Received: 1 April 2022 | Revised: 25 August 2022 | Accepted: 30 August 2022

DOI: 10.1111/ajt.17189

ORIGINAL ARTICLE

Epidemiology of surgical site infections after solid organ transplants in the period 2015–2019: A single-center retrospective cohort study

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Surgical site infections (SSI) are severe complications of solid organ transplant (SOT). This retrospective study assessed the epidemiology of and outcomes associated with invasive primary SSI (IP-SSI) occurring within 3 months of transplantation in adult SOT recipients at Duke University over a 5-year period (2015–2019). Among 2073 consecutive SOT recipients, 198 IP-SSI were identified. The IP-SSI rate declined over the period (14.4% in 2015 vs. 8.3% in 2019) and was higher among multi-organ compared with single-organ transplants (33.9% vs. 8.1%, $p < .01$). SOT recipients with IP-SSI had longer hospital stays than patients without SSI (30.0 vs. 17.0 days, $p < .01$). Transplant hospitalization (9.6% vs. 2.2%, $p < .01$), 6-month (11.6% vs. 3.3%, $p < .01$), and 1-year mortality (15.7% vs. 5.8%, $p < .01$) were higher in SOT recipients with IP-SSI than in those without. While Gram-positive bacteria were the most common pathogens, urogenital Mollicute and atypical Mycobacteria were identified as an unexpected cause of IP-SSI, particularly among lung transplant recipients. The median time to IP-SSI was 24.0 (IQR 13.8–48.3) days, although the time to IP-SSI varied based on organ transplanted and the causative pathogen. IP-SSI is an important and potentially modifiable complication of SOT, associated with prolonged hospitalizations and reduced survival, particularly in the lung transplant population.

KEYWORDS
clinical research / practice, complication: infectious, infection - mycobacterial: nontuberculous, infection and infectious agents – bacterial, infection and infectious agents – fungal, infectious disease

Abbreviations: CDC, Centers for Disease Control and Prevention; EMR, electronic medical record; IP-SSI, invasive primary surgical site infections; IQR, interquartile ranges; I-SSI, invasive surgical site infections; LOS, length of hospital stay; MDR, multidrug resistance; NHSN, National Healthcare Safety Network; SOT, solid organ transplant; SSI, surgical site infections; US, United States of America.

1 | INTRODUCTION

Despite improvements in infection control practices, surgical site infections (SSI) still account for almost 20% of all hospital-acquired infections and are associated with adverse outcomes[1] including increased morbidity, mortality, length of hospital stay, and hospitalization cost.[2,3] Transplant surgery is characterized by a substantial risk of SSI because of the baseline comorbidities of solid organ transplant (SOT) recipients, the surgical complexity of transplant procedures, and the need for post-transplant immunosuppression.[4] These factors may significantly influence both the timing and type of pathogens that cause SSI in this population.

Studies to date have shown that SSI after transplant surgery impairs post-transplant recovery and leads to graft failure and death.[5] The reported rate of SSI among SOT recipients ranges from 2.0% to 46.2%, with the lowest rates historically reported among kidney transplants and the highest among multi-organ transplants.[6,7] While several studies over the past 20 years have evaluated the burden and risk factors for SSI after abdominal organ transplantation,[6–29] very few data are available in the thoracic organ transplant setting. Based on a 2008 multi-center prospective study, SSI was estimated to occur after 4.8% of heart transplant surgeries,[30] while two single-center retrospective studies in 2013 and 2017 documented SSI complicating 5% and 9% of lung transplantations, respectively.[31,32] Despite these individual reports, to the best of our knowledge, there has not been a comprehensive assessment of the epidemiology of SSI across all SOT types (Table S1). In this study, we assessed the epidemiology and outcomes of SSI among SOT populations over a 5-year period in a major US transplant center.

2 | METHODS

2.1 | Study design

We performed an observational single-center retrospective cohort study of all patients who underwent a SOT procedure between January 1, 2015 and December 31, 2019 at Duke University Hospital (Durham, NC, USA), a high-volume solid organ transplant center that has been performing adult and pediatric SOT 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.

2.2 | Study population

Eligible patients were 18 years of age or older and met all the following criteria: (i) SOT performed at Duke University Hospital during the 5-year study period, (ii) at least 12-month post-transplant clinical follow-up available unless death occurred before the 12-month mark, and (iii) administration of peri-operative antimicrobial prophylaxis and induction immunosuppression as per institutional protocols (Table S2–S3).

2.3 | Definitions and adjudication process for surgical site infections (SSI)

Using the Centers for Disease Control and Prevention (CDC) - National Healthcare Safety Network (NHSN) definitions for SSI, SSI needed to occur within 3 months after the transplant procedure.[1] Infections were defined as primary or secondary superficial incisional SSI, primary or secondary deep incisional SSI, and organ/space SSI. Deep incisional SSI and organ/space SSI were considered invasive SSI (I-SSI). For the primary analyses, only invasive primary SSI (IP-SSI) were considered: secondary (not involving the primary incision) and superficial (more difficult to retrospectively adjudicate) SSI were excluded. Detailed criteria used for the diagnosis and categorization of SSI are reported in Table S4. 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 (EMRs) of adult SOT recipients were reviewed annually. A manual review of EMRs was performed for all adult SOT recipients fulfilling at least one of these three criteria: (i) positive culture collected from a sterile site within 3 months after the transplant procedure, (ii) transplant ID consultation within 3 months after the transplant procedure, and (iii) diagnosis of surgical site infection based on ICD-10 coding. For SOT performed in the year 2015, SOT was reviewed manually independently by two reviewers with expertise in transplant infectious diseases. SSI cases were subsequently manually 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 2016–2019 was manually 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 months after the transplant procedures. The final adjudication decision (SSI vs. no SSI) and relevant surgical, infectious diseases, and microbiology data were manually entered into the Duke University Surgical Site Infection in Solid Organ Transplants (SSI-SOT) database (created for quality improvement/assurance). Relevant baseline data (including age, gender, date of transplant, admission date, and discharge date) were automatically extracted and entered into the SSI-SOT database.

