

Bacteremia During the First Year After Solid Organ Transplantation: An Epidemiological Update

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Background. There are limited contemporary data on the epidemiology and outcomes of bacteremia in solid organ transplant recipients (SOTr).

Methods. Using the Swiss Transplant Cohort Study registry from 2008 to 2019, we performed a retrospective nested multicenter cohort study to describe the epidemiology of bacteremia in SOTr during the first year post-transplant.

Results. Of 4383 patients, 415 (9.5%) with 557 cases of bacteremia due to 627 pathogens were identified. One-year incidence was 9.5%, 12.8%, 11.4%, 9.8%, 8.3%, and 5.9% for all, heart, liver, lung, kidney, and kidney-pancreas SOTr, respectively ($P = .003$). Incidence decreased during the study period (hazard ratio, 0.66; $P < .001$). One-year incidence due to gram-negative bacilli (GNB), gram-positive cocci (GPC), and gram-positive bacilli (GPB) was 5.62%, 2.81%, and 0.23%, respectively. Seven (of 28, 25%) *Staphylococcus aureus* isolates were methicillin-resistant, 2/67 (3%) enterococci were vancomycin-resistant, and 32/250 (12.8%) GNB produced extended-spectrum beta-lactamases. Risk factors for bacteremia within 1 year post-transplant included age, diabetes, cardiopulmonary diseases, surgical/medical post-transplant complications, rejection, and fungal infections. Predictors for bacteremia during the first 30 days post-transplant included surgical post-transplant complications, rejection, deceased donor, and liver and lung transplantation. Transplantation in 2014–2019, CMV donor-negative/recipient-negative serology, and cotrimoxazole *Pneumocystis* prophylaxis were protective against bacteremia. Thirty-day mortality in SOTr with bacteremia was 3% and did not differ by SOT type.

Conclusions. Almost 1/10 SOTr may develop bacteremia during the first year post-transplant associated with low mortality. Lower bacteremia rates have been observed since 2014 and in patients receiving cotrimoxazole prophylaxis. Variabilities in incidence, timing, and pathogen of bacteremia across different SOT types may be used to tailor prophylactic and clinical approaches.

Keywords. bacteremia; bloodstream infection; clinical outcomes; epidemiology; risk factors; solid organ transplant; timing.

Bacteremia represents a relatively common complication after a solid organ transplant (SOT) and is historically associated with high morbidity and mortality [1–9]. The incidence, pathogens, and risk factors of bacteremia in SOT recipients have been described in older series from the 1990s and early 2000s; however, contemporary data are lacking [2, 4–7, 10–21]. We have

previously reported on infectious disease complications during the first year post-transplant with data on SOT recipients between 2008 and 2014 using the Swiss Transplant Cohort Study (STCS) registry [10]. Bacterial infections represented the bulk (63%) of infectious disease complications during the first year post-transplant, 22% of which were bacteremia. In that study, bacteremias were unequally distributed during the first year after an SOT, with 34% of bacteremias observed during the first month, and 44% and 22% between 1 and 6 and after 6 months, respectively. We performed a retrospective observational multicenter cohort study to describe the epidemiology, risk factors, and outcomes of bacteremia during the first year post-transplant using the STCS database between 2008 and 2019.

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METHODS

Study Design

The STCS is a multicenter cohort study prospectively enrolling >95% of SOT recipients in all Swiss transplant centers since

2008 [11]. Data are prospectively collected at prespecified scheduled patient visits, are event-driven, for example, in case of rejection, graft failure, or infectious diseases leading to hospitalization, and are regularly monitored with quality audits, as previously described [10, 11]. All consecutive adult (≥ 18 years) patients who received a heart, liver, lung, kidney, or kidney-pancreas transplant between May 1, 2008, and December 31, 2019, with a minimum of 12-month follow-up and who signed an informed consent form were included in this study. For patients who received >1 transplant, only the first transplant was considered, and patient follow-up was stopped at the time of their second transplant. The study was approved by the STCS Scientific Committee and the relevant ethics committees.

Objectives

The primary objective was to describe the cumulative incidence and timing of bacteremia during the first year post-transplant, overall and according to the type of transplant. As secondary objectives, we described the (a) epidemiology of bacterial pathogens, (b) primary site of infection, (c) risk factors, and (d) all-cause mortality in SOT recipients with bacteremia during the first year post-transplant.

Definitions

Infection definitions were developed by the STCS Infectious Diseases Working Group, based on published recommendations and guidelines [10–13]. As previously described, proven bacteremia required isolation of a bacterial pathogen in a blood culture with associated clinical signs and symptoms and administration of appropriate antibiotic treatment [10, 11]. In case of potential skin contaminants (ie, coagulase-negative *Staphylococcus* spp., *Bacillus* spp.), a proven bacteremia was defined as identification of a pathogen in at least 2 positive blood cultures with associated clinical signs and symptoms prompting administration of appropriate antibiotic treatment [10, 11]. Patients could have 1 single or >1 bacteremia episode during the study period. For patients with >1 bacteremia episode, a bacteremia with the same pathogen was considered a new episode when it occurred >14 days after the primary bacteremia. Infections were defined as mono- and polybacterial if only 1 or >1 bacterial pathogen was identified in the same blood culture, respectively. Infections were considered very early, early, and late if they occurred 0–30 days (1 month), 31–180 days (2–6 months), and >180 days (>6 months) post-transplant, respectively. Data on bacterial drug resistance were systematically collected after 2012, and multidrug resistance was defined as previously reported [14]. Surgical post-transplant complications included vascular, anastomosis, biopsy-related bleeding, and surgical site complications. Medical post-transplant complications included diabetes mellitus, hypertension, metabolic disorders, cardiopulmonary disease, transplanted organ tumor, and/or primary disease recurrence.

Clinical Attitudes

Administration of antibacterial perioperative, viral, and *Pneumocystis*-related prophylaxis and immunosuppression were center-based and depended on local institutional protocols [10]. All SOT recipients received perioperative antibacterial prophylaxis and oral nystatin or amphotericin-B prophylaxis during the first 2 weeks post-transplant [10]. Administration of cotrimoxazole as primary *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis is administered in all kidney, heart, lung, and high-risk liver transplant recipients for a minimum of 6 months post-transplant at all centers [15].

Statistical Analysis

Patient and donor characteristics were described as counts and percentages for qualitative data and as medians and interquartile ranges (IQRs) for quantitative data. The cumulative incidence method was used to estimate the probability of first bacteremia within 1 year post-transplant dealing with death, graft failure, and second transplant as competing events. The Gray test was used to compare cumulative incidence curves separated by transplant type, by number of pathogens (mono- vs polymicrobial bacteremia), and by type of pathogen for monomicrobial bacteremia. To visualize the temporal tendency of bacteremia infections, we analyzed the incidence proportions of patients infected during the first year after transplant date by transplant year via locally weighted scatterplot smoothing with a span of 1.5, a nonparametric local regression approach. Cause-specific Cox proportional hazard models were constructed to determine risk factors for bacteremia occurrence. The time from transplantation to each of the first bacteremia episodes within 30 days and within 1 year after transplantation was considered. Follow-up information observed after transplantation until first bacteremia, death, graft failure, or second transplantation, whichever came first, was modeled as time-dependent. Potential risk factors considered in the final multivariable model were chosen based on a combination of clinical relevance and consistency with transplant types. Models were applied in the total population and within subgroups defined by transplant types. To quantify 30-day mortality among patients with bacteremia, the Kaplan-Meier method was used, and Cox proportional hazard models were applied to identify risk factors for death. The Fleming-Harrington test was used to compare survival curves by transplant type, by number of pathogens (mono- vs polymicrobial bacteremia), and by type of pathogen for monomicrobial bacteremia. R, version 4.2.1, was used for statistical analysis.

