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Major Article

Microbiology of surgical site infections in patients with cancer: A 7-year review

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Background: Health care–associated infections (HAIs) have arisen as major sources of multidrug-resistant bacteria. Surgical site infections (SSIs) are the most frequent HAIs in many countries, with high antimicrobial-resistant prevalence.
Methods: A 7-year retrospective review (2008-2014) of microbiologic data within a prospective surveillance program on patients with SSI at a cancer hospital in Mexico.
Results: There were 23,421 surgeries performed during the study period. The SSI rate was 7.9%. Gram-negative bacilli (GNB) were found in 56.5% of samples. *Escherichia coli* was the most frequent microorganism (27.5%), followed by *Staphylococcus aureus* (16.3%). SSI caused by *S aureus* showed a decreasing trend ($P = .04$). Extended-spectrum β-lactamase (ESBL)–producing *E coli* increased from 39.5% in 2008 to 72.5% in 2014 ($P < .001$). Fluoroquinolone resistance also increased in all members of the *Enterobacteriaceae*. Methicillin-resistant *S aureus* (MRSA) was isolated in 32% of cases with no significant increase (*P* value is not significant).
Conclusions: GNB caused most SSIs, with an increase of ESBL *E coli* strains. In breast and thoracic surgery, *S aureus* remained the most frequent isolate. MRSA remained stable throughout the study period. We observed a decreasing trend in *S aureus*. These findings show the differences in the microbiology of SSIs in a middle-income country and the increasing trend of ESBL enterobacteria and other multidrug-resistant organisms, such as *Enterococcus faecium*.

BACKGROUND

Surgical site infections (SSIs) are one of the most frequent health care–associated infections (HAIs) in low- and middle-income countries,[1,2] where 75% of the world's population resides.[3] The incidence of SSI in Mexico and other Latin American countries is higher than that reported by the U.S Centers for Disease Control's National Health Safety Network and in a recent review from the International Nosocomial Infection Control Consortium.[4,5]

SSIs increase health care costs, increase hospital readmissions, and are associated with higher morbidity and mortality.[2] Patients with SSI have a 60% increased rate of admission to the intensive care unit (ICU), a 15 times higher risk of rehospitalization within 30 days after discharge, and 6.5 extra hospitalization days.[6] In patients with cancer, the number of SSIs tends to be increased, with a negative impact on patients quality of life.[7,8] In addition to these observations, oncologic patient populations might be uniquely and more severely affected by emerging antimicrobial-resistant strains[9] because patients with cancer are frequently exposed to multiple antimicrobial regimens, creating selective pressure on this population. In regions with a high prevalence of antibiotic resistance, nearly one-half of gram-negative bacilli (GNB) isolated from surgical wards were found to be multidrug resistant (MDR).[10]

In the United States, gram-positive cocci are the most frequent bacteria found in SSIs.[2,5] Methicillin-resistant *Staphylococcus aureus* (MRSA) is highly prevalent, representing >40% of isolates in some series. GNB are becoming more important as etiologic agents of SSI.[4] Extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* have increased in many regions of the world, and in some

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regions, they are the most frequent isolates of HAI.[11] Other MDR gram-negative bacteria, such as *Acinetobacter baumannii*, although less frequent as a causative agent, have also increased in surgical infections, especially among severely ill patients hospitalized in the ICU.

SSIs have comprised the most prevalent HAIs at the Instituto Nacional de Cancerología (INCan) since 1992, when a prospective surveillance program was initiated, with rates between 8% and 14%. *Escherichia coli* has been the most frequent isolate from SSIs during the last 20 years, and a steady increase in ESBL strains has been observed since 2008.

Despite the increased rate of HAI caused by MDR bacteria, there is little recent information on the pathogens causing SSIs. In the present report, we describe the microbiology and susceptibility patterns of SSI at a cancer referral center in Mexico City.

METHODS

Study population and case definition

The INCan is a 130-bed referral and teaching hospital for adult patients with cancer, with >3,500 surgical procedures performed each year. Seventy percent of patients at this institution are women, 30% are between 30 and 50 years old, and 63% are >50 years. Breast and cervical cancer are the 2 most common neoplasms, followed by other colorectal, ovarian, and prostate cancer. More than one-half of patients exhibit advanced disease stages and comorbidities, such as diabetes mellitus (19%), hypertension (32%), and obesity (15%).

