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Blood stream infections in children in the first year after liver transplantation at Wits Donald Gordon Medical Centre, South Africa

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Abstract

Children who undergo liver transplantation and subsequently develop BSI are at risk for adverse outcomes. Research from high-income settings contrasts the dearth of information from transplant centers in low- and middle-income countries, such as South Africa. Therefore, this study from Johannesburg aimed to describe the clinical and demographic profile of children undergoing liver transplantation, and determine the incidence and pattern of BSI and associated risk factors for BSI during the first year after liver transplant. Pediatric liver transplants performed from 2005 to 2014 were reviewed. Descriptive analyses summarized donor, recipient, and post-transplant infection characteristics. Association between BSI and sex, cause of liver failure, age, nutritional status, PELD/MELD score, graft type, biliary complications, and acute rejection was determined by Fisher's exact test; and association with length of stay by Cox proportional hazards regression analysis. Survival estimates were determined by the Kaplan-Meier method. Sixty-five children received one transplant and four had repeat transplants, totaling 69 procedures. Twenty-nine BSI occurred in 19/69 (28%) procedures, mostly due to gram-negative organisms, namely *Klebsiella species*. Risk for BSI was independently associated with biliary atresia (44% BSI in BA compared to 17% in non-BA transplants; $P = .014$) and post-operative biliary complications (55% BSI in transplants with biliary complications compared to 15% in those without; $P = .0013$). One-year recipient and graft survival was 78% (CI 67%-86%) and 77% (CI 65%-85%), respectively. In Johannesburg, incident BSI, mostly from gram-negative bacteria, were associated with biliary atresia and post-operative biliary complications in children undergoing liver transplantation.

KEYWORDS

blood stream infection, end stage liver disease, liver transplant, low and middle income country, mortality, pediatric

[Corrections added on February 17, 2020, after first online publication: In the article title the word "wits" changed to "Wits".]

Abbreviations: BA, , biliary atresia; BMI, , body mass index; BSI, , blood stream infections; CI, , confidence intervals; CMV, , Cytomegalovirus; EBV, , Epstein-Barr Virus; ESLD, , end-stage liver disease; MELD, , model for end-stage liver disease; MTB, , mycobacterium tuberculosis; MTB, , mycobacterium tuberculosis; NAT, , nucleic acid testing; PELD, , pediatric end-stage liver disease; PTLD, , post-transplant lymphoproliferative disorder; SA, , South Africa; sSA, , sub-Saharan Africa; WDGMC, , Wits Donald Gordon Medical Centre.

1 | INTRODUCTION

Post-transplant BSI are a leading cause of morbidity and mortality in pediatric solid organ transplant recipients, presenting a common clinical challenge worldwide.[1,2] These infections can have multiple origins (donor-derived, healthcare-associated, community-acquired), and management is complicated by immunosuppressive therapy, emerging healthcare-associated antibiotic resistance, and the need to carefully dose adjust immunosuppression to prevent allograft rejection. Immunosuppressive medications are a well-known and significant risk factor for BSI in pediatric solid organ transplant recipients, and higher levels of immunosuppression increase the severity of post-transplant BSI.[1] BSI can be classified by the time frame in which they occur after transplant as <30 days, 30 days–6 months, and 6 months onwards.[1]

Although international studies from high-income settings have considered the profile of post-transplant BSI in pediatric liver transplant recipients, comprehensive data from SA are scarce.[3-6] In our program, as in other parts of the world, the most common cause of ESLD in children requiring transplantation is BA. However, there are many factors in our setting that potentially impact on the clinical course and outcomes of our pediatric liver transplant recipients. These include delayed diagnosis and referral; few specialist treatment centers with the expertise to care for children with ESLD and even fewer options for transplantation; differential access to specialist centers which is influenced by health insurance status and urban vs rural location; and the socio-economic status of the family or caregiver. Often, children travel with a desperate parent, far from their home and support networks, and incur substantial out of pocket expenses to access care.[2,7] We have observed that many children are severely malnourished when we first evaluate them in our center, corroborating similar experiences in children with ESLD around the world.[2,7,8] These children require intensive nutritional rehabilitation before transplantation and, although not ideal, this may require prolonged hospital stays before the transplant procedure. Delayed access to appropriate care, poor socio-economic circumstances, and extended hospital stays before transplant increases the risk of post-transplant BSI in these fragile children.

