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Major Article

Colonization by fecal extended-spectrum β-lactamase-producing Enterobacteriaceae and surgical site infections in patients with cancer undergoing gastrointestinal and gynecologic surgery

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Key Words:
Multidrug resistance
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Cross infection
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Background: Cancer patients are at increased risk of infection. Fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) may increase this risk. There are few studies on the prevalence of ESBL-PE colonization and surgical site infections (SSIs).

Methods: This prospective cohort study included patients with gastrointestinal and gynecological malignancies who were admitted to the hospital for elective surgery. Rectal swab cultures were obtained on the day of admission and during the postoperative period every 5 days. Prevalence of ESBL-PE fecal colonization and risk factors for the development of SSI were assessed.

Results: We included 171 patients, 30 (17.5%) of whom were colonized with ESBL-PE at admission. This proportion increased to 21% (37 of 171) of the samples during the hospital stay. Incidence of SSI was 14.6% (n = 25). Ten of 37 (27%) patients colonized by ESBL-PE developed SSI versus 15 of 134 (11%) of the non-ESBL-PE (relative risk [RR], 2.163; 95% confidence interval [CI], 1.201-3.897; $P = .016$). Five patients developed a bloodstream infection, and 4 patients were colonized with ESBL-PE (RR = 4.02; 95% CI, 1.2-3.89; $P = .008$).

Conclusions: The rate of ESBL-PE fecal colonization in surgical patients was 17.5%. Colonization of ESBL-PE duplicated the risk of SSI by the same strain and, by a factor of 4, the risk of bloodstream infections.

Cancer treatment has improved the patient's survival in recent years; however, the incidence of infections in this susceptible population has increased.[1] Oncological treatment frequently involves surgery and, in some cases, radical and complex procedures that increase the risk of hospital-acquired infections (HAIs). Surgical site infections (SSIs) are the most frequent complication after surgery, accounting for 31% of all HAIs among hospitalized patients. SSIs represent a considerable burden for health care systems, particularly in low- and middle-income countries.[2] In some cases, such as in colorectal surgery, SSI prevalence is 15%-30%.[3] Deaths attributable to SSI have been estimated at 3%, and increased health care costs and long-term disability have also been described as a consequence. In oncological patients, SSI may also delay adjuvant treatment, with negative consequences for the patient's overall survival.[4]

Infections caused by resistant gram-negative bacteria comprise a global threat worldwide, leading to treatment failure, elevated costs, and higher mortality. The increase of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) is of particular concern, and in many low- and middle-income countries, these are highly prevalent.[5] More recently, in other high-income countries ESBL-PE have shown a rapid increase.[6]

At our institution, we observed a brisk increase in the isolates of ESBL-producing *Escherichia coli,* from 39% in 2008 up to 75% in 2014.[7]

There are few studies on the prevalence of ESBL-producing microorganisms and SSI. Previous studies have demonstrated an association between ESBL fecal carriage and an increased risk of infection in

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Table 1
Characteristics of the study population according to ESBL colonization status at admission

Variable	Total (n = 171)	ESBL carriers (n = 30)	Non-ESBL carriers (n = 141)	*P* value
Age (y, mean ± SD)	54.5 ± 13.9	56.1 ± 15.8	54.2 ± 13.5	.545
Female, n (%)	133 (77.8)	25 (83.3)	108 (76.6)	.354
Type of malignancy				.053
Ovary	44 (25.7)	4 (13.3)	40 (28.3)	—
Colon	28 (16.4)	4 (13.3)	24 (17)	—
Endometrium	25 (14.6)	4 (13.3)	21 (14.9)	—
Gastric	21 (12.2)	2 (6.7)	19 (11.1)	—
Rectum	17 (9.9)	3 (10)	14 (9.9)	—
Cervix	11 (6.4)	4 (13.3)	7 (4.9)	—
Pancreas, small intestine, liver, and biliary tract	19 (11.1)	8 (26.6)	12 (8.5)	—
Others	4 (2.3)	1 (3.3)	4 (2.8)	—
Breast	2 (1.2)	0	2 (1.4)	—
BMI kg/m^2, mean ±SD	26.3 ± 5	25.7 ± 4.5	26.4 ± 5.1	.451
Obesity	37 (21.6)	6 (20)	31 (21.9)	.866
Smoking	55 (32.1)	10 (33.3)	45 (31.9)	.823
Alcohol use disorder	20 (11.7)	5 (17.2)	15 (10.6)	.338
Diabetes mellitus	24 (14)	2 (6.7)	22 (15.6)	.379
Hypertension	33 (19.3)	6 (20)	27 (19.1)	.86
Antimicrobials within the past 3 mo	67 (39.2)	19 (63.3)	48 (34)	.002
Hospitalization within the past 3 mo	37 (21.6)	11 (36.7)	26 (18.1)	.023
Chemotherapy within the past 3 mo	31 (18.1)	3 (10)	28 (19.9)	.219
Previous radiation therapy	13 (7.6)	2 (6.7)	11 (7.8)	1.000

