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Infections among pediatric transplant candidates: An approach to decision-making

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Abstract

Introduction: The presence of infections in the immediate pretransplant period poses challenges in decision-making. Delaying transplantation because of these infections may be required, but is associated with a risk to the potential recipient. The aim of this project was to develop a structured framework based on expert opinion to guide decision-making regarding the safety of transplantation for candidates with infection immediately before transplant, and to show how this framework can be applied to clinical scenarios.

Methods: Categories were created as follows: Category A: no delay; Category B: brief delay (≤1 week); Category C: intermediate delay (>1 week); and Category D: more prolonged or indefinite delay. A survey containing 59 clinical scenarios was sent to members of the IPTA ID CARE committee. Answers were reviewed, and the level of agreement was characterized as follows: Level 1: ≥75% agreement; Level 2:51%-74% agreement; and Level 3: ≤50% agreement. 95% CIs were calculated for the mean overall agreement across 59 scenarios.

Results: Among the panel, the agreement level ranged from 33% to 92% with the mean overall agreement across the 59 scenarios being 61%. For 7/59 scenarios, the lower bound of 95% CI was greater than 50%, indicating a difference at the 5% level of significance between the observed proportion and the chance level of 0.5.

Summary: The document provides expert opinion regarding the need to delay transplantation in the setting of different infections. The most important points in the decision to proceed to SOT included the urgency of transplantation and the severity of infection.

KEYWORDS

candidate, infection, pediatric, solid organ transplantation

Abbreviations: AST-IDCOP, American society of transplantation infectious diseases community of practice; CARE, clinical care, advocacy, research and education; CI, confidence interval; CLABSIs, central line–associated bloodstream infections; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; ID, infectious diseases; IPTA, International Pediatric Transplant Association; LRTI, lower respiratory tract infection; NTM, non-tuberculous mycobacteria; RSV, respiratory syncytial virus; SOT, solid organ transplantation; URTI, upper respiratory tract infection; UTI, urinary tract infection; VAD, ventricular assisted devices; VZV, varicella-zoster virus.

1 | INTRODUCTION

The role of SOT in the management of end-organ failure is well established. In preparing potential organ recipients for transplant, efforts are made to minimize or eliminate the risk of infection after transplantation. Several factors predispose to post-transplant infections. First, the organ being transplanted influences not only the anatomical site of early post-transplant infection, but also the need for induction therapy, the choice of immunosuppressants, and the net state of immunosuppression, with each factor being associated with different infectious risks.[1] The age of the recipient also significantly contributes to the risk of infection, with younger children being at higher risk of severe respiratory viral infections, more likely to experience donor-derived herpesvirus infections, and less likely to be fully immunized prior to SOT.[2] Other factors such as underlying illnesses and intraoperative and donor-derived factors also contribute to the overall risk of infection following SOT.[2]

In the immediate pretransplant period, the presence of a new or ongoing infection can pose a risk for successful transplantation. In some situations, this may result in the transplant being delayed in an effort to minimize risks. In this regard, clinicians are often faced with the task of balancing the risk of morbidity or mortality from an acute or recently diagnosed chronic infection against the risk of dying on the waiting list. The decision to delay SOT because of concern for the presence of infection in the potential recipient is influenced by several factors including the urgency of the transplant, the nature of the infection, and the perceived magnitude of risk that the infection will present in the post-transplant period. Because these events are rare and difficult to study, there is a lack of data and definitive guidance is lacking. In an effort to address these deficiencies, we conducted a survey of pediatric transplant infectious disease experts using a structured framework to develop guidance recommendations for these situations.

2 | METHODS

The project was designed by the IPTA ID CARE committee. At the time of the study, the committee included 13 members consisting of transplant ID physicians as well as solid organ transplant physicians, referred to as panel members in the manuscript. The respective expertise of each panel member is detailed in Table S1.

2.1 | Categories of action

Ordinal categories were created as follows: Category A: no need to delay SOT; Category B: brief delay (≤1 week) until cultures are negative or infection controlled; Category C: intermediate delay (>1 week); and Category D: more prolonged or indefinite delay (Table 1). The categories are referred to as the IPTA ID CARE (IPTA-IDC) categories.

2.2 | Design of survey

An extensive review of the current literature and existing guidelines was performed which served as a guide in creating a survey consisting of 59 clinical scenarios. The survey was sent to a panel consisting of each member of the IPTA ID CARE committee. The IPTA-IDC categories were used to classify the potential responses of the panel members. Each panel member was asked to assign a category of action for each of the clinical scenarios. When a panel member provided more than one answer for a defined scenario, results were removed from the analysis a posteriori.

2.3 | Levels of agreement

The survey provided an opportunity to examine the level of agreement among panel members. Answers were reviewed, and percentage agreement between members for each scenario was defined as follows: Level 1: ≥75% agreement; Level 2:51%-74% agreement; and Level 3: ≤50% agreement (Table 1).