RESULTS

Of 6016 SOT recipients enrolled in the STCS during the study period, 4383 patients were included, with 415 (9.5%) patients with 557 bacteremia episodes due to 627 pathogens during

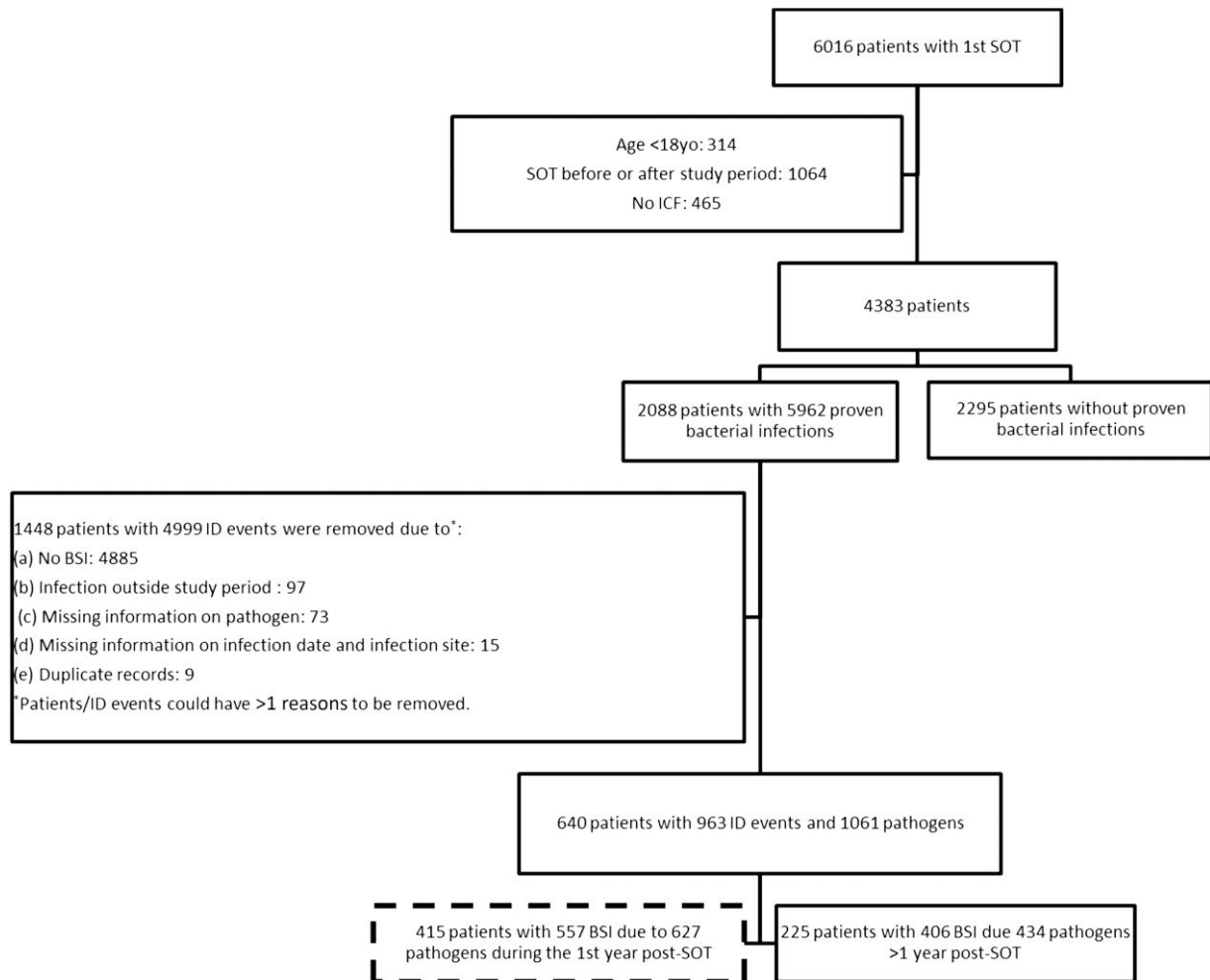


Figure 1. Study flowchart. Abbreviations: BSI, bloodstream infection; ICF, informed consent form; ID, infectious disease; SOT, solid organ transplant.

the first year post-transplant (Figure 1). The patient baseline characteristics are described in Table 1.

Incidence

The 1-year cumulative incidence of bacteremia was 9.5% for all SOT recipients (95% CI, 8.63%–10.36%): 12.8% for heart (95% CI, 9.6%–16.5%), 11.4% for liver (95% CI, 9.6%–13.4%), 9.8% for lung (95% CI, 7.2%–12.7%), 8.3% for kidney (95% CI, 7.2%–9.4%), and 5.9% for kidney-pancreas transplant recipients (95% CI, 2.4%–11.6%; $P = .003$) (Figure 2A, B). Most patients (317/415, 76.4%) had 1 single bacteremia episode during the study period, while 98 (23.6%) patients were diagnosed with >1 distinct bacteremia episode during the first year post-transplant: 69, 19, 5, and 5 patients with 2, 3, 4, and 5 bacteremia episodes, respectively. More than 1 bacteremia episode was more frequently observed in heart (34.8%, 16/46), liver (26.9%, 32/119), and kidney (22.9%, 46/201), as compared with lung (9.3%, 4/43), transplant recipients. Monomicrobial bacteremia was observed in 379 patients (91.3%), with a 1-year incidence

of 8.65% compared with 0.82% for polymicrobial bacteremia (Figure 2C). Cumulative incidence for monomicrobial bacteremia due to gram-negative bacilli (GNB), gram-positive cocci (GPC), and gram-positive bacilli (GPB) was 5.62%, 2.81%, and 0.23%, respectively (Figure 2D). Incidence significantly decreased during the study period from 2008–2013 to 2014–2019 (hazard ratio [HR], 0.66; $P < .001$).

