*, and other Gram-negative bacteria were considered multidrug-resistant (MDR) if they showed resistance to fluoroquinolones, cephalosporins, and carbapenems.

Table 1
Hospital-acquired infections (HAI), overall mortality, and infection-related mortality in an intensive care unit (ICU)

Year	2007	2008	2009	2010	2011
HAI rate	8.6	8.9	11.5	9.5	17.4
Patients admitted to the ICU (*n*)	341	296	277	273	252
ICU overall mortality (%)	19	18	17	18	18
HAI mortality (%)	19	31	29	25	53
ICU stay, days, median (IQR)	4 (2–4)	2 (1–4)	2 (1–6)	3 (1–6)	4 (2–5)
Infection rate by site					
VAP	3.8	4.7	4.3	3.7	9.5
VAP/1000 ventilator-days	11.7	15.8	14.4	12.2	31.7
CA-UTI	2	3	3.9	3.7	2.6
CA-UTI/1000 catheter-day	3.4	5	6.6	6.1	3.6
CLABSI	0.8	0	0.4	0	0.8
SSI	0.3	1.3	1.8	1	2.1
Abdominal sepsis	0.6	1	1.1	2.2	2
Prevalence (%) MDR-HAI pathogens[a]	37.5	33.3	29.4	33.3	65.1

IQR, interquartile range; VAP, ventilator-associated pneumonia; CA-UTI, catheter-associated urinary tract infection; CLABSI, central line-associated bloodstream infection; SSI, surgical site infection; ESBL, extended-spectrum beta-lactamase; XDR, extensively drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococcus.

[a] MDR, multidrug-resistant bacteria (ESBL *Escherichia coli*, MDR/XDR *Pseudomonas aeruginosa*, MDR *Acinetobacter baumannii*, MRSA, VRE).

2.1. Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous data were compared by means of the Mann–Whitney *U*-test or the Student *t*-test according to the data distribution. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. *p*-Values of ≤0.05 were considered statistically significant. Device utilization ratios, site-specific incidence rates per 100 patients, and site-specific incidence densities per 1000 days at risk or per 1000 patient-days were calculated. Data were analyzed using Epi-Info (v. 7) and STATA (v. 12) statistical software.

3. Results

During the study period there were 1418 admissions to the ICU. There were 159 HAI in 134 patients (110 with one, 23 with two, and one with three HAI episodes). The overall incidence of HAI in the ICU was 11.2 per 100 patients and 32.2/1000 patient-days (Table 1).

The median patient age was 50 years; 65 patients (48.4%) were male. The most frequent causes of ICU admission were septic shock (43%), hypovolemic shock (25%), respiratory failure (15%), and postoperative care (10%). Other demographic and clinical characteristics are shown in Table 2.

Seventy-two patients (45.3%) had ventilator-associated pneumonia (VAP), 41 (25.8%) had a catheter-associated urinary tract

Table 2
Demographic and clinical characteristics in intensive care unit (ICU) patients with hospital-acquired infections (HAI) (2007–2011)

Characteristic, *n* (%)	Patients (*N* = 134)
Age, years, median (range)	50 (16–93)
Male	65 (48.5%)
Underlying oncological disease	
Genitourinary	32 (23.9)
Lymphoma	16 (11.9)
Acute leukemia	14 (10.4)
Esophagus and stomach	10 (7.5)
Colon and rectum	9 (6.7)
Breast	6 (4.5)
Status of cancer at ICU admission	
Recent diagnosis	83 (64)
Progression	11 (8.5)
Complete remission	16 (12.3)
Recurrence	12 (9.2)
Non-response	8 (6.1)
ICU admission diagnosis	
Septic shock	58 (43)
Hypovolemic shock	33 (25)
Respiratory failure	20 (14.9)
Postoperative surgical care	14 (10.4)
Other reasons	6 (4.4)
Chemotherapy within 2 months	26 (19.4)
Mechanical ventilation	131 (97.8)
Comorbidities	
No comorbidities	97 (72.4)
Hypertension[a]	17 (12.7)
Diabetes mellitus	14 (10.4)
Chronic renal failure	6 (4.5)
Other[b]	7 (5.2)

[a] Six patients had two co-morbidities.