There are two pediatric liver transplant centers in SA, one in Johannesburg and the other in Cape Town. The program in Johannesburg at WDGMC began in 2005 and is now the largest volume pediatric liver transplant unit in the country. WDGMC also hosts the only living donor pediatric liver transplant program in sSA. These characteristics make WDGMC a unique site at which to study the profile of BSI after liver transplant in a middle-income setting. In this study, we aimed to (a) describe the clinical and demographic profile of children undergoing liver transplantation in our program; (b) determine the incidence and pattern of BSI occurring in these children in their first year after transplantation; and (c) investigate associated risk factors for BSI during the same period. The clinical implications of our findings could assist other similarly placed pediatric transplant programs in low- and middle-income settings, such as others in sub-Saharan Africa, Brazil, Columbia, Costa-Rica, and Iran.[9]

2 | PATIENTS AND METHODS

Study subjects: We obtained approval for this retrospective record review from the University of the Witwatersrand Human Research Ethics Committee (Medical) [M160257]. We included all pediatric patients who underwent liver or combined liver-kidney transplantation from January 2005 to December 2014, and we followed them up for 12 months after transplant, or until death. Pediatric patients were defined as any recipient less than 18 years of age on the day of transplant. We extracted the following data from clinical records and laboratory pathology reports: for donors—age, sex, donor type (living or deceased), blood group, ABO-incompatible transplants, serology for hepatitis A, B, and C, HIV, and syphilis; for recipients—age, sex, population group, blood group, type of ESLD (chronic/acute), etiology of ESLD, pretransplant anthropometry based on age group (MUAC z-score, weight, BMI z-score), PELD, or MELD score; transplant number (first/retransplant), transplant type (liver-only, combined liver-kidney); graft type (whole/partial), post-operative

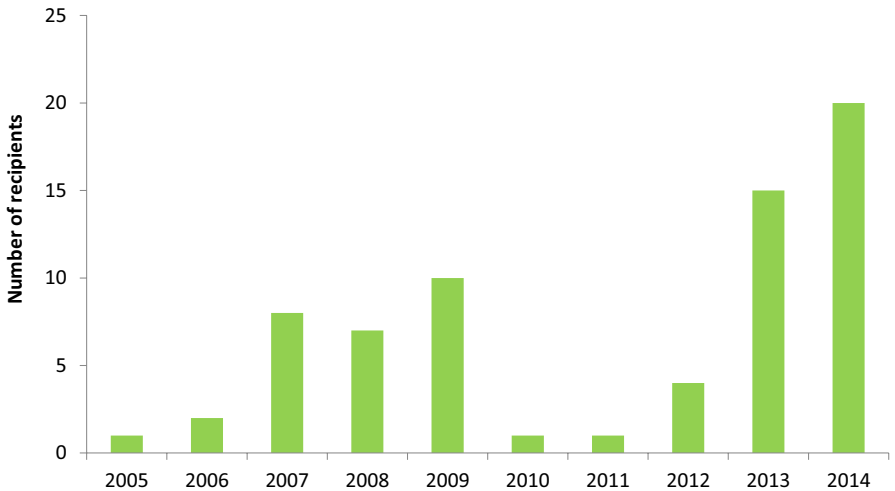

FIGURE 1 Number of pediatric liver-only and combined liver-kidney transplants performed from inception of the liver transplant program at WDGMC (2005-2014)