Timing of Bacteremia

The median time from transplantation to the first bacteremia episode (IQR) was 71 (16–164) days. The median time to bacteremia (IQR) was shorter among lung (5.5 [0–53] days), compared with heart (37.5 [8–123] days), kidney-pancreas (50.5 [5–103] days), liver (67 [12–171] days), and kidney transplant recipients (95 [36–195] days; $P < .001$). Almost one-third of infections (189/557, 34%) were observed during the first month post-transplant, followed by 248/557 (44.5%) and 120/557 (21.5%) between 2–6 and 7–12 months post-transplant, respectively (Figure 3). More than half of infections in lung (30/48,

Table 1. Patient Baseline Characteristics of Solid Organ Transplant Recipients Overall and Based on the Presence of a Bloodstream Infection During the First Year Post-transplant

		All Patients (n = 4383), No. (%)	BSI (n = 415), No. (%)	No BSI (n = 3968), No. (%)
Recipient demographics				
Median age (IQR), y	...	55.7 (45.3–62.7)	58.6 (49.7–64.5)	55.3 (44.8–62.5)
Sex, female	...	1535 (35.0)	150 (36.1)	1385 (34.9)
Recipient comorbidities				
Renal failure	...	208 (11.3)	32 (15.5)	176 (10.8)
Diabetes mellitus	...	921 (21.9)	112 (27.0)	809 (20.4)
Hypertension	...	2643 (60.3)	246 (59.3)	2397 (60.4)
Cardiovascular/pulmonary disease	...	2482 (56.6)	275 (66.3)	2207 (55.6)
Metabolic/endocrine disease	...	3496 (79.8)	332 (80.0)	3164 (79.7)
Malignancy	...	977 (22.3)	93 (22.4)	884 (22.3)
Donor				
Median age (IQR), y	...	54 (42–63)	55 (43–65)	53 (42–63)
Sex, female	...	2053 (47.1)	189 (45.6)	1864 (47.2)
Donor status				
...	Living	1083 (24.7)	76 (18.3)	1007 (25.4)
...	DBD	2933 (66.9)	310 (74.7)	2623 (66.1)
...	DCD	367 (8.4)	29 (7)	338 (8.5)
Transplant information				
Transplant year				
...	2008–2013	1937 (44.2)	234 (56.4)	1703 (42.9)
...	2014–2019	2446 (55.8)	181 (43.6)	2265 (57.1)
Median cold ischemia time (IQR), median days	...	356 (150–520)	369 (185–515)	354 (148–520)
Transplant type				
...	Heart	359 (8.2)	46 (11.1)	313 (7.9)
...	Kidney	2437 (55.6)	201 (48.4)	2236 (56.3)
...	Liver	1044 (23.8)	119 (28.7)	925 (23.3)
...	Lung	441 (10.1)	43 (10.4)	398 (10.0)
...	Kidney-pancreas	102 (2.3)	6 (1.5)	96 (2.4)
Induction immunosuppression	Basiliximab	3241 (80.9)	289 (79.0)	2952 (81.1)
...	Thymoglobulin	862 (21.5)	85 (23.2)	777 (21.3)
...	Other	285 (7.1)	36 (9.8)	249 (6.8)
Donor-recipient information				
Blood group incompatibility	...	166 (3.8)	22 (5.3)	144 (3.6)
CMV D/R serology status				
...	CMV R+	2600 (60.2)	264 (64.4)	2336 (59.8)
...	CMV D+R-	855 (19.8)	90 (21.9)	765 (19.6)
...	CMV D-R-	861 (19.9)	56 (13.7)	805 (20.6)

Abbreviations: BSI, bloodstream infection; CMV, cytomegalovirus; D, donor; DBD, donor after brainstem death; DCD, donor after circulatory death; HLA, human leucocyte antigen; IQR, interquartile range; R, recipient.

62.5%) and 47% (31/66) in heart transplant recipients were observed in the first month post-transplant.

Pathogen Distribution

Among 627 pathogens identified, there were 389 (62%), 215 (34.3%), 21 (3.4%), and 2 (0.3%) GNB, GPC, GPB, and GNC, respectively (Table 2). Enterobacterales were the most frequently identified pathogens in almost half of cases (48/627, 48%), followed by enterococci (121/327, 19.3%) and staphylococci (70/627, 11.2%), including 42/627 (6.7%) coagulase-negative *Staphylococcus* and 28/627 (4.5%) *S. aureus*. Overall, GNB were the most frequently encountered pathogens in heart (44/

69, 63.8%), kidney (227/291, 78%), and kidney-pancreas (5/7, 71.4%) SOT recipients. Infections due to non-lactose-fermenting GNB were more frequently encountered in lung (16/54, 29.6%) and kidney-pancreas (3/7, 42.9%) transplant recipients. Proportionally, bacteremia episodes due to *Staphylococcus* spp. were more frequent in lung (14/54, 25.9%) and heart (15/69, 21.7%) transplant recipients.

Antibiotic Resistance

Data on antibiotic resistance were not systematically collected until 2012 and were missing for some patients thereafter. Overall, multidrug-resistant (MDR) pathogens, including

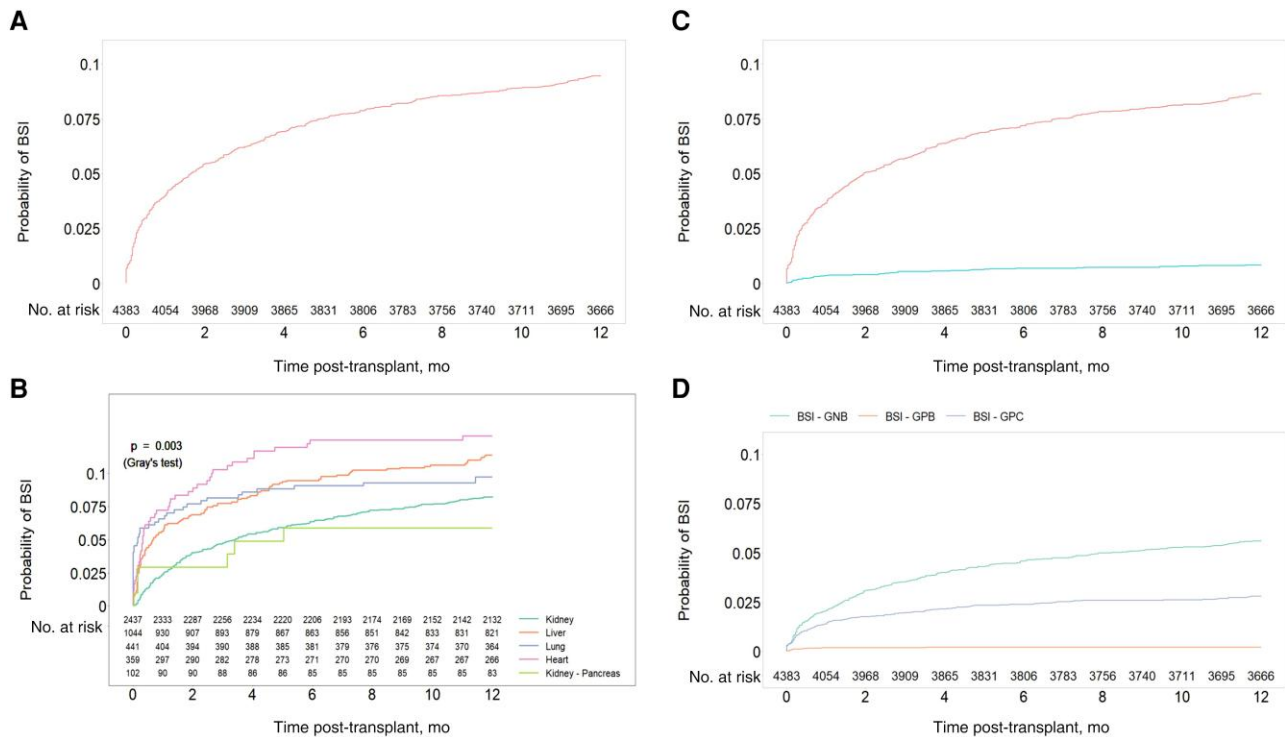


Figure 2. Estimated cumulative incidence of bacteremia during the first year post-transplant: (A) in the overall cohort; (B) per transplant type; (C) based on the number of pathogens identified: mono- vs polymicrobial bacteremia; and (D) based on the type of pathogen for monomicrobial bacteremia events (gram-positive cocci vs gram-negative bacteria vs gram-positive bacteria). The temporal tendency of bacteremia during the study period is presented in (E), showing the incidence proportions of patients infected during the first year after transplant date by transplant year via locally weighted scatterplot smoothing with span 1.5, a nonparametric local regression approach. Abbreviation: BSI, bloodstream infection.