Prospective surveillance of all surgical procedures is regularly conducted with a full chart review 30 days after discharge.

For the purpose of this study, we included all surgical specimens (wound, abscess, pus aspirate, or tissue) cultured at the microbiology laboratory between January 1, 2008, and December 31, 2014, regardless of surgery type or cancer diagnosis. Plating in blood, chocolate, and MacConkey agar was regularly conducted for microorganism identification. Identification of isolates was performed with MicroScan (AutoScan4, Dade, Behring, Germany) from 2008-2010. In 2011, the automated equipment was changed to BD Phoenix 100 (BD, Sparks, MD). Since 2014, isolates have been processed using matrix-assisted laser desorption/ionization–time of flight mass spectrometry. Susceptibility to antimicrobial agents was determined according to current Clinical Laboratory Standards Institute criteria. Susceptibility tests were identified by means of an automated microbiology system (BD Phoenix 100; BD, Sparks, MD). Resistant microorganisms were confirmed through a disk diffusion method.

Case definition

SSI was defined if any of the following conditions were met: (1) the surgical procedure registry or the medical chart was consistent with a diagnosis of SSI, or (2) the hospital surveillance system reported an SSI according to the Centers for Disease Control and Prevention's definition criteria. Duplicate cultures of a previously identified SSI were excluded from the analysis.

Identification and susceptibility testing

The following MDR bacteria were evaluated: MRSA, vancomycin-resistant *Enterococcus faecium* (VRE), ESBL-producing *E coli* and *Klebsiella* spp, and *Pseudomonas aeruginosa* and *Acinetobacter* spp resistant to third-generation cephalosporins and carbapenems. Other GNB were considered MDR if they were resistant to fluoroquinolones, third-generation cephalosporins, and carbapenems.[12]

Each sample was cross-referenced with the patient's medical record. Age, sex, surgical procedure, type of surgery (clean, clean-contaminated, contaminated, or infected), and SSI type were recorded. Cases with SSI that occurred within 30 days of surgery were included, or within 1 year if a prosthesis was inserted.

Statistical analysis

A descriptive analysis was conducted. Microbiologic findings were subcategorized by type of surgical procedure; frequency and susceptibility trends were described for each year and for the group of surgical procedures. Changes over time of selected microorganisms were evaluated by means of linear regression, and the annual changes in proportions of resistant isolates over this 7-year period were compared by the χ^2 test for trends. Data were analyzed using SPSS version 19.0 statistical software (SPSS, Chicago, IL).

RESULTS

During the study period, 23,421 surgeries were performed: 12,439 were clean (class I); 8,763 were clean-contaminated (class II); 578 were contaminated (class III); and 1,641 were infected (class IV). We identified 1,863 (7.9%) microbiologic proven SSI in 1,458 patients. Nine hundred eighty-six (67.6%) SSIs occurred in women, and 472 (32.4%) occurred in men. Mean age of patients was 54 ± 14.4 years.

There were 3,149 cultures taken; of these, 2,399 (76.2%) were positive. There were 2,782 isolates identified in 1,863 SSIs (7.9% of the surgical procedures performed). Class III surgeries had the highest infection rate (21%), followed by class II (8.2%), and class I (8.1%). SSIs in which a culture was obtained and that demonstrated a positive isolate were more frequently found from abdomen and pelvis (525 infections of 2,962 surgeries = 14.5%), breast (497 infections of 5,050 surgeries = 10.4%), and soft tissue and sarcoma (189 infections of 2,685 surgeries = 7.04%) surgical procedures.

Sixty percent of infections (1,137) were monomicrobial, and 40% (n = 726) were polymicrobial. GNB were the most prevalent microorganisms, accounting for 56.5% (n = 1,561) of the isolates, regardless of the surgery type. Overall, *E coli* was the most frequent microorganism (n = 759, 27.3%), followed by *S aureus* (n = 451, 16.2%), *Enterococcus faecalis* (n = 258, 9.3%), and *P aeruginosa* (n = 215, 7.7%), as depicted in Figure 1. The proportion of SSI caused by *E coli* increased from 25% in 2008 to 34.7% in 2014 (linear regression $R^2 = 0.313$, $P = .1917$), whereas *S aureus* significantly decreased from 19.5% in 2008 to 7.4% in 2014 (linear regression $R^2 = 0.5736$, $P = .0486$).

