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Risk Factors for Invasive Surgical Site Infections Among Adult Single Liver Transplant Recipients at Duke University Hospital in the Period 2015–2020

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Background. Invasive primary surgical site infections (IP-SSI) are a severe complication of liver transplant surgery. Identification of risk factors for IP-SSI is critical to IP-SSI prevention. **Methods.** All adult single liver transplants performed at Duke University Hospital in the period 2015–2020 were reviewed for IP-SSI occurring within 90 d of transplant. Risks for IP-SSI were identified using least absolute shrinkage and selection operator variable selection procedure. A 2-sided *P* value of <0.05 was considered statistically significant. **Results.** IP-SSI were identified in 34/470 (7.2%) adult single liver transplants. Repeat transplantation, spilt liver, Roux-en-Y biliary anastomosis, anastomotic leak, and post-transplant renal replacement therapy were positively associated with IP-SSI. IP-SSI were associated with increased length of index transplant hospitalization (24.5 versus 10.0 d, $P<0.01$) and 1-y all-cause mortality (14.7% versus 4.1%, $P=0.02$). Gram positive bacteria were the main pathogens (51.7%), followed by Gram negative bacteria (24.1%) and *Candida* (24.1%). Multidrug resistance bacteria increased over time (27.3% in 2015 versus 66.7% in 2020, $P=0.17$). **Conclusions.** In the setting of routine antimicrobial prophylaxis and an overall low rate of IP-SSI, surgical factors were the main determinants of IP-SSI among adult liver transplant recipients. IP-SSI had a negative impact on the length of index transplant hospitalization and 1-y mortality. While the surgical factors associated with an increased risk of IP-SSI are not easily modifiable, their impact may be best contained by close clinical monitoring and tailored antimicrobial therapy.

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INTRODUCTION

Despite improvements in surgical techniques and postoperative management, surgical site infections (SSI) still represent a frequent complication after liver transplant surgery and remain a major cause of post-transplant morbidity and mortality.[1-18] Specifically, SSI after liver transplant have been associated with prolonged index transplant hospitalization, need for rehospitalization, graft loss, and in-hospital mortality.[10] In addition, SSI after liver transplant result in increased health care–related costs and expenses.[1,7,10,12,16,19] Identifying risk factors for SSI is a crucial step in the prevention of these infections. While several research groups attempted to achieve this goal, their analyses are not contemporary (majority of the studies performed in the period 1990–2010) and suffered multiple limitations. These include small sample size (median n = 250), variable surveillance window for the identification of SSI (ranging from hospital discharge up to 365 d post-transplant), and inclusion of both superficial and invasive SSI, with superficial SSI being prone to recall bias in the context of retrospective studies (Table S1, SDC, http://links.lww.com/TXD/A709).[1-12] Our study aimed to identify risk factors for invasive primary surgical site infections (IP-SSI) within 90 d of transplant surgery among a

large, contemporary cohort of adult single liver transplant recipients at Duke University Hospital.

METHODS

Study Design

We performed an observational single-center retrospective cohort study of all adult patients who underwent a single liver transplant between January 1, 2015, and December 31, 2020, at Duke University Hospital (Durham, NC), a high-volume solid organ transplant center, which has been performing adult and pediatric solid organ transplants since 1965. This study was approved by the Duke University Health System Institutional Review Board (IRB number: Pro00104142). All study data were maintained on a secured REDCap platform offered by the Duke Office of Clinical Research. The study was performed in accordance with the STROBE guidelines.[20]

Study Population

Eligible patients were 18 y of age or older and met all the following criteria: (i) single liver transplant performed at Duke University Hospital during the 6-y study period and (ii) at least 12-mo post-transplant clinical follow-up available, unless death occurred before the 12-mo mark.

Definitions and Adjudication Process for Invasive Primary Surgical Site Infections

Centers for Disease Control and Prevention (CDC)—National Healthcare Safety Network (NHSN) definitions for SSI were used. Accordingly, SSI were defined as primary or secondary superficial incisional SSI, primary or secondary deep incisional SSI, and organ/space SSI.[21] Deep incisional and organ/space infections involving the primary surgical incision were considered invasive primary surgical site infections (IP-SSI). Detailed criteria used for the diagnosis and categorization of SSI are reported as supplementary digital contents (Table S2, SDC, http://links.lww.com/TXD/A709). Surgical site infections that occurred within 90 d after the transplant procedure were included. The date of SSI diagnosis was defined as the date when the first criterion used to meet the SSI definition occurred.

