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EVOLUTION OF PEDIATRIC LIVER TRANSPLANT: FROM INCEPTION TO MODERN PRACTICE

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This article explores the historical development of pediatric liver transplantation (LT), tracing its evolution from the first experimental procedures to modern high-tech approaches. Throughout its history, LT in children has been a catalyst for innovation and novel surgical techniques. The earliest attempts at pediatric LT faced numerous technical and immunological challenges and were associated with extremely high mortality rates. A major breakthrough occurred in the 1980s with the introduction of cyclosporine A. During this period, pioneering advances such as reduced-size grafts, split-liver transplantation, and the first successful living-related donor procedures marked a new era. The 1990s witnessed further progress in surgical techniques, introduction of tacrolimus, and the development of right-lobe living donor transplantation. These innovations not only expanded the donor pool significantly but also improved surgical outcomes. Entering the 21st century, the field experienced further breakthroughs with the implementation of ABO-incompatible transplantation and the adoption of MELD and PELD scoring systems for organ allocation. In addition, the integration of minimally invasive laparoscopic and robot-assisted approaches reduced donor morbidity and improved postoperative recovery. Today, pediatric LT is recognized not only as a life-saving treatment for end-stage liver failure in children but also as a driving force of innovation in modern transplant practice. The article underscores the importance of continuous refinement of surgical techniques and personalization of immunosuppressive regimens as key strategies to improve long-term survival and enhance the quality of life in pediatric LT recipients.

Keywords: pediatric liver transplantation, history, innovations, donation, immunosuppression.

INTRODUCTION

The development of liver transplantation (LT), one of the landmark achievements of 20th-century medicine, is inextricably linked to pediatric practice. In many respects, pediatric LT not only adapted technologies from adult surgery but also served as a true catalyst for innovation in this complex field. It is remarkable that the very first attempts at human LT – marked by both tragic failures and the first glimmers of hope – were carried out in children [1, 2]. This fact lent a special ethical and dramatic dimension to the discipline, as it was about saving the lives of young patients for whom other treatment methods had been exhausted.

Unlike other areas of surgery and transplantology, where pioneering procedures were initially performed on adults and only later extended to children, LT from the outset accounted for the unique anatomical, physiological, and nosological characteristics of the pediatric population [3]. The urgent need to treat children with end-stage liver disease largely determined the key directions of transplant hepatology.

The challenge of adapting adult donor organs to small recipients spurred the development of groundbreaking surgical techniques. The introduction of the reduced-size liver graft, first applied in children, represented a major breakthrough that laid the foundation for wider clinical use [4, 5]. This pioneering concept subsequently gave rise to further advances such as split-liver transplantation, enabling a single donor organ to serve both an adult and a child, and living-related donor liver fragment transplantation, which has revolutionized therapeutic strategies not only in pediatrics but also in adult practice [6, 7].

Moreover, in-depth study of the unique features of the pediatric immune system – its plasticity and capacity for tolerance – led to the development of protocols for LT across ABO-incompatible barriers, thereby further expanding the therapeutic options available for saving young patients [8, 9]. Thus, throughout its history, pediatric LT has not been a passive recipient of advances in "adult" medicine but has acted as a powerful engine of progress, driving the search for unconventional solutions and broadening the overall horizons of transplantation. Some of the most important historical milestones along this path will be discussed below.

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EXPERIMENTAL PERIOD AND EARLIEST ATTEMPTS (1950s–1970s)

The historical development of LT in the 1950s–1970s was an intense and often dramatic era, characterized by a shift from bold but largely unsuccessful experimental interventions to the gradual accumulation of knowledge, refinement of surgical techniques, deeper understanding of immune mechanisms, and emergence of the first pharmacological approaches to immunosuppression. This formative stage laid the groundwork for modern transplantology and eventually led to the recognition of LT not merely as an experimental endeavor, but as an effective, life-saving treatment for patients – including children – with end-stage liver disease [10, 11].

A crucial step forward was the extensive series of animal experiments, primarily in dogs, which enabled researchers to refine the fundamental surgical steps of the procedure, study the physiological changes in recipients, and clarify the basic principles governing the function of transplanted organs. Among the pioneers, Thomas Starzl – later known as the "father of transplantology" in Western literature – conducted groundbreaking experiments in Denver, where he developed and standardized the technique of orthotopic LT. His work established the essential stages of hepatectomy in the recipient, followed by implantation of the donor liver with meticulous reconstruction of vascular anastomoses [12].

