Pediatric Solid Organ Transplantation

A Practical Handbook

Ron Shapiro
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Sidharth Kumar Sethi
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Editors
Ron Shapiro
Recanati/Miller Transplantation Institute
Mount Sinai Hospital
NY, USA

Rupesh Raina
Department of Nephrology
Akron General Medical Center at
Cleveland Clinic Foundation
and Akron Children's Hospital
OH, USA

Minnie M. Sarwal
Division of Transplant Surgery
University of California
San Francisco, CA, USA

Sidharth Kumar Sethi
Kidney and Urology Institute
Medanta, The Medicity
Gurugram, Haryana, India

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'Dedicated to our patients and their families who inspired us for this initiative'

– Ron, Minnie, Rupesh & Sidharth

Foreword

Dear Colleagues

Pediatric Solid Organ Transplantation has become firmly established as a specialty within itself, with input from multidisciplinary teams to facilitate the best management with good quality outcomes for children requiring transplantation.

These teams consist of professionals from a wide variety of clinical laboratory and research backgrounds as well as supportive services in very many forms, to ensure that preparation prior and during transplantation as well as long-term care occurs. This illustrates the notion of "it takes a village to raise a child and support a pediatric transplant patient."

Pediatric transplantation is now possible as a goal and in fact a reality even in low resource settings, with teamwork between adult and pediatric colleagues and the implementation of good quality affordable generic medication.

In well-resourced settings, "Precision" or individualized transplant management is now accepted practice. Overall goals of long-term outcomes includes living many happy years with a stable transplanted organ. This needs to be balanced together with all the other normal stages of childhood development leading to successful transition to adult services when the time is right while maintaining function of a transplanted organ.

International input from over 40 well-respected international authors have had input to make this a handbook with high-quality chapters and protocols in pediatric solid organ transplantation including kidney, intestinal, pancreas, liver, heart, and lung transplantation. This book covers organ-specific topics as well as more generalized areas including immunosuppression and regulation thereof, infections, lymphoproliferative concerns as well as transition.

The era of COVID-19 has introduced new issues relating to immunosuppression and vaccination while maintaining this important service to our patients.

We would like to dedicate this book to our pediatric transplant patients across the world who have taught us so much while we care for them.

May this book become a firm favourite in your teaching tool set.

Stay safe and take care

Best wishes

Mignon McCulloch

Clinical Unit: Renal and Organ Transplant
Red Cross War Memorial Children's Hospital
Rondebosch, Cape Town, South Africa

IPTA (International Pediatric Transplant Association)
Austin, TX, USA

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About the Editors

Ron Shapiro is the Surgical Director of the kidney and pancreas transplant program at Mount Sinai's Recanati/Miller Transplantation Institute, New York, USA. Dr. Shapiro, a leading surgeon with more than 30 years of experience in the field of transplantation, was trained at the University of Pittsburgh under Dr. Thomas E. Starzl, a transplant pioneer. Prior to returning to Mount Sinai, Dr. Shapiro was a professor of surgery at the University of Pittsburgh and the Robert J. Corry Chair in Transplantation Surgery at the Thomas E. Starzl Transplantation Institute, Pittsburgh, USA. After 26 years with the University of Pittsburgh, Dr. Shapiro left his endowed chair in Pittsburgh to return to The Icahn School of Medicine at Mount Sinai, where he had completed his internship and residency. Dr. Shapiro graduated with his medical degree from the Stanford School of Medicine. He is board certified in surgery with special expertise in renal transplant and pancreas transplantation. He is also Secretary of the Transplantation Society, and former president of the International Pediatric Transplantation Association (until March 2015). He is also on the editorial boards of *Pediatric Transplantation* and is Editor in Chief of *Clinical Transplantation*.

Dr. Shapiro has co-authored four books: *Atlas of Organ Transplantation*, *Renal Transplantation*, *Pancreatic Transplantation*, and *Living Donor Organ Transplantation*. He has published more than 440 articles, 75 book chapters, and has given more than 560 lectures. Dr. Shapiro has been repeatedly named by Castle Connolly, Ltd. as one of "America's Top Doctors."

Minnie M. Sarwal is Medical Director of the Kidney Pancreas Transplant Program at the University of California, San Francisco (UCSF) and a Professor in Residence in Surgery, with courtesy appointments in Medicine and Pediatrics at UCSF. She is the Director of the Precision Transplant Lab, an NIH and Chan Zuckerberg funded translational lab. She has an Adjunct appointment at the University of Berkeley as a Capstone mentor of the Masters in Translational Medicine Dr. Sarwal is a Consulting Professor at Stanford University where she was Medical Director of the Pediatric Kidney Transplant program, and Professor in Pediatrics, Immunology, and Surgery. Dr. Sarwal's research interests include clinical trials, bioinformatics, translational immunogenetics, genomics, and proteomics. Dr. Sarwal received her M.D. from India, completed her residency in the UK, and a fellowship in pediatric and adult nephrology at Guy's Hospital, London, UK. She holds a Ph.D. in molecular genetics

from Cambridge University (Christ's College), under the mentorship of Nobel Laureate Sydney Brenner; a diploma in child health from London, UK; membership of the Royal College of Physicians and elected fellow of the Royal College of Physicians, UK.

Dr. Sarwal is an internationally recognized leader in the fields of renal and transplant translational medicine and immunology. She has founded multiple companies, spun out of academia and IP generated in her lab, with an emphasis on personalized diagnostics in transplant medicine.

Dr. Sarwal has been an Asian-American and Women's Mentor at Stanford University, is a Capstone mentor of the Masters in Translational Medicine program at Haas/Berkeley and UCSF, and currently the Senior Treasurer of The Transplantation Society. She is the Chief Editor of *Frontiers in Nephrology* and associate editor for *Clinical Transplantation*. Dr. Sarwal has been the recipient of numerous awards and distinctions, inclusive of the NKF Cuneo Richardson Award for Scientific Excellence and the TTS-Roche Award for Outstanding Transplant Research. Dr. Sarwal serves on the FDA Science Board, NIH study sections and Chairs the Congressionally Directed Research Tissue/Transplant Program for the Department of Defense.

Rupesh Raina is an Adult-Pediatric Kidney Disease/Hypertension Nephrologist at Akron Children's Hospital, and Akron General Medical Center at Cleveland Clinic Foundation. He is a Professor of Medicine and Professor of Pediatrics at Neomed Medical University and Case Western Reserve University, Cleveland, Ohio. He is Council Member for Facility of Internal Medicine Council at Neomed. Dr. Raina is M-4 director for Neomed College of Medicine. Dr. Raina is the Pediatric Education Committee Member for the International Society of Nephrology, International, International Pediatric Transplant Association. He is Fellow of the National Kidney Foundation and the American Society of Nephrology. Additionally, Dr. Raina serves the National Kidney Foundation Advisory Board NKF, Ohio. Dr. Raina's practice includes care of patients with disorders of the kidney including chronic kidney disease, nephrotic syndrome, glomerulonephritis, tubular disorders, cystic kidney disease, kidney malformations, neonatal AKI, kidney stones, and hypertension. He also provides medical supervision to dialysis treatments, plasma exchange, and kidney transplantation in adults and children. Dr. Raina's clinical research interest includes transition of adolescent with chronic renal diseases to adulthood care, renal replacement therapies in acute renal failure, bone marrow transplant, and inherited metabolic diseases. Basic science research includes but not limited to identify non-invasive biomarkers (urine endothelin (ET-1) and others) to predict ADPKD disease progression.

Sidharth Kumar Sethi is currently Senior Consultant, Pediatric Nephrology and Pediatric Renal Transplant Medicine, Kidney and Urology Institute, Medanta, The Medicity, India. He was trained as a fellow (International Pediatric Nephrology Association Fellowship) and senior resident in pediatric nephrology at All India Institute of Medical Sciences, India and Division of Pediatric Nephrology and

Transplant Immunology, Cedars Sinai Medical Centre, Los Angeles, California. His main areas of interests are acute kidney injury, dialysis, and pediatric renal transplantation. He has been actively involved in the care of children with all kinds of complex renal disorders, including acute kidney injury, dialysis, nephrotic syndrome, tubular disorders, urinary tract infections, hypertension, chronic kidney disease, and renal transplantation. He has been a part of 8-member writing committee for the Indian guidelines of Steroid Sensitive Nephrotic Syndrome and expert committee involved in the formulation of guidelines of pediatric renal disorders including Steroid-Resistant Nephrotic Syndrome and urinary tract infections. He has more than 150 indexed publications in pediatric nephrology and chapters in reputed nephrology textbooks. He is a part of the Board of Directors, PCRRT-ICONIC Foundation, a foundation which aims to create awareness and spread education regarding critical care pediatric nephrology. He is Editor, *Springer's Handbook of Critical Care Pediatric Nephrology & Pediatric Dialysis* along with Dr. Bunchman, Dr. Raina, and Dr. McCulloch. He was awarded in 2014 by Case Western Reserve University, for his outstanding contributions to the field of Pediatric Nephrology.

Part I

Renal Transplant

Pediatric Kidney Transplantation: A Historic View

1

Rachel M. Engen and Priya S. Verghese

> My interest in transplantation began when I was a medical student. I was particularly stimulated by the consistent lack of encouragement and negative response which my naïve suggestions were met. Taking care of a youngster about my own age with Bright's disease… I was told by the senior consultant that we would have to make him as comfortable as possible for the two weeks of life which remained. I asked if he could receive a kidney graft and was told no; I then asked why not and was told because it cannot be done. – *Roy Calne* [1].

1.1 The Triangulation Technique

In 1894, French president Sadi Carnot was assassinated in a knife attack in Lyon, France, dying from a lacerated portal vein. General consensus was that the president could not have been saved, but Alexis Carrel, a medical student at the University of Lyon, argued that surgeons should be able to repair blood vessels like any other tissue. In 1896, after Matthieu Jaboulay's successful repair of a divided carotid artery, Carrel began experiments on techniques for suturing small blood vessels. He obtained needle and thread from a wholesale haberdashery near his home and learned the manual dexterity required for fine work from a local embroideress [2]. Carrel carried out his experiments while working as a house officer and, in 1902, published his first article on vascular anastomosis [3]. Using this technique, he was able to autotransplant the kidney of a dog, replicating a procedure first performed by Emerich Ullmann that same year.

R. M. Engen (✉) · P. S. Verghese
Department of Pediatrics, Division of Kidney Diseases, Ann and Robert H Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: rengen@luriechildrens.org

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Over the next 10 years, Carrel published extensively on transplantation, reporting that autografts were successful, but allografts eventually failed after a brief period of function for reasons unknown at that time. By the beginning of World War I, interest in organ transplantation was low. Carrel changed his focus to other areas, including tissue culture, and, along with Charles A. Lindbergh, the development of the first organ perfusion pump. In 1914, he spoke at the International Surgical Association. "The surgical side of the transplantation of organs is now completed, as we are now able to perform transplantations of organs with perfect ease and with excellent results from an anatomic standpoint. But as yet the methods cannot be applied to human surgery, for the reason that homoplastic transplantations are almost always unsuccessful from the standpoint of functioning organs. All of our efforts must now be directed toward the biologic methods which will prevent the reaction of the organism against foreign tissue and allow the adapting of homoplastic grafts to the hosts" [4].

1.2 An Immunologic Barrier

Brazilian-born zoologist Peter Medawar was a 24-year-old recent graduate assigned by Thomas Gibson to study whether skin allografts could be used to help treat victims of the Battle of Britain [5]. At the time, skin grafting had been practiced for over 100 years, but common knowledge at the time was that allografts "cannot be used to form a permanent graft in human beings, except, without a doubt, between monozygotic twins" [6]. Medawar and Gibson reported the case of a 22-year-old woman with severe burns who received multiple rounds of skin autografts and allografts (from her brother). The autografts did well, but the first round of allografts showed evidence of inflammation by day 5 and significant degeneration by day 15. Importantly, the second round of skin allografts degenerated even faster, by day 8 [6]. From this and studies in rabbits, Medawar concluded that "the mechanism by means of which foreign skin is eliminated belongs in broad outline to the category of actively acquired immune reactions," [7] an early description of allograft rejection.

Six years later, Medawar was at a cocktail party with his colleague, Hugh Donald, who was looking for a way to differentiate identical twins from fraternal twins in cattle. Medawar suggested using skin grafts, as fraternal twins should reject the graft from their twin. He enlisted his first graduate student, Rupert Billingham, grandson of a dairy farmer, to help. Medawar initially thought the outcome was predictable, but instead the results showed that most twin cows accepted the skin graft, even when the twins were of different genders. Seeking to explain their results, Medawar went back to Donald, who directed him and Billingham to the research of Frank Lillie on the interconnected placental circulation of twin Freemartin cattle and Ray Owen, who discovered that Freemartin cattle carry two red blood cell types – their own and their twin's [8]. They hypothesized that the twin cattle exchanged blood in utero, leading to donor cell chimerism in adulthood, and that this chimerism would exist for white blood cells as well. It was the first description

of immune tolerance [9]. Medawar and Billingham, along with Leslie Brent, moved on to confirm their studies in mice ("Thank God we've left those cows behind," Medawar reportedly said) [8], and, while not immediately clinically applicable, their findings raised hopes that the immunologic barrier could be breached in human transplantation [10].

Meanwhile, George Snell was studying tumor transplantation and found that certain genes were associated with the failure of tumors transplanted from one strain of mice to another. His across-the-hall neighbor named them H genes, or "histocompatibility" genes [11]. In France, Jean Dausset had become interested in the biology of blood transfusions while working as a medic in World War II and was widely published on the topic. In 1952, he wondered "If there existed individual differences carried by red blood cells, why wouldn't there exist others, carried on white blood cells" [3]. He combined the white blood cells of one individual with the serum of another individual, one who had received multiple blood transfusions. "With the naked eye, I saw the formation of enormous clumps of agglutinins" [3]. By 1958, Dausset had described the human equivalent of Snell's H gene, which he initially called "Mac." Seven years and over 900 skin graft trials later, Dausset, along with Czech researchers Pavol and Dagmar Ivany, clarified the genetic region and multiple loci today known as the human leukocyte antigens [3].

1.3 "Science Fiction": The Beginnings of Human Transplantation

The first attempted human-to-human kidney transplantation was performed by Ukranian Yuriy Voronoy in 1933 on a 26-year-old woman with acute kidney injury from mercury poisoning. Voronoy was hopeful that the immunosuppressive effects of the mercury would allow the graft to survive long enough for the native kidneys to recover. The kidney was transplanted into the right thigh and initially made urine but, after transfusion with a different blood type, the graft failed, and the patient died 48 hours after surgery [12]. Voronoy tried six more times in the following 16 years; none of the kidneys functioned for any appreciable length of time [4]. In 1945, Charles Hufnagel, David Hume, and Ernest Landsteiner at the Brigham Hospital in Boston transplanted a human kidney to arm vessels. The kidney functioned briefly, with little urine output, but despite this spurred increased interest in transplantation at both Brigham Hospital and elsewhere [13].

In the early 1950s, teams in Boston and Paris began pursuing human kidney transplantation, but results remained poor, with graft survival lasting days to months. In Paris, urologist René Küss was initially using kidneys donated by prisoners condemned to death who consented to postmortem procurement. The donor nephrectomies were performed minutes after decapitation "on the ground, by torchlight…which strongly offended the sensitivity of some of us" [14]. The kidneys made urine transiently, but all recipients died within days to weeks. Across town, Jean Hamburger performed the first living related kidney transplant on a 16-year-old carpenter who ruptured a solitary right kidney in a fall from scaffolding. "The boy's mother pleaded

with us to attempt to transplant one of her kidneys to her son" [15]. Hopeful that the close biologic relationship between mother and son would prevent rejection, surgeons agreed and performed the procedure on Christmas Eve. The graft functioned immediately with normalization of the boy's blood urea levels, but on postoperative day 22, the kidney developed rejection and the patient died.

In October 1954, David Miller was caring for 23-year-old Richard Herrick at the Public Service Hospital in Brighton, MA. Richard was diagnosed with chronic kidney disease secondary to chronic nephritis and his death seemed imminent. Richard's older brother Van had asked Dr. Miller if he could give a kidney to his brother. Dr. Miller told him it was impossible, but then remembered that Richard had an identical twin brother, Ronald. He was aware of ongoing transplant research and sent the brothers to nephrologist John Merrill at Peter Bent Brigham Hospital in Boston.

Over the next 2 months, the Brigham team grappled with the ethical issues in removing a kidney from a healthy individual, consulting physicians, clergy, lawyers, and insurance actuarial tables before finally leaving it up to Ronald. "I had heard of such things," Ronald remembered, "but it seemed in the realm of science fiction. [We] were caught up in the enthusiasm, but I felt a knot in the pit of my stomach…the only operation I'd ever had before was an appendectomy, and I hadn't much liked that" [10]. Even Richard, the recipient, had last minute thoughts. "Get out of here and go home," Richard wrote to Ronald the night before the surgery. "I am here, and I am going to stay," Ronald responded. On December 23, urologist J. Hartwell Harrison removed Ronald Herrick's left kidney and surgeon Joseph Murray transplanted it into Richard Herrick. The kidney functioned immediately; urine "had to be mopped up from the floor" [10]. Richard married his recovery room nurse, had two children, and lived 8 more years before dying in 1962 from recurrence of his original disease. Ronald lived to the age of 79 years. The first successful kidney transplantation was front-page news that rekindled interest in transplant research around the world; seven identical twin transplants would be performed in the next year, including two unsuccessful attempts in children (one due to recurrence of glomerulonephritis and one due to primary nonfunction) [16]. The effect of this new treatment was, however, limited. The immunologic barrier remained, and most with kidney disease would not have an identical twin.

1.4 Breaking the Barrier

Medawar had shown that immunologic tolerance was possible with his skin grafting experiments, and research endeavors turned to suppression of the immune system. E. Donnall Thomas had been a hematologist at the Brigham Hospital and was involved, for a short time, in the care of Richard Herrick. In 1955, he and surgeon John Mannick were studying bone marrow transplantation using irradiation at Mary Imogene Bassett Hospital in Cooperstown, New York, where the "cold winters of that upstate New York rural community were conducive to the conduct of research" [17]. In 1959, they reported the successful transplantation of a kidney into a beagle who had received total body irradiation followed by bone marrow allograft from the

kidney donor. The kidney functioned normally until the dog died 49 days later from pneumonia; on autopsy, the kidney pathology was normal [18]. Murray's team in Boston began experimenting with Thomas and Mannick's protocol in dogs and 12 humans. In January 1959, they performed a kidney transplant between 24-year-old John Riteris and his fraternal twin brother using sublethal irradiation. John lived 27 years before dying of congestive heart failure. The only time he ever discussed his transplant with his brother was in an inscription in a book he gave to Andrew just before his death. It read, "To Andrew – Thanks for the second drink" [10]. The immunologic barrier had been broken for the first time, but it was the only success out of 12 attempts. The infectious complications of irradiation were unacceptably high.

Roy Calne was teaching anatomy at Oxford University in 1956 when he attended a seminar given by Peter Medawar on immunologic tolerance. "He had the audience spellbound with his brilliant oratory and the content of his message," Calne recalled. "When he finished, a medical student asked if there were a potential application of the work; Medawar's reply was short, in fact two words, "Absolutely none!" [1]. Calne disagreed and asked his Department Head if he could have a letter of recommendation to join Medawar's lab. The Department Head replied that Medawar "was a very busy man and since I wanted to be a surgeon I had better go and learn to do hernias" [1]. Calne did so and obtained a residency position at the Royal Free Hospital, which had neither facilities nor funding for research. Nevertheless, Calne obtained permission to begin trying kidney transplants, first in mice and then in dogs. He had no more successes than others. Irradiation had a track record of failure; he wondered if cancer drugs might prove a viable alternative.

Calne reached out to Ken Porter, a pathologist who had used thiotepa to prolong survival of skin grafts in rabbits. Porter pointed Calne to a paper published that same week by Robert Schwartz and William Damashek reporting the induction of immunologic tolerance in rabbits treated with 6-mercaptopulrine (6-MP). Calne began treating his canine transplant recipients with 6-MP, resulting in some prolonged survivals. Excited by the results, he called Ken Porter; "before I could give him my news, he said "You remember the 6-MP experiments, well it did not have any significant effect on rabbit skin allografts so I wouldn't bother to try it in the dogs" [1]. Calne published his results in *The Lancet* in 1960, prompting at least one letter to the editor that implied his results were not accurate. As Calne was a junior surgeon publishing his first paper, the response caused him "some distress." After some prompting, he contacted Medawar's office to discuss his results. "[I] very meekly asked if I might sometime have a chance to speak with him. [His secretary] said, "I'll put you through;" I was protesting, "Oh no, no- he's a very busy man!" By then I was speaking to the great man who gave me the impression that he had all the time in the world" [1].

Calne's results sparked interest, and soon Charlie Zukoski and David Hume had published independent replication of his results. Calne received permission to use 6-MP in clinical kidney transplantation. Their first case, a woman with polycystic kidney disease with a potential donor who died from a subarachnoid hemorrhage, was cancelled when the donor kidney was also found to be polycystic. "I have never

since forgotten the association of polycystic disease with berry aneurysms… It seemed that perhaps transplantation was not meant to start at that time" [1]. Calne took an 18-month research sabbatical to Boston, where he collaborated with George Hitchings and Gertrude Elion, researchers at Burroughs Wellcome laboratories who were working on synthesizing purine analogs with a better therapeutic index than 6-MP. The best of these was BW57–322, known today as azathioprine. On his return to St. Mary's Hospital, Calne and Porter began trialing kidney transplants with azathioprine and steroids.

Jean Hamburger and René Küss were re-energized by the success in Boston and the advances in immunology. Hamburger was working in the same hospital as Jean Dausset, the man responsible for the identification of the HLA gene. In February 1962, Hamburger performed a kidney transplant between an 18-year-old boy with nephronophthisis and his first cousin, selected as donor from among multiple family members using the "leukocyte group" detection available at the time, with preoperative irradiation. It was the first successful non-twin transplant. The patient "was so impressed by the whole event that he decided to study medicine and became a cardiologist" [15]. The kidney functioned for 15 years, and the patient was still alive 30 years later with a second transplant. Meanwhile, Küss performed ten transplants using varying combinations of irradiation and 6-mercaptopurine, but only three patients survived [14]. In September 1963, Küss was one of 20–25 transplant surgeons and physicians who met in Washington, DC. "Each of us presented the results of his experience, which overall was fairly disastrous…" with only 10% of grafts surviving 3 months [9, 14]. "The review caused some of us to doubt the real value of renal transplantation when, at the end of the meeting, a newcomer amongst the group of pioneers, Thomas Starzl, unraveled three rolls of paper which he carried under his arm and raised our hopes by presenting his results obtained with azathioprine and cortisone" [14].

Starzl was a late addition to the program, invited only at Will Goodwin's request. "I felt like someone who had parachuted unannounced from another planet onto turf that was already occupied." He remembers the "naked incredulity about our results," [19] which reported 70% graft survival at 1 year. Luckily, he'd been warned to bring the patient charts with him as proof. Starzl's early career had been mired in frustrations, his clinical practice hampered by departmental politics, and his research presentations ignored or mocked [19]. In December 1961, he had taken a position at the University of Colorado, and by March of 1962, his team had successfully performed its first kidney transplant between identical twins.

A few weeks after public announcement of that transplant, 12-year-old Royal Jones was referred to the University of Colorado, with his mother as a potential donor. Joe Holmes, chief of the University of Colorado nephrology program, agreed to try and maintain Jones on chronic hemodialysis, itself a relatively novel treatment, until the transplant program was ready to attempt a non-twin transplant. Jones' case "was enough to mobilize an army, and this was exactly what happened" [19]. Laboratory and surgical teams were recruited, anesthesia machines refurbished, and research funds diverted from other programs. The team performed eight to ten dog transplants per day to perfect techniques and study different

immunosuppression regimens. A supply of azathioprine, then under clinical trials, was obtained. By summer of 1962, 20–25% of dogs with kidney transplants were surviving for 100 days after transplant, but Royal was running out of vascular access for dialysis.

On November 24, 1962, Royal received a renal transplant from his mother with a combination of irradiation, azathioprine, and prednisone for immunosuppression. He was kept in one of the operating rooms for 1 month after transplant to decrease the risk of infection, suffered one episode of early rejection that was reversed with prednisone, and returned to school a few weeks later. His initial allograft lasted 6 years before requiring a second transplant, from his father, that survived a further 14 years. Thirty years later, he was still alive and waiting for a third kidney [19]. Between 1962 and 1964, 16 children would receive kidney transplants in Colorado, ten of them were still alive at 25 years of follow-up [20].

By 1970, there were five published case series of kidney transplantation in children, with mortality (13%) that was similar to adult reports. Nearly all of these were living donor transplants, for which outcomes were significantly better compared to deceased donor grafts. Death was typically caused by infection [21], with the risk seeming to correlate with the steroid dose [22]. Most children underwent bilateral nephrectomy and splenectomy either prior to or at the time of transplant.

1.5 Youthful Rebellion and Tissue Typing

The discovery that leukocyte antibodies form during pregnancy, by the Dutch team of Jon van Rood, Aad van Leeuwen, and George Eernisse in 1958, provided substrate to begin testing potential tissue donors for HLA type, though the initial study results remained uninterpretable until computer analysis arrived in the early 1960s. Armed with this new technique, van Rood, van Leeuwen, Ali Schippers, and Hans Bruning traveled to transplant centers around the world – Brussels, Louvain, Edinburgh, Boston, Denver, and Minneapolis – to collect tissue samples from over 100 kidney transplant recipients and their sibling donors. They found that those with a perfect HLA match were significantly more likely to survive than those without. Their results led to the founding of Eurotransplant in 1967, the first large-scale effort to implement transplant immunology in clinical transplantation [23]. The initial analyses of Eurotransplant outcomes in 1969 were disappointing. “There was really very little to be said about the effects of matching,” [23] though the results (68% graft survival at 1 year) were much better than those in the International Registry for Kidney Transplantation (approximately 40% graft survival at 1 year). However, with follow-up, it became clear that matching led to improved long-term graft survival and decreased lymphocyte infiltrate in the kidney, despite the fact that they were only matching for the “Leiden antigens”: A2, A28, and the cross-reactive groups of HLA-B.

In 1955, Paul Terasaki was a zoologist studying immune tolerance in chick embryos at the University of California, Los Angeles, when he realized his work was mainly retreading the studies of Billingham, Brent, and Medawar. In search of

a new direction, he applied for a research position in Medawar's lab; he was denied based on lack of space. Undeterred, he made a visit to Ray Owen's laboratory at Cal Tech, where Brent was spending a year, to get their opinions on his research. A month later, Medawar called Terasaki offering a position in his London lab; apparently Brent had put in a good word [24]. After a year in London, Terasaki "somehow came to the conclusion that humoral immunity was more important than cellular immunity," the exact opposite of Medawar's research. "To this day, I'm not sure whether this view was simply youthful rebellion" [24].

Terasaki was interested in Jean Dausset's leukoagglutination test, but felt it was "too capricious" for clinical use. "Many hours in the laboratory were required to learn what would NOT work, despite publications to the contrary" [24]. The lymphocyte microcytotoxicity test, developed with John McClelland in 1964, used a piece of aluminum foil taped to the edge of a cover glass to create an oil chamber. Reagents were limited, so the testing used the smallest volume that could be dispensed – 0.001 mL, or one lambda. By 1970, the microcytotoxicity test was the primary form of tissue typing. Blood samples were shipped to the Terasaki lab using a two-chamber plastic bag with nylon wool in the top. Granulocytes in blood injected into the bag would stick to the nylon wool, while red cells and lymphocytes would fall into the lower chamber, which contained a tampon. Upon arrival in the lab, a large vise was used to squeeze blood out of the tampon for testing. Using this system, nearly every kidney transplant in the United States between 1965 and 1968 underwent typing [24].

1.6 "It Seemed Too Good to be True": Pharmacologic Immunosuppression

The search continued for immunosuppressive medications that could decrease or replace steroids and limit their significant side effects. In 1899, Ilya Ilyitch Metchnikov had developed antilymphocyte serum (ALS), made by injecting guinea pigs with cells from rat spleen and lymph node. Medawar was enthusiastic about this idea, but clinicians were reluctant to risk their success with azathioprine and steroids. The injection of animal serum into humans was "not a particularly palatable idea, especially when the dosage into the abdomen would be several gallons if experimental information was applied to clinical practice" [19]. Beginning in 1964, K.A. Porter and Yoji Iwasaki began using horses to raise serum and then identified and purified the gamma globulin fraction. The first patients were treated in the summer of 1966 and "could be picked out of a crowd… The ALG (antilymphocyte globulin) was given into the muscles of the buttock and caused such severe pain and swelling that patients constantly walked the floors trying to rid themselves of what felt like a charley horse. They sat crookedly on chairs and formed their own support groups to exchange tall tales, and especially complaints" [19]. The initial study was a success, with reduced rates of early rejection and a 50% decrease in prednisone dose [25]. The concept was further refined by Ben Cosimi when he used newly developed cell culture techniques to produce a monoclonal antilymphocyte antibody – OKT3 – first

used in 1980 [19]. However, antilymphocyte antibodies could not be used long term because of the inevitable development of an immune reaction to the horse protein and the higher incidence of viral infections and malignancies.

In 1976, Jean Borel, a researcher at Sandoz pharmaceutical company in Switzerland, presented preclinical data on the potential immunosuppressive effects of a metabolite of the *Tolypocladium inflatum* fungus called cyclosporine [26]. Meanwhile, in the Cambridge lab of David White, visiting research fellow, Alkis Kostakis was reaching 2 years without significant success. Worried his professors in Greece would be upset if he returned home without any research product, Kostakis transitioned studying immunosuppression. Borel had given White a bottle of cyclosporine, which White passed along to Kostakis for experimentation. Two months later, he called Calne reporting significant prolongation of rat heart allograft survival [1]. "It seemed too good to be true," so Calne had him repeat the studies. The results were even better when Kostakis dissolved the drug in the olive oil his mother had sent him, "worried that he might starve whilst he was in England" [1]. Initial clinical trials of cyclosporine monotherapy showed no better outcomes than the conventional azathioprine-prednisone combination with increased complications, but a regimen combining a lower dose with prednisone showed success [19]. Cyclosporine was approved for use in the United States in 1983 and resulted in a 20% decrease in 1-year graft loss [27] and lower doses of prednisone [19].

In the years since, the search for better immunosuppression medication – more targeted, more effective, fewer side effects – has continued. In 1986, Takenori Ochiai first presented preliminary data on FR900506, an extract of *Streptomyces tsukubaensis*, that was found in soil samples from the base of Tsukuba mountain in Japan. The results of the first clinical trials of this new drug, shortened to FK-506, were so exciting to the public that they were first published by the *Pittsburgh Post-Gazette*, scooping the official *The Lancet* publication [19]. The original hope that it could work synergistically with cyclosporine, replacing prednisone in a two-drug regimen, was dashed when it was discovered that the medications were both calcineurin inhibitors. FK-506 was approved by the US Food and Drug Administration (FDA) in 1994 as tacrolimus. A Cochrane review of tacrolimus ultimately found that it decreased the risk of graft loss by nearly 50% at 3 years [28] relative to cyclosporine.

In the 1970s, South African geneticist Anthony Allison and Argentinian biochemist Elsie M Eugui were studying children with defects in purine metabolism. They noted that de novo purine synthesis is inhibited in adenosine deaminase deficiency, an immunodeficiency, while purine salvage pathways are blocked in Lesch-Nyhan syndrome, a neurodevelopmental disorder. Their hypothesis that targeted inhibition of de novo purine synthesis might serve as an immunosuppressant led to identification of mycophenolate mofetil, an ester derivative mycophenolic acid, which was studied as an antibiotic in 1896 but abandoned due to toxicity [29]. Mycophenolate mofetil prolonged allograft survival and reduced the occurrence of graft rejection and was approved by the US FDA in 1995. As of 2018, over 95% of pediatric kidney transplants were managed using a combination of tacrolimus and mycophenolate mofetil, with or without prednisone [30].

Surendra Nath Sehgal was studying soil samples from the island of Rapa Nui when he found that isolates of *Streptomyces hygroscopicus* produced a compound with activity against *Candida albicans*. Further study, however, showed that the compound had immunosuppressive properties that made it impractical as an antifungal. Undeterred, Sehgal sent the compound to the National Cancer Institute, where it was found to block growth in several tumor cell lines, but the research was dropped in 1982 after a laboratory closure. In 1988, Sehgal successfully advocated for renewed research on this compound, and in 1999, the US FDA unanimously approved sirolimus, also called rapamycin after its island origin [31]. Sirolimus lacks the nephrotoxic side effects of tacrolimus and cyclosporine, making it an attractive option for reducing or eliminating calcineurin inhibitor exposure; however, studies in children showing an increased risk for posttransplant lymphoproliferative disease with a high-dose sirolimus regimen have limited its widespread use [32]. As of 2014, approximately 7.7% of US pediatric renal transplant recipients were using sirolimus at 1 year posttransplant, and studies about its efficacy and side effects in children remain ongoing [33].

1.7 A Framework for Allocation

In the early 1960s, deceased donor donation in the United States required that the potential donor's heartbeat be allowed to stop, after which the medical team would move rapidly to restart circulation and ventilation to preserve kidney oxygenation. Conversely, teams in Sweden and Belgium would continue ventilator support for patients with *le coma depassé* (literally "a state beyond coma"). The ethical debate about the appropriateness of this continued through 1968, when the Ad Hoc Committee of Harvard Medical School, led by medical ethicist Henry Beecher, published "A Definition of Irreversible Coma," laying out criteria to diagnose brain death. This definition was soon given legal standing in the United States and elsewhere, although its acceptance is not universal [34].

With a definition of "brain death," there was increased opportunity to obtain higher-quality organs from deceased donors, but early kidney allocation systems were ad hoc, informal networks between hospitals. Paul Taylor, the first organ procurement officer at the University of Denver in the 1960s, would "visit hospitals throughout the region and identify victims of accidents or disease whose organs might still be useable" [19]. After the 1968 guidelines on the dead donor rule, the first organ procurement organization (OPO) in the United States, the New England Organ Bank, was established. OPOs in the United States remained unregulated and often informally run through the 1970s [19]. By 1969, the National Transplant Communications Network was maintaining a file of kidney transplant candidates with their tissue and blood type from 61 centers in the United States and Canada. Printouts of these lists were sent to participating centers monthly; installing a computer at each center was thought to be "too great an extravagance" [35]. If a deceased donor kidney became available, and could not be used at the procurement hospital or a hospital nearby, the procuring team could consult the list and directly contact

the physicians of the potential recipient with the best match to the donor [35]. There were not always clear organ allocation principles, and even Starzl's large Pittsburgh program was dependent on donated corporate jet access to fly to procurements. In 1984, the United States passed the National Organ Transplant Act (colloquially known as the "Gore Bill") establishing a national Organ Procurement and Transplantation Network, providing funding for transplantation medications, and outlawing the sale of human organs (in response to an unpopular proposal by a Virginia physician to establish a kidney brokerage business) [19].

After passage of the Gore Bill, "no one knew what to do with it" [19]. There was no accepted method for allocating organs nationwide. Olga Jonasson chaired a task force that held public hearings for over a year before issuing broad guidelines rejecting discrimination on the basis of gender, race, nationality, or economic class and cautioning the use of age, lifestyle, and measures of social worth in allocation decisions. These guidelines were incorporated into the original 1986 contract with the United Network for Organ Sharing (UNOS). Under pressure to develop a more detailed system for organ allocation, UNOS largely adopted the "points" system that was used at the University of Pittsburgh (initially in response to accusations of allocation improprieties) [19]. Patients waitlisted for a kidney at Pittsburgh were awarded points based on wait time, HLA match, panel reactive antibody (PRA), medical urgency, and if the kidney's cold ischemia time was greater than 24 hours at the time of allocation, logistics. Patients with a six out of six HLA match were given priority. Children less than 10 years of age or 27 kg were on a separate waitlist from adults [36].

Pediatric priority has remained a core component of organ allocation in the United States. Initially, children were awarded extra points to minimize wait time; however, pediatric transplantation rates remained lower than desired. In 1998, UNOS instituted a policy in which a child would be moved to the top of the allocation sequence if they had not received a transplant by a predetermined time: 6 months for children less than 5 years, 2 months for children 6 to 10 years, and 18 months for children 11 to 17 years of age. While this improved transplant offers, these organs were often declined due to poor organ quality. In 2005, the decision was made to give pediatric patients high priority from donors aged less than 35 years [37]. "Share 35" significantly improved pediatric wait times, but there was a concurrent 27% decline in living donor transplant rates [38]. In 2014, UNOS transitioned to a new kidney allocation system and introduced the Kidney Donor Profile Index (KDPI), an estimate of the likely survival of an allograft relative to all others. In this scheme, children are given priority for the best 35% of kidneys after multiorgan transplant recipients, recipients with zero HLA mismatches to the donor, prior living donors, and highly sensitized recipients. The new system has resulted in a decrease in pediatric donor kidneys transplanted into pediatric recipients, as the Kidney Donor Profile Index assigns worse scores to kidneys from donors less than 18 years old. An early analysis showed no increase in wait time and no increase in transplant rate for pediatric transplant recipients under this system, but long-term data is pending [39].

1.8 "The Greatest Application": Pediatric Transplantation

Early on, some questioned whether transplantation in children was ethical given the challenges of pediatric dialysis and the uncertain long-term outcomes of the procedure [40]. Initially, most pediatric transplants used adult-sized kidneys, as they were living donor transplants. As deceased donor transplantation became more common, interest focused on transplanting pediatric deceased donor kidneys into children "to increase the number of cadaver kidneys" [41]. Outcomes were dismal. The first two case series included nine children, of whom four died within 2 months [41, 42]. Some programs tried using kidneys donated by anencephalic infants; 43% never functioned, primarily due to vascular thrombosis [43]. As late as 1994, outcomes for deceased donor kidney transplantation in children less than 5 years of age were described as "disappointing" [43] and worse than those of older children and adults [44], although it was acknowledged that transplant was the only available treatment for children with ESRD [44]. In 1992, the North American Pediatric Renal Trials and Collaborative Studies report showed that 1-year graft survival for recipients of donors 0–5 years of age was 63%, 73% for recipients of donors 6–10 years of age, and 80% for recipients of donors greater than 10 years old [45]. Results were even worse among donor kidneys from children less than 3 year of age that were placed in similarly aged children [46]. When a transition was made to placing larger donor kidneys into children, 1-year deceased donor graft survival improved significantly [43]. As of 2018, pediatric kidney allograft survival is 97% at 1 year and 60.6% at 10 years, generally similar to adult outcomes [30].

With more experience, the particular complications of transplant in young children emerged. Children less than 12 years or 35 kg may not have room in the iliac fossa for placement of an adult donor kidney in children less than 12 years, necessitating development of an intraperitoneal organ placement via a midline incision [47]. The postoperative diuresis may be more severe in an infant or young child; one of Starzl's initial 22 pediatric transplants died of iatrogenic hyponatremia and hyperkalemia on post-op day 1. Young children clear cyclosporine approximately twice as fast as adults; the initial rapid improvement in adult outcomes with the introduction of cyclosporine was not seen in children until this was recognized in dosing protocols [43].

Steroid side effects were particularly notable in children, especially growth arrest, delayed puberty, cataracts, weight redistribution, acne, and the associated psychological reactions [47]. "Soon the eye clinics were flooded with moon-faced children and young adults who were going blind" Starzl wrote. Then "the orthopedic clinics were filled with moon-faced kidney recipients whose… bones might break with a movement as slight as a cough. Muscles wasted away" [19]. In a long-term follow-up study of 25 children transplanted at the University of California, San Francisco, between 1964 and 1970 and still alive in 1991, 14 had cataracts and 5 had skeletal problems, mainly aseptic necrosis [48]. Due to these concerns, steroid minimization and avoidance has been studied since the 1970s [43]. While early studies of these protocols showed decreased hypertension and improved linear growth, there was also a high rate of acute rejection leading to permanent declines in

function or graft failure [49–51]. However, when these studies were repeated using tacrolimus and mycophenolate mofetil for maintenance immunosuppression, there was no difference in graft survival between protocols that did and did not include steroids [52, 53]. As of 2018, 37.5% of pediatric kidney transplants use a steroid-free immunosuppression protocol [30].

Beyond the basics of patient and graft survival, the central question for pediatric transplantation, given the risks and complications, was whether the recipients would be able to live a quality life. Even in the earliest days of transplant, it was apparent that the answer was yes. In 1976, Weil et al. reported follow-up of 57 children who received a kidney transplant between 1962 and 1969. At follow-up, 61% of children were alive, most of whom had experienced "catchup growth" after transplant and were working or attending school full-time [22]. Similarly, in 1991, Potter et al. reported outcomes of 37 children transplanted between 1964 and 1970. Of the 25 survivors, 18 were either employed outside the home or as homemakers and 6 had children of their own. No patient had a Karnofsky Performance Status score of less than 80% on a scale of 0–100% [48].

Research continues to seek improvements in pediatric kidney transplant outcomes. Clinical trials are investigating novel immunosuppression therapies and refinement of current protocols. Observational studies are using unprecedented access to large databases, such as the North American Pediatric Renal Trials Collaborative to provide a more detailed understanding of risk factor, including at the molecular level. New technology allows the creation of learning health systems, such as the Improving Renal Outcomes Collaborative, for large-scale quality improvement. A focus on the psychosocial contributors to graft survival drive studies on adherence and transitions to adult care.

"Kidney transplantation burst onto the scene so unexpectedly in the early 1960s that little forethought had been given to its impact on society. Nor had its relation to existing legal, philosophic, or religious systems been considered. Procedures and policies were largely left to the conscience and common sense of the transplant surgeons involved" [19]. Faith in humanity and people who were willing to persist through failure with grit and determination are responsible for the legacy of transplantation. From the lessons of the past, we have much to accomplish as we continue to learn and grow the field of pediatric transplantation.

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Transplant Immunobiology

2

Licia Peruzzi and Enrico Cocchi

2.1 Introduction

When a solid organ is transplanted from a nonidentical individual into a recipient, several actors start to play a role to develop an immune response aiming at getting rid of the foreign tissue.

This response is called "allorecognition" and involves cells belonging to the recipient's immune system and to the graft, interacting in a process ultimately evolving to rejection if not properly prevented pharmacologically.

Some peculiar events occur already before transplant, in particular when dealing with deceased donor, which may have suffered from sepsis or hemodynamic stress or have undergone extracorporeal procedures inducing pro-inflammatory responses with effects on the vascular tree of all organs, further amplified during the ischemic phase just before transplant and by an additive damage induced by the violent reperfusion.

These non-immunological events have a high impact on the immediate outcome of the transplant but also on later events, influencing subsequent adaptation responses and immunological trigger.

Immediately after vascular connection and declamping, vascular endothelium is the first site of the graft exposed to donor cells. From this primary contact, a cascade of events involving inflammatory and innate immune response followed by a more tailored adaptive specific response are triggered, leading to the immediate rejection of the foreign organ, if adequate measures are not properly adopted. This concept was evident since the origin of the transplant era, when it was immediately clear the importance of preventive modifications of the immune system to render it unoffensive. This preventive adaptation of the immune system to accept a foreign graft is defined "induction therapy."

L. Peruzzi (✉) · E. Cocchi
Pediatric Nephrology Dialysis and Transplant Unit,
Regina Margherita Children's Hospital, Turin, Italy
e-mail: licia.peruzzi@unito.it

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Endothelial cells (ECs) are semiprofessional antigen-presenting cells (APCs) and can express all the resting histocompatibility complex (MHC) antigens of class I as well as of class II upon a flogistic stimulus, such as the ischemic condition or the high oxygen tenor of reperfusion. ECs moreover can express other sets of minor antigens that can be recognized by immune cells as foreign.

Therefore, in the vascular tree of the graft is where the first encounter between donor and recipient occurs and where the host immune system will continue for all the graft's life to discriminate between self and non-self.

Allograft rejection is clinically categorized as hyperacute, acute, or chronic, depending on the time of onset after the transplant procedure. On a biological point of view, basing on the principal mechanism involved, cell-mediated or antibody-mediated rejections are schematically distinguished, although strict and interdependent interactions of the two pathways occur, rapidly recruiting other systems such as complement, coagulation, and inflammation.

2.2 EC Activation Starts before Transplant

Activation of ECs is a multifactorial process that starts long before the donor's brain death. Factors associated with critical illness, pain, infections, and treatment as well as procedures such as perfusion or cardiopulmonary bypass contribute to ongoing EC injury and activation [1, 2].

A large amount of experimental data demonstrated that the vascular tree of transplanted organs from deceased donors is already damaged during brain death, before the process of transplantation is initiated. ECs become activated in response to a multitude of stimuli and facilitate leukocyte-endothelial interactions through overexpression of adhesion molecules, release of chemotactic cytokines, and reduced release of protective substances [3, 4] (Fig. 2.1).

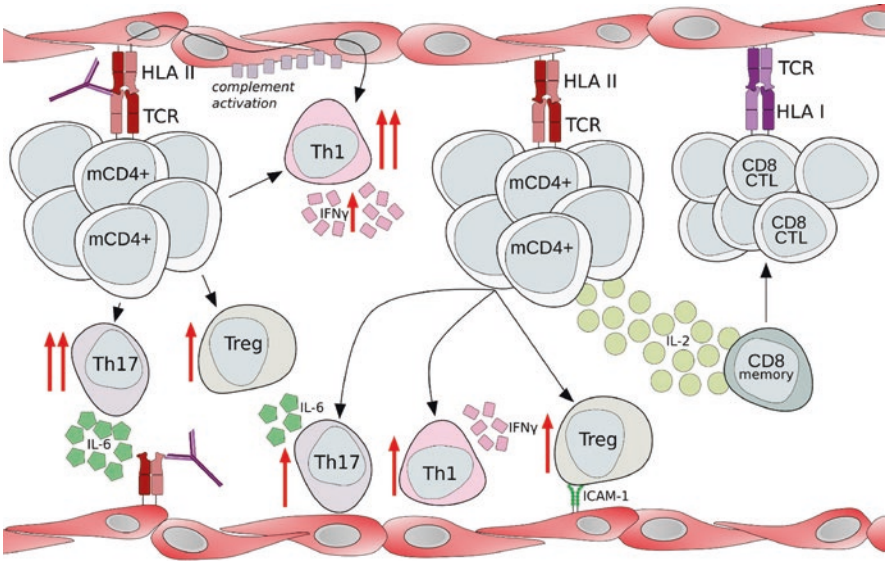

Fig. 2.1 Key role of endothelial cell in allorecognition: Graft-activated endothelial cells express HLA class II antigens and present donor alloantigens to recipient T cells, inducing CD4 triggering to secrete IL-2 and stimulate alloproliferation. IL-2 also facilitates differentiation of memory CD8 into cytotoxic T cells, able to target donor's HLA I and induce rejection. CD4 activation recruits also Th17 (capable of a pro-inflammatory action) and Treg provided with anti-inflammatory and regulatory immunosuppressive effects and Th1 subsets. DSA further induce endothelial activation and amplify the pro-inflammatory cascade. Abbreviations: *CD8-CTL* CD8 cytotoxic T lymphocytes, *TCR* T cell receptor, *mCD4* memory CD4 T lymphocytes, *Th17* lymphocytes' T helper 17, *Treg* regulatory T lymphocytes *Th1* T helper 1, *IL-2* interleukin 2, *IL-6* interleukin 6, *IFNγ* interferon gamma, *ICAM-1* intercellular adhesion molecule 1

2.3 The Grafted Organ Comes from an Ischemic Period: Role of the Hypoxic Phase and of Reperfusion

During the ischemic phase of the organ, when blood flow is reduced during the surgical phase of organ isolation and explantation from the donor or suppressed during the storage phase, several non-immunological events further increase the endothelial disruption already initiated [5].

The worse damage occurs during reperfusion, particularly in the microcirculation tree.

The endothelial dysfunction mainly consists of increased vascular permeability associated to apoptosis, autophagy, and necrosis of the ischemic tissue coexisting with regeneration areas.

EC, after the reperfusion phase, acutely overexpress P selectin, stored in the Weibel-Palade bodies and translocated to the membrane, E selectin, and ICAM-1, thus favoring neutrophil adhesion. Upon neutrophil adhesion, the ECs undergo

transformations induced by Ca++ influx, with stress fiber formation from actin F, myosine L chain activation, tension generation, and release of reactive oxygen species (ROS), resulting in necrosis and inflammatory response.

Other non-immunological events including pro-coagulatory and pro-thrombotic changes on the surface of the damaged endothelium may result in vascular occlusion [6].

Glycocalyx in patients suffering from sepsis is the target of leukocyte-endothelial interactions, thrombotic status consequences, and vascular permeability. These modifications of EC favor the attachment of monocytes and alter nitric oxide synthase homeostasis. Additional mediators released in the extracellular environment are adenosine triphosphate (ATP) and adenosine diphosphate (ADP), able to further catalyze platelet aggregation and to amplify the formation of microthrombi.

Prolonged ischemic time is associated with higher ROS release and vascular damage; a direct correlation is present with early allograft dysfunction.

Physical factors therefore contribute heavily to the damage of the vascular tree of the organs that further will be transplanted.

Ischemia reperfusion (IR) triggers a cross talk between neutrophils, macrophages, and dendritic cells (DC), through extracellular vesicles (EVs) which carry inflammatory and anti-inflammatory potentials addressed to local tissues.

EC and epithelial cells in the ischemic phase release huge amounts of EVs, particularly in response to hypoxia-inducible factor (HIF), an activator of over 70 target genes, which can remodel the plasma membrane and induce a cascade of actions as vasoconstriction, vascular inflammation, rarefaction of peritubular capillaries until chronic hypoxia, interstitial fibrosis, and tubular atrophy.

Renal proximal tubular cells are very vulnerable to the ischemic damage due to the mitochondrial high oxygen requirement and can easily release EVs with different effects involving also the immune system [7].

2.4 Endothelial Cells Talk with the Immunological System

Endothelial cells are the interface between the graft and the recipient's immunity, and the primary target for host recognition. Upon ischemia the graft ECs develop the activated status, express adhesion molecules and chemokines attracting macrophages and natural killer cells, molecules able to start the coagulation and complement cascade. Moreover ECs upregulate HLA I and HLA II, becoming the first target of specific alloresponse and of acute rejection.

Hyperacute rejection occurs within minutes after organ reperfusion, being the underlying mechanism the presence of preformed circulating anti-HLA donor-specific antibodies.

Antibodies binding to the EC surface are sufficient to activate the complement cascade until the terminal attack complex and through the upregulation of the expression of adhesion molecules to attract platelets and activate the coagulation cascade until the formation of thrombi.

Pre-formed anti-HLA antibodies can derive from previous transplants, from repeated transfusions, and in females in case of multiple pregnancies, particularly with different spouses.

Nowadays, this event is extremely rare due to the routinary assay of the presence of antibodies through pretransplant crossmatch and specific anti-HLA antibodies' identification with the modern high sensitive flow cytometry technique [8, 9].

2.5 T and B Cells Are the Main Effectors of Acute Rejection

Acute rejection can occur days or months after transplantation, involving all the actors participating in the innate and the adaptive immune response.

Although histologically T cell-mediated acute cellular rejection is prevalent, often the mechanism involves also the B cells, in an interdependent system.

Antigen presentation to the host immune system involves multiple modalities, deriving from engagement of graft antigens, graft antigen-presenting cells, and recipient antigen-presenting cells with the recipient's lymphocytes.

T cells can recognize directly the intact foreign HLA molecule presented by a donor-derived antigen-presenting cells (APCs), by donor-activated EC or by donor APC migrated in the host lymphoid organs.

The recipient APC can present HLA peptides from digested graft HLA molecules to T lymphocytes also in an indirect manner.

T cell engagement secondarily induces B cell activation, which plays a crucial role in developing antibody-mediated rejection, by antibodies against HLA I and HLA II and other immunogenic targets on the surface of graft ECs [10–12].

2.6 The Pathways of T Cell Allorecognition

Direct pathway: CD4 and CD8 T lymphocytes recognize intact MHC class I and class II directly on the surface of donor APC, either in the graft or migrated to the host secondary lymphoid tissue.

Indirect pathway: alloantigens are processed and presented to CD4 and CD8 T lymphocytes by the recipient APC, within the self-MHC.

Although infinite peptides can be theoretically generated, the immune response is usually generated against a limited number of immunodominant epitopes.

Semi-direct pathway*:* recipient T cells recognize intact alloantigen, which are presented as intact molecule by the recipient DC.

The intact alloantigen is transferred to the recipient DC most probably via transfer of extracellular vesicles.

The three different pathways will last for different time and thus influence the timing and persistence of rejection.

Direct recognition has been usually considered as a short lasting type of response, limited to a few weeks; however, recent studies suggest that "direct" pathway activation is largely due to recognition of intact alloantigen acquired by transfer of donor-derived extracellular vesicles to host APC. According to this hypothesis, direct pathway CD4 T cell activation can occur also at late time points after transplantation.

CD4 T cell response against processed alloantigens can last much longer than against intact antigens; the indirect pathway is more involved in chronic rejection and it is hypothesized that memory T cells are derived upon this pathway (Fig. 2.2).

CD8 T lymphocytes are generally activated by the presentation of intact MHC class I alloantigens by migrating donor DC, and the process is particularly efficient in an inflammatory environment, but requires the presence of CD4 T helper cells.

Experimental models support the hypothesis that immediately after transplantation, strong CD8 T cytotoxic response can be generated upon efficient CD4 T help by direct and semi-direct presentation of MHC I. It is still not clear how long in the life of the transplantation these mechanisms last, since so far no clear evidence of late direct alloreactive CD8 T stimulation is available.

The immunological synapse defines the engagement of the T cell with the dendritic cell through HLA of the APC and the T cell receptor (TCR). The TCR is composed of an alpha chain and a beta chain and several associated molecules named CD3 chains.

The strict contact between HLA and TCR/CD3 triggers a cascade of intracellular signals (signal 1).

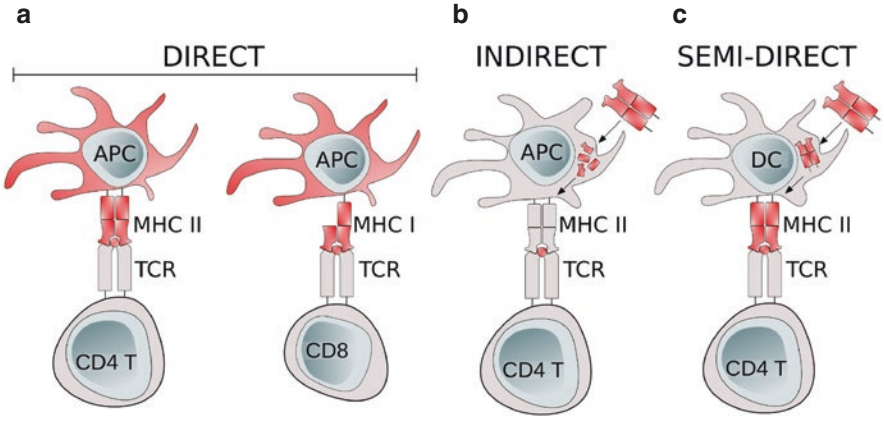

Fig. 2.2 T cell allorecognition: (**a**) Direct pathway: donor antigen-presenting cells (APCs) present intact allo-MHC class II to CD4 T lymphocytes and MHC class I to CD8 T lymphocytes. (**b**) Indirect pathway: recipient APCs internalize donor MHC I and II alloantigens and digest and present peptide fragments within the MHC complex to self-CD4 T lymphocytes. (**c**) Semi-direct pathway: recipient dendritic cells present conformationally intact allo-MHC to self-CD4 T lymphocytes. Abbreviations: *APCs* antigen-presenting cells, *DC* dendritic cells, *MHC I* major histocompatibility complex class I, *MHC II* major histocompatibility complex class II

Simultaneously, a hinge between other molecules on both sides generate a second signal defined costimulatory signal (signal 2), essential for effective T cell activation, since its blockage blunts T activation and induces anergy and apoptosis.

Signal 1 and signal 2 activate three main downstream pathways of signal transduction: the calcium- calcineurin pathway, the RAS-mitogen-activated protein kinase (MAPK) pathway, and the IKK-nuclear factor κB (NF-κB) pathway.

The signals originating from these pathways are transferred to the nucleus where they activate gene transcription factors including the nuclear factor of activated T cells (NFAT), activated protein-1, and NF-kB inducing the transcription of several activation molecules, cytokines, mainly interleukin-2 (IL-2) and interferon-γ (IFN-γ), and cytokine receptors as CD25.

IL-2 is the key activator of T cell activation and can bind either its own receptor on the surface of the same T cell with an autocrine mechanism (signal 3) or on other T cells, triggering further other downstream pathways and amplifying activation. Mammalian target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K), and Janus kinase/signal transducers and activators of transcription protein (JAK/STAT) are the most explored pathways.

The activated T cells undergo the cell division cycle and clonal expansion of donor HLA/peptide-specific effector (CD8+ cytotoxic T cells) T cells.

CD8 T cells have a cytotoxic function, help macrophage-induced CD4-Th1 response, and help B cells for antibody production (CD4+ Th2).

2.7 T Cell-Mediated Cytotoxicity

Cytotoxicity is mediated by CD8+ T cells through engagement of TCR within MHC class I, expressed on all nucleated cells.

Killing occurs either by a calcium-dependent secretory mechanism or a calcium-independent mechanism upon strict contact through TCR and costimulatory molecule engagement.

The activation pathway induces calcium influx and exocytosis of cytolytic granules, containing lytic enzymes perforin and granzymes capable of lysing the target cell.

In the absence of calcium, *fas* ligand is upregulated on T cells, thus binding *fas* expressed on target cells: upon this contact, the T cell proceeds toward apoptosis, programmed cell death with nuclear fragmentation, not eliciting an inflammatory response.

2.8 The Costimulatory System

The interaction between the APC and the CD4T is not sufficient to properly activate the alloresponse and requires the help of several other molecules that altogether are known to provide the “costimulatory” signal. These molecules have the characteristics of specific receptors providing a further physical contact between the APC and

the lymphocyte. Costimulation not only provides activatory signals but also can trigger inhibitory signals to limit and control T activation.

Several molecules have been identified to provide this function and among them the best characterized are the CD28:B7 and the TNF-related families, complemented by some adhesion molecules and a growing list of other candidates (reviewed in Mardomi et al. and Esposito et al.) [13, 14].

2.8.1 The CD28:B7 Family

Belong to this family the pairs receptor-ligand: CD28/CTLA4: B7.1/B7.2, ICOS:ICOSL, and PD-1:PDL1/PDL2.

B7-H3 and B7-H4 are candidates of this family but still not demonstrated in human.

The CD28:B7 family is able to provide either stimulatory or inhibitory signals, modulating T cell activation.

CD28 belongs to the immunoglobulin superfamily and is constitutively expressed on T cells. Upon interaction with the ligands B7.1 (CD80) or B7.2 (CD86), expressed on APC, full activation of T lymphocyte can occur [15].

CTLA4 (cytotoxic T lymphocyte-associated antigen 4/CD152) is structurally homologous to CD28, but with higher avidity for the ligands CD80 and CD86 and acts as a competitor of CD28, inducing the dissociation of the complex CD28:CD80-CD86, thus providing a negative downregulatory signal to the T cell.

ICOS (induced costimulatory molecule) belongs to the same family: it is not constitutively expressed on T cells but is induced on activated T cells, its expression remaining also in memory and T effector cells [16].

ICOS can bind to B7-homologue or to B7-related homologue expressed on APC and provide a positive signal for T cell activation involving also B cell recruitment.

PD-1 (programmed death-1) is expressed on peripheral T cells, NK cells, B cells, and monocytes: after binding to PD-L1 (B7-H1) and PD-L2 (B7:DC) induces a potent inhibitory signal in the early phases of the T cell activation process inducing a cell cycle arrest in G0/G1 phase, blocking also cytokine production [17].

The importance of PD-1/PD-L1 axis in the establishment of tolerance against allografts is demonstrated in a growing amount of literature.

B7-H3 and B7-H4 are B7 homologues, inducible in immune and hematopoietic cells and with the dual capacity to induce either stimulatory or inhibitory signal, but with still unidentified putative receptors in humans [18].

2.8.2 The TNF-Related Family

The TNF superfamily includes several molecules able to influence T cell-mediated response. The most characterized are the pairs CD40:CD40L, OX40:OX40L, CD30:CD30L, CD27:CD70, CD137:CD137L, glucocorticoid-induced TNF receptor-related protein (GITR):GITRL, and herpes virus entry mediator (HVEM): LIGHT [19].

These receptors have similar structure and share the capacity upon ligation to recruit TNF receptor-associated factors (TRAFs), which mediate the intracellular transcription of MAP kinase and NF-kB pathways.

CD40:CD40L (CD154) is the most studied pair of this family. CD40 is mainly expressed on B cells, but also on monocytes, dendritic cells, endothelial cells, smooth muscle cells, and fibroblasts. Its ligand CD40L (CD154) is expressed on activated T cells upon T cell receptor engagement, but also on platelets and inflammatory cells. Signaling through CD40 is critically important for DC activation, B cell activation, antibody isotype switch clonal expansion, formation of germinal centers, and maturation until the generation of long-lived plasma cells [24, 25]. Moreover, CD40/CD40L pathway stimulation induces also CD80 CD86 expression and the co-activation of the CD28 pathway [20, 21].

OX-40:OX40L: OX40 (CD134) is expressed on activated T cells, Tregs, NK cells, and neutrophils, and its ligand OX40L(CD252) on APC and B cells, in an inducible modality. Engagement of this receptor induces mainly B lymphocyte activation with proliferation and differentiation. A role in clonal expansion of effector and memory T cells has also been described: memory alloreactive T cells are less dependent on conventional costimulatory pathways such as CD28/CD80 or CD40/CD154. Instead, they seem to rely more on the OX40/OX40-L signaling.

Due to the wide expression of OX40L on nonimmune cells upon induction, OX40/OX40L axis is one of the important axes in cross talks between immune and nonimmune cells.

Other molecules belonging to the TNF superfamily are able to modulate the immune response, T cell polarization, and long-term maintenance of T cell response.

HVEM or TNFRS14 (herpesvirus entry mediator): BTLA (B and T lymphocyte attenuator) TNFRS14 is expressed on a wide range of hematopoietic and non-hematopoietic cells and is the major ligand with a co-inhibitory function for BTLA and a costimulatory signal via LIGHT. BTLA is mainly expressed on lymphocytes, belongs to the CD28 family, and has by itself a co-inhibitory function. Its expression seems to be related to tolerance.

GITR (glucocorticoid-induced TNF-related protein): GITRL – GITR is a transmembrane protein, member of the TNFR superfamily, mainly expressed on Tregs, and upregulated upon T cell activation. Its natural ligand GITRL is expressed on DCs, macrophages, and endothelium. Upon GITR-GITRL binding, co-activation of NK cells and APC simultaneous downregulation of Tregs occur.

2.9 Adhesion Molecules

These molecules facilitate T cell adhesion to APC favoring all the costimulatory pathways and maintain a costimulatory function themselves. β2 integrins (CD11/CD18) are a wide family of adhesion molecules mediating leukocyte interaction among leukocytes and to endothelial cells and other APC. They all share a common β-chain (CD18) associated with different α-subunits (CD11).

CD11a/CD18 (LFA-1, lymphocyte function-associated antigen 1): ICAM-1 intracellular adhesion molecule 1, CD54): this pair plays an important role in the initial phases of T cell activation, being CD11a/CD18 expressed on the T cell, but also on B cells, neutrophils, and macrophages and ICAM on APCs.

LFA-1 is a positive costimulatory molecule, inducing cytokine release, T cell activation, and differentiation [22].

TIM (T cell Ig and mucin domain) molecules: this family of transmembrane proteins bear an extracellular immunoglobulin and mucin domain and are expressed on a wide variety of innate and adaptive immune cells.

In human, the three molecules TIM1, TIM3, and TIM4 are described.

TIM1 is expressed on T cells and TIM4 is its ligand. The disruption of this pair breaks peripheral tolerance and activates T cells. TIM1 is also a regulatory B cell marker.

TIM4 has been observed on activated and IFN-γ-producing B cells during rejection and is also expressed on liver Kupffer cells and upregulated in transplanted liver.

Galectin 9:TIM3: galectin 9 is an homeostatic molecule with either adhesion and costimulatory function or immunoregulatory activity, such as the capacity to influence cytokine secreting-Th1 and Th17 and to expand the population of CD4+, CD25+, and Fox-P3+ Tregs.

VISTA (domain immunoglobulin suppressor of T cell activation): is a checkpoint molecule mostly expressed on DC, able to negatively regulate T cell responses. Its ligand is still undefined and possibly functions either as receptor or ligand. Structurally, it is similar to PD1.

HLA-G and HLA-E: these nonclassical MHC molecules are involved in the immunologic tolerance process; the expression of HLA-G and HLA-E inhibitory receptors and the role of these molecules in the regulation of alloreactive immune responses however, to date, are still not fully defined (Fig. 2.3).

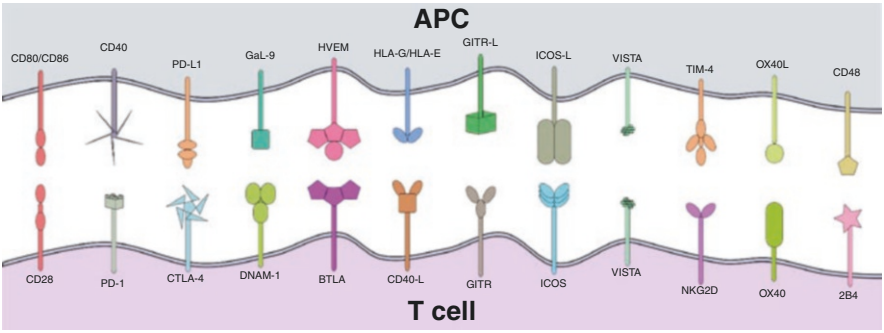

Fig. 2.3 The costimulatory system: several molecules contribute to strengthen the interaction between antigen-presenting cell and T lymphocyte, defined "costimulatory molecules." The signal transmitted by these molecules is necessary to fully activate the immune response. Some of them are also provided with an inhibitory function. These molecules are fundamental in the alloresponse and are target of many new drugs in transplantation immunological treatment. Details and abbreviations in text

2.10 B Cells' Role in Transplantation

B cell activation, switch to memory B cells and to antibody-producing plasma cells (PC) are important tiles in the comprehension of transplantation immunobiology and the complex mechanisms of the multifaceted actions involved in rejection [23].

B cells can respond acutely leading to massive production of antibodies against the graft (donor-specific antibodies), possibly evolving to acute humoral rejection, but are also capable of being recalled in chronic rejection upon continuous subliminal stimulation and continuous DSA synthesis.

Upon exposure to alloantigen, the B cells undergo a series of transformation until the generation of memory B cells and antibody-secreting cells, short-lived plasmablasts, and long-lived plasma cells (PC).

The initiation of B cell response requires that the antigens are transferred to secondary organs (spleen and tributary lymph nodes) where they are transferred to DC as intact molecules, in a sort of semi-direct manner, driven by the donor's DC transferred then to the follicular resident DC. Here, opsonized antigens are able to stimulate the rearranged specific B cell receptor (BCR), complement receptors (in particular CR2), and other activatory receptors as FcγRII, CD22, and CD72 (reviewed in Cyster et al. [24]).

Upon antigen priming, the B cell undergoes a transformation which upregulates chemokine receptors CCR7 and EBI2, necessary for the B cell to exit the lymph station and migrate toward T cell help. The T-B interaction transforms the B cell into an active APC, able to internalize the bound antigen, process it, and re-expose the peptides within self-MHC II to T CD4 cells.

Antibody-secreting B cells express antibodies functioning as opsonins to favor DC activation and T cell responses.

Indirect presentation of alloantigen by recipient B cells to recipient T CD4 cells: the binding of alloantigens by BCR results in the activation of B cells and induces the processing and subsequent presentation of the alloantigens in the context of MHC class II.

In fully mismatched transplantation, recipient alloreactive B cells can engage interactions with recipient T CD4 but not T CD8 lymphocytes, and only via indirect pathway.

B cells acts as APCs to T follicular helper cells in secondary lymphoid organs: activated B cells migrate to the lymphoid tissue where they meet cognate interactions with T follicular helper cells (Tfh), previously activated by DCs.

Upon this T:B interaction, B cells undergo extrafollicular differentiation into memory B cells or short-lived PCs, or alternatively entry into a germinal center (GC). Here class-switching and somatic hypermutation occur together with selection of high-affinity B cells upon Thf drive [25].

Costimulation through CD40:CD154, CD28:B7, and ICOS:ICOSL allows optimized B cell differentiation and B cell affinity maturation.

Lower-affinity B cells emerge early from the GC as memory B cells, whereas higher-affinity B cells will emerge later as antibody-secreting cells.

Recipient DC at the same time pick up the non-self-antigens, migrate in the lymph nodes, and transfer either intact or processed antigens, via exosomes and other subcellular mechanisms, to resident DC and present the alloantigens to T CD4.

The B-T interaction is a key process, involving T cell receptor (TCR) and a panel of costimulatory molecules on both sides: primarily LFA1, CD28, and CD154 on T cells and CD80/86 and CD40 on B cells.

Upon T CD4 help B cells differentiate alternatively into memory B cells or into secreting cells or migrate to the follicular center of the lymph node. Here they undergo switch rearrangement becoming class-switched memory B cells, and long-lived plasma cells.

Memory B cells: there are two types of memory B cells belonging to two generations. Extrafollicular pre-germinal center memory B cells are the first appearing upon alloantigen exposure. Germinal center memory B cells have fewer somatic hypermutations and are released in the phase of the germinal response. The earlier extrafollicular B cells are mainly IgM, while the germinal B cells have undergone class-switch recombination and express the BCR with other Ig isotypes. The events influencing the ratio of IgM and IgG memory B cells are not known.

IgM and IgG memory B cells have different functions, according to their BCRs: the level of somatic hypermutation and the affinity of the BCR determines the longevity of memory B cells.

2.11 Plasma Cells

Antibody-secreting cells can be differentiated into "short-lived," transiently detectable in the blood post-immunization, and "long-lived" plasma cells homed in the bone marrow, lymphoid tissues, and solid organs (lung, intestine, chronically inflamed tissues), based on the loss of B cell marker CD19 expression and acquisition of the plasma cell markers, CD38 and CD138, as well as Ki-67, HLA-DR, and FcγRIIb. The acquisition of stronger CD28 expression mainly characterizes long-lived plasma cells [26].

2.12 Cells Participating in the Immune Response: Not Only T and B Cells

Mammalian immunity has endless capacity to "adapt" the receptor of T and B lymphocytes to recognize foreign antigens with a high molecular specificity, to expand clonally, and to differentiate to maintain the memory of the antigens, in a very precise process defined as "adaptive immune response."

The full activation of the T lymphocyte needs two well-regulated signals, which require multiple steps and inevitably some time: the first derives upon the

engagement of the T cell receptor with the antigenic peptide presented within the grove of the major histocompatibility complex (MHC) molecules expressed on the activated antigen-presenting cells (APCs). The second signal comes instead, as reviewed above, from costimulatory molecule or cytokine receptor interactions expressed on lymphocytes with a counterpart on the activated dendritic cell (DC).

2.13 Dendritic Cells in Allograft Rejection

Dendritic cells are the most efficient antigen presenter and are capable of inducing T lymphocyte proliferation 100 folds more efficiently than macrophages, particularly when activated by an inflammatory stimulus. DCs are present in lymphoid organs but are also spread throughout the body, within the organs including the kidney.

The inflammatory phase preceding the transplant is an extremely efficient priming for kidney resident DC that acquire the capacity not only to present MHC peptides to the recipient's lymphocytes but also to migrate to the recipient's lymph nodes to directly stimulate the nodal lymphocytes.

Host T lymphocytes can therefore be activated after transplant in two modalities: one through "direct" alloantigen presentation by the donor resident DC and the other through presentation of donor alloantigens by its own DC in lymphoid organs in an "indirect" pathway [27].

2.13.1 Which DC: From the Donor's or the Recipient's?

Several experimental settings addressed to solve this issue allowed to understand that donor DCs contribute to but are not essential for rejection: donor DCs migrate out of the transplant to secondary lymphoid organs where they are surrounded and killed by the recipient's NK and the recipient's immune system. It seems so highly improbable that donor DCs can play a significant role in activating recipients T lymphocytes and initiate the alloresponse.

The most probable role of donor's DC is as carrier of alloantigens to the recipient's lymphoid organs where the non-self-MHC fragments are caught and processed by recipient's DC and presented to T lymphocytes, in a cross exchange of peptides.

T lymphocytes are therefore activated either directly or indirectly by recipient's DC presenting the alloantigen in the context of self MHC II, mainly in the lymphoid organs (lymph nodes, spleen) but also in other sites, including the graft.

In the kidney, continuous interaction between the graft's DC and the recipient's T lymphocytes persists for the all life of the graft, mainly with perivascular DC going to the bloodstream and to the interstitium and T lymphocytes transmigrating across the endothelium.

2.14 Innate Immune Response

The series of well-regulated and orchestrated actions so far described are preceeded by an immediate action defined as "innate immunity", which is the first aspecific response, immediately activated to induce prompt activation of dendritic cells through primitive and aspecific pathways ready to be recruited.

The process of innate recognition is triggered by the engagement of molecular patterns present on different pathogens, defined pathogen-associated molecular patterns (PAMPs) by the Toll-like receptors (TLR), receptors widely diffused on the cells and able to immediately activate simple and aspecific activation patterns. This type of recognition is more ancient and conserved in the phylogenesis, less specific, but very sensitive in stimulating an immediate response.

This modality is active also in allograft rejection, pointing out the multiple actors and mechanisms participating in allorecognition, potential targets of therapy [28].

A large number of experimental evidences and observations, also in human, demonstrated that innate immune cells, in particular monocytes and macrophages, are capable of responding to allogeneic non-self-antigens independently from the more professional cells usually involved in allorecognition.

Response is crucial to initiate the more specific adaptive T lymphocyte response by inducing tailoring and prompting of antigen-presenting cells, necessary to drive the T response. Monocyte- macrophages moreover retain their killing and phagocytic capacity on allogenic targets.

The mechanisms of innate allorecognition are complex and still under full comprehension.

One hypothesis is that one mechanism is mediated by CD47 differential binding on monocytes to polymorphic SIRPα (signal regulatory protein alpha), a polymorphic IgSF (immunoglobulin superfamily) protein expressed on neurons and myeloid cells, but also present or induced on myocytes, epithelial cells, and endothelial cells' of the donor [29].

They showed that SIRPα triggers monocyte activation via CD47 and that amino acid polymorphisms in SIRPα determine the strength of the innate alloresponse by modulating binding to CD47.

Under steady-state conditions, bidirectional interactions between CD47 and self-SIRPα are of equal affinity and monocyte activation is prevented. In case of transplantation, non-self-SIRPα on donor cells disturbs the balance between activation and inhibitory signals mediated by CD47 allowing monocytes to differentiate into DC.

This model has been hypothesized also for NK allorecognition, where other polymorphic ligands/receptors could be involved in fine-tuning the innate alloresponse.

The innate immune system is well established to be an important component of allorecognition, but the available data demonstrate that by itself it is not sufficient for allograft rejection.

2.15 Memory Can be Present Also in Non-lymphoid Cells

The concept of immunological memory traditionally belongs to T and B lymphocytes; however, a growing amount of data, mostly in mice models, converge in expanding the concept of memory also to many other cells types. Myeloid strain cells (monocyte-macrophages and NK cells), dendritic cells, and cells of nonimmune (epithelial stem cells) origin have been demonstrated to acquire memory to infectious agents and alloantigens [30, 31].

The molecular mechanisms for memory to allogenic MHC I molecules in monocyte and macrophages occur through polymorphic PIR-A (paired immunoglobulin-like receptor A) molecules expressed on monocytes and macrophages, upon SIRPα-CD47 pathway priming. Non-immunological memory lasts days or weeks, longer than the life on a monocyte, and tailors the monocyte-macrophage to an epigenetic modification, clonal expansion, and proliferation. In humans, these mechanisms are still partially defined and further studies are necessary to translate these promising findings into clinical transplantation [31–33].

2.16 Tubular Epithelial Cells as Immunoregulator

Upon dendritic cells' interaction with antigen-specific T cells, abundant IL-1 is released, exerting an activator effect on tubular epithelial cells (TEC). Other cytokines such as IFN-γ, TNF-α, IL-18, and IL-17, released from leukocytes after infiltration to the interstitium, may play an analogous effect, transforming TEC into an immunologically reactive cell. Upon priming TEC can play a critical role in allorecognition and rejection, through the secretion of IL-6, TNF-α, IL-18, IL-15, transforming growth factor beta (TGF-β), and various types of chemokines (CC, CXC, and CX3C) and upregulating inducible nitric oxide synthase (or NOS type 2 [NOS2]).

Activated TEC can secrete complement fraction C3, further attracting infiltrating leukocyte through complement receptors, and auto-downregulate the inflammatory process through the secretion of TGF-β1.

IFN-γ and TNF-α, moreover, activate TEC inducing upregulation of MHC I and neo-expression of MHC II; costimulatory molecules B71, B7–2, and CD40; the co-inhibitory molecules PD-L1 and PD-L2; and adhesion molecules (intercellular adhesion molecule 1 [ICAM-1], lymphocyte function-associated antigen 3 [LFA-3], vascular cell adhesion molecule 1 [VCAM-1]).

Above further amplification of T cell attraction TEC can transform into an active APC, although the precise role of this interaction in allorecognition and rejection is controversial [34].

2.17 Extracellular Vesicles Mediate Cellular Cross Talk between Immune System and Graft

Extracellular vesicles (EVs) are membrane structures released by all cell types through different pathways: after fusion of endosomes with the plasma membrane (exosomes), shed from plasma membrane (microvesicles), or released during apoptosis (apoptotic bodies). These three entities differ in size (exosomes, 30–150 nm; shedding microvesicles, 150 nm – 1 μm; apoptotic bodies, 1–5 μm) and partly in content.

After cellular shedding, EVs are taken up by neighboring or distant target cells by endocytosis, phagocytosis/pinocytosis, membrane fusion, or receptor-mediated endocytosis. EVs are cargo of biomolecules such as microRNA, proteins such as cytokines or growth factors and nucleic acids [35].

Most EVs do not express HLA molecules; therefore, they escape immune recognition and fuse with target cells through mechanisms influenced also by local pH and electric charge.

The effects evoked after fusion depend on the transferred molecule; therefore this system is a very versatile pathway for intercellular communication.

EVs released by DC, macrophages, and NK cells have been demonstrated to have an important immunomodulatory role in allorecognition; therefore, many studies addressed to explore their therapeutic potential in transplantation immunology are being carried out [36, 37].

PMN-derived EVs have globally anti-inflammatory and immunosuppressive effects, mainly on DCs and macrophages through the suppression of pro-inflammatory cytokines and the upregulation of TGF-β1.

EVs released from apoptotic PMN bodies are able to blunt T cell activation through the suppression of IL-2 production and IL-2 receptor expression. The stimulation of Tregs has been described, via annexin V release [38].

EVs released from macrophages exert pro-inflammatory effects, amplifying the attraction of other leukocytes. DCs expressing TLR4 in the early phases of inflammation are able to transfer TLR4 included in EVs among bone marrow EVs, activate the NF-κB signaling pathway, and transfer miRNA useful to enhance DC mutual activation.

DC-derived EVs have also an important role in allorecognition, since the graft releases EVs carrying on their surface MHC I, MHC II, other non-HLA donor antigens, costimulatory and pro-inflammatory molecules.

Donor DCs can release EVs expressing peptides within the donor MHC which are presented directly to T cells, but can also transfer EVs containing intact donor antigens to the recipient's APC which will present these peptides within the recipient's MHC to recipient's T cells.

Donor-derived EVs moreover can transfer directly to recipient's APC donor MHC peptides, which will be further presented without any processing to recipient's T cells [39].

Recent data demonstrate that EVs exert their function mainly as antigen transporter and that this modality is probably the main mechanism for alloantigen presentation from donor APC to host lymphocytes (Fig. 2.4).

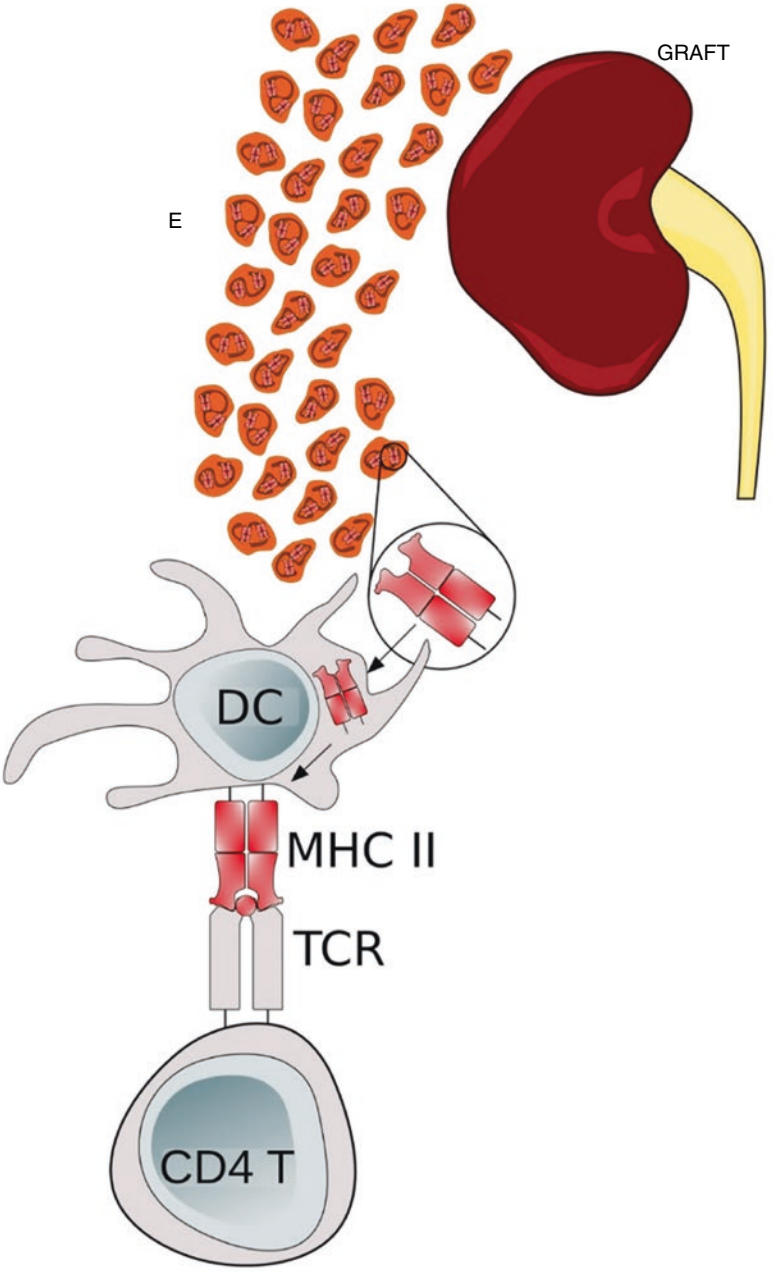

Fig. 2.4 Role of extracellular vesicles released from the graft in alloantigen presentation to T lymphocytes: Extracellular vesicles participate to semi-direct antigen presentation to T lymphocyte CD4 positive through cross-dressing antigen-presenting cell with graft-derived extracellular vesicles bearing alloantigens. Abbreviations: *DC* dendritic cells, *MHC II* major histocompatibility complex class II, *CD4 T* T lymphocytes CD4 positive, *TCR* T cell receptor

Complement cascade can be activated or inhibited by EVs released by the graft or by the recipient's T cells. T cell-derived EVs can activate complement through immunoglobulin binding, while EVs derived from other cell types activate C1q providing adhesion to C1q and classic pathway activation.

EVs of endothelial origin are shed during inflammatory processes and can carry complete membrane attack complex and express a procoagulant phenotype, which will further activate coagulation and complement cascade.

EVs can exert complement inhibitory effect through a scavenging action of complement fractions bound to cell membranes of various cell types including glomerular cells.

EVs released from leukocytes, if complement coated, can be rapidly phagocytosed by PMNs, thus abolishing the complement harming effect. EVs can also carry complement inhibitors in the form of protein or mRNA and deliver them in the inflammatory sites.

EVs of platelet and endothelial origin are promoters of coagulation, tissue regeneration, and chemotaxis.

2.18 Role of Antibodies

Antibodies against a transplanted tissue are nowadays clearly identified as a major challenge and thorough assessment at wait-listing, at time of transplant, and during posttransplant follow-up is increasingly paid [40].

Antibodies against several alloantigens can be circulating before transplantation, as a result of previous sensitization through foreign antigen exposure. Apart from previous transplantation, alloantigen sensitization can occur via blood transfusions, with platelets or leukocytes contaminating red blood cell preparations not properly filtered or leukocyte depleted. In women sometimes multiple pregnancies, when the mother is exposed to the partner HLA and non-HLA antigens, may represent a sensitizing occasion.

These antibodies are defined as "preformed" or "donor-specific antibodies" and are usually detected in advance, most frequently at time of wait-listing or at pretransplant crossmatch.

Their presence can favor immediate or later antibody-mediated rejection through recruitment of multiple mechanisms; therefore, a wide technology investment was set up in the last decades reaching widespread availability of advanced techniques to detect the antibodies, which is described in other sections of this book.

Antibodies appearing after transplantation are defined as *de novo* donor-specific antibodies (DSA): they are generally against HLA class I, expressed on all graft cells, or class II (expressed on activated tubular and endothelial cells), but also against minor histocompatibility antigens (MICA) and non-HLA antigens.

The clinical significance of the presence of DSA is not easily predictable, since their harmful effects depend on several characteristics of the immunoglobulin itself and of the host [41, 42].

2.18.1 How Antibodies Damage the Graft

Antibodies directed against HLA are more deeply explored than the others in their harmful effect, which is now recognized to stimulate three pathways: (a) EC activation, (b) complement activation, and (c) leukocyte interaction/activation. The severity of the rejection results from the host capacity to modulate these systems which is also influenced by the biochemical characteristics of the immunoglobulin like isotype/subclass, glycosylation, and affinity [43].

The first contact between the allograft and the recipient occurs on the endothelium, which can be activated by IFNγ to overexpress HLA and P-selectin and undergo mammalian target of rapamycin (mTOR)-dependent migration, proliferation, and protein synthesis [44].

Activated EC facilitates leukocyte attraction to inflammatory sites and proliferates and induces smooth muscle proliferation, increasing intima thickness, a hallmark of chronic AMR in all solid organ transplants [45].

Antibodies against HLA can bind efficiently complement according to isotype and subclass: IgM, IgG3, and IgG1 are the most efficient subclasses to induce complement activation. The multiple complement regulatory proteins can affect the intensity of complement activation and the cellular damage.

Leukocyte recruitment and activation depends either on EC activation or on chemotactic complement factor release. Neutrophil, NK cells, and macrophages are usually identified in AMR, in different solid organs. IgG subclass has different Fc receptor binding affinity, with different leukocyte activation and attraction capacity. IgG3 DSAs are strong drivers of acute AMR, while IgG4 are more frequently found in smoldering subclinical AMR and chronic rejection.

The variable terminal glycosylation of the anti-HLA immunoglobulins can influence different local responses with sialic acid inducing a more tolerogenic environment and galactose residues more pro-inflammatory (Fig. 2.5).

Non-HLA antibodies are less explored but they have the same capacity to elicit EC, complement, and leukocyte activation. AT1R antibodies mediate endothelial cell activation and vasoconstriction by binding to the second extracellular loop of the AT1R and act as an angiotensin II agonist, promoting downstream activation of transcription factors AP-1 and NF-κB [46].

Their harmful effect is mainly addressed to the microvascular tree, even though non-HLA antibodies have also been identified in CMR in renal transplantation, suggesting that additional mechanisms of action different from anti-HLA DSA are elicited, still poorly known.

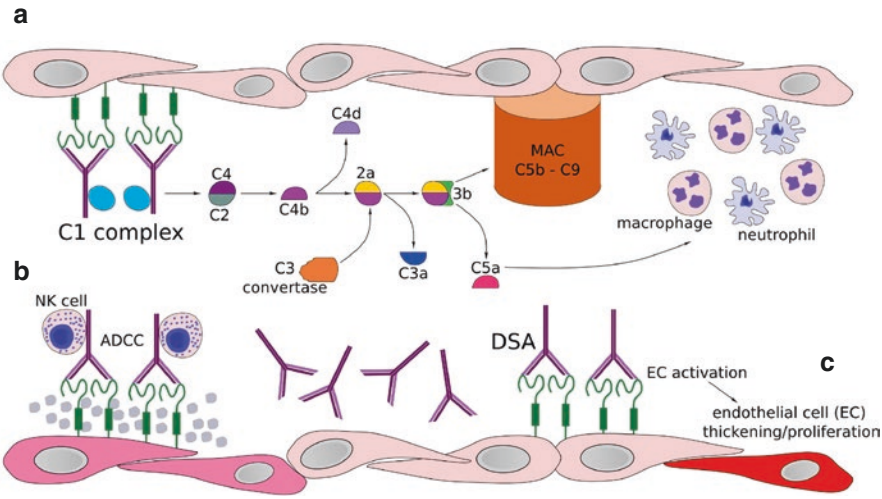

Fig. 2.5 Mechanisms of antibody-mediated graft damage: (**a**) immune complexes bind complement C1q and trigger the classical complement cascade until the formation of the membrane attack complex C5b–C9 on the endothelium. (**b**) Antibodies against multiple alloantigens can bind to Fc receptors expressed by natural killer (NK) cells which will proceed with antibody-dependent cellular cytotoxicity (ADCC) of the underlying cell. (**c**) Antibodies binding to the endothelial cell can induce direct endothelial activation further amplifying the inflammatory response. Abbreviations: *DSA* Donor-Specific Antibodies, *NK* Cells Natural Killer Cells, *ADCC* Antibody-Dependent Cellular Cytotoxicity, *EC* Endothelial Cell, *MAC* Membrane Attack Complex

2.18.2 Clinical Effects

De novo DSAs are produced in about 25% of solid organ transplants within 10 years, and their presence is correlated with worse outcome, for higher incidence of rejection and shorter graft survival. However, a subset of patients does not seem to have poorer outcome in spite of DSA, and the fine immunological mechanisms silencing their potential harm are still not fully defined.

Three situations can occur:

(a) DSA with stable function and without development of antibody-mediated rejection (AMR): about 20% of histologically negative protocol biopsies at 1 year already have de novo DSA, and about 50% of the cases of recent development of de novo DSA do not have histological signs of rejection.
(b) Subclinical AMR: is usually detected in protocol biopsies, while might be missed in biopsies performed only on clinical indication. In these cases, C4d deposition and peritubular capillaritis indicative of "smoldering" inflammation are detected. These cases have worse outcome than the DSA negative counterparts.

(c) Clinical dysfunction with overt AMR: nearly 50% of subjects with DSA develop AMR. Often DSAs are observed at time of biopsy performed on a function impairment, and nowadays the appearance of DSA is clearly attributed to non-adherence in most of the cases. AMR is characterized by peritubular and peri-capillary deposition of C4d and neutrophil peritubular infiltrate followed by cellular infiltrate and a broad range of allograft injury (acute tubular injury, tubulitis, glomerulitis, capillaritis, fibrinoid necrosis). Chronic antibody-mediated rejection has the same lesions, evolved to damage of the peritubular capillary basement membrane with multilayering, interstitial fibrosis, intimal fibrosis, and persistence of C4d staining in peritubular capillaries. These cases have generally a worse 5-year outcome than cases with T cell-mediated rejection, due to the lack of an efficacious treatment.

Persistent antibody production can elicit chronic latent or overt rejection (chronic ABMR) [47–52] where the same lesions evolve to damage of the peritubular capillary basement membrane with multilayering, interstitial fibrosis, intimal fibrosis, and persistence of C4d staining in peritubular capillaries.

2.19 Role of Complement

The complement system is a complex and multifunctional cascade of mediators that provides a stringent link between innate and adaptive immunity involving at the same time the coagulation system, playing a key role in allorecognition and rejection if not properly controlled [53, 54].

Complement and the coagulation system have in common a serine protease cascade with production of interlinking molecules, such as C5a and C5b–C9, which increase tissue factor production from endothelial cells triggering the coagulation system and release of thrombin: thrombi are the final event isolating the graft in hyperacute, rarely observed, untreated rejection.

Complement components and regulators are soluble or membrane proteins which catalyze the breakdown of converting enzyme complexes or convertases leading to the formation of membrane attack complex C5b, C6, C7, C8, and C9 (C5b–C9), causing cell perforation and lysis.

Activation of the complement cascade occurs through three pathways: the classical, lectin, and alternative cascades.

The classical pathway is triggered by antigen-antibody immune complexes formed upon B cells' immune surveillance against alloantigens and involves the activation of C4, C2, and C3.

The lectin pathway is initiated by lectins such as mannose binding lectin and ficolins, which bind to carbohydrate ligands on the surface of pathogens, forming C4b, C2a, and C3 convertase.

The alternative pathway is activated by spontaneous hydrolysis of C3 or by C3b binding to the activated cell surface, thus amplifying the cascade, using Factors B, D, and P to form the alternative C3 convertase C3bBb.

C3 is the first checkpoint of complement activation, where the three pathways converge: the cleavage of C3 forms C3a and C3b.

C3b triggers the formation of the second checkpoint point: the C5 convertase, the protease cleaving C5. Cleaved C5 triggers the formation of the final attack complex C5b–C9.

The cleaved fractions C3a and C5a retain a strong biological activity, behaving as anaphylatoxins and exerting a potent pro-inflammatory action able to attract and activate leukocytes to migrate in the graft.

The complement system is finely controlled at multiple steps of the cascade by inhibitors and regulators to prevent spontaneous auto-activation and local tissue damage: CD35 (CR1), CD46 (MCP), CD55 (DAF), C4BP (C4b-binding protein), and Factor H are complement inhibitors which favor degradation or inhibit the assembly of the subfractions.

Complement engagement can occur via three different triggers: (a) by anti-HLA or non-HLA immunoglobulins triggering complement activation through the classical pathway, (b) by the cellular membranes of the other cell populations of the graft, and (c) by the carbohydrate residues on the cell surface of the graft.

The main complement source is the liver but it is not negligible the peripheral synthesis of complement fractions by tissue resident cells and inflammatory infiltrating cells.

In the kidney, graft complement activation starts from the ischemia/reperfusion phase, mainly from endothelium and tubular epithelial cells, even though almost all renal resident cells can be upregulated to synthesize C3 and to release it in response to pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), and intercellular adhesion molecule 1 (ICAM-1) [55].

The complement system is deeply involved in the rejection mechanisms joining the gross defense mechanism set up by innate response to the coagulation cascade and to the finalized adaptive allorecognition.

C3a and C5a have a potent effect on APC increasing their ability to stimulate efficiently alloreactive T cells via nuclear factor-kB (NF-kB) signaling and costimulatory molecule upregulation.

T cells express various complement receptors such as C3aR and possibly CD88, involved in T cell survival and activation.

C5a induces proliferation and expansion of CD8+ T cells and CD4+ T cells help CD8+ T cells expansion during allograft rejection.

Complement is the main effector of antibody-mediated rejection: anti-HLA antibodies bind C1q and trigger the classical pathway cascade starting from the deposition in the graft of C4, and its splice product C4d.

Deposition of the complement fragment C4d on ECs was the first complement marker recognized for acute allograft rejection and as a predictor for long- term graft loss.

Persistent DSA production can lead to chronic AMR (CAMR) evolving from an initial injury involving DSAs and complement activation with chemotaxic effects and inflammatory cell infiltration, to persisting continuous damage with peritubular glomerulitis and capillaritis.

Long-lasting endothelial and smooth muscle cell activation by DSAs can then amplify the initial inflammatory process in a self-maintaining process.

The binding of alloantibodies to the graft endothelium triggers contemporarily both complement and coagulation cascades with a pro-inflammatory and procoagulant response, immediate thrombosis and infarction of the graft.

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3 Deceased Donor Allocation Policy and Kidney Allocation System on Young Pediatric Recipients

Amy E. Gallo, William F. Parker, and Lainie F. Ross

3.1 Kidney Transplant's Impact on Young Pediatric Recipients

The size of the kidney deceased donor pool in the United States does not meet the medical demands of the country. Tens of thousands of patients wait years or decades for an appropriate organ, and thousands each year die waiting. According to the OPTN, there were 16,534 deceased donor kidney transplants performed in the United States in 2019 (and an additional 6867 living donor kidney transplants), but over 94,000 patients are still waiting; this represents a serious deficiency for all age groups. Long wait times for pediatric patients can be especially devastating, given their added vulnerabilities.

End-stage renal disease (ESRD) burdens all age groups both physically and mentally, but one of the major challenges unique to children is the adverse impact that ESRD has on their growth and cognition, which can dramatically alter the trajectory of their life. For example, studies have shown that patients under 21 years of age

A. E. Gallo (✉)
Department of Surgery, Stanford University, Palo Alto, CA, USA
e-mail: agallo@stanford.edu

W. F. Parker
Department of Medicine, University of Chicago, Chicago, IL, USA

MacLean Center for Clinical Medical Ethics, University of Chicago, Chicago, IL, USA
e-mail: wparker@uchicago.edu

L. F. Ross
Department of Medicine, University of Chicago, Chicago, IL, USA

MacLean Center for Clinical Medical Ethics, University of Chicago, Chicago, IL, USA

Department of Pediatrics, University of Chicago, Chicago, IL, USA

Department of Surgery, University of Chicago, Chicago, IL, USA
e-mail: lross@uchicago.edu

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with chronic kidney disease (CKD) have at least one standard deviation lower intellectual functioning, lower academic achievement, and decreased executive function compared to children without CKD [1]. The negative impact on cognition is exacerbated by disease severity, with ESRD having a greater adverse impact than other stages of CKD. The exact cause is unknown but it is likely to be multifactorial. Proposed mechanisms include exposure to increased plasma levels of uremic solutes [2], anemia, poor nutrition, rapid changes in blood pressure from dialysis [3], and/or hypercalcemia from secondary hyperparathyroidism [4].

Renal failure stunts growth as well [5]. Severe and moderate growth failure in children with ESRD is associated with higher hospitalization rates, infection, and death [6]. A shorter final height in these patients also correlate with lower education, less pay, and decreased independent living [7].

In addition to impairing physical growth, time spent on dialysis can also slow the social development of children. Chronic absenteeism because of dialysis sessions and procedures makes children more likely to dissociate from school and feel less connected to the learning process [8].

Fortunately, a kidney transplant can dramatically redirect a pediatric patient's health trajectory. Almost immediately following a successful transplant, some of the factors that are thought to contribute to worsening cognition resolve [2]. Data from the late 1990s found that growth rates of young transplant recipients ages 0.5–4 years reportedly showed a delta of 3.1 cm/yr. and those patients ages 5–9 years showed a delta of 2.0 cm/yr. compared to patients on peritoneal dialysis [9]. Height gain may be even greater now that programs are more likely to employ a steroid-free approach to transplant immunosuppression [10].

Most importantly, as with adult patients, transplantation for children is clearly a lifesaving procedure [11]. Compared to dialysis, pediatric patients with transplant have decreased all cause 1-year mortality [12]. The risk of death on dialysis has been reported as high as four times the associated risk of kidney transplantation [13].

3.2 Deceased Donors for Pediatric Recipients

Like all candidates for kidney transplantation, children can benefit from a living or deceased donor graft [14]. Living donors have always played an important role in pediatric kidney transplantation, comprising more than half of all pediatric transplants in the 1970s and still constituting approximately one-third of all pediatric kidney transplants in the last two decades. In 2019, 241 (31%) of the 770 pediatric kidney transplants were living donors, and 114 (47%) of those were from parents. There are many reasons why parents are unable to be living donors for their children—from health issues to social and financial reasons [15, 16]. As such, many children will need to join the deceased donor waitlist.

3.2.1 Ethical Arguments for Pediatric Priority for Deceased Donor Kidney Transplantation

The ethical arguments to give children priority over adults in deceased donor kidney allocation are justice-based: persons who develop ESRD in youth are among the "worst off" [17] and therefore should get priority for the most effective treatment to help them achieve a normal lifespan and a reasonable quality of life [18, 19]. The equity concept of fair innings maintains that those developing ESRD at younger ages are worse off than those developing ESRD when older because they have had fewer healthy life years [18, 19]. A similar argument is provided by Norman Daniels who argues that age rationing is justified in cases of scarcity. Daniels argues that one must distinguish between equity among age groups and equity among birth cohorts [20]. One should not judge the value of one age (or stage) of life as more valuable, but only to judge that those who are younger have had less life-years and therefore less opportunity to achieve a normal lifespan [18, 19, 20].

In addition to giving children more kidneys, there is an efficiency-based ethical argument to give children priority for the highest quality kidneys. Children should be offered kidneys that are expected to function for a long time because children are expected to live a long time (efficient use of the organ) and a long-functioning graft minimizes the need for multiple re-transplants.

3.3 The "Old" and "New" Allocation Systems

3.3.1 Share 35

On September 28, 2005, "Share 35" was initiated to provide a pediatric advantage in the kidney allocation system (KAS). Under the "Share 35" model, all deceased donor kidneys from donors <35 years of age were first allocated locally to pediatric patients <18 years of age. Only multi-organ candidates, paybacks, or a zero-mismatch kidney had higher priority. Under this "old" allocation system, children are also qualified to receive points, which were approximately equivalent to years of waiting time (Table 3.1) [21]. Children younger than 11 years old were given the biggest advantage and assigned 4 extra points. Children between 11 and 18 years old were assigned 3. Additional points were assigned to children identical to adults. Patients with pre-formed circulating antibodies represented by a calculated panel reactive antibody (cPRA) level higher than 80% would receive 4 points or approximately 4 years of wait time. Points were also assigned based on the quality of the DR match. The net result was a slight advantage to younger children over older children and sensitized patients over unsensitized patients.

Table 3.1 Key points from the "old" allocation system (Modified from Chaudhuri et al. (2015) and used with permission from John Wiley and Sons) [21]

Initial criteria for allocation	
ABO match—Organs are offered to like blood types only	
HLA 6 antigen match patients Extended criteria donors offered only to those patients that consented for this criteria	
Donor age < 35 years first to recipients <18 years old	
Additional awarded points	
All age patients with a cPRA >80%	4 points
Pediatric patients <11 years old	4 points
Pediatric patients 11–18 years old	3 points
No DR mismatch	2 points
One DR mismatch	1 points

The intention of "Share 35" was to provide children high-quality organs quickly. And it worked: pediatric patients received deceased donor kidneys on average 84 days earlier than prior to "Share 35" [22]. There was also a modest improvement in access to deceased donor kidneys across races [22]. The unforeseen consequence was a decline in living donor transplants from 58.4% to 41.6% [22], and an increase in the number of HLA-mismatched transplants. A closer look, however, suggested that the living donor decline was the continuation of a trend that pre-dated "Share 35" [23]. Regardless, there was a push by professional societies to continue to promote living donation to children despite the improved availability of deceased donor organs [24].

3.3.2 Changes in Pediatric Priority under KAS

"Share 35" improved the needed access to transplantation for children. And yet, there was momentum to revise the system less than a decade later, not because of pediatric concerns, but rather, due to inefficiencies and inequities in the adult waitlist. KAS was implemented on December 4, 2014, to improve organ longevity by getting kidneys with more long-term potential to patients with longer expected posttransplant survival and to increase access to clearly underserved patient populations (Table 3.2). KAS implemented a new formula that ranked kidneys by a kidney donor profile index (KDPI) based on adult kidney transplant outcomes. The KDPI includes more donor variables, namely, donor age, height, weight, ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, hepatitis C virus status, and donation after circulatory death, to summarize the likelihood of graft failure in adults. Once a donor kidney is assigned a KDPI, it is placed in an allocation grouping sequence A, B, C, or D, ranked from best predicted graft outcome to worst predicted graft outcome (Table 3.3). The best 20% of kidneys assessed by KDPI (sequence A) were then directed to candidates with the longest expected posttransplant survival (EPTS).

Table 3.2 A comparison of the "old" and "new" allocation systems (Modified from Chaudhuri et al. (2015) and used with permission from John Wiley and Sons) [21]

Allocation prior to KAS	Allocation post KAS
Wait time	
Adult	
Starts when listed with a GFR ≤ 20 mL/min	Starts when listed with a GFR ≤ 20 mL/min or from the date the patient initiated dialysis
Pediatric	
Starts when listed with a GFR ≤ 60 mL/min	Starts when listed with a GFR ≤ 60 mL/min or from the date the patient initiated dialysis
Priority based on survival benefit	
Adult	
None	Top 20% EPTS offered KPDI ≤20% kidneys
Pediatric	
Offered local kidneys from donors <35 years old before adults that are not dual organ recipients	Offered local kidneys from donors KDPI <35% before adults that are not dual organ recipients, PRA 98–100%, or prior living donors
Expanded criteria donor classification	
Based on donor age, hypertension history, creatinine, and cause of death	KDPI >85%: Based on donor age, hypertension history, creatinine, cause of death and height, weight, ethnicity, diabetes history, hepatitis C status, and donation after circulatory death
Awarded points	
cPRA >80% 4 points	cPRA >20% receive points based on a sliding scale
DR zero or single DR mismatch, 2 or 1 points	DR zero or single mismatch, 2 or 1 points
	Prior living donor, 4 points
Pediatric	
0–10 years old, 4 points, 11–17 years old, 3 points	< 10 years old, 1 point
	0–10 years old zero mismatch, 4 points 11–17 years old zero mismatch, 3 points
Blood type	
Allocated to blood type identical recipients	Blood type B candidates may be eligible for type A2
Payback	
Payback for zero-mismatch kidneys sent to another OPO	All payback credits eliminated

Pediatric allocation, however, was an afterthought. Although UNOS stated it wanted to preserve the "Share 35" advantage for pediatrics, for simplicity and logistics of the new system, a major change occurred in accordance with the overhaul. Rather than children being eligible for kidneys from donors <35 years old, they were now eligible for kidneys from donors whose kidneys were ranked KDPI <35%, sequences A and B (Table 3.3).

We discuss three problems with this change. First, the predictive accuracy of KDPI is modest at best (c = 0.6) and again was derived only using adult recipients.

Table 3.3 Sequences A–D in the kidney allocation system

Sequence A KDPI ≤ 20%	Sequence B KDPI > 20% but < 35%	Sequence C KDPI ≥ 35% but ≤ 85%	Sequence D KDPI > 85%
Local CPRA 100	Local CPRA 100	Local CPRA 100	Local CPRA 100
Regional CPRA 100	Regional CPRA 100	Regional CPRA 100	Regional CPRA 100
National CPRA 100	National CPRA 100	National CPRA 100	National CPRA 100
Local CPRA 99	Local CPRA 99	Local CPRA 99	Local CPRA 99
Regional CPRA 99	Regional CPRA 99	Regional CPRA 99	Regional CPRA 99
Local CPRA 98	Local CPRA 98	Local CPRA 98	Local CPRA 98
Zero mismatch (top 20% EPTS)	Zero mismatch	Zero mismatch	Zero mismatch
Prior living organ donor	Prior living organ donor	Prior living organ donor	Local + regional
Local pediatrics	**Local pediatrics**	Local	National
Local top 20% EPTS	Local adults	Regional	
Zero mismatch (all)	Regional pediatrics	National	*all categories in sequence D are limited to adult candidates
Local (all)	Regional adults		
Regional pediatrics	**National pediatrics**		
Regional (top 20%)	National adults		
Regional (all)			
National pediatrics			
National (top 20%)			
National (all)			

Physiologically, younger (< 10 years of age) pediatric patients are significantly different from both adolescents and adults [25], and therefore not surprisingly, the KDPI has been demonstrated to be even less accurate for pediatric recipients [26].

Second, it has also been demonstrated that the KDPI is highly inaccurate in its quality assessment and KDPI assignment of young pediatric donor kidneys, typically assigning them KDPI ≥35 percentile scores, which are worse than their actual measured graft function [27]. With the new allocation formulation, height and weight are significantly weighted into the assumption that lower height and weight equate to reduced renal mass and worse graft outcomes. This assumption, combined with the incorrect assumption that kidney quality increases linearly with age for

donors <18, results in KDPI ranking almost every pediatric donor under age 10 with a KDPI ≥35% [27]. Therefore, virtually all pediatric donor kidneys are assigned to sequence C or D and would now be allocated to adult recipients and not to children (Table 3.3). This shift disregards the fact that that there is no statistically significant difference in graft survival in pediatric recipients with pediatric kidneys classified by KDPI into sequence A, B, C, or D (Fig. 3.1) [27].

Third, under KAS, not only children are no longer eligible for pediatric kidney donor grafts, but also pediatric patients are now placed behind several adult populations on the allocation sequences (those who were highly sensitized anywhere in the country—kidney candidates with a cPRA of 100%, listed at the local, regional, and national levels followed by candidates with a cPRA of 99% at the local and regional levels, followed by candidates with cPRA of 98% at the local level, followed by zero-antigen mismatched candidates, and former living donors) (Table 3.3). Although pediatric patients did not see an overall decline in the number of offers [28], the quality of the offers shifted [29].

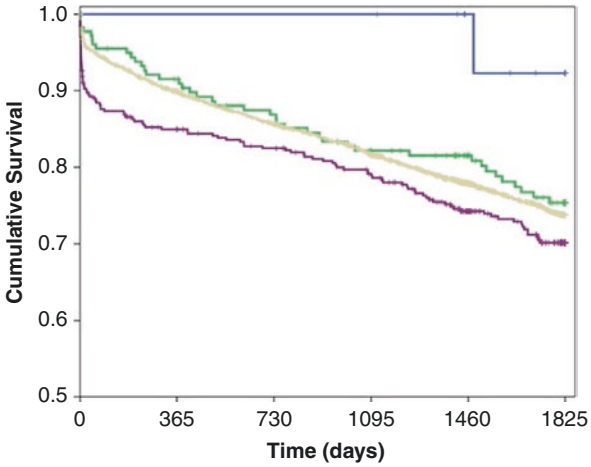

Fig. 3.1 Kaplan-Meier survival curves for child (<10 years old) donor kidneys from 2000 to 2010 based on KDPI. Blue: KDPI-A constituting 0.4%of all child donor kidneys, Kaplan-Meier 5-year survival of 92.3%. Green: KDPI-B constituting 4.6% of all child donor kidneys with a Kaplan-Meier 5-year graft survival of 75.4%. Tan: KDPI-C: constituting 84.8% of all child donor kidneys with a Kaplan-Meier 5-year graft survival of 73.7%. Purple: KDPI-D: constituting 10.1% of all child donor kidneys with a Kaplan-Meier 5-year graft survival of 70.2%. By the log rank test, no KDPI sequence had significantly different survival than any other. *P* values by log rank test are as follows: KPDI-A versus KPDI-B:$P = 0.111$, KDPI-A versus KDPI-C:$P = 0.082$, KDPI-A versus KDPI-D:$P = 0.05$, KDPI-B versus KDPI-C:$P = 0.599$, KDPI-B versus KDPI-D:$P = 0.146$, KDPI-C versus KDPI-D:$P = 0.071$ (Reproduced from Parker et al. (2016) and used with permission from John Wiley and Sons) [27]

3.4 The KAS Effect on Young Recipients

More than 5 years after the implementation of KAS, emerging data show it has improved transplantation rates in highly sensitized adults and improved racial disparities in adult allocation [30]. However, it has had an unintended negative impact on young pediatric recipients. The effect varies across regions but overall, pretransplant dialysis times are longer, transplant rates are decreased, and delayed graft function is increased (Fig. 3.2) [29, 31, 32]. Given the short time period, data do not show worse overall outcomes but many of the younger, more complex patients are still waiting for organs, and long-term data are not complete (reported at 2 years) [32]. The majority of the published data detail graft function and patient survival, but it is clear from studies on the impact of early transplant that more specific endpoints will need to be evaluated to appreciate the scope of the change. In analysis of 3777 deceased donor kidney transplants in pediatric recipients between 2006 and 2016, delayed graft function alone is associated with a 13% reduction in 5-year graft survival (Fig. 3.3) [29]. Increasing DGF is speculated to be secondary to a shift in the donor quality, specifically age [29]. From 2014 to 2016, young pediatric

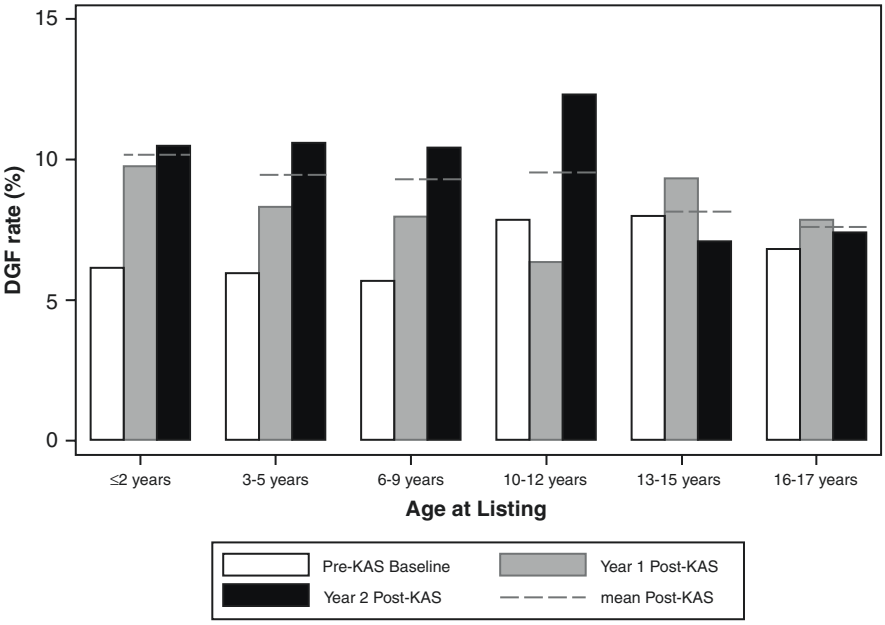

Fig. 3.2 Delayed graft function (DGF) rates pre-post KAS by age of listing for pediatric recipients (white = pre-KAS, gray = year 1 post-KAS, black = year 2 post-KAS, dashed line = mean post-KAS). Delayed graft function was defined by need for dialysis in the first week after transplant. Young pediatric recipients (<10 years old at listing) had DGF 5.96% of the time pre-KAS and 9.67% of the time post-KAS ($P = 0.024$). Older pediatric recipients (≥10 years old at listing had DGF 7.47% of the time pre-KAS and 8.28% of the time post-KAS ($P = 0.477$) (Reproduced from Parker et al. (2018) and used with permission from John Wiley and Sons) [29]

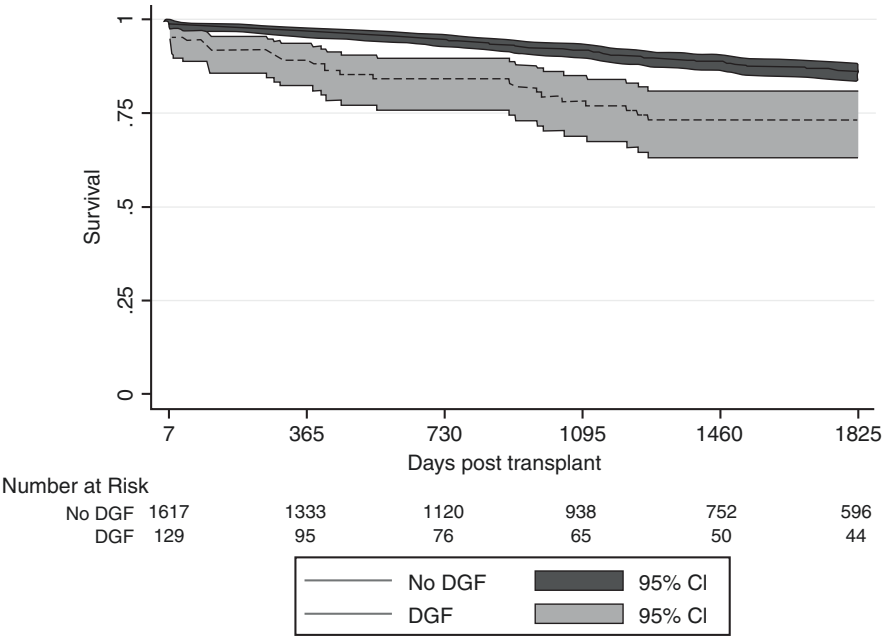

Fig. 3.3 Graft survival for young pediatric recipients by delayed graft function (DGF), 2006–2016. Kaplan-Meier survival estimates and 95% CI are displayed for each group. Grafts with DGF had significantly lower 1-year (89% vs 97%), 3-year (78% vs 92%), and 5-year (73% vs 86%) survival than grafts without DGF ($P < 0.01$ for all comparisons) (Reproduced from Parker et al. (2018) and used with permission from John Wiley and Sons) [29]

recipients received 34% fewer deceased donor kidneys from pediatric donors overall (32% pre-KAS and 21% post-KAS, $P < 0.01$) and a 76% decrease in deceased donor kidneys from young pediatric donors (7% pre-KAS and 1.7% post-KAS, $P < 0.01$) [29].

