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ORIGINAL ARTICLE

Ventilator-associated pneumonia and bloodstream infections in intensive care unit cancer patients: a retrospective 12-year study on 3388 prospectively monitored patients

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Abstract

Purpose Some publications suggest high rates of healthcare-associated infections (HAIs) and of nosocomial pneumonia portending a poor prognosis in ICU cancer patients. A better understanding of the epidemiology of HAIs in these patients is needed.

Methods A retrospective analysis of all the patients hospitalized for ≥ 48 h during a 12-year period in the 12-bed ICU of the Gustave Roussy hospital, monitored prospectively for ventilator-associated pneumonia (VAP) and bloodstream infection (BSI) and for use of medical devices.

Results During 3388 first stays in the ICU, 198 cases of VAP and 103 primary, 213 secondary, and 77 catheter-related BSIs were recorded. The VAP rate was 24.5/1000 ventilator days (95% confidence interval [CI] 21.2–28.0); the catheter-related BSI rate was 2.3/1000 catheter days (95% CI 1.8–2.8). The cumulative incidence during the first 25 days of exposure was 58.8% (95% CI 49.1–66.6%) for VAP, 8.9% (95% CI, 6.2–11.5%) for primary, 15.1% (95% CI 11.6–18.5%) for secondary and 5.0% (95% CI 3.2–6.8%) for catheter-related BSIs. VAP or BSIs were not associated with a higher risk of ICU mortality.

Conclusions This is the first study to report HAI rates in a large cohort of critically ill cancer patients. Although both the incidence of VAP and the rate of BSI are higher than in general ICU populations, this does not impact patient outcomes. The occurrence of device-associated infections is essentially due to severe medical conditions in patients and to the characteristics of malignancy.

Keywords Healthcare-associated infections · Intensive care unit · Risk factors · Catheter-associated infections · Ventilator-associated pneumonia

Introduction

Intensive care unit (ICU) patients develop life-threatening healthcare-associated infections (HAIs) more frequently than other patients due to their acute illness and invasive procedures. Infection surveillance networks provide comparative HAI data that can be adjusted, at least partially, for intrinsic and extrinsic risk factors in patients [1]. The HAI rates differ

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according to the ICU type and patient mix [1]. Among the HAIs, ventilator-associated pneumonia (VAP), clinical sepsis and bloodstream infections (BSIs) are associated with a poorer prognosis [2].

A growing number of cancer patients are admitted to ICUs and regular improvement of their prognosis has been observed [3]. The rare publications available show high HAI rates [4] and the poor prognosis of nosocomial pneumonia in critically ill cancer patients [5]. There is a need for a better understanding of the epidemiology, risk factors, and outcomes concerning HAIs in this population.

Patients and methods

Our main objective was to report the incidence of VAPs and BSIs in critically ill cancer patients based on a 12-year prospective cohort in our oncology ICU. Our secondary objectives were to describe pathogen distribution and assess the risk factors for HAIs and their potential influence on ICU mortality.

The Gustave Roussy Cancer Centre is a tertiary care hospital treating exclusively patients with solid or hematological malignancies. The average annual admission volume in the 12-bed medical surgical ICU is 400 to 450 patients. A dedicated infection control team is in place since 1999.

We collected data from the hospital activity and associated expenditure database (*Programme de Médicalisation des Systèmes d'Information*, PMSI) and from the ICU case report forms for stays ≥ 48 h.

The PMSI national database contains information on admission categories, patient demographics, disease characteristics, Eastern Cooperative Oncology Group performance status (ECOG-PS [6]), and Simplified Acute Physiology Score (SAPS II [7]).

