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Original Article

Clinical characteristics associated with hospital-onset bacteremia and fungemia among cancer and transplant patients

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Abstract

Objective: This study quantified the burden of hospital-onset bacteremia and fungemia (HOB) among cancer and transplant patients compared to other patients.

Methods: A retrospective cross-sectional study used data from 41 hospitals between October 2015 and June 2019. Hospitalizations were segmented into categories using diagnosis-related groups (DRG): myeloproliferative (MP) cancer, solid tumor cancer, transplant, and non-cancer/non-transplant ("reference group"). To quantify the association between DRG and HOB, multivariable adjusted Poisson regression models were fit. Analyses were stratified by length of stay (LOS).

Results: Of 645,315 patients, 59% were female and the majority 41 years of age or older (76%). Hospitalizations with MP cancer and transplant demonstrated higher HOB burden compared to the reference group, regardless of LOS category. For all hospitalizations, the >30 days LOS category had a higher burden of HOB. The median time to reportable HOB was within 30 days regardless of duration of hospitalization (reference, 8 days; solid tumor cancer, 8 days; transplant, 12 days; MP cancer, 13 days).

Conclusion: MP cancer and transplant patients had a higher burden of HOB compared to other hospitalized patients regardless of LOS. Whether these infections are preventable should be further evaluated to inform quality metrics involving reportable bacteremia and fungemia.

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Introduction

Hospital-acquired infections (HAIs) are a significant driver of increased morbidity, mortality, and financial cost.[1–4] HAI measures, in particular the National Healthcare Safety Network (NHSN)-defined central line-associated bloodstream infection (CLABSI) rates, are quality metrics evaluated by the Centers for Medicare and Medicaid Services (CMS) and private insurers as indicators of patient safety and can potentially affect reimbursement through CMS' Hospital-acquired Conditions Reduction Program and the 2015 Value-Based Performance Program.[5] Since 2011, CLABSIs have been included in the CMS national reporting programs but may be impacted by subjectivity and interrater variability.[6] Decreasing national CLABSI rates have facilitated discussions on expanding the metric to a more encompassing measure beyond central lines to include broader sources of BSI in the form of hospital-onset bacteremia and fungemia (HOB).[1]

At the time of current writing, HOB reporting is unique in that a bacteremia or Candida species fungemia might be reportable irrespective of the original source, possibly including bacteremia and fungemia from other HAIs not specific to CLABSI. The provisional definition may also capture currently excluded but clinically significant entities, including midline-associated BSI, and peripheral intravenous (IV) associated infections.[7,8] In fact, the World Health Organization just released in May 2024 guidelines for preventing BSIs due to peripheral IVs.[9] HOB is objective, easier to electronically capture, automated, and removes the adjudication process as is currently required for catheter associated urinary tract infection (CAUTI) and CLABSI.[10,11] HOB is associated with significant incremental mortality, length of stay (LOS), and cost of care. Higher mortality rates among patients with noncentral line-associated BSI and $20,000 in additional costs have been reported.[12] In a recent case-matched analysis, CLABSIs and non-CLABSI HOB were associated with significantly higher costs and longer LOS for both ICU and non-ICU patients; and a greater than 3.5-fold increased risk of mortality in ICU patients.[1] Opinions from the Society for Healthcare Epidemiology of America (SHEA) Research Network suggest many hospital epidemiologists and infection prevention specialists (54%) view HOB as a measure of a hospital's quality of care. Indeed, 29% of those surveyed reside in organizations implementing HOB testing. The majority of those surveyed (57%) favored publicly reporting HOB alone (22%) or in addition to CLABSI (35%), with 34% favoring CLABSI alone.[10] Therefore, HOB may represent a stand-alone or adjunct quality of care safety metric to aid in the improvement of infection prevention and patient outcomes.

