Recommended Curriculum for Training in Pediatric Transplant Infectious Diseases

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A working group representing the American Society of Transplantation, Pediatric Infectious Diseases Society, and International Pediatric Transplant Association has developed a collaborative effort to identify and develop core knowledge in pediatric transplant infectious diseases. Guidance for patient care environments for training and core competencies is included to help facilitate training directed at improving the experience for pediatric infectious diseases trainees and practitioners in the area of pediatric transplant infectious diseases.

Key words. curriculum; fellowship; pediatric infectious disease; transplantation.

Transplant infectious diseases (TID) has emerged as a subspecialty within infectious diseases over the past 2 decades. The core knowledge for TID practitioners encompasses unique issues, which have been previously explored and communicated as guidelines for subspecialty training in TID by the American Society of Transplantation Infectious Diseases Community of Practice Educational Initiatives Working Group [1]. These guidelines, however, do not address issues that may be specific for pediatric transplant patients or training in pediatric TID.

An increasing number of pediatric infectious disease specialists are focusing their careers on transplant infectious diseases. While published content specifications for general training in pediatric infectious diseases identify a basic level of knowledge relevant to transplant-related infectious diseases, the core knowledge and directed training necessary to effectively establish expertise in TID in children are not fully described. In an effort to provide directed guidance in pediatric TID, the American Society of Transplantation (AST), Pediatric Infectious Diseases Society (PIDS), and International Pediatric Transplant Association (IPTA) collaboratively established a workgroup to develop a core curriculum to augment the training in the field of pediatric TID. Differences from adult TID training guidelines include the need to recognize the role of physical and psychological growth and development, as well as evolving immunologic maturation in assessment of the pediatric organ recipient, the increased risk for primary infections and community-based infectious exposures after transplantation, and the complexity of immunization-related issues before and after transplant. The following document provides guidance and recommendations for the training for individuals seeking a basic level of competency as a general pediatric infectious diseases practitioner to evaluate transplant recipients as well as those who require greater knowledge and expertise to pursue a specialized focus in pediatric TID. It is not meant to be all encompassing, but provides a framework for practitioners at different levels. The document supports subspecialty (fellowship) training programs in recognizing the specific issues related to pediatric TID. An additional fellowship is not suggested by the document or its contents, although additional training may be sought by individuals who wish to pursue a career in this sub-specialty.
PATIENT CARE ENVIRONMENT

- Basic competency for trainees
  Many pediatric infectious diseases training programs provide exposure to solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) populations; however, some programs have limited or no routine access to these patients. Many training programs have access to some but not all transplant types and will see patient volumes that vary widely by specific organ recipient type.
  - If inadequate patient volumes (fewer than two transplant-related consults per month on average) exist within a specific institution, augmenting experience with directed case-based learning is recommended.
- Specialized focus on pediatric TID
  It is recommended to pursue training at a pediatric center with the following resources:
  - The presence of an HSCT and at least 2 types of SOT programs
  - Sufficient patient volumes in HSCT and SOT to provide clinical exposure to common opportunistic infections
  - Proximity to adult transplant centers to expand experience is supportive but not essential; rotations with available adult TID services are strongly recommended, particularly if pediatric TID is limited
  - Opportunity for mentorship from at least one individual with clear expertise in pediatric TID is strongly encouraged.
  - Access to didactics designed to augment both clinical and research education in pediatric TID.
  - Experience in working with laboratories with expertise in bacterial, fungal, and viral diagnostics and resistance testing is encouraged.

COMPETENCIES

Medical Knowledge
General competency in medical knowledge of preventing, evaluating, and treating infections that occur after transplantation is expected for all trainees planning to sit for the American Board of Pediatrics Pediatric Infectious Diseases subspecialty or equivalent examination [2, 3], as described in the current Content Outline [2]. However, an increased depth of understanding should be achieved by those who anticipate careers focused on pediatric TID. The main areas of medical expert knowledge that should be acquired during pediatric TID training are summarized below. Medical expert knowledge for SOT and HSCT overlap in many areas, but specific differences are highlighted.