2.4 | Other study definitions

Length of hospital stay (LOS) was defined as the number of days from the 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. Six-month and 1-year mortality was defined as all-cause mortality from the time of transplant to 180 days and 365 days after transplant, respectively. Multidrug resistance (MDR) among Gram-negative organisms was defined as resistance to at least 1 agent in at least 3 antimicrobial categories.[33]

2.5 | Study objectives

The primary aim of this study was to determine the rate over time, the microbiology, the timing of diagnosis after transplant, and the clinical outcomes (length of transplant hospital stay, mortality during the transplant hospitalization, 6-month and 1-year mortality post-transplantation, and 1-year graft failure) associated with IP-SSI among all SOT recipients and for each SOT group during the study period. Secondary aims included: (i) determining the cumulative rate of all SSI (including superficial, invasive, primary, and secondary SSI) among all SOT recipients and for each SOT group during the study period; and (ii) evaluating the rate of invasive SSI (I-SSI), including both primary and secondary SSIs, among all SOT recipients and for each SOT group during the study period.

2.6 | 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. Comparisons between groups were made with the chi-square test or independent t-test, as appropriate. The log-rank test was used to estimate the equality of survival functions. A two-sided p-value of <0.05 was considered statistically significant. SSI rates were calculated based on the total number of SOT (denominator) and the total number of SSI (numerator). Statistical analyses were performed using IBM SPSS Statistics (version 28.0; IBM).

3 | RESULTS

Twelve-month post-transplant clinical follow-up was available for 2073 of 2074 adult SOT recipients whose procedure was performed at Duke University Hospital during the study period (2015–2019). Of the 2073 SOT recipients, 1955 received single and 118 received multi-organ SOT (Figure 1).

3.1 | SSI rates

Two hundred thirty-seven SSI, including 210 I-SSI and 198 IP-SSI, were identified among all organ transplants during the study period (Table 1). The cumulative rate of IP-SSI was significantly higher among multi-organ transplants than among single organ transplants (33.9% vs. 8.1%, $p < .01$). Lung transplants were characterized by a significantly higher rate of IP-SSI than the heart (13.2% vs. 7.9%, $p = .02$), liver (13.2% vs. 6.6%, $p < .01$), and kidney (13.2% vs. 5.1%, $p < .01$) transplants. The cumulative rate of IP-SSI among SOT declined over time from 14.4% in 2015 to 8.3% in 2019 ($p < .01$) (Figure 2). A similar trend in the rate of IP-SSI was seen for both single (12.1% to 7.0%, $p = .01$) and multi-organ (52.4% to 31.0%, $p = .12$) organ transplants. Among single organ groups, liver and kidney transplants were characterized by a global decline in the rate of IP-SSI (from 14.3% to 3.6%, $p = .01$; and from 10.3% to 3.3%, $p < .01$, respectively) over the 5-year reporting period. Conversely, while the rate of IP-SSI declined substantially from 2015 to 2016 (14.3% vs. 9.4%, $p = .28$) for lung transplants, the rate of IP-SSI up-trended thereafter, albeit without reaching the 2015 rate. Among heart transplants, after trending down between 2015 and 2017, the IP-SSI rate was higher in 2019 than at the beginning of the study period (9.5% in 2015 to 10.7% in 2019, $p = .04$) (Figure 2).

3.2 | Transplant hospital length of stay

For SOT recipients with IP-SSI, the median LOS during the index transplant admission was 30.0 days (IQR 12.0–79.3) and was similar among single organ and multi-organ transplants (30.0 days vs. 33.0 days) (Table 2). This LOS was significantly longer than LOS for SOT recipients without SSI (30.0 days vs. 17.0 days), when the overall study population was analyzed (Table 2). A prolonged LOS was associated with IP-SSI among the lung, heart, liver, and kidney transplant sub-groups, but no significant difference in LOS among recipients with IP-SSI and recipients without SSI was identified in the multi-organ transplant sub-population.

3.3 | Mortality and graft failure

All-cause in-hospital mortality among SOT diagnosed with IP-SSI was significantly higher than among SOT without SSI (9.6% vs. 2.2%, $p < .01$) (Table 2 and Table S5). There was no significant difference in transplant hospitalization mortality for a single organ compared with multi-organ transplants (9.5% vs. 10.0%, $p = .92$) (Table 2). However, in-hospital mortality was significantly higher among lung transplants with IP-SSI than among heart, liver, and kidney transplants (18.8% vs. 2.3%, $p < .01$) (Table 2).

Six-month and 1-year mortality was also significantly higher among SOT diagnosed with IP-SSI than among SOT without SSI (11.6% vs. 3.3%, $p < .01$; 15.7% vs. 5.8%, $p < .01$, respectively) (Table 2 and Figure 3). Six-month and 1-year mortality rates for SOT with IP-SSI were similar among single-organ and multi-organ transplants (Table 2). Six-month and 1-year mortality rates were significantly higher among lung transplants with IP-SSI than among heart, liver, and kidney transplants (18.8% vs. 5.7%, $p = .01$; 24.6% vs. 9.2%, $p < .01$, respectively).