Young children who need pediatric kidneys may be even more severely disadvantaged. Improvements in neonatal dialysis have created a larger cohort of younger patients with end-stage renal disease with vascular complications. In addition, there are patients in this population who are hypercoagulable from nephrotic syndrome and others who have inherited thrombophilias [33], causing thrombosis in the vessels that are usually targeted for transplant. At Stanford University alone, since KAS, six young patients with inferior vena cava clots have been listed for whom a pediatric donor is the only technical option (Gallo, personal data). The pediatric donor is preferred in order for the venous outflow to be accommodated by the collateral pelvic venous system draining the pelvis and lower half of the body or the portal vein. In the current allocation system, emergency listing is often the only way to get a pediatric kidney allocated to a pediatric recipient because the KDPI of kidneys less than 10-year-old are routinely ≥35%. Even with emergency listing, the wait times are severely prolonged and during the wait time dialysis access is tenuous.

The pediatric transplant community has tried to adapt to the new donor pool and the logistics of the new allocation. Data suggest that acceptance practices are

different than in the pre-KAS era; in particular the acceptance rates of KDPI kidneys between ages 18 and 35 with a KDPI <35% have decreased [28]. The reasons for this practice change are not yet delineated, but decline reasons might help shed light on the discrepancy. Some in the transplant community are encouraging the use of a higher percentage of increased infectious risk donors and donors after cardiac death for pediatric patients [34, 35, 36]. The long-term outcomes of these practice changes are unknown because historically these kidneys were rarely accepted for children. Centers are also now publishing on the pediatric experience with en bloc transplants in order to provide more options for children; however, these kidneys will still infrequently be offered to children given that their KDPI ≥35 [37]. The use of the mechanical pump is also being evaluated to allow for longer cold ischemia times to avoid delayed graft function in situations where cold ischemic time is unpreventable.

3.5 Eliminating Donation Service Area

In 2019, a modification to the kidney and pancreas allocation system was proposed and accepted and projected to be implemented in December 2020. The change mimics the allocation policy revision for liver and intestinal transplant, which came into effect in February 4, 2020, where organ distribution occurs based on the distance of a recipient center to the donor hospital and not on whether or not the donor hospital is in a particular donation service areas (DSAs). This policy's mission was to eliminate the disparities that arise from discrepancies in size, shape, and population within the 58 DSAs in the United States. The statistical modeling behind the proposal suggests that the modification will reduce wait time variability across the country and increase transplant rates for certain groups of candidates. Pediatric recipients are a group targeted to benefit. Currently, pediatric patients are only offered kidneys from outside their DSA, when all local patients turn down a kidney first. The only exceptions are zero-HLA-mismatch or high PRA (99–100%) offers (Table 3.3). Therefore, the vast majority of children will only be eligible for quality kidneys within their DSA. If a DSA does not have a pediatric center or pediatric candidates listed, the kidney with a KDPI <35% will first be offered to an adult within that DSA. With the use of 250 nautical miles, instead of DSA boundaries, a particular donor with a KDPI <35% could reach a child in another DSA before an adult within the same DSA. The impact of this change on pediatric recipients will need to be studied after the policy is implemented.

3.6 Conclusion

Data show that young (prepubertal) children are more seriously harmed by prolonged dialysis time than their adult counterparts. To avoid the cognitive and growth harms that ESRD causes in prepubertal children, they need to be transplanted

quickly with well-matched high-quality kidneys to minimize threats to their quality of life and to help them achieve a full lifespan. To date, KAS has failed to properly consider its adverse impact on this vulnerable population.

There are a multitude of factors that must be considered to create a fair and efficient allocation system. It is important that UNOS is transparent about the ethical principles behind their decision to make changes and that they consider both intended and unintended (but anticipatable) consequences. Underlying principles and mathematical models should be discussed by a broad array of stakeholders to ensure that the modifications are designed to achieve their intended goals. This means re-evaluating how deceased donor kidneys are scored and to whom they are offered. It also may mean considering a major revamp to the entire algorithm or at least to the pediatric portion of the algorithm [27, 38].

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Donor-Recipient Size Mismatch in Pediatric Renal Transplantation

4

Min Hyun Cho

4.1 Cause of Donor-Recipient Size Mismatch

Many researchers have tried to confirm the characteristics of the ideal kidney donor for pediatric recipients and have suggested several considerations, including donor criteria, such as age and renal function, and degree of human leukocyte antigen (HLA) matching [1]. Donation after cardiac death or from donors with acute kidney injury can predispose the recipient to delayed graft function and a poorer long-term outcome. If the donor kidney is from a very young donor, graft thrombosis due to the small size of the anastomotic vessels can occur. In addition, kidneys from HLA- or ABO-mismatched donors are not actively recommended in pediatric kidney transplantation (KT) compared to adult KT because most pediatric recipients require re-transplantation [2]. Unfortunately, in order to meet these optimal kidney donor criteria for pediatric recipients, longer waiting times would be inevitable [3]. Therefore, kidneys from adult donors, rather than age- and size-matched pediatric donors, are utilized in most pediatric recipients, making donor-recipient size mismatch a common problem in pediatric KT.

The opposite donor-recipient size mismatch also happens, especially in adolescent patients receiving a kidney from a younger donor. Several studies have suggested that small-for-size renal transplants lead to poorer allograft function, probably due to glomerular hypertrophy and hyperfiltration-induced injury from nephron underdosing [4–9]. It recently was reported that a low donor-recipient body surface area (BSA) ratio (<0.9) or a donor-recipient weight mismatch exceeding 30 kg, with the recipient weighing more than the donor, is associated with an increased risk of graft loss [10, 11].

M. H. Cho (✉)
Department of Pediatrics, Kyungpook National University, School of Medicine, Daegu, South Korea
e-mail: chomh@knu.ac.kr

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This chapter primarily will discuss donor-recipient size mismatch between pediatric recipients and adult donors ("small recipient vs big donor").

4.2 Overcoming Hemodynamic Imbalance

There is a basic discrepancy in hemodynamic mechanism between the pediatric cardiovascular system and a kidney donated from an adult. Kidneys at rest receive one-fifth (20%) of the cardiac output [12]. For a healthy adult weighing 70 kg, resting cardiac output is about 5 L/min, and approximate blood volume is 5 L, meaning that an adult kidney receives roughly 500 mL/min of blood. On the other hand, the estimated blood volume of infants and children is about 75 and 80 mL/kg body weight, respectively. For an infant weighing 10 kg, estimated blood volume is about 800 mL. Therefore, a renal transplant from an adult donor needs more than 60% of an infant's whole blood volume for an effective renal blood flow. Consequently, donor-recipient size mismatch usually results in graft hypoperfusion and delayed graft function, which is further complicated by the significantly lower resting blood pressure of small children [3]. According to a previous report by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), infants receiving living donor adult-size kidneys have a 10% incidence of dialysis-dependent acute tubular necrosis (ATN) and poor graft survival rates, as ATN in the immediate postoperative period is a major independent risk factor for graft failure in infants and small children; adult recipients have an extremely low incidence of dialysis-dependent ATN [13]. However, several recent studies have revealed that adult-size kidneys can be transplanted to small pediatric recipients with excellent long-term outcomes, comparable to those of size-matched kidneys [14, 15]. In particular, based on data obtained from the Scientific Registry of Transplant Recipients, Lepeytre et al. reported that donor age exhibits a stronger association with graft survival than donor-recipient size mismatch, and that, consequently, younger donors may yield more favorable outcomes than older donors in size-mismatched KT [15].

The administration of large quantities of intravenous fluids or blood transfusions, as well as the concomitant use of inotropes, may be required to manage hypoperfusion caused by donor-recipient size mismatch [16]. It was reported that in infants with adult-size kidneys, aortic blood flow increases more than twofold; the increased aortic blood flow is sustained for at least 4 months after transplantation and appears to be driven by the blood flow demand of the adult-size kidney [17]. Sarwal et al. recommended the following protocol for long-term aggressive fluid maintenance, and all infants and small children who are recipients of an adult-size kidney have since been maintained for a mean of 9 months on assisted nasogastric/gastrostomy tube fluids at 3,000 ± 500 mL/m^2/day, with a mean sodium content of 10 ± 4 mEq/kg/day. Blood pressures were maintained in the 95th percentile for age until 6 months after transplantation to ensure adequate perfusion of the allograft [18]. Lee et al. suggested that the intraoperative administration of vasoactive agents and aggressive fluid resuscitation using crystalloids, albumin, and packed red blood cells is essential for successful outcomes in small pediatric recipients of adult-size

donor kidneys [19]. However, the management of this fluid status can also aggravate the burden on the cardiovascular system [1]. To maintain adequate renal perfusion as well as reduce the burden on the cardiovascular system in cases of donor-recipient size mismatch, Voet et al. suggested that cardiac output monitoring using transpulmonary thermodilution appears to be safe and leads to excellent renal results, with a trend toward a reduced use of fluids in favor of norepinephrine [20].

4.3 Surgical Techniques

The surgical technique utilized for an adult kidney transplant is similar to that used in pediatric patients with a body weight > 30 kg. In pediatric patients with a body weight of 10–30 kg, surgeons individualize the incision and allograft sites based on the child's anatomy. A midline intraperitoneal approach is usually utilized in small children with a body weight < 10 kg. Since the space between the peritoneum and the subcutaneous fascia is restricted, the kidney needs to be placed intraperitoneally, and the renal vein and artery of the graft are anastomosed to the recipient's inferior vena cava and aorta [21].

More recently, the extraperitoneal approach has increased in popularity, with one study suggesting that this new method has several advantages over the traditional procedure, including preservation of the peritoneal cavity for future dialysis, lower risk of bowel complications, and easier access for transplant biopsy [22]. In addition, any collections, such as postoperative abscesses, urinomas, and chyle leaks, would be self-contained in the extraperitoneal space and, therefore, more likely to be amenable to percutaneous drainage [23].

Vitola et al. reported a 62-patient study in which an extraperitoneal approach was used to perform KT in pediatric recipients weighing < 15 kg [24]. The researchers concluded that the extraperitoneal approach is practical for KT in small pediatric patients, offering favorable outcomes and an acceptable rate of complications, such as lymphoceles and renal artery thrombosis and stenosis. In a report from Japan, Muramatsu et al. also reported that there was no significant difference in 5-year survival rates between the extraperitoneal and intraperitoneal approaches in pediatric patients weighing < 15 kg who received a living-related donor kidney transplant and that both the intraperitoneal and extraperitoneal transplant approaches are acceptable for low-weight pediatric recipients of an adult-size kidney [25].

4.4 Graft Survival and Adaptation

Although there have been studies directly comparing graft survival and outcomes in children receiving kidneys from adult versus pediatric donors, there are conflicting data. The findings perhaps originate from various factors, including differences in operative experience, the presence of hypercoagulability, and donor age [3]. Some reports have shown a higher incidence of infection and vascular complications with pediatric donors [26]; conversely, other researchers have recommended that

pediatric donor kidneys be given to pediatric recipients because corrected glomerular filtration rate (GFR) and graft size growth were significantly higher in pediatric patients who had received a pediatric graft kidney [27]. Unfortunately, if this latter finding is right, a longer waiting list in pediatric patients with end-stage renal disease (ESRD) would be inevitable, owing to the scarcity of pediatric donors.

To resolve this confusion, Goldsmith et al. conducted a retrospective study of 1-year graft survival in two groups—recipients of weight-matched donor grafts and recipients of mismatched donor grafts. Finding no significant differences between the two groups, the researchers concluded that adult-size kidneys can be safely transplanted into small pediatric recipients [28]. Based on the results of 61 KT recipients weighing < 20 kg with five years of follow-up, Amesty et al. also reported that there were no significant differences in long-term GFR, proteinuria, rejection, and graft or patient survival of small pediatric recipients between adult donors and size-matched donors [14]. Interestingly, there is some literature on adaptive changes in mass and function after the transplantation of size-mismatched kidneys in pediatric recipients. Feltran et al. reported that graft volume and function increase in renal transplants with a low graft mass/recipient size ratio without an increase in proteinuria. At the other extreme, pediatric patients with a high graft mass/recipient size ratio show a reduction in graft volume and stable graft function [29].

There is one more point to consider here—the reliability of serum creatinine or estimated GFR calculated from serum creatinine in pediatric patients with a donor-recipient size mismatch. Theoretically, it is possible that the glomerular filtration potency of a kidney from an adult donor could be relatively higher than the body volume or muscle mass of the pediatric recipient, masking the elevation in serum creatinine from various causes of graft dysfunction, such as acute rejection, calcineurin inhibitor nephrotoxicity, and BK virus nephropathy, especially during the first posttransplant year. It has been reported that the decisive factor for graft-estimated GFR is the weight or BSA of the recipient, meaning that recipient metabolic demand is the most important determinant of graft function [30].

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Medical Evaluation of the Living Donor for Pediatric Kidney Transplantation

5

Fahima Mahir and Veronica Delaney

5.1 Introduction

The optimal and most cost-effective modality of kidney replacement therapy is kidney transplantation [1]. It provides superior patient outcomes and significantly more quality of life than dialysis for the treatment of end-stage kidney disease (ESKD). The demand for transplants continues to rise. The kidney waiting list is about six-fold greater than the number of transplants performed [2]. Increasing the available pool of grafts is becoming a necessity. Living donor transplantation is an ideal option due to increased waiting time across transplant centers in the United States (US) for deceased donor transplantation and superior graft and patient survival [1, 2].

The purpose of the living donor evaluation is to minimize short- and long-term risks after donation, in particular the development of kidney failure requiring dialysis or transplantation [3]. Postdonation risk depends on predonation demographics and health characteristics, and so it is imperative to identify any conditions that may increase the risk of developing CKD or ESKD. Due to the lack of large and long-term prospective studies in the field of living kidney donation evaluation, there is uncertainty surrounding long-term outcomes after donation, especially for young donors who have more life years ahead of them to develop ESKD or complications of donation. Studies comparing living donors to similarly screened healthy non-donors have shown an increased risk of ESKD, although the magnitude of absolute risk was small [4], and increased cardiovascular and all-cause mortality in living donors [5]. Expert work groups have established guidelines to aid the transplant community to better assess the living kidney donor candidate. These guidelines describe postdonation risk with regard to a single predonation characteristic in

F. Mahir (✉) · V. Delaney
Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mt. Sinai, New York, NY, USA
e-mail: fahima.mahir@mountsinai.org; veronica.delaney@mountsinai.org

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isolation and do not consider risk in the context of multiple predonation characteristics assessed together [3, 6, 7]. The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) has proposed a more comprehensive approach to postdonation risk evaluation [3]. The guideline encourages an integrative risk-based approach in which the donor candidate's demographic and health characteristics are assessed together rather than individually to determine the overall postdonation risk, as well as risks attributable to donation. The guidelines encourage transplant centers to develop quantitative thresholds of acceptable risk for each postdonation adverse outcome and to apply these thresholds consistently across all donor candidates.

We will consider the most important parameters commonly evaluated in the donor selection process, with a focus on the 2017 KDIGO guidelines and maintaining an integrative risk-based approach to the medical evaluation.

5.2 Donor Age

Living donor candidates must be adults. The minimum age at some centers for donation is 21 years old, whereas other centers may accept candidates as young as 18 years old. There is no upper limit for donors in terms of age; however, candidates of advanced age may have other medical comorbidities that exclude them from donation.

In addition, advanced age must be integrated and assessed in combination with other factors, especially the predonation glomerular filtration rate (GFR) [6]. Unilateral nephrectomy decreases GFR by 50%, but the compensatory response by the contralateral kidney limits the decrease to 30% of the predonation GFR 1 year after donation [8–10]. The aging process may diminish compensatory hyperfiltration and decrease postdonation GFR. In donor candidates of advanced age, it is essential to accurately assess predonation GFR. GFR measured using iothalamate may complement 24-hour urine collection [8].

5.3 Kidney Function

Evaluation of the GFR is essential to the living donor screening process. A sufficient GFR is necessary to rule out the presence of kidney disease and ensure an adequate postdonation GFR that affords the donor normal renal function after donation.

Recommended methods for evaluating GFR are based on the 2012 KDIGO Chronic Disease Guidelines [2]:

- Estimate glomerular filtration rate (GFR) using serum creatinine-based estimating equations.
- Confirm GFR with one or more of the following based on availability: measured GFR using an exogenous filtration marker, measured creatinine clearance, estimated GFR from the combination of the serum creatinine and cystatin C, or repeat estimated GFR from serum creatinine.

Candidates with a GFR of 90 mL/min per 1.73m^2 or greater should be considered acceptable for kidney donation, while donor candidates with a GFR less than 60 mL/min per 1.73 m^2 should not donate. The decision to approve donor candidates with GFR between 60 and 89 mL/min per 1.73 m^2 should be individualized based on prediction of long-term ESKD risk.

All donor candidates must be counseled that the risk of developing kidney failure requiring treatment with dialysis or transplantation is higher as a result of donation; however, the magnitude of the absolute risk is low [5, 6].

5.4 Hypertension

Hypertension is a known cause of chronic kidney disease, and loss of kidney function may accelerate the rise in blood pressure over time in the setting of uninephrectomy. In addition, hypertension can reduce the renal reserve and limit compensation postdonation.

The exact risk for the development of hypertension attributable to donation is difficult to assess due to the lack of controlled studies and prolonged follow-up. Some studies have suggested there is an increased risk of hypertension after donation [11, 12, 13].

Per KDIGO guidelines, blood pressure evaluation should be based on measurements taken on at least two occasions prior to donation. Donor candidates with hypertension that can be controlled to less than 140/90 mmHg using one or two antihypertensive agents, and do not have evidence of target organ damage, may be acceptable to donation.

For donor candidates in whom the presence of hypertension is unclear based on history and clinic measurements, ambulatory blood pressure monitoring should be obtained for further evaluation.

Most centers consider uncontrolled hypertension or hypertension with target organ damage (i.e., proteinuria, albuminuria, left ventricular hypertrophy, and hypertensive retinopathy) as absolute contraindications to living donation.

Donor candidates must be counseled that blood pressure may rise with aging, and donation may accelerate the need for antihypertensive treatment over that expected with normal aging.

5.5 Diabetes and Glucose Abnormalities

Compared to Type I diabetes, which is an absolute contraindication to kidney donation, Type II diabetes is not an absolute contraindication to living kidney donation, although many centers will not consider these individuals.

The presence of impaired fasting glucose or impaired glucose tolerance increases the risk for diabetes by 5–10% per year depending on ethnicity and family history [14]. Among US transplant centers, there has been an increase in acceptance of living donor candidates with glucose abnormalities despite the correlation between

prediabetes and subsequent development of diabetes. This is significant because hyperfiltration in the setting of uninephrectomy is known to contribute to progression of diabetic kidney disease.

Donor candidates with prediabetes and diabetes must be assessed looking at the global cardiovascular risk and the risk of developing diabetes. Available data do not suggest a high risk in the short- and long-term follow-up for low-risk prediabetic donors [15]. While the risk for donors of developing diabetic kidney disease is low, a recent study identified Type II diabetes as a leading cause of late postdonation ESKD [16].

According to the 2017 KDIGO guidelines, a 2-h glucose tolerance test or hemoglobin A1c should be performed in donor candidates with elevated fasting blood glucose, history of gestational diabetes, or family history of diabetes in a first-degree relative.

Donor candidates with prediabetes and diabetes must be counseled that their condition may progress over time and may lead to end-organ complications.

5.6 Obesity

In parallel with trends in the general US population, the mean body mass index (BMI) of donors has increased with the proportion of living donors with a BMI greater than 30 kg/m^2 approximately 23% [2]. Obesity is strongly correlated with an increased risk for CKD and/or proteinuria. It is also an additional metabolic risk factor for diabetes and hypertension that increases the risk of developing postdonation CKD and/or proteinuria [17, 18].

Assessing these patients is challenging because the BMI cutoff above which donation is no longer safe is unknown.

5.7 Proteinuria

Microalbuminuria is an established risk factor in the progression of nephropathy and increased cardiovascular risk in the general population [19, 20].

Based on recommendation from the KDIGO 2012 CKD guidelines:

- Assess albuminuria using albumin-to-creatinine ratio in an untimed urine specimen.
- Confirm albuminuria with albumin excretion rate (AER) in a timed urine specimen or by repeating the albumin-to-creatinine ratio if the AER cannot be obtained.

Urine AER less than 30 mg/d should be considered acceptable for kidney donation.

Donor candidates with urine AER greater than 100 mg/d should not donate.

The decision to approve donor candidates with AER 30 to 100 mg/d should be individualized and based on the prediction of the long-term ESKD risk.

5.8 Hematuria

A common definition for persistent microscopic hematuria is greater than two to five red blood cells on high-power field on two to three separate occasions that is unrelated to exercise, trauma, sexual activity, or menstruation. A positive dipstick does alone does not define microhematuria, and evaluation should be based on findings from microscopic examination of the urinary sediment. The presence of hematuria is abnormal and should always be evaluated when found a donor candidate.

The evaluation can help to determine if the hematuria is due to a reversible cause (urinary tract infection, nephrolithiasis), a malignancy affecting donor health and/or disease transmission, or glomerular disease that may be associated with an increased lifetime risk of ESKD.

Testing should include a urinalysis and urine culture to assess for infection, cystoscopy and imaging to screen for urinary tract malignancy, 24-hour urine stone analysis, and/or kidney biopsy.

Candidates with hematuria from a reversible cause that resolves may be acceptable for donation. Donor candidates with IgA nephropathy or Alport's syndrome should not donate. Donor candidates with thin basement membrane disease with normal blood pressure and kidney function appear to be acceptable donor candidates [21, 22].

5.9 Kidney Stones

Evaluation of past asymptomatic and symptomatic stones in a living donor candidate is important due to the high risk of acute kidney injury (AKI) as well as the high prevalence of stones in donors [21]. The risk for developing a kidney stone after living kidney donation in donors who did not have a stone history is the same for selected non-donors. One or more episodes of stones have been associated with twofold higher risk for ESKD [8].

Evaluation with imaging and biochemical studies in case of current or prior stones is recommended to assess the risk of recurrence.

Major metabolic disorders and/or bilateral kidney stones are considered contraindications for donation. Donor candidates with past or current kidney stones with no or minor disorders can be considered for donation despite lack of evidence regarding outcomes.

The affected kidney for accepted donations should be used to protect the donor from obstructive AKI.

5.10 Malignancy

Cancer screening should be performed per local guidelines.

Screening is necessary to identify cancers that require management to protect the health of the donor candidate. Decreased kidney function may compromise long-term health outcomes in individuals requiring cancer treatments with nephrotoxic or cardiovascular side effects. Evaluation also reduces risk of transmission from the donor to the recipient.

Cancer screening should be current at the time of donation.

Donor candidates with active malignancy should be excluded. In some cases of active malignancy with low transmission risk, a donor may be considered with a clear management plan and minimal donor health implications. Donor candidates with a history of treated cancer that has a low risk of transmission or recurrence may be acceptable candidates.

5.11 Screening for Transmissible Infections

Screening for infections identifies illness that may require management and helps to prevent transmission to the recipient.

Screening tests for the following infections should be obtained predonation:

- Human immunodeficiency virus.
- Hepatitis B virus.
- Hepatitis C virus.
- Cytomegalovirus.
- Epstein-Barr virus.
- *Treponema pallidum* (syphilis).
- Urinary tract infection.
- Other potential exposures based on geography and environmental exposures.

5.12 Psychological Issues

Donors must be cleared psychologically and must have a living donor advocate. Lack of coercion should be established by the donor evaluation team.

5.13 Conclusion

Living kidney donation is a critically important part of kidney transplantation, especially for pediatric patients. The evaluation of the living donor must be comprehensive to ensure that the donor has the lowest possible incidence of medical and psychological complications postdonation.

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Surgical Management of the Pediatric Renal Transplant Patient

6

Dagny von Ahrens and Ron Shapiro

6.1 Introduction

Surgical management in pediatric kidney recipients varies according to the size of the recipient. Teenage patients over 30 kg will behave surgically much like small adult patients. Infants and young children between 9–10 and 20 kg will require a different surgical approach, requiring vessel anastomoses to larger recipient vessels. Older children between 20 and 30 kg will fall somewhere in between.

6.2 Timing of Transplantation

Indications for transplantation according to the Pediatric Committee of the American Society of Transplantation include symptoms of uremia not responsive to standard therapy, failure to thrive because of limitations in total caloric intake, delayed psychomotor development, hypervolemia, hyperkalemia, and metabolic bone disease because of renal osteodystrophy [1]. Time on dialysis has been shown to be an independent risk factor for transplant outcomes; however, dialysis should not be avoided if it will mitigate surgical risk due to electrolyte abnormality or volume status [2]. Many pediatric centers prefer a recipient weight of >10 kg to minimize the risk of vascular thrombosis and to accommodate the larger adult-sized kidney [3]. A multicenter retrospective case-controlled cohort study of infants weighing

D. von Ahrens
Albert Einstein College of Medicine, Abdominal Transplant Surgeon, Montefiore Einstein Center for Transplantation, Montefiore Medical Center, Bronx, NY, USA
e-mail: Dagny.Vonahrens@mountsinai.org; Dvonahr@montefiore.org

R. Shapiro (✉)
Mount Sinai Hospital Recanati/Miller Transplantation Institute, NY, USA
e-mail: ron.shapiro@mountsinai.org

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<10 kg versus 10–15 kg did, however, show good long-term outcomes, with comparable patient and graft survival as well as vascular complications [4]. Recipient size of 10–20 kg was protective in a large cohort study for 10-year graft survival, presumably due to large graft size and nephron "dose" [2].

6.3 Donor Selection

Size matching is potentially a challenge, as both small and large grafts can pose risks. Smaller vascular anastomoses are at higher risk for graft thrombosis [5]. Large grafts, however, can be a challenge in small recipients to create enough space for a secure tension-free fascial closure and to minimize the risk of abdominal compartment syndrome, itself a risk factor for graft thrombosis [6]. Pediatric donors can be used, but depending on donor size, en bloc grafts should be considered for donors <20 kg; in practice, en bloc kidneys have been used uncommonly in pediatric recipients and, if they are used, should be transplanted into older children, at least 8–10 years of age. The most recent data indicate that older donors (age 35–40) had similar graft survival, although a younger teen age or adult donor is generally preferred [2]. Donors over 40 years of age would generally be limited to living donors, usually parents.

6.4 The Operation

Preoperative workup should include a thorough update of the history and physical with particular attention to ensure that recipients are free of infection. Many pediatric patients are transplanted for urologic abnormalities and have a risk of UTI at baseline. Crossmatch should be up to date, and donor and recipient EBV/CMV serologies should be assessed preoperatively. Electrolytes and volume status should be assessed, as well as the potential need for dialysis; however, hypovolemia should be avoided to minimize the risk of graft thrombosis and hypotension with anesthesia and reperfusion. A large graft in a small recipient requires adequate volume to perfuse the patient and the graft. Significant hypotension can be encountered due to the increased volume of the donor kidney, so close communication with the anesthesia team should be maintained throughout the case. Minimizing blood loss as a basic operative principle holds true in children, but transfusion may be required simply due to a large graft which can sequester a large percentage of the recipient's blood volume. Steroids are typically administered at the beginning of the case prior to induction immunosuppression. Mannitol and Lasix are given during the implantation of the kidney to facilitate diuresis and scavenging of reactive oxygen species accumulated during clamping and cold time.

6.5 Incision and Graft Placement

In the adult and larger adolescent patients, a "hockey stick," Gibson, or Rutherford Morison incision is typically made to expose the retroperitoneum. The incision can be extended up to the costal margin to accommodate a larger graft. In smaller children (<20–30 kg), a midline incision may be preferable for a transperitoneal approach to allow enough space for the allograft and vessels to lie without pressure or kinking. Surgical preference is variable; some surgeons will always place the kidney in the retroperitoneum, even in 10 kg infants. Consideration of venous outflow of the bowel during the operation should be considered and may require a larger incision to allow for exposure [7]. If the aorta and IVC are used for anastomosis, the kidney is placed on the right after mobilization of the right colon and cecum. The graft may or may not need to be secured to the abdominal wall, as the bowel overlies and protects it. Again, this is to some extent a function of surgical preference, as torsion of an intra-abdominal kidney is possible in an active pediatric patient posttransplantation.

6.6 Vessels

The renal artery and vein are typically implanted in teenagers and adults at the level of the external iliac artery and vein. Small pediatric patients will generally require vascular anastomoses at the level of the common iliac vessels or the aorta and inferior vena cava. Partial clamping is preferable using a side-biting clamp if vessel caliber allows, although surgical preferences vary. Recipient vessels and small or young donor vessels can have a tendency for spasm, so liberal use of verapamil or papaverine with close communication with anesthesia can improve graft perfusion. Consideration of antiplatelet or systemic anticoagulation intra- or postoperatively can be assessed on a case-by-case basis by vessel size, quality, and underlying risk for thrombosis but is not required on a routine basis; that said, routine use of low-dose aspirin is common in most transplant programs for both pediatric and adult patients. Small caliber vessels may need to be anastomosed in an interrupted fashion, and renal artery and vein length should be relatively short to prevent graft thrombosis; again, surgical preference will play a big role in these decisions.

6.7 Native Nephrectomy

At times, if native kidneys have severe hydronephrosis or have been chronically infected, concomitant native nephrectomy should be considered and is typically accomplished through a transperitoneal midline approach. This decision will have been made pretransplantation by the pediatric nephrologist and the surgeon.

6.8 Ureteral Implantation

On occasion, patients have undergone prior urologic interventions including ureteral reimplantation or bladder augmentation. Preoperative planning should consider the possibility of scar tissue or altered anatomy. Postoperative planning should be discussed with the patient and/or family if continued intermittent catheterization will be needed in the case of neurogenic bladder. An intraperitoneal kidney can still have a retroperitoneally placed ureter and bladder to minimize postoperative bowel complications. A tunneled Lich-Gregoir is typically performed with 6–0 Maxon or PDS suture to prevent vesicoureteral reflux (VUR). Placement of a stent to protect the ureteroneocystostomy is often surgeon and center dependent; some surgeons always leave a stent for several weeks, some never do, and some do so on a case-by-case basis. Cystoscopic stent removal is generally straightforward and is performed under general anesthesia for pediatric patients. Bladder capacity has been shown to increase significantly after transplantation, even in atrophic bladders. Although an atrophic bladder is an independent risk factor for posttransplant reflux, the incidence is low, and a recent study suggested no difference in renal function at 5 years [8]. In the case of en bloc grafts, the ureters may be syndactylized (partially anastomosed) or implanted individually.

6.9 Postoperative Management

Careful fluid, electrolyte, and blood pressure management are required postoperatively to account for increased volume of distribution, variable graft function, and concentrating ability. Adequate perfusion of the graft is imperative, and high urine output should be replaced diligently; however, significant volume overload can lead to risks of abdominal compartment syndrome, and graft thrombosis [9]. Respiratory and acid-base status should be carefully monitored, and need for diuresis assessed on an hourly basis in the early postoperative period. Intra-abdominal placement of a graft can lead to postoperative ileus due to intra-op bowel manipulation, so bowel function and abdominal distention should be monitored by the surgical team. Permissive hypertension should be allowed for graft perfusion and managed judiciously. Glycemic control in the setting of postoperative stress, steroid administration, and osmotic diuresis should also be managed carefully. Graft ultrasound should be obtained postoperatively to assess for perfusion, hydronephrosis, and collections which may include hematoma, lymphocele, or urine leak. An extraperitoneal graft can be more susceptible to compression from a moderate-sized collection, whereas an intraperitoneal fluid collection may go unrecognized due to a larger space for fluid to accumulate. Thus, these complications should be considered if a sudden drop in urine output or hemoglobin is encountered. If a surgical drain is placed intraoperatively, fluid can be assessed if a lymphocele, urine leak, or bleed is suspected.

Depending on the institution, most pediatric renal transplant recipients will be managed initially in the pediatric intensive care unit postoperatively. When the patients have stabilized over the first few days, they may be transferred to the floor. They may be discharged once taking adequate po fluids and having bowel function, and adequate patient/parent/guardian teaching has taken place. Careful attention should be paid to emphasizing adherence, and any medication administration challenges should be addressed prior to discharge.

6.10 Conclusions

Surgical implantation of a kidney in a pediatric patient requires attention to the size of the recipient and demands perfect technique and excellent communication with the anesthesia team, the pediatric nephrology team, and the ICU team. Routine success can be obtained with careful attention to the details of the individual patient.

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7 Management of the Pediatric Renal Transplant with Posterior Urethral Valves for Successful Transplantation

Eric Bortnick and Jeffrey A. Stock

7.1 Introduction, Epidemiology, and Clinical Presentation

Posterior urethral valves (PUV) are obstructing membranes within the lumen of the urethra that extend distally from the verumontanum. Occurring only in males, PUV are the most common cause of congenital bladder outlet obstruction in infants that can result in a spectrum of damage to both the lower and upper urinary tract. With an incidence estimated to be approximately 1 in every 5000–8000 male infants, PUV are the number one congenital cause of renal failure and renal transplantation in the pediatric population.

With the modern use of prenatal imaging, many PUV patients are found on prenatal ultrasound, with studies ranging in antenatal diagnosis rates of 37–53% [1, 2]. Features indicative of PUV on prenatal ultrasound included a distended, thick-walled bladder with a dilated posterior urethra (often referred to as a "keyhole sign"), hydronephrosis, and potentially oligohydramnios. If not detected on prenatal imaging, postnatal diagnosis may be made immediately after birth or years later depending on the degree of obstruction. Immediate postnatal respiratory distress may be present if severe oligohydramnios was present prenatally, as this leads to pulmonary hypoplasia, the most common cause of death in the postnatal setting. Postnatal infants may also present with severe sepsis and azotemia owing to the renal dysplasia present from the long-standing obstruction. In the patient with the less severe obstructing membrane, diagnosis may be made in the neonatal period by palpating an abdominal mass (a distended bladder), or later in childhood as a presentation of voiding dysfunction.

E. Bortnick
Pediatric Urology Fellow, Boston Children's Hospital, Boston, MA, USA

J. A. Stock (✉)
Pediatric Urology, Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: jeffrey.stock@mountsinai.org

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Initial management in the neonate includes catheter placement immediately after birth in patients diagnosed prenatally to aid in urinary drainage. This is subsequently followed by surgical intervention with cystoscopy and valve ablation so as to restore flow of urine through the urethra and enable normal filling and emptying of the bladder. Advances in technology and surgical equipment have made this possible for smaller sized infants, though the surgical option of vesicostomy for urinary diversion still exists for those patients too small for a cystoscope to pass through the urethra.

7.2 Pathophysiology of Renal Dysfunction in ESRD

The initial obstruction caused by PUV during fetal development leads to a wide variety of downstream effects on the lower and upper urinary tract that can persist after birth and worsen as the child grows. As a result of the obstruction, the bladder wall hypertrophies, leading to higher voiding pressures that help to maintain complete bladder emptying. These increased voiding pressures lead to remodeling of the bladder wall musculature, further increasing voiding pressure. As emptying begins to fail due to excessive remodeling, higher post-void residuals remain, and poorly contracting bladders lead to increased upper tract dilation.

The increase in intravesical storage pressures leads to increased pressure on the ureter, renal pelvis, and ultimately the renal parenchyma and nephrons. This increased pressure causes architectural and functional changes. Renal dysfunction is due to two etiologies—renal dysplasia and obstructive uropathy. Irreversible dysplastic changes occur during fetal obstruction and persist at term even after the obstruction is relieved. It is this renal dysplasia that leads to worsening renal function over time and potentially the eventual need for transplantation.

7.3 Risk Factors for End-Stage Renal Disease in PUV

End-stage renal disease (ESRD) in patients with PUV is common, with a lifetime prevalence of 20–50%. Despite immediate treatment with urethral catheter placement in the neonatal setting and even some prenatal treatments, nothing has been shown to protect against the further development of ESRD. One of the strongest risk factors for ESRD in children with PUV is the nadir creatinine. A serum creatinine greater than 1.2 mg/dL at 1 year of age predicts a high risk of ESRD, while a creatinine less than 0.8 mg/dL portends minimal risk. Nadir serum creatinine at 1 year is more predictive than nadir serum creatinine at 1 month.

Age at diagnosis of PUV has been mentioned as a potential risk factor for development of ESRD, with the hypothesis that earlier diagnosis is linked to earlier treatment, improved outcomes, and a lower incidence of ESRD. A contrasting hypothesis that late presentation is better is based off the assumption that those who present later have a milder form of the disease. As expected, research studies on this topic have been mixed. In one study of 315 patients with PUV, those who were diagnosed

prenatally were less likely to develop chronic kidney disease at a mean follow-up of 5.5 years compared to those were diagnosed postnatally [3]. In contrast, a review in 1988 found that 41% of those presenting before 1 year of age had poor long-term renal function compared to only 15% of those presenting after 1 year [4].

Renal dysplasia, with or without vesicoureteral reflux, recurrent urinary tract infections, and bladder dysfunction have also been shown to be risk factors for future ESRD. As available imaging techniques have improved and become more widespread, renal sonography and nuclear scintigraphy have given information on how to quantify renal dysplasia. Hyperechogenic kidneys, cystic changes in the cortex, and loss of corticomedullary differentiation signify a poor prognosis.

7.4 Preoperative Workup/Evaluation

Renal transplant in patients with PUV presents a unique and challenging scenario. As a result of the valves and their sequela, the urinary bladder is usually thick-walled, poorly functioning, and/or hypercontractile. In addition, as a result of the poorly functioning bladder and high intravesicular pressures, the ureters can be hydronephrotic due to vesicoureteral reflux. Therefore, it is imperative that the appropriate workup is done to monitor bladder function prior to transplantation. The goal is to ensure that the two primary functions of the bladder are working appropriately: storage of urine at adequate capacity with storage pressures less than 35 cm of water and emptying completely and reliably.

Videourodynamics should be performed on patients with a history of bladder issues prior to performing transplantation. This study helps to determine the function of the bladder, specifically the filling, storage, and voiding pressures as well as the contractile function. If abnormal, the patient can be started on overnight catheterization or clean intermittent catheterization in an attempt to help the bladder regain normal function and optimize the bladder for transplantation. Clean intermittent catheterization can also be performed though a continent catheterizable stoma (e.g., a Mitrofanoff appendicovesicostomy) if already present or if spontaneous voiding is not possible. In the case of an anuric patient, if the bladder was functioning well prior to the development of ESRD, it should function well after the transplant; bladder function can also be tested with bladder cycling. Pretransplant nephrectomy is rarely indicated and is usually reserved for severe proteinuria or polyuria.

For patients with poorly functioning, low-capacity bladders with unsafe storage pressures, an augmentation cystoplasty may be considered. While different surgical options exist for bladder augmentation, the most common method is an enterocystoplasty with either the small bowel or colon. The goal of this procedure is to create a low-pressure, compliant reservoir in order to protect the upper urinary tract and restore a functional lower urinary tract. Studies have not shown a difference in outcome between performing augmentation in a separate procedure prior to renal transplant and at the time of the transplant. It is safe to perform renal transplantation in patients with augmentation or conduits, and studies have shown that it does not

negatively affect survival outcomes. In a 2014 single institution retrospective review by Lopez Pereira et al., 12 patients with PUV and augmentation cystoplasty who underwent renal transplantation were compared to a cohort of 24 patients with PUV and no augmentation cystoplasty who underwent renal transplantation. The 10-year graft survival rate was not different between the two groups, and graft function at the end of the study was similar. The rate of urinary tract infection was significantly higher in the augmented group, and in those patients with more than three recurrent UTIs, noncompliance with CIC was a cause in 40%. The UTI incidence was not affected by whether CIC was performed through urethra or Mitrofanoff conduit [5]. A recent review by Marchal et al. in 2020 came to a similar conclusion. One hundred twelve patients with lower urinary tract malformation who underwent renal transplantation (49 of which were PUV) found that while enterocystoplasty and continent urinary diversion exposed grafts to more frequent episodes of graft pyelonephritis, patient and graft survival rates at 10 years were similar to those who had kidney transplants with ureteral implantation into the native bladder [6].

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RISE to Transition: A Structured Transition Protocol for Renal Transplant Recipient

8

Rupesh Raina, Zubin Mahajan, and Ronith Chakraborty

8.1 Introduction

Pediatric patients after renal transplantation experience numerous challenges when they reach adolescence and initiate self-management of their disease [1]. They are expected to learn how to direct their insurance and adhere to their appointments and medications among other responsibilities previously managed by their parents or providers [1]. Additionally, this transition phase overlaps their period of high-risk behavior on account of psychosocial and cognitive development [2–4]. Furthermore, the normal adolescent tendencies of testing independence and questioning of authoritative figures predispose them to reject medical advice and treatment. Medication non-adherence due to above stated factors contribute to a 20% greater risk of graft failure in this age group as compared to adults [5]. These findings prompt requirement of an appropriate transition protocol to transfer care from pediatric to adult providers.

The American Academy of Pediatrics describes transition as a process "to maximize life-long functioning and potential through the provision of high-quality, developmentally appropriate health care services that continue uninterrupted as the individual moves from adolescence to adulthood" [6]. The concept of transition

Rupesh Raina and Zubin Mahajan contributed equally with all other contributors.

R. Raina (✉)
Department of Nephrology, Akron General Medical Center at Cleveland Clinic Foundation, and Akron Children's Hospital, OH, USA
e-mail: rraina@akronchildrens.org; raina@akronnephrology.com

Z. Mahajan · R. Chakraborty
Department of Nephrology, Cleveland Clinic Akron General/Akron Nephrology Associates, Akron, OH, USA

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Table 8.1 World Health Organization (WHO) classification of factors contributing to non-adherence

Patient factors	Healthcare factors	Disease-related factors	Therapy-related factors	Socioeconomic factors
Age < 24	Insurance	Diagnosis	Side effects	Socioeconomic status
Patient knowledge	Organization of care	Disease severity	Number of doses/day	Family support
Patient education	Culture of care	Disease progression	Number of medications	Family structure
Cognitive ability	Poor communication		Complex regimen	Race
Mental status			Cost of medications	Culture
				Social support

originated in 1990 and is gaining increasing consideration over the past few decades [2]. The main goal of transition care is to establish self-reliant adult medical care. This requires transitioning patients to have a comprehensive understanding of their medical condition, its associated complications, and treatments.

Multidisciplinary transition teams and dedicated transition clinics aid to address the majority of the transition complications. However, the financial cost and organization of all teams in a single hospital unit limit the establishment of such transition clinics [7]. Adherence may be defined as the extent to which patients can follow recommendations for prescribed treatment [8, 9]. For renal transplant recipients, the term adherence simply refers to their successful management of immunosuppressive medication. There are no universal recommendations for assessment of adherence, but it can be evaluated using patient's report, medical team collateral report, and drug assays [10–12]. The factors contributing to non-adherence depend on the patient, healthcare, socioeconomic status, disease, and treatment. The World Health Organization classifications of these factors are provided in Table 8.1.

8.2 Problems of Transition and Consequences of Non-adherence to Transition

The Scientific Registry for Transplant Recipients reported a 5-year allograft survival rate in adolescents of 55% and 72% for deceased and living donors, respectively [13]. It has been demonstrated that 43.8% of adolescent patients were non-adherent to all the stages of transition as compared to the 22% of pediatric patients younger than the adolescent age group indicating that the adolescent population are at a greater risk for non-adherence [4]. The components of adherence to a treatment regiment are provided in Table 8.2 and the consequences of non-adherence

Table 8.2 Components of adherence to treatment

Components of adherence to treatment regimen	
Pharmacological	Non-pharmacological
Drug adherence	Scheduling clinical appointments
Dosage adherence	Completing blood work
Timing adherence	Returning provider calls
Duration adherence	Proper diet and exercise
Not skipping doses	Avoid alcohol, smoking
Collecting prescriptions from pharmacy	Avoid high-risk behavior

may be broadly classified into clinical and economic consequences. Clinical consequences can be examined by estimating the effect of non-adherence on clinical outcomes or by retrospectively observing for causes of acute rejections or graft losses. Lack of adherence is accountable for 50% of graft failure cases in adults and additionally, accounts for high graft failure rates in adolescents between 17 and 24 years [5, 14, 15]. Several studies show that 14.4% of the grafts lost in pediatric renal transplant recipients and 23.2% of the late acute rejection episodes were attributed to lack of adherence [16–22]. Eighteen studies estimated the contribution of non-adherence in the etiology of graft losses and acute rejections, attributing up to 64% of the graft failures [23–27] and 80% of the delayed acute rejections [28, 29]. In addition to its detrimental impact on health, non-adherence also has some economic consequences. According to the 2009 annual United States Renal Disease System (USRDS) data, the estimates of annual healthcare system costs for adherent kidney transplant recipients were $16,844 (USD) versus $82,765 for a patient with graft failure and $70,581 for a dialysis patient [30].

8.3 Transition Process in Various Studies and Challenges of Transition

Transition from pediatric to adult care provider is a challenging time period in the life of an adolescent (Table 8.3). Adolescents face difficulties adjusting with their emotional needs in addition to keeping pace with the transition process [1]. They are expected to independently schedule their appointments and demonstrate adherence to posttreatment routines. In addition, they are expected to recognize the requirement to seek medical attention in urgent or emergent circumstances and should be well versed with all their medications, dosages, time of administration, side effects, and reason for their use. They should also display the ability to refill medications and be consistent with laboratory testing as per recommendations of the healthcare provider [2–4].

Table 8.3 Challenges encountered by adolescents during transition

Challenges encountered by adolescents during transition process
• Autonomously scheduling appointments and attending clinics
• Demonstrating adherence to post-transition procedures
• Identifying when and how to pursue urgent/emergent medical therapy
• Recognizing all medications: Name, dosing, administration times, side effects, and reason for their need
• Being able to refill medications
• Being able to change medication doses over the phone
• Comprehending the cause of their organ failure and the need for transplant
• Completely appreciating their medical history
• Being able to describe the short- and long-term consequence of treatment, e.g., cancer surveillance, reproductive health/pregnancy/sexual activity, infection prevention
• Being able to discuss potential complications with medical team
• Maintaining consistency with routine blood work
• Adolescents with chronic medical illness are vulnerable to experience anger, aggression, hyperactivity, and internalizing symptoms such as depression, anxiety, social withdrawal, and blunt affect with loss of self esteem
• These adolescents are prone to vulnerable child syndrome, school phobia, body over-concern, or professional underachievement

Multiple studies have assessed the state of transition from pediatric to adult care (Table 8.4) [31–45]. A study conducted by McQuillan et al. exhibited that the use of a proper transfer clinic is associated with a better treatment adherence and long-term outcomes in renal transplant patients [33]. Weitz et al. conducted a retrospective study to evaluate the use of transition programs and concluded that the mean decline in estimated GFR in the transition group was −11.3 ± 44 (−6) in comparison to the mean decline of the control group which was −28.4 ± 33 (−23.3). This demonstrates that the reduction in estimated GFR of transplant patients in the transition group was lower in comparison to the control group, indicating better graft survival with use of transition programs [31]. Similarly, a study conducted by Harden et al. displayed that use of a joint pediatric-adult clinic was associated with 0% graft losses in comparison to the 67% graft loss in the control group [45]. Prospective studies have shown parallel results as well. A prospective study by Prestidge et al. showed that 24% patients in the control group had graft failure, whereas 0% died or had graft failure in the transition group [39]. However, a prospective study conducted by Pape et al. demonstrated that use of a transition clinic was not associated with any short-term benefits on graft survival and outcome [37].

Table 8.4 Transition tools used and the clinical outcome in various transition studies

Author	Year of study	Type of study	Sample size	Transition tools	Results	Conclusion
Weitz et al. [31]	2015	Retrospective study	59	Transition program	Decline in eGFR was significantly lower at 3 years after transition despite age of graft in TP group was almost twice the age of graft in control group	Standardized multilevel TP has a positive impact on reduction in kidney function and AR episodes in pediatric kidney transplant patients
Marchak et al. [32]	2015		49	Readiness for transition Questionnaire-provider (RTQ-provider), RTQ-teen, and RTQ-parent	RTQ has ability to strengthen interpersonal communication among patients, families, and healthcare providers to assess and recognize factors that affect transition readiness	Future research is required to demonstrate predictive validity of this intervention post transition to adult care
Mcquillan et al. [33]	2015	Retrospective study	32	Transfer clinic	Improved adherence and renal function in transplant patients	May improve long-term graft outcomes in transplant patients
Kreuzer et al. [34]	2015		112	Standardized questionnaire to assess current transition care practices in Germany and Austria	Significant rise in serum creatinine levels noted in 21% of patients during last visit to pediatric clinic. Majority of patients demonstrated coefficient of variation for immunosuppressive medication trough levels <20% which was indicative of good medication compliance evidenced by reduced rates of transplant rejection (coefficient of variation for tacrolimus trough levels <40% not found to be associated with increase in risk of transplant rejection)	Transition care varies significantly between centers despite existence of highly specialized care. Recommended for improvement in transition and psychosocial care including patient education

(continued)

Table 8.4 (continued)

Author	Year of study	Type of study	Sample size	Transition tools	Results	Conclusion
Akchurin et al. [35]	2014	Retrospective	97	Tacrolimus trough levels and its variability used to assess differences in transition and control group on the basis of medication compliance before and after transition	No statistically significant difference in medication compliance was found in the transitioned group before and after transition, and between transitioned group and control group who had renal transplantation under adult care. However, medication noncompliance rate was found to be higher in non-transitioned adolescent control group who had graft loss when they were still under pediatric care in comparison to the transitioned group	Medication compliance was not related to transition from pediatric to adult care in the same center, but adolescent age was shown to be risk factor for non-compliance

Annunziato et al. [36]	2013	Prospective cohort	34	Transition coordinator	Results indicated that medication adherence was significantly better among the transition coordinator group compared to the historical cohort. Patients in the transition coordinator group were adherent prior to transfer and this trend continued, whereas in the historical control group, adherence was poor prior to transfer and this situation worsened. In comparison with the historical group, mortality improved post-transfer (zero deaths vs. four deaths in historical group) and no patients were lost to follow-up. Likewise, scores for both physical and mental health quality of life in the transition coordinator group were above norm-based mean scores and remained stable pre- and post-transfer	This approach is both feasible and effective, highlighting the importance of establishing relationships with patients during the transition process

(continued)

Table 8.4 (continued)

Author	Year of study	Type of study	Sample size	Transition tools	Results	Conclusion
Pape et al. [37]	2013	Retrospective study	66	Transition clinic	Patients transferred to transition clinic showed high level of satisfaction and small number of medication regimen changes compared to the other two groups transferred to nephrologists in private practice and general transplantation clinic. However, there were no significant differences in renal function decline among three groups in short term	Transfer to specialized clinic was not associated with short-term benefits in terms of graft function and survival
Andreoni et al. [38]	2013	Retrospective cohort	16,809	NA	Patients between 14 and 16 years of age were found to have high risk of graft loss with black adolescents having worst outcome. Further, patients who had deceased donor and government insurance were found to have highest risk of death compared to those with living donor and private insurance	Adolescents between 14 and 16 years of age are at higher risk of renal transplant failure with highest risk observed among black population and patients with government insurance

Prestidge et al. [39]	2012	Prospective cohort study	46	Transition clinic	Twenty-four percent patients in control group had graft failure, whereas 0% died or had graft failure in transition group. Cost estimates suggested similar costs of care between the two groups, but substantial additional costs due to induction of dialysis and death in the historical group	Transition care associated with better graft survival and lesser mortality rate. Control group care expenses were more than transition group due to requirement for dialysis
Gilleland et al. [40]	2012	Prospective cohort study	48	Readiness for transition questionnaire	The RTQ showed good internal consistency and inter-rater reliability and demonstrated construct validity. Increased adolescent responsibility and decreased parental involvement predicted higher transition readiness. Additionally, greater adolescent adherence factors predicted greater transition readiness	The preliminary psychometrics of the RTQ appear to be supported. Additional research should evaluate healthcare transition programming to identify clinical components related to improved transition readiness, adolescent responsibility, and medical outcomes
Van den heuvel et al. [38]	2010	Retrospective cohort study to determine the effect of transition on the renal graft survival	162	NA	Acute graft rejection episodes were significantly higher before transition. The risk of graft rejections reduced after transition to adult care, and this reduction was more pronounced in native Dutch patients compared to immigrants	Acute graft rejection risk reduced after transition to adult care

(continued)

Table 8.4 (continued)

Author	Year of study	Type of study	Sample size	Transition tools	Results	Conclusion
Rutishauser et al. [41]	2010	Cross-sectional study	283	NA	The barriers to transition were feeling at ease with the pediatrician (45%), anxiety regarding transition (20%), and lack of information about the adult specialist and healthcare (18%). Fifty-three percent of adolescents and 69% of parents preferred a joint transfer meeting with the pediatric and adult specialist, and 24% of these adolescents declared that their health professional had offered this option	Establishment of a comfort zone with the pediatric team, anxiety, and a lack of information of both adolescents and their parents were among the most important barriers for a smooth and timely transfer according to adolescents and parents
Chaturvedi et al. [42]	2009	Retrospective study	11	Transition questionnaire was used to demonstrate level of satisfaction and perception of transition process	This study demonstrated that adolescent's participation in transition planning and preparation before transfer to adult care were insufficient	Adolescents should be involved actively in transition planning from the beginning
Koshy et al. [43]	2009	Retrospective cohort study to examine effect of transition on graft survival	115	NA	There was no increase in risk for renal allograft failure during transition. Furthermore, hospitalizations for graft rejection or biopsy were found to be lower after 18 years of age	Transition to adult care does not increase risk of graft failure

Ferris et al. [44]	2006	Prospective cohort study	142	Transition score, transition readiness survey, health passport	Sixty-three percent of these adolescents were able to present their passports 6 to 9 months after receipt. Age was associated independently with sustained passport-carrying (adjusted odds ratio 1.50 [95% CI: 1.18, 1.90]). Adolescents younger than 17 years had a significantly lower transition score than older teens and young adults. Age < 14 was associated with lowest transition score	As age increases, there is better adherence to transplant therapy. Transition programs that involve patients, families, pediatric and adult health care providers, and interdisciplinary collaboration are key to ensuring a successful transfer to adult-focused health services
Harden et al. [45]	2006	Retrospective study	21	Pediatric/adult joint transition clinic	Results indicated that six transplants were lost in control group (67%), whereas no transplant losses were observed in transition group	These results suggest that the integrated transition clinic, coupled with the young adult clinic, may improve patients' medication adherence and healthcare engagement

8.4 Survey of Pediatric Nephrologists and Concern for Transition Process

The RISE protocol was established by Raina et al. to transition pediatric patients to adult care [46]. In order to assess the current state of transition care, a survey was administered to various nephrologists across the United States. The investigators distributed a total of 150 surveys in 87 nephrology centers and received 60 responses from 49 centers (40% response rate). Simultaneously, the authors also conducted a thorough systematic literature review to analyze existing literature on transition care approaches and tools used for patients with renal transplant [46].

8.5 RISE Protocol

8.5.1 Importance of RISE Protocol

Adolescent transplant patients frequently find it problematic to adhere to treatment regimen resulting in loss of transplant, leaving dialysis as their only treatment alternative [2–5]. This is a major impediment to the acquisition of self-management and healthcare utilization skills by adolescent transplant patients since in many cases they are still treated as pediatric patients. Currently, there is no standardized transition protocol in place to guide this process for children with renal transplants. As a result, the transition of adolescents is not optimized from both a physician and a patient standpoint. A recent survey indicated that only 33% of pediatric nephrologists provide a written healthcare transition (HCT) plan to their patients and families [46]. This lack of proper transition increases the mortality and morbidity of patients with renal transplants [5, 14]. This clearly prompts to a requirement for a multidimensional, multicentric systematic protocol to ensure successful transition of adolescent renal transplant patients from pediatric to adult care providers. The RISE protocol aims to test the efficacy of the RISE as a tool to diagnose and monitor the process of transition over time for children with renal transplant. Another aim is to test the utility of the adapted RISE Transition Readiness Survey as a self-reported tool about issues of transition among adolescents and to test the feasibility and utility of Akron Children's Hospital's adapted RISE health passport to improve disease self-management and medication knowledge among adolescents with renal transplant.

8.5.2 Transition Age

Although the recommended age for active transition is 18–21 years, the process of training regarding transition should commence after 12 years [46]. However, it is significant to understand that age criteria are not set in stone and some adolescents

and young adults may not be sufficiently mature for acquisition of their own responsibility and require a delay of active transition. Therefore, the best strategy is to assess readiness prior to transition and decide the timing of active transition process based on individual patient assessment [46].

8.5.3 Elements of the RISE Protocol

The RISE protocol focuses on ensuring competency in four specific areas prior to the transition stage. The primary area that necessitates competency before transition is the recognition of the disease process, reason for transplant, and the healthcare system. The second area is insight into the short- and long-term impact of their disease, therapy, consequences of non-adherence, and their emotional needs. Another area to ensure capability is self-reliance in scheduling and attending appointments, refilling medications, and identifying urgent/emergent deviations to their health. Lastly, it is important to establish healthy lifestyle choices, lifelong adherence to medications and follow-up, psychosocial skills, and educational/vocational goals.

8.5.4 Transition Clinic

The transition clinic is recommended as the fundamental location for the entire transition process with the clinic being supervised by the transition team. The reason for establishment of the transition clinic is to provide a single area for the patients to meet their entire medical team, improve collaboration, and establish bidirectional flow of information between pediatric and adult teams [33, 37, 45]. The transition clinic utilizes valid, reliable, and evidence-based transition tools for children and adolescents with chronic health conditions, and the implementation of these tools will be used to guide transition intervention and education strategies [31–45]. The transition clinic also incorporates in-person interviews, questionnaires, medical record reviews, and communication with external providers (i.e., schools, pharmacies, hospitals, etc.) [33, 37, 40, 44].

8.5.5 Transition Team

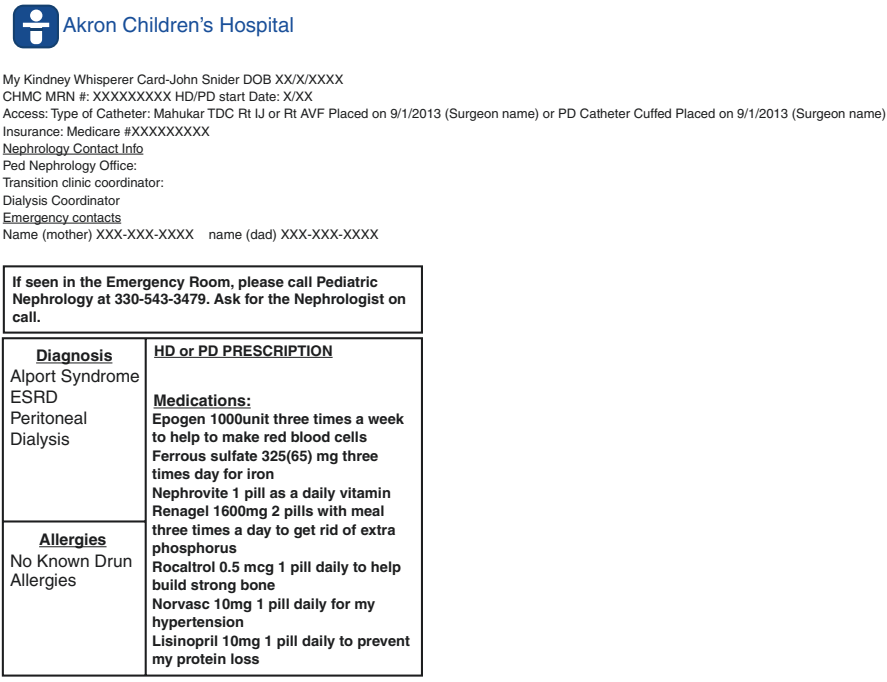
The transition process is facilitated by five groups that must function cohesively to provide optimal transition care, and this includes the patient and family, along with pediatric and adult transplant team.

Transplant team, transition team, and the primary care physician. The transition team comprises of a Med-Peds nephrologist, social worker, transition coordinator, allied health professionals, and community resource providers [45, 46].

8.5.6 Transition Tools

The RISE transition protocol uses various tools such as a medical passport, milestone, etc.

Checklist, kidney transplant questionnaire, and a transition readiness assessment to facilitate smooth transition [31–45]. The medical passport is designed to provide critical information, such as medical history, diagnosis, date of transplant, medications, providers, etc., regarding the patient in an event of emergency (Fig. 8.1) [44]. It contributes to the areas of recognition, self-reliance, and establishment of good healthcare habits [47, 48]. In order to maintain the efficacy of passport use, it should be updated during each visit, and a survey should be conducted at 3 months and 6 months into the transition. Another tool employed during the protocol is the Milestone checklist, which is used to track progress across the four competencies and through transition [46]. A basic checklist is provided in Table 8.5 and Table 8.6, which has been adjusted accordingly by both the adult and pediatric team for each patient. During the initiation of transition, a baseline assessment is conducted using the kidney transplant questionnaire. This will serve to increase the understanding regarding the patient's disease, its complications, and treatment and thus, will help the transition team to focus their attention on areas of knowledge deficit. Transition readiness assessments of the patient and family should also be completed every 6 months (Tables 8.7 and 8.8) [40, 44].



Akron Children's Hospital

My Kindney Whisperer Card-John Snider DOB XX/X/XXXX
CHMC MRN #: XXXXXXXXX HD/PD start Date: X/XX
Access: Type of Catheter: Mahukar TDC Rt IJ or Rt AVF Placed on 9/1/2013 (Surgeon name) or PD Catheter Cuffed Placed on 9/1/2013 (Surgeon name)
Insurance: Medicare #XXXXXXXXX
Nephrology Contact Info
Ped Nephrology Office:
Transition clinic coordinator:
Dialysis Coordinator
Emergency contacts
Name (mother) XXX-XXX-XXXX name (dad) XXX-XXX-XXXX

If seen in the Emergency Room, please call Pediatric Nephrology at 330-543-3479. Ask for the Nephrologist on call.

Diagnosis	**HD or PD PRESCRIPTION**
Alport Syndrome ESRD Peritoneal Dialysis	**Medications:** **Epogen 1000unit three times a week to help to make red blood cells** **Ferrous sulfate 325(65) mg three times day for iron** **Nephrovite 1 pill as a daily vitamin** **Renagel 1600mg 2 pills with meal three times a day to get rid of extra phosphorus** **Rocaltrol 0.5 mcg 1 pill daily to help build strong bone** **Norvasc 10mg 1 pill daily for my hypertension** **Lisinopril 10mg 1 pill daily to prevent my protein loss**
Allergies No Known Drun Allergies	

Fig. 8.1 Health passport

Table 8.5 Milestone checklist for pediatric team

• Understanding of the principal cause of their organ failure, need for transplantation
– Use passport and ensure understanding by repetition
• Cognizance of the long- and short-term implications of the transplant condition on their overall health and additional aspects of their life (e.g., infection prevention, cancer surveillance, academic and vocational aspirations)
• Comprehension of the influence of their illness on their sexual and reproductive health, including:
– The outcome of pregnancy on their own welfare
– The result of their medications on fertility and potential teratogenicity
– The part of genetic counseling, and genetic risk of their disease recurrence in future offspring, if pertinent to their condition
– Their own increased vulnerability for sexually transmitted disease
• Demonstration of a sense of responsibility for their own healthcare
– Information of the names, shapes/colors, indications, and dosages of their transplant and ancillary medications
– Call for their own prescription refills and renewals
– Formulate their own medication dose boxes, if not done by their pharmacist
– Independently communicate their healthcare requirements to their providers
– Teach them when and how to seek urgent medical attention, including health emergency telephone number(s)
– Ability to make, keep a calendar of, and follow through with their own healthcare appointments
– Understanding of their medical insurance coverage and eligibility criteria
• Capacity to provide most self-care independently
• An expressed readiness to transfer into adulthood
• Ownership of their medical information in a concise portable accessible summary
• Make them CEO of their own health problem

8.5.7 Transition Stages

Pre-transition stage: This stage commences when the patients are 14–18 years of age and is controlled by the pediatric team (Fig. 8.2). The main objective of this stage is to advance the quality of life of these adolescents by targeting the psychosocial aspects of transplant and transition process [49, 50]. The pediatric team creates a well-organized transition framework where they communicate to the patient, their family, and the adult healthcare team. Patients should be provided with a portable, concise, and up-to-date summary of their medical/surgical history and medications. They should also provide the adult team with an updated health passport of the transplant patient and organize for an adult primary care physician during this period [44]. Family-led education during the pre-transition stage is vital for the success of the transition process. A checklist is provided to both pediatric and adult teams that ensures that they conduct a thorough wholesome transition process (Table 8.9). Education regarding the process is provided to the patient and their family during this stage [46].

Table 8.6 Adult provider checklist

• Do you have a joint transplant clinic operational with pediatric and adult transplant physicians, nurses, and a social worker, with other health professionals available as needed? Y/N
• Do you have a clinic environment that is welcoming to young adults and adolescents? Y/N
• Does your clinic have all relevant educational and age-appropriate reading material and diversional activities (computer, internet, etc.) with youth friendly décor? Y/N
• Do you have insurance and healthcare service that works for your facility before transition into adulthood? Y/N
• Did you have your adult specialty physician or nurse meeting the adolescent in the pediatric clinic prior to transfer, a pediatric team member accompanying the patient to his/her first adult site visit, overlap/alternating visits between the pediatric and adult sites, and fully shared adolescent-adult clinics? Y/N
• Do you have all validated instruments to assess transition readiness and decision-making capacity? Y/N
• Do you have a written healthcare transition plan compiled together with the young person and family? Y/N
• Do you have all medical record providers at transfer and incorporate areas in need of attention, including individualized information about methods most successfully used to optimize immunosuppressive medication adherence? Y/N
• Do you have a patient's portable concise, up-to-date summary of their medical/surgical history and medications? Y/N
• Did you have a primary and preventive healthcare (PCP adult) establishment of partnerships with primary care providers and referral of patients to them well in advance of transfer? Y/N
• Did you provide education to primary care providers and patients on transplant-specific healthcare guidelines, such as reproductive health, cancer screening, immunizations, dental health, and high-risk behaviors? Y/N
• Do you have mechanisms for joint meetings of adult and pediatric teams? Y/N
• Do you have process and procedures for follow-up of outcomes of adolescent patients after transfer to adult care for both quality assurance and care improvement? Y/N
• Do you have structured clinical and social network support that incorporate the following:
1. More frequent clinic/nursing visits: Y/N
2. More contact phone, text, and email: Y/N
3. Healthcare provider continuity: Y/N
4. Peer group support and mentoring: Y/N
• Do you have stepwise approach to education and treatment regimen?
1. Medications (purpose, name, dose, schedule, side effects): Y/N
2. Enhance with booklets, DVD, and labels: Y/N
3. Assess comprehension: Y/N
• do you have in place various behavioral strategies to deal with medication nonadherence?
1. Simplify the regimen: Y/N
2. Individualize and tailor the medication schedule: Y/N
3. Recording of medications, use of labels, alarms, and text: Y/N
4. Link medications to ADL, e.g., brushing teeth and meals: Y/N
• Do you have a pharmacist, drug monitoring, and tools to assess immunosuppression? Y/N

Table 8.7 Transition readiness assessment of patient

	Assessment of adherence to treatment regimen					
Section A	Never	Almost never	Sometimes	Almost always	Always	Not needed for my care
1. How often did you make an effort to understand what your doctor told you?	☐	☐	☐	☐	☐	☐
2. How often did you take your medicines on your own?	☐	☐	☐	☐	☐	☐
3. How often did you ask your doctor or nurse questions about your illness, medicines, or medical care?	☐	☐	☐	☐	☐	☐
4. How often did you make your own appointments?	☐	☐	☐	☐	☐	☐
5. How often did you need someone to remind you to take your medicines?	☐	☐	☐	☐	☐	☐
6. How often did you use things like pillboxes, schedules, or alarm clocks to help you take your medicines when you were supposed to?	☐	☐	☐	☐	☐	☐
7. How often did you use the internet, books, or other guides to find out more about your illness?	☐	☐	☐	☐	☐	☐
8. How often did you forget to take your medicines?	☐	☐	☐	☐	☐	☐
9. How often did you work with your doctor to take care of new health problems that came up?	☐	☐	☐	☐	☐	☐

(continued)

Table 8.7 (continued)

	Assessment of facts regarding the medical condition					
Section B	Nothing	Not much	A little	Some	A lot	Not needed for my care
10. How much do you know about your illness?	☐	☐	☐	☐	☐	☐
11. How much do you know about taking care of your illness?	☐	☐	☐	☐	☐	☐
12. How much do you know about what will happen if you don't take your medicines?	☐	☐	☐	☐	☐	☐
	Assessment of communication with doctors					
Section C	Very hard	Somewhat hard	Neither hard nor easy	Somewhat easy	Very easy	Not needed for my care
13. How easy or hard is it to talk to your doctor?	☐	☐	☐	☐	☐	☐
14. How easy or hard is it to make a plan with your doctor to care for your health?	☐	☐	☐	☐	☐	☐
15. How easy or hard is it to see your doctor by yourself?	☐	☐	☐	☐	☐	☐
16. How easy or hard is it to take your medicines like you are supposed to?	☐	☐	☐	☐	☐	☐
17. How easy or hard is it to take care of yourself?	☐	☐	☐	☐	☐	☐
18. How easy or hard do you think it will be to move from pediatric to adult care?	☐	☐	☐	☐	☐	☐

Table 8.8 Assessment of concerns of family regarding patient transition

Assessment of concerns of the family regarding patient transition
• Does my child have abstract knowledge of treatment requirements and complication prevention?
• Does my child understand transplant organ rejection, why signs and symptoms may be minimally apparent, even with significant organ injury?
• Does my child know how to ensure completion of necessary routine management tasks, e.g., taking medication on time (alarm watch, cues linked to daily routine)?
• Does my child know each of medication, major side effects, and consequences of taking them irregularly?
• Do I participate in appointment making to go for well-baby checkup for my child?
• Will my child be able to effectively ask for assistance in complex situations when my child needs help?
• Will my child read books, pamphlets, or the internet to learn more about transplantation and the underlying condition that originally lead to my child's kidney failure?
• Does my child achieve sense of self as a capable manager of the kidney transplant condition?
• Does my child reach critical milestones prior to adult care transfer?
• Does my child integrate realities of transplant care with the invincible nature of their peers?
• Does my child appreciate the benefits that constraints of transplant management allow?
• Does my child continue to develop more independent clinic and community support network with transition to adult-based services?
• Does my child pledge to make commitment to lifetime of treatment for his kidney?

Active transition stage: The active transition stage ensues when the patients are 18–21 years of age. The pediatric team initiates this process by first assessing the level of readiness of the patient and their family [40, 44]. This is achieved through the use of standardized assessments such as Rapid Estimate of Adolescent/Adult Literacy in Medicine (REALM) and Appointment and Medication Adherence Report, Family Relationship Index and Social Support (SSQSR) [32, 40]. The assessment of readiness aids the teams in distinguishing the areas in which the patient knowledge is deficient. During the primary visit, all teams are present when the pediatric team hands over the written transition plan, medical passport, and all the patient records to the adult team. The pediatric team communicates with adult providers at transfer and brings forth the areas of need to attention, including individualized information about methods most successfully used to optimize immunosuppressive medication adherence. The adult team then explains their expectations and also communicates with the primary care provider (PCP). During this stage, the transition team will act as a conduit between the pediatric and adult care team and ensure proper readiness of the patients for transition by conducting surveys every 6 months. Adult practitioners may benefit from cultivating partnerships with their pediatric colleagues and participation in bidirectional information sharing. Adult team may need to study about care of adolescents at various developmental levels, the impact of childhood chronic disease on development, and management of childhood causes of end-stage organ failure and congenital diseases [33, 37, 45, 46].

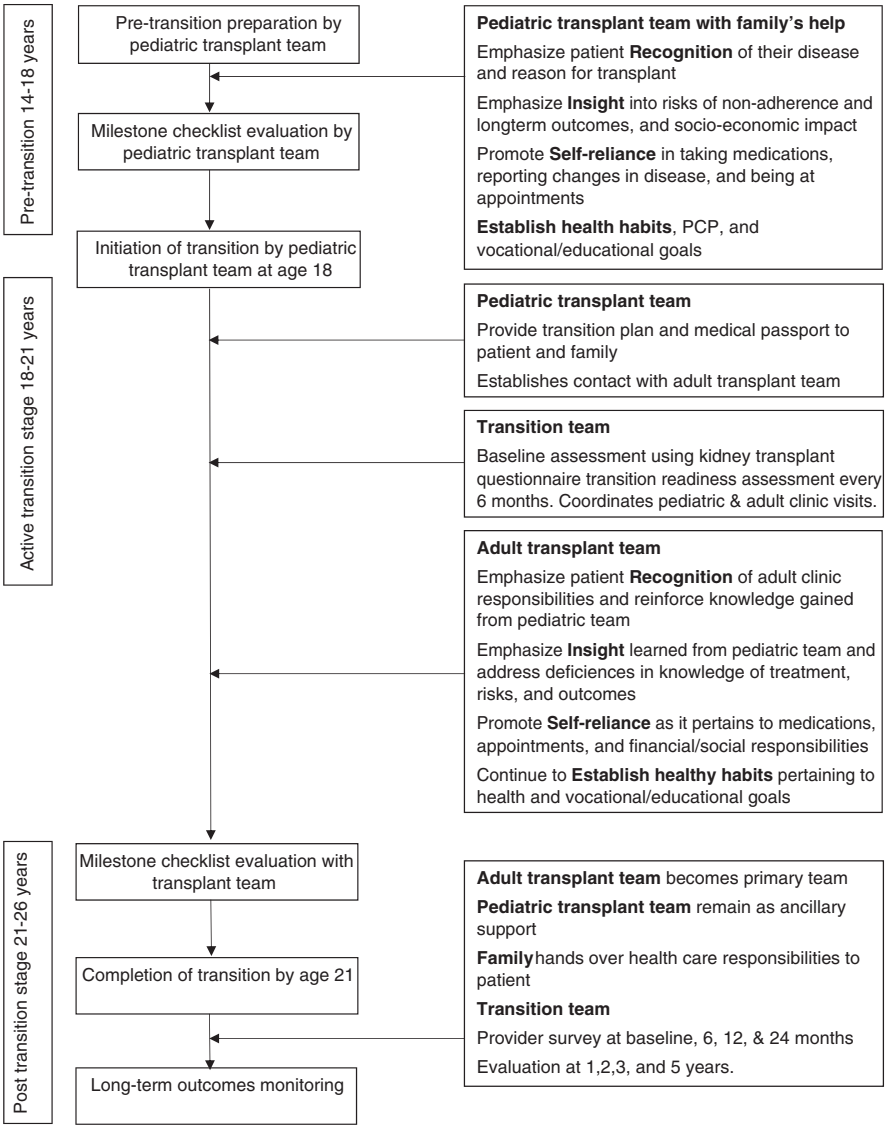


Fig. 8.2 Flow diagram representing the transition process

Table 8.9 Checklist tasks for pediatric and adult team

Checklist for pediatric team	Checklist for adult team
Demographics	Orientation of adolescent to adult practice
Transplant date and organ	Address concerns of adolescents regarding transition
Provide history and physical examination summary, last clinical note, and lab work	Discuss confidentiality, access to information, and shared decision-making
Evaluate insurance status, medication list, and current problems with transition or health	Encourage direct provider communication in patients with complex health or psychosocial needs
Provide the young adult with an updated health passport	Communicate with pediatric team regarding their residual of care
Check milestones prior to transition and assess transition readiness	Provider works with young adult to strengthen self-care skills
Present the case to transition committee and adult team	Establish plan for further consultation with the pediatric team if need arises
Create a written healthcare transition plan with patient and family	Use of community resource information and culturally appropriate support
Review the process both verbally and via letter	
Arrange PCP and pharmacy	
Schedule a combined adult-pediatric clinic	

Post-transition stage: The post-transition stage occurs from 21 to 26 years and the adult team has a principal role in this stage. By this stage, the proper communication channels are established between the patient, adult team, and the PCP [36, 45]. In addition, the patient competency in RISE areas should be established. The pediatric team will remain available as ancillary support if their input is required. Additionally, the transition team continues to follow up with the patient and acts as a safety net for them until transition is completed [46].

8.5.8 Limitations of RISE Protocol

The RISE protocol creates an appropriate and a systematic transition outline for guiding patients toward adult care providers. However, it has certain limitations, such as it does not consider the quality of healthcare services in other parts of world, especially in underdeveloped and developing countries. Additionally, the financial cost of implementing such a multidisciplinary protocol might be inflated. The major obstacle in implementation of this protocol is mobilization of all the healthcare resources in a single hospital unit.

8.5.9 Implementation of RISE Protocol

The transition protocol was applied to a pilot study conducted at Akron Children's Hospital, Akron, Ohio. Seventeen patients (6 females and 11 males, mean age 14.5 years), who received a renal transplant in the preceding 2–9 years (mean 5.6 years, median 7), went through the RISE transition protocols. The transition process spanned 2 years to overlap medical care between pediatric nephrologists and crucial adult physicians and related services. The final transition was completed at 21 years of age. The transition clinic allowed for sufficient time to prepare the patient, caregivers, and physicians to leave pediatric care for adult care (satisfaction score 90%). Educating the young person and their family regarding transition and the process involved, their kidney condition, healthcare privileges, the adult healthcare environment, and about how it is diverse from the pediatric health care services were identified as the key factors for RISE transition (90th percentile).

Adolescents and parents did not differ significantly in their overall outlook and stated that they would appreciate the support provided by a transition program. However, the parents had additional appreciation of the transition services as compared to the adolescents. Eighty-five percent of patients and family felt generally well informed of the RISE transition protocol. Nevertheless, 70% preferred to receive additional information about their disease and overall health during their transfer period. When asked for the key person during the transfer, 62% of respondents mentioned the pediatrician, 30% stated the nurses, and 6% stated "others." The relevant issues during transfer were cited as medication (35%), education and employment (27%), disease knowledge (13%), and environment in the adult service (25%).

8.6 Conclusion

Healthcare transition (HCT) is a process that requires preparation as a continuum from pediatric- to adult-focused services. Transition requires a formal transition program to improve medical and psychosocial outcomes in transplant patients. There is a need to assess the impact of various transition elements on outcomes, transition readiness, and the role of patients and their family. The RISE protocol and its four competency areas is the core element for successful transition to an adult care provider. Self-reliance and the establishment of healthy choices aim to improve patient autonomy and emotional burden and to minimize disruptions in their daily lives. Recognition and insight aim to educate the patient regarding all aspects of their disease. Education about medical, social, vocational/educational, and interpersonal effects of their disease and treatment will help to improve adherence as well as modify patient perspectives of their disease. Proficiency in all four areas will allow the patient to RISE to transition and establish him/herself in the adult medical world. The use of RISE protocol is expected to significantly reduce the rates of graft failure accounted to non-adherence among pediatric patients. The main limitation of this protocol is the financial cost and coordination failure during implementation of

RISE protocol. Transition cost analysis conducted by comparing the cost of graft failure and the cost of transition programs will demonstrate the benefit of these programs with respect to the long-term consequences.

Conflict of Interest The authors declare that there is no conflict of interest.

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Induction Therapy in Pediatric Renal Transplant Recipients

9

Olga Charnaya, Asha Moudgil, and Dechu Puliyanda

9.1 Introduction

Induction therapy is the initiation of intense immunosuppression at the time of, or prior to, transplantation intended to prevent allograft rejection upon contact of the recipient's immune system with the donor antigens. Induction therapies have been divided into biological agents that include monoclonal and polyclonal antibodies and chemical agents such as calcineurin inhibitors (CNI), antiproliferative agents including mycophenolate mofetil (MMF), and methylprednisolone (MP). Other induction therapies include plasmapheresis and intravenous immunoglobulin (IVIG). Most data comes from adult studies and pediatric data is provided when available.

Historically, induction therapy was primarily intended to provide intensive T-cell depletion at the time of transplantation. Recently, newer induction agents and strategies have also targeted B-cells, particularly in the highly sensitized recipients.

O. Charnaya
Department of Pediatrics, Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: ocharna1@jhmi.edu

A. Moudgil
Department of Nephrology, Children's National Medical Center, Washington, DC, USA
e-mail: amoudgil@childrensnational.org

D. Puliyanda (✉)
Department of Pediatrics, Division of Pediatric Nephrology and Transplant Immunology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: dechu.puliyanda@cshs.org

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9.2 Aims of Induction Therapy

The main purpose of induction therapy has been to decrease the incidence, severity, and frequency of acute rejection (AR) episodes after transplantation with the intent of prolonging the life of the allograft. This is accomplished by interfering with the anticipated immune response to foreign antigens.

The immune response mounted against a transplanted allograft occurs due to the cognate interaction between the innate and adaptive immune systems, which is most intense at the time of transplant and continues throughout the entire life of the allograft. At the time of transplant, the innate immune system is activated in response to tissue injury sustained during organ retrieval and resultant ischemia, known as ischemia-reperfusion injury (IRI), which initiates and amplifies the adaptive response. Production of inflammatory cytokines (IL-1, IL-6, TNF-α, and γ-interferon), chemokines, and P-selectins induces permeability changes in endothelial cells causing release of antigens from the graft and stimulating migration of donor-derived antigen-presenting cells (APCs) from the transplant to the recipient's lymphoid tissue. Both donor-derived and recipient APCs present foreign antigens in the form of peptides present on their cell surface in the groove of the histocompatibility antigen (HLA) molecules to the recipient CD4+ T-cells. This ensures that all allopeptides are presented to T-cells with the optimal T-cell receptor (TCR) specificity and affinity. Proliferation of CD4+ T-cells is driven by further co-stimulatory signaling from APCs [1]. Activated CD4+ cells stimulate many other types of cells that include effector cytotoxic T-lymphocytes (CD8+), inflammatory T-cells (Th17), and B-cells to generate cell-mediated graft destruction and develop HLA antibodies and long-term immunological memory. The adaptive immune response further directs innate immune components such as complement, neutrophils, and phagocytic cells to the site of allograft injury [2]. T-regulatory (Treg) cells are also produced during this interaction which helps regulate these inflammatory responses to limit the destruction.

The aim of induction therapy is to prevent these inflammatory responses at the time of transplantation and to provide adequate immunosuppression until the oral immunosuppressive agents can take over this task. In patients with delayed graft function (DGF), defined as the need for dialysis within the first week after transplantation, there is an upregulation of HLA molecules on the allograft causing an increased propensity for AR and therefore, the need for intensification of immunosuppression [3]. Successful induction therapy agents and protocols need to be safe and cost-effective and should not cause excessive immunosuppression, with the goal of minimizing the risk of infectious complications and malignancies, such as posttransplant lymphoproliferative disease (PTLD). The effect of any induction agent on long-term patient and graft survival should be assessed prior to its widespread use.

9.3 Historical Induction Agents

Total lymphoid irradiation (TLI) was one of the first induction modalities used in the early transplantation era in human organ transplantation [4, 5]. TLI caused lympholysis and produced sufficient immunosuppression to prolong the survival of a variety of organ allografts in experimental animals [6, 7]. The length of effective immunosuppression was dose-dependent and was limited by the toxicity that occurred with the higher doses. The next step in evolution of induction immunosuppression came with utilization of polyclonal antibodies, obtained by immunizing laboratory animals with human lymphoid cells from cell cultures, peripheral lymphocytes, thymus, or spleen. The pooled sera are pre-absorbed on erythrocytes and platelets and purified to extract the IgG fraction. Polyclonal antibody agents have evolved over time and are the most commonly utilized induction agents today.

9.4 Currently Utilized Induction Agents

Current induction therapies can be broken down into three broad categories: lymphocyte-depleting, non-lymphocyte-depleting, and chemical agents. Numerous studies have compared different induction immunosuppression regimens. However, these studies are often underpowered, are predominantly performed in adult patients, and have not demonstrated a superiority of a single optimal induction regimen. Therefore, most pediatric transplant centers use induction agents based on their clinical experience rather than guided by the available data.

9.4.1 Lymphocyte-Depleting Agents

Rabbit antithymocyte globulin (rATG) under the brand name Thymoglobulin® received FDA approval in 1998 for the treatment of steroid-resistant AR in transplant recipients; in the last few years, it was also approved as an induction agent. It is created by immunizing rabbits with human thymocytes and purifying the resulting IgG fraction. The antibodies in Thymoglobulin are polyclonal, and although their effect is predominantly anti T-cell, it also has a lesser degree of activity against B-cells, monocytes, and neutrophils due to shared antigens between different immune cells [8]. Data show that rATG induces a proportionally larger decrease of CD4+ Foxp3- cells compared to CD4 + CD25 + Foxp3+ Treg cells resulting in relative preservation of Treg cells [9].

Brennan et al. performed the first studies to demonstrate the safety, effectiveness, and superiority of Thymoglobulin over another polyclonal horse-derived preparation (ATGAM) and basiliximab [10–12]. These landmark studies changed the clinical approach to induction immunosuppression as evidenced by a persistent and

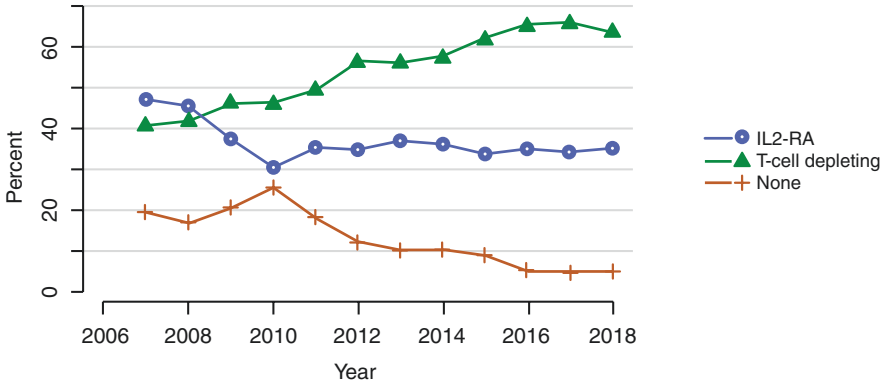

Fig. 9.1 2018 SRTR/OPTN annual report. Use of induction immunosuppression by agent in pediatric kidney transplant by year [133]

steady increase in rATG induction compared to no-induction or basiliximab (Fig. 9.1). While pediatric studies are limited, rATG induction followed by CNI, MMF, and prednisone was demonstrated to be a safe and effective immunosuppression regimen in pediatric patients with 1 year of follow-up, with a low incidence of AR, symptomatic cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection, or PTLD [13]. A single-center study of 198 children and adolescents showed decreased rates of AR when compared to an ATGAM-induction historical cohort; however, there were increased rates of EBV viremia with Thymoglobulin® but similar patient and graft survival [14].

Thymoglobulin® can be administered through a large peripheral vein or central venous access and is usually given daily (1.5–2.0 mg/kg/day) to achieve total cumulative dose ranging from 4.5 to 7.5 mg/kg [11, 15–17]. The current FDA dosing guidance recommends a minimum of four doses of rATG at 1.5 mg per kg for a cumulative dose exposure minimum of 6 mg per kg for induction purposes [18]. Individual centers use varying doses of rATG for induction based on the center's experience and preferences.

Rounding the daily dose to the nearest 25 mg increment (but still ensuring the complete total dose), dosing guided by CD3+ T cell counts as well as delayed administration of doses can help to reduce the cost of this therapy [19]. More recently, low-dose (3–4.5 mg/kg) Thymoglobulin induction regimens have been studied in adult patients and shown to have similar rates of biopsy proven AR, delayed or slow graft function, graft loss, and leukopenia [20, 21].

Alemtuzumab (Campath-1H®, Genzyme, Cambridge, MA), a monoclonal antibody targeted at the CD52 antigen present on T- and B-lymphocytes and monocytes, received FDA approval in 1998 for the treatment of chronic lymphocytic leukemia. It has been used extensively off label in solid organ transplantation as an induction agent. The nature and kinetics of lymphocyte repopulation depends on the maintenance immunosuppression. Similar to rATG, alemtuzumab also proportionally increased CD4 + CD25 + Foxp3+ Treg cell population independent of the

maintenance immunosuppression regimen [22, 23]. This suggests that repopulation of the lymphoid compartment after T-cell depletion with alemtuzumab results in long-term increases of Treg cells.

Initial adult trials were aimed at CNI and steroid avoidance with alemtuzumab induction; however, they resulted in an unacceptably high incidence of acute cellular and humoral rejection [24–26]. Five-year follow-up results of alemtuzumab induction in 33 renal transplant recipients with half-dose CSA monotherapy compared with patients treated with conventional immunosuppression with CSA, azathioprine (AZA), and steroids showed comparable patient and graft survival, graft loss, incidence of infections, and serious adverse events and incidence of AR [27]. The results of this study suggested that alemtuzumab induction was safe in the long term. However, it was noted that it may cause delayed onset of AR, and therefore continued surveillance for AR is needed.

As with most induction agents, pediatric data are limited by small sample size and short follow-up. Alemtuzumab induction was first shown to be safe and effective with tacrolimus monotherapy immunosuppression in a pilot study of 17 unselected pediatric patients. Tacrolimus was begun posttransplantation with subsequent lengthening of intervals between doses with the hypothesis that heavy posttransplant immunosuppression may contribute to long-term immunosuppression dependence by subverting tolerogenic mechanisms [28]. Steroids were added temporarily to treat rejection in two patients (both rATG subgroup) or to treat hemolytic anemia in two others. After a mean follow-up of 22 months, patient and graft survival were 100% and 94%, respectively. Following the same protocol, Sung et al. reported data on 25 pediatric patients receiving alemtuzumab induction with 100% actuarial patient and graft survival at 3 years, and only one graft was lost at 4 years due to nonadherence [29]. At the 4-year follow-up, 48% remained on tacrolimus monotherapy maintenance immunosuppression, 32% on dual therapy (tacrolimus and an antiproliferative agent), and 16% on triple therapy (tacrolimus, antiproliferative agent, and glucocorticoids). Early acute rejection (< 12 months) occurred in 12%, late acute rejection episodes occurred in 16% of patients, and 20% of patients developed de novo donor-specific antibodies (dnDSA). Similarly, Tan et al. showed favorable 4-year outcomes in patients receiving a living donor kidney transplant with alemtuzumab induction and tacrolimus monotherapy [30]. Acute cellular rejection was seen in 4.8% of patients and no antibody-mediated rejection (AMR) was seen; 17% developed dnDSA. The mean HLA mismatch in the cohort was only 2.6, notably better than many transplants done today.

Alemtuzumab is given at the time of organ reperfusion (0.3–0.6 mg/kg, max 30 mg) IV or as a subcutaneous injection at similar doses [31]. Most commonly, a single dose is used in pediatric patients; however, in some adult protocols, a second dose is administered after 24 hours resulting in prolonged lymphocyte depletion [32]. In 2013, the manufacturer changed their distribution model for alemtuzumab and it is no longer commercially available. It is now provided only through the Campath® Distribution Program free of charge for patients deemed appropriate. While this is an economic advantage to centers at the present time, concern remains for the future and availability of alemtuzumab in the long term [19].

A recent Cochrane review analyzed 99 studies (8956 adult and pediatric participants) with the aim of evaluating the relative and absolute effects of lymphocyte-depleting agents and to determine differences in adverse effects. They found that both rATG and alemtuzumab reduce AR rates compared to no-induction, at the cost of increased CMV infections, while patient-centered outcomes (death and toxicity) do not appear to be improved [33].

9.4.2 Non-lymphocyte-Depleting Agents

Basiliximab (Simulect®, Novartis Pharmaceuticals Corp, East Hanover, NJ) is a chimeric (75% human, 25% murine) monoclonal antibody that targets the CD25 molecule on the IL-2 receptor and selectively prevents the clonal expansion of activated T-cells. Daclizumab is a humanized monoclonal antibody, which is no longer on the market and will not be discussed in this chapter.

The IL-2 receptor is comprised of three chains: α chain (CD25), β chain (CD122), and γ chain (CD132). Only the β and the γ chain are expressed on the surface of the resting T-cells. In response to antigenic stimulation, the activated T helper lymphocyte (CD4) can induce activation of the IL-2 receptor α chain (CD25) and form the activated IL-2 receptor heterotrimeric complex. This leads to the clonal expansion of activated helper and cytotoxic T-cells. An important caveat to consider is that Treg cells are depended on IL-2 signaling for ongoing activity and therefore their function can be impaired by this therapy. Studies have shown that basiliximab therapy led to a profound, but transient, reduction in $CD4^+CD25^+FOXP3^+$ Treg within 7 days of treatment lasting for approximately 90 days after transplant [34].

Several single-center and a few multicenter studies have reported their experience with IL-2 receptor antagonist (IL2-RA) induction in pediatric renal transplantation, with triple immunosuppression consisting of CSA or tacrolimus, and MMF or AZA and steroids, as maintenance immunosuppression. Although most of the reports have a small sample size, the incidence of AR at 1 year has varied between 6% and 17%, with 1-year graft survival between 86 and 98% [35–37]. Pooled data from NAPRTCS reported 284 patients treated with daclizumab, 166 with basiliximab, and 711 with no-induction therapy as controls [38]. One-year incidence of AR was 23–26%, lower than 34% observed in no-induction controls. Graft survival was significantly higher with 95–97% versus 93% in no-induction controls. There was no increase in the incidence of side effects in those treated with IL2-RA compared to no-induction control group. Smith et al. reported decreased incidence of graft thrombosis in those treated with IL2-RA induction (1.07%) compared with those treated with no-induction therapy (2.40%, OR 0.44, 95% CI 0.23, 0.84, $p = 0.014$) in a retrospective analysis of data reported to NAPRTCS [39]. All these studies, though mostly single-center and/or retrospective, point to the fact that IL2-RA can prevent AR without increasing side effects.

A 2010 Cochrane review compared basiliximab with no-induction or rATG [40]. When compared to rATG, there was no difference in graft loss at any time point, but there was a reduction of biopsy-proven AR at 1 year (RR 1.30, 95% CI 1.01 to 1.67)

with rATG but a 75% increase in malignancy and 32% increase in CMV disease. Notably in this review, despite the homogeneity of results across the populations of the pooled studies, there was underrepresentation of high-risk participants and in particular of children.

Basiliximab is given on day 0 and day 4 of transplant as 20 mg/dose in adults and 12 mg/m^2/dose in children. In a cost comparison between basiliximab and placebo (including steroid therapy), no significant differences in costs were seen in terms of immunosuppressive therapies, total hospitalization, laboratory tests, outpatient visits, postoperative dialysis, or total costs at 6 or 12 months from an institutional perspective [41].

Belatacept (Nulojix®), approved in June of 2011, is indicated for the prophylaxis of organ rejection in adult patients receiving a renal transplant. A soluble fusion protein, it binds to CD80 and CD86 on APC inhibiting CD28-mediated costimulation of T-lymphocytes [42]. Unlike the lymphocyte-depleting agents, the effect on circulating Treg cells is unclear with studies showing both decreased and increased counts and function [34, 43–45].

Belatacept was introduced as a CNI-sparing agent for maintenance immunosuppression. Early studies (BENEFIT trial) showed an increased risk of early ACR episodes and increased risk for PTLD in EBV-seronegative patients [42, 46]. In both a Cochrane review and the 7-year follow-up studies, patients treated with belatacept were shown to have more AR but better renal function, less hypertension, improved lipid parameters, and less new-onset diabetes compared to patients receiving CSA-based maintenance immunosuppression [47–50]. To address the increased risk for AR, Wojciechowski et al. studied a protocol of low-dose rATG combined with belatacept induction followed by belatacept and everolimus maintenance therapy. This study of 44 adult patients showed an 11.3% 1-year AR rate, which was numerically lower than that seen in the BENEFIT study [51]. Kirk et al. showed that the increased early acute rejection risk could be overcome with a CNI and steroid-free regimen when belatacept is paired with alemtuzumab induction and sirolimus maintenance in adult patients [52]. The initial cohort consisted of 20 living donor kidney transplant recipients. Half of the cohort received donor bone marrow infusion as there is evidence that mTORi can promote the effects of co-stimulatory blockade, especially with high levels of circulating donor antigen. No patients in this trial developed DSA or had clinical rejection (three patients with subclinical rejection) in the first year, and 7/20 patients were able to successfully wean to belatacept monotherapy after 1 year. The 5-year follow-up study of an expanded cohort of 40 patients including deceased donor transplant recipients, expanded criteria donors, and those with pre-formed alloantibody did not include donor bone marrow infusions [53]. DSA developed in 5/40 patients, 4 had subclinical rejection detected on protocol biopsy in the first year, and only 2 patients experienced a clinical rejection event. There were no grafts lost due to rejection and 12/40 patients were able to wean to monotherapy with belatacept. These two studies showed that co-stimulatory blockade could successfully be employed at the time of transplant with comparable complication rates to standard induction protocols.

9.4.3 Comparison of Antibody Induction Agents

A prospective study compared the effects of alemtuzumab, rATG, and basiliximab on AR in high- and low-immunological risk patients. All patients had the same early steroid withdrawal, and CNI/MMF maintenance immunosuppression regimen. High-risk patients received either alemtuzumab or rATG, and low-risk patients received either alemtuzumab or basiliximab. By the first year after transplant, biopsy-confirmed AR was less frequent with alemtuzumab than with conventional therapy in the low-risk group, but no apparent difference was detected in the high-risk group [54]. Koyawala et al. compared outcomes in adult KT recipients based on induction agent utilizing OPTN data linked with Medicare claims data. The study showed higher mortality risk and odds ratio of AR with alemtuzumab and basiliximab, and higher risk of allograft failure in the alemtuzumab group compared to matched rATG recipients [55]. Similarly, Tanriover et al. compared outcomes based on induction regimen in adult living and deceased donor KT recipients. They showed that compared with no-induction therapy, IL2-RA induction was not associated with better outcomes when TAC/MPA/steroid maintenance was used. However, rATG appears to offer better graft survival compared to IL2-RA in steroid avoidance protocols [56, 57].

For patients considered to be at high-immunological risk including African Americans (AA), high HLA mismatch, and DGF, lymphocyte-depleting induction therapy as compared with IL2-RA reduces the risk of rejection, graft loss, and death [12, 58–61].

9.4.4 Chemical Agents (CNI, Corticosteroids)

Chemical agents for induction include corticosteroids, CSA, and tacrolimus. These are the same drugs that are used for maintenance immunosuppression except they may be used intravenously and usually in higher doses.

Corticosteroid induction followed by maintenance therapy has played a central role in the evolution of renal transplantation. It was and remains a cornerstone of immunosuppression in the majority of patients. Most studies have used 10–15 mg/kg of methylprednisolone (MP) in the operating room followed by steroid taper. Corticosteroids prevent T-cell activation by preventing release of T-cells and APC-derived cytokines such as IL-1, IL-2, IL-3, IL-6, TNF-α, and γ-interferon. In addition, corticosteroids are beneficial in reducing IRI, especially in deceased donor organ transplantation. In steroid avoidance protocols, steroids are still used for the first 5 days after transplant to help reduce IRI.

Tacrolimus is a highly protein-bound drug that binds to the immunophilin, FK-binding protein, within the cytoplasm of the cell. This causes inhibition of the calcineurin pathway preventing the generation of IL-2 and therefore inhibiting the proliferation of T-lymphocytes. The drug was introduced in the late 1980s and has been extensively used as a maintenance immunosuppressive drug since the mid-1990s. The side effects of tacrolimus are similar to those of cyclosporine,

except that fewer cosmetic side effects such as hirsutism and gingival hyperplasia are observed with tacrolimus. However, tacrolimus has more pronounced side effects on the neurological system and may have an increased incidence of post-transplant diabetes and PTLD as compared to CSA [62].

Studies with the use of IV tacrolimus as an induction agent are extremely limited and are really of historic interest only.

Mycophenolate mofetil (MMF) has been administered anywhere from 12 hours up to 14 days prior to transplant to allow for lower maintenance CNI doses [63]. Initial pharmacokinetic studies were done with patients on CSA and determined an ideal starting dose of 1200 mg/m2/day. Tacrolimus does not have the same effect on MMF metabolism and therefore lower starting doses (600–900 mg/m2/day) should result in similar AUC [64].

Other than IV methyl prednisolone, chemical agents are rarely used for induction.

9.5 Induction Strategies Based on Patient Risk

9.5.1 Induction Therapy in Standard-Risk Group

In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) guideline for "Care of Kidney Transplant Recipients" recommended induction therapy in all kidney transplant recipients (Level 1A) [65]. This guideline recommended children with standard immunological risk receive IL2-RA (basiliximab) as first-line therapy, but children at high-immunological risk receive lymphocyte-depleting induction. There is presently no consensus among pediatric kidney transplant centers regarding the use and optimal regimen for immunosuppressive induction therapy.

9.5.2 Induction Therapy with Steroid Avoidance

Sarwal et al. from Stanford University subsequently conducted single-center pilot trial that enrolled 57 pediatric renal transplant recipients in a steroid-free protocol using extended daclizumab induction followed by tacrolimus and MMF maintenance [66]. Study patients underwent serial protocol biopsies. The control group included 50 historical-matched steroid-based children receiving tacrolimus. In this study, 98% graft and patient survival was achieved in the steroid avoidance group. At 1 year of analysis, steroid-free recipients showed significant improvements in clinical AR, graft function, hypertension, and growth without an increase in infectious complications. Since that time, numerous studies have been published showing long-term (up to 5 years) safety and efficacy with early steroid withdrawal protocols utilizing lymphocyte depletion induction [67–72]. The benefits seen in all of these protocols are improved cardiovascular risk factors (blood pressure and lipids) and improved growth with comparable rates of AR and graft survival.

A direct comparison of alemtuzumab and rATG induction with complete steroid avoidance protocols was recently completed and showed no difference in 1-year

graft survival, low corticosteroid conversion in both groups, similar incidence of DSA, and biopsy-proven AR [73]. Notable differences between the groups included more leukopenia in the alemtuzumab group and more CMV viremia in the rATG group. However, there were other center-specific practices regarding MMF and valganciclovir dosing that may have contributed to the differences; therefore, they cannot be attributed to induction agent alone.

9.5.3 Induction Therapy in Diseases with a High Risk of Recurrence

9.5.3.1 Focal Segmental Glomerulosclerosis (FSGS)

Primary idiopathic FSGS recurs in 30% of patients receiving their first kidney transplant, >80% in a second transplant, and is associated with a high risk of graft failure [74]. The current theory that a humoral circulating factor is responsible for the disease has led to the specific targeted therapies added to standard induction immunosuppression [75].

Plasma exchange (PLEX) removes the patient's plasma and replaces it with pooled donor fresh frozen plasma (FFP) or albumin with the aim of removing the suspected offending circulating agent. This therapy is currently the mainstay of treatment of posttransplant FSGS recurrence. Two of the first prospective studies of preemptive use of PLEX in kidney transplant in adult and pediatric patients, utilizing varying numbers of PLEX treatments with differing time of initiation depending on living donor or deceased donor transplant, showed a reduced rate of FSGS recurrence; however, the numbers in both studies were very small (n = 10 and n = 21) [76, 77]. More recently, pediatric-specific data has not shown a benefit of preemptive PLEX in reducing recurrence of FSGS [78–80]. Given the cost and potential complications of this therapy, careful consideration of the risk/benefit in each individual patient is recommended as we await better powered studies to provide evidence-based guidance.

Rituximab is an anti-CD20 monoclonal antibody that depletes B-cells and suppresses antibody production. The mechanism of action in FSGS is not completely understood but thought to be through interference with the production of a circulating factor involved in FSGS pathogenesis, either through its direct effects on B-cells or through its indirect effects on T-cells [81]. In addition, some direct effect on podocyte structure has been theorized [82]. Rituximab has been used for treatment of documented recurrence and has been shown to help sustain remission in combination with PLEX; however, its use as an induction agent is limited [83]. Case reports have shown effectiveness of rituximab to prevent posttransplant FSGS [80, 81]. Rituximab was used successfully in a patient receiving a second kidney transplant, and in another patient, it was used as the only induction agent in an actively nephrotic patient with no disease recurrence with up to 30 months of follow-up [84, 85]. Ofatumumab (a fully humanized monoclonal antibody to CD20) has been used in three children with recurrent FSGS with attainment of full or partial remission after failing PLEX, CSA, and rituximab [86, 87]. This drug has not been used as part of an initial induction regimen and needs to be studied further.

Protein adsorption column and LDL apheresis have been described as treatment options for recurrence in a few case reports [88, 89]. There is one case report of five adult patients with primary FSGS who received perioperative LDL apheresis with a short follow-up time (60 days–22 months) with no recurrence events in this cohort [90].

Cyclosporine A has shown some degree of efficacy in pediatric patients with an up to 81% percent reduction in proteinuria in patients with recurrent disease. However, this is usually in combination with other therapies such as PLEX, and therefore the individual effect of this drug is difficult to determine [91, 92]. Unless we have reliable biomarkers of FSGS recurrence or these therapies are tried in a large number of patients in a randomized manner, the role of preemptive therapies remains anecdotal and speculative since only 30% patients have recurrence.

9.5.3.2 Atypical Hemolytic Uremic Syndrome (aHUS)

The unifying pathogenesis of aHUS is dysregulation of the alternative complement pathway caused by one or a combination of genetic mutations in the various regulatory proteins required to suppress this constitutively active pathway. Risk of recurrence is very high, up to 80% within the first 2 years, depending on which mutation is identified. There are three primary strategies to minimize risk of recurrence: [1] kidney transplant + PLEX, [2] kidney transplant + eculizumab, and [3] combined liver-kidney transplant [93].

PLEX with FFP replacement can ameliorate symptoms of aHUS by replacing the missing factor where the underlying pathophysiology is a deficiency of regulatory proteins. However, this therapy will be ineffective in the mutations caused by membrane cofactor protein (MCP) and can exacerbate aHUS in gain-of-function mutations. This regimen is associated with a high rate of complications and therefore is not an ideal option for patients with aHUS.

Eculizumab, a recombinant humanized monoclonal antibody that binds C5 and effectively stops its cleavage thus inhibiting the formation of terminal membrane attack complex (C5b-9), has revolutionized the care of adults and children with complement disorders. This drug should be used in combination with a standard induction regimen, the first dose to be given either given prior to surgery or within the first 24 hours following reperfusion. It should be continued indefinitely after transplant [94–96].

9.5.3.3 C3 Glomerulopathy (C3GN)

C3GN is a membranoproliferative glomerulonephritis mediated by alternative complement pathway dysregulation and has an estimated 50% risk of recurrence in the allograft. Recurrence usually occurs within the first 1–2 years and is characterized by decreasing renal function, proteinuria, hematuria, and/or hypocomplementemia [97]. Eculizumab has been used to treat recurrent C3GN; however, there are no data to support the prophylactic use of this drug as part of an induction regimen [94, 98].

9.5.4 Induction Therapy in Immunologically High-Risk (HLA-Sensitized) Patients

Patients are considered HLA sensitized if their panel reactive antibody (PRA) is greater than 30%. They are considered broadly sensitized if their PRA is >80% [99]. These antibodies make it difficult for them to receive a kidney transplant with a negative crossmatch (both with living and deceased donors); and wait times on dialysis are longer than the average low-risk patients. After transplant, they are at high risk for AMR and have a higher risk of graft loss [100]. Therefore, this group of patients presents a unique challenge to the transplant physicians.

Prior to consideration for transplantation, measures are undertaken to remove these antibodies and to suppress their production. This process is referred to as desensitization or immunomodulation. Several protocols for immunomodulation are available and have been studied; however, this is beyond the scope of this chapter [101–104].

Once the patient has undergone immunomodulation, and a kidney with an acceptable crossmatch is available, the induction immunosuppression regimen is intense and may consist of one or more of the following agents [105]. It is important to note that almost all studies of induction therapies in highly sensitized patients are in adults. It is also important to note that most studies are with a combination therapy, and therefore it is difficult to assess the efficacy of individual induction agents.

9.5.4.1 Intravenous Immunoglobulin: IVIg

IVIg has been the mainstay in the repertoire of induction agents used for HLA-sensitized patients. It was the very first agent used for desensitization and continues to be used as an induction agent in combination with other agents. IVIg is efficacious in reducing anti-HLA antibodies in vitro and in vivo [106]. This action is perhaps mediated through an anti-idiotypic antibody-blocking effect; it is also a modifier of complement activation and injury [107].

The IG02 placebo-controlled study assessed the use of IVIg vs placebo as an induction agent in 24 highly sensitized adult kidney transplant recipients. Patients received 2grams/kg IVIg (maximum dose of 140 grams). IVIg was superior to placebo for the reduction of HLA antibodies and improving the rates of transplantation, with similar rates of adverse events in both groups [101]. A single pediatric study showed the efficacy of IVIg along with rATG induction in successful transplantation of a 7-year-old highly sensitized child [108].

IVIg products are derived from pooled human sera, and several IVIg preparations are currently available on the market, differing with regard to excipient compounds. The adverse effects of each preparation differ based on the excipient used, and therefore proper product selection is important [109]. In general, sucrose-free products decrease the risk of acute kidney injury (AKI), and splitting the dose of IVIg and giving over a longer period of time might mitigate the risk of thrombosis seen with these products [110].

9.5.4.2 Alemtuzumab

Alemtuzumab has been used for induction in highly sensitized pediatric patients. In a pediatric study, 15 highly sensitized patients underwent induction with alemtuzumab (15–30 mg as a one-time subcutaneous injection) [111]. This group was compared to 35 non-sensitized patients who had received basiliximab induction. Although there was a higher risk of acute cellular rejection in the highly sensitized group, the rates of AMR were comparable. WBC count and absolute lymphocyte count were significantly lower in the alemtuzumab group at 30 days and 1 year; however, the rates of viral, bacterial, and fungal infections were comparable. Patient survival was 100% with excellent graft survival in both groups. In another pediatric study, three highly sensitized patients were successfully transplanted after desensitization and alemtuzumab induction with stable 3-year graft function [112].

9.5.4.3 Antithymocyte Globulin

Various dosing regiments of rATG have been used in highly sensitized patients ranging from a single dose at 9 mg/kg given in the perioperative period to 1.5 mg/kg/day for 4–5 days for a total of 6 mg/kg [113, 114]. The incidence of AR was comparable to low-risk patients receiving non-lymphocyte-depleting agents for induction [115]. A study comparing rATG to alemtuzumab induction in adult highly sensitized patients showed a significantly lower incidence of AR and DGF with alemtuzumab [116]. However, the incidence of AR decreased when rATG was combined with rituximab for induction therapy [21].

There are reports of two highly sensitized children treated with rATG induction who had stable graft function and no detectable CMV, EBV, and BK viremia, at 1-year posttransplantation [108, 112].

9.5.4.4 Rituximab

Rituximab has been successfully used in desensitization protocols in combination with IVIg and PLEX. The typical dose for induction is 375 mg/m2 as a one-time dose given in the perioperative period. Several adult studies have shown beneficial effect and stable allograft function with the use of rituximab alone or in combination with IVIG or rATG [21, 117, 118].

Rituximab may be associated with increased risk of hypogammaglobulinemia and infections. However, two reports did not show increased risk of infectious complications in highly sensitized renal transplant recipients treated with rituximab either for induction or for the treatment of AMR [119, 120].

9.5.4.5 Eculizumab

In a rat model of acute AMR after kidney transplant, terminal complement blockade preserved allograft function resulting in significantly longer graft survival than in those not treated with C5 blockade [121]. Eculizumab has been used as an induction agent in highly sensitized adult patients to mitigate the risk of AMR. Nine weeks of eculizumab (starting on the day of transplant) was used in 80 highly sensitized

patients in combination with rATG induction, and the drug was well tolerated [111, 122]. At 36 months, graft and patient survival rates were 83.4% and 91.5%, respectively. Similar results have been noted in other studies [123, 124].

Because of the association between terminal complement inhibition and *Neisseria meningitidis* infection, patients are required to be vaccinated for it at least 14 days before receiving the first dose of eculizumab or to be vaccinated at the time of transplant and receive prophylaxis with an appropriate antibiotic for 14 days after the vaccination.

9.5.4.6 C1-INH (Berinert; CSL Behring, King of Prussia, Penn)

C1-INH is a serine protease inhibitor which inhibits complement activation by interrupting C1s and C1r in the classic complement pathway [125]. It is also a potent inhibitor of the lectin complement pathway by neutralizing lipopolysaccharides, thereby inhibiting both sepsis and endotoxin shock in animal models. It plays an important role in vascular permeability and its deficiency leads to hereditary angioedema [126].

In a placebo-controlled trial in highly sensitized adult transplant recipients, C1-INH used with alemtuzumab induction was noted to be safe with no significant adverse events. No AMR episodes were observed, and C1-INH therapy led to reductions in levels of C1q HLA antibodies, thus indicating its role in prevention of AMR. It has also been shown to prevent DGF in a randomized placebo-controlled trial [127].

9.5.4.7 Bortezomib

The drug works by inhibiting proteasomes, cellular complexes that break down proteins, and specifically target antibody-producing plasma cells. It has been used in conjunction with pheresis to treat AMR and for desensitization, but reports of its use as an induction agent are very limited. Bortezomib is associated with peripheral neuropathy in 30% of patients [128].

9.5.4.8 Imlifidase

Imlifidase contains the IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS), an endopeptidase that cleaves human IgG into $F(ab')_2$ and Fc fragments inhibiting both complement-dependent and antibody-dependent cytotoxicity. Imlifidase therefore can be useful as an induction agent in highly sensitized patients.

IdeS was administered to 25 highly HLA-sensitized patients (11 patients in Stockholm, Sweden, and 14 in Los Angeles, USA) before the transplantation of a kidney from an HLA-incompatible donor. Frequent monitoring for renal function, adverse events, outcomes, donor-specific antibodies, and renal biopsies were performed. Maintenance immunosuppression consisted of tacrolimus, MMF, and steroids. IdeS reduced or eliminated donor-specific antibodies and permitted HLA-incompatible transplantation in 24 of 25 patients [129]. In a study by Lonze et al., Ides was used in seven highly sensitized patients prior to renal transplantation. Three out of seven patients had rebound in DSA and ABMR that responded to standard of care. Therefore, patients in the Ides study in the USA also received IVIg and rituximab after transplantation to prevent antibody rebound [130].

Very few highly sensitized pediatric patients have received renal transplant after desensitization due to availability of other options for children including receiving an organ though donor exchange registries or by preferentially allocating kidneys to these children as was done in a recent Italian study [131]. However, there are a few patients who are running out of dialysis access due to prolonged time on dialysis and may benefit from such therapies. Due to lack of sufficient data, most treatments in children are guided by adult studies. However, it is very important to have long-term follow-up data in children to assess if these therapies have unique effects on growth and development in children and young adults.

9.6 Current Practices in the USA

The KDIGO guidelines recommended induction therapy in all kidney transplant recipients (Level 1A) [65]. They recommend children with standard immunological risk receive IL2-RA (basiliximab) as first-line therapy and that polyclonal agents be reserved for patients determined to have high-immunological risk (black race, allosensitization, younger age). Peritransplant events such as DGF, prolonged cold ischemia time, high number of HLA mismatches, and in recipients of donors with higher kidney disease profile index (KDPI) may also warrant antibody induction therapy [12].

Despite these recommendations to stratify induction immunosuppression based on patient risk, this is not reflected in an analysis of practice patterns. Dharnidharka et al. evaluated induction immunosuppression for all adult and pediatric patients who received a kidney transplant from 2005 to 2014 utilizing the SRTR database and found that only a minority of variation in induction immunosuppression choice was a result of donor/patient factors, and the majority was a result of center-practice patterns [132].

The 2018 UNOS/OPTN report shows that the most commonly used induction agents are T-cell-depleting preparations, followed by IL2-RA, and no-induction agent staying static over the last 2 years [133, 134].

9.7 Conclusions

The goal of available induction therapies in conjunction with maintenance immunosuppression is to prevent AR and its deleterious effects on the allograft. It is pertinent to find the least toxic, steroid-sparing, and cost-effective induction regimen. Currently, induction is commonly used for most pediatric transplants and for all high-risk patients including those who are receiving a re-transplant, highly sensitized, cross-match positive and with DGF or those at risk for DGF, and those at risk of recurrence of their native kidney disease. Most recently, innovative induction protocols are being used to minimize maintenance immunosuppression. However, more pediatric data is needed to ensure risks and safety profile in growing children and adolescents.