The ICU registry is based on a questionnaire, filled out by the same two physicians since 1999. The case report forms include information on the following: invasive devices (mechanical ventilation [MV] and central venous catheters [CVCs]), HAIs (VAP, primary BSIs, catheter-related BSIs, and secondary BSIs), neutropenia (white blood cell [WBC] count < 1000/mm^3 or acute leukemia) before admission (duration and nadir), and outcomes at discharge from ICU (infections [date of diagnosis, pathogen] and death. MV by intubation or tracheotomy and CVCs (including totally implanted ports and hemodialysis lines) were studied. As the majority of long-term CVCs were used throughout the ICU stay, we did not differentiate between long-term and temporary central lines. All patients were prospectively monitored for infections from admission to 48 h after discharge. All the ICU stays between January 1, 2000, and December 31, 2011, were considered. During this period, the main change in routine practice was the use of a sedation scale for mechanically ventilated patients since 2004. The data are strictly confidential and available only to authorized clinicians and staff. (Medical procedures are described in the supplementary material)

Diagnostic techniques and infection criteria remained unchanged during the study period. All cases of pneumonia and BSIs were audited by two authors (AS, FB) in 2013–2014, using the microbiology data and medical records. All clinically suspected VAP were confirmed using a quantitative culture of distal respiratory tract secretions, "blindly," or via a fiberoptic bronchoscope (or sometimes a semi-quantitative culture of sputum after extubation). For details, see web supplements. Bacteremia or fungemia were defined as at least one positive blood culture (except for skin commensals). BSIs were classified as primary, secondary, or catheter-related BSI (CR-BSI) (see supplementary material).

Statistical analysis

We retrospectively described the use of invasive devices in terms of the number of devices, median placement time, and inter-quartile ranges (IQRs). Device usage rates (ratio of the duration of device use to the duration of the stays) were calculated separately for the first (per patient) ICU stays and for the remaining stays. We computed the rates of HAIs as 1000 times the ratio of the total number of infections to the total number of ICU days. HAI rates were calculated as (1000×) the ratio of the total number of infections (VAP and CR-BSIs) to the total duration of the device.

For patients with several stays exceeding 48 h, only the first stay was included in the prognostic analyses. Analogously, only the first HAI was considered. To verify whether the infection risk was constant over time, we compared the exponential estimation of the cumulative incidence to the 95% confidence bands of the Kaplan–Meier estimate.

We identified factors associated with infection using logistic models adjusted for the exposure time. We computed univariate models, then multivariate models via stepwise selection based on likelihood ratio tests ($\alpha_{in} = 0.2$, $\alpha_{out} = 0.05$). The methods used for sensitivity analyses and factors associated with mortality are shown in the supplementary material. All analyses were performed using SAS 9.3 and R 3.1.

Results

The number of ICU stays was 4554, of which 554 lasted < 48 h (flowchart: Figure S1). The number of first stays ≥ 48 h was 200 to 300 per year until 2008, then it increased. The median length of the ICU stay was constantly about 6–7 days (Figure S2).

Table 1 describes patient characteristics. Among the 4000 stays ≥ 48 h, 3388 were first stays (median duration 6 days). Most of the patients (1938; 57%) were admitted for medical

reasons; 2640 (79%) had solid tumors, and 1461 (43%) had metastatic disease. At ICU admission, 320 patients (9%) had experienced leukopenia, for more than 7 days in 108 (3%) cases. The ICU mortality rate was constantly 14%.

Invasive devices

Among the first stays ($N = 3388$), 930 patients (27%) experienced one or more episodes of MV (median duration 4 days) and 2806 patients (83%) underwent at least one CVC placement (median dwell time 7 days; le S1). The total CVC dwell time (33,498 days) exceeded the total duration of stays (31,670 days) because most patients had several catheters, including CVCs (preexisting and implanted in the ICU). The ICU device usage rate was 25.5% for MV and 105.8% for CVCs. Figure 1 shows the yearly number of stays ≥ 48 h with devices and median device duration.

Healthcare-associated infections

During the first stays (Table 2), we recorded 198 cases of VAP ($N = 153$ patients) and 393 BSIs ($N = 296$): 103 were primary ($N = 96$), 77 CR-BSIs ($N = 73$), and 213 secondary ($N = 171$).