The most frequent microorganisms for selected surgical procedures are summarized in Figure 2. For detailed information regarding the most common procedures, and the most frequent microbial isolates for specific group of surgeries, see Supplementary Appendix S1.

Antimicrobial susceptibility

From 2008-2014, fluoroquinolone resistance increased for all members of the *Enterobacteriaceae* family; *E coli* resistance increased from 60.7% to 80.8% (χ^2 for trend = 11.22, $P = .0008$), *Klebsiella pneumoniae* increased from 16.7% to 55.2% (χ^2 for trend = 8.399, $P = .0038$), and ciprofloxacin-resistant *P aeruginosa* increased from 23.1% to 37.8% (χ^2 for trend = 0.7751, $P = .3787$). ESBL-producing *E coli* also increased from 39.5% to 72.5%, (as illustrated in Fig 3) (χ^2 for trend = 45.05, $P < .001$). *K pneumoniae* was rare (n = 83), but ESBL *K pneumoniae* accounted for 22.9% (n = 19) of all these isolates. Most were found during 2012-2013.

Of *P aeruginosa* isolates, 32 out of 215 (14.9%) were resistant to carbapenem over the study period, decreasing from 25.6% in 2008 to 8.3% in 2014 (χ^2 for trend = 4.059, $P = .0439$). MDR *P aeruginosa* isolates were uncommon (n = 25, 11.6% of *P aeruginosa*). MDR isolates