- Pre-transplant evaluation
  - Identify individual risks for infection that may compromise the patient’s ability to undergo transplant, that require treatment prior to transplantation, or that indicate need for delay in transplant (eg, adequate treatment of infections in kidney transplant candidates on dialysis)
  - Conduct appropriate pre-transplant evaluation and assess risks in family members (eg, need for tuberculosis testing)
  - Assess prior immunity to vaccine-preventable infectious agents and recommend expedited immunization schedule where indicated
  - Understand screening strategies important in pre-transplant evaluation (serologic, radiographic, demographic, medical history)
  - Appreciate limitations of screening serology due to:
    - Underlying organ dysfunction, as for patients with nephrotic syndrome, chronic liver disease, or protein-losing enteropathy
    - History of immunomodulatory therapy such as immunoglobulin administration or receipt of cellular therapy (ie, rituximab or bortezomib)
    - Passive antibody presence due maternal antibody during infancy or receipt of blood products
  - Appreciate differences in infection risk based on type of transplant
  - Organ-based (liver, kidney, heart, lung, intestine)
  - HSCT (autologous, allogeneic—matched, unrelated, cord, etc.)
  - Provide education about transplant infections and strategies for safe living after transplantation to patients and families
- Donor selection
  - Understand donor risk factors that potentially confer risks to recipients and be able to advise physicians and families regarding potential donor suitability
  - Assess infectious work-up for living—related donors
- Donor-derived infections
  - Understand the pathogenesis of donor-derived infections
  - Understand the timetable of donor-derived infections
  - Understand the difference between anticipated and unanticipated donor-derived infections
  - Perform risk assessment for specific donor/recipient pairs
  - Know about available effective interventions against the development of anticipated donor-derived infections
  - For SOT
    - Recognize limitations of deceased donor histories to accurately identify the risks for potentially transmissible infectious diseases
Understand the potential risks associated with variable geographic exposures of the potential organ donor (eg, coccidiomycosis, strongyloidiasis, and trypanosomiasis).

Be aware of risk profiles that place donors at increased risk for:
- Unexpected infection with human immunodeficiency virus, hepatitis B virus, and hepatitis C virus
- Unexpected central nervous system infection

Understand ethical and regulatory requirements to notify recipients, families, as well as the organ procurement organization (OPO) and Organ Procurement Transplant Network (OPTN) of unanticipated donor-derived infections.

For HSCT:
- Recognize potential donor-derived pathogens from stem cell sources
- Understand manipulation involved in HSCT collection, including umbilical cord collection, bone marrow preservation, T-cell depletion
- Know screening measures used to evaluate stem cell sterility at time of transplant

Immunizations:
- Understand the importance of optimizing the immunization status of children undergoing SOT
- Plan pre-immunization strategy for transplant candidates (primarily relevant for SOT or nonmyeloablative HSCT)
- Understand post-transplant immunization strategies
  - For SOT in relation to immunosuppression, rejection, and time from transplant
  - For HSCT recipients, in relation to engraftment, ongoing immunosuppression, time from transplant, and graft-versus-host disease (GVHD)
- Understand vaccine strategies including:
  - Active and passive immunization
  - Live versus nonlive vaccine, including risk–benefit analysis of live vaccine administration in SOT and HSCT
- Appreciate emerging data specific to vaccination in transplant candidates and recipients, including new vaccines and formulations
- Recognize importance of immunizing close contacts and health-care workers and contraindications to immunization in these populations for selected live vaccines (ie, smallpox vaccination)