The VAP rate was 24.5/1000 MV days (95% confidence interval [CI] 21.2–28). This rate varied remarkably over the years (Figure S3, left). CVCs were responsible for 19.5% of all BSIs (77/393). The CR-BSI rate was 2.3/1000 CVC days (95% CI 1.8–2.8), with small variations over time (Figure S3, right; Fig. 2).

The most common secondary BSIs were of abdominal origin (58.7%, 125/213). Thirty-four BSIs were due to VAP and 23 to urinary tract infections.

Figure 3 shows the number of stays with at least one HAI of each type. Among the 379 patients with infections, 75% (286) experienced only one type of infection, 73 two types, 19 three, and 1 all four types.

Microbiologic findings

The most common pathogens (Table S2) were Gram-negative aerobes bacilli (373 isolates, 49.8%) and Gram-positive cocci (271 isolates, 36.2%). Candida species and other fungi accounted for 34 isolates (4.5%). Polymicrobial infections were recorded in 37/153 (24.2%) VAPs (first episodes) and 35/340 (10.3%) BSIs: 6/96 (6.3%) primary BSIs, 20/171 (11.7%) secondary BSIs, and 9/73 (12.3%) CR-BSIs. Almost 5.5% of bloodstream isolates ($N = 24$) were *Candida* species, 29% ($N = 7$) of which were *Candida albicans*.

Risk factors for infections

Figure 2 shows the cumulative incidence rates of VAP and primary and secondary BSIs and CR-BSIs. The results of multivariate prognostic analyses are summarized in Table 3, and details are provided in the supplementary material (Tables S3–S6).

Among the 930 patients with MV, 45 were excluded from the prognostic analyses (10 had VAP) due to missing values among risk factors. VAPs were recorded for 143 (16%) of the

Table 1 Patient characteristics

	1st stays	2nd + stays
ICU stays		
Number of stays	3388	612
Total duration (days)	31,670	5798
Median duration (q25–q75)	6 (3–10)	6 (3–10)
Sex		
Male	1844 (54%)	364 (59%)
Female	1544 (46%)	248 (41%)
Age (years)		
Median (q25–q75)	56 (46–65)	55 (46–64)
SAPS II score		
Median (q25–q75)	31 (22–43)	34 (25–43)
Admission category		
Medical	1938 (57%)	454 (74%)
Scheduled surgery	1083 (32%)	54 (9%)
Unscheduled surgery	367 (11%)	104 (17%)
Type of neoplasia		
Benign tumor	110 (3%)	14 (2%)
Hematological malignancy	606 (18%)	114 (19%)
Solid tumor	2640 (79%)	478 (79%)
Missing data, *N*	32	6
Presence of metastases		
No	1927 (57%)	336 (55%)
Yes	1461 (43%)	276 (45%)
WHO score		
0/1/2	1842 (56%)	249 (41%)
3/4	1444 (44%)	357 (59%)
Missing data, *N*	102	6
Leukopenia before admission		
No	3068 (91%)	561 (92%)
Yes	320 (9%)	51 (8%)
1–7 days	212 (6%)	21 (3%)
> 7 days	108 (3%)	30 (5%)
Death in ICU		
No	2901 (86%)	528 (86%)
Yes	487 (14%)	84 (14%)
Death at the hospital (including ICU)		
No	2836 (84%)	520 (85%)
Yes	549 (16%)	92 (15%)
Missing data, *N*	3	0

ICU intensive care unit, *SAPS* Simplified Acute Physiology Score, *WHO* World Health Organization, *q25* first quartile, *q75* third quartile