2.4 | Results presentation

Consensus agreement was then developed as follows: For each scenario, a category of action and a level of agreement were defined based on the answers of the panel members. For example, if 67% of panel members proposed a brief delay for a given scenario, this

TABLE 1 Categories of action and classification of level of agreement between experts

Categories of action	
A	No delay
B	Brief delay (≤1 wk) until cultures are negative or infection controlled
C	Intermediate delay (>1 wk)
D	More prolonged or indefinite delay
Classification of level of agreement between experts	
1	≥75% agreement
2	51%-74% agreement
3	≤50% agreement

For example, if more than 75% of experts considered that there should be a brief delay of transplantation in the case of bacteremia, this scenario would be labeled as B1.

scenario was characterized as B; 2. When agreement was below 50%, the most frequently chosen options were taken into account (ie, B/C; 3), unless one option was selected by at least two more panel members than other options (ie, B; 3).

2.5 | Statistical analysis

For each scenario, a 95% CI was calculated for the mean overall agreement. A lower bound of 95% CI greater than 50% indicated a difference at the 5% level of significance between the observed proportion and the chance level of 0.5.

3 | RESULTS

3.1 | Survey results

The response rate was 13/13 (100%) among the panel members. One or more panel members did not respond to a given scenario on 27 occasions (3.5%). More than one answer was provided in 41 (5.3%) of the potential total of 767 responses from the entire panel. Among the panel, agreement ranged from 33% to 92% with the mean overall agreement across the 59 scenarios being 61% (95% CI of the mean: 0.56-0.65). The point estimate of agreement was >50% in 39/59 scenarios. However, only 7/59 scenarios showed statistical significance above 50% agreement level, as shown in Figure 1 and Table S2. The pooled results of the survey by category of clinical scenario are shown in Tables 2-4. This shows the IPTA-IDC categories along with the recommendations from the panel. CIs are created based on the extent of agreement among respondents.

3.2 | Application of IPTA ID CARE categories to common clinical scenarios

3.2.1 | Bacteremias

For bacterial bloodstream infections (including CLABSIs), 75% of panel members recommended a brief delay before SOT, waiting until cultures are sterile, and evidence that the infection is controlled (B; 1) with emphasis on the urgency of SOT and the causative pathogen (Table 2).