Cases of SSI were retrospectively adjudicated based on CDC-NHSN definitions by a team of transplant surgeons and infectious diseases specialists. Specifically, electronic medical records of adult SOT recipients were reviewed annually. For SOT performed in the year 2015, each SOT was reviewed independently by 2 reviewers with expertise in transplant infectious diseases. SSI cases were subsequently reviewed by a SOT surgeon. By virtue of the high degree of concordance (>95%) in the adjudication of SSI for the year 2015, each SOT performed in the period 2016–2020 was reviewed by a single reviewer with expertise in transplant infectious diseases. The review process included an in-depth manual evaluation of all surgical operative notes, infectious diseases consultation notes, and microbiology results obtained within 3 mo post-transplant procedures. Additional details on the adjudication process for SSI can be found in our previous publication.[22]

Other Study Definitions

Standard antimicrobial prophylaxis was defined as the administration of cefazolin (ciprofloxacin plus metronidazole in penicillin allergic patients) and clotrimazole in accordance with the institutional antimicrobial prophylaxis protocol in place during the study period (Table 1). Standard immunosuppression regimens used during the study period are reported as supplementary digital contents (Table S3, SDC, http://links.lww.com/TXD/A709). Anastomotic leak was defined as a visceral or biliary anastomotic leak occurring after liver transplant surgery. Return to the OR for abdominal surgery within 3 mo of transplant was defined as any abdominal surgery (including fascia closure) within 3 mo of transplant. For patients diagnosed with SSI, only abdominal surgeries performed before the diagnosis of SSI were included. Multidrug resistance (MDR) among Gram negative organisms was defined as resistance to at least 1 agent in at least 3 antimicrobial categories.[23] Extended-spectrum beta-lactamase (ESBL) *Enterobacteriaceae* were identified in accordance with the recommendations of the Clinical and Laboratory Standards Institute.[24] MDR Gram negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococci* were considered MDR bacteria. Length of hospital stay (LOS) was defined as number of days from admission date to the date of discharge during the index transplant hospitalization. In-hospital mortality was defined as all-cause mortality during the index transplant hospitalization. One-year mortality was defined as all-cause mortality from date of transplant to 365 d after transplant.[22]

Study Objectives

The primary aim of this study was to determine risks for IP-SSI during the study period among adult liver transplant recipients. Secondary aims included: (i) evaluating the rate of IP-SSI over time; (ii) assessing the microbiology of IP-SSI; and (iii) determining the clinical outcomes associated with IP-SSI among adult liver transplant recipients.

TABLE 1.

Perioperative antibacterial and antifungal (excluding *Pneumocystis jiroveci*) prophylaxis protocols for adult liver transplant surgery at Duke University Hospital in the period January 1, 2015–December 31, 2020

Antibacterial prophylaxis protocol	Antifungal prophylaxis protocol	Relevant protocol changes during study period
Standard Cefazolin (for 24 h; ciprofloxacin/metronidazole if penicillin allergy)	**Standard** Clotrimazole (for 3 mo)	Starting in 2018, if intraoperative transfusion requirements were ≥40 units of blood products, prophylaxis was modified as follows: piperacillin/tazobactam plus vancomycin plus fluconazole (for 5 d or as clinically indicated)
Fulminant liver failure Piperacillin/tazobactam (for 5 d or as clinically indicated)	**Fulminant liver failure** Fluconazole 400 mg q24h (for 5 d or as clinically indicated)	
Split liver Piperacillin/tazobactam (for 2 d or as clinically indicated)	**Split liver** Fluconazole 400 mg q24h (for 2 d or as clinically indicated)	

If history of pretransplant infection in donor or recipient, antibacterial and antifungal prophylaxis regimens were individualized.

Statistical Analysis

Continuous variables were calculated as medians with interquartile ranges (IQR). Categorical variables were calculated based on frequencies and percentages of the specified group. IP-SSI rates were calculated based on the total number of single liver transplants (denominator) and total number of IP-SSI (numerator). A univariate analysis for risk factors for IP-SSI was performed: odds ratios and *P* values were calculated. To identify features associated with IP-SSI, least absolute shrinkage and selection operator (LASSO) was implemented as a variable selection procedure. Based on epidemiologic plausibility and collinearity considerations, the following variables were entered in the initial model: BMI, repeat transplantation, split liver, Roux-en-Y biliary anastomosis, units of packed red blood cells required during transplant surgery, anastomotic leak, post-transplant renal replacement therapy, and return to the OR for abdominal surgery within 3 mo of transplant. Continuous variables were standardized before entering into the model. The tuning parameter that resulted in the minimum deviance (selected via tenfold cross validation) gave the final model. The (unregularized) odds ratios for the variables selected by LASSO model were presented with confidence intervals derived using a post selection inference procedure (R package Selective Inference).[25] Since some patients died within 90 d without diagnosis of IP-SSI, a sensitivity analysis was conducted, which refit the model above excluding patients that died within 90 d without IP-SSI diagnosis. Statistical analyses were performed using IBM SPSS Statistics (version 29.0; IBM, Armonk, NY) and R version 4.4.0 (R Package Selective Inference).

RESULTS

During the 6-y study window, 470 adult single liver transplants were performed at Duke University Hospital and a 12-mo post-transplant clinical follow-up was available for all. The median age of recipients was 58.6 (IQR 50.1–64.4) y, and the majority were Caucasian (82.6%) and male (68.1%) (Table 2). Among the 470 liver transplant recipients, 34 (7.2%) developed an IP-SSI within 90 d from transplant surgery (Figure 1). IP-SSI were diagnosed a median of 13.5 (IQR 12.1–25.5) d after transplant and 11 (32.4%) occurred despite receipt of perioperative antimicrobial prophylaxis with activity against the pathogens later identified as the cause of IP-SSI. None of the IP-SSI documented were donor derived. The rate of IP-SSI declined over the study period, but the variation was not statistically significant (14.3% in 2015 versus 9.9% in 2020, $P = 0.44$) (Figure 2).