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Maintenance Immunosuppression in Kidney Transplantation

10

Deepti Narla, Christina Nguyen, Shefali Mahesh, and Rupesh Raina

10.1 Introduction

Maintenance immunosuppression is essential to decrease the risk of transplant rejection and prolong the long-term viability of an allograft. Immunosuppressive agents target T-cell activation at different signaling stages. Signal 1 involves interaction of T-cell receptor major histocompatibility (MHC) and antigen. Signal 2 involves interaction of costimulatory molecule CD28 on T-cell with C80/86 on antigen-presenting cells. Signals 1 and 2 together through calcium-dependent calcineurin pathway, RAS-mitogen-activated protein kinase pathway, and nuclear factor-κβ pathway lead to IL-2 production and other cytokines. Signal 3 is the downstream activation resulting in T-cell proliferation and amplification through binding of IL-2 to its receptor activating mammalian target of rapamycin (Fig. 10.1) [1, 2].

Transplant immunosuppressive treatment has been utilized since the late 1950s (Fig. 10.2). Initial immunosuppressive management was combination of total body irradiation and prednisone, but this approach was limited by serious and sometimes fatal infections. In the early 1960s, azathioprine in combination with prednisone was adopted with improved allograft survival. But it was not until the 1980s that significant improvement in allograft survival was accomplished with introduction of cyclosporin. Triple therapy with azathioprine, prednisone, and cyclosporin became

D. Narla · S. Mahesh
Department of Pediatric Nephrology, Akron Children's Hospital, Akron, OH, USA

C. Nguyen
Department of Pediatric Nephrology, University Hospital, Cleveland, OH, USA

R. Raina (✉)
Department of Nephrology, Akron General Medical Center at Cleveland Clinic Foundation, and Akron Children's Hospital, OH, USA
e-mail: RRaina@akronchildrens.org

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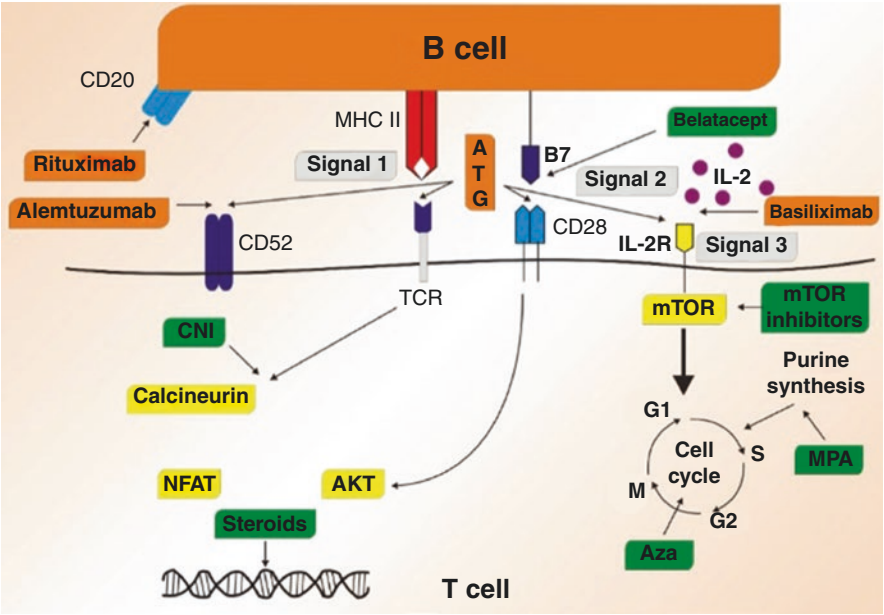

Fig. 10.1 T-cell activation pathway and targets of immunosuppressive drugs [1]

the common maintenance immunosuppressive regimen [3, 4]. With FDA approval of Cellcept in 1995 and tacrolimus in 1997 for renal transplantation, most maintenance immunosuppression protocols now have tacrolimus and Cellcept with or without steroids as the mainstay maintenance immunosuppression [5] (Fig. 10.3). Please refer to end of the chapter for examples of maintenance immunosuppression protocol.

While adequate immunosuppression is essential for allograft survival, it is important to consider the multiple adverse effects of immunosuppressive medications including risk of infection, malignancy, and long-term morbidity associated with these medications. Using a combination of medication with different mechanism of action at reduced doses increases the efficacy of treatment while decreasing the adverse effects [6].

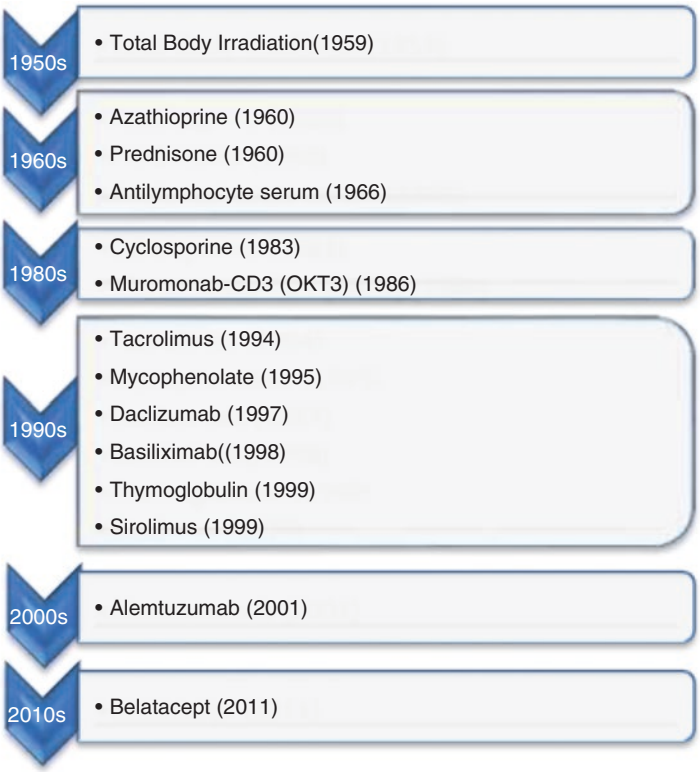

Fig. 10.2 Timeline of utilization of various immunosuppressive agents in kidney transplant

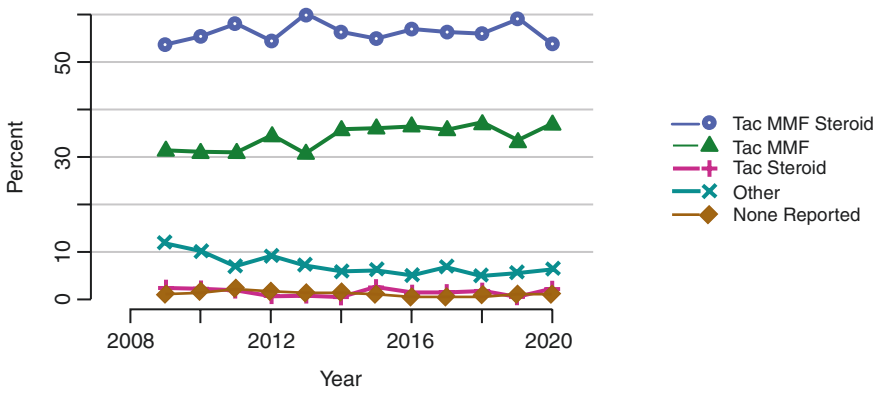

Fig. 10.3 Maintenance immunosuppressive regimen in pediatric transplant patients. At the time of discharge, the most common combination was tacrolimus, MMF, and steroids (54.1%) followed by tacrolimus and MMF (36.8%) [5]

10.2 Corticosteroids

Corticosteroids are synthetic analogues of cortisol that predominantly have glucocorticoid effects with minimal mineralocorticoid effects. Glucocorticoid effects include anti-inflammatory, immunosuppressive, and antiproliferative actions exerted through multiple pathways. Broadly, these can be categorized into genomic and non-genomic effects. Genomic effects are mediated by the binding of glucocorticoids to the glucocorticoid receptors, which translocate into the nucleus where it activates anti-inflammatory genes, such as Annexin A1, or represses pro-inflammatory factors such as Nf-kB and activator protein 1. These effects are dependent on the cumulative dosage over the duration of glucocorticoid administration. The mechanism of non-genomic effect is less well understood and is thought to be mediated by membrane-bound receptor that modulates antioxidant and anti-inflammatory effects. These effects tend to be rapid onset with a short duration of activity [7, 8]. Therefore, glucocorticoid administration leads to inhibition of production of T-cell cytokines such as IL-2, IL-6, and interferon-gamma which reduces the response of lymphocytes and macrophages to the transplant allograft. In addition, it also suppresses T-cell activity by suppressing antibody and complement binding. Moreover, it causes migration of T-cells to lymphoid tissue [2, 9, 10].

Corticosteroids were the mainstay maintenance immunosuppression therapy. However, given the side effect profile (see Table 10.1), steroid avoidance, early steroid withdrawal (within 7 days of posttransplant), and late withdrawal (6–12 months posttransplant) are utilized to minimize these side effects. Initial randomized clinical trials have supported higher rates of acute rejection in steroid avoidance/withdrawal protocols, but these studies were with cyclosporin and azathioprine as maintenance immunosuppressive medication. Later studied utilizing tacrolimus and MMF as maintenance immunosuppressive agents did not find significant increase in acute rejection nor graft loss [11–13]. The use of steroid avoidance/withdrawal has increased in pediatric transplant patients given the benefits of growth acceleration especially in prepubertal children, bone health, and

Table 10.1 Side effect profile of steroids

Cardiovascular	Hypertension, sodium and fluid retention, hyperlipidemia, arrhythmias
Endocrine/metabolic	Truncal obesity, moon facies, buffalo hump, adrenal insufficiency, glucose intolerance/diabetes
Gastroenterological	Peptic ulcer disease/gastritis, pancreatitis, steatohepatitis
Immune system	Leukocytosis, increased risk of infections, increased risk of malignancy
Neurological/ psychiatric	Pseudotumor cerebri, depression, mania, psychosis, mood liability
Skeletal and muscle	Impaired linear growth, decreased bone mineralization, fractures, avascular bone necrosis, myopathy/muscle weakness
Skin	Skin thinning, striae, ecchymosis, hirsutism, delayed wound healing, acne
Ophthalmic	Increased intraocular pressure, posterior subcapsular cataracts, glaucoma, exophthalmos

improvement in cardiovascular risk factors (obesity, hypertension, and hyperlipidemia) compared to steroid-based protocols. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) data showed use of prednisone 30 days post-transplant decreased from 97.8% in 1996 to 2001 to 59.7% in 2008–2017. Caution is advocated for use of steroid avoidance/withdrawal protocol in patient with PRA > 60% and recipients with primary GN [13].

10.3 Calcineurin Inhibitors (CNIs)

Alloantigen binding to T-cell receptor results in increase in intracellular calcium concentration which activates the calcineurin heterodimer that constitutes subunit A and B. Calcium binds to calcineurin B subunit resulting in the activation of phosphatase activity of calcineurin A subunit. This causes dephosphorylation of transcription factor, NFATc, which then translocates into the nucleus along with calcineurin. As a result, cytokines' transcription such as IL-1 and IL-2 and costimulatory molecules such as CD40 ligand are upregulated which leads to growth and differentiation of T-cells [14] (Fig. 10.4).

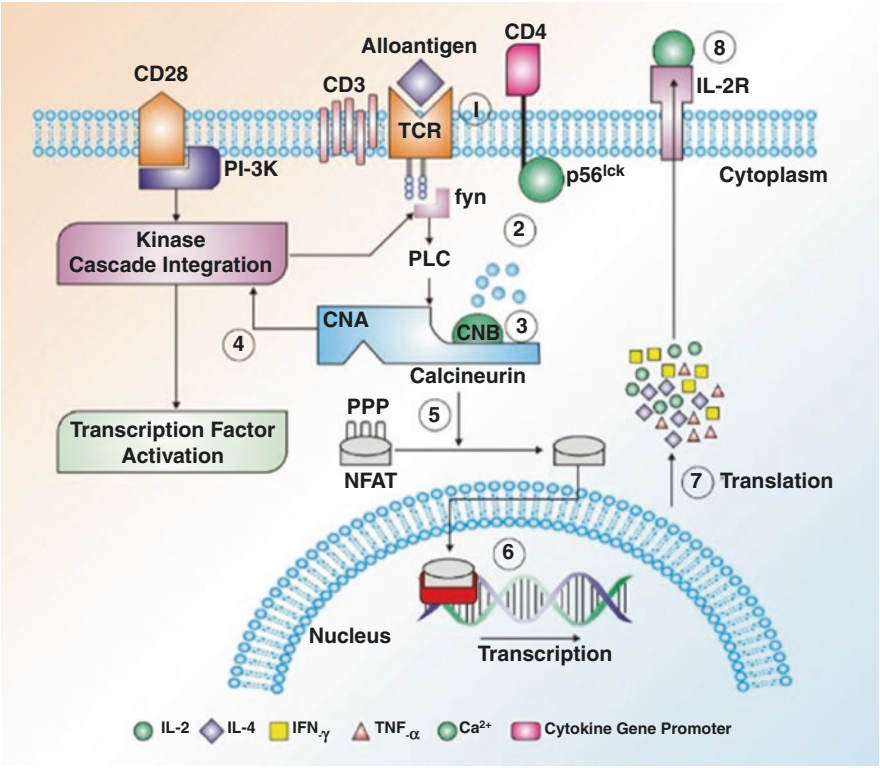

Fig. 10.4 Role of calcineurin in T-cell activation [14]

CNIs' mechanism of action is dependent on their high-affinity binding to specific cytoplasmic receptors such as cyclophilin and FK binding protein, usually termed immunophilins. This complex competitively inhibits the activity of calcineurin which prevents translocation of the NF-AT family of transcription factors into the nucleus. This in turn leads to reduced transcriptional activity of TNF-alpha, IL-2, IL-3, IL-4, and other cytokine genes. Reduced transcriptional activity of cytokine genes leads to inhibition of T-cell activation, proliferation, and differentiation [2, 4, 9, 10, 13].

Calcineurin inhibitors include cyclosporin and tacrolimus. CNIs have a narrow therapeutic range. Given acute allograft rejection is highest during the first 3 months posttransplant period, higher drug levels are maintained initially followed by reduction in doses to decrease the overall side effects [6]. However, high drug levels increase the risk of nephrotoxicity.

CNI causes vasoconstriction resulting in elevated blood pressures and diminished renal perfusion. This effect is dose dependent and in acute setting, causes renal ischemia and acute tubular necrosis [2]. CNIs also increase the risk of de novo thrombotic microangiopathy. Though the exact mechanism is not known, it is postulated to be secondary to CNI-induced vascular endothelial cell injury. Chronic CNI use can lead to CKD and ESRD. This is likely secondary to CNI-induced vascular endothelial injury and arteriolar vasoconstriction leading to allograft ischemia and chronic hypoperfusion. On kidney biopsy, CNI-induced nephropathy findings include obliterative arteriolopathy/hyalinization of the afferent arteriole, ischemic collapse or glomerular scarring, tubule vacuolization, focal and global segmental glomerulosclerosis, focal interstitial fibrosis associated with macrophage influx, and tubular atrophy (striped fibrosis) [15].

Tacrolimus and cyclosporin have similar adverse effect but vary in severity. The risk of new-onset diabetes, tremor, headaches, dyspepsia, vomiting, diarrhea, and hypomagnesaemia was significantly higher in tacrolimus group compared to cyclosporin group, while constipation, hirsutism, and gingival hyperplasia were more significant in cyclosporin group [4] (Table 10.2). Tacrolimus compared to cyclosporin had lower acute rejection and better early graft survival in a meta-analysis of randomized trial data [16].

Table 10.2 CNI adverse effects

Renal	TMA, decreased renal blood flow, CNI-induced nephropathy
Electrolyte disturbance	Hyperkalemia, metabolic acidosis, hypomagnesemia, hypercalciuria
Endocrine/ metabolic	Diabetes, hyperuricemia
Cardiovascular	Hypertension, dyslipidemia
Neurotoxicity	Tremor, neuralgia, peripheral neuropathy, psychoses, hallucinations, dysarthria, vision loss, seizures, PRES, cerebellar ataxia, paresis, and leukoencephalopathy
Other	Gingival overgrowth and hair growth (seen with cyclosporin)

FDA approved extended-release tacrolimus capsules Astagraf in 2013 and Envarsus in 2015. These are not interchangeable. Astagraf may initially require higher doses to achieve similar trough level to twice daily tacrolimus, while Envarsus requires a lower dose to achieve the same trough level secondary to better bioavailability. Daily tacrolimus has similar efficacy and safety profile to BID tacrolimus, but the daily formulation has decreased toxicity [17, 18].

Cyclosporin and tacrolimus are metabolized by cytochrome P450 enzymes specifically CY3A4 and CYP3A5. Genetic variability in the expression of CYP3A5 enzyme leads to variation in absorption and metabolism of these drugs. Children who express at least one CY3A5*1 allele are fast metabolizers and will need a higher dose (1.5-to-two-fold increase in dose) to achieve the same target trough level [4, 19]. Moreover, many foods and drugs can alter the drug levels by inducing/inhibiting CYP3A4/5 and P-glycoprotein (Fig. 10.5).

CNI levels, especially tacrolimus level, are also affected by diarrhea. Tacrolimus is transported out of intestinal enterocytes by P-glycoprotein efflux pump leading to exposure of intestinal CYP3A which results in decreased bioavailability. However, in diarrhea/enterocolitis, P-glycoprotein carrying epithelial cell are destroyed resulting in decrease exposure to CYP3A and increased drug level [4]. Therefore, drug levels need close monitoring with persistent diarrhea.

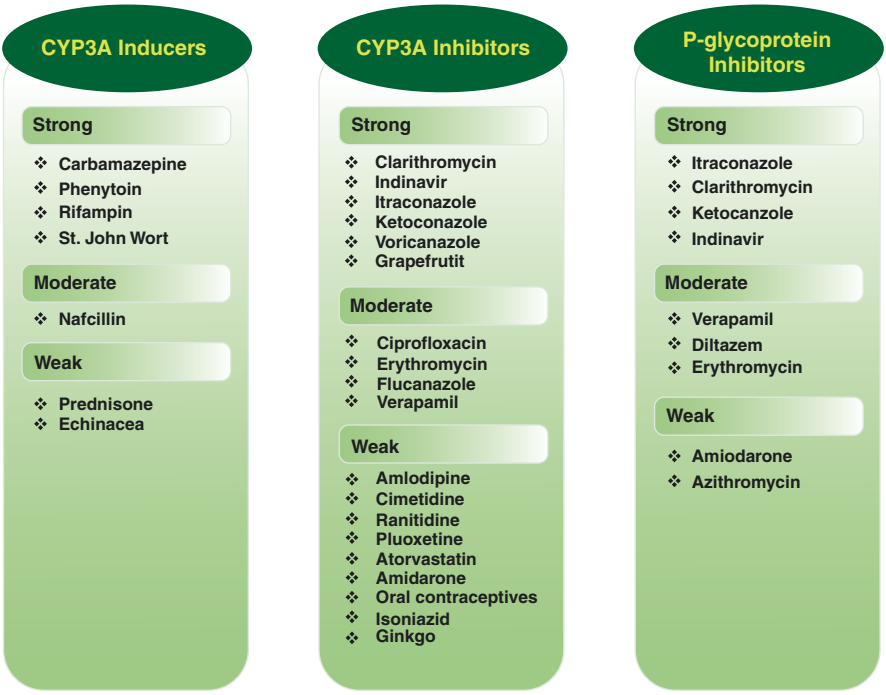

Fig. 10.5 Drug and food that can affect CNI levels. CYP3A inducers decrease CNI levels, while CYP3A and -glycoprotein inhibitors increase CNI levels

10.4 Antimetabolite Agents

Antimetabolite agents commonly used in kidney transplant patients are mycophenolate mofetil (MMF) and azathioprine. These agents function by blocking de novo nucleotide synthesis. In the case of MMF, it is metabolized in the liver and converted to the active compound mycophenolic acid. This active compound blocks inosine-5′-monophosphate dehydrogenase (IMPDH) which is a critical enzyme for the rate-limiting step for de novo biosynthesis of guanine nucleotide. Unlike most cells that have two pathways (IMPDH pathway and salvage pathway) for generation of guanosine nucleotides, lymphocytes do not have salvage pathway and therefore MMF selectively blockades lymphocyte proliferation. Specifically, MMF inhibits IMPDH type II isoform which is exclusively found in activated lymphocytes. This blockage of guanine synthesis induces cell cycle arrest in S-phase [2, 4, 9, 10].

Azathioprine blocks purine biosynthesis by formation of thio-inosinic acid which specifically targets lymphocytes due to lack of salvage pathway for purine synthesis. Azathioprine is metabolized to 6-mercaptopurine (6-MP) which is further converted to 6-thiouric acid, 6-methyl-MP, and 6-thioguanine (6TG). These metabolites stop replication by incorporating into a replicating DNA. In addition, azathioprine affects CD28 co-stimulation of alloreactive T lymphocyte leading to the induction of apoptosis of T-cells [4, 10].

Active metabolites of azathioprine are inactivated by the enzyme thiopurine methyltransferase (TPMT) and enzyme nudix hydrolase 15 (NUDT15). Therefore, in patients with significant myelosuppression, TMPT phenotype/genotype testing and NUDT15 genotype testing are recommended. FDA recommends alternative therapy for individuals with known homozygous TPMT and/or NUDT15 deficiency and decreased doses for heterozygous for TPMT or NUDT15 deficiency [4, 20].

MMF is considered first line of antiproliferative agent [6]. Randomized controlled trials in the 1990s supported improved short-term outcomes for patients on MMF mainly from decreased acute rejections. However, Australian arm of the Tricontinental Mycophenolate Mofetil Renal Transplantation Study showed no significant benefit in patient or graft survival, cancer incidence, or estimated kidney function at 15 years posttransplantation [21]. The decreased risk of acute rejection noted in these trials was found to be less significant with use of CNIs. There is no strong evidence that MMF is superior to azathioprine with respect to long-term outcomes [6, 22].

The most common side effects of MMF are diarrhea, vomiting, leukopenia, anemia, and infection. These adverse effects are more common in children <6 years of age. MMF is contraindicated in pregnancy given the increased risk of first trimester pregnancy loss and congenital malformations. The most common side effects of azathioprine are bone marrow suppression, nausea, and vomiting [4]. It can occasionally cause liver impairment, hepatic veno-occlusive disease, and cholestatic jaundice [10].

10.5 Mammalian Target of Rapamycin (mTOR) Inhibitor: Sirolimus

mTOR is a serine/threonine kinase that regulates cell growth [23]. mTORi binds to intracellular immunophilin FK506 binding protein forming a complex with FKBP12. This complex has high affinity to mTOR, thereby inhibiting it and resulting in the arrest of T-cell cycle in the G1 phase. Therefore, signal transduction from IL-2 and other cytokines is blocked [4]. Sirolimus also blocks calcium-independent CD28-induced costimulatory pathway [24].

There was no significant difference in graft survival or patient survival when mTORi were used as replacement for either CNI or antiproliferative agents. mTORi use is limited by the side effect profile especially with hyperlipidemia and bone marrow suppression [8]. In addition, development of interstitial pneumonitis is an important consideration which is dose dependent and resolves with discontinuation of the medication. Other side effects include hypertension, edema, diarrhea, poor wound healing, and proteinuria [13, 20]. There is decreased incidence of viral infection with mTORi. But there is an increased incidence of PTLD when used in combination with CNIs and steroids, and therefore, this combination should be avoided [4].

10.6 Costimulation Blocker: Belatacept

Belatacept is a bioengineered Fc fragment of immunoglobulin IgG1 that binds with high affinity to CD80 and CD86 ligands. As a result, it blocks CD28-mediated costimulatory pathway preventing T-cell activation and proliferation [4]. Loss of costimulatory pathway signaling causes T-cells to become immunologically unresponsive. They are unable to secrete inflammatory cytokines, proliferate, and undergo apoptosis [9].

Costimulation blocker, belatacept, has been investigated as an alternative to CNI in order to limit the nephrotoxicity side effect of CNI and increase graft life. Belatacept regimen has lower rates of donor-specific antibody development and better estimated glomerular filtration rate compared to cyclosporin regimen. However, there is increased risk of PTLD with belatacept especially in the EBV (−) recipients [25]. Therefore, belatacept is not recommend in EBV (−) recipients.

Below are examples of induction and maintenance immunosuppressive protocols.

Steroid withdrawal immunosuppressive protocol adopted from Cincinnati Children's Hospital Medical Center.

Definitions

Standard risk	Steroid sparing	High risk	Delayed graft function
PRA < 80% and no DSAs and two or fewer of the following risk factors: • African American • 6/6 HLA mismatch • Deceased donor • Repeat transplant • Initial non-function	More than usual risk for posttransplant diabetes Obesity (BMI > 90%) Significant bone disease Exclusion criteria • High immunologic risk	PRA > 80% or DSAs or Two or more of the following risk factors: • African American • 6/6 HLA mismatch • Deceased donor • Repeat transplant • Initial non-function	Hemodialysis within 7 days of transplant Oliguria for 24–36 hours and < 10% decrease in serum creatinine Risk factors: • Prolonged cold ischemia time (>24 hours) or warm ischemia time (>40 min) • Obesity • Poor donor (higher donor serum creatinine or older age) • Donation after cardiac death

Induction immunosuppression

	Standard risk	Steroid sparing	High risk	Delayed graft function
Basiliximab	POD: 0,4 <35 kg: 10 mg ≥35 kg: 20 mg			
Thymoglobulin		1.5 mg/kg/dose daily Reduce dose by 50% for: ANC < 1200 cells/uL or PTL < 80,000 cells/uL Hold dose if: ANC < 800 cells/uL or Plt < 50,000 cells/uL		
		Four doses. Start intraoperatively		Start on day of determination of DGF and continue for four doses or until tacrolimus restarted

Maintenance immunosuppression

	Standard risk	Steroid sparing	High risk	Delayed graft function
Steroids	3–6-month taper based on risks and benefit	Rapid tapering over 1 week	6-month taper down to 0.1 mg/kg/do or max of 5 mg every other day	3–6-month taper based on risks and benefit
Tacrolimus trough levels ng/ml	First mo: 10–15 Second–sixth mo: 7–10 >6 mo: 4–7	First mo: 10–15 Second–sixth mo: 7–10 >6 mo: 4–7	First–sixth mo: 10–15 >6 mo: 7–10	Hold tacro initially and restart when creatinine is improving but no later than POD 4
CellCept	Initial 600 mg/m2 BID (max 1500 mg) Reduce to 450 mg/m2 BID POD 15	Initial 600 mg/m2 BID (max 1500 mg) Reduce to 450 mg/m2 BID POD 15	600 mg/m2 BID	Based on standard or high risk

Rapid taper of steroids

1-week taper	
POD 1–2	2 mg/kg (max 80 mg)
POD 2–3	1 mg/kg (max 40 mg)
POD 4–5	0.5 mg/kg (max 20 mg)
POD 6	Off

Steroid taper

3-month taper	6-month taper	
Week 1	Week 1	1.5 mg/kg/dose (max 60 mg)
Week 2	Week 2	1 mg/kg/dose (max 40 mg)
Week 3	Week 3	0.75 mg/kg/dose (max 30 mg)
Week 4–5	Week 4–7	0.5 mg/kg/dose (max 20 mg)
Week 6–7	Week 8–11	0.35 mg/kg/dose (max 15 mg)
Week 8–9	Week 12–15	0.2 mg/kg/dose (max 10 mg)
Week 10–12	Week 16–24	0.1 mg/kg/dose (max 5 mg)
Month 3	Month 4	Off

Tacrolimus starting dose

CY3A5 non-expression	0.1 mg/kg/dose q12 hours up to 5 mg
CY3A5 expressors	0.15 mg/kg/dose q12 hours up to 7 mg

Steroid avoidance protocol adopted from University Hospital
Induction: thymoglobulin 1.5 mg/kg/dose daily for four doses.

Maintenance:

Tacrolimus: 0.07 mg/kg/dose q12 hours up to 2 mg to be started on post-op day 1 after adequate graft function.

Posttransplant	Tacrolimus goal (mg/ml)
Day 1–week 4	10–12
Month 1–3	8–10
Month 3–6	7–9
Month 6–12	5–7
≥12 months	4–5

MMF: 300 mg/m2/dose BID (max dose of 1.5 g BID). Started on day of transplant

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Pediatric ABO-Incompatible Renal Transplant

11

Pranaw Kumar Jha and Sidharth Kumar Sethi

11.1 History of ABOi Renal Transplants

Kidney transplantation is the best form of renal replacement therapy for a patient with end-stage kidney disease. Blood group incompatibility is an important immunological barrier for kidney transplantation. The initial attempts to transplant kidney across the incompatible blood groups led to hyperacute rejection and graft loss, and soon it was realized that the blood group compatibility is a prerequisite for renal transplantation.

Interest in ABO-incompatible renal transplant rekindled after realizing the potential use of plasmapheresis for the removal of anti-blood group antibodies. In 1988, Alexandre et al. from Belgium published first successful series of ABO-incompatible renal transplants using plasmapheresis and splenectomy in the preconditioning protocol. The popularity of ABO incompatible transplant increased due to the efforts by the Japanese groups in late 1980s, due to absence of a deceased donor program. Subsequently, it spread to the USA and other parts of the world. With the advent of newer immunosuppression, the success rate of such transplants has increased over the past few decades.

11.2 Blood Group Antigens and Blood Group Compatibility

The blood group antigens appear in the sixth week of fetal life. A, B, and H are the blood group antigens. These antigens are present on the red blood cells (RBCs) and other tissues like the salivary gland, pancreas, kidney, and body fluids. H antigen is universally present in all the individuals. Those with A or B blood group have specific carbohydrate determinant added to the H antigen. This is determined by the A- or B-allele-encoded glycosyltransferase gene expression.

P. K. Jha · S. K. Sethi (✉)
Kidney Institute, Medanta, The Medicity, Gurgaon, Haryana, India

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Table 11.1 Donor and recipient blood groups in an ABO-compatible transplant

Donor blood group	Recipient blood group
A, B, AB, O	AB
A, O	A
B, O	B
O	O

Table 11.2 Donor and recipient blood groups in an ABO-incompatible transplant

Donor blood group	Recipient blood group
A, B, AB	O
B, AB	A
A, AB	B

As mentioned, blood group antigens are also found on the endothelium of the kidneys. Hence, if a kidney is transplanted across the blood group barrier, it gets rejected as the naturally forming anti-blood group antibodies present in the recipient attack the antigens present on the graft endothelium leading to complement activation, microthrombi formation, and hyperacute rejection.

Acceptable blood group of a donor and recipient pair in a regular blood group-compatible transplant is shown in Table 11.1, while Table 11.2 shows the blood groups in an ABOi renal transplant.

11.3 Anti-Blood Group Antibodies and Methods of Determination

The anti-blood group antibodies are formed against specific blood group antigens which depends upon the blood group of the person. These antibodies are formed within first 3 to 6 months of life, stabilizes by 5 to 6 years of age, and then declines in the old age. These are believed to be formed as cross-reactive antibodies formed against non-self-antigen such as food and environmental antigens. It is produced by the bone marrow and lymph gland cells. The antibodies are of both IgG and IgM type. The IgG type is thought to be functionally more significant and it is the one which is usually monitored, although it is still not clear which one of them is the one causing the antibody-mediated rejections (AMR).

There are three methods of antibody determination:

- Tube
- Gel
- Flow cytometry

There is a discrepancy in the titer measured by different methods and the reproducibility varies. Flow cytometry is the most reproducible one followed by gel and tube methods. In a study done by Kobayashi et al., the variation in IgG was from 16 to 256, while that of IgM was from 8 to 32 for the same sample in different labs when done by tube method.

11.4 Preconditioning Protocol

For a successful ABOi transplant, a preconditioning protocol is needed to remove the anti-blood group antibodies and deplete the source of antibody production. A preconditioning protocol in an ABOi transplant consists of the following:

- Anti-blood group antibody removal by extracorporeal methods of regular plasmapheresis, double filtration plasmapheresis (DFPP), or immunoadsorption (IA). A regular plasmapheresis requires removal of large amount of plasma and subsequent replacement with albumin or fresh frozen plasma. In DFPP specifically immunoglobulins are removed. It is a two-step process involving separation of plasma and then passing it through a pore size-based filter column leading to removal of immunoglobulin. Immunoadsorption is the most specific method of isoagglutinin removal and can be antibody specific or nonspecific. The ABO column is coated with blood type A or B antigen which adsorbs the corresponding anti-blood group antibodies. It has a low risk of infection and bleeding complications when compared to other extracorporeal methods, but it is the most expensive of all the three methods.

  Figure 11.1 shows different extracorporeal methods of isoagglutinin removal. All antibody removal techniques, namely, conventional PP (plasmapheresis),

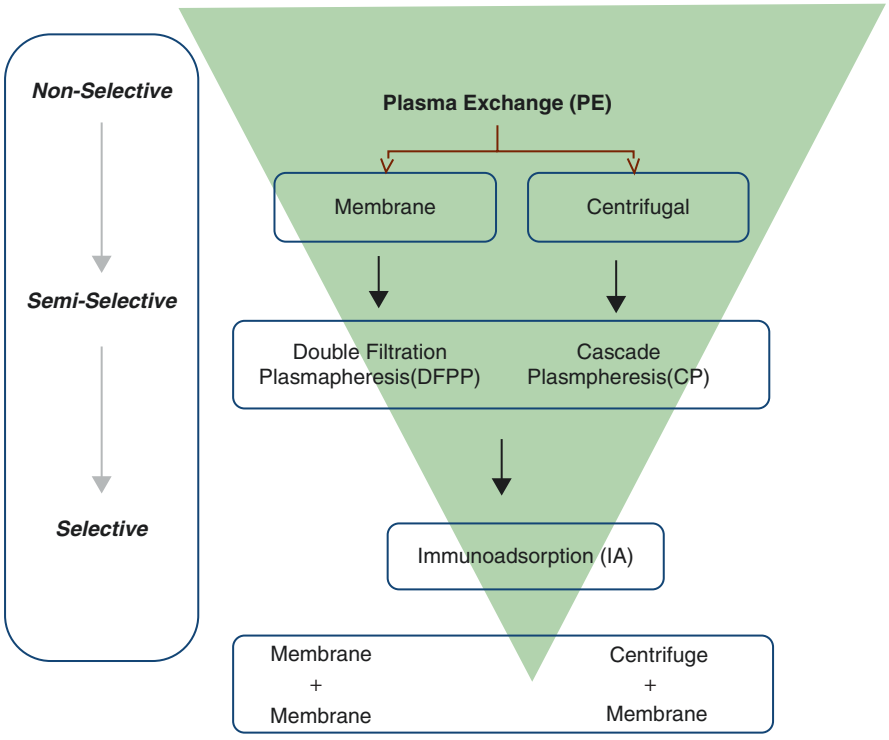

Fig. 11.1 Apheresis technology and selectivity. Taken from Sethi et al., Pediatr Transplant. 2018 May;22(3):e13138 with permission

DFPP (double filtration plasmapheresis), and semi-selective and antigen-selective IA (immunoadsorption), effectively reduce the isoagglutinin titer in the recipient. DFPP and IA modalities allow treatment of higher plasma volumes without requiring any post-procedural substitution fluid replacement with less side effects of plasma infusions. Based on the current evidence, there appears to be no significant differences in survival, graft function, rejection episodes, number of treatments, mean titer step reduction, and titer rebound with the use of different antibody removal strategies. It is important to note that there is a higher incidence of bleeding complications reported in pediatric as well as adult ABOi transplant undergoing IA. The risk appears to correlate with number of apheresis treatments and nonspecific binding of coagulation factors to the membrane. Thus, it is recommended to follow the bleeding parameters and fibrinogen levels in apheresis procedures, especially in IA treatments. Our center recently reported our data of adult and pediatric ABOi transplants with satisfactory outcomes (AK Tiwari et al., 2020). Figures 11.2, 11.3, and 11.4 depict immunosuppression pro-

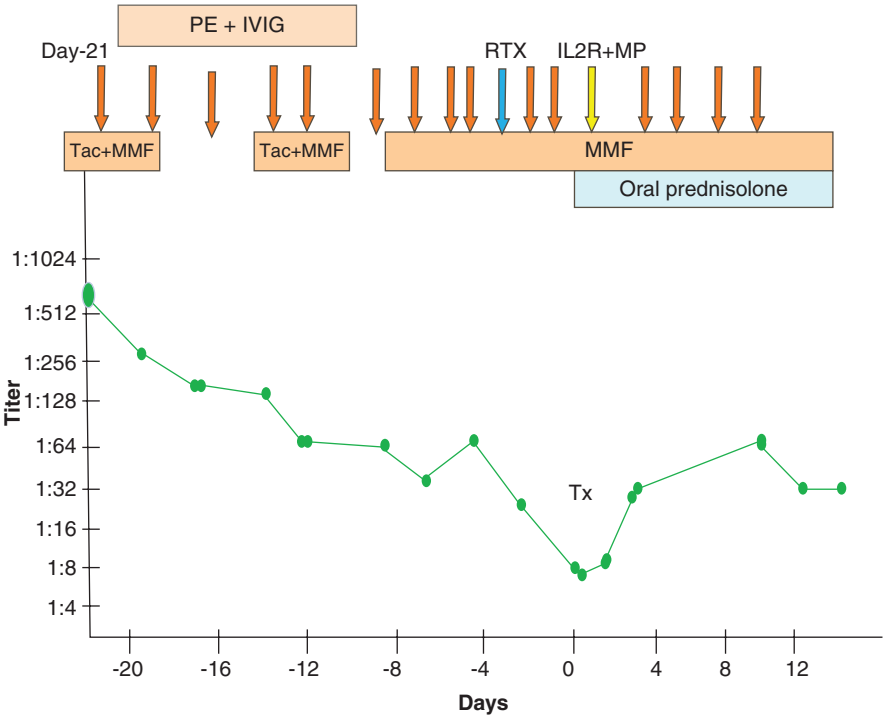

Fig. 11.2 Blood group antibodies trend in a 19-year-old adolescent [B to O] using rituximab, plasmapheresis, and ivIg desensitization. Abbreviations: *PE* plasmapheresis; *ivIg* iv immunoglobulin; *RTX* rituximab; *IL2R* basiliximab; *MP* iv methylprednisolone; *Tx* date of transplant. Taken from Sethi et al., Pediatr Transplant. 2018 May;22(3):e13138 with permission

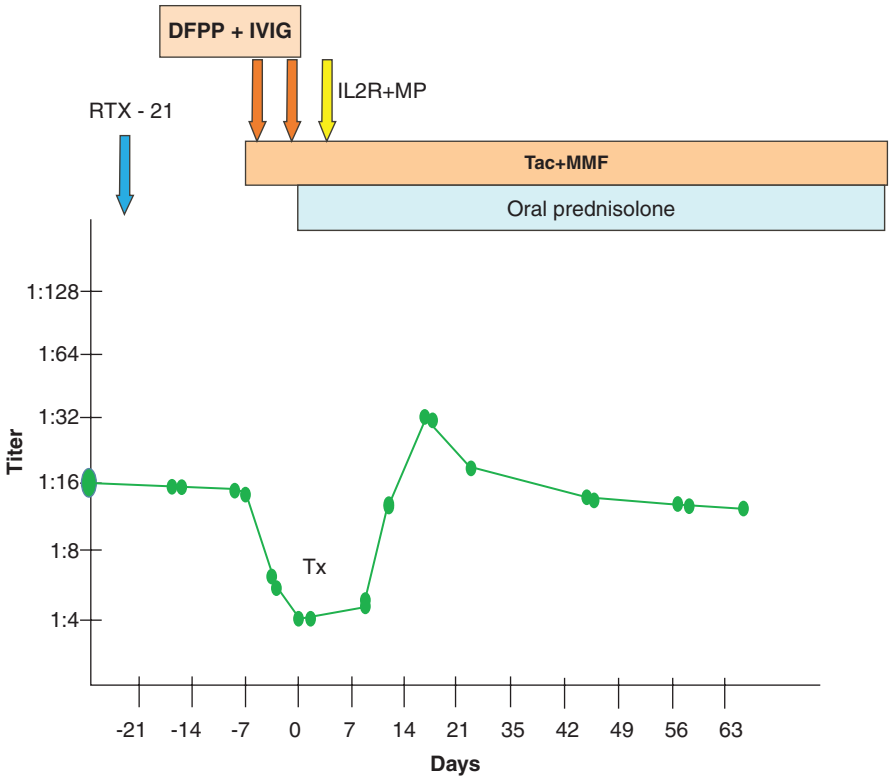

Fig. 11.3 Blood group antibodies' trend in a 12-year-old adolescent [AB to B] using rituximab, double filtration plasmapheresis, and ivIg desensitization. Abbreviations: *DFPP* double filtration plasmapheresis; *ivIg* iv immunoglobulin; *RTX* rituximab; *IL2R* basiliximab; *MP* iv methylprednisolone; *Tac* tacrolimus; *Tx* date of transplant. Taken from Sethi et al., Pediatr Transplant. 2018 May;22(3):e13138 with permission

tocols used in children using various forms of apheresis techniques—plasmapheresis (PE), double filtration plasmapheresis (DFPP), and immunoadsorption (IA), respectively.

- B-cell depletion—Splenectomy used to be the procedure for this purpose earlier, but it was associated with significant morbidity and mortality. Later, injection of rituximab came into use for this purpose in early 2000 and it is being continued presently as well. Although there are rituximab-free preconditioning protocols coming up, few of the studies showed the long-term outcome is better with rituximab.
- Maintenance and induction immunosuppression—In addition to the above, the triple drug maintenance immunosuppression is used consisting of a calcineurin inhibitor, MMF, and steroid. These are started anywhere from 4 days to 1 week pretransplant. The induction consists of an IL2 receptor antagonist such as basiliximab or antithymocyte globulin (ATG).

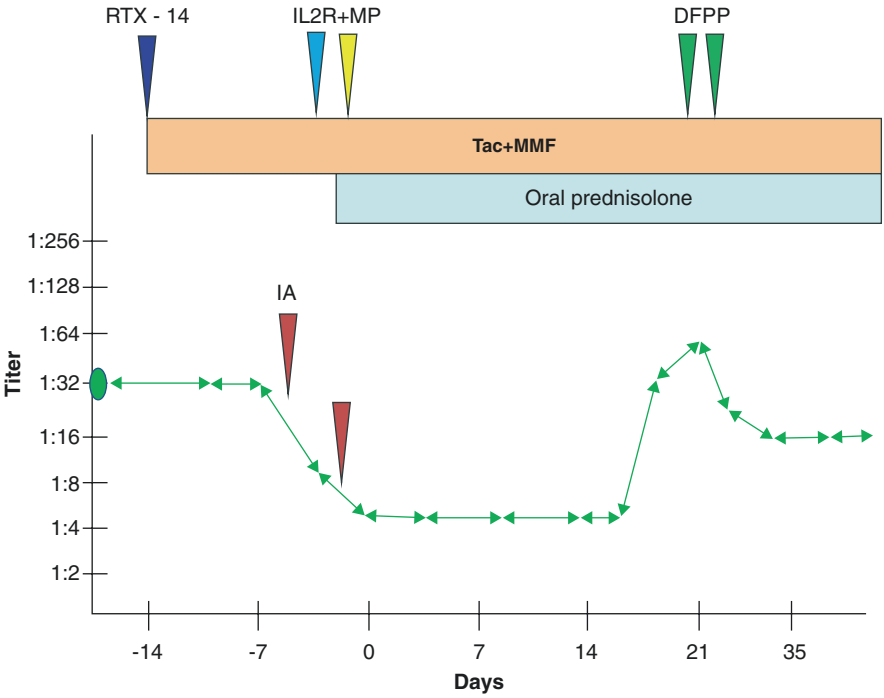

Fig. 11.4 Blood group antibodies' trend in a 3-year-old child [A to B] using rituximab, immunoadsorption, and ivIg desensitization. Abbreviations: *IA* immunoadsorption; *DFPP* double filtration plasmapheresis; *ivIg* iv immunoglobulin; *RTX* rituximab; *IL2R* basiliximab; *MP* iv methylprednisolone; *Tac* tacrolimus; *Tx* date of transplant. Taken from Sethi et al., Pediatr Transplant. 2018 May;22(3):e13138 with permission

11.5 Accommodation

Accommodation is defined as the phenomenon by which the graft rejection is avoided despite the reemergence of incompatible antibody. Whenever an ABO-incompatible kidney is placed in a recipient, one of the three responses are expected:

- Anti-blood group antibodies reacting with the ABO antigen on the graft leading to hyperacute rejection.
- Immunologic tolerance to ABO antigen in which case no antibodies are produced.
- Accommodation—in this case, the antibodies are produced but do not lead to any rejection.

Accommodation as described by an American Society of Transplantation consensus in 2006 is said to occur if there is a structurally and functionally normal graft in the presence of C4d in blood vessels on a kidney biopsy.

The mechanism leading to accommodation is not clear though there are few proposed mechanisms as follows:

- There is a change in the function of anti-donor antibody (Ishida et al., Transpl Int 2005).
- There are changes in the antigen itself.
- Acquired resistance in the graft through the expression of anti-apoptotic genes.
- Expression of complement regulatory protein such as CD59 (Griesemer et al., Transplant 2009).
- Shift to IgG2 isotype of immunoglobulin which is thought to be less effective at complement activation (Kirk et al. 2007).

11.6 Significance of Antibody Titer

There has been a debate about the importance of titer. Initial studies showed that the long-term allograft survival is poor with high-titer levels (Shimmura et al., Transplant 2000). Gloor and Toki et al. showed that high pre-op titer is a predictor of AMR. Gloor et al. also observed that a rapidly increasing titer posttransplant is associated with AMR and graft loss. Tobian et al. showed that high titer at 1–2 weeks posttransplant was associated with higher chances of AMR. However, the studies published later raised questions about the significance of titer in the present era of maintenance immunosuppression of tacrolimus, mycophenolate mofetil (MMF), prednisolone. Most of the centers have their own threshold of acceptable immediate pretransplant titer which has varied from 4 to 32 mostly. There have been occasional centers who have transplanted with a titer of 128 without doing any plasmapheresis.

11.7 Outcomes in Children

Most of the evidence on long-term outcomes of ABOi in children stem from Japanese studies, which report comparable long-term outcomes, as compared to blood group-compatible renal transplants. Recent data from Japan also showed satisfactory outcomes in children with antibody titer $\leq$1:64 using rituximab twice and routine immunosuppression and no apheresis procedures. Recent data from Sweden by Tyden et al. also reports excellent 3-year outcomes. Tyden et al. also recommend not doing routine posttransplant apheresis procedures for rebound unless associated with graft dysfunction. Our center also does not routinely do posttransplant apheresis unless associated with significant titer rebound and acute graft dysfunction. Excellent data from the UK suggests a tailored densensitization protocol in smaller children undergoing ABOi transplant. Data from UK suggests that children wait listed for deceased donor transplant could get ABOi with satisfactory outcomes. They suggest IA for titers 1:64 or more; 1:16–1:32 titers receive DFPP. They did not give apheresis and rituximab in titer 1:8 or less.

The risk of malignancy is not reported to be high in adults undergoing ABOi as compared to blood group-compatible transplants. It is important to note that the recent meta-analysis done on adults undergoing ABOi (including 40 studies and 7098 ABOi transplants) reports excess mortality and graft losses in first 3 years posttransplant. This may be related to early infectious complications and acute rejections. Long-term outcomes after 5 years were equivalent in the recent meta-analysis in terms of graft and patient survival. Thus, it is important to follow these pediatric ABOi recipients closely for infections and acute rejections, especially in the early 3–5 years of transplant.

11.8 Unanswered Questions

Although ABOi renal transplant offers hope to a blood group-incompatible pair of kidney transplantation, there are quite a few unanswered questions. The first and foremost is the phenomenon of hyperacute antibody-mediated rejection in ABO-incompatible renal transplant. It is unpredictable and usually happens within the first 2 weeks of the transplant. The graft biopsy in such cases has been found to contain predominant thrombotic microangiopathy lesions. Various methods have been used to salvage treat a kidney with an acute antibody-mediated rejection. This included plasmapheresis, splenectomy, rituximab, and eculizumab. Most of the attempts to salvage such a kidney is futile and ends up in graft nephrectomy.

Second is the importance of immediate pretransplant antibody titer. The practice is variable and there have been reports of successful transplants with titer as high as 128 without the need for plasma exchange.

Third, the optimal preconditioning protocol is not clear. The protocols have varied. Many centers do plasmapheresis to achieve desired titer before transplantation, while there are others who just use a fixed number of sessions pretransplantation. Even the use of plasmapheresis in posttransplant period is not clear. Few centers do a fixed number of plasmapheresis posttransplantation, while most of the others don't do it regularly. However, there are few who do it if the antibodies increase progressively and cross a certain number posttransplant. The role of rituximab is also not clear.

11.9 Conclusions

With improved understanding in the immunology of transplants, ABO-incompatible kidney transplant is an acceptable option to expand the donor pool if a living-related ABO blood group-compatible donor or paired exchange is not available. There is now extensive data showing equivalent short- and medium-term outcomes for renal allografts and patient survival in adults.

Suggested Readings

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Overview of Biomarkers of Rejection in Pediatric Renal Transplantation

12

Praveena Velpurisiva and Minnie M. Sarwal

Solid organ transplantation is a practical next treatment step to those suffering from end-organ injury and has been in practice since 1954 [1, 2]. According to 2018 SRTR (Scientific Registry of Transplant Recipients) annual report, there was a 24.6% increase in kidney transplants (tx) in the United States, due to higher availability of living and deceased donor allografts [3]. One- and 5-year graft survival rates among pediatric tx patients are 93–95% and 77–85%, respectively [4, 5]. A few known reasons for kidney damage that cause the patients to undergo kidney tx are renal dysplasia, obstructive uropathy, reflux nephropathy, focal segmental glomerulosclerosis, and lupus nephritis [5].

Graft failure or poor acceptance of transplant is accompanied by telltale clinical signs such as higher serum creatinine levels, hypertension, fatigue, elevated temperature, and decreased urine output [6]. To clinically confirm the rejection, an allograft biopsy is obtained, and a histopathological analysis is performed using Banff criteria. At this point, the graft is completely rejected by the immune system and leaves patient with an only option to undergo a second tx surgery. A wide array of factors such as age, health, sensitization risk, and compliance to medication pre- and posttransplantation play a vital role in the success of allograft as shown in Fig. 12.1.

Heterologous immunity, relating to cross-reactivity between the immune response to infectious pathogens and alloimmunity [7], is an important factor that drives varied risk of rejection, stratified by age. A recent study by Aziz et al. also highlights that transplant recipients exposed to the SARS-CoV-2 coronavirus

P. Velpurisiva
Department of Surgery, University of California, San Francisco, CA, USA

M. M. Sarwal (✉)
Department of Surgery, University of California, San Francisco, CA, USA

Department of Medicine, University of California, San Francisco, CA, USA
e-mail: minnie.sarwal@ucsf.edu

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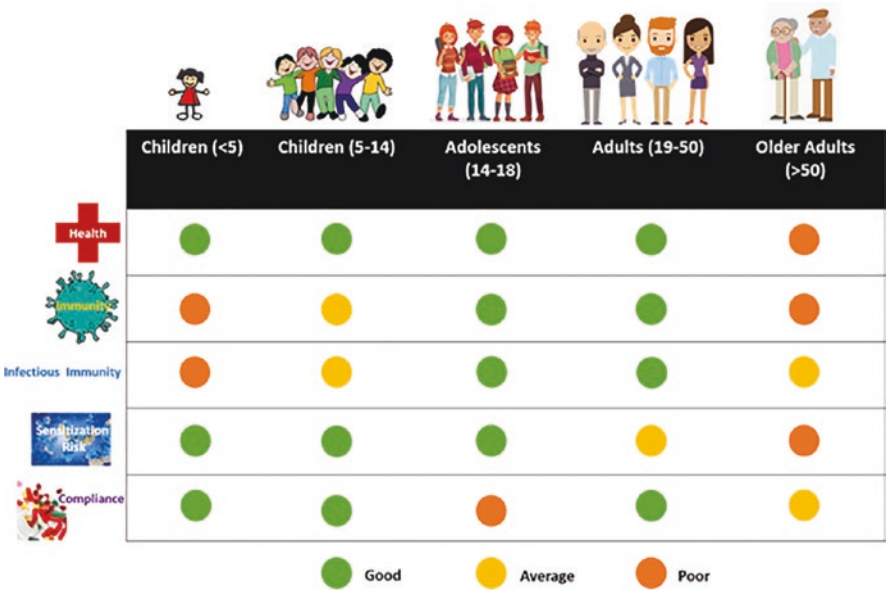

Fig. 12.1 General factors that play a role in the management of transplant recipients across the spectrum of age

(COVID-19) can have a higher risk of acute rejection [8]. To prevent graft deterioration and identify the rejection, even before the clinical parameters fluctuate, early detection of rejection using biomarkers remains a crucial unmet need. Especially in the pediatric population, noninvasive biomarkers, which can have high sensitivity and specificity for acute rejection, and can avoid invasive biopsies, are relevant.

A biomarker is defined as a molecular indicator to identify, monitor, and predict a biological process in a diseased or a healthy state. Based on the end point measurement, biomarkers are categorized as prognostic, predictive, and surrogate end points [9]. Prognostic biomarkers usually refer to scenarios where a future clinical event is assessed with the patient's known preexisting conditions and medical history; predictive biomarkers record change in response to the treatment; surrogate markers have a correlation to the clinical end points as an effect of an intervention, where they only provide information such as a change in a clinical parameter but not causation.

Developing potential molecular biomarkers is essential in determining early kidney rejection, as delay in screening not only results in kidney malfunction but also casts a lasting effect on the health of other vital organs. A biomarker is said to be effective when it lies in the optimal sensitivity-specificity region, with maximum area under the curve in the receiver's operating characteristic (ROC) curve. This optimal region varies from person to person and depends on factors illustrated in Fig. 12.1.

12.1 Invasive Molecular Markers

Many advancements have been made in determining biomarkers from the samples collected in an invasive manner using various genomic tools. Tissue biopsy

followed by histological confirmation remains the gold standard to confirm allograft rejection, till date. Some examples of use of genomic tools include use of DNA microarrays to study gene expression [10–12] profiles from tissue biopsy [13, 14], as well as the reduction of selected genomic markers to PCR for assessment of minimal gene sets for biopsy diagnosis [15–17].

Blood draws provide a minimally invasive approach for biomarker assessment. A blood draw was used to predict acute rejection (AR) by determining 5-gene set and 17-gene signature via kidney Solid Organ Response Test (kSORT) assay [18, 19]. Another well-known INTERCOM cohort study points out that antibody-mediated rejection (ABMR) transcriptome score could diagnose rejection with an accuracy of 85% which the histology failed to capture [11]. Assessment of donor-derived fractions of cell-free DNA in plasma that require DNA amplification and sequence information also provides an opportunity for detection of allograft injury as it relates to acute rejection and chronic graft injury [20–22]. TruGraf DNA microarray-based assay is another validated biomarker test that uses blood to determine the performance of the allograft without the need for biopsy [23, 24].

12.2 Noninvasive Biomarkers

Despite this progress on the invasive procedure front, there is a clear unmet need to expand noninvasive ways to determine biomarkers for tissue rejection. Time-consuming, intensive, and expensive surgical procedures followed by patient visits to address any symptoms or infection, requirement of a trained clinician to obtain biopsy, and repetitive blood draws emphasize the need to identify and validate biomarkers that can predict tissue rejection. Urine provides a powerful biofluid to assess its different compartments to reflect the state of renal allograft health and injury. Urine RNA, though subject to degradation, can still be amplified successfully to assess specific markers such as granzyme B, perforin, granulysin, FasL, FoxP3, and IL10 [9, 25–28]. Lim et al. showed that the urinary exosomes are promising markers for acute T-cell-mediated rejection [29]. Urine supernatant has been studied extensively at the proteome [30–32] and peptidome level [33, 34]. Extensive research has been performed by Sigdel et al. in optimizing the amount of protein recovery [35, 36] from urine for biomarker identification, identifying and validating upregulated fibrinogen proteins using quantitative proteomics [32], and validating acute rejection specific urine markers using shotgun proteomics approach [31]. Urine metabolomics was used to monitor the allograft status as well as immunosuppression in pediatric tx recipients [37] and detect antibody-mediated rejection in children [38]. Despite these research studies on urine as a repository to vital biomarkers, they require detailed and extensive sample analysis and consistent handling protocols.

More recently, multianalyte DNA, protein, and metabolite markers, using custom-designed immunoprobes and assays, have allowed stabilization of urine samples for 3–5 days, without any need for processing at site, and can analyze urine samples and compute a quantitative scaled score (ranging from 0 to 100), called a Q score, which has a > 90% sensitivity and specificity for acute rejection [39]. This study was performed with adult and pediatric urine samples that was validated and

compared against the biopsy results for both types of rejection (TCMR and ABMR) and clinical and subclinical acute rejection.

Over the decades, the field has been progressively transitioning from invasive biopsy to successfully validating invasive, less invasive markers to noninvasive biomarkers. The future of predicting the tx rejection lies in relying on a clinically validated noninvasive biomarker detection kit that can soon replace the current gold standard. Robust performance was seen in biomarkers present in blood and urine as shown in Table 12.1, which paved the road to FDA approval. Single cell sequencing and omics approach will pave a better path in determining specific biomarkers as well as cater personalized treatment to the patients.

Table 12.1 List of validated and exploratory minimally or noninvasive biomarkers for kidney rejection. *FDA approved and commercially available

Biomarker classification	List of biomarkers	First authors	Sample type	Recipient
Validated	miRNA-210 [40]	Lorenzen, J.M. et al.	Urine	Adults
	Three-gene signature (CD3εE,IP-10 mRNA, 18 s rRNA,) [41]	Suthanthiran M. et al.	Urine	Adults
	miRNA-155-5p, CXCL10 [42]	Millan, O. et al.	Urine	Adults
	*CXCL9 [43]	Hricik, D.E., et al.	Urine	Adults, children
	CXCL10 [43]	Hricik, D.E., et al.	Urine	Adults, children
	Q score [39]	Yang et al.	Urine	Adults
	uCRM score [44]	Sigdel, T.K., et al.	Urine	Adults
	Tetraspanin-1, Hemopexin [29]	Lim, J.H., et al.	Urine	Adults
	HLA-DRB1, FGB, FGA, KRT14, HIST1H4B, ACTB, KRT7, DPP4 [32]	Sigdel, T.K., et al.	Urine	Children
	17-gene set based on kSORT assay [19]	Roedder, S., et al.	Blood	Adults
	5-gene set [18]	Li, L., et al.	Blood	Children
	10-gene set [45]	Li, L., et al.	Blood	Children
	*$CD154^{+}$ cytotoxic T cells [46]	Ashokkumar, C., et al.	Blood	Adults
	Dd-cfDNA [20, 21]	Bloom, R.D., et al., Goussous, N., et al.	Blood	Adults
	*TruGraf [23, 24]	First M.R.et al., Peddi V.R. et al.	Blood	Adults
	Soluble galectin-9 [47, 48]	Naka, E.L., et al., Shahbaz, S.K., et al.	Blood, urine, tissue	Adults
	Soluble TIM-3 [47–49]	Naka, E.L., et al., Shahbaz, S.K., et al., Chen, D., et al.	Blood, urine, tissue	Adults

Table 12.1 (continued)

Biomarker classification	List of biomarkers	First authors	Sample type	Recipient
Exploratory	FOXP3 [50]	Aquino-Dias, E.C., et al.	Blood, urine	Adults
	Soluble KIM-1 [48, 51, 52]	Shahbaz, S.K., et al. Chaturvedi, S. et al. Jin, Z.K., et al.	Blood, urine	Adults
	Granzyme B, perforin, FasL [25]	Vasconcellos, L.M., et al.	Blood	Adults, children
	$CD4^{+}CD25^{high}CD45RO^{+}$ [53]	Sorof, J.M., et al.	Blood	Adults
	Soluble CD30 [54]	Hirt-Minkowski, P., et al.		
	Osteopontin [52]	Jin, Z.K., et al.	Blood	Adults
	TTN, LBP, CFD, MBL2, SERPINA10, AFM, KNG1, LCAT, SHBG [55]	Freue, G.V., et al.	Blood	Adults
	NF-κB, STAT1, STAT3, and 63 other proteins [56]	Wu, D., et al.	Blood	Adults
	TRIB-1 [57]	Ashton-Chess, J., et al.	Blood	Adults
	TIPE2 [58]	Jia, L., et al.	Blood	Adults
	mRNA for OX40,OX40L, PD-1, FOXP3 [59]	Afaneh, C., et al.	Blood	Adults
	UMOD, PEDF, CD44 [31]	Sigdel, T.K., et al.	Urine	Adults
	IGFBP7, VASN, EGF, LG3BP [30]	Loftheim, H., et al.	Urine	Young adults, children
	ANXA11, integrins (β3,α3), TNF α [60]	Srivastava, M., et al.	Urine	Adults

12.3 Current Challenges

Although many biomarkers were successfully validated, performance of many biomarkers is challenged by confounding risk factors like bacterial and viral infection such as cytomegalovirus (CMV), BK virus, etc. and chronic injury seen in tx recipients. Immunosuppressants administered to these patients also have an impact on certain immunological markers that may otherwise provide a status on the allograft status. These factors interfere in validating biomarkers, as they cast an effect on upregulation or downregulation of proteins or metabolites.

One of the challenges that lie in biomarker discovery and validation is the lack of large cohorts to definitively conclude on the specificity and reliability to be able to predict the outcome in different patient demographics. The missing gap in the field also lies in capturing the subclinical conditions at an earlier stage that are usually not detected further down the road to graft failure. In addition to the research on

biomarkers on predicting the rejection posttransplantation, biomarkers that can thoroughly assess the organ quality prior to transplantation and predict the consequence are invaluable [61]. This information can help in classifying the "good" vs "bad" quality organs that can provide a matrix with deceased, live (healthy and those with comorbidities) donors and match them with recipients with a different matrix of health conditions.

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Adherence in Pediatric Transplant Recipients

13

Bethany J. Foster

13.1 Introduction

Poor treatment adherence is believed to be among the most important barriers to long-term graft survival [1–3]. Poor medication adherence may be the most important cause of late acute rejection and graft failure—especially among young people [2–5]. Quality of life is poorer [6, 7], and both hospitalization and mortality rates are higher [8] among poorly adherent than adherent patients. Daily intake of immunosuppressive medications on a strict schedule is necessary to prevent rejection. In addition, regular monitoring of graft function via blood testing, imaging, and/or biopsies is needed for early detection and treatment of rejection. Adolescents and young adults are at particularly high risk for graft failure [9–11]. Although the reasons for the higher risks in this age group are incompletely understood, suboptimal treatment adherence is likely an important contributor. Whether other factors, such as greater immune reactivity in this age group, also play a role is unconfirmed. Regardless of the reasons, this age group should be considered at higher risk, warranting closer surveillance.

S*atisfactory adherence* has been defined as sufficient concordance between the prescribed treatment plan and the patient's behavior such that outcome is unaffected by any deviations from the plan [12]. Unfortunately, the magnitude and frequency of deviations needed to affect outcomes are not known and likely vary from patient to patient [13]. In some cases, even fairly small deviations from the prescribed immunosuppressive regimen may have important consequences [14].

This chapter will review the different components of adherence, review factors that influence adherence, highlight the most common barriers to adherence among

B. J. Foster (✉)
Departments of Pediatrics and Epidemiology, Biostatistics and Occupational Health, McGill University and Montreal Children's Hospital of the McGill University Health Centre, Montreal, Quebec, Canada
e-mail: bethany.foster@mcgill.ca

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young people, and consider the strengths and limitations of different methods of measuring adherence. I will also consider possible intervention strategies to improve adherence. I will focus primarily on medication adherence. However, the impact of poor adherence to other aspects of treatment, including attendance at clinic visits and blood testing [15], is also recognized.

13.2 Components of Adherence

Difficulties with adherence are classified as problems of *initiation, implementation*, and/or *persistence* [16]. Initiation is rarely a problem in transplantation; immunosuppressive medications are started in hospital, and failure to continue the medications as an outpatient is exceedingly rare. Most adherence difficulties among transplant recipients are problems of implementation and include issues with *taking* all of the prescribed doses, with appropriate *timing* of doses, and with appropriate *dosing* [16].

Missing doses intermittently or regularly is a common problem: in one study, 27% of kidney transplant recipients 11–20 years old reported missing at least one dose of medication within the prior week [17]. Poor taking adherence is linked to higher acute rejection and graft failure rates [18, 19]. Even more risky than occasional missed doses are "drug holidays," defined as missing ≥2 consecutive doses [18, 20]. It must be acknowledged that almost all patients will miss doses occasionally. Patients may be encouraged to honestly report missed doses by asking how often they miss doses, rather than whether they ever miss doses.

Off-schedule dosing indicates a problem with "timing adherence" and is the most common form of poor adherence. Over 75% of kidney transplant recipients 11–20 years old reported taking medications at least 1 h late at least once in the prior week [17]. In the 3-month run-in period of the TAKE-IT trial, in which adherence was monitored electronically, only about 65% of all doses (across all patients) were taken within 3 h before or after the scheduled time [21]. The impact of off-schedule dosing on rejection risk and graft outcomes is unknown, but there is some evidence for a relationship with late acute rejection in heart [22] and kidney [18, 23] transplant recipients. An expectation of perfect timing adherence is unrealistic. A window of 1–2 h around the expected dosing time is considered acceptable by most healthcare professionals [24, 25]. It is important that the expected dosing schedule be discussed with transplant recipients, and the importance of correct dose timing emphasized.

Incorrect dosing of medications may be due to either dosing errors or deliberate modification of the dose by the patient. Dosing errors, which are usually easily corrected after identification, may result from prescribing errors, dispensing errors, miscommunication between the patient and the physician or pharmacist, or misunderstanding on the part of the patient. Patients may deliberately reduce the dose of medication due to adverse effects and beliefs about the medication or in an effort to make the supply last longer in the face of financial constraints [26–29]. The risk of graft failure was 70% higher among those who reduced doses by more than 50%

compared with no reduction [30]. Treating teams must directly acknowledge the practice of dose modifications with patients in order to identify and correct the reasons for this problem.

Problems with *persistence*, defined as continuing the medication regimen for as long as the condition is being treated [16], are fortunately uncommon in transplant recipients. One study showed discontinuation of medication to be associated with an 8.3 times higher risk of graft failure [30].

13.3 Unintentional Vs. Intentional Poor Adherence

Among adolescents, most poor adherence is "unintentional" [29]. Organizational problems (58%) [31] and forgetting (29–56%) [31, 32] are the most commonly cited reasons for missing medications among adolescent renal transplant recipients, often triggered by disruptions in normal routines [27, 29]. Adherence tends to be poorer on weekends than weekdays [33], and in the evening compared with morning [24, 25, 33]. An understanding of these common organizational challenges can be useful in helping adolescents plan how they will maintain adherence during routine disruptions. Intentional poor adherence, which may reflect attempts to "be normal," represents less than 5% of reasons given by adolescents for poor adherence [31]. This type of nonadherence is more difficult to address as it may be associated with a lack of acceptance of the condition being treated, or with beliefs about the relative risks of medications compared with the condition being treated [26]. Such beliefs may be tightly linked to culture and to trust.

13.4 Determinants of Adherence

Understanding the determinants of adherence is helpful in planning interventions to support adherence and in considering the needs of individual patients. Factors associated with treatment adherence were classified by the World Health Organization (WHO) as patient-related, social and economic, therapy-related, condition-related, healthcare team-related, and healthcare system-related [34]. This classification was further refined by Berben et al. who conceptualized the determinants of adherence at different "levels" [35]. Berben's framework includes patient-level (WHO patient-, condition-, and therapy-related factors), "micro"-level (social factors and interactions with the care team), "meso"-level (organization and expertise of the healthcare team and care processes), and "macro"-level (high-level healthcare systems factors, including care and medication cost coverage, and overall care environment) factors. Figure 13.1 provides a schematic representation of the likely causal links between the different factors influencing adherence. While highlighting the importance of care processes and structures in promoting adherence, the framework shown in Fig. 13.1 also emphasizes that the effects of meso- and macro-level factors must be mediated through modifiable patient-level factors. Ultimately, only the patient can change their adherence.

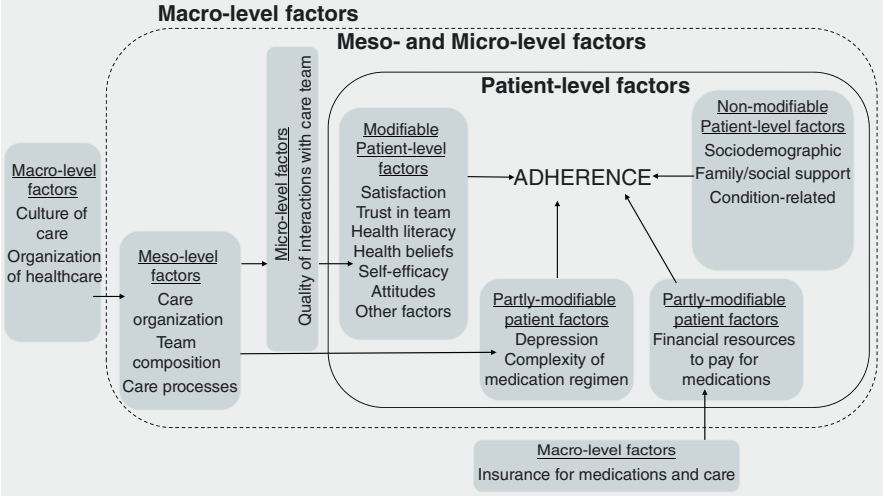

Fig. 13.1 Factors influencing treatment adherence at the "macro-," "meso-," "micro-," and patient levels are shown in concentric boxes. Arrows indicate the likely causal relationships. Note that the influence of macro-, meso-, and micro-level is mediated through patient-level factors

Numerous patient-level risk factors for poor adherence have been identified. Some, including male gender [36], longer time since transplant [18, 37], and lower socioeconomic status, are not modifiable [38]. Recognition of these characteristics as risk factors may be helpful, but it must be recognized that our ability to predict adherence based on non-modifiable risk factors is imperfect. Modifiable risk factors deserve more attention. Healthcare professionals have the opportunity to influence many patient-level factors associated with adherence. Simplification of the medication regimen may help improve adherence [32, 39, 40]. Greater self-efficacy, defined as a sense of control over one's environment and behavior, is also associated with better adherence [25]; greater self-efficacy may start with improved disease and treatment knowledge. While lack of parental supervision and support, poor parent-patient communication, and poor family functioning may be difficult to modify, they may be potent drivers of poor adherence among children and adolescents [39, 41, 42]. Therefore, these factors merit attention.

Financial factors related to the way medications and medical care are insured have also been recognized to have a major impact on adherence [43]. Inability to pay for medications, less common in children than adults, has been reported as a cause of poor adherence in 10 to >20% of patients in US kidney transplant programs [28, 29].

13.5 Transfer to Adult-Oriented Care and Adherence

The period following transfer from pediatric to adult-oriented care is recognized as a high-risk time for transplant recipients [44]. It is difficult to separate the effects of age from those of care environment. However, some studies suggest that adult-oriented healthcare processes are poorly matched to the developmental needs of adolescents and young adults, contributing to poorer adherence [45]. Preparation for the changes in care philosophy, practices, and resource availability that usually accompany the transfer to adult care is important to maintaining adherence [42, 45]. Ongoing efforts to promote adaptation to the new adult care environment may also help ensure adequate adherence after transfer [46].

13.6 Pretransplant Adherence as a Predictor of Posttransplant Adherence

The risk of poor posttransplant medication adherence was eight times higher at 1 year posttransplant [47] and three times higher at 3 years posttransplant [48] among adult solid organ transplant recipients with poor pretransplant adherence compared with those with good adherence pretransplant. However, our ability to predict posttransplant adherence from pretransplant adherence is poor: the prevalence of poor adherence 1 year posttransplant is less than half of that pretransplant [48]. Furthermore, there is little information on the adherence trajectories of children and adolescents before and after transplant [49]; behavior may be even less predictable in this age group since it is likely to change with age. An assessment of adherence pretransplant is generally recommended, but should not be used to make decisions about transplant candidacy unless health-compromising nonadherent behavior continues despite intervention [50].

13.7 Methods of Measuring Adherence

Accurate assessment of medication adherence is challenging, since no perfect method exists. Therefore, most suggest that multiple methods should be used whenever feasible for optimal adherence assessment [51]. Assessment methods potentially useful in clinical practice are summarized in Table 13.1.

Direct methods: The only direct method available to clinicians is measurement of blood drug levels. Low or undetectable trough levels of immunosuppressive medications may provide evidence of very recent poor adherence, and recurrent low

levels serve as a red flag. It has also been suggested that high variability in the trough levels of medications, as measured using the standard deviation [52] or coefficient of variation [53], may reflect poor adherence. Only variability in tacrolimus levels has been shown to correlate with outcomes. Variability in cyclosporin levels appears less useful [54], and mycophenolic acid levels and azathioprine metabolites are not routinely monitored and have not been studied. The standard deviation of tacrolimus trough levels has been repeatedly shown, across multiple organ types [52, 55], to be associated with higher risks of rejection and graft failure—which is

Table 13.1 Methods of measuring adherence in clinical practice

Method		Strengths	Limitations
Direct			
Drug levels	Measure blood drug levels	• Objective.	• Only reflects very recent adherence. • Not available for all relevant medications.
	Determine variability in tacrolimus trough levels (standard deviation or coefficient of variation)	• Objective. • Easily calculated. • Relatively inexpensive.	• Requires multiple levels. • Other reasons for variable levels (besides poor adherence). • Validated only for tacrolimus.
Indirect			
Self-report	Unstructured questioning or various self-report tools may be used with different time windows	• Simple. • Inexpensive.	• Poor recall. • Overestimates adherence due to social desirability bias.
Pill counts	Remaining pills counted and compared with number expected if adherence was perfect	• Simple. • Relatively inexpensive.	• Patients must bring pills for counting. • Assumes missing pills were consumed. • No information about timing of missed doses or about times of day that medications are taken.
Pharmacy records	Compare number of pills dispensed over a given interval with number expected to be consumed within that interval	• Relatively inexpensive. • May help identify dosing errors, deliberate dose modifications.	• Estimates may be inaccurate due to patients' pill "stockpiles" or if patient uses more than one pharmacy. • Cumbersome to call pharmacy. • No information about timing of missed doses or about times of day that medications are taken.

Table 13.1 (continued)

Method		Strengths	Limitations
Electronic monitoring	Single pill-bottle device records date and time of bottle opening	• Portable, simple. • Detailed information on both taking and timing. • Captures changes over time. • Can be used to provide dose reminders only when needed.	• Assumes medication is consumed when bottle is opened. • May be cumbersome among those who use a multidose pillbox. • Relatively expensive. • Requires adherence to use of device. • Requires expertise in using and interpreting data.
	Multidose electronic pillbox records date and time of opening of each compartment	• Easy to use. • Detailed information on both taking and timing. • Captures changes over time. • Can be used to provide dose reminders only when needed.	• Assumes medication is consumed when compartment is opened. • Not portable. • Relatively expensive. • Requires adherence to use of device. • Requires expertise in using and interpreting data.

a strength. A standard deviation <2.0 was associated with better graft survival. However, it is not clear if this measure reflects adherence only. Data from two trials in kidney transplant recipients showed no correlation between electronically monitored adherence and standard deviation of tacrolimus trough levels [21, 56]. Other factors including consumption of medications with or without food or interactions with other medications or foods could also influence tacrolimus exposure [57]. Furthermore, calculation of the standard deviation requires at least three drug levels; even if levels are measured monthly, variability in levels will inevitably reflect past behavior. The delay needed to determine standard deviation of tacrolimus levels may be too long to be very helpful in the clinic.

Indirect methods: Indirect methods include self-report, pill counts, pharmacy refill data, and electronic monitoring. In general self-report tends to overestimate adherence [58]. However, using a validated tool to capture self-reported adherence may improve accuracy by ensuring a clear and reasonable time frame for reporting. Normalizing adherence lapses and remaining neutral and nonjudgmental will also improve accuracy. Self-report correlates moderately well with other assessment methods, such as electronic monitoring [58].

Although pill counts seem simple and potentially useful, they have significant limitations. Patients often forget to bring pills for counting. Counts also assume that missing pills have been consumed. Furthermore, pill counts can only estimate if doses were missed; they provide no information on the timing of missed doses or about times of day that medications were taken. Pharmacy records may be useful to

verify doses and determine if refills are collected at the expected intervals. However, pharmacy records have similar limitations to pill counts. In addition, if patients have "stockpiles" of medication, left over after dose changes, it may be difficult to accurately determine adherence.

Electronic monitoring is considered the "gold standard" for adherence assessment [58]. Electronic monitors provide the richest type of adherence information, capturing of patterns of missed and late (or early) doses, and changes in adherence over time. Adherence data can be captured in real time on a web-based system accessible to both patients themselves and healthcare professionals. However, electronic monitoring assumes that the medication is consumed every time the electronic device is opened and that no medication was consumed if the device is not opened. When these assumptions are incorrect, inaccuracies result. A number of monitoring systems are available, including pill bottles with an electronic cap that records a date and time "stamp" each time the bottle is opened (such as the Medication Event Monitoring System, MEMS) and multidose electronic pillboxes such as the Vaica SimpleMed device. While bottle devices have the advantage of being portable, they can only store one medication, and therefore may be unacceptable to people who use a multidose pillbox to organize their medications [59]. Some bottle devices must be placed on a reader to upload the data. Multidose electronic pillboxes have their own limitations. They are not portable and may depend on a reliable Internet connection. There is some debate as to whether electronic monitors capture adherence to using the monitor as much or more than adherence to the medication regimen.

13.8 Improving Adherence for all Patients

Before implementing patient-level interventions to improve adherence, it is important to consider the foundation upon which these interventions will rest. The organization and delivery of care, as well as the quality of the interactions with patients, may also influence adherence [35]. A transplant program with an adherence-supporting culture recognizes that poor adherence is difficult to assess, and often undetected. Further, an adherence-supporting pediatric transplant program recognizes the critical importance of working with young recipients and their families to develop patients' autonomy regarding self-care, including medication-taking; treatment adherence is inextricably linked with autonomy in self-care [60]. Pediatric transplant programs must integrate adherence education and some form of adherence monitoring into routine care for all patients. Consistently asking about medication adherence at every clinic visit, in a nonjudgmental way, not only reminds patients of the importance of adherence, but may help improve adherence. Regular monitoring of blood drug levels and graft function may serve as an additional reminder of importance of medication adherence and alert care providers to potential problems. Protocols to increase the frequency of visits and/or blood tests for patients in whom adherence is suboptimal may also be helpful [61]. Creating an adherence-promoting culture within a transplant program is not cost-free. Supporting

adherence takes time. Staffing must be planned accounting for the time needed to promote good adherence and to develop patients' autonomy in medication-taking.

Given the importance of the quality of interactions between healthcare providers and patients in supporting adherence [35], transplant program staff also need appropriate training. Nurses are generally well-trained to support patients' adherence. Motivational interviewing training may further enhance the skills of all personnel to better support adherence [62, 63].

It may also be helpful to preemptively address organizational problems and "forgetting," two of the most commonly identified barriers to adherence, by teaching patients to use a multidose pillbox [31, 32], and to use a reminder system, such as a watch or cellphone alarm. Smartphone applications and web-based tools to promote better self-care and medication adherence may also be helpful for some patients [64].

It is also important have systems in place to identify individual patients who are struggling with adherence so that they can receive additional interventions. Tools such as the Adolescent Medication Barriers Scale may be helpful in identifying personal barriers to adherence and can be used to tailor interventions to address the most relevant barriers [65]. Low drug levels or large variability in tacrolimus trough levels may also be helpful in identifying patients in need of more intensive intervention.

Four randomized trials testing adherence-promoting interventions, one in children and adolescents (TAKE-IT), showed superior adherence in the intervention than the control group [21, 56, 66, 67]. The intervention in one of these included only electronic monitoring with dose reminders (plus or minus provider notification of adherence lapses) [56]. The other three interventions (TAKE-IT, MAESTRO-TX, MAGIC) were similar in that they all included dose reminders, feedback of electronically monitored adherence data, social support, problem-solving with development of action plans to address specific adherence barriers, and regular reassessment of these action plans. One criticism of such multi-component interventions is that it is not possible to determine which are the 'active ingredients' [68]. However, it is possible that different components are more or less effective for different people, and therefore multiple components are necessary.

13.9 Targeted Intervention

Both the MAESTRO-TX and MAGIC trials targeted only those patients with demonstrated poor adherence for intervention [66, 67]. This is a logical and efficient strategy. The challenge in applying this approach in clinical practice lies in accurately identifying those in need of intervention before development of an adverse outcome. Both trials used an interval of electronic monitoring to identify high-risk patients. While this may be an effective method, it is not clear how often, and when, monitoring would need to be done to identify patients at risk. This is a particular challenge in young people, in whom adherence is likely to change over time with increasing independence from parents. It may be helpful to track adherence barriers using a questionnaire administered at regular intervals and intervene when new

barriers appear. It may also be useful to intervene preemptively when there are major changes in usual routines or in lifestyle (e.g., leaving home for college) [20, 59]. To be effective, interventions should be administered repeatedly at regular intervals rather than in single session or concentrated formats [69–73].

13.10 Conclusions

Pediatric solid organ transplant recipients require many decades of graft function. One of the most important ways of optimizing graft survival is to ensure scrupulous adherence to immunosuppressive medications. The responsibility for excellent adherence is shared between transplant care providers, parents, and young people themselves. Transplant care providers must develop programs with an adherence-supporting culture, in which adherence is openly discussed and routinely assessed. Interventions aimed at improving adherence and in developing young people's autonomy in medication-taking should be integrated into regular care. Staff must have adequate time for adherence-supporting activities. Results of the first randomized trials suggest that multicomponent intervention strategies are effective in improving adherence, particularly among those identified to be at high risk. Future work must determine the effectiveness of these approaches in improving clinical outcomes.

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14 Recent Advances in the Diagnosis and Treatment of Antibody-Mediated Rejection in Pediatric Kidney Transplants

Katherine Twombley

14.1 Diagnosis

14.2 Detection of Donor-Specific Antibodies

Cell-based techniques were first described by Terasaki and Patel (Fig. 14.1), when they showed immediate graft failure in 80% of the patients with circulating donor-specific antibodies (DSA) identified by the complement-dependent cytotoxicity (CDC) assay [1]. This test only tells you that there are antibodies present that are activating complement; it does not tell you which antibodies are present. At the time that this assay was developed, the assumption was that positive crossmatches always represented clinically relevant human leukocyte antigen (HLA) antibodies and that a negative crossmatch would ensure long-term graft survival, which is now known not always to be the case.

This test is performed by incubating the recipient's serum with donor lymphocytes. If the recipient's serum has complement-fixing antibodies directed toward the donor HLA antigens, then addition of complement (typically rabbit) will result in cell death/lysis. The more complement-fixing antibodies present, the more cells that die, leading to a strong crossmatch and a higher concern for subsequent ABMR. A score of 0 means no reaction (little risk) and a score of 8 is the strongest score (highest risk), providing the clinician with a semiquantitative result. You can also perform a "titered crossmatch." In this test, the serum of the recipient is serially diluted to 1,2,4,8,16,32,64,128, etc. The result is reported as the lowest dilution that gives you a negative reaction (e.g., 1:128). The main advantage of the CDC assay is that it specifically picks up complement-fixing antibodies that are known to pose a risk to

K. Twombley (✉)
Department of Pediatrics, Division of Nephrology, Medical University of South Carolina, Charleston, SC, USA
e-mail: twombley@musc.edu

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Fig. 14.1 Cell based Assays (**a**) CDC Cross Match (**b**) Flow Cross Match. Recipient's sera containing anti-HLA donor specific antibodies. Donor lymphocytes+ complement or fluorescent-conjugated antihuman globulin

the allograft. One of the disadvantages is that complement-fixing antibodies that are present at low titers or potentially clinically relevant weak IgG HLA-specific antibodies that may be rendered negative during the preparation may not be picked up by this assay. In addition, CDC assay may be positive in the setting of antibodies directed toward non-HLA antigens (autoreactive antibodies).

The next tests that were developed were the solid-phase antibody detection systems (Fig. 14.2), and they include enzyme-linked immunosorbent assay (ELISA), flow cytometry, and Luminex® (Luminex Corporation, Austin, TX). As Gebel and Bray summarized in their paper titled "HLA Antibody Detection With Solid Phase Assays: Great Expectations or Expectations Too Great?" [2], they have changed the field for better and/or for worse. The main advantage of these assays is that they have allowed for the determination of specific anti-HLA antibodies.

Flow cytometry (lymphocyte crossmatch) is currently considered the gold standard for identifying the presence of HLA donor-derived antibodies [3]. It uses microparticles coated with purified HLA class 1 and class 2 antigens [4]. The process usually starts by using multiple antigen beads that delineate between the presence of antibodies directed toward HLA class 1 or class 2, and the intensity of these antibodies in flow cytometry screen is expressed as mean channel shift (MCS) [5]. Once there is a positive flow screen, then single bead testing can be performed to identify the specific antibodies. This is typically done by flow cytometry or Luminex®. The main difference between these two tests is that with Luminex® there are fluorescence beads, with antibody binding to antigen beads on a plate. With flow, the reaction takes place in suspension. The main disadvantage of these tests is that there is no information as to whether the antibodies detected are able to activate complement. The main advantage of these tests is that once the specificities of the recipient HLA antibodies have been determined, the crossmatch can be more accurately interpreted, making up for the main disadvantage. For example, if recipient solid-phase testing does not show any donor-derived HLA antibodies, then the

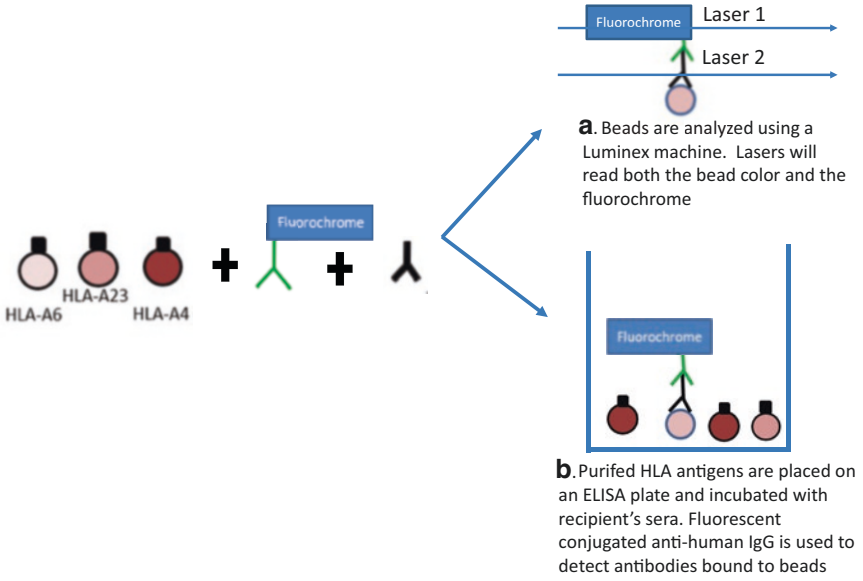

Fig. 14.2 Solid Phase Assays (**a**) Luminex (**b**) ELISA. Internally dyed color coded microsphere beads are coated with a single HLA class I or class II molecules. The recipient's sera is incubated with the beads and fluorescent conjugated anti-human IgG. (**a**) Beads are analyzed using a Luminex machine. Lasers will read both the bead color and the fluorochrome (**b**) Purifed HLA antigens are placed on an ELISA plate and incubated with recipient's sera. Fluorescent conjugated anti-human IgG is used to detect antibodies bound to beads

lymphocyte crossmatch would be predicted to be negative. But if the solid-phase testing is positive, a positive lymphocyte crossmatch could be interpreted as not due to HLA antibodies [6].

With flow and Luminex®, the clinician obtains a semiquantitative measure of the amount of antibodies present expressed in terms of median fluorescence intensity (MFI) or molecules of equivalent soluble fluorochrome (MESF). While studies have demonstrated an association between the strength of DSA and the risk of development of ABMR, response to treatment of ABMR, and subsequent allograft survival [5], one of the main problems is that there is currently no way to develop a consensus on the cutoff strength of DSA that is clinically relevant. Even when protocols and reagents are exactly identical, there is still around 20–25% variability in the level of antibody activity reported by laboratories. There are several reasons for this. It is difficult to standardize flow due to variability in cytometers, fluorochromes, antiglobulin reagents, and cell-to-serum ratios [7]. Luminex® is affected by several factors, including antibody concentration in the serum, density, conformation, and orientation of the antigen, as well as by the antibody avidity toward the respective antigen [8]. Currently, it is recommended that each lab make their own cutoffs and always test subsequent samples in the same lab. More recent analyses have suggested a consensus significance of an MFI of 1400 or greater.

The reporting of MFIs or MESFs has led clinicians to believe that those values represent the strength of the antibodies, but this is not always the case. We now know that all HLA antigens are not the same, and this has led to some labs to make some MFI thresholds more locus specific. Sullivan et al. described their practice with antibodies against C-locus [9]. They noted that antibodies against C-locus specificities do not tend to be clinically significant until they reach higher thresholds (5000 MFI) compared to other HLA class 1 loci (2000 MFI), as antigen cell surface expression for the C-locus is lower [10]. More recently, epitope and eplet matching has come to the forefront and is gaining traction in the field of transplantation. An epitope is the sequence of amino acids on an antigen where an antibody can bind, and each HLA antigen can be composed of multiple overlapping epitopes. An eplet is when amino acids are not in sequence but are in close enough proximity in the quaternary structure to allow for antibody binding. A single antibody to a shared amino acid sequence (epitope or eplet) can react with multiple antigens**.** Online tools that assist with the identification of shared epitopes have been developed and include HLAMatchmaker (http://www.epitopes.net) and the HLA Epitope Registry (http://www.epregistry.com.br/terms/index).

It has become clear that de novo DSA (dnDSA) development is one of the biggest risk factors in developing ABMR post renal transplantation [11], underscoring the need for the best possible matches. A single antigen can have multiple epitopes that can be pathogenic and just like antigens, not all epitopes are the same. It has now been shown that less dnDSA developed when matching was done with HLA class II antigen and eplet matching only compared to antigen matching alone [12]. There are minimal data on the use of this new technology in pediatrics [13, 14], and none of the long-term outcomes of pediatric kidney transplant patients that were matched by epitopes or eplets have been reported to date. There is still a great deal to learn about this technology and how it will apply to children.

14.3 Surveillance DSA Monitoring

The routine monitoring for dnDSA development post kidney transplantation has not been universally adopted by the pediatric kidney transplant community, but it is becoming more common. There are arguments for and against this practice. Ginevri et al. in showed that the development of dnDSA preceded the development of ABMR by a median time of 1 year in pediatric kidney transplant patients [15] and that the patients who developed dnDSA were at a higher risk of developing ABMR, renal dysfunction, and graft loss. Chaudhuri et al. showed that the presence of de novo antibodies (HLA and MHC class 1-related chain A) was associated with significantly higher rates of acute rejection, chronic graft injury, and decline in graft function, but not all patients who developed dnDSA had rejection [16]. This is partly why the presence of isolated dnDSA without histologic changes suggestive of ABMR continues to be a point of debate in terms of treatment approach.

14.4 Histology

Performing a kidney biopsy is still a key component in the diagnosis of ABMR in children, and the histologic diagnosis of ABMR has changed recently. Historically, the diagnosis consisted of features that showed the evolution of events during ABMR as we understood them at the time: presence of circulating DSA, evidence of complement activation (deposition of C4d along the peritubular capillaries) with histologic evidence of tissue injury, and acute kidney injury characterized by elevation in serum creatinine [17–19]. We now recognize that ABMR can occur in the absence of C4d positivity, and we now have criteria for the recognition of increased expression of gene transcripts/classifiers in the biopsy tissue that have been validated and strongly associated with ABMR. The definition for DSA has also been expanded to include nonhuman leukocyte (HLA) antibodies (angiotensin type 1 receptor (AT1R) antibodies, vimentin antibodies, etc.).

14.4.1 Detection of C4d by Immunostaining

C4d staining has come full circle from being required as a diagnostic criterion for antibody-mediated rejection in kidney allografts in 2003 [20] to being removed as a required criterion in 2014 with the acceptance of C4d-negative ABMR [21]. The presence of C4d indicates complement has been activated once an antibody/antigen interaction has occurred. C3a and C5a are also generated, but they mainly serve as anaphylatoxins that signal recruitment of other inflammatory cells [22]. While it is possible to stain for C3 as well as other complement components, C4d forms covalent bonds with the tissue that allows it to have a longer half-life to remain at the site of complement activation longer [22] and withstand tissue processing. Thus, it serves as a footprint of ABMR picked up by immunohistochemistry or immunofluorescence much more reliably [22].

The use of C4d in diagnosing rejection is not perfect, as it is not always associated with rejection. Occasionally, C4d staining may be observed in organs years after transplantation without other evidence of rejection. It has also been shown that biopsies with histological features of ABMR such as capillaritis, glomerulitis, interstitial fibrosis, and tubular atrophy, without C4d staining when found with circulating DSA, were found to lead to transplant glomerulopathy [23] and have poor long-term outcomes [22]. Treatment of these patients appears to prevent or at least delay the occurrence of transplant glomerulopathy [24]. However, the presence of C4d staining in an allograft may not always be pathologic. In fact, diffuse C4d staining is often found in ABO-incompatible allografts without evidence of allograft dysfunction and is thought to be more associated with accommodation rather than rejection [22, 25].

14.5 Histologic Changes of Tissue Injury

A biopsy of the renal cortex stained with hematoxylin-eosin (H&E) and periodic acid Schiff (PAS) stains will demonstrate an array of histologic changes. The histologic features can vary depending on the timing of the biopsy starting from margination of neutrophils and mononuclear leukocytes and later on monocytes and macrophages in peritubular and glomerular capillaries, thrombotic microangiopathy, and in severe cases, necrotizing arteritis [24]. It is now recognized that intimal arteritis may also occur in ABMR, perhaps as frequently as it does in cellular rejection [23]. It is not uncommon to find concurrent changes of cellular and antibody-mediated rejection in one specimen.

With the recognition of C4d-negative ABMR, there has been a focus on other histologic findings in an attempt to better define the presence of early antibody-mediated renal allograft injury. Adult studies on protocol and for cause biopsies have compelling evidence that the presence of microvascular injury (glomerulitis and/or peritubular capillaritis) is a better indicator of graft survival rather than C4d staining [26–28]. The Banff 11th meeting recognized that microvascular injury can be seen in early protocol biopsies and correlates with an increased risk for the developmental of transplant glomerulopathy [17]. Future studies in children will need to be done to confirm these findings.

14.6 On the Horizon

Current diagnostic testing is not perfect. To do a renal allograft biopsy on a child requires sedation and sometimes an admission which are time-consuming and costly [29]. Children have a small body surface area compared to the large kidney allograft, and a great deal of damage can be done before there is a change in creatinine [30], underscoring the need for detection of damage earlier. Most concerning is that children with lower body surface areas had higher fibrosis scores over time, possibly related to undetected acute rejections [31–33].

Recently, there has been new technology developed which is donor, i.g. graft, derived cell-free DNA (dd-cfDNA) that can be found in the plasma of the recipient. While there are currently no studies in pediatric kidney patients on this test, it is definitely a promising technology.

Children typically obtain disproportionately large renal grafts compared to adults, and this can potentially be problematic with dd-cfDNA testing in children. Studies done on other organs have shown that size does matter when comparing levels of dd-cfDNA; liver and lung recipients have higher levels than kidney and cardiac recipients [34, 35]. This suggests that smaller children could have potentially have higher levels than older children, where the graft size is more proportionate to the recipient's body, but this is not known. This therapy needs to undergo rigorous testing in all children before it can be put into routine practice.

14.7 Treatment of Antibody-Mediated Injury

The optimal therapy for ABMR is not well defined in children or adults. There are variable reported treatment options in the literature, but the data on children treated for ABMR are rare. Table 14.1 gives some of the most commonly used treatments,

Table 14.1 Dosing, duration and side effects of common medications used in antibody mediated rejection treatment

Drug	Dose	Duration	Common Adverse Side Effects
Prednisone	1–30 mg/kg/dose	Used as either a premedication for other drugs or as multiple standalone single doses	Obesity, hyperactivity, insomnia, hyperglycemia, acne, hypertension among others
IVIgG	1–2 g/kg total cumulative dose	Can be given at alone either at the beginning and/or end of treatment, but 100 mg/kg can be given after each pheresis session.	Aseptic meningitis, acute renal failure, thrombotic events, anaphylactic reactions, fever, chills
SQIgG	0.5 mg/kg divided twice weekly over a month	Unknown	Injection site reactions
Rituximab	375 mg/m^2/dose or 750 mg/m2/dose	Anywhere from 1–4 doses	Fever, chills, infection, hypotension during infusion, asthenia, progressive multifocal leukoencephalopathy, and activation of hepatitis B
Bortezomib	1.3 mg/m^2/dose	4 doses every 72 h	Diarrhea, vomiting, thrombocytopenia, hypercalcemia, paresthesias
Eculizumab	5–20 kg = 300 mg/dose 20-40 kg = 600 mg/dose >40 kg = 900 mg/dose	Weekly for 1–4 weeks	Neisseria meningitidis infections
TPE	1–1.5 volume exchange with either FFP, 5%albumin, or IVIgG replacements	Every 48-74 h for 5 treatments	Bleeding, infection, hypocalcemia, hypotension, nausea, dizziness, chills
Anti-thymocyte or anti-lymphocyte globulin	1–1.5 mg/kg/dose	1–7 treatments Q24-48 h	Chills, nausea, leukopenia, fever, nausea

Kg kilograms, *IVIgG* intravenous immunoglobulin, *mg* milligrams, *m*^{2} meters squared, *TPE* therapeutic plasma exchange, *SQ* subcutaneous

doses, duration, and side effects of these treatments, but this can be variable depending on the biopsy finding as well as other treatments that are being given. Children also have naive immune systems compared to adults, making infections a significant concern when treating ABMR [36–38]. There is not one single medication or therapy available at this time to treat pediatric ABMR, but use of these medications in combination is more likely to have better results. The big question that remains unanswered is which combination is most beneficial.

14.8 Removal/Neutralization of Antibody

Intravenous immunoglobulin G (IVIgG) and therapeutic plasma exchange (TPE) were two of the first and are still two of the most widely used therapies in the treatment of ABMR. TPE was first reported in the treatment of ABMR in the early 1980s as it is known to remove circulating antibodies. One of the first case reports for TPE use in treating ABMR was in 1983 by Soulillou et al., and not surprisingly, they did not find a benefit when TPE treatment was used alone [39]. This underscores the concept that it is not enough to just remove the circulating antibodies, but it is also necessary to stop the production of more antibodies.

The benefit of TPE depends on several factors: [40] the tissue compartments in which each immunoglobulin subclass resides and [41] the type of immunoglobulin being targeted. Different types of immunoglobulins have different characteristics. For example, IgM is found in the intravascular space and is easily removed in large quantities; therefore, it does not repopulate by re-equilibration following TPE. IgG and IgA on the other hand are both intravascular and extravascular and re-equilibrate into the intravascular space between TPE treatments, therefore requiring multiple TPE treatments to remove a significant amount of total body antibody [42–44].

The exact mechanisms of action of IVIgG are not entirely clear, although IVIgG is thought to have immunomodulatory as well as anti-inflammatory actions. One of the more well-known mechanisms of IVIgG is its ability to inhibit complement activation, which can be a crucial step in ABMR allograft dysfunction. Other mechanisms include inhibition of costimulatory molecule CD80/86 expression and suppression of HLA class I/II expression [45]. IVIgG is also thought to decrease the secretion of interleukin (IL)-12 and increase the secretion of IL-10, suggesting that treatment started at the time of antigen presentation could potentially induce a beneficial regulatory rather than damaging inflammatory pathway. Lastly, IVIgG is thought to induce significant B-cell apoptosis in vitro through Fc receptor-dependent mechanisms [46].

Jordan et al. first reported the beneficial effects of IVIgG in the treatment of ABMR in 1998 [47]. This led to the development of subsequent protocols that included either high-dose IVIgG alone or a combination of TPE and low-dose IVIgG [48–50]. However, this alone is not usually enough to stop the injury. More recently, there has been the development of subcutaneous IgG (SQIgG) that is being used off label for the treatment of chronic ABMR. SQIgG infusions are typically administered biweekly, resulting in more constant steady-state concentrations.

These infusions can be done at home and for extended periods of time. To date, there are limited to no pediatric data on this treatment in pediatric renal ABMR.

14.9 B-Cell Depletion

Anti-thymocyte globulin (ATG) and antilymphocyte globulin (ALG) also have some B-cell activity [51–53] and have had varying success in the treatment of ABMR. ATG is made by taking pediatric human thymus tissues that are removed routinely during pediatric cardiac surgery. The predominant cell population that is harvested is CD3+ T cells [51], but there is some B-cell lymphopoiesis that occurs in the human thymus, so it is not unexpected that there are CD20+ as well as CD138+ cells in these preparations [52, 54]. Both ATG and ALG have been shown to induce apoptosis in naive and activated human B cells and plasma cells. ATG has also been shown to increase the number of T-regulatory cells in vitro and in vivo [55–58]. Furth et al. published one of the first successful pediatric case reports using TPE, cytomegalovirus-specific IVIgG, and ALG in 1999 [59], followed by Shah et al. demonstrating that ATG with TPE to effectively treat acute ABMR [60]. [*The usefulness of ATG in ABMR is not very high*.]

Rituximab is a chimeric monoclonal anti-CD20 antibody. CD20 is found on the surface of most B cells, but it is not found on mature plasma cells [61, 62]. It has been used in the treatment of ABMR with varying degrees of success [63–66]. Through antibody-dependent cell-mediated and complement-dependent cytotoxicity in addition to direct signaling that leads to apoptosis, rituximab ultimately leads to less CD20+ cells than can turn into antibody-producing plasma cells [67–69].

Reports of successful rituximab therapy in pediatric renal transplant recipients with ABMR are found in the literature with varying degrees of success. Billing et al. treated six children with chronic antibody-mediated rejection with IVIgG and rituximab which led to an improvement in GFR within 12 months [70, 71]. Others have used rituximab in combination with steroid pulses, IVIgG, and/or PP in the treatment of AMR in children [67]. Unfortunately, rituximab did not have a significant effect on antibody intensity [63]. This is concerning when used also as failure to significantly reduce or remove the antibodies can lead to chronic allograft injury. Rituximab, like TPE and IVIgG, is likely not an effective therapy when used alone.

14.10 Depletion of Plasma Cells

Mature plasma cells are the main cells that produce DSA, which is why targeting them is so attractive [56]. The proteasome inhibitor bortezomib was approved in 2003 for the treatment of multiple myeloma, and now there are reports of its use in the treatment of ABMR. The power of these mature plasma cells is significant, as evidenced by the production of antibodies at a rate of several thousand per second. These antibodies can appear as early as 1 week after antigen presentation and persist for months [72, 73]. The process of antibody production leads to increased protein

synthesis and accumulation of unfolded proteins in the endoplasmic reticulum of the plasma cells, and proteasome inhibitors prevent the clearance of these unfolded proteins which ultimately leads to plasma cell death [74, 75].

Everly and associates were the first to report the beneficial effects of bortezomib treatment in patients with refractory acute ABMR [76]. More recently, there have been published data on pediatric cases. Twombley et al. were the first to describe its use in pediatric kidney patients. The most important finding of this paper was that there were no reported serious side effects and no infections 2 years posttreatment [77]. Subsequently, Pearl et al. showed stabilization of estimated glomerular filtration rate 1 year after treatment with bortezomib [78]. A multicenter retrospective study showed that the use of bortezomib led to a 25% reduction in the MFI levels of the immune-dominant DSA in 56% of the patients 1–3 months posttreatment [79]. There is still much to be learned about the potential benefits and long-term outcomes of bortezomib use in the treatment of pediatric renal ABMR. [You might want to mention that bortezomib is used in conjunction with pheresis.]

14.11 Complement Inhibition

Eculizumab is a humanized monoclonal antibody that blocks the cleavage of human complement component 5 and prevents the formation of the membrane attack complex (MAC) [80]. It has been successfully used to prevent posttransplantation recurrence of atypical hemolytic uremic syndrome after kidney transplantation [81, 82]. Some have now started to use it as not only a treatment of ABMR but to also potentially prevent ABMR in highly sensitized patients. Stegall et al. have reported their experience with eculizumab in the prevention of ABMR. Despite avoiding ABMR with eculizumab use, some patients still had evidence of chronic humoral injury with eculizumab use [83]. Also published was a case of biopsy-proven severe ABMR despite adequate levels of eculizumab and C5 blockade [84]. These reports suggest that ABMR might involve more proximal components of the complement pathway (e.g., C3a anaphylatoxin) or that some ABMR episodes might be completely complement independent in some patients.

14.12 Summary

There have been many advances in the field of transplantation, but little has changed in the treatment outcomes of ABMR. There is still little consensus on the treatment of ABMR. There are promising new techniques in the area of prevention of DSA with epitope or eplet matching that will hopefully lead to progress. With these newer advancements, some progress is in sight, but we still have a long way to go.

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Acute Vascular Rejection

15

Manpreet Grewal and Amrish Jain

Acute vascular rejection (AVR) after kidney transplantation is an alarming complication that develops in the posttransplant period and often is resistant to the conventional antirejection therapies. It encompasses all the vascular lesions occurring in the transplant allograft during the rejection episode.

15.1 Terminology and Evolution

Till the early 1990s, in the absence of a systematic international classification for reporting of renal allograft biopsies, there was a considerable heterogeneity among pathologists in reporting of the biopsies. The Banff working group proposed the first systematic classification in 1993, and it has undergone noteworthy changes over the past three decades with the Banff group meeting every few years, and new updates have been added [1].

Histopathologically, acute vascular rejection encompasses intimal arteritis and endarteritis of the graft vessels. According to the first Banff classification in 1993, intimal arteritis was defined as intimal thickening with inflammation of arterial subendothelial space ranging from rare intimal inflammatory cells to necrosis of the endothelium with deposition of fibrin, platelets, and inflammatory cells. The cellular infiltrate is composed of lymphocytes and monocytes. Severity of the arteritis was determined by the number of vessels affected as well as by the intensity of individual lesions [1]. As for transmural arteritis, it was defined as injury and inflammation of the whole arterial wall, including the media, necrosis of the medial smooth muscle cells, fibrin insudation, and cellular infiltration with mononuclear as well as polymorphonuclear leukocytes [1].

M. Grewal · A. Jain (✉)
Division of Pediatric Nephrology and Hypertension, Children's Hospital of Michigan, Detroit, MI, USA
e-mail: ajain@med.wayne.edu

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The initial Banff schema classified intimal arteritis and endarteritis as a part of acute rejection Grade II and Grade III, respectively. In the revised Banff classification in 1997, the vascular lesions were further quantified as follows: v0, no arteritis; v1, mild to moderate intimal arteritis in at least one arterial cross section; v2, severe intimal arteritis with at least 25% of the luminal area lost in at least one arterial cross section (Fig. 15.1a and b); and v3, transmural arteritis and/or arterial fibrinoid changes (Fig. 15.2a and b) and medial smooth muscle necrosis with lymphocytic infiltrates in the vessel [2].

After multiple revisions, at the 2005 Banff meeting, the basic classification of rejection was changed from acute and chronic to its pathophysiologic basis, i.e., antibody-mediated (ABMR) and T-cell-mediated (TCMR), either of which could be acute or chronic [3]. Initially, intimal or transmural arteritis was categorized as a classical lesion of only TCMR; however, multiple studies showed that lesions of AVR were not only seen in TCMR but were also reported in allograft biopsies with ABMR [4–9]. Thus, the lesions of AVR were included in the Banff classification as acute T-cell-mediated rejection (TCMR) Type IIA corresponding to cases with v1,

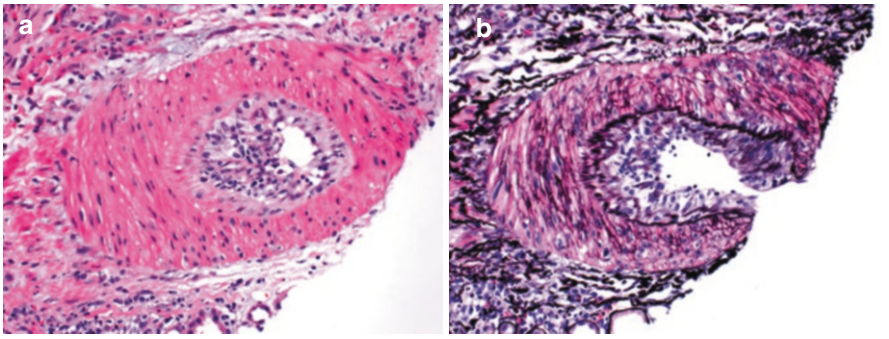

Fig. 15.1 Intimal arteritis (V2) in vascular transplant rejection on hematoxylin and eosin (**a**) and Jones silver (**b**) staining – 200X power. Courtesy: Dr. Alejandro Best, MD

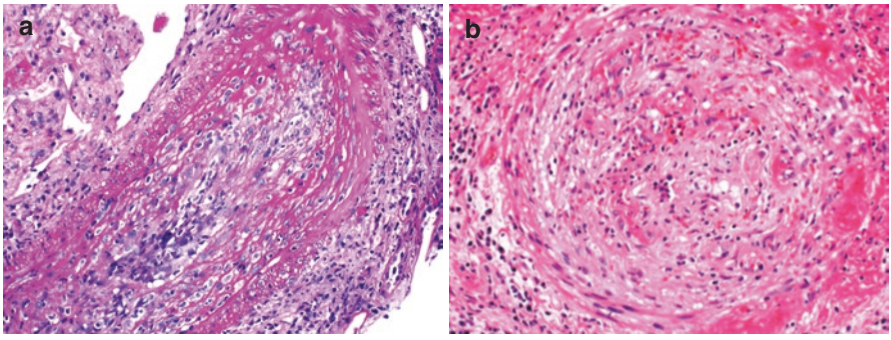

Fig. 15.2 Transmural arteritis (V3) in vascular transplant rejection on hematoxylin and eosin (**a**) and periodic acid Schiff (**b**) staining – 200X power. Courtesy: Dr. Alejandro Best, MD

acute TCMR Type IIB corresponding to cases with v2, acute TCMR Type III corresponding to cases with v3, and acute ABMR Type III to include cases with v3, having circulating anti-donor antibodies (DSAs) and C4d positivity in the peritubular capillaries (PTC) [4].

Restricting acute ABMR to only the v3 lesion was challenged by studies demonstrating renal allograft biopsies with ABMR with v1 and v2 lesions. Shimzu et al. reported 17 patients with lesions of AVR on allograft biopsies and demonstrated that features of ABMR in the form of peritubular capillaritis, C4d staining, and positive DSAs were seen in some patients with v1 and v2 lesions as well [8]. They later reported that 26 out of their 28 renal transplant patients with biopsy-proven AVR had either v1 or v2 lesions. Acute ABMR was diagnosed in five of these 26 cases based on the histopathological findings of peritubular capillaritis and/or glomerulitis with circulating DSAs and C4d deposition in PTC [9]. Carmen Lefaucheur and colleagues retrospectively tested DSAs in the sera of 302 kidney transplant recipients with biopsy-proven acute rejection. They reported acute antibody-mediated vascular rejection in 64 (21%) of the 302 patients. Nearly half of these patients had intimal arteritis v2 or higher [10]. On the basis of these studies, v1 and v2 vascular lesions were included in the diagnostic criteria for acute ABMR as well [11]. Currently, lesions of AVR, i.e., intimal arteritis of any degree and endarteritis, are included in the histopathological criteria for ABMR, TCMR, or mixed ABMR/TCMR.

15.2 Pathogenesis

The immune system of a recipient responds to any foreign antigen including those on the allograft via recognition of alloantigens, leading to activation of the innate immune system. This sets off a chain of reactions causing the release of various inflammatory mediators and chemo-attractants and ultimately the activation of host lymphocytes and macrophages [12]. CD4 T cells, CD8 T cells, and macrophages adhere to the endothelial adhesion molecules on activated endothelial cells and invade the subendothelial matrix and intima of muscular arteries of the graft tissue and cause widespread microvascular inflammation leading to the destruction of the graft tissue [13–15].

The humoral immunologic reactions associated with AVR are believed to be triggered by circulating antibodies called DSAs that can be directed against the donor human leukocyte antigens (HLA), non-HLA, or ABO antigens [16]. The DSAs bind to these antigens and cause activation of the classical complement pathway. The C3 convertase generated as a result of fixation of C1q eventually leads to the formation of the membrane attack complex (C5b–C9) (Fig. 15.3) [17, 18]. The membrane attack complex damages the vascular endothelium resulting in increased recruitment and activation of the inflammatory and coagulation cascades, in turn leading to widespread microvascular injury. C4d is generated as a split product of C4 activation in the classical complement pathway, and it binds to the endothelial and collagen basement membranes, thereby serving as a marker of antibody-mediated injury.

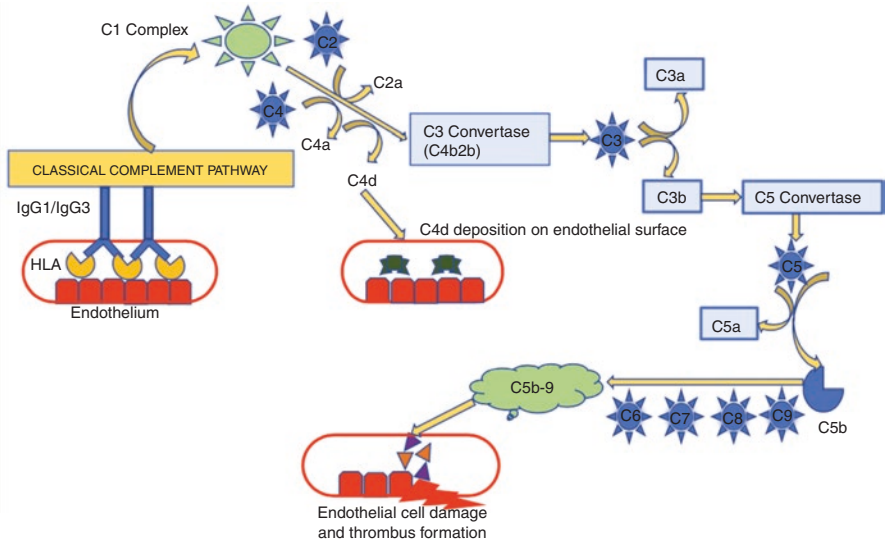

Fig. 15.3 Activation of the classical complement pathway causing generation of the membrane attack complex, leading to widespread microvascular injury

Thus, C4d staining of the PTCs of the allograft is a specific marker of ABMR, and it can serve as a surrogate in cases with false-negative DSAs or if DSA testing is not available [19–21]. However, not all patients with ABMR have positive C4d staining on allograft biopsies but have significant risk of graft loss [22]. Thus, C4d-negative ABMR was also included in the Banff classification in 2013.

DSAs are most commonly directed against major histocompatibility complex (MHC) class I and II antigens. However, over the past two decades, there has been a spiraling curiosity in elaborating the role of antibodies against the minor non-donor-specific antigens in impaired graft survival or graft loss. The most commonly identified non-donor-specific antigens include MHC class I-related chain A (MICA) antigens, MHC class I-related chain B (MICB) antigens, antibodies against the angiotensin type 1 receptor (AT_1R), endothelin type A receptor (ET_AR), platelet-specific antigens, and polymorphisms involving chemokines and their receptors [23–25]. Since these antigens are not expressed on lymphocytes, antibodies directed against them are not detected with the methods generally used for the crossmatching during the pretransplant period.

The most extensively studied are the antibodies against the MICA antigens. MICA genes are highly polymorphic genes expressed in epithelial cells, keratinocytes, and endothelial cells but not on the lymphocytes [26–28]. About two decades ago, Zwirner et al. demonstrated MICA antibodies as a new alloantigen recognized by antibodies in the sera of organ transplant recipients [29]. Since then, extensive research has been done on the role of these antibodies in renal allograft rejection. Zou et al. measured anti-MICA antibodies in the stored sera from 1910 recipients of deceased donor kidney transplants and compared the 1-year graft survival in

anti-MICA-positive versus anti-MICA-negative patients. They found a statistically significant difference among both groups with a shorter 1-year graft survival in recipients with anti-MICA antibodies [30]. The mechanism of action of these antibodies is similar to the HLA DSAs which cause activation of the classical complement cascade. Sanchez-Zapardiel et al. showed that 23% of anti-MICA-positive sera from transplant patients could trigger complement-dependent cytotoxicity leading to endothelial damage and thrombosis formation by fixing C1q and activating the classical complement pathway [31].