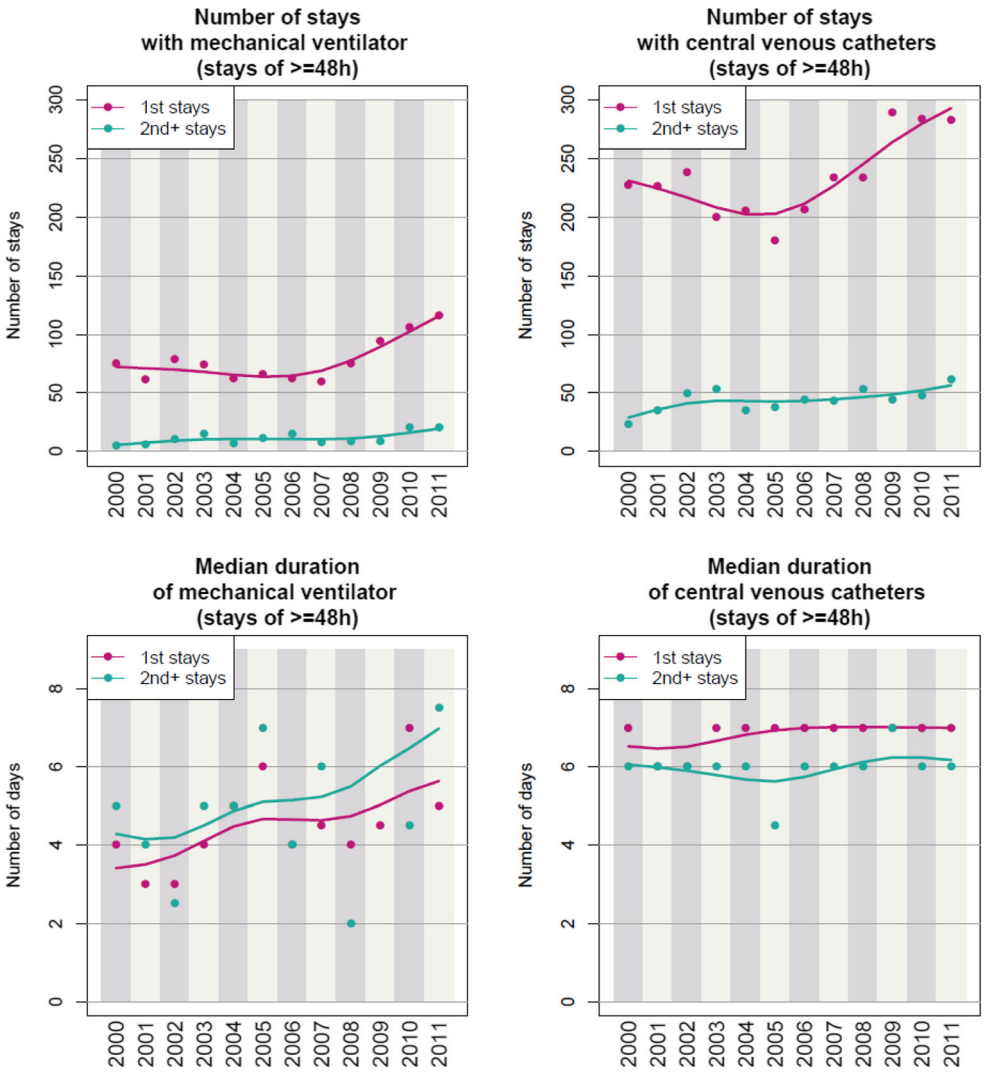

Fig. 1 Device utilization in the ICU at Gustave Roussy Hospital between 2000 and 2011

remaining 885 stays. The risk of developing VAP was constant over time. The cumulative risk of VAP after 25 days of MV was 58.8% (95% CI 49.1–66.6%; Fig. 2). The duration of MV, older age, scheduled surgery, and solid tumors were VAP-specific risk factors (Table S3).

Among the 3388 first stays, 134 were excluded from the prognostic analyses for the risk of BSI (2 had primary and 8 secondary BSIs) because of missing values among risk factors. Primary BSIs were recorded for 94 (3%) of the remaining 3254 stays. The cumulative risk of primary BSI after a 25-day ICU stay was 8.9% (95% CI 6.2–11.5%; Fig. 2). The length of stay, a high SAPS II score, scheduled surgery, ECOG-PS > 2, absence of metastases, and recent leukopenia were significant risk factors (Table S4).