IP-SSI Risk Factors

Per Table 2, repeat transplantation status (14.7% versus 1.6%), receipt of pretransplant immunosuppressive therapy (17.6% versus 6.9%), and prior hepatobiliary surgery (52.9% versus 27.1%) were more common among patients who developed an IP-SSI compared with those patients who did not. Concordance with institutional antimicrobial prophylaxis recommendations was high among both groups, and patients who received the standard prophylaxis regimen (cefazolin; ciprofloxacin plus metronidazole if documented penicillin allergy) were less likely to develop an IP-SSI compared with those who received a nonstandard regimen (65.4% versus 38.2%).

Operative factors that were more common among patients who developed an IP-SSI included living donor status (11.8% versus 0.7%), split liver procedure (17.6% versus 2.8%), Roux-en-Y biliary anastomosis (50.0% versus 13.1%), operative time above 8 h (41.2% versus 12.2%), higher intraoperative blood product requirements (5.0 (IQR 1.0–9.3) versus 3.0 (IQR 0.0–6.0) packed red blood cells units), and peritoneal contamination due to accidental entry into the gastrointestinal tract (11.8% versus 0.2%).

Among post-transplant factors, development of an anastomotic leak (44.1% versus 2.8%), need for post-transplant renal replacement therapy (35.3% versus 10.8%), and return to the OR for abdominal surgery within 3 mo of transplant (44.8% versus 17.7%) were more frequent among patients with IP-SSI (Tables 2 and 3). Based on epidemiologic plausibility and collinearity considerations (eg, collinearity between living donor status and split liver procedure; prior hepatobiliary surgery and repeat liver transplantation), the following 8 variables were entered in the initial LASSO model: repeat transplantation, split liver, Roux-en-Y biliary anastomosis, units of packed red blood cells required during surgery, anastomotic leak, post-transplant renal replacement therapy, return to the OR for abdominal surgery within 3 mo of transplant, and BMI. Although peritoneal contamination due to accidental entry into the gastrointestinal tract was of interest as a potential predictor, we did not include this in the model, since there were very low cell counts, which resulted in large odds ratios and unstable confidence intervals. The tuning parameter that resulted in the minimum deviance (selected via tenfold cross validation) gave a model that selected 6 variables: repeat transplantation, split liver, Roux-en-Y biliary anastomosis, anastomotic leak, post-transplant renal replacement therapy, and BMI. All variables were found to be positively associated with IP-SSI except for BMI (Table 4). Since some patients died within 90 d without diagnosis of IP-SSI, a sensitivity analysis was conducted, which refit the model above excluding the 7 patients that died within 90 d without IP-SSI diagnosis. This sensitivity analysis gave similar results as the main analysis (Table 4).

IP-SSI Microbiology

Among the 34 IP-SSI, 18 (52.9%) were monomicrobial and 16 (47.1%) polymicrobial. Fifty-eight pathogens were isolated from samples collected at the infected sites. Of the pathogens isolated, 30 (51.7%) were Gram positive bacteria, 14 (24.1%) Gram negative bacteria, and 14 (24.1%) *Candida* species. While no statistically significant variation in pathogen distribution was observed over time, Gram negative bacteria tended to be responsible for a higher proportion of cases at the end of the study period (13.3% in 2015 versus 41.7% in 2020, $P = 0.19$) (Figure 3).

Among 30 Gram positive bacteria, more than half (16, 53.3%) were *Enterococci* of which 8 (50.0%) were vancomycin resistant. Four *Staphylococci* were isolated, and all were methicillin susceptible. Among 14 Gram negative bacteria, MDR was identified in 10 (71.4%); one was carbapenem resistant and 4 were ESBLs producers. The proportion of MDR organisms among Gram negative bacteria increased over time without reaching statistical significance (50.0% in 2015 versus 80.0% in 2020, $P = 1.00$). Similarly, when the

TABLE 2.

Baseline characteristics of 470 adult patients who underwent a single liver transplant at Duke University Hospital in the period January 1, 2015–December 31, 2020, stratified by development of IP-SSI within 90 d of transplant surgery