Other groups of minor antigens that have emerged as a significant cause of refractory vascular rejection are the AT_1R and ET_AR. Both receptors are expressed at the vascular endothelium and play a major role in the regulation of blood pressure. The anti-AT_1R autoantibodies are IgG antibodies that serve as AT_1R agonists, resulting in the overactivity of the AT_1R. As a result, these patients develop malignant hypertension and present with accelerated vascular rejection. Giral et al., in a cohort of 599 kidney transplant recipients, demonstrated that patients with AT_1R-autoantibody level > 10 U had 2.6-fold higher risk of graft failure 3 years after transplant and nearly twice the risk of acute rejection within the first 4 months of transplantation [32]. The antiendothelial antibodies (AECA) against the ET_AR have been reported to cause early acute rejection. Sun et al. evaluated the association between de novo AECA and the risk of developing early acute rejection. Fifty percent of their patients who developed de novo AECAs had an acute rejection with presence of glomerulitis and PTC inflammation on renal biopsies leading to graft dysfunction [33].

15.3 Clinical Presentation and Diagnosis

AVR may present as hyperacute or acute rejection. Hyperacute rejection is caused by preformed DSAs and frequently results in allograft loss within the first 24 hours. Hyperacute rejection is diagnosed in the operating room or in the immediate postoperative period as the well-perfused kidney becomes mottled and cyanotic and the patient remains oligo-anuric. Renal scans or Doppler studies show scanty or absent renal blood flow. Before establishing a diagnosis of hyperacute rejection, other causes of delayed or poor graft function should be considered. These include prolonged ischemia or vascular injury during the intraoperative period leading to acute kidney injury, thrombosis or embolization of the renal artery or vein, urologic abnormalities like urinary leak, or hematoma.

Acute rejection on the other hand usually manifests within the first 6 months after transplantation. Most patients who have acute rejection are asymptomatic, and rejection is usually detected by an increase in the serum creatinine, proteinuria, and new-onset or worsening hypertension. Occasionally, patients may present with fever, malaise, oliguria, and graft pain and/or tenderness.

Hyperacute or acute ABMR despite negative flow crossmatch during the pretransplant testing should raise the suspicion of presence of antibodies against minor antigens like MICAs, AT1R, and ETAR. Patients with MICA antibodies have been

demonstrated to have more accelerated rejection as compared to those with only anti-HLA antibodies. Development of malignant hypertension posttransplant has been found to be closely linked to antibodies against AT_1R and ET_AR. Dragun et al. showed that 20 of the 33 kidney transplant recipients with acute vascular rejection secondary to AT_1R antibodies had no DSAs, and 80% of these DSA-negative patients had malignant hypertension [34].

Renal biopsy of the allograft is the most important diagnostic test to establish the diagnosis of AVR. Diagnosis of TCMR is established by the presence of tubulitis and significant interstitial inflammation along with variable level of intimal arteritis depending on the stage of TCMR. Diagnosis of ABMR, on the other hand, requires histological evidence of acute tissue injury, C4d staining in peritubular capillaries, and/or serologic evidence of circulating DSAs. Previously, all three criteria were used to diagnose ABMR, but in the Banff 2017 update, C4d-positive staining alone, in the absence of DSA positivity, was also categorized as ABMR in the presence of characteristic histologic changes [35].

15.4 Treatment

Initial management of acute rejection is use of high-dose glucocorticoids; however, patients with vascular rejection respond poorly to the conventional treatment. Use of anti-lymphocyte-antibody therapy with anti-thymocyte globulin (ATG) has been recommended in severe acute vascular rejection refractory to steroids. ATG acts via blocking membrane proteins causing impaired function and apoptosis of lymphocytes leading to prolonged lymphopenia and thereby limiting the production of antibodies [9, 36].

Acute ABMR secondary to the antibodies against minor antigens is also often refractory to the traditional treatment modalities (e.g., steroids). Sun et al. in their study of 226 kidney transplant recipients demonstrated that patients with de novo AECAs had more severe and more frequent rejection episodes and had a greater likelihood of being steroid-resistant [33]. As a consequence, therapies directed at removing the pre-formed alloantibodies and decreasing their further production remain the mainstays of treatment.

Plasmapheresis/Plasma Exchange Plasmapheresis/plasma exchange or immunoadsorption removes alloantibodies from the plasma. Immunoadsorption involves the removal of antibodies by passing them over a matrix lined with specific ligands. In plasmapheresis, the patient plasma is discarded, and replacement donor plasma is given to the patient, while in immunoadsorption patient's own remaining plasma components are returned to the patient without the need for plasma exchange. Both processes remove the intravascular antibodies and help in reducing the effective immune response [37–39].

Intravenous Immune Globulin (IVIG) The mechanism of action of IVIG is not entirely known, but it is thought that it neutralizes alloantibodies as well as diminishes plasma cell production by inducing apoptosis of B cells. Despite plasmapheresis and IVIG being the most commonly used therapies to decrease the alloantibodies, there is paucity of well-designed clinical trials proving their efficacy. The frequency, duration, and dosing of these treatments are variable [37–40]. Use of plasmapheresis and IVIG has been reported in patients with anti-MICA antibodies and has been found to be associated with improvement in renal function with declining levels of these antibodies [25, 38, 41, 42].

Therapies directly targeting mature plasma cells, memory B cells, or plasma blasts have also been used to prevent the development of alloantibodies by preventing the generation of new plasma cells. *Rituximab* is an anti-CD20 monoclonal antibody and has cytotoxic activity against B-lymphocytes and thereby leads to a reduction in the antibody levels [43]. Many prospective randomized controlled trials (RCT) and retrospective studies have evaluated the use of rituximab in the management of ABMR, with variable results suggesting a beneficial role [43–45]. *Bortezomib* is a proteasome inhibitor, which acts by inhibiting protein biosynthesis, thereby leading to apoptosis of the antibody-producing plasma cells. More than 30% of the patients taking bortezomib experience significant side effects, and there is limited literature supporting its use [46–48]. *Eculizumab*, a humanized monoclonal antibody directed against C5, acts by inhibition of membrane attack complex formation and halting activation of the complement cascade [49, 50]. The 2019 Expert Consensus from the Transplantation Society Working Group recommend that these agents may be considered as adjunctive therapies to plasmapheresis, IVIG, and corticosteroids especially when the risk of graft loss is high [51].

Imlifidase is a novel agent undergoing phase 2 clinical trials in kidney transplant recipients. It is made from an endopeptidase derived from the bacterium *Streptococcus pyogenes* and cleaves the IgG in the hinge region resulting in the formation of Fab and Fc fragments. This mechanism inhibits all IgG-mediated immunity and prevents rejection of a transplanted kidney [51, 52].

15.5 Prognosis

AVR has a poor prognosis and it is considerably refractory to conventional anti-rejection therapies. Van Saase et al. evaluated the graft survival among 482 deceased donor kidney transplant recipients and reported a 48% 1-year graft survival rate in patients with AVR [53]. Haas et al. also reported a significantly poor response to anti-rejection therapy in patient with severe intimal arteritis as compared to those with mild to moderate intimal arteritis [54]. Teo et al. in a study of 274 patients from Australia and New Zealand Dialysis and Transplant Registry found that AVR associated with ABMR was associated with the poorest outcome with over one-fourth of the grafts being lost within 3 months after transplantation [55].

Thus, AVR continues to be a diagnostic and therapeutic challenge to clinicians. Although the optimal treatment remains unknown, treatment regimens that target both cellular and humoral immunity and include therapies directed at depletion of plasma cells along with plasmapheresis and IVIG could potentially improve graft survival.

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Infectious Complications in Pediatric Renal Transplantation

16

Masaki Yamada and Michael Green

Abbreviations

KTx	Kidney transplantation
ESRD	end-stage renal disease
UTI	urinary tract infection
SSI	surgical site infection
CRBSI	catheter-related bloodstream infection
HSV	herpes simplex virus
CMV	cytomegalovirus
EBV	Epstein-Barr virus
PTLD	post-transplant lymphoproliferative disorder
BKPyV	BK polyomavirus
PyVAN	polyomavirus-associated nephropathy
HBV	hepatitis B virus

M. Yamada (✉)
Department of Advanced Medicine for Viral Infections, National Center for Child Health and Development, Tokyo, Japan

Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
e-mail: yamada-mas@ncchd.go.jp

M. Green
Surgery and Clinical and Translational Science, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Transplant Infectious Diseases, Division of Infectious Diseases, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA
e-mail: Michael.green@chp.edu

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Kidney transplantation (KTx) is the treatment of choice for children with end-stage renal disease (ESRD). While patient and graft survival following KTx continue to improve, infections remain a major cause of morbidity, graft loss, and mortality after pediatric KTx. This chapter highlights the risks and timing for these infections, highlighting current recommendations for their diagnosis, management, and prevention.

16.1 Predisposing Factors

Factors predisposing to infections after KTx can be divided into three categories: pre-transplant factors, intraoperative factors, and post-transplant factors.

Pre-operative factors impacting the risk of infection after KTx include underlying renal disease (e.g., obstructive uropathy, autoimmune nephropathy), age at transplantation, nutritional and immunization status, and the infectious history of the donor and recipient [1]. For example, younger children undergoing KTx are more likely to be immunologically naïve against cytomegalovirus (CMV) and Epstein-Barr virus (EBV), increasing their risk for developing severe disease from these pathogens. Similarly, lacking immunizations before transplantation increases the risk of developing vaccine-preventable diseases following it. Finally, the infectious history of the donor, including results of serologic and microbiologic screening, is another important pre-transplant factor that modifies the risk of infection after transplantation. Critical donor results include their CMV and EBV serostatus and any cultures obtained from the donor at the time of organ recovery. Recipient factors should be carefully reviewed as part of the pre-transplant evaluation and again at the time of transplantation when donor results become available (see Sect. 16.3).

The intraoperative factors affecting infectious risk relate to the transplant surgical procedure, including cold and warm ischemia time, operative time, contamination of the operative field, the amount of bleeding, and the placement of a urinary stent. They may directly predispose to post-KTx infections (e.g., contamination of the operative field) and serve as surrogates for the complexity of the surgical procedure (e.g., prolonged operative time and greater complexity are associated with greater risk for infection). Surgical decisions, such as placing a urinary stent predisposing to UTI and allograft pyelonephritis, also affect risks [2].

A range of post-operative factors impacts the risk of infection after KTx. The presence of surgical complications (e.g., lymphocele, ureteral stricture) can lead to graft dysfunction and infection of the graft or related surgical sites. The net state of immunosuppression is perhaps the critical factor for the clinician to be aware of as it predicts risk for both frequency and severity of infections. Finally, additional factors such as graft dysfunction, ongoing rejection, the individual risk for opportunistic pathogens, and exposures to common pathogens (e.g., influenza, respiratory syncytial virus) significantly increase the risk of post-KTx infections [3].

16.2 Timing of Infections After KTx

The timing of presentation is one of the most clinically relevant predictors of likely causes of post-KTx infections (Table 16.1). Post-KTx infections can be grouped into three timeframes: early (the first month after KTx), intermediate (1 to 6 months), and late (>6 months). The likelihood that a type of infection occurs within a given timeframe is primarily explained by its underlying cause. In general, infectious complications attributable to technical complications of KTx tend to occur in the early time period, while those related to immunosuppression tend to occur in the intermediate and late time periods.

16.2.1 Early Post-KTx Period (the First Months After KTx)

16.2.1.1 Surgical Site Infections (SSIs) [5]

SSIs occur in approximately 3–11% of children and adults undergoing KTx. SSIs range from simple superficial wound infections to complicated, deep perinephric

Table 16.1 Timeframe of common infections after pediatric kidney transplantation [4]

Timing	Type of infections	List of common pathogens
Early period The first months	Surgical site infections Urinary tract infections Bacteremia and sepsis Respiratory infections	Herpes simplex virus Hepatitis B virus West Nile virus Zika virus SARS-COV-2 Seasonal virus
Intermediate period 1–6 months	Opportunistic infections (primary infection and reactivation)	Herpesviruses Polyomaviruses Papillomaviruses Adenovirus Zika virus SARS-COV-2 *Listeria monocytogenes* *Mycobacterium tuberculosis* Atypical mycobacteria Nocardia Fungal disease *Pneumocystis jirovecii* Parasitic disease Seasonal virus
Late period >6 months	Community-acquired infections Urinary tract infections Opportunistic infections	*Streptococcus pneumoniae* Herpesviruses Hepatitis B and C virus Zika SARS-COV-2 Seasonal virus

SARS-COV-2, severe acute respiratory syndrome coronavirus 2

abscesses. The use of closed suction drainages, early removal of peritoneal drainages, and use of perioperative antibiotics for up to 24 hours post-KTx contribute to decreasing the incidence of SSI.

The clinical manifestations of SSI vary. SSI may present as a febrile illness without focus, skin erythema, wound dehiscence, abdominal pain with tenderness over the allograft, or prolonged need for post-operative peritoneal drainage. When present, fluid or pus obtained from either the superficial wound or deep surgical site should be cultured for bacterial, mycobacterial, and fungal organisms [5].

Empiric therapy for a presumptive SSI should cover staphylococci, streptococci, Enterobacteriaceae, and *Candida* species if suspected [6]. In general, achieving adequate source control for SSI can lead to a shorter duration of therapy, while the inability to achieve it may require longer courses. The usual duration of therapy for an SSI in a patient showing improvement is 10–14 days but may be longer for more complicated infections (e.g., deep abscess).

16.2.1.2 Urinary Tract Infections [7]

UTIs are the most common post-KTx infection, affecting up to 79% of recipients throughout their post-transplant course. The clinical spectrum of post-KTx UTI includes asymptomatic bacteriuria, cystitis, and complicated UTI, including graft pyelonephritis (Table 16.2) [7]. Complicated UTI accounts for more than 30% of all bacteremic episodes in KTx recipients and can lead to acute and chronic graft dysfunction, potentially shortening allograft survival. The incidence of UTI is highest during the early and intermediate periods, although they can develop at any time post-KTx. UTIs occurring early appear to be more frequently associated with graft loss than episodes occurring later in the post-KTx course [8].

Table 16.2 Classification of asymptomatic bacteriuria (AB) and urinary tract infection in kidney transplant recipients [7]

Classification	Description	Laboratory investigations of urine
Asymptomatic bacteriuria	No urinary[a] or systemic symptoms[b] of infection	$>10^5$ CFU/mL uropathogen
Acute simple cystitis	Positive urinary symptoms, but no systemic symptoms and no ureteral stent/nephrostomy tube/chronic urinary catheter	>10 WBC/mm^3 $>10^3$ CFU/mL uropathogen
Acute pyelonephritis/ complicated UTI	Positive systemic symptoms without other apparent etiology, flank/allograft pain, bacteremia with the same organism as in urine Urinary symptoms may or may not be present	>10 WBC/mm^3 $>10^4$ CFU/mL uropathogen
Recurrent UTI	≥3 UTIs in prior 12-month period	As above

UTI urinary tract infection; *WBC* white blood cell; *CFU* colony-forming units/milliliter
[a]urinary symptoms: dysuria, urinary urgency/frequency, or suprapubic pain
[b]systemic symptoms: fever, chills, malaise, hemodynamic instability

The management of asymptomatic bacteriuria in pediatric KTx recipients remains controversial; retrospective studies assessing the benefit of treating asymptomatic bacteriuria have not shown a benefit, at least for recipients out more than 2 months from KTx. Current consensus guidelines recommend against the treatment of asymptomatic bacteriuria occurring later than 2 months post-KTx [7].

16.2.1.3 Respiratory Tract Infections

The onset of respiratory infection within the first month after KTx is often associated with the need for prolonged ventilatory support. Most healthcare-associated respiratory infections are caused by Gram-positive and Gram-negative bacteria, *Streptococcus pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa*, and other Enterobacteriaceae commonly recovered. Empiric therapy should include the use of a fourth-generation cephalosporin or piperacillin/tazobactam, with or without vancomycin, depending on the host factors, Gram stain results, and local antibiogram. However, the combination of piperacillin/tazobactam and vancomycin has been associated with increased risk of nephrotoxicity, prompting the need for caution if used in this patient population [9]. Of note, respiratory tract infections due to opportunistic pathogens rarely occur during the early post-KTx periods.

16.2.1.4 Clinical Sepsis

Clinical sepsis refers to a condition associated with significant alterations in vital signs (e.g., fever, tachycardia, and hypotension), which can be attributable to post-surgical fever, rejection, and infection. Clinical sepsis occurs more frequently during the early post-KTx period and is often associated with the presence of SSI, UTI, and device-related infections, including catheter-related bloodstream infections (CRBSI). The common causative organisms for SSI and CRBSI in KTx recipients include coagulase-negative staphylococci, *Staphylococcus aureus,* and less frequently *Candida* spp. When UTI is the source of sepsis, pseudomonas and both Gram-positive and Gram-negative enteric organisms should be considered. For patients with uncomplicated bloodstream infections, the typical duration of treatment is 10 to 14 days depending on the causative pathogens. Longer treatment may be indicated for complicated infections such as a perinephric abscess.

16.2.1.5 Viral Infections

HSV is the most common viral pathogen causing symptomatic infections during the early post-KTx period. Historically, the incidence of HSV infection in pediatric KTx recipients was as high as 8%. However, this has been substantially decreased in the era of prolonged anti-CMV prophylaxis with ganciclovir and valganciclovir, which also cover HSV.

Community-acquired respiratory/gastrointestinal viral infections can also occur during the early post-KTx period. Development of community-acquired respiratory viral infections during the early post-KTx period has been associated with worse outcomes compared to acquisition later in the post-transplant course. Therefore, the KTx recipients should avoid exposure to symptomatic household members and other close contacts.

16.2.2 Intermediate Time Period (1–6 Months After KTx)

The cumulative effect of immunosuppression becomes evident during the intermediate time period, predisposing to infection with opportunistic pathogens such as CMV, EBV, BK polyomavirus (BKPyV), and *P. jirovecii* during this time interval. As opposed to the reactivation of previously acquired latent pathogens seen in many adult KTx recipients, pediatric KTx recipients often acquire a primary infection of these opportunistic pathogens from the graft and develop clinically significant diseases.

16.2.2.1 Viral Infections

The Herpesviridae share the biologic properties of latency and reactivation, which frequently occur in children receiving immunosuppressive medications. Hence, Herpesviridae is the most important pathogen group affecting the clinical course after KTx.

Cytomegalovirus

CMV may cause a primary infection (acquired via the renal allograft or blood product transfusion) in the seronegative recipient (R-) or a secondary infection in seropositive recipients (R+) via reactivation of latent virus or infection with a new strain from the donor. CMV infection is diagnosed by detection of CMV DNA by PCR in blood, bronchoalveolar lavage, or tissue, while CMV disease is usually defined by the presence of symptoms and end-organ damage attributed to active CMV infection.

Clinical manifestations of CMV range from asymptomatic infection to symptomatic disease, including a febrile syndrome associated with leukopenia, thrombocytopenia, and atypical lymphocytosis, and tissue-invasive disease, most commonly involving the liver, lungs, or gastrointestinal tract. In addition, CMV has an immunomodulatory effect, which has been linked to the development of allograft dysfunction, nephropathy, and other opportunistic infections [10].

The frequency of CMV infections after transplant has led to efforts to prevent development of CMV disease. Preventive strategies include universal chemoprophylaxis, surveillance monitoring of the CMV viral load to initiate preemptive therapy, and more recently, the use of surveillance monitoring after prophylaxis. Of note, some centers monitor the CMV viral load even while transplant recipients are receiving chemoprophylaxis.

Current guidelines recommend that universal chemoprophylaxis be accomplished using intravenous ganciclovir or oral valganciclovir for D+/R- KTx recipients, and oral valacyclovir for R+ KTx recipients [11, 12]. While duration of prophylaxis may vary among centers, current guidelines recommend 6 months for D+/R- or 3 months for R+. Prophylaxis is generally logistically easier to apply than the other preventive strategies. This advantage may be offset by the higher drug cost and prolonged exposure to ganciclovir and valganciclovir, potentially leading to side effects, including leukopenia, and potentially selecting for antiviral resistance. Preemptive therapy requires weekly CMV viral load monitoring for the first 12 weeks post-KTx. Antiviral therapy is initiated if a positive CMV viral load is

detected. While the cost of monitoring is higher and infrastructure must be in place to manage testing and track results, fewer patients are exposed to antiviral therapy, reducing the risk of side effects and concern for selection of antiviral resistance. Some institutions have also adopted surveillance after prophylaxis (also known as the "hybrid approach") with the initial use of shorter periods of prophylaxis followed by longer periods of surveillance monitoring to inform preemptive ganciclovir or valganciclovir therapy in those developing elevated CMV loads. Reduction of immunosuppression should be considered in patients receiving preemptive antiviral therapy for either of the latter two strategies. Transplant clinicians can choose the appropriate strategy for their patients depending on the presence of specific risk factors (e.g., D+/R-) and adequate infrastructure to manage and track results necessary for the preemptive therapy approach. Most centers have developed institutional protocols to guide decision-making (Table 16.3) [11].

Current guidelines recommend treating all pediatric KTx recipients with symptomatic CMV disease. The antiviral agents for CMV currently approved for the children in North America are ganciclovir, valganciclovir, foscarnet, and cidofovir. Children with mild CMV disease can be managed with oral valganciclovir, while moderate to severe disease requires initial use of intravenous therapy until the CMV disease starts to resolve and the CMV load starts to fall. Foscarnet and cidofovir have significant renal toxicity. Their use should be limited to patients for whom there is a concern for ganciclovir resistance. When suspected, the presence of resistance should be confirmed using molecular methods. The efficacy and safety of letermovir are under investigation in pediatric hematopoietic cell transplant recipients or in adult KTx recipients. Although it may be a reasonable choice of primary and secondary prophylaxis for patients with a history of ganciclovir-resistant CMV infection, pediatric KTx-specific data is lacking. Maribavir has not been approved for children by FDA as of the end of 2022. However, the adult data has shown the efficacy of antiviral-resistant CMV infection [13]. Therefore, safety, tolerability, pharmacokinetics, and antiviral activity for pediatric HCT and solid organ transplantation are under investigation.

Epstein-Barr Virus [14, 15]

EBV infection in pediatric KTx recipients may be asymptomatic or associated with clinical syndromes ranging from non-specific viral syndrome to post-transplant lymphoproliferative disorder (PTLD). While some EBV infections are self-limited, EBV-associated PTLD remains a serious complication potentially affecting both

Table 16.3 Recommendations for cytomegalovirus prevention in kidney transplant recipients [11]

Serostatus	Type of prevention	Duration	Level of evidence
D+/R-	Antiviral prophylaxis	6 months	Strong, high
	Preemptive therapy	Weekly monitoring for 3 months	Strong, high
R+	Antiviral prophylaxis	6 months	Strong, high
	Preemptive therapy	Weekly monitoring for 3 months	Strong, high

Edited from AST IDCOP guideline [11]

graft and patient survival. The incidence of PTLD in pediatric KTx recipients is 0.9% at 1 year and 1.8% at 5 years post-KTx, which is 2–5 times higher than that observed in their adult counterparts [16]. Risk factors for the development of PTLD include mismatch of EBV serostatus (D+/R-), developing primary EBV infection after KTX, recipient younger age, and exposure to lymphocyte depleting agents. Of note, EBV disease is uncommon in KTx recipients who are EBV seropositive prior to transplant.

EBV is transmitted via exposure to saliva and other body fluids, blood transfusion, or, most frequently, in transplant recipients, through the transplanted organs. Children undergoing KTx are frequently EBV naïve prior to transplant, placing them at risk for primary infection and at increased risk of developing EBV disease and PTLD compared to adult KTx recipients [17].

Initial laboratory diagnosis of EBV infection in pediatric KTx recipients is typically made by detection of EBV DNA in peripheral blood by PCR. The presence of EBV DNA in blood usually precedes development of EBV-associated disease and PTLD, but may also be detected in those who will not develop the disease. Thus, an elevated load, even a high load, is sensitive but not specific in predicting risk of progression to EBV disease, including PTLD. The fact that the load typically rises prior to the onset of EBV disease has led to broad use of EBV viral load monitoring to allow for the preemptive reduction of immunosuppression over the last decades, with the latest incidence of EBV-associated PTLD appearing to have decreased in association with the use of this approach. The preemptive use of anti-CD20 antibodies (e.g., Rituximab) and EBV-specific cytotoxic T lymphocytes for patients with elevated loads has also been considered. Definitive data demonstrating the benefits and potential side effects of these approaches are lacking.

Although a few prospective studies have shown the positive impact of antiviral therapy with ganciclovir or valganciclovir in high-risk pediatric KTx recipients, whether antiviral therapy could prevent EBV transmission remains controversial [18]. Systematic review in both adults and pediatric organ recipients, has not been able to show the effect to prevent EBV infection or disease [19]. A recently published international consensus conference on the prevention and management of PTLD did not endorse use of ganciclovir or valganciclovir as prevention for EBV disease including PTLD [20].

Treatment decisions for EBV infections after KTx depend upon the clinical presentation and histologic characterization of the EBV disease. Patients with symptomatic EBV disease should be evaluated to determine the extent of their disease. CT imaging of the neck, chest, and abdomen should be performed. Imaging of the head may also be included, especially if there are central nervous system symptoms. The use of a PET CT scan is widely recommended. Pathology remains the gold standard to diagnose EBV disease and PTLD. Results of histology, including the degree of structural destruction, as well as type and clonality of infected cells, commonly dictate the choice of treatment. Reduction of immunosuppression is a common initial treatment step and is maintained at least until the diagnosis is confirmed and the pathology is characterized [14]. As many as two-thirds of patients respond to reduction or temporary withdrawal of immunosuppression alone, though concern

for rejection may limit this approach. Depending on the results of histology, treatment might shift to the initial use of rituximab or a multi-drug chemotherapy regimen. Both strategies may also be used in response to a failure of initial therapies.

BK Polyomavirus [21]
BKPyV is a human polyomavirus that infects most children, with seroprevalence estimated to be 90% by 4 years of age. Despite this high seroprevalence, clinical disease due to BKPyV is almost exclusively recognized in immunocompromised individuals. In KTx recipients, BKPyV is associated with ureteral stenosis, hemorrhagic or chronic cystitis, interstitial nephritis with graft failure, and allograft nephropathy (PyVAN, polyomavirus-associated nephropathy) [21]. The latter is the most important, as it can lead to allograft dysfunction and graft loss if untreated. An added concern is its clinical resemblance to allograft rejection, potentially confusing management and increasing the likelihood of progression to graft loss.

The overall incidence of PyVAN in adult and pediatric KTx recipients is reported as 1–10%. PyVAN typically presents in the intermediate to late post-KTx periods. Younger age, primary BKPyV infection after KTx, lymphodepleting induction, intense immunosuppression, and mycophenolate mofetil are considered risk factors for PyVAN. Although the clinical signs of PyVAN, such as an increase in serum creatinine, graft dysfunction, and allograft rejection, may precede the diagnosis of PyVAN, most children experience progression to PyVAN without clinical symptoms such as fever and hematuria. Progression from sustained, high-level BKPyV viruria to BKPyV-DNAemia and PyVAN is thought to occur serially over time, and viral loads may be elevated in the presence of other causes of allograft dysfunction. Thus, a positive pathologic diagnosis on an allograft biopsy is the gold standard for confirming the diagnosis of PYVAN.

To prevent the development of PyVAN, current guidelines recommend monthly measurement of BKPyV DNA in plasma until 9 months, and then every 3 months until 2 years post-KTx; extended screening after 2 years may be considered in pediatric KTx. Reduction of immunosuppression should be considered when the BKPyV DNA in urine is $>10^7$ copies/mL, or when BKPyV DNA in plasma is $>10^3$ copies/mL. Current evidence does not support the use of antiviral agents, such as cidofovir or brincidofovir, for prevention or treatment of BKPyV infection [21].

16.2.2.2 Fungal Infections

Fungal infections occur less frequently in KTx recipients compared to recipients of other organs. This low incidence may be explained by the type of surgical procedures performed during KTx and the lower level of immunosuppression required to maintain most renal allografts. Despite their lower incidence, fungal infections can be serious and life-threatening. Accurate diagnosis is crucial to optimize the choice of antifungal medications and use of invasive procedures to achieve source control. The diagnosis should be established by isolation of fungi from sputum, tracheal aspirate, bone marrow, tissue, or fluid. Serum galactomannan and 1–3-β-D-glucan levels may support the clinical diagnosis, although their performance specifications

in children are suboptimal. Identification and susceptibility testing can be performed on recovered fungal isolates and should be used to guide therapy whenever possible.

Fungal infections in KTx recipients primarily occur due to the presence of immunosuppressive therapy. Some pathogens are acquired after KTx, while others may be present and reactivate because the child is immunosuppressed.

Candida spp. including *C. albicans*, *C. krusei*, *C. glabrata*, *C. tropicalis*, and *C. auris* are the most frequently isolated fungi, causing esophagitis, pneumonitis, urogenital infection, and bloodstream infections. *Candida* infections usually occur during the first 2 months post-KTx and are associated with the presence of indwelling intravascular and urinary catheters. Echinocandins are the drug class of choice for invasive *Candida* infection as they have broader fungicidal activity against *Candida* spp. and less interaction with calcineurin inhibitors than azoles [22]. Invasive aspergillosis occurs in less than 0.5% of pediatric KTx recipients. It usually occurs within 3 months post-KTx. Known risk factors include the longer duration of renal replacement therapy and leukopenia. Other infections with filamentous fungi are uncommon. *Cryptococcus neoformans* is rarely seen in pediatric KTx recipients.

Pneumocystis jirovecii pneumonia (PCP) remains an important cause of severe pneumonitis. PCP occurs typically 3–6 months post-KTx. The use of universal PCP prophylaxis during the first 6–12 months post-KTx has led to current incidence rates being as low as 0.8 per 1000 KTx recipients. The primary risk factors for PCP are not being on prophylaxis. Other risk factors include lymphopenia, CMV infection, hypogammaglobulinemia, treatment of allograft rejection, and corticosteroids. Typical symptoms of PCP include fever, dyspnea, tachypnea, hypoxemia, and nonproductive cough. Interstitial pulmonary infiltrates are typical radiographic findings. Bronchoalveolar lavage or lung biopsy is necessary to confirm a diagnosis. However, empiric treatment should be considered when clinically suspected. High-dose intravenous trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for PCP and is given for 14–21 days. Adjunct use of corticosteroids within 72 h of the onset of hypoxemia is also recommended [23].

Low-dose oral TMP-SMX provides effective prophylaxis against PCP and also UTIs when given on a daily basis. Daily TMP-SMX is recommended for the first 6 months post-KTx, with some centers extending this out to a year. The benefit of providing longer prophylaxis after 1 year post-KTx has been discussed due to occasional late cases, but this remains a research question; a few programs maintain three times weekly prophylaxis indefinitely.

Alternative choices, including atovaquone, dapsone, and aerosolized pentamidine are occasionally used for KTx recipients who do not tolerate TMP-SMX.

Endemic Fungal Infections

Endemic fungal infections in North America include histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis. These organisms are geographically restricted and should be considered when KTx recipients live in or travel to areas where these infections are common. Endemic mycoses typically present during the intermediate or late post-KTx periods and can be life-threatening

if untreated. Disseminated disease may develop in KTx recipients with primary infection or reactivation of latent infection in previously infected patients. Experience unique to Coccidioidomycosis has led to the recommendation that kidney transplant recipients who are serologically positive for *Coccidioides*, as well as those receiving a renal allograft from a seropositive donor, should remain on lifelong prophylaxis with fluconazole. Accordingly, serologic monitoring of donors and recipients for Coccidiodiomycetes should be performed on donors and recipients with an epidemiologic risk of exposure. The use of serologic monitoring and prophylaxis for the other endemic mycoses is not recommended at this time, as these pathogens tend not to recur after transplant.

16.2.3 Late Post-KTx Period

Infectious complications occurring beyond 6 months after KTx tend to be less severe than those experienced in the earlier time periods, especially when immunosuppression has been minimized with favorable graft function. However, a history of repetitive episodes of rejection increases the risk of opportunistic infections. In those cases, constant vigilance for CMV infection, EBV-associated PTLD, PyVAN, as well as other community-acquired infections should continue even in this later time period. Although the clinical impact of UTI occurring in late post-KTx periods is less compared to the earlier time periods, the risk of developing a UTI remains, especially in recipients with residual anatomical issues. Community-acquired infections with respiratory pathogens, such as influenza virus and *Streptococcus pneumoniae,* are also common, emphasizing the need for all recommended vaccinations before and after KTx (see Sect 16.3).

KTx recipients may have chronic hepatitis virus infection with HBV or HCV. These infections may result in chronic liver disease, cirrhosis, and liver failure in late periods. If the KTx recipients are already infected with HBV or HCV, the careful monitoring of viral activity and liver function should be included in the routine care, and a pediatric hepatologist should be consulted.

16.3 Management

16.3.1 Pre-transplant Evaluation

Referral to pediatric infectious disease specialists to complete pre-transplant evaluation is recommended to allow for a comprehensive assessment of the KTx candidate. The typical checklist during the pre-KTx evaluation is detailed and summarized in Table 16.4 [4]. Key components of this evaluation include taking a careful history of multi-drug-resistant organisms as well as immunization status; this allows for recommendations to prepare the child for KTx and prevent infections afterward. Other key questions include identifying both where the child lives and any travel history to help assess the risk for endemic infectious diseases (e.g., tuberculosis,

Table 16.4 Guidelines for pre-transplant evaluation in pediatric kidney transplant [4]

History:
Past infectious diseases
Other past medical histories
Travel to or birth or residence in areas endemic for fungal or parasitic diseases or Zika virus/ SARS-COV-2 transmission
Tuberculosis exposure
Animal exposure
Diet preferences and water resources
Vaccinations
Reactions or allergies to antimicrobial agents
Current or past immunosuppression
Physical examination:
Search for active or latent focus of infection
Nutritional status
Screening tests:
Purified protein derivative (PPD: All ages)
Interferon-γ release assay (IGRA: Age older than or equal to 2 years)
Chest radiograph
Urinalysis and urine culture
Viral serology IgG and/or IgM for HSV, CMV, EBV, VZV, HAV, HBV, HCV, HIV, BK virus, WNV, ZV, and others depending on the history
Baseline HSV, CMV, and EBV DNA PCR, HCV, and BK virus if seropositive or post-transplant monitoring is anticipated
Fungal and parasitic testing if travel or exposure history is positive; sputum or stool tests as indicated
Anticipatory guidance
Update vaccines
Counsel regarding measures to reduce infection risk
Consider antimicrobial or viral prophylaxis if at risk

SARS-COV-2 severe acute respiratory syndrome coronavirus 2; *PPD* purified protein derivative; IGRA interferon-γ release assay; *CMV* cytomegalovirus; *EBV* Epstein-Barr virus; *HAV* hepatitis A virus; *HBV*, hepatitis B virus; *HCV* hepatitis C virus; *HIV* human immunodeficiency virus; *HSV* herpes simplex virus; *PCR* polymerase chain reaction; *VZV* varicella-zoster virus; *WNV* West Nile virus; *ZV* Zika virus

HTLV-1, Zika virus, West Nile virus, SARS-COV-2, *Histoplasma*, and other endemic mycoses, such as *Trypanosoma cruzi*). Diet preferences, water resources, pet animal exposure, allergy to medication, and pre-KTx use of immunosuppressants (for some autoimmune kidney diseases) should also be noted [1]. Serologic screening should be performed as described in Table 16.4. An evaluation for MTB infection should also be performed, including documenting prior history of Bacillus Calmette-Guerin (BCG) vaccination and exposure as well as performing either interferon-γ release assay (IGRA, validated age above 2) or tuberculin skin test (TST, in all ages) to screen for latent MTB infection [24]. Risk stratified management for each opportunistic pathogen, including prevention of CMV and EBV, should be discussed as part of the evaluation, as should strategies for safe living and general hygiene following KTx [3].

16.3.2 Post-KTx Immunization [25]

A plan should be implemented to ensure that transplant recipients are up to date on their immunizations following KTx. In general, the standard immunization schedule of inactivated vaccines for the general population should be followed, with a goal to provide catch-up vaccines prior to KTx whenever possible. The inactivated vaccines can generally be given after 3 months post-KTx, though this may be delayed in children requiring higher levels of immune suppression due to a history of rejection. Influenza vaccines may be given as early as 1 month after KTx during the endemic season. Optimization of vaccination against HBV and *S. pneumonia* should continue after transplant. Hepatitis B surface antibody titer should be assessed yearly for high-risk KTx recipients, and if titers fall below 10 IU/mL, re-vaccination should be considered.

Historically, most centers have not provided live virus vaccines after transplant. However, a recent consensus conference endorsed vaccination for selected pediatric recipients who are at baseline immunosuppression and without recent concern for rejection. Use of live vaccines in this population should be carried out in consultation with both the transplant nephrologist and the pediatric transplant infectious disease specialist at the patient's transplant center.

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Post-Kidney Transplant Hypertension in Children

17

Dunya Mohammad and Gaurav Kapur

17.1 Introduction

Hypertension (HTN) is a common medical problem among kidney transplant recipients in the pediatric population [1]. It is a known risk factor for cardiovascular morbidity and mortality in all patients with and without chronic kidney disease (CKD) or a renal transplant [2]. Additionally, in adults hypertension is identified as the most important non-immunological indicator related to graft failure. Early detection and proper control of blood pressure (BP) is universally considered important for avoiding complications related to hypertension and improving allograft survival in post-transplant patients.

17.2 Hypertension Epidemiology Post-Renal Transplant

Overall prevalence of hypertension in the pediatric population is increasing and based on current estimates, is around 3%, which is much lower than adult estimates at 45% [3, 4]. However, hypertension prevalence among children post-kidney transplant is much higher at 47–82% and closer to adult estimates at 50–80% [2]. Results of studies estimating the prevalence of hypertension vary based on parameters used to define HTN and the study cohort. In the immediate post-transplant period systolic BP is the highest but gradually decreases over time [5]. According to the North

D. Mohammad
University of South Alabama, Mobile, AL, USA
e-mail: dmohammad@health.southalabama.edu

G. Kapur (✉)
Central Michigan University, Children's Hospital of Michigan, Detroit, MI, USA
e-mail: gkapur@med.wayne.edu; kapur1g@cmich.edu

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American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), antihypertensive medication use decreased to 59% at 24th month compared to 70% at the first month post-transplant [6].

Another study evaluating the rate of transitioning to hypertension after 4 years of transplant in 126 normotensive pre-transplant children (mean age of 7.8 years at baseline) reported a cumulative hypertension incidence rate of 37.7% and 49.5% at 2- and 4-year post-transplant, respectively [7].

Adult studies have estimated the annual risk of cardiovascular events post-kidney transplant to be 50-fold higher than the general population [8]. One of the earliest studies (analysis of 1380 deaths from 1990 to 1996 reported in US Renal Data Systems) by Parekh et al. reported cardiovascular mortality >1000 times that of age-matched peers in children who received therapy for end-stage renal disease (ESRD) and died before 30 years of age [8]. The study also reported cardiac death rates of 2.1 and 1.3 per 1000 patient-years, in black and white patients with renal transplant, respectively. Recent analysis of the US Renal Data System reported a 15–20-year shorter life expectancy for youths with end-stage renal disease (ESRD) compared to youth in the general population [9].

According to the 2014 NAPRTCS annual report; among 11,117 index transplants (from 1996 to 2013), death reports were available in 591 patients (5.3%). Of these, infection (n = 168, 28.4%) was the most common cause of death followed by cardiopulmonary (n = 86, 14.6%) and malignancy/cancer (n = 68, 11.5%) [10]. The Australian and New Zealand Dialysis and Transplant (ANZDATA) registry reported 40% (n = 174) mortality from cardiovascular causes in a cohort of 1810 children with renal transplant. In this study, 81% of the time under observation was spent with a functioning transplant, and 33.6% (n = 608) of the patients received more than one transplant during a median follow-up time of 13.4 years. Despite only 19% of the observation time reported in the study spent on dialysis, the ANZDATA reported a median time and age of death of 10 years (IQR, 4–20) and 24 years (IQR, 18–35), respectively. The findings of the ANZDATA gain further importance when viewed in light of studies reporting suboptimal cardiovascular care in children with kidney disease [11, 12]. In retrospective analysis of 221 patients with kidney transplant with 24-h ambulatory blood pressure measurement (ABPM), based on clinic BP measurements, 49% had normal BP, 34% had pre-hypertension, and 17% had hypertension. However, hypertension was identified more frequently based on ABPM and 22–26% were hypertensive based on mean ABP and 42–45% based on BP load [13]. The higher hypertension prevalence on ABPM was attributed to nocturnal hypertension and identification of masked hypertension (associated with left ventricular hypertrophy), trends which are missed on clinic BPs alone. Guidelines from the National Kidney Foundation and American Heart Association stress on the importance of cardiovascular care in post-transplant patients similar to CKD and ESRD patients on [14, 15]. Despite these recommendations, the quality of cardiovascular disease care post-transplant is shown to be suboptimal compared to non-transplant CKD patients. A multicenter study evaluating the prevalence of CKD stages and the degree of achieving Kidney Disease Improving Global Outcomes (KDIGO) guideline treatment goals in a cohort of 2160 kidney transplant patients

(mean age of 53 years) reported >50% of the patients with CKD (54.4%, 13%, and 2.3%, for stages III, IV, and V, respectively) and suboptimal BP control (≥130/80 mmHg) with high cholesterol levels despite statin therapy [16].

17.3 Consequences of Hypertension in Post-Transplant Patients

According to the 2009 KDIGO guidelines, it is unlikely that a large randomized controlled trial in recipients of kidney transplant will be conducted to evaluate the effect of lowering BP on graft survival or cardiovascular mortality [17]. The validity of the statement is obvious as it has been conclusively shown in the general adult population by different reports (observational and randomized controlled trials (RCT)) that hypertension is an independent risk factor for cardiovascular and chronic kidney disease, and reducing BP reduces the risk and progression of cardiovascular and chronic kidney disease in low- and high-risk groups (diabetes and chronic kidney disease) [15].

In adults, the overall prevalence of hypertension in transplant recipients is around 85%. Hypertension can increase cardiovascular morbidity and mortality due to increased risk of ischemic heart disease, congestive heart failure, coronary artery disease, increased arterial stiffness, and stroke. Graft rejection is noted to be more prevalent in girls and young women compared to their male counterparts [18]. A recent retrospective analysis of 815 patients showed graft survival is directly related to degree of BP control; inversely patients with highest BP had the worst survival rate especially patients with SBP more than 140 mmHg [19]. However, the precise effect of strict control of BP is difficult to assess because of the negative effect of decline in allograft function on BP control and detrimental effect of elevated BP on allograft function [20].

In pediatric post-transplant patients, cardiovascular mortality is the second most common cause of death after infection. However, pediatric post-kidney transplant patients are at higher risk of cardiovascular mortality than the general population. Despite the significant post-transplant reduction in renal-related cardiovascular morbidity and mortality, hypertension remains one of the most important modifiable risk factors in pediatric patients [21]. A study by Stabouli et al. which included 74 pediatric transplant patients (median age 11 years) showed pre-transplant BP control at 16.7% compared to 43.8%, 66.7%, and 42.9% at 1, 5, and 10 years post-transplant, respectively [22]. Despite the improvement in BP control over time, the prevalence of HTN remains high for many years post-transplant. The same study also reported that after 10 years of transplant hypertensive patients had 8 times higher hazard of graft loss in comparison to non-hypertensive patients (95% CI 1.561–41.807, $P < 0.05$).

Additionally, hypertension has been associated with neuropsychological impairment in both adult and pediatric populations [23, 24]. This effect has been more pronounced in CKD patients, ranging from 50% to 87%, secondary to changes in blood pressure, high homocysteine levels, anemia, and subclinical vascular and

brain white matter changes in this population [25, 26]. Post-kidney transplant patients have shown better general cognitive functioning when compared to pre-transplant CKD patients, but significantly lower compared to matched healthy individuals [27]. A recent study in kidney transplant patients with cognitive outcome suggests possible positive association between impaired cognition and all-cause graft loss in post-transplant patients [28]. This is clinically relevant, because impaired cognition in areas of memory affects medication compliance, which is crucial in post-transplant patients.

17.4 Diagnosis of Hypertension and Importance of ABPM

Casual BP measurement should be a routine in all pre- and post-transplant clinic visits. The recommendations in the section on high-risk patients in the 2017 clinical practice guidelines on screening and management of high BP in children and adolescents [29] should be followed to diagnose hypertension in children with renal transplant. Per the guidelines, oscillometric BP machines validated for use in children can be used for initial screening, followed by confirmation with auscultatory measurements in patients with high BP reading (>90th percentile for age, gender, and height).

Recent reports and the 2017 guidelines have highlighted the usefulness of ABPM in identification and characterization of BP in this population [30, 31]. ABPM records BP periodically throughout the day (usually every 20–30 min) while the patient is in his home environment following a daily routine. The updated 2014 scientific statement from the American Heart Association should be followed for performance and interpretation of ABPM results in pediatric post-transplant patients [32].

ABPM studies of post-renal transplant in children have shown a poorly controlled BP in more than 50% of the patients (50–80%) [33, 34]. This is attributable to identifying masked, white coat, and nocturnal hypertension and abnormalities of circadian BP rhythms (daytime and nighttime hypertension and dippers and non-dippers) with ABPM use. Of note, studies have not shown long-term benefit regarding cardiovascular morbidity/mortality with reversal from non-dipper to dipper or a higher risk of cardiovascular disease in patients with elevated nighttime BP [35].

In a recent retrospective cohort of 202 post-transplant patients (median age 16.7 years), 123 had baseline and follow-up ABPM (for mean 2.3 years); improved HTN control was reported in those with ABPM compared to those without ABPM (45% vs. 26%, $P = 0.002$) [13]. This study also reported high baseline 24-h mean BP as an independent risk factor for persistently elevated BP at follow-up. These study findings support a role for ABPM in not only diagnosis but also in assessing long-term prognosis of HTN in this high-risk population. Furthermore, studies have shown that routine ABPM use to achieve BP control in children with CKD correlates with improvement in left ventricular mass index [36, 37]. A recent case series

of 68 patients (mean age 9.1 ± 5.3 years), who had routine ABPM immediately post-transplant and annually thereafter (6.2 ± 2.8 years mean of last follow-up), reported significant improvement in LVH [38].

Despite these reports ABPM use is limited. This could be attributed to (a) ABPM cost and reimbursement in the pediatric population; (b) logistical issues related to machines available, return of machines, and weekdays versus weekends for the studies; (c) current recommendations for performing ABPM in children are confusing as vigorous exercise or contact sports are to be avoided but routine activities are encouraged; and (d) sleep hindrance with 24-h BP monitoring leading to incomplete studies. Furthermore, ABPM interpretation is limited as it references normative data derived from ABPM studies of nearly 1100 predominantly Caucasian children, lack of ethnic diversity in the cohort, and minimal diastolic BP variability and limited data on children with height less than 140 cm [39].

17.5 Pathophysiology

Hypertension post-transplantation has a complex and multifactorial etiology. In addition to the traditional risk factors such as age, gender, race, obesity, and family history, additional factors contribute to increased prevalence of hypertension post-transplantation including recipient, donor, surgery, and immunosuppression medication-related factors [5, 40] (Table 17.1).

Table 17.1 Traditional and nontraditional risk factors for post-transplant hypertension [41, 42]

Traditional risk factors
• male gender • African American race • family history of hypertension • preexisting hypertension in recipient or donor • donor age • preexisting left ventricular hypertrophy and cardiac function abnormalities • body mass index (BMI)
Nontraditional risk factors
• presence of native kidney • deceased donor transplant • En-block kidney transplant • volume overload • ischemia-reperfusion injury • post-transplant proteinuria • medications (steroids and calcineurin inhibitors) • surgical complications (transplant real artery stenosis, lymphocele, ureteric stenosis) • renal allograft-related factors (delay graft function, graft failure, recurrent primary disease, thrombotic microangiopathy) • metabolic disease (secondary hyperparathyroidism and hypercalcemia)

17.6 Pre-Transplant Factors

Commonly known risk factors associated with hypertension such as male gender, African American race, family history of hypertension, and obesity have been associated with hypertension in the kidney transplant recipients too.

Pre-transplant hypertension is present in almost all recipients as chronically deteriorating renal function is associated with elevated BP, with reports of more than 80% documented hypertension in children with CKD stages 3–5 [43]. Major contributing factors to increased incidence of hypertension with CKD progression are (1) salt and water retention resulting in increased cardiac output and peripheral vascular resistance, (2) activation of renin-angiotensin-aldosterone system (RAAS) causing direct vasoconstriction through angiotensin II and salt retention with volume expansion through aldosterone-induced salt retention, (3) sympathetic overactivation, (4) impaired endothelium-dependent vasodilatation, and (5) chronic hyperparathyroidism due to the parathyroid-induced intracellular hypercalcemia which increases sensitivity of endothelial cells to calcium and catecholamine with resultant vasoconstriction and stiffening of blood vessels [44]. A detailed discussion of CKD factors contributing to hypertension is beyond the scope of this chapter and the readers are referred to other reviews [45–47]. Pre-transplant hypertension not only doubles the risk of CKD progression, but also remains a major risk factor for persistent hypertension and ESRD post-transplant [5, 48]. A recent adult study by Pourmand et al. tried to answer the question of whether kidney transplantation cures pre-transplant hypertension by resolving most of the factors contributing to hypertension in CKD stage 5 post-transplant. Their results showed that more than half of patients with hypertension continued to be hypertensive post-transplant (56.8%) and hypertension was the main risk factor for ESRD in their cohort [49]. This in part can be explained by the effect of long-standing hypertension on blood vessels resulting in decreased vascular compliance with vascular stiffness, which is more pronounced in patients with a history of prolonged volume access [50, 51].

Obesity (body mass index (BMI) ≥30) has been linked to hypertension, kidney injury, and poor graft survival in both adult and pediatric post-transplant patients [52, 53]. Although most studies define obesity based on BMI, a recent pediatric study identifies waist-to-height ratio as the most sensitive predictor of cardiovascular risk factors in post-transplant patients compared to BMI and waist circumference [54]. The mechanism of hypertension in individuals with high BMI is complex. The main two factors that are more of a direct consequence of obesity are (1) localized (kidney and muscle) sympathetic nervous system activation by visceral fat deposition and (2) renin release from the adipose tissue with activation of RAAS from renal compression by visceral fat. These two factors together increased intravascular volume and peripheral vascular resistance which directly elevates BP [55–57]. The worldwide obesity pandemic applies to the pre-transplant pediatric population with renal transplant as a possible exacerbating factor [55].

Native disease—glomerular versus non-glomerular: Studies have shown an association between hypertension and degree of CKD; the association is stronger when considering the etiology of the primary renal disease (i.e., glomerulopathy versus tubulopathy). In the ESCAPE (Effect of Strict Blood Pressure Control and ACE inhibition on the Progression of Chronic Renal Failure in Pediatric Patients) trial survey, hypertension prevalence was 88% in children with glomerulopathy compared to 38% in children with hypoplastic/dysplastic kidneys, regardless of CKD stage [58]. This can be in part related to the fact that patients with renal dysplasia are non-oliguric salt wasters and usually do not require hypertension-inducing treatment like steroids.

Although the role of native kidneys in post-transplant hypertension and cardiovascular morbidity is not well understood, some studies show reduction in the need for antihypertensive medications after native nephrectomy in kidney transplant patients [59]. In current practice, native nephrectomy before or at the time of transplant is not a routine. Native nephrectomy remains limited to cases with expected risk to recipient or graft secondary to underlying anatomical anomaly, severe proteinuria, primary kidney disease-related refractory hypertension, chronic kidney infection, or malignancy [60, 61].

Preemptive and living donor transplant: Both adult and pediatric studies show the positive effect of preemptive and living donor transplantation on immediate and late onset post-transplant hypertension [62, 63]. A recent study by Pagonas et al. assessing 815 adult post-transplant patients showed overall lower BP in recipients of live young donors [64]. This effect could partially be explained by the overall better graft function and survival in preemptive living donor renal transplant. Preemptive transplantation avoids patient exposure to dialysis. This is important, because the duration of dialysis exposure has been reported as an independent risk factor for cardiovascular morbidity and mortality not only while the patient is on dialysis but also after transplantation [65–67].

Donor factors: Donor age, female gender, preexisting hypertension, and poor-quality donor (as identified by gross anatomy, vascular flow, and resistance measurements and histologic abnormalities) are factors that have been independently associated with increased risk of post-transplant hypertension [68]. Studies have shown recipients of expanded criteria donors (any donor 60 years or older or patients 50–59 years old with history of two of the following: hypertension, serum creatinine >1.5 mg/dl, or death from cerebrovascular disease) have higher prevalence of hypertension and cardiovascular disease [69]. It's also important to note that donor genetic variants such as variants of $APOL_1$ gene and polymorphism of genes encoding ABCC2, ABC1, and CYP3A5 have been associated with subsequent hypertension in post-transplant patients with decreased allograft survival [1, 70, 71]. Another donor factor associated with increased risk of post-transplant hypertension is the size of the donor kidney relative to the recipient. A disparity between donor and recipient size can lead to a decreased number of nephrons relative to recipient size and could lead to maladaptive response of glomerular hyperfiltration, hypertrophy, and hypertension [72, 73].

17.7 Immediate and Early Post-Transplant Period

Hypertension prevalence is high in the immediate post-transplant period; it gradually increases over the first few weeks reaching around 95% by the end of the first month [74]. It is important to investigate new onset hypertension post-transplant as the underlying cause guides therapy [2, 69].

Increased intravascular volume and vasoconstriction are the main immediate causes of hypertension post-transplant [75]. To avoid perioperative volume contraction, which has been linked to high incidence of acute tubular necrosis and delay graft functioning (DGF) post-transplant, peri- and intraoperative volume expansion and achieving goal BP > 90th percentile are the standard of care in almost all transplant centers [76]. Consequently, volume overload resulting from administration of crystalloids and occasionally colloid solutions intraoperatively is the main contributor to 80–90% prevalence of hypertension in the immediate post-transplant period [49, 75]. DGF, reported in up to 25% of deceased donor transplants, is an additional factor related to hypertension in this period by decreasing free water excretion and inappropriate production of renin [77]. Hyperacute or early acute rejection, which is rejection within the first 24 h to the first few weeks' post-transplantation, can present with renin-mediated hypertension, although the most common presentation is asymptomatic increase in serum creatinine level, in the current immunosuppression era.

Commonly used immunosuppressive medications such as steroids, calcineurin inhibitors (CNIs), and mTOR inhibitors have been associated with de novo or worsening hypertension in the immediate or late post-transplant period [62, 78–80]. Sodium retention leading to volume expansion is the underlying mechanism common to these immunosuppressants. Additionally, corticosteroids increase BP via permissive effect on vasopressors with a decrease in nitric oxide production. Corticosteroid effects appear to be dose dependent prompting the use of lower-dose corticosteroids and steroid-sparing approaches based on immunologic risks in transplant patients [81]. Steroid doses of 10 mg and less per day have shown minimum effect on BP [82].

Calcineurin inhibitors (tacrolimus and cyclosporine) induce renal vasoconstriction which in turn causes renal hypoperfusion and contributes to their nephrotoxic effect. CNI vasoconstriction is mediated by increased activity of endothelin, thromboxane 2, TGF-beta, angiotensin 2 (renal vasoconstrictors), decreased production of prostaglandins, nitric oxide (renal vasodilators), and stimulation of the renin-angiotensin system [83]. The reported frequency and severity of hypertension is less with tacrolimus compared to cyclosporine, and currently tacrolimus-based immunosuppression is the standard of care [82]. Additionally, CNIs have been associated with post-transplant hemolytic uremic syndrome or posterior reversible encephalopathy syndrome (PRES), both disorders associated with significant BP elevation. These rare side effects may necessitate change in immunosuppressive therapy.

External compression of the allograft by a hematoma, seroma, lymphocele, urinoma, and transplant renal artery stenosis are the other considerations in the immediate postoperative period. Perinephric fluid collection especially hematoma and

seroma is common post-transplant and usually is diagnosed on allograft ultrasound. Intervention is based on size, site, and appearance of symptoms like pain, decreased urine output, hypertension, or increase in creatinine [84]. Transplant renal artery stenosis (TRAS) is reported in 10–23% of transplant patients and accounts for up to 5% of persistent refractory post-transplant hypertension [85, 86]. It is a relatively common complication that usually happens within the first 2 years, commonly within the first 6 months post-transplantation [87]. Structurally it happens at the anastomosis site, although pseudo-renal artery stenosis has been reported in adults with atherosclerosis proximal to anastomosis [2, 88, 89]. The identified causes of TRAS include suture techniques, trauma to donor or recipient vessels during the surgery, atheroma of the artery, or immune-mediated vascular damage [90]. The mechanism of hypertension is stenosis-induced hypoperfusion resulting in renin-mediated hypertension. TRAS directly compromises graft survival and has also been associated with premature death (adjusted hazard ratio 2.84, 95% CI 1.70–4.72) in transplant patients [87, 91]. Activation of RAAS in TRAS patients leads to fluid retention, severe worsening hypertension, and increase in creatinine in the absence of rejection. A bruit over the graft might be heard on examination [90]. Flash pulmonary edema from cardiorenal syndrome (Pickering syndrome) has been reported as a rare presentation of TRAS [91]. For diagnosis, color Doppler ultrasound is a sensitive primary screening tool but angiography remains the gold standard. Percutaneous transluminal angioplasty is currently considered safe and effective treatment option for TRAS patients, with reports of significant improvement in both hypertension and graft function [92, 93].

17.8 Late Post-Transplant Factors

Hypertension prevalence decreases with time post-transplant, especially beyond 6 months [75]. This trend is most likely secondary to gradual weaning of steroids and accepted lower target troughs of CNIs. Pre-transplant hypertension, low GFR, and chronic allograft failure (CAF) are recognized as the main contributing factors to new onset or persistent late post-transplant hypertension [82].

Data on hypertension late in the post-transplant period is limited in children. A retrospective study of 70 renal transplant patients (age < 18 years) evaluated multiple risk factors such as age of recipient and donor age; pre-transplant hypertension; GFR at 1, 3, and 6 months post-transplant; cumulative dose of corticosteroids; cold ischemia time > 24 h; transplant type (living related or cadaveric donor); recipient BMI at follow-up; and delayed graft function. Of these factors, only GFR at 3 and 6 months post-transplant (92+/−29 and 83+/−20 ml/min per 1.73 m2 at 3 and 6 months, in the non-hypertensive patients, versus 74+/−23 and 70+/−21 ml/min per 1.73 m2, respectively, in the hypertensive group) had a statistically significant association with hypertension [74].

CAF is identified as one of the most common causes of pediatric graft failure by the NAPRTCS data; it can be both the cause and the consequence of poorly controlled hypertension as well [6]. Obesity is a known risk factor for hypertension in

children with and without chronic kidney disease. This effect is also seen in late post-transplant with a study showing positive association between BMI at 1 year post-transplant and hypertension at third year post-transplant [5]. Multiple studies report an increase in weight (15–45%) and emergence of metabolic syndrome (MS) (defined by having three or more of the following: abdominal obesity, hypertension, glucose intolerance, increased triglycerides, or low HDL cholesterol in one-third of patients post-transplant [94–97]. In the post-transplant period, the first year, young age (6–12 years), male patients with low baseline BMI, and steroid immunosuppression are identified as risk factors for weight gain [94, 96, 98]. Despite the fact that steroid exposure is a well-known risk factor for hypertension and obesity, studies have shown a steroid-independent association between hypertension and obesity in pediatric post-transplant patients [99]. Thus, obesity can be a target of modification in prevention and management of hypertension, knowing its association with graft loss and cardiovascular morbidity post-transplant [53, 55, 95].

Noncompliance with dietary salt restriction or medication, acute rejection episodes, high CNI drug levels (medication error, changes in gastrointestinal absorption or metabolism associated with other medications, fruits), nonsteroidal anti-inflammatory drug use other than acetaminophen, nasal decongestants, excessive alcohol intake, and untreated obstructive sleep apnea are other considerations for hypertension in the outpatient setting for renal transplant patients. Renal biopsy could lead to subcapsular hematoma or biopsy-related AV fistula, which could also lead to hypertension.

17.9 Management

Improved pediatric survival (90–95%) post-kidney transplant magnifies the importance of long-term management of modifiable risk factors that affect long-term morbidity and mortality in these patients. BP control and management is aimed at improving allograft survival and minimizing long-term cardiovascular complication risk [51].

17.10 Targeted Blood Pressure in Post-Transplant Patients

There is no current consensus on the ideal BP post-transplant. Kidney Disease Improving Global Outcomes clinical practice guidelines (2012 and the updated 2020 draft), similar to that of the American College of Cardiology, recommend a target BP of <130/80 mmHg in transplant patients 18 and older [100, 101]. These are in agreement with SPRINT trial results, which showed a 28% mortality reduction in CKD patients (28% of study cohort) with target BP <130/80 mmHg [102]. In children (<18 years) with CKD, current KDIGO recommendation based on ABPM recommends target mean 24-h arterial pressure (MAP) of ≤50th percentile for age, sex, and height [101]. These recommendations are supported by the ESCAPE trial and multiple small trials showing the benefit of low BP targets [36].

Chronic Kidney Disease in Children Study (CKiD) data too shows that lower MAP (<50th percentile) may have an additional benefit to MAP targets <90th percentile in children with CKD [103]. A target range of 50–90th percentile could be considered in children with renal transplant. The concerns for lower target BP in both adult and children are the risk of hypotension, AKI, and graft dysfunction. The ESCORT trial (a pediatric RCT, $n = 21$) reported no difference in annual reduction in eGFR in children (age range 6.2–16.8 years) randomly assigned to standard (24-h MAP 50–95th percentile) or intensified (MAP <50th percentile) BP targets [104].

17.11 Non-pharmacological Interventions

All pediatric kidney transplant patients need to undergo diet and lifestyle modifications with support from a dietitian. The standard recommendations in hypertensive adults and children with and without CKD are low sodium diet (<2 g per day) and dietary approaches to stop hypertension (DASH) diet. A recent meta-analysis in non-CKD hypertensive patients showed low sodium intake (<3.5 g per day) was beneficial in reducing both BP and cardiovascular disease risk [105]. However, dietary approach must be individualized. A low sodium diet might be detrimental in a subpopulation of patients with salt wasting and transplant receipts with high-output CKD because of risks of hypotension. Additionally, a high potassium diet or salt substitutes that have high potassium content especially in patients with hyporeninemic hypoaldosteronism could cause hyperkalemia in the presence of poor or declining transplant function. Patients should be encouraged to keep an active lifestyle with regular aerobic exercise (at least 150 minutes/week) if compatible with their cardiovascular status and maintain weight at normal range for age and sex (BMI ≤25).

17.12 Pharmacotherapy

There are no pediatric recommendations on when and which antihypertensive to first start in treating hypertension post-transplant. In adults, almost 90% of patients need antihypertensive therapy post-renal transplantation. Adequate BP control is more important than specific medication used, since comparisons of antihypertensive have not shown benefits of one over the other. In addition to known medication side effects, other considerations for selecting antihypertensive medication in a transplant patient include alteration in graft perfusion, risk of anemia, and effects on metabolism of immunosuppressant medications [106]. Attention should also be paid to induction or inhibition of cytochrome P450 pathway by antihypertensives and its subsequent effect on calcineurin metabolism, the mainstay of current immunosuppressive therapy. Non-dihydropyridine calcium channel blockers (CCB) (verapamil and diltiazem) are CYP450 inhibitors (diltiazem dose of 120 mg/day is sufficient to decrease CNI dose by 60%) and can increase the risk of supratherapeutic CNI levels with nephrotoxicity risk for the allograft [107].

17.13 Management in the Immediate Post-Transplant Period

Intravenous (IV) route is the most commonly used and preferred route for antihypertensive medication in the immediate post-transplant period. Hypertension in this period is mainly related to fluid overload and pain. IV diuretics (loop diuretics: furosemide or thiazide) are commonly used for volume overload in the presence of a functioning graft with urine output. For rapid action in case of hypertensive urgency vasodilators like hydralazine are preferred. Hydralazine is historically the most commonly used medication for treatment of rapid elevation in BP. Two recent pediatric studies looked into its efficacy and safety, with reports of 43% clinical response, mild adverse events (9%), and excessive (>30%) drop in BP [108, 109]. Alternatives for both pediatric and adult patients include dihydropyridine CCB (nicardipine, isradipine) that have rapid onset and short duration of action.

Fenoldopam is a selective dopamine 1 (DA1) receptor agonist. It's a rapid-acting, effective agent for intravenous control of BP in children. It results in natriuretic and renal vasodilatation through direct activation of DA1 receptors in proximal convoluted tubule and renal vasculature, respectively. Studies have shown its role in improving kidney perfusion in case of mild to moderate AKI without causing hemodynamic disturbance in critically ill children compared to low-dose dopamine [110]. However, its effect in the prevention of ischemia-reperfusion injury in renal transplantation patients has not been clinically significant and there are no studies on its role in post-transplant hypertension management [111].

Other IV medications like labetalol (combined α1- and β-adrenergic blocking) and esmolol are available as bolus or continuous infusions for treatment of hypertensive urgency, but their role in pediatric post-transplant hypertension is not studied. ARB and ACE-I should be avoided in the immediate post-transplant period because of the effect of these medications on GFR and rise in creatinine which can mask rejection as a cause of creatinine elevation. Immunosuppression (mainly steroid) reduction is associated with improved BP after the initial induction phase.

17.14 Long-Term Management

Based on KDIGO guidelines, review of data from multiple adult randomized controlled trials shows dihydropyridine CCB (such as amlodipine and nifedipine) and angiotensin receptor blockers (ARB) (such as losartan and valsartan) compared to placebo have a significant effect on reducing the rate of graft loss [112–114]. Yet these mediations have not shown any effect on overall mortality and cardiovascular-related mortality like stroke and myocardial infection [17, 101]. Pediatric data on the frequency of antihypertensive medication use in all age groups post-transplant show CCB, alpha-agonist, and diuretic use in 60.8%, beta blockers in 30%, ACE-I/ARBs in 23.2%, and vasodilators in 4.5% [115].

In patients with hypertension and proteinuria, ARB and angiotensin-converting enzyme inhibitors (ACE-I) slow the progressive decline in GFR and remain the antihypertensive of choice. In the first year post-transplant increased risk of hyperkalemia has been reported with ACE-I and ARB, attributed to decreased aldosterone secretion and interference with potassium secretion in the collecting duct [116]. Additionally, increased risk of anemia has been reported with ACE-I/ARB use in immediate post-transplant period [117]. Over time, progressive decline in renal allograft function along with increasing proteinuria is associated with preference for ACE-I and ARB as antihypertensive medications. Data on other classes of antihypertensive medications such as diuretics and beta blockers in post-transplant patients is limited.

A new emerging interesting treatment for drug-resistant post-transplant hypertension is sympathetic renal denervation (SRD) of the native kidneys. This procedure has shown some promising results in limited number of cases. A recent adult study on 18 post-transplant patients with multidrug-resistant hypertension, followed for 6 months after SRD, showed SRD to be significantly effective in reducing office BP (P = 0.001) and improving nocturnal hypertension (10.38 ± 12.8 mmHg (P = 0.06) and interestingly more patients who were non-dippers converted to dippers (P = 0.035) [8, 118].

For long-term management, the easiest to use medication with assessment for standardized response via BP monitoring can be implemented with active monitoring of medication side effects. Studies have shown simplifying treatment regimen for patients and clinicians will have positive impact on management of chronic medical conditions, although such regimen is not yet standardized in this specific patient population [119, 120].

Finally, to ensure effective BP control it is of paramount to take a multidisciplinary approach in addition to the above pharmacological and non-pharmacological therapies, minimize use of CNI and steroids to lowest possible dose, and have regular BP monitoring in between provider visits by ancillary providers and patient counseling on adherence to medications.

17.15 Summary

Hypertension underdiagnoses and inadequate control are frequently encountered in pediatric post-transplant patients. High incidence of masked and nighttime hypertension underscores the importance of a 24-h ABPM monitoring in addition to office BP measurements. Post-transplant hypertension has a multifactorial etiology associated with hypertension diagnoses and timing of the renal transplant. Effective BP control with non-pharmacologic and pharmacologic therapy reduces the risk of cardiovascular morbidity and mortality and improved allograft survival (Table 17.2).

Table 17.2 Treatment of hypertension in kidney post-transplant patients

1: *Calcium channel blockers (most commonly used)* [121, 122]		
Medication	*Dose and frequency*	*Comments*
Amlodipine Nifedipine (extended release) Isradipine (immediate release)	Oral: <6 years: 0.1 mg/kg/dose once daily (max dose 0.6 mg/kg/day or 5 mg/day) Oral: ≥6 years 2.5 once daily (max dose 10 mg/day) Oral: 0.25–0.5 mg/kg/day once daily or divided into two doses every 12 h; do not exceed 60 mg initially (max dose 3 mg/kg/day up to 120 mg/day) Oral: 0.05–0.1 mg/kg/dose 2 to 3 times daily (max dose 0.6 mg/kg/day or 10 mg/day)	Can cause reflex tachycardia, lower extremity edema, and gingival hypertrophy Amlodipine and isradipine can be compounded into stable suspensions Isradipine onset of action in <60 minutes can be used as an oral agent in conditions with acute rise in BP Isradipine not recommended for long-term use Non-dihydropyridines (verapamil and diltiazem) are not routinely used in children
2: Beta *blockers* [122–126]		
Labetalol *Carvedilol (immediate release)* *(extended release capsules)* *Propranolol (immediate release)* *(sustained release)* Atenolol	Oral: 1–3 mg/kg/day in 2 divided doses (max dose 10–12 mg/kg/day up to 1200 mg/day) IV (intermittent bolus): 0.2–1 mg/kg/dose (max dose 40 mg/dose) Adolescence ≥18 years Oral: Initial: 6.25 mg twice daily, can be increased to 12.5 mg twice daily in 1–2 weeks (max dose 50 mg/day) Oral: Initial: 20 mg/day, can be increased to 40 mg/day in 1–2 weeks (max dose 80 mg/day) Oral: Initial: 1–2 mg/kg/day divided into 2–3 doses (max dose 4 mg/kg/day up to 640 mg/day) 1–2 mg/kg/day once daily (max dose 4 mg/kg/day up to 640 mg/day) Oral: Initial: 0.5–1 mg/kg/day once daily or into two divided doses (max dose 2 mg/kg/day up to 100 mg/day)	Relative contraindications include asthma and heart failure Bradycardia, hyperlipidemia, and hyperglycemia are possible side effects Can impair compensatory sympathetic response in patients who are athletes Atenolol dose should be adjusted based on eGFR
3: **Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blocker (ARB) [122–127]**		
Enalapril Lisinopril Losartan	Oral: Initial: 0.08 mg/kg/dose once daily (max dose 40 mg) Oral: Initial: 0.07 mg/kg/day once daily (max dose: 0.6 mg/kg/day up to 40 mg/day) ≥6 years: Oral: Initial: 0.7 mg/kg/day once daily (max dose 1.4 mg/kg/day up to 100 mg/day)	Usually not used in the first 6 months post-transplant for concerns of hyperkalemia and decrease allograft perfusion Dry cough and angioedema less common in newer ACE-I and ARB Urine pregnancy test should be made at the start and frequently afterwards in teenage females because of teratogenicity

Table 17.2 (continued)

1: *Calcium channel blockers (most commonly used)* [121, 122]		
Medication	*Dose and frequency*	*Comments*
4: Alpha blocker and agonists [122]		
Clonidine (central) Prazosin (peripheral)	0.1–0.2 mg/day up to 2.4 mg/day (max) 0.05–0.1 mg/kg/day up to 0.5 mg/kg/day (15 mg/day max)	Clonidine available as transdermal preparation Not used in infants and toddlers Rebound hypertension occurs if stopped suddenly Heavy sedation could limit its use May cause hypotension and syncope, especially after the first dose

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Recurrent Renal Disease After Transplantation

18

Shanthi S. Balani and Paul R. Brakeman

18.1 Introduction

In the pediatric population, primary glomerulonephritis diseases, including focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), and membranoproliferative GN (MPGN), are the second most common cause of end-stage renal disease (ESRD), representing 21.1% of all pediatric ESRD patients [1]. In addition, secondary glomerular diseases, including systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV), and complement-mediated glomerular disease, are the fourth leading cause of ESRD, representing 8.0% of pediatric patients with ESRD [1]. These conditions can recur after transplantation with varying effects on the allograft and long-term transplant outcomes (Table 1). The goal of this chapter is to describe the epidemiology, pathophysiology, treatment options, and allograft outcomes for patients in whom these conditions recur after transplant.

18.2 Focal Segmental Glomerulosclerosis

Focal segmental glomerular sclerosis (FSGS) is the most common acquired glomerular disease causing ESKD in pediatric and adult patients. FSGS is a histopathologic description of glomerular scarring with a heterogenous pathogenesis. FSGS can be genetic, primary/idiopathic, or secondary with post-transplant recurrence primarily occurring in primary/idiopathic forms of FSGS [2, 3]. FSGS recurrence is common, affecting up to 55% of first pediatric transplants and up to 80% of subsequent transplants after FSGS has recurred in a previous transplant [4–6].

S. S. Balani
Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

P. R. Brakeman (✉)
Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA
e-mail: paul.brakeman@ucsf.edu

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The molecular pathogenesis of primary FSGS is incompletely understood, with the central event being podocyte damage leading to podocyte loss and glomerular scarring. The mechanism for primary FSGS likely involves a circulating factor that causes increased glomerular permeability. The hypothesis that there is a circulating factor that can trigger increased glomerular permeability is supported by data that plasma from a human with FSGS can trigger increased glomerular permeability when infused into a rat and that FSGS recurrence can occur within hours of implantation of a renal allograft. There has been exhaustive work to identify this circulating factor or factors; however, to date the definitive identification of this factor remains elusive [7]. Podocyte damage occurs in secondary FSGS as a result of viruses, hyperfiltration related to obesity or drug toxicity, and other environmental factors [2]. It is likely that some patients with presumed primary FSGS have an unidentified secondary cause for their FSGS.

18.2.1 Incidence

The overall reported rate of recurrent FSGS in children is 6–58% [4, 6]. This large variability may reflect different definitions of recurrence (clinical versus biopsy-proven) and/or incomplete reporting of data in large data sets. Center-specific retrospective pediatric cohort studies show generally high rates of recurrence between 30% and 55% [8–10]. Most recurrences occur within the first week after transplant and can occur as early as post-operative day 1 [8, 11].

18.2.2 Risk Factors

Risk factors for recurrence include younger age at onset of disease, more rapid progression to ESRD, white race, and previous recurrence in an allograft [4–6]. Of note, many patients with very-early onset FSGS will have a genetic cause for their disease and are unlikely to recur, although recurrence has been reported for a small number of patients with identified homozygous mutations in *NPHS2* [12, 13]. The use of a living donor or deceased donor has not been observed to affect disease recurrence [9].

18.2.3 Diagnosis and Treatment

Identification of FSGS recurrence is usually made based on significant new proteinuria and/or reduced allograft function after transplantation. After transplantation, patients should be monitored daily, then weekly, and eventually monthly with a spot urine protein/creatinine ratio [14]. An elevated protein/creatinine ratio should be confirmed with a 24-h urine collection. In order to reduce thrombotic risk and also to allow for identification of recurrence, transplant recipients with ongoing nephrotic-range proteinuria should undergo native nephrectomy prior to transplant

or have pre-transplant urinary protein loss aggressively reduced with renin-angiotensin-aldosterone system blockade (RAASB) and/or non-steroidal anti-inflammatory medications such as indomethacin followed by native nephrectomy at the time of transplant [15]. There are no specific guidelines for which patients should undergo nephrectomy prior to transplantation. Definitive diagnosis requires allograft biopsy which early on usually shows histologic features of minimal change disease with normal-appearing glomeruli on light microscopy with foot-process effacement on electron microscopy. Serial biopsies of patients who do not respond to therapy show progressive development of podocyte detachment and epithelial hypercellularity, accumulation of intracapillary foam cells, and the segmental scarring that is classic for FSGS in native kidneys [16].

Management of FSGS recurrence is difficult due in part to a lack of randomized clinical trials as well as specific guidelines. Based on the evidence for a circulating factor, plasmapheresis has been a commonly used treatment for FSGS recurrence since 1985. To date there are still few randomized trials evaluating plasmapheresis, but there have been many case series reporting efficacy in inducing remission of recurrent FSGS that often persists even after discontinuation of plasmapheresis [4, 5, 11, 17]. A typical plasmapheresis regimen is plasmapheresis with 5% albumin replacement daily for 3 days followed by alternate day treatment (3 times per week) for a total of nine treatments or longer depending on response [14]. Treatment is more likely to be successful if started early on in a relapse. In a meta-analysis of many, primarily adult, case series, plasmapheresis induces complete remission (<0.5 G/day) of proteinuria in 47% of patients and partial remission (<1 G/day) of proteinuria in 28% of patients [11]. Studies in pediatric cohorts are limited, but plasmapheresis also appears to be efficacious in pediatric patients [4–6, 18].

Additional management strategies for recurrent FSGS include immunoadsorption instead of plasmapheresis, intensifying immunosuppression with cyclosporine, and using rituximab or similar biologics such as ofatumumab [4–6]. Immunoadsorption is an alternate extra-corporal option for acute therapy for recurrent FSGS [19–21], and a recent case series in children demonstrated efficacy similar to plasmapheresis [19]. Some authors have advocated using high-dose cyclosporine as part of prevention and treatment of FSGS recurrence, but there are no randomized trials directly comparing cyclosporine-based immunosuppression to tacrolimus-based regimens [15, 22]. There have been many case series and case reports describing the use of rituximab for FSGS recurrence reporting generally good success [5, 6]. The appropriate dosing and frequency of rituximab administration is variable and still not completely defined, with one case report even demonstrating efficacy with a single low dose of rituximab [23]. Rituximab is an anti-CD20 antibody B-cell-depleting agent; however, its efficacy in FSGS may be via immune and non-immune mechanisms as it has been shown to bind directly to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein and regulate acid sphingomyelinase activity in the podocyte [24, 25]. Ofatumumab is another B-cell-depleting agent that has also demonstrated efficacy in FSGS although with only a few cases reported [26, 27]. Ofatumumab may be a useful option for patients who do not tolerate rituximab due to anaphylaxis.

Pre-transplant regimens to prevent recurrence have also been evaluated, as the recurrence rate for the highest risk patients is very high [28, 29]. One regimen that has been reported in a relatively large prospective cohort of patients included giving 1–2 doses of 375 mg/m^2 of rituximab and giving 3–10 sessions of therapeutic plasma exchange in the perioperative period [29]. This trial demonstrated similar rates of recurrence for very high-risk patients receiving this regimen compared to lower-risk patients receiving no pre-emptive preventative therapies [29]. Recurrence of FSGS in subsequent allografts remains a nearly insurmountable problem in patients where a prior allograft has failed due to FSGS recurrence and requires further clinical investigation.

18.2.4 Prognosis

Allograft survival for pediatric patients with FSGS is reduced. Using data from the USRDS from 2000 to 2009, Wang and colleagues reported a 5-year allograft survival of 64% for pediatric patients with FSGS compared to 79% for other causes of ESRD [30]. These differences persisted, with 10-year allograft survival being 47% for pediatric patients with FSGS compared to 61% for other causes of ESRD [30]. Similar data have been reported by Koh and colleagues using the NAPRTCS database with a 5-year allograft survival of 74% for pediatric patients with FSGS compared to 87% for other patients with other glomerular diseases [31]. Encouragingly, both of these studies report improved allograft survival for transplants performed after 2000.

18.3 IgA Nephropathy

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and recurs at a high rate post-transplantation with recurrence rates as a high as 50% reported for pediatric patients [32–34]. IgAN in the native kidney often progresses slowly and IgAN recurrence in the allograft can likewise have an indolent presentation. However, IgAN recurrence does lead to significant allograft dysfunction in a small percentage of patients, and there is some evidence that treatment of recurrent IgAN can prolong allograft survival.

The pathogenesis of IgAN Nephropathy in the native kidney is not completely defined and involves generation of aberrantly glycosylated IgA1, development of anti-glycan autoantibodies and deposition of these IgA-antibody complexes in the glomeruli. This deposition of IgA1-antibody complexes in the glomeruli leads to the pathognomonic finding of diffuse mesangial IgA1 staining that is the hallmark of IgAN. These immune complexes then trigger inflammation mediated by complement as well as other inflammatory mediators such as B cell activation factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) [32, 34]. The pathogenesis of IgAN recurrence appears to involve these same mechanisms.

18.3.1 Incidence

The overall reported rate of recurrent IgAN in adults is between 10 and 61 percent [34, 35] with most authors citing about a 30% recurrence rate [34–37]. Most studies have reported the time to recurrence to be between 3 and 5 years [34]. The variability in the reported recurrence rate is likely related to variability in performing biopsies as well as variability in assigning a diagnosis of recurrent IgAN. Some case series have defined recurrence of IgAN as having hematuria and/or proteinuria, while others have only required the presence of IgA deposits on biopsy to define recurrence of IgAN. In one small case series comparing adult and pediatric kidney transplant patients, the pediatric recurrence rate (age < 20) was reported to be 53.8% compared to only 23.3% for patients >20 years old [33].

18.3.2 Risk Factors

Young age at renal transplantation, male gender, and rapidly progressive original disease have all been associated with a higher risk of IgAN recurrence [34, 35, 38]. The presence of crescents in the native kidney has also been shown to be predictive of post-transplant recurrence [38]. There is conflicting evidence on whether living-donor kidneys are more likely to have recurrence [34, 35, 39], and a further lack of data that living donation affects patient or allograft survival in patients with ESKD due to IgAN [34]. Currently, IgAN is not listed as a contraindication to living-donor transplantation in several transplant guidelines.

Large registry reviews as well as smaller case series have demonstrated that use of steroid-based immunosuppression is associated with a lower rate of IgAN recurrence [40–44]. Use of other specific immunosuppressive agents has not been shown to definitively affect the rates of IgA recurrence, although there is some evidence that the use of tacrolimus and mycophenolate over cyclosporine and azathioprine may be associated with lower rates of IgAN recurrence [34, 35].

Post-transplant IgAN appears to have the same pathophysiologic mechanism as native IgAN. Post-transplant serum IgA1 levels are predictive of post-transplant recurrence of IgAN [45], and serum levels of galactose-deficient immunoglobulin (Ig)A1 also predict IgAN recurrence [46]. Increased levels of APRIL have been shown to precede transplant recurrence of IgAN [47].

18.3.3 Diagnosis and Treatment

In most cases IgAN recurrence is identified based on biopsies performed for other clinical indications; however, IgAN recurrence may be identified during evaluation for proteinuria and/or allograft dysfunction. Diagnosis can only be made based on biopsy findings of IgAN. Histopathology for IgAN recurrence is very similar if not identical to IgAN in the native kidney, and the Oxford classification system also predicts outcome for recurrent IgAN [48]. Interestingly,

not all patients with IgAN recurrence on biopsy have hematuria or proteinuria [49, 50], although more severe histological disease is almost always associated with proteinuria [50].

There are no treatments for recurrent IgAN that have been tested in randomized-controlled trials. As with primary IgAN, treatment of IgA recurrence is focused on limiting proteinuria and achieving a tight blood pressure control as recommended in KDIGO transplant guidelines [34, 35, 51, 52]. KDIGO guidelines for primary IgAN are to control blood pressure with an angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor (ARB) blocker, with a goal to lower the blood pressure to less than 130/80 mm Hg in patients with protein less than 1 g per day and less than 125/75 in patients with protein greater than 1 g per day. For pediatric patients younger than 13 years of age, blood pressure should be lowered ideally to 50% for age, gender, and height. For patients with recurrent IgAN, this tight blood pressure control should be the goal but may be impossible due to unacceptable decreases in GFR with aggressive renin-angiotensin-aldosterone system blockade (RAASB) or other side effects such ass hyperkalemia. With or without hypertension, in those with proteinuria greater than 0.5 g per day, RAASB should be initiated. There is some evidence in small trials that this treatment strategy is efficacious [53–56].

While steroid withdrawal and steroid avoidance have been associated with IgAN recurrence, there is no randomized trial demonstrating efficacy for treatment of recurrent IgAN with either IV or oral steroids. Data to support use of tonsillectomy post-transplant to treat recurrent IgAN are limited and have generally only been reported in Japanese patients; thus the validity in other ethnicities has not been confirmed [34]. In severe cases of IgAN recurrence rescue therapy with steroids, eculizumab and cyclophosphamide have been attempted with variable success [3, 4, 20].

18.3.4 Prognosis

Outcome of recurrent IgAN is highly variable. Some patients have detectable IgA deposition on biopsy and never develop hematuria or proteinuria, while in other patients recurrent IgAN is associated with development of proteinuria and early allograft failure. Short-term allograft outcomes are generally unaffected by recurrence of IgAN; however, 10- and 15-year death-censured allograft survival are moderately reduced in patients with IgAN recurrence [57–59]. Worse prognosis is predicted by more severe histopathologic classification, presence of crescents, and heavier proteinuria similar to primary IgAN [50, 51, 57, 60–62].

18.4 Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) has a higher rate of allograft failure compared to other glomerulonephritides, and recurrence contributes to a significant proportion of allograft failure [63, 64]. Studies have shown variable rates of

MPGN recurrence from 27% to 65%. This large variability is attributed to small numbers, lack of protocol biopsies, presence of different subtypes, and variable periods of observation [65].

MPGN was previously classified into three types: Type 1, Type 2, and Type 3 based on location of immune complex deposition found on electron microscopy. However, with increased pathophysiologic understanding of the disease, the classification has evolved to be based on the mechanism of glomerular injury and distinguishable by immunofluorescence. The new proposed classification includes immune complex-mediated glomerulonephritis characterized by deposition of immunoglobulins and complement components, or complement-mediated glomerulonephritis characterized by complement deposition in the absence of immune complexes mediated by abnormal activation of the alternate complement pathway [66, 67]. Rarely, a third type without immune complexes or complement is seen, caused by endothelial injury.

Recurrence of MPGN post-kidney transplantation is now being studied in the light of the new classification. This is very helpful since the risk of recurrence, prognosis, and treatment differ substantially among subtypes.

18.5 Immune Complex-Mediated MPGN

18.5.1 Incidence

The overall reported rate of recurrent idiopathic MPGN is between 19% and 48% [65, 68, 69], with over 50% of recurrences occurring within the first 2 years after transplantation [70]. MPGN with polyclonal immunoglobulin deposits has a relatively low rate of recurrence of 30–35% and tends to have a more benign course [71]. MPGN with monoclonal immunoglobulin deposits has a higher rate of recurrence, closer to 66% with a more aggressive course [72, 73].

18.5.2 Risk Factors

Several studies have raised concern of MPGN recurrence being higher among recipients of living-related-donor kidneys, compared with deceased-donor kidneys [65, 69, 74–76] and recommend exercising caution with living donation. This was attributed to a possible common genetic predisposition. However, this was not corroborated in a large cohort study [63]. The data on living donation continue to remain limited and conflicting, and currently living donation is not listed as a contraindication in several transplant guidelines.

Risk of recurrence is also found to be associated with persistent or recurrent hypocomplementemia – either C3 or C4 or both, especially in MPGN with polyclonal immunoglobulin deposits [65, 68, 69].

A few other studies reported increased risk of recurrence with the presence of serum monoclonal globulins [65, 68, 69]. There was one study which showed an

association between the human leukocyte antigen phenotype B8DR3 and recurrent disease [75].

ATG induction therapy was found to be associated with a lower risk of recurrence of MPGN [77].

18.5.3 Diagnosis and Treatment

A strong index of suspicion is necessary in patients with ESRD from MPGN who develop hematuria/proteinuria or declining renal function of the allograft.

Diagnosis is confirmed with biopsy with a special importance of immunofluorescence staining patterns. It should be distinguished from transplant glomerulopathy (which may have similar appearance on light microscopy) by the presence of electron dense deposits on EM.

It is also important to rule out secondary causes of MPGN – including infections (Hep B, Hep C, HIV), autoimmune conditions, and monoclonal gammopathies.

No specific guidelines exist on treatment, and it is usually based on the severity of the disease process.

ACEi/ARB may be sufficient in mild disease cases (proteinuria <3.5 g/day), similar to treatment offered in primary MPGN.

In moderate disease with proteinuria >3.5 g/day or steadily declining renal function, immunosuppression is intensified in addition to ACEi/ARBs. Options available include high-dose steroids, cyclophosphamide [78], rituximab [79], antimetabolites (azathioprine/mycophenolate), and plasmapheresis [80]. Rituximab may be specifically beneficial in monoclonal IgG MPGN [65, 79].

Recurrent MPGN can be poorly responsive to immunosuppressive therapy, with less than half of patients responding to high-dose steroids, rituximab and/or plasmapheresis, or eculizumab to preserve their renal allografts, as shown in a study published in 2016 [69].

Thus, it is important to fully characterize the GN pre-transplant, as it will direct management and prognosis post-transplant.

18.5.4 Prognosis

Recurrent MPGN in the transplant kidney has a grave prognosis, with a 5-year allograft survival post-recurrence of only 30% [81]. There is a higher incidence of graft loss in MPGN associated with monoclonal IgG deposits of about 50% [72, 73], whereas MPGN associated with polyclonal IgG has a better prognosis with graft loss of 10% [71].

One study showed the mean duration of graft survival following the diagnosis of recurrent disease was 40 months [75].

MPGN recurrence increases the risk of recurrence in subsequent transplants. Four out of five patients who received a second transplant after losing the previous allograft due to recurrent MPGN showed recurrence in the second allograft [75].

18.6 Complement-Mediated MPGN (C3GN/Dense Deposit Disease)

C3 glomerulopathy [comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD)] is characterized by the glomerular deposition of C3 in the absence of immunoglobulin deposition. The underlying abnormality is uncontrolled activation of the alternate pathway of the complement system. Both can be morphologically distinguished by the nature and ultrastructural characteristics of these electron dense deposits.

18.6.1 Incidence

The reported recurrence rate of C3 glomerulonephritis (C3GN) is greater than 50 percent, and the recurrence rate of dense deposit disease (DDD) is much higher and approaches approximately 80 to 100 percent [82–84].

The timing and clinical presentations of patients with C3GN and DDD are different; DDD is more likely to recur later in the post-transplant period and is often associated with no clinical manifestations other than allograft dysfunction.

A large cohort study with long-term follow-up contested the largely held belief that Type 2 MPGN has a higher recurrence rate and poorer outcome. They demonstrate that rather than the MPGN type, the severity of initial glomerular injury, particularly younger age at diagnosis and the presence of cellular crescents on the initial biopsy, influenced renal survival [85].

18.6.2 Risk Factors

Monoclonal gammopathy is associated with earlier and more aggressive recurrent disease and was seen in 21% of patients with recurrent C3 glomerulopathy in one case series of patients [82].

Persistent or development of new hypocomplementemia and living donation is also shown to be associated with a higher risk of recurrence in the case of immune complex-mediated MPGN [69].

Levels of C3 nephritic factors have not been shown to correlate with disease activity or recurrence risk [86].

18.6.3 Diagnosis and Treatment

A biopsy with analysis of tissue by light microscopy, immunofluorescence, and electron microscopy should be performed in all transplant recipients who have either DDD or C3GN as a cause of end-stage renal disease (ESRD) in the native kidney and who present with unexplained new or worsening proteinuria, hematuria, or worsening renal function.

It is very important to perform a comprehensive genetic and functional evaluation of the complement system if this has not been done previously, as the identification of an abnormality in the alternative complement pathway informs immunosuppressive therapy.

Mild disease (stable renal function and non-nephrotic-range proteinuria) can be managed with the addition of ACEi/ARBs.

However, most recurrences tend to be moderate to severe in presentation, and due to the rarity of the disease and small numbers of recurrent disease, no treatment options have been rigorously tested in clinical trials.

It is unclear if intensification of immunosuppression, especially nonspecific agents such as cyclophosphamide or mycophenolate, is beneficial. Chronic infusions of fresh frozen plasma to replace missing complement factors may be beneficial in cases of genetic mutations in CFH. Rituximab and plasma exchange can be trialed in cases of pathogenic antibodies.

The role of eculizumab is rapidly evolving in the prevention and treatment of recurrent C3 glomerulopathy since the first reported study showing benefit in 2012 [87]. Several studies since have shown variable response to eculizumab. Six patients with C3GN and DDD, of whom three had recurrent disease, from a prospective single-arm pilot study were given eculizumab for 1 year, and all responded to therapy [88].

Eculizumab binds to C5 and blocks its binding to a second surface-bound C3b, making it very effective in aHUS. However, the pathophysiology of C3GN is less well understood and substantially more complex than in aHUS. Eculizumab is effective in patients in whom the dominant process is activation of C5 convertase and the terminal complement cascade. Conversely, in C3G patients in whom the dominant process is upstream dysregulation at the level of C3 convertase, as evidenced by elevated levels of C3 split product, it is likely not to be effective.

This again highlights the importance of disease characterization pre-transplant, so that it may aid in treatment post-transplant. However, efforts to prevent post-transplant recurrence with either rituximab or eculizumab have not been shown to be consistently effective [71].

18.6.4 Prognosis

There is a high rate of graft loss associated with post-transplant recurrence for both C3GN and DDD, with over 50% of patients reported to experience allograft failure, although the number of patients in these studies was relatively small with a median time from recurrence of disease to failure of 18 months [82, 89].

Transplant recipients with DDD have been shown to have a significantly reduced allograft survival. In a series of 75 pediatric patients, Braun et al. demonstrated a 5-year allograft survival of 50% compared to 74% in their transplant cohort as a whole [83]. The UNOS review reported a 10-year death-censored allograft survival

of 57.5% for recipients whose primary pathology was DDD compared to 65.2% for those with other forms of glomerulonephritis [90].

When patients with failed allografts from recurrent C3GN are evaluated for a second transplant, the risk of recurrence may be deemed to be unacceptably high [89].

18.7 Anti-neutrophil Cytoplasmic Antibody-Associated Vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of small- to medium-vessel vasculitic conditions associated with the presence of ANCA on serologic testing. The vasculitis seen in AAV can cause necrotizing inflammation in multiple organs, including the kidneys, lungs, upper airway tissue, gastrointestinal tissue, joints, eyes, skin, and/or nervous system [91]. The specific antibodies that have been identified are anti-proteinase 3 (anti-PR3) and anti-myeloperoxidase (anti-MPO) antibodies which are found in the cytoplasmic region of the neutrophil. The identified AAV conditions include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), renal limited vasculitis, and eosinophilic granulomatosis with polyangiitis with GPA and MPA being the most common AAV syndromes to cause ESKD in children.

While there is a strong association of AAV and ANCAs, the pathophysiology is incompletely understood, as ANCA titers do not consistently vary with disease activity, nor do specific ANCAs always associate and/or segregate with the specific AAV syndromes (i.e., GPA versus MPA). Passive transfer of anti-MPO antibodies can cause AAV in mouse models; however, the pathogenesis of AAV elucidated in these anti-MPO models also involves activation of neutrophils, adherence and degranulation of neutrophils in the microvasculature, endothelial injury, complement activation, and release of other inflammatory cytokines and chemoattractants [92, 93]. Interestingly, robust PR3-AAV animal models do not currently exist, and while there are many in vivo data indicating that human PR3-AAV pathophysiology is similar to MPO-AAV disease, this has not been validated in animal models [92].

18.7.1 Incidence

Relapse of AAV is rare post-transplant. In adult series of patients, relapse rates vary between 0.006 and 0.1 per patient per year with time to relapse ranging from 5 days to more than 13 years [94]. Similar data are limited for pediatric patients, but in two recent small series there were no relapses reported [95, 96]. At the University of California, San Francisco, we have had one pediatric patient with a relapse of AAV post-transplant and can report anecdotally, at least, that recurrence of AAV post-transplant for pediatric patients is possible and can be treated successfully.

18.7.2 Risk Factors

With such limited data available for pediatric patients, risk factors for recurrence have not been defined. For adult patients, it appears that modern mycophenolate-based immunosuppression has yielded lower rates of recurrence compared to azathioprine-based immunosuppression regimens [97, 98], indicating that more intensive immunosuppression likely reduces recurrence. Ongoing disease activity is also thought to be a risk for recurrence, and there is a KDIGO recommendation to perform renal transplant in AAV only if the disease has been quiescent for at least 1 year [52]. It is important to note that complete elimination of ANCA is not required to achieve quiescence and to be ready for kidney transplantation [52]; however, there is some evidence that persistent ANCA positivity is associated with a higher recurrence rate post-transplant and thus patients with persistent positivity should be carefully monitored for clinical signs of disease activity before and after kidney transplantation [99].

18.7.3 Diagnosis and Treatment

Recurrence of AAV can be identified post-transplant by unexplained decrease in allograft function, new significant hematuria and proteinuria, allograft biopsy, and/or new-onset extra-renal symptoms such as pulmonary hemorrhage [94, 99]. Identification of recurrent extra-renal symptoms of AAV such as new cough with anemia can be difficult, as these symptoms can be subtle and often mimic infection. Ultimately, renal recurrence is diagnosed by allograft biopsy. There is no standard monitoring protocol for AAV post-transplant, but a reasonable monitoring schedule could include ANCA testing monthly for the first 6 months and then q3 months after that, with urinalysis at every visit to evaluate for new-onset hematuria and/or proteinuria that would trigger further evaluation.

Treatment for recurrent AAV disease should be similar to treatment for primary disease [94, 99]. Severe AAV has been treated with high-dose IV glucocorticoids, plasma exchange, and/or cyclophosphamide and these therapies can be considered for severe transplant recurrence as well [94, 98, 99]. More recently, data have suggested that rituximab provides similar outcomes to cyclophosphamide, with an improved safety profile [91, 99]. There are case reports describing the successful use of rituximab post-transplant for both recurrent and de novo AAV [100, 101] and rituximab can be considered for use as the sole induction agent for recurrent AAV depending on the severity of the recurrence.

18.7.4 Prognosis

In general, the prognosis for kidney transplantation for patients with AAV is good based on recent adult data. Patient and graft survival is at least as good for AAV patients as it is for patients with non-diabetic ESKD [99, 102]. In addition, the many

case reports and case series describing AAV recurrence in adult patients report generally good success treating AAV recurrence, although these reports are likely to be significantly biased.

18.8 Lupus Nephritis

Although the incidence of ESKD from lupus nephritis (LN) has decreased as a result of advances in lupus treatment, it still affects 10–20% of children 10 years after diagnosis and accounts for 4% of kidney transplants [103]. It is generally agreed that remission of lupus activity is important prior to proceeding with transplantation, and most patients with recent significant renal or extra-renal activity and ESRD receive a period of dialysis to achieve "burn out." However, there are currently no established guidelines for how long a patient with ESKD from LN should wait before undergoing kidney transplantation. This remains a source of debate, since it has been shown that serological activity does not always correlate with clinical activity to determine transplant eligibility [104]. Studies have also shown that pre-emptive transplantation is a safe option in LN patients who are in remission and is associated with superior graft survival and patient outcomes [105].

18.8.1 Incidence

The incidence of clinically significant recurrent LN (rLN) is 2–11%, but can range from 0% to 44% depending on the study [106]. Pediatric specific recurrence data are scarce and thought to range from 0% to 30% [107]. It may, in fact, be more prevalent, as suggested by a surveillance biopsy study in which 54% had biopsy-proven recurrence of LN. The majority of the cases were subclinical and characterized as class I/class II LN [105, 108].

Recurrent LN can occur as early as 5 days and up to 16 years post-transplant, with the median time to recurrence approximately 4 years post-transplant [106, 109, 110]. The clinical and histologic pattern of recurrence varies, although it is usually more benign in histology and clinical manifestation than the patient's original disease [111].

18.8.2 Risk Factors

A large OPTN study of kidney transplant recipients with ESKD due to LN revealed a 1.88-fold higher risk for non-Hispanic black race, a 1.70-fold increased risk for female gender, and a 1.69-fold greater risk for recipients younger than 33 years old [112]. A surveillance biopsy study reported a higher association of recurrence in patients with lupus anticoagulant [108]. There are no studies that have been published describing the risk factors in the pediatric population. Post-transplant recurrence is not found to be reliably predicted by serological measures such as complement and anti-double-stranded DNA antibody levels.

18.8.3 Diagnosis and Treatment

Recurrent LN can present as an increase in serum creatinine, new-onset proteinuria, and/or new-onset hematuria. A kidney biopsy has to be obtained to make a definitive diagnosis, as it is recognized that serology can be inconsistent and is not adequate to make a diagnosis [109]. Additionally, a kidney biopsy must include light microscopy, immunofluorescence, and electron microscopic examination to maximize diagnostic yield, as light microscopic findings may be subtle or non-specific [110]. The histopathologic lesion with rLN may be different than that in the native kidney and is usually less severe, with mesangial proliferation or Class II being the most common [106, 109]. A study of allograft biopsies from patients with LN demonstrated that while typical immune complex GN was frequently observed, atypical pauci-immune proliferative GN and segmental glomerular sclerosis were also observed, implying a role for nonimmune complex-mediated glomerular injury in rLN [113].

Patients who have subclinical disease (Class I or II) do not need any change to their immunosuppression regimen unless there is clinical evidence of a lupus flare. Patients with proteinuria >0.5 g/day, similar to nontransplant patients, should be treated with renin-angiotensin-aldosterone system inhibition to reduce proteinuria and slow the progression of renal disease. Patients having clinically evident disease with deterioration of kidney function in the setting of Class III or IV LN may be treated with higher doses of mycophenolate mofetil (MMF) 2–3 g/day. If they fail to respond or have severe crescentic lesions on biopsy, IV cyclophosphamide can be used in place of the prescribed antimetabolite with pulse dose steroids. Some authors suggest a trial of rituximab in refractory cases although there are no published reports supporting its benefit [106, 109]. Due to the lack of evidence supporting the benefit of further immunosuppression, caution should be exercised to avoid the complications associated with overimmunosuppression such as BK nephropathy, opportunistic infections, and malignancy.

18.8.4 Prognosis

Patients with rLN had a fourfold increased risk of graft failure as reported by a UNOS study [112], but only 7% of graft failure events were attributed to rLN. Other single-center studies have similarly found that graft loss and patient survival are not adversely affected by rLN [111, 114–116]. Although allograft survival was comparable between lupus and non-lupus recipients in a pediatric study, it was associated with a worse patient survival rate, with a 1.8 relative risk of mortality [117].

18.9 Idiopathic Membranous Nephropathy

Idiopathic membranous nephropathy (IMN) is a glomerular disease that usually presents with nephrotic syndrome and is characterized histopathologically by extensive foot-process effacement and subepithelial deposits on electron microscopy and

glomerular basement membrane matrix spike formation that progresses over time [118]. IMN is found in ~1–9% of all pediatric native kidney biopsy samples [119–121] and progresses to ESKD in about 30% of pediatric patients within 10 years [119]. Pediatric membranous nephropathy is often a secondary disease caused by other primary diseases such as SLE, infections such as hepatitis B or C, and/or various medications [121]. Secondary MN does not typically recur post-transplant. Since 2009, it has been demonstrated that auto-antibodies against multiple antigens are the primary driver of IMN [122, 123]. Anti-M-type phospholipase A2 receptor (PLA2R) is the most common antigen in IMN with ~70% of adult patients [122] and ~45–75% of pediatric patients [124, 125] with IMN having measurable anti-PLA2R antibodies and/or glomerular PLA2R staining. Antibodies against these antigens lead to histologic changes by in situ binding to glomerular components, formation of immune complexes, and activation of the immune system [123].

18.9.1 Incidence

Recurrence of MN post-kidney transplant is estimated to occur in 10–50% of adult patients [86, 126, 127]. The rate of recurrence in pediatric patients is not clear, as <1% of pediatric kidney transplants are performed for ESKD secondary to IMN, with only 10 transplants reported for ESKD secondary to IMN in the United States from 2015 to 2019 [1]. In addition, in the adult kidney transplant population de novo MN occurs in ~2% of adult transplants and may have a different pathophysiology, being associated with rejection and other types of inflammation [128, 129].

18.9.2 Risk Factors

With such limited data available for pediatric patients, risk factors for recurrence in the pediatric population have not been defined. For adult patients, both pre-transplant and post-transplant titers of anti-PLA2R antibodies predict recurrence in the allograft [130–133]. In addition there may be a donor-genetic component to recurrence as specific single nucleotide polymorphisms (SNPs) in the HLA-DRB1, HLA-DQA1, HLA-D, and the PLA2R1 loci of the donor are associated with recurrence of IMN in the allograft [134].

18.9.3 Diagnosis and Treatment

Recurrence of IMN is usually first identified by recurrence of proteinuria, and periodic monitoring for proteinuria using a monthly spot urine protein to creatinine ratio for the first 1–3 years after transplant is recommended [131, 132]. An elevated protein/creatinine ratio should be confirmed with a 24-h urine collection. Given the association between anti-PLA2R-ab and recurrence, some centers also routinely monitor anti-PLA2R titers [132].

MN recurrence tends to occur 1–3 years post-transplant, and it is important to note that other causes of proteinuria several years into the life of an allograft include acute rejection, transplant glomerulopathy, overweight/obesity, diabetes mellitus, malignant hypertension, mTOR inhibitors, and/or chronic CNI toxicity. Definitive diagnosis is made by allograft biopsy including staining for IgG subtypes and PLA2R antigen [131, 132]. Many times subclinical de novo or recurrent MN (rMN) is diagnosed on surveillance biopsies.

Treatment of rMN is similar to treatment for primary IMN in terms of the use of rituximab; however, there is no significant evidence that additional steroids, alkylating agents, calcineurin inhibitors, and mycophenolic acid provide any benefit in rMN [132]. All patients with rMN should receive supportive care including RAS blockade, strict blood pressure control, statin therapy if nephrotic with hyperlipidemia, symptomatic treatment with diuretics, and anticoagulation if indicated. Many centers reserve additional immunosuppression to higher-risk rMN where there is persistent proteinuria of >1 G/day despite treatment with RAS blockade. Multiple case series in adult patients have described good responses to rituximab using most commonly 1 G of IV rituximab for 2 doses of 375 mg/m^2/dose [131, 132].

18.9.4 Prognosis

In general, the prognosis in kidney transplantation for patients with rMN is guarded compared to patients with primary IMN. Most subclinical rMN progresses to overt proteinuria over time, and the likelihood of achieving a spontaneous remission is reduced in rMN compared to IMN in native kidneys [131, 132]. One large study by Pippias and colleagues in >700 adult patients with IMN (both with and without rMN) demonstrated a relative risk for death-censured graft loss of 1.60 (1.34–1.91) at 10 years and 1.65 (1.40–1.95) at 15 years compared to ADPKD controls with no risk for recurrent disease [135]. Death-censored kidney allograft survival rates were also lower in 167 patients in the Australia and New Zealand Dialysis and.

Transplant (ANZDATA) Registry, although overall patient survival post-transplant was better for patients with MN than for patients with ESKD due to other causes [126].

18.10 Conclusion

There is significant variability in allograft survival across subtypes of disease recurrence in pediatric transplantation. Our current strategies for treatment of the most common recurrent diseases such as FSGS and IgA nephropathy are good enough that disease recurrence can usually be treated and/or attenuated with only mild to moderate effects on allograft survival for most patients. Other recurrent diseases such as complement-mediated C3GN are associated with severely reduced allograft survival. Definitive data from randomized trials on the efficacy of specific therapeutic strategies do not exist for any recurrent disease in

pediatric kidney transplantation. Therefore, recurrent disease in pediatric kidney transplantation is generally treated using the same modalities we use to treat primary disease. While we await more complete and informative data from pediatric trials on recurrent disease post-kidney transplantation, with small numbers of patients being transplanted for most recurrent diseases and with only a portion of these patients having recurrent disease, we are unlikely to see significant randomized trials in pediatric patients for most types of recurrent disease. We likely will need iterative improvement strategies with standardized treatment protocols rather than randomized clinical trials to lengthen allograft survival in patients with rare and severe recurrent conditions.

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Post-Transplant Lymphoproliferative Disorders

19

Vikas R. Dharnidharka

19.1 Introduction

PTLDs were very rare in the early days of solid organ transplantation. The first cases were reported by Starzl et al. in 1969 [1]. With the advent of more powerful immunosuppressive regimens, PTLD began to be reported more frequently in the 1980s [2, 3]. The cumulative frequency of PTLDs rises with longer time on immunosuppression, though EBV-positive PTLDs have an early increase in incidence, particularly in the setting of an EBV seropositive donor/EBV seronegative recipient [4]. PTLD incidence density, calculated as number of cases divided by time, months, or years under immunosuppression, is highest in intestinal, lung, or heart transplantation and less in liver or kidney transplant. Children have a higher proportional PTLD incidence than adults, due to lack of prior immunity to EBV in the recipient [5].

19.2 Pathogenesis

PTLD origin mechanisms are still not fully known [6]. The linkage of PTLD to EBV was serendipitous, but then confirmed through different types of epidemiologic and laboratory investigations [7]. Epstein-Barr virus (EBV), now known as human herpesvirus 4 (HHV4), is a ubiquitous, yet perplexing, gammaherpes DNA virus. Primary infection with EBV has a wide range of outcomes ranging from asymptomatic infection to self-resolving infectious mononucleosis, to the development of EBV-associated malignancies including

V. R. Dharnidharka (✉)
Division of Pediatric Nephrology, Hypertension and Pheresis, Washington University School of Medicine, Saint Louis, MO, USA

St Louis Children's Hospital, St. Louis, MO, USA
e-mail: vikasD@wustl.edu

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Burkitt lymphoma, Hodgkin's disease, nasopharyngeal carcinomas, and B-cell lymphomas in transplant recipients and AIDS patients [8]. EBV infection is typically acquired in childhood, such that EBV infects more than 95% of world's adult population, though less so in developed countries. The primary EBV infection in childhood is usually asymptomatic, but during adolescence it may manifest as infectious mononucleosis (IM). After primary infection in the immunocompetent host, EBV persists in the B-cell compartment of the infected host in a latent state of infection and reduced immunogenicity, with occasional episodic lytic viral reactivations [9]. In its lytic phase, EBV elicits potent CD8 T cell immune responses that successfully keep both its latency and reactivation phases under tight control in immunocompetent humans. When cellular immunity is impaired, the growth-transforming function of some of the EBV latent oncogenes can lead to several malignancies [10]. Chronic pharmacologic immunosuppression, as occurs in transplant recipients, leads to dominant expression of regulatory cytokines (e.g., IL-10, IL-6) and of inhibitory molecules (e.g., PD-1). EBV displays multiple evasion mechanisms from host immune responses [11], such as suppressing host cell microRNA-194 to override control of IL-10 expression [12]. Together, these mechanisms contribute to the attenuation of antiviral innate and adaptive immune control and allow for an autocrine growth of EBV in its target cells, leading to malignancy.

At a genetic or molecular level, host genetic lesions seen in PTLD include mutations in DNA mismatch repair mechanisms, aberrant somatic hypermutation, and mutations of proto-oncogenes. Other frequently observed abnormalities include dysregulation of transcriptional control including aberrant hypermethylation and altered microRNA expression [13]. However, EBV-positive PTLDs show different alterations in host gene expression than EBV-negative PTLDs. The latter have alterations in B-cell development gene expression patterns more similar to lymphomas in immunocompetent hosts, whereas EBV-positive PTLDs have altered expression patterns of genes related to anti-EBV immune response [14]. This supports the theory that the pathogenesis of lymphomas that occur in the context of host immunosuppression shares many common drivers to those that occur in the "overtly" immunocompetent.

19.3 Risk Factors

Several different types of risk factors (host, infectious, transplant, immunosuppression) are associated with PTLD development [15]. Epstein-Barr virus infection is the single most important risk factor, and therefore, recipient EBV seronegativity at the time of transplant is associated with higher risk. Other established risk factors include the overall intensity of immunosuppression, white race, pediatric age group, and the type of organ transplant (Table 19.1), while some other risk factors such as specific induction agents or concomitant CMV infection are inconsistently reported [2].

Table 19.1 Non-modifiable and modifiable risk factors for PTLD in children

• **Non-modifiable** – *Consistent* Younger recipient age at transplant Caucasian race EBV seromismatch – *Inconsistent* Recipient HLA alleles	• **Modifiable** – *Consistent* Intensity of immunosuppression Induction: OKT3, ALG, Thymoglobulin, and alemtuzumab Belatacept Sirolimus use de novo Tacrolimus/MMF combination Quadruple immunosuppression – *Inconsistent* Antiviral prophylaxis

19.4 Clinical Features

The clinical syndromes of presentation can be numerous [16]. Non-specific symptoms can include fever or weight loss. Lymph node enlargement may be seen externally. Mass effects from tumors can create symptoms that depend on the localization. Knowledge of the differential diagnosis is important in preventing missed diagnoses of non-PTLD diseases such as *Bartonella* cat-scratch disease or tuberculosis [17]. The gold standard for diagnosis remains histopathology of a biopsy specimen, which also enables disease characterization and classification based on the 2016 revision of the World Health Organization classification of lymphoid neoplasms.

19.5 Pathology

PTLDs are categorized into four major categories using the 2016 World Health Organization classification [18]. Non-destructive PTLDs are polymorphic lymphoplasmacytic proliferations without tissue architecture disruption, further subdivided into plasmacytic hyperplasia PTLD, infectious mononucleosis (IM) PTLD, and florid follicular hyperplasia. The polymorphic PTLDs include lymphocytes of varied types, sizes, and shapes and plasma cells, do not have a predominance of transformed cells, and cannot fulfill the criteria for a classic malignant lymphoma. Monomorphic PTLDs resemble either a B-cell lymphoma, a plasma cell neoplasm, or a T/NK-cell lymphoma. They are further subcategorized based on the type of lymphoma they most closely resemble. In contrast to registry data, in the WHO classification, most small B-cell lymphomas are not considered to be a PTLD [6]. The fourth category of PTLD is classic Hodgkin's lymphoma type. In rare cases the histology may show both rejection and PTLD.

19.6 Prevention and Preemptive Strategies

Approaches to preventing EBV disease and PTLD include chemoprophylaxis using antiviral agents or immunoprophylaxis (including adoptive immunotherapy such as intravenous immunoglobulin), but no vaccine against EBV currently exists. Some centers use the antiviral agents acyclovir and ganciclovir for the prevention of EBV/PTLD. Data in support of this practice are conflicting, as most EBV is believed to be in latent phase, where antiviral agents may not work. Data from a European multicenter trial suggest that chemoprophylaxis with valganciclovir can reduce the incidence of EBV DNAemia in pediatric kidney transplant patients. Currently, universal chemoprophylaxis as a preventive strategy is not recommended, but is commonly utilized by many pediatric kidney transplant programs for 3–12 months. Another approach involves viral load monitoring to trigger preemptive strategies such as reduction of immunosuppression. At present, serial monitoring of the EBV viral load and reduction of immunosuppression for increasing EBV DNAemia are the recommended approaches for solid organ transplant recipients, though details of such protocols vary highly by center. The use of rituximab at the time of EBV DNAemia has been established as an effective preemptive strategy for stem cell transplant recipients [19] but data are much more scant in solid organ transplant recipients.

Quantification of EBV DNA in peripheral blood is an important component of strategies for PTLD prevention, diagnosis, and management. The different DNA assays available in clinical laboratories have many important variations related to EBV cell tropism, EBV DNA dynamics, and the biologic forms of EBV DNA in the cellular and acellular fractions of peripheral blood during acute and persistent EBV infection and in EBV+ PTLD [20]. Each of these factors influences the choice of testing matrix (whole blood, plasma leucocytes), EBV DNA assay design (EBV gene, amplicon), and result interpretation (different denominator units) when using quantitative EBV DNA assays in specific clinical settings [21]. Further laboratory assay harmonization is needed in terms of standards and calibrators, nucleic acid extraction methods, target and probe design, and other factors to reduce result variability.

19.7 Treatment

Randomized controlled trial data for PTLD therapies after solid organ transplantation do not exist, so available phase II trial data help guide therapeutic decision making. Reduction or cessation of immunosuppression is performed at the time of diagnosis in almost all patients, though efficacy varies. There is little evidence that antiviral agents improve outcomes, though ganciclovir and related antiviral agents are still often used in EBV-positive disease as EBV lytic transcripts have been found in PTLDs [22, 23]. Some patients require no additional therapy beyond reduction in immunosuppression, though in both adults and children there is increasing use of

rituximab early after diagnosis, and this appears to have improved outcomes in certain populations. Rituximab monotherapy is used in almost all patients with CD20-positive B-cell PTLD not responding to an initial attempt of immunosuppression reduction. The European adult PTLD-1 trial demonstrated excellent 2-year overall response rates with a sequential strategy: patients with complete response after four doses of rituximab receive four additional doses of rituximab monotherapy, while patients with partial or no response should generally receive CHOP-based chemotherapy (cyclophosphamide, hydroxyrubicin, vincristine, prednisone) as used for non-Hodgkin's lymphoma [24]. Pediatric recipients with primary EBV infection often respond to reduction in immunosuppression, though there is increasing evidence to support the use of rituximab monotherapy, as in adults. Many children not responding to rituximab have achieved responses with modified (and less toxic) chemotherapeutic regimens [25]. Rituximab followed by extended rituximab monotherapy or CHOP chemotherapy has become a standard in the treatment of CD20-positive B-cell PTLD in adults. Classical Hodgkin's disease and Burkitt lymphoma PTLD are generally managed with conventional multidrug chemotherapy at diagnosis. Primary central nervous system (CNS) disease or systemic disease with CNS involvement carries a poor prognosis [26], though newer regimens suggest better outcomes [23]. More recently, adoptive cellular immunotherapy with third-party EBV-specific cytotoxic T cells has become available and is currently being tested in phase 3 trial patients failing rituximab and/or chemotherapy [27].