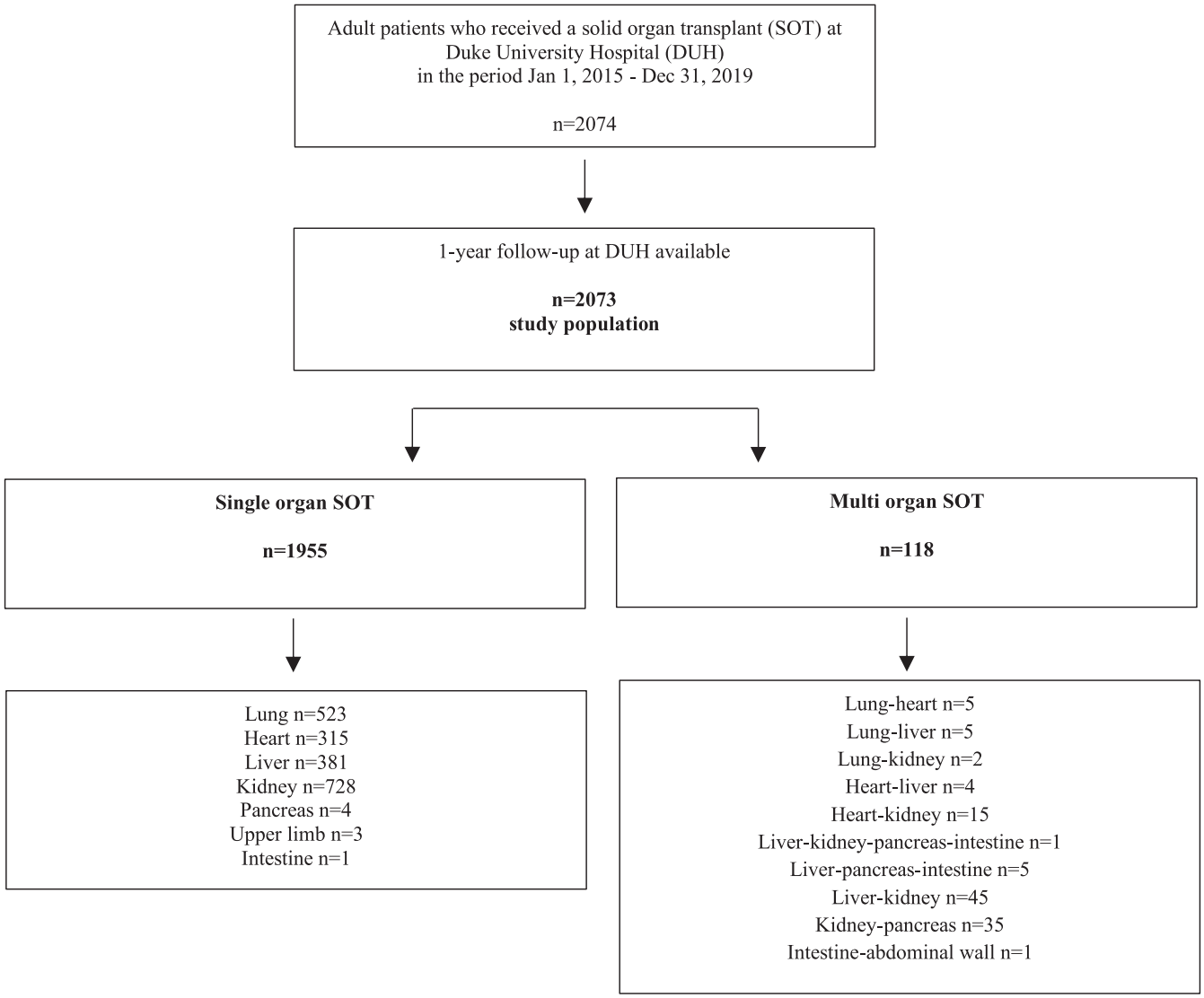

FIGURE 1 Study population.

When 1-year graft failure was evaluated, it was more commonly encountered among SOT with IP-SSI than among SOT without SSI (24.2% vs. 7.0%, $p < .01$). A significantly higher rate of 1-year graft failure among SOT with IP-SSI than among SOT without SSI was detected in all organ transplant sub-populations except for heart and liver transplants (Table 2).

3.4 | SSI microbiology

Among the 198 IP-SSI diagnosed, 2 (1.0%) were culture negative, 125 (63.1%) were monomicrobial and the remaining 71 (35.9%) were polymicrobial. Per Tables 3, 303 total pathogens were isolated. Gram-positive bacteria accounted for the majority (136, 44.9%); *Enterococcus species* (44, 32.4%), coagulase-negative *Staphylococcus* (27, 19.9%), and *Staphylococcus aureus* (22, 16.2%) were the most represented Gram-positive pathogens. Gram-negative bacteria accounted for 87 (28.7%) isolates; *Escherichia coli* (18, 20.7%), *Pseudomonas aeruginosa* (16, 18.4%), and *Klebsiella* species (14, 16.1%) were the most frequently encountered pathogens in this group. MDR was identified in 44.8% of Gram-negative bacteria in the study period: specifically, MDR was detected in 37.5% of *Pseudomonas aeruginosa isolates* and 66.0% of Enterobacteriaceae isolates. The rate of MDR among Gram-negative isolates increased from 42.9% in 2015 to 52.2% in 2019, but this difference was not statistically significant ($p = 0.58$).

Yeasts accounted for 62 (20.5%) isolates. Among *Candida* isolates, 44 (70.9%) were *non-albicans Candida* species. Ten Mollicute (6 *Ureaplasma* spp. and 4 *Mycoplasma* spp.), five mold (3 *Mucor* spp., 1 *Aspergillus ustus*, and 1 *Curvularia* spp.), and three nontuberculous mycobacteria (2 *Mycobacterium abscessus* complex and 1 *Mycobacterium fortuitum*) infections were also diagnosed (Table S6).