	N = 470	No IP-SSI n = 436	IP-SSI n = 34
Male gender, n (%)	320 (68.1)	297 (68.1)	23 (67.6)
Race, n (%)			
Caucasian	388 (82.6)	361 (82.8)	27 (79.4)
African American	49 (10.4)	46 (10.6)	3 (8.8)
Asian	11 (2.3)	7 (1.6)	4 (11.8)
American Indian or Alaska Native	6 (1.3)	6 (1.4)	0 (0.0)
Other	6 (1.3)	6 (1.4)	0 (0.0)
Declined	10 (2.1)	10 (2.3)	0 (0.0)
Age (y), median (IQR)	58.6 (50.1–64.4)	58.7 (50.3–64.4)	54.6 (41.8–63.5)
BMI, median (IQR)	29.9 (26.3–33.4)	29.9 (26.4–33.5)	28.4 (23.2–32.6)
Underlying disease leading to transplant, n (%)			
Hepatocellular carcinoma	92 (19.6)	88 (20.2)	4 (11.8)
Drug-induced acute hepatic Necrosis	3 (0.6)	3 (0.7)	0 (0.0)
Acute hepatic necrosis other	8 (1.7)	7 (1.6)	1 (2.9)
Cirrhosis biliary (primary and secondary)	15 (3.2)	13 (3.0)	2 (5.9)
Cirrhosis alcoholic	84 (17.9)	80 (18.3)	4 (11.8)
Cirrhosis autoimmune	13 (2.8)	10 (2.3)	3 (8.8)
Cirrhosis cryptogenic	24 (5.1)	23 (5.3)	1 (2.9)
Cirrhosis NASH	97 (20.6)	94 (21.6)	3 (8.8)
Cirrhosis HBV related	7 (1.5)	6 (1.4)	1 (2.9)
Cirrhosis HCV related	60 (12.7)	54 (12.4)	6 (17.6)
Cholangiocarcinoma	4 (0.9)	3 (0.7)	1 (2.9)
Hepatic epithelioid Hemangioendothelioma	4 (0.9)	3 (0.7)	1 (2.9)
Primary sclerosing cholangitis	40 (8.5)	34 (7.8)	6 (17.6)
Alpha 1 antitrypsin deficiency	8 (1.7)	8 (1.8)	0 (0.0)
Hemochromatosis	1 (0.2)	1 (0.2)	0 (0.0)
Other	10 (2.1)	9 (2.1)	1 (2.9)
Pretransplant immunosuppressive therapy, n (%)	36 (7.6)	30 (6.9)	6 (17.6)
Pretransplant diabetes, n (%)	152 (32.3)	140 (32.1)	12 (35.3)
Pretransplant end stage renal disease, n (%)	20 (4.6)	20 (4.6)	0 (0.0)
Antibiotic use in the 4 mo before transplant, n (%)	349 (74.3)	324 (74.3)	25 (73.5)
Ascites, n (%)	293 (62.3)	274 (62.8)	19 (55.9)
Prior hepatobiliary surgery, n (%)	136 (28.9)	118 (27.1)	18 (52.9)
Days admitted before transplant, median (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–5.5)
MELD score at transplant, median (IQR)	19.5 (14.0–27.0)	19.0 (14.0–27.0)	21.5 (15.8–28.8)
Standard antimicrobial prophylaxis regimen, n (%)	298 (63.4)	285 (65.4)	13 (38.2)
Concordance of antimicrobial prophylaxis administered with institutional protocol, n (%)	422 (89.8)	393 (90.1)	29 (85.3)

(Continued)

TABLE 2.
Continued

	N = 470	No IP-SSI n = 436	IP-SSI n = 34
Repeat transplantation, n (%)	12 (2.6)	7 (1.6)	5 (14.7)
Living donor status, n (%)	7 (1.5)	3 (0.7)	4 (11.8)
Split liver, n (%)	18 (3.8)	12 (2.8)	6 (17.6)
Cold ischemic time (min), median (IQR)	295.0 (237.0–366.5)	294.0 (236.0–363.0)	313.5 (248.8–421.5)
Warm ischemic time (min), median (IQR)	39.0 (34.0–43.0)	39.0 (35.0–43.0)	35.5 (32.0–40.0)
Primary closure, n (%)	455 (96.8)	424 (97.2)	31 (91.2)
Transplant surgery > 8 h, n (%)	67 (14.3)	53 (12.2)	14 (41.2)
Roux-en-Y biliary anastomosis, n (%)	74 (15.7)	57 (13.1)	17 (50.0)
Peritoneal contamination due to accidental entry into GI tract, n (%)	5 (1.1)	1 (0.2)	4 (11.8)
Units PRBC required during surgery, median (IQR)	3.0 (0.0–6.0)	3.0 (0.0–6.0)	5.0 (1.0–9.3)
Anastomotic leak, n (%)	27 (5.7)	12 (2.8)	15 (44.1)
Post-transplant renal replacement therapy, n (%)	59 (12.6)	47 (10.8)	12 (35.3)
Return to the OR for abdominal surgery within 3 mo of transplant, n (%)	90 (19.1)	77 (17.7)	13 (44.8)

BMI, body mass index; CI, confidence interval; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end stage liver disease; NASH, nonalcoholic steatohepatitis; PRBC, packed red blood cells.

cumulative proportion of MDR among Gram positive and negative bacteria was evaluated, MDR increased from 27.3% in 2015 to 66.7% in 2020 ($P = 0.17$) (Figure 4A,B).

Candida albicans accounted for 5 (35.7%) of the 14 *Candida* isolates. *Candida glabrata* was the most common *non-albicans* species (77.8%), and all *Candida glabrata* isolates were susceptible dose-dependent to fluconazole. A detailed description of all the pathogens isolated is reported in Table S4 (SDC, http://links.lww.com/TXD/A709).

IP-SSI Outcomes

Recipients who developed an IP-SSI required a complex multidisciplinary management, which included antimicrobial therapy in all the cases (34, 100%) and surgical reoperation in approximately half of the cases (16, 47.1%). Recipients who developed an IP-SSI had longer index transplant hospitalization (24.5 versus 10.0 d, $P < 0.01$) and higher 1-y mortality (14.7% versus 4.1%, $P = 0.02$) compared with adult single liver transplant recipients, who did not develop an IP-SSI. In-hospital mortality and 30-d mortality did not differ significantly among the study groups (Table 5).