TABLE 1 Donor characteristics at the time of transplant

Variable	overall (n = 69); n (%)[a]
Median donor age; *years (IQR)*	25.0 (17.1-34.0)
Donor sex	
Male/Female	34 (49)/35 (51)
Donor type	
Deceased/Living	53 (77)/16 (23)
Donor blood group	
A	14 (20)
B	9 (13)
O	46 (67)
AB	0
ABO-incompatible transplants	
O to A or B or AB; A to AB; B to AB	17 (25)
Hepatitis A IgM	
Negative	64 (93)
Missing	5 (7)
Hepatitis B SAg	
Negative	62 (90)
Missing	7 (10)
Hepatitis B SAb	
Positive	26 (38)
Negative	37 (54)
Missing	6 (9)
Hepatitis B core ab	
Positive	6 (9)
Negative	61 (88)
Missing	2 (3)
Hepatitis C	
Negative	69 (100)
HIV antibody[b]	
Negative	69 (100)
TPHA/RPR	
Negative	61 (88)
Missing	8 (12)

[a]Percentages have been rounded, so may add to more or less than 100.
[b]HIV antibody-positive living and deceased donors were excluded. However, one deceased donor tested antibody negative but was in the window period of HIV infection and resulted in HIV infection of a pediatric recipient. The window period was confirmed with subsequent HIV nucleic acid testing, which tested positive.

surgical complications, induction and maintenance immunosuppression, laboratory-confirmed BSI, biopsy-proven graft rejection in the first year after transplant, length of hospital stay at time of transplant, recipient and graft survival. All data were collected using REDCap.[10]

Nutritional Status: We use indices recommended by the World Health Organization according to age.[11] For children ≤5 years of age,

TABLE 2 Characteristics of pediatric liver transplant recipients at WDGMC (2005-2014)

Characteristic	Overall (n = 69); n(%)[a]
Before Transplant	
Median age *(IQR); range*	49 mo (27-152); 9-216 mo
Sex	
Male/Female	27(39)/42(61)
Population Group	
Black	35(51)
White	24(35)
Indian/Asian	6(9)
Mixed	4(6)
Blood Group	
O	31(45)
A	25(36)
B	11(16)
AB	2(3)
Type of liver failure	
Chronic/Acute	65(94)/4(6)
Nutritional status for children ≤ 5 y old (n = 41)	
Median weight *(IQR); range*	11 kg (9-13 kg); 5-20 kg
Severe malnutrition	9(22)
Moderate malnutrition	9(22)
Mild malnutrition	4(10)
Well nourished	12(29)
Missing	7(17)
Children aged > 5 y old (n = 28)	
Median weight *(IQR); range*	37 kg (27-47 kg); 14-81 kg
Severe malnutrition	3(11)
Moderate malnutrition	2(7)
Mild malnutrition	5(18)
Well nourished	14(50)
Missing	4(14)
MELD/PELD Score	
≥35	3(4)
30-34	2(3)
15-29	32(46)
<15 1	26(38)
Missing	6(9)
At time of transplant	
Transplant number	
First/Retransplant	65(94)/4(6)
Type of transplant	

(Continues)

TABLE 2 (Continued)

Characteristic	Overall (n = 69); n(%)[a]
Liver-only/Combined liver-kidney	62(90)/7(10)
Type of graft	
Partial/Whole	43 (62)/26(38)
Post-transplant	
Surgical complications	
Re-look laparotomy (n = 66)	20(29)
Primary non-function of graft (n = 68)	3(4)
Biliary complications (n = 68)	22(32)
Strictures	11/22
Leaks	11/22
Vascular complications (n = 68)	8(12)
Hepatic Artery (thrombosis)	3/8
Hepatic Vein (thrombosis/stenosis)	2/8
Portal Vein (thrombosis)	3/8
Median length of stay *(IQR); range*	24 d (13-42 d); 1-129 d
Biopsy-proven rejection in the first year	18 (26)

[a]percentages have been rounded, so may add to more or less than 100.

we used MUAC z-scores and BMI z-scores where MUAC data were not available, and for children >5 years old, we used BMI z-scores. Both indices classify malnutrition as follows (a) mild malnutrition: z-score −1 to −1.9; (b) moderate malnutrition: z-score −2 to −2.9; (c) severe malnutrition: z-score less than or equal to −3. For this analysis, we defined children with MUAC and BMI z-scores greater than or equal to 0, as well nourished.