MDR and extended-spectrum beta-lactamase (ESBL)-producing GNB, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE), remained relatively stable during the study period (Figure 4A, B). Among 67 of 121 (55.4%) isolates of *Enterococcus* spp. with known resistance patterns, 36/67 (53.7%), 29/67 (43.3%), and 2/67 (3%) were pan-susceptible, penicillin-resistant, and VRE, respectively. There were 28 isolates of *S. aureus*, 7 (25%) of which were MRSA. Resistance data were available for 250/389 (64.3%) GNB: 17/250 (6.8%) and 32/250 (12.8%) were MDR and ESBL-producing pathogens, respectively. Among the 32 ESBL-producing GNB, there were 20, 11, and 1 *E. coli*, *Klebsiella* spp., and *Enterobacter* spp., respectively, observed in kidney (18/32, 56.3%), liver (10/32, 31.3%), heart (3/32, 9.4%), and lung (1/32, 3%) transplant recipients. There were no carbapenemase-producing GNB identified.

Bacteremia Source

The source of bacteremia was recorded in 302/557 (54.2%) bacteremia events. In 279/302 (92.4%), 21/302 (7%), and 2/302 (0.7%) events, there were 1, 2, and 3 sources reported, respectively, for a total of 327 different sources. Overall, urinary tract infections were the most frequently identified bacteremia

source (156/327, 47.7%), followed by liver (35/327, 10.7%), gastrointestinal tract (34/327, 10.4%), respiratory tract (30/327, 9.2%), catheter-related (30/327, 9.2%), surgical site (28/327, 8.6%), mucocutaneous (10/327, 3.1%), bone and joint (2/327, 0.6%), and heart (2/327, 0.6%) infections.

Risk Factors

Risk factor analysis for bacteremia was performed to identify bacteremia predictors during the first year post-transplant (Table 3). Recipient age (HR, 1.19; $P < .001$), diabetes (HR, 1.82; $P = .02$) and cardiopulmonary comorbidities before and/or at transplant (HR, 1.38; $P = .005$), surgical (HR, 3.13; $P < .001$) and medical (HR, 2.32; $P = .001$) post-transplant complications, acute rejection (HR, 2.24; $P < .001$), and invasive fungal infections (HR, 3.55; $P < .001$) were identified as significant risk factors. In contrast, transplantation between 2014 and 2019 (HR, 0.61; $P < .001$), CMV donor-negative/recipient-negative serology status (HR, 0.66; $P = .006$), and administration of cotrimoxazole as prophylaxis (HR, 0.55; $P < .001$) were protective against bacteremia. Similar analyses were performed to identify predictors of very early bacteremia during the first month post-transplant. Liver (HR, 1.69, $P = .03$) and lung transplant recipients (HR, 2.78; $P < .001$), surgical complications

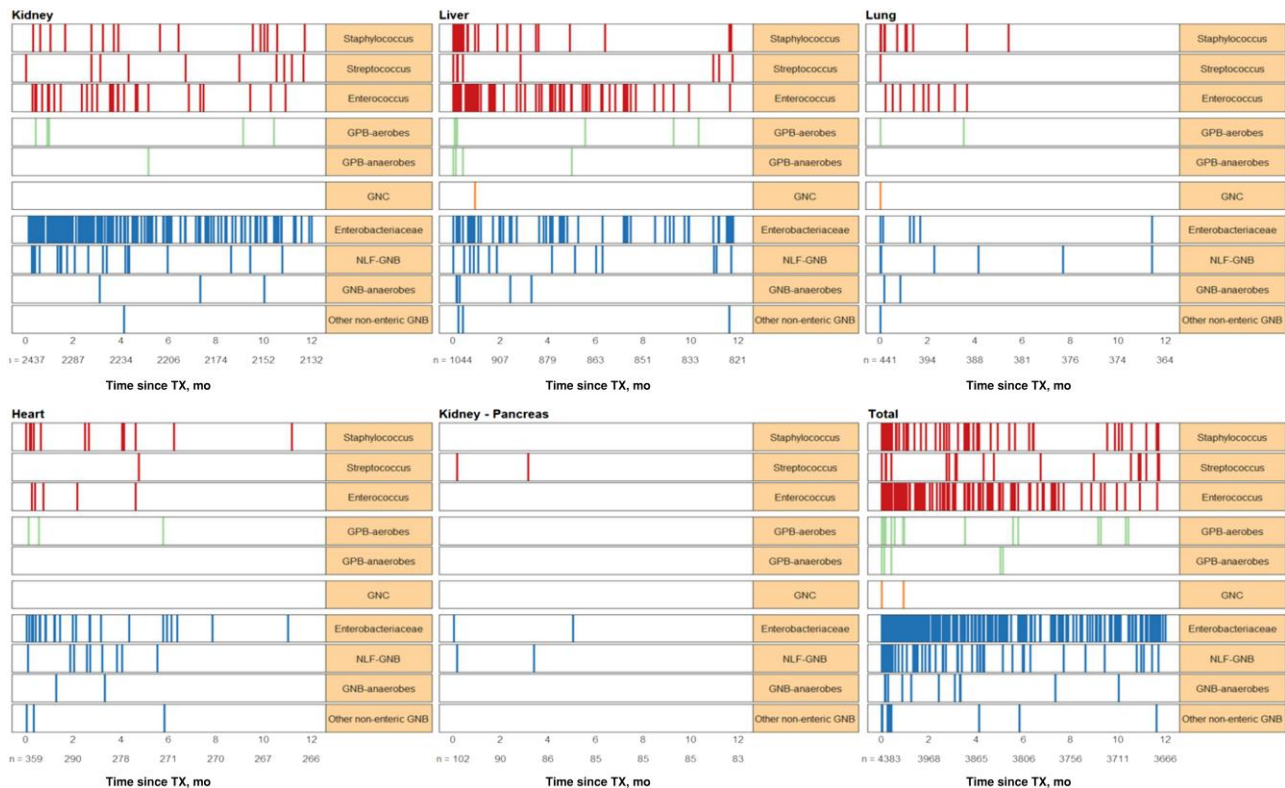


Figure 3. Infection density by pathogens causing bacteremia during the first year after a solid organ transplant overall and by transplant type.

post-transplant (HR, 2.45; $P < .001$), and acute rejection (HR, 2.76; $P < .001$) were independent predictors of early bacteremia. Transplantation between 2014 and 2019 (HR, 0.67; $P = .009$) and administration of cotrimoxazole (HR, 0.41; $P < .001$) were protective against very early bacteremia.