DISCUSSION

This study documented a low overall rate (7.2%) of IP-SSI among adults undergoing single liver transplant at Duke University Hospital during a recent 6-y period. Notably, rates of IP-SSI remained low during year 2020 despite the COVID pandemic and its adverse consequences on transplant systems. While historical rates of SSI after liver transplant surgery reported in the literature have ranged from 8.8% to 37.5%,[1-7,9-18] direct comparison of rates between studies is not possible. While we excluded superficial SSI from our analysis owing to lower diagnostic certainty, our assessment was also more comprehensive than most as we elected to include all IP-SSI occurring within 90 d of the transplant surgery rather than only those occurring during the index transplant hospitalization or within the first month after transplant to be in line with CDC-NHSN definitions.[2,3,5,6,8,9,12,16] Using these definitions and in the setting of relatively high compliance with a standardized antimicrobial prophylaxis protocol, surgical factors (repeat transplantation, split liver, Roux-en-Y biliary anastomosis, anastomotic leak) were among the main determinants of IP-SSI, which resulted in longer index transplant hospital stay and which had a negative impact on 1-y all-cause mortality. Notably, these findings are in line with historical risks and are related to the complexity of the surgical procedure and are therefore not easily modifiable.[2-4,6,10,11,26,27] Whether longer duration or broader spectrum antimicrobial therapy would be effective in preventing such infections and improving outcomes is unclear.

Relative to spectrum of coverage, our data emphasize several observations worthy of consideration. While there were no MRSA infections documented, *Enterococci* (and VRE specifically) were responsible for a substantial proportion of the IP-SSI caused by Gram positive bacteria in our cohort.[3,4] While this is in line with historical reports documenting increasing rates of SSI due to VRE in the liver transplant population at other centers, the 2018 changes to our institutional prophylaxis protocol wherein vancomycin was added in cases of liver transplant surgeries with massive blood product

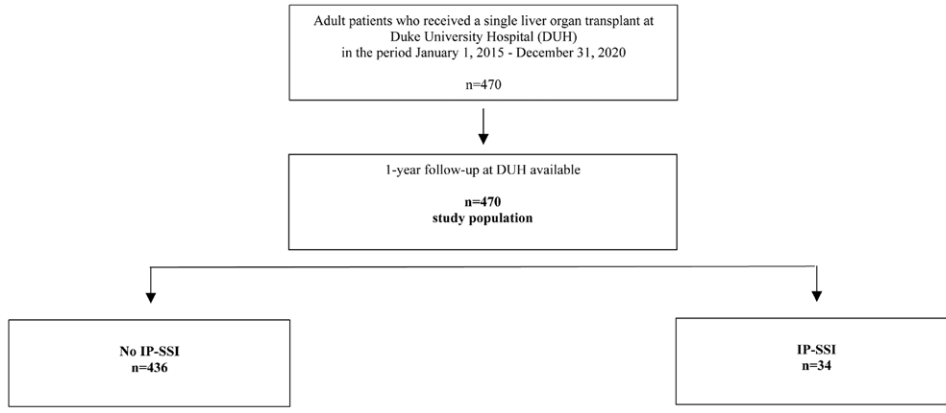

FIGURE 1. Study population.

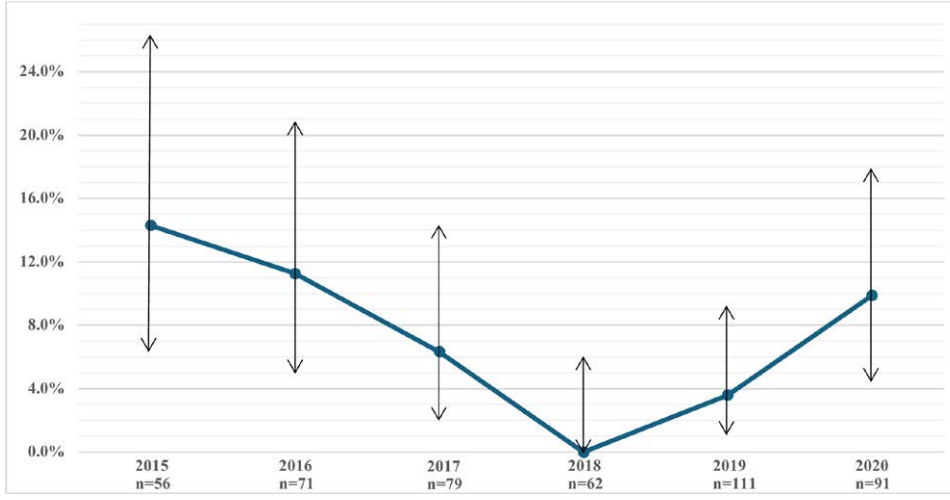

FIGURE 2. Rates (and 95% CI) of IP-SSI within 90 d of transplant surgery among adult single liver transplant at Duke University Hospital in the period January 1, 2015–December 31, 2020. CI are shown by black arrows. 95% CI, confidence intervals; IP-SSI, invasive primary surgical site infections.