HOB is thought to be preventable or at least partially preventable.[13] Nevertheless, specific patient populations may be

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at a higher risk for HOB, especially those with nonmodifiable risk factors such as inherently immunocompromised patients (eg, myeloproliferative (MP) disease and cancer patients), and long-term surgical patients and/or prolonged exogenous immune suppression (eg, transplant recipients).[14] Another clinical consideration based on the currently available HOB definition is that only the first positive blood culture determines HOB or community-onset bacteremia (COB) designation; therefore, subsequent or recurrent blood cultures during the HO period may not be considered for required reporting. While guidelines support more vigilant infection-control practices in these vulnerable populations, the development of HOB likely disproportionately impacts these patients.[15,16] The current study primarily aims to quantify the burden of HOB among adult cancer (solid tumor cancer and MP cancer) and transplant (solid organ and bone marrow (BMT) recipient) patients compared to patients with other diagnosis-related groups (DRG). Secondary aims include the incidence of non-reportable HOB admissions (eg, subsequent HOB, commensal organisms, and other non-reported organisms), and describing the pathogens driving HOB infections.

Methods

This was a retrospective observational study that included data from inpatient adults age 18 years or older from 41 acute-care hospitals in the BD Insights and Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ) between October 2015 and June 2019. Details of the data collection system have been previously described and include pharmacy, microbiology data and other laboratory measurements, administrative data, patient demographics, and admission, discharge, and transfer data feeds.[17,18] The New England Institutional Review Board/WCG Human Subjects Research Committee (Wellesley, MA) approved the study as involving use of a limited retrospective data set for an epidemiology study and granted an exemption from consent.

Definitions

Exposure groups

Hospitalizations were categorized into four disease groups based on their corresponding DRG code description: solid tumor cancer, MP cancer, transplant (including solid organ and BMT), or non-cancer, non-transplant DRG code (here on described as the "reference").

Hospital-onset bacteremia and fungemia: reportable and subsequent infections

Reportable HOB cases were defined by the currently available definition per the CDC (ie, a first positive blood culture and was collected in the hospital-onset period, on or after day 4 of hospitalization) for an eligible BSI organism as defined by the NHSN bloodstream pathogen list.[1,19,20]

"Subsequent HOB" was defined with 3 requisite qualifiers: (1) occurred after an index reportable HOB event; (2) the pathogen was not the same as the index HOB; and (3) contained an eligible BSI organism (as outlined earlier). A "non-duplicated pathogen for a subsequent HOB event" was defined with 2 mutually exclusive requirements, either: (1) a subsequent HOB event that was a different pathogen from the first (ie, Reportable) HOB or (2) a subsequent HOB event that had the same pathogen as the index HOB but occurred 30 days after the index HOB event and had a different antimicrobial susceptibility test result.

The prevalence of commensal bacteria or other pathogens (defined as not listed in either the NHSN pathogen list or commensal list) isolated in blood cultures were also evaluated in our analyses. To better understand the epidemiology of the microorganisms that are associated with HOB, species of organisms were grouped into pathogens categories based on previously published data.[1]

Other variables

Sex, age, LOS, DRG, 30-day readmissions, ICU during hospitalization, hospital cost per admission, in-hospital mortality, insurance payor, and hospital by demographics, staffed bed size, teaching status, and urban/rural location were variables collected in administrative data. ICU LOS was a derived variable from admission, discharge, and transfer data and quantified the number of days in the ICU. Severity of illness was measured by a quantified marker of risk for mortality during the same admission, the Acute Laboratory Risk of Mortality Score (ALaRMs) and was derived using laboratory data and administrative data with Agency of Healthcare Research and Quality (AHRQ)'s clinical classification software, the methods and use of which have been previously published.[1,21]

Statistical analysis

The distribution of patient, clinical, and hospital characteristics were described using frequencies for categorical variables and medians with interquartile ranges for continuous variables overall and by DRGs.

Because hospitalizations tended to be longer in patients with MP cancer and transplant compared to other DRG groups, analyses were stratified by LOS (≤30 or >30 days). The rate of HOB was estimated per 1,000 admissions. We compared the rate of HOB by DRG using prevalence rate ratio (RR) with multivariate adjusted Poisson regression. In admissions with HOB, the association between DRG with subsequent HOB, commensal bacteria, and other pathogen infection was evaluated using frequencies and multivariable adjusted logistic regressions.