Additional organ-specific risk factor analyses were performed, including variables considering clinical plausibility and limitations associated with the smaller number of events per SOT type (Table 4). Recipient age (HR, 1.29; $P < .001$), deceased donors (HR, 1.58; $P = .004$), surgical (HR, 2.58; $P = .002$) and medical (HR, 4.06; $P = .002$) post-transplant complications, and rejection (HR, 2.79; $P < .001$) were risk factors for bacteremia in kidney transplant recipients. In contrast, transplantation between 2014 and 2019 (HR, 0.65; $P = .003$) and administration of cotrimoxazole as prophylaxis (HR, 0.41; $P < .001$) were protective against bacteremia. For liver transplant recipients, surgical complications (HR, 2.74; $P < .001$) and rejection (HR, 2.58; $P < .001$) predicted bacteremia, while bacteremia were less likely if transplantation occurred between 2014 and 2019 (HR, 0.46; $P < .001$). For thoracic organ transplant recipients, surgical (HR, 3.23; $P < .001$) and medical (HR, 3.03; $P = .02$) post-transplant complications and CMV infection (HR, 7.52; $P = .05$) were independent risk factors for bacteremia. CMV serology donor-negative/recipient-negative

(HR, 0.43; $P = .01$) and cotrimoxazole prophylaxis (HR, 0.46; $P = .01$) were protective against bacteremia.

Outcomes

All-cause 30-day mortality in SOT recipients with bacteremia was 3% (12/415) (Figure 5A) and did not significantly differ based on SOT type: 2% (1/46), 2% (4/201), 4% (5/119), 5% (2/43), and 0% (0/6) for heart, kidney, liver, lung, and kidney-pancreas SOTr, respectively ($P = .29$) (Figure 5B). All-cause 30-day mortality was 3% (11/379) and 3% (1/36) in patients with mono- vs polymicrobial bacteremia ($P = .6$) (Figure 5C). No predictors, including SOT type, time from SOT to bacteremia, or GNB bacteremia, were found to significantly affect mortality postbacteremia (data not shown).

DISCUSSION

In this 12-year cohort study, almost 1 in 10 patients developed a bacteremia during the first year post-transplant, consistent with previously reported rates of an incidence ranging between 7% and 35%, depending on different transplant types [5, 16–18]. We observed the highest incidence in heart transplant recipients, as previously reported, with incidence rates up to 15% [5, 17]. A significant decline in bacteremia in the latter study

Table 2. Distribution of Bacterial Pathogens Among Solid Organ Transplant Recipients With a Bloodstream Infection During the First Year Post-transplant

	Overall ^a (n = 627), No. (%)	Heart (n = 69), No. (%)	Liver (n = 206), No. (%)	Lung (n = 54), No. (%)	Kidney (n = 291), No. (%)	Kidney-Pancreas (n = 7), No. (%)
Gram-negative bacilli	389 (62.0)	44 (63.8)	87 (42.2)	26 (48.1)	227 (78.0)	5 (71.4)
Enterobacterales	301 (48.0)	30 (43.5)	65 (31.6)	7 (13)	197 (67.7)	2 (28.6)
<i>E. coli</i>	182 (29.0)	8 (11.6)	36 (17.5)	4 (7.4)	133 (45.7)	1 (14.3)
<i>Enterobacter</i> spp.	21 (3.3)	6 (8.7)	7 (3.4)	0	7 (2.4)	1 (14.3)
<i>Klebsiella</i> spp.	67 (10.7)	8 (11.6)	12 (5.8)	1 (1.9)	46 (15.8)	0
<i>Proteus mirabilis</i>	5 (0.8)	0	0	0	5 (1.7)	0
<i>Serratia marcescens</i>	8 (1.3)	4 (5.8)	2 (1)	0	2 (0.7)	0
Other ^b	18 (2.9)	4 (5.8)	8 (3.9)	2 (3.7)	4 (1.4)	0
Non-lactose-fermenting	67 (10.7)	9 (13)	14 (6.8)	16 (29.6)	25 (8.6)	3 (42.9)
<i>Pseudomonas aeruginosa</i>	57 (9.1)	9 (13)	9 (4.4)	13 (24.1)	23 (7.9)	3 (42.9)
Other ^c	8 (1.3)	0	3 (1.5)	3 (5.6)	2 (0.7)	0
Other nonenteric ^d	8 (1.3)	3 (4.3)	3 (1.5)	1 (1.9)	1 (0.3)	0
Anaerobic	13 (2.1)	2 (2.9)	5 (2.4)	2 (3.7)	4 (1.4)	0
<i>Bacteroides fragilis</i>	4 (0.6)	0	1 (0.5)	1 (1.9)	2 (0.7)	0
Other ^e	9 (1.4)	2 (2.9)	4 (1.9)	1 (1.9)	2 (0.7)	0
Gram-negative cocci ^f	2 (0.3)	0	1 (0.5)	1 (1.9)	0	0
Gram-positive bacilli	21 (3.4)	3 (4.3)	10 (4.9)	2 (3.7)	6 (2.1)	0
Aerobic ^g	16 (2.6)	3 (4.3)	6 (2.9)	2 (3.7)	5 (1.7)	0
Anaerobic ^h	5 (0.8)	0	4 (1.9)	0	1 (0.3)	0
Gram-positive cocci	215 (34.3)	22 (31.9)	108 (52.4)	25 (46.3)	58 (19.9)	2 (28.6)
<i>Staphylococcus</i> spp.	70 (11.2)	15 (21.7)	24 (11.7)	14 (25.9)	17 (5.8)	0
<i>S. coagulase</i> -negative	42 (6.7)	8 (11.6)	14 (6.8)	8 (14.8)	12 (4.1)	0
<i>S. aureus</i>	28 (4.5)	7 (10.1)	10 (4.9)	6 (11.1)	5 (1.7)	0
<i>Enterococcus</i> spp.	121 (19.3)	6 (8.7)	75 (36.4)	10 (18.5)	30 (10.3)	0
<i>Streptococcus</i> spp. ⁱ	24 (3.8)	1 (1.4)	9 (4.4)	1 (1.9)	11 (3.8)	2 (28.6)

^aPatients could have bloodstream infections with ≥ 1 bacterial pathogen.

^bOther Enterobacterales included *Citrobacter braakii* (2), *Morganella morganii* (3), *Pantoea agglomerans* (1), and other not-otherwise-specified organisms (12).

^cOther non-lactose-fermenting gram-negative bacilli included *Acinetobacter* spp. (3), *Aeromonas hydrophila* (1), *Burkholderia cepacia* (3), *Pseudomonas (Flavimonas) oryzzihabitans* (1).

^dOther nonenteric gram-negative bacilli included *Campylobacter* spp. (1), *Haemophilus influenzae* (2), *Haemophilus parainfluenzae* (2), and other not-otherwise-specified organisms (3).

^eOther anaerobic gram-negative bacilli included *Bacteroides* spp. (3), *Parabacteroides distasonis* (1), and other not-otherwise-specified organisms (5).

^fGram-negative cocci included *Moraxella* spp. (1), *Veillonella* spp. (1).

^gAerobic gram-positive bacilli included *Bacillus* spp. (1), *Corynebacterium* spp. (1), *Lactobacillus* spp. (2), *Lactococcus lactis* (1), *Listeria monocytogenes* (1), *Micrococcus luteus* (1), *Pedococcus acidilacti* (1), *Ruminococcus* spp. (1), *Spiroplasma* spp. (1), and other not-otherwise-specified organisms (6).

^hAnaerobic gram-positive bacilli included *Bifidobacterium* spp. (1), *Clostridium* spp. (3), *Cutibacterium acnes* (1).

ⁱIn addition to *Streptococcus* spp., *Gemella* spp. (1) and *Granulicatella* spp. (1) were also included.

period was observed. This may, in part, be attributed to improved clinical practices in surgical and medical management, but also improved follow-up and monitoring of patients through the years. Notably, multivariable analyses confirmed a protective effect against bacteremia for SOT occurring during 2014–2019 compared with 2008–2013.