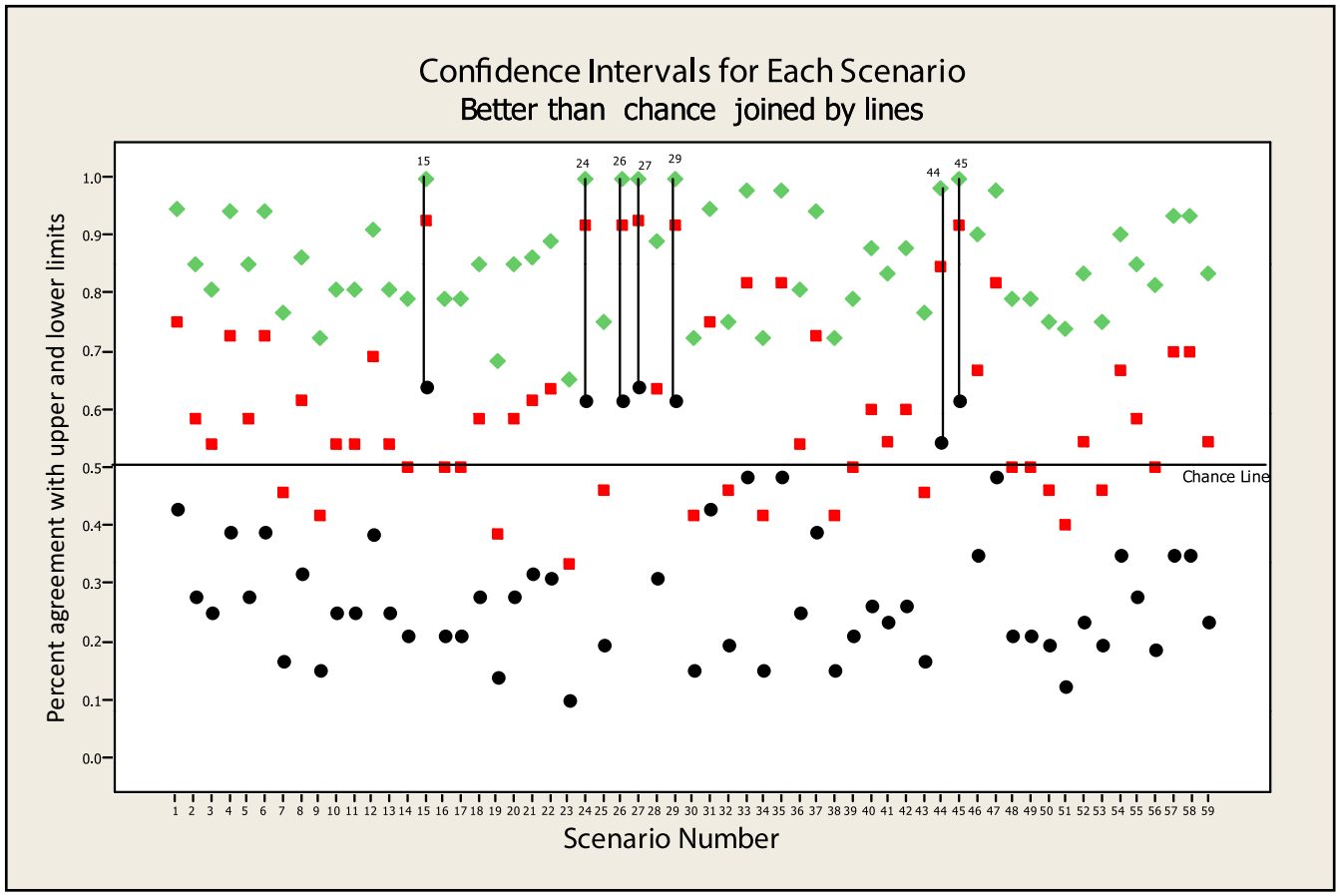

FIGURE 1 Confidence intervals for each clinical scenario. Green and black dots: upper and lower limits of the 95% confidence interval of agreement, respectively; red dots: observed agreement. Scenarios with vertical lines indicate those where the agreement was above chance; 15: mild-moderate gastroenteritis due to a virus without potential for dissemination in a candidate awaiting urgent SOT; 24: urinary tract in a kidney transplant candidate; 26 and 27: urinary colonization in a kidney and non–kidney transplant candidate, respectively; 29: active tuberculosis; 44 and 45: human immunodeficiency virus infection, respectively well controlled and poorly controlled

TABLE 2 Recommendations and percentage agreement for common clinical scenarios

Scenarios	Clinical conditions	Recommendations	95% Confidence Interval	
			Lower CI	Upper CI
1	**Bacteremia or bacterial CLABSI**	B1	0.43	0.95
	URTI			
2	Elective SOT, virus known	B2	0.28	0.85
3	Elective SOT, virus unknown	C2	0.25	0.81
4	Urgent SOT, virus known	A2	0.39	0.94
5	Urgent SOT, virus unknown	A2	0.28	0.85
	LRTI			
6	Lung transplant, mild-moderate	C2	0.39	0.94
7	Lung transplant, severe	C3/D3	0.17	0.77
8	Non–lung transplant, mild-moderate	C2	0.32	0.86
9	Non–lung transplant, severe	C3/D3	0.15	0.72
	Gastroenteritis			
	Elective SOT, mild-moderate			
10	Virus unknown	B2	0.25	0.81
11	Virus known, no potential for dissemination	B2	0.25	0.81
12	Virus known, potential for dissemination	C2	0.39	0.91
13	Elective SOT, severe	C2	0.25	0.81
	Urgent SOT, mild-moderate			
14	Virus unknown	A3/B3	0.21	0.79
15	Virus known, no potential for dissemination	A1	0.64	1.00
16	Virus known, potential for dissemination	B3	0.21	0.79
17	Urgent SOT, severe	B3/C3	0.21	0.79
	Central nervous system infections			
18	Bacterial meningitis	B2	0.28	0.85
19	Viral meningitis/encephalitis (non-HSV)	C3/D3	0.14	0.68
20	HSV encephalitis	C2	0.28	0.85
21	Meningoencephalitis of unknown origin	D2	0.32	0.86

CI, confidence interval; CLABSI, central line–associated bloodstream infection; HSV, Herpes simplex virus; SOT, Solid organ transplantation.

3.2.2 | Viral upper respiratory tract infections

In the case of an URTI in a candidate awaiting an elective SOT, 58% of panel members recommended a brief delay if the virus is identified (B; 2), whereas 33% recommend an intermediate delay. If the virus was unknown, 54% recommended an intermediate delay (C; 2) and 31% a brief delay. In the case of an urgent need for SOT, 73% and 58% of panel members recommended no delay, whereas 27% and 33% recommended a brief delay whether etiology was known or unknown, respectively (A; 2).

3.2.3 | Lower respiratory tract infections

For children presenting with evidence of LRTI, the recommendations varied depending on the severity of the acute infection, the type of transplant, and urgency of transplant. If a lung transplant candidate presented with evidence of mild/moderate LRTI in the immediate pre-transplant setting, 73% of panel members recommended an intermediate delay (C; 2), whereas the level of agreement was poor and equally divided between intermediate and prolonged delay in the case of severe LRTI (C/D; 3). The panel's position was similar if LRTI occurred in

TABLE 3 Recommendations and percentage agreement for other bacterial and fungal infections