The regression models were adjusted for sex, age, ICU stay during the hospitalization, ALaRMS, payor, and hospital characteristics (staffed bed size, teaching status, and urbanicity) with hospital as random effect to account for within-cluster correlation of data. In hospitalizations with HOB, unadjusted Kaplan-Meier plots were generated to visualize the median time to reportable HOB by DRG group. The prevalence of pathogen categories at the reportable (first) HOB were estimated using frequencies by LOS and DRG. All analyses were conducted using R software version 4.1.2 software (R Foundation for Statistical Computing, Vienna, Austria) with R Studio (Boston, MA).

Results

Patient demographics

The present analysis included 645,315 hospitalizations (0.83% MP cancer, 1.61% solid tumor cancer, and 0.36% transplant, Table 1). Approximately 60% of the analytic cohort were female and the vast majority were 41 years or older (33% age 41–64 years and 43% age 65 years or older). LOS was higher in patients hospitalized for MP cancer or transplant compared to solid tumor cancer or non-cancer, non-transplant DRG. The median ALaRMS score was higher among all groups in comparison to the reference group (38.0). The median ALaRMS was highest for the transplant group

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Table 1. Patient, clinical, and hospital characteristics overall and by diagnosis related groups

Characteristic	Overall	Reference	Solid Tumor Cancer	Myeloproliferative Cancer	Transplant
	n = 645,315	**n = 627,250**	**n = 10,361**	**n = 5,356**	**n = 2,348**
Female	378309 (58.6%)	369,409 (58.9%)	5720 (55.2%)	2289 (42.7%)	891 (38.0%)
Age group					
18–40	155284 (24.1%)	153614 (24.5%)	467 (4.5%)	804 (15.0%)	399 (17.0%)
41–64	212219 (32.9%)	204246 (32.6%)	4227 (40.8%)	2330 (43.5%)	1416 (60.3%)
65–80	185356 (28.7%)	178965 (28.5%)	4075 (39.3%)	1786 (33.3%)	530 (22.6%)
>80	92456 (14.3%)	90425 (14.4%)	1592 (15.4%)	436 (8.1%)	3 (0.1%)
LOS Days (Median [Q1, Q3])	4.0 [2.0, 6.0]	4.000 [2.000, 6.000]	4.0 [3.0, 7.0]	5.000 [3.000, 10.0]	10.0 [5.0, 21.0]
LOS (≤30 days)	640220 (99.2%)	622681 (99.3%)	10315 (99.6%)	5089 (95.0%)	2135 (90.9%)
Ever ICU Status	117436 (18.2%)	114384 (18.2%)	1294 (12.5%)	572 (10.7%)	1186 (50.5%)
ICU LOS Days (Median [Q1, Q3])	2.20 [1.18, 4.37]	2.22 [1.19, 4.39]	1.77 [0.920, 3.03]	2.57 [1.18, 5.31]	1.52 [0.980, 4.92]
30 Day readmission	72603 (11.3%)	68200 (10.9%)	1586 (15.3%)	2238 (41.8%)	579 (24.7%)
In-Hospital Death	14751 (2.3%)	13636 (2.2%)	757 (7.3%)	299 (5.6%)	59 (2.5%)
Total Cost (Median [Q1, Q3])	8370 [4990, 15400]	8270 [4960, 15100]	9850 [5990, 16200]	15500 [8700, 29300]	127000 [82200, 194000]
ALaRMS Score (Median [Q1, Q3])	38.0 [25.0, 52.0]	38.0 [25.0, 52.0]	43.0 [33.0, 56.0]	41.0 [30.0, 54.0]	46.0 [35.0, 62.0]
Payor Class					
Medicaid	90918 (14.1%)	89368 (14.2%)	942 (9.1%)	469 (8.8%)	139 (5.9%)
Medicare	333713 (51.7%)	324331 (51.7%)	5776 (55.7%)	2413 (45.1%)	1193 (50.8%)
Private	177127 (27.4%)	171550 (27.3%)	2783 (26.9%)	2033 (38.0%)	761 (32.4%)
Uninsured	25392 (3.9%)	24960 (4.0%)	286 (2.8%)	137 (2.6%)	9 (0.4%)
Missing	1114 (0.2%)	1088 (0.2%)	22 (0.2%)	4 (0.1%)	0 (0%)
Other	17051 (2.6%)	15953 (2.5%)	552 (5.3%)	300 (5.6%)	246 (10.5%)
Staffed Bed Size		**Hospital-level characteristics**			
<100	22507 (3.5%)	22226 (3.5%)	215 (2.1%)	66 (1.2%)	0 (0%)
100–300	180471 (28.0%)	177094 (28.2%)	2451 (23.7%)	917 (17.1%)	9 (0.4%)
>300	442337 (68.5%)	427930 (68.2%)	7695 (74.3%)	4373 (81.6%)	2339 (99.6%)
Teaching	409773 (63.5%)	396539 (63.2%)	6961 (67.2%)	4064 (75.9%)	2209 (94.1%)
Urban	528455 (81.9%)	512804 (81.8%)	8780 (84.7%)	4732 (88.3%)	2139 (91.1%)