In line with reduced numbers of bacteremia in the most recent part of the study period, mortality among patients with bacteremia in this cohort was low at 3%. This is in contrast to previously published data with mortality rates as high as 25% to 50% [2, 5, 6, 8, 17, 19, 20]. Although we were not able to definitively assess attributable mortality in this retrospective study, we report 30-day all-cause mortality, considering this relatively representative of a potential effect of bacteremia on survival outcomes. Improved contemporary transplant practices with close patient follow-up leading to early diagnosis of infectious complications and prompt treatment initiation might

have, in part, contributed to the lower mortality rates observed in our cohort.

Older age has been previously identified as a bacteremia predictor in kidney and liver transplant recipients, suggesting that older patients may be more fragile, with more comorbidities, and at higher risk to present complications post-transplant, such as bacteremia [21, 22]. In alignment with prior published data, we found that diabetes and cardiopulmonary complications were significant risk factors for bacteremia [5, 8, 21, 23]. Similarly, surgical complications were identified as an important predictor of bacteremia, as has already been identified in previous studies, particularly in liver and lung transplant recipients [4, 16, 18, 24–28]. Acute rejection and medical complications post-transplant were found to be significantly associated with bacteremia during the first year as well. Rejection has been previously identified as a significant risk factor for bacteremia in both kidney and liver transplant recipients

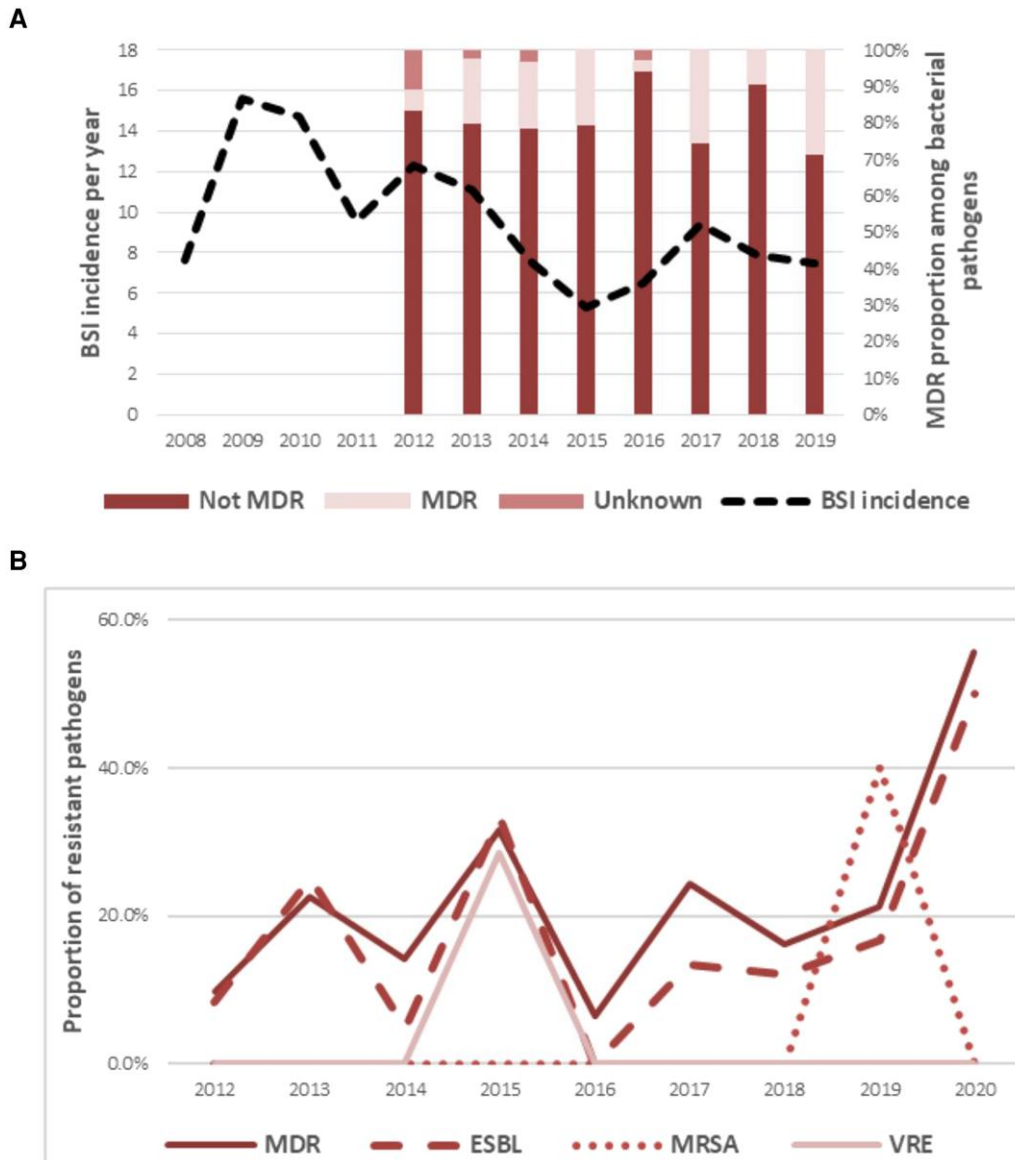


Figure 4. A, Distribution of MDR pathogens through the study period. MDR pathogens included MDR and ESBL-producing GNB, MRSA, and VRE. MDR GNB definitions were based on previously published guidelines [14]. Results are presented as stacked bar charts including the proportions of MDR pathogens, non-MDR pathogens, and pathogens with unknown resistance patterns. B, Distribution of resistant pathogens through the study period, including MDR and ESBL GNB, MRSA, and VRE. MDR GNB definitions were based on previously published guidelines [14]. Results are presented as the proportion of resistant pathogens over the number of pathogens with known antibiotic susceptibilities per year. Data on bacterial drug resistance were collected after 2012; hence results are presented between 2012 and 2019. Antimicrobial resistance patterns were not available for all pathogens between 2012 and 2019. Abbreviations: BSI, bloodstream infection; ESBL, extended-spectrum beta-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

[21, 26]. It is likely that the impact of those complications on bacteremia may be related to their direct and/or indirect effects on the net immunosuppression status of those patients. Liver and lung transplant recipients were more likely to develop an early bacteremia compared with other organs, consistent with the high risk for infectious complications early post-transplant in those patient categories.