Scenarios	Clinical conditions	Recommendations	95% confidence interval		Comments/discussion points
			Lower CI	Upper CI	
	Bacterial infections				
	Endovascular infections				
22	Bacterial endocarditis	C2	0.31	0.89	Some centers postpone SOT for >2 wk after documentation of negative blood cultures when possible. If SOT is urgent, SOT can occur as soon as blood cultures are sterile If heart transplantation is considered as a curative approach in patients who failed medical or surgical treatment,[3] SOT can be considered as soon as cultures are sterile
23	VAD infection	B3/C3/D3	0.10	0.65	VAD infection usually prompts heart transplantation.[4] The AST-IDCOP recommends infection to be controlled before SOT. Septic shock and hemodynamic instability are absolute contraindications for immediate heart transplant.[5]
	UTI				
24	Kidney transplant candidate	B1	0.62	1.00	The European Association of Urology recommends treating the UTI and resolving predisposing factors such as obstruction, reflux, or infection focus before kidney transplant.[6]
25	Non–kidney transplant candidate	A3/B3	0.19	0.75	UTI shortly before liver transplantation was not associated with increased infection-related morbidity or mortality.[7,8]
	Urinary colonization				
26	Kidney transplant candidate	A1	0.62	1.00	
27	Non–kidney transplant candidate	A1	0.64	1.00	
28	**Resp. MDR bacteria colonization, lung transplant candidate**	A2	0.31	0.89	There is debate about contraindication for lung transplant in cases of MDR bacteria such as *B cenocepacia*.[9,10]
	Mycobacteria				
29	Tuberculosis, active disease	D1	0.62	1.00	The AST-IDCOP recommends documenting microbiological (at least negative AFB stains) and radiographic resolution before SOT unless risks outweigh benefits, especially because of challenges of TB treatment after SOT such as potential disease severity and interactions between immunosuppressants and antibacterials.[11,12]
30	Tuberculosis, latent infection	C3/D3	0.15	0.72	Rule out active disease. The AST-IDCOP recommends considering treatment based on additional risk factors for TB disease such as recent tuberculin skin test (TST) conversion, past medical history of TB disease, contact with a confirmed active TB case, travel or residency in an endemic region, and profound immunosuppression.[12] It is therefore recommended that if LTBI treatment is indicated, SOT should be delayed until LTBI treatment is completed unless risks outweigh benefits, and not to delay SOT if no treatment is needed.[12]

(Continues)

TABLE 3 *(Continued)*

Scenarios	Clinical conditions	Recommendations	95% confidence interval		Comments/discussion points
			Lower CI	Upper CI	
31	NTM, active disease	D1	0.43	0.95	Treat appropriately with documentation of microbiological and radiographic resolution before SOT due to potential severity of infection and interactions between medications. Based on increased mortality data, some experts believe that transplant is contraindicated if 3 mo of treatment have not been completed.[13] Take into consideration the NTM species and the organ to be transplanted. For example, *M abscessus* is considered by some experts as a contraindication for lung transplantation because of poor outcomes[9,10]; however, if lung transplant is considered, the infection must be adequately treated before and after transplant to avoid reactivation.[10]
32	NTM, colonization	B3	0.19	0.75	Rule out active NTM disease using the 2007 American Thoracic Society criteria.[14]
33	**Bacterial peritonitis**	C1	0.48	0.98	The infection-related morbidity or mortality is not increased in patients with SBP early before SOT[7,8,15] and the risk of post-transplant sepsis is not increased in liver transplant candidates with SBP if they received 3-4 d of antibiotics before SOT.[16] If peritoneal dialysis catheter-associated peritonitis, refer to IDSA guidelines regarding catheter removal.[17] Even if the microorganism does not require prompt removal of the catheter, removing the catheter might help to hasten clearance
	Fungal infections				
	Candida				
34	Bloodstream infection	B3/C3	0.15	0.72	IDSA guidelines recommend to remove CVL in the case of *Candida* CLABSI.[17]
35	Endocarditis	D1	0.48	0.98	Some centers try to document 2 wk of negative cultures before SOT but might agree to transplant if urgent as soon as blood cultures are sterile. If heart transplantation is considered as a curative approach, SOT could probably be considered as soon as cultures are sterile.[3]
36	Invasive infection (other)	C2	0.25	0.81	The European Association of Urology recommends treating *Candida* UTI and to resolve predisposing factors before SOT.[6]
23	VAD infection	B3/C3/D3	0.10	0.65	The approach is similar to bacterial VAD infection
	Aspergillus				
37	Respiratory colonization, lung transplant candidate	A2	0.39	0.94	Pretransplant respiratory fungal colonization increases the risk of pulmonary fungal infection after lung transplant in children.[18] The AST-IDCOP recommends starting prophylaxis before lung transplant in the case of *Aspergillus* colonization and continuing it up to 6 mo after SOT.[19]
38	Respiratory colonization, non–lung transplant candidate	A3/C3	0.15	0.72	Some adult SOT experts suggest antifungal prophylaxis in heart transplant patients if a case of invasive aspergillosis has been diagnosed in their program within the last 2 mo,[19] whereas other experts have considered antifungal prophylaxis for other SOT candidates with respiratory colonization.[20]
39	Invasive infection	C3/D3	0.21	0.79	Regardless of the organ to be transplanted, the AST-IDCOP recommends ruling out invasive aspergillosis in any case of colonization and, if invasive infection confirmed, deferring SOT until clinical resolution, whenever possible.[9]