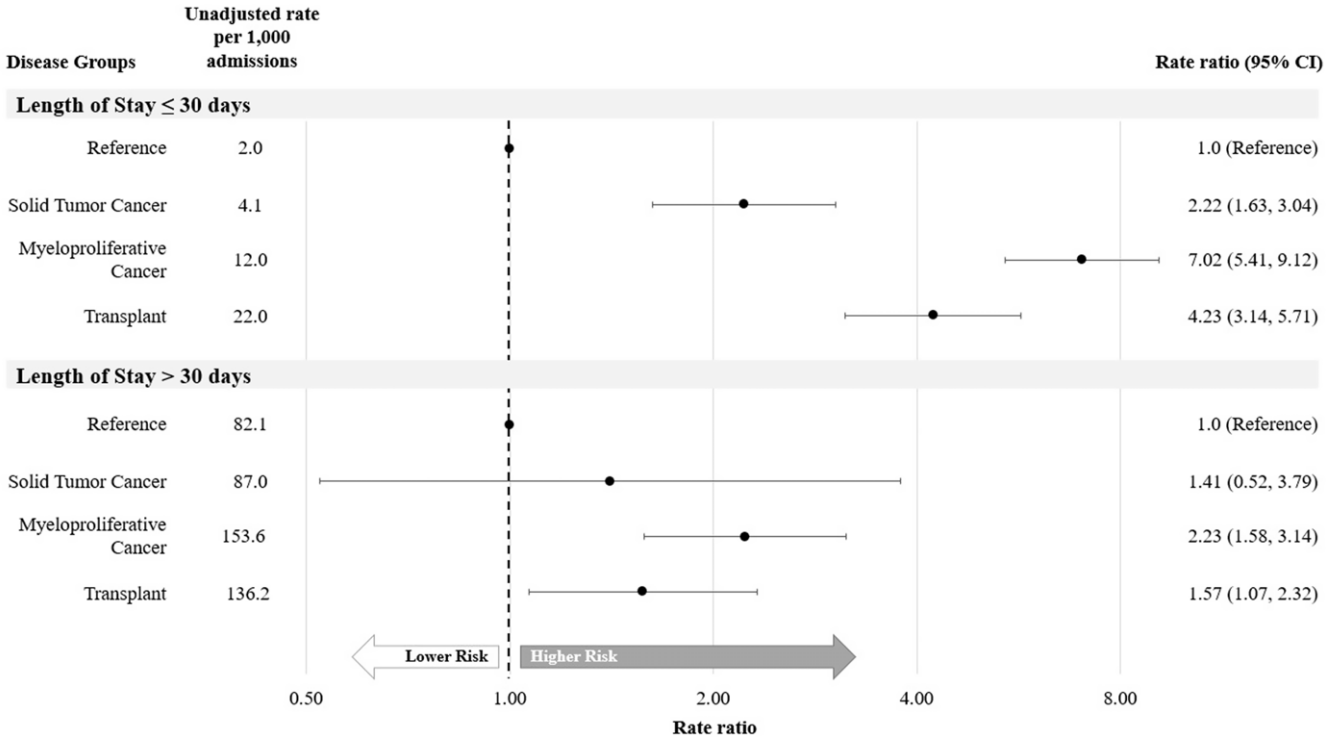

Figure 1. Prevalence rate ratio of HOB by DRG group and stratified by length of stay (≤30 days and >30 days). Models were adjusted for age, sex, diagnosis related groups (DRG) code, ICU status, Acute Laboratory Risk of Mortality Score (ALaRMS), payor type, and hospital-level variables (staffed bed size, teaching status, urbanicity).