BMI, body mass index; *ESBL*, extended-spectrum β-lactamase.

transplant patients,[8] as well as bacteremia in patients with hematological malignancies.[9] Because oncologic patients are at higher risk for being hosts to multidrug-resistant (MDR) bacteria and SSI represent a considerable burden in hospitals, we sought to describe the prevalence of ESBL-PE fecal carriage in cancer patients prior to surgery (at time of admission) and during their hospital stay, and whether carriers have a major risk of infectious complications.

METHODS

Study design, setting, and participants

From September 2014 to December 2015, we conducted a prospective cohort study of adult patients, with gynecological or gastrointestinal malignancies, who were admitted to the hospital for elective abdominal and pelvic surgical procedures. This single-center study was conducted at the Instituto Nacional de Cancerología, a 135-bed public tertiary-care, teaching cancer hospital in Mexico City, with an annual mean of 7,500 hospital discharges and 3,500 surgeries per year.

Written informed consent was obtained from all participants enrolled in the study. The study was approved by the Institutional Review Board (014/016/INI) (CEI/906/14).

Patients and follow-up

At admission, patients who agreed to participate were screened for ESBL-*E coli* through a rectal swab. Data collected included the following: length of hospital stay, gender, age, weight, height, obesity (body mass index ≥ 30 kg/m^2), smoking status, alcohol use disorder (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition [DSM-V]), diabetes, high blood pressure, hospital admissions, antibiotic use, chemotherapy and radiotherapy within 3 months, central venous catheter placement, ileostomy, colostomy, gastrostomy, blood cell count, Model for End-Stage Liver Disease, type and duration of surgery, surgical blood loss, reoperation, parenteral nutrition, blood transfusion, postsurgical drainages, and the use of antibiotic prophylaxis. Information on the characteristics of patients and neoplasia is provided (Table 1). Additional rectal swabs were obtained on days 5, 10, 15, 20, and 25 of the hospital stay.

During the length of hospital stay, study subjects were evaluated every other day by 1 of the investigators. Information on clinical evolution, wound appearance, drains, and antibiotic use was collected. Investigators and attending physicians were blinded to the rectal swab result. Before discharge, study participants were instructed on SSI symptoms and when to contact a physician. Surgical patients had weekly appointments during the first 2 postoperative weeks, and at least 1 additional appointment 30-40 days after surgery. If a complication occurred, the number of appointments varied.

The primary outcome variable was SSI, defined by US Centers for Disease Control and Prevention (CDC) criteria.[10] Pneumonias, urinary tract infections, and bloodstream infections were also evaluated as outcomes variables.

All patients were evaluated for at least 30 days after surgery for SSI or any other health-related infection. SSI surveillance was conducted on a regular basis. The Instituto Nacional de Cancerología has a broad hospital program with postdischarge surveillance of up to 30 days or up to 1 year if prosthetic material is inserted. All surgical patients are registered in a database. Infection-control nurses see the patients and follow their postoperative course 2-3 times per week until discharge. All cultures are reviewed daily at the Microbiology Laboratory, along with readmission records. This information is cross-checked, and between 30-45 days after surgery (up to 1 year if prosthetic material is inserted) the medical chart is reviewed to determine whether an infection has occurred.

Microbiology analysis

A rectal swab was obtained at the time of admission and every 5 days until discharge or on postoperative day 25. Only 1 rectal swab was obtained per time point from each patient. All samples were plated in blood, MacConkey, and chocolate agar and incubated at 37°C for 24 h. Species identification was performed with the BD Phoenix 100 Automated System (Franklin Lakes, NJ). ESBL-producing microorganisms were confirmed by means of the double disc diffusion method.