requirements may have influenced these findings. Use of vancomycin may have prevented MRSA infections, while selecting for vancomycin-resistant *Enterococci*. Notably, however, no MRSA infections occurred before the use of vancomycin and only a quarter of VRE cases occurred after the 2018 protocol changes. Since pretransplant VRE colonization is a known risk for VRE SSI among liver transplant recipients and given that none of the patients with VRE IP-SSI in our cohort received microbiologically appropriate perioperative prophylaxis, VRE screening pretransplant and targeted antimicrobial prophylaxis at time of transplant for those colonized seem reasonable considerations.[10,28] Further, whether vancomycin should be routinely employed, even in the setting of high-volume transfusion requirements, particularly considering its potential for acute kidney injury in patients with competing risks for renal injury, requires further study.[29]

Regarding Gram negative coverage, only 25% of the IP-SSI in our study were caused by Gram negatives and was limited to only 4 ESBL producers and 1 carbapenem-resistant pathogen over the 6-y period. While the proportion of MDR Gram negative pathogens increased over time in our study population, the percent was similar to the trend observed in the non-transplant population at our institution, where the prevalence of ESBL among *Escherichia coli* isolates rose from 5% in 2015 to 21% in 2020. The current overall low rate of IP-SSI in our liver population suggests that our current Gram negative coverage recommendations still work reasonably well at our institution, but warrants closely monitoring.

In studies from other institutions, however, Gram negatives are responsible for up to 50% to 75% of SSI in the liver population,[2,6,14] with high rates of carbapenem resistance reported from some.[4] While the impact of antimicrobial prophylaxis choice on emergence of MDR in the liver transplant population is uncertain, it should be taken into careful consideration alongside programmatic rates of MDR infections. Broader prophylaxis to cover MDR organisms may cause selective antimicrobial pressure favoring the emergence of even more resistant strains, particularly in the setting of unrepaired anatomical abnormalities that also serve as an ongoing source for infection. As demonstrated by the development of IP-SSI even in patients receiving microbiologically appropriate prophylaxis in our cohort, broadening antimicrobial prophylactic regimens would not necessarily prevent all IP-SSI in patients with such risks. A multipronged and individualized approach inclusive of real time monitoring for accruing IP-SSI risks, early surgical intervention for biliary and anastomotic leaks and antimicrobial therapy tailored according to pathogens detected may be the most effective intervention.

TABLE 3.

Risk factors for invasive primary surgical site infection (IP-SSI) within 90 d of transplant surgery among 470 adult single liver transplants performed at Duke University Hospital in the period January 1, 2015–December 31, 2020, univariate analysis

	OR (95% CI)	*P* value
Male gender, n (%)	1.0 (0.5-2.2)	1.00
Race, n (%)		
Caucasian	Reference	0.59
Non-Caucasian	1.2 (0.5-3.0)	
Age (y), median (IQR)	0.9 (0.9-1.0)	0.08
BMI, median (IQR)	0.9 (0.9-1.0)	0.07
Underlying disease leading to transplant, n (%)		
Hepatocellular carcinoma	Reference	0.23
Nonhepatocellular carcinoma	1.9 (0.7-5.6)	
Pretransplant immunosuppressive therapy, n (%)	**2.9 (1.1-7.5)**	**0.03**
Pretransplant diabetes, n (%)	1.1 (0.6-2.4)	0.70
Pretransplant end stage renal disease, n (%)	0.9 (0.9-0.9)	1.00
Antibiotic use in the 4 mo before transplant, n (%)	0.9 (0.4-2.1)	0.92
Ascites, n (%)	0.7 (0.4-1.5)	0.42
Prior hepatobiliary surgery, n (%)	**3.0 (1.5-6.1)**	**<0.01**
Days admitted before transplant, median (IQR)	1.0 (0.9-1.1)	0.17
MELD score at transplant, median (IQR)	1.0 (0.9-1.1)	0.26
Standard antimicrobial prophylaxis regimen, n (%)	**0.3 (0.2-0.7)**	**<0.01**
Concordance of antimicrobial prophylaxis administered with institutional protocol, n (%)	0.6 (0.2-1.7)	0.34
Repeat transplantation, n (%)	**10.6 (3.2-35.4)**	**<0.01**
Living donor status, n (%)	**19.2 (4.1-89.9)**	**<0.01**
Split liver, n (%)	**7.6 (2.6-21.7)**	**<0.01**
Cold ischemic time (min), median (IQR)	1.0 (0.9-1.0)	0.43
Warm ischemic time (min), median (IQR)	1.0 (0.9-1.0)	0.07
Primary closure, n (%)	0.3 (0.8-1.1)	0.07
Transplant surgery >8 h, n (%)	**5.1 (2.4-10.6)**	**<0.01**
Roux-en-Y biliary anastomosis, n (%)	**6.6 (3.2-13.8)**	**<0.01**
Peritoneal contamination due to accidental entry into GI tract, n (%)	**58.0 (6.3-535.3)**	**<0.01**
Units PRBC required during surgery, median (IQR)	**1.1 (1.0-1.1)**	**0.01**
Anastomotic leak, n (%)	**27.9 (11.5-67.8)**	**<0.01**
Post-transplant renal replacement therapy, n (%)	**4.5 (2.1-9.7)**	**<0.01**
Return to the OR for abdominal surgery within 3 mo of transplant, n (%)	**3.8 (1.8-8.3)**	**<0.01**

Statistically significant results are presented in bold.BMI, body mass index; CI, confidence interval; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; IP-SSI, invasive primary surgical site infection; MELD, model for end stage liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PRBC, packed red blood cells.