Antimicrobial prophylaxis: Perioperative antibacterial prophylaxis was commenced in theater with piperacillin/tazobactam (100 mg/kg/dose, 8 hrly) and continued for 24 hours post-operatively. For children transplanted for acute liver failure, the antibacterial prophylaxis was continued for 7 days, with additional antifungal prophylaxis in the form of micafungin (150 mg/kg/dose) for the same duration. After transplant, oral sulphamethoxazole/trimethoprim suspension (200 mg/40 mg per 5 mL) was administered three times weekly (0.5 mL/kg) for the first 6 months post-transplant as prophylaxis against *pneumocystis jirovecii* infection. For children 18 months and older, based on donor (D) and recipient (R) serology for CMV infection, only children at highest risk for CMV infection (CMV IgG D+/R−) were given valganciclovir prophylaxis (14 mg/kg/d) for 3 months and low-risk patients received acyclovir prophylaxis for 3 months. All children younger than 18 months were considered high risk and given CMV prophylaxis. We did not administer routine prophylaxis against tuberculosis infection.

Immunosuppression: We used corticosteroids and calcineurin inhibitor-based therapy, namely tacrolimus. Intravenous methylprednisolone (10 mg/kg) was administered intraoperatively at transplant, followed by oral prednisone from day 1 (1 mg/kg/d), which was tapered and stopped within 6 months post-transplant. Tacrolimus was started from day 1 with therapeutic drug monitoring to maintain trough levels of 12-15 mg/mL for the first month post-transplant and then 5-10 mg/mL over the next 6 months.

Definition of BSI: A BSI was confirmed if there were clinical signs of infection and a positive culture of a pathogen identified from a single laboratory-confirmed blood culture. Skin contaminants, for example, *micrococcus* spp., *corynebacterium* spp., and coagulase-negative staphylococci, were excluded. In the case of polymicrobial BSI, each isolate was considered a pathogen. We verified BSI using clinical records and pathology laboratory reports. Investigations to confirm infection were initiated by clinicians, based on clinical signs and symptoms in the recipient.

Data analysis: Descriptive analyses were performed to summarize donor, recipient, and post-transplant infection characteristics. The association between recipients who experienced no vs one or more BSI after transplant and the following variables: sex; cause of liver failure (BA vs other); at time of transplant: age (<2 years vs ≥2 years), nutritional status (malnourished vs well nourished), PELD/MELD score (<15 vs ≥15), graft type (partial vs whole);

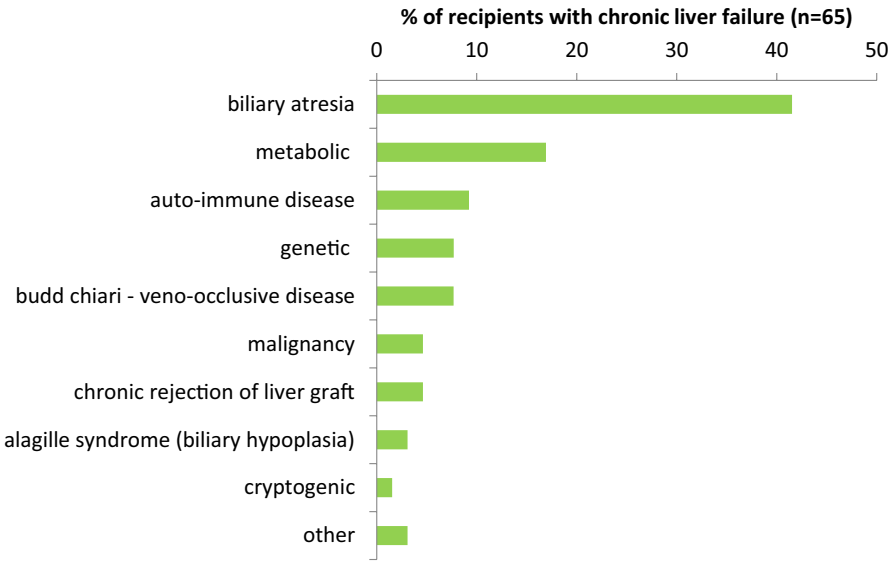

FIGURE 2 Causes of chronic ESLD in children presenting for liver-only and combined liver-kidney transplantation at WDGMC (2005-2014)