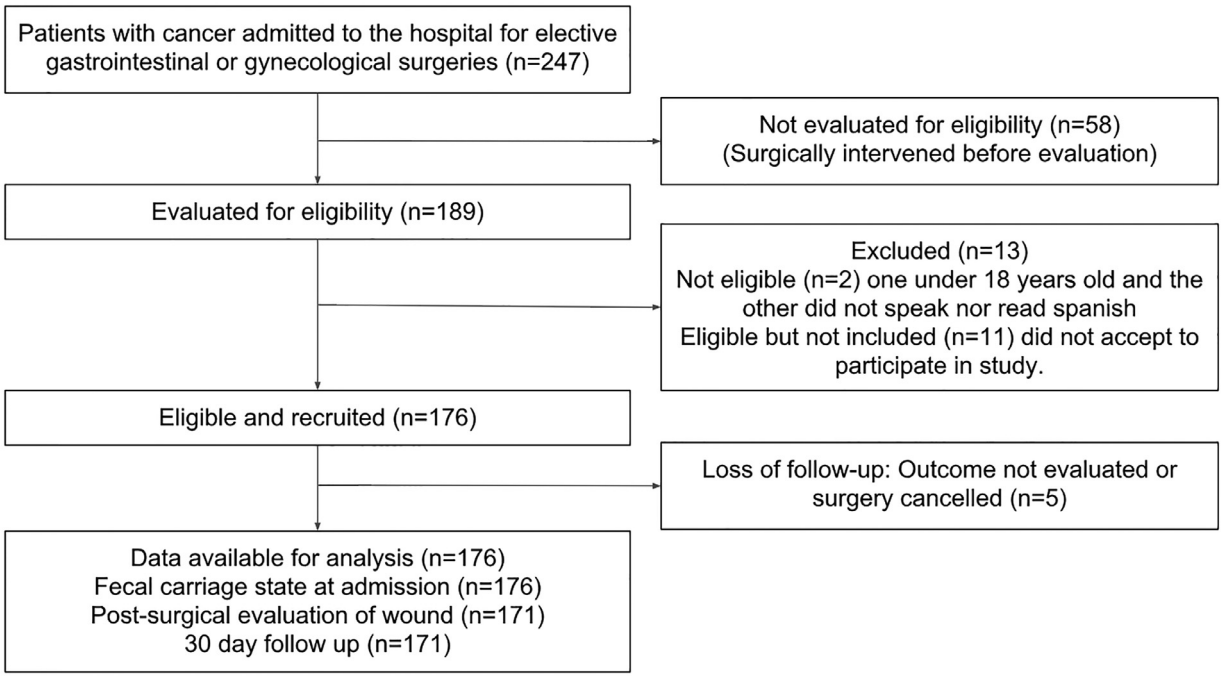

Fig 1. Flow chart of patients included in this study.

Study sample

Recruitment of patients was performed by means of convenience sampling. Sample size was calculated using Epi Info software version 6 (CDC, Atlanta, GA), with an historical 37% prevalence of ESBL-producing bacteria[7] taken as expected frequency, with an acceptable error margin of 5%, and a confidence level of 80%. The estimated sample size to detect ESBL-PE colonization was 174 patients, considering a potential dropout of 20%.

Genetic characterization and ESBL determination

All *E coli*, *Klebsiella pneumoniae,* and *Klebsiella oxytoca* strains were stored at −70°C. Molecular analysis was performed at the Instituto Nacional de Salud Pública , Mexico. For ESBL-producing determination, all selected samples were confirmed by the double disk synergism method as recommended by the Clinical and Laboratory Standards Institute.[11]

Polymerase chain reaction amplification for each ESBL gene was detected using the specific oligonucleotides *bla*CTX-M,[12] *bla*SHV, and *bla*TLA-1,[13] which have been reported previously. Phylogenetic EC group was performed by polymerase chain reaction obtaining fragments of the genes *Chua*, *yja*A, and TSPE4.[14]

Molecular DNA genotyping of the 57 ESBL-producing isolates was performed by pulsed-field gel electrophoresis (PFGE), and whole-cell DNA was obtained according to the method described by Kaufman.[15] The gels were stained and analyzed according to the criteria of Tenover et al[16] and GelCompar II software (Applied Maths, Austin, TX, USA).