In parallel, the innovative contributions of our compatriot Vladimir Petrovich Demikhov earned him recognition as the founding father of experimental transplantology. His wide-ranging research, which included pioneering experiments on the head, heart, lungs, kidneys, esophagus, and limbs, as well as creation of artificial circulatory systems, gained worldwide recognition. Importantly, Demikhov also devoted significant attention to LT. In the 1950s, he explored the feasibility of heterotopic LT and even combined LT with other organs such as the adrenal glands and pancreas, investigating their interactions and the potential role of the liver in modulating immune responses [13, 14]. This work significantly enriched the experimental foundation of the field and spurred further scientific exploration in this direction.

The earliest attempts at LT in humans were fraught with immense challenges. Surgeons faced massive, uncontrollable bleeding, driven both by the technical complexity of the procedure and by the severe coagulopathy inherent in patients with liver failure. Transplant rejection, poorly understood at the time, led to rapid graft failure, while postoperative infections, exacerbated by inadequate immunosuppressive therapy, further contributed to the high mortality rates.

A historic milestone was reached in 1963, when Thomas Starzl performed the world's first orthotopic liver transplant in a human. The recipient was a three-year-old child with cirrhosis caused by biliary atresia [1, 12]. Although the surgery itself was technically successful, the child succumbed in the early postoperative period to massive hemorrhage and severe coagulopathy. This case, followed by several other unsuccessful attempts, prompted a temporary moratorium on liver transplants.

Yet, Starzl and his team persisted. On July 23, 1967, they carried out what is regarded as the first successful LT. Once again, the recipient was a child, a one-and-a-half-year-old girl with an extensive malignant liver tumor, most likely hepatoblastoma [12, 15, 16]. Remarkably, she survived for 400 days before dying from recurrence and systemic spread of the cancer. This case proved for the first time that a transplanted liver could function long-term and sustain the recipient's life.

The tragic fate of this little patient, whose portrait reportedly hung above Starzl's bed until his final days, became a symbol of both the formidable obstacles and the extraordinary perseverance of the pioneers of transplantology.

In parallel with their American colleagues, European surgeons were also making early attempts at LT. In 1968, in Cambridge, UK, Sir Roy Calne, another iconic pioneer in the field, performed a liver transplant on a 10-month-old child with biliary atresia. Tragically, the patient died intraoperatively from cardiac arrest [3, 17]. A year later, in Brussels, Jean-Bernard Otte – who would go on to become one of Europe's foremost pediatric transplantologists – carried out a liver transplant in a 15-month-old child with biliary atresia. The patient survived for seven weeks before succumbing to massive bleeding triggered by graft biopsy [3].

By the early 1970s, a modest body of clinical experience in LT had been gathered worldwide, though the outcomes were overwhelmingly negative. One-year survival rates, particularly in pediatric patients, rarely exceeded 30–40% [3, 18]. Still, these pioneering efforts, often undertaken in children because of the absence of therapeutic alternatives, laid the groundwork for future progress. They underscored the critical challenges that needed to be overcome: refinement of surgical techniques, development of effective and safer immunosuppressive strategies, optimization of perioperative care, and prevention of postoperative complications.

However, a transformative breakthrough came in 1972, when Jean-François Borel and Hartmann Stähelin, working at the Swiss pharmaceutical company Sandoz, accidentally discovered cyclosporine A. This substance, isolated from the fungus *Tolypocladium inflatum*, was found to possess highly selective immunosuppressive properties [19, 20]. This event was a turning point, paving the way for new achievements in the following decade.

THE ERA OF CYCLOSPORINE AND THE EMERGENCE OF CLINICAL TRANSPLANTATION (1980s)

The early 1980s ushered in a transformative era for LT and for clinical transplantology as a whole. The decisive breakthrough came with the introduction of cyclosporine A into clinical practice – the first immunosuppressant that was both effective and relatively selective. For the first time, physicians had a drug that could reliably control rejection, dramatically improving both short-term but also long-term graft outcomes [20, 21].

The clinical application of cyclosporine began with Roy Calne's pioneering work in Cambridge on kidney transplantation, where the problem of rejection was particularly acute. The success of these early trials quickly extended to LT, where the benefits proved equally striking [20]. The impact was so profound that, in 1983, the U.S. National Institutes of Health (NIH) convened a consensus conference and formally recognized LT as a clinically valid and effective treatment for end-stage liver disease [22, 23].

This decision was a major milestone, paving the way for wider use of the method, standardization of approaches, and creation of specialized transplant centers.