[b] Four patients with systemic lupus erythematosus, one with fever and neutropenia, one with HIV, and one with deep venous thrombosis.

infection (CA-UTI), 21 (13.2%) had a surgical site infection (SSI), 20 (12.6%) were cases of abdominal sepsis, and five (3.1%) had a central line-associated bloodstream infection (CLABSI).

The CA-UTI rate was 17.1/1000 catheter-days. The mean VAP rate was 8.2/1000 ventilator-days. The mean number of days of mechanical ventilation in the patients who developed VAP was 14.4 ± 10.2 days.

Of all nosocomial infections, 145 (91.2%) were culture-confirmed and 14 (8.8%) were clinically defined as culture-negative infections. There were 266 microorganisms isolated, of which 105 were considered MDR; the overall prevalence was 39.5%. These bacteria were distributed as follows: 148 Gram-negative (55.6%), 86 Gram-positive (32.3%), and 32 yeasts (12.1%). The most frequent organisms were *E. coli* (n = 54, 20%; 94.4% of these were ESBL producers), *S. aureus* (n = 32, 12%; 90.6% of these were MRSA), *E. faecium* (n = 32, 12%; 18.7% were VRE), *P. aeruginosa* (n = 29, 11%; 14% were MDR), and *Acinetobacter baumannii* (n = 15, 6%; all MDR) (Table 3).

The mean number of days of ICU hospitalization was greater in patients who developed MDRB-HAI compared to patients with HAI with susceptible bacteria (16 ± 10 vs. 12 ± 6 days, p = 0.02). MDRB were most frequently isolated in patients who developed VAP (p = 0.03) and bacteremia (p = 0.003). Appropriate empirical antimicrobial treatment was initiated in 75 patients (56%), although it did not influence mortality (p = 0.9), even in the presence of MDRB (p = 0.8).

The SOFA score at ICU admission was 8.4 ± 3.3, and at HAI diagnosis was 7.4 ± 4.1 (p = 0.03), with no statistical difference between patients who developed and those who did not develop MDRB-HAI (7.1 ± 3.5 vs. 7.4 ± 4.1, respectively p = 0.5).

The mortality rate of patients with hematological malignancies did not differ from that of patients with solid tumors, even in those with MDRB (p = 0.7).

Among patients admitted to the ICU (n = 1418) during the study period, 252 died (17.8%). Fifty-eight patients (23%) had an HAI, and 51 (88%) of these had an MDRB isolated. The mortality related to MDRB-HAI was significantly higher than that for non-MDRB-HAI (p = 0.05).

In 2011, the ICU experienced a 5-month outbreak of MDR *A. baumannii*, isolated from bronchial secretions of 13 patients (also isolated from blood in one patient, urine and surgical site infection in one patient each); in two patients it was isolated only in blood cultures. Eleven patients died (73%) increasing the HAI mortality to 53%.

4. Discussion

Cancer is a leading cause of death worldwide, accounting for 13% of all deaths in the year 2008.[13] Along with its higher incidence, more cancer patients receive multimodal treatment, with chemotherapy, radiation therapy, surgery, and/or molecular targeted therapies, with increased rates of remission and cure. Within in-hospital medical care, patients with cancer admitted to the ICU are becoming more common.[14–17]

ICU-HAI rates are higher than in general hospital wards due to the complex interactions between the patient's underlying diseases, comorbidities, severity of illness, type of ICU, length of stay, and use of multiple invasive devices.[2,18] A study conducted in patients with hematological malignancies admitted to the ICU showed that mechanical ventilation and the failure of two or more organs were independently associated with in-hospital mortality. Mortality reported in the ICU, in-hospital, and at 6 months were 34%, 46%, and 59%, respectively.[15] Another study reported that mortality in cancer patients was negatively influenced by respiratory failure and the development of septic shock during the ICU stay.[16]

A previous study at our institution showed an overall mortality over a 6-year surveillance period of 18% (302 deaths/1670 patients), but there were no data on the related infections.[8] In this study, mortality was reported in 18%; 23% of all cases were associated with an HAI.