19.8 Prognosis

The patient survival after PTLD has generally been poor, ranging from 30% to 70% [28–30]. However, some recent data on patient survival after PTLD depict an improved survival compared to older eras. In children with kidney transplants [31], registry data showed that patient survival was 90.6% at 1 year and 87.4% at 3, 4, and 5 years post-PTLD, improved if more recent year of PTLD diagnosis (adjusted hazard ratio AHR 0.86, $p < 0.001$).

For non-kidney pediatric organ transplants, death is most common in the first 2 years after diagnosis and may be due to progressive disease or complications of therapy, including infection or allograft loss due to acute or chronic rejection [32]. Therefore, success of therapy must also include evaluation of allograft outcomes. Despite remaining one of the most reliable prognostic systems, the International Prognostic Index does not fully hit the mark in regard to the complexity of PTLD and new proposed prognostic factors [33]. Age, performance status, disease stage, and elevated LDH continue to be apropos prognostic factors in PTLD. Anellovirus positivity within tissues has been reported to associate with worse prognosis, perhaps as an indicator of higher overall degree of immunosuppression [32].

Gaps in PTLD knowledge remain in several areas including pathophysiology, surveillance, and monitoring, as well as in optimal prevention and treatment strategies.

Teaching Points

1. PTLDs occur in 1–10% of organ transplant recipients, with a cumulatively increasing burden with greater time on immunosuppression.
2. Epstein-Barr virus oncogenic transformation of lymphoid cells is seen in 50–70% of cases, with no etiologic agent found in EBV-negative PTLDs.
3. Clinical presentations vary by tumor location.
4. No preventive EBV vaccine exists and chemoprophylaxis efficacy is controversial.
5. Preemptive interventions at the EB DNAemia stage seem to reduce the risk of subsequent PTLD.
6. If PTLD occurs, management strategies include reduction or discontinuation of immunosuppression, anti-B-cell agents, and lymphoma chemotherapy, usually in sequential fashion.
7. Despite good results with the above strategies, morbidity and mortality post-PTLD remain high.

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How to Manage Children with Chronic Kidney Allograft Dysfunction

20

Martin Garcia-Nicoletti, Richard J. Baker, and Stephen D. Marks

20.1 Introduction

Over the last few decades there have been advances in preventing acute renal allograft loss and failure in the first year following transplantation [1]. However, the reduction in long-term renal allograft loss has not been as pronounced [2].

CAD is often asymptomatic and is normally identified with an increase in serum creatinine, development or increase in proteinuria, hypertension and corresponding decrease in glomerular filtration rate (GFR). CAD is related to fibrosis and scarring which affects all of the anatomical components of the nephron leading to functional obsolescence. The glomeruli may develop segmental or global sclerosis with accumulation of mesangial matrix, with thickening of arterial intima and/or glomerular capillary walls, and the interstitial membrane may thicken leading to interstitial fibrosis with progressive tubular atrophy [3]. These changes develop in a multiphase process with the early phase involving cytokines and inflammatory cells and activation of fibroblasts and myoblasts, which leads to polymerisation of collagen into a thickened layer having the appearance of a mature scar [4].

M. Garcia-Nicoletti
Department of Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

R. J. Baker
Renal Unit, Lincoln Wing, St. James's University Hospital, Beckett Street, Leeds, UK
e-mail: richard-j.baker@nhs.net

S. D. Marks (✉)
Department of Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London Great Ormond Street Institute of Child Health, London, UK
e-mail: stephen.marks@gosh.nhs.uk

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Data from the UK Renal Registry (UKRR) showed that as of 31 December 2019 there were 652 children aged 16 years and younger who had received a kidney transplant [5]. The Organ Procurement and Transplantation 2019 annual report from the United States of America stated that in the period from 2017 to 2019, 1517 children underwent a kidney transplant; of those 124 (8.2%) were re-transplanted [6]. A Dutch study of 249 children who had undergone kidney transplantation and were followed up for a median of 25.3 years found that 34% (85) had undergone 2 transplants, 17% (43) had 3, and 4.8% (12) had undergone more than 3 transplants [7].

Consequently, it is essential to ensure that management of a failing renal allograft be as comprehensive as possible to preserve residual renal allograft function and to ensure that pre-emptive re-transplantation is maximised, although some patients may require dialysis if the transition to dialysis is sudden. Clinicians should aim to minimise time spent on dialysis and ensure that outcomes post re-transplantation are optimal. This will depend on clinical infrastructure and timely management along local pathways.

20.2 Evaluation of Kidney Allograft Function

20.2.1 Serum Creatinine

Creatinine is a product of muscle metabolism and is formed at a reasonably constant rate [8]. As it is derived from muscle metabolism, it can be greatly affected by age, gender, ethnicity and differences in body mass [9]. Serum creatinine is useful in identifying acute kidney injury but is not as reliable in detecting chronic changes. The GFR is a more accurate measurement for the assessment of allograft function [10]. Baseline GFR in each renal transplant recipient is determined by various factors which include organ donor factors such as type (living or deceased), age of donor, cold ischaemia time as well as events in the early post-transplant period such as use of nephrotoxic drugs, infection and acute rejection. The gold standard for measuring GFR is inulin clearance, but due to the high costs involved, in clinical practice, a simpler option is to calculate the estimated GFR from factors such as weight, height and serum creatinine. In the adult population, the two most widely accepted calculation methods are the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, with Kidney Disease Improving Global Outcomes (KDIGO) using CKD-EPI equation in their guidelines due to it being found to be more accurate, as it controlled for differences in muscle mass and diet according to race, ethnicity and geographic area [10].

In the paediatric population, the updated Schwartz formula remains the most widely used [11, 12]. The UK Renal Registry data showed that 2.1% of children with a renal transplant had an eGFR of <30 mL/min/1.73 m^2 [5]. However, many clinicians are now measuring cystatin C and utilising various equations to estimate GFR, including the pediatric eGFR calculator from the National Kidney Foundation (https://www.kidney.org/professionals/kdoqi/gfr_calculatorped; accessed 27 March 2022).

20.2.2 Proteinuria

Proteinuria in patients with chronic kidney has been strongly associated with progression to end-stage kidney disease [13]. Proteinuria in the adult post-transplant population is variable, with a prevalence between 7.5% and 45% [14]. Proteinuria can be quantified by several methods including 24-h collection, shorter timed collections and spot urine protein-creatinine (UPCR) or spot urine albumin-creatinine ratio (UACR). Due to the difficulty in performing 24-h urine collection, spot urine protein-creatinine or albumin-creatinine ratio is commonly used in the determination of proteinuria. In adults, proteinuria is defined as spot UPCR of >200 mg/g or spot UACR of >17 mg/g in women and > 25 mg/g in men [10]. In children, proteinuria is defined as spot UPCR of >0.2 mg/mg in children 2 years and older and >0.5 mg/mg in children aged 6–24 months or a spot UACR of >30 mg/g in children [10]. A systematic review by Akbari et al., which looked at diagnostic accuracy of spot urine albumin-creatinine or protein-creatinine ratios vs 24-h collection in adult kidney transplant recipients, looked at 8 studies with a total of 1871 transplant recipients and showed a correlation of spot ratio to 24-h collection ranging from 0.772 to 0.998, with a median value of 0.92 [15].

The KDIGO 2012 guidelines for evaluation and management of chronic kidney disease (CKD) currently include albuminuria in their prognosis and risk stratification for the development CKD even in those who have a normal GFR [16]. A single centre study by Bucsa et al. evaluated the KDIGO risk stratification in 231 adult transplant recipients and found that proteinuria was associated with either graft loss or a 30% decline in GFR from 6 months to 2 years post-transplantation [17]. This highlights the importance of including proteinuria when assessing and stratifying the risk of allograft dysfunction.

Risk prediction models for predicting allograft failure have been developed. Shabir et al. developed a risk assessment tool for predicting 5-year allograft function in adults which included age, sex, rejection in the first year, urine albumin-creatinine ratio and GFR; the weighted coefficient in the model for urine albumin-creatinine ratio was equivalent to rejection and greater than GFR in predicting graft failure [18]. Loupy et al. developed the iBox prediction algorithm which predicts allograft survival at 3, 5 and 7 years; this is the first validated tool to predict allograft function. The authors noted that proteinuria was significantly related to allograft failure ($p < 0.001$) [19].

A retrospective study by Gulleroglu et al. looked at proteinuria at 3 months post-transplant in paediatric renal transplant recipients and investigated its effect on allograft rejection, graft loss and GFR at 3 years. They looked at 67 transplant recipients and found that 39 children (58%) had proteinuria of >500 mg/day, but did not show a relationship between proteinuria and allograft loss or GFR; however, they did show a positive relationship between proteinuria and acute rejection [20].

KDIGO currently recommends measuring urine protein excretion within the first month after transplantation and every 3 months in the first year and annually thereafter [10].

20.2.3 Ultrasound

Doppler renal transplant ultrasound is commonly used for the evaluation of renal transplant recipients, including its routine use in the first few hours or days post-transplant to assess blood flow [21]. A renal arterial resistance index of 0.80 or higher has been shown to be a strong predictor of renal allograft failure. A study of American adult renal transplant recipients who were at least 3 months post-transplantation found that 20% of patients had a resistive index (RI) of 0.80 or more, and 69% of those with the higher RI had an increase of 50% or more in serum creatinine compared to 12% of those with an RI of less than 0.80 [22]. More detailed Doppler assessment using "cine-loops" has shown a correlation between loss of peripheral cortical allograft perfusion and chronic allograft nephropathy as defined by the Banff histological criteria but was insensitive to minor allograft damage [23]. Doppler ultrasound provides some useful information as it can provide diagnostic information in those who suffer from CAD; however, it cannot assess function, and chronic allograft injury appears similar regardless of the cause, with progressive volume loss and diffuse cortical atrophy [24].

20.2.4 Histopathology

The concept of protocol biopsies was initially used to look at early immunological response to the transplant and to detect the incidence of subclinical acute rejection, but did not gain widespread clinical use, as results have been difficult to interpret, and immunosuppression has become more potent, reducing the incidence of subclinical rejection [25, 26].

Protocol biopsies were examined as a way of investigating, categorising and preventing CAD. A study in Germany by Schwarz et al. looked at 258 adult transplant recipients who underwent protocol biopsies at 6, 12 and 26 months post-transplant [27]. Of those transplant recipients, 190 patients completed all 3 biopsies at the specified timepoints. Histological changes associated with CAD appeared early; 37% of transplant recipients had chronic tubulointerstitial changes that affected more than 5% of the cortical area after 6 months [27]. It is a weakness of the study that no pre-implantation biopsies were conducted and thus there was no baseline for comparison.

The KDIGO clinical practice guideline for the care of kidney transplant recipients recommends an allograft biopsy in all patients with declining renal allograft function of unclear cause to detect potential reversible causes [10].

The Banff Classification of Allograft Pathology was developed in 1991 to develop a standardised classification system for reporting solid organ biopsies. Chronic antibody-mediated rejection is characterised by transplant glomerulopathy and multi-lamination of the capillary basement membrane and can be accompanied by other non-specific changes such as tubular atrophy, interstitial fibrosis and arteriopathy [28].

A single centre retrospective study which looked at 56 paediatric transplant recipients who underwent a biopsy for allograft dysfunction found 7 cases of chronic antibody-mediated rejection, and of those 50% (3) had to reinitiate dialysis, and found that the 2013 Banff classification was superior in identifying antibody-mediated rejection than the previous 2003/2007 classification [29].

20.2.5 Outcomes

A meta-analysis which looked at approximately 250,000 adult transplant recipients with allograft failure found that mortality was highest in the first year, 12%, falling to 6% in the second year and then 5% annually thereafter [30]. It has also been shown that individuals who commence dialysis following failure of the renal allograft have reduced quality of life and increased mortality compared to transplant-naïve patients who commence dialysis – those with a failed allograft having a 32% higher all-cause mortality than transplant-naive patients [31].

The poorer outcomes of those who commence dialysis after a failed allograft are likely multi-factorial; it has been shown that patients who commence dialysis following renal allograft failure had lower serum albumin, lower haemoglobin and higher PTH within the first 3 months of commencing dialysis compared with transplant-naïve patients [32]. The presence of a failed renal allograft may also be a source of chronic inflammation and may contribute to the inflammatory burden that dialysis carries [33]. The psychosocial impact of allograft failure must also not be underestimated with individuals suffering feelings of shock, grief and anger at the loss of their "previous life" [34].

A qualitative study by Ouellette et al. interviewed 15 adults who had suffered allograft failure and returned to dialysis and found common themes of life disruption on returning to dialysis as well as the shock and anger of this disruption [35]. The study also found that most of the participants eventually identified some benefits with having experienced allograft failure, with some using the experience to refocus themselves [35]. This was also found by Gill and Lowes who interviewed eight adults with a failed allograft and their partners, and found that after return to dialysis they grieved for the loss of their "previous" life, and this loss is often not recognised by health-care professionals [34].

20.3 Treatment

20.3.1 Immunosuppressive Therapy

The weaning of immunosuppression is complicated; balancing advantageous factors such as decreasing sensitisation and rejection, maintaining urine output and avoiding nephrectomy against the risk of malignancy, infection, cardiovascular and drug side effects. This is becoming more complicated during COVID-19, as adults

who are immunocompromised have a reduced humoral response in the post-vaccination period [36].

A retrospective study by Lachman et al. looked at 54 adults with renal allograft failure, divided into 3 groups: A ($n = 28$) had graft nephrectomy and withdrawal of immunosuppression, B ($n = 24$) had graft nephrectomy and continued immunosuppression, and C ($n = 14$) had withdrawal of immunosuppression. The study found those who had a graft nephrectomy had a predominant increase in HLA class I donor-specific antibodies, while those who had a withdrawal of immunosuppression without graft nephrectomy had an increase in predominantly HLA Class II donor-specific antibodies [37]. Another retrospective study which looked at 131 patients found that donor mismatch at the time of the first transplant in HLA-A, HLA-B, HLA-C, HLA-DR and HLA-DQ loci is associated with the development of HLA donor-specific antibodies after allograft failure, with a risk ratio of 1.40 for each mismatch [38]. It is unclear whether graft nephrectomy leads to the sensitisation or if the inflammation necessitates the graft nephrectomy.

The British Transplantation Society has published guidelines that state sera should be screened at 3 monthly intervals and following a sensitising event such as blood transfusion [39].

20.3.2 Nephrectomies

The indication for graft nephrectomy can be divided into absolute or relative indications, as detailed in [40]:

Absolute:

1. Unsalvageable venous or arterial renal allograft thrombosis.
2. Graft malignancy not appropriate for less invasive management.

Relative:

1. Localising signs that could indicate a chronic alloimmune response such as graft pain, increased inflammatory markers and generalised malaise.
2. Recurrent or severe graft pyelonephritis that does not respond to treatment.
3. To enable complete withdrawal of immunosuppression.
4. To create space for re-transplantation.

Analysis of registry data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) found that over a 13-year period (1992–2004), of 1451 children who restarted dialysis following a failed allograft, 421 (29%) had undergone a graft nephrectomy [41].

A single centre retrospective study conducted by Minson et al. found that 34 children developed renal allograft failure over 10 years, and of those 18 required a graft nephrectomy (53%). Children who developed allograft failure in the first year were four times more likely to require a graft nephrectomy [42].

In another single centre retrospective study, Zerouli et al. identified 63 cases of graft failure over 12 years where all patients had graft nephrectomy if renal allograft failure was within the first month after transplantation compared to 68% in those patients who had renal allograft failure after the first year (and 86% for those who lost their allograft between 1 and 12 months after transplantation). They also reported that graft nephrectomy-associated morbidity was seen in 38% of all nephrectomies with all individuals having a full recovery [43].

20.4 Chronic Kidney Disease (CKD) Management

There are no specific recommendations on when to plan for re-transplantation or to start dialysis when a renal allograft has failed. Decline in allograft function is often less predictable than in those patients who suffer CKD in their native kidneys; clinicians and patients can both at times be reluctant to anticipate allograft failure [44]. Currently, KDIGO defines chronic kidney disease as abnormalities of kidney structure or function, present for more than 3 months, with implications for health [16]. The British Transplantation Society has published guidelines for the management of the failing kidney transplant, and they recommend that patients with a failing allograft have access to a low clearance multi-disciplinary team, and that joint care be initiated at least 6 to 12 months before the anticipated need for dialysis or re-transplantation [45].

A single centre retrospective study done by Sinha et al. which found that of the 129 children who were followed up for median of 3.8 years, 66% (85) had CKD stage III or IV [46]. The children in this study also showed a high incidence of CKD complications, with hypertension in 53% (68), anaemia in 50% (65), albuminuria in 60% (78), abnormal serum calcium in 13% (17), abnormal serum phosphate in 19% (24) and short stature in 29% (37) [46].

As CKD progresses, malnutrition is common in children due to decreased appetite, decreased intestinal absorption of nutrients and disruption in acid base regulation which can be detrimental for growth. The Kidney Disease Outcomes Quality Initiative (KDOQI) from the National Kidney Foundation published guidelines in 2008 which recommend increased energy intake for children with CKD stages:

- Stage III CKD: 100–140% of daily recommended intake.
- Stage IV and V CKD: 100–120% of daily recommended intake [47].

Successful transplantation corrects many of the underlying abnormalities that contribute to metabolic bone disease in children. Prior poorly controlled bone disease including hyperphosphatemia and pre-existing hyperparathyroidism may lead to slower recovery of bone density. In children with a failing allograft, it is recommended that they undergo ongoing monitoring of serum calcium, phosphate, PTH, bicarbonate and 25-hydroxyvitamin D, as per CKD guidelines [48].

Post-transplant anaemia has been shown to be associated with increased mortality and decreased allograft function [49, 50]. Analysis of European registry data

over a 12-year period looked at data from 3669 children with a functioning graft and found that 49.8% of children were anaemic as per KDOQI 2007 guidelines and 7.8% according to 2015 NICE guidelines [51]. The analysis also found that anaemia was associated with an increased risk of renal allograft loss; a haemoglobin of <90 g/L equates to a hazard ratio of 1.89 ($p = 0.001$) compared to those with a reference value haemoglobin of 110–120 g/L [51].

This shows the importance of managing post-transplant anaemia. Currently in the UK, the National Institute for Health and Care Excellence (NICE) published guidelines in 2021 which recommended a target haemoglobin of 110 g/L (105 g/L < 2 years) and to consider investigation and managing the anaemia if levels fell below that or if they had developed symptoms attributed to anaemia such as tiredness, palpations or shortness of breath [52]. The KDIGO clinical practice guidelines published in 2012 define anaemia in children as haemoglobin concentration of <110 g/L in ages 6 months to 1 year, <115 g/L for 5–12 years of age, <120 g/L for ages 12–15 and < 120 g/L in females and < 130 g/L in males for ages 15+ [53].

A multi-centre open label randomised controlled trial in adults used epoetin-beta to normalise haemoglobin values to between 130 and 150 g/L. In the group where haemoglobin was 130–150 g/L versus 105–115 g/L, the authors found they had a slower rate of decline in allograft function and improved quality of life with no associated increase in adverse effects [54].

When to initiate dialysis in a failing allograft is a complex and difficult decision with GFR often declining rapidly in the 3 months just prior to the initiation of dialysis [55]. A 5-year retrospective multi-centre study within a single organisation showed that in 747 adult patients who returned to dialysis after a failed allograft, a higher eGFR at initiation of dialysis was associated with a higher mortality, with a hazard ratio of 1.06 ($p = 0.02$) [56]. Although another retrospective study which looked at 292 adult patients who initiated dialysis after a failed allograft found that both new onset of diabetes mellitus after transplantation (HR 1.96, $p = 0.03$) and hypoalbuminaemia (HR 0.42, $p = 0.03$) were associated with increased mortality, GFR at initiation was not associated [57].

When outcomes were investigated, there was no difference on survival in both the short and long term on choice of dialysis modality, but those patients who are transplanted pre-emptively had the greatest survival benefit [58]. A single centre retrospective study by Sinha and Marks which looked at 129 children who had undergone transplantation found in those who had undergone pre-emptive transplantation (30%, 39), in the pre-emptive group a significantly lower proportion had progressed to CKD IV 3% (1) vs 16% (14) ($p = 0.02$) and a lower incidence of CKD complications, but only hypertension and acid base status were found to be significant [59].

The British Transplantation Society guidelines state that the decision-making process and management of end-stage kidney disease in the context of failing allografts are largely the same as in those who suffer from chronic kidney disease and are transplant naïve, and advocate access to a dedicated multi-disciplinary team and pre-emptive re-transplantation when possible or the re-initiation of dialysis in a planned fashion [45].

20.5 Conclusion

CAD is complex subject, and its management requires a multi-disciplinary team approach. The goal of clinicians and the team is to preserve existing allograft function, with planning for pre-emptive re-transplantation, if possible; if not, re-initiation of dialysis should be planned. The challenge facing both paediatric and adult nephrologists is the paucity of data on how best to manage these patients and the psychological barrier to both clinician and patient of accepting that the allograft is failing in order to promote timely advance care planning.

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Part II

Intestinal Transplant

Indications for and Management of Pediatric Intestinal Transplant Patients

21

Stuart S. Kaufman and Cal S. Matsumoto

21.1 Introduction

Replacement of the small intestine with or without other parts of the digestive system such as the stomach, liver, pancreas, and colon represents the ultimate treatment for *intestinal failure*, the state of permanent dependence on parenteral nutrition for support of life with an anatomically or functionally inadequate gastrointestinal tract [1]. Intestinal transplantation was first performed in humans as an experimental, end-of-life procedure by Lillihei and coworkers in 1968 [2]. The operation was consistently unsuccessful at that time because of the failure of then available immunosuppressive agents to prevent rejection of a solid organ with the largest population of lymphocytes of any transplanted organ [3, 4], as well as the overwhelming infectious complications observed from the augmented immunosuppression required. Interest in intestinal transplantation faded over the next two to three decades, which were without meaningful improvements in the immunosuppressive armamentarium, when parenteral nutrition became increasingly available for use in the home setting. Interest in intestinal transplantation returned during the late 1980s and early 1990s as limitations of extended parenteral nutrition therapy for intestinal failure became increasingly apparent and as immunosuppressive agents with markedly increased efficacy, specifically the calcineurin inhibitor tacrolimus, became available for clinical use [3, 5]. Despite improved immunosuppressive therapy, morbidity and mortality were extremely high during the first decade of clinical intestinal

S. S. Kaufman
Pediatric Intestinal Rehabilitation and Transplantation, MedStar Georgetown Transplant Institute, Washington, DC, USA

C. S. Matsumoto (✉)
Center for Intestinal Care and Transplantation, MedStar Georgetown Transplant Institute, Washington, DC, USA
e-mail: csm5@gunet.georgetown.edu

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transplantation, because severe allograft rejection and secondary post-operative sepsis and multi-organ failure were frequent. The often desperately ill state of patients, the scarcity of suitable donor organs, the non-sterile nature of the intestine itself, and the limitations of available laboratory and imaging methods contributed to poor outcomes during these early years. In fact, 5-year patient survival through the 1990s was markedly inferior to contemporaneous outcomes following most other solid organ transplants [6]. Subsequent refinements in patient selection, operative techniques, immunosuppressive therapy, and post-operative rehabilitation comprehensively managed by integrated teams of transplant surgeons, physicians, nurses, dieticians, social workers, and others have improved outcomes. Data from the 2019 Intestinal Transplant Registry indicate steady improvement in long-term pediatric intestinal transplant survival in each 5-year era increment from 1995 to 2015 [7]. Despite these improvements in survival, the decision to pursue intestinal transplantation in infants and children continues to remain a complex one. Once relegated as a second-tier therapy for intestinal failure, the improvements in outcome for intestinal transplantation in infants, children, and adolescents may outpace parallel improvements in intestinal rehabilitation, thus offering an attractive treatment alternative for those suffering from intestinal failure. The current approach to pediatric intestinal transplantation is summarized in this chapter.

21.2 Intestinal Transplantation in the Management of Intestinal Failure

Intestinal transplantation has not superseded extended parenteral nutrition as the primary therapeutic modality for intestinal failure in infants and children [8], even though the estimated annual cost after successful transplantation that results in extended withdrawal of parenteral nutrition is less than that of continued parenteral nutrition by 1–3 years following surgery [9, 10]. Rather, pediatric patients with intestinal failure are candidates for intestinal transplantation only if they are either failing or can reasonably be predicted to fail parenteral nutrition therapy. There are at least two reasons for the continued secondary role of intestinal transplantation in the management of pediatric intestinal failure. First, there is often considerable uncertainty, particularly in infants following major intestinal resection, whether true intestinal failure, i.e., unequivocally permanent parenteral nutrition, is present [11]. In fact, about 55% to 80% of infants who are committed to parenteral nutrition because of intestinal resection in the neonatal period have transient intestinal insufficiency rather than intestinal failure and eventually adapt to full enteral feeding [12–15]. Second, survival following intestinal transplantation has historically been no better than and in some circumstances inferior to long-term survival of pediatric intestinal failure patients receiving extended parenteral nutrition [6, 8, 12, 16]. Five-year patient survival following intestinal transplantation with or without the liver is approximately 60–65% [17]. Although intestinal transplantation may eventually replace extended parenteral nutrition therapy as the most appropriate therapeutic

option for pediatric patients with intestinal failure [3], the numerous hazards associated intestinal transplantation combined with an improved outlook for long-term management of intestinal failure using parenteral nutrition make an initial trial of potentially indefinite parenteral nutrition the preferred approach in most circumstances [8]. Undoubtedly, these factors have contributed to the recent reduction in intestinal transplant activity. Even at its peak in 2007, intestinal transplantation was performed infrequently, 198 procedures in the United States including 111 in patients below age 17 years. Just 91 intestinal transplants were performed, including 34 in children in the United States in 2020 [18]. Worldwide, the United States remains the most active in intestinal transplantation, as there were 0.8 patients per million population on the active waitlist and 0.5 patients per million transplanted with or without inclusion of other organs in 2010. In comparison, there were 0.7 and 0.3 patients per million population in the United Kingdom and 0.4 and 0.1 in France waiting for transplant and to be transplanted, respectively, at the same time [19].

21.3 Indications for Intestinal Transplantation

From the Intestinal Transplant Registry data collected worldwide from 1985 to February 2013, the majority of disease states that eventually led to the transplantation of the intestine in pediatric recipients was anatomic short gut (Table 21.1). 1611 pediatric patients received an intestinal graft in 55 transplant centers with gastroschisis (22%), volvulus (16%), necrotizing enterocolitis (14%), and intestinal atresia (4%) being the main contributors of anatomic short gut. Intestinal pseudo-obstruction (18%) and chronic enteropathy (8%) comprised the majority of functional intestinal disorders, and retransplantation (8%) and tumors (1%) accounted for additional indications [20, 21].

Life-threatening complications of intestinal failure and parenteral nutrition therapy that indicate intestinal transplantation are summarized in Table 21.2. These complications include (1) progressive and irreversible parenteral nutrition-associated liver disease, in this context more appropriately designated *intestinal failure-associated liver disease* [3, 22], (2) loss of central venous access required to deliver parenteral nutrition, (3) recurring life-threatening infection related to the pathological state of the remaining gut, and (4) intra-abdominal neoplasia that requires visceral exenteration to obtain a reasonable chance of cure [8].

Table 21.1 Indications for intestinal transplantation in children based on diagnosis

Anatomic Short Gut (61%)		Functional (30%)		Other (9%)	
Gastroschisis	22%	Pseudoobstruction	18%	Retransplant	8%
Volvulus	16%	Malabsorption	8%	Tumor	1%
NEC	14%	Other	4%		
Atresia	4%				
Other	5%				

Adapted from: Ganoza et al. [20] and Grant et al. [21]

Table 21.2 Indications for intestinal transplantation evaluation

Intestinal failure-associated liver disease
Total bilirubin ≥6 mg/dL
AND
Platelet count ≤220 × 10^3/μL and albumin ≤3.0 g/dL
OR
Platelet count ≤168 × 10^3/μL and albumin ≤3.5 g/dL
Intestinal failure with loss of half of standard central venous access sites
Infant 2/4 (jugular, subclavian)
All others 3/6 (jugular, subclavian, femoral)
Intestinal failure with recurrent life-threatening infection attributable to central venous catheter and/or diseased remnant gastrointestinal tract
Total intestinal loss from congenital malformation, necrotizing enterocolitis, vascular accident, or non-metastatic tumor

Adapted from Kaufman et al. [25] and Kaufman et al. [35]

21.3.1 Intestinal Failure-Associated Liver Disease (IFALD)

Progressive, life-threatening IFALD has historically been the most common indication for intestinal transplantation in the pediatric age group, because the infant liver is more easily damaged by the deleterious effects of intestinal failure and parenteral nutrition therapy than the mature organ. This fact has been emphasized by the preponderance of liver-inclusive intestinal transplants performed in infants less than 1 year of age, about 80–90% of all intestinal transplants in this age group. However, the incidence of severe IFALD in infancy sufficient to indicate early intestinal transplant has fallen considerably. Whereas in 2007, 94 infants under age 1 year were placed on the US national waitlist for intestinal transplant, only 7 infants were placed on the waitlist in 2020. Similarly, in 2007, 37 intestinal transplants were performed in infants less than 1 year, whereas in both 2017 and 2018 only 1 case was performed in each year [18]. Overall, 80% of intestinal transplants in children of all ages incorporated liver in 2007, whereas 50% of pediatric intestinal transplants included a liver allograft in 2020. The apparently declining frequency of advanced IFALD in pediatric patients, especially infants, may be due to new methods of parenteral nutrition management, particularly reduction in calories provided by the conventional, hepatotoxic soy-based lipid emulsion, use of alternative lipid products including those containing fish oil, and continued consolidation of care at multidisciplinary intestinal rehabilitation centers [23, 24].

Improvements in the care of patients with intestinal failure notwithstanding, some patients, especially those with neonatal intestinal failure, die because of chronic liver failure in infancy or at a later time, the majority between ages 7–18 months [12, 14–16, 25]. The challenge to the clinician remains the identification of patients who, without a transplant, will progress to hepatic failure and die from its complications. Prognosis of IFALD, particularly in infants, is determined by the interactions of evolving cholestasis, portal hypertension, and synthetic

dysfunction; all carry similar weight [25]. Early, mild IFALD, as indicated by the combination of a total serum bilirubin level of 6 mg/dL, low-normal platelet count of 220,000 μ/L, and low-normal albumin of 3.5 g/dL, within the first 6 months after birth predicts a probability of liver failure leading to death or transplant of between 35% and 40%. Escalation of total bilirubin to 12 mg/dL, reduction of the platelet count to 170,000 μ/L, and reduction in serum albumin to 3.0 g/dL increase the probability of liver failure to about 85% in the same time period. Intermediate levels of each variable in various combinations produce correspondingly intermediate risks of liver failure. These tests are more reliable indicators of hepatic deterioration than the physical examination that tends to demonstrate only jaundice and abdominal distention due to hepatosplenomegaly; clinically important ascites and large esophageal varices such as are typical in patients with decompensated, end-stage liver disease and an anatomically normal gastrointestinal tract are rare due to the marked reduction in superior mesenteric vein blood flow associated with loss of all or the most the midgut [5, 26]. Rather, bleeding in IFALD due to portal hypertension emanates mainly from the mucocutaneous interface of abdominal wall stomas [27], and malnutrition is absent due to parenteral nutrition support.

There remains no formal consensus as to the magnitude of progressive IFALD risk that indicates referral for transplant. Listing for transplant is based on consideration of the balance between estimated life expectancy during evolution of IFALD compared to the probability of ending parenteral nutrition before IFALD-related death is predicted. Predicting liver recovery as enteral feeding increases is complicated by the fact that no specific percentage of enteral caloric intake has been shown to prevent or reverse established IFALD [28]. Patients unlikely to need transplant referral are those with anatomic short bowel with high probability of eventual intestinal rehabilitation (Table 21.3) and estimated risk of fatal IFALD no higher than 35–50%. Patients with a very low or no probability of ending parenteral nutrition should be referred for transplant with the emergence of even mild IFALD [29, 30].

Table 21.3 Risk factors for permanent parenteral nutrition

Anatomic short bowel syndrome
Infants
Less than 40 cm of remnant small bowel without ileocecal valve.
Less than 20 cm of remnant small bowel with ileocecal valve.
Older patients
Less than 65 cm of remnant small bowel without ileocecal valve.
Less than 30 cm of remnant small bowel with ileocecal valve.
Functional intestinal failure
Chronic intestinal pseudo-obstruction syndromes: Continuous parenteral nutrition.
Congenital secretory diarrhea syndromes, e.g. microvillus inclusion disease.

Adapted from Mousaet al. [29], Kaufman et al. [35], Galea et al. Short-bowel syndrome: a collective review. J Pediatr Surg 1992;5:592–6, and Messing et al. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999;117:1043–50

21.3.2 Loss of Central Venous Access

Intestinal transplantation that is indicated by threatened loss of ability to deliver parenteral nutrition safely is likely to increase, as more patients with less than optimal rehabilitation potential but no evidence of IFALD remain on parenteral nutrition for extended periods [31]. The most obvious challenge is maintenance of indefinite central venous catheterization. Venous occlusion is closely associated with catheter-related bloodstream infection, a common occurrence in patients with intestinal failure [32]. Coincidental genetic thrombophilia may increase the cumulative risk of venous occlusion [33]. Four central venous access sites are routinely available in infants, the two internal jugular and two subclavian veins. In older patients, central access via the femoral veins is generally feasible. The degree of lost venous access that defines parenteral nutrition failure is influenced by two principles from the perspective of intestinal transplantation. First, morbidity and mortality of transplant candidates and recipients increase when central venous catheter placement is inordinately difficult [34]. Second, central venous access may be needed for a prolonged period after transplant, up to several weeks to months. For these reasons, the prevailing philosophy of most transplant centers is, somewhat arbitrarily, that *loss of half of all central venous access sites in the setting of permanent parenteral nutrition* despite optimal catheter care provided by a center with expertise in intestinal rehabilitation is sufficient to recommend intestinal transplantation [35].

21.3.3 Recurring, Life-Threatening Bloodstream, or Metastatic Infection

The position of the American Society of Transplantation is that repeated life-threatening infection, both within the bloodstream and elsewhere, in the setting of protracted central vein catheterization despite presumably optimal management by an intestinal rehabilitation center justifies consideration of intestinal transplantation [35]. The source of infection in affected patients is rarely known with certainty but potentially results from repeated external catheter contamination and vascular seeding from a chronically ischemic, inflamed, and/or dysmotile bowel [36]. The total number of infections, sites of infection distant from the bloodstream, or specific infective agents that are necessary to meet this indication for intestinal transplantation remain undefined. Spleen or brain abscess and endocarditis are probably appropriate indications for transplant once the infection has been eradicated. It is also highly desirable that patients with recurring infections be considered for transplantation before they are colonized with highly resistant bacteria such as extended spectrum beta-lactamase-producing coliforms, *Pseudomonas* sp., and vancomycin-resistant enterococci, because these pathogens are often extremely difficult to manage successfully in immunosuppressed patients, particularly those with poor vascular access [37]. In practice, recurring infection is rarely the sole indicator of parenteral nutrition failure; rather, recurring infection typically coexists with and accelerates the tempo of progressive liver failure and declining vascular access in a vicious cycle.

21.3.4 Intra-Abdominal Neoplastic Disease

There are isolated reports of intra-abdominal congenital malformations for which cure may require near-complete bowel resection, resulting in a greatly increased risk of secondary liver failure [38]. More commonly, this situation arises in adolescent patients with familial adenomatous polyposis and colectomy who have developed extensive intra-abdominal and pelvic desmoid tumors [39]. Immediate referral for intestinal transplantation is justified in these patients, because absence of the alimentary tract beyond the esophagus or stomach is not only a major risk of liver failure but also for repeated life-threatening fluid and electrolyte imbalances. In contrast with intestinal transplantation for desmoid tumors that are only locally invasive, transplantation for intra-abdominal neoplasms that have distant metastases is contraindicated.

21.4 Evaluation for Transplant

The decision to list a patient for intestinal transplantation is based on several factors that include (1) a clear and convincing indication for the operation based on the foregoing considerations, (2) absence of contraindicating co-morbid disorders, and (3) establishing that the intended recipient's family has or will have a social support structure that would permit them to deliver appropriate post-operative care.

21.4.1 Confirmation of an Indication for Intestinal Transplant

In most cases, the need for intestinal transplantation is clear based on an unequivocal diagnosis of anatomic or functional intestinal failure that predicts little or no tolerance of enteral nutrition and a high risk of rapidly progressive IFALD or future inability to deliver parenteral nutrition. On other occasions, the need for intestinal transplant may be uncertain at referral. Useful testing may include endoscopic biopsy, as demonstration of a relatively atrophic mucosa despite enteral nutrition implies a low probability for additional rehabilitation, particularly if functional studies such as plasma citrulline concentration are not encouraging [40]. Conversely, contrast radiography of the upper and lower gastrointestinal tracts may reveal new or evolving stricture, stenosis, or dysfunctional segments that indicate intestinal reconstruction, stoma closure, or related procedures rather than immediate listing for transplant [41, 42].

21.4.2 Isolated Intestinal vs. Combined Liver and Intestinal Transplantation

Historically, there was great urgency in identifying patients at risk for progressive IFALD because of the extraordinarily high mortality of patients on the waitlist for

both a liver and intestinal allograft that approximated 35% to 40% of those listed [43]. The risk of death on the waitlist for combined liver and intestinal transplant has fallen, since allocation rules in the United States now prioritize patients with chronic liver disease in need of additional organs such as the small bowel [17, 23]. However, declining waiting times and waitlist mortality have not decreased the gravity of the decision to include liver, which remains an extremely scarce resource, in the composite allograft. The usual clinical scenario for isolated intestinal transplant is an increasing total serum bilirubin concentration that remains less than 10 mg/dL, mild splenomegaly, and a platelet count in the low-normal range [44], whereas the combination of severe hepatosplenomegaly, hyperbilirubinemia that often exceeds 10 mg/dL, and thrombocytopenia not attributable to recent infection, with or without recurring gastrointestinal tract hemorrhage and coagulopathy, indicates inclusion of liver in the proposed transplant. When severity of liver disease is ambiguous based on clinical and laboratory data, a biopsy may discriminate mild from advanced and irreversible disease. Historically, fully established cirrhosis or extensive, i.e., grade 3, bridging fibrosis indicates liver (and intestinal) transplantation, while purely portal fibrosis (grade 1) or portal plus mild bridging fibrosis (grade 2) supports isolated intestinal transplantation [25, 45]. Regression of fibrosis after isolated intestinal transplant is inconsistent [46, 47]. A risk of isolated intestinal transplant in the setting of moderate to severe liver disease is precipitation of early post-operative hepatic decompensation.

There is a limited role for isolated liver transplantation for pediatric patients partially dependent on parenteral nutrition with impending hepatic decompensation. Clinical experience indicates that the operation should be performed only in patients who are likely to end parenteral nutrition following restoration of normal liver function, that is, patients who do not have intrinsic intestinal failure. The criteria that have been validated over time that indicate isolated liver transplantation in patients with end-stage liver disease and intestinal insufficiency rather than true intestinal failure include at least 50 cm of intact small bowel in the absence of an ileocecal valve (ICV) or 30 cm with ICV; a minimum of 50% of the estimated daily energy requirement supplied via the gastrointestinal tract, the tolerance of which has been proven by weight gain; and no history of recurrent central line infections in the presence of dilated dysmotile bowel [48, 49].

21.4.3 Inclusion of Additional Organs in the Transplant

A full "multivisceral transplant" includes *liver, stomach, duodenum, and pancreas* with small bowel, i.e., jejuno-ileum. Multivisceral transplantation is most often performed in infants and children because of profound gastroduodenal dysmotility that coexists with intestinal failure. Foregut disease may be primary as in chronic idiopathic intestinal pseudo-obstruction or secondary to extensive neonatal necrotizing enterocolitis and congenital anomalies; desmoid tumors involving the foregut in patients with familial adenomatous polyposis are also in this category [50]. In the clinical scenario where the liver remains preserved but the native stomach,

duodenal-pancreatic complex, and intestine need replacement due to either tumor encroachment or a functional disorder, a liver-sparing, multivisceral transplant or a *modified* multivisceral transplant is indicated.

Assessment may include contrast fluoroscopy of the upper gastrointestinal tract, nuclear gastroduodenal imaging, and, in ambiguous cases, antroduodenal manometry. Patients with desmoid tumors may benefit from evaluation at a transplant center at initial diagnosis in order to coordinate tumor and bowel resection with transplantation [39]. The colon substantially improves body fluid and electrolyte conservation. Consequently, for patients, including those with long-segment Hirschsprung disease, intestinal pseudo-obstruction, microvillus inclusion disease, and familial adenomatous polyposis, who lack both functional colon and small intestine, inclusion of the *colon* in a composite allograft is highly desirable and adds no extra morbidity to the transplant [51].

21.4.4 Venous Access

Determining patency of central veins requires venography, because ultrasonography is less sensitive [52]. CT angiography and magnetic resonance venography have largely replaced conventional fluoroscopy for this purpose. During the transplant evaluation, a plan for maintaining adequate central venous access in the perioperative period can be formulated that may include dilatation and stenting of partially thrombosed vessels [34]. Rarely, the inability to guarantee adequate venous access contraindicates intestinal transplantation.

21.4.5 Assessment of Co-Morbid Disorders

Cardiac function. Formal cardiac evaluation is generally indicated for all intestinal transplant candidates in light of the potential for structural cardiovascular disease associated with protracted central venous catheterization and for subtle congenital anomalies, the presence of which may be overshadowed by intestinal failure. When congenital or acquired cardiovascular disease necessitates surgical intervention, the transplant and cardiovascular teams must jointly determine whether repair should be attempted before or after the transplant.

Pulmonary function. A history of chronic respiratory disease is relatively common in pediatric candidates for intestinal transplantation because of the frequency of extreme prematurity associated with necrotizing enterocolitis. Most relevant to transplant surgery is past or current oxygen dependence. A history of lung disease before transplant is likely to prolong mechanical ventilation after transplant significantly and to increase the probability of tracheostomy. X-rays or computed tomography of the chest is generally indicated at evaluation as well as echocardiography to assess secondary right ventricular hypertrophy and pulmonary hypertension. Pulmonary function tests may be useful if available. Sustained oxygen dependence (room air saturation <92–93%) often contraindicates transplant.

Renal function. Intestinal failure predisposes to renal insufficiency [53]. Contributory factors include repeated exposure to nephrotoxic drugs such as aminoglycoside antibiotics, chronic under-hydration, and conjugated hyperbilirubinemia in patients with IFALD [54]. Significant urinary tract dilatation and renal dysfunction are common features of some intestinal dysmotility syndromes such as megacystis-microcolon-intestinal hypoperistalsis syndrome. Assessment of renal function during evaluation is essential, because pre-existing renal impairment complicates peri-operative fluid management and amplifies the nephrotoxic effects of numerous drugs typically employed after transplant, notably tacrolimus. Ultrasound or computed tomography of the kidneys is an essential part of the evaluation to detect renal atrophy, nephrocalcinosis, or hydronephrosis. Since plasma urea nitrogen and creatinine concentrations are relatively insensitive measures of renal function, nuclear renal imaging and estimation of glomerular filtration using cystatin-c may be useful [55]. Markedly impaired renal function may require formulation of alternative immunosuppressive and infection prophylaxis strategies or concurrent kidney transplantation [30].

Neuro-developmental function. Concerns about intellectual functioning most commonly arise in infants with intestinal failure that results from necrotizing enterocolitis associated with extreme prematurity. Less often, neuromuscular and developmental disabilities may be severe enough to contraindicate intestinal transplantation, including syndromic Hirschsprung disease and mitochondrial diseases such as mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome [56, 57]. In the absence of precise guidelines that define the magnitude of disability that should contraindicate transplant, most centers follow the dictum that the patient should be functional enough, both at referral and for the foreseeable future, to obtain improved life quality from the operation [11]. Developmental assessment is useful for all pediatric intestinal transplant candidates. Testing of visual acuity and hearing is important before transplant to guide future rehabilitation. Additional studies such as magnetic resonance imaging of the brain are obtained in selected individuals based on history and examination.

Psycho-social status. Care of the pediatric intestinal transplant recipient following hospital discharge to home is complicated and demanding, initially exceeding the challenge of caring for the patient with intestinal failure. The transplant center is obliged to estimate the ability of a patient's family to deliver adequate post-transplant care, to initiate supportive or corrective interventions in concert with the referring center where possible, and potentially to deny transplantation if a family provides clear and ongoing indications that it is not likely to be able to deliver adequate care and if alternate care arrangements cannot be made in conjunction with social service agencies. The key predictor of successful family care after transplant is successful family care before referral. Events that cast doubt about a family's willingness or ability to care for an intestinal transplant recipient include a history of delayed hospital discharge due to an inadequate home environment, reliance on professional home health providers to perform basic tasks such as connecting and disconnecting parenteral nutrition infusions, and previous involvement of child protective agencies.

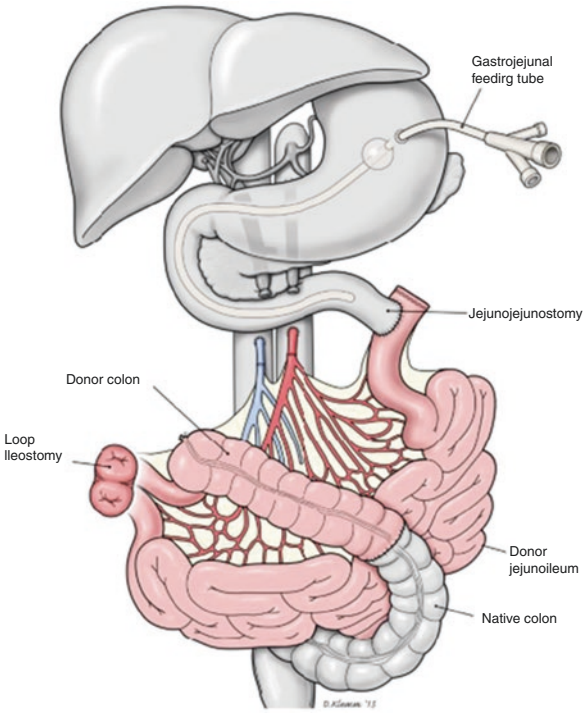
Infection and immune status. As with transplantation of other organs, the frequency of and dangers posed by opportunistic infections after intestinal transplantation require determination of susceptibility to primary infection and reactivation of

latent infection with agents that include but are not limited to herpes simplex virus [58], varicella zoster [59], cytomegalovirus [60], Epstein-Barr virus [61], hepatitis C virus [62], and *Toxoplasma gondii* [63]. Serological testing may not accurately indicate disease susceptibility in candidates less than 1 year of age because of persisting maternal antibodies. A negative test for human immunodeficiency virus is generally mandatory before listing. The not infrequent necessity of transplantation under age 1 year undermines completion of pre-transplant immunization. However, live-attenuated vaccines can be given as early as age 6 months [64]. Finally, candidates are tested for the presence of anti-HLA antibodies, the development of which is promoted by frequent blood transfusions and infections. The concept of heterologous immunity is thought to be responsible for the development of anti HLA that is observed in patients without typical sensitizing events such as transfusion, retransplantation, and pregnancy] that are common in patients with long-term central vein access.

21.5 Intestinal Transplant Allograft Types

21.5.1 Isolated Intestinal Transplantation

There are two technical options in isolated intestinal transplantation based on whether allograft venous outflow is directed to the native portal venous system, i.e., mesenteric vascular reconstruction, or shunted to the inferior vena cava, i.e., systemic vascular reconstruction (Fig. 21.1). The underlying recipient intestinal disease, severity of IFALD, and recipient venous anatomy determine which of the two reconstruction methods is utilized, as the choice has no impact on nutritional outcome [1, 65, 66]. *Mesenteric vascular reconstruction* is generally appropriate for isolated intestinal transplant recipients with congenital secretory diarrhea syndromes and pseudo-obstruction, in whom the presence of all or most of the native small intestine preserves mesenteric vasculature. Mesenteric reconstruction is also required when thrombosis of the recipient inferior vena cava secondary to previous catheterization precludes systemic vascular reconstruction. In contrast with functional intestinal failure, most patients with short bowel syndrome require *systemic vascular reconstruction*, because loss of all or most of the midgut produces an undersized recipient portal venous system that cannot accommodate the high-volume mesenteric venous outflow emanating from an intact midgut, i.e., the allograft. Hepatic fibrosis, albeit insufficient to justify concurrent liver transplantation, also contraindicates mesenteric vascular reconstruction, not only because of the risk of inducing hepatic decompensation, but also because secondary portal hypertension may lead to acute intestinal allograft congestion and necrosis [67]. Arterial flow to the isolated intestinal allograft is established directly from the recipient infrarenal aorta; the technical challenge is obtaining a tension-free anastomosis under the weight of bowel that avoids the sequence of arterial traction, thrombosis, and necrosis of the allograft. Another key technical objective essential to good, early allograft function is ligation of tissues around the base of the mesentery in order to minimize the risk of post-transplant chylous ascites [68].



Isolated small bowel transplant: detail of mesenteric reconstruction options

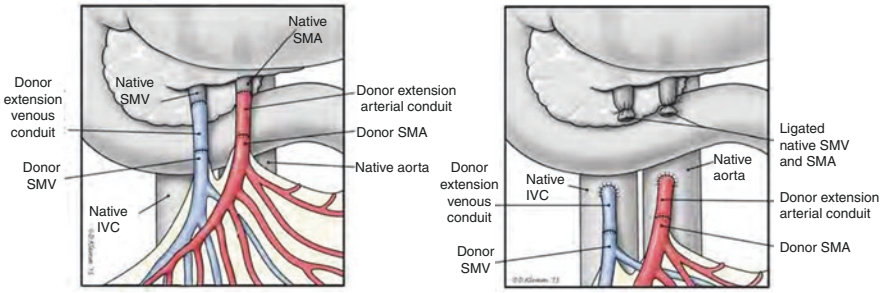


Fig. 21.1 Isolated enbloc small bowel/colon transplant using systemic vascular reconstruction (inferior vena cava) with short extension vascular grafts. Allograft is in color, native viscera are shaded. Proximal and distal enteric continuity are obtained with a jejunojejunostomy, loop ileostomy, and distal colocolostomy, respectively. Inset illustrating in detail the two potential vascular reconstruction configurations with (left) mesenteric reconstruction, and (right) systemic reconstruction

Allograft continuity with remnant native gut is usually established proximally beyond the native ligament of Treitz. However, a native-to-recipient duodenojejunostomy can be performed if native jejunum is inadequate. Distal continuity is routinely established in conjunction with the formation of an ileostomy that provides access for surveillance endoscopy. A twin lumen, i.e., loop ileostomy, may be constructed, the efferent limb of which is anastomosed to the native left colon. Alternatively, if colon is included in the allograft, an anastomosis is fashioned between allograft distal transverse colon and native distal sigmoid colon. As an alternative to loop ileostomy, a single lumen "chimney" ileostomy with internal end to side anastomosis to native colon may be performed. The transplant is completed with placement of one or more abdominal drains plus tubes for intestinal lumen access; a combined gastrojejunal tube or separate gastric and jejunal tubes can be placed; either option avoids prolonged post-operative nasogastric suction and facilitates enteral nutrition. Jejunal feeding is usually needed transiently, because early post-operative gastroparesis and inefficient peristalsis across the native-to-graft enteroenteric anastomosis are common [69, 70].

21.5.2 Combined Liver-Intestinal-Pancreas Transplantation

In current practice, the organs are most commonly implanted en bloc as a single unit attached at the porta hepatis, thereby including much of the donor duodenum and either the pancreatic head or whole organ as a composite allograft (Fig. 21.2). The advantage of the en bloc technique, particularly for infants, is that it avoids biliary and hepatic arterial dissection that can easily injure small hilar structures [71, 72]. Arterial blood flow is established from the infrarenal aorta via a transposed donor thoracic aortic graft. The native spleen is usually preserved along with the native foregut and is drained by shunting splenic vein flow to the inferior vena cava via a porto-systemic shunt. Cholecystectomy is routine, and enteral continuity is accomplished in the same manner as in isolated intestinal transplantation.

21.5.3 Multivisceral Transplantation

Multivisceral intestinal transplantation differs from combined liver-intestinal-pancreas transplantation in that the entire splanchnic circulation is removed as a consequence of resection of the pancreas, spleen, stomach, root of the intestinal mesentery, and the liver, obviating the need for a native to native porto-systemic shunt (Fig. 21.3). Allograft hepatic veins are anastomosed to the recipient inferior vena cava, and arterial flow to the allograft may be accomplished with a single anastomosis of donor infrarenal aorta to the infrarenal aorta of the recipient. Gut lumen continuity may be established proximally with anastomosis of the native esophagus to the cardia of the

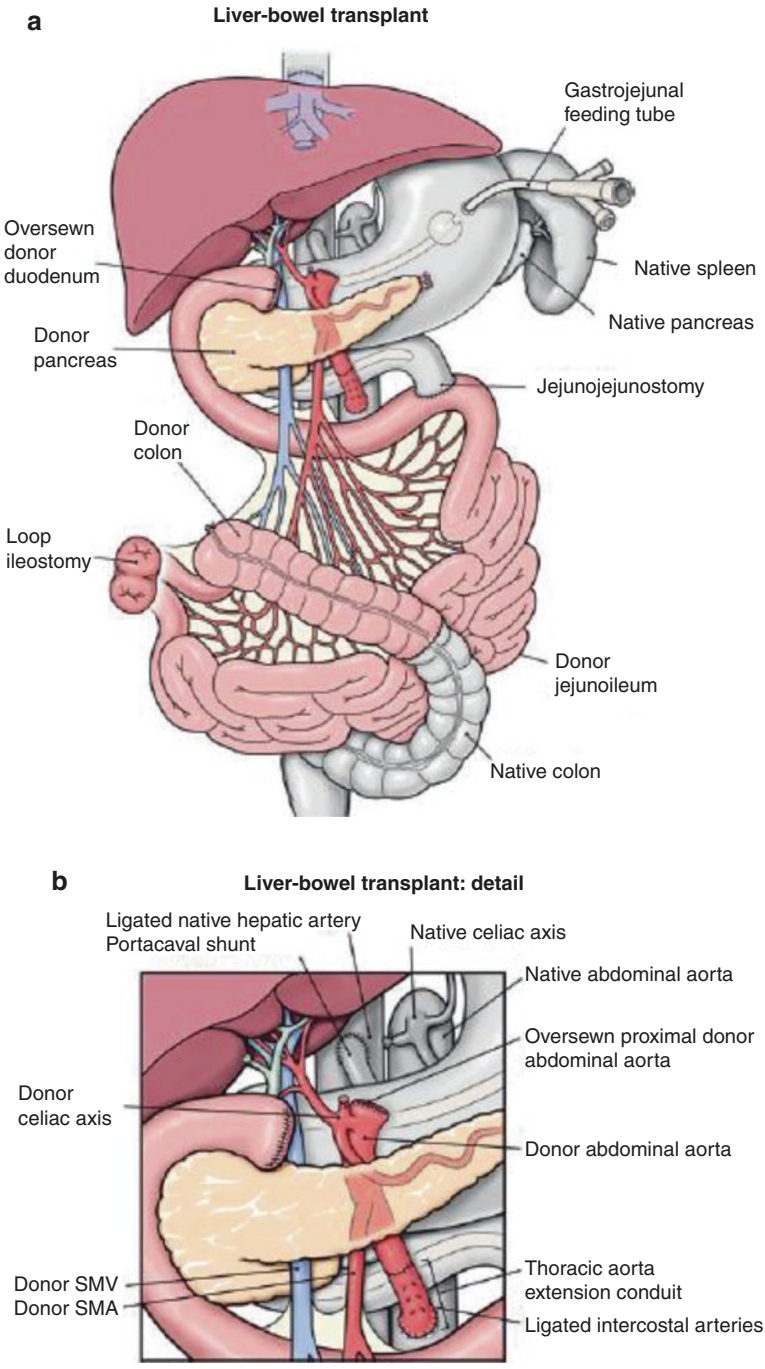


Fig. 21.2 Composite liver-intestinal-pancreas transplant, including duodenum and head of pancreas. Allograft is in color, native viscera are shaded (Fig. 21.2a). Native stomach, splenopancreatic complex is intact with venous drainage via native porto-caval shunt (Fig. 21.2b). Allograft arterial inflow is via aorta-aorta anastomosis and venous outflow via "piggyback" hepatic venous drainage. Distal gastrointestinal reconstruction as shown in Fig. 21.1

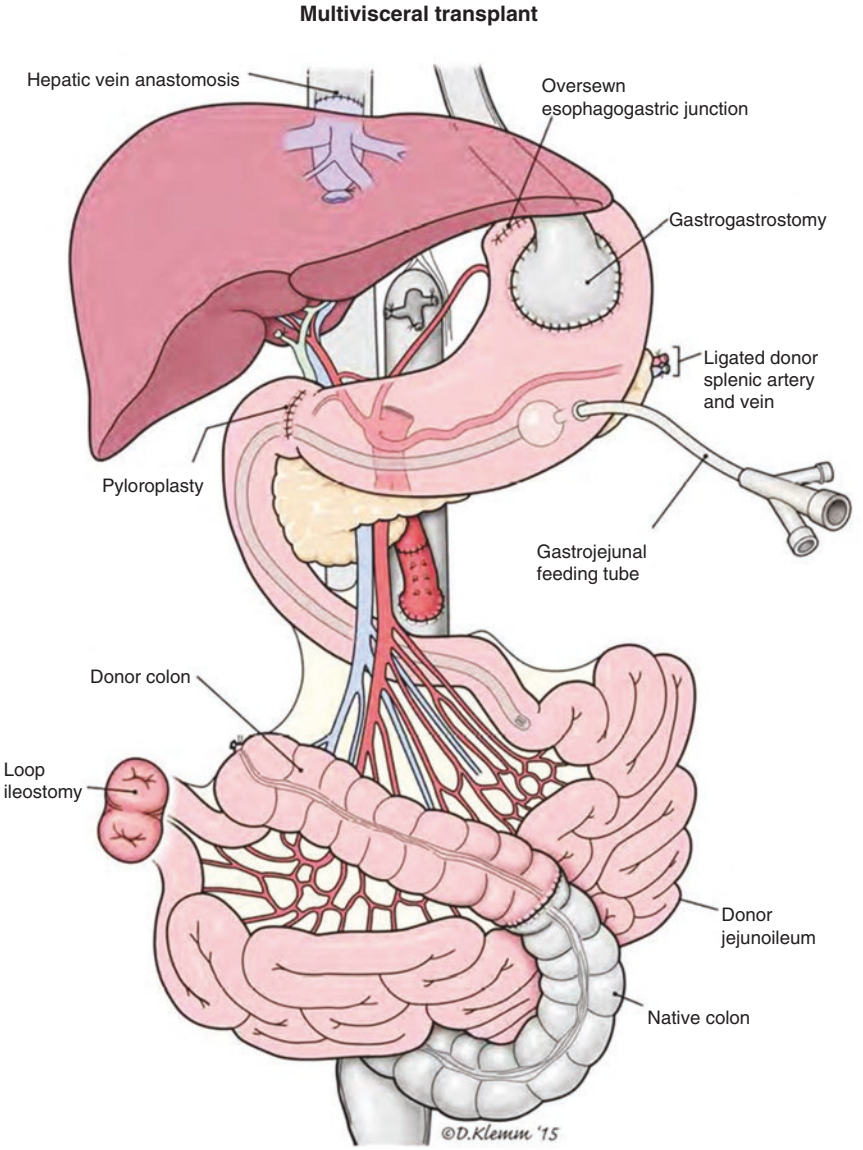


Fig. 21.3 Multi-visceral transplant with "piggyback" hepatic venous drainage to native vena cava and an inflow conduit from the recipient infrarenal aorta. A gastrogastric anastomosis and standard distal reconstruction are employed. A pyloroplasty facilitates gastric drainage

gastric allograft, although proximal gastrogastric anastomosis may reduce the risk of anastomotic leak [73]. Pyloroplasty promotes emptying of the denervated stomach. Gastric decompression is mandatory, usually with a combined gastrojejunal tube that allows early feeding into the graft jejunum. Distal enteral continuity is reestablished with loop ileostomy construction and colon anastomosis as described above. The

modified multivisceral transplant graft preserves the native liver; therefore, the allograft outflow is via the graft portal vein placed as an end-to-end anastomosis to the native portal vein [74]. Bile duct reconstruction is necessary with this graft type, usually with an end-to-end reconstruction (Fig. 21.4).

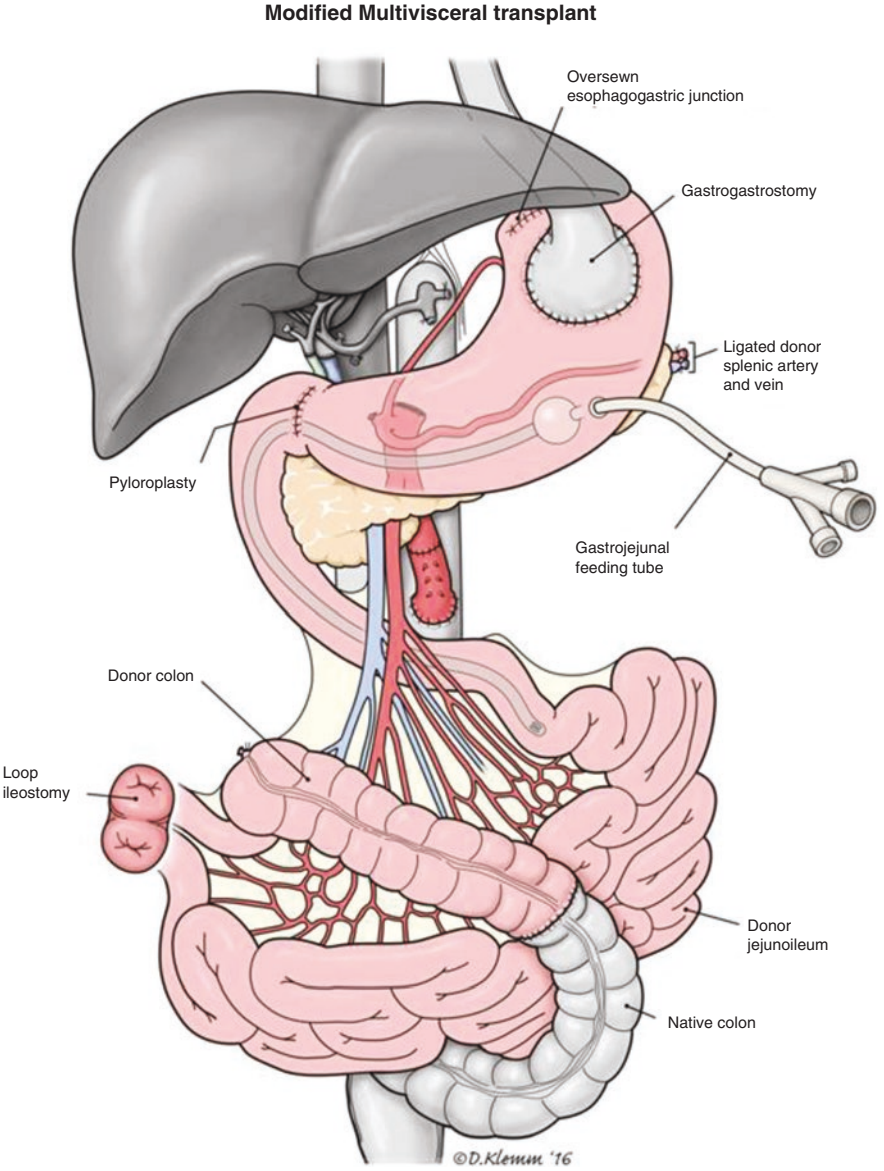


Fig. 21.4 Modified multi-visceral transplant preserving the native liver. Allograft organs include the stomach, pancreas, duodenum, small bowel and colon. Arterial inflow is via aorta-aorta anastomosis and graft venous outflow is via graft portal vein- native portal vein anastomosis. Native hepatic arterial inflow is preserved and enteric reconstruction is performed as for a full multivisceral graft. Biliary reconstruction is accomplished with a choledochocholedochostomy

21.6 Management Following Intestinal Transplantation

21.6.1 Post-Operative Management

Patients undergoing isolated intestinal transplantation are generally not critically ill at the time of surgery, and the early post-operative course is similar to that following any major abdominal operation. Extubation is usually accomplished within 24–48 h. In contrast, recovery following a combined liver-intestinal-pancreas transplant is often prolonged, since the operation has taken place in the setting of pre-operative liver as well as intestinal failure that typically includes renal insufficiency, fluid overload, infection, and protracted hemodynamic stress; mechanical ventilation may be required for several weeks. Illustrative is one series that demonstrated a 6-month mortality following liver-inclusive small bowel transplant of about 20%, whereas no recipients of an isolated small bowel allograft died within the same time frame [75]. In all intestinal transplant variants, marked intra-abdominal third space fluid losses are typical and require aggressive fluid resuscitation within the first 24 to 36 post-operative hours. The challenge in the intensive care unit is to maintain hemodynamic stability and fluid balance in a way that optimizes allograft and renal perfusion but avoids persistent and frank pulmonary fluid overload that prolongs mechanical ventilation. Blood flow to the allograft may be assessed by frequent Doppler ultrasound of the ileostomy at the bedside, whereas overlying bowel gas limits the utility of trans-abdominal ultrasonography. The intestinal vasculature is sensitive to vasoconstricting agents, particularly alpha-adrenergic agonists, and they should be avoided.

Routine post-transplant medical therapy typically includes a proton pump inhibitor to forestall acute gastric mucosal erosive hemorrhage [76]. Broad-spectrum prophylactic, anti-bacterial, and anti-fungal therapy is maintained for several days to a few weeks after transplant; endoscopic confirmation of allograft mucosal integrity and initial tolerance of enteral nutrition may serve as thresholds for discontinuation. Prophylaxis against *Pneumocystis jirovecii* is accomplished with trimethoprim-sulfamethoxazole or, in the presence of continued bone marrow suppression that is common in patients with pre-transplant liver failure, intravenous pentamidine.

21.6.2 Enteral Nutrition

In the absence of post-operative cardio-pulmonary instability or surgical complications that require abdominal exploration, ileus generally resolves within 3–5 days, at which time enteral feeding, generally via jejunostomy with an amino acid or peptide formula, is introduced and increased gradually thereafter. Formulas with reduced long-chain triglyceride content or enriched with medium-chain triglycerides are often used, since lymphatic drainage cannot be established surgically, e.g., Vivonex RTF® or Peptinex® [77]. Parenteral nutrition, which is usually re-introduced 2 or 3 days post-operatively, is tapered as enteral feeding is increased. Intestinal allograft transit is generally rapid, which has been attributed to allograft denervation that removes the inhibitory influence of the central nervous system on bowel

motility [69]. Anti-peristaltic agents such as loperamide (Imodium®), alone or in combination with diphenoxylate-atropine (Lomotil®), are almost always necessary to reduce ileostomy output, generally to less than 30–40 mL/kg/day, in order to permit gradual reduction in intravenous fluid intake [78]. Side effects of these agents that include abdominal distention, vomiting, and lethargy are rare, even in small infants. In the absence of allograft dysfunction that is mainly due to rejection, respiratory instability, or sepsis, total caloric needs can usually be delivered entirely through the allograft within 4–6 weeks.

The objective of intestinal transplantation is the acquisition or restoration of the ability to consume an unrestricted or minimally restricted, age-appropriate diet. Within certain limitations, this objective eventually can be met in most patients. Continued tolerance of enteral feeding is also a practical, ongoing test of allograft function. Once total enteral nutrition has been established via jejunostomy, feeding can be transitioned to the gastric and oral routes as native foregut motility improves. Re-establishment of retroperitoneal lymphatic drainage, also by around 4 weeks after transplant, permits a mixed diet and/or formula with standard fat content without producing chylous ascites or other overt symptoms of lipid intolerance [77]. A polymeric formula may be substituted if there is no history of cow milk intolerance (see below). Fried and other fatty foods often continue to produce diarrhea that is only partially responsive to anti-peristaltic drugs. High osmolality, sugary fluids also often increase stool output dramatically in intestinal transplant recipients of all ages. In many patients, this phenomenon may improve or resolve over time. Because median net energy absorption remains only about 85–90% indefinitely [79], enteral caloric intake necessary to meet metabolic requirements is at least twofold greater than resting energy expenditure [80]. Ongoing malabsorption, particularly for lipid, contributes to the prolonged need for supplemental tube feeding to deliver sufficient calories for growth. Infants who have eaten little or nothing by mouth prior to intestinal transplantation tend to remain highly dependent on formula feeding delivered by tube, and extensive occupational therapy may be necessary to teach infants and children to eat. Depending on intake, fat-soluble vitamin supplementation may be necessary, and a need for iron supplementation is common. It is unclear whether high iron requirements are due to frequent blood sampling, occult bleeding from an otherwise intact allograft, or inefficient iron absorption.

21.6.3 Immunosuppressive Therapy

Although there are many variations in immunosuppressive practices among transplant centers, there are also numerous areas of consensus, including (1) the need for allograft lymphocyte depletion before implantation, (2) the benefit of antibody induction for the recipient, and (3) the continued suitability of the calcineurin inhibitor tacrolimus (Prograf®)-based immunosuppression in most instances [17]. Allograft lymphocyte depletion is most commonly accomplished by treatment of the donor with anti-lymphocyte globulin, usually Thymoglobulin®, before removal of the bowel [10]. Tacrolimus dose and frequency are based on achieving a whole

blood trough concentration initially of around 15–25 ng/mL. Induction antibody therapy for the recipient generally employs either a lymphocyte-depleting agent such as rabbit anti-thymocyte globulin (Thymoglobulin®) or alemtuzumab (Campath®) or basiliximab (Simulect®), an agent that inhibits activated IL-2 receptor [6]. Intravenous corticosteroids as methylprednisolone are usually given in high dose for several days, later replaced by prednisone or prednisolone.

In the absence of allograft rejection, both corticosteroids and tacrolimus are gradually reduced during the first post-transplant year by 50–75% [70]. Some programs favor steroid discontinuation if allograft rejection has been absent or infrequent for an extended period, while others favor minimal or no maintenance steroid therapy from the beginning when Thymoglobulin® is used for initial induction [81]. Because of the side effects and limitations of prolonged, high-dose tacrolimus therapy in preventing allograft rejection, another immunosuppressive agent is often added. The rationale is that low doses of two drugs, with or without corticosteroids, are both safer and more efficacious than a high dose of a single agent. Sirolimus, also known as rapamycin (Rapamune®), is usually favored on the basis of established efficacy and bioavailability [82], and mycophenolate mofetil (CellCept®) can also be used.

21.6.4 Surveillance of the Allograft

Protocol endoscopy of the allograft remains an essential component of intestinal transplant care. No non-endoscopic test of enterocyte function or inflammation, including plasma citrulline and fecal calprotectin, provides sufficient sensitivity or specificity to displace endoscopy [83]. The intent of endoscopic surveillance is detection of rejection while still histologically mild and either asymptomatic or minimally symptomatic, and therefore most likely to be reversed with only modest intensification of immunosuppressive therapy. Surveillance endoscopy is generally done once or twice weekly for the first few post-operative weeks and then at least biweekly to monthly for several months thereafter. Many centers continue to recommend annual endoscopic surveillance indefinitely in addition to endoscopy ad hoc for assessment of symptoms.

The ileostomy is the endoscopic access site of choice when available. Ileoscopy in infants and children generally utilizes a gastroscope inserted 5–20 cm into the allograft. Endoscopic grasp biopsy during each endoscopy session remains the standard of care, because visual inspection alone is only about 50% sensitive compared to biopsy for detection of allograft rejection, particularly in its early stages. Use of a zoom endoscope does not increase sensitivity, most likely because allograft rejection originates in the crypts of Lieberkűhn rather than villi [83]. Two to four specimens are taken at each session, and all areas within reach of the endoscope should be sampled [84]. Use of 1.8 mm forceps may be preferable because of the increased risk of intra-mural and luminal hemorrhage from the allograft compared to native small bowel, even when blood coagulation is normal.

Although findings in the ileum are usually representative of the entire allograft, discordance between the ileum and jejunum may occur in about 25% of cases when

both sites are sampled simultaneously, emphasizing that negative or ambiguous ileal findings in the setting of symptoms of graft dysfunction indicate immediate assessment of the proximal side of the allograft [83]. When the distal end of the allograft, i.e., ileum, is anastomosed to remnant native colon, it is usually possible to pass the endoscope into the colon for detection of opportunistic infection and graft vs. host disease. It is also comparatively easy to pass an endoscope from the ileum orthograde through the ileocecal valve in order to assess allograft colon when present; in this case a separate proctosigmoidoscopy is usually the most practical means of evaluating the native colon, although there is no consensus as to how often native colon should be inspected. If the upper native to graft anastomosis is located distal to the native duodenum, intubation of the allograft may be facilitated if an infant gastroscope can be passed through the gastrostomy orifice.

21.6.5 Growth and Development After Intestinal Transplantation

Assessment of growth is confounded by differing clinical practices and differing patient populations among centers, including the decreasing number of patients undergoing transplant because of liver failure [85]. Most studies report impaired linear growth at transplant and mean height Z-scores ranging between −2.8 and − 1.8 [86–88]. Because patients awaiting intestinal transplantation are supported with parenteral nutrition by definition, impairments in weight at transplant are usually less profound than impairments in height; the reported weight Z-scores range between −2.6 and − 1.0.

Patients who obtain good allograft function within a few months after transplant that permits ending of parenteral nutrition and who continue to require little or no supplemental intravenous fluids during subsequent years have demonstrated significant growth improvement in some studies [86, 87] but not in others [88, 89]. Selection bias may be operative, because the most striking improvements in growth occur in those patients with the most severe initial impairment, viz., height Z-scores < −2.0 [85]; in one such a group, average height Z-scores increased from −4.71 at transplant to −3.59 at 1 year and − 2.43 at 2 years after surgery [90]. Steroid-free immunosuppression regimens have been suggested to improve linear growth [81]. Even when significantly improved linear growth has been documented following intestinal transplantation, eventual attainment of average to above-average body size is uncommon. Acute allograft rejection (as compared to chronic rejection) does not appear to interfere with growth significantly [85, 86].

21.6.6 Quality of Life After Intestinal Transplantation

Objectives of intestinal transplantation include not only obtaining long-term survival after potentially fatal intestinal failure but also reintegration of the patient into society. Relatively little information is available concerning quality of life after intestinal transplantation in either children or adults. A return to work or school is

now achieved in most patients despite re-hospitalizations that are particularly frequent during the first few post-operative years [9, 91]. Common sense dictates that patients and their parents should perceive improved life quality following intestinal transplantation when good allograft function permits early ending of parenteral nutrition, at least some tolerance of foods by mouth, and elimination of the illness that indicated transplantation, including recurrent infections, pain-producing procedures, and repeated hospitalizations. A positive relationship between allograft function and patient perception of post-transplant life quality has been demonstrated in adults [92]. Similarly, pre-adolescent patients with good allograft function have self-perceptions of physical and emotional well-being that are comparable to those of healthy children [93], although potentially inferior school performance may be an important exception [94]. In contrast, parents of intestinal transplant recipients tend to perceive the functioning of their children as inferior to normal children, particularly in general and physical health and participation in family activities. Parent evaluations of their children also seem to be inferior to patients' personal assessments, perhaps reflecting an inherently greater adaptive potential of children and the relatively greater anxieties of parents.

21.6.7 Coordination of Care After Intestinal Transplantation

Following discharge to ambulatory status, most transplant centers insist that patients remain in their care for periods that vary from several weeks to months, since an experienced transplant center is best equipped to manage complications that remain frequent during the first several post-transplant months. These complications include episodes of fever, increased stoma output or other indications of rejection, opportunistic infection, electrolyte disturbances, and marked fluctuations in blood immunosuppressive drug concentrations. A period of relative clinical stability enables patients to return home to the care of their referring physicians or others who will assume responsibility for digestive care. The relatively greater and more prolonged medical fragility of intestinal transplant recipients compared to other solid organ transplant recipients requires maintenance of a close working relationship between the transplant center and referring physicians. This dictum is particularly apt for patients who live most distant from the transplant center.

There are no formal guidelines that govern how an intestinal transplant team should maintain collaboration with local physicians. Procedures will undoubtedly continue to vary based on the established practices of transplant teams, the individual interests and knowledge bases of local physicians, and ability of patients and their families to return to the transplant center for periodic follow-up. In general, most transplant centers expect to determine the immunosuppressive therapy including targeted blood levels when applicable. Surveillance colonoscopy and upper endoscopy can usually be performed by the local gastroenterologist. Well patients generally undergo blood testing including chemistries, hemograms, PCR monitoring, and immunosuppressive levels monthly to bimonthly; most transplant centers prefer to receive these data along with local physicians. Decisions concerning

nutrition support, monitoring of growth and development, and management of ancillary medical problems such as glucose intolerance, renal insufficiency, and hypertension are generally made locally, the transplant center serving as consultant. Acute illness that requires hospitalization does not necessarily require transfer to the transplant center, particularly if the reason is not directly related to the transplant and if alteration of immunosuppressive therapy does not appear to be warranted. Conversely, transfer back to the transplant center is generally appropriate when there are indications of serious allograft dysfunction, e.g., markedly increased fecal volume over several days without definable cause or lower gastrointestinal bleeding that suggests rejection or invasive opportunistic infection. Serious opportunistic infection elsewhere, e.g., the lower respiratory tract, may also warrant transfer in the event that major reductions in immunosuppressive therapy are required.

21.6.8 Allograft Loss and Long-Term Outcomes of Intestinal Transplantation

Within the first post-transplant year, refractory acute rejection is the most common cause of transplant failure and allograft removal in the isolated intestinal transplant recipient. Because the liver-intestinal-pancreas or multivisceral allograft is difficult to remove without immediate retransplant, refractory acute rejection is typically fatal in these two groups. Similarly, the most common late cause of allograft loss or death is chronic rejection, with or without superimposed acute rejection [95]. In all, refractory acute or chronic rejection is responsible for about one-third of post-intestinal transplant deaths. Opportunistic infection not directly related to rejection is the cause of death of an additional third, and various miscellaneous causes are responsible for the remainder [90]. Severe opportunistic infections that may or may not be precipitated by intensified immunosuppressive therapy for treatment of severe rejection are most common within the first 6 months after transplantation, when immunosuppressive therapy is usually maximal. Nevertheless, opportunistic infection remains a risk at any time after transplant.

21.7 Conclusion

Intestinal transplantation represents the ultimate treatment of intestinal failure. It has not supplanted extended parenteral nutrition as the primary therapy for affected pediatric patients in light of its enormous complexities and hazards. Indications for transplantation and the organs to be included in the operation require careful consideration. Intestinal transplantation may not be appropriate for all pediatric patients and their families. Families and health-care providers must recognize that, as with any solid organ transplant, intestinal transplantation does not represent a cure in the conventional sense but, rather, is intended to convert a fatal disorder into a manageable challenge of daily living. Because long-term success in intestinal

transplantation requires appropriate management of immunosuppressive therapy, nutrition, fluid and electrolyte balance, and surveillance for and treatment of allograft rejection and infection, families and health-care providers must be prepared to commit an enormous amount of physical and intellectual energy to the process indefinitely.

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Intestinal and Multivisceral Transplantation in Children: Outcomes and Complications

22

Masato Fujiki, Charles B. Chen, Mohamed Osman, Giuseppe D'Amico, Kadakkal Radhakrishnan, and Kareem Abu-Elmagd

22.1 Indications for Visceral Transplantation

Long-term dependence on parenteral nutrition (PN) can be associated with life-threatening complications, including catheter-related bloodstream infections, loss of central venous access, liver failure, metabolic bone disease, and impaired QoL. These complications of PN warrant consideration for intestinal transplantation. Table 22.1 shows indication for transplantation in children as reported by the Intestinal Transplant Registry.

A single center experience of visceral transplantation including 376 patients was reported [1]. One hundred and sixty-three (43%) in the series were pediatric patients with the mean age of 26 years. With increased awareness, more patients are being referred for transplantation before development of PN-associated liver failure and thus receive liver-free allografts. Early referral and transplantation should be considered before the development of other complications. The study just mentioned showed favorable outcomes following early transplantation, with better graft survival and improved QoL [2]. Liver-inclusive visceral transplantation is only

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M. Fujiki · M. Osman · G. D'Amico · K. Abu-Elmagd (✉)
Center for Gut Rehabilitation and Transplantation, Department of General Surgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: abuelmk@ccf.org

C. B. Chen
Department of Child Health, University of Missouri School of Medicine, Columbia, MO, USA

K. Radhakrishnan
Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH, USA

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Table 22.1 Indications of visceral transplant in children

Causes of gut failure
Gastroschisis
Necrotizing enterocolitis
Intestinal atresia
Volvulus
Trauma
Radiation enteritis
Crohn's disease
Dysmotility syndrome
Neoplastic disorders
Enterocyte dysfunction
Aganglionosis
Microvillus inclusion disease
Tufting enteropathy
Portomesenteric thrombosis

indicated for patients with advanced liver damage, and for end-stage liver disease patients with diffuse portomesenteric venous thrombosis who are not suitable candidates for isolated liver transplantation.

22.2 Global Trends

The Intestinal Transplant Registry report of global activity and trends showed that, between 1985 and 2013, 1611 pediatric visceral transplants were performed in 55 centers. Of these, 620 (38%) were liver-free visceral transplants (582 isolated small bowel and 38 modified multivisceral), and 1001 (62%) were liver-inclusive visceral transplants (734 liver-intestine and 257 full multivisceral) [3]. Increased transplant activities have occurred in South America and Asia, reflecting the growing worldwide interest in the field [4]. Despite increased practicality, total annual activities have decreased over the last few years, particularly in the pediatric population [3]. Such a decline can be partially explained by the growing activity in gut rehabilitation, with a comprehensive multidisciplinary approach, including medical therapy and bowel lengthening procedures. Continued evolution of PN therapy may further reduce the risk of associated liver damage and subsequent need for visceral transplantation.

22.3 Immunosuppressive Management

Immunosuppression has evolved through various eras as described in recent publications [2, 5, 6]. The current immunosuppressive regimen at the Cleveland Clinic consists of induction therapy with methylprednisolone, with the anti-CD52 monoclonal antibody alemtuzumab or the polyclonal rabbit anti-thymocyte globulin, and

tacrolimus-based maintenance therapy. The tissue typing laboratory can run a virtual crossmatch at the time of the organ offer and facilitate the decision to accept an organ. When transplants are performed with the presence of preformed DSA with high titers (> 4000 MFI), a desensitization protocol that includes rituximab may be added to the standard immunosuppressive therapy. The laboratory monitors preformed DSA as well as newly developing de novo DSA.

22.4 DSA and Liver's Immunological Protective Effect

The impact of preformed DSAs and de novo DSA has received increased attention in recent years. Preformed DSAs are present in 13% to 38% of recipients and de novo DSA occurs in 18% to 33% of cases, and both have a negative impact on acute rejection, chronic rejection, and graft survival [7, 8]. The inclusion of the liver in visceral allograft is protective and associated with clearance of preformed DSA, prevention of de novo DSA formation, and reduced risk of chronic rejection, contributing immunological benefit, especially in the long term [7–9]. The national registry data showed that long-term graft survival of liver-inclusive allografts is superior to that of liver-free graft, which can be explained partially by the liver's immunological protective effect [10] (Fig. 22.1). This is most pronounced when the visceral transplant is performed with a positive crossmatch and the presence of preformed DSA. The largest single center experience of intestinal transplants with a positive crossmatch ($n = 55$) revealed that the liver allograft alleviated the detrimental effect of DSA on outcomes of visceral allografts (Fig. 22.2).

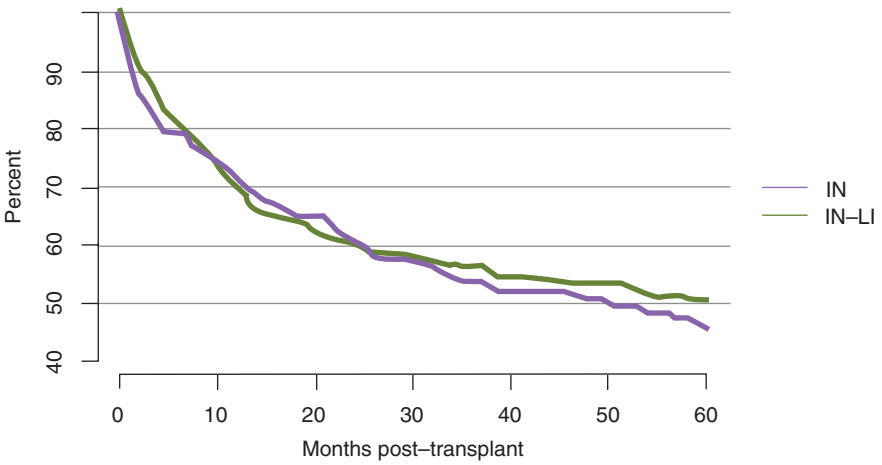

Fig. 22.1 Graft survival among pediatric and adult intestine transplant recipients, 2008–2010, by transplant type. *IN* liver-free visceral transplant, *IN-LI* liver-inclusive visceral transplant (Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2016 Annual Data Report: Intestine. Am J Transplant. 2018;18 Suppl 1:254–290)

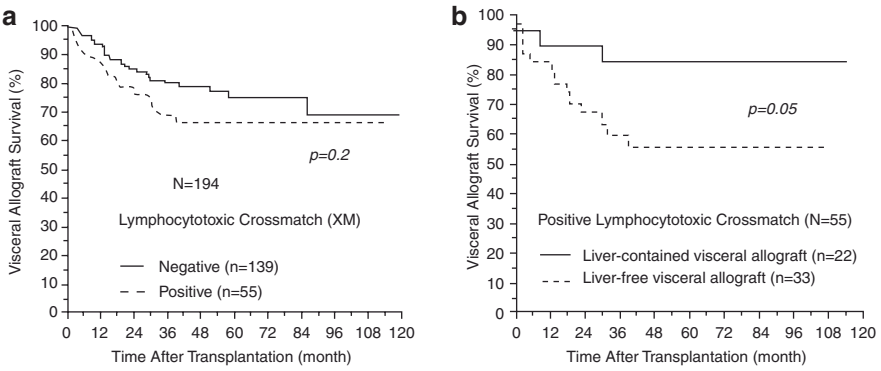

Fig. 22.2 (**a**) Kaplan-Meier survival of the total visceral allografts calculated according to the status of the complement-dependent lymphocytotoxic crossmatch (CDC-XM). (**b**) Allograft survival in recipients with positive CDC-XM considering the type of transplanted organs (Modified from Abu-Elmagd KM, Wu G, Costa G, et al. Preformed and de novo donor specific antibodies in visceral transplantation: long-term outcome with special reference to the liver. Am J Transplant. 2012;12:3047–3060)

22.5 Complications

22.5.1 Acute Rejection

Acute cellular rejection continues to be the leading cause of graft failure. Acute cellular rejection of the intestinal allograft is graded as indeterminate, mild, moderate, and severe, based on apoptosis count in 10 consecutive crypts and presence of confluent apoptosis and ulceration (Table 22.2) [11]. Acute cellular rejection is treated with steroids and/or Thymoglobulin. Some centers use Thymoglobulin up to 20 mg/kg with monitoring of CD3+ T cell in peripheral blood [12]. However, it should be noted that complete depletion of CD3+ T cell in peripheral blood does not mean effective depletion of graft CD3+ T cell and memory effector cells that play a major role in cellular rejection. Kroemer et al. reported that the degree of T cell depletion in Thymoglobulin-treated grafts was significantly higher in responders than in non-responders. Unfortunately, T cell depletion in the grafts cannot be monitored routinely in clinical practice; thus, the treatment dose of lymphocyte-depleting agents should be determined by serial histological assessment, clinical condition, infectious complications, and tolerability of the medication. Second-line agents for Thymoglobulin-resistant rejection include infliximab and alemtuzumab [12–14]. Infliximab specifically targets TNF-alpha-producing cells and thus is likely to deplete IL-17 and TNF-alpha-positive cells, which is the major effector T cell population of rejection [12].

Histological features of antibody-mediated rejection of the intestinal allograft were described previously, and its diagnosis is based on vascular changes including congestion, thrombosis, and extravasation in the mucosal capillaries, with positive

Table 22.2 Grades of acute cellular rejection of intestinal allograft

Grade of ACR	Major histologic findings
Indeterminate	Minimal localized inflammatory infiltrate, minimal crypt epithelial injury, increased crypt epithelial apoptosis <6 apoptotic bodies/10 crypts
Mild	Mild localized inflammatory infiltrate with activated lymphocytes, mild crypt epithelial injury, increased crypt epithelial apoptosis > = 6 apoptotic bodies/10 crypts
Moderate	Widely dispersed inflammatory infiltrate in lamina propria, diffuse crypt epithelial injury, increased crypt apoptosis with focal confluent apoptosis, more prominent architectural distortion
Severe	Features of moderate ACR plus mucosal ulceration; possible severe intimal arteritis or transmural arteritis

ACR acute cellular rejection

C4d staining [15–18]. Severe antibody-mediated rejection in the bowel has several prominent characteristic features, but it is an uncommon, albeit destructive, entity [16]. Therefore, it is likely that milder forms are not being suitably assessed in mucosal bowel biopsies. To date, there is no consensus regarding the treatment of humoral rejection. Plasmapheresis and intravenous immunoglobulin aim at depleting or inactivating the DSAs. Rituximab prevents the relapse of DSA synthesis. Eculizumab and bortezomib act on the last effectors of the immune reaction, the complement cascade [19], or proteasomes, respectively [20, 21].

22.5.2 Viral Infections

Recent advances in polymerase chain reaction technology have allowed closer monitoring of Epstein-Barr virus and cytomegalovirus after transplantation. Patients can get weekly titers, and consistently rising titers can be promptly treated with reduction of immunosuppression. The first-line CMV treatment includes ganciclovir with standard or high doses based on drug resistance testing. Resistant/refractory CMV results in significant morbidity and involves the use of both older (foscarnet, cidofovir) and novel agents such as maribavir, brincidofovir, and letermovir [22].

22.5.3 Graft-Versus-Host Disease (GVHD)

GVHD is a rare complication following solid organ transplant, with the highest incidence in visceral transplant recipients in up to 10% [23, 24]. Pediatric liver-inclusive visceral allograft recipients, who have had splenectomy or lymphocyte-depleting agents, are prone to develop this complication. The presence of circulating or tissue-penetrating donor immunocytes is an essential requirement for the diagnosis of clinically suspected GVHD. This potentially fatal complication is induced by a hereditary or acquired immune deficiency, which is thus a relative contraindication for visceral transplantation. Preceding or simultaneous bone marrow

transplantation to reconstitute the immune system, followed by visceral transplantation, has been reported with successful outcomes [25]. Previous studies have documented total repopulation of the recipient immune system with donor-derived multilineage complete chimerism in a few cases [2, 26]. Steroids remain the first line of treatment along with modulation of the primary immunosuppression. Steroid-refractory patients remain a challenge and, to date, no consensus has been achieved for a single agent second-line therapy [27].

22.5.4 Posttransplant Lymphoproliferative Disorder

With a combination of high-dose immunosuppression and an immature immune system, pediatric intestine recipients have a higher risk of developing posttransplant lymphoproliferative disorder (PTLD) than any other solid organ recipients [28]. The other likely contributing factor includes the large number of donor lymphocytes in the allograft [29]. With modification of immunosuppressive regimens over time, the incidence of PTLD in this population has fallen from 31% to 12–15% [28, 30]. Such improvement is likely to be related to increased use of lymphocyte depletion for induction, followed by lower maintenance immunosuppression. Risk factors for disease development include recipient age, EBV serostatus, degree of immunosuppression, splenectomy, and prior rejection.

Clinical presentation of PTLD varies depending on onset time and location. PTLD can present in the GI tract, occasionally at the stoma site [28], involving the risk of GI perforation, bleeding, and intussusception [31]. Later disease often presents as classic nodal lymphoma in the mesentery, lung, and central nervous system [32].

The most common subtype of PTLD is monomorphic PTLD, specifically DLBCL, among other subtypes; early lesions consist of plasma cell-rich lymphoid hyperplasia, polymorphic PTLD, and classical Hodgkin lymphoma-type PTLD [33]. Like other solid organ recipients, fist-line management of PTLD is with reduction of immunosuppression. Previous studies showed that rituximab alone has shown efficacy in intestinal transplant recipients with a high complete response rate [34, 35]. Localized tumor can be the target of surgical resection or radiation therapy. For refractory disease, conventional intensive chemotherapy may be indicated. Other treatment options include EBV-specific cytotoxic lymphocyte infusion therapy from a third party [36].

22.6 Outcomes

22.6.1 Patient and Graft Survivals

The most important outcome measures include patient and graft survival, establishment of nutritional autonomy, and QoL. In a University of Pittsburgh series, long-term outcomes following visceral transplantation in children and adults improved steadily with a 5-year patient and graft survival of 68% and 53%, respectively, with improvements in immunosuppression protocols (Fig. 22.3). Causes of graft loss in

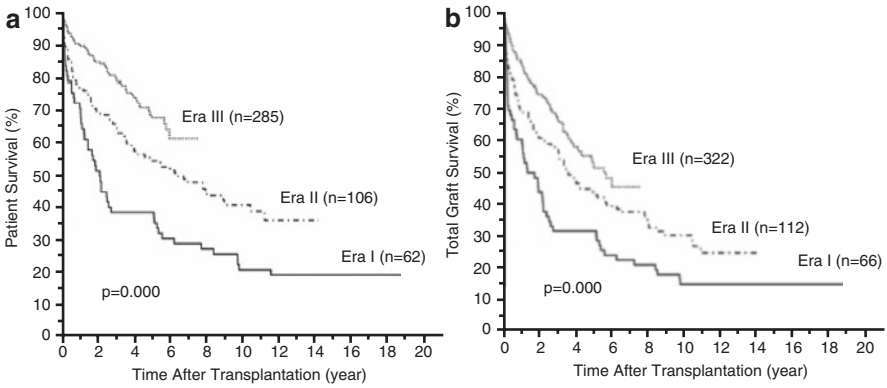

Fig. 22.3 Patient (**a**) and graft (**b**) survivals according to era of transplant in a single center. Era I, 5/90–5/94; Era II, 1/95–6/01; Era III, 7/01–11/08 (Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg. 2009;250:567–581)

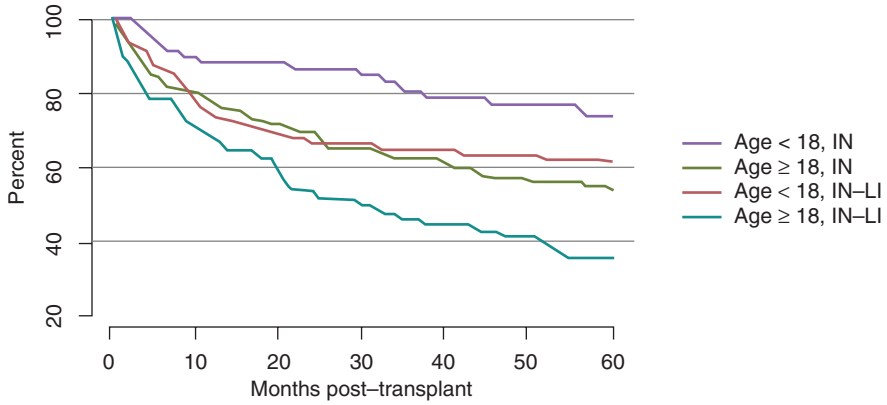

Fig. 22.4 Patient survival among visceral transplant recipients, 2008–2010, by age and transplant type. 1- and 5-year survival of pediatric intestine recipients was 88.1% and 74.6%, respectively. IN, liver-free visceral transplant; IN-LI, liver-inclusive visceral transplant (Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2016 Annual Data Report: Intestine. Am J Transplant. 2018;18 Suppl 1:254–290)

this series included technical complications (11%), rejection (20%), GVHD (1%), infections (11%), and PTLD (3%). Death beyond 5 years following transplantation was mainly from rejection and infection.

Current data from registry and large centers has shown 1-year patient and graft survival rates between 76% and 90% [2, 10, 37]. At 5 years, the global report showed patient and graft survival of 58% and 50%, respectively, with significant differences based on recipient age and graft type [3, 10]. Pediatric patients had a better survival compared to adults (Fig. 22.4). Differences in outcome are heavily

affected by center volume. According to the most updated data from large US centers, including Georgetown University and the Cleveland Clinic, a 5-year pediatric patient survival has continued to improve to 78–85% [37].

22.6.2 Growth and Nutrition

Oral aversion may persist after intestinal transplantation and can be a significant challenge for parents, physicians, and speech pathologists. The reported oral aversion rate following transplant is quite variable. One study showed that 45% of children continued to require enteral feeding within 2 years of transplantation [38]. A recent report focusing on 10-year outcome after pediatric intestinal transplantation revealed that 79% of recipients are maintained on exclusive oral diet, and only a small number require supplemental enteral nutrition in the long term, due to oral aversion or eating disorders [39].

Several studies documented improving growth and nutrition following visceral transplantation. Sudan et al. reported normal growth in 75% of 31 children [40], with more marked initial growth improvement followed by a gradual decrease in improvement. Venick et al. identified shorter hospitalizations and absence of rejection as markers of growth, while the use of peptide formulas and lower corticosteroid doses was associated with long-term growth and weight gain [41]. Additionally, long-term use of corticosteroids and other immunosuppressive medications often has a negative impact on physical growth. Steroid-free regimens were reportedly associated with improved growth and a lower rate of growth failure compared to regimens that include steroids. In one large study of 109 children receiving intestinal transplant, patients on a steroid-free regimen reached nutritional autonomy approximately 5 months sooner than patients on a regimen that included steroids. While Z-scores for height improved in both groups, there was a greater increase in Z-score in the steroid-free group (48% vs. 44%) [42].

22.6.3 Quality of Life

With an increased number of surviving patients, QoL has become an increasingly important subject in pediatric visceral transplant recipients. With the use of the child health questionnaires, well-designed studies showed physical and psychosocial function similar to that in healthy, normal children. These studies have shown improvement in many QoL domains with a better overall rehabilitative index than TPN [1, 43, 44]. The multifaceted QoL parameters in this population have been recently addressed in a comprehensive report reflecting the largest single center experience with more than two decades of follow-up[1]. Despite the lack of complete catch-up growth, the maintained intestinal graft function and nutrition in the long term allows many children to become independent from their parents and pursue education and employment. In this study, 66% of the survivors who were pediatric patients at the time of transplantation completed high school or college, with the

remaining currently attending special skills classes or high school. Seven survivors gave birth or fathered children after transplantation. The study identified a variety of developmental, neurologic, and behavioral disorders among visceral allograft recipients. Pediatric patients were noted to have a higher risk of neurologic, developmental, and behavioral disorders than adults. These include autism, developmental delay, attention-deficit/hyperactivity disorder, deafness, and paraplegia. This was attributed to organic brain dysfunctions that occurred as PN-associated complications during the early phases of neuronal, emotional, and physical development. A high education index was reported among all respective age groups with sustained cognitive, psychosocial, and physical function, including high scores on the Lansky and Karnofsky performance scales with normal functional activities in most survivors. In recent reports [1, 40, 45], transplant recipients had better QoL, with 12 domains scoring significantly better than those of the PN-dependent patients. These domains are anxiety, appearance, coping, sexuality, digestive symptoms, sleep, energy, optimism, impulsiveness/control, social support, and leisure activities. Depression continued to be a discriminating factor, with unfavorable scores before and after transplantation.

In another report, psychological, emotional, and social QoL measures improved significantly ($P < 0.05$) following transplantation. Morbidities included dysmotility (59%), hypertension (37%), osteoporosis (22%), and diabetes (11%), with a significantly higher incidence among adult recipients [43]. 88% of current survivors had normal functional status according to the Lansky and Karnofsky performance scales. Patients who had low performance scores had a history of neuropsychiatric disorders or had experienced allograft enterectomy or graft dysfunction.

A more recent report on a series of 34 long-term survivors of pediatric intestinal transplants focused on QoL in different pediatric age groups. Overall, QoL in pediatric intestinal recipients was acceptable compared to the standard population and improved with age and time from transplant. In preschoolers (age under 4 years) the physical domains such as feeding problems or sleeping disturbances scored low according to the evaluation of the parents, whereas physical and psychological well-being scored higher in older children, likely as a result of improvement of everyday life associated with the increase in time interval from the critical posttransplant phase and progressive increased acceptance of the posttransplant status [44].

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Long-Term Management of Intestinal Transplant Patients

23

Kadakkal Radhakrishnan and Charles B. Chen

23.1 Nutrition

The nutritional assessment is an integral component of the pre-transplant evaluation and helps to determine if a patient requires intestinal transplantation or if an intestinal rehabilitation program would be more appropriate. For those patients who undergo intestinal transplantation, monitoring nutritional status before and after surgery is critical to ensure that patients are meeting their goal nutritional requirements. Malnutrition may develop due to decreased intake, nutrient losses, and changes in metabolism. This can have a profound effect on pediatric patients and significantly impair their growth and development.

One of the main goals following transplantation is early initiation of enteral feeds [1, 2]. However, anatomical changes as well as the risk of rejection may make restoration of enteral autonomy difficult [3]. While almost all patients will initially be on parenteral nutrition, the initiation of enteral feeds is determined by multiple factors, including return of bowel function and adequate ostomy output [4]. Depending on the patient's ability to tolerate enteral nutrition, parenteral nutrition can be slowly weaned.

There is evidence that hydrolyzed or elemental formula can help nutrient absorption and limit food antigen overload which may trigger immune stimulation and increase the risk of graft rejection [3]. At our institution, both hydrolyzed and elemental formulas have been used extensively in transplant patients. The rate of feed advancement and choice of formula varies significantly. High stoma output and electrolyte abnormalities can complicate advancement of feeds in the post-operative period and may require cessation of enteral feeds. There is also debate about the optimal route of feed delivery, as some centers prefer jejunal feeds due to concern

K. Radhakrishnan (✉) · C. B. Chen
Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH, USA
e-mail: radhakk@ccf.org

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for gastroparesis following transplant [2]. At our institution, both gastric and jejunal feeds have been used. Oral feeds may be tried if a patient demonstrates tolerance of enteral feeding. However, patients who had difficulty with feeding prior to surgery can have significant oral aversion following transplantation. This may arise in patients on prolonged tube feeds or parenteral nutrition and requires oral rehabilitation therapy [5].

Micronutrient deficiencies are also frequently observed in intestinal transplant patients. Both macronutrient and micronutrient deficiencies may occur due to high stoma output, malabsorption, and poor intestinal motility [6]. One study reported micronutrient deficiencies in 95% of its post-transplant patients with iron, magnesium, zinc, and vitamin D deficiency being the most common [7]. Other complications include chylous ascites, fat malabsorption, and development of food allergies [3, 8]. The frequency of assessing nutritional laboratory studies at our institution is outlined in Table 23.1.

Anthropometric measurements along with nutritional requirements should be routinely assessed. Monitoring growth is critical, as many patients develop linear growth retardation at the time of the transplant, that may persist for years afterwards [9]. In younger patients receiving transplants, a positive trend in linear growth has been noted in individuals with earlier initiation of enteral feeds [10]. The use of corticosteroids and periods of feed discontinuation both contribute significantly to impairment of growth. Given these challenges, future research is needed to investigate new methods of nutritional evaluation as well as strategies to prevent growth retardation.

Table 23.1 Routine assessment of nutritional laboratory studies at the Cleveland Clinic

Laboratory study	Frequency of testing
Complete blood count Complete metabolic panel Magnesium Phosphorus Gamma-glutamyl transferase International normalized ratio	Initially every 1–2 weeks; can gradually decrease in frequency
Vitamin A Vitamin D Vitamin E Vitamin B12 Total and free carnitine	Every 3 months
Triene/tetraene ratio Copper Selenium Zinc Manganese	Every 3–6 months
Vitamin B1 Vitamin B6 Methylmalonic acid Folic acid	Every 6 months

23.2 Infections

Infections are one of the most common complications in the post-transplant period and represent a major cause of graft loss as well as morbidity and mortality [11–13]. Infections often occur despite decontamination of the gut following transplant and the use of prophylactic medications [14]. Close monitoring and treatment of developing infections is critical in this immunocompromised group. Additionally, careful consideration must be given to the choice of antibiotic, antiviral, and antifungal regimens as resistance may develop given their frequent use. While the timing of different infections may be variable, Table 23.2 shows a list of the most common infections as well as their typical time of presentation after transplant.

More than 70% of pediatric patients developed bloodstream infections, with the majority of these infections occurring within 3 months of transplant [15]. Bacterial infections can be seen in up to 93% of transplant recipients, with frequent sources being central venous catheters and intra-abdominal infections. *Enterococcus* species are one of the most common bacterial organisms and in one study were found in 52% of post-transplant patients [11, 15]. The higher rate of bloodstream infections in intestinal transplants compared to other solid organ transplants may be due to multiple factors, including greater immunosuppression and disruption of the gastrointestinal barrier due to surgery [11].

Fungal infection is also a feared complication and occurs in up to 25% of pediatric small bowel transplant patients [11, 16]. Patients receiving total parenteral nutrition and antibiotics had a significantly higher risk of developing fungemia [17]. The most common organisms are *Candida* species; however, *Aspergillus* infections have also been frequently described and have a much higher morbidity [16]. *Mucormycosis*

Table 23.2 Common infections following intestinal transplant

Infections	General timing of infections after transplant
Bacteria *Enterococcus* Coagulase-negative *staphylococcus* *Streptococcus* *Pseudomonas* *Enterobacter* *Klebsiella* *Escherichia coli*	Often within 1 month but can occur anytime, especially in patients with central lines [22]
Virus EBV CMV Adenovirus Other respiratory viral infections	Variable EBV: Variable, can occur years later CMV: Generally after 2 months [14] Adenovirus: Often within 6 months [21]
Fungus *Candida* *Aspergillus*	*Candida*: Intra-abdominal infections occur early (within 1 month); candidemia occurs late (after 6 months) [16] *Aspergillus*: Variable [23]

is particularly difficult to control, with a high mortality rate despite early therapy and debridement [18]. Intra-abdominal fungal infections typically occur within 1 month after transplant, while fungemia tends to occur more than 6 months after transplant [16]. Although data support the use of antifungal prophylaxis, the optimal regimen remains controversial [19].

Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are the most well-known viral infections following intestinal transplant. Infection with EBV prior to transplant affords a level of protection against development of the infection post-operatively [20]. EBV status is extremely important, as those who are donor positive/recipient negative (D+/R-) are at highest risk, while those who are donor positive/recipient positive (D+/R+) are at intermediate risk. Post-transplant lymphoproliferative disorder (PTLD) is one of the most dreaded complications of EBV infection. Many patients remain on long-term antiviral prophylaxis with ganciclovir, although the duration of treatment varies across institutions [1, 2]. Surveillance includes routine monitoring of EBV and CMV DNA in blood and tissue samples. Aside from EBV and CMV, other respiratory viruses including adenovirus must be considered [11]. Adenovirus can manifest with gastrointestinal and respiratory symptoms and may increase the risk of rejection. In one study, it was reported in up to 24% of patients and was most often found in the first 6 months after transplant [21].

Many institutions have implemented preventative strategies to decrease the frequency of infectious complications. Determination of immunization status as part of the pre-transplant evaluation is critical [20]. Both the donor and recipient must be carefully screened for infectious diseases, including CMV and EBV. Post-operatively, immunosuppression must be carefully managed, and the risk of rejection must be weighed against the risk of infection. Patients presenting with fever must be immediately evaluated, given the concern for sepsis and rejection. Patients should have a thorough infectious workup and be started on broad-spectrum antibiotics, with possible addition of antivirals and antifungals as well.

23.3 Monitoring Allograft Function and Surveillance for Rejection

One of the most significant challenges of intestinal transplantation is the development of acute or chronic rejection [24]. Periodic endoscopies through a temporary stoma may be performed in the early post-operative period to monitor for rejection [25]. Some institutions have implemented surveillance with twice weekly endoscopies during the first week after transplant, followed by reduction to weekly, then biweekly endoscopies [26]. The frequency of surveillance depends on multiple factors, but is often determined by clinical suspicion of rejection, such as the presentation of fever, abdominal pain, and increased stoma output.

The gold standard for monitoring allograft function is by endoscopic biopsies with subsequent histopathological examination [25]. However, current research has focused on the examination of non-invasive biomarkers in allograft surveillance. The presence of donor-specific antibodies (DSA) has been associated with rejection

and graft loss, and post-transplant DSAs have been found in up to 40% of intestinal transplant patients [25]. Although the significance in the pathophysiology of rejection has yet to be elucidated, the presence of de novo or pre-formed DSAs has been shown to negatively impact graft survival and lead to worse clinical outcomes [26]. Many transplant centers have implemented routine monitoring of DSA, although how DSA affects the next step in evaluation or management varies.

Other biomarkers include serum citrulline, which is produced by enterocytes, and can serve as a marker of small bowel mass [27]. One series of studies found that those who presented with acute rejection were noted to have lower citrulline levels [28], although other studies have disputed this association [29]. Nevertheless, the data suggest that citrulline has an excellent negative predictive value especially in ruling out severe acute rejection [30]. Another set of biomarkers include granzyme B and perforin, which play roles in the induction of apoptosis by cytotoxic T lymphocytes and natural killer cells [31]. These can be elevated during episodes of rejection; however, they may also rise in PTLD and viral infections. While these biomarkers have been used in certain situations, unfortunately they are generally not practical.

Visual graft surveillance represents a simpler, more accessible means of monitoring after intestinal transplantation [25]. However, traditional endoscopic surveillance has been reported to be normal in up to 37% of cases of histologically determined mild or moderate rejection [32]. The endoscopic appearance of the mucosa in rejection includes mucosal hyperemia, edema, loss of vascularity, and granularity [33]. Gross endoscopic appearance does not correlate well with histologic features, as one study showed normal endoscopic findings in up to 45% of patients with biopsy-proven rejection [34]. Multiple institutions have also used zoom-video endoscopy, which can magnify an image up to 100-fold and allows individual microvilli to be observed. However, the challenge again remained that while it could more reliably detect cases of severe rejection, it was more liable to miss cases of mild and moderate rejection [35].

Even with endoscopic biopsies, one challenge is that the distribution of rejection may be variable, and biopsies in only one region of the transplanted intestine may be insufficient to diagnose rejection [32, 33]. Therefore, sampling of different regions of the graft is important to maximize detection. Jejunal biopsies should be obtained in patients where there is clinical suspicion of rejection but the ileoscopy biopsies are negative [32].

23.4 Immunosuppression and Management of Rejection

Acute cellular rejection (ACR) is the leading cause of graft loss within the first 2 months after transplant. Histological changes associated with ACR include apoptotic bodies, increase in lamina propria inflammation, and mucosal injury [33]. The grading system for acute cellular rejection is shown in Table 23.3. Antibody-mediated rejection (ABMR) is less commonly encountered; however, histological features of ABMR include capillary congestion, neutrophilic infiltration, and

Table 23.3 Grading of acute cellular rejection[a]

Grade	Histopathology	Frequency (percent of total episodes of rejection)
0 (no ACR)	Normal intestinal mucosa and villous architecture	33.9
Indeterminate	Mild villous blunting, slight increase in inflammatory infiltrate in lamina propria, rare crypt apoptotic bodies	49.1
1 (mild ACR)	Mildly increased inflammatory infiltrates in lamina propria, increased crypt apoptotic bodies	12.6
2 (moderate ACR)	Marked villous blunting, moderate increase in inflammatory infiltrates in lamina propria, numerous apoptotic bodies, crypt dropout	3.7
3 (severe ACR)	Mucosal breakdown, significant increase in inflammatory infiltrates in lamina propria, crypt damage and loss	0.8

[a]From Ruiz et al. [48] and Remotti et al. [33]

epithelial injury [36]. Chronic rejection is more progressive and can be a cause of late graft failure. Histologic features include ischemic changes, low-grade apoptosis, and fibrosis of the lamina propria [33]. Chronic rejection can be insidious and may require surgical exploration for adequate detection. Intestinal transplants that include the liver have a lower rate of rejection, as the presence of a transplanted liver allograft is thought to protect other organs from rejection [37, 38].

The most commonly used first-line immunosuppressive agents include corticosteroids and tacrolimus [39]. However, some institutions have used tacrolimus for maintenance without corticosteroids. Target serum tacrolimus trough levels in the first 3 months after transplant are generally 10–15 ng/dL [39]. At our institution, the tacrolimus goal is reduced to 6–8 ng/dL at 3 months after transplant if there are no episodes of rejection. Corticosteroids are also used as adjunctive therapy and slowly weaned if rejection does not occur.

Tacrolimus, a calcineurin inhibitor, has several major side effects including hyperkalemia, hypomagnesemia, hyperglycemia, nephrotoxicity, and hypertension [40]. This has prompted some centers to use sirolimus for maintenance immunosuppression, either in combination or as an alternative to tacrolimus. Studies have shown that sirolimus helps to decrease the rate of rejection when used in conjunction with tacrolimus [41, 42]. This has allowed sirolimus to become a rescue therapy to avoid potential adverse effects associated with high-dose tacrolimus [40]. Nevertheless, the increased risk of thrombosis and decreased wound healing associated with sirolimus has made it less desirable as a first-line immunosuppressant [40]. Other less frequently used medications include mycophenolate mofetil and cyclosporine [43].

When patients present with an episode of acute rejection, one frequently used regimen is to first administer one or multiple intravenous boluses of corticosteroid followed by a steroid wean. Some centers increase the tacrolimus dose to a goal level of 10–15 ng/dL, although the effectiveness of this approach is not clear. Antilymphocyte antibodies may be given in cases of more severe or corticosteroid-unresponsive rejection.

Many institutions also routinely use induction therapy, with alemtuzumab, antithymocyte globulin, or basiliximab [2, 44, 45]. Our institution has used intravenous immunoglobulin, infliximab, and rituximab in several regimens for treating rejection. One regimen that has been well described is administration of a lymphoid depleting agent as pretreatment, followed by immunosuppression with low-dose tacrolimus. Such multi-drug regimens have been shown to decrease the incidence of PTLD but are associated with a higher rate of infections [46, 47]. There is evidence to suggest that these induction regimens also help to improve graft survival rates and clinical outcomes [42].

23.5 Renal Dysfunction and Hypertension

Complications of intestinal transplantation may lead to renal dysfunction, including the development of acute kidney injury (AKI) and chronic kidney disease (CKD) [49]. Many risk factors are implicated in the development of renal dysfunction, including older age and previous episodes of AKI following transplantation. Further worsening of renal function may occur as a result of preoperative, intraoperative, and post-operative complications such as sepsis, ischemia, and hypotension [50]. Medications also play a significant role. In particular, calcineurin inhibitors can cause nephrotoxicity, likely through a direct toxic effect on the renal tubule and vascular endothelium [50, 51]. Tight control of calcineurin levels and minimizing nephrotoxic medications are critical in patients who are at risk of renal dysfunction. This has led to the use of sirolimus as an alternative therapy in order to minimize calcineurin inhibitor use. Additionally, maintaining appropriate volume status is often difficult when patients develop increased ostomy losses or other causes of volume loss [49]. Volume depletion and fluid shifts, when coupled with alterations in circulation, may increase the risk of CKD.

There is evidence to suggest that pediatric patients may have greater ability to regain renal function compared to adults [52]. Nevertheless, patients with more severe renal disease may require renal replacement therapy including dialysis or even renal transplantation [53]. Management of renal disease is particularly challenging in this population as immunosuppression may have to be frequently adjusted due to other comorbid conditions including rejection and infection. It is therefore imperative to perform routine monitoring of kidney function to help prevent or delay progression to CKD.

Hypertension has also been reported as a long-term complication and can affect more than 20% of pediatric patients [53]. Hypertension in transplant patients may be especially difficult to treat and may require multiple anti-hypertensive medications including calcium channel blockers, angiotensin-converting enzyme inhibitors, and beta blockers. On the other hand, diabetes is less frequently observed and was reported in only 4% of patients in one study [53]. Both of these complications are partly iatrogenic, owing to the use of immunosuppressive regimens including calcineurin inhibitors and corticosteroids.