CMV donor-negative/recipient-negative serostatus was associated with fewer bacteremia episodes—overall, very early,

and for thoracic organ transplant recipients in particular, likely due to fewer hospitalizations of those patients associated with CMV reactivation and infections and also fewer CMV-treatment associated toxicities, predominately cytopenias, associated with (val)ganciclovir. Notably, CMV infection was associated with higher bacteremia rates only in thoracic organ transplant recipients. It is known that heart and particularly lung transplant recipients are at high risk for CMV reactivation, which is associated with dismal clinical outcomes

Table 3. Results of Multivariable Analyses to Identify Risk Factors for Bloodstream Infections During the First Year Post-transplant: (A) Overall, (B) Very Early (0–30 Days) vs Later; for the Purposes of Those Analyses, Kidney-Pancreas Transplant Recipients Were Considered With Kidney Transplant Recipients, due to the Small Number of Kidney-Pancreas Transplants

	Overall			Very Early BSI ^a		
	HR	95% CI	P	HR	95% CI	P
Demographics recipient/donor						
Recipient age, 10 y	1.16	1.05–1.29	0.003	0.99	0.86–1.14	0.9
Recipient sex, male vs female	0.86	0.69–1.08	.2
Donor age, 10 y	1.05	0.98–1.12	.14	1.03	0.93–1.13	.6
Baseline comorbidities						
Diabetes mellitus, yes vs no	1.42	1.12–1.8	.004	1.33	0.92–1.91	.18
Hypertension, yes vs no	1.05	0.81–1.35	.7	0.98	0.67–1.45	>.9
Cardiopulmonary disease, yes vs no	1.39	1.09–1.77	.007	1.21	0.83–1.77	.3
Malignancy, yes vs no	0.79	0.6–1.06	.12
Transplant-related variables						
Donor status, deceased vs living	1.28	0.94–1.74	.11	1.88	1.02–3.44	.04
Transplant year, 2014–2019 vs 2009–2013	0.66	0.54–0.82	<.001	0.73	0.53–1.01	.05
Induction immunosuppression, Thymoglobulin vs other	0.98	0.73–1.32	>.9	1.28	0.8–2.07	.3
CMV serology status, D-/R- vs R+	0.62	0.46–0.86	.003	0.57	0.35–0.94	.03
CMV serology status, D+/R- vs R+	1.04	0.8–1.34	.8	0.9	0.6–1.35	.6
Transplant type (compared with kidney)						
Heart	1.1	0.72–1.67	.7	1.54	0.85–2.81	.2
Liver	0.98	0.69–1.39	>.9	1.52	0.9–2.56	.11
Lungs	1.02	0.68–1.53	>.9	2.65	1.5–4.67	<.001
Post-transplant time-dependent variables						
Surgical complications, ^b yes vs no	3.09	2.21–4.33	<.001	2.4	1.59–3.61	<.001
Medical complications, ^c yes vs no	2.27	1.3–3.98	.004
Rejection, ^d yes vs no	2.37	1.76–3.19	<.001	2.77	1.66–4.63	<.001
Invasive fungal infection, ^d yes vs no	3.14	1.57–6.27	.001
Any viral infection (excluding CMV), ^d yes vs no	1.08	0.39–2.96	.9
CMV infection, ^d yes vs no	1.8	0.66–4.87	.2
Administration of TMP/SMX as prophylaxis, yes vs no	0.5	0.38–0.65	<.001	0.4	0.27–0.6	<.001

Abbreviations: BSI, bloodstream infection; CMV, cytomegalovirus; D/R, donor/recipient; HR, hazard ratio; TMP/SMX, trimethoprim/sulfamethoxazole.

^aDue to the limited number of BSI events during the first month post-transplant, a smaller number of independent variables was considered based on clinical plausibility and available literature data, excluding the following variables from this model: malignancy before transplant, post-transplant medical complications, invasive fungal infections, and viral infections.

^bSurgical post-transplant complications within 30 days of BSI included vascular, anastomosis, biopsy, bleeding, and surgical site complications.

^cMedical transplant-related complications within 1 year of BSI included diabetes mellitus, hypertension, metabolic disorders, cardiopulmonary disease, transplanted organ tumor, and/or primary disease recurrence.

^dRejection and invasive fungal or viral/CMV infections were considered within 90 days of BSI.

[29]. CMV reactivation may have direct, but also indirect, effects on rejection and graft loss and on the net state of immunosuppression of those patients, and hence increase their susceptibility to opportunistic infections [30–32]. Our data support this already established body of literature suggesting that CMV reactivation post-heart/lung SOT may predispose patients to other complications, including bacteremia.

Administration of cotrimoxazole prophylaxis against PJP was found to be protective against bacteremia overall but also in the early 30-day post-transplant period and for kidney and thoracic organ SOT recipients. Most data on the effect of cotrimoxazole prophylaxis on bacterial infection prevention come from the kidney transplant literature. For instance, administration of cotrimoxazole PJP prophylaxis was shown to have no significant effect on decreasing asymptomatic bacteriuria, cystitis, or allograft pyelonephritis in a single-center

before-and-after retrospective study on kidney transplant recipients [33]. Similarly, in another single-center retrospective study on kidney transplant recipients, when PJP prophylaxis with cotrimoxazole was compared with dapsone, there was no difference in risk for urinary tract infections in the overall patient population [34]. However, cotrimoxazole had to be discontinued in almost half of patients. When analysis was performed in the subset of older (>47-year-old) patients who received dapsone (either up front or as a switch from cotrimoxazole), a potential benefit of cotrimoxazole prophylaxis in reducing urinary tract infections was noted. This observation was consistent with another smaller, single-center retrospective study on renal transplant recipients showing lower incidence of urinary tract infections in patients who received cotrimoxazole vs aerosolized pentamidine as PJP prophylaxis [35]. Similarly, administration of cotrimoxazole as primary prophylaxis during

Table 4. Results of Multivariable Analyses to Identify Risk Factors for Bloodstream Infections During the First Year Post-transplant for (A) Kidney, (B) Liver, and (C) Heart and Lung Transplant Recipients

	Kidney ^a			Liver ^a			Heart and Lung ^a		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Demographics Recipient/donor									
Recipient age, 10 y	1.29	1.14–1.47	<.001	1.16	0.97–1.39	.11	1.02	0.86–1.2	.9
Recipient sex, male vs female	0.79	0.59–1.06	.12
Donor age, 10 y	1.09	0.99–1.2	.07
Transplant-related variables									
Donor status, deceased vs living	1.57	1.13–2.18	.007
Transplant year, 2014–2019 vs 2009–2013	0.74	0.56–1.0	.05	0.46	0.32–0.68	<.001	0.7	0.45–1.07	.1
Induction immunosuppression, thymoglobulin vs other	1.16	0.84–1.6	.4
CMV serology status, D-/R- vs R+	0.73	0.48–1.09	.13	0.67	0.37–1.21	.2	0.43	0.22–0.85	.01
CMV serology status, D+/R- vs R+	0.97	0.67–1.41	.9	1.14	0.72–1.81	.6	0.99	0.61–1.59	>.9
Post-transplant time-dependent variables									
Surgical complications, ^b yes vs no	2.79	1.54–5.04	<.001	2.74	1.65–4.54	<.001	3.23	1.83–5.71	<.001
Medical complications, ^c yes vs no	4.23	1.71–10.5	.002	1.64	0.83–3.23	.2	3.03	1.18–7.74	.02
Rejection, ^d yes vs no	3.05	2.08–4.47	<.001	2.58	1.54–4.32	<.001	1.61	0.84–3.07	.15
Invasive fungal infection, ^d yes vs no	1.97	0.61–6.34	.3
Any viral infection (excluding CMV), ^d yes vs no	0.89	0.12–6.37	>.9
CMV infection, ^d yes vs no	0.66	0.09–4.76	.7	2.77	0.66–11.6	.2	7.52	1.02–55.7	.05
Administration of TMP/SMX as prophylaxis, yes vs no	0.37	0.25–0.55	<.001	0.83	0.56–1.24	.4	0.46	0.25–0.84	.01

Abbreviations: BSI, bloodstream infection; CMV, cytomegalovirus; D/R, donor/recipient; HR, hazard ratio; TMP/SMX, trimethoprim/sulfamethoxazole.