(Continues)

TABLE 3 *(Continued)*

Scenarios	Clinical conditions	Recommendations	95% confidence interval		Comments/discussion points
			Lower CI	Upper CI	
	Other fungi				
40	*Cryptococcus*	D2	0.26	0.88	The AST-IDCOP as well as other expert groups recommend completing induction therapy, to confirm microbiological clearance, and declining antigen before SOT.[21,22] The AST-IDCOP also recommends waiting for complete clinical resolution and complete at least 1 y of therapy if possible.[21]
41	*Coccidioides*	D2	0.23	0.83	The AST-IDCOP recommends long-term antifungal prophylaxis in the case of positive serology or past medical history in order to avoid reactivation.[23] In the cases of active disease, delaying SOT until clinical, radiological, and serological resolution cases should be strongly considered and performing SOT earlier is advised only if benefits outweigh risks.[24]
42	*Histoplasma*	D2	0.26	0.88	The AST-IDCOP recommends antifungal prophylaxis in candidates with past history in the previous 2 y; no recommendations in the case of active infection.[23]

AST-IDCOP, American society of transplantation infectious diseases community of practice; CI, confidence interval; CLABSI, central line–associated bloodstream infection; CVL, central venous line; IDSA, Infectious Diseases Society of America; MDR, multidrug resistant; NTM, non-tuberculous mycobacteria; SBP, spontaneous bacterial peritonitis; SOT, solid organ transplantation; UTI, urinary tract infection; VAD, Ventricular assisted device.

a non–lung transplant candidate (mild/moderate: C; 2; severe: C/D; 3). In any case, the urgency of SOT as well as the etiology of LRTI (if known) was considered important in the decision-making process.

3.2.4 | Gastrointestinal tract infections

If a candidate presented with acute gastroenteritis, respondents felt that the urgency of SOT, disease severity, and the potential risk of disseminated infection related to the pathogen (if known) needs to be considered in making a recommendation. If the transplant was elective and the disease mild/moderate, 54% of panel members recommended a brief delay whether etiology was known and there was no potential for disseminated infection or whether etiology was unknown (B; 2), whereas 31% and 38% of the panel respectively recommended an intermediate delay. In contrast, if disease was mild/moderate but there was a potential for disseminated infection, 69% of panel members recommended an intermediate delay (C; 2). Fifty-four percent of the panel recommended an intermediate delay in the case of severe gastroenteritis in a patient awaiting elective SOT, regardless of the etiology, whereas 38% recommended a prolonged delay (C; 2).

For recipients in urgent need of a transplant, 92% of panel members recommended no delay in the case of mild/moderate gastroenteritis if etiology was known and there was no potential for disseminated infection (A; 1). Opinions were equally divided between no delay and brief delay if etiology was unknown and disease mild/moderate (A/B; 3). In the case of a mild/moderate infection where the causative agent has the potential for disseminated disease, 50% of panel members recommended a brief delay and 33% of the panel recommended an intermediate delay (B; 3). A lack of agreement was noted in the case of severe gastroenteritis, with opinions being divided between a brief and an intermediate delay, regardless of the etiology (B/C; 3).

3.2.5 | Central nervous system infections

For bacterial meningitis, 58% of panel members recommended a brief delay, although a minority advised waiting longer (B; 2). In the case of HSV encephalitis, 58% recommended an intermediate delay, whereas 33% recommended a prolonged delay (C; 2). In the case of meningitis/meningoencephalitis caused by a known virus other than HSV, the overall agreement was poor and equally divided between an intermediate and a prolonged delay (C/D; 3). Sixty-two percent of panel members recommended a prolonged delay in the case of meningoencephalitis of unknown origin (D; 2). For these three last scenarios, some panel members advised postponing SOT for ≥2 weeks whenever possible.

3.3 | Application of IPTA ID CARE categories to other clinical scenarios

3.3.1 | Bacterial infections

Endovascular infections

In the case of bacterial endocarditis, 64% of panel members recommended an intermediate delay and 36% a prolonged delay (C; 2)

(Table 3).[3-17] Respondents indicated the importance of the urgency of transplant, patient stability, and microorganism virulence. In the case of VAD infection, there was no consensus among the panel members and answers were equally distributed between brief, intermediate, and prolonged delay (A/B/C; 3).

Urinary tract infection and colonization

In the case of UTI, 92% of panel members recommended a brief delay for kidney transplant candidates (B; 1). Interestingly, opinions were equally divided between no delay and brief delay in the case of a UTI in a candidate awaiting organs other than the kidney (A/B; 3). In the case of urinary colonization, 92% of panel members recommended no delay whether candidates were awaiting either a kidney or another organ (A; 1).