23.6 Graft vs Host Disease

Graft vs host disease (GVHD) is a well-known complication of intestinal transplantation with reported rates of 5–10% in pediatric patients [54]. It is thought that the large quantity of alloreactive lymphocytes in the small bowel graft increases the risk of GVHD. Risk factors include multivisceral transplant, younger age, and a history of recipient splenectomy [55, 56]. The bone marrow and skin are often affected and the diagnosis is made clinically with supporting histological features [55]. This is in contrast to bone marrow GVHD, where more systemic manifestations are observed. Methods of evaluation include endoscopy for patients with a high suspicion of gastrointestinal involvement and skin biopsies for those with cutaneous findings. Donor T-cell chimerism in the post-operative period can serve as a marker of GVHD, with treatment of GVHD being associated with decreasing chimerism [57].

The primary treatment of GVHD is with corticosteroids. For those with steroid-resistant GVHD, secondary agents have been used that target either the cytotoxic action on effector cells or inhibit cytokines in the GVHD pathway. Although patients who respond to high-dose steroids have a good prognosis, those who fail to respond after 5 days of steroids have a much higher mortality [54]. The management of steroid-resistant GVHD is more controversial, although tacrolimus and antithymocyte globulin have been frequently used in treatment protocols with variable efficacy [54]. Infection is a common cause of mortality, seen in 55% of GVHD patients in one large study of adult and pediatric patients [56]. Infection prophylaxis is an important part of the treatment to help prevent the development of opportunistic infections [57]. Patients may develop hematologic abnormalities such as neutropenia which may necessitate the use of granulocyte colony-stimulating factors. As GVHD often presents early in the post-transplant period, delays in diagnosis may result in a missed opportunity to implement early intervention [55]. Consultation with a bone marrow transplant specialist is critical in order improve outcomes for the patient.

23.7 Malignancy

There is an increased risk of de novo malignancies or recurrence of existing malignancies after intestinal transplant. Malignancies have been increasingly observed as more patients are surviving longer following transplant. The risk is increased with continued use of immunosuppressive medications which impairs the body's ability to perform immunologic surveillance [58, 59]. It is also thought that there is an increased exposure to environmental oncogenes in the setting of dysfunctional immune surveillance [13, 46]. Although PTLD is the most commonly reported malignancy, non-lymphoid cancers such as non-melanotic skin cancers may also develop [46].

PTLD is seen more frequently in patients with intestinal transplants compared to other solid organ transplants [60, 61]. PTLD has been reported in more than 30% of intestinal transplant patients, although the incidence has decreased to

12–15% with recent advances in monitoring [62]. The large volume of lymphoid tissue in the allograft and increased immunosuppression are thought to increase the risk of PTLD [63].

The incidence of PTLD is greatest in patients who are EBV(−) who receive a graft from an EBV(+) donor [64], although other risk factors include younger age at transplant, use of immunosuppressive medications, and treatment for rejection [46]. The risk is especially high in patients under the age of 25, in which there is a 50-fold increase in the risk of developing de novo cancers [59]. The most important method of controlling EBV proliferation and decreasing the risk of PTLD is by reducing immunosuppression; however, this must be balanced with the increased risk of rejection [64]. Rituximab has been used for treatment of PTLD as well as for pre-emptive treatment of elevated EBV titers [65, 66]. Periodic monitoring of viral loads is therefore critical. One study reported that EBV viral loads of less than 40 genome copies per 10,000 peripheral lymphocytes for 6 months after intestinal transplantation had a high negative predictive value for the development of PTLD [67]. In some cases, the intestinal graft may need to be explanted if it is affected by PTLD.

Close monitoring and routine screening are critical, as malignancies may not develop until many years after transplant. Treatment of malignancies often requires additional surgeries for resection of tumors, radiotherapy, or chemotherapy [46]. Cancers that develop in transplant patients are often more aggressive compared to those in non-transplant patients [68]. The need to treat both intestinal transplant and malignancy increases morbidity and mortality and may make management more challenging. Another risk for the development of malignancy is the high lifetime exposure to ionizing radiation, which is generally due to frequent imaging such as with computed tomography. The use of alterative imaging techniques such as ultrasound can help to minimize radiation exposure in these individuals [58, 69].

23.8 Long-Term Development and Quality of Life

Given the numerous advances in the field, more patients are surviving longer after transplantation. As mentioned previously, many children have problems with growth, and nutritional status should be routinely evaluated. Close monitoring of bone health is critical given prolonged use of corticosteroids and other medications that increase the risk of osteopenia [2]. From a neurodevelopmental standpoint, patients may be susceptible to cognitive and motor delays, which can persist for years after transplant [70]. The need for anesthesia with various procedures or surgeries throughout a patient's life can also impact their neurocognitive development [71]. Additionally, patients with prior developmental delay may continue to experience delays post-operatively [72]. As patients may require special education and other services such as speech and physical therapy, referral for early intervention can help to maximize a patient's developmental potential [73].

In addition to optimizing medical management, evaluating and monitoring psychosocial functioning is important in improving the patient's quality of life. The pre- and

post-transplant period can be a significant source of stress for both patients and caregivers alike. The addition of a mental health specialist to the transplant team can be beneficial in helping pediatric patients manage their psychosocial issues. There may be differences in perception between patients and their caregivers, which could affect compliance with the plan of care. One study reported that pre-adolescent transplant patients often perceived their physical and psychosocial functioning as similar to that of normal school children, while parents perceived lower general health and physical functioning in those patients compared to normal children [74, 75].

Socioeconomic status and caregiver education also play important roles in long-term development and quality of life [76]. Frequent hospital admissions and treatments can lead to family disruption and affect continuity with school and extracurricular activities. Additionally, intestinal transplant patients who have reached adolescence may become less compliant with taking their medications and increase their risk of developing complications [76]. The transition from pediatrics to adult care may be difficult and would benefit from a multidisciplinary team to facilitate the needs of the patient. Given all of these challenges, further research is needed to elucidate factors that improve quality of life and develop interventions to ameliorate psychosocial comorbidities.

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Part III

Pancreatic Transplant

Pediatric Pancreas Transplantation

24

Jens G. Brockmann

24.1 Introduction

Guidelines for pancreas transplantation became first available in 2021 in the form of recommendations generated by a group of experts at a world conference [1]. Their main message was that both simultaneous pancreas-kidney transplantation (SPK) and pancreas transplantation alone (PTA) can improve long-term survival, and all types of pancreas transplantation will improve the quality of life. Pancreas transplantation may also improve secondary complications of diabetes. Therefore, advantages of pancreas transplantation apparently surpass its potential disadvantages. PTA is reported to increase risk of mortality only in the early period after transplantation, but is associated with improved life expectancy thereafter. Additionally, preemptive SPK, when compared to SPK performed in patients undergoing dialysis, appears to be associated with improved outcomes. Inevitably, time on dialysis has negative prognostic implications in SPK recipients. Increased long-term survival, improvement in the course of diabetic complications, and amelioration of quality of life justify preferential allocation of kidney grafts to SPK recipients. Unfortunately, the level of evidence supplementing these recommendations is weak and is basically all based on the experience gained in adult pancreas transplantation. Initial reports of pediatric transplantation were not encouraging and might have haltered the pancreas transplantation in the pediatric population. For adults most pancreas transplants are performed as either SPK or PAK transplants; the majority of recipients suffer from advanced diabetic nephropathy, a condition that has been associated with an increase in all-cause mortality due to higher incidence of micro- and macrovascular complications of diabetes. Additionally, pancreas transplantation is a relatively low volume but high complexity procedure that has never gained widespread acceptance and few patients are referred for pancreas transplant alone at

J. G. Brockmann (✉)
Organ Transplant Centre of Excellence, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

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a stage when extrarenal diabetic complications are still reversible in nature. Recently, there is an additional decline in the number of pancreas transplants in the United States, Europe, and the United Kingdom.

The above-mentioned recommendations for pancreas transplantation should also be valid for the pediatric population despite a clear position statement by the American Diabetes Association where one recurrent theme of this position statement paper is that "children are not little adults," although in those latest recommendations transplantation is not mentioned at all [2]. Pediatric-onset diabetes is different from adult diabetes because of its distinct epidemiology, pathophysiology, developmental considerations, and response to therapy [3, 4].

24.2 Incidence of Diabetes in the Young

The SEARCH for Diabetes in Youth study found a 21 percent rise in prevalence of type 1 diabetes from 2001 to 2009 in youth aged 0–19 years, with increases observed in all sex, age, and race/ethnic subgroups except those with the lowest prevalence (0–4 years old and American Indians) [5]. Incidence of type 1 diabetes in pediatrics has also increased. Adjusted risk for developing type 1 diabetes increased by 1.4% annually between 2002 and 2012, with significant increases in all age groups except those 0–4 years old [6].

Type 1 and 2 diabetes in adolescents with normal renal function confer a significantly increased risk for ESRD. Type 1 accounting to approximately 85 percent of the diabetes of the young is associated with younger age at ESRD onset (median age, 36.0 vs. 40.5 years), while type 2 is associated with higher mortality rates. During a follow-up period of 1183 adolescents with type 1 and 196 with type 2, mortality rates were higher in type 2 diabetes as compared with type 1 and controls (8.7%, 2.2%, and 2.7%, respectively) [7].

Nowadays earlier onset of either type 1 or type 2 diabetes results in a longer duration of diabetes at any adult age than in former years. Thus, women with youth-onset diabetes are now more likely to have diabetes during their pregnancies resulting in increased offspring risk for both obesity and diabetes. In addition, complication development is duration dependent, so persons with youth-onset diabetes now face chronic kidney disease and dialysis, myocardial infarction, and stroke at younger ages than persons who develop diabetes as adults, resulting in greater life-years lost and higher health-care costs [8].

24.3 Incidence of Diabetes Mellitus and End-Stage Renal Disease (ESRD) in the Young

Diabetes is the single largest cause of ESRD in the United States. In 1985, the adjusted prevalence of treated ESRD attributed to diabetes was 103 cases per million population, these patients accounting for 19 percent of prevalent treated ESRD in the United States; by 2012, the prevalence had risen to 731 cases per million

population, representing 35 percent of prevalent treated ESRD in the United States (44% of dialysis patients and 23% of kidney transplant patients). About 30 percent of persons with type 1 diabetes and 10–40 percent of those with type 2 diabetes eventually develop kidney failure.

In 1985, the adjusted incidence of treated ESRD attributable to diabetes was 45 cases per million population. The rate increased to 170 per million by 2005 and leveled off thereafter. The increasing prevalence of diabetes and more inclusive criteria for initiating renal replacement therapy contributed to higher incidence rates of diabetes-related ESRD over time. Trends in the incidence of treated ESRD due to diabetes differ broadly by age and race/ethnicity. A shift towards a younger age at onset of type 2 diabetes among some minority populations may be partly responsible for the secular trends in ESRD incidence observed in the younger groups. Epidemiologic data on racial/ethnic differences in the incidence of treated ESRD in type 1 diabetes are sparse. Young persons or those who are treated with insulin are often misclassified as having type 1 diabetes. According to USRDS data, of all new cases of treated ESRD due to diabetes between 2008 and 2012, 91% were attributable to type 2 diabetes. In total the age group from 0 to 19 years contributes only to one percent of patients suffering from ESRD [9]. The reason for the very little incidence of ESRD in children is that diabetes usually requires long-lasting course (median approximately 20 years) to irreversibly alter kidney function.

24.4 Pancreas Transplantation for Pediatric Recipients

Although the first documented simultaneous pancreas and kidney transplant (SPK) in a pediatric recipient was reported in 1981, there is no or just very little published evidence for whole-organ pancreas transplantation for the pediatric age group. Until 1995 referring to the International Pancreas Transplant Registry there were only eight reported cases for SPK in this age group [10]. Only one single case of PTA in a child has been reported thus far for a 13-year-old male recipient suffering from severe labile diabetes and hypoglycemic unawareness resulting in frequent episodes of hypoglycemia and hospital admissions [11]. Combined kidney and islet transplantation has been described only once for a pediatric recipient aged 6. Despite a better glucose control this recipient did not achieve insulin independence applying this approach [12]. A much bigger body of evidence exists for total pancreatectomy and islet cell autotransplantation (TPIAT) for pediatrics suffering from chronic pancreatitis achieving insulin independence of 40–60 percent at 1 year following this particular procedure [13, 14]. Utilization of the genuine recipient islets for TPIAT does not require posttransplant immunosuppression for this particular group of patients, but is unfortunately available in few specialized centers providing capacity for islet separation only.

Referring to the OPTN (Organ Procurement and Transplantation Network) database as of end of June 2022 out of a total of 35,794 pancreas transplants, 809 were performed for patients aged 0–17 years. Their absolute and relative distribution is presented for solitary and SPK transplantation as presented in Table 24.1. Only one living donation has been described within the age group of 11–17 years for SPK [15].

Table 24.1 OPTN numbers for pancreas and pancreas/kidney transplantation stratified for different pediatric age groups as of end of June 2022 [15]

Total	Pancreas transplant *n* = 9219	Kidney/pancreas transplant *n* = 26,575
Pediatric	*n* = 736 (0.7%)	*n* = 73 (0.2%)
Recipient age	***n* (%)**	***n* (%)**
<1 year	179 (2)	8 (0.03)
1–5 years	376 (4)	23 (0.08)
6–10 years	94 (1)	18 (0.07)
11–17 years	87 (1)	24 (0.09)

Stratification for the type of diabetes revealed that only one pancreas transplant each for the age group <1 year, as well for the age group 1–5 years, two for the age group 6–10 years, and six for the age group 11–17 years were performed for type I diabetics. Type I diabetes for SPK recipients was only described for two in the age group 6–10 years and five within the age group 11–17 years. The latter age group revealed the one additional type II diabetic as indication for transplantation [15].

Scarcity of publication for pancreas transplantation in the pediatric population with the consequent lack of outcome analysis renders interpretation hypothetical. Nevertheless, it appears logic that the recommendations for the adult population should as well apply for the young. Failure to thrive secondary to end-stage organ disease in the infant and pediatric age groups provides even stronger reason for the mandate of solid organ transplantation in these age groups. Not just physical, but even more important mental development will be regained following solid organ transplantation for especially renal anddiabetically impaired children.

24.5 Reason for Pediatric Pancreas Transplantation

As in adults, cardiovascular disease is the most important cause of death in adolescents and young adult patients suffering of end-stage renal disease (ESRD) since childhood [16]. This concerns patients on dialysis as well as transplant recipients given that a long duration of dialysis during childhood is an extra mortality risk factor [17]. Congenital anomalies of the kidney and urinary tract (CAKUT) are the single most frequent causes for ESRD in children, associated with lower mortality, when compared to other causes of ESRD in childhood [18]. Age at dialysis initiation is a key determinant of patient survival. Registry data consistently showed that compared with adolescents, mortality risk is approximately four times higher in children <5 years of age at dialysis initiation, and 1.5 times higher in children >5 years of age [19–21]. Mortality risk remains the highest in neonatal and infant dialysis patients [22], who are technically challenging to treat due to small body size, a high risk of infection, difficulties in nutrition and growth, and a high prevalence of severe comorbidities [23, 24]. These challenges and a perceived unacceptable quality of life are important factors in the decision to withhold or withdraw treatment in some of these children [25, 26]. Moreover, transplantation is often not

feasible due to the small size of the child relative to the large donor kidney and is usually recommended after 18 months of age or having beyond 10 kg of body-weight. Growth retardation, which is highly prevalent in these children, further delays transplantation and thus increases time on dialysis, which in turn increases mortality risk in this already vulnerable population [23, 26]. Nonetheless, relatively good clinical outcomes have been reported, and survival has improved significantly in this group. An international collaboration recently demonstrated a 5-year survival of 76 percent and a transplant probability of 55 percent, concluding that relatively good survival may be achieved in neonates despite the high prevalence (73%) of comorbidities [23].

Growth failure in the pediatric RRT (renal replacement therapy) population may reflect disease severity and is associated with increased mortality. In the United States, every SDS decrease in height increased mortality risk by 14 percent. This effect is particularly evident in children <14 years of age [27]. A report from North American Pediatric Renal Trials and Collaborative Studies demonstrated that mortality risk was twice as high in children with a height SDS <2.5 compared with those of normal height. Both short (<third percentile) and tall (>third percentile) stature at RRT initiation were associated with an increased risk of death, although tall stature was seen only in a small group of white children with elevated BMI (>95th percentile) [28].

No studies have specifically investigated a possible effect of sex on mortality in the pediatric ESRD population, but girls seem to have a higher mortality risk than boys [29]. In the United States, girls >5 years of age on dialysis had a 27% increased mortality risk compared with boys, although this effect was less pronounced in younger children. Girls had an 18 percent higher cardiovascular-related and a 37 percent higher infection-related mortality risk compared with boys [30, 31]. A potential explanation was suggested by a European study demonstrating a 23 percent decreased probability of preemptive transplantation in girls compared with boys. This disparity was mostly explained by the fact that girls tended to progress faster to ESRD and by differences in age and primary renal disease distribution. Other potential nonmedical factors, such as patient, parental, and physician attitudes toward transplantation, may also play a role [32].

Time spent on dialysis impacts mortality risk, which is highest during the first year of treatment, and reflects the intrinsic mortality risk of initiating dialysis. In the United States, mortality rates reach 48 per 1000 patient-years during the first month, peak during the second month at 57, then slowly decrease to 28 during months 9–12 [29]. Although there is lacking data in the pediatric population, two single-center US studies demonstrated that infants with oligoanuria had a higher mortality risk compared with infants with residual renal function [33–35], and others have demonstrated a positive effect of residual renal function on growth and nutrition [36–38]. Kidney transplantation, therefore, is considered the treatment of choice for ESRD in children [30, 39], because it is associated with a better quality of life, productivity, and growth of children and longer patient survival than what can be achieved by any other modality of long-term dialysis [40]. The most favored ESRD treatment modality in children is renal transplantation, but a lack of health-care resources and high patient mortality in the developing

world limit the global provision of RRT and influence patient outcome [41]. Now most registries report that approximately two-thirds of children and adolescents on ESRD programs have a transplant [42]. Beginning with the first kidney transplants in the 1950s, children experienced poorer patient and graft survival rates than adult patients. Today pediatric kidney transplant outcomes are markedly improved and younger children today experience better long-term graft survival than adults [43]. There is no clear evidence how much impact pancreas transplantation in the form of SPK can contribute to improvement in survival and of the ability to thrive in young diabetic suffering from ESRD. For non-uremic children suffering from severe labile diabetes and episodes of life-threatening hypoglycemic unawareness, PTA might be an attractive therapeutic option. However, a minority of pancreas transplants performed worldwide are PTA because the risks of surgery and especially life-long immunosuppression counterbalance the potential benefits of an insulin-free state. About 5% of all PT have been PTA overall, but only 0.4% of PT have involved recipients under 21 years of age [44].

Evolution of pancreas transplantation might have been halted due to initial unfavorable results such as from the University of Minnesota group describing four PTA cases in pediatric recipients [45]. In three, a deceased donor graft was used and all of them have lost their graft within the first 6 months due to different causes (rejection, infection, or pancreatitis); the fourth pediatric recipient had a living donor and lost the graft 5.5 years post-transplant to rejection [46]. Long-term pancreas graft survival appeared to be a challenge in pediatric.

Refinements in surgical technique [47–49], constant improvement in perioperative management, mid- and long-term immunosuppression, and superior outcomes for pediatric kidney transplantation should nowadays qualify children suffering from severe labile diabetes and episodes of life-threatening hypoglycemic unawareness the option for PTA and SPK for children suffering from ESRD and insulin-dependent diabetes mellitus no matter whether ESRD is secondary to diabetes or initial hemolytic uremic syndrome. Restoration of endocrine hemostasis with its obvious benefits for physical and mental development might be yet another strong argument considering pediatric patients for pancreas transplantation and giving the pediatric waiting list patient higher priority as it is already been practiced for the children awaiting a kidney transplant only.

24.6 Transplantation of Pediatric Donor Organs

The shortage of deceased donors for simultaneous pancreas-kidney transplantation has prompted the use of deceased donor organs from pediatric donors. Reluctance due to potential higher technical complications has been overcome following superior result in utilizing pediatric donor kidneys only. For SPK transplantation from donors aged <18 years, there was significant improvement for the 10-year kidney and pancreas graft survival rates which are 80 percent and 72 percent, respectively, compared to pancreas and kidney graft survival rate which is 61 percent from donors ≥18 years. Additionally, 5 years post-transplant, blood glucose, HbA1c, and creatinine clearance were significantly better in recipients from pediatric donors [50].

24.7 Summary

ESRD and insulin-dependent diabetes present with increasing incidences worldwide for adults and children. In the pediatric population ESRD is associated with higher mortalities disfavoring younger age and female sex. Youngest patients requiring renal replacement therapy bear the highest mortality risk. Global disparities persist in the provision of RRT and outcomes in the pediatric ESRD population, even among middle- and higher-income countries. Patient survival has improved substantially over recent decades in both dialysis and transplant populations. Patient survival is multifactorial, largely dependent on access to treatment, country health expenditure, disease etiology, age, transplant feasibility, growth failure, sex, BMI, race, and presence of comorbidities.

- PTA (pancreas transplant alone) should be offered for pediatrics with severe labile diabetes and life-threatening episodes of hypoglycemic unawareness.
- SPK should be offered to insulin-dependent pediatrics with ESRD considered for kidney transplantation for there is no difference in immunosuppression once a pancreas graft is included.
- Islet auto-transplantation should be offered to children with chronic pancreatitis with indication for total pancreatectomy.

Pediatric donors represent a valuable source of organs, providing excellent short- and long-term outcomes. Age matching of deceased donor organs and prioritization of young pancreas waiting list recipients should be applied in pancreatic organ allocation as it is already practised in kideny transplantation.

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25 Total Pancreatectomy and Islet Auto-Transplantation for Chronic Pancreatitis Children: Pre-Surgical Evaluation, Patient Selection, the Surgical Procedures, Islet Isolation Procedure, and the Early Inpatient Management

Ellen Florek and Srinath Chinnakotla

Abbreviations

CP	Chronic Pancreatitis
IEQ	Islet Equivalents
TP-IAT	Total Pancreatectomy Islet Auto-transplantation

25.1 Introduction

Chronic pancreatitis (CP) is an uncommon diagnosis in children, with an estimated incidence of less than 1 case per 200,000 [1]. Unlike adults, the etiology of chronic pancreatitis in children is most commonly due to genetic mutations, PRSS1, SPINK1, and CFTR genes [2, 3]. A recent study of children with chronic pancreatitis demonstrated a genetic etiology in 67% of cases, while obstructive etiologies, including biliary calculi and congenital anatomic abnormalities, made up 33% [3]. Some of these patients had both genetic and obstructive etiologies, and 11% of patients at no known risk factors at all (idiopathic). Congenital anatomic abnormalities associated with pancreatitis include pancreas divisum, annular pancreas, intestinal duplication cysts, anomalous pancreaticobiliary junction, and choledochal cysts [4–8].

E. Florek · S. Chinnakotla (✉)
Department of Surgery, University of Minnesota Medical School, Minneapolis, MN, USA

University of Minnesota Masonic Children's Hospital, Minneapolis, MN, USA
e-mail: chinni@umn.edu

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The first line of treatment of childhood CP includes narcotic analgesics, pancreatic enzyme supplementation to minimize pancreatic stimulation, nerve block procedures, and endoscopic decompression of obstructive disease by stone extraction, sphincterotomy, stricture dilation, and stent placement [9, 10]. Children who fail medical or endoscopic interventions qualify as surgical candidates. The various surgical interventions include partial resection (Whipple's procedure, distal pancreatectomy), drainage procedures such as lateral pancreaticojejunostomy (such as Puestow), or variants (such as Frey, Beger, or Duval procedures) [11]. Patients can obtain pain relief from these procedures, but due to the diffuse nature of CP, pain eventually recurs in up to 50% of patients [12–17]; Despite the aforementioned interventions, exocrine and endocrine insufficiency can still develop over time [18].

A novel approach to treatment of CP was developed in 1977, when the first human total pancreatectomy with islet auto-transplantation (TP-IAT) was performed by Dr. David Sutherland at the University of Minnesota [19, 20]. The total pancreatectomy removes the source of the pain and theoretically eliminates risk of pancreatic cancer. In isolation, however, a total pancreatectomy would lead to a lifetime of brittle diabetes. The goal of the islet auto-transplantation is to prevent or minimize TP-related diabetes. Isolated islets of Langerhans are infused back into the patient, most typically via the portal vein, and eventually engraft in the sinusoids of the liver [19]. Following success at our institution, TP-IAT is now increasingly being used to treat children with chronic pancreatitis refractory to medical and endoscopic treatment. To date, over 200 cases have been performed worldwide [21–23]. This book chapter will review the indications, surgical procedure, islet isolation, and early post-operative care.

25.2 Selection of Patients for TP-IAT

TP-IAT should be considered in children who have failed medical and endoscopic therapy and have impaired quality of life as indicated by the inability to attend school or participate in ordinary activities [21–25]. Due to the extensive nature of the operation and the potential complication of lifelong diabetes, patients must be carefully selected to ensure that a TP-IAT will provide more benefit than harm. Reliable family support and treatment of mental health comorbidities are essential for successful post-operative outcomes in children [24].

The child should have an unequivocal diagnosis of chronic pancreatitis before undergoing TP-IAT. The Minnesota Criteria guide selection of appropriate patients at our institution and are listed in Table 25.1 [21, 25]. All patients are discussed at a multidisciplinary committee, and surgery is scheduled only after approval from the committee.

Pre-operative evaluation of islet function should include fasting glucose, hemoglobin A1C, C-peptide levels, and oral or intravenous stimulatory tests [22, 24]. Such measures may help estimate the likelihood of successful islet isolation [26].

Table 25.1 Criteria for a TP-IAT, University of Minnesota

Definitions
Chronic pancreatitis (CP)
Chronic abdominal pain, lasting more than 6 months; features consistent with CP; and evidence of CP by at least one of the following:
1. Morphologic or functional evidence of CP [per computed tomography (CT) of abdomen indicating calcifications, or per endoscopic retrogradecholangiopancreatography (ERCP)]
2. At least 6 of 9 criteria positive for CP per endoscopic ultrasound (EUS)
3. At least 2 of the following:
a. Findings suggestive of CP (abnormal duct or side branch) per secretin-enhanced magnetic resonance cholangiopancreatography (sMRCP) or magnetic resonance imaging (MRI) T1 evidence of fibrosis
b. At least 4 of 9 criteria positive for CP per EUS
c. Abnormal exocrine pancreatic function test results (peak bicarbonate <80)
OR
Relapsing acute pancreatitis (relapsing AP)
1. Three or more episodes of documented AP (elevated amylase or lipase, CT evidence) with ongoing episodes for more than 6 months and with disabling interval pain similar to AP pain
2. No evidence of current gallstone disease (patients with gallstones should undergo a cholecystectomy) and no evidence of other correctable conditions such as AP
OR
Documented hereditary pancreatitis with compatible clinical history
Indications for a TP-IAT (must have all of below)
1. Documented CP or relapsing AP with chronic or severe abdominal pain, directly resulting in at least one of the following:
a. Chronic narcotic dependence (narcotics required on a daily or near-daily basis for >3 months)
b. Impaired quality of life (QOL), per the RAND Medical Outcomes Study 36-item Short Form (SF-36) health survey
2. Complete evaluation with no reversible cause of CP or relapsing AP present or untreated
3. Unresponsiveness to maximal medical therapy and endoscopic therapy
4. Ongoing abdominal pain requiring routine narcotics for CP or relapsing AP
5. Adequate islet function (i.e., either no diabetes or noninsulin-requiring diabetes with positive C-peptide levels)
Contraindications for a TP-IAT
• Active alcoholism (to be considered for a TP-IAT, patient must be abstinent for 6 months with documented success of therapy)
• Pancreatic cancer
• End-stage pulmonary disease, cirrhosis, or severe arteriosclerotic heart disease
• Poorly controlled psychiatric illness
• Inability to comply with post-operative regimen
• Intraductal papillary mucinous neoplasia (patient should undergo an IAT only as part of a clinical trial)
• Illegal drug usage (to be considered for a TP-IAT, patient must be abstinent for 6 months with documented success of therapy)

25.3 Surgical Considerations in Pediatric Patients [21]

The resection is shown in Fig. 25.1. The main variation in the surgical technique for children receiving an islet auto-transplantation is preserving the blood supply to the pancreas until the dissection is completed for resection, thus minimizing the warm ischemia time and maximizing islet cell preservation. In addition, important surgical steps in the pediatric patient include special attention to avoid any inadvertent injury or spasm of the small vessels to pancreas, pylorus preservation, and use of a Roux-en-Y loop for duodenojejunostomy to minimize post-operative gastrointestinal complications such as bile reflux gastritis (Fig. 25.2). For the procedure, we use a midline incision, as it is associated with less pain compared to a bilateral subcostal incision. After opening the abdominal cavity, performing any necessary adhesion lysis, a Kocher maneuver is performed to completely mobilize the duodenum and the pancreatic head until the left renal vein and the superior mesenteric artery are well visualized. The peritoneum on the anterior surface of the portal triad is opened; the gastroduodenal artery is dissected and looped. Papaverine (1%) is sprayed on the artery to prevent spasm. The short gastric vessels are divided; the spleen is mobilized by dividing the spleno-renal and spleno-colic ligaments. Using the spleen as a handle, the tail and body of the pancreas are mobilized all the way medially to the level of the superior mesenteric vein. The fibro-fatty tissue around the splenic artery and splenic vein both anteriorly in front of and behind are

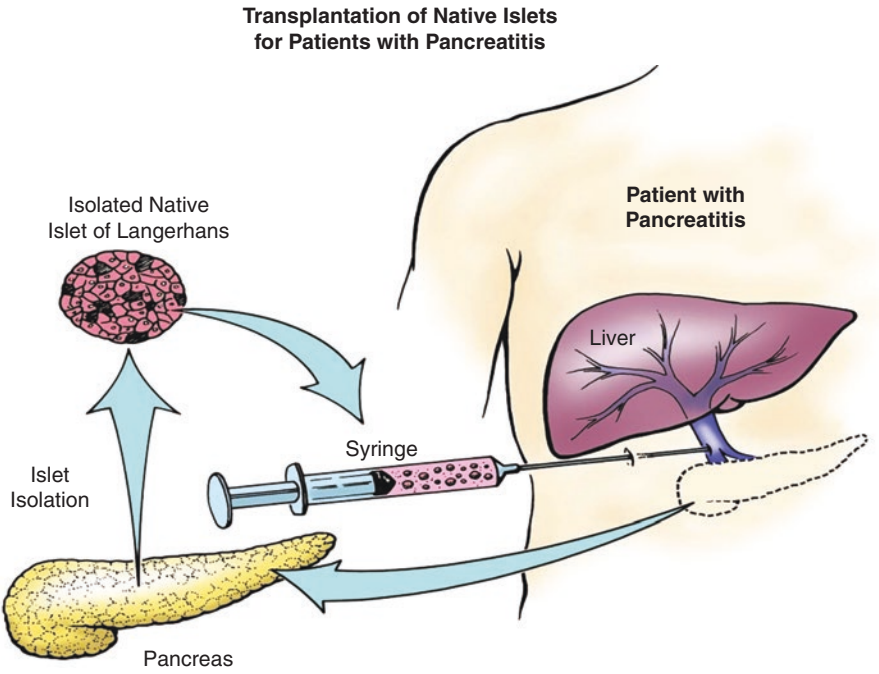

Fig. 25.1 Transplantation of native islets for patients with pancreatitis

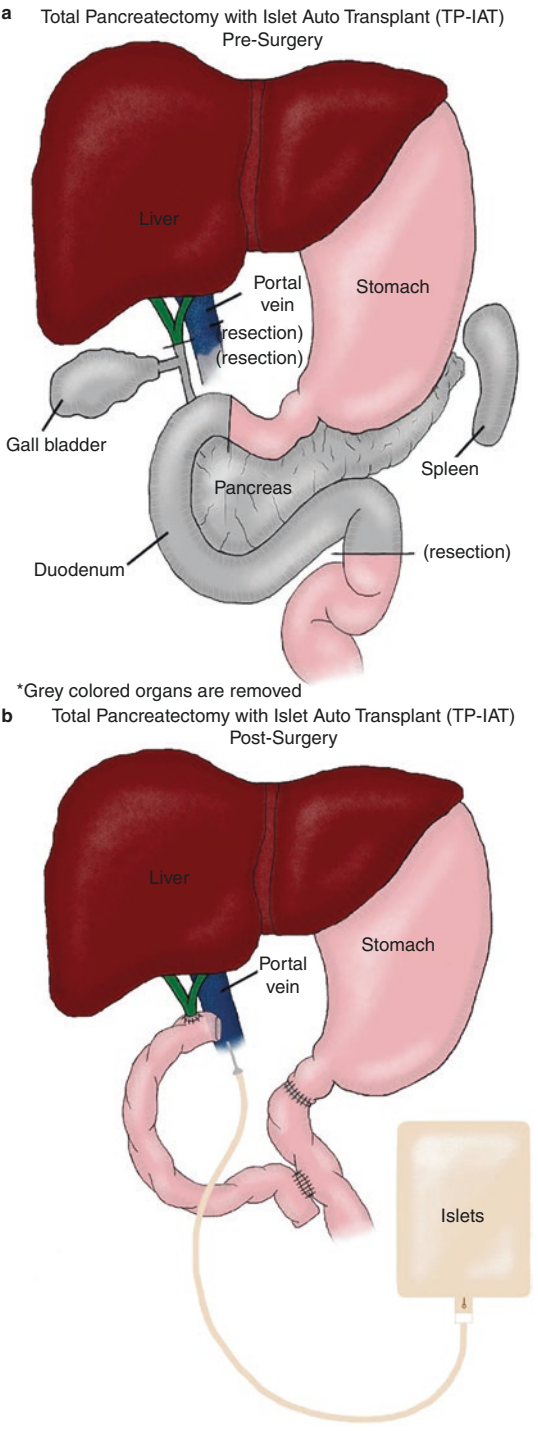

Fig. 25.2 (**a**) Total pancreatectomy with islet auto-transplant (TP-IAT) pre-surgery. (**b**) Total pancreatectomy with islet auto-transplant (TP-IAT) post-surgery

dissected, and the splenic artery is identified and looped on the superior border of the pancreas. The splenic vein is looped distal to the entry of the inferior mesenteric vein. The duodenum is transected 3 cm distal to the pylorus using a GIA stapler (1 proximate, reloadable linear cutter stapler 55 mm, Ethicon Endo-Surgery, USA). The right gastric and gastro-epiploic blood vessels are preserved and the stomach is reflected upwards and laterally to expose the head and body of the pancreas. The distal duodenum is transected at the ligament of Treitz. The superior mesenteric vein is identified and carefully dissected. The pancreatic neck is elevated off the portal vein. The bile duct is identified and transected at the superior border of the pancreas. Careful examination is done to look for any accessory right hepatic artery arising from the superior mesenteric artery. If one exists, it is carefully preserved. The uncinate process of the pancreas is mobilized off the portal vein by dividing all the small tributaries to the portal vein. At this stage the pancreas is connected only by its vascular structures and the islet cell isolation team is alerted.

The vascular structures are divided in the following order: gastroduodenal artery, splenic artery, and splenic vein. The pancreas is then immediately placed in cold sterile preservative solution and transported to the islet isolation laboratory. While the processing of the pancreas is continued in the laboratory, gastrointestinal reconstruction is initiated as follows: the proximal jejunum is mobilized and brought into the infra hepatic region on the right side. A choledochojejunostomy end-to-side (end of bile duct to the side of jejunum) is constructed using multiple interrupted absorbable sutures. Twenty centimeters downstream, the jejunum is divided using a GIA stapler. A 40 cm Roux-en-Y limb is fashioned. A duodenal jejunostomy is constructed in an end-to-side fashion in two layers using multiple absorbable interrupted sutures. A gastro-jejunostomy tube is placed in the stomach using the Stamm technique and the tip of the jejunal tube placed in the distal jejunum.

We have recently started performing this procedure laparoscopically. In a case controlled study where 21 patients who received the laparoscopic procedure were compared to matched controls, the surgical complications and islet graft outcomes were similar. The laparoscopic approach allows for a smaller incision and better scar satisfaction [27].

25.4 Islet Isolation and Infusion

For pediatric pancreata, the recommended enzyme mixture is a high proportion of intact class 1 (C1) and class 2 (C2) collagenases combined with neutral proteases, all from the organism *Clostridium histolyticum*. This specialized enzyme mixture has been shown to improve islet yields from pediatric pancreata without compromising their functional capacity in vivo [28, 29]. After ductal perfusion of the enzymes, the pancreas is digested using a modified Ricordi's semi-automated method [23, 30]. Of note, younger patients benefit from a prolonged stationary digestion time prior to mechanical digestion compared with adults [23, 28]. The digested tissue is not typically purified for autologous transplantation unless volume

reduction is required. Despite the small size of the pediatric pancreas, consistently high islet yield per gram pancreas can be obtained in children compared to adults [23, 28, 29]. Following isolation, the islet product is suspended in albumin-based media and returned to the operating room for infusion.

25.5 Islet Cell Infusion

Prior to starting islet infusion, the patient is given 35 units per kilogram of heparin, allowing the heparin to circulate for at least 3 min. The islet product also contains 35 units per kilogram of heparin. The patient is also started on dextran 0.5 cc per kilogram to a maximum of 10 cc per hour continuous infusion. Dextran specifically inhibits the extrinsic pathway of coagulation [21]. The splenic vein stump or the middle colic vein is cannulated and attached to pressure tubing with an in-line manometer, which is typically zeroed prior to starting the infusion. The islet preparation is infused by gravity into the portal vein system. Baseline portal pressure is first recorded and the pressure is measured every 3 min. If the pressure increases to greater than 25 cm of saline, infusion is paused for 15 min and the pressure measured. Most of the time, there is auto-regulation and the portal pressure decreases. Infusion is restarted and pressures measured at 3-min intervals. It is important to closely monitor pressure changes at 3-min intervals in children. If the pressure is less than 25 cm of saline, the infusion is restarted. If the pressure is more than 25 cm saline (after waiting for 15 min to auto-regulate), or if a total tissue volume is 0.25/Kg of patient body weight, the portal infusion is stopped and the rest of the islet preparation is implanted in the peritoneal cavity as a thin film. The total time spent on infusing islets ranged from 60 to 110 min [21].

25.6 Post-Operative Care

Patients are admitted to the intensive care unit for post-operative monitoring, including frequent blood glucose checks [21, 22]. A continuous infusion of insulin is adjusted to maintain blood glucose between 80 and 120 mg/dL. This is converted to subcutaneous insulin, which is continued upon discharge. Tube feeds are cycled and diet is advanced as gastric emptying improves. Tube feeds are stopped when the child can demonstrate adequate oral intake of calories and protein. Mean duration of hospitalization is 16–21 days.

Regular use of digestive enzymes is required after total pancreatectomy. The target dose is 1500 lipase units/kg per meal and half this amount for snacks [21]. Patients also take fat-soluble vitamin supplementation (AquADEKs®) and are counseled to consume a low-oxalate diet to prevent kidney stones [21].

Nearly all pediatric patients receive exogenous insulin during the first 3 months post-TP-IAT to relieve beta cell functional stress during the engraftment (neovascularization) stage [30]. During this time, islets rely on diffusion to obtain nutrients and oxygen and are particularly at risk of injury by hyperglycemia in an anoxic environment. Subsequently,

insulin is gradually discontinued provided that blood glucose levels remain in a near-normal target range. Target range is a fasting glucose of <125 mg/dL, post-prandial glucose of <180 mg/dL, and glycosylated hemoglobin ≤6.5% [25]. If these parameters are not met, then the patients must continue insulin use. Corticosteroids and other medications that induce hyperglycemia should be avoided whenever possible [30].

25.7 Pain Management

Patients are post-operatively started on intravenous narcotics, and as they resume gastrointestinal function, oral narcotics are started. Patients are weaned off narcotics in the outpatient clinics.

25.8 Splenectomy Management

Nearly all children who undergo TP-IAT will have their spleen removed as part of the procedure due to the technical difficulty of spleen preservation in this population and risk of post-operative splenic congestion [21, 22]. Vaccination is completed at least 2 weeks pre-operatively and includes immunizations against Haemophilus influenzae type b, meningococcus, and pneumococcus. All children are maintained on prophylactic antibiotics for 1 year post-operatively [21]. This differs from adults, who do not undergo antibiotic prophylaxis following TP-IAT. Pediatric patients and their caretakers also receive counseling regarding the risks of infection following splenectomy and strategies for risk reduction.

25.9 Surgical Morbidity and Mortality

The operative mortality after TP-IAT in pediatric patients is very low (0–1%) [21–23]. In one series, surgical complications occurred in 15 (20%) patients and included abdominal hemorrhage (5.3%), bowel obstruction (5.3%), abdominal abscess (4%), enteric leak (2.6%), biliary leak (1.3%), and wound infection (1.3%) [21]. Of note, in this series, the complication rate was significantly lower in younger children <12 years of age ($p = 0.041$). Interestingly, all four patients who developed intraabdominal bleeding had elevated islet infusion portal pressures (>25 mmHg). In another series, complications included acute respiratory distress syndrome, pneumonia, urinary tract infection, and central line-associated bloodstream infection [22]. None of the patients had long-term sequelae from their complications.

Post-splenectomy thrombocytosis (platelet count $>10^6$/μL) occurs in 40% of patients and is managed with hydroxyurea [21]. Although there is a risk of portal vein thrombosis with islet infusion, no pediatric cases have been reported thus far. Portal vein stenosis requiring a surgical shunt for correction has been reported in one patient [21].

25.10 Narcotic Use and Pain After TP-IAT

Prior to TP-IAT, pediatric patients required on average 32.7 mg morphine equivalents daily [22]. Following their operation, patients remain on narcotics for acute post-operative pain, and the dose is gradually tapered. Narcotics can be discontinued in the majority of patients, with 79–90% reported as narcotic-free on follow-up [21, 22]. On post-operative surveys, patients report that pancreatitis-type pain and the severity of pain significantly improve over time ($p = < 0.001$) following TP-IAT [21].

25.11 Islet Function After TP-IAT

In the largest series of pediatric patients to date, 41.3% achieved insulin independence following TP-IAT, and 90.3% of these patients did so within 1 year [21]. Younger children (<12 years) are more likely to achieve insulin independence than older children (12–18), 56.0% versus 40.5% ($p = 0.05$) [21]. In another series, 29% were insulin independent, and an additional 57% required less than 20 U/day of insulin daily [22]. Insulin independence has been observed for longer than 10 years after TP-IAT [21].

It is important to remember that without pancreatectomy, 30–50% of pediatric CP patients will develop diabetes in their lifetime solely from progression of their disease [18]. Also, even the children who have partial function and must use some insulin on a daily basis have been shown to have improved quality of life compared to their pre-TP-IAT status [21].

25.12 Factors Predicting Insulin Independence

There are several patient factors which are associated with a higher probability of insulin independence. These factors include younger age, lack of prior Puestow procedure, lower body surface area, higher IEQ/Kg body weight, and total IEQ transplanted [21–23]. Total IEQ given is by far the strongest factor associated with insulin independence (OR = 2.62; p value <0.001) [21]. Patients who received the most islets, >5000 IEQ/kg body weight, fared the best, with an insulin independence rate of 76% at 2 years post-op. This is in stark contrast to the 13% insulin independence rate of children who receive <2500 IEQ/kg [21].

Prior pancreatic surgery has been shown to have a significant impact on outcomes of TP-IAT. While previous surgery does not increase complication rates, drainage procedures such as the Puestow lead to significantly lower islet yields and increased the risk of insulin dependence [21]. It is important to counsel parents accordingly when considering a patient for TP-IAT post-surgical drainage procedures.

25.13 How Young Is Too Young for TP-IAT

Fear of diabetes and major surgery have deterred referral of younger children for TP-IAT and resulted in these children suffering with intractable pain and poor quality of life. We evaluated outcomes in our youngest TP-IAT recipients and noted that they in fact do well. Among 17 children between ages 3 and 8 who underwent TP-IAT, all (100%) had relief of pain, and all were off narcotics [31]. Fourteen of the 17 (82%) were insulin independent, higher than the 41% rate observed in patients older than 8 years [31]. There was no operative mortality. Although the decision to proceed to TP-IAT must be carefully considered in the management of young children with chronic pancreatitis, taking into consideration the risks of major surgery and age and size of the child does not negatively affect outcomes. Younger age is not a contraindication to referral [31].

25.14 Conclusions

Chronic pancreatitis, though rare in children, is a debilitating disease that often leads to severe abdominal pain, pancreatic insufficiency, loss of school days, and narcotic dependence. Pancreatitis is increasingly recognized as a cause of chronic abdominal pain in children. Ongoing pain, such as that experienced by children with CP, has been associated with mental health issues such as anxiety, depression, low self-esteem, and also chronic physical health problems.

If medical or endoscopic interventions do not provide adequate relief for pediatric patients, a provider should consider total pancreatectomy to remove the underlying cause of the patient's pain.

With improvements in islet isolation, infusion, and engraftment, the complication of brittle diabetes can be avoided or minimized. As a rule, pediatric patients experience sustained pain relief and acceptable long-term glycemic control. Quality of life improves dramatically after TP-IAT, with most children reporting full-time return to school. Early referral to an experienced center allows for evaluation and surgical treatment before extensive damage to the pancreas has occurred. Further advances in islet isolation technique will allow increasing numbers of patients to remain insulin-independent.

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26 Total Pancreatectomy with Islet Autotransplantation (TPIAT): Postoperative Management and Outcomes

Kendall R. McEachron, Mackenzie Moore, and Melena D. Bellin

26.1 Introduction to TPIAT in Children

The first total pancreatectomy with islet autotransplantation (TPIAT) was performed in 1977 to treat painful chronic pancreatitis (CP) in an adult patient at the University of Minnesota [1]. After this patient successfully achieved insulin independence, utilization of TPIAT for the treatment of adult CP increased slowly, but it was not until 1989 that the first reported TPIAT in a child was performed [2].

The indication for TPIAT in children is CP and/or recurrent acute pancreatitis (RAP) that has failed to respond to medical and endoscopic therapy and is limiting quality of life via frequent hospitalizations and chronic pain [3, 4]. For these children, TPIAT offers the potential for reduced pain and improved quality of life and has therefore gained popularity as the initial surgical treatment of pediatric CP/RAP, especially in the last 10–15 years [5, 6]. Unlike adults, children rarely develop pancreatitis as a result of alcohol or gallstones. Instead, they are far more likely to have genetic predispositions for lifelong RAP and CP such as mutations involving the cationic trypsinogen (*PRSS1*) gene, mutations in trypsin inhibitor pathways including the serine protease inhibitor Kazal type 1 (*SPINK1*), mutation in the chymotrypsin C (*CTRC*) gene, or mutations in the cystic fibrosis transmembrane receptor (*CFTR*) impairing bicarbonate secretion in the pancreatic ductal secretions [7]. For genetic etiologies of CP, TPIAT removes the diseased pancreas in its entirety, eliminating risk of future CP recurrence, and treats cases of small duct disease that would otherwise make the option of a drainage procedure technically impossible. In children with other CP/RAP etiologies, such as pancreatobiliary obstruction or idiopathic disease, TPIAT has also developed as a popular initial surgical treatment, with similar success in eliminating pancreatic pain. Regardless of CP etiology,

K. R. McEachron · M. Moore · M. D. Bellin (✉)
Departments of Surgery and Pediatrics, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: Bell0130@umn.edu

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drainage procedures (Puestow, Frey) or other pancreas-sparing surgeries in children result in a high rate of pain recurrence and, if performed prior to TPIAT, result in lower islet yield and worse diabetes outcomes [8].

Specific indications for TPIAT in children, preoperative assessment, surgical and islet isolation techniques, and initial postoperative management are covered elsewhere. In this chapter, the authors will discuss the early outpatient management of diabetes, pain, and nutrition in children who have undergone TPIAT, followed by a summary of pediatric TPIAT outcomes at 1 year posttransplant and beyond.

26.2 Diabetes Management in the Outpatient Setting after TPIAT

After TPIAT, the islets have been necessarily devascularized from their native environment of the pancreas, and the process of revascularization occurs over a period of 3 months after transplantation into the liver (or alternate site) [9]. Hyperglycemia during this critical period is a source of metabolic stress on the islets, and animal models of islet transplant suggest that islet apoptosis occurs more frequently in hyperglycemic conditions after transplant [10–13]. Therefore, maintaining euglycemia (blood glucose range 80–120 mg/dL) and avoiding prolonged hyperglycemia are primary goals during this period of engraftment. Patients undergoing TPIAT are started on an intravenous infusion of insulin intraoperatively at the time pancreatectomy. Subsequently, children are maintained on intravenous insulin until insulin needs and nutritional intake are sufficiently stable to permit transition to a subcutaneous insulin regimen [14]. Once transitioned to subcutaneous insulin, it is our practice to continue insulin for at least 3 months to reduce metabolic stress on the islets during engraftment. Subcutaneous insulin can be administered via multiple daily injections of long- and rapid-acting insulin analogs, or by continuous infusion of a rapid-acting analog using an insulin pump. In children, we have found the latter method to be more convenient for administering the very low doses of insulin that may be required. Continuous glucose monitoring (CGM) technology is also safe when clinically indicated [15, 16] and may assist the child in returning to school or play without frequent need to perform finger-stick blood glucose measurements.

Children in our practice remain in close contact with a pediatric endocrinologist (typically once-weekly visits with interval updates on blood glucose levels as needed) in the first 4–6 weeks of outpatient management. Weaning off insulin, if indicated after the 3-month engraftment period, can be performed in clinic or remotely. Insulin is weaned slowly as tolerated, to keep fasting glucose <125 mg/dL and 2-h post-prandial glucose <150–180 mg/dL. Patients are considered insulin independent if they are off insulin completely and maintaining a HbA1c ≤6.5%. Children who become insulin independent most often wean off insulin therapy between 6 and 15 months post-TPIAT (Fig. 26.1). Beta cell function after engraftment is monitored at 3, 6, and 12 months posttransplant, and yearly thereafter, with laboratory testing including hemoglobin A1c (HbA1c) and mixed-meal tolerance testing (measurements of glucose and C-peptide fasting and

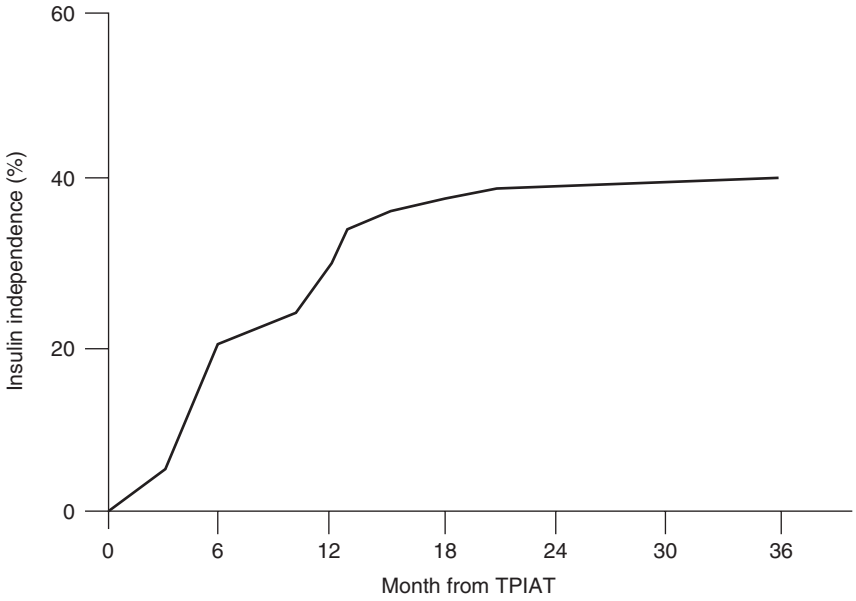

Fig. 26.1 Percent of children who are insulin independent following total pancreatectomy with islet autotransplantation (TPIAT) over time (internal data from the University of Minnesota). The majority of children who will ultimately become insulin independent do so between 6 and 15 months after surgery

post-prandial following ingestion of 6 mL/kg [max 360 mL] of a Boost High Protein supplement). Patients who are insulin independent are expected to have some islet attrition and will usually need to resume partial insulin therapy at some point [17], with the longest documented duration of insulin independence to date of 15 years in a child and 20 years in an adult (internal data). Because of this known risk for recurrent insulin need, even insulin-independent patients are instructed to periodically monitor blood glucoses.

26.3 Pain Management in the Outpatient Setting after TPIAT

Refractory pain from chronic pancreatitis that is lifestyle-limiting is the primary indication for TPIAT in children. Children who meet these criteria have had many episodes of severe pain treated with recurrent or chronic administration of opioids, predisposing them to opioid-induced hyperalgesia [18]. Chronic pancreatitis can also result in hypersensitivity to pain through central sensitization [14, 19–21]. These unique circumstances of patients undergoing TPIAT have led to special emphasis on multimodal postsurgical pain management, with judicious administration of opioids and incorporation of non-pharmacologic pain management methods.

The multimodal approach to pain management after TPIAT begins in the hospital, where children are given a combination of opioids and non-opioid analgesics.

Gabapentin (or alternatively pregabalin) is also used, as it has been shown to improve the central sensitization of chronic pancreatitis pain processing [22, 23]. Alpha-2 agonists and regional anesthesia techniques are also important components of an opioid-sparing approach to pain management in the acute postoperative period [24, 25].

After recovery from surgical pain, the goal in children in the outpatient setting is to wean off opioids entirely [4]. Acetaminophen, NSAIDs, and gabapentinoids remain important pharmacologic measures for pain management during this transition period, but non-pharmacologic therapies are perhaps the most important tools in accomplishing the goal of opioid independence [14]. Physical therapy is one important component of the non-pharmacologic recovery process, and at our institution, the first interaction with a physical therapist occurs prior to TPIAT. Psychological therapies for pain management, such as cognitive behavioral therapy (CBT) and mind-body techniques such as deep breathing or self-hypnosis, have been shown to reduce pain intensity in children with chronic pain, can improve the child's ability to cope with pain, and counteract the central sensitization from chronic pancreatitis pain [19, 26–28]. Finally, if children develop episodes of abdominal pain mimicking that of pancreatitis, other types of abdominal pain, or non-abdominal pain syndromes, opioids should be avoided for pain management in the absence of a clear indication. Patients and their caregivers should be educated that continued use of opioids in these instances can perpetuate the cycle of central sensitization and hyperalgesia and even worsen the severity or duration of pain episodes [29].

26.4 Management of Exocrine Pancreatic Insufficiency after TPIAT

Pancreatectomy results in exocrine pancreatic insufficiency (EPI), which leads to inadequate digestion and absorption of carbohydrates, fats, and proteins, and ultimately malnutrition [30–32]. Absorption of fats and fat-soluble vitamins is impacted most [31, 33]. Increased amounts of undigested fat in the stool increase transit time through the gastrointestinal tract, which further exacerbates malabsorption and contributes to the clinical symptoms of steatorrhea, loose stools, flatulence, and abdominal pain [31, 34, 35]. In children, complications of EPI may include weight loss, poor growth, and deficiencies of the fat-soluble vitamins A, D, E, and K [31, 33, 35]. Poorly controlled EPI after TPIAT can also make the management of diabetes more difficult, due to altered carbohydrate absorption and increased gastrointestinal transit time [32, 34].

Lifelong pancreatic enzyme replacement therapy (PERT) is necessary following TPIAT in order to prevent malabsorption and treat the symptoms associated with EPI [31–33, 36]. PERT has been shown to improve symptoms and the objective parameters of fat and nitrogen absorption [31, 37]. Enzymes are generally well tolerated but are expensive, and the frequency with which they must be administered makes adherence difficult [31, 32, 38]. Adherence with PERT is historically poor in adults after pancreatic surgery [39], and post-TPIAT, up to 20% of patients (adults and children combined) either do not use enzymes at all or do not use as directed [32]. PERT formulations contain lipase, amylase, and peptidase and are typically

capsules filled with enteric-coated microspheres that are designed to prevent inactivation by the acidic gastric environment [31, 32, 36, 38]. Enteric-coated formulations are preferred over non-enteric-coated formulations as they are less likely to be inactivated by gastric acid. Proton pump inhibitors (PPI) are initiated or resumed after TPIAT to reduce risk of gastrointestinal ulcers during postsurgical healing but have an added benefit of preventing inactivation of pancreatic enzymes in the stomach and may decrease required PERT dose [38]. While most children at our institution are weaned off PPI therapy 1 year after surgery, long-term PPI treatment may be a consideration for patients who have signs of exocrine insufficiency despite appropriate PERT dosing and adherence.

PERT should be taken with all meals and snacks with weight-based (1000–2000 lipase units/kg/meal) or fat content-based (2000–4000 lipase units/gram of fat) dosing [32]. A half dose is given for snacks. Enzymes timing (at start, middle, or end of meal) is somewhat debated, but enzymes do need to be taken *with* the meal and not before [38]. Weight-based dosing is more convenient, but dosing based on fat content is more physiologic. In practice, weight-based dosing is often applied, and the patient may be instructed to take a slightly higher dose for a particularly fatty meal or snack [31]. Because the microspheres in the capsules are enteric coated, they should not be chewed. For younger patients who are unable to swallow pills, the capsules can be opened and the spheres mixed into food at the beginning of a meal or snack [38].

Changes in dosing of enzymes are based on symptoms of EPI. The presence of symptoms should prompt a discussion of adherence, but if this is adequate, the dose of enzymes may need to be changed. If there is not an improvement of symptoms despite adherence to an appropriate dose of enzymes, other causes of malabsorption should be considered with special attention to the diagnosis of small bowel bacterial overgrowth (SIBO) as this condition can produce a similar clinical picture [32, 35]. The current protocol at the University of Minnesota is to empirically treat for SIBO when suspected [32]. Other non-pancreatic causes of symptoms such as celiac disease should also be considered [40].

In both adult and pediatric TPIAT patients, gastrointestinal symptoms are common pre- and postoperatively. The most common complaint in pediatric patients is diarrhea with a prevalence of 80% at 1 year post-TPIAT, but other intestinal complaints including constipation are also common. Interestingly, diarrhea has been found to occur independent of PERT dose and patient reported adherence, making diarrhea without steatorrhea an unclear indication for dose modification [32].

Another common gastrointestinal complication of both chronic pancreatitis and pancreatic surgery is delayed gastric emptying (DGE), with an estimated prevalence of 45–50% and 14–20%, respectively, in all patients (adults and children) [41]. In a single institution assessment of postoperative delayed gastric emptying in 33 TPIAT patients, mostly adults, 45% of them experienced symptoms of DGE, and 12% of cases were severe [42]. The symptoms of DGE are nausea, vomiting, poor appetite, and constipation which can hinder the achievement and maintenance of nutrition pre- and postoperatively for patient with chronic pancreatitis who undergo TPIAT [41]. Because all patients experience some slowing of gastric motility early after

TPIAT surgery, we place a gastrojejunostomy tube intraoperatively to provide nutrition, medication administration, and management of early postoperative gastric dysmotility [43]. The mechanisms for ongoing DGE beyond the initial postoperative recovery and weaning off opioids are poorly understood and require further study to determine the most effective treatments. While there are no uniform guidelines on the management of exocrine insufficiency in the setting of DGE, some experts recommend that individuals with significant DGE may benefit more from taking PERT throughout their meal, rather than at one discrete time [31].

26.5 Nutrition Management after TPIAT

Nutritional considerations after TPIAT are particularly important for children, who are still undergoing growth and development and face lifelong risk of secondary complications like osteoporosis if macro- and micronutrients are not appropriately provided. Nutritional compromise can result from both EPI and the altered gastrointestinal anatomy (partial duodenectomy with Roux-en-Y duodenojejunostomy).

Children with EPI, in general, have higher caloric requirements than healthy age-matched children [30], and those who have undergone TPIAT, in particular, have higher energy requirements due to the stress of surgery. Early after surgery, oral intake is often not feasible, and therefore supplemental feeding is administered via gastrojejunostomy for 6–8 weeks postoperatively. A healthy, balanced, age-appropriate diet is recommended once the child is able to tolerate oral intake. High sugar beverages should be avoided entirely. While some patients may be more readily able to wean off insulin therapy with a carbohydrate-limited diet, restricting healthy carbohydrates is often inappropriate for the growing child, and a very low carbohydrate diet is generally not recommended. A pediatric dietitian should be involved in the child's management before and after TPIAT, with growth parameters and symptoms of EPI monitored routinely at clinic visits.

Fat-soluble vitamin digestion and absorption are particularly affected by EPI and may not be optimized even with PERT. Because of altered intestinal anatomy, iron deficiency is common in this population, and although less commonly seen in our clinical practice, patients are also at risk for deficiencies of zinc and vitamin B12. Patients should receive supplementation with a multivitamin and regular monitoring of these micronutrients (Table 26.1). Essential fatty acids can also be depleted after TPIAT (internal unpublished data) and may require supplementation. Although data in children with CP is currently lacking, adults with CP are at higher risk for osteoporosis and fractures compared with healthy controls [44]. Bone mineral density measurements may prove helpful in assessing the clinical endpoints of body fat mass, lean body mass, and bone density in children with CP who are undergoing TPIAT [45].

One final nutritional consideration is the risk for calcium oxalate nephrolithiasis, which is observed with increased frequency in CP [46]. Fat malabsorption in the intestine leads to oxalate hyperabsorption and thus the risk for renal calculi. Dietitian assessment and education should include teaching a low oxalate diet, and patients should be judicious with intake of high oxalate foods.

Table 26.1 Management considerations for exocrine pancreatic insufficiency and other potential nutritional concerns after TPIAT.

Nutritional parameters	Exocrine pancreatic insufficiency	General diet	Fat-soluble vitamins	Micronutrients
Intervention	PERT: 1000–2000 lipase units per kg per meal. Increase for high-fat meals	Pediatric dietitian; healthy age-appropriate, balanced, diet of fats, carbohydrates, and protein	Supplementation of vitamins A, E, and D	Multivitamin with iron, calcium, zinc, vitamin B12
Monitoring	Symptoms of EPI; growth	Growth; blood glucose levels and insulin requirements	Laboratory monitoring; symptoms of nutrient deficiency	Hemoglobin; growth; symptoms of nutrient deficiency
Special considerations	Proton-pump inhibitors; consider SIBO or celiac disease	Eliminate high-sugar beverages	DEXA	MCV/MCH/RDW; avoidance of high-oxalate foods

PERT pancreatic enzyme replacement therapy, *SIBO* small intestinal bacterial overgrowth, *DEXA* dual-energy x-ray absorptiometry

26.6 Other Considerations

Splenectomy is most often performed at the time of TPIAT. Children should be managed in accordance with current Centers for Disease Control and American Academy of Pediatrics (Red Book) guidelines. This includes appropriate vaccinations before and after TPIAT surgery and, based on current guidelines, prophylactic antibiotics for 1 year after splenectomy in those <18 years of age.

26.7 Outcomes of Pediatric TPIAT

26.7.1 Opioid Use and Pain Relief

The primary indication for TPIAT in children is refractory, lifestyle-limiting pain of chronic pancreatitis. In the largest series of pediatric TPIAT patients to date, 100% (n = 75) were on opioids prior to TPIAT [4]. Relief of pain and eventual weaning off opioids are the primary goals and important outcome measures following TPIAT. In children, reducing pain and sustaining opioid independence are feasible goals. In the aforementioned series of 75 children undergoing TPIAT at the University of Minnesota, prevalence of opioid use 1 year after TPIAT went from 100% to 20% and continued to decline subsequently, with the prevalence of opioid use remaining

below 20% through 10 years of follow-up. Likewise, pain severity decreased significantly in the first 3 months following TPIAT and was also sustained in the 10-year follow up cohort. In a more recent series including 30 patients under age 18, the overall prevalence of opioid use and persistent pain at 10 years was 16.7% and 11.8%, respectively [17]. Outcomes may be even more favorable for very young children (age under 8 years) undergoing TPIAT. In the largest series of this age group, 100% of patients were off opioids by 6 months postoperatively [5].

26.7.2 Insulin Independence

The strongest predictor of islet graft function after TPIAT is the islet mass transplanted, or islet equivalents (IEQ) per kilogram of body weight [4, 6, 17, 47, 48]. While the majority of patients (~84%) have clinically meaningful islet graft function at 1 year after surgery [4], only about 40% of children will wean completely off insulin (Fig. 26.1). However, age < 18 at the time of transplant is associated with better long-term metabolic outcomes compared with adults [6, 17]. This difference is likely driven by higher rates of insulin independence seen in the youngest children undergoing this procedure; the highest rates of success have been observed in those under 9–12 years of age [4]. Long-term follow-up demonstrates graft attrition over time, though children have shown potential to sustain islet graft function out to 10 years and beyond. Any patient undergoing TPIAT should be counseled before surgery on the high lifelong risk for diabetes mellitus and the management of diabetes. Factors that appear to be associated with lower rates of insulin independence include prior pancreatic operations and a higher body surface area (which correlates with patient age) at the time of transplant [4]. In particular, the success of the islet isolation procedure is impaired by a prior lateral pancreaticojejunostomy (Puestow), because optimal collagenase digestion of the pancreas relies on an intact pancreatic duct. For these reasons, and because the risk of pain recurrence is high, Puestow or Frey procedures are generally not recommended as temporizing measures for surgical management of chronic pancreatitis in children. The presence of beta cell autoantibodies at the time of TPIAT also appears to convey a poorer prognosis for islet graft function [49].

26.7.3 Quality of Life

Children with chronic pancreatitis have lower quality of life on standardized assessments, compared to normative values [50, 51]. They are repeatedly hospitalized, miss school, and may be unable to engage in other normal childhood activities. Children who have undergone TPIAT report improved quality of life, and their parents report fewer days of school missed and fewer limitations in daily activities [4, 50]. The authors have previously reported improvement in the physical component summary (PCS) and mental component summary (MCS) scores obtained from the Medical Outcomes Study Short Form-36 (SF-36) in children who have undergone

TPIAT, sustained over 5 years of follow-up [4, 17, 50]. In general, well-selected pediatric patients undergoing TPIAT can expect improvements in health-related and overall quality of life.

26.8 Conclusions

Children with disabling CP refractory to medical and endoscopic management may be candidates for TPIAT. While TPIAT is a major surgery that should be reserved for only severely affected children, diagnosing CP and referring severely affected children early in the course of disease may benefit TPIAT outcomes, in light of data indicating that children (especially young children) have improved metabolic outcomes and decreased residual pain burden. In general, other pancreatic surgeries for CP should be avoided, as they may prolong duration of pain and impair metabolic outcomes from eventual TPIAT. Postoperative management of pediatric TPIAT patients requires a highly skilled and close-knit multidisciplinary team, including pain management experts, physical and occupational therapists, endocrinologists, dieticians, and gastroenterologists. When appropriately managed after TPIAT, children can experience a high rate of pain remission, reduced burden of diabetes, and overall improved quality of life after TPIAT. In short, they can return to a normal childhood.

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Part IV

Heart Transplant

Indications and Outcomes of Heart Transplantation in Children

27

Diana Torpoco Rivera and Swati Sehgal

27.1 Indications of Heart Transplant in Pediatrics and in Adults with Congenital Heart Disease

The first pediatric heart transplant (HT) was performed by Dr. Kantrowitz and his team on an infant with congenital heart disease (CHD) for which there was no surgical repair available at that time [1]. In the fifty plus years since that first transplant, indications for HT have evolved with the diversification of the etiology of heart failure and available surgical options in children [2].

The general indications for heart transplant in children are:

(i) Cardiomyopathies.
(ii) Unrepaired congenital heart disease without good surgical repair options.
(iii) Repaired congenital heart disease with failure of the palliation.
(iv) Retransplantation.
(v) Others like idiopathic malignant arrhythmias, refractory to medical therapy, and cardiac tumors.

The primary indication for transplant varies by age, with CHD being the most common indication in infants (57%) and cardiomyopathy in older children (53% in children aged 11–17 years) [3].

D. Torpoco Rivera · S. Sehgal (✉)
Division of Pediatric Cardiology, Central Michigan University College of Medicine, Children's Hospital of Michigan, Detroit, MI, USA
e-mail: sehga1s@cmich.edu

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27.2 Cardiomyopathies

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy encountered in children. Children with cardiomyopathy listed for transplant include 83% with DCM, 11% with hypertrophic cardiomyopathy, and 6% with restrictive cardiomyopathy [4]. Children undergoing HT for chemotherapy-induced cardiomyopathy are a very small fraction of all cardiomyopathies, comprising 0.04% of all DCM patients as per a recent multicenter registry data report [5].

27.3 Unrepaired Congenital Heart Disease

In this day and age, there are very few congenital heart diseases that are not amenable to surgical repair. In the 1980s, when the Norwood operation was initially offered to children with hypoplastic left heart syndrome (HLHS), the outcomes were poor, and many children with HLHS were offered HT as a superior alternative. With improved survival after the Norwood operation and shortage of the infant heart donor pool, transplant is now only offered to a subset of patients with this cardiac defect who are expected to have poorer outcomes after Norwood, e.g., HLHS with severe dysfunction of the systemic right ventricle [6, 7].

27.4 Repaired Congenital Heart Disease

Children and adults with CHD who undergo repair early in life may develop refractory heart failure years after repair. In their cohort of adults with congenital heart surgery undergoing transplantation, Irving and colleagues showed that 41% of their patients had univentricular physiology and 59% had biventricular physiology [8]. Patients with d-transposition of the great arteries who underwent repair via atrial switch procedure, corrected transposition of the great arteries, and tetralogy of Fallot are at higher risk for heart failure and arrhythmias later in life requiring HT [9].

A large group of repaired CHD patients requiring transplant later in life are those who were born with a functionally univentricular heart and undergo 2 or 3 stage palliation culminating in a Fontan procedure [10, 11]. Patients with univentricular physiology develop heart failure either due to dysfunction of the systemic ventricle or due to failure of the Fontan circulation with chronically elevated central venous pressures resulting in challenging complications, including protein losing enteropathy, plastic bronchitis, arrhythmias, and liver disease [12].

27.5 Retransplantation

International Society for Heart and Lung Transplantation (ISHLT) registry documented anywhere between 14 and 38 retransplants annually in the pediatric population from 2004 to 2014 [13]. Using the ISHLT registry data from 1988 to 2010, Conway and colleagues found that out of nearly 10,000 heart transplants recorded

in that time frame, 602 (6.1%) were retransplants [14]. Coronary allograft vasculopathy, rejection, and primary graft failure are the most common reasons for requiring a retransplant [15–17]. The number of patients undergoing retransplantation has decreased in the most recent era to <3% of all transplants, primarily due to improved survival of the primary graft [3].

27.6 Changing Indications in Current Era

Since the first successful pediatric heart transplants in the 1980s, there has been a major shift in the indications for heart transplants. Early on, patients with HLHS were directly offered HT due to poor outcomes of the Norwood procedure [6, 7, 18, 19]. Later on as Norwood outcomes improved, and the shortage of infant donor hearts continued, HT was only reserved for the HLHS patients who were poorer candidates for the Norwood procedure [20–22]. As a result of successful palliation of congenital heart defects like HLHS, there is a large group of children in their adolescence and young adulthood who develop failure of the palliation resulting in heart failure and/or arrhythmias and poor quality of life. This group comprises a big portion of the indications for HT in the current era [10, 23, 24] (Fig. 27.1).

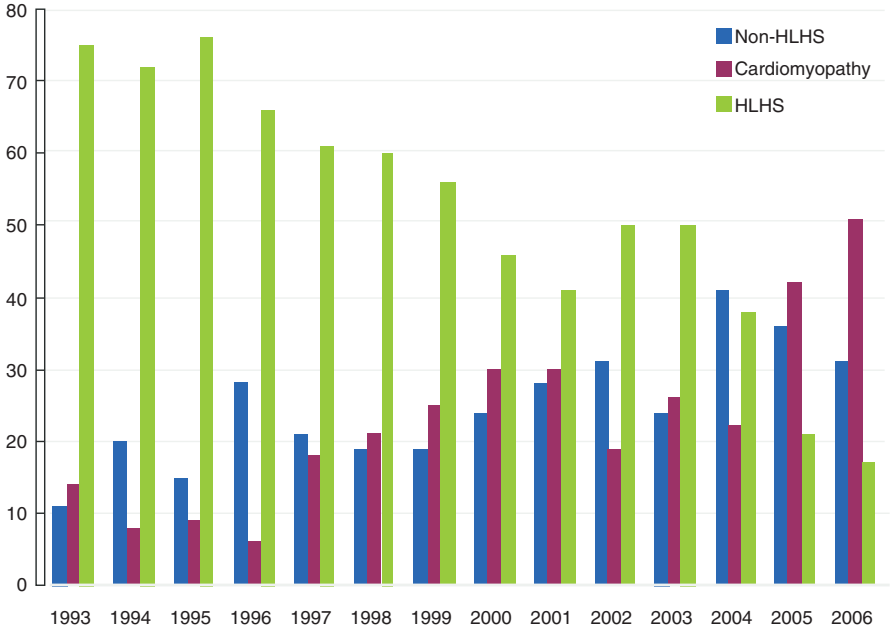

Fig. 27.1 Changing indications of heart transplant. The distribution of number of patients listed for HT in the Pediatric Heart Transplant Study in each year from 1993 to 2006 with cardiomyopathy, hypoplastic left heart syndrome HLHS), and other congenital heart disease (non- HLHS). (*Reprinted from* Guleserian KJ, Schechtman KB, Zheng J, et al. Outcomes after listing for primary transplantation for infants with unoperated on non-hypoplastic left heart syndrome congenital heart disease: a multi-institutional study. J Heart Lung Transplant. 2011;30:1023–1032; with permission) [22]

27.7 Outcomes

The latest report from the ISHLT registry reported an overall median survival of 18 years for a pediatric HT recipient. The highest median survival is seen in infant transplant recipients, 24.5 years. The lowest median survival is noted for recipients between 11 and 17 years of age, 14.3 years [3].

There are many other factors that determine post-transplant outcomes. Diagnosis before transplant is a crucial determinant of outcome. Children undergoing HT for DCM have a higher survival rate compared to children undergoing HT for CHD. This has been demonstrated by many single center reports as well as collective data from multiple registries [3, 8, 25].

Mora and colleagues described their single center experience and reported an overall survival of 72% for DCM at 10 years; in comparison, patients with CHD had a survival of 66% at 10 years. They did a sub-analysis of patients with single ventricles undergoing HT and noted the worst survival in this group—50% at 10 years [8]. Similar outcomes were reported for children undergoing HT for cardiomyopathy, CHD, and specifically single ventricle lesions after failed palliation, by Voeller et al. [26].

Reasons for poor outcomes in children undergoing HT for CHD are as follows:

(i) Patients with CHD undergoing transplant are more likely to have one or more operations prior to transplant that increases their risk of bleeding and technical complications during transplant surgery. Longer ischemic times contribute further to poor outcome due to graft dysfunction [9, 27].
(ii) The higher number of prior operations (and associated blood transfusions) increases their likelihood of having preformed antibodies, increasing the risk of allograft rejection after transplant [9, 27].
(iii) Suboptimal end organ function, for example, chronic kidney disease at baseline that increases their likelihood of requiring renal replacement therapy pre- or post-transplant.
(iv) Elevated pulmonary vascular resistance which increases their need for cardiopulmonary support post-transplant [27].

It is important to note that the initial difference in survival in cardiomyopathy vs. CHD patients was negated by 10 years post-transplant, with survival being 70% and 68%, conditional upon 1 year survival [13]. This finding strengthens the premise that the causes of poor outcome in CHD population are related to factors that affect the early postoperative and short-term course.

There is a 30% risk of early mortality in adults with CHD undergoing HT [12]. All of the reasons cited above for poor outcomes in patients with CHD hold true for adults undergoing transplant. Additionally, pulmonary artery reconstruction was found to be associated with increased risk of short-term and long-term survival [28].

27.8 Cardiomyopathies

Children undergoing HT for DCM have better outcomes than children undergoing HT for other cardiomyopathies. Multiple studies have demonstrated that 10-year survival after transplant is best in patients with DCM followed by restrictive cardiomyopathy and is the worst in hypertrophic cardiomyopathy (72%, 63%, and 47%, respectively) [4, 29–32].

The difference in outcome is related to a number of factors. Children with restrictive and hypertrophic cardiomyopathy may be sicker at the time of transplant, have limited available therapies aimed at the type of cardiac dysfunction seen in these patients, and have increased risk of arrhythmias and limited mechanical cardiac support options as compared to children with DCM. The form of mechanical cardiac support that is commonly employed in HCM and RCM patients is ECMO. It is known that patients supported on ECMO as bridge to transplant have poorer outcomes after transplant compared to patients supported on a VAD [13]. Additionally, the likelihood of high pulmonary vascular resistance in patients with RCM predisposes them to a higher risk for primary graft failure.

27.9 Retransplantation

Overall survival after retransplantation is lower than after primary transplantation. Candidates for retransplantation are immunocompromised from maintenance immunosuppression, likely to be allosensitized, and have baseline chronic kidney disease, all of which increase the risk of morbidity and mortality after transplant.

ISHLT data over a period of 22 years demonstrated that survival was 81% at 1 year, 63% at 5 years, 46% at 10 years, and 26% at 20 years after retransplantation as compared to 84% at 1 year, 72% at 5 years, 60% at 10 years, and 42% at 20 years after primary transplant [14]. Mahle and colleagues reported a survival half-life after retransplantation of 5.6 years, as compared to 13.2 years after primary transplantation [15]. In terms of the indication, retransplantation for coronary allograft vasculopathy, which is by far the most common cause of retransplant, has a better prognosis than retransplantation performed for early primary graft failure [8, 14, 15]. Earlier studies also reported that a shorter interval (<1 year) between primary transplant and retransplant portends a poor prognosis [15, 16].

27.10 ABO-Incompatible (ABOi) Heart Transplant Outcomes

Animal research in the 1950s found that infants have an immunological immaturity that provides a window of opportunity for better acceptance of transplanted organs. This immunologic immaturity in infants makes them unable to produce anti-A or anti-B isohemagglutinins.

West and colleagues pioneered the art of ABOi heart transplantation and reported successful outcomes [33, 34]. The advantage of ABOi transplantation is a reduction in waiting time and waiting list mortality by expanding the pool of eligible donors for these infants. Ten-year follow-up of their largest single center cohort that included 35 ABOi heart transplants in infants and other multi-institutional studies revealed no difference in outcome between ABO-compatible and ABO-incompatible heart transplants [35–37] (Fig. 27.2). There is evidence that these patients develop low titers of antibodies to the donor blood group post-transplant that persist but do not cause allograft rejection suggesting the development of tolerance and/or accommodation [37, 38]. Currently, UNOS recommends ABOi HT to be limited to infants or children under 2 years of age and the isohemagglutinin (IH) titer to be less that 1:16. Some centers have pushed these boundaries and have performed ABOi with IH titer as high as 1:256. They had a higher incidence of antibody-mediated rejection in their cohort that required aggressive treatment for antibody removal, but there was no mortality [39].

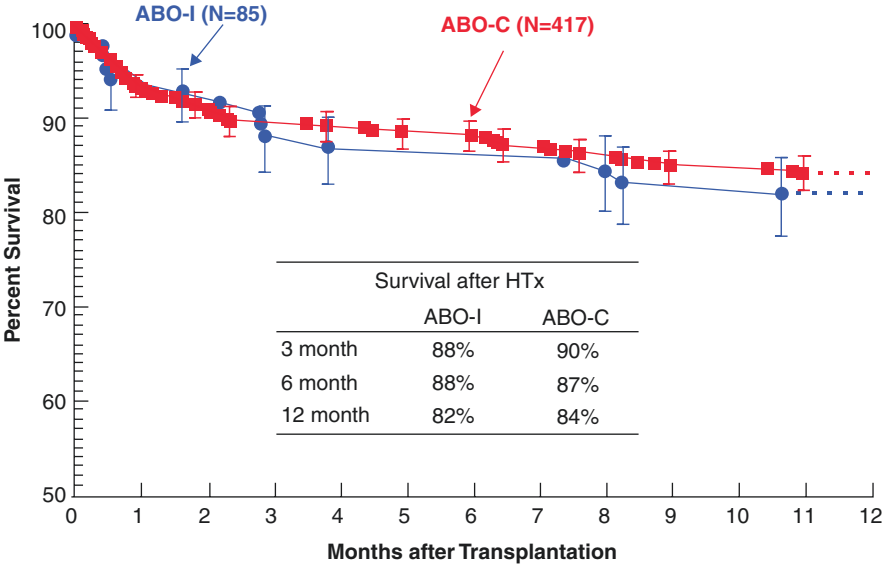

Fig. 27.2 Freedom from death in ABOc and ABOi heart transplants from a multi-institutional study. (*Reprinted from* Henderson HT, Canter CE, Mahle WT, et al. ABO-incompatible heart transplantation: analysis of the Pediatric Heart Transplant Study (PHTS) database. *J Heart Lung Transplant*. 2012;31(2):173–179; with permission) [36]

27.11 Mechanical Cardiac Support and Outcomes Post-Transplant

More and more pediatric HT recipients are being supported by mechanical support devices prior to transplant. In 2017, 37% of children receiving HT were on mechanical support as a bridge to transplant – majority of them on ventricular assist devices (VAD), with a smaller number on extracorporeal membrane oxygenation (ECMO) [3] (Fig. 27.3). Children supported with mechanical devices are able to undergo physical rehabilitation and achieve improved nutritional status that in turn improves pre- and post-transplant outcomes [40, 41]. When comparing outcomes between ECMO and VAD as a bridge to HT, waitlist and post-transplant survival are noted to be poorer in ECMO patients. Jeewa and colleagues reported a waitlist mortality of 38% on ECMO compared to 13% on VAD. Survival post-HT to hospital discharge was also better in the group on VAD support (92% vs. 80%) [40].

Analysis of the UNOS database also resulted in similar outcomes for patients bridged to HT with a VAD. However, patients bridged to transplant with ECMO had lower survival [42]. The factors negatively affecting post-ECMO outcomes are likely related to the patient factors necessitating ECMO in the first place. These patients are more likely to be smaller and younger, have CHD, and are more likely to be sicker at the time of ECMO institution, as ECMO placement is reserved mainly for the urgent/emergent setting, whereas VAD placement is a planned/scheduled procedure.

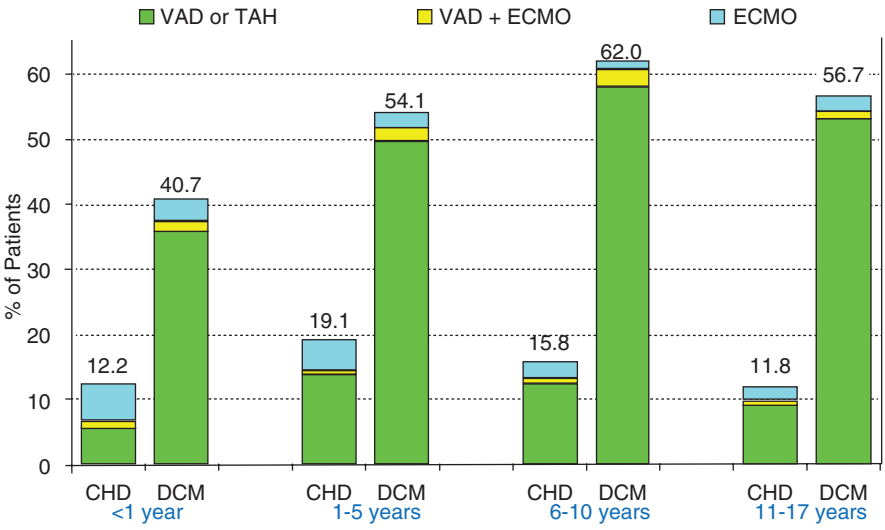

Fig. 27.3 Mechanical cardiac support prior to heart transplant. (*Reprinted from* Rossano JW, Singh TP, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric heart transplantation report - 2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant. 2019 Oct;38(10):1028–1041; with permission) [3]

27.12 Morbidity

27.12.1 Rejection

Acute allograft rejection is common in the first year post-transplant (also called early rejection). However, the incidence of treated rejection in the first year has decreased in the recent era (13% from 2010 to 2018 as compared to 24% between 2005 and 2009) [3, 43, 44]. This is likely related to increasing use of tacrolimus over time as opposed to cyclosporine [3]. Late rejection (rejection beyond the first year post-transplant) also has declined in the recent era [45]. With respect to antibody-mediated rejection (AMR) specifically, a recent study analyzing data from Pediatric Heart Transplant Society (PHTS) reported that freedom from AMR was 88% and 82% at 1 and 3 years, respectively [46]. AMR is commonly associated with hemodynamic compromise, is more difficult to treat, and portends a poorer prognosis compared to acute cellular rejection. One- and 3-year survival after AMR diagnosis was found to be 88% and 77% based on the PHTS data [46]. Unlike the improvement noted in the incidence of rejection overall, there is not much decline observed in the incidence of AMR with severe hemodynamic compromise in the recent era [47]. Risk factors for AMR in this cohort included early rejection, presence of anti-HLA antibodies, older recipient age, African-American race, and non-adherence to medications [47]. The 1- and 5-year survival was 66% and 49%, respectively, in this cohort [47]. Despite the ability to detect and treat rejection more effectively in the acute phase, late rejection and antibody-mediated rejection have a higher risk of mortality, moderate-severe coronary allograft vasculopathy, or retransplantation [45, 46].

27.12.2 Coronary Allograft Vasculopathy (CAV)

Coronary allograft vasculopathy is characterized by diffuse and progressive thickening of the intima along the entire length of the epicardial and intramyocardial arteries. CAV is the leading cause of graft loss beyond 3 years after transplant [13]. As per the data from the most recent ISHLT cohort, 50% of the pediatric HT recipients develop CAV by 15 years of age. CAV increases the risk of graft loss and mortality, with a nearly 50% mortality within 5 years of diagnosis irrespective of the age of the recipient [3].

Older donor age, older recipient age, presence of human leukocyte antigen (HLA) mismatch, allosensitization, frequent cellular rejection, and rejection with hemodynamic compromise are associated with an increased risk of CAV in children [47–50]. Induction therapy in the peritransplant period was found to be a protective factor, whereas a rejection episode in the first year post-transplant increases the risk of CAV in the following 3 years [3]. Treatment options for CAV are limited to percutaneous stent placement and ultimately retransplantation. There are data that proliferation signal inhibitors such as sirolimus and everolimus may delay or halt the progression of CAV in adults [51]. Results from a similar trial in children are pending at this time.

27.12.3 Infections

During the post-transplant period, infections remain a significant cause of morbidity and mortality. Most common causative agents for infections in pediatric HT recipients include bacterial (60%), followed by cytomegalovirus (CMV) (18%), other viral infections (13%), fungal (7%), and protozoal (2%) [52]. The highest risk of infection in these patients is during the early post-transplant period, with bacterial and fungal infections being more common in the first month after transplantation. Viral infections are the most common in the second month after transplantation, with CMV being the most common viral infection.

Factors affecting the frequency, severity, and type of infections include type and dose of immunosuppressive therapy, use of invasive devices, age at transplant, immunization status prior to transplant, and prolonged hospitalization [53].

27.12.4 Renal Dysfunction

Renal dysfunction is a well-known chronic complication of pediatric HT. Children who develop renal disease after transplantation have a ninefold increased risk of death compared to those who do not [54]. Risk factors associated with decline in renal function in children after HT include abnormal pre-transplant renal function, African-American race, and use of calcineurin inhibitors. The eighth pediatric report from the registry of ISHLT reported that within 7 years after transplant, about 10% of patients had some degree of renal dysfunction [55].

Chronic use of calcineurin inhibitors has been associated with histologic changes in the kidneys, including glomeruli, arterioles, and tubulointerstitium [56]. Prevention of nephrotoxicity caused by tacrolimus can be achieved by maintaining the systemic blood levels of this drug at the lowest range possible (consistent with avoiding rejection) in order to decrease local renal exposure to calcineurin inhibitors and their metabolites.

27.12.5 Hypertension and Hyperlipidemia

Hypertension is common in pediatric HT recipients. According to the 11th report of the ISHLT, 69% of children surviving 8 years after HT are hypertensive [57]. Hypertension in this population is multifactorial. After recovering from the immediate postoperative state, the primary drivers of hypertension are the immunosuppressive agents, mainly calcineurin inhibitors and steroids [58].

Hyperlipidemia is seen in 25% of HT patients [57]. Lipid abnormalities are affected by the immunosuppression regimen administered. Cyclosporine can increase levels of cholesterol, plasma triglycerides, and LDL cholesterol. Prednisone raises total cholesterol and HDL cholesterol and causes obesity and insulin resistance, thereby also affecting triglycerides levels. The use of statins is recommended in children with hyperlipidemia following HT as they have

been shown to be highly effective in controlling lipid disturbances with a low incidence of serious adverse effects [59].

27.12.6 Diabetes

New-onset diabetes (NOD) is a recognized complication of solid organ transplantation in adults and is being increasingly recognized in pediatric HT recipients. There have been many single center reports from an earlier era [60–62] and two recent registry-based larger studies, describing the incidence and risk factors of NOD after transplant. Sehgal et al. analyzed the OPTN (Organ Procurement and Transplantation Network) data and found a prevalence of 11% over a median follow-up of 3 years [63] (Fig. 27.4). Older age at transplant, female gender, African-American race, obesity, transplant before the year 2000, and steroid use at 30 days after transplant have been found to be risk factors for NOD after transplant [63, 64].

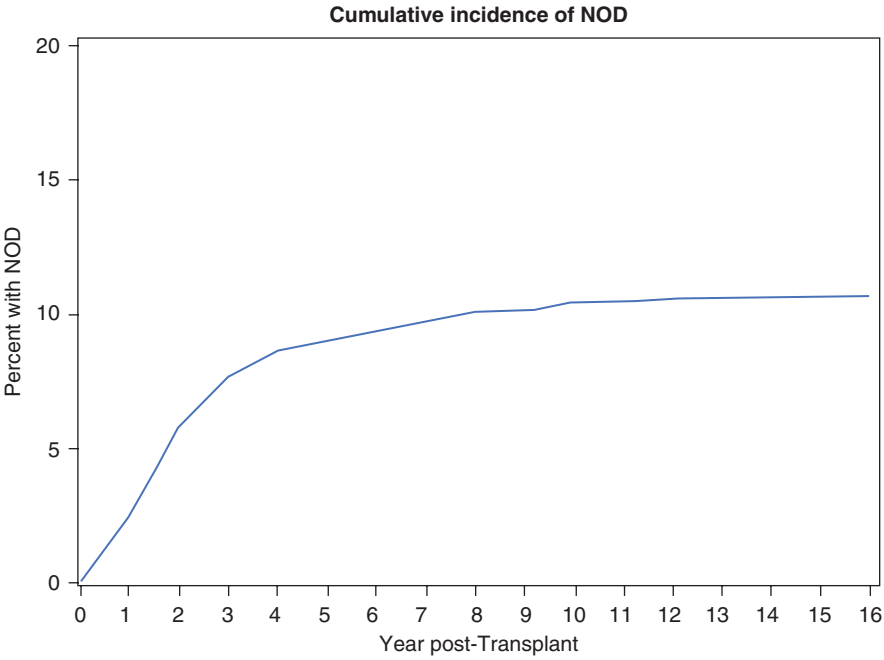

Fig. 27.4 Cumulative incidence of new-onset diabetes after heart transplant. (*Reprinted from* Sehgal S, Bock MJ, Louks Palac H, et al. New-onset diabetes mellitus after heart transplantation in children - Incidence and risk factors. Pediatr Transplant. 2016;20(7):963–969; with permission) [63]

27.12.7 Post-Transplant Lymphoproliferative Disease (PTLD) and Other Cancers

Post-transplant lymphoproliferative disorders (PTLD) are heterogeneous lymphoid disorders ranging from indolent polyclonal proliferations to aggressive lymphomas. Timely and accurate diagnosis, usually based on histopathology, is crucial for early intervention [65]. PTLD is a significant cause of morbidity and mortality after HT.

Manlhiot et al. described their center's experience with PTLD. They had 23 cases of PTLD among 173 patients at a median of 4 years from HT. PTLD affected 9%, 15%, and 28% of patients at 3, 5, and 10 years, respectively. Freedom from death or PTLD recurrence after PTLD diagnosis was 72%, 58%, and 50% at 1, 3, and 5 years, respectively [66]. Risk factors associated with PTLD include younger age at transplant [67], higher cumulative doses of cyclosporine (but not tacrolimus) [67], longer induction therapy [66], higher EBV load [66, 68–70], and higher frequency of allograft rejection [71]. It should be noted that there is a form of EBV-associated PTLD with low or undetectable levels of EBV [72].

27.12.8 Functional Status, Exercise Capacity, and Limitations

There are encouraging data on the functional status of children following heart transplant. As per a recent study, 64% of the heart transplant recipients had no functional limitation, and an additional 21% had only minor limitations with strenuous activity [73].

With respect to vigorous aerobic physical activity, children with HT experience some limitations. In pediatric transplant recipients, the maximal oxygen consumption declines over time, and this could be explained by diastolic graft dysfunction, chronotropic impairment from denervation, or musculoskeletal abnormalities [74]. Some studies have proposed that there is some partial cardiac reinnervation after HT and this might contribute to some improvement of heart rate response to exercise [75]. Children with HT are able to participate in a variety of sports under the guidance of their transplant team.

27.12.9 Quality of Life

The goal of cardiac transplantation is to increase the duration and quality of the life of the recipient. Post-cardiac transplant management can be extremely challenging for recipients and their families, especially in the first year after transplant. Frequent clinic visits and laboratory blood draws, polypharmacy, and procedures like cardiac catheterizations place a significant burden on the patient and family immediately

post-transplant. Even though the HT recipients and their families report improvement in quality of life with respect to their physical abilities, there is a constant feeling that post-transplant care is the biggest controlling factor in their life [76]. As such, it is the biggest responsibility of the heart transplant team to be supportive of these families and provide the best care with the utmost compassion.

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Pediatric Heart Transplant Immunosuppression

28

Jessica A. Laks and Anne I. Dipchand

28.1 Introduction

Post-heart transplant immunosuppression has seen considerable evolution over the last 60 years. Steroids were the mainstay of transplant immunosuppression back in the 1960s while transplant was first being attempted; however, survival outcomes were poor which led to abandoning cardiac transplantation [1]. The discovery of cyclosporine led to renewed attempts at heart transplantation in the 1980s and eventually to our modern era approaches of combination antirejection medications [2]. The goal of our current immunosuppression regimens is to target different areas of the immune system in order to minimize both acute and chronic rejection while limiting side effects to the patients. This is done through specific peri-transplant immunosuppression regimens as well as maintenance immunosuppression with the most common approaches reviewed below and summarized in Table 28.1. As well, we will discuss the common immunosuppression side effects and complications.

J. A. Laks
Heart Institute, Johns Hopkins All Children's Hospital, St Petersburg, FL, USA
e-mail: jlaks1@jhmi.edu

A. I. Dipchand (✉)
University of Toronto, Labatt Family Heart Centre, Hospital for Sick Children, Toronto, ON, Canada
e-mail: anne.dipchand@sickkids.ca

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Table 28.1 Commonly used immunosuppression drugs, dosing and therapeutic ranges/monitoring used in heart transplant patients

Peri-Transplant Immunosuppression			
Generic Name	**Type**	**Typical Dosing Protocols**	**Monitoring**
Induction Therapy			
Rabbit anti-thymocyte globulin	Rabbit polyclonal	• Cumulative dose—3.5 mg/kg to 7.5 mg/kg IV • Given as 1.5 mg/kg/dose IV q24h for 3–5 days • Infused over >6 h	• Platelets, leukocytes, neutrophils and CD3+ counts
Basiliximab	Monoclonal IL-2 receptor antibody	• <35 kg: two 10 mg IV doses • ≥35 kg: two 20 mg IV doses – 1st dose given during OR and 2nd dose given POD 4	N/A
Peri-operative Therapy			
Methylprednisolone	Corticosteroid	• Intra-op dosing: 10-20 mg/kg IV – 1st dose on induction, 2nd dose on release of aortic cross-clamp • Post-op taper: – Day 1-4 – 2mg/kg IV once daily reducing by 0.5 mg/kg each day – Day 5 – 0.25 mg/kg IV	N/A
Maintenance Immunosuppression			
Generic Name	**Type**	**Typical Dosing Protocols**	**Monitoring**
Cyclosporine	Calcineurin inhibitor	• First 3-6 mos: 8-15 mg/kg/day enterally divided q12h • > 3-6 mos: 4-6 mg/kg/day enterally divided q12h • Affected by drugs that influence cytochrome P450 3A4 metabolizing pathway	• TDM via trough levels • General target levels (ng/mL): – 0–3 mos post-tx – 300-350 – 4-12 mos post-tx – 250-300 – >12 mos post-tx – 150-200 • Levels 2 hours post-dose (C2) more accurately estimate AUC and may result in lower doses

Tacrolimus	Calcineurin inhibitor	• < 40 kg: starting dose ~0.05-0.2 mg/kg/day enterally divided q12h • ≥ 40 kg: starting dose 1-2 mg enterally q12h • Affected by drugs that influence cytochrome P450 3A4 metabolizing pathway	• TDM via trough levels • General target levels (ng/mL): – 0–3 mos post-tx – 10-12 – 3–6 mos post-tx – 8-10 – 6–12 mos post-tx – 6-8 – 1–2 years post-tx – 5-7 • Targets dependent on clinical course
Azathioprine	Purine antimetabolite	• Pre-transplant: 3-5 mg/kg/dose IV or enterally x 1 • Post-transplant: 1-3 mg/kg/dose enterally daily	• Monitoring of levels not clinically available • Consider decrease or discontinue for WBC < 3000-4500
Mycophenolate mofetil	Purine biosynthesis	• 20-80 mg/kg (600-1200 mg/m^2/day) enterally divided q12h • Initial doses lower to mitigate GI side effects • Up-titration q2-3 days until target dose achieved • Maximum dose not to exceed 1.5 g twice daily	• MPA (MMF metabolite) therapeutic drug monitoring trough levels • Predominant role of monitoring is supportive (drug not titrated to levels) • MMF dose modifications for side effects: GI symptoms and/or severe neutropenia
Sirolimus (Rapamycin)	mTOR inhibitor	• <40 kg: loading dose 3 mg/m^2 enterally x 1, then 1 mg/m^2 enterally daily or divided q12h • ≥40 kg: loading dose 6 mg enterally x 1, then 2 mg enterally daily	• TDM via trough levels of 5–15 ng/mL
Everolimus	mTOR inhibitor	• Currently being studied	• TDM via trough levels of 3–8 ng/mL
Prednisone	Corticosteroid	• Variable use and dosing (institution and program-specific)	N/A

d/c discontinuation, *TDM* therapeutic drug monitoring, *GI* gastrointestinal, *MMF* mycophenolate mofetil, *AUC* area under the curve, *CNI* calcineurin inhibitor

28.2 Peri-Transplant Immunosuppression

28.2.1 Induction Therapy

Induction therapy is the administration of intensive immunosuppression during the perioperative period, with the rationale being that the risk of rejection is greatest early post-transplant. The overall goal is to reduce the frequency and intensity of acute rejection and allow for the delayed introduction of nephrotoxic maintenance immunosuppression drugs [3, 4]. Induction therapy has also been used as a successful prelude to steroid-free protocols [5]. Concerns about the effect of induction therapy on post-transplant infections or post-transplant lymphoproliferative disorder (PTLD) exist; however, no association has been firmly established in pediatric heart transplantation [6]. Induction therapy has been increasingly utilized over the last 15 years. According to data from the International Society for Heart and Lung Transplantation (ISHLT) registry, nearly 75% of pediatric heart transplant recipients received induction therapy from January 2010 to June 2018, which was a significant increase from 64% in 2005 to 2009 [7]. The two most common induction agents used are anti-lymphocyte or anti-thymocyte globulin and interleukin-2 receptor antagonists, which were used in 57% and 18% of pediatric heart transplant recipients, respectively.

28.2.2 Polyclonal Anti-Thymocyte Globulin

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG) are both polyclonal antibodies produced by injecting human lymphocyte or thymus tissue into another mammalian species and then harvesting and concentrating the resultant anti-human lymphocyte antibodies produced by that animal [8]. Rabbit ATG is the most frequently used preparation, although prior generations of products were also produced in horses [9]. Polyclonal antibodies have a broad specificity and target T cells, B cells, plasma cells, monocytes, and dendritic cells (DCs) [10]. They act in three major ways: activating or altering the function of lymphocytes, lysing lymphoid cells, and altering the traffic of lymphoid cells and sequestering them, which ultimately results in depletion of lymphoid effector cells [3, 9]. The underlying mechanism of action of ATG in depleting T cells is through complement-dependent lysis in the blood compartment and apoptosis and subsequent phagocytosis by macrophages in the lymphoid tissue. ATG has also been found to downregulate adhesion molecules and chemokine receptors inhibiting lymphocyte proliferation and recruitment to the allograft especially during periods of ischemia-reperfusion injury [10]. Side effects can be seen with ATG, as by triggering T cells and the subsequent release of tumor necrosis factor alpha (TNFα), interferon γ (IFN- γ), and other cytokines, symptoms of fever and chills can occur [3].

Dosing of ATG varies in clinical practice; however, the literature has shown that a total cumulative dose of 3.5–7.5 mg/kg appears to be adequate for children at standard immunological risk receiving calcineurin inhibitor (CNI)-based maintenance therapy [11]. Dosing can be tailored according to overall risk of the patient

based on factors including age, immunologic risk (e.g., presence of pre-transplant donor-specific antibodies (DSA) or a positive crossmatch), prior cardiac surgery, and retransplantation, among other factors. However, a total dose below 3.5 mg/kg is not recommended [11, 12]. Hematological triggers of platelets, leukocytes, neutrophils, lymphocytes, and CD3+ counts are used in adults for dose modification or discontinuation and can also be applied to children [11].

28.2.3 Monoclonal Interleukin-2 Receptor Antagonists

Interleukin-2 (IL-2) is a key autocrine growth factor that induces T cell proliferation [3]. IL-2 receptor antagonists bind to the alpha subunit of the IL-2 receptor complex and block binding, thus preventing IL-2 receptor-mediated lymphocyte activation and proliferation [9]. Basiliximab is a chimeric monoclonal antibody against CD25 (IL-2 receptor alfa) and also inhibits an additional proliferation signal mediated via IL-15. Full receptor saturation can occur after a single dose with effects after two intravenous doses lasting 4–6 weeks in children [13].

28.2.4 Basiliximab Vs Anti-Thymocyte Globulin

As the use of induction therapy continues to rise in pediatric heart transplant patients, studies over the last few years have begun to compare the use of basiliximab and ATG. An analysis of pediatric heart transplant patients from the United Network for Organ Sharing (UNOS) database reviewed 2275 patients who received induction therapy with 685 receiving basiliximab and 1590 receiving ATG [4]. Basiliximab was associated with poorer long-term survival at 5 and 10 years (68% vs 76% at 5 years [$p < 0.001$] and 49% vs 65% at 10 years [$p < 0.001$], respectively). Basiliximab was associated with higher risk of death secondary to graft failure ($p = 0.013$) but not death attributable to cardiovascular causes, infection, or malignancy. Compared to ATG, use of basiliximab remained significantly associated with all-cause mortality after multivariate analysis (hazard ratio, 1.27; 95% CI, 1.02–1.57; $p = 0.030$) [4]. A study analyzing ISHLT registry data confirmed many of these findings with improved 5- and 10-year graft survival for ATG on conditional 1-year survival analysis (87.4% vs 82.1% at 5 years and 71.0% and 58.3% at 10 years [$p < 0.01$], respectively) [14]. The basiliximab cohort was more likely to experience rejection prior to discharge (17.5% vs 13.3%, $p = 0.04$) and had a higher likelihood of being discharged home on steroid maintenance (90% vs 60%, $p < 0.01$). PTLD and death due to infection did not differ between the two groups; however, infection prior to discharge did occur more frequently in the ATG cohort (23.2% vs 21.1%, $p = 0.03$) [14]. An analysis of the PHTS database comparing the impact of induction therapy on outcomes after stratifying patients by diagnosis and risk found that overall, patients who did not receive any induction therapy had lower survival ($p < 0.01$) [15]. Both ATG and IL-2 receptor antagonists were associated with an improved freedom from first rejection in patients transplanted for cardiomyopathy ($p < 0.01$).

28.2.5 Perioperative Steroids

Exact protocols, dosing, and timing of administration of perioperative IV steroids are difficult to find in the literature; however, the majority of pediatric heart transplant programs give IV methylprednisolone in the perioperative period for 2–5 days including a rapid wean to either maintenance steroids or a steroid-free regimen [9]. Timing of the initial methylprednisolone dose often aligns with the initiation of cardiopulmonary bypass and/or the release of the aortic cross-clamp. Often, methylprednisolone will be co-administered with ATG induction therapy to prevent ATG infusion reactions [16]. Practice patterns within the pediatric heart transplant community support the use of perioperative IV corticosteroids as evidenced by the fact that the term "steroid avoidance" does not mean complete avoidance but rather is generally defined as complete withdrawal of steroids from the immunosuppression protocol after the induction period [5, 9].

28.3 Maintenance Immunosuppression

Maintenance therapies are used to prevent acute rejection over the long term. Triple and dual therapy are the most commonly employed regimens and work by inhibiting T cell activation via differing pathways [16].

28.3.1 Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Calcineurin inhibitors have been the pillar of maintenance immunosuppression since cyclosporine revolutionized the field in the early 1980s [9, 16]. Calcineurin is a component of the T cell receptor (TCR) signaling pathway, which is responsible for activation and proliferation of the T cell. Cyclosporine and tacrolimus both inhibit T cell activation through calcineurin inhibition but through different steps in the activation pathway. Cyclosporine is a lipophilic molecule that binds to cyclophilins, which then complexes with calcineurin and inhibits its activity. Tacrolimus or FK506 is a macrolide antibiotic that binds to the FK-binding proteins, which then complexes with calcineurin and inhibits its activity. Pediatric data on the efficacy of cyclosporine and tacrolimus is limited [17].

There has been a trend towards an increasing use of tacrolimus over cyclosporine in pediatric heart transplant recipients based on pediatric ISHLT registry data. In the 2008 registry report, 41% of patients were receiving cyclosporine, and 56% were receiving tacrolimus at 1-year post-transplant compared to 84% of patients receiving tacrolimus at 1-year post-transplant in the 2019 registry report [16, 18]. This is likely a result of a number of factors including ease of tacrolimus administration and monitoring as well as the cosmetic influences of cyclosporine causing hirsutism and gingival hyperplasia, resulting in compliance issues especially in the teenage years [16].

28.3.2 Antiproliferative Agents: Azathioprine and Mycophenolate Mofetil

Antiproliferative agents are typically the second maintenance agent in dual- and triple-drug regimens and work by blocking B and T cell proliferation via different pathways [16]. Azathioprine is a prodrug that is metabolized to 6-mercaptopurine, which is converted to its active metabolite and subsequently interferes with nucleic acid synthesis inhibiting T and B lymphocytes [19]. Mycophenolate mofetil (MMF) is an antimetabolite that interrupts purine metabolism in T and B lymphocytes [16].

Azathioprine was primarily used in early clinical trials; however, MMF use in pediatric heart transplant patients has increased over the years with ISHLT registry data demonstrating that 94% of patients were discharged on MMF in the most recent era and 81% of patients remained on MMF at 1-year post-transplant [18]. The shift from azathioprine to MMF has been a result of large adult studies including a randomized controlled trial demonstrating that patients who received MMF over azathioprine (in addition to cyclosporine and corticosteroids) had a significant reduction in mortality at 1 year (18 [6.2%] vs 33 [11.4%], $p = 0.031$) and a significant reduction in the requirement for rejection treatment (65.7% vs 73.1%, $p = 0.026$) [20]. Similarly, an analysis of the joint UNOS/ISHLT registry database for outcomes of adult heart transplant patients treated with azathioprine versus MMF found that actuarial survival was greater in patients treated with MMF compared to azathioprine (1 year, 96% vs 93%; 3 years, 91% vs 86%, $p = 0.0012$) [21].

Pediatric studies also support the beneficial effects of MMF. Dipchand et al. reported a single-center experience on 21 pediatric heart transplant patients on calcineurin inhibitors who were switched from azathioprine to MMF [22]. The rationale for switching included rejection (66%), inability to wean steroids (14%), ABO donor-recipient mismatch (10%), coronary artery vasculopathy (CAV) (5%), and immunosuppressant side effects (5%). Of those switched for rejection, 93% demonstrated resolved or improved rejection and corticosteroids were reduced or discontinued in 48% [22]. Another single-center experience reported significantly less rejection when treating pediatric heart transplant patients with MMF in combination with a calcineurin inhibitor compared with azathioprine or corticosteroids [23].

28.3.3 Proliferation Signal Inhibitors: Sirolimus and Everolimus

Proliferation signal inhibitors (PSI) are used in immunosuppressive therapies for prevention of both acute and chronic rejection. Sirolimus is a macrolide antibiotic with a structure similar to that of tacrolimus. It binds to FK-binding protein-12, inhibiting a protein kinase, the mammalian target of rapamycin (TOR), which results in inhibition of the clonal expansion of T cells. Activation of TOR also signals proliferation of smooth muscle cells and endothelial cells in response to growth factors [16, 19]. Everolimus is an analog of sirolimus that differs by one hydroxyl group at position 40 of the molecule. It arrests the cell cycle of lymphocytes and inhibits IL-2- and IL-15-mediated T and B cell proliferation [16].

PSIs, specifically sirolimus, have been used for alternative maintenance immunosuppression, predominantly for its renal-sparing effects and to promote regression of or prevent CAV. An early pediatric single-center experience with sirolimus demonstrated it to be a valuable immunosuppressant for the management of rejection and significant renal dysfunction with improvement on follow-up biopsies and glomerular filtration rates [24]. Balfour et al. studied the renal function of 15 pediatric heart transplant patients taking calcineurin inhibitors who had sirolimus introduced to their immunosuppressant regimen. Patients were given a lower dose of calcineurin inhibitor with it completely discontinued in five patients. Renal function significantly improved in the patients within 30 days without a meaningful increase in rejection [25]. More recent data comparing utility and safety of total replacement of a calcineurin inhibitor with PSIs versus calcineurin inhibitor minimization with concomitant use of PSIs revealed on a multivariate analysis that improvement of renal function was primarily seen in patients with PSI usage within 5 years of transplantation especially in those with the total replacement strategy ($p = 0.049$) [26]. Asante-Korang et al. conducted a single-center, retrospective study of 19 patients converted from calcineurin inhibitors to either sirolimus ($n = 15$) or everolimus ($n = 4$) [27]. There were four treatment failures for rash, bone marrow suppression, rejection and renal transplantation, and one patient with recurrent rejection necessitating resumption of tacrolimus. Median creatinine was found to be higher pre-switch ($p = 0.016$), and median eGFR was lower pre-switch ($p = 0.0004$) indicating that conversion from calcineurin inhibitor to PSI can be safely accomplished [27].

A prospective study on the use of everolimus as primary immunosuppressive therapy followed 36 pediatric heart transplant patients over a 4-year period. Median calculated GFR increased from 40.7 to 48.7 ml/min, although this was not statistically significant. Median arterial blood pressure as well as triglyceride and cholesterol levels did not change significantly. Overall, this study demonstrated that calcineurin inhibitor-free immunosuppression with everolimus is an effective and safe approach [28]. However, PSIs remain second line in most pediatric heart transplant program protocols pending further experience in pediatrics.

28.3.4 Corticosteroids

Corticosteroids have been a fundamental part of heart transplant immunosuppression since its inception. Corticosteroids are nonspecific immunosuppressive medications affecting the number, distribution, and function of all types of leukocytes as well as endothelial cells [19]. The major effect on lymphocytes is through binding to nuclear factor kappa B and inducing an inhibitory protein. This prevents translocation of nuclear factor kappa B into the nucleus and transcription of pro-inflammatory cytokines [9]. Corticosteroids are associated with a number of detrimental adverse effects including impaired constitutional growth, facial swelling, acne, weight gain, osteopenia, avascular necrosis, fractures, gastritis, abnormal hair growth, adrenal insufficiency, hypertension, and psychiatric conditions [9, 16, 19].

Prednisone use in the pediatric population is decreasing with ISHLT registry data demonstrating that 66% of recipients were discharged on prednisone in the most recent era (January 2010–June 2018) compared to 74% in the previous era (January 2005–December 2009) [18]. Single-center pediatric studies have reported that corticosteroids can be avoided in pediatric heart transplant recipients with negative donor-specific crossmatch and induction with ATG with 92% freedom from rejection at 6 months and 87% at 1 year, and overall post-transplant survival rates of 91% at 6 months and 88% at 1 year [5]. Analysis of the Organ Procurement and Transplantation Network (OPTN) database for patients undergoing heart transplant between 1990 and 2010 for conditional 30-day graft loss and death based on maintenance steroid use showed no difference between propensity-matched cohorts [29]. This led the authors to conclude that a steroid-free regimen avoids complications of steroid use without compromising graft survival. A similar analysis was performed using the PHTS database for patients transplanted between 1993 and 2011 revealing no difference in graft loss or graft loss secondary to rejection. At 1-year post-transplant, there was no difference in freedom from rejection or malignancy, but there was higher incidence of rejection with severe hemodynamic compromise and infection in the steroid-free cohort [30].

A multicenter, prospective, cohort study reported 1-year outcomes among recipients without pre-transplant DSAs who received induction with ATG and maintenance immunosuppression with tacrolimus and MMF and no steroid use beyond 1 week [31]. Patients without DSAs at transplant and managed with a steroid-free protocol had excellent short-term survival (94.5%) and a low risk of first-year diabetes and PTLD.

28.4 Side Effects of Immunosuppression

Each immunosuppressive regimen has a different set of risks and benefits. It is important to have an understanding of the adverse effects associated with each medication and how to manage them.

28.4.1 Gastrointestinal Symptoms

Gastrointestinal symptoms are generally a side effect of MMF and can lead to nausea, vomiting, diarrhea, abdominal pain, and weight loss [9]. These symptoms are generally responsive to a decrease in dosage; however, at times, it requires discontinuation of MMF [19].

28.4.2 Myelosuppression

Myelosuppression is a universal side effect seen in almost all immunosuppressant medications, and complete blood counts should be monitored. Azathioprine

specifically can cause complete bone marrow failure with leukopenia, anemia, and thrombocytopenia [16]. Patients with polymorphisms in the TPMT gene can especially be affected with alterations in the metabolism of azathioprine resulting in marrow toxicity and life-threatening reactions [32]. These side effects are generally dose-dependent, however, and usually resolve within 7–10 days of dose reduction [19]. MMF is more commonly associated with anemia and neutropenia; however, thrombocytopenia does occur [19]. Sirolimus is also associated with thrombocytopenia, anemia, and leukopenia. The thrombocytopenia seen with sirolimus tends to be dose related and reversible, and severe thrombocytopenia is rare [19].

28.4.3 Diabetes Mellitus

New-onset diabetes mellitus (NODM) is a significant complication as it contributes to a number of factors that affect graft function and survival, including coronary artery disease, chronic kidney disease, and peripheral vascular disease. Tacrolimus and corticosteroid use at discharge were found to be independent risk factors for the development of NODM in adult heart transplant recipients [33]. Hyperglycemia is especially common at higher doses of tacrolimus and in certain subgroups including women and black race. As well, NODM has been shown to be more common when tacrolimus is combined with azathioprine over MMF [34]. Once patients develop NODM on tacrolimus, switching to a CNI-free regimen is unlikely to reverse the course; however, weaning corticosteroids can provide adequate glycemic control. A pediatric study reviewing NODM in heart transplant recipients from the OPTN database did not find immunosuppressive medications to be an independent risk factor [35]. The major modifiable risk factor identified in this study was obesity highlighting the importance of diet, exercise, and preventative intervention strategies. Transplantation before the year 2000 was also an independent risk factor for NODM in this study, and the authors speculate that this is related to the decreased use of maintenance corticosteroids after this era [35].

28.4.4 Impaired Wound Healing

Impaired wound healing has been reported to be associated with PSIs. This is a result of these medications inhibiting the translation of transcription factors such as vascular endothelial growth factor (VEGF) resulting in reduced angiogenesis and interference with wound healing [27]. Adult heart transplant studies using primary initiation of everolimus have not shown significant differences in overall rates of wound dehiscence or sternal complications; however, the combined rate of serious incisional complications was increased [36]. This has led to some discouraging the de novo use of PSIs due to the high percentage of early withdrawal. However, a recent pediatric study demonstrated only 1 wound infection out of 13 surgical procedures, suggesting that sirolimus can be used or continued in pediatric patients undergoing major surgical procedures during the perioperative period [37]. These

results may be associated with the fact that in many studies, only BMI is significantly associated with wound healing complications and elevated BMI may play a more significant role than PSIs [36].