post-transplant: biliary complications, acute rejection within 90 days was determined by Fisher's exact test. Cox proportional hazards regression was performed to examine the association between no vs one or more BSI after transplant and length of hospital stay censored for death. Survival estimates were determined by the Kaplan-Meier method. Patient and graft survival were estimated at 90 days and 1-year post-transplant. Data analysis was carried out using SAS 9.4 (SAS Institute, Cary, NC). A 5% significance level was used.

TABLE 3 Details of laboratory-confirmed bloodstream infections (BSI) in pediatric recipients in the first year after liver transplant

Characteristic	n (%)[a]
Number of transplant procedures complicated by BSI	19/69 (28)
Number of BSI per transplant procedure (n = 69)	
0	50 (72)
1	11 (16)
2	6 (9)
3	2 (3)
Organisms Identified (n = 29)[b]	
Bacterial	26 (90)
Fungal	3 (10)
Gram-Positive Bacteria (n = 7)	
Enterococcus faecium	7 (100)
Gram-Negative Bacteria (n = 22)	
Klebsiella pneumoniae	10 (45)
Klebsiella oxytoca	1 (5)
Klebsiella aerogenes	1 (5)
Klebsiella sp	2 (9)
Eschericia coli	4 (18)
Enterobacter cloacae	2 (9)
Pseudomonas aeruginosa	1 (5)
Pseudomonas stutzeri	1 (5)
Fungal Organisms (n = 3)	
Candida parapsilosis	3 (100)

[a]percentages have been rounded, so may add to more or less than 100.
[b]three BSI were polymicrobial, making total number of organisms identified greater than the total number of BSI: two BSI identified two gram-negative organisms; one BSI identified one gram-positive and one gram-negative organism.

3 | RESULTS

The number of transplant procedures increased steadily during the study period (Figure 1), and overall, we performed 69 transplants in 65 patients. The living donor liver transplant program only began in 2013, explaining the predominance of deceased donor grafts (53/69; 77%) over living donor grafts. The donor and recipient characteristics are summarized in Tables 1 and 2, respectively. Of the four recipients transplanted for acute liver failure, two were for acute hepatitis A infection, one had primary non-function of the graft, and data were not available for one child. The remainder presented with chronic ESLD, of which the most common indication for transplant was BA (Figure 2). Many children were malnourished at the time of transplant, particularly at younger ages. From available data on 34/41 children aged ≤5 years, 22/34 (65%) were moderately or severely malnourished at the time of transplant (Table 2).

Of the 69 liver transplant procedures performed during the study period, 19 procedures (28%) were complicated by laboratory-confirmed BSI's (Table 3) and most occurred within the first 6 months of transplant (Figure 3). Most children developed a single BSI; however, there were a few with two and three BSI episodes (Table 3). Barring one exception, all BSI were treated as inpatients (28/29, 97%). From the blood culture results, bacterial infections were the most common (90%), and of these, gram-negative organisms dominated—in particular—*Klebsiella pneumoniae*. Of the gram-positive organisms, *Enterococcus faecium* was the only pathogen isolated, and there was no documented MTB infection (Table 3). Of potential factors (Table 4)