Mycobacterial infections

Mycobacterial infections are divided into *M tuberculosis* and NTM. For latent tuberculosis, panel members recommended an intermediate and prolonged delay in 42% and 33%, respectively (C/D; 3), whereas 92% recommended a prolonged delay in the case of active disease (D; 1). In the case of NTM colonization, the agreement between respondents was poor, but a brief delay was the most frequently chosen response by 46% of members (B; 3); 75% of panel members recommended a prolonged delay in the case of NTM disease (D1).

MDR colonization

Sixty-four percent of panel members recommended no delay in cases of MDR bacterial colonization of the respiratory tract in patients awaiting lung transplantation (A; 2).

Bacterial peritonitis

Eighty-two percent of our panel recommended an intermediate delay for cases of peritonitis (C; 1).

3.3.2 | Fungal infections

Invasive candidiasis

With respect to *Candida* bloodstream infections, the panel's opinions were equally divided between brief and intermediate delay (B/C; 3) (Table 3).[3,6,9,17-24]. Respondents suggested that the urgency of need for SOT, rapidity of fungemia clearance, and the possibility of removing the CVL in the cases of CLABSI should be taken into account. In the case of *Candida* endocarditis, 82% of panel members recommended a prolonged delay (D; 1). The approach of the panel for *Candida* VAD infection was similar to that of bacterial VAD infection (B/C/D; 3). For all other invasive *Candida* infections, 54% of the panel recommended an intermediate delay (C; 2).

Aspergillus infection and colonization

For *Aspergillus* spp colonization in the respiratory tract, 73% of the panel members recommended no delay for lung transplant candidates (A; 2). For candidates awaiting other organs, our panel's opinions were again divided between no delay and intermediate delay (A/C; 3). Regarding invasive aspergillosis, the panel was divided between intermediate and prolonged delay (C/D; 3).

Other infections

For *Coccidioides*, *Histoplasma*, and *Cryptococcus* infections, panel members recommended a prolonged delay in 55%, 60%, and 60%, respectively (D; 2).

3.3.3 | Viral infections

BK Virus

In the case of BK virus infection in a kidney transplant candidate, agreement was poor, although no delay was the most frequently chosen option by 45% of members (A; 3) (Table 4).[25-32]

HIV

Eighty-five percent of panel members recommended no delay for children awaiting transplant with well-controlled HIV infection (undetectable viral load, adequate CD4 T-cell counts, and appropriate adherence to antiretrovirals) (A; 1), and 92% recommended a prolonged delay with poorly controlled HIV, awaiting until the disease is well controlled (D; 1).

Hepatitis viruses

Sixty-seven percent of panel members recommended no delay if the patient was a hepatitis B (HBV) carrier (A; 2), whereas 82% recommended a prolonged delay in the case of acute HBV infection, unless there was HBV causing fulminant hepatitis requiring SOT (D; 1). In the case of chronic HBV infection, the overall agreement was poor and mainly divided between no delay and intermediate delay (A/D; 3). For hepatitis C (HCV) infection, the agreement was poor, with panel members recommending no delay and a brief delay in 50% and 33% of cases, respectively, if patient is a carrier (A; 3). In the case of chronic active HCV, the overall agreement was poor and mainly divided between no delay (46%) and intermediate delay (38%) (A/C; 3).

Herpes group viruses

Fifty-five percent of panel members recommended an intermediate delay in cases of EBV DNAemia (C; 2); however, in the case of a clinical illness consistent with infectious mononucleosis in the last 6 weeks, agreement was poor, although a prolonged delay was the most frequently chosen option by 46% of members (D; 3). For children awaiting transplant with CMV DNAemia, the level of agreement was also poor with recommendations equally divided between a brief and an intermediate delay (B/C; 3).

For primary VZV infection (chickenpox) or reactivation (shingles), panel members recommended an intermediate delay in 67% and 58%, respectively (C; 2). The usual approach is to wait until all lesions are crusted, if possible. There was no consensus in the case of mucocutaneous HSV infection although an intermediate delay was most frequently chosen by 50% of members (C; 3). The recommended approach depended on the urgency of SOT, presence or absence of DNAemia, and whether it is primary infection or reactivation.

TABLE 4 Recommendations and percentage agreement for other viral and parasitic infections