Secondary BSIs were recorded for 163/3254 stays (5%). The cumulative risk of secondary BSIs after a 25-day ICU stay was 15.1% (95% CI 11.6–18.5%; Fig. 2). The length of stay, surgery, and leukopenia were significant risk factors for secondary BSI (Table S5).

Among the 2806 patients with a CVC, 109 were excluded (1 had CR-BSI) because of missing risk factors. CR-BSIs were recorded for 72 (3%) of the remaining 2697 stays. The cumulative risk of CR-BSIs after a 25-day CVC dwell time was 5.0% (95% CI 3.2–6.8%; Fig. 2). No significant risk factors were associated with the risk of CR-BSI, probably due to a lack of power (the low number of CR-BSIs; Table S6). Sensitivity analyses (Tables S7–S14) confirmed the robustness of these results.

Mortality

The occurrence of a VAP episode or BSI was not associated with a higher risk of ICU mortality in the univariate or multivariate analyses (Table S15). A significantly higher risk of death was observed for high SAPS II and ECOG-PS values, medical admission, and the presence of metastases.

Table 2 Incidence of healthcare-associated infections in the intensive care unit

	VAPs	pBSI	sBSI	CR-BSI	Total
HAIs, *N*	198	103	213	77	591
Stays with at least one HAI, *N* (%)	153 (4.5)	96 (2.8)	171 (5)	73 (2.2)	379 (11.2)*
HAIs per 1000 ICU days, rate (95% conf. interval)					
All patients	6.3 (5.4–7.2)	3.3 (2.7–3.9)	6.7 (5.8–7.6)	2.4 (1.9–3.0)	18.7 (17.2–20.2)
Patients with leukopenia	10.1 (6.8–13.7)	12.2 (8.6–16.1)	8.7 (5.7–12.0)	2.4 (0.9–4.2)	33.4 (27.4–39.7)
Patients without leukopenia	5.8 (4.9–6.7)	2.2 (1.7–2.8)	6.5 (5.6–7.5)	2.4 (1.8–3.0)	16.9 (15.4–18.4)
HAIs per 1000 device days, rate (95% conf. interval)					
All patients	24.5 (21.2–28.0)	–	–	2.3 (1.8–2.8)	–
Patients with leukopenia	24.1 (16.3–32.6)	–	–	1.8 (0.7–3.1)	–
Patients without leukopenia	24.6 (20.9–28.5)	–	–	2.4 (1.8–3.0)	–

The total duration of the ICU stays was 31,670 days; the total duration of the mechanical ventilator use was 8077 days; the total duration of central venous catheter use was 33,498 days

HAI healthcare-associated infections, *ICU* intensive care unit, *CI* confidence interval, *VAP* ventilator-associated pneumonia, *pBSI* primary bloodstream infections, *sBSI* secondary bloodstream infections, *CR-BSI* catheter-related bloodstream infections