Risk of infection:
- Understand typical timing relative to transplant of presentation of infection with different pathogens
- Incorporate the time from transplant into the evaluation strategy of febrile transplant recipients
- Appreciate risks specific to transplant type and underlying disease requiring transplant
- Understand the relationship between depth and duration of neutropenia and its associated risk of infection
- Understand the potential impact of technical complications of surgery (eg, anastomotic stenosis or thrombosis) on subsequent and potentially recurrent infections
- Understand impact of environment on infectious risk
  - Community exposures
  - Health-care-associated exposures

Prevention of infection:
- Define differences, benefits, and limitations for prevention strategies including prophylaxis and preemptive therapy
- Understand the potential role and limitations of viral load monitoring for the prevention of disease in transplant recipients
- Apply hospital prevention strategies for health-care-associated infections to transplant candidates and recipients
  - Hand hygiene, isolation policies, surgical site infection prevention bundles
  - Understand and enforce preventive vaccination strategies for family members, contacts (eg, influenza, pertussis)
- Recognize the increased prevalence of and need for surveillance for multidrug-resistant bacterial infections in this population
- Appreciate different surveillance measures potentially indicated for recipients from diverse geographic areas
- Understand the impact of prolonged viral shedding in immunocompromised hosts

Antimicrobial stewardship:
- Understand the need and methods for prospective utilization of antimicrobial stewardship in transplant populations
- Understand potential interactions between antimicrobial agents and immunosuppressive medications
- Understand alterations in pharmacokinetics and tissue penetration of antimicrobial agents in organ failure and transplant recipients

Disease categories (general):
- Bacteria
  - Gram positives: drug-resistant pathogens (eg, vancomycin-resistant Enterococcus, methicillin-resistant Staphylococcus aureus); sepsis caused by viridans streptococci
Gram negatives: understand different patterns and mechanisms of resistance and the appropriate approaches to antibiotic therapy for organisms with ampC and Extended-spectrum beta-lactamase (ESBL), carbapenem-resistant Enterobacteriaceae, as well as other multidrug-resistant organisms.

- Fungal (Pneumocystis, Candida spp., Aspergillus, other molds, endemic fungi, emerging fungi)
- Mycobacterial (M. tuberculosis and atypical mycobacteria)
- Parasitic (Toxoplasma, Cryptosporidium, Strongyloides, Giardia, Trypanosoma cruzi)
- Viral
  - DNA viruses with potential for latency: herpesviruses, adenovirus, parvovirus, polyomaviruses
  - RNA viruses: enterovirus, respiratory viruses, enteric viruses (eg, rotavirus, norovirus), measles and subacute sclerosing panencephalitis
  - Antiviral agents and immunotherapy (including adoptive T-cell transfer strategies)
- Important and common pediatric post-transplant infections
  - Cytomegalovirus (CMV)
    - Stratify disease risk based on donor/recipient serostatus
    - Understand CMV infection and disease manifestations
    - Know the typical timing of CMV infection and disease in the presence or absence of preventive strategies
    - Devise prevention strategies and understand benefits and limitations of different strategies including prophylaxis, pre-emptive monitoring/treatment or a sequential combination
    - Understand biomarkers that may help evaluate disease specific immunity (eg, ELISPOT, tetramer, and interferon-γ-release assays)
    - Understand diagnostic methods (molecular, virologic, pathologic, serologic) and compare their uses and limitations
    - Provide treatment strategies (route, regimen, and duration) for CMV disease based on the location (CMV syndrome versus tissue invasive disease) and severity of illness
    - Understand the underlying mechanisms of, when to suspect, and how to diagnose and treat antiviral-resistant CMV infection.
  - Epstein Barr virus (EBV)
    - Stratify risk based on donor/recipient serostatus and type of transplant
    - Understand the spectrum of EBV infection (eg, asymptomatic infection to post-transplant lymphoproliferative disorder (PTLD) and malignancy)
    - Know the typical timing of onset of clinical manifestations of EBV infection
    - Understand diagnostic methods and compare their uses and limitations
    - Recognize use and limitations of monitoring strategies
    - Recognize available therapeutic options and their limitations for the treatment of EBV/PTLD in SOT and HSCT recipients
    - Understand when and how to evaluate a patient for PTLD and understand the pathologic classification of disease
    - Know the difference in clinical behavior and therapeutic responsiveness of early versus late onset EBV-associated PTLD
    - Understand the rationale of stepwise approaches to treatment of EBV infection
  - Varicella-zoster virus (VZV)
    - Understand risk for primary or reactivation disease after transplantation based on serologic and immune status
    - Understand issues related to pre-transplant vaccination for SOT
    - Be able to define a significant exposure and strategies to prevent infection after VZV exposure
    - Roles of passive immune globulin and acyclovir prophylaxis
    - Know treatment strategies for primary infection (varicella) and reactivation (zoster) after transplantation
  - Candida infections
    - Recognize risk factors associated with type of transplant, therapies for rejection, GVHD
    - Recognize disease presentation from candidemia to disseminated visceral disease
    - Understand strategies for primary and secondary prevention (including risk factors for non-albicans infection), diagnosis (including histopathology, culture, biomarker and radiologic uses), and therapeutic strategies (azole, echinocandins, polyenes, 5-fluorocytosine)
  - Aspergillus infections
    - Recognize risk factors associated with type of transplant, and pre-transplant infection, colonization
    - Recognize disease presentation: pulmonary, cutaneous, sinus/central nervous system, anastomotic site
    - Recognize the trimodal risk periods in HSCT: pre-engraftment, acute GVHD, chronic GVHD
Understand strategies for:
- Primary and secondary prevention (including prevention of healthcare-associated aspergillosis)
- Diagnosis (including histopathology, culture, biomarker, and radiologic uses)
- Therapeutic strategies (azoles, echinocandins, polyenes, combination therapy)