TABLE 4.

Risk factors for IP-SSI within 90 d of transplant surgery among 470 adult single liver transplants performed at Duke University Hospital in the period January 1, 2015,–December 31, 2020, Lasso model

Variables	Main model aOR (95% CI)	Sensitivity analysis aOR (95% CI)
Repeat transplantation	3.4 (0.1-19.8)	3.3 (0.1-19.9)
Split liver	2.3 (0.1-17.1)	2.9 (0.1-262.3)
Roux-en-Y biliary anastomosis	5.8 (2.1-17.6)	5.7 (2.1-59.2)
Anastomotic leak	27.1 (8.6-94.8)	26.8 (5.0-79.8)
Post-transplant renal replacement therapy	6.9 (2.4-19.3)	7.1 (2.3-19.9)
BMI	0.7 (0.5-5.5)	0.8 (0.6-269.0)

95% CI, 95% confidence intervals; IP-SSI, invasive primary surgical site infection.

Candida represented 24% of pathogens causing IP-SSI in our study, with a high proportion of isolates (64.3%) being *non-albicans Candida* with dose-dependent susceptibility to fluconazole. This rate of *Candida* SSI among liver transplant recipients is higher than those reported in the literature wherein they ranged from 2.5% to 15.0%.[2,6,10] Our center adopted a tailored antifungal prophylaxis strategy, reserving systemic antifungal agents only to those patients with fulminant liver failure, split liver procedure, and extensive intraoperative blood products requirements. However, our current data challenges this approach and suggests the need for more comprehensively covering the other well-known risks specific for *Candida* in this population. In addition, the high proportion of *non-albicans Candida* isolates with dose-dependent susceptibility to fluconazole queries the appropriateness of our currently recommended prophylactic fluconazole dosing (400 mg daily).

Relative to antimicrobial prophylaxis duration, our center administered antimicrobial prophylaxis for 24 h after liver transplant surgery. Prophylaxis was extended only in case of split liver procedures (48 h) and fulminant liver failure leading to transplant (5 d). This is in line with the recommendations of the American Society of Transplantation and the American Society of Health System Pharmacists, which suggest limiting the duration of prophylaxis to 24–48 h after liver transplant surgery.[30,31] In our cohort, IP-SSI occurred at

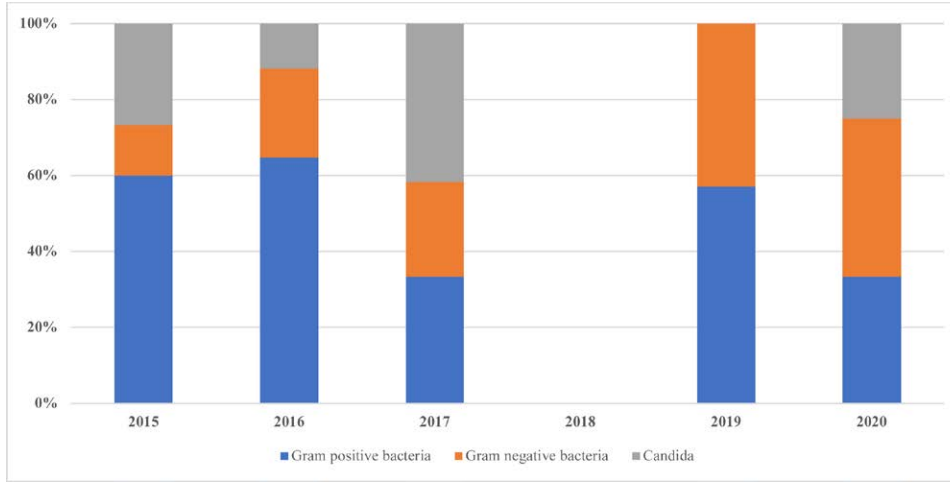

FIGURE 3. Causative pathogens of IP-SSI within 90 d of transplant surgery identified among adult patients who underwent a single liver transplant at Duke University Hospital in the period January 1, 2015– December 31, 2020. IP-SSI, invasive primary surgical site infections.