28.4.5 Hyperlipidemia

Hyperlipidemia and hypertriglyceridemia are seen with the use of PSIs. Despite elevated triglyceride levels, adult heart transplant studies show that everolimus is efficacious in preventing CAV when compared to other immunosuppressive medications [38]. In the single-center, retrospective pediatric study of conversion from CNI to PSIs as primary immunosuppressive therapy, median LDL, total cholesterol, and triglyceride levels increased from before to after the switch [27]. These increases were all statistically significant; however, it did not seem to affect graft function or development of CAV. Overall, the authors suggest that all patients over the age of 10 years be prescribed HMG-CoA reductase inhibitors and that patients on PSIs should be monitored and may require additional lipid-lowering medications [27].

28.4.6 Chronic Kidney Disease (CKD)

Calcineurin inhibitors can cause nephrotoxicity by limiting renal blood flow caused by constriction of the afferent arterioles in the glomerulus [39]. The effect on the kidneys can be exacerbated by dehydration, as well as concomitant use with NSAIDs, ACE inhibitors, and multiple other drugs. Given the widespread development of CKD in heart transplant recipients on CNIs and the associated morbidity and mortality, multiple adult and pediatric studies have focused on modifications to the immunosuppression regimens. A single-center, retrospective pediatric review evaluated the effect on renal function of a CNI minimization protocol using sirolimus in pediatric heart transplant recipients with CNI-induced renal insufficiency and demonstrated improved renal function as measured by GFR at 2 years ($p = 0.018$) [40]. Another pediatric single-center experience demonstrated improvement in renal function in two out of three patients who underwent minimization of tacrolimus and addition of sirolimus for renal dysfunction [24].

28.4.7 Post-Transplant Lymphoproliferative Disorder (PTLD)

The risk of malignancies develops over time post-transplant with 16% of survivors developing malignancy at 15 years post-transplant according to ISHLT registry data [18]. The majority of the malignancies are lymphomas or PTLD. Primary Epstein-Barr virus (EBV) infections after transplantation and insufficient EBV-directed cellular immunity have been linked as key pathogenic mechanisms for PTLD development [41]. Pediatric studies on PTLD have demonstrated that higher maximum EBV load ($p = 0.004$) and longer duration of induction therapy ($p = 0.02$) were

associated with increased risks of PTLD [42]. That being said, no specific immunosuppressive agents or regimens have been specifically linked to an increased risk for the development of PTLD. Most programs aim to minimize risk by using the lowest amount of immunosuppression deemed safe based on an individual patient's risk profile and clinical picture. Reduction or temporary discontinuation of immunosuppression at the time of PTLD diagnosis is used by most centers as a component of initial treatment in order to allow one's native immunoregulation to reverse lymphoproliferation [42, 43].

28.5 Conclusions

Post-transplant immunosuppression has evolved over the years for pediatric heart transplant recipients. In general, the majority of pediatric heart transplant recipients receive induction therapy with ATG followed by maintenance immunosuppression with a combination of tacrolimus and MMF. Many centers continue to use corticosteroid maintenance; however, there is increasing use of steroid-free and rapid steroid weaning protocols. There is also a rise in programs converting patients to PSI-based regimens demonstrating that the evolution in this field is ongoing. As transplant clinicians, it is imperative to not only be aware of the different regimens that exist but to also carefully balance drug side effects and comorbidities. The ultimate goal is to establish a regimen that optimizes the pediatric heart transplant recipient's quality of life and overall patient and graft survival.

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Part V

Liver Transplant

Pediatric Liver Transplantation

29

Eliza J. Lee and Khashayar Vakili

29.1 Introduction

Since the first successful pediatric liver transplant performed by Dr. Starzl in 1967, refinements in perioperative management, organ preservation, surgical technique, and immunosuppression have steadily improved both short- and long-term outcomes for children undergoing liver transplantation [1, 2]. With these advancements, the indications for liver transplantation (LT) in children have broadened and include a variety of congenital, genetic, and oncologic diseases. In 2018, 700 new active candidates were added to the pediatric liver waiting list [3], and approximately 90% of children on the waitlist will eventually undergo liver transplantation, due in large part to increasing utilization of living donor and technical-variant deceased donor allografts [4]. With 5-year patient survival of over 80% across allograft types, further improvement in survival requires reduction of long-term complications related to chronic immunosuppression, chronic rejection, and medication noncompliance. In this chapter, we will discuss the indications and workup of children undergoing liver transplantation, surgical techniques, common postoperative complications, and outcomes and long-term medical management of children following liver transplantation.

E. J. Lee · K. Vakili (✉)
Department of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: Khashayar.vakili@childrens.harvard.edu

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29.2 Indications for Liver Transplantation in Children

Consideration for liver transplantation should weigh the risks of living with a diseased liver against the risks of transplantation. In some cases, such as acute liver failure, end-stage liver disease, or unresectable hepatoblastoma, the decision to offer transplantation is of clear benefit; however, in some other circumstances, the potential benefit may be less clear. The indications for LT in children vary across age groups and may broadly be divided into several categories (Fig. 29.1) [1]: (1) cholestatic liver disease (e.g., biliary atresia, sclerosing cholangitis, Alagille syndrome); (2) metabolic disorders (e.g., alpha-1 antitrypsin deficiency, urea cycle defects, tyrosinemia, primary hyperoxaluria); (3) acute liver failure; and (4) primary liver malignancy. Further discussion and disease-specific considerations will be highlighted in the sections below.

29.2.1 Cholestatic Liver Disease

Biliary atresia (BA) remains the most common indication for pediatric liver transplantation, affecting nearly 30% of all pediatric patients undergoing liver transplantation [3]. Although nearly all patients with BA first undergo a hepatic portoenterostomy (Kasai procedure) to improve biliary drainage as infants, patients

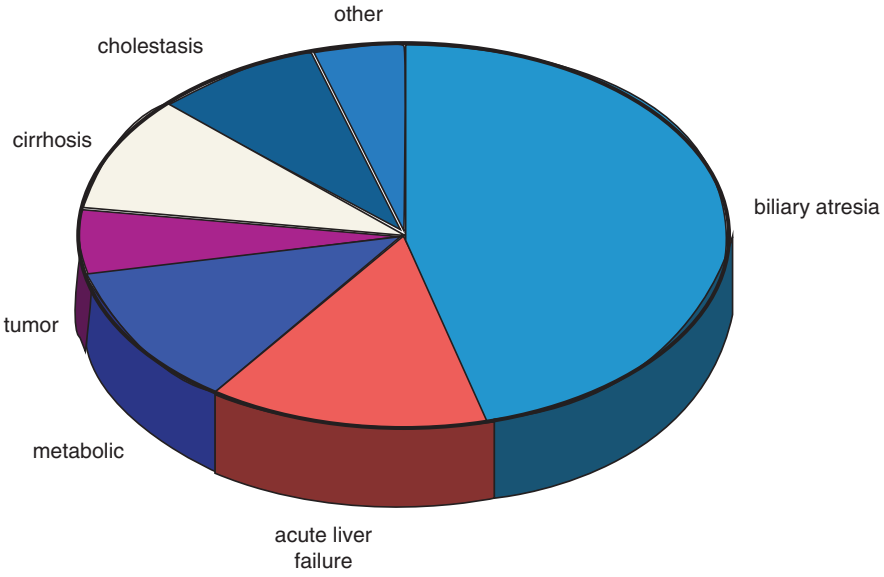

Fig. 29.1 Indications for liver transplantation in children (Source: Rawal N, Yazigi N. Pediatric Liver Transplantation. Pediatr Clin North Am. 2017;64(3):677–84)

may suffer long-term complications arising from recurrent cholangitis, cirrhosis, and sequelae of portal hypertension. The timeline for the development of such complications remains variable, as 30–40% of patients may demonstrate excellent initial biliary decompression for several years; however, nearly all patients will eventually require evaluation for liver transplantation [5].

Primary sclerosing cholangitis (PSC) is a rare disease process in children. PSC is characterized by progressive stricture formation within the biliary tree with subsequent cholestasis, cholangitis, cirrhosis, and portal hypertension [6]. PSC in children tends to be clinically milder compared to adults and is more responsive to immunosuppressive therapies. However, some children experience intractable symptoms related to their liver disease or complications secondary to medical therapy which prompts consideration for liver transplantation. An international cohort study of over 700 children diagnosed with PSC demonstrated a survival of 70% at 10 years following diagnosis with 14% of patients requiring liver transplantation at a median of 4 years following diagnosis with a median age of 15 years [6].

Alagille syndrome (AS) is an autosomal dominant disorder caused by mutation in *JAG1* or *NOTCH2* genes resulting in cardiac or pulmonary vascular structural abnormalities as well as liver injury. AS is most commonly identified on workup of persistent neonatal jaundice with a hallmark histopathologic finding of paucity of intrahepatic bile ducts [7]. Other common findings in patients with AS include butterfly vertebrae, distinct facial structures, and ophthalmologic defects. Liver-related problems in AS commonly arise from cholestasis with resultant jaundice, development of xanthomas, and rickets due to malabsorption of fat-soluble vitamins (A, D, E, and K). Although many patients are able to be treated medically for symptoms of severe cholestasis, select patients may require biliary diversion or LT if adequate symptom control, growth, and quality of life are not achieved through medical therapy [7, 8]. It is currently estimated that liver transplantation is required in 10–30% of patients with AS. These patients should be screened for cardiac abnormalities (echocardiogram, cardiac catheterization) before proceeding with transplant surgery [9, 10]. Post-transplant, patients with AS have been reported to have a 1-year patient survival rates ranging from 71% to 100% across several series [10].

29.2.2 Metabolic Liver Diseases

Metabolic disorders compromise a wide range of diagnoses for which pediatric patients would benefit from liver transplantation. Typically, these disorders are the result of genetic mutations which alter the metabolism of metals, lipids, and proteins or affect mitochondrial function. In some of these disorders, such as alpha-1 antitrypsin deficiency, Wilson's disease, or tyrosinemia, the underlying metabolic defect can result in cirrhosis and in some cases acute liver failure [11]. In others, such as maple syrup urine disease, urea cycle defects, and certain mitochondrial

disorders, patients have intact synthetic liver function; however, they exhibit significant metabolic or extrahepatic derangements such as hyperammonemic crises which can lead to brain injury. These patients generally have strict dietary restrictions which can be a significant burden on their quality of life. In patients with certain metabolic disorders, LT serves to introduce the normal gene into the body and decrease progression of clinically significant extrahepatic disease [4, 11]. While LT alone may correct the underlying metabolic derangement in some patients, transplantation with another organ, such as lung or kidney, may be required for those patients suffering from cystic fibrosis or primary hyperoxaluria, respectively.

29.2.3 Primary Liver Malignancy

Hepatoblastoma (HB) is the most common primary liver malignancy in children which requires LT in patients with surgically unresectable disease. The incidence of primary liver tumors, particularly hepatoblastoma, has risen steadily from 0.6 to 1.2 cases per million between the 1970s and the 1990s [12, 13]. HB is associated with certain genetic conditions such as Beckwith-Wiedemann and familial adenomatous polyposis syndromes, in addition to prematurity.

Currently, neoadjuvant chemotherapy followed by surgery remains the mainstay for treating children diagnosed with HB. These tumors are classified based on the PRETreatment EXTent of disease (PRETEXT) staging system which categorizes it based on the overall disease burden within four defined sections of the liver (PRETEXT I–IV), in addition to vascular involvement or metastatic spread. All patients with PRETEXT IV and some patients with PRETEXT III lesions will benefit from LT in order to achieve complete resection of the tumor. These generally include patients with either extensive disease throughout the liver or tumors which demonstrate significant vascular involvement which makes surgical resection not a feasible approach for obtaining adequate gross disease control [14]. Outcomes for patients undergoing LT for HB have improved markedly over the past several decades, with 10-year post-transplant survival as high as 84% in one series [15]. Early referral of patients with unresectable tumors on diagnosis to transplant centers is critical for optimizing neoadjuvant chemotherapy regimens in conjunction with LT and minimizing waitlist time and the risk of pre-transplant disease spread [16].

With an incidence of 0.3–0.45 cases per million, hepatocellular carcinoma is the second most common primary liver malignancy in children [17]. Unlike adult patients with HCC, the vast majority of children diagnosed with HCC do not have underlying liver disease or cirrhosis, making surgical resection the preferred mode of treatment in this population [17]. HCC in children may arise in patients with tyrosinemia or long-standing cirrhosis. The same surgical principles apply to HCC as they do to HB. However, HCC is far less chemoresponsive than HB, thus making its overall survival more inferior with long-term survival ranging from 60 to 85% in some series [17, 18].

29.3 Recipient Evaluation and Contraindications to Transplantation

Pediatric patients are evaluated for liver transplantation by a multidisciplinary team consisting of hepatologists, surgeons, social workers, psychologists, nurses, and pharmacists. The decision to proceed with LT should weigh the risk of transplantation against the risks of living with the diseased liver. The recipient is also evaluated for contraindications to transplantation which include (1) the presence of unresectable extrahepatic malignancy; (2) uncontrolled systemic infection; (3) multi-system organ failure; and (4) end-stage non-hepatic organ failure that will not improve with medical treatment or transplantation [4].

Prior to transplantation, it is important to optimize medically the health of the patient with regard to liver-related issues as well as screening for other organ dysfunction (e.g., renal, cardiac, or pulmonary), identifying potential living donors, ensuring appropriate nutritional reserve prior to surgery, and educating both patients and caregivers about the risks, benefits, and expected outcomes following liver transplantation [19].

29.4 Donor Assessment

About 90% of liver transplants performed in the United States utilize allografts from deceased donors, and the remainder is from living donors. Potential liver donors are assessed based on a combination of clinical history, appropriate blood group matching, and laboratory testing to determine overall liver function. In addition, the donors are also screening for viral diseases (HIV, hepatitis B and C).

Aside from assessing organ function, another important factor in evaluating potential liver donors is determining an appropriate size match between donor and recipient so as to ensure both a good anatomic fit within the recipient and adequate liver mass. Although whole liver allografts may be utilized from donors within 80–150% of a recipient's weight, appropriately size-matched pediatric donors are rare, thus making technical-variant deceased donor grafts and living donor grafts of key importance for timely transplantation of children. Specifically, left lateral segment, left lobe, and right lobe allografts have been obtained from both living and deceased donors for transplantation into children ranging in size from infants to teenagers with excellent outcomes [20].

In light of the ongoing deceased donor organ scarcity, the use of living donor allografts has become increasingly important for pediatric patients to help minimize waitlist mortality [11]. Although the specifics of evaluating potential living donors are outside of the scope of this chapter, in general, potential living liver donors undergo thorough medical and psychiatric evaluations to ensure the likelihood for full recovery following donation with a suitable social and mental health infrastructure to allow for fully informed consent and a safe postoperative recovery. While living donor liver transplantation (LDLT) constitutes a small proportion of transplants in the United States, the use of living donor grafts in children has increased

over time, with approximately 11% of pediatric liver transplant recipients undergoing LDLT in 2018 as compared to just 6% of patients in 2013 [3, 4]. Despite the relatively few numbers of pediatric LDLT recipients, the future for living donation remains promising as long-term outcomes in this population are excellent, with 5- and 10-year graft failure rates of 5% and 10%, respectively [3].

29.5 Recipient Operation

The recipient operation generally begins via a subcostal incision with or without a midline extension depending upon the patient's size and body habitus. In small children, a transverse upper abdominal incision is commonly used. Once the subcutaneous tissues are dissected and the abdomen inspected, the portal structures, including the hepatic artery, common bile duct, and portal vein, are transected as close to the liver as possible so as to ensure adequate length for subsequent anastomosis to the donor liver. The first deceased donor whole liver transplants were performed using a bicaval technique in which the native liver is removed en bloc with the retro-hepatic vena cava and is replaced with the donor inferior vena cava (IVC) as part of the liver allograft (Fig. 29.2a) [21]. The current, more common approach is the piggyback technique which is employed for both pediatric and adult liver transplants. Using this method, the recipient's native liver is mobilized off of the inferior vena cava by dividing the minor venous branches which drain directly from the caudate lobe and the right lobe into the vena cava (Fig. 29.2b) [21]. Once this this completed, the hepatic veins are fully isolated and divided near the liver, and the native liver is removed.

Implantation of the liver allograft usually begins with reconstruction of the venous outflow. This should be accomplished in a manner which minimizes kinking and disruptions to venous flow. This is particularly important with the use of split liver grafts. In general, maintaining a short hepatic vein on the donor may minimize the risk of outflow obstruction. In the piggyback technique, the donor hepatic veins or suprahepatic IVC are anastomosed to the recipient confluence of hepatic veins. Alternatively, some prefer a cavocavostomy method for whole liver allografts in which the donor and recipient inferior vena cavas are anastomosed in a side-to-side fashion.

Reconstruction of the portal vein is achieved via an end-to-end anastomosis between the donor and recipient portal veins, taking care to ensure that there is no kinking between the two vessels or stenosis at the anastomosis itself. In select cases, such as patients with atretic portal veins or those with portal vein thrombosis, additional measures such as a portal vein thrombectomy or use of a deceased donor iliac vein interposition graft may be required.

Once portal vein inflow and hepatic vein outflow have been restored, a blood flush is performed after reperfusing the portal vein in order to mitigate hemodynamic and electrolyte abnormalities which may be caused by hyperkalemia and hypothermia related to a sudden rush of cold preservation solution into the recipient's circulatory system. After the patient is stabilized following portal reperfusion,

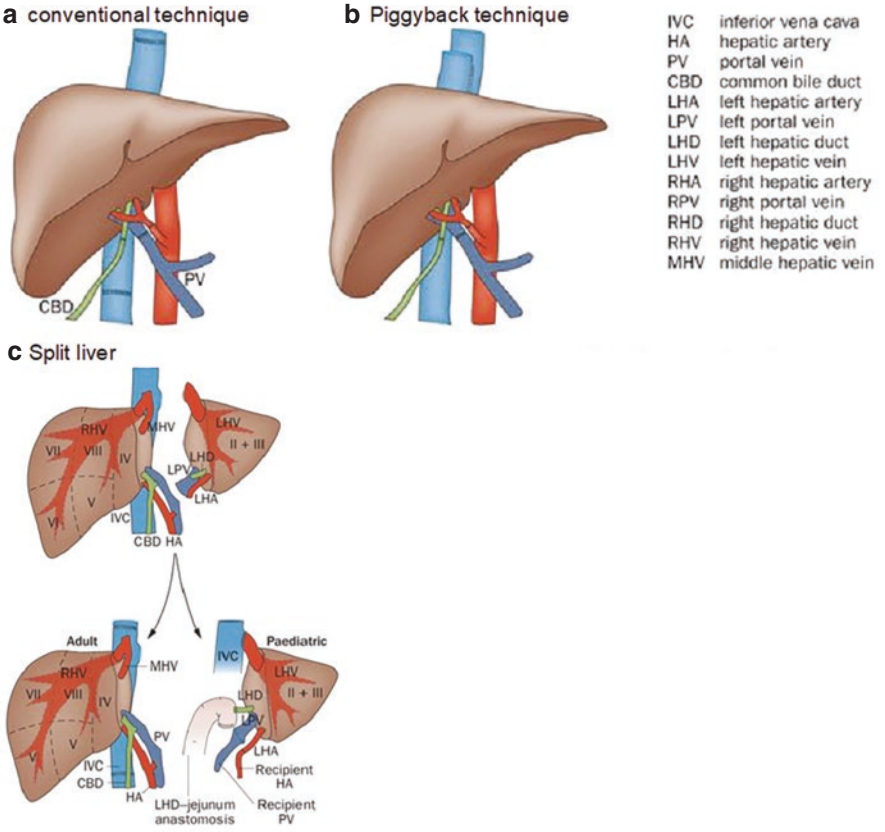

Fig. 29.2 Anatomy of transplanted livers using (**a**) conventional bicaval whole liver technique, (**b**) piggyback whole liver technique, and (**c**) split liver allografts (Source: Zarrinpar A, Busuttil RW. Liver transplantation: past, present and future. Nat Rev. Gastroenterol Hepatol. 2013 Jul;10(7):434–40)

arterial inflow is achieved by anastomosing the recipient and donor arteries in an end-to-end fashion. Commonly the recipient proper or common hepatic arteries are used as inflow vessels. At times placement of an arterial conduit from the recipient aorta using donor iliac artery may be required if the recipient celiac or hepatic artery branches are not suitable as inflow vessels.

Reconstruction of the biliary system is performed following the vascular reconstructions and after adequate hemostasis is assured. In pediatric liver recipients, typically those weighing less than 15 kg, or those with biliary atresia, bile duct reconstruction is achieved via a Roux-en-Y hepaticojejunostomy in which the donor bile duct is sewn to a side of the recipient's small bowel (Fig. 29.2c). Otherwise, biliary reconstruction is commonly via an end-to-end anastomosis between the donor and recipient common bile ducts.

Following vascular and biliary reconstruction, the patient's abdomen is again inspected to ensure excellent hemostasis prior to placement of surgical drains and closure of the abdomen. In rare instances where the recipient's abdomen does not easily accommodate the new liver, delayed closure methods are used in a staged fashion to eventually close the abdominal wall.

29.6 Immunosuppression

Immunosuppressive therapies are commonly initiated at the time of transplantation. While the majority of pediatric liver transplant recipients do not receive induction immunosuppressive therapy, IL-2 receptor antagonists and T-cell depleting agents are utilized in as many as 30.1% and 14.0% of pediatric patients, respectively, according to the most recent 2018 Scientific Registry of Transplant Recipients (SRTR) report [3]. Calcineurin inhibitors, typically tacrolimus or cyclosporine, are used by the majority of centers for maintenance immunosuppression. Some centers may additionally use an anti-metabolite agent for maintenance therapy such as mycophenolate mofetil or azathioprine. The majority of pediatric programs aim to wean recipients off steroids within weeks to months after transplant. Other agents, such as sirolimus and everolimus, are also used in select instances when patients develop complications related to first-line maintenance immunosuppression. Ultimately, regardless of the specific immunosuppressive therapy, careful titration of dosages is required to ensure adequate immunosuppression while also mitigating long-term risks associated with these medications, such as nephrotoxicity, opportunistic infections, hematologic abnormalities, and malignancy (most commonly post-transplant lymphoproliferative disease [PTLD]) [11].

29.7 Postoperative Surgical Complications

29.7.1 Primary Non-function

While definitions of primary non-function (PNF) vary, PNF is a relatively rare complication of LT, with a reported incidence varying between 0.9% and 7.2% across adult and pediatric recipients [22, 23]. Characterized by a marked rise in serum transaminase levels to the 1000s as well as hyperbilirubinemia, PNF is believed to be the result of severe, ongoing ischemia/reperfusion injury when no underlying organic cause (technical or immunologic) can be found. Although the exact etiology which underlies PNF remains unknown, it is believed that donor−/allograft-specific issues such as hypoxemia, hypotension, prolonged warm or cold ischemic times, and significant steatosis may contribute to its development [12, 24]. Clinically, this process manifests as coagulopathy, metabolic derangements, and altered mental status. Similar to patients with acute liver failure, PNF can result in cerebral edema, herniation, and death. Therefore, patients with signs of PNF should be re-listed for emergent liver re-transplantation.

29.7.2 Biliary Complications

With an incidence reported in the literature ranging between 10% and 45%, biliary complications such as leaks or anastomotic strictures are the most common complication following LT in children [25]. Although very rarely the cause for allograft loss or patient death, biliary complications may impede overall healing postoperatively, prolong length of hospital stay, and predispose patients to infectious complications. Bile leaks are generally observed in the early postoperative period and may be from the anastomosis or a biliary radical along the cut-edge of a split liver graft. Biliary strictures may occur early or months to years following transplant and may require endoscopic stents, percutaneous transhepatic stents, or operative revision.

29.7.3 Vascular Complications

Occurring in some 5.7–8.4% of pediatric liver transplant recipients, hepatic artery thrombosis (HAT) is the most common postoperative vascular complication in children and is a significant source of potential graft loss [4, 11]. In the literature, a variety of patient and technical factors, including hepatic arterial anatomy/size, recipient age, postoperative hypotension, rejection, and underlying hypercoagulability syndromes, have been attributed to the development of HAT [26–28]. HAT commonly occurs within the first week following transplant and most commonly results in biliary ischemia and biliary cholangiopathy with resultant cholangitis or development of cirrhosis in the subsequent months or years. In some instance, HAT results in fulminant liver failure requiring an emergent re-transplantation as a life-saving measure. Significant elevation in AST or ALT following transplantation should alert the clinician for potential HAT. Urgent duplex ultrasound or a CT angiogram should be performed to assess for HAT. Immediate return to operating room for arterial thrombectomy and revision is necessary to salvage the graft and minimize injury. Patients who develop biliary complications may require either percutaneous or endoscopic procedures to manage leaks or strictures. In some instances, operative revision of the biliary anastomosis is required. Regardless of the mode of treatment pursued, patients with ischemic cholangiopathy secondary to HAT are prone to long-term complications such as recurrent cholangitis and/or cirrhosis requiring repeated hospitalizations and in some instances re-transplantation [4, 29].

Portal vein thrombosis (PVT) is estimated to occur in 5–10% of children post-liver transplant and is a particular risk in recipients with a diminutive native portal vein as seen in biliary atresia [11, 30]. Clinically characterized by thrombocytopenia, worsening ascites, and gastrointestinal bleeding, portal vein thrombosis is diagnosed by ultrasonography or cross-sectional imaging such as CT scan or MRI. In cases where PVT is detected soon post-transplant, operative management remains the standard of care and typically consists of portal vein thrombectomy and revision of the anastomosis. Patients with late developing PVT may present with sequelae of

portal hypertension. The management of these patients typically involves the use of percutaneous methods to establish flow through the portal vein. In patients with portal vein strictures, percutaneous balloon venoplasty and stenting may be utilized [11].

In very rare instances, thrombosis or kinking of the hepatic veins may occur leading to graft thrombosis and potential graft loss. Although more common in segmental grafts due to the potential for the liver to twist around the hepatic vein anastomosis, hepatic vein thrombosis may be seen in whole allografts as well. Regardless of the cause, the treatment requires emergent reoperation and typically involves repositioning the allograft and revising the hepatic vein anastomosis if necessary. Chronic hepatic vein thrombosis or stenosis may also develop, and in addition to pursuing a hypercoagulable workup and anticoagulation, these patients are best treated by percutaneous venoplasty [31].

29.8 Post-Transplant Medical Complications

29.8.1 Acute and Chronic Rejection

As many as 50–60% of pediatric liver transplant recipients develop at least one episode of acute cellular rejection (ACR) in the weeks and months following transplant [4, 31]. The majority of patients tend to be asymptomatic; however, some may develop fever and malaise. Laboratory tests commonly demonstrate elevated AST, ALT, and GGT. Definitive diagnosis is established following liver biopsy and histologic examination. Histologically, ACR is characterized by endothelialitis, bile duct injury, and lymphocytic infiltration. It is graded via the Banff scheme into mild, moderate, and severe [31, 32]. The treatment for ACR commonly involves high dose steroids, which are tapered over several months, along with close monitoring of maintenance immunosuppression to ensure consistent and adequate serum drug levels.

Chronic rejection (CR) frequently has a more indolent course over the course of many years and manifests as progressive fibrosis that can lead to cirrhosis, cholestasis, and eventual liver dysfunction. About 10% of liver recipients develop CR. As with ACR, CR is diagnosed by liver biopsy, with characteristic findings of vanishing bile ducts and areas of ischemic necrosis with fibrosis [32]. Chronic rejection remains difficult to treat, with therapies predominantly focused on increasing maintenance immunosuppression and minimizing symptoms related to cholestasis. In cases where CR results in end-stage liver disease, re-transplantation may ultimately be required [31].

29.8.2 Infections

Given that LT recipients are frequently hospitalized prior to transplant, thus increasing their risk of colonization with multidrug-resistant organisms, combined with the immunosuppressive drugs that are required postoperatively to prevent allograft rejection, infectious complications are the most common source of significant

morbidity and mortality for patients following LT [4, 31]. Patients are particularly prone to bacterial infections in the immediate postoperative period, with causative microbes typically including gram-negative organisms, enterococci, and staphylococcal species [31]. Patients are also susceptible to fungal infections, making a broad infectious workup necessary in cases with hemodynamic changes and fevers. Although patients are typically treated initially with broad-spectrum antibiotic and antifungal coverage in cases of suspected postoperative sepsis, careful review of microbial sensitivities, prior culture data, and close discussion with infectious disease providers are necessary to minimize exposure and the risk of developing drug resistance in transplant patients.

Viral infections with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are common viral infections seen in post-transplant pediatric recipients. The highest risk of these viral infections is in a seronegative recipient of a liver from a seropositive donor. Antiviral therapies, prophylactic protocols, and close monitoring of viral loads are required to manage these patients. Patients may present with viremia or at times with tissue-invasive disease.

Particular attention must be paid to pediatric patients with no prior exposure to EBV, as infection with this disease either at the time of transplantation or postoperatively poses a significant risk factor for the development of post-transplant lymphoproliferative disorder, which is caused by expansion of EBV-related B cells. PTLD is more commonly found in children than adults post-transplant [11, 31]. Some types of PTLD such as those with polyclonal expansion may respond to a decrease in the level of immunosuppression; however, the monoclonal forms of PTLD may require additional therapies such as rituximab alone or in combination with cyclophosphamide and prednisone [4].

29.9 Long-Term Outcomes

Due to advances in surgical and preservation techniques, as well as perioperative management and immunosuppressive therapies, liver transplantation has become a viable therapeutic option for children with end-stage liver disease resulting from a variety of congenital, metabolic, or malignant etiologies. Where once survival post-transplant was measured in months, 1-, 5-, and 10-year patient survival rates are currently reported at over 90%, 80%, and 70%, respectively [4, 20]. Although this is an outstanding achievement over the past several decades, more work is required, particularly in the fields of novel immunosuppression development, wider adaptation of technical-variant grafts, and cellular therapies such as human hepatocyte transplantation, in order provide as many patients as possible with life-saving therapies and improve their overall quality of life.

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Perioperative Management after Liver Transplantation

30

Naresh Shanmugam and Anil Dhawan

There is wide variation in perioperative management of liver transplantation in children. Apart from age and disease-specific factors, every institute has its own protocol [1]. The indications for liver transplantation (LT) can be broadly classified into acute liver failure (ALF), chronic liver disease (CLD), metabolic liver disease (MLD) and liver tumours [2]. The overall principles of perioperative care remain the same with minor variations based on disease type. Perioperative management can be divided into preoperative assessment, intraoperative management and postoperative care.

30.1 Pre-Transplant Assessment

Most of the children with CLD and MLD are managed in primary centres and referred to tertiary or regional centres when LT is indicated. These children require a thorough re-evaluation at the transplant centre before being listed for LT. During the assessment, liver disease aetiology-associated comorbidities such as cardiac anomalies in Alagille syndrome, vascular anomalies in biliary atresia, etc., along with comorbidities that may have developed due to the course of liver disease such as hepatopulmonary syndrome, osteoporosis, etc., should be evaluated. The pre-transplant assessment consists of a number of biochemical, radiological and clinical evaluations that are discussed in a multidisciplinary meeting so that the team is aware of anticipated complications. The extent of these tests varies by centre, and some of the comments in this chapter reflect our institutional practice.

N. Shanmugam
Dr Rela Institute & Medical Centre, Chennai, India

A. Dhawan (✉)
Paediatric Liver, GI and Nutrition Center and Mowat Labs, King's College Hospital, London, UK
e-mail: anil.dhawan@nhs.net

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30.2 Liver Function and Associated Complications

Biochemical parameters looking at synthetic and detoxification function of the liver can help to assess the functional capacity of the liver. These biochemical indices are used to calculate the disease severity score that helps in prioritising the patients on the deceased donor waiting list [3]. Contrast-enhanced computed tomography (CECT) of the abdomen helps not only to assess the vascular anatomy and plan the surgery but also to look at certain disease-specific associated congenital anomalies like situs inversus and vascular anomalies in biliary atresia. Ascitic fluid culture is not part of routine pre-transplant assessment and is only needed when there is a history of recurrent spontaneous bacterial peritonitis (SBP). Routine screening endoscopy for varices is not recommended for children who have never had bleeding [4].

Renal Function Serum urea and creatinine are not perfect markers of renal function, and the gold standard test, isotopic glomerular filtration rate (GFR), is expensive and cumbersome. The estimated GFR using modified Schwartz formula has shown to predict more reliably the GFR in children [5]. Cystatin C is a non-glycosylated protein that is secreted by the kidney and completely catabolised in the proximal tubule with no re-absorption, which is a better screening tool for renal function. Samyn et al. showed that serum cystatin C is a reliable marker of kidney function, and a level of 1.06 mg/L was found predicting 51Cr-EDTA GFR < 80 mL/min/1.73 m^2 with a sensitivity of 91% and a specificity of 81% [6]. In clinical practice, however, the serum creatinine is used much more frequently.

Developmental Assessment It is a well-known fact that children with liver disease, particularly those with cholestasis during infancy, may have neurodevelopmental delay, and this delay would affect all the domains of development such as physical/motor mental/cognitive/and language [7]. Severe neurological impairment seen in few of the MLD patients is due to neuronal damage caused by ammonia and/or toxins. Early LT is advocated in such cases to prevent further damage. Formal developmental assessment using standardised scales during pre-transplant period will help in monitoring and supporting the patients during post-transplant period.

Nutritional Assessment Protein energy malnutrition (PEM) increases mortality and morbidity after liver transplantation [8]. PEM adversely affects wound healing and muscle strength and prolongs ventilator dependency. Organomegaly, ascites and peripheral oedema interfere with routine anthropometric measurements and make them unreliable. Mid-arm muscle circumference (MAMC) and triceps skin fold thickness in small children can provide an inexpensive and easy measure of their nutritional status, as the upper arm is less likely to be affected by oedema. The concept of skeletal muscle mass (SMM) in the body in proportion to weight gives more accurate measurement of nutritional status. Psoas muscle cross-sectional area at the L3 vertebral level by computed tomography (CT) scan or magnetic resonance imaging (MRI) gives reliable information on skeletal muscle mass (SMM). More accurate measurements can be done using bioelectrical impedance which can give data on

muscle mass, fat and fluid. These measurements could help in identifying sarcopenic obesity, where the muscle has fat infiltration and an increase in visceral fat [9].

Vaccination and Virology Screening It is imperative that the children undergoing LT should be up to date on their vaccinations as there were safety concerns and efficacy of live vaccines after transplant [10]. More recent international consensus confirms the safety of measles mumps rubella and/ or varicella vaccine in children after 1 year of liver or kidney transplant and 2 months after acute rejection episode and on "low-level" immune suppression. If possible, paediatric patients should receive all missed vaccines as per the recommended immunisation schedule. In case of live vaccination, LT should not be offered for 4 weeks after vaccination. Recipient serologic status for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) helps with planning immune prophylaxis based on donor serology.

30.2.1 Cardiopulmonary Assessment

Cardiovascular abnormalities such as structural heart disease, myocardial abnormalities, vascular anomalies and conduction defects can cause hemodynamic instability intraoperatively or after the transplant. Appropriate diagnostic tests and treatment are very important. Diagnostic tests include pulse oximetry in the upper limb and lower limb, electrocardiography (ECG), echocardiography (ECHO), contrast-enhanced ECHO and cardiac catheterisation, if necessary. Some of the common problems encountered are peripheral pulmonic stenosis in Alagille syndrome, and it is crucial to evaluate the right heart pressure, as elevated pressure can cause graft congestion and failure. If pressures are high, remedial measures such as balloon angioplasty can be offered prior to transplant if feasible. RV pressure more than 60 mm HG may be considered to be severe obstruction, and if no intervention can be done to decrease the pressure, then these patients cannot be listed for LT. The same principle applies to patients with severe portopulmonary hypertension. If, in spite of medical management, there is a persistent mean pulmonary artery pressure > 45 mm of Hg, this is a contraindication for LT. Patients with no structural heart defect and with an O2 saturation < 95% on room air should have a contrast ECHO/CT pulmonary angiogram to look for hepatopulmonary syndrome (HPS).

Pre-transplant evaluation might require additional specialist consultation with a dentist, ENT surgeon, etc., if there is suspicion of a septic focus. These specialist consultations are usually done based on the recommendation of the treating hepatologist after thorough clinical examination of the patient.

With completion of the pre-transplant assessment, the patient is presented at a multidisciplinary meeting consisting of hepatologist, transplant surgeon, anaesthetist, intensivist and transplant coordinator SOCIAL WORKER, NUTRITIONIST, PHARMACIST, AND INSURANCE COORDINATOR. Once the team agrees that the evaluation and risk assessment are complete, the patient is listed for transplant. There are scoring systems, such as the paediatric end-stage liver disease [PELD], which are used to prioritise children on the deceased donor list. Higher scores are associated with increased post-transplant morbidity such as prolonged hospital

stay, ionotropic requirement, kidney injury, etc. [3]. There are certain conditions where PELD exceptions are given, such as transplant for liver malignancy, but it has been shown that 48% of listed children received the organ either due to a PELD exception or prioritisation due to sudden deterioration of the patient's condition [11].

30.2.2 Pre-Transplant: Admission

Patients are generally admitted a day prior to the liver transplant for a living donor case, or whenever there is a deceased donor organ for the patient. Clinical examination and biochemical tests are performed to look for any biochemical abnormality or infection. The common electrolyte abnormality noted in CLD is hyponatremia. A serum sodium lower than 130 meq/L was associated with neurologic disorders, renal failure and infectious complications within the first month after transplantation [12]. In the pre-transplant scenario, it is ideal to gradually raise serum sodium to 125 meq/l prior to surgery, as the use of sodium containing fluids intraoperatively can raise the serum sodium dramatically over a short period of time. Rapid serum sodium elevation can result in central pontine myelinolysis, quadriplegia, coma, etc. For children with metabolic disorders, a written plan is attached with case notes regarding preoperative and intraoperative metabolic medications and precautions.

30.2.3 Intraoperative Care

LT is a major surgery with long operative time, and it is essential to identify hemodynamic fluctuations early so that appropriate interventions can be implemented. Pulse oximetry, core body temperature, invasive central venous pressure (CVP) and arterial blood pressure monitoring, along with frequent arterial blood gas analysis, are routine for monitoring cardio-respiratory dynamics. LT can be associated with a large volume of blood loss, particularly in patients with a previous Kasai portoenterostomy [13]. In liver disease, there is a decrease in both procoagulant and anticoagulant levels, platelets, etc., and haemostasis is altered [14]. Surgery in a coagulopathic patient is a challenge as overcorrection can trigger a thrombotic cascade and undercorrection can be associated with increased bleeding.

Prothrombin time (PT)/international normalised ratio of PT (INR)/activated partial thromboplastin time (aPTT) assess only plasma events in haemostasis and do not reflect how platelets and other cellular components contribute to coagulation. Haemostasis in liver disease is best assessed using viscoelastic tests such as thromboelastography (TEG) and thromboelastometry (TEM) that assess clot formation in whole blood, including plasma and cellular components [15]. TEG provides a graphical representation (Fig. 30.1) of assembly of a clot in whole blood and provides an assessment of overall haemostasis [16]. Intraoperatively, TEG helps in choosing the appropriate blood components for correcting the coagulopathy. Table 30.1 shows TEG parameters and its correlation with coagulation cascade.

Changes in ventilatory parameters (increase in peek inspiratory pressure to deliver the same set tidal volume) while closing the abdomen, particularly when

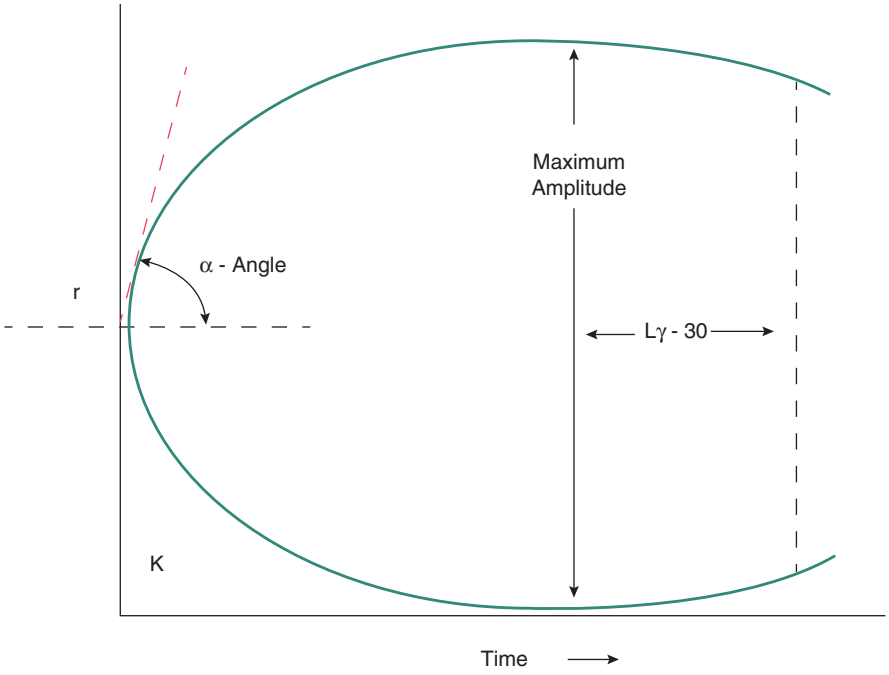

Fig. 30.1 Figure showing standard TEG in a normal person. Reproduced with permission from Shanmugam N., V.K., *Coagulopathy in Liver Disease*, in *Pediatric Liver Intensive Care*, D.A. Shanmugam N., Editor

Table 30.1 TEG parameters and its correlation with coagulation cascade [16]

TEG parameters	Normal range	Corresponds to	Correlates with
Reaction time in minutes (r)	2.5–7.5 min	Time between beginning of the clotting cascade and the initial formation of fibrin	Procoagulant factor levels, INR and aPTT
Kinetic time in minutes (k)	0.8–2.8 min	Time between initial fibrin formation to reach a specific clot firmness	Fibrinogen levels and platelet function/ number
α-angle in degrees	55.2–78.4	Deals with kinetics of clot formation Rate of fibrin formation and cross-linking of platelets	Fibrinogen levels and platelet function/ number
Maximum amplitude in mm	50.6–69.4	Measures the maximum clot strength	Fibrinogen levels and platelet function/ number
Clot lysis at 30 minutes (Ly-30; in percentage)	0.0–7.5	Percentage of clot dissolution within 30 mins of maximum amplitude	Fibrin degradation products

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there is a large graft in a small child, warrant either skin closure or PTFE graft closure of the abdomen. Tight abdominal closure can cause compartment syndrome and also make ventilation difficult.

30.2.4 Postoperative Care

Postoperative handover is usually done by the anaesthesiologist to the paediatric intensivist and the nurse. Important intraoperative events to be discussed at handover and parameters to be checked by the receiving team are outlined in Table 30.2. Post-transplant parameters which require immediate notification of the transplant surgeon are shown in Table 30.3.

Table 30.2 Important intraoperative events to be discussed at handover and patient checklist on receiving

• Issues at induction of anaesthesia, ET size, central lines, arterial lines
• Donor issues if any, condition of donor liver.
• Cold ischemic time, graft recepient weight ratio (GRWR), graft weight
• Duct to duct or Roux-en-Y
• Type of abdominal closure and airway pressures on closure
• Blood loss, amount of blood products transfused, fluid balance and requirement of inotropes
• Urine output, electrolyte imbalances
• Peak INR, peak lactate, shifting INR, platelet and lactate, TEG report
• Time of antibiotics, antifungal and immunosuppression
Parameters to check by the receiving team
• **Airway (tube position, leaks)**
• **Breathing (air entry, chest rise)**
• **Circulation (CRT, BP)**
• Temperature (need for warmer—WHAT IS THIS?)
• ABG on receiving (see BE, pH, lactate)
• X-ray chest (line position, ET position, NG position)
• Send bloods for urea and electrolytes, full blood count and INR

Table 30.3 Parameters which require immediate alert to transplant surgeons

1. Hb > 11 or < 9 gm/dL
2. Platelets <20,000 (hypersplenism/sepsis/platelet dysfunction)
3. Drain fluid is bloody/turbid/bilious
4. Increasing serum lactate
5. Increased RI in liver (>0.8)
6. Electrolyte imbalances
7. Unexplained tachycardia
8. Altered flow signals of hepatic vasculature on Doppler ultrasound

30.3 Airway and Ventilation

The mode of ventilation is based on local practice and expertise; usually, a standardised inspiratory volume is used, as intra-abdominal pressure can affect the peak inspiratory pressure (PIP). It has been shown that children with difficulty in closing the abdomen due to graft size had prolonged ventilation [17]. Peek end expiratory pressure (PEEP) is kept at 5–8 cm. Inadequate PEEP will lead to alveolar collapse, and high PEEP can cause decreased vascular return. Pressures and FiO2 should be adjusted so as to maintain arterial saturations over 95% and PaCO2 between 35 and 45 mmHg. In case of hepatopulmoary syndrome (HPS) use, minimal Fio2 is utilised to keep saturation just above 88%. When saturation is persistently lower than 85% despite 100% oxygen, add nitric oxide at a standard dose (max 20 ppm). Management of post-transplant hypoxemia in HPS is outlined in Fig. 30.2 [18]. Right lower lobe collapse and pleural effusion are common after liver transplantation, and a chest drain for pleural effusion can be placed if necessary [17]. Right hemidiaphragm elevation and right lower lobe atelectasis are common and should be treated conservatively; bronchoscopy is indicated if conservative measures fail or the atelectasis is thought to be the cause of delay in extubation. Patient is gradually weaned off ventilator support and extubated when hemodynamically stable with improving LFTs

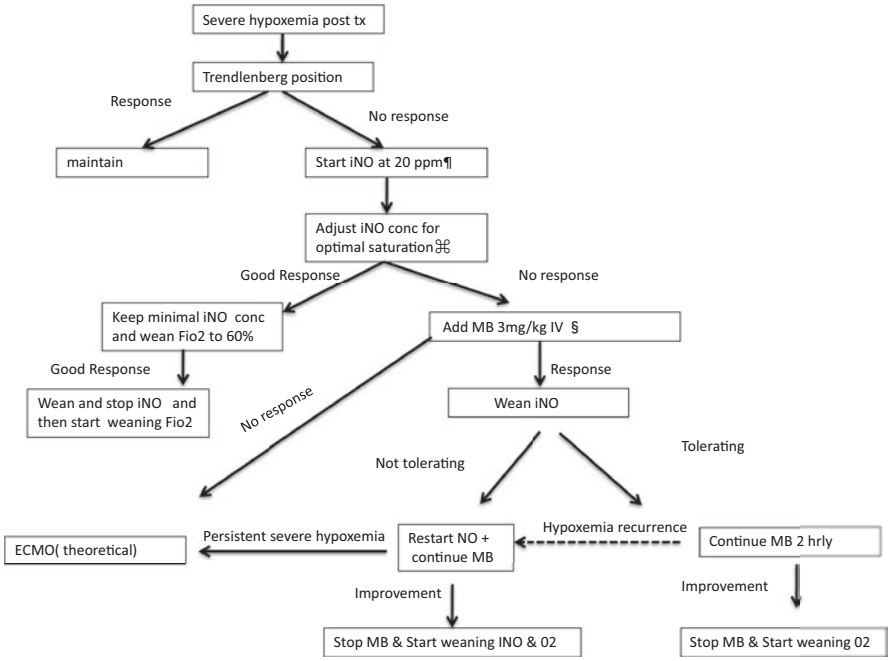

Fig. 30.2 Practical management protocol of hepatopulmonary syndrome during post-liver transplant period. Reproduced with permission from Sundaram K., D.A., Shanmugam N., *Pulmonary Complications of Liver Disease*, in *Pediatric Liver Intensive Care*, D.A. Shanmugam N., Editor

and lactate levels and a normal doppler ultrasound of liver. Good chest physiotherapy and incentive spirometry post extubation helps in minimising respiratory complications.

30.4 Fluids and Nutrition

LT is associated with large volume fluid shifts due to blood/fluid loss and replacement with colloids and crystalloids. It is difficult to access the intravascular fluid status accurately based on simple input/output. CVP can be used as a surrogate marker of intravascular fluid status and is maintained around 8–10 CMS of water. Under filling (low CVP) can cause low blood pressure and reduce perfusion to the graft, while over filling (high CVP) can cause passive graft congestion. Though CVP gives a fair idea about intravascular fluid status, it is not the most sensitive way of measuring intravascular volume [19]. Though there are no recommended guidelines on post-LT fluid management, maintenance fluids are started at 2/3 of daily requirements. Glucose and electrolytes are added to maintenance fluids to give a glucose infusion rate (GIR) of 4–6 mg/kg/h, sodium of 2–4 meq/kg/day and potassium of 1–2 meq/kg/day. Adult studies have shown that a restrictive fluid management strategy, either intraoperative or in the postoperative period, did not increase the risk of acute kidney injury and in fact was helpful in decreasing ICU stay, pulmonary complications [20], etc. Potent diuretics such as IV bolus dosage should be avoided, as sudden large volume diuresis can cause hypotension and decreased graft perfusion and increase the viscosity of blood and can predispose to vascular thrombosis. Lactate is used as surrogate marker of graft recovery, and it reaches a peak before reperfusion of the graft and then gradually comes down. Progressive rise in the lactate is a serious concern as sepsis, hypotension and decreased/absent hepatic vascular flow can cause this. Rarely, transient post-surgical insulin resistance leading to anaerobic metabolism and a rise in the lactate is treated with insulin and a dextrose drip. Children will require adequate protein, calories and vitamin supplements for post-transplant liver regeneration and wound healing [21]. Based on the type of bile duct anastomosis (duct to duct, old/new roux loop), enteral feeds are started between post-op days (POD) 1 to 5. Consider TPN from POD 1 in malnourished children and in those (bowel perforation) in whom it would take a few days to reach full enteral feed.

30.5 Inotropes

Adequate blood pressure has to be maintained for good allograft liver perfusion. Consider vasopressors in patients having low blood pressure which is unresponsive even after adequate fluids are given. Though CVP gives a rough idea about intravascular fluid status, it is not an ideal test. IVC collapsibility on ultrasound and ultrasonic cardiac output monitor (USCOM) gives more accurate measures of intravascular fluid status and helps in choosing fluid replacement or pressors [22]. Noradrenaline is the vasopressor of choice due to its alpha effects increasing both

systolic and diastolic blood pressure. Vasopressin or its synthetic analogue terlipressin is used as a second line when hypotension secondary to decreased SVR is refractory to norepinephrine.

30.6 Immunosuppression

There is wide variation in immunosuppression protocols among centres. The standard LT immunosuppression protocol described below reflects our practice.

All LT patients will receive IV methylprednisolone at a dose of 10 mg/kg before reperfusion of the allograft. On postoperative day (POD) 1, a dose of 2 mg/kg (max 40 mg) is given as a single dose IV in morning and continued for 3–5 days. Then it is gradually weaned over the next few weeks to a long-term maintenance oral dose of 1 mg daily [23]. A slightly higher dose is continued as maintenance in children who had LT for autoimmune liver disease [24]. Once the patient can tolerate feeds, steroids can be given orally.

Of the calcineurin inhibitors (CNI), tacrolimus is used as first-line immunosuppression as it has maximum efficacy with a relatively low side effect profile. Usually 0.15 mg/kg is given in two divided doses, and the dosage is titrated to maintain tacrolimus trough levels between 8 and 12 ug/L initially. Low to high normal trough levels are maintained based on clinical need. In patients with renal dysfunction or frequent infection/high viral titres of EBV/CMV, lower levels are maintained. In the case of late acute cellular rejection, a decision may be made to run higher levels of tacrolimus instead of adding in an additional agent. Cyclosporine is rarely used as first line and is used only when tacrolimus is contraindicated. One of the major side effects of tacrolimus is renal dysfunction. Either MMF or azathioprine (or in certain cases sirolimus) may be added to tacrolimus (in the case of sirolimus after the 28th POD as there is an association with hepatic artery thrombosis in this time period), thus allowing a lower level of tacrolimus without loss of efficacy.

Basiliximab is a monoclonal antibody directed against the α chain of the IL-2 receptors (CD25) used in combined liver kidney transplant with significant renal dysfunction prior to transplant; it is given at the time of the transplant and on postop day 4 to allow lower levels of tacrolimus in the first few weeks particularly. Some transplant programmes use basiliximab induction as a part of a steroid-free or low steroid regimen [25].

30.7 Renal Dysfunction

Patients transplanted with the usual surgical technique are at risk for acute tubular necrosis (ATN) due to the vena cava being clamped above the renal veins. Urinary sodium helps to distinguish between hepatorenal syndrome (HRS) and ATN. Urine sodium will be low in HRS and high in ATN. Adult studies have shown that preexisting hepatorenal syndrome, intraoperative blood transfusion >2.5 units, hypotension and low intravascular volume status can cause kidney dysfunction immediately post-surgery [26].

In the case of renal dysfunction-associated acidosis, electrolyte imbalance, hyperammonemia, uraemia and fluid overload will require renal replacement therapy (HD/CVVH).

30.8 Radio Imaging

Ultrasonography (USG) along with Doppler ultrasound (DUS) is the preferred post-LT screening of the allograft liver. It can detect vascular and biliary complications, intra-abdominal fluid collections and blood flow dynamics in the transplanted organ. During routine post-LT DUS, the hepatic artery and its intrahepatic branches, main portal vein and its branches, hepatic veins and IVC are screened. The resistive index (RI) of the hepatic artery is a calculated index using peak systolic velocity (PSv), diastolic velocity (Dv) and systolic acceleration time (Sat); the time taken to reach PSv after trough Dv RI is calculated using the formula (PSv – Dv/PSv), which usually range between 0.6 and 0.8 in the normal liver. An elevated RI indicates increased resistance to arterial flow seen when the graft becomes stiff, such as in acute rejection.

Thrombosis and anastomotic stenosis are the common complications affecting the portal vein (PV) after LT. Frequency and duration of the ultrasound screening following LT vary by program and the individual patient. Our policy is to do daily DUS for first 5 days post-op. In high-risk patients (small vessels, interposition graft, etc.), twice daily Doppler US is performed. If there is any concern regarding arterial/venous flow signals, a CT is performed [27]. Early identification of vascular thrombosis helps with appropriate surgical/radiological interventions. Figure 30.3a demonstrates a hepatic angiogram done on POD 1 with no flow due to hepatic artery thrombosis; Fig. 30.3b shows good intrahepatic flow following thrombolysis.

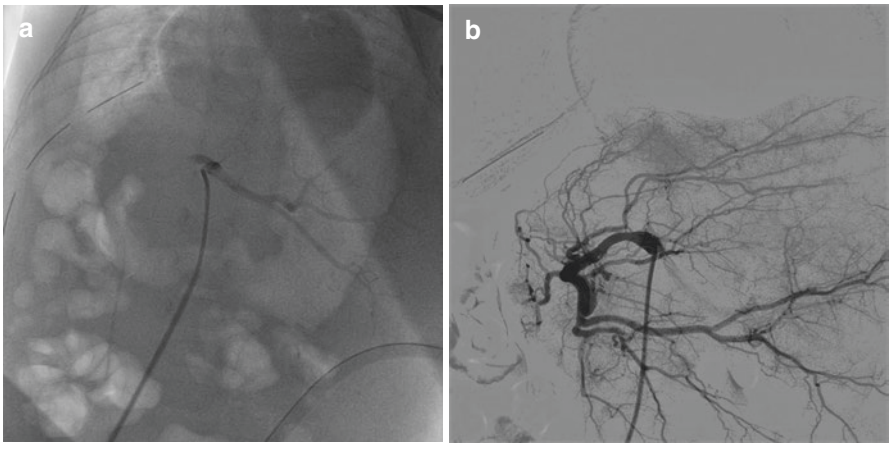

Fig. 30.3 (**a**) Hepatic angiogram of left lateral segment after hepatic artery thrombosis. (**b**) Hepatic angiogram after thrombolysis

30.9 Infection Control

Empiric antibiotics are given to all LT patients; the type and the duration of the course vary according to the centre. Patients are prone to infections because of impaired polymorphonuclear leukocyte function, impaired cell-mediated and humoral immunity and diminished opsonic and complement activity. Some of the factors that predispose to infection are presence of indwelling catheters, bile leak, acid suppressants and immunosuppressant drugs. Usually, the antifungal fluconazole (6 mg/kg/day) is given intravenously for 5 days and then orally. It can be stopped after 2 weeks. There are no recommendations regarding long-term antibiotic prophylaxis. Sometimes, early signs of sepsis could be subtle, including food intolerance, hypoglycaemia and irritability. During the postoperative period, children with hyperthermia/hypothermia and unexplained tachycardia/tachypnoea should be investigated for sepsis. Ganciclovir treatment is initiated if recipient is negative and donor is positive for CMV IgG. Treatment is usually given for 2 to 3 weeks and short-term prophylaxis in the form of a once-a-day oral dosing for 3 months, depending on local institutional policy.

30.10 Anticoagulation

Post-LT anticoagulation is used in nearly all LT programs, to prevent thrombosis of the hepatic vessels. There is no specific recommendation on the type and duration of anticoagulation prophylaxis. Voulgarelis et al. in survey-based study showed that the majority of centres performing paediatric LT used heparin [28]. Our practice is to start anticoagulation when the INR <2 and platelets >50,000. We use low molecular weight heparin—Fragmin 50 U/kg/dose Q12H or Clexane 1 mg/kg/dayQ24H. Heparin is used only for high-risk patients where there was intraoperative thrombosis or if there was some concern about vascular flow on intraoperative DUS. Usually 75 U/kg is given as a loading dose followed by 20 U/kg/h, and the dose is titrated to maintain aPTT levels between 80 and 100. Once graft function is stable and there are no planned interventional procedures such as liver biopsy, LMH is changed over to oral aspirin 3–5 mg/kg/day. It has been shown that early HAT was not significantly associated with anticoagulation and antiplatelet strategies [29].

30.11 Immediate Post-Transplant Complications

30.11.1 Primary Non-function (PNF) of the Liver Graft

Graft does not function in immediate postoperative period without vascular issues or rejection. More common with deceased donor transplants and usually associated with factors such as older donor age, prolonged donor ICU stay, prolonged cold ischemic time, etc., this situation warrants emergency re-transplantation.

30.11.2 Vascular Complications

The risk for hepatic artery thrombosis (HAT) and portal vein thrombosis should be closely monitored, especially in the first 5 days following transplantation. Regular DUS screening will help in identifying the problem. If there is suspicion of HAT, a CT angiogram is recommended as sometimes collaterals can mimic hepatic artery flow [30]. Venous outflow obstruction is less frequently encountered and may present as large volume drain output/graft dysfunction with a biopsy showing sinusoidal dilatation.

30.11.3 Complications Due to a Large Graft

Graft-to-recipient weight ratio (GRWR) is the ratio of graft weight in kgs/body weight in kgs × 100. GRWR >4 is considered to be a large graft, and problems such as difficult abdominal closure and the possibility of abdominal compartment syndrome and respiratory compromise can be anticipated. In such a scenario, either skin closure without muscle closure is done or abdomen is closed temporarily using PTFE mesh. Portal hypoperfusion can happen in a large allograft which can elevate the liver enzymes.

30.11.4 Functional Small for Size Syndrome

GRWR <0.8 is considered to be a small graft. It is of concern in adult living donor and split LT, while in the paediatric LT setting, the recipient is relatively smaller, and so we rarely encounter this issue. However in some cases, even with an adequate size organ, the patient can have functional small for size due to portal hyper perfusion (preexisting severe portal hypertension) or due to a steatotic donor liver. A progressive increase in bilirubin, intractable ascites and coagulopathy indicates a small size graft. Drugs that decrease portal flow such as propranolol, octreotide and terlipressin or splenic artery embolisation or ligation may be helpful.

30.11.5 Bleeding

Change in the colour/volume of the drain fluid from clear to blood stained or frank blood should raise the suspicion of intra-abdominal bleeding. It is imperative that the hemogram and coagulation parameters are checked and the patient is stabilised with blood transfusion and coagulation correction before being taken to the operating room for re-exploration. Acute portal vein thrombosis can occasionally present as a variceal bleed, and bleeding from the bile duct anastomosis (the Roux-en-Y hepaticojejunostomy) may also present as melena. CT angiogram can help in identifying an arterial bleed, which can be treated by radiological intervention.

30.11.6 Abdominal Drain Fluid

Colour and volume of the drain fluid indicate the type of fluid. A bile leak can originate from the bile duct anastomosis or from the cut surface of the liver. It may also present as a loculated collection which maybe asymptomatic or manifest systemic symptoms. Tissue oedema at the anastomotic site could temporarily increase intrabiliary pressure and could cause a leak. Waiting for a few days for the oedema to settle down and establish patency of the biliary anastomosis may be helpful. Large volume bile leaks or leaks with signs of infection need biliary stenting or surgical re-exploration. Turbid drain fluid or a bile leak with raised fluid amylase is suggestive of intestinal perforation. With extensive surgical dissection of the retrocaval space, lymphatic leak may be encountered. Chylous drainage can be managed with fat-free or MCT-based feeds, but if it persists for a longer time, medications such as octreotide with or without total parenteral nutrition can be given.

30.12 Conclusion

Though there is variation in perioperative care among centres, the principles of treatment remain the same. The LT process involves many specialists, and it is essential to have roles and responsibilities of each person on the team clearly defined so that there is coherence in communication among the team members and with the parents. With improved intensive care management and improvised surgical techniques, patient survival and graft survival have greatly improved. This leads to the long-term commitment of the transplant team to continued follow-up and patient education, focusing on improving the quality of life after LT, in addition to optimising survival.

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Immunosuppression after Liver Transplantation in Pediatric Population

31

Veysel Umman, Murat Zeytunlu, and Sukru Emre

31.1 Introduction

Pediatric liver transplantation has become the standard of care for children with end-stage liver disease, owing to advancement of surgical techniques including split liver transplantation and living donor liver transplantation which increased available organs. Furthermore, technological advancements, better understanding of disease process, patient selection and improved pre- and postoperative ICU care, better managing of short- and long-term complications secondary to increasing experience, and team effort have played important role for patient outcomes and satisfaction. In addition to these factors, understanding the immunological issues and development of new immunosuppressive medications have made the field of liver transplantation as an acceptable treatment modality. These advancements improved outcomes dramatically to 94% 1-year survival [1, 2]. Immunosuppressive therapy has substantial contribution in these results by prevention of rejection and early complications. On the other hand, immunosuppressive management of pediatric recipients has continued to be challenging for various reasons. In this chapter we aim to overview the current immunosuppressive medications, their mechanism of actions, pharmacokinetics, pharmacodynamics, side effects, and immunosuppressive strategies/protocols.

31.2 Background

Beginning from the early days of LT, immunosuppressive regimens showed continuous evolution. Corticosteroids and azathioprine were the main regimens until the 1980s, when initially with the introduction of cyclosporine [3] and later with the

V. Umman · M. Zeytunlu · S. Emre (✉)
Department of General Surgery, School of Medicine, Liver Center of Excellence/Bornova, Ege University, İzmir, Turkey

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development of FK506, tacrolimus [4] and calcineurin inhibitors (CNI) improved 1-year survival rates drastically. Although CNI became the mainstay of immunosuppressive therapy in organ transplant patients and was used for induction regimen as well as in the rescue protocol in a state of rejection, the frequency of side effects, mostly renal and neuro toxicities, continued the quest for novel immunosuppressive agents with less side effect profiles. In 1995, mycophenolate mofetil (MMF) and later in 1999 sirolimus (SRL) were approved for use in transplantation [5]. In order to limit the side effects of CNI, lately selective monoclonal antibodies (Abs) targeting the interleukin-2 receptor (IL-2R) were introduced.

With all the new available agents and gathering data, immunosuppressive protocols in pediatric liver transplantation differ among transplant centers. Varying protocols are based on early post-transplant complications, early occurrence of rejection episode(s), side effects profile, recipients' growth curve, and availability of new immunosuppressive agent around the world. Since there is no tool to define an "immune threshold" of a given patient, finding the optimal level of immunosuppression is always challenging. Therefore, starting immunosuppressive medication with higher doses immediately after liver transplantation (LT), gradually tapering their doses, and discontinuing some of the immunosuppressive medications have been the only rational way surgeons and physicians have been following.

However, as we all know, children are not small adults. Therefore, laws of pharmacokinetics and pharmacodynamics for immunosuppressive medications in relation to metabolization rate of drugs, surface area of children, and drug absorption demonstrate differences in pediatrics. We should keep this in mind and try to focus on evidence-based data gathered from children and liver transplantation, not just concentrate on studies about immunosuppressive therapy involving adults or other organ recipients but especially from pediatric liver transplantation studies. This lack of data and guidelines contributed to variations of protocols among centers in terms of both selected agents and their doses.

Another area of concern that comes with immunosuppression is infections. While the majority of the pediatric recipients are naïve to EBV and CMV pretransplant (especially in the USA and Europe), most of their donors are positive, setting the stage for post-transplant opportunistic viral infections and related problems such as post-transplant lymphoproliferative disorder (PTLD). In addition to creating vulnerability for opportunistic infections, immunosuppressive medications have many side effects, which are mainly dose related (Table 31.1). As a result, physicians' task of managing the immunosuppressive medications requires a cautious balance between avoiding all side effects of these medications including infections, nephro- and neurotoxicities, cancer development, or post-transplant lymphoproliferative disorder (PTLD) while making sure that patients will not develop rejection episodes.

Lastly, in addition to the importance of immunosuppressive agent itself and managing/adjusting this medication, long-term graft survival also depends heavily on recipient's adherence to medications in pediatrics, especially in teenagers. After improved survival rates over the years, the frontier in pediatric liver transplantation has shifted to improving quality of life after liver transplantation and prevention of

Table 31.1 Immunosuppressive drugs used in liver transplantation

Drug group	Agent	Target	Affect	Side effect
Steroid	Corticosteroid	Intracellular glucocorticoid receptor	Block transcription of genes that code for ILs (IL 1,2,6) and cytokines (TNF- α, IFN- γ) Decrease B cell expression Inhibit T cell proliferation Suppress COX expression	Osteoporosis, DM, hyperglycemia, weight gain, increased infections, adrenal insufficiency, growth failure, glaucoma, central obesity, mood swings
Calcineurin inhibitors	Cyclosporine	Binds to cyclophilin and competitively binds and inhibits phosphatase activity of calcineurin	Inhibit calcineurin phosphatase which inhibits T cell signal transduction and activation more selectively and block IL-2 secretion	Nephrotoxicity, glucose intolerance, hyperlipidemia, hypertension, DM, high K level, neuropsychiatric problems, malignancy, hirsutism, gingival hyperplasia, susceptibility to infections
Calcineurin inhibitors	Tacrolimus	Binds to FKBP-12 and competitively binds and inhibits phosphatase activity of calcineurin	Inhibit calcineurin phosphatase which inhibits T cell signal transduction and activation more selectively and block IL-2 secretion. IL-3,4, granulocyte-macrophage colony-stimulating factor, interferon gamma, and TNF-alpha are also decreased	Nephrotoxicity, neurotoxicity, glucose intolerance, hypertension, hyperkalemia, hypomagnesemia, hypophosphatemia, alopecia, pruritus, headaches, lack of appetite, gout, increased susceptibility to infection, and malignancy

(continued)

Table 31.1 (continued)

Drug group	Agent	Target	Affect	Side effect
Antimetabolites	Azathioprine Mycophenolate mofetil	Metabolites bind DNA Inosine monophosphate dehydrogenase	Inhibits purine synthesis. Blocks DNA and RNA synthesis Inhibits inosine monophosphate dehydrogenase, thus preventing de novo guanosine synthesis. Suppress primarily T cell and B cell production and antibody formation	Bone marrow suppression Vomiting, diarrhea, abdominal pain and cramps, fatigue, hair loss, bone marrow suppression mainly neutropenia, increased opportunistic infections, sepsis
mTOR inhibitors	Sirolimus Everolimus	FKBP-12	Blocks IL-2 secretion at cell division level by interfering with B and T cell activation	Wound healing, incisional hernia, hepatic artery thrombosis[a], hyperlipidemia, mouth ulcers, pleural effusion, dermatitis, joint pains, bone morrow suppression, proteinuria
IL-2 receptor blockers	Daclizumab was removed from the market Basiliximab	IL-2 receptor alfa chain (CD 25 antigen)	Block the IL-2 receptor on the activated T cells, depleting them and preventing signal transduction	Coughing, fever, tremors, loss of energy, weakness, pain or burning with urination, easy bruising or bleeding, swelling of body or face, body aches, unusual, insomnia, flu symptoms, nausea, vomiting

[a]Hepatic artery thrombosis related to sirolimus has been discussed in detail under mTOR subtitle

immunosuppression side effects and their complications, followed by better adherence, especially in teenagers, which can be assured only by open communication and close relationship of the patient and family with their physicians. By achieving this adherence, a better quality of life and a normal growth and development of the child can be accomplished.

31.3 Immunosuppressive Agents

When we look at the last SRTR reports, we see a trend for decrease in the chronic use of steroids. In 2017 annual SRTR report, 56.6% of pediatric liver transplant recipients did not receive any induction therapy, while 27.6% received interleukin-2 receptor antagonists, and 16.7% received a T cell depleting agent [6]. The most preferred initial immunosuppression regimens were tacrolimus and steroids (50.6%) and tacrolimus, mycophenolate mofetil, and steroids (25.0%).

In the 2020 annual SRTR report, pediatric liver transplant recipients who did not receive any induction therapy increased to 63.5%. The preference for initial immunosuppression regimens also changed, and the commonly preferred regimes were tacrolimus, MMF, and steroids with 38.6% and tacrolimus and steroids with 36.9% [7].

31.3.1 Corticosteroids

Corticosteroids have played an essential role in immunosuppression since the early days of transplantation. They are useful for both as an induction agent and for treatment of rejection. Most centers rely on corticosteroids, and patients use them at the time of discharge and for the first 30 days post-transplantation [8].

Mechanism of Action Corticosteroids act via intracellular glucocorticoid receptors which are existent in almost every cell in the body. They act via suppression of antibody production and cytokine synthesis (IL-1, IL-2, IL-6) and reduce T cells, B cells, as well as neutrophil activity [5].

Side Effects Although they are traditionally and commonly used, there are well-established adverse effects of corticosteroids, especially in high doses and with cumulative effect. Growth impediment has been found in earlier studies investigating long-term survivors of liver transplantation [9], and the SPLIT registry revealed that 23% of 10-year survivors of pediatric liver transplantation experienced impaired linear growth [2]. Steroid use was also linked to diabetes, hyperlipidemia, weight gain, hypertension, and increased infections in the post-transplant period [10]. Cushingoid facies and striae along with mood swings can also be seen. Although these side effects resolve and the growth catch-up is achieved when steroids are weaned, weaning should be performed carefully to avoid adrenal insufficiency [11, 12].

Current Strategies of Optimal Use Concern for these side effects of steroids encouraged pediatric transplant centers to minimize their use, or completely switch to steroid-free protocols [13–15]. Withdrawal time differs among programs between 3 months and 12 months [16]. The choice of which children to be weaned from steroids is still vague, although those with autoimmune hepatitis have a high incidence of recurrence and should not be weaned [17]. However, compared to minimi-

zation of steroid dose, or withdrawal during the first year, complete steroid avoidance and replacing steroid with basiliximab to combine with tacrolimus have shown better overall results, including both growth and graft function [18, 19].

31.3.2 Calcineurin Inhibitors

Although they are among the early agents of immunosuppressive therapy, together with corticosteroids, CNI are the backbone of immunosuppression. Tacrolimus and cyclosporine are two main calcineurin inhibitors.

With the introduction of cyclosporine, there has been a drastic change in the outcomes of solid organ transplantation, but unfortunately cyclosporine has a narrow therapeutic window [20]. Nephrotoxicity associated with tacrolimus led experts to concentrate on therapeutic monitoring of these drugs to minimize the side events, as well as to detect sub-therapeutic dosing. Although major side effect profiles of CNI inhibitors are similar, especially in pediatric liver transplantation, tacrolimus is the preferred agent due to cyclosporine side effect of hirsutism [12].

Mechanism of Action Tacrolimus binds to cyclophilin and cyclosporine binds to FKBP-12, which are both a family of intracellular proteins called immunophilins. When the drug and immunophilin complex are formed, it competitively binds to and inhibits the phosphatase activity of calcineurin, which ends up indirectly blocking the transcription of cytokines especially interleukin-2 genes in T cells. Moreover, transcription of IL-3, IL-4, granulocyte-macrophage colony-stimulating factor, interferon gamma, and TNF-alpha is also decreased [21].

Side Effects Dose-dependent nephrotoxicity, neurotoxicity, glucose intolerance, hypertension, increased susceptibility to infection, and malignancy are common side effects for all CNI. Nephrotoxicity in children can be subtle and hard to estimate via creatinine and blood measurements; therefore, if necessary dose adjustments are not done, patients might experience chronic renal failure and even require renal transplantation following CNI therapy [2, 15]. However, with timely adjustments, early acute renal dysfunction associated with CNI therapy can improve when CNIs are withdrawn, although hyperlipidemia may not be completely resolved [12].

CNIs can result in hypertension, caused by renal vasoconstriction and sodium retention. They can also cause hyperkalemia and hypomagnesemia; therefore, potassium and magnesium levels should be closely monitored. Due to neurotoxicity, manifestations such as headaches, mild tremor, twitch, or seizure can be seen [22]. Hyperuricemia and gout are among other metabolic side effects [23]. Lastly, while hirsutism and gingival hyperplasia can be seen with cyclosporine only, lack of appetite is expected to be seen with tacrolimus [16, 24].

Both cyclosporine and tacrolimus are metabolized in the liver and small intestine by enzymes of the cytochrome P450 3A family (CYP3A) and excreted in bile. Therefore, both drugs share common drug interactions. Due to cytochrome

enzyme interaction, absorption and metabolism of the drugs can be altered by certain fruits such as grapefruit and pomegranate. Certain drugs inhibit CYP3A metabolism by causing an increase in immunosuppressant blood concentration. These drugs include amiodarone, azole antifungals (e.g., fluconazole, posaconazole, voriconazole), HIV protease inhibitors (e.g., atazanavir, nelfinavir, saquinavir), macrolide antibiotics, non-dihydropyridine calcium channel blockers, and grapefruit juice. Drugs that induce CYP3A metabolism end up decreasing effective immunosuppressive concentration; examples of these drugs are antiseizure medications, carbamazepine, phenobarbital, phenytoin, primidone, enzalutamide, nafcillin, rifamycins (e.g., rifabutin, rifampin, rifapentine), and St. John's wort. Numerous factors including pharmacokinetic factors, any infection, any change in gastrointestinal motility like diarrhea or constipation affecting absorption, drug toxicity, and rejection can affect optimal concentrations; thus, close drug monitoring is necessary.

Current Strategies of Optimal Use Studies comparing tacrolimus and cyclosporine showed greater patient and graft survival with tacrolimus in addition to less steroid-resistant rejection [25]. Tacrolimus has almost 100 times more potent immunosuppressive effect [26] which results in higher incidence PTLD [27]. Elimination half-life of tacrolimus in children is 50% higher compared to adults, and clearance is correspondingly two to four times faster [5, 28, 29]. Therefore, in order to achieve similar concentrations, children require higher doses of drug.

31.3.3 Mycophenolate Mofetil (MMF)

Mechanism of Action MMF is an inactive molecule, and it is rapidly converted in the liver to its active metabolite, mycophenolic acid (MPA), by ester hydrolysis. MPA is a selective purine analog inhibitor, which acts via selective inhibition of inosine monophosphate dehydrogenase, thus preventing de novo guanosine synthesis. Since both B and T lymphocytes cannot employ alternative pathways for nucleotide synthesis, such as neutrophils, and rely specifically on the purine synthesis for their proliferation, MMF provides selective inhibition of B and T cells and thus antibody formation [30, 31].

Side Effects As an antimetabolite, MMF was developed after azathioprine to serve as both a maintenance and rescue therapy during rejection, with less side effects of bone marrow toxicity. Complete absorption of MMF via oral route and the side effects are dose dependent. Gastrointestinal side effects like vomiting, diarrhea, and abdominal pain/cramping are most common, followed by bone marrow suppression. These symptoms do not require discontinuation and are overcome by dose reduction. Severe side effects such as neutropenia, increased opportunistic infections, and sepsis can also be seen [12, 32].

Interruption to oral absorption of MMF by other drugs such as antacids can create variation in the blood level [5]. Also, MPA undergoes enterohepatic circulation

and is excreted by the kidney; therefore, in cases with renal impairment or when enterohepatic circulation is altered (cholestyramine use), special attention should be paid to drug monitoring and individualized dosing.

Current Strategies of Optimal Use MMF serves to spare CNI or steroid treatment since it has no side effects of nephrotoxicity or neurotoxicity. It can also be used as an adjunctive therapy helping to reduce required dosing of CNI. Although the prospective studies investigating adjunct use are ongoing, starting at a low dose to prevent side effects, increasing the dose with tolerance or temporary reduction in case of side effects, and adjusting according to the individual blood level via drug monitoring are effective strategies [5].

31.3.4 mTOR Inhibitors

Molecular target of rapamycin (mTOR) receptor is an intracellular regulator of protein kinases. Sirolimus (SRL) and everolimus are mTOR inhibitors, which enter the cytoplasm and reversibly bind to FK-binding protein (FKBP12), which later binds to mTOR causing inhibition of interleukin (IL)-2 signal transduction with subsequent cell cycle arrest in the G1-S phase triggering apoptosis [16].

31.3.4.1 Sirolimus

Mechanism of Action Isolated from the fungus *Streptomyces hygroscopicus*, SRL (rapamycin) was originally used as an antifungal agent, and later its immunosuppressive potency was discovered. Although SRL and tacrolimus both use the same binding protein, sirolimus interferes with B and T cell activation and thus proliferation by cytokines via blocking IL-2 signal transduction, whereas CNIs inhibit cytokine production via IL-2 gene transcription [16].

Side Effects SRL is quickly absorbed from the gastrointestinal system and has a long half-life (40–86 h) [33]. It is metabolized by the CYP3A enzyme family, which requires thorough investigation for drug-drug interaction. Side effects in the acute postoperative period are delayed wound healing, incisional hernia, and hepatic artery thrombosis (5.5%) [32, 34]. Although there were also several trials contrasting this outcome showing no increased incidence of hepatic artery thrombosis [35, 36], in 2008 FDA recommendation for not using sirolimus in de novo liver transplantation recipients led to consideration of this agent as a second-line agent [37]. With chronic use, hyperlipidemia, dermatitis, joint pains, oral ulcers, peripheral edema, and bone marrow suppression have also been reported [38].

Current Strategies of Optimal Use SRL can provide a safe alternative to tacrolimus with no associated nephrotoxicity and neurotoxicity. Although SRL can be used as a single primary immunosuppressive therapy, acute rejection rates of 80% have been reported with monotherapy [37]. It can also be combined with steroids,

CNIs, and MMF. There were small series which studied combined effects of SRL with a CNI [39]. Synergistic effect allowed low rates of acute rejection with low-dose use of CNI [40]. SRL can also be used as a rescue agent in cases with chronic rejection. In a study involving 38 pediatric liver transplantations, the two main indications for SRL use were rejection (42%) and renal impairment (29%) [41]. Although 53% of the patients developed complications, following dose reduction, 65% of them were able to continue SRL therapy. Meanwhile, for patients starting on SRL for renal impairment, recovery of renal function with decrease in creatinine levels was observed.

31.3.4.2 Everolimus

Everolimus is a derivative of sirolimus with more solubility. Being a mTOR inhibitor, everolimus shares similar features as well as side effects with sirolimus. Everolimus might also contain some direct antiviral properties according to a cohort study involving pediatric kidney transplant recipients [42]. Everolimus-based immunosuppressive regimen was associated with decreased 3-year incidence of CMV-associated disease following transplant compared to standard-dose calcineurin inhibitor-based regimen.

Data on use of everolimus in the pediatric liver transplant group is limited. A study of 56 pediatric liver transplant recipients investigated the use of everolimus with reduced CNI. It was shown that renal function was improved with maintained antirejection potency; however, serious infections suggested that these patients were over-immunosuppressed, so the study stopped recruitment [43]. Randomized controlled trials in the adult liver transplant recipients have shown improved renal function, no differences in rejection or graft loss, but higher infection rates with the use of everolimus [44]. There are also studies of kidney and heart transplantation in pediatric patients. 28 pediatric heart transplant recipients received everolimus combined with MMF, without any CNI, has shown improvement in glomerular filtration rate [45]. Likewise, use of everolimus in combination with MMF was investigated for longitudinal growth over 2 years in steroid-free pediatric patients, and it was concluded that low-dose everolimus does not appear to negatively impact short-term growth in pediatric renal transplant recipients [46]. Although in different patient groups these studies suggest possible use of everolimus especially for patients with diminished renal function, further randomized trials to demonstrate safety and efficacy in pediatric liver transplant population are necessary.

Lastly, mTOR pathway inhibitors have been investigated for their antitumor effects due to involvement in cell growth and their anti-angiogenetic effects. Everolimus is licensed for use in renal cell carcinoma [47], and its use in hepatocellular carcinoma has been also studied. A meta-analysis compared mTOR inhibitors with calcineurin inhibitors in post-transplant patients, and it was found that mTOR inhibitor-based immunosuppression improved recurrence-free survival over at least 3 years compared to conventional CNI-based protocols, without any increase in the rates of acute rejection or hepatic artery thrombosis [48]. Another study involving

sirolimus concluded outcome could improve after LT in patients with AFP evidence of higher tumor activity [49]. There have been other trials studying combined use of sorafenib and mTOR inhibitors. HCC curative resection was used as the predictor of overall survival, and it was shown that with early start of sorafenib in combination with mTOR inhibitors, overall survival improved [50]. Further studies with larger groups and meta-analyses are required for confirmation of effectiveness of this treatment.

31.3.5 IL2 Receptor Blockers

Mechanism of Action Immediately after implantation of liver allograft, immune process will ensue to gain control of the new foreign tissue. Engagement of antigen presenting cells with antigen will activate the pathway, which will eventually cause activation of markers and IL-2 receptors on the surface of the T cells. Since interleukin-2 receptors are found on activated T cells, a targeted T cell clonal expansion is inhibited via IL-2 receptor blockers. Basiliximab is the only available immunosuppression agent in this group after daclizumab was removed from the market. Basiliximab, which is a partially humanized monoclonal antibody, binds to alpha subunit of the interleukin-2 receptor on activated T cells, and it has tenfold higher binding affinity compared to daclizumab [51].

Side Effects Although these drugs are generally very well tolerated, they are relatively new, and long-term studies are required to confirm their adverse effects. Hypersensitivity reaction, abdominal pain, vomiting, insomnia, edema, hypertension, anemia, dysuria, cough, dyspnea, and fever might be seen [12]. Also, attention should be paid to give it as an infusion since a bolus delivery may cause nausea, vomiting, and local pain at injection site [10].

Current Strategies of Optimal Use IL-2 receptor antagonists are frequently employed as an alternative to steroids for induction in liver transplant recipients. They show improvement in rates of both acute and chronic rejection with decreased need for immunosuppression and decreased rates of infections. Introduction of calcineurin inhibitors and thus their nephrotoxic effects were postponed with the use of daclizumab. This was valuable especially in patients undergoing liver transplant with impaired kidney function or renal insufficiency. Studies showed that results are satisfactory with no increase in the risk of rejection [52, 53]. Although studies involving basiliximab use are mainly in adult population, there are limited numbers of studies in pediatric population showing beneficial use of basiliximab. One of the earlier studies showed better growth and reduced need for antihypertensive medication with the use of basiliximab induction and steroid-free regimen [54]. In addition, rates of rejection-free graft survival were also higher. The renal sparing effects of basiliximab and its use as an alternative in the treatment of steroid resistant rejection have also been shown [55, 56].

31.4 Immunosuppression Withdrawal and Tolerance

Current immunosuppressive strategies are successful in preventing graft loss. On the other hand, long-term use of immunosuppressive medications has many complications such as CNI-related kidney failure, opportunistic infections and related morbidity and mortality, cancer development, psychological and social problems, and peer pressures. These issues adversely affect patient's quality of life, decrease life span, and contribute to nonadherence [57]. In order to diminish the cumulative toxic burden of lifelong immunosuppression, withdrawal of immunosuppressive treatment has gained interest. Self-stopping of immunosuppression treatment in noncompliant children, or discontinuation of immunosuppressive therapy in cases with life-threatening complications without graft rejection or loss, has been shown before [58, 59]; however, elective withdrawal has been a novel area of interest. Operational tolerance has been used to describe acceptance of a graft by a recipient without the need for maintenance immunosuppression [5]. In a tolerant host, withdrawal of immunosuppression is sustained, and in up to 60% of the children, graft function remains normal with stable graft histopathology [60].

A recent multicenter trial investigated 88 children and found 33 (37.5%) were operationally tolerant [61]. 16 patients were found to be non-tolerant by histology (with biochemical changes but no histological criteria), and 39 were non-tolerant by rejection (shown with subtle liver inflammation in trial entry biopsies). In cases non-tolerant to withdrawal, no incidence of death, graft loss, or chronic, severe, or refractory rejection occurred. In the follow-up of 4 years, fibrosis stage, or the expression level of a rejection gene set, did not show any increase in tolerant or non-tolerant subjects, redeeming safety and potential benefits of withdrawal or immunosuppressive minimization. Earlier single center experiences demonstrated similar results with approximately 34–42% successful immunosuppression withdrawal rates [62–64].

Safety of withdrawal, how to induce graft acceptance, personalized characteristics of patients related to successful withdrawal, as well as biomarkers for surveillance are still ongoing topics of research [62].

31.5 Problems with Teenagers: Adherence

Adherence to medications plays a significant role in determining outcome for both adult and pediatric transplantation. Chronic and late rejection are the most common causes of late graft loss, and nonadherence is the major reason in 35–50% of adolescent transplant recipients [65–67]. In pediatric population, there are multiple different considerations and barriers compared to adult population. Firstly, children require caregivers, and an inconsistent caregiver or previous abuse of the child can be the reason for nonadherence. Peer pressure and risk-taking behavior can be another reason for nonadherence. Also the medications are usually unpalatable, and children might require nasogastric tubes for administration. Lastly, with a longer

period of exposure to these drugs, children might experience growth retardation, increased infections, and malignancy and possibly develop nonadherence [12].

A clinical adherence-improvement protocol was suggested and introduced by Shemesh et al. 23 children were identified as nonadherent by measurement of tacrolimus levels and frequency of clinical visits were increased in this group [68]. It was found that the number of patients with high alanine aminotransferase levels decreased significantly and the number of rejection episodes and degree of adherence improved.

A study investigated 400 pediatric liver transplants for 2 years, to assess any relation between Medication Level Variability Index (MLVI) and adherence. It was found that 53% of the adolescents who had MLVI>2 in year 1 had late acute rejection by the end of year 2, when compared with 6% of those with year 1 MLVI≤2 [67]. Around 9 years, 30% of children start to take responsibility for taking their medication, and this is the critical period for nonadherence [69]. Forgetfulness and vomiting (70%), followed by bad taste (60%) and interruptions in routine (60%), were found to be the most reported barriers to adherence [70]. In the same study, factors improving adherence were reported as having medication with you at all times, having to take fewer medications, and having fewer regimen changes over time [70].

Addressing these issues of physical and psychological barriers early and having continuous follow-up with repeated visits under control of a multidisciplinary team, formed by a dedicated pediatrician, child life specialist, social worker, and transplant pharmacist, help these patients with adherence as well as improve long-term outcomes.

31.6 Transition to Adulthood

Adolescence becomes even harder to adopt for pediatric liver transplant recipients with changing medical and psychosocial needs. As children go through the transition to adulthood, they might experience more risk-taking behaviors, might have poorly expressed anger and psychological issues such as depression and anxiety, and might consider using alcohol or recreational drugs and start smoking with their peers [69]. Weight gain because of steroid use, or hirsutism and cosmetic changes such as gingival hyperplasia due to use of cyclosporine, can be hard to accept for teenagers and might be reasons for nonadherence in combination with a sense of invulnerability [10].

Families should be aware of this complicated and busy period and should be under the guidance of professional help while dealing with these issues as well as with managing immunosuppression and other medications. As patients mature into adulthood, this transition process should also include effective and safe transition of care from pediatricians to adult healthcare providers. The family should orchestrate this transition smoothly to avoid anxiety, confusion, and distress to child, which could increase nonadherence [71].

Assessment of adolescent executive function skills has been suggested as a guide to individualize the transition readiness guidelines [71]. One of the transition tools is the Readiness for Transition Questionnaire, which can be used starting from 11 to 12 years of age [72]. Identifying high-risk patients, improving detection methods, and planning earlier interventions are crucial for long-term outcomes.

31.7 Summary

Management of immunosuppression in pediatric population is challenging and requires knowledge of different pharmacokinetics and pharmacodynamics than adults. Side effect profiles and dosing should be carefully maintained in children. Although corticosteroids are still used predominantly, especially for induction therapy, tacrolimus and corticosteroid-free regimens are gaining popularity. With a longer life expectancy compared to adults, minimizing the cumulative side effects of immunosuppression and avoiding late acute rejection are two goals.

Successful withdrawal reports and with more trials focusing on personalized characteristics of patients related to successful withdrawal, as well as biomarkers for surveillance, in the future there might be avoidance of immunosuppression for maintenance.

Management of an immunosuppression regimen in order to minimize side effects on growth and development, infections, and higher rates of PTLD while avoiding rejection, continuing adherence, and lastly providing a smooth and well-thought transition process from pediatric to adult care providers are requirements and guarantors for improved outcomes.

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Combined Liver-Kidney Transplantation for Primary Hyperoxaluria Type 1

32

Charles B. Chen, Kadakkal Radhakrishnan, and Koji Hashimoto

32.1 Introduction

Primary hyperoxaluria type 1 (PH1) is an extremely rare, autosomal recessive condition caused by the buildup and deposition of oxalate. Of the three main types of primary hyperoxaluria, PH1 is the most common and accounts for about 80% of all cases [1]. The oxalate deposition can have significant effects on the kidneys and urinary tract, where it can lead to the development of nephrocalcinosis and urolithiasis [2, 3]. Additionally, it can also affect multiple other organs in later stages of the disease, causing symptoms of systemic oxalosis.

This condition is reported in one to three people per one million individuals, although it is found more frequently in several Middle Eastern populations and other groups with high rates of consanguinity [3, 4]. However, it is likely that this number is underestimated [5]. The rarity of this condition means that diagnosis can often be delayed, leading to worse clinical outcomes [6, 7]. PH1 is a complex disease with significant heterogeneity, not only in clinical presentation and disease course but also in genetic and biochemical variation.

C. B. Chen · K. Radhakrishnan
Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH, USA

K. Hashimoto (✉)
Department of General Surgery, Digestive Disease & Surgery Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: hashimk@ccf.org

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32.2 Genetics and Pathophysiology

PH1 is due to a mutation in the AGXT gene located on chromosome 2q37.3, which is responsible for the production of alanine-glyoxylate aminotransferase (AGT) (Table 32.1) [5, 8]. This enzyme is responsible for the conversion of glyoxylate to glycine. Normally, the enzyme AGT is found almost exclusively in hepatic peroxisomes. However, mutations in the AGXT gene cause either a deficiency of AGT or misdirection of the enzyme toward the mitochondria rather than the peroxisome [2, 9]. This leads to a buildup of glyoxylate which is converted to oxalate (Fig. 32.1). Calcium oxalate crystals subsequently deposit in the renal tubules along with other organs and produce the deleterious effects of this condition [10].

Although more than 150 mutations have been identified in the gene, 2 primary mutations (Gly170Arg and Ile244Thr) are responsible for more than 30–40% of the mutant alleles found in PH1 [2, 11]. Certain mutations are also found more frequently in particular populations, such as the Ile244Thr mutation in patients of North African origin [12–14]. These mutations can lead to a variety of effects such as loss of enzymatic activity, aggregation, and abnormal targeting. While the

Table 32.1 Overview of enzymatic abnormalities and genes involved in primary hyperoxaluria

Condition	Abnormal enzyme	Defective gene
Primary hyperoxaluria type 1	Alanine-glyoxylate aminotransferase	AGXT
Primary hyperoxaluria type 2	Glyoxylate reductase-hydroxypyruvate reductase	GRHPR
Primary hyperoxaluria type 3	4-hydroxy-2-oxoglutarate aldolase	HOGA1

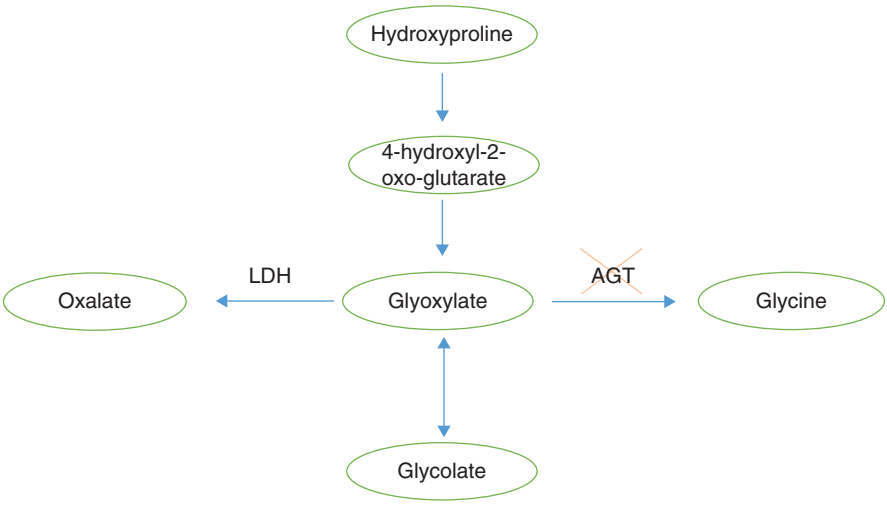

Fig. 32.1 Pathway showing defect in AGT enzyme in primary hyperoxaluria type 1

Gly170Arg mutation has been shown to be associated with improved renal outcome, there is unfortunately little other evidence to suggest that specific genotypes can help to predict disease severity or outcome [14].

32.3 Clinical Presentation

PH1 can have significant variation in clinical presentation between individuals. As mentioned previously, deposition of calcium oxalate leads to the formation of nephrocalcinosis and urolithiasis. This can result in symptoms such as hematuria, dysuria, or the development of recurrent urinary tract infections [1]. In one large study, the presenting symptoms involved the urinary tract in 82% of patients [15]. Renal dysfunction is also a frequent manifestation, with a large number of patients developing end-stage renal disease (ESRD) [3, 9]. While some patients may be asymptomatic for most of their lives and present with significant renal failure, others may have frequent symptoms but still retain good renal function. Even multiple affected members of the same family can have significantly different presentations [5].

PH1 can present at any age, although the median age at onset of symptoms is 3–5 years [1, 14, 15]. The infantile form of PH1 may be especially difficult to manage, as the presentation may be more severe, and the outcome is often poor [8]. These infants generally develop renal dysfunction within the first few months of life, and 80% of patients develop ESRD by 3 years of age [12]. These individuals can develop anemia and metabolic acidosis secondary to renal failure, and growth may be compromised [5]. A more common form of PH1 is seen in young children and adolescents who develop recurrent urolithiasis and progressive renal failure. A third form is seen in older adults who present with occasional passage of stones [8]. The rate of disease progression also varies among individuals, with one study showing that 26% of pediatric patients had developed ESRD and 42% had developed renal dysfunction at the time of diagnosis [16].

Patients with PH1 generally have normal hepatic function despite the enzymatic defect. Fibrosis is usually absent, and histological changes are minimal. Nevertheless, there are reports of significant oxalate deposition as well as cirrhosis in PH1, although these cases are generally described in adults [17, 18]. Patients who develop renal failure have poor clearance of oxalate and therefore can have systemic manifestations due to the accumulation and deposition of oxalate in various organs. This can lead to cardiac, thyroid, ocular, bone, gastrointestinal, and dermatologic abnormalities [3]. Patients can develop skeletal manifestations, including spontaneous fractures, spondylolysis, myopathy, and arthritis [10, 19]. Oxalate deposition in the myocardium can lead to arrhythmias, heart block, and cardiac failure [20].

32.4 Diagnosis

The diagnosis of PH1 should be considered in patients with recurrent renal calculi. Additionally, this condition should also be suspected in patients with nephrocalcinosis or urolithiasis who have clinical or laboratory evidence of renal dysfunction,

including decreasing GFR (glomerular filtration rate) [3]. The workup for PH1 generally includes a combination of laboratory, imaging, histopathologic, and genetic tests. Analysis of urine samples for increased urinary oxalate excretion is often the first step in the diagnostic workup for PH1. This includes 24-hour urine collection for oxalate, with a urine oxalate of greater than 0.5 mmol/1.73 m^2 per day defined as elevated urinary oxalate excretion [3].

Diagnosis can be made with a liver biopsy to assess the catalytic activity of the AGT enzyme [5]. Histologic examination can demonstrate absence of the AGT enzyme in peroxisomes. Molecular genetic testing reveals biallelic pathogenic variants in the *AGXT* gene which establishes the diagnosis of PH1. DNA analysis may be especially useful for prenatal testing, as well as for screening an affected individual's relatives [3]. Unfortunately, the clinical course of the disease cannot be predicted by results of genetic testing.

Renal biopsies performed in some patients may reveal oxalate crystals. Additionally, patients under treatment may pass kidney stones that are high in calcium oxalate monohydrate, which is suggestive of PH1 [21]. Patients with systemic oxalosis can also present with radiographic findings, especially with bone involvement. Bone x-rays may reveal radiodense metaphyseal bands in some patients [5, 19]. Electrocardiogram and echocardiogram can be used to detect cardiac abnormalities, and ophthalmic examination can reveal retinal calcium oxalate deposits [20, 22].

32.5 Treatment

It is important for newly diagnosed patients to be treated immediately in order to preserve renal function and improve long-term outcomes. Patients with more mild disease can often be treated conservatively. Initial treatment includes aggressive hydration. This may be difficult for infants and young children, who may require nasogastric or gastrostomy tubes to ensure adequate fluid intake [3]. Dietary modifications are only minimally effective, despite restriction of dietary oxalate being recommended by some healthcare providers. Although these conservative treatments can be effective, the need for strict adherence may compromise the effectiveness of these therapies [7].

Medications for PH1 treatment include the use of calcium oxalate crystallization inhibitors such as potassium citrate [8]. Pyridoxine can also be used as an adjunct therapy, as it serves as a cofactor for AGT and helps to decrease urinary oxalate excretion [3, 4, 21]. Pyridoxine can help to delay progression to end-stage renal disease, but the response varies among patients, and some individuals are not pyridoxine-sensitive [23]. The data on the efficacy of medical management is equivocal. Some studies suggest that aggressive hydration and medical therapies do not prevent progression to ESRD [11], while others show that early and aggressive treatment may help in preserving renal function [24, 25]. Nevertheless, therapeutic delays are associated with decline in renal function [24]. Additionally, patients experiencing urolithiasis and nephrolithiasis may require urologic interventions,

such as extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy, and ureteral stenting [3].

Dialysis is another treatment modality, although one significant challenge is that in order to remove the amount of oxalate produced by the liver, patients will generally need to undergo an intense regimen of hemodialysis and/or peritoneal dialysis. Even this is often not successful in removing the necessary amount of oxalate. Specific indications for the use of dialysis include pediatric patients awaiting organ transplantation. Dialysis can also be used as a method to deplete excessive oxalate burden in patients awaiting a kidney transplant and as a temporary measure for post-transplant patients to expedite recovery of renal function [7].

32.6 Transplantation

When pharmacological therapy and dialysis are unsuccessful, transplantation remains an option [11]. The three main types of transplant that can be performed include isolated liver transplant, isolated kidney transplant, and combined liver-kidney transplant (LKT). Multiple factors must be considered prior to transplantation, including patient age, condition, comorbidities, severity of disease, and organ availability [26]. Ideally, transplantation should occur prior to the development of systemic oxalosis; however, pediatric patients must also be of sufficient size to receive the graft. The decision of which transplant to perform should be based on an assessment of how quickly clinical improvement is anticipated, as well as the risks, benefits, and long-term outcomes and complications of the surgeries.

Isolated liver transplant can be performed preemptively to correct the enzymatic defect without necessitating a subsequent kidney transplant. This is a reasonable choice for patients with residual kidney function and is ideally performed before systemic complications develop. There is also evidence that preemptive liver transplants in patients with good renal function may help slow the progression to ESRD [27]. One major challenge is determining the timing of the transplant given the variability of the disease course [11, 28]. For PH1 patients, liver transplants have been classified as either early or late, with each having a different purpose [26]. Early liver transplants are performed in patients with a GFR between 40 and 60 mL/min/1.73 m^2, at which point tissue oxalate deposition often starts to occur [26]. Transplants performed at this early stage aim to avoid the need for a renal transplant and the development of systemic oxalosis. Late liver transplants are performed in patients where the GFR is less than 30 mL/min/1.73 m^2 and aim to stabilize renal function and delay the need for a renal transplant. In young children, the risks and complications of liver transplant must be weighed against the effect on the quality of life due to symptoms from oxalate deposition. Patients may suffer from the effects of residual oxalosis from tissues that are slow to turn over, even after successful liver transplantation [26].

While isolated kidney transplantation is an option, it is generally only a temporary solution and is not commonly performed. The kidney transplant can help remove oxalate but unfortunately does not correct the underlying genetic defect.

Although there is evidence that isolated kidney transplants decrease plasma oxalate levels more than dialysis, oxalate deposition nevertheless continues to occur in various tissues of the body [29]. Isolated kidney transplants have poor prognosis due to the risk of recurrence of disease and continued deposition of oxalate in the new renal graft [11]. In one study of patients under 19 years of age, kidney graft survival was only 14% at 5 years post-transplant for isolated kidney transplants compared to 76% in combined LKT [30].

The combined LKT offers the greatest benefit in that it is able to both correct renal dysfunction and replace the deficient hepatic AGT enzyme, thereby restoring normal oxalate production. Since initially performed for PH1 in the 1980s, combined LKT has become progressively more widely practiced as the definitive treatment for this condition. Pediatric and adult data from the European PH1 Transplant Registry over 20 years (1984 to 2004) showed that for patients receiving LKT, the patient survival rate at 5 and 10 years was 80% and 69%, respectively [31]. The US Renal Data System showed that in patients with oxalosis, death-censored graft survival at 8 years in LKT was 76%, compared to only 48% in those receiving kidney transplants alone [32]. The data in the pediatric population is less well defined. One study of eight pediatric LKT patients found that patient and graft survival were both 75% at an average follow-up of 7.4 years [33]. Overall, combined LKT has become accepted as a definitive treatment option that has produced good long-term outcomes [34].

Combined LKT is often performed for patients with more advanced renal disease or end-stage renal disease, and evidence suggests that it should be considered when the GFR is between 15 and 40 mL/min/1.73 m^2 [34, 35]. Despite the benefits of a combined transplant, shortage of suitable donor organs may lead to long wait times, which may increase the need for dialysis [27]. This waiting period may lead to further mobilization of oxalate from tissues in patients with systemic oxalosis, which can cause damage to the renal allograft even after transplantation.

Combined LKT can be performed either simultaneously or sequentially, with organs obtained from either deceased or living donors. Simultaneous LKT has the advantage of immediately correcting both the enzymatic and renal defects [35]. The simultaneous transplant also obviates the need for a second operation, unless the patient needs to have a re-transplantation or reoperation for other reasons. The functional renal graft can help to decrease the morbidity associated with long-term renal dysfunction.

Evidence suggests that when both the liver and kidney for simultaneous transplants are from the same donor, the kidney has some added protection against rejection [36, 37]. Although not specific to PH1, the immunological protection of the kidney graft in pediatric patients has been demonstrated in an analysis of the 1995–2005 UNOS database. This analysis showed significant improvement in the renal graft survival at 5 years post-transplant in the combined LKT group compared to the kidney transplant group [38]. Interestingly, at 6 months post-transplant, the data showed a much higher rate of renal graft loss in combined LKT. Therefore, although there may be increased complications in the immediate postoperative period, the long-term outcomes are favorable for combined LKT.

Sequential transplantation consists of an initial liver transplant followed by a kidney transplant performed at a later time. It is thought that the initial liver transplant helps decrease the oxalate burden and protects the renal graft from the deleterious effects of hyperoxaluria [39]. Sequential LKT may be required in small patients where the abdominal cavity is unable to accommodate both grafts or in patients who are not deemed stable enough to undergo a simultaneous transplant [40]. However, waiting for a patient to be large enough for a simultaneous LKT may lead to progression of systemic oxalosis [41]. One series of eight cases of living donor sequential LKT showed that the interval between liver and kidney transplants ranged between 51 days and 10 months [42]. The timing of the second transplant is very important and must take into account factors such as progression of renal disease and need for dialysis. If the kidney transplant occurs while a patient still has adequate residual renal function, the immunosuppression from the previous liver transplant can further hasten renal decline [35]. There is strong evidence to initiate renal replacement therapy after liver transplant and prior to the kidney transplant [41].

Due to a shortage of deceased donor organs, living donor transplantation has become more widespread in recent years. This can be performed from either the same donor or different donors and performed simultaneously or sequentially [40]. The risks to the living donor must be carefully considered, especially in the case of a simultaneous LKT [43]. The availability of living donors may also present a challenge, especially for patients who are likely to require both organs.

More research is needed, however, to further understand LKT for PH1. The data for sequential LKT from the same living donor are limited. In one case series of 23 patients, the interval between liver and kidney transplantation was approximately 6 months. Follow-up at 2.3 years showed liver and kidney graft survival rates were 88.5% and 90.5%, respectively, while patient survival was 88.5% [44]. Data on sequential LKT from separate donors have also been reported, including both living donor and deceased donor liver transplantation followed by living donor renal transplantation [41, 45]. Single donor sequential LKT remains more popular, as most recipients are only able to identify one living donor, and this process makes best use of the donor organs [40].

The data for simultaneous LKT from the same living donor are even more scarce [37]. As mentioned previously, simultaneous LKT provides an immunologic advantage as the liver transplant can help protect the kidney transplant from rejection. There are also reports of simultaneous LKT by separate donors, with three cases noted in one study [40]. Unfortunately, the latter does not provide the same immunologic protection. Nevertheless, in both cases, while the metabolic abnormality is corrected, residual systemic oxalosis can continue to damage the new renal allograft. See Table 32.2 for a comparison of sequential and simultaneous LKT.

The role of domino liver transplantation and its impact on patients with PH1 is a topic of debate. Evidence indicates that structurally and morphologically normal livers from donors who have metabolic diseases, such as PH1, can be used for certain recipients [46]. However, recipients of PH1 livers have been found to develop oxalosis and renal dysfunction [47]. One series of five patients who received livers

Table 32.2 Comparison of sequential and simultaneous liver-kidney transplants. Data from Narasimhan et al. [40]

Type of transplant	Advantage	Disadvantage
Sequential LKT	Suitable for infants with systemic oxalosis Suitable for small patients where abdominal cavity is unable to accommodate both new grafts at the same time Allows for renal function in native kidney to improve after liver transplant (thus avoiding need for a renal transplant)	Frequent need for continued dialysis following liver transplant
Simultaneous LKT	Corrects both enzymatic and renal defects Provides immunologic advantage as liver transplant can help protect kidney transplant from rejection Generally avoids need for long-term dialysis following liver transplant	Continued risk of damage to newly transplanted kidney due to systemic oxalosis

from PH1 donors showed that all of the recipients developed renal failure within four weeks of transplant and four of the patients subsequently died [48]. Despite the fact that these livers are normal aside from the enzymatic defect, they still pose the risk of subsequent hyperoxaluria to the recipient. While it is suggested that heterozygous carriers should not be candidates as living donors due to the possibility of decreased enzymatic function, the clinical evidence is unclear. As family members may consider being a donor, their AGT enzymatic activity should be assessed, as some relatives may be heterozygous for the mutation. A study by Sasaki et al. showed several cases of decreased AGT catalytic activity from livers donated by possible heterozygous carriers [41]. The recipients of those liver transplants, however, did not suffer any adverse effects. Therefore, the decision to use a liver from a PH1 patient or carrier should be made carefully after consideration of the risks.

The decision to perform a single or combined transplant, either sequentially or simultaneously, must be made on an individual basis. Multiple factors should be taken into account, including the degree of systemic oxalosis, renal dysfunction, recipient body size, and risk of renal allograft failure from oxalate deposition [40]. The risk to the donor must also be taken into consideration, especially if both kidney and liver are obtained from the same living donor.

32.7 Postoperative Management

In addition to the usual complications of transplant, such as rejection and infection, there may be additional postoperative challenges in transplant patients with PH1. Infants and younger children are at higher risk for postoperative challenges, especially since they often have more severe disease at the time of transplantation. Cardiovascular instability has been described in at least two cases of infantile PH1 due to oxalate deposition in coronary vessels [11]. Postoperative complications for

renal grafts include acute tubular necrosis, and therefore renal function must be closely monitored.

For patients who undergo combined LKT, those with higher systemic oxalate load may be at risk of developing recurrent nephrolithiasis and urolithiasis [3]. Aggressive hydration often is recommended, and crystallization inhibitors may be continued following transplant. Patients may require additional dialysis to optimize renal function and normalize urine oxalate levels, especially in those with delayed graft function [49, 50].

Immunosuppression must also be managed carefully, especially since calcineurin inhibitors can lead to nephrotoxicity. Little data exist on the optimal regimen for post-transplant patients with PH1, with corticosteroids, calcineurin inhibitors, mTOR inhibitors, and other agents used in various combinations [51]. Induction therapy with monoclonal or polyclonal antibodies has been implemented as a way to avoid use of calcineurin inhibitors until renal function improves [52].

Long-term growth and development should also be routinely assessed although few studies have analyzed these factors in PH1 patients undergoing transplant. Many pediatric patients experience growth failure, although the etiologies are multifactorial [52]. One series of 24 pediatric patients who underwent LKT showed that while surgery can improve growth outcomes, it does not lead to full catch-up growth in the majority of patients [53]. Early transplantation to avoid long-term dialysis, early steroid withdrawal, and optimizing post-transplant renal function may all help to reduce the degree of growth retardation.

32.8 Conclusion

Although many advances have been made in the diagnosis and treatment of PH1, outcomes in pediatric patients are still worse compared to other conditions that cause ESRD [7]. Lack of awareness as well as underdiagnosis of the condition may have a significant impact, especially for patients who are in the earlier stages of their disease. In terms of treatment for PH1, early, aggressive management is important to protect renal function and prevent systemic oxalosis. However, as patients can quickly develop systemic oxalosis, timely referral for transplantation is critical. The optimal timing, as well as the type of transplant, must be carefully considered.

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Human Hepatocyte Transplantation

33

Minh Phuong Nguyen, Vandana Jain, and Anil Dhawan

33.1 Introduction

Liver transplantation (LT) is the standard of care for patients with acute liver failure, end-stage liver diseases and liver-based metabolic disorders (LBMDs) [1]. LT in the UK has good 1-year and 5-year post-transplantation survival rates: 94% and 82.7% in adults and 96.8% and 91.5% in children, respectively [2]. However, the shortage of donor organs is a major limitation, leading to increased waiting list mortality. In addition, LT is a costly, major surgical procedure, with potential postoperative complications, requiring lifelong immunosuppression to help prevent graft rejection. Hence, there is an urgent need to develop alternative therapies to LT.

Clinical human hepatocyte transplantation (HT) is a promising alternative option either to replace LT or act as a bridge while awaiting LT, for the following two scenarios: (i) liver-based metabolic disease (LBMD) and (ii) acute liver failure (ALF) [3]. The key principle relies on the infusion of functional hepatocytes, from donor livers unsuitable for LT, and their successful engraftment in the recipient's liver parenchyma, delivering the missing hepatic function of the defective native cells. The safety of clinical human HT and its initial clinical benefits have been shown [4]. Several advantages over LT can be demonstrated—(i) it is less invasive; (ii) it has a lower risk profile; (iii) it is less expensive; (iv) isolated cells from a single donor liver can be used for several recipients; (v) multiple injections for one recipient are possible, if needed; (vi) cells can be cryopreserved for storage, ready for immediate

M. P. Nguyen · V. Jain
Dhawan Lab at the MowatLabs, Institute of Liver Studies, King's College Hospital, London, UK

A. Dhawan (✉)
Paediatric Liver GI and Nutrition Center and MowatLabs, King's College Hospital, London, UK
e-mail: anil.dhawan@kcl.ac.uk

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use [5, 6]; and (vii) the native liver remains in place in case of cell graft failure or native liver regeneration in ALF and the presence of a potential target for future gene therapy for LBMD. However, the widespread clinical application of HT has been inhibited by a limited supply of donor livers from which high-quality hepatocytes can be isolated, along with issues achieving optimal cell viability, engraftment and immunogenic tolerance [4, 7]. Innovative techniques to overcome these constraints of HT are imperative for the further development of this field.

33.2 Hepatocyte Processing and Transplantation Protocols

33.2.1 Source of Hepatocytes

Primary hepatocytes are the functional units of the liver, making up the largest proportion of the organ and carrying out synthetic and detoxification functions. They are isolated from unused donor livers, due to being suboptimal for transplantation for one of the following reasons: severe steatosis, older donors, trauma or anatomical abnormalities, extended cold ischemia time or leftover segments I and IV after a split procedure. However, such marginal livers often do not yield high enough quality hepatocytes for HT [8]. Hence, alternative sources for obtaining hepatocytes are being explored. Explanted livers from patients with LBMD are a potential source of cells, as their missing enzymatic function would be performed by the recipients native liver, similar to the concept of 'domino' LT [9]. Foetal and neonatal livers are a potential promising alternative source of hepatocytes, which will be discussed later in the chapter.

33.2.2 Hepatocyte Isolation

All liver tissues are processed in accordance with Good Manufacturing Practice (GMP), in GMP-certified facilities. Cells are isolated using an established *three-step collagenase perfusion* with a peristaltic pump (Fig. 33.1) [10]: (1) hepatic vessels are cannulated and perfused with a balanced salt buffer containing egtazic acid (EGTA), which chelates calcium ions, hence interrupting calcium dependent cell-to-cell adhesions, known as desmosomes. (2) Tissue is washed thoroughly with plain salt buffer to remove any residual EGTA. (3) Tissue is flushed with calcium-dependent collagenase, at strictly 37°C with oxygenation, to digest the extracellular matrix. Detached cells are then filtered and centrifuged at low speed to remove non-parenchymal cells. Cells are quantified for viability and total number using a trypan blue assay. Cells can be used fresh for transplantation or cryopreserved. Cryopreservation involves placing 1.0–1.5 × 10^7 cells/ml in a freezing medium composed of University of Wisconsin 10% dimethyl sulfoxide and 5% glucose, before placing in controlled-rate freezers and stored long term in specialized nitrogen liquid biobanks [11].

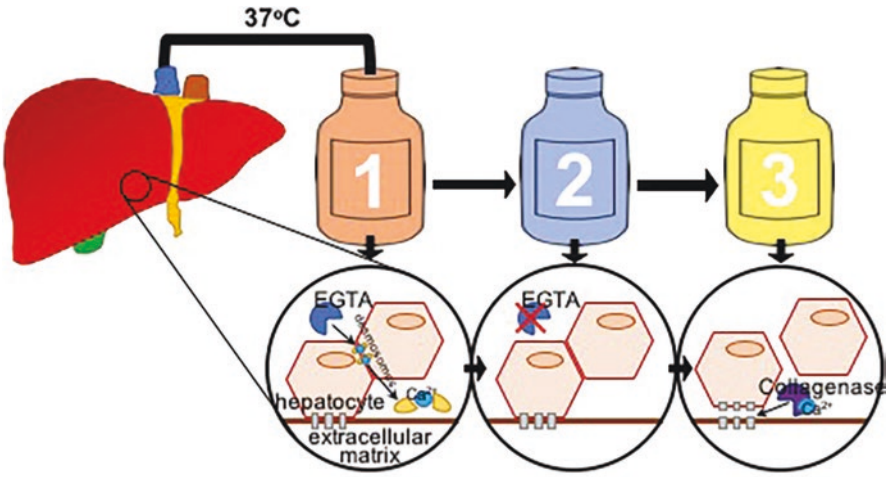

Fig. 33.1 A simplified diagram showing hepatocyte isolation steps using a standard collagenase perfusion technique at 37 °C: (1) Perfusion with EGTA-enriched solution aims to chelate the calcium ions, to break the links between the desmosomes and loosen the tissue; (2) solution is required to remove any trace of EGTA, as calcium ions are required for the next step; (3) a collagenase solution rich in calcium ions is used to digest the extracellular matrix in order to release hepatocytes (figure modified from [6])

33.2.3 Quality Control of Hepatocytes

Isolated human hepatocytes go through rigorous screening at each production stage, to ensure the optimal condition of the cells prior to transplantation. Microbiological analysis is undertaken to ensure no microbial contamination and cell viability is assessed, usually using the trypan blue exclusion test, to ensure optimal cell engraftment. At King's College Hospital, only hepatocytes with at least 60% cell viability are accepted for clinical transplantation. This protocol is especially critical for cryopreserved cells, as freeze-thawing impairs mitochondria, affecting cell respiration with a dramatic drop of ATP levels [12] and potentially inducing apoptosis. In addition to viability assessment, monitoring cells for early signs of apoptosis and metabolic function has also been proposed [13].