Statistical analysis

Continuous variables were compared by the Student t or Mann-Whitney U test as appropriate. Qualitative variables were compared with the X^2 or Fisher exact test. Logistic multinomial regression was performed with variables with *P* values <.1 and with those considered as possible confounders (age, sex, albumin, and type of malignancy). Data were analyzed with SPSS version 19.0 statistical software (SPSS, Inc, Chicago, IL).

RESULTS

Participants

We included 171 patients. The recruitment process is depicted in Figure 1.

The mean age of study participants was 54.5 ± 13.9 years, and 77.7% (n = 133) were female. The most common oncological diagnoses were as follows: ovary (25.7%; n = 44), colon (16.9%; n = 29), endometrial (15.2%; n = 26), gastric (12.3%; n = 21), and rectal (9.9%; n = 17) cancer. Comorbidities included the following: 32.6% (n = 55) were current or former smokers, 21.6% (n = 37) were obese, 19.3% (n = 33) had hypertension, 14% (n = 24) had type 2 diabetes mellitus, and 11.7% (n = 20) had some degree of alcohol use. Variables including demographic characteristics, type of neoplasia, comorbidities, and oncological treatment (chemotherapy or radiotherapy) are summarized in Table 1.

At admission, 39.2% (n = 67) of patients had been recently exposed to antimicrobials, 21.6% (n = 37) had been hospitalized within the previous 3 months; 18.1% (n = 31) had received chemotherapy, and 7.6% (n = 13) had been administered radiation therapy.

The most prescribed antibiotics for surgical prophylaxis in the study were cefuroxime (40 patients, 22.7%), metronidazole (21, 11.9%), ceftriaxone (17, 9.7%), ciprofloxacin (9, 5.1%), clindamycin (7, 4%), and cephalotin (1 patients, 0.6%). A combined regimen with cefuroxime plus metronidazole was used for colorectal surgeries and other clan-contaminated procedures.

ESBL-PE were recovered from rectal swabs in 30 (17.5%) patients at admission. This proportion increased to 21.6% (n = 37) samples during the hospital stay (median 4 days, interquartile range [IQR] 3-6 days). Therefore, 7 of the original non-ESBL patients became “ESBL-colonized” at some point during their hospital stay. Four of the