Understand the natural history of treated and untreated *Aspergillus* infection, including immune reconstitution syndrome

Diagnostic tools
- Understand the benefits and limitations of infection-related diagnostic tools including but not limited to culture techniques, molecular diagnostics, immune function assays, and pathology
- Be familiar with the implications of maternal antibody for interpreting serologic test results in infants
- Appreciate differences in viral diseases considering congenital infection, primary infection, reactivation, asymptomatic shedding, disease
- Recognize the role and limitations of viral load assessment for monitoring response to treatment for specific viral diseases
- Recognize the importance of imaging and other modalities to define the functional status of vascular/anatomic anastomoses and their relationship to infectious disease pathogenesis

Infectious risk after hospital discharge
- Counsel patients and families on safer living practices for home, school, travel, pets, hobbies, and eating

Net state of immunosuppression
- Understand the concept of net state of immunosuppression and its cumulative impact on risk for infection
- Recognize the enhanced risk for infection associated with augmentation of immune suppression
- Recognize role of infection in net state of immunosuppression (eg, immunomodulatory effects of CMV)
- Understand humoral and cellular effects of major immunosuppressive medications and impact on risk for infection
- Understand mechanisms of newer biologic agents in terms of targets and infection risk
- In SOT
  - Recognize impact of major antirejection treatment modalities, including the variation in duration and intensity of effect with different agents
- In HSCT
  - Understand the timetable and process of immune recovery, considering timing of engraftment, and presence or absence of GVHD

Recognize specific risks portended by GVHD and its treatment

Immunology
- Understand the concepts of innate and adaptive immunity
- Know the mechanisms by which immune responses facilitate or prevent disease, including but not limited to cytokines, GVHD, and transplant rejection
- Understand the effects of emerging therapies, including diverse monoclonal antibodies that selectively target specific components involved in host response

INTERPERSONAL COMMUNICATION SKILLS AND PROFESSIONALISM

Pediatric TID physicians facilitate the doctor–patient relationship, informed consent, and the dynamic exchanges that occur between individuals at different stages during the transplant process.