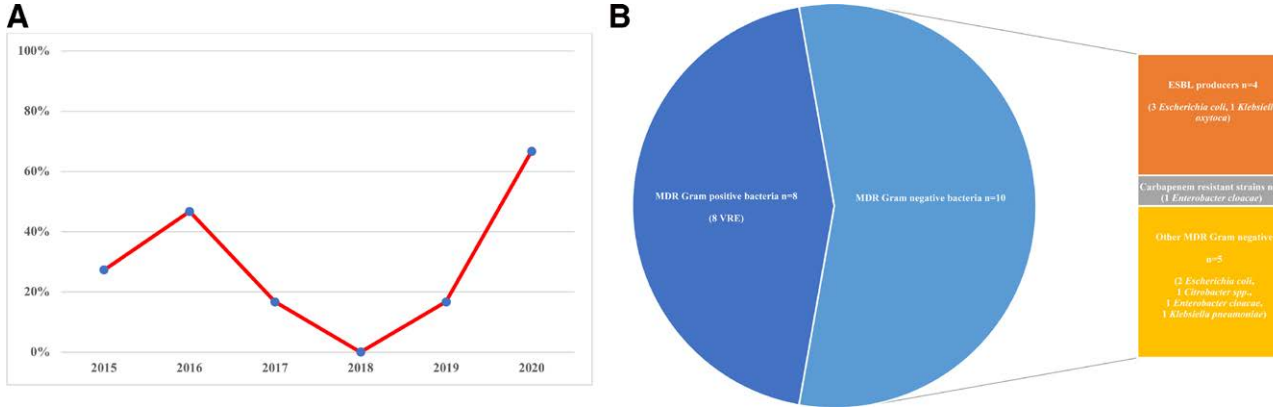

FIGURE 4. A, MDR bacteria causing IP-SSI within 90 d of transplant surgery identified among adult patients who underwent a single liver transplant at Duke University Hospital in the period January 1, 2015–December 31, 2020. B, MDR bacteria causing IP-SSI within 90 d of transplant surgery identified among adult patients who underwent a single liver transplant at Duke University Hospital in the period January 1, 2015–December 31, 2020. IP-SSI, invasive primary surgical site infections; MDR, multidrug resistance.

TABLE 5.

Outcomes of adult patients who underwent a single liver transplant at Duke University Hospital in the period January 1, 2015–December 31, 2020 stratified by development of IP-SSI within 90 d of transplant surgery

	No IP-SSI n = 436	IP-SSI n = 34	*P* value
Length of hospital stay (d), median (IQR)	10.0 (7.0-16.0)	24.5 (11.8-46.3)	**<0.01**
In-hospital mortality, n (%)	4 (0.9)	1 (2.9)	0.31
30-d mortality, n (%)	5 (1.1)	2 (5.9)	0.09
1-year mortality, n (%)	18 (4.1)	5 (14.7)	**0.02**

Statistically significant results are presented in bold. 95% CI, 95% confidence intervals; IP-SSI, invasive primary surgical site infection; IQR, interquartile range.

a median of 13.5 d after transplant, querying the utility of prolonged antimicrobial prophylaxis. Recent studies, including a randomized control trial, did not show any benefit on the incidence of SSI in extending the duration of antimicrobial prophylaxis above 24 h post liver transplant surgery.[32,33] Given the unclear benefit posed by extended antimicrobial prophylaxis and the potential risks associated with this approach (including emergence of resistant pathogens and *Clostridium difficile* infections), limiting prophylaxis to 24–48 h after liver transplant surgery and monitoring closely patients in the post-surgical period seems a reasonable approach. Further studies are needed to refine the duration of antimicrobial prophylaxis in the context of high-risk liver transplant surgeries, such as split liver procedures and fulminant liver failure.

The development of IP-SSI was associated with increased duration of index transplant hospitalization and higher 1-y mortality in our liver transplant population. While there

is consensus on the profound effect of SSI on the duration of the transplant hospitalization, the need for readmission, and increase in health care costs, the contribution of SSI on mortality is more controversial.[1,7,10,12,16,19] Hellinger, Kirkland, and Viehman reported a statistically significant association between the occurrence of SSI and mortality among liver transplant recipients, while no effect on mortality was observed by Freire and Hollebeak.[1,4,5,10,19] Deciphering the impact of competing risks on mortality is difficult at best, as sicker patients require more complex surgery and are often at increased risk for other complications that also portend poor outcome. Further studies are needed to clarify the effect of SSI on the survival of liver transplant recipients.

There are several limitations of our retrospective study. While we believe the impact of selection bias is negligible (no lost to follow-up over 470 patients), information bias may have occurred. To minimize the risk of information bias arising from possible incomplete reporting of superficial SSI in source documents, we limited our evaluation to IP-SSI cases only. Our study also lacks information regarding pretransplant colonization with MDR bacteria as systematic screening for colonization with MDR bacteria in liver transplant candidates was not routinely performed at our center during the study period. Our study also lacks information on adverse events associated to antimicrobials, such as *Clostridium difficile* infections. Finally, the external validity of this study is hampered by its single-center design and low number of IP-SSI. Data generated by this study reflect the epidemiology, outcomes, and management practices associated with IP-SSI among adult single liver transplant recipients at a single institution over the period 2015–2020.[22] However, we believe our contemporary experience provides invaluable insight for other liver transplant centers contemplating IP-SSI preventive measures for their programs.

In conclusion, in the setting of a standardized prophylactic approach, we documented an overall low rate of IP-SSI among liver transplant recipients at our center over a recent 6-y period. Despite low rates of IP-SSI, the exercise provided helpful information that could be used to refine the prophylactic approach at our center. Importantly, surgical factors were found to be the main drivers of IP-SSI risk. As surgical factors are not easily modifiable, their impact may be best contained by close clinical monitoring, early surgical intervention for leaks, and with the spectrum of antimicrobial therapy tailored to pathogens detected and according to the patients' specific circumstances. Importantly, our data suggest that broadening antimicrobial prophylaxis alone in an attempt to cover MDR pathogens may not be sufficient to reduce the development of IP-SSI in this setting, but rather, may favor the emergence of even more resistant organisms. Further studies are needed to evaluate the most effective preventive approach in liver transplant recipients at high risk for IP-SSI.

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