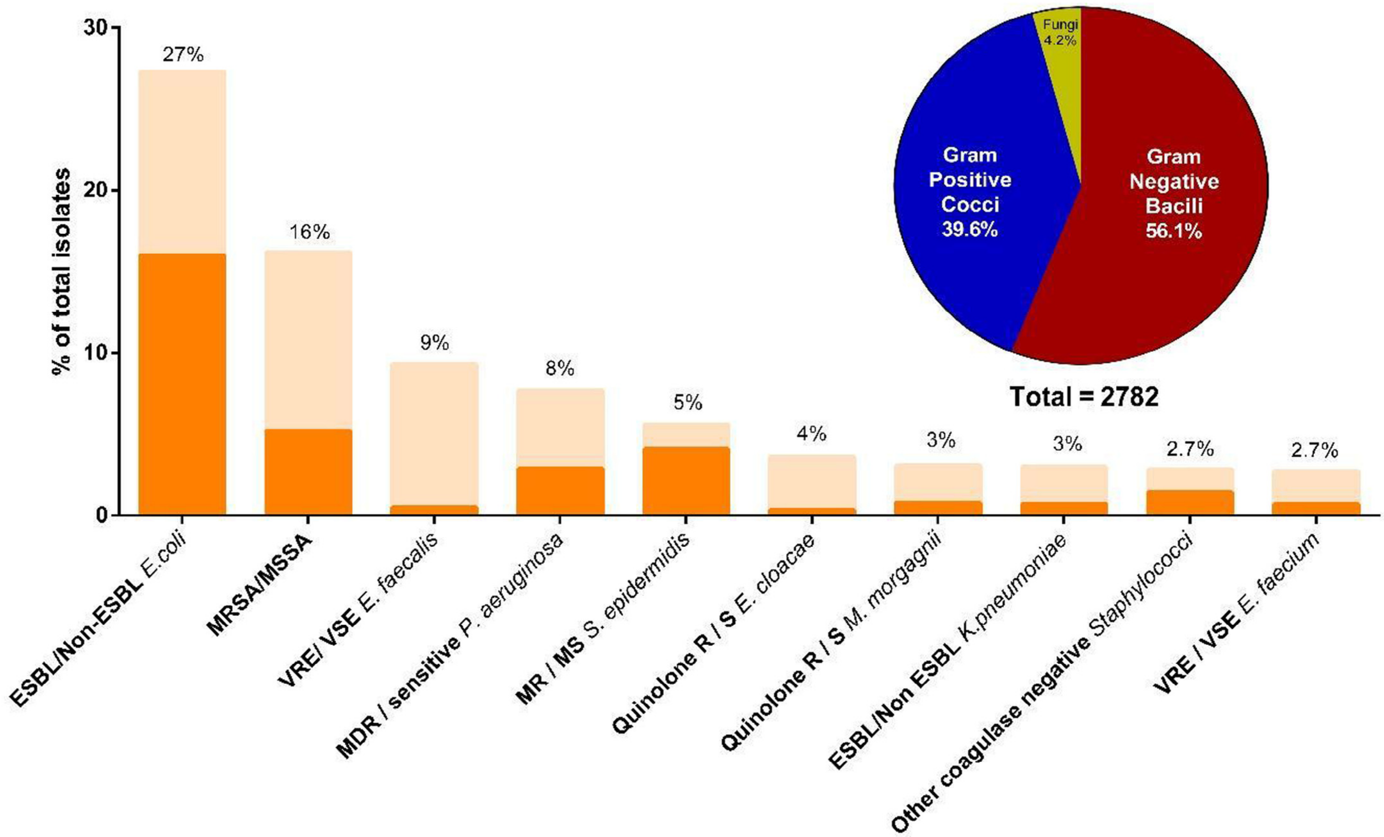

Fig 1. Most frequently isolated bacteria from surgical site infections. The bars represent the percentage of total isolates, and the dark bars represent resistant isolates within that species. *ESBL*, extended-spectrum β-lactamase; *MDR*, multidrug resistant; *MR*, methicillin resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MS*, methicillin sensitive; *MSSA*, methicillin-sensitive *S aureus*, *VRE*, vancomycin-resistant *Enterococcus faecalis*; *VSE*, vancomycin-sensitive *Enterococcus faecalis*.