*Not the row sum, but the number of ICU stays with at least one HAI of any type

$ There were 3388 patients with a stay exceeding 48 h

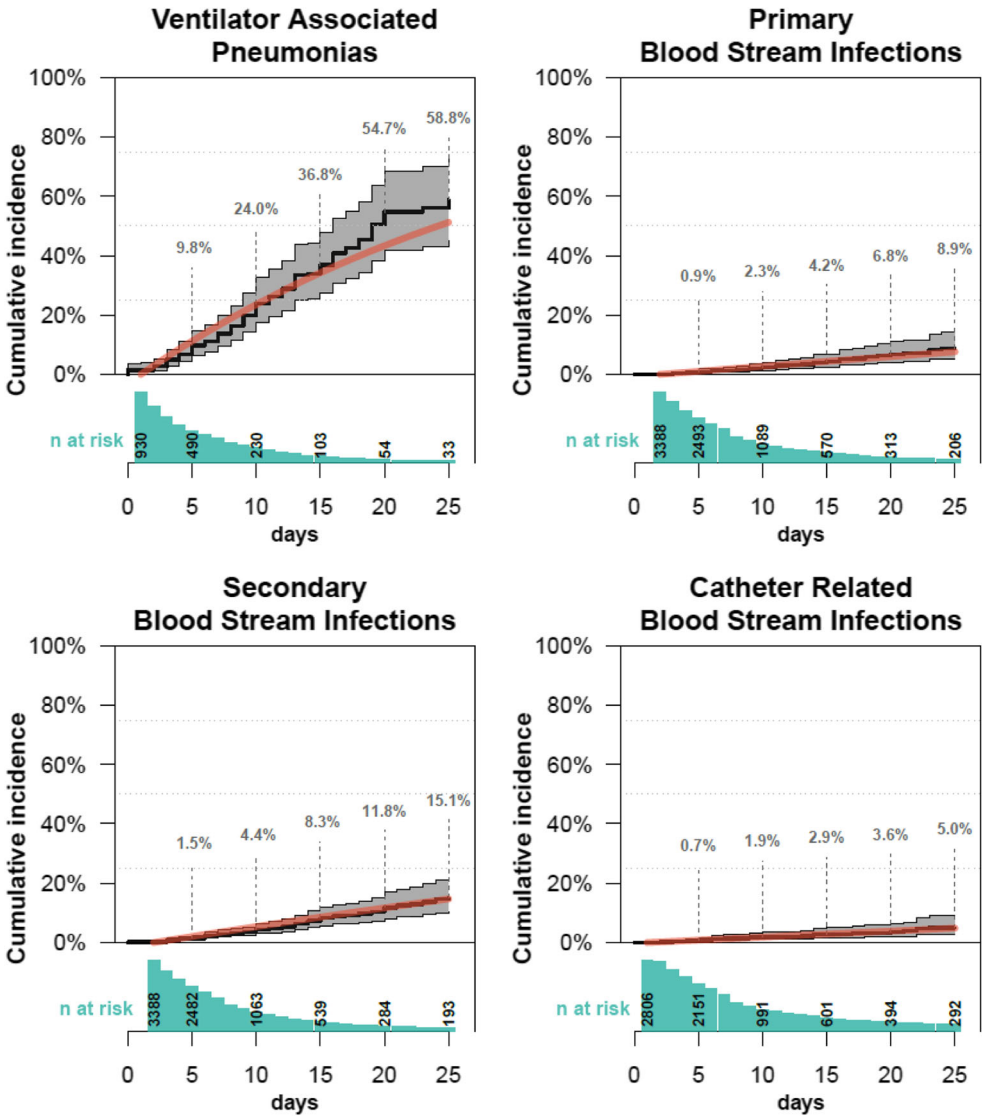

Fig. 2 Cumulative incidence of intensive care unit associated infection in the first 25 days of exposure. Black lines are one minus the Kaplan–Meier estimator, with their 95% confidence bands. Red lines are the exponential estimator, under the hypothesis of constant risk over time. In all these cases, the hypothesis of constant risk over time is compatible with 95% confidence bands of the non-parametric Kaplan–Meier curves