(46.0), followed by solid tumor cancer (43.0), and MP cancer (41.0).

Burden of HOB by LOS groups

The rate of HOB was 2.0 per 1,000 admissions in LOS ≤30 days and 82.1 per 1,000 admissions in LOS >30 days. In patients with LOS ≤30 days, the unadjusted rate was lowest in the reference group (2 per 1,000 admissions; Figure 1) and highest for patients hospitalized for transplant (22.0 per 1,000 admissions). In multivariable adjusted analyses, the risk of HOB in MP cancer was 7-fold higher (RR: 7.02, 95% CI: 5.41, 9.12) and fourfold higher in transplant (RR: 4.23; 95% CI: 3.14, 5.71) compared to the reference group. Despite the overall burden of HOB being higher in patients with longer hospitalizations, the higher risk for HOB in MP cancer and transplant vs the reference group were consistent. The risk of HOB was 2-fold higher for MP cancer and 57% higher for transplant compared to the reference group ($RR_{MP\ cancer\ vs\ reference}$: 2.23; 95% 1.58, 3.14 and $RR_{transplant\ vs\ reference}$: 1.57; 95% CI: 1.07, 2.32). In both LOS groups, there were no statistically significant differences in the risk of HOB between solid tumor cancer and the reference.

Median time to reportable HOB

The median time between an admission and HOB event was within 30 days for all DRG groups (Figure 2). The median time to HOB was 8 days in solid tumor cancer and 8 days in the reference group. Patients hospitalized by MP cancer and transplant had a statistically significantly longer median compared to the reference group (13- and 12- days vs 8 days, both $P < 0.001$, respectively).

HOB with other BSI events

In patients with HOB, the risk for subsequent HOB were generally similar by DRG. The exception were patients with LOS ≤30 days, MP cancer was associated with a 4.5-fold higher risk for subsequent HOB compared to the reference group (OR: 4.50, 95% CI: 1.81–11.22, Table 2).

The risk of commensal bacteria or infection with other pathogen was not statistically different by DRG or LOS in hospitalizations with reportable HOB (Supplemental Table 1).

Pathogen composition

Pathogen composition of reportable HOB by LOS and DRG group is presented in Figure 3. The top three prevalent pathogens were *Enterobacteriaceae, Enterococcus* spp., and *Staphylococcus aureus* in both LOS groups (Figure 3, Panel A) and DRG groups (Figure 3, Panel B). *Enterobacteriaceae* was the most prevalent pathogen for both LOS groups (34.6% in LOS ≤30 days and 28.5% in LOS >30 days). In LOS ≤30 days, *S. aureus* was the second most prevalent pathogen followed by *Enterococcus* spp. (25.2% and 13.7%, respectively. Whereas in the LOS >30 days, *Enterococcus* spp. was more prevalent than *S. aureus* (24.2% vs 15.8%).

The most prevalent pathogen for all DRG groups was *Enterobacteriaceae.* The second most prevalent pathogen for MP cancer, solid tumor cancer, and transplant groups was *Enterococcus* spp.; however, *S. aureus* was the second most prevalent for the reference group.