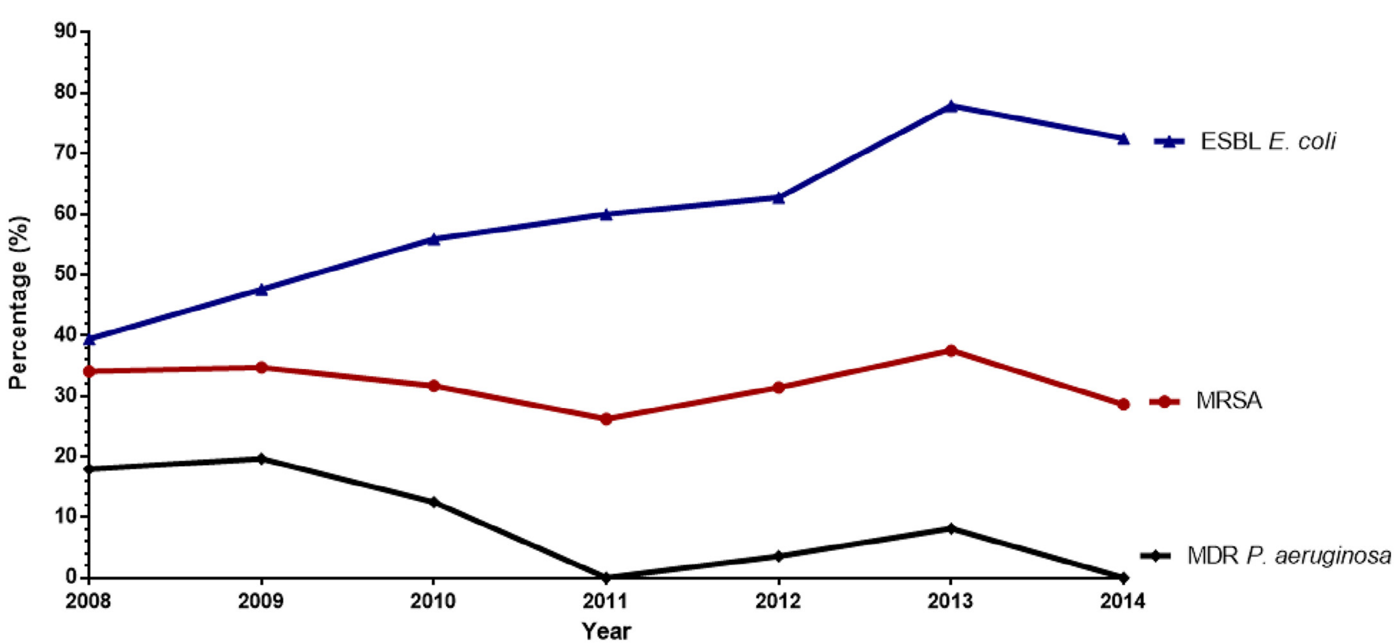

Fig 2. Resistance patterns per year of the most frequent microorganisms. In blue, isolates of susceptible and ESBL *Escherichia coli* in surgical site infections (2008-2014) (χ^2 test for trends = 45.05, $P < .001$). In red, isolates of susceptible and MRSA in surgical site infections (2008-2014) (χ^2 test for trend = 0.1649, $P = .6847$). In black, isolates of MDR *Pseudomonas aeruginosa* in surgical site infections (2008-2014) (χ^2 for trend = 8.992, $P = .0027$). Vancomycin-resistant *Enterococcus* is not plotted because of the small number of isolates (n = 19) (χ^2 test for trend was = 3.118, $P = .0774$). *ESBL*, extended-spectrum β-lactamase; *MDR*, multidrug resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*.

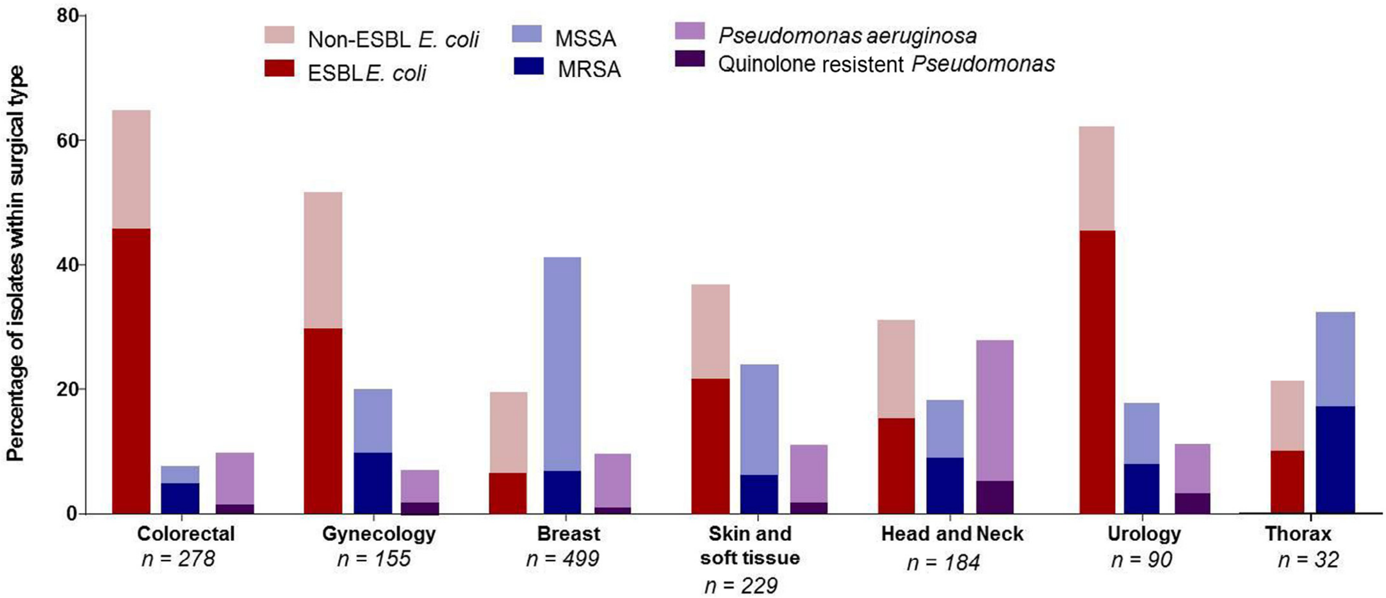

Fig 3. Isolates by group of surgeries. Resistance patterns are shown, and the darker bars represent resistant bacteria. *ESBL*, extended-spectrum β-lactamase; *MDR*, multidrug resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-sensitive *S aureus*.