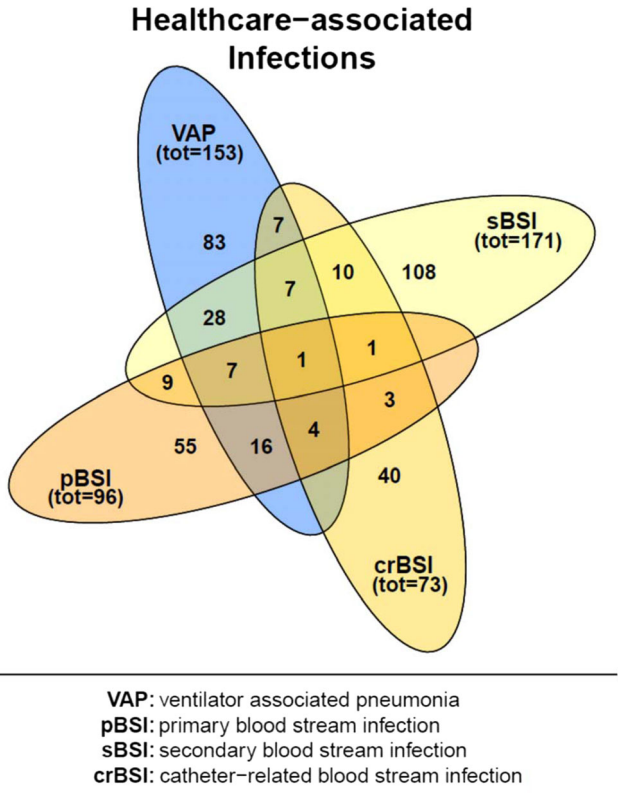

Fig. 3 Number of first stays in the intensive care unit (total = 3388) with at least one of each type of infection. VAP ventilator-associated pneumonia, pBSI primary bloodstream infections, sBSI secondary bloodstream infections, CR-BSI catheter-related bloodstream infections

Discussion

We presented the results of a retrospective study on prospectively collected data, with drastic quality control measures which eliminated some inconsistencies. The stability of the admission categories, severity scores, and length of stay suggest that the case mix has not changed over time. To our knowledge, this study is the largest prospective series (3388; 12 years) on HAIs in cancer patients (see supplementary material). The study began after the introduction of alcohol-based hand gels. The main change in routine practice was the use of a sedation scale for mechanically ventilated patients since 2004.

Specific comments on device usage rates, slightly different from those reported previously, are given in the online supplementary material. Briefly, the rate of catheter use is higher (almost all of our patients have a long-term intravascular device) and the MV rate is lower [4] but has been increasing over time. As we focused on avoidable device-associated infections only, the overall incidence cannot be compared with other non-cancer populations.

We observed a higher VAP rate (24.5/1000 ventilator days) than in other studies (12/1000 at the end of the 90s to < 6/1000 during the past decade [8, 9]), but lower than the VAP rate in the only study in cancer patients (42/1000 [4]). The incidence of VAP may have been underestimated given that microbiological samples were postponed when palliative care was decided, and some patients may have died with untreated pneumonia (or, similarly, with undiagnosed BSI…). Immunodeficiency due to malignancies and anticancer therapies can explain the high rate of VAP in cancer patients. However, neutropenia did not appear to be a risk factor for VAP, which is consistent with other studies [10, 11].

We observed a higher BSI rate (11.6/1000 ICU days) than that reported in a mixed population of French ICU patients (4.5/1000) [12] and by the French National Surveillance Network [13] (3.53/1000). Our CR-BSI rate (2.3/1000 catheter days) is higher than those reported in the USA [14]. Mixing long-term and short-term CVCs in our study makes interpretation difficult: the REACAT study excluded long-term and pre-inserted CVCs. Interestingly, when CR-BSI secondary to long-term and short-term CVCs were examined in a post hoc analysis, a very similar infection rate was observed for catheters previously inserted when in the operating room (including totally implanted ports) and those inserted during the ICU stay. Unlike the steadily declining device-associated infection rates often reported [8, 15], our incidence of CR-BSI increased between 2006 and 2009 and then decreased to below 2/1000 CVC days (Figure S3, right). We focused on CR-BSIs because they are more sensitive to preventive interventions than central line-associated BSIs and more relevant for comparisons between ICUs [16].

The distribution of germs is relatively close to that of general ICU populations, except for yeasts and anaerobic organisms. *Candida* species represented 5.5% ($N = 24$, including 11 cases of candidemia during leukopenia) of the isolated blood culture organisms, a rate that is similar to [8] or higher than [17] that of previous reports. Indeed, our population exhibited many recognized risk factors for candidemia [18]. Our high rate of anaerobic germs (13%) is mainly due to the numerous heavy abdominal surgery cases admitted in our center.