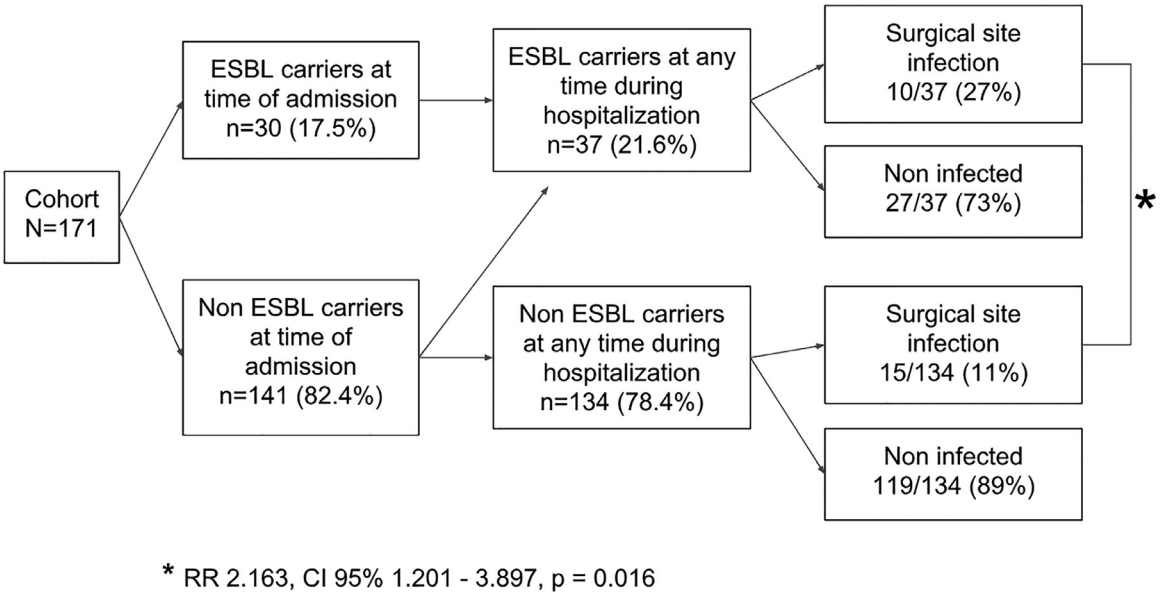

Fig 2. Cohort of patients admitted for surgery, ESBL carriers, and noncarriers and their outcomes regarding SSI. (*) The risk of developing an SSI in ESBL carriers versus non-ESBL carriers (RR, 2.163; 95% CI, 1.201-3.897; *P* = .016. *CI*, confidence interval; *ESBL*, extended-spectrum β-lactamase; *RR*, relative risk; *SSI*, surgical site infection.

patients (57.1%) became ESBL carriers on day 5, 2 (28.6%) became colonized on day 10, and 1 patient (14.2%) became colonized on day 15. At admission, ESBL carriers had a higher frequency of previous antibiotic exposure (63.3%) compared to noncolonized subjects (33.3%) (*P* = .002).

The following surgeries were performed: 42 (24.7%) exploratory laparoscopies; 26 (15.3%) hysterectomies; 22 (12.9%) hysterectomies with oophorectomy; 16 (9.4%) hemicolectomies; 13 (6.5%) gastrectomies; 12 (7.1%) rectal resections; 9 (5.3%) ileostomies; 7 (4.1%) colostomies; 6 (2.6%) Whipple procedures; 5 (3%) laparoscopic cholecystectomies; 5 (3%) partial hepatectomies; 3 (1.8%) pelvic exenterations; 2 (1.2%) abdominal wall reconstructions; 2 (1.2%) oophorectomies; 1 (0.6 %) splenectomy, and 1 (0.6%) bilateral pelvic lymphadenectomy.

From the whole sample, 25 patients (14.6%) developed an SSI: 14 (56%) of these were classified as organ/space SSI, 5 (20%) as deep incisional, and 6 were superficial incisional. Median time of SSI diagnosis was 8.5 days (IQR 4.25-11.75 days) after surgery.

In 16 (64%) of the 25 SSI, the causal microorganism was isolated and 13 were Enterobacteriaceae: 10 ESBL-producing *Escherichia coli*; 1 ESBL-producing *K pneumoniae*; 1 non-ESBL producing *E coli*; 1 non-ESBL producing *K oxytoca*, and 3 other microorganisms.

Ten of the 37 (27%) patients with pre or postsurgical intestinal colonization by ESBL-PE developed an SSI versus 15 of 134 (11%) of the never-colonized ESBL bacteria group (relative risk [RR] 2.163, 95% confidence interval [95% CI], 1.201-3.897; *P* = .016). Cohort colonization and SSI from the beginning of follow-up are depicted in Figure 2. Of the 25 SSI, 10 (40%) were caused by ESBL-PE. Four of 10 of the ESBL-colonized patients had an SSI with an ESBL pathogen: all were organ/space infections and were caused by ESBL-producing *E coli* (3 cases) and ESBL *K pneumoniae* (1 case). Six of the non-ESBL-colonized patients had an ESBL SSI (6 of the 15 clinical infections), with ESBL-producing *E coli,* the causative microorganism in all 6 of these cases, including 3 organ/space infections, 2 superficial, and 1 deep incisional.

Other infectious outcomes

Other infectious complications were recorded in 16 patients (9.4%): 9 (56.2%) patients had urinary tract infections, 5 (32.1%) had bloodstream infections, and 2 (12.5%) patients had pneumonia. A comparison of these complications in the group of patients who were ESBL carriers versus the group of noncarriers is summarized in Table 2.

The median time of diagnosis of infectious complications other than SSI was 16 days (IQR, 10-23 days). Thirteen patients (81.3%) had positive cultures. Eight (61.5%) were Enterobacteriacea (6 were ESBL-producing *E coli*, 1 was ESBL-producing *K pneumonia*, and 1 was non-ESBL-producing *E coli*), and the remaining 5 were non-Enterobacteriacea (2 were *Staphylococcus aureus*; 2 were *Streptococcus epidermidis,* and 1 was *Streptococcus viridans*). Five patients required reoperation, of which 3 patients had reoperations due to surgical complications, and 2 patients had 2-stage procedures.