Scenarios	Clinical conditions	Recommendations	95% confidence interval		Comments/discussion points
			Lower CI	Upper CI	
	Viral Infections				
43	**BK virus infection**	A3	0.17	0.77	Consider longer delay in the cases of viremia compared to isolated viruria
	HIV				
44	Well controlled	A1	0.55	0.98	The panel's opinion concurred with the AST-IDCOP recommendations[25]
45	Poorly controlled	D1	0.62	1.00	Ensure undetectable viral load, adequate CD4 T-cell counts, and therapeutic adherence
	HBV				
46	Carrier	A2	0.35	0.90	The AST-IDCOP recommends evaluating the need for treatment of all HBsAg-positive candidates.[26]
47	Acute infection	D1	0.48	0.98	Differentiate situations where HBV is causing end-organ failure requiring SOT from situations where a patient needs SOT for reasons unrelated to HBV
48	Chronic infection	A3/C3	0.21	0.79	
	HCV				
49	Carrier	A3	0.21	0.79	The AST-IDCOP recommends evaluating the need for treatment of all HCV-positive candidates.[26]
50	Chronic infection	A3/C3	0.19	0.75	Differentiate situation where HCV is causing end-organ failure requiring SOT from situation where a patient needs SOT for reasons unrelated to HCV
	Herpesvirus infections				
51	CMV DNAemia	B3/C3	0.12	0.74	Consider urgency of SOT, viral load, presence of symptoms or signs of organ disease, rapidity of response to treatment, and whether it is thought to be primary infection or reactivation (the recommended delay would likely be longer in the cases of primary infection to allow for immunity to develop)[27,28] Primary EBV infection increases the risk of post-transplant lymphoproliferative disorder.[29,30] Asymptomatic CMV replication before SOT increases the risk of post-transplant CMV disease.[31]
52	EBV DNAemia	C2	0.23	0.83	
53	Infectious mononucleosis, <6 wk ago	D3	0.19	0.75	
54	Chickenpox	C2	0.35	0.90	More severe or disseminated in SOT patients.[32] The usual approach is to wait until all lesions are crusted, if possible. Consider urgency of SOT, presence or absence of DNAemia, and whether it is primary infection or reactivation (a longer delay would be recommended in the cases of primary infection due to the absence of preexisting immunity).
55	Zoster	C2	0.28	0.85	
56	Mucocutaneous HSV	C3	0.19	0.81	Consider urgency of SOT, presence or absence of DNAemia, and whether it is primary infection or reactivation (a longer delay would be recommended in the cases of primary infection due to the absence of preexisting immunity).
	Parasitic infections				
57	*Schistosoma* infection or positive serology	C2	0.35	0.93	Kidney transplant candidates who received a single dose of praziquantel before transplant for *S haematobium* infection did not show increased mortality or disease recurrence after transplantation [33]; therefore, it seems reasonable to treat infection before SOT.

(Continues)

TABLE 4 (Continued)

Scenarios	Clinical conditions	Recommendations	95% confidence interval		Comments/discussion points
			Lower CI	Upper CI	
58	*Echinococcus* infection	C2	0.35	0.93	The AST-IDCOP and the WHO guidelines recommend deferring SOT until cysts are removed and 7-10 d of albendazole are completed, and to consider long-term post-transplant antiparasitic therapy.[34,35] There is debate whether extrahepatic disease in patients with *Echinococcus*-associated liver failure contraindicates SOT.[34,36]
59	*Strongyloides* infection (positive stools or serology)	C2	0.23	0.83	SOT recipients are at increased risk of post-transplant disseminated strongyloidiasis,[37] a severe and often fatal entity due extra-intestinal dissemination of the parasite. As treatment can be completed in 48 h,[38] it is recommended to complete treatment before SOT.

AST-IDCOP, American society of transplantation infectious diseases community of practice; BK, BK polyomavirus; CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; SOT, solid organ transplantation; WHO, World Health Organization.

3.3.4 | Parasitic infections

For Strongyloides, 55% of our panel recommended an intermediate delay (C; 2) (Table 4).[33-38] The panel noted that the approach to *Schistosoma* infection depends on the clinical scenario. Overall, 70% of our panel members recommended an intermediate delay (C; 2). However, the panel noted that it is important to differentiate swimmer's itch where SOT would not necessarily need to be delayed from severe systemic *Schistosoma* infection where SOT should be postponed. In the case of Echinococcus infection, 70% of panel members also recommend an intermediate delay (C; 2).

4 | DISCUSSION

Infections in the immediate pretransplant period pose challenges in the decision-making process regarding the need to delay or not to delay SOT. Current literature and published guidelines do not address most of these scenarios nor provide guidance to inform decision-making relevant to these situations. To address these challenges, we first developed a structured framework describing specified categories of delay and used this framework to capture decisions made by an expert panel using both common and potentially uncommon scenarios that could be encountered in the clinical practice of pediatric SOT. The performance of the survey using a structured framework of responses provided us an opportunity to assess recommendations for the duration of delay in undergoing SOT in different infectious scenarios and to highlight the level of agreement in making those recommendations among the expert panel completing the survey. Additional relevant discussion points that relate to the results are embedded in Tables 3 and 4. We are not aware of a similar effort to aid the decision-making for situations where candidates are diagnosed with specific infections or infectious syndromes when being called in for transplantation. It is important to highlight that these recommendations do not provide levels of evidence, but rather summarize expert opinion and demonstrate the degree of variability in their responses. These opinions were informed by the clinical experience (with an average of more than 18 years in the care of organ transplant recipients) of our panel along with their knowledge of available information in the literature.