decreased steadily over the study period (from 18% to 0%, χ^2 for trend = 8.992, P = .0027). Fifteen (7.0%) isolates of *P aeruginosa* exhibited extended drug resistance; they also decreased over time (from 12.8% to 0%, χ^2 for trend = 6.724, P = .0095). There were 9 cases of SSI caused by MDR *A baumannii*. All these patients had been admitted to the ICU during an outbreak of MDR *A baumannii* in 2011, with no other cases presenting since then.

In other enterobacteria, the global frequency of carbapenem resistance was 3.9%. Out of 1,560 isolations of GNB, there were 63 isolates (3.9%) resistant to carbapenems (*P aeruginosa*, n = 32; *E coli*, n = 16; *A baumannii*, n = 9; *Stenotrophomonas* spp, n = 1; *Acinetobacter wolffii*, n = 1; *K pneumoniae*, n = 1; *Pseudomonas* spp, n = 1, and *Proteus* spp, n = 1). The nonfermenters showed a higher resistance to carbapenems than the rest of the enteric GNB (19.2% vs 1.69%, respectively; $P < .0001$).

The proportion of MRSA remained stable at approximately 32%, with no significant increase (χ^2 for trend = 0.1649, P = .6847), as observed in Figure 3. There were no vancomycin-resistant *S aureus* strains. VRE, although infrequent (n = 19), increased from 0% in 2008 to 33% in 2014 (χ^2 for trend = 3.118, P = .0774), as shown in Figure 3. A timeline describing the infection control policies implemented at our institution during the study period is depicted in Figure 4. In Figure 3, we show the changes in proportions of ESBL *E coli*, MRSA, and MDR *P aeruginosa* for each year.

DISCUSSION

In this series, GNB were the predominant bacteria, regardless of the type of surgery. Overall, *E coli* was the most frequent bacteria in clean-contaminated and contaminated procedures in gastrointestinal, gynecologic, urologic, and head and neck surgeries. *S aureus* was the second most common bacteria isolated, behind *E coli*. However, *S aureus* was the most common cause of SSI in clean procedures, in breast and thoracic surgery.

Most published series on SSI include general, cardiovascular, gynecologic, orthopedic, and thoracic surgery; however, cancer surgery is frequently excluded or underrepresented. To our knowledge, this is the largest series in patients with cancer and one of the longest duration series reporting the microbiology of SSI.

The frequency of SSI proven microbiologically during the study period was 7.6%. In this same period, the general SSI rate was 8.3% (regardless of having a microbiologically proven SSI or not). The SSI rate in our series is higher than other reports.[13,14] In the study by Sammon et al, in which the authors reported the prevalence of HAI in a sample of 8 major oncologic surgical procedures, from the Nationwide Inpatient Sample in the United States, the rate of SSI for elective surgeries was 3.2%, much lower than our rate.[4]

The rate of SSI varies according to surgery type, surveillance intensity, postdischarge surveillance, resources available for microbial detection, hospital type, among others. At the INCan, there has been a prospective program with postdischarge surveillance for all major surgeries since 1993, allowing accurate detection of SSI, and underreporting is probably low. This may also contribute to a higher prevalence when compared with other studies without postdischarge surveillance.

The proportion of ESBL isolates found in our series, especially ESBL *E coli*, is very similar to that reported by Shah et al from India,[15] and other authors from middle- and low-income countries,[16] where it has become endemic and shows an increasing burden in HAIs. ESBL *E coli* increased from 40% in 2008 to 72% in 2014, resembling the results from the SENTRY Antimicrobial Surveillance Program, which reported an increase from 34% in 2008 to 48.4% in 2010.[17] Our results are also consistent with a previous report from our institution on bloodstream infections in patients with hematologic malignancies.[18]

In countries like Mexico, ESBL *E coli* has become endemic, and it is also found in the community. Fecal colonization rate of ESBL enterobacteria at time of admission in our institution is 14%, increasing up to 25% after prolonged hospitalization. The frequent exposure to the hospital environment and aggressive therapeutic and prophylactic interventions may disrupt the gut microbiota, exerting selective pressure. The latter partially explains ESBL *E coli* as the most frequent cause of SSI in most patients undergoing abdominal, pelvic, and other clean-contaminated surgeries. At our institution ESBL *E coli* is now endemic.