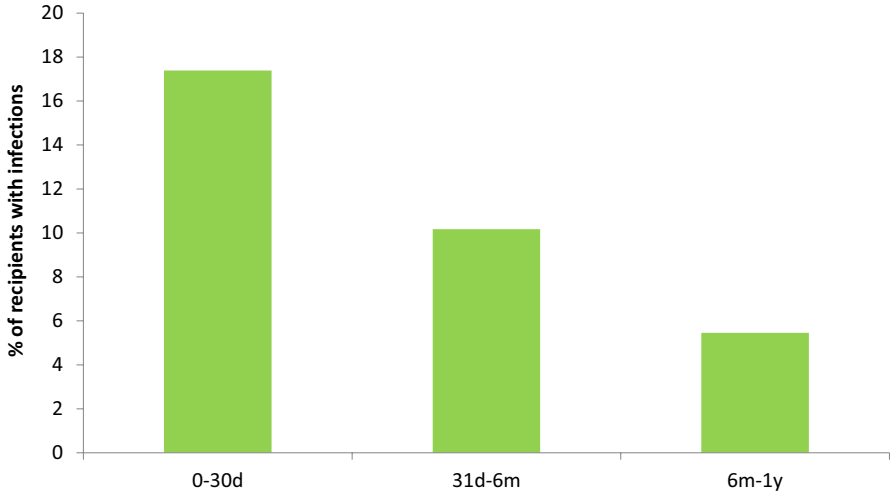

FIGURE 3 Distribution of laboratory-confirmed BSI in the first year after liver transplant

TABLE 4 Risk factors for BSI in pediatric liver transplant recipients

Variable	Category	Overall n (%)	BSI None n (row %)	BSI ≥1 n (row %)	*P*-value for between-group comparison
n		69	50	19	
Graft type	Partial	43 (62)	28 (65)	15 (35)	.10
	Whole	26 (38)	22 (85)	4 (15)	
Biliary complications (n = 68)	No	46 (68)	39 (85)	7 (15)	.0013
	Yes	22 (32)	10 (45)	12 (55)	
Age at transplant	<2 y	15 (22)	12 (80)	3 (20)	.53
	≥2 y	54 (78)	38 (70)	16 (30)	
Gender	Male	26 (38)	18 (69)	8 (31)	.78
	Female	43 (62)	32 (74)	11 (26)	
PELD/MELD	<15	26 (38)	21 (81)	5 (19)	.38
	≥15	37 (54)	25 (68)	12 (32)	
Cause of liver failure	Biliary atresia	27 (39)	15 (56)	12 (44)	.014
	Other	42 (61)	35 (83)	7 (17)	
Acute rejection within 90 d	No	51 (74)	40 (78)	11 (22)	.074
	Yes	18 (26)	10 (56)	8 (44)	
LOS[a] (d) (censored for death): median (95% CI)		24 (18-30)	20 (15-27)	31 (23-45)	.088
Malnourished[b] (all) (n = 58)	No	26 (45)	17 (65)	9 (35)	.27
	Yes	32 (55)	25 (78)	7 (22)	
Malnourished[b] (≤5 y) (n = 34)	No	12 (35)	6 (50)	6 (50)	.18
	Yes	22 (65)	16 (73)	6 (27)	
Malnourished[b] (>5 y) (n = 24)	No	14 (58)	11 (79)	3 (21)	.47
	Yes	10 (42)	9 (90)	1 (10)	

[a]Length of stay.

[b]Malnutrition (mild, moderate and severe) defined as pretransplant MUAC or BMI (for recipients aged ≤ 5 y) and BMI (for recipients aged > 5 y) with z-score of ≤−1.

that might be associated with BSI, the only significant risk factors identified were (a) BA as a cause of liver failure (44% BSI in BA transplants compared to 17% in non-BA transplants; P = .014) and (b) the development of post-operative biliary complications (55% BSI in transplants with biliary complications compared to 15% in those without; P = .0013). There was a trend toward significance with length of stay and acute rejection within 90 days. The prevalence of malnutrition, by age group, for those with and without BSI, is given in Table 4. There was no significant association between malnutrition status and BSI prevalence.

As per protocol, most children (63/69; 91%) received intravenous methylprednisolone and tacrolimus (58/69; 84%) for immunosuppression in the immediate post-transplant period. There were 26 biopsy-proven acute rejection episodes with a mean Banff score of 5.2 (SD 1.4, range 3-8), and the median length of hospital stay for all children after transplant was 24 days (IQR 13-42 days). Median patient follow-up time was 2.4 years with recipient and graft survival shown in Figure 4. Twenty-three (23) recipients died in the first year following transplant, and of these, seven had a laboratory-confirmed BSI at the time of death.