The group of patients who developed an SSI had more complications (40%, 10/25) compared with the group that did not develop an SSI (8.2%, 12/146) (RR, 7.5; 95% CI, 2.8-20.3; *P* < .001).

Univariate analysis of risk factors for SSI development suggested that presurgical serum glucose ≥180 mg/dL (RR, 9.14; 95% CI, 1.91-43.74; *P* = .009); surgical drainages (RR, 2.71; 95% CI, 1.1-6.4; *P* = .02);

Table 2
Comparison of infectious complications in ESBL carriers versus noncarriers at time of admission for elective surgery

Outcome	ESBL carriers n = 37 (%)	Non-ESBL carriers n = 134 (%)	RR	95% CI	*P* value
SSI	10 (27)	15 (11.2)	2.163	1.201-3.897	.016
Blood stream infection	4 (10.8)	1 (0.7)	4.024	2.359-6.865	.008
Pneumonia	1 (2.7)	1 (0.7)	2.347	0.570-9.671	.387
Urinary tract infection	2 (5.4)	7 (5.2)	1.029	0.293-3.615	1

CI, confidence interval; *ESBL*, extended-spectrum β-lactamase; *RR*, relative risk; *SSI*, surgical site infection.

hospital stay >10 days (RR, 9.41; 95% CI, 3-29.21; $P < .001$), and ESBL carriage at any point during hospitalization (RR 2.9, 95% CI, 1.2-7.3; $P = .032$) were associated with SSI development. By logistic regression analysis, after adjusting for confounders, hyperglycemia (≥180 mg/dL) at time of surgery (RR, 17.9; 95% CI, 2.8-115.7; $P = .002$) and more than 10 days of hospital stay (RR, 8.8; 95% CI, 1.8-42.4; $P = .006$) persisted as statistically significant risk factors.

Molecular analysis

Molecular analysis was performed in 57 samples from 18 patients. Phylogenetic concordance was found in 4 (22.2%): 2 of these belonged to the A phylogenetic group, 1 belonged to the B2 phylogenetic group, and the remaining 1 belonged to the D phylogenetic group (dendogram, Supplementary Fig S1).

The ESBL enzyme was analyzed in 33 (57.9%) samples (28 *E coli*, 4 *K pneumoniae*, and 1 *K oxytoca*). Strains of *E coli* were distributed in the following groups: 9 (27%) were CTX-M; 3 (9.1%) were SHV (2 *Klebsiella* spp and 1 *E coli*), and 2 (6.1%) had both CTX-M and SHV (both were *K pneumoniae*).

The PFGE analyses did not reveal clonal relationship between the samples of the same patient, with the exception of 1 patient, in whom we identified the same ESBL producer *E coli* obtained from stools and surgical site with the same molecular characteristics of PFGE pattern, phylogroup D, and ESBL type of CTX-M. Additionally, there was another patient case in which *E coli* isolated from the stool and infection site shared the same PFGE pattern, but that obtained from stools was a non-ESBL producer and the second was CTX-M.

DISCUSSION

Key results

ESBL-PE are an emerging threat globally, as individuals may either be colonized at the hospital or in the community. Traveling, prior antibiotic use, and patients admitted to hospitals from abroad are increasing the number of individuals who are colonized with ESBL-PE.[17] As humans are increasingly colonized by ESBL-Enterobacteria, the risk for an HAI caused by a MDR bacteria is also probably growing.[18]

In growing patients with malignancies, MDR bacteria are of special concern. These pathogens have been associated with delays in the initiation of appropriate antimicrobial therapy and worse clinical outcomes.[19] In patients with hematological malignancies under myelosuppressive chemotherapy, colonization by MDR microorganisms has increased in the past few years[9].

In this study, we evaluated the prevalence of colonization and ESBL-colonizing strains as a risk factor for SSI. Colonization rate by ESBL-Enterobacteria occurred in nearly one-fifth (17%) of the patients admitted for elective abdominal and pelvic surgeries, which is lower than the rate reported by Ogban et al[20] in surgical patients from Nigeria (27.1%) and lower than the rate reported by Manoharan et al[21] (34.3%) in healthy individuals without previous exposure to antibiotics. Our rate is very similar to that reported in pediatric cardiac surgery in Morocco (15%).[22] In this latter cohort of surgical patients, gut colonization was lower than the rate observed in hematological patients from our institution, which showed a prevalence of 29.2% (Cornejo-Juárez P, unpublished data, July 2018).