In most series from the United States, *S aureus* is the most frequent pathogen isolated in SSIs. In the current report, this did not occur; in contrast, we found a significant decrease in SSIs caused

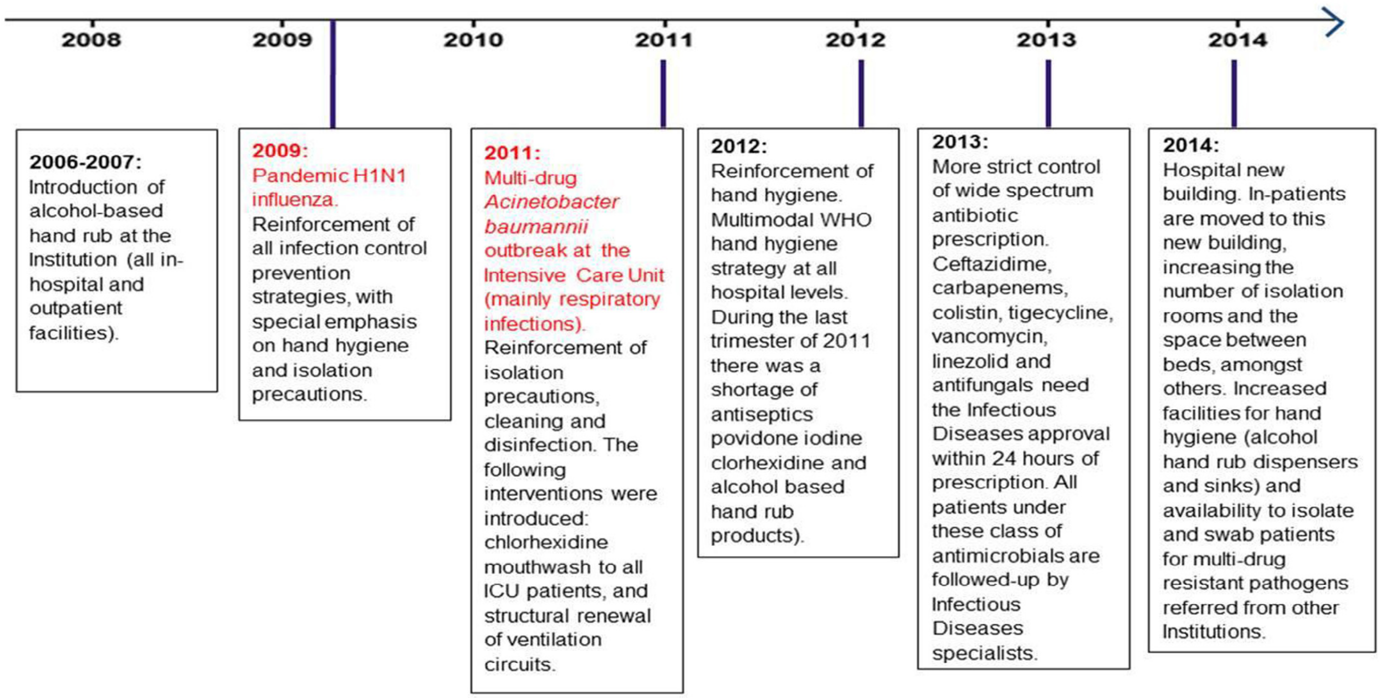

Fig 4. Timeline of infection control practices implemented through the study period. In red, outbreaks are highlighted. *ICU*, intensive care unit; *WHO*, World Health Organization.

by *S aureus*, and this could be because of the intensification on hand hygiene policies, introduction of alcohol-based handrub solutions, and introduction of other preventive measures deployed during the 2009 H1N1 pandemic influenza outbreak (Fig 4). During the influenza pandemic year, isolation precautions, hand hygiene, and more strict policies for visitors were reinforced.