Discussion

The current report explored the demographics and clinical characteristics of hospitalizations at risk for HOB. When looking at initial and subsequent HOB events, a bimodal distribution was

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Table 2. Burden of Subsequent HOB by DRG and LOS

LOS	Group	% HOB admissions with subsequent HOB	
		% (n/SubTotal)	**OR (95% CI)**
≤30 days	Overall	4.1 (57/1406)	
	Reference	3.9 (49/1256)	1.0 (Reference)
	Solid Tumor Cancer	2.4 (1/42)	0.72 (0.09, 5.39)
	Myeloproliferative Cancer	11.5 (7/61)	4.5 (1.81, 11.22)
	Transplant	0 (0/47)	n/a
>30 days	Overall	14.5 (65/449)	
	Reference	14.9 (56/375)	1.0 (Reference)
	Solid Tumor Cancer	0 (0/4)	n/a
	Myeloproliferative Cancer	12.2 (5/41)	0.77 (0.27, 2.18)
	Transplant	13.8 (4/29)	0.72 (0.23, 2.24)

HOB, hospital-onset bacteremia and fungemia; DRG, diagnosis related groups; LOS, length of stay; OR, odds ratio; CI, confidence interval; n/a, not applicable.
Models were adjusted for age, sex, diagnosis related groups (DRG) code, Acute Laboratory Risk of Mortality Score (ALaRMS), payor type, and hospital-level variables (staffed bed size, teaching status, urbanicity).

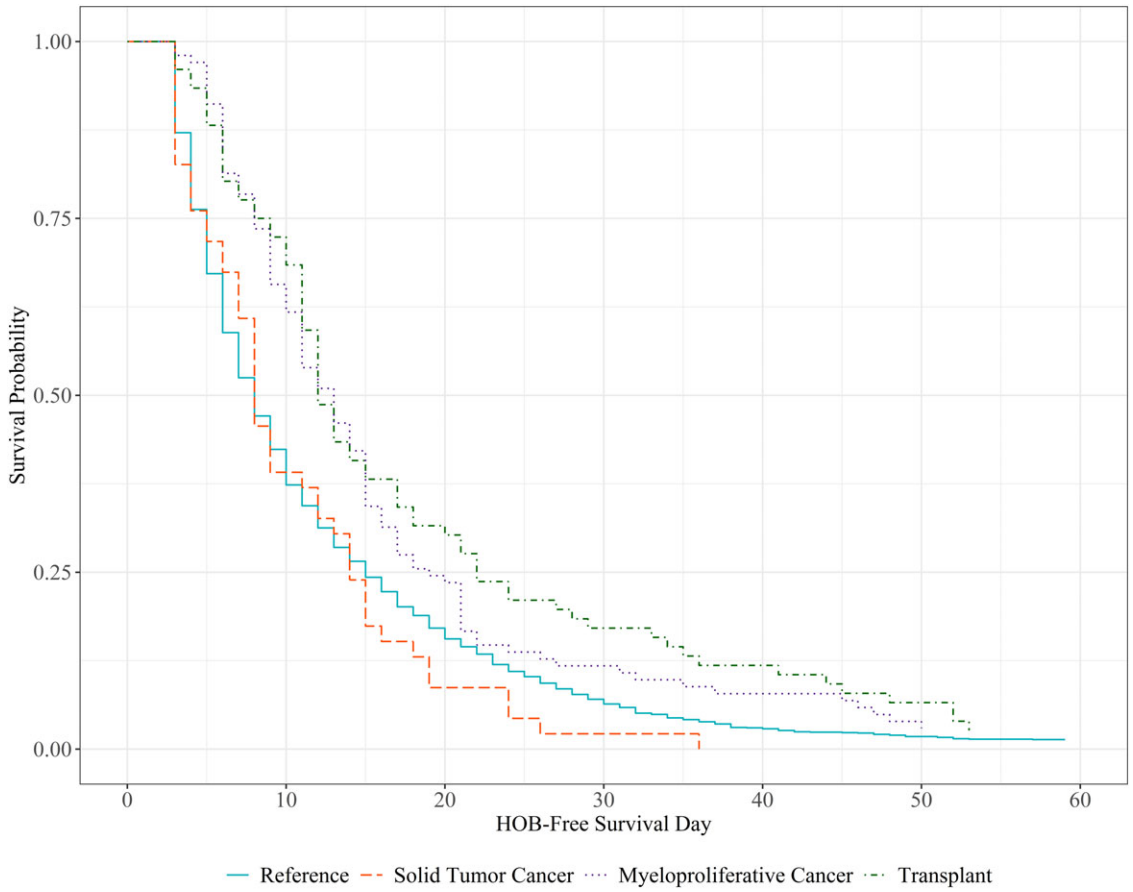

Figure 2. Unadjusted Kaplan-Meier survival plot for days from admission to reportable (first) HOB by DRG. * Median days from admission start to reportable HOB.

seen peaking at a time point within 30 days and >30 days of admission (data not shown). Most of these cases were in cancer and transplant patients which made clinical sense as both populations are at risk for prolonged immune suppression and/or often experience protracted and complicated hospitalizations. Therefore, this analysis focused on these patient populations compared to a reference group with further stratification of cancer patients into those with solid tumor vs MP cancer types.