No significant differences were found in the IP-SSI microbiology among heart, liver, kidney, and multi-organ transplants when compared to the IP-SSI microbiology in the overall study population (Table S7). The IP-SSI microbiology in the subgroup of lung transplants was similar to the IP-SSI microbiology in the overall

TABLE 1 Adult solid organ transplants performed at Duke University Hospital in the period January 1, 2015–December 31, 2019 and complicated by surgical site infections

	All SSI,[a] *n* (%)	Invasive SSI,[b] *n* (%)	Invasive Secondary SSI,[c] *n* (%)	Invasive Primary SSI,[d] *n* (%)
All SOT (*n* = 2073)	237 (11.4)	210 (10.1)	12 (0.6)	198 (9.6)
Single organ SOT (*n* = 1955)	195 (10.0)	168 (8.6)	10 (0.5)	158 (8.1)
Lung (*n* = 523)	77 (14.7)	70 (13.4)	1 (0.2)	69 (13.2)
Heart (*n* = 315)	39 (12.4)	34 (10.8)	9 (2.9)	25 (7.9)
Liver (*n* = 381)	31 (8.1)	25 (6.6)	0 (0.0)	25 (6.6)
Kidney (*n* = 728)	46 (6.3)	37 (5.1)	0 (0.0)	37 (5.1)
Pancreas (*n* = 4)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)
Intestine (*n* = 1)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)
Other (*n* = 3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multi-organ SOT (*n* = 118)	42 (35.6)	42 (35.6)	2 (1.7)	40 (33.9)
Lung-heart (*n* = 5)	2 (40.0)	2 (40.0)	0 (0.0)	2 (40.0)
Lung-liver (*n* = 5)	2 (40.0)	2 (40.0)	0 (0.0)	2 (40.0)
Lung-kidney (*n* = 2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart-liver (*n* = 4)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)
Heart-kidney (*n* = 15)	7 (46.7)	7 (46.7)	0 (0.0)	7 (46.7)
Liver-kidney-pancreas-intestine (*n* = 1)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)
Liver-pancreas-intestine (*n* = 5)	3 (60.0)	3 (60.0)	0 (0.0)	3 (60.0)
Liver-kidney (*n* = 45)	14 (31.1)	14 (31.1)	1 (2.2)	13 (28.9)
Kidney-pancreas (*n* = 35)	11 (31.4)	11 (31.4)	0 (0.0)	11 (31.4)
Intestine-abdominal wall (*n* = 1)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)

[a]Includes all SSI (primary and secondary site infections as well superficial and invasive infections).
[b]Invasive SSI (excludes superficial SSI, primary and secondary are included).
[c]Includes only invasive secondary site infections (i.e., ECMO cannulation sites).
[d]Includes only invasive primary site infections (excludes superficial and secondary infections).

study population, with two important exceptions. First, Mollicute infections were diagnosed almost exclusively in the lung transplant population. Second, IP-SSI due to yeasts among lung transplants decreased from 80.0% in 2015 to 15.0% in 2019 (Table S7).

When clinical outcomes were analyzed among monomicrobial IP-SSI based on the etiologic agent of infection, IP-SSI due to Mollicutes and nontuberculous mycobacteria were characterized by prolonged LOS; high mortality and graft failure rates were also reported for IP-SSI due to molds (Table S8).

3.5 | Time to SSI

The median time from transplant surgery to IP-SSI diagnosis was 24.0 (IQR 13.8–48.3) days. This varied based on organ transplants, with an earlier diagnosis of IP-SSI among abdominal than thoracic transplants. Specifically, while IP-SSI was diagnosed 35.0 days (IQR 18.0–54.0) after lung and 29.0 days (IQR 18.5–58.5) after a heart transplant, IP-SSI tended to occur less than 30 days after kidney and liver transplants [kidney 28.0 days (IQR 14.0–46.0); liver 14.0 days (IQR 7.5–23.0)].

The time to development of IP-SSI differed based on the pathogen type. Although there was overlap, the median time to diagnosis of monomicrobial Mollicute (18.0 days), yeast (20 days), Gram-negative (24.5 days), and Gram-positive (28 days) infections was usually within the first 30 days of transplant whereas monomicrobial mold (47.5 days) infections occurred later. Two monomicrobial nontuberculous mycobacterial IP-SSI were diagnosed at a median of 23.0 days after transplant (Figure 4). Of note, we also identified 23 IP-SSI occurring beyond 90 days of transplant surgery: however, these infections were not included in the analysis as they were outside the 90-day follow-up for SSI per study definitions.

4 | DISCUSSION

This study provides insights on the epidemiology of IP-SSI in a large cohort of adult single and multi-organ SOT at Duke University