Analyzing the infection rate by site, there was a clear increase in VAP in 2011 related to the Acinetobacter outbreak described above. The prevalence of MDR-HAI pathogens was significantly higher in the same year. Analyzing the remainder of the study period (2007–2010), there was no significant variation in the infection rate. Of note, the CLABSI rate remained less than 1, which

Table 3
Most frequent microorganisms isolated in intensive care unit (ICU) patients with hospital-acquired infections (HAI) (2007–2011)

Microorganisms	Pneumonia	Urinary tract infection	Surgical site infection	Bloodstream infection	Abdominal sepsis	Total
Escherichia coli						
ESBL	10	7	10	11	4	42
Non-ESBL	4	4	0	3	1	12
Staphylococcus aureus						
MRSA	13	0	7	9	0	29
MSSA	1	0	0	1	1	3
Enterococcus faecium						
VRE	0	1	2	3	0	6
Vancomycin-sensitive	3	9	4	9	1	26
Other Gram-negative[a]	16	5	11	3	1	31
Pseudomonas aeruginosa[b]						
MDR	2	0	0	2	0	4
XDR	3	0	0	1	0	4
Non-resistant	15	5	3	5	1	29
Acinetobacter baumannii[c]						
MDR	12	1	2	5	0	20
Enterococcus faecalis[d]	3	6	8	3	0	20
Klebsiella spp[d]	8	2	0	1	0	11
Total						
MDR	40	9	21	31	4	105
Non-MDR	50	31	26	25	5	137

ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*. MSSA, methicillin-sensitive *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococcus;

[a] Other Gram-negative: Enterobacter cloacae, Enterobacter aerogenes, Morganella morganii, Serratia marcescens, Klebsiella oxytoca, Citrobacter freundii, Proteus mirabilis, Stenotrophomonas maltophilia, Acinetobacter lwoffii.

[b] MDR, multidrug-resistant (resistant to fluoroquinolones and cephalosporins); XDR, extensively drug-resistant (also resistant to carbapenems).

[c] All *A. baumannii* strains were MDR (except for tigecycline and colistin). All were isolated in 2011 corresponding to an ICU outbreak.

[d] These bacteria were not MDR.

is due to the strict management of vascular central lines in our hospital.

The risk of infection with MDRB has been related to a number of factors, including previous antimicrobial therapy, cross-transmission, and length of hospital stay.[3,19] Critically ill cancer patients admitted to the ICU have a major risk of MDRB-HAI infection that will impact negatively on mortality,[2,20] rendering the enormous efforts to cure and control the cancer wasteful and inefficient. Eighty-eight percent of our patients who developed an HAI and died had an MDRB isolated, reflecting the relationship between these multi-resistant bacteria and the high risk of mortality.

As previously reported, the increase in mortality among patients with MDRB-HAI, even with appropriate therapy, is higher compared to increases in other series of non-cancer patients.[20] In agreement with other studies, we found a higher mortality in patients with MDRB-HAI, regardless of whether or not they had received appropriate antimicrobial therapy. These findings may be explained by the morbidity and organ failure present in ICU patients acting as independent factors related to mortality. In a previous report from our institution involving patients with hematological malignancies and bacteremia due to ESBL *E. coli*, mortality was twice that of patients with non-ESBL *E. coli* isolated.[12] The percentage of isolates observed to have antimicrobial resistance in our ICU reflects the common and increasing problem of emerging resistance patterns in all types of hospital wards.[21]

In 2011, the HAI rate and HAI mortality increased in relation to an MDR-*Acinetobacter spp* outbreak. This bacterium has become an emerging nosocomial pathogen, particularly in the ICU setting, and is frequently associated with outbreaks, most commonly of VAP.[22–24] It has often been attributed to contaminated medical equipment and materials in contact with water, as well as environmental surfaces.[19,25] When other resistant microorganisms were evaluated, none was associated with a high mortality or longer duration of hospitalization, although estimates are imprecise given the low number of these latter isolates.

Our institutional program enhances antimicrobial stewardship and monitors antimicrobial resistance. These measures have been reinforced since 2011, including ICU antimicrobial restriction and consultation with an infectious diseases specialist, de-escalation of therapy, and antimicrobial dose optimization.

The emergence of MDRB poses a difficult task for physicians, who have access to limited or non-existent therapeutic options. Critically ill cancer patients admitted to the ICU are at major risk of MDRB-HAI that will impact adversely on mortality, despite enormous efforts and expense.

Conflict of interest: All authors declare no conflicts of interest. The study authors conducted the data collection and analysis. There was no funding source for the research study. We agree to allow the journal to review data if requested.

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