- Competency for general infectious diseases trainees
  - All trainees of pediatric infectious diseases should have understanding of issues of confidentiality for patient and family

- Specialized focus on pediatric TID
  - Develop skills to effectively communicate risks and available strategies to prevent infectious complications in transplant recipients to patients and families
  - Demonstrate cooperation and integration with all members of the multidisciplinary transplant team to facilitate complicated patient care needs
  - Understand sources of relevant data, including results of donor evaluation, recipient pretransplant evaluations, and OPOs
  - Understand the responsibilities of transplant centers and OPOs to report potential donor-derived disease transmission events and the role of the pediatric TID specialist to help recognize these events and assure appropriate reporting
  - Understand the processes of consent, donor, and recipient selection (including issues of brain death and donation after cardiac death), allocation systems, and considerations regarding retransplantation and limited resource utilization

SCHOLARLY ACTIVITIES AND CLINICAL PRACTICE

Practice-Based Learning and Improvement
- The pediatric infectious diseases specialist is expected to demonstrate a lifelong commitment to reflective learning,
as well as the creation, dissemination, application and translation of medical knowledge. Knowledge of the logistics and operational issues of the transplant process is essential.

- Competency for all pediatric infectious diseases trainees
  - All pediatric infectious disease trainees should be aware of the resources that are available. These include but are not limited to the American Society of Transplantation’s ID guidelines [4], relevant approved guidelines from Infectious Diseases Society of America (IDSA) that specifically address immunocompromised hosts [5], and sections of HSCT guidelines related to TID [6].

- Specialized focus on pediatric TID
  - For those individuals seeking to focus on pediatric TID, additional resources are available and should be sought out. Specialized textbooks and journals focused on transplantation in general and TID in particular are available. Reports of consensus conferences on specific issues in TID have been published and are available. An increasing number of online resources are also available through the academic transplant societies (http://www.myast.org/cop/infectious-disease-cop; http://www.tts.org), United Network for Organ Sharing (UNOS) (http://www.unos.org/donation/index.php?topic=professional_education), and other agencies and organizations. Currently, the AST provides to members an online question-and-answer curriculum, primarily with adult literature, that covers significant infectious events in the transplant candidate and recipient. In addition, participation in transplant-focused continuing education is recommended to develop and maintain an understanding of noninfectious issues in transplantation.

**Systems-Based Practice**
- All pediatric infectious diseases trainees should be aware of the complexity of transplant logistics.
- Specialized focus on pediatric TID:
  - Specialists practicing pediatric TID should be exposed to and understand transplant logistics including the role of OPOs, UNOS/OPTN and its ad hoc Disease Transmission Advisory Committee, and National Bone Marrow Donor Programs (in Canada, the Stem Cell and Marrow Network).
  - Participation in Quality Improvement efforts is recommended and may include collaborations on development, evaluation, or revision of protocols related to infectious diseases in transplantation.

**HEALTH ADVOCACY**

As health advocates, pediatric TID physicians use their expertise and influence to advance the health and well-being of individual patients, communities, and populations on issues relating to infections in organ transplantation.

Key and enabling competencies for advocacy by pediatric TID specialists include, but are not limited to:

- The ability to identify the determinants of health for the populations that they serve, and promote the health of individual patients, communities, and populations
- The ability to address health needs and patient care issues at both the level of the individual patient and as they may affect communities of transplant patients
  - Advocacy to obtain affordable medication (including pediatric antimicrobial formulations), legal assistance, and safe housing, through referrals to social services, community organizations, and legal aid
  - Recognize characteristic age-related pediatric and adolescent behavior issues, and behaviors that place patients at risk for transplant-related infections, such as recreational drug use, excessive alcohol consumption, unsafe travel, sexual practices, and recommend strategies to reduce those risks
  - Provide guidance for food handling, sports, or pet-handling practices and recommend strategies to reduce those risks
  - Recognize and respond to misconceptions regarding vaccines and vaccination effectiveness and safety in transplantation and related settings
  - Support cocooning as a strategy to protect pediatric transplant patients from vaccine-preventable diseases