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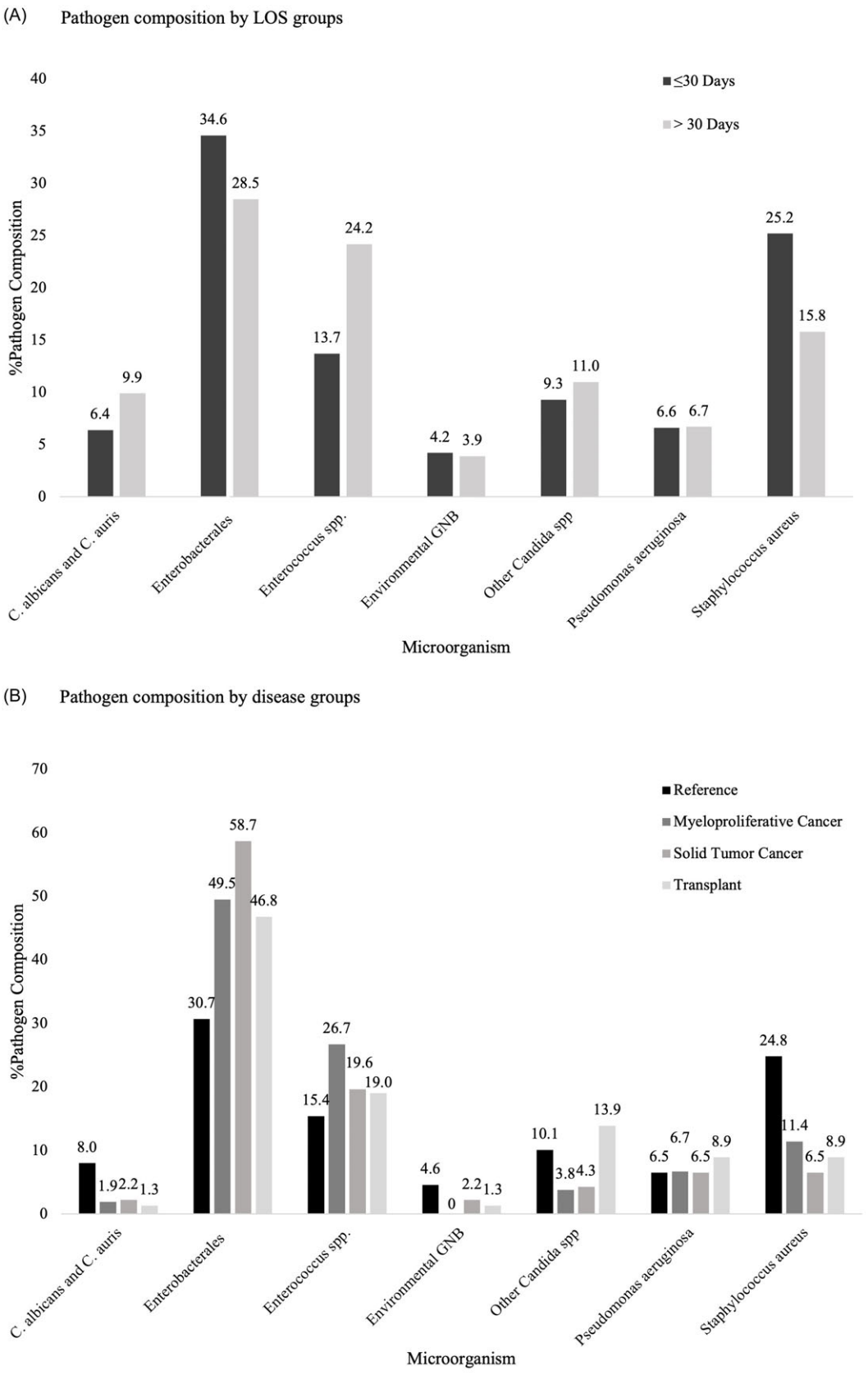

Figure 3. Prevalence of pathogen in reportable HOB (%) by LOS and DRG group. C. albicans and C. auris, Candida albicans and Candida auris; GNB, gram-negative bacteria.