ESBL-Enterobacteriaceae are now common isolates in many Mexican hospitals,[23] as they are in Latin America and Asia. In many low- and middle-income countries, ESBL isolates have become endemic. This also resembles the results from the SENTRY Antimicrobial Surveillance Program.[24]

Similar to what has been described for bloodstream infections in patients with hematological malignancies,[9] patients colonized with an ESBL-Enterobacteriaceae at admission more frequently developed postoperative bacteremia and an SSI, although the risk was much weaker for the latter (Table 2). By multivariate analysis, ESBL carriage was not associated with an increased risk of SSI caused by an ESBL-Enterobacteriaceae. The latter may be related to the small sample size for SSI.

The CTX-M gene was the most frequent (27.3%) in our samples, as previously reported in Mexico and abroad.[9,25] The clonality study (4/18 pairs of samples tested = 22.2%) revealed a weak correlation between fecal ESBL-producing *E coli* colonization strains and those isolated from wounds and/or organ spaces, which is different from reports on fecal colonization and bloodstream infections in cancer patients.[9,25] As suggested on the clonality study, *E coli* and *Klebsiella* spp from the surgical site probably acquired the ESBL via a plasmid conjugation from other bacteria. Considering that the majority of SSI were detected on an ambulatory basis and that these wounds might have been extensively manipulated by health care workers, patients, and patients' relatives, the acquisition of ESBL-producing strains probably occurred via other sources, such as hands or even contaminated water outside the hospital environment.[26]

We also investigated risk factors for ESBL-Enterobacteriaceae carriage. Antibiotic use 3 months prior to surgery and being admitted to the hospital within the 3 previous months correlated with a higher ESBL fecal-colonization rate. Patients with pancreatic and hepatobiliary neoplasia were more frequently colonized by ESBL-producing strains, probably related to the fact that endoscopic procedures for diagnosis and obstruction management are frequent, with an increased rate of colonization and infection with resistant bacteria. In this group of patients, antimicrobial prophylaxis targeted to ESBL-Enterobacteriaceae may be advised, as has been discussed previously.[27]

In our patients, the frequency of SSI was 14.6%, similar to what has been reported for gastrointestinal and gynecologic cancer surgery. It is noteworthy that SSI showed a higher frequency in patients who were carriers of ESBL producers than in noncarriers, although it did not show to be an independent risk factor for SSI by the multivariate analysis. As has been described previously, in both gastrointestinal and gynecologic cancer surgery, hyperglycemia and the prolonged use of surgical drains were a risk factor for SSI. Although both variables may in part reflect the complexity of the surgeries performed, the sample size was not powered to evaluate risk factors for SSI.

Strengths and limitations

This study has limitations inherent in the type of design. Although this is a prospective study with close follow-up, selection bias may have occurred, as the majority of patients were women with gynecological cancer. Analysis of the risk factors identified is limited, as associations do not necessarily represent causality and this study was not powered for SSI risk factors. Although we conducted active surveillance of signs of infection for at least 30 days, and our institution has a broad SSI surveillance program, another possible limitation is the underestimation of SSI in patients who were discharged and followed only through the outpatient clinic.

This study was only conducted at 1 oncological referral center from a middle-income country, which limits generalizability of the results. Despite this ant the high community colonization rate expected in Mexico, ESBL increased with prolonged hospitalization, similar to other reports in patients with hematological malignancies and bloodstream infections..[28] Finally, the study was designed to estimate the prevalence of fecal carriage at admission; therefore, the remainder of the conclusions should be interpreted with caution. The lack of statistical power to conclude that fecal carriage is a risk factor for the development of SSI should be considered in a future study.

CONCLUSIONS

The rate of ESBL-PE fecal colonization at hospital admission was 17.5%, and this proportion increased to 21% during hospital stay. Colonization of ESBL-PE duplicated the risk of SSI by the same strain and, by a factor of 4, the risk of bloodstream infections. Our results suggest that this is a niche population that needs more attention. However, larger multicenter studies that potentially account for varying ESBL prevalence in different regions are required to confirm this trend.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2019.01.020.

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