One child contracted HIV from a deceased donor after transplantation—the first index case documented from SA. When this occurred, the national policy for the screening of donors for HIV infection required an ELISA antibody test. Subsequently, national policy was reviewed, and donor HIV NAT adopted as a standard requirement with ELISA antibody testing. To date, the child remains well on antiretroviral treatment.[3,4,12,13]

4 | DISCUSSION

Our study is the first contemporary description of BSI in the first year after pediatric liver transplantation in SA. To some extent, our

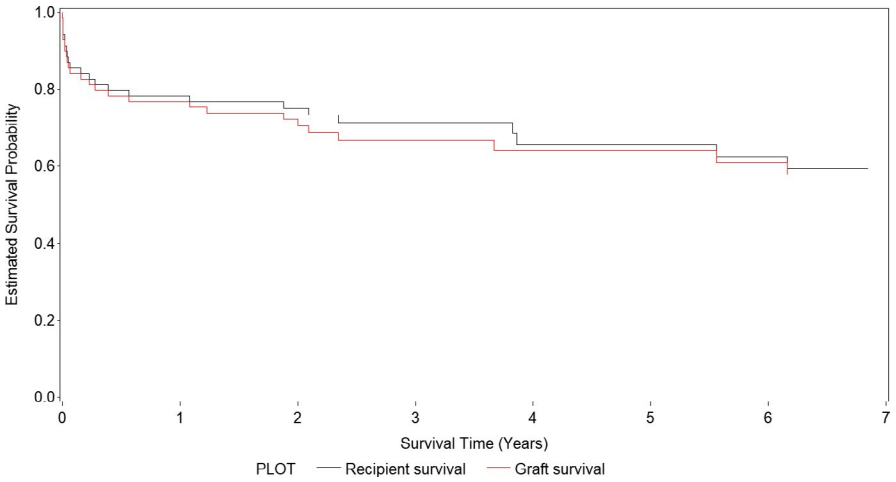

FIGURE 4 Recipient and graft survival. Using 95% CI, 90 d recipient and graft survival was 83% (CI 71%-90%) and 81% (CI 70%-89%,) respectively; 1-year recipient and graft survival was 78% (CI 67%-86%) and 77% (CI 65%-85%), respectively

findings in Johannesburg mirror those briefly reported in the pediatric liver transplant program of the Red Cross Children's Hospital in Cape Town between 1991 and 2003. Biliary atresia was the most common cause of liver failure in our program, a finding that is reflected worldwide and in the earlier Cape Town study.[14,15]

In this study, 29 BSI occurred in 19 transplants (28%)—a slightly higher incidence than reported in studies from Japan and Korea (25% and 21.5%, respectively), but on par with studies from Italy (28%) and a review from USA which reported BSI incidence between 19% and 40%.[3,4,12,13] Most of our BSI occurred in the first 6 months after transplant surgery, which is consistent with published data.[5,12,13.] Bacterial pathogens were most frequently isolated, of which gram-negative pathogens, in particular, *Klebsiella species* were most common. The predominance of gram-negative BSI in the early post-transplant period is known.[3,5,12,13] However, we do have fewer gram-positive organisms than in other studies.[3,5,12,13.] Our results may reflect the definition of BSI we used, where potential contaminants such as coagulase-negative *staphylococci* were excluded. Despite this, our relative burden of gram-positive infection is still much lower than the studies cited above, and our rates of fungal infection (10%) higher than studies from Italy and Japan (3%-4%).[3,12]

We did not demonstrate an increased risk for BSI in the first year after liver transplant with partial grafts (when compared to whole grafts), or malnourished children (compared to well-nourished children).[2,7,16] While these findings contradict available literature from high-income settings, they may have resulted from our small sample size. The only significant risks for BSI that we identified were post-operative biliary complications and children with biliary atresia as a cause of liver failure. Studies from Japan, Korea, and France, and a review of 17 studies on risk factors for BSI after pediatric liver transplantation all concur with these findings as independent risk factors for BSI.[4,5,17,18]