Results of the survey clearly highlight that the perceived urgency for SOT impacts both the decision to delay transplant and the duration of this delay. This was generally true regardless of the pathogen or scenario. Most clinicians consider the urgency of transplant to be mainly related to end-organ failure; however, in some settings of severe organ shortage, a child might be urgently transplanted despite the absence of end-organ failure because refusing an organ may increase the risk of death. It is also important to understand that elective and urgent transplants are both extremes of a spectrum, thereby requiring every situation to be assessed separately. Regardless of the reason for the urgency, the presence of bridging therapies for several organs such as dialysis or VAD also needs to be weighed in these situations.

Another important factor that the survey highlighted is the clinical presentation of the infectious episode. When considering the entire list of clinical scenarios, results indicated more agreement in situations where the infectious illness was not severe. This suggests that other factors are taken into account when deciding recommendations on a case-by-case basis. In the case of URTI, differences in opinion likely reflect the importance of other factors such as time since symptom onset, presence or absence of fever, and the organ being transplanted, as a URTI in a lung transplant candidate may be more concerning than in another transplant candidate.

With respect to a given clinical syndrome, the causative organism is important in decision-making. For example, the availability of treatment for most bacterial infections is likely associated with shorter delays compared with similar syndromes caused by viruses. Indeed, some studies have shown that invasive bacterial infections diagnosed and appropriately treated during the 4 weeks before liver transplantation were not associated with worse outcome.[7,8] Patients with respiratory viral infection due to RSV, influenza, adenovirus, and parainfluenza soon after transplant are at higher risk of severe infection[39,40]; despite the paucity of pretransplant data in SOT candidates, this could probably be extrapolated to pretransplant candidates with impending immunosuppression. On the other hand, successful SOT during active influenza infection in patients who received immediate neuraminidase inhibitors treatment has been reported .[41,42] Despite the lack of strong evidence, the AST-IDCOP currently recommends delaying SOT in cases of URTI in order to allow immunity to develop.[9] Similarly, gastrointestinal pathogens such as enterovirus and adenovirus are more likely to cause disseminated infections than other gastrointestinal viruses.[43,44] Overall, data are scarce for gastroenteritis in the transplant setting and are mainly focused on rotavirus where outcomes have been variable .[45,46] In this context, an approach might depend on the causative virus; obtaining a multiplex PCR on respiratory or gastrointestinal specimens is probably helpful in decision-making as long as results can be available in a short turnaround time frame.

The anatomical relationship between the transplanted organ and the infection needs to be taken into account. Although data have shown that infection-related morbidity or mortality did not increase in liver transplant candidates with bacterial LRTI as long as patients were adequately treated,[7,8,15] this might not be true when lungs are transplanted, because of the direct contact between the graft and the pathogen. Similarly, small bowel transplant patients could be at increased risk in the case of gastroenteritis because of the direct contact between the pathogen and the graft.

Depending on the severity of the infection pretransplant, the ethical issues related to the potential sequelae also need to be taken into account; for example, in the cases of HSV encephalitis.

Several limitations of the work presented herein are noted. The size of the panel is relatively small, and it is possible that some members lacked experience in some specific areas or uncommon scenarios, although the panel includes an international cohort of experienced senior clinicians (mean 18 + years of practice) with expertise in pediatric transplant ID. The size of the panel likely contributes to the fact that agreement level reached significance in only 7 scenarios, even if the agreement level was above 50% in the majority of the scenarios. The fact that scenarios were artificial, might also explain the lack of agreement between panel members. This explains why every patient needs to be assessed and managed individually. Another limitation of this work is that it was not possible to capture all scenarios, but we have focused on what we perceived to be the major common scenarios that are encountered in clinical practice. We also tried to cover a wide variety of categories of common and uncommon pathogens and clinical syndromes. Finally, an important limitation of this work is the fact that some recommendations are constantly being updated, such as HCV, and therefore, some recommendations generated by this work may require updating in the future to remain valid.

In summary, the IPTA-IDC gives expert opinion for the pediatric transplant candidate with clinical or laboratory evidence of infections. The application of this framework to common scenarios is presented in this paper. The naming and description of the specific categories provides advantages. First, the framework is explicit and reproducible and thereby facilitates easy communication within centers and across centers. Second, the categories are ordinal and provide a separation between patients who are assigned different categories. Third, although we did not pursue assigning scores, the ordinal categories are amenable to modifications that enable scores to be assigned that reflect the likelihood of the transplant proceeding. There will be the need for validation of these practices in the clinical setting.

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AUTHOR CONTRIBUTION

AGL, MG, and UDA: Designed the survey; LDI, AC, BH, DVDL, LG, MIA, AV, HME, MMC, MGM, and KMPB: Reviewed the survey; MG, LDI, AC, BH, DVDL, LG, MIA, AV, HME, MMC, MGM, KMPB, and UDA: Answered the questionnaire; AGL and DS: Analyzed the data; AGL, MG, DS, and UDA: Drafted the manuscript; and all authors: Critically reviewed the manuscript.

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SUPPORTING INFORMATION

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

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