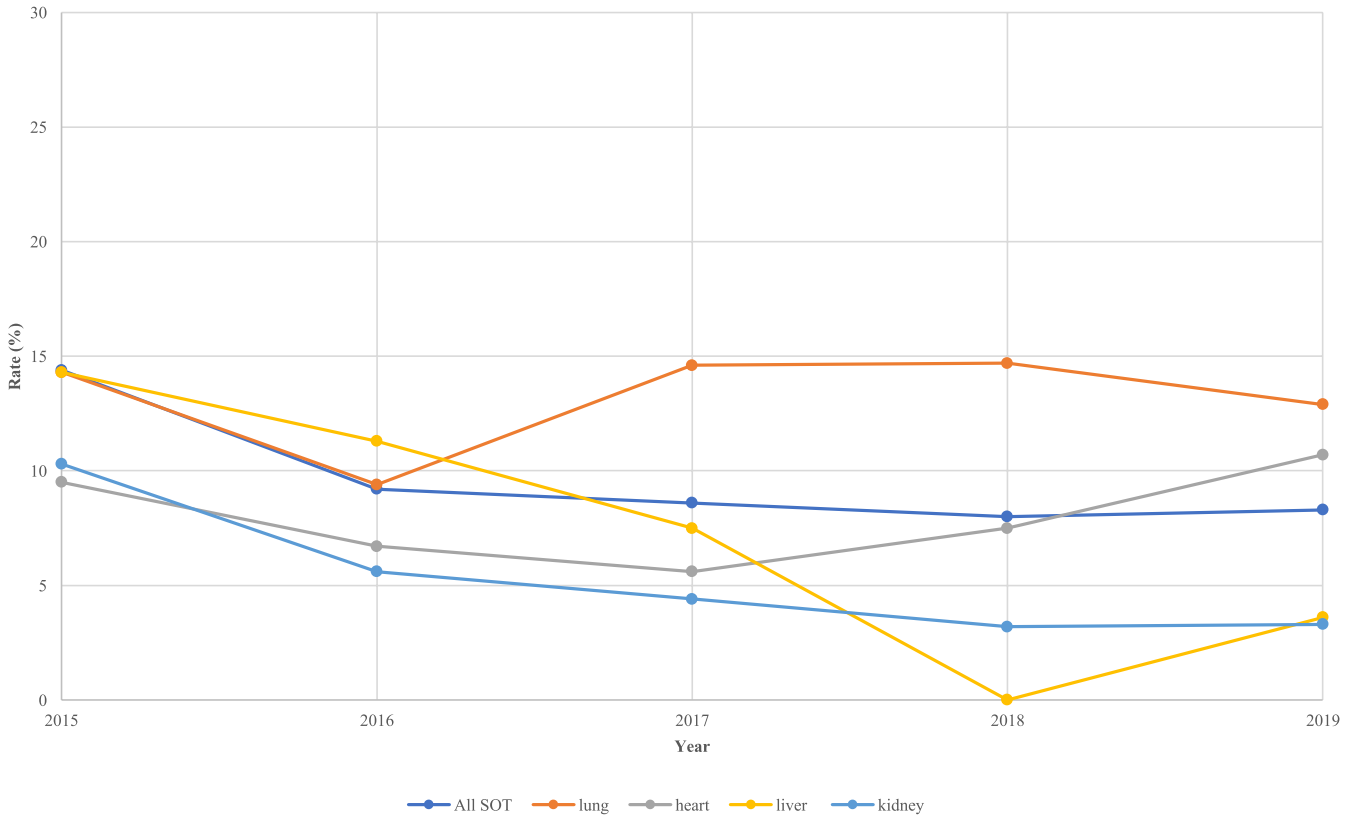

FIGURE 2 Rate of invasive primary surgical site infections (IP-SSI) in the first year after transplant among adult recipients of a solid organ transplant (SOT) at Duke University Hospital in the period January 1, 2015–December 31, 2019.

Hospital over a recent five-year period (2015–2019). Although we found a declining rate of IP-SSI over the study period, IP-SSI continued to affect a relevant proportion of SOT (approximately 1 out of 10 SOT at the end of the study period) and was associated with increased transplant hospitalization length of stay, graft failure, and mortality.

The lung and heart transplant subpopulations differed from the overall SOT population, as they were characterized by an initial decline followed by an increase in the rate of IP-SSI. This temporal trend may reflect the response to reporting and improvements in preventive measures (infection detection and control practices including changes in antimicrobial prophylaxis) concurrent with more recent increases in the severity of patients' pre-transplant clinical status. For example, the decrease in IP-SSI due to yeast in our lung transplant program may be attributed to incorporating fluconazole into the standard prophylaxis protocol in 2015. Concurrently there were increases nationally in the median lung allocation score and age at transplant of lung recipients over the same period.[34] Similarly, in the heart transplant subpopulation, 2015–2019 was characterized by a rise in listings with extracorporeal membrane oxygenation and intra-aortic balloon pumps.[35]

In accordance with reports from prior studies,[4,7] we identified a significantly higher rate of IP-SSI among multi-organ compared with single organ transplants, which can be attributed to the extensive disruption of anatomical barriers in the setting of multi-organ transplants.

The rate of IP-SSI among lung transplants in our center was substantially higher (13.2%) than the rate reported by two other major US transplant centers (5.0% at the University of Pittsburgh in the period 2006–2010 and 9.0% at Barnes-Jewish Hospital in the period 2010–2014).[31,32] We hypothesize that this difference may be due to: (i) the progressively higher complexity and medical urgency of lung transplants in the period 2015–2019 compared to the prior decade, and (ii) the exclusion of re-transplants from the studies performed in the other two centers. Differences in SSI surveillance methods and surgical and prophylactic approaches may also contribute.

IP-SSI was associated with a significantly prolonged transplant LOS, increased 1-year graft failure, and increased mortality (in-hospital, 6-month, and 1-year mortality) compared to SOT without SSI. Although causal inference cannot be made based on observational data, IP-SSI was associated with significantly lower post-transplant survival. Similar results were reported by Shields and collaborators.[31] The increased mortality associated with IP-SSI in our overall study population seems to be largely driven by the adverse outcomes reported in the lung transplant sub-population.