The absence of MTB infection during the study period was counterintuitive, as we do not administer prophylaxis after transplantation. While the WHO classifies SA as having one of the highest burdens of MTB in the world, this is strongly associated with the HIV epidemic, and prevalence rates differ substantially across the country.[19] For example, in our province of Gauteng, MTB prevalence is half that of the Western and Eastern Cape. None of our recipients were HIV-positive at the time of transplant, which could also have mitigated their risk. These findings support our approach, which is not to provide routine MTB prophylaxis in our pediatric transplant program.

Our inadvertent, donor-derived, HIV-transmission also warrants further discussion as SA has high-HIV prevalence. The transplant in question took place in 2013 as part of a national organ share. The donor had no identifiable high-risk practices for HIV. At the time of donation, HIV fourth-generation ELISA testing was performed as per standard protocols. This method was most feasible in our setting in terms of cost considerations, turnaround time, and laboratory logistics. Because such a transmission had not taken place before, we did not appreciate the limitations of this testing protocol at that time. Both donor kidneys were transplanted at the center in Cape Town, and the liver graft was split between an adult and pediatric recipient at WDGMC. Post-transplant, both kidney recipients were admitted with repeated infectious complications, and HIV seroconversion was ultimately confirmed. We were notified of the seroconversion and subsequently tested our liver recipients, both of whom had seroconverted. This prompted our policy change to NAT testing—in additional to fourth-generation ELISA—in all donors. Screening with NAT, while more costly, results in healthcare savings that exceed screening costs particularly in high-HIV prevalence regions like SA. We urge other high-prevalence regions with transplant programs to consider implementing routine donor screening with NAT. Our 1-year patient and graft survival rates are comparable with similar LMIC pediatric liver transplant programs.[20-22] However, they are inferior to the outcomes achieved by transplant centers in high-income countries and might be due to the heavy reliance on deceased donation in our cohort.[23,24]

This study has several limitations, namely the relatively small sample size; the absence of reliable data on the antibiotic resistance profiles of gram-positive and negative bacterial isolates, which prevented in-depth analysis of the pattern of hospital-acquired infections; prior to 2010, the lack of standardized prevention of central line-associated BSI (CLABSI) bundles; at the start of the program,

we did not have a dedicated pediatric ICU, nor did we have appropriately trained pediatric staff. Also, this study reflects a single-center experience, and our findings might not be generalizable. Future studies are underway to address these knowledge gaps.

In spite of these limitations, this study provides valuable insights into the profile of incident BSI in the first year after transplant in our pediatric recipients, and our lessons learned might assist others in low- and middle-income countries who participate in pediatric solid organ transplantation.

5 | CONCLUSION

In this study from WDGMC in Johannesburg, SA, the incidence and pattern of BSI in the first year after pediatric liver transplantation was comparable to that described in high-income countries. Postoperative biliary complications and biliary atresia—as a cause of liver failure—were independent risk factors for BSI post-transplant, although more extensive studies are needed to explore other risks for BSI in our setting and ultimately improve outcomes.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

Mary Duncan: conceptualized the study, collected the data, and edited the final draft of the paper; Anne DeVoll-Zabrocki: conceptualized the study, collected the data, and edited the final draft of the paper; Harriet Etheredge: contributed to writing the first draft of the manuscript, editing subsequent versions, and the final draft; Heather Maher: contributed to data collection and edited the final draft of the paper; Carolyn Bouter: contributed to writing the first draft of the manuscript, editing subsequent versions and the final draft; Petra Gaylard: biostatistical analysis and edited the final draft of the paper; Jerome Loveland: contributed to conceptualizing the study and edited the final draft of the paper; June Fabian: wrote the first draft of the manuscript and edited subsequent versions; Jean F Botha: contributed to conceptualizing the study and edited revised versions and the final draft of the paper.

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