Scheduled surgery and a solid tumor were VAP-specific risk factors, mainly due to hyperthermic intraoperative peritoneal chemotherapy (HIPEC) surgeries and esophagectomies, with regular complications requiring MV. Surgery (scheduled or not) and leukopenia were risk factors for secondary BSI, which could be due to HIPEC, often complicated by leukopenia and peritonitis. Nevertheless, after excluding 1051 scheduled surgery patients (Table S11), unscheduled surgery and leukopenia remained significant risk factors. Mucosal barrier injury (BSI), due to neutropenic enterocolitis, is not preventable and is classified as a secondary BSI in our study: in this case, leukopenia is not only a risk factor but also the

Table 3 Prognostic factors for ventilator-associated pneumonia and bloodstream infections

	VAP			pBSI			sBSI		
C-index	0.704			0.825			0.744		
Prognostic factors	Pr (VAP)	95% CI	*P*	Pr (pBSI)	95% CI	P	Pr (sBSI)	95% CI	*P*
Exposure time			< 0.001			< 0.001			< 0.001
2 days	10%	8–12%		1%	1–1%		2%	1–2%	
8 days	19%	12–28%		2%	1–4%		5%	3–8%	
Age (years)			0.008						
≤ 50	9%	5–16%							
50–60	13%	7–22%							
> 60	18%	11–26%							
Sex									
Male									
Female									
SAPS II						0.002			
≤ 40				1%	1–3%				
40–50				2%	1–5%				
> 50				4%	1–8%				
Admission category			0.006			0.02			< 0.001
Medical	12%	7–21%		1%	0–2%		2%	1–4%	
Scheduled surgery	22%	12–35%		3%	1–6%		6%	3–9%	
Unscheduled surgery	11%	5–21%		1%	0–3%		6%	3–11%	
Type of neoplasia			0.009						
Solid tumor	16%	9–26%							
Benign tumor	2%	0–11%							
Hematological malignancy	12%	6–22%							
Presence of metastases						0.01			
No				2%	1–4%				
Yes				1%	0–2%				
ECOG PS						0.02			
0/1/2				1%	1–3%				
3/4				2%	1–4%				
Leukopenia before admission						< 0.001			0.006
No				1%	1–3%		3%	2–5%	
1–7 days				7%	3–15%		7%	3–13%	
> 7 days				3%	1–9%		8%	4–17%	

Estimated probabilities (Pr) with their 95% confidence interval (95% CI) from univariate and multivariate analyses, adjusted for the ICU length of stay. For each category, the probability is computed for a mean profile of the other factors

VAP ventilator associated pneumonia, *pBSI* primary bloodstream infection, *sBSI* secondary bloodstream infection, *SAPS* Simplified Acute Physiology Score, *ECOG PS* Eastern Cooperative Oncology Group performance status

cause of the BSI. The fact that ICU mortality was not influenced by the occurrence of VAPs or BSIs means that nosocomial infections mainly reflect the severity of the underlying disease or of the patient's condition. Nevertheless, we had no information on the adequacy of initial antimicrobial treatment, a key point in mortality attributable to VAP [19]. Finally, the design of our study does not allow a detailed analysis of the real prognostic burden of each HAI on mortality; aggregation of data into broad categories, such as VAPs and BSIs, lessens the actual impact of some types of HAI on the prognosis. Thus, the occurrence of a deep fungal infection in a neutropenic patient obviously has a greater impact on the prognosis than a catheter-related fungemia, for example. Identifying the mortality *indeed attributable* to each HAI (rather to underlying conditions) would require further analysis and studies.

Conclusions

The occurrence of device-associated infections is essentially due to severe medical conditions in patients and to the characteristics of the malignancy, but these infections do not influence the outcome of ICU cancer patients. Given the data were obtained in an oncology ICU in a specialized cancer center, extrapolation from these findings should be made very cautiously. However, these data may be useful for comparative studies with other oncology ICUs and for developing quality improvement activities. They could be also useful for comparison with HAI rates in the era of innovative treatments such as immunotherapy.

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and FR had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions AS and FB contributed to conception and design. AS, MW, and MM were involved in the data acquisition. FR and JPP planned and performed the statistical analyses. All the authors were involved in the interpretation of the results, read, and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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