The microbiology of IP-SSI among adult SOT in the period 2015–2019 was dominated by Gram-positive bacteria among both single-organ and multi-organ transplants. A presumed common pathway of SSI acquisition is through the skin, and Staphylococci, a common skin commensal, composed the largest proportion of Gram-positive organisms. Enterococci, responsible for 32.4% of the Gram-positive infections, are more typically considered enteric organisms and

TABLE 2 Clinical outcomes among adult solid organ transplant recipients transplanted at Duke University Hospital in the period January 1, 2015–December 31, 2019 and diagnosed with invasive primary surgical site infections (IP-SSI) vs. those not diagnosed with surgical site infections (no-SSI) by organ population

	Length of hospital stay, days (median, IQR)			In-hospital mortality, all-cause mortality, *n* (%)			6-month mortality, all-cause mortality, *n* (%)			1-year mortality, all-cause mortality, *n* (%)			1-year graft failure, *n* (%)		
	IP-SSI	no-SSI	*p*-value	IP-SSI	no-SSI	*p*-value	IP-SSI	no-SSI	*p*-value	IP-SSI	no-SSI	*p*-value	IP-SSI	no-SSI	*p*-value
All SOT	30.0 (12.0–79.3)	17.0 (10.0–34.0)	<0.01	19 (9.6)	40 (2.2)	<0.01	23 (11.6)	61 (3.3)	<0.01	31 (15.7)	107 (5.8)	<0.01	48 (24.2)	129 (7.0)	<0.01
Single organ SOT	29.0 (12.0–66.8)	17.0 (10.0–34.0)	<0.01	15 (9.5)	36 (2.0)	<0.01	18 (11.4)	56 (3.2)	<0.01	25 (15.8)	100 (5.7)	<0.01	35 (22.2)	121 (6.9)	<0.01
Lung	44.0 (24.5–100.0)	23.0 (15.0–39.0)	<0.01	13 (18.8)	20 (4.5)	<0.01	13 (18.8)	21 (4.7)	<0.01	17 (24.6)	42 (9.4)	<0.01	19 (27.5)	46 (10.3)	<0.01
Heart	51.0 (30.0–105.0)	44.0 (21.0–61.0)	0.01	2 (8.0)	12 (4.3)	0.33	2 (8.0)	20 (7.2)	0.70	5 (20.0)	27 (9.8)	0.11	5 (20.0)	30 (10.9)	0.17
Liver	25.0 (11.0–41.0)	9.0 (7.0–15.8)	<0.01	0 (0.0)	3 (0.9)	1.00	2 (8.0)	7 (2.0)	0.12	2 (8.0)	14 (4.0)	0.29	3 (12.0)	12 (3.4)	0.07
Kidney	7.0 (4.0–13.0)	5.0 (4.0–7.0)	<0.01	0 (0.0)	1 (0.1)	1.00	1 (2.7)	8 (1.2)	0.38	1 (2.7)	17 (2.5)	1.00	8 (21.6)	33 (4.8)	<0.01
Multi-organ SOT	33.0 (9.5–101.0)	10.0 (7.0–32.0)	0.11	4 (10.0)	4 (5.3)	0.44	5 (12.5)	5 (6.6)	0.31	6 (15.0)	7 (9.2)	0.37	13 (32.5)	8 (10.5)	<0.01

were recovered more often among single and multi-organ abdominal transplants. The contribution of multi-drug resistant organisms, namely methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* was relevant: methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium* (VRE) accounted for 54.5% of *S. aureus* isolates and 52.3% of *Enterococcus* spp. isolates, respectively. Most cases of MRSA were isolated among thoracic organ transplants (75.0%), with lung transplants accounting for the majority (50.0%). Interestingly, MRSA IP-SSI tended to develop in the weeks after vancomycin prophylaxis was discontinued (75% of the MRSA IP-SSI among lung transplants occurred after the discontinuation of vancomycin, which typically occurred at the time of chest tube removal). Of note, all MRSA isolates recovered in this study were vancomycin susceptible. On the other hand, the vast majority of VRE isolates were encountered among lung and liver transplants. We hypothesize that the emergence of vancomycin-resistant strains in the lung population was due to the prolonged post-transplant vancomycin exposure in this group since vancomycin is the standard Gram-positive antimicrobial prophylaxis used in this setting. On the contrary, the occurrence of VRE IP-SSI among liver transplants may have resulted from pre-transplant enteric/biliary colonization with VRE. These findings have implications for the antimicrobial prophylaxis regimens used in SOT surgery. In order to refine prophylactic approaches for each organ group, studies to examine factors associated with the development of IP-SSI that take into account the pathogens involved are needed.

MDR was identified in 44.8% of the Gram-negative organisms causing IP-SSI in our study population and this rate remained relatively stable during the study period. The presence of MDR was associated with more prolonged LOS, highlighting the increased clinical complexity of recipients developing MDR Gram-negative IP-SSI.

Yeasts accounted for 20.5% of the isolates causing IP-SSI. In the lung transplant sub-population, we noticed a dramatic decrease over time in the number of IP-SSI caused by yeasts, from 80.0% of isolates in 2015 to only 12.9% of isolates in the period 2016–2019. This substantial decrease in the lung transplant population followed the universal addition of systemic fluconazole for 90 days to our standard antifungal prophylaxis regimen (inhaled amphotericin B complex) after lung transplant. The predominance of *non-albicans* candidiasis over *Candida albicans* infections likely reflects the use of fluconazole in the peri-transplant period.[35]

Ten Mollicute IP-SSI were identified in 9 adult SOT recipients. Of these, 6 were lung transplants, 2 were combined lung-heart transplants, and 1 was a combined heart-kidney transplant recipient. These urogenital Mollicute infections, predominantly among lung transplant recipients, raise concern for transmission of extragenital Mollicutes from lung donors and raises the question of whether lung donors should be screened for respiratory colonization with urogenital Mollicute species.[37]

We documented nontuberculous mycobacteria (2 *M. abscessus* complex and 1 *M. fortuitum*) as etiologic agents of three IP-SSI in our study population. Of these infections, 2 *M. abscessus* complex SSI occurred among heart transplants in 2015 (one single-heart