Key findings from this study include a higher burden of HOB and admission rates in MP cancer and transplant groups compared to the reference group.

MP Cancer and transplant patient populations have several clinical features in common that increase susceptibility to infection. Both groups are likely to be immunocompromised:

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transplant patients by intentional immune suppressive agents to enhance transplanted organ viability, and MP cancer by the underlying illness and/or antineoplastic chemotherapy. Solid tumor cancer patients likely have more admissions related to debulking and staging procedures and therefore may not be as chronically immune compromised until receiving antineoplastic or immunomodulating therapy. This may be why the HOB rates are more similar between not only the MP cancer and transplant patients but also between the solid tumor and reference group patients. Both groups can have protracted stays and are more prone to having invasive procedures with open or large post-surgical sites and frequently used vascular access devices for laboratory and therapeutic monitoring. These clinical realities could plausibly increase the risk for BSI, reportable HOB, and—for MP and transplant patients—subsequent HOB events.

A recent study evaluating HOB prevention in a tertiary care hospital setting determined that 56.0% of HOBs were not preventable by providers. The study attributed this to patients with HOB presenting with more complex disease states.[22] Unadjusted HOB may be a marker for overall patient acuity rather than the quality of care. The goal of HOB is to provide an actionable metric for patient safety. To achieve this goal, an HOB-related quality metric ideally would standardize populations that account for acuity. Options include risk adjustment for specific patient-level risk factors to inform the HOB standardized infection ratio or excluding specific high-risk populations altogether, recognizing that prevention may not be realistic. These data would suggest that taking one of these approaches may be useful to evaluate quality of care fairly and accurately for hospitals with extensive transplant or cancer patient populations.

At the time of writing, the proposed HOB definition indexes on a first positive blood culture, which is agnostic to subsequent HOB events occurring in high-risk, prolonged stay populations. While highlighting a disproportionate risk for HOB, these data are insufficient to explore how preventable these events are in this high-risk population, which should drive the ultimate decision to risk adjust or exclude these populations altogether. This is a critical area of future research.

From a patient safety standpoint, visibility to the preferential burden of HOB (reportable or not) and in which at-risk populations, may help better prepare infection prevention programs and antimicrobial stewardship programs (ASP) for optimal HOB prevention, identification, and care. Understanding the pathogens associated with HOB in at-risk populations can further support efforts as certain organisms can originate from known reservoirs (ie, Enterobacteriaceae from GI sources, *S. aureus* from skin or soft tissue, etc.). Ostensibly, an infrastructure already exists to execute on focused infection prevention efforts and timely definitive therapy if a bloodstream infection event does occur given the CMS ruling that requires acute care hospitals to have an ASP as a condition of participation. Furthermore, ASP committees should have representation by infection prevention, microbiology lab and quality department leaders.

Conclusions

The results from this study demonstrated a higher burden of HOB in MP cancer and transplant hospitalizations, regardless of LOS. Across all DRG groups, the median time to first HOB event occurred within the first 30 days of admission; however, the MP cancer and transplant groups had a significantly longer time from admission to HOB event compared to the reference group. Finally, there was a higher risk of subsequent HOB in MP cancer hospitalizations. Should HOB become a mandatory metric, adjustment for hospitals caring for these patients is crucial to ensuring that the comparisons between facilities are meaningful.

Regardless as to whether HOB becomes a mandatory metric, delineating populations with a disproportionate burden of HOB and subsequent HOB represents a patient safety issue given the documented higher risk for mortality, LOS, readmission, and cost of care.[1] These data identify a high priority focus area for future research in HOB prevention.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2024.160.

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