33.2.4 Hepatocyte Infusion

Fresh or cryopreserved hepatocytes, representing around 5–10% of the total liver mass, are infused through the portal vein (PV), with prior radiological or surgical insertion of the catheter. Once injected, the cells cross the sinusoidal barrier, causing disruption to the local endothelium, before migrating to the liver parenchyma. The cells that successfully engraft show remaking of their cell membrane and formation of hybrid cell junctions between the new cells and the native hepatocytes [14].

Multiple administration of hepatocytes is possible, if a higher number of cells are required to achieve a beneficial effect [15, 16]. However, portal pressure has to be carefully monitored during transplantation, using a Doppler ultrasound, to avoid portal hypertension and risk of portal thrombosis; the number of cells allowed per transplantation session is dictated by portal pressure [17, 18]. Alternative infusion routes are preferred in specific clinical scenarios. An intra-splenic approach can be considered for recipients with cirrhotic livers, as the remodelled tissue structure could have a negative impact on cell engraftment [19]. Patients with ALF have been treated with hepatocytes instilled into the peritoneal cavity, which is easier to access and has a larger capacity for cells [20]. However, transplantation via the peritoneal route means that the cells have no site for attachment and will be rapidly cleared by the host immune response.

33.2.5 Immunosuppression

Immunosuppressive protocols, including steroids and calcineurin inhibitors, similar to those used in LT, are often adapted for HT. Although the liver is considered an immune-privileged organ, which in select patients can lead to graft tolerance, and the gradual withdrawal of immunosuppression, hepatocytes do not seem to have this same privilege, possibly because other hepatic cells, such as stellate cells or liver sinusoid endothelial cells, contribute to liver tolerance or because hepatocytes lose their tolerogenic potential in an allogenic environment. Both innate and adaptive immune processes have been shown to be involved in rejection of the transplanted hepatocyte, hence the need for continuous administration of immunosuppressive medication.

33.3 Clinical Indications for HT

HT was first attempted in 1976 on hyperbilirubinemic Gunn rats, as a new technique for the treatment of Crigler-Najjar syndrome type 1 (CN1) [21], followed by the first human HT, performed in 1992, using autologous cells in patients with cirrhotic livers [22]. Over the past three decades, clinical application of HT in humans has been published in over 100 case series internationally, with the safety of the technique being well established. For LBMD, the aim of HT is to provide a sufficient number of engrafted cells, estimated at ~5–10% of the theoretical liver mass, to substitute a single enzyme defect. Hence, infants or children with metabolic defects would no longer require specialized diets to prevent toxic metabolites, or be at risk of metabolic crises that can lead to irreversible neurologic sequelae. In ALF, the principle behind HT is to provide some functional mass, and pro-regenerative signals from the transplanted cells [23], to support the failing liver and ‘bridge’ the patient to LT or, ideally, to full recovery without LT.

33.3.1 Liver-Based Metabolic Diseases (LBMD)

An initial biochemical and clinical benefit has been observed with HT for LBMD; however, a sustained response has been lacking, with most cases showing a decline in cell function after approximately 9–12 months (Table 33.1).

1. **Urea cycle defects** are genetic metabolic disorders wherein the urea cycle is unable to be completed, therefore leading to build-up of blood ammonia or urea cycle intermediaries. Patients commonly present soon after birth, but can present at older ages, and without intervention lead to negative neurological outcomes and death. Despite ongoing research, outcomes for these patients are poor [43]. Among LBMDs, urea cycle defects have more commonly been treated with HT. Before 2010, HT had been used to treat 12 patients with urea cycle defects: 8 with ornithine transcarbamylase deficiency (OTC) [35–39], 1 with argininosuccinate lyase deficiency (ASL) [42], 2 with carbamoyl phosphate synthetase 1 (CPS1) deficiency [39] and 1 with citrullinemia [39]. All patients showed some initial metabolic stabilization, but HT ultimately did not prevent subsequent LT or death. Since 2010, four further cases (three OTC, one CPS1) are recorded in the literature. A 12-year-old [28] and neonate [41] with OTC both showed an initial reduction in ammonia levels post-transplant; however, the 12-year-old subsequently died of septic shock. The neonate remained stable at 3 months post-HT; no further outcome is known. In two alternative approaches, Soltys et al. [40] made use of radiotherapy administered to the right lobe of the liver in a 4-month-old with CPS1, and a 7-month-old with OTC, aiming to improve cell engraftment, prior to the infusion of fresh hepatocytes via PV. However, significant biochemical improvements did not occur, and after protein advancement, the patients showed elevated blood ammonia, and both needed subsequent LTs (see Table 33.1).
2. **Crigler-Najjar type 1 (CN1)** is caused by a defective UDP glucuronosyltransferase (UGT) enzyme, which leads to elevated unconjugated hyperbilirubinemia and subsequent neurological injury and death. An initial therapy is daily phototherapy, but this loses efficacy over time. HT has been demonstrated to produce short-term reduction in bilirubin levels, although it did not avert the long-term need for LT [25, 26, 30]. In the past 10 years, four cases of HT have been reported for CN1. Two of these cases also involved partial hepatectomy to enhance cell engraftment, but both needed LT after an initial biochemical improvement [30]. In one encouraging case [28], HT caused a 50% reduction in bilirubin levels with sustained reduction after 1 year, as well as reduced need for phototherapy (12 hours vs 24 hours) and improvements in motor abilities.
3. **Glycogen storage disease type 1 (GSD1)** refers to a collection of autosomal recessive metabolic disorders where patients have deficient activity of the glucose-6-phosphatase (G6Pase) complex, causing excessive accumulation of fat and glycogen in the kidneys and the liver. In two adult patients, HT has pre-

Table 33.1 Clinical experience with hepatocyte transplantation in patients with inborn errors of metabolism (updated/modified from [4] and with permission taken from [6])

Study	Patient age	Transplanted cells ($\times 10^9$)	Delivery route	Cell viability (%)	Cell type	Follow-up	Outcome
	Crigler-Najjar syndrome type 1						
Fox et al. [24]	10 years	7.5	PV	90	F	↓ 50% bilirubin, enzyme activity in the liver	OLT after 4 years
Darwish et al. [15]	8 years	7.5	PT	NA	F/C	↓ 40% bilirubin for 6 months	OLT at 20 months
Ambrosino et al. [25]	9 years	7.5	PV	60–80	F	↓ 30% bilirubin for a few weeks	OLT after 5 months
Dhawan et al. [26]	18 months	4.3	PV	NA	C	↓ 50% bilirubin	OLT after 8 months
	3 years	2.1	PV	NA	F/C	↓ 30% bilirubin	Follow-up
Allen et al. [27]	8 years	1.4	PV	93	F	↓ 30% bilirubin, ↓ phototherapy	OLT after 11 months
Lysy et al. [16]	9 years	6.1	JV	80	F/C	↓ 35% bilirubin for 6 months	OLT waiting list
	1 year	2.6	PV	83	F/C	↓ 25% bilirubin, ↓ phototherapy for 4 months	OLT after 4 months
Ribes-Koninckx et al. [28]	7 months	6.7	PV	66 ± 7	C	↓ 50% bilirubin, improved neurology	Stable at 1 year follow-up on 12 hours phototherapy
Meyburg et al. [29]	11 years	0.18	PV	63 ± 6	C	↓ 20% bilirubin	OLT waiting list
Jorns et al. [30]	13 years	2.2 and 9	PV	87–100	C	↓ 50% bilirubin	OLT after 19 months
	11 years	5.3	PV	87–100	C	↓ 50% bilirubin >6 months	OLT after 32 months
	Familial hypercholesterolemia						
Grossman et al. [17]	5 patients (7–41 years)	1.0–3.2	PV	90–95	F	Up to ↓ 20% LDL in three patients	NA

	Factor VII deficiency						
Dhawan et al. [31]	3 months	1.1	PV	80–90	C	↓ 70% rFVII requirement for 6 months	OLT after 7 months
	35 months	2.2	PV	50–90	F/C	↓ 70% rFVII requirement for 6 months	OLT after 8 months
	Glycogen storage disease type I						
Muraca et al. [32]	47 years	2	PV	NA	F	Normal diet, ↑ fasting time	NA
Lee et al. [33]	18 years	6	PV	75–82	F/C	Normal G6Pase activity up to 7 months	NA
Ribes-Koninckx et al. [28]	6 years	2.35	PV	66 ± 7	C	↓uric acid/glucose/cholesterol	Sustained glucose control at 1-year follow
	Infantile Refsum disease						
Sokal et al. [34]	4 years	2	PV	50–90	F/C	↓ 40% pipecolic acid after 18 months	NA
	Progressive familial intrahepatic cholestasis type 2						
Dhawan et al. [26]	32 months	0.2	PV	60	F	No benefit, cirrhosis established	OLT after 5 months
	16 months	0.4	PV	87	F	No benefit, cirrhosis established	OLT after 14 months
	OTC deficiency						
Strom et al. [35]	5 years	1	PV	NA	F	↓ NH_3, 0.5% of normal liver OTC activity	Death 42 days later
Horslen et al. [36]	10 h	9	PV	51–94	F/C	↓ NH_3, ↑ protein tolerance for a short period	OLT at 6 months
Stephenne et al. [37]	14 months	2.4	PV	70	C	↓ NH_3, ↑ urea, psychomotor improvement	OLT after 6 months
Puppi et al. [38]	1 day	1.6	PV	85–95	F/C	↓ NH_3, ↑ urea under normal protein diet	APOLT at 7 months

(continued)

Table 33.1 (continued)

Study	Patient age	Transplanted cells ($\times 10^9$)	Delivery route	Cell viability (%)	Cell type	Follow-up	Outcome
Meyburg et al. [39]	6 h	0.6[a]	UV	71	C	↓ NH_3, ↑ urea, normal urinary orotic acid excretion	Death at 4 months
	9 days	0.6[a]	UV	64	C	↓ NH_3, ↑ protein intake, urinary orotic acid normal at 6 months	OLT waiting list
Soltys et al. [40]	7 months	2	UV/PV	76.9	F	No improvement in NH_3	OLT at 11 months age
Enosawa et al. [41]	11 days	0.14	UV/PV	89.1, 82.6	C	↓ NH_3	Stable at 3-month follow-up
	ASL deficiency						
Stephenne et al. [42]	42 months	4.7	PV	81–90	F/C	↓ NH_3, psychomotor catch-up. Donor liver cells detected in the liver	OLT after 18 months
	CPS1 deficiency						
Meyburg et al. [39]	2.5 months	1.4	PV	74	C	↓ NH3, ↑ urea for 11 months	OLT waiting list
Soltys et al. [40]	4 months	6.89	UV/PV	88	F	No improvement in NH3	OLT 3.5 months later
	Citrullinemia						
Meyburg et al. [39]	36 months	1.5[a]	PV	77	C	Normal NH_3, ↑ 40% urea, ↑ protein intake	NA

APOLT auxiliary partial orthotopic liver transplantation, *ASL* argininosuccinate lyase, *C* cryopreserved, *CPS1* carbamoyl phosphate synthetase, *F* fresh, *JV* jejunal vein, *NA* not available, *OLT* orthotopic liver transplantation, *OTC* ornithine transcarbamylase, *PV* portal vein, *PT* percutaneous transhepatic route, *rFVII* recombinant factor VII, *UV* umbilical vein

[a] Hepatocytes isolated from the same donor

viously been demonstrated to lead to short-term improvement in glucose control with improving G6Pase activity and triglyceride levels to normal ranges [32, 33]. A 6-year-old paediatric patient with GSD1a who had regular episodes of symptomatic hypoglycaemia was treated with HT and had sustained glucose control 1 year later [28].

A number of other LBMDs have been shown in case reports and case series to have short-term improvement in outcomes following HT, including factor VII deficiency (FVII) [31], familial hypercholesterolemia (FH) [17], tyrosinemia type 1 [28] and several others [44]. In FVII, patients showed up to 70% decreased need for recombinant factor VII treatment, and patients with FH showed reduced low-density lipoprotein production [17, 31]. Patients with tyrosinemia treated with HT showed reduced bilirubin levels and improved clotting factors [28]. Several cases, including those previously described, have combined HT with partial hepatectomy, which stimulates the liver to regenerate with elevated hepatocyte growth factors and hence improved engraftment and cell functionality [30, 45]. These findings indicate the potential significant role of HT in LBMD going forward, improving the patients' clinical condition as well as quality of life.

33.3.2 Acute Liver Failure (ALF)

ALF in children, although rare, carries significant morbidity and mortality due to the abrupt loss of hepatic function. The aetiology is age-dependent. LBMD, herpes simplex virus (HSV) and gestational alloimmune liver disease (GALD) are the leading causes of ALF in infants, whereas drug overdose, viral infections, Wilson disease and autoimmune liver disease are more common causes in older children [46]. HT experience in ALF (Table 33.2) often reveals an improvement in biochemical parameters and even clinical (e.g. improvement in hepatic encephalopathy) scenarios in some patients. Successful 'bridging' to full recovery has been demonstrated [47, 48], but most cases result in LT or death. As there are currently no optimal prognostic scoring models [49] to predict which patients with ALF will spontaneously recover or need LT, or any randomized controlled trials, it is challenging to assess the true efficacy and overall survival benefit of the treatment. Of the more recent studies, Meyburg et al. [29] performed HT in a 3-week-old with HSV and showed a transient reduction of ammonia levels and a decrease in plasma demand, but ultimately the patient died after 11 days due to a complicating hemophagocytic lymphohistiocytosis. Another study showed that 37 patients, including children as young as 3.5 months old, treated with hepatocytes for drug- or viral-induced ALF revealed some positive outcomes; 2 were cured without need for LT, and 3 were bridged to LT with full recovery [50]. More recent results from human hepatocyte alginate microbead transplantation (see Sect. 33.4.6 *Cell Encapsulation to Evade Immune System*) showed safety and feasibility of this technique; four out of eight ALF patients avoided LT, and three were successfully bridged to LT [48].

Table 33.2 Clinical results of hepatocyte transplantation in patients with acute liver failure (updated/modified from [4] and with permission taken from [6])

Study	Patient age	Transplanted cells ($\times 10^9$)	Delivery route	Cell viability (%)	Cell type	Outcome
	Alginate microbead hepatocytes					
Dhawan et al. [48]	15 days	0.02/kg	IP	≥ 60	C	Survived without transplant
	6 years	0.015/kg	IP	≥ 60	C	OLT on day 8
	3 days	0.025/kg	IP	≥ 60	C	Survived without transplant
	1 day	0.024/kg, 0.03/kg	IP	≥ 60	C	OLT on day 28
	8 days	0.026/kg	IP	≥ 60	C	Died
	14 days	0.021/kg	IP	≥ 60	C	Survived without transplant
	41 days	0.03/kg, 0.023/kg	IP	≥ 60	C	OLT on day 44
	17 months	0.02/kg	IP	≥ 60	C	Survived without transplant
	Drug-induced acute liver failure					
Bilir et al. [51]	32 years	1.3	IS	54	C	Death on day 14
	35 years	10	IS	74	C	Death on day 20
	55 years	39	IS	52	C	Death in 6 h
Strom et al. [19]	13 years	1	PV	NA	NA	Death on day 4
	43 years	NA	NA	NA	NA	Death on day 35
Fisher et al. [52]	27 years	0.03	IS	NA	NA	OLT on day 10
	26 years	1.2	IS	NA	NA	OLT on day 2
Fisher et al. [50]	21 years	0.94	IS	NA	NA	Death on day 1
	35 years	5.4	PV	NA	NA	Death on day 18
	35 years	3.7	PV	NA	NA	Full recovery
	51 years	3.9	PV	NA	NA	Death on day 3
Habibullah et al. [47]	32 years	0.06/kg[a]	IP	NA	NA	Death in 30 h
	29 years	0.06/kg[a]	IP	NA	NA	Death in 37 h

Table 33.2 (continued)

Study	Patient age	Transplanted cells ($\times 10^9$)	Delivery route	Cell viability (%)	Cell type	Outcome
	20 years	0.06/kg[a]	IP	NA	NA	Death in 48 h
	20 years	0.06/kg[a]	IP	NA	NA	Full recovery
	24 years	0.06/kg[a]	IP	NA	NA	Full recovery
	Viral-induced acute liver failure					
Fisher et al. [50]	4 years	3.4	PV	NA	NA	Death on day 2
	54 years	6.6	PV	NA	NA	Death on day 7
Bilir et al. [51]	29 years	10	PV and IS	64	C	Death in 18 h
	65 years	30	PV and IS	62	C	Death on day 52
Strom et al. [19]	28 years	0.17	IS	NA	NA	OLT on day 3
	37 years	0.12	IS	NA	NA	Death on day 5
	43 years	0.73	PV	NA	NA	OLT on day 1
Fisher et al. [53]	37 years	0.88	IS	96	C	Full recovery
Habibullah et al. [47]	40 years	0.06/kg[a]	IP	NA	NA	Death in 13 h
Meyburg et al. [29]	3 weeks	0.57	PV	78	C	Death on D11
	Idiopathic acute liver failure					
Sterling and Fisher [54]	3.5 months	0.18	PV	NA	NA	OLT on day 1
	23 years	0.44	IS	NA	NA	OLT on day 5 and death on day 13
Fisher et al. [50]	48 years	0.75	PV	NA	NA	Death on day 1
Habibullah et al. [47]	8 years	0.06/kg[a]	IP	NA	NA	Full recovery
	Mushroom poisoning-induced acute liver failure					
Schneider et al. [44]	64 years	4.9	PV	62	C	Full recovery
	Postsurgical acute liver failure					
Strom et al. [19]	69 years	0.53	IS	NA	NA	Death on day 2
	Acute liver failure induced by acute fatty liver of pregnancy					
Khan et al. [20]	26 years	0.3[a]	IP	NA	NA	Full recovery

C cryopreserved, *F* fresh, *IP* intraperitoneal, *IS* intrasplenic, *NA* not available, *OLT* orthotopic liver transplantation, *PV* portal vein

[a] Foetal hepatocytes

33.4 Optimizing and Advancing HT

Human HT, as an alternative to LT, holds great potential. However, as discussed in this chapter, its widespread clinical application and success are challenged by a limited supply of donor livers from which high-quality hepatocytes can be isolated, along with issues achieving optimal cell viability, engraftment and immunological tolerance. This next section summarizes attempts made to tackle these issues.

33.4.1 Alternative Source of Hepatocytes

Potential alternative sources of hepatocytes are foetal and neonatal donors, as they are currently not being utilized for LT, due to their size and risk of hepatic artery thrombosis [55, 56]. Although cells are not fully mature, they express the principal enzymes needed for hepatic-detoxifying functions [57]. Furthermore, recent studies have suggested the superiority of neonatal cells compared to adult hepatocytes (Fig. 33.2), in terms of higher viability, better recovery after cryopreservation [12] and greater expression of adhesion molecules (β1-integrin, β-catenin and E-cadherin) implying improved engraftment [8, 57]. Cell suspensions from neonatal isolation also contained a higher percentage of hepatic progenitor cells, indicating they could participate in liver regeneration [8]. More recently, preclinical data have suggested that neonatal cells trigger a weaker response of native immunity when tested in a blood coagulation loop model [58]. The translation of this success to human studies is awaited.

33.4.2 In Vitro Expansion of Human Hepatocytes

Approaches to expand human hepatocytes on a large scale, in order to overcome the limited organ supply, have been recently described. Zhang et al. [60] recently reported defined medium conditions allowing 10,000-fold expansion of human hepatocytes. Under hypoxic conditions, cells were able to proliferate for more than 1 month. These proliferating human hepatocytes displayed biphenotypic features of mature hepatocytes (typical polygonal morphology, albumin synthesis, cytochrome P450 metabolic activity, ureagenesis) and liver progenitor cells (expressed early gene markers). Furthermore, these proliferating cells repopulated immune-deficient Fah-knockout mice and underwent maturation following transplantation in vivo.

Similarly, Kim et al. [61] established a culture medium in which human primary hepatocytes were reprogrammed back to hepatic progenitor status. These cells expressed classical markers of early hepatocyte precursors, pluripotent stem cells and endoderm. When transplanted into an ALF mouse model, hepatic progenitors gained properties of mature hepatocytes (albumin and α1-antitrypsin secretion for at least 3 weeks after transplantation).

Despite the promising potential of in vitro hepatocyte expansion, these approaches used non GMP-compliant reagents (e.g. foetal bovine serum, Matrigel), and the

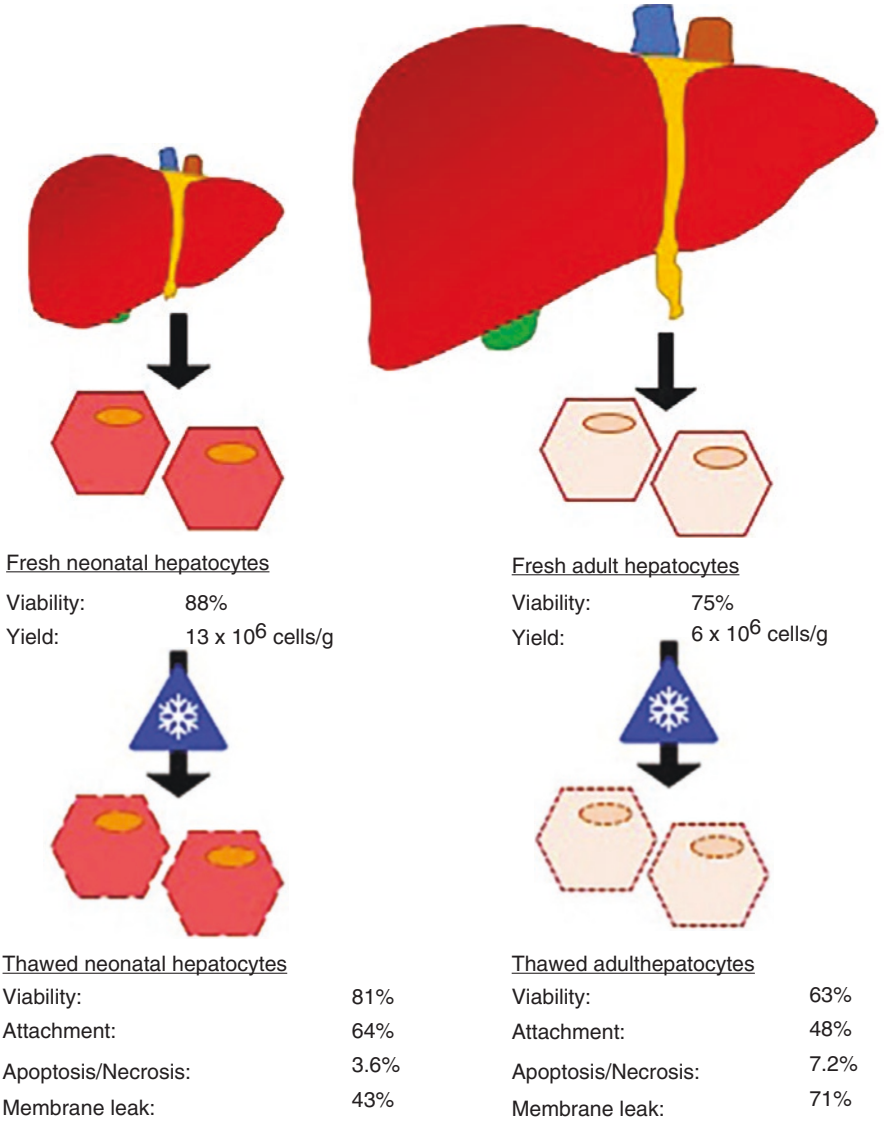

Fig. 33.2 Quality of isolated human hepatocytes (fresh and cryopreserved) from neonatal vs adult liver tissues, including cell recovery and function on thawing [8, 57–59]

newly obtained cells are classified as a medicinal product (due to deliberate expansion in culture or genetic manipulation), requiring regulated legislation and a high number of nonclinical studies to verify safety, biodistribution, toxicology, tissue clearance and tumorigenicity. Optimization of these factors could allow for successful translation of in vitro expansion of human hepatocytes to clinical use.

33.4.3 Generation of Hepatocyte-like Cells from Stem Cells

Adult human pluripotent stem cells (hPSCs), such as embryonic stem cells (ESCs; from the inner cell mass of the fertilized egg) [62–65], and induced pluripotent stem cells (iPSCs; reprogrammed from fully differentiated somatic cells) [66–68] have been used to generate hepatocyte-like cells (HLCs). HLCs are generated from hPSCs based on the embryonic development of the liver (from endoderm differentiation, via hepatic specification to liver maturation). Advantages of hPSCs include better availability, greater capacity to expand in vitro and in vivo and autologous transplantation (removing the need for immunosuppression); however, low scalability and phenotypic immaturity have limited their clinical use.

Pettinato et al. [69] proposed a protocol to generate fully functional hepatocyte-like organoids based on human embryoid bodies (EBs) containing human iPSCs and human adipose microvascular endothelial cells (HAMECs). This combination showed enhanced differentiation of iPSCs-derived HLCs to express liver-specific genes and characteristics (cytochrome P450 metabolism, albumin and fibrinogen production, urea cycle) which were comparable to human primary hepatocytes. Moreover, transplanted HLCs in D-galactosamine ALF rats bridged the animal through the critical phase. The majority of the recent work on iPSC-derived HCLs relies on 3D culture systems, where cells are induced to differentiate towards the hepatic lineage, and their morphology resembles primary hepatocytes more than cells grown on 2D plates [70].

Fourrier et al. [71] attempted to produce GMP-approved HLCs by producing hepatic stem cells (HSCs) from human iPSCs, cultured in xeno-free, feeder-free, chemically defined settings. When transplanted into tacrolimus-suppressed Gunn rats (animal model for Crigler-Najjar syndrome), HSCs reduced bilirubin levels by 30% for 6 months. Protocols have also been described for placenta-derived stem cells, including human amnion epithelial cells (hAECs), to be converted into HLCs [72–74]. They have favourable immunomodulatory properties, can differentiate into different cell types, lack telomerase and are non-tumorigenic when transplanted [75–78]. When transplanted into immunocompetent mouse models of LBMDs (without immunosuppression added), hAECs demonstrated resolution of symptoms and no signs of rejection, highlighting their immune-privileged status [79–81].

33.4.4 Hepatocyte Co-Culture with Mesenchymal Stromal Cells

Mesenchymal stromal cells (MSCs) are a population of immature cells, present in all mammalian stromal tissues, easily isolated from adipose tissue, the umbilical cord, bone marrow and the liver [82–84]. They provide an attractive option for regenerative medicine, as they can differentiate into other cells from the mesodermal origin (chondrocytes, adipocytes, osteoblasts) [85], and have a robust proliferative capacity, which can withstand freeze-thawing cycles after cryopreservation [86]. Furthermore, MSCs have been shown to have immunomodulatory potential, which has shown encouraging results in inducing tolerance in organ transplantation

(kidney, liver) [87] and preventing rejection in allogeneic islet cell transplantation [88, 89]. Studies have shown that MSCs, when cultured alongside human hepatocytes, significantly boosted their viability, survival and liver-specific functions (improved albumin gene expression and secretion, enhanced urea synthesis and metabolic activities), compared to hepatocyte-only monocultures [90–92]. Hence, co-culturing MSCs with hepatocytes could further improve clinical HT.

33.4.5 Strategies to Enhance Primary Hepatocyte Engraftment

Hepatocytes are required to efficiently engraft into the recipient liver for a persistent therapeutic effect.

33.4.5.1 Liver Preconditioning

Several approaches, such as liver preconditioning through partial hepatectomy [30], portal embolization [93] and irradiation [40], have been developed to provide a selective advantage for the transplanted cells to proliferate. A recent study administered 10^6 primary hepatocytes with external focal irradiation and hepatic mitogen GC-1 (a thyroid hormone receptor-β agonist) [94, 95] to an ApoE-deficient mouse model of dyslipidemia. The treatment was tolerated and allowed robust liver repopulation, so that circulating ApoE was detectable and serum cholesterol decreased, and there was a reduction of atherosclerotic plaque formation. Although efficacy has been demonstrated in animal models, the translation of preconditioning to humans has been less successful. As described above, adjunct radiotherapy with HT in a 4-month-old with CPS1 and a 7-month-old with OTC [40] did not demonstrate biochemical or clinical improvement, and partial hepatectomy in two CN1 patients receiving HT showed initial biochemical improvement, which was not sustained [30].

33.4.5.2 Alpha-1 Antitrypsin Co-Administration

The innate immune system, via an early phagocytic immune response, plays a key role in eradicating up to 70% of transplanted hepatocytes, soon after transplantation. Instant blood-mediated inflammatory reaction (IBMIR) [96] describes one mechanism for this phagocytosis process. Injected hepatocytes release tissue factor, triggering a rapid cascade of coagulation and complement pathways (Fig. 33.3) [97]. Formed fibrin clots, thrombin-activated complement proteins and platelets entrap hepatocytes and infiltration of polymorphonuclear leukocytes result in the loss of transplanted cells [98]. The co-administration of alpha-1 antitrypsin (A1AT), a natural immune-modulator normally produced by hepatocytes, with known anti-inflammatory and anti-apoptotic properties [99, 100], has been shown to dampen this reaction in islet cell transplantation [101]. Recently, Lee et al. [102] used an in vitro Chandler tubing system to elicit acute IBMIR, by combining human hepatocytes with ABO-matched blood, and demonstrated its suppression with the addition of A1AT (4 mg/ml). Reduction in both platelet consumption and pro-inflammatory cytokines (IL-1β, IL-6 and IFN-γ) was observed. In the animal

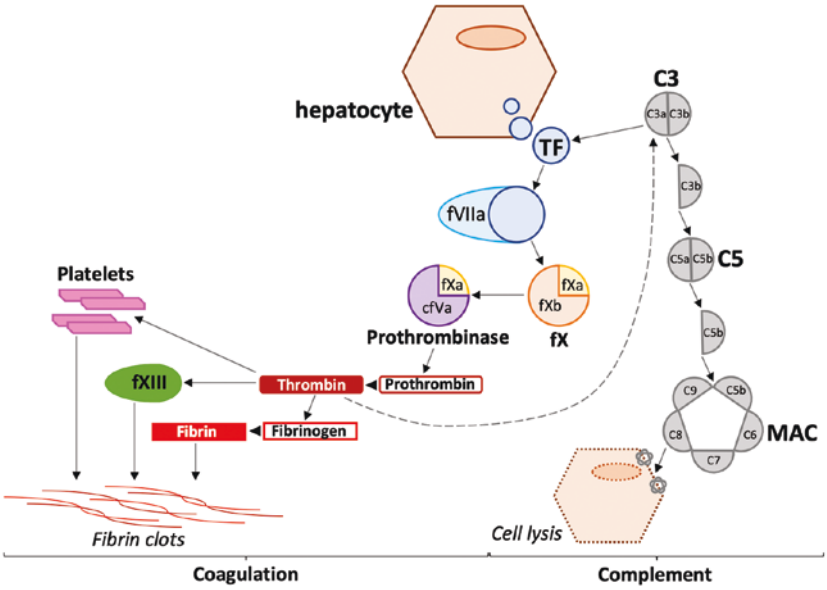

Fig. 33.3 Activation of complement and coagulation pathways during IBMIR. Tissue factor (TF) released from transplanted hepatocytes binds to clotting factor VIIa (fVIIa) causing cleavage of factor X (fX). The resulting prothrombinase, consisting of fXa and cofactor Va (cfVa), converts prothrombin to thrombin which then causes the formation of fibrin clots by transforming fibrinogen into fibrin, activating factor XIII (fXIII), causing fibrin to cross-link and enlisting platelets to aggregate. Cleavage of complement protein C3 to C3a and C3b causes the C5 convertase to generate C5b and form the membrane attack complex (MAC) with C6-9 complement proteins. This is another way thrombin initiates the complement signalling process. MAC attaches to the cellular membrane and generates holes that lead to cell lysis [96, 97]

model, engraftment of male rat hepatocytes into female recipients was significantly improved when intrasplenically infused with A1AT (120 mg/kg). This was demonstrated by measuring labelled hepatocytes expressing the sex-determining region Y gene, present only in donor cells. Increased engraftment correlated with reduced IBMIR. Clinical trials using A1AT are currently being planned.

33.4.6 Cell Encapsulation to Evade Immune System

An exciting new direction for HT is the encapsulation of hepatocytes in alginate beads [103]. Alginate (alginic acid) [104] is a bio-inert material which creates a physical yet permeable barrier, protecting hepatocytes from immune attack while allowing the movement of substrates and proteins for functions of the liver to be performed (Fig. 33.4). The immune privilege offered by alginate permits cell transplantation without using immunosuppression. The efficacy and safety of this technique have been shown in multiple animal models with ALF [105–108].

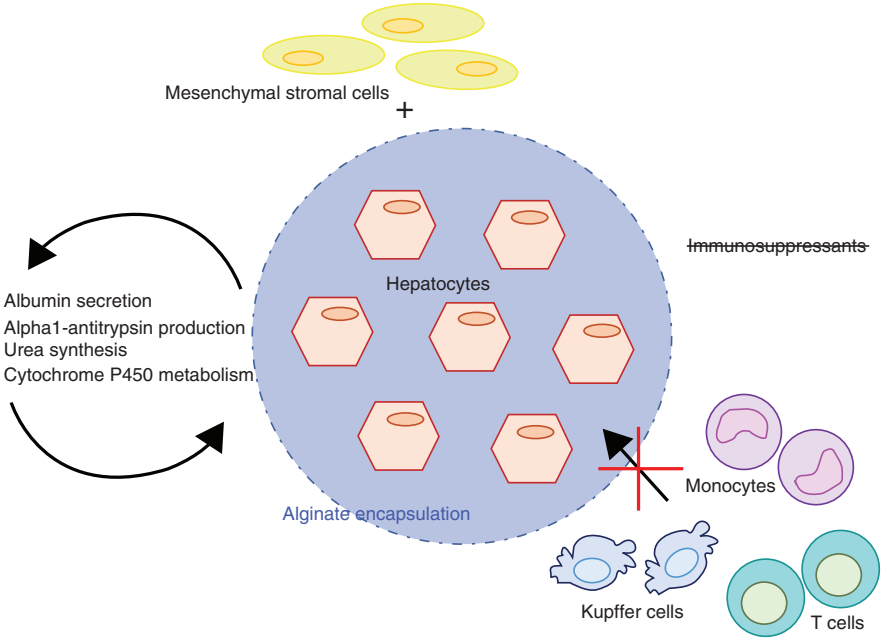

Fig. 33.4 The concept of alginate-encapsulated hepatocytes is protection against immune effector cells (lack of host immune response means no rejection of donor cells, without the need for immunosuppression) while fulfilling liver-specific activities. Further Improvements may include co-encapsulation with cells such as mesenchymal stromal cells, to enhance long-term survival and functionality

The first paper documenting the human experience with encapsulated hepatocytes has recently been published by King's College Hospital [48]. Eight children with ALF (four neonatal haemochromatosis, two viral infections and two children with unknown cause at the time of infusion) received intraperitoneal infusion of GMP grade alginate-encapsulated hepatocytes, at a median age of 14.5 days (range 1 day–6 years). The procedure was well tolerated, without complications in all patients. Of the eight children, four avoided LT while three were successfully bridged to LT following the intervention. One patient, who died, was not considered a suitable LT candidate. Furthermore, cells retrieved after infusions (at the time of LT) were structurally intact, were free of host cell adherence and contained viable hepatocytes with preserved function. This study is pivotal in demonstrating safety and efficacy of encapsulated hepatocytes in ALF patients, including sick neonates. There is also evidence to suggest that the co-administering of other cell types, such as MSCs [109], can prolong the survival and function of encapsulated hepatocytes and that cryopreserving encapsulated hepatocytes is associated with less freeze-thaw damage [110].

33.5 Conclusions

HT has immense potential for LT candidates, overcoming the drawbacks of whole LT. Use of alginate-embedded human hepatocytes has been a major advance in the management of ALF. Extensive efforts are being made to address the key limitations of this modality, to enable future widespread clinical application.

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Split Liver Transplantation

34

Lucas Rabaux, Christophe Chardot, and Carmen Capito

34.1 Introduction

How to get a new liver when you are 2 years old?

Although the first liver transplantation was performed in a child by Thomas Starzl's team in 1963 [1], it soon became obvious that pediatric transplantation could not be considered without finding a solution to the mismatch between the number of small size donors (fortunately very limited) and the number of children suffering from end-stage liver failure. A solution was proposed in 1984, when, almost concomitantly, Henri Bismuth and Christoph Broelsch performed the first transplantation with a reduced-sized adult liver in a child [2, 3]. Reduced but not split. It was in 1988 that the first split liver transplantation was performed by Rudolf Pichlmayr's team, allowing two transplants from one adult liver, one in an adult with the right lobe and one in a child with the left lobe [4]. Thanks to this technique and the development of living donor transplantation, mortality on the waiting list in the pediatric population has been considerably reduced from 40% in the 1980s to less than 5% nowadays [5, 6]. Thus, the split liver is today an essential procedure in the organization of a liver transplantation system. It probably remains underperformed because of the complex organization that it requires and the specific complications that are attributed to splitting the liver. This is why it is still an issue, which needs understanding of both the organization of the donor allocation system that allows it and the technical challenges it represents, as well as its specific complications [3].

L. Rabaux · C. Chardot · C. Capito (✉)
Pediatric Surgery and Transplantation Department, Hôpital Necker Enfants Malades, Paris, France

APHP, Université Paris Centre, Paris, France
e-mail: carmen.capito@aphp.fr

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34.2 Donor Selection

Everything begins with a phone call, most of the time in the middle of the night: "We have a donor." Then it all starts, all the steps that lead from the retrieval to the split and the transplantation. However, long before that, there is a donor allocation system, without which nothing would happen.

34.2.1 Graft Allocation

In France, it is ruled by the *Agence de la biomédecine*, the French organ-sharing authority. The allocation is partly made according to the age of the donor and regardless of MELD/PELD scores. Donors under 18 years old are allocated in priority to pediatric recipients, and donors between 18 and 30 years old are allocated in priority to pediatric recipients as long as a split is proposed by the pediatric team for an adult surgical center [7]. In the United States, the algorithm is more complex and includes not only MELD/PELD score but also recipient/donor geographical proximity and age of the donor. Pediatric livers are prioritized to regional pediatric patients or national status 1A younger than 11 years old and then regional adult patients with status 1A. Interestingly, national pediatric 1A patients between 11 and 18 years old will come after the regional pediatric/adult round. For donors above 18 years old and who fall under the OPTN criteria of split, the graft is allocated first to the regional patient with the highest MELD/PELD score but with no obligation to split, and then the other lobe could be offered to other regional patients in order of decreasing MELD/PELD score [8]. In the United Kingdom, there is an "intention to split policy," meaning that if the graft meets the criteria for splitting, it is offered to the pediatric center for a split [9]. An equivalent strategy was introduced in Italy beginning in August 2015, under the name "mandatory-split liver policy": donors aged 18–50 years at standard risk are offered for split liver transplantation [10]. Those allocation rules are extremely important, as they significantly change the number of split livers in each country and thus increase or decrease the access to transplant for pediatric recipients. In the United States, UNOS data demonstrate that less than 1.5% of donor livers are split for transplant. In France, 3.8% of donor liver are split [6], and in Italy, the split liver transplantation rate increased from 6% to 8.4% with the new policy [10]. These results could probably be even higher, as evidenced by some centers (such as Birmingham in the United Kingdom) whose rate goes up to 15% of split livers [9].

34.2.2 Donor Criteria

The most critical factor for success is the choice of the donor/recipient pair. Although some marginal donors can be chosen, and successfully, for adult liver transplantation [11], for a split the donor must be chosen carefully because of the increased

cold ischemia time that it implies. Will the liver we have chosen be able to withstand this additional insult?

The split remains a stressful procedure for the liver, whose ischemia time will necessarily be prolonged. Moreover, the vessels to be anastomosed will be of reduced diameter, and there will be a hepatic cut. It is therefore necessary to choose a graft capable of withstanding these constraints, without forgetting that two transplants will result from the split, one of them in a child, who will need to keep the graft for many years.

Regarding total ischemia time, the cutoff generally accepted in splitting teams is 12 hours. Stahl and colleagues showed in a meta-analysis that primary non-function was significantly increased after that time [12].

Criteria that identify a donor's liver, as one with the potential to be split, have been established by UNOS/OPTN in the United States [13]. They are noted in Table 34.1. Our team's criteria are based on the same criteria, with some differences [14].

To summarize, the ideal donor for a split is young, hemodynamically stable with a short resuscitation required, not abusing drugs and alcohol, and no history of liver disease or other complex diseases. We limit donor age to 50 because the liver's regeneration capacity is perhaps compromised by aging, but this upper limit is, of course, balanced by the urgency. Regarding static biochemical tests, the ideal donor has no severe electrolyte disturbances or deteriorating trends. Although Kaseje et al. recently demonstrated no difference in primary non-function incidence in pediatric liver transplantation with a donor sodium above 160 mM, in our center we keep this as the upper allowable limit [15]. For liver enzymes, we have a quite high cutoff but as a function of the cause of death. A post trauma donor is more prone to have elevated liver enzymes; in contrast, we will be more concerned if it is a neurological accident with elevated hepatic enzymes. Another pitfall to watch out for is that extensive necrosis will prevent the liver from producing any enzymes. We are also very suspicious of motor vehicle accident donors on a weekend evening because of

Table 34.1 Donor selection- UNOS/OPTN and local criteria

UNOS/OPTN criteria	Criteria in our center
1. Less than 40 years old 2. On a single vasopressor or less 3. Transaminases no greater than three times the normal level 4. Body mass index (BMI) of 28 or less	1. ≤50 years, BMI < 30 2. Heart beating, brain death 3. No asphyxial death (drowning, hanging) 4. Cardiac arrest <30 min 5. Non-alcoholic (elevated GGT or MCV?) 6. No hard drug abuse 7. No complex medical history 8. Na + ≤160 meq/L 9. Decrease of liver tests since death and initial ALT<500UI/l 10. No alcohol on first blood tests 11. Hemodynamic stability (nor adrenaline <2γ/kg/min) 12. <10 days in ICU 13. No active infection

the risk of acute hepatitis or primary non-function induced by severe acute alcohol abuse.

The last thing to evaluate for the donor's choice is the ratio of the weight of the donor liver to the recipient. The aim is to obtain a functional hepatic mass of 1 to 3 percent of the recipient weight. Although multiple formulae exist to calculate the donor's liver volume [5], we use a simplified and practical estimation that is the following:

$$\text{Donor Weight} = 4 - 10\,\text{X}\,\text{Recipient Weight} = \text{Left lateral segment}\left(\text{LLS}\right)$$

$$\text{Donor Weight} = 2 - 4\,\text{X}\,\text{Recipient Weight} = \text{Left lobe}\left(\text{LL}\right)$$

If the graft-to-recipient weight ratio is below 1%, the recipient is at risk of small-for-size syndrome, which will be characterized by excessive portal flow, cholestasis, major ascites, and extensive necrosis of the liver parenchyma [16]. On the other side, a ratio too high will lead to large-for-size syndrome, with a main and potentially dramatic complication that is acute graft venous outflow obstruction.

34.3 Liver Procurement

The first step in liver retrieval is the macroscopic evaluation. The liver is inspected and palpated, and a recoloration time is performed to identify arguments for significant steatosis. The recoloration time is defined as the number of seconds it takes for the liver to recover its initial color after pressure, going from purple red to yellow and then back to purple red. A liver with minimal steatosis will have a recoloration time of less than 3 s. Even if very empirical, we consider it as a good evaluation index. If there is any doubt, both because of donor characteristics and of the graft gross appearance, a biopsy is performed, with frozen sections requested. If the biopsy shows a macrovesicular steatosis of more than 30%, the organ should not be split. The reason for this is to avoid primary non-function, one of the main risks for which is macrovesicular steatosis [17].

34.3.1 In Situ Split

In the United States, two-thirds of splits are performed in situ [18] unlike in France where less than 10% are performed in situ, the main reason being organizational. Indeed, as it is a complex procedure, it implies that a senior surgeon be involved in the procurement. Most of our teams cannot afford this human expense all year long, and because of comparable long-term results [19] if ischemia time remains below 12 h, we perform ex situ split. In situ split advantages are a reduced cold ischemia time, meaning a quicker recovery of the liver function after transplantation and a better control of the bleeding on the cut surface. The ex situ split is indeed an independent predictor of intraoperative bleeding [20].

34.3.2 Ex Situ Split

In France, the majority of splits are performed ex situ. The advantages of this technique are as follows: first, there is a reduction of the procurement operative time, which can be essential if the donor becomes hemodynamically unstable, and, second, a resident trained to perform the procedure quite quickly can perform the retrieval. The dissection of the pedicle is limited, and the liver can even be retrieved en bloc with the pancreas, which avoids potential difficulties related to arterial anatomical variations and allows venous reconstruction if needed as the splenic and superior mesenteric veins are also harvested in continuity with the portal vein. It is important to keep in mind that vascular anatomy is standard in only 50–75% of cases [21].

34.4 Split

One organ has been accepted, but two transplants are targeted. To achieve this, the liver must be shared. All splitting procedures are based on the segmental liver anatomy described by Couinaud [22]. The most accepted split is to create a left lateral segment and extended right lobe grafts for a child and adult pair. A segment II/III graft is achieved by dividing the hepatic parenchyma at the falciform ligament. However, they are some other feasible splits, which we will discuss below.

It is important to keep in mind that hepatic biliary anatomy should be assessed prior to cutting any vessels because some anatomic variations of the biliary anatomy, such as crossing right bile ducts, may preclude the procedure. In this regard, we use a perioperative cholangiogram on the back table before any sections and before giving the OK to the adult team awaiting the right liver.

At the vascular level, only intrahepatic bifurcation of the portal vein is an absolute barrier to splitting. Other vascular and biliary variants are not barriers, irrespective of the numbers and difficulty of the anastomoses required. The subsequent risk of stenosis should be balanced with the urgency of the transplantation for the recipient.

In the following presentation, we have chosen to present each step of a left lateral segment split in a chronological order.

34.4.1 Before Starting

During the split, the liver is immersed in a 4 °C preservation solution maintained at this temperature by ice. If the gallbladder has not been removed during the liver retrieval, it is removed now, and the cystic duct is ligated.

34.4.2 First Step: Dissection

Vena Cava The liver is placed with the posterior side in front of you. The vena cava is defatted, and any diaphragmatic and adrenal veins are ligated. The retrohepatic vena cava is tested for sealness. The inferior vena cava will stay with the right graft.

Portal Vein Still with the posterior side in front of you, the portal vein is dissected along its entire course up to its bifurcation, which is marked by a loop. The only absolute contraindication of splitting is intrahepatic division of the portal vein. In these cases, we will not share and keep the portal vein totally for the more urgent recipient, so either a liver reduction for the child or the whole liver for the adult recipient.

Hepatic Artery The liver is then placed anterior face in front of you. The hepatic artery is dissected to the beginning of the gastroduodenal artery, which is ligated. It is then dissected along its left edge up to the start of the right hepatic branch. The dissection must be minimized as much as possible, in order not to alter the vascularization of the main bile duct.

Bile Duct A probe is introduced into the main bile duct, to locate the start of the left bile duct, with the presence of a common II–III trunk. The bile duct is dissected only at its division, and here again, minimal dissection is needed. A metallic clip is put close to the left bile duct origin, at the presumed level of section. This will allow it to be located during cholangiography. Imaging is performed, which allows us to assess the position of the duct of segments II and III and especially segment IV bile duct and thus determine the ideal position for sectioning the left duct.

Once this step is achieved, we can proceed to the section of the vessels.

34.4.3 Second Step: Hilar Vessel's Section

Portal Vein The left portal vein is cut at its roots or just after the division segment IV branches if any. The portal trunk and the right portal vein will stay with the right graft. The orifice in the portal trunk is closed with 7.0 monofilament. In the first centimeters of the left portal vein, the small branches going to the Spiegel lobe are ligated and cut. This allows more length of the left portal stump, which will be precious during anastomosis.

Hepatic Artery The right hepatic arterial branch is sectioned at its origin, and its orifice is ligated. The coeliac trunk will usually stay with the left graft because the right branch is larger than the left one [23].

Bile Ducts The left bile duct will be cut sharply at its termination with a scalpel in order to maintain continuity between the right and the main hepatic duct. If the seg-

ment IV bile duct is located at the very first centimeters of the common left bile duct, it could be acceptable to shift the section location before. It is possible that you will not encounter a common bile duct but separate bile ducts for segments II and III; in this case, you need to cut them individually, and you will be doing separate biliary anastomoses.

34.4.4 Third Step: Parenchymal Transection

It is performed with Kelly clamp crushing technique and specific ligatures. For the first two superficial centimeters and for small ligatures, we gladly use thermofusion (Ligasure®) which ensure a safe bile and vascular stasis. Ideally, for this step, once you approach the hilum, you need to flip the liver on its anterior side (posterior side in front of you). This will avoid damaging the vascular and biliary structures of each graft.

34.4.5 Final Step: Hepatic Vein

The path of the middle and left hepatic vein is located with a metallic probe. The middle hepatic vein will stay with the right graft in case of a left lateral segment graft. At the end of the parenchymotomy, using scissors we will separate the left hepatic vein from the middle one. The hole on the middle vein will be closed either with a venous patch or transversally if not narrowing the lumen.

34.4.6 Alternative Split

As previously stated, arterial anatomy is modal in only 50–60% of cases. A variation of vessels can vary the split procedure. In the case of a replaced right hepatic artery coming from the superior mesenteric, splitting the arteries can be greatly facilitated: the right hepatic artery and the superior mesenteric patch will stay with the right graft, and the common one and the celiac trunk will stay with the left graft. If a large replaced left hepatic artery comes from the left gastric artery, one may simply cut at the origin of the common hepatic artery, leaving the common hepatic artery with the right graft and the celiac trunk and left hepatic artery with the left graft [24].

Beyond the arterial variations, alternative cutting lines are possible. The liver can be split to create a right and left liver (with the middle hepatic vein), which can be used for two adults or an adult and a teenager pair. Furthermore, according to the size and weight of the pediatric recipient, if a heavier graft is necessary, you can split a left lateral segment plus half of segment IV without the middle hepatic vein. Still in this idea of adaptation to the size of the recipients, we can practice monosegmental grafts. Usually segment III will be removed [25]. This technique can be useful for neonates, but most small infants will be able to cope with a certain degree

of large for size (>4% GBWR) provided that a delayed closure of the abdomen is performed (silicon or Vicryl mesh for the first postoperative week with or without closure of the skin and final closure thereafter) [26].

34.5 Hepatectomy

Most of the time, hepatectomy is made in parallel with the split. It is probably the most critical step of all the transplantation procedure. Although the technique is not different from adult recipients, it has some pediatric particularities. Indeed one-third of the pediatric recipients have liver failure from biliary atresia, and a large majority of them have already had a Kasai procedure [6, 27]. Hepatectomy will thus be performed on a previously operated abdomen. This situation associated with cirrhosis will induce vascular adhesions all around the liver, which will make the dissection more difficult and bloody. However, it is mandatory to reduce perioperative bleeding to a minimum. Indeed, it has been identified as a predictive factor of increased mortality. In this regard, the dissection must be precise, as bloodless as possible, and if impossible, the liver must be removed quickly. The vena cava is preserved by ligation of the spigelian veins from bottom to top as described by Russell Strong from Brisbane [28].

On the other hand, everything must be done during the Kasai operation to limit inflammation and future adhesions: minimal dissection of the hilum and hepatic pedicle and no drainage after the Kasai procedure. Furthermore, the application of hyaluronate-based membrane (Seprafilm®) on the liver prevents those adhesions and has been identified as a protective factor for intraoperative bleeding [23, 27].

34.6 Transplantation

In the same spirit as before, we will describe the steps of graft implantation and its particularities in a pediatric recipient.

34.6.1 Before Starting

It is important to note that during the graft implantation period, the liver will be subject to warm ischemia. In our center, we infuse the portal vein with a 4 °C albumin 5% solution, until the portal anastomosis is performed. One of the reasons is that we think it will minimize the warm ischemia during the hepatic vein anastomosis; other advantages will be described below.

34.6.2 First Step: Hepatic Vein Anastomosis

According to the technique described by Russell Strong (Brisbane technique) in 1988, during hepatectomy the recipient liver has been resected off the inferior vena cava, which has been left in situ [28]. Still following this technique, the liver is placed orthotopically in the recipient, and the first step will be the anastomosis of the donor hepatic vein end to side to the inferior vena cava of the recipient. In order to ensure an adequate venous outflow and to prevent the liver from kinking, the anastomosis will be done using the triangulation technique described by Jean Emond [29]. The orifices of all three hepatic veins of the recipient will be merged into one single orifice (Fig. 34.1a) and widened by a vertical incision of the anterior aspect of the vena cava below the original opening. A widening of the graft left hepatic vein by a vertical incision will be also performed (Fig. 34.1b) to avoid mismatch. The anastomosis is then performed by three running sutures starting from the inferior tip of the triangle (Fig. 34.1c, d).

When it is completed, we carefully examine the cut surface, and thanks to the albumin flow, we can identify any leaks from the vena cava or the cut surface that mandate additional ligation before unclamping. Once that is done, we clamp the graft portal vein with the graft filled with albumin. This will avoid hypotension at unclamping by vascular steal in an empty large organ.

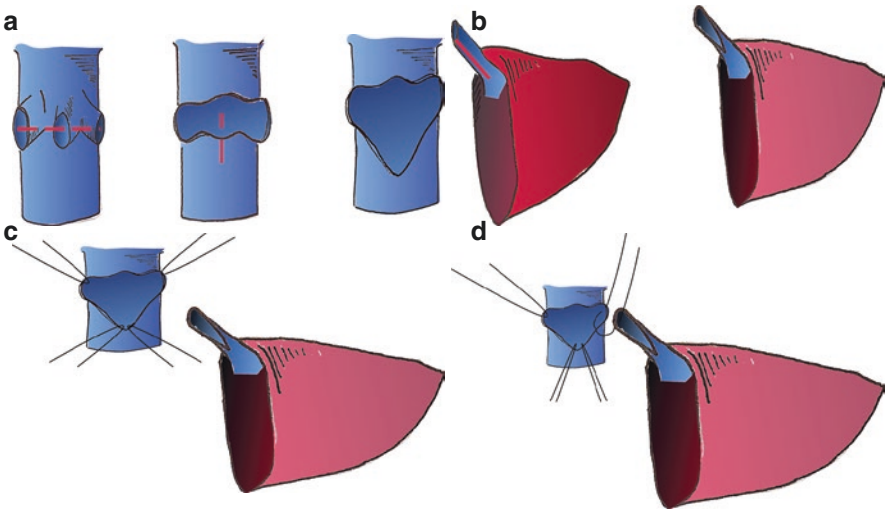

Fig. 34.1 Schematic representation of the triangulation technique according to Emond. (**a**) Section lines on the recipient vena cava. (**b**) Section lines of the graft hepatic vein. (**c**) Hepatico-cava anastomosis. (**d**) Hepatico-cava anastomosis

34.6.3 Second Step: Portal Vein Anastomosis

Most of the time, the portal anastomosis is done end to end. The most common issue that makes it impossible is a diameter mismatch with a smaller recipient portal vein diameter. If so, there are two kinds of techniques that must be known (Fig. 34.2).

The first one does not require a vein graft. If we are facing a diameter mismatch, we will perform an end-to-end-side anastomosis starting at the confluence of the superior mesenteric vein and the splenic vein of the recipient. The incision on the recipient portal vein is a Y-inverted shape (Fig. 34.2a, b) as described by Koichi Tanaka's team in 1999 [30]. This precludes mobilization and control of this bifurcation behind the pancreas during the hepatectomy. This anastomosis is feasible when the graft left portal branch is not too short, and it requires a parachute-running suture for the beginning of the anastomosis.

The second ones will use vein grafts and will be used when the direct anastomosis is technically difficult (short graft portal branch). It can be performed either with the interposition of a vein graft to gain length (Fig. 34.2c) or with a vein patch sutured on the confluence of the superior mesenteric vein and the splenic vein and the small recipient portal trunk to gain length and width. In our center, our preference goes to the portoplasty with a patch (Fig. 34.2d). Indeed, De Magnée et al. published in 2011 a retrospective study that showed that there was an increased risk of thrombosis associated with interposition of a vein graft as compared to the portoplasty with patch or end-to-end anastomosis when feasible [30, 31].

Before completing the portal anastomosis, we systematically retrieve 10 ml/kg of portal blood in children with minimal or absent portal hypertension (fulminant hepatitis, tumors, or organic aciduria patients mainly) compensated by the same amount of red cell and platelet transfusion. The idea is to reduce reperfusion injury due to an accumulation of metabolites produced by the 1 or 2 h of mesenteric ischemia.

34.6.4 Third Step: Hepatic Artery Anastomosis

The hepatic artery anastomosis will be end-to-end interrupted sutures, with an 8.0 nonabsorbable monofilament (prolene), if the caliber of the recipient artery allows it. If it is too small, we will willingly use an iliac conduct (Fig. 34.3) that will be anastomosed to the infrarenal aorta during cold ischemia time while waiting for the split to be completed. Then we will perform a standard running suture end-to-end anastomosis between the iliac graft and the common hepatic artery or the coeliac trunk of the graft. This type of anastomosis is of upmost importance particularly when hepatectomy has been difficult or the graft appears less viable than expected. Indeed, in these situations you need a good and quick graft arterial supply.

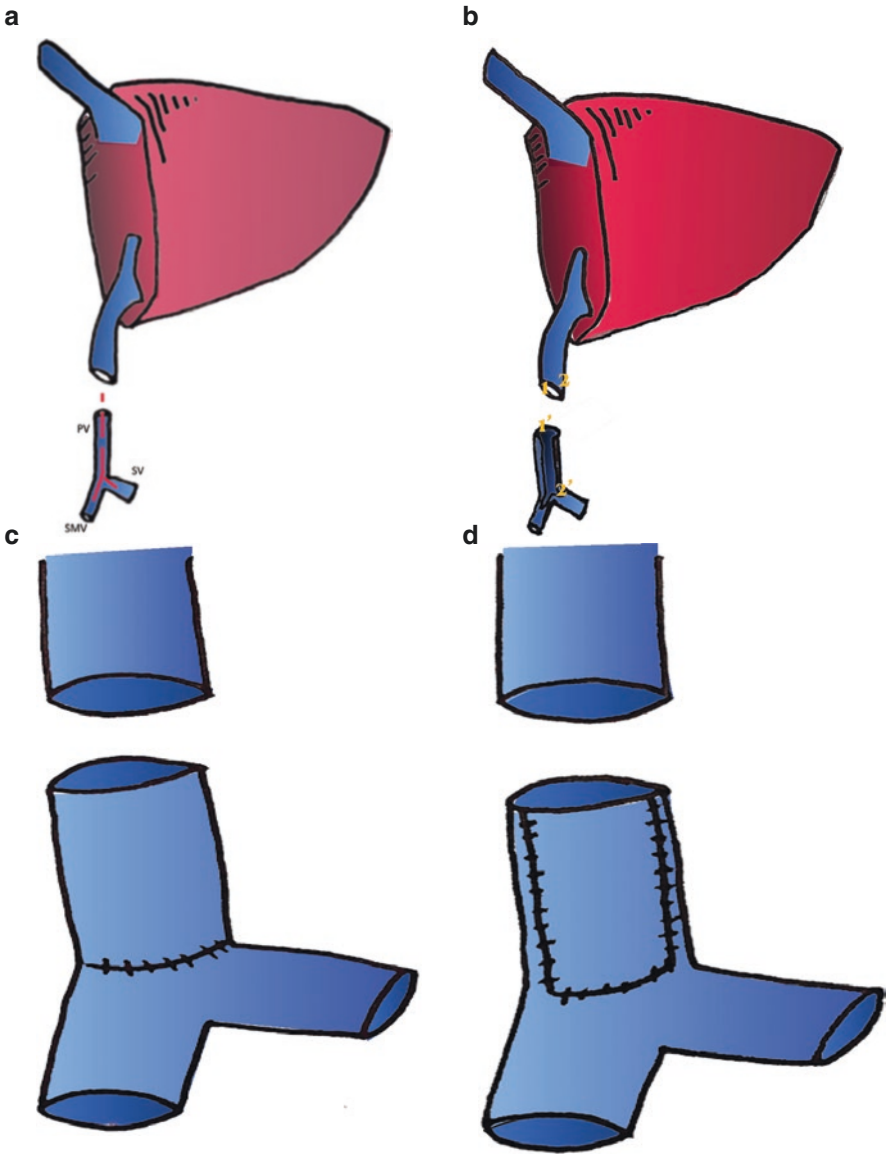

Fig. 34.2 Schematic representation of portoplasty without patch. (**a**) Section line on the portal (PV), mesenteric (SMV) and splenic (SV) veins. (**b**) Anastomosis without a patch. Schematic representation of portoplasty with grafts. (**c**) vein graft interposition (**d**) vein patch interposition

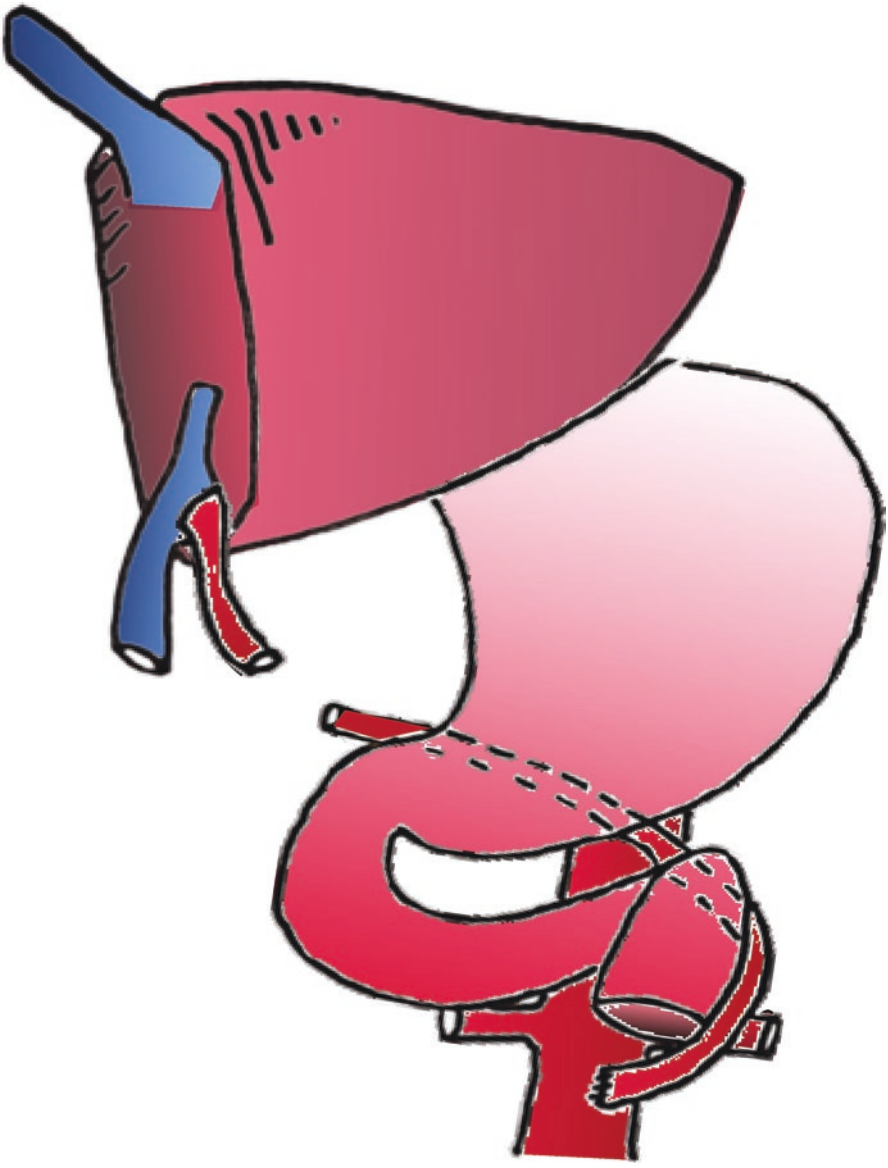

Fig. 34.3 Schematic representation of the donor iliac artery graft anastomosed to the infrarenal aorta

34.6.5 Fourth Step: Biliary Anastomosis

The biliary anastomosis is always a Roux-en-Y choledochojejunostomy, with interrupted sutures, as described by Thomas Starzl [32]. It is sometimes necessary to make two anastomoses, if the bile ducts from the segments II and III are separate. Before starting the anastomosis, one needs to check with a metallic probe that the two branches from segments II and III are present.

34.6.6 Final Step: Closing

When all fourth anastomoses are completed, we will attach the liver to the diaphragm in proper position, to prevent any rotation, which could lead to a kinking of hepatic veins, an immediate Budd-Chiari syndrome, and a permanent loss of the graft.

It is mandatory that the closure be tension free. If this is not possible, the parietal closing must be delayed, and a Gore-Tex mesh and VAC dressing must be used instead. Our belief is that this should be generalized to all situations where transplantation has been difficult (significant blood loss, prolonged clamping time, redo anastomosis, prolonged warm ischemia, and patchy recoloration of the liver). It prevents postoperative abdominal compartment syndrome and further compression of the graft by parietal edema that will necessarily occur if the graft does not reperfuse well postoperatively. Furthermore, our experience and recent studies tend to show that it does not increase the infectious risk [26].

34.7 Results

A number of studies have shown that there are no significant differences in patient and graft survival between split liver transplantation and whole liver transplantation [33–36]. This seems to be true in the short and also in the long term and applies for pediatric recipients and for adult recipients as well [37]. The results have greatly improved with experience and can no longer be an obstacle to the extended practice of the split liver transplantation.

34.8 Complications

Patient and graft survival and biliary and vascular complications are reported to be not more frequent in split liver transplantation compared to whole liver transplantation [38, 39]. That said, the presence of more than one bile duct in the graft is an independent risk factor for the development of biliary complications after pediatric

liver transplantation [40]. With regard to vascular complications, the pediatric rates of hepatic artery and portal vein thromboses are significant and higher than those observed in adults [33] or in pediatric living donor liver transplantation [41]. A recent review of the pediatric literature showed rates of 0–28.1% for hepatic artery thrombosis and 1.5–11.2% for portal vein thrombosis with lower rates seen in pediatric living donor liver transplantation [42]. In our center, we have experienced low rates despite a majority of deceased donor ex situ split liver transplantation (2.3% incidence of hepatic artery thrombosis). Our protocol of thrombosis prophylaxis includes antithrombin substitution starting in the operating room. Indeed, in a study that we have recently conducted, and not yet published, we have identified that there is a real shift in favor of prothrombotic factors during the first 5 days of transplantation despite the low PT seen. The correction occurs after about 5 days. In addition to antithrombin substitution, we add low molecular weight heparin. Finally, a switch to aspirin is made at day 10 if the liver produces sufficient ATIII at that time.

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Part VI

Lung Transplant

Pediatric Lung Transplantation: Indications and Outcomes

35

Raphael Werner and Christian Benden

35.1 Introduction

For children and adolescents with end-stage chronic parenchymal and vascular pulmonary disease, lung transplantation is often the last therapeutic option. Since the first pediatric lung transplant in 1986 [1], the management of pediatric patients has developed rapidly, and currently lung transplantation is an accepted treatment in carefully selected children and adolescents, offering a net survival benefit and an improved quality of life [2–4]. While the overall survival after pediatric lung transplant has improved in recent years, rates of chronic lung allograft dysfunction (CLAD) and late mortality have essentially remained unaltered [2, 4]. Thus, the latest improvements have resulted from a reduction in early mortality, mainly due to infectious complications [2, 4]. According to the International Society for Heart and Lung Transplantation (ISHLT) Thoracic Transplant (TTX) Registry, a total of 101 pediatric lung transplants were performed worldwide in 2017. These cases were distributed among 37 centers, but only 5 centers performed more than 4 procedures [5]. While most pediatric lung transplants are performed in high-volume adult centers achieving excellent results [6], recent publications have shown that also the centers' pediatric experience greatly influences the outcome [7]. Especially for the management of patients with cystic fibrosis (CF) undergoing lung transplant, pediatric and CF-specific knowledge is crucial, predicting better long-term survival [7].

While chronic obstructive pulmonary disease (COPD) is the most common indication for adult lung transplantation, most pediatric patients undergo lung transplantation for end-stage CF. However, the primary indication for lung transplantation

R. Werner
Division of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

C. Benden (✉)

Faculty of Medicine, University of Zurich, Zurich, Switzerland

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in pediatric patients is age-dependent, ranging from congenital heart disease in children younger than 1 year to CF and idiopathic pulmonary arterial hypertension (IPAH) in older children and adolescents [5]. Different approaches in the management of chronic pulmonary diseases and organ allocation also account for regional differences in the primary indication for pediatric lung transplantation [3]. Re-transplantations are hardly ever carried out in children, with only 103 cases worldwide documented in the ISHLT TTX Registry between 2000 and 2017 [5]. The leading cause for re-transplantation was CLAD, most commonly presenting as CLAD – bronchiolitis obliterans syndrome (BOS) [3, 5]. Similarly, a decreasing trend in numbers of combined heart-lung transplantations has been observed worldwide, as reported in the ISHLT TTX Registry: while nine children underwent such a procedure in 2014, only three cases were documented in 2017 [5]. The particular indications, as well as the intra- and early postoperative management of patients undergoing heart-lung transplantation, go beyond the scope of this chapter and will not be addressed.

Lung transplantation in children comprises a variety of additional challenges compared to adults, such as the adapted surgical approach, the developing pediatric immune system and its influence on immunosuppression, as well as the psychological and social impact during adolescence. Children are not "just small adults" but deserve an individually tailored approach to lung transplantation. In this chapter, we describe the essential aspects of pediatric lung transplantation, providing an update on the latest developments in the management of these patients.

35.2 Transplant Evaluation

In all children with end-stage parenchymal or vascular pulmonary disease who have exhausted medical and/or surgical treatment and have a predicted life expectancy of less than 2 years, a lung transplant should be assessed and discussed at a lung transplant center [8, 9]. Due to the lack of adequately sized organs for younger children, a potentially longer time on the waiting list has to be expected, requiring an early referral as well as timely listing for transplant [10]. These circumstances intensify the fact that a careful selection of possible candidates is absolutely crucial. Even though clinical evidence on the selection of lung transplant candidates is scarce, with no prospective, randomized trials available, the ISHLT provides a consensus document with disease-specific recommendations regarding the timing of referral and listing for transplant [10]. While this document provides support from expert opinions to place a patient on the waiting list, it is not a replacement for a careful individual evaluation of each potential candidate [10]. Based on the current data, absolute contraindications for lung transplantation in children are generally similar to those in adults. However, relative contraindications vary between different centers [10]. For patients with CF, referral criteria are similar to adult practice: in brief, maximal medical therapy, a forced expiratory volume in 1 s (FEV_1) <30%, a 6-minute walk distance <400 m, or pulmonary hypertension at rest [3, 10]. Furthermore, CF patients with an increasing frequency of exacerbations,

noninvasive ventilation (NIV), prolonged recovery from exacerbations and accumulating antibiotic resistance, pneumothorax, major hemoptysis, and/or worsening nutritional status despite adequate supplementation should also be evaluated for lung transplantation [3, 10]. Maximal medical therapy in CF patients should—whenever applicable based on an individual's CF genotype—include new disease modulators that act by improving production, intracellular processing, and/or function of the defective CF transmembrane conductance regulator (CFTR) protein as the basic defect. The promising early results show that even in advanced CF disease, modulating agents may lead to clinical stabilization or may at least prolong the time until lung transplantation is indicated [3, 11, 12].

In particular, in young females with CF, a low body mass index is associated with a rapid decline in respiratory function, necessitating early referral. However, an underweight habitus per se does not predict poor outcome after lung transplantation, as shown in an analysis of the ISHLT TTX Registry [2]. Patients with end-stage CF should be placed on the waiting list in case of hypoxic (PaO2 < 8 kPa or < 60 mmHg) and/or hypercapnic (PaCO2 > 6.6 kPa or > 50 mmHg) respiratory failure, a rapid decline of pulmonary function with frequent hospitalizations, WHO Functional Class IV, long-term NIV, pulmonary hypertension, and/or rapid pulmonary function decline [10].

An infection with *Burkholderia cepacia* complex has been shown to be associated not only with a more rapid progression of pulmonary disease in CF patients depending on its genomovar but also with worse outcome after transplantation [13, 14]. It is therefore essential to exclude *B. cepacia* complex during transplant assessment. Patients with *B. cenocepacia* are especially at increased risk of recurrent disease post-transplant, ideally undergoing transplant assessment at experienced centers [10, 14]. Similarly, the presence of non-tuberculous mycobacteria (NTM) should be identified upon referral and guideline-conforming diagnostics, and treatment should be initiated before transplant listing. If the optimal NTM therapy is not tolerated, lung transplantation should not be performed [10]. In some centers, the isolation of *M. abscessus* subspecies *abscessus* would be considered a contraindication for a lung transplant [3]. In general, the appropriate treatment of the present pathogens should be evaluated and implemented in cooperation with a transplant infectious diseases specialist well before listing [3]. When evaluating a pediatric CF patient for lung transplant, the presence of extrapulmonary, systemic manifestations has to be assessed carefully. This includes endo- and exocrine pancreatic insufficiency, chronic sinusitis with potentially multiresistant pathogens, CF-associated liver disease, CF-associated bone disease, as well as bowel problems such as recurrent episodes of distal intestinal obstruction syndrome [3, 9].

With the difficulty of estimating waiting list mortality in children with IPAH and other pulmonary vascular diseases, the correct timing of referral and listing remains challenging. The favorable response to multidrug treatment with phosphodiesterase inhibitors, endothelin receptor antagonists, and prostanoids further complicates the decision to place a patient on the waiting list, leading to variabilities in standard of care between different transplant centers [10, 15]. For children with pulmonary

vascular diseases, listing criteria include a NYHA functional class of III or IV, despite maximal medical treatment, a cardiac index <2 liters/min/m^2, a 6-minute walk distance <350 m, or a right atrial pressure > 15 mmHg. A listing should also be evaluated in the presence of a rapid clinical decline with major hemoptysis, pericardial effusion, and signs of right ventricular failure such as hepatic or renal insufficiency [10].

At pediatric lung transplant candidate assessment, the child and his/her family need to be properly informed about the planned transplantation and subsequent mandatory long-term follow-up. The commitment to follow treatment and instructions provided by the transplant team is essential even in children, requiring careful evaluation prior to listing. Since the majority of CLAD cases originate from nonadherence to medical treatment, this subject should be especially articulated in adolescents at transplant evaluation [16]. The child's family support is crucial, and it should be supported and strengthened throughout the transplantation process and follow-up [8, 9].

35.3 ECMO as Bridge to Transplant

At some centers, long-term mechanical ventilation prior to pediatric transplantation is still considered a relative contraindication to listing for transplant due to the high short-term morbidity and mortality reported [17]. However, more recent data have shown that in carefully selected pediatric patients, extracorporeal life support (ECLS) as a bridge to transplant has no negative effect on post-transplant survival [18–20]. Especially in smaller children, suitable donor organs are scarce, and progressively advancing organ failure is often seen during the long period on the waiting list. In such cases, ECLS may stabilize the child until a suitable donor organ is allocated. The ideal candidates for ECLS as a bridge to transplant present with single-organ failure and good rehabilitation potential. Children, as well as adults, on ECLS as a "bridge strategy" should ideally be kept awake and spontaneously breathing, in order to continue regular physiotherapy, avoiding rapid physical deconditioning [21–23]. Additionally, in younger children, where the range of applicable sedatives is limited, duration of perioperative sedation can be reduced if intubation and mechanical ventilation are avoided [21]. The contraindications for pre-transplant ECLS in adult patients, as published by the ISHLT Pulmonary Council, also apply to children and include septic shock and multi-organ failure [10].

In most centers, awake ECLS as a bridge to transplantation is therefore preferred to long-term mechanical ventilation. Recent data also show promising results of the use of ECMO as an alternative option to conventional cardiopulmonary bypass intraoperatively. With lower rates of bleeding, primary graft dysfunction, or renal failure, many high-volume, mostly adult, centers prefer ECMO as the tool of choice for intraoperative cardiopulmonary support, a mode of intraoperative support predominantly used in older children [24]. The different techniques of ECMO and intraoperative cardiopulmonary bypass are beyond the scope of this chapter.

35.4 Donor Acceptability Criteria and Graft Size Reduction

Worldwide, lung transplantation is mainly limited by the scarcity of suitable donor organs. In pediatric lung transplantation, the challenges of finding a suitable organ are even greater due to the frequently faced problem of donor-recipient (D/R) size mismatch [25, 26]. The allograft-thorax match is known to have a considerable effect on postoperative outcome: the transplantation of oversized lung allografts potentially results in complications like atelectasis or distortion of the bronchial anatomy (on a segmental or sub-segmental level) with subsequently impaired airway clearance and increased predisposition to recurrent respiratory infections [3, 27, 28]. On the other hand, an undersized allograft is associated with lower expiratory airflow, higher pulmonary vascular resistance, persistent pneumothorax, an increased risk for primary graft dysfunction, and an increased risk for CLAD [29, 30]. Solutions to overcome the lack of availability of small organs include advanced operative strategies to downsize the donor organ [31]. Most commonly, peripheral segmental resections are performed [32, 33]. Lobar and split lung transplants are further options to provide an adequate match between donor lung and recipient thorax [27, 33, 34]. The decision regarding choice of graft size reduction is often only made during back-table preparation based on visual assessment of the size discrepancy [27]. A study by Inci et al. demonstrated that bilateral lobar transplantation is a feasible option for patients unable to wait for an appropriately size-matched organ, offering a comparable long-term survival to standard bilateral lung transplantation [27]. A case report by the Zurich Group even described a simultaneous bilateral lobar lung transplant from an adult, 190 cm tall donor into two adolescents with good lung function and no signs of CLAD more than 10 years post-transplant [35]. While this approach will certainly not become standard of care due to its considerably high logistic complexity and rare concurrence of critical circumstances, it demonstrates that this approach remains a valuable option to increase the donor pool [35].

Further strategies to use so-called "marginal" donor organs include donation after circulatory death (DCD) and ex vivo lung perfusion (EVLP) of donor organs initially presenting with borderline gas exchange, both used predominantly in adult lung transplantation to date.

35.5 Management of Pediatric Patients Receiving a Lung Transplantation

The median overall survival of pediatric lung transplant recipients is 5.7 years with similar survival across all pediatric age groups [5]. A publication by the Zurich Group showed a 5-year survival rate of 75% in a population of children and adolescents up to 20 years of age [6]. While the highest risk of death is during the first year after transplantation, the median survival in pediatric recipients surviving the first year rises to 9.1 years [5]. However, there is controversial discussion on the survival

benefit of lung transplantation in children with advanced CF pulmonary disease. Several studies, including a report from Zurich, describe a clear survival benefit independent of pediatric age. The report from Zurich was based on 80 CF patients with a predicted 5-year survival of 33% without surgery, compared to a 5-year post-transplant survival of 67% [36]. In contrast, a model designed by Liou et al. estimated that only 5 out of 514 children with end-stage CF pulmonary disease on the waiting list would have a significant benefit following lung transplantation [37]. Subsequently, the composition of future studies assessing the survival benefit of lung transplantation in pediatric CF patients was widely discussed [38]. Unfortunately, no recent data on this matter are available yet.

Following lung transplantation, immunosuppressive treatment is the cornerstone to prevent lung allograft rejection. In various smaller studies, the use of an induction immunosuppression has been associated with reduced rates of acute cellular rejection in children [39, 40]. An analysis of the United Network for Organ Sharing (UNOS) database confirmed a significantly positive effect with higher median survival times after induction immunosuppression with the commonly applied agents basiliximab and alemtuzumab [41]. A randomized, double-blinded and placebo-controlled trial on the use of the anti-CD20 antibody rituximab as an induction immunosuppressive agent has been initiated in 2014 and closed recruitment in 2019.

Maintenance immunosuppressant treatment in children is generally similar to adults and includes a triple treatment with an interleukin-2 receptor antagonist, mycophenolate mofetil, and steroids [3, 39]. In a retrospective single-center study, the use of the interleukin-2 receptor antagonist tacrolimus was associated with a positive effect on survival in pediatric lung transplantation [42]. Regarding the choice of the interleukin-2 receptor antagonist, tacrolimus is therefore more commonly used than cyclosporine. Consequently, the International Pediatric Lung Transplant Collaborative (IPLTC) recommends a protocol including tacrolimus, mycophenolate mofetil, and prednisolone (Goldfarb S, personal communication). While the prevention of allograft dysfunction is crucial, immunosuppressant-related side effects such as interleukin-2 receptor antagonist-induced nephrotoxicity are common complications during the postoperative course. In order to prevent potentially irreversible renal damage, strategies such as a precise therapeutic drug monitoring are required to keep target levels of interleukin-2 receptor antagonists as low as possible and as high as necessary. Especially in children with a good and stable FEV1 in the postoperative course and no signs of CLAD, an individualized therapeutic approach with tailored target levels of interleukin-2 receptor antagonists is recommended [9].

Early mortality and morbidity during the first year after transplantation in children are often caused by infections, to which the young and immunosuppressed patients are particularly susceptible. Cytomegalovirus infections remain a serious complication after pediatric lung transplant. Compared to adult patients, children are more commonly CMV naïve at the time of transplant and are more likely to acquire a primary CMV infection in the postoperative course [43]. Therefore, children at high risk for CMV, such as donor +/recipient, should receive universal CMV

prophylaxis starting within the first 10 days after transplantation [3, 44]. For prophylaxis, oral valganciclovir is currently the commonly used drug. Although no exact duration of CMV prophylaxis is defined in the current guidelines, a finite period of 3–6 months is recommended [43]. A preemptive therapy approach by weekly CMV viral load surveillance for 3–4 months has shown comparable results of CMV disease prevention in solid organ transplantation. However, this approach is often difficult to coordinate, and less frequent screening resulted in higher rates of CMV disease compared to prophylaxis [43]. In many centers, a "hybrid approach" is pursued by combining universal prophylaxis with weekly CMV viral load surveillance during the first postoperative months. Respiratory viral infections are still a commonly encountered complication after pediatric lung transplantation, and a single episode of a respiratory viral infection is associated with an increased risk for death or re-transplantation. Prior to being put on the transplant waiting list, all children should be vaccinated in order to prevent commonly vaccine-preventable diseases [3]. Vaccination of family and peer contacts is also greatly recommended [3, 45].

The prevention and management of CLAD is one of the major challenges after pediatric lung transplantation. As mentioned above, BOS, the most common form of CLAD, is the most frequent cause of re-transplantation and the leading cause of death beyond the first year after transplantation [3, 46]. The Thoracic Transplant Registry of the ISHLT documents a cumulative 5-year incidence of 36.9% [46]. BOS is thought to be caused by a combination of inflammation, destruction, and fibrosis of the small airways with a progressive obliteration and a persistent decline of allograft function [47]. A decrease in FEV1 to ≤80% of the baseline post-transplant FEV1 for 3 weeks is considered a surrogate marker for BOS [48]. According to the ISHLT/ATS/ERS clinical practice guidelines, treatment recommendations for BOS include augmented immunosuppression with a course of systemic steroids, a trial of azithromycin, extracorporeal photopheresis, and total lymphoid irradiation [3, 47]. In children with end-stage BOS refractory to other therapies, re-transplantation should be evaluated by an experienced thoracic surgeon [47].

35.6 Conclusion

In pediatric patients of all age groups including infants, lung transplantation has successfully been performed with excellent long-term survival rates. The development of CLAD and infectious complications remain challenges in the postoperative management of these patients and necessitate close follow-up. The shortage of adequately sized organs, especially in smaller children, requires an early thorough and efficient assessment of potential candidates to maximize the overall survival benefit after transplantation. The use of ECMO as a bridge to transplant and a variety of surgical approaches address D/R size mismatch and help to overcome the challenge of finding a suitable organ.

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Paediatric Lung Transplantation

36

Rossa Brugha, Helen Spencer, and Paul Aurora

36.1 Introduction

The first lung transplantation was performed in 1963. A single lung was transplanted into a 58-year-old man (who happened to be in prison, serving a life sentence) with a bronchial carcinoma obstructing his left main bronchus. After performing a left thoracotomy, the team discovered that their recipient had an empyema, alongside metastatic lung cancer. They continued with the procedure, and despite ABO mismatch, the recipient survived 18 days, until succumbing to renal failure. Subsequent experience has served to improve listing and matching criteria. Combined heart-lung transplantation followed in 1968, the first patient a 2-month-old child. The first paediatric single lung transplant followed 19 years later in 1987, in a 16-year-old boy with pulmonary fibrosis, and in 1988 the first double lung transplant was successfully performed in a 42-year-old woman with emphysema secondary to alpha-1 antitrypsin deficiency [1].

Lung transplantation in a child is a rare event. The International Society of Heart and Lung Transplantation (ISHLT) Registry reports 2430 paediatric lung transplants and 345 heart-lung transplants in the 26 years from 1992 to June 2018 [2]. With between 35 and 50 centres internationally submitting activity data year on year, the great majority report between 1 and 4 procedures per annum [2]. Most doctors (and many paediatricians) will never meet a child who has had a lung transplant. Lung diseases in childhood are changing: cystic fibrosis has been the most common indication for paediatric lung transplantation (65% of transplants in adolescents from 2002 to 2018) yet is expected to become less common in the era of CFTR potentiator/corrector therapies [3]. In contrast, increased early diagnoses of interstitial lung disorders, advances in technologies facilitating awake (or even ambulant)

R. Brugha · H. Spencer · P. Aurora (✉)
Cardiothoracic Transplant Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK
e-mail: rossa.brugha@gosh.nhs.uk; p.aurora@ucl.ac.uk

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extracorporeal oxygenation, and an expanding donor pool (following changes in legislation toward "opt-out" registers) are all postulated to increase lung transplantation activity in the paediatric population.

Post-transplantation, the lungs sit in the front line of the body's immune response to inhaled pathogens, allergens, and pollutants. Pathology related to immune suppression, and adherence to drug regimens, is a challenge for children, their families, and professionals. Despite this, survival post-transplantation continues to improve. Median unconditional survival is 6.3 years for the 2002–2009 cohort (increased from 4.0 years for the 1992–2001 cohort), with conditional median survival (adjusted to reflect those surviving to 12 months post-transplant) increasing from 7.3 years for those transplanted between 1992 and 2001, to 9.4 years for the 2002–2009 cohort [2].

36.2 Indications for Lung Transplantation

The primary role of the lungs is to provide a large surface area for gas exchange. Long-standing pathologies that impair air flow (airway and parenchymal disorders), gas transport between alveolus and capillary, or blood flow (vascular disorders) will eventually result in hypoxia, hypercapnia, or a combination of the two. These will manifest as combinations of exercise intolerance and fatigue, breathlessness, cyanosis, and, in infants, failure to thrive. Children, families, and the professionals caring for them need to consider and balance two broad concepts when considering whether or not to be placed on the lung transplant list, these being quality of life and potential duration of life [4]. This is difficult, and controversial [5–7], as lung disorders causing this level of impairment in children are rare, and prospective data on which to base decision-making is limited.

The commonest indication for lung transplantation in childhood varies by age [4]. In the adolescent age group (11–17 years), it is cystic fibrosis (CF); in children aged 1–10 years, CF and idiopathic pulmonary arterial hypertension (IPAH); and in those under 1 year, childhood interstitial lung diseases (chILD), a large proportion of which are due to primary disorders of surfactant metabolism [2]. The great majority of children receive a bilateral lung transplant, with heart-lung procedures (approx. 10 per year reported to the ISHLT) limited to those children with concomitant left ventricular failure or complex congenital heart disease [8]. "Domino" procedures (where the first recipient receives a heart-lung block and donates their heart to a second recipient) are now very rare, as is single lung transplantation in children [8].

36.3 Referrals and Candidate Selection

The accepted threshold at which lung transplantation is offered is when professionals estimate that a child is more than 50% likely to die of their disorder within 2 years, despite maximal medical therapy [9]. This assessment is based on a number

Table 36.1 Criteria for priority 1 paediatric lung transplant candidature under the lung allocation scoring system. Exception cases to be included as priority 1 may be included by a review board. Adapted from reference [69]. Cardiac index = cardiac output (L/min)/body surface area (m^2)

Paediatric priority 1 lung transplant candidates meet one or more of the following criteria:	
Respiratory failure	**Pulmonary hypertension**
– Requiring continuous mechanical ventilation – Requiring supplemental oxygen delivered by any means to achieve Fi02 > 50% in order to maintain oxygen saturations >90% – Arterial or capillary PC02 > 6.67 kPa (50 mmHg), or venous PC02 > 7.47 kPa (56 mmHg)	– Pulmonary vein stenosis involving three or more vessels – Suprasystemic PA pressure on cardiac catheterization or by echocardiogram estimate – Cardiac index <2 L/min/m^2 – Recurrent syncope – Haemoptysis

of physiological assessments, which, by the nature of the intervention, are challenging to evaluate prospectively in randomised controlled trials, due to the inherent biases in comparing groups [6]. These assessments include the 6-minute walk test, spirometry (forced vital capacity), pulmonary artery pressures, functional status, and need for supplemental oxygen. Along with other variables, these are combined into a "Lung Allocation Score" (LAS), which is used by the United Network for Organ Sharing (UNOS, USA) and Eurotransplant, as well as Germany and the Netherlands, to determine which recipients aged 12 years and above will receive donor organs as they arise. Children aged less than 12 years are ranked according to criteria that result in a "priority status" 1 or 2 (Table 36.1). This system, introduced in 2005, replaced a previous system in the United States where lungs were allocated on the basis of time spent on the waiting list.

Timing of referral of paediatric patients is crucial, with transplant teams preferring early contact and assessment rather than late in a disease course; this allows for open discussions about prognosis, risks, and benefits and any possible additional therapies as well as the suitability of transplantation. It also reduces, but does not obviate, the possibility of children referred later in their disease dying while waiting for offers of donor organs. Sadly, children will still die while on the waiting list, as matching must be done by blood group and donor height, and suitable offers from paediatric donors are limited. The median waiting time for a paediatric lung transplant in the United Kingdom between 2012 and 2015 was over 1 year [10].

36.4 Contraindications and Exclusion Criteria

In 2014 the ISHLT published consensus criteria for the selection of candidates for lung transplantation, which included a paediatric-specific section [4]. A number of absolute and relative contraindications to surgery may affect decisions to list children and adolescents for lung transplantation. The ISHLT consensus document lists these for adults, and an adapted paediatric list is reproduced in Table 36.2; relative

Table 36.2 Absolute and relative contraindications to lung transplantation in children, adapted from reference [4]

Absolute contraindication	Relative contraindication
Recent (<2–5 years) history of malignancy (depending on the malignancy)	Progressive or severe malnutrition
Untreatable significant dysfunction of another organ system (unless combined transplantation can be performed)	Extensive previous chest surgery with lung resection (note that previous pleural procedures may complicate the transplantation procedure but are not necessarily a contraindication)
Acute medical instability (e.g. sepsis, acute liver or renal failure)	Mechanical ventilation or extracorporeal life support[a]
Non-correctable bleeding disorder	
Uncontrolled infection with highly virulent or highly resistant pathogens, including active *Mycobacterium tuberculosis* infection	Colonisation or chronic infection with highly resistant bacteria, fungi, or viruses; certain strains of mycobacteria. Extrapulmonary infection expected to deteriorate secondary to long-term immune suppression
Significant chest wall or spinal deformity expected to result in severe respiratory restriction post-transplantation	Hepatitis B or C, with stable disease, without significant evidence of cirrhosis or portal hypertension
Current, repeated, or previous prolonged episodes of nonadherence to medical therapy	Known HIV positive with undetectable HIV RNA and compliance with antiretroviral medications
Psychiatric or psychological condition resulting in inability to work with healthcare team or adhere to medication regimes	Infection with *Burkholderia cenocepacia*, *Burkholderia gladioli*, and multidrug-resistant *Mycobacterium abscessus* if infection sufficiently treated preoperatively with expectation of adequate control postoperatively
Inadequate social support	
Severely limited functional status with poor rehabilitation potential	Concomitant medical conditions (epilepsy, diabetes, gastro-oesophageal reflux disease) should be optimized before transplantation
Active substance abuse (e.g. alcohol, tobacco)	

[a]*May be an absolute contraindication in some centres*

contraindications may differ between centres [11]. Transplanting individuals who are on a ventilator increases mortality risk; however, some centres will accept patients who are ventilated [8]; extracorporeal membrane oxygenation (ECMO) is not a contraindication to transplantation in some centres if it has not been used for a prolonged period of time (this is undefined), and in some adult ICUs, it is possible to ambulate on ECMO as a bridge to transplantation. Lung transplantation outcomes following bridging on ECMO appear to be best for awake, ambulant adult patients who can actively participate in rehabilitation [12], as time on the waiting list is much shorter compared to children and outcomes depend on rapid access to donor lungs.

36.5 Donor Criteria

The main criteria for suitable offers of lungs for children are donor height and ABO compatibility. Size mismatch is an important consideration as oversized allografts may be physically constricted inside the recipient's thorax, affecting airway calibre and clearance of secretions, or affecting parenchymal inflation resulting in atelectasis [13]. Undersized allografts (albeit less common in paediatric practice) are hypothetically associated with increased relative inflation pressures and relative barotrauma and in adults have a higher risk of primary graft dysfunction [14]. Donor lungs can be "downsized" (with either lobar or sub-segmental reduction) by the receiving surgical team, with a single centre case series of five vs. five children (the majority with CF) reporting similar outcomes across groups when using this technique [15].

With older donors, ischaemic time of >6 h is associated with poorer outcomes [16]. Ex vivo lung perfusion (EVLP) has the potential to salvage potential donor lungs [17], and EVLP devices are licensed by the US Food and Drug Administration [18]. Approaches to maximize the potential of EVLP donor lungs by instilling antibiotics [19] and by lavaging and administering surfactant if contamination has occurred from the stomach (in a porcine model) [20] are described. One single-centre case series in adults reports similar outcomes for 30-day mortality vs. non-EVLP control donor lungs [21] and suggests a potential 20% increase in the potential donor pool; this experience was not replicated in a multicentre study in the United Kingdom [22]. Should overall benefit be demonstrated, EVLP technology needs to be adapted for smaller, paediatric donor lungs [8].

36.6 Perioperative Management and Surgery

36.6.1 The Donor

Following confirmation of brain or circulatory death, measures should be put in place to protect the potential donor lungs while discussions begin with the family of the donor. These include a cuffed endotracheal tube (to protect the airways from aspiration of pharyngeal secretions in the absence of protective airway reflexes), elevating the head of the bed to approx. 30 degrees, volume-targeted ventilation with end expiratory pressures that aim to minimize atelectasis, and investigations including plain radiograph, airway cultures, and inspection of the potential donor lungs by bronchoscopy [23]. The "ideal donor" is aged under 55 years, arterial oxygen tension >300 mmHg while ventilated with 100% oxygen with a peak end expiratory pressure 5 cmH_2O, less than 20 years smoking pack history, clear chest radiograph, no chest trauma, and no aspiration or purulent secretions with a negative Gram stain or sputum culture; these "ideal" criteria are often not met [24].

36.6.2 The Recipient

Induction immunotherapy is started on the day of transplantation with either an anti-CD25 (alpha subunit of the IL-2 receptor) monoclonal antibody (basiliximab) or an anti-CD52 monoclonal antibody (alemtuzumab). Basiliximab prevents T cell replication and activation of B cells; alemtuzumab labels mature lymphocytes for destruction by neutrophils. In our centre, mycophenolate mofetil and tacrolimus are given orally once it is confirmed that the transplantation is to go ahead, with basiliximab given within 2 h before organ implantation and methylprednisolone starting when the patient comes off bypass.

36.7 Surgical Approach

Surgery is usually performed on cardiopulmonary bypass or while on ECMO. A bilateral transverse incision is made anterolaterally (the "clamshell" incision) at the fourth intercostal space. The pulmonary vasculature is divided and dissected from the main bronchi, which are then divided. The donor lungs arrive en bloc; the bronchi are divided, with the airways trimmed to approximately two cartilaginous rings from the origin of the upper lobe bronchus. The lungs may be "trimmed" in order to attempt to match the size of the recipient thorax. A bilateral sequential transplantation is then performed with end-to-end anastomoses [8], or telescoped anastomoses if there is a significant size mismatch [25].

36.8 Early Complications

36.8.1 Surgical Complications

Early postoperative complications relating to surgery include bleeding, and issues with the airway anastomosis including ischaemia and necrosis, which may lead to dehiscence. Dehiscence (either partial or complete) is reported to have an incidence of between 1% and 10% [25]. Later airway complications include stenosis and malacia due to loss of supportive cartilage [25]. Airway complications are likely due to reduced blood supply to the donor lung mucosa and cartilage, as the bronchial arteries, which supply the airway, are divided when the lungs are retrieved. Surgical techniques have developed to mitigate this risk by reducing the length of the donor bronchus [25] and in some centres by covering the anastomosis with peribronchial or pericardiac lymphatic tissue [8]. Vascular complications (patency of the anastomoses, thrombus formation) can be assessed postoperatively on echocardiography; this is usually with transoesophageal echocardiography while still in theatre [8].

Risk factors for airway complications include prolonged (>50 hours) mechanical ventilation of the donor lungs, high end-expiratory pressure requirements postoperatively, need for organ preservation techniques, infection, and prolonged ischaemic time. Mis-sized organs (including after trimming) may result in distorted

large airways [13]. Acute cellular rejection has been shown to decrease perfusion of graft tissue, but this is controversial as a risk factor for airway complications [25]. Sirolimus (an mTOR inhibitor) has been shown to impair healing at the anastomosis [26], and the recommendation is that mTOR inhibitors are not used for immune suppression until there is bronchoscopic evidence of healing at the site [25].

Other immediate complications of surgery include injury to the recurrent laryngeal nerve (resulting in vocal cord dysfunction), the phrenic nerve (causing diaphragmatic palsy), and afferent and efferent cough reflexes [8]. Ciliary beat frequency is reduced in the transplanted lung [27]. These factors may all impair cough and mucus clearance postoperatively.

36.8.2 Primary Graft Dysfunction

The syndrome of acute, early lung injury following lung transplantation is termed primary graft dysfunction (PGD) [28]. The definition is clinical, based on the ratio of inspired to arterial oxygen and chest x-ray appearances (Table 36.3), with the features considered to occur as a consequence of mechanical, immune, inflammatory, and possible infective factors [28]. PGD is associated with early and late mortality and with bronchiolitis obliterans syndrome (BOS); it is an important outcome measure in trials of new therapies related to lung transplantation [28]. PGD is graded at time 0 h (when the second pulmonary arterial cross clamp is removed) and then at 24 h, 48 h, and 72 h, with grade 3 PGD at 48 h and 72 h being most predictive of subsequent poor outcomes [28]. Treatment is supportive, with fluid restriction, and avoidance of barotrauma [29], inhaled nitric oxide, and/or temporary ECMO support may be required [30].

36.8.3 Hyperacute Rejection

Hyperacute rejection is mediated by pre-existing donor-specific antibodies (DSAs) to human leukocyte antigen (HLA). It occurs within minutes to hours following transplantation, with DSAs binding to the graft endothelium, resulting in activation of the classical complement cascade. This triggers formation of the membrane attack complex, causing endothelial injury, which in turn triggers local inflammation, neutrophil recruitment, and thrombosis formation. The result is severe allograft

Table 36.3 2016 International Society for Heart and Lung Transplantation Primary Graft Dysfunction Definition, adapted from reference [28]

Primary graft dysfunction grade	Pulmonary oedema on chest x-ray?	PaO_2/FiO_2 ratio
0	No	Any
1	Yes	>300
2	Yes	200–300
3	Yes	<200

PaO_2 partial pressure of arterial oxygen (in mmHg), FiO_2 fractional inspired oxygen

dysfunction with pulmonary oedema, haemorrhage, and markedly impaired gas exchange and diffuse infiltrates on chest x-ray [31]. Children are tested for pre-formed HLA antibodies (panel-reactive antibody, PRA), and a virtual cross-match is undertaken as part of the initial panel of investigations pre-listing, which has made hyperacute rejection a rare event.

36.9 Immune Suppression

Following discharge from hospital, first-line long-term immune suppression in our centre consists of tacrolimus, mycophenolate mofetil (MMF), and oral prednisolone. Target tacrolimus levels are initially maintained at a relatively high level in lung transplant recipients, depending on high vs. low risk of rejection, with trough levels between 12–15 and 10–12 ng/ml, respectively. Children at high risk of rejection are those with a previous episode of acute rejection or multiple HLA mismatches.

At discharge, children and families are asked to contact the transplant team if they are unwell, if new medications are suggested by their local team, or if they begin to experience side effects of medications. Tacrolimus is associated with nephrotoxicity, tremor, neurotoxicity, diabetes and hypertension, MMF with bone marrow suppression, nausea, constipation and/or diarrhoea, and hyperglycaemia; this list is not exhaustive. A recent open label study in 130 adults post-lung transplantation demonstrated greater renal function in patients on a quadruple regime (everolimus, tacrolimus, prednisone, and MMF) as tacrolimus levels could be reduced [32].

36.10 Home Monitoring

Children are discharged with a spirometer to use daily at home and asked to make a diary of readings and to telephone the team if there is a fall in values. Close working with the local referring team, with shared protocols, is essential as children may live a long way from the specialist centre. Live vaccines (MMR, BCG, oral rotavirus) should be avoided; we recommend annual inactivated influenza immunization for the child and family.

36.11 Following the Transplantation

36.11.1 Acute Rejection: Cellular and Antibody Mediated

Rejection of the allograft by the recipient immune system is a common cause of post-transplantation morbidity. The ISHLT data to 2019 reports that 28% of paediatric lung transplant patients experienced an episode of rejection between discharge and follow-up at 1 year [2].

Episodes of rejection manifest clinically as cough and shortness of breath, and there may be low-grade fever. Patients may have normal findings on examination, or there may be crackles, pleural rubs, or even effusions [33]. These symptoms are

nonspecific and can be differentiated from infection via sampling of upper and lower airway cultures, plus transbronchial biopsy. Infection and rejection may occur concurrently. Biopsy findings are used to differentiate acute rejection into cellular or antibody mediated, as this determines treatment choices, and the two phenomena may co-exist.

Patients may be asymptomatic, with routine surveillance biopsy demonstrating abnormal findings suggestive of rejection [34]. At our centre we perform routine surveillance bronchoscopies at 1 week, 1 month, 3 months, 6 months, and 1 year post-transplantation.

Surveillance spirometry is a useful tool, with a 10% fall in the forced expiratory volume in 1 s (FEV1) suggestive, but nonspecific, for episodes of rejection. There may be bilateral infiltrates on chest x-ray, or ground glass opacities on chest CT [33].

36.11.2 Acute Cellular Rejection (ACR)

ACR occurs when T cells drive immune responses following recognition of non-self human leucocyte antigen (HLA) expressed on the surface of cells in the allograft [35]. It is an important complication, associated with mortality and in the longer term with chronic lung allograft dysfunction (CLAD), predominantly the bronchiolitis obliterans syndrome (BOS) [33, 36]. Younger children (under 3 years) appear to be at lower risk of rejection in comparison to older children and adults [8]. In addition to changes on chest x-ray and spirometry values, peripheral blood eosinophils $>0.4 \times 10^9$/l, or a raised fractional exhaled nitric oxide, are nonspecific biomarkers for ACR [33, 37]. Chest CT may be more discriminatory (with a positive predictive value of 80%, negative predictive value 90%) on the basis of a single centre report [38]. In practice the diagnosis of ACR can only be confirmed by lung biopsy, which is usually obtained bronchoscopically.

At bronchoscopy, following lower airway lavage for microbiological samples, a transbronchial biopsy is undertaken to obtain tissue for histopathological assessment of the presence (or absence), and severity, of ACR. Biopsies may be performed using either biopsy forceps or via cryobiopsy, although the latter approach is rarely used in children [39]. Complications include bleeding, pneumothorax, and desaturations [33].

When assessing for ACR, the histopathologist looks at two areas: around the small blood vessels and small airways. The hallmark of ACR is a mononuclear cell (lymphocyte and monocyte/macrophage) infiltrate [35]. The presence and severity of the infiltrate are graded according to the 2007 ISHLT diagnostic criteria [40] (Table 36.4), with the perivascular infiltrate (with or without endothelial inflammation) used to determine grade of acute rejection ("A"); this may or may not be accompanied by features of small airways rejection ("B"), typically a lymphocytic bronchiolitis. The grading is subjective, with both inter- and intra-observer variability reported [35, 41, 42]; this in part may be related to sample quality and the patchy nature of disease [35].

Along with symptoms, grade of ACR determines treatment, with consensus regarding treating patients who are symptomatic with grade A2 rejection on biopsy. Treatment of minimal (A1) or mild rejection (A2) in the absence of symptoms is

Table 36.4 Classification of acute cellular rejection, ISHLT 2007, from reference [40]

Acute rejection		Small airways inflammation—lymphocytic bronchiolitis	
ISHLT grade	Definition	ISHLT grade	Definition
A0	None	B0	None
A1	Minimal	B1R	Low grade
A2	Mild	B2R	High grade
A3	Moderate	BX	Ungradable
A4	Severe		

more controversial [33, 35]. Minimal rejection has been associated with an increased risk of subsequent chronic lung allograft dysfunction (CLAD) in a large case series in adults [43]; this finding is not universally reproduced in studies, and additional biomarkers (such as CXCL9, a chemokine that induces chemotaxis and leucocyte differentiation) in bronchial lavage fluid may aid decision-making [44].

Treatment involves an increase in immune suppression with pulsed methylprednisolone, or in some centres with oral prednisolone in mild or moderate rejection [33]. ACR that does not respond to steroids should prompt clinicians to re-evaluate their diagnosis (with infection, antibody-mediated rejection, and post-transplantation lymphoproliferative disorder (PTLD) as potential differentials). Additional immune suppressive agents (everolimus/sirolimus, alemtuzumab) may be used. Extracorporeal photopheresis (ECP) may be used for recurrent episodes of acute rejection [45]; the technique is postulated to increase circulating numbers of T regulatory lymphocytes, which induce tolerance to antigens expressed in the graft [46]. Anti-thymocyte globulin is now rarely used.

36.11.3 Antibody-Mediated Rejection (AMR)

Antibody-mediated, or humoral, rejection is a well-described phenomenon in heart and kidney transplant recipients and more recently defined for lung transplant recipients by the ISHLT in 2016 [47]. It is defined as "a process of immune activation, whereby allospecific B cells and plasma cells produce antibodies directed against donor lung antigens" [47]. Opsonisation of donor cells by donor-specific antibody (DSA) triggers complement-dependent and complement-independent inflammatory cascades, resulting in tissue injury and the clinical sequelae as described previously. Diagnosis of AMR is made on the basis of a triad of allograft dysfunction (which may be symptomatic or asymptomatic), identification of DSAs, and appearance on transbronchial biopsy; in AMR, this is typically a neutrophilic capillaritis (as opposed to the mononuclear infiltrate in ACR), with >50% C4d immunostaining considered positive [35, 47]. Subsequent studies suggest that DSA may be identified within an explanted graft in the absence of DSA in the circulation, in the setting of graft rejection [48]. Novel biomarkers may therefore be required in order to detect cases of AMR in the absence of circulating DSA [49].

Treatment includes plasmapheresis, intravenous immunoglobulin, rituximab (anti CD20), and bortezomib (a proteasome inhibitor, which induces apoptosis of

plasma cells) [35]. Eculizumab (an anti-complement C5 monoclonal antibody) has been used in case reports [50, 51]. Data on outcomes are limited by varying definitions prior to the 2016 ISHLT document; overall the results from multiple case series indicate that AMR is difficult to treat and outcomes are poor [47], with an increased risk of chronic lung allograft dysfunction [52]; the development of de novo DSA is associated with an accelerated, severe form of the bronchiolitis obliterans syndrome [53].

36.11.4 Infection

Children routinely receive intravenous antibiotics at the time of transplantation, if possible guided by the results of prior airway cultures. Following transplantation, in our centre, prophylaxis against opportunistic infection by yeast, fungi, and *Pneumocystis jirovecii* is maintained with nystatin, posaconazole (if chronic suppurative lung disease was the indication for transplantation), and co-trimoxazole. If both donor and recipient are cytomegalovirus (CMV) naïve, then acyclovir prophylaxis is continued for 12 months. If the donor was or the recipient is CMV positive, then valganciclovir is used for up to 12 months if tolerated.

As the lungs are constantly exposed to pathogens, typical and opportunistic infections may occur post-transplantation as a result of immune suppression. Repeated respiratory viral infections are common in younger children and may result in significant morbidity and mortality; they are also associated with an increased risk of CLAD [8]. For confirmed viral infection, cidofovir (selective viral DNA polymerase inhibitor, therefore active against DNA viruses; cytomegalovirus, herpesviridae, adenovirus) and ribavirin (nucleoside analogue, active against RNA viruses; respiratory syncytial virus, parainfluenza) may be used. Diagnosis of CMV infection may be challenging, as CMV may be found in bronchoalveolar lavage in asymptomatic patients, and the presentation of CMV pneumonitis (cough, respiratory distress, inspiratory crackles, and bilateral infiltrates on chest x-ray) is similar to that of rejection; positive CMV histochemistry on transbronchial biopsy, along with clinical features, aids diagnosis [8].

36.12 Post-Transplantation Lymphoproliferative Disorder (PTLD)

PTLD is the result of uncontrolled proliferation of lymphocytes, predominantly B lymphocytes, as a consequence of immune suppression [54]. PTLD is associated with Epstein-Barr virus (EBV) on 90% of occasions [55]. After those receiving an intestinal transplant, lung transplant recipients are at the highest risk of developing PTLD with risks between 3% and 12% quoted for adults and children [56]. ISHLT data to June 2017 reports that 22 of the 235 survivors recorded at 7 years (9.4%) have received a diagnosis of lymphoma [2]. The majority of cases arise in the first 12 months following transplantation, when immune suppressive regimes are at their most intense [56].

In the majority of cases, EBV primary infection, or reactivation following the initiation of immune suppression, may drive a clonal expansion of B cells and plasma cells [54]. PTLD is more common in children than adults, as a greater proportion of paediatric transplant recipients are EBV naïve. In healthy individuals, cytotoxic T lymphocytes remove these B cells, but as immune suppressant chemotherapy impairs the T cell population, the B cell activity continues.

PTLD may arise, and therefore manifest clinically, both within and outside the allograft, typically within the reticuloendothelial system. The site at which disease initially presents is associated with risk of mortality [57]. Typical systemic signs and symptoms include swollen lymph glands, weight loss, fever and/or night sweats, sore throat, and malaise/lethargy [56]. Localized lymph node hyperplasia may result in abdominal pain, anorexia and nausea, or focal neurology in cases of central nervous system disease. Prospective surveillance by screening using repeated measures of whole blood or bronchoalveolar lavage EBV viral load by PCR in paediatric lung transplant recipients was not predictive for PTLD in a multicentre study [58]; these studies are difficult due to the small numbers of individuals affected; only 4 of the 61 children recruited prospectively developed PTLD over the 5 years of follow-up [59].

Diagnosis is made via clinical suspicion, serial EBV titres in whole blood, cross-sectional imaging (including positron emission tomography-computed tomography (PET-CT) scan), and ultimately on histopathology of biopsied lymph nodes, if they are accessible. Classification is based on the 2016 WHO classification [60].

Treatment of PTLD post-lung transplantation is similar to that of other solid transplants, with the proviso that lung transplant recipients do not tolerate reduction in immune suppression to the same degree as recipients of other solid organ transplants (children receiving liver transplants may have tacrolimus stopped altogether). If reduction of immunosuppression, or switching from a calcineurin inhibitor to an mTOR inhibitor, is unsuccessful, then anti-CD20 therapy (rituximab) is indicated. Data from adults suggests that using rituximab as a first-line therapy is associated with increased survival, and this is the approach in our centre [61]. If unsuccessful, this is followed by CHOP chemotherapy (cyclophosphamide, doxorubicin, oncovin (vincristine), and prednisolone) [56].

36.13 Chronic Lung Allograft Syndrome (CLAD)

CLAD describes the long-term decline in spirometry seen in the majority of children following lung transplantation. It is an umbrella term encompassing four phenotypes: bronchiolitis obliterans syndrome (BOS); restrictive allograft syndrome (RAS); a mixed phenotype with features of both BOS and RAS; and an undefined phenotype [62]. Of the 858 children post-lung transplantation included in the 2019 ISHLT data (January 1995 to June 2017), 45% were free of the BOS phenotype at 5 years post-transplantation, with 23% free at 10 years [2]. Allograft failure is the major cause of death (greater than 40% of cases) after the first year post-lung transplantation [62].

Historically, the BOS phenotype (with obstructive spirometry and radiological and histological findings similar to that of post-infectious constrictive obliterative bronchiolitis) has been well recognized, with RAS (typified by restrictive spirometry along with persistent opacities on chest imaging) introduced as a term in 2011 [63].

CLAD is defined as "a substantial and persistent decline (≥20%) in measured FEV1 value from the reference (baseline) value" [62], which is the mean of the best two postoperative measurements of absolute FEV1 (in litres), taken more than 3 weeks apart. Maximal baseline FEV1 post-lung transplantation is normally attained at around 6 months post-transplantation in adults. In children and adolescents, this is less straightforward to define, as FEV1 is considered in relation to height-, age-, and gender-matched norms (as percent predicted or number of standard deviation scores from the mean). Therefore while absolute FEV1 may rise over time, percent-predicted FEV1 may fall in relation to the "normal" values, and close attention should be paid to the reference equations used by local and transplant centres, as these may differ by over 10% predicted for the same absolute FEV1 [64]**.** In view of this, CLAD may be suspected in paediatric patients where the criteria have not been met.

Clinical features include shortness of breath, pleuritic pain, non-productive cough, and weight loss; there may be crackles on examination [65]. In order to diagnose CLAD, the team must exclude other causes for a fall in FEV1, including the normal fall in absolute FEV1 (in litres) as the patient ages (in adults), pulmonary oedema, persistent pleural effusion, airway stenosis, acute or subacute infection or rejection, aspiration (including reflux aspiration) lung disease, and myopathy.

Investigations for these phenomena should be triggered at a fall of 10% in FEV1 and treated if found. Following this, in adult recipients, if FEV1 remains low less than 3 weeks after the initial decline, a label of "possible CLAD" may be applied, whereas between 3 weeks and 3 months, the term "probable CLAD" is used, with investigations and treatment ongoing as appropriate. Beyond 3 months, if FEV1 (with or without a fall in FVC) remains at or below 80% of baseline, "definite CLAD" is attributed, and the phenotype of CLAD is determined on the basis of spirometry, total lung capacity (on plethysmography), and CT chest appearance (Table 36.5) [62]. It could be argued that the definition of CLAD in children should be looser, but as yet there is no consensus on this.

Table 36.5 Phenotypes of chronic lung allograft syndrome (CLAD) adapted from reference [62]

	Obstructive spirometry (FEV1/FVC <0.7)	Restrictive plethysmography (TLC decline ≥10% from baseline)	CT opacities
BOS	Yes	No	No
RAS	No	Yes	Yes
Mixed	Yes	Yes	Yes
Undefined	Yes	May or may not be present	No

BOS bronchiolitis obliterans syndrome, *RAS* restrictive allograft syndrome, *TLC* total lung capacity, *CT* computed tomography

Azithromycin prophylaxis decreases the prevalence of CLAD and improves lung function and exercise capacity [66]. Montelukast slows the rate of FEV1 decline in CLAD [67]. A Nissen fundoplication may be indicated if concerns arise regarding gastro-oesophageal reflux-aspiration lung disease, and conversion of immune suppression from cyclosporine to tacrolimus is beneficial [62]. Total lymphoid irradiation and extracorporeal photopheresis are additional options [24]. Management of RAS is challenging [65], with small effects seen in single cases or small series following the use of pirfenidone, nintedanib (a tyrosine kinase inhibitor), or alemtuzumab [62]. A European trial of pirfenidone in BOS (NCT02262299) was scheduled to complete in late 2019 [68].

36.14 Summary

Lung transplantation is a life-saving and life-extending treatment for children with end-stage lung disease, with outcomes improving over time. Selecting the children most likely to benefit from transplantation, in the face of relative paucity of organs in comparison to other solid organs, remains a significant challenge for paediatric lung transplant teams, and the need for relatively high levels of immune suppression may result in a significant burden of disease. Future efforts directed to elicit the underlying processes driving chronic lung allograft dysfunction may result in further improvements in longevity following lung transplantation, and we hope an expanding donor pool will reduce waiting list mortality.

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Correction to: Intestinal and Multivisceral Transplantation in Children: Outcomes and Complications

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