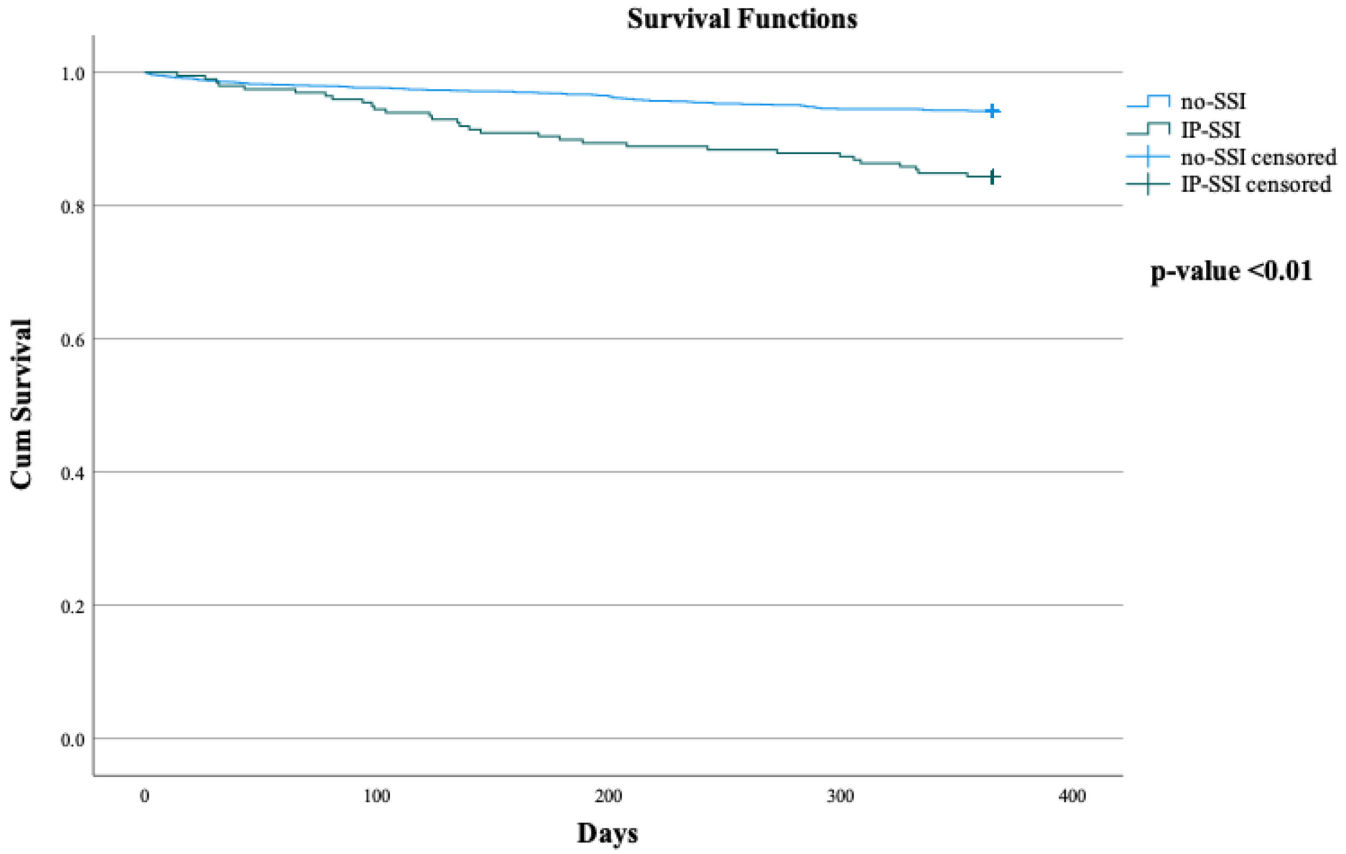

FIGURE 3 Survival curve in the first year after transplant for adult solid organ transplant (SOT) recipients transplanted at Duke University Hospital in the period January 1, 2015–December 31, 2019 and diagnosed with invasive primary surgical site infections (IP-SSI) vs. those not diagnosed with surgical site infections (no-SSI).

TABLE 3 Isolates were identified among all solid organ transplant recipients diagnosed with an invasive primary surgical site infection (IP-SSI) at Duke University Hospital in the period January 1, 2015–December 31, 2019

	2015	2016	2017	2018	2019	2015–2019
Gram-positive bacteria, *n* (%)	30 (40.5)	36 (53.7)	22 (48.9)	21 (40.4)	27 (41.5)	136 (44.9)
Gram-negative bacteria, *n* (%)	14 (18.9)	21 (31.3)	10 (22.2)	19 (36.5)	23 (35.4)	87 (28.7)
MDR Gram-negative bacteria, *n* (% among Gram-neg)[a]	6 (42.9)	6 (28.6)	3 (30.0)	11 (57.9)	12 (52.2)	38 (43.7)
Yeasts, *n* (%)	25 (33.8)	9 (13.4)	11 (24.4)	7 (13.5)	10 (15.4)	62 (20.5)
Mollicute, *n* (%)	2 (2.7)	1 (1.5)	1 (2.2)	1 (1.9)	5 (7.7)	10 (3.3)
Molds, *n* (%)	1 (1.4)	0 (0.0)	1 (2.2)	3 (5.8)	0 (0.0)	5 (1.7)
Nontuberculous mycobacteria, *n* (%)	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (1.0)
Total isolates, *n*	74	67	45	52	65	303

[a]Percentages are calculated based on the total number of organisms identified during each period, with the exception of MDR Gram-negative organisms where the percentage is calculated on the number of Gram-negative organisms isolated during each period.