^aDue to the limited number of BSI events for each individual organ transplantation, different numbers of independent variables were considered based on clinical plausibility and available literature data.

^bSurgical post-transplant complications within 30 days of BSI included vascular, anastomosis, biopsy, bleeding, and surgical site complications.

^cMedical transplant-related complications within 1 year of BSI included diabetes mellitus, hypertension, metabolic disorders, cardiopulmonary disease, transplanted organ tumor, and/or primary disease recurrence.

^dRejection and invasive fungal or viral/CMV infections were considered within 90 days of BSI.

the first months after a kidney transplant to prevent urinary tract infections has been shown to be an effective and relatively safe approach, albeit at doses higher than PJP prophylactic doses [36, 37]. Our data suggest that administration of cotrimoxazole as PJP prophylaxis may contribute to lower bacteremia rates, not only very early, during the first month, but also extending through the first year post-transplant.

Collectively, GNB were more commonly identified, representing the majority of bacteremia episodes in heart, kidney, lung, and kidney-pancreas transplant recipients, as previously reported [5, 17, 38–40]. Consistent with prior reports, GPC were frequent pathogens in liver transplant recipients, with *Enterococcus* spp. encountered quite often [16, 17]. The latter might, in part, be related to frequent colonization of the biliary tract of liver transplant recipients with enterococci, leading to higher numbers of bacteremia due to those pathogens [41]. In contrast to prior reports on the emergence of MDR bacterial pathogens in SOT recipients, there were only 2 infections due to vancomycin-resistant enterococci, while a large number of *Enterococcus* spp. were still susceptible to penicillin [4, 41]. Similarly, rates of bacteremia due to other non-*Enterococcus* MDR pathogens were relatively low, with few infections due to ESBL-producing GNB and no infections identified due to carbapenemase-producing GNB. This is in contrast to MDR

pathogen rates as high as 20%–25%, 8%, and 57% in kidney, liver, and lung transplant recipients, respectively [4, 6, 39, 42]. The low MDR incidence in SOT recipients in our cohort reflects the general trend of infections due to MDR bacterial pathogens in Switzerland, as reported by the ANRESIS network [43, 44]. Although those data are in accordance with the general epidemiology in our country, they also suggest that close control and monitoring of transplant prophylactic and treatment strategies by experienced transplant infectious disease teams in all transplant centers in Switzerland might have contributed to keeping antibiotic resistance low in this fragile patient population. Continuous surveillance and monitoring of MDR bacterial pathogen epidemiology in SOT recipients should be maintained in order to identify timely potential trends of MDR development in the future, which could affect clinical practices and patient outcomes.

Despite its limitations, associated with its retrospective design and occasional lack of resistance and other data, our findings complement the existing body of literature with results spanning a 12-year study period reporting on >4000 SOT recipients. In conclusion, we report low bacteremia incidence associated with low mortality rates during the first year after SOT. Improved clinical practices might have led to lower rates of bacteremia in the latter part of the study period and the

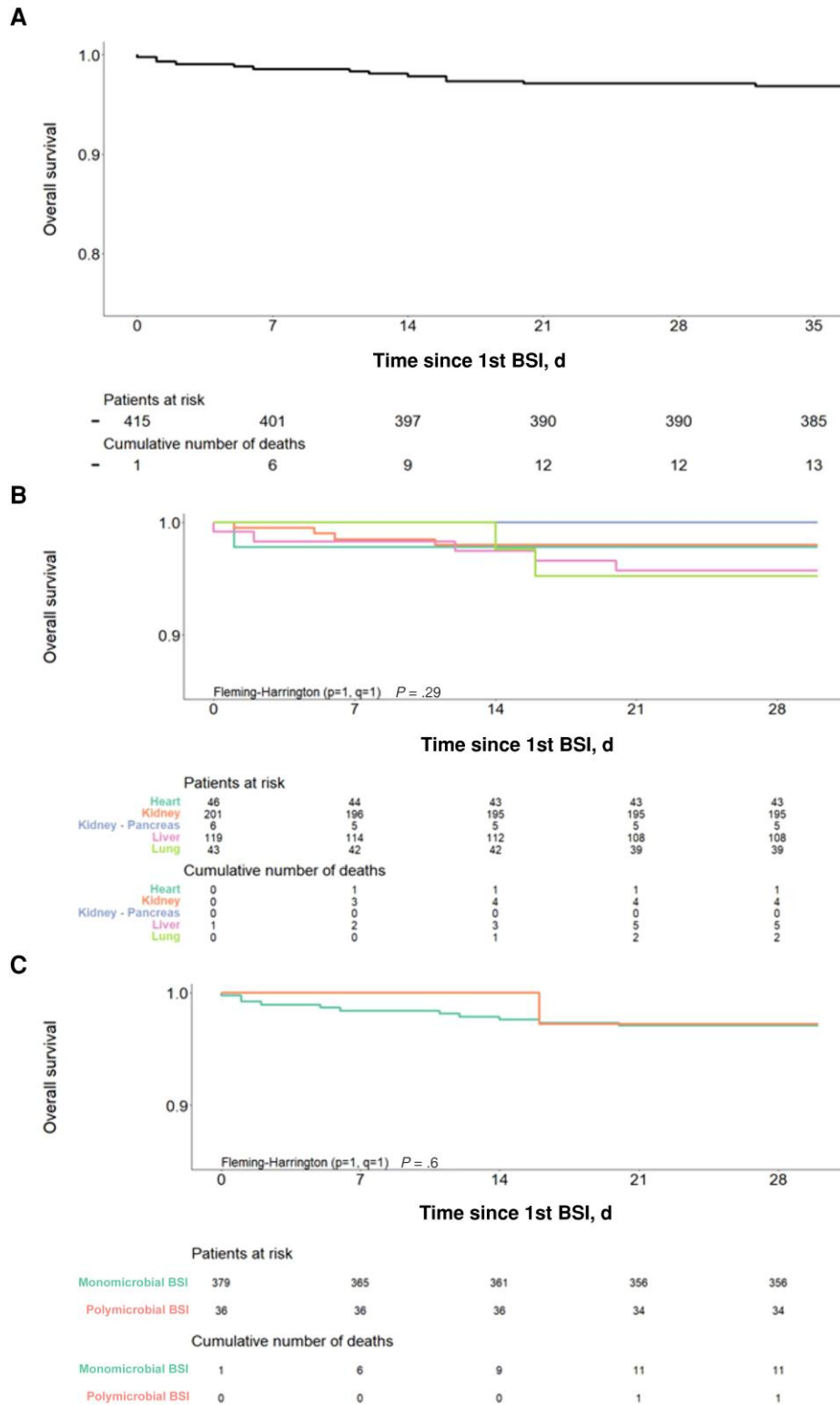


Figure 5. All-cause 30-day mortality of SOT recipients with bacteremia: (A) overall, (B) by SOT type, (C) number of pathogens identified (mono- vs polymicrobial). Abbreviation: SOT, solid organ transplant.

observed low mortality rates. Continuous review and assessment of the epidemiology and risk factors of bacteremia may impact prophylactic and other approaches and allow for even better clinical outcomes in the future.

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Patient consent. All patients included in this study signed an informed consent form to participate in the STCT.

Ethical approval. This study has been approved by local ethical committees.

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