**RESEARCH**

For those with a specialized focus on pediatric TID, a research component of training is strongly encouraged. The trainee’s research should ideally relate to clinical issues, disease pathogenesis, basic science, or health systems approaches relevant to pediatric TID. Research may be basic science, translational, clinical, outcomes-based, or health systems-related. As with all pediatric infectious diseases training, it is recommended that

- Trainees have at least one research project for which they are primarily responsible
- The overall goals of the research training must be commensurate with the time available and the experience of the trainee
Table 1. Examples of Types of Studies and Required Skills for Academic Research in Transplant Infectious Diseases

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<th>Type of Research</th>
<th>Examples of Skills</th>
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<tr>
<td>Basic science studies</td>
<td>Standard laboratory techniques (tissue culture, PCR, fluorescence microscopy, Western blotting) as well as those specific to the study of infectious pathogens (virus titration, bacterial culture) and/or immunology (ELISA, ELISPOT, flow cytometry)</td>
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<tr>
<td>Translational studies</td>
<td>Standard and specialized laboratory techniques as above, and clinical research tools as for clinically oriented research, below</td>
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<tr>
<td>Clinical studies</td>
<td>Epidemiologic methods, data management, biostatistics, human subjects protection training, good clinical practice methodology, pharmacokinetics/pharmacodynamics, experience performing multicenter studies</td>
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<tr>
<td>Outcomes research</td>
<td>Quality improvement, cost-effectiveness, and systems-based methods, use of large datasets (eg, OPTN), experience performing multicenter or multidisciplinary studies</td>
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Abbreviations: ELISA, enzyme-linked immunosassay; ELISPOT, enzyme-linked immunosorbent spot; OPTN, Organ Procurement Transplant Network; PCR, polymerase chain reaction.

In addition, pediatric TID training should ensure that

- Trainees obtain direct experience in design, implementation, data collection, analysis, and reporting of at least 1 research study relevant to pediatric TID
- Presentation at a national or international meeting with a section focused on TID is encouraged (eg, American Transplant Congress, IPTA, IDSA, and Pediatric Academic Societies).
- A manuscript should be drafted and, ideally, submitted and published during the training period
- Mentoring should include close supervision and training by at least 1 research mentor with relevant expertise and should be supplemented by regular periodic review of the trainee’s progress by other experts (eg, a Scientific Oversight Committee).
- Given that all pediatric ID trainees may not be at a center with dedicated expertise in pediatric TID, mentorship opportunities with adult TID locally and/or pediatric TID from other institutions could be explored.
- Individuals inclined to pursue academic pediatric TID and independent research after fellowship should be identified early, encouraged, and assisted with organizing the submission of an application for a National Institutes of Health K award or similar training grant mechanism on an appropriate timeline.
- Specific studies should be tailored to the interests of the individual fellow, and aimed at developing the skills required for independent research in that area (Table 1).
- Clinical, translational, outcomes-based, and health systems research training may include formal course work in Public Health or alternate scientific training programs (eg, Master’s in Clinical Science), with or without completion of the requirements for a Master’s Degree.
- Although prospective cohorts or clinical trials typically represent stronger study designs, studies using existing data/specimens may be better suited to be pediatric ID trainee projects in light of time constraints (usually 2–3 years).
- Given the relatively small numbers of pediatric transplants performed at most centers, opportunities for multicenter or multidisciplinary collaborations for clinically oriented research should be considered whenever possible.

SUMMARY

This curriculum provides a guide for pediatric infectious disease training focused on specialization in pediatric TID. As the field progresses, we realize that additional issues will emerge requiring updates to the curriculum as with any area in infectious diseases. In addition, development of pediatric-specific case-based learning and educational conferences is needed from the Pediatric TID community.

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REFERENCES