transplant and one heart-kidney transplant): at that time our hospital was experiencing an outbreak of *M. abscessus* complex, presumably due to the contamination of heater-cooler units of cardiopulmonary bypass machines.[36,38] No other outbreaks were documented during the study period. Of note, we identified two additional nontuberculous mycobacterial IP-SSI which occurred beyond 90 days of transplant surgery: however, these infections were not included in the analysis as they were outside the 90-day follow-up for SSI per CDC-NHSN definition. Similarly, we identified 21 IP-SSI due to agents other than nontuberculous mycobacteria outside the 90-day follow-up for SSI per CDC-NHSN definition. The identification in our study of 23 IP-SSI beyond the 90-day follow-up for SSI should prompt clinicians to maintain a high index of suspicion for SSI even after the traditional 90-day

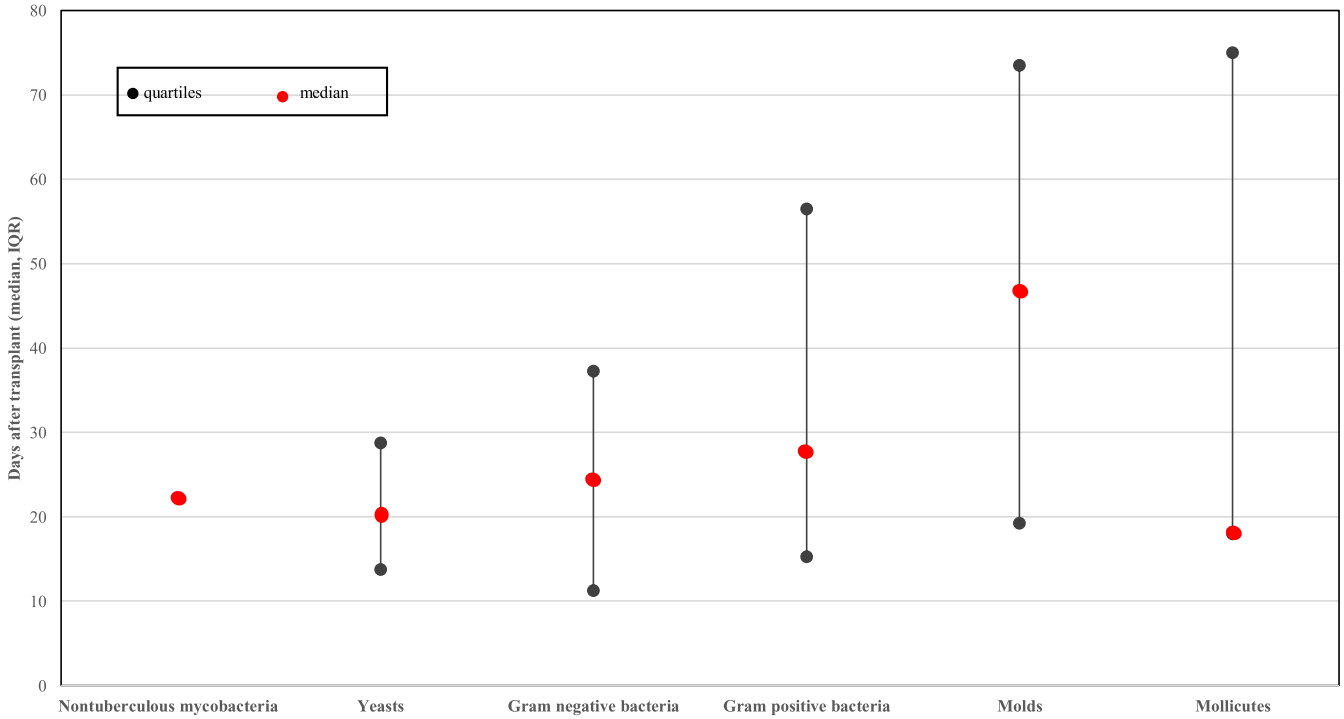

FIGURE 4 Time from transplant to development of invasive primary surgical site infection (IP-SSI) among adult patients who received a solid organ transplant (SOT) at Duke University Hospital in the period January 1, 2015–December 31, 2019. Analysis is limited to monomicrobial IP-SSI and stratified by pathogen category.

follow-up period proposed by the CDC-NHSN definition and may also suggest re-evaluate and possibly modify the CDC-NHSN definition for SSI in the setting of solid organ transplantation.

This study has multiple limitations. Since this is a retrospective study, it is prone to selection and information bias. While we believe the impact of selection bias on our results is negligible (1 lost to follow-up over 2074 patients), information bias may have occurred despite the extensive manual review process. Specifically, information bias may have substantially affected data acquisition regarding superficial SSI. Hence, because of the possible incomplete reporting of superficial SSI in source documents (patients' EMRs), our primary study aim was limited to the evaluation of IP-SSI. Prospective studies are needed to assess the contribution of superficial SSI to the outcome of SOT. Second, the external validity of this study is hampered by its single-center design. Data generated by this study reflected the epidemiology and the outcomes associated with IP-SSI among adult SOT at Duke University Hospital in the period 2015–2019. Third, we did not investigate the occurrence of donor-derived infections.

In conclusion, although the IP-SSI rate declined over time, IP-SSI continued to be a frequent and severe complication of SOT, compromising post-transplant survival and graft function. A high index of clinical suspicion for IP-SSI should be maintained by providers caring for SOT in the post-transplant setting. In addition, we hypothesize that there are modifiable risk factors for IP-SSI unique to each type of SOT. Prospective studies are needed to delineate unique risks and identify interventions aimed at decreasing the incidence of IP-SSI in the SOT population.

ACKNOWLEDGMENT

The authors would like to thank those involved in data management and study administration, including Kelly Stanley and Katherine Link.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Carugati M, Arif S, Sudan DL, et al. Epidemiology of surgical site infections after solid organ transplants in the period 2015–2019: A single-center retrospective cohort study. *Am J Transplant*. 2022;00:1-10. doi:10.1111/ajt.17189