Although we had very few SSIs caused by *E faecium*, we observed a trend toward an increase of VRE isolates (*P* is not significant), consistent with the increasing MDR bacteria observed in most series. Furthermore, between 2008 and 2010 there was an increase in MRSA isolates in blood and surgical infections, with a more frequent prescription of vancomycin to treat those infections. As explained in the report by Alatorre-Fernández et al, this probably exerted antimicrobial pressure in the hospital environment, with an increase in the isolation of VRE. In their report, the molecular analysis of vancomycin-resistant *E faecium* in blood specimens turned out to be polyclonal.[19]

S aureus was the predominant isolate after breast cancer surgery, as shown in Figure 3. As expected, most of these surgeries were clean procedures, and 69% (345/497) were monomicrobial, in agreement with reports by other authors.[5,20] Overall, breast surgery showed a high SSI rate, with a sustained increase in MRSA isolates and a stable proportion of GNB over the study period. Similar to our report, other studies have also found a high proportion of GNB in breast isolates, despite it being a clean procedure.[20] In all these series, *Pseudomonas* has also been identified in approximately 25% of cases.[20,21] An increased rate of SSI caused by GNB may result from prior exposures of the patient to the health care environment, previous broad-spectrum antimicrobial therapy, and resistance to the aforementioned prophylactic agents, mainly cefazolin and cefuroxime.[20,22]

The proportion of isolates of *P aeruginosa* was 8%, similar to other reports[6] of SSI. *P aeruginosa* was more prevalent in infections occurring in head and neck surgery and in patients undergoing abdominal-thoracic resections for soft tissue tumors. In head and neck surgeries involving the opening of oral cavity mucosa, *P aeruginosa* developed in 37 of 132 SSIs (28%). In a recent review of SSIs after head and neck surgeries with flap reconstruction, GNB were responsible for 44% of the infections.[23] It has been suggested that *Pseudomonas*, and *Enterobacteriaceae*, can be part of the normal microbiome in wet skin areas, facilitating their entry during the surgical procedure or through tracheostomy tube manipulation.[23,24]

The resistance of *P aeruginosa* to ciprofloxacin and third-generation cephalosporins is increasing, and in some settings, resistance to carbapenem has also become a problem.[25] In our series, ciprofloxacin-resistant *P aeruginosa* augmented over time, from 20% in 2008 to 40% in 2014. These findings are consistent with those of other reports in Mexico and elsewhere,[25,26] and this needs to be considered when initiating empirical antimicrobial treatment after head and neck surgeries, or in those settings with a high prevalence of *Pseudomonas* infection. In contrast, in our population, ceftazidime resistance decreased over the study period, being <10% since 2012. This could be the result of an antibiotic de-escalation, along with more frequent prescription of other antipseudomonal antibiotics, such as meropenem and piperacillin-tazobactam.

Our study has several limitations inherent to its design. As in any retrospective study, several biases were probably introduced, despite using standard definitions for SSI and a prospective, continuous surveillance program. Although some infections were probably misclassified, we consider that this behaved as a random error. Another limitation of the study is lacking quantitative wound bacterial cultures, in that they are not routinely performed at our institution.

Despite these limitations, our study possesses several strengths. In the current series, a fair amount of surgical procedures and SSIs were included, with the advantage of a prospective surveillance program during the last 20 years. This program has constantly collected information from different sources on surgeries and infections, including medical and nursing charts (with systematic chart review at the 30th postoperative day), microbiology reports, and readmissions to the hospital. During data capture, microbiologic and clinical data were available for review, with high verification rates.

CONCLUSIONS

The frequency of SSI was 7.9%, similar to other reports in patients with cancer, and consistent with rates of SSI from Mexico and other limited-resources countries.

In contrast with other studies from developed countries, gram-negative bacteria were the most frequent isolates, above gram-positive cocci. This study contributes to our field by providing a clear definition of causative microbiologic agents of SSI in low- and middle-income countries, and in hospital settings where ESBL enterobacteria are increasing in prevalence.

MDR pathogens, such as *E faecium* and *P aeruginosa*, are an emerging threat in surgical patients, increasing the burden of surgical infections, which are highly preventable and represent the most frequent HAIs in resource-limited countries.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ajic.2017.02.023.

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