Paediatric LT during this period faced a set of unique challenges that required innovative solutions. One of the most pressing issues remained the shortage of appropriately sized donor organs, which contributed to persistently high mortality rates among children on waiting lists [3, 24]. The technical complexity of performing transplantation on young patients – with their delicate anatomical structures and limited abdominal cavities – added further obstacles.

Nevertheless, it was the need to save children's lives that continued to stimulate surgical thinking. The concept of reduced-size LT, first pioneered in the late 1970s by Henri Bismuth and others, began to find wider and more consistent application in the 1980s, particularly as outcomes improved in the cyclosporine era [4, 5, 25]. This made it possible to use part of an adult donor's liver for transplantation into a child and somewhat alleviate the growing problem.

Another important achievement, driven by the urgent needs of pediatric recipients, was the first successful split LT, performed in 1988 in Hanover by a German team led by Rudolf Pichlmayr [6, 26]. This groundbreaking procedure made it possible to divide a single donor liver into two functionally independent grafts and transplant them into two recipients – most often an adult and a child. The success of split transplantation was underpinned by advances in the study of segmental liver anatomy, refinement of precision parenchymal transection techniques, and significant improvements in organ preservation methods. Following the Hanover breakthrough, split LT was soon reproduced with success in other leading European centers, notably in Paris and Brussels, which further confirmed the feasibility and promise of the approach [27].

Soviet transplantologists also played a significant role in advancing this field. The experimental and later clinical studies of Evsey Galperin and Valery Shumakov, particularly in the area of heterotopic transplantation of the left hepatic lobe, stimulated scientific discussion and attracted the attention of the international transplant community [28, 29].

The late 1980s witnessed another transformative event in liver transplantation, one that was particularly crucial for pediatric patients: the first successful attempts to transplant a fragment of the liver from a living related donor. The idea of using part of a living donor's liver to save a child in the face of a critical shortage of cadaveric organs had long been considered, but its realization required not only advanced surgical expertise, but also remarkable courage and the resolution of complex ethical issues.

The first clinical attempt was made in Brazil by Silvano Raia and his colleagues in 1988 (according to some sources, in 1987), when a mother donated the left lateral sector of her liver to her child. Sadly, the recipient died in the early postoperative period [30, 31].

A true breakthrough came in 1989 in Sydney (Australia), when Professor Russell Strong and his team performed the world's first successful living-donor LT, transplanting the left lateral lobe from a mother to her young son [7, 32]. The case was widely publicized, causing a sensation in the medical community and marking the start of a new chapter in the history of LT.

Almost simultaneously, also in 1989, a team in Chicago (USA) led by Christoph Broelsch – already experienced in reduced-size and split LT – launched the first structured program of living-related donor LT in children [33, 34]. After returning to Germany, Professor Broelsch and his team continued to successfully develop all these areas.

Thus, the era of cyclosporine not only radically improved transplant outcomes overall, but also gave rise to a series of innovations, many of them driven by the urgent need to improve care for children with end-stage liver disease. Once again, pediatric transplantation became a catalyst for progress, stimulating the development and refinement of techniques such as reduced-size LT, split transplantation, and ultimately living-related donor transplantation. On the wave of these achievements, the young science of clinical transplantology entered the next decade poised for rapid expansion.

TECHNICAL ACHIEVEMENTS AND INNOVATIONS IN TRANSPLANTATION (1990s)

The 1990s marked another qualitative leap in the development of LT, a period that not only significantly

reduced mortality among patients on waiting lists, but also brought substantial improvements in both short-term and long-term survival rates, particularly in the most challenging group: young children [35, 36].

By this time, the fundamental principles and core surgical approaches to LT had gained broad recognition and clinical acceptance. In most developed countries, the legislative framework regulating organ donation had been consolidated, and the criteria for determining brain death had been standardized, both of which were critical steps in expanding the pool of deceased donors [37].

At the same time, surgical hepatology advanced rapidly, supported by the introduction of new imaging technologies, significant improvements in instruments for parenchymal dissection, and a deeper understanding of the segmental anatomy of the liver.

These achievements directly facilitated the further refinement and broader adoption of techniques for reducing graft size and, most importantly, split LT. During the 1990s, transplant surgeons began to actively implement *in situ* division of the liver from deceased donors, that is, splitting the organ directly within the body while maintaining blood flow. This approach significantly minimized warm ischemia of the graft fragments and improved their functional quality [38, 39].

Importantly, these complex operations were no longer isolated, experimental procedures but began to be performed in series at leading transplant centers worldwide. This shift enabled more systematic analysis of outcomes for different types of grafts, accumulation of collective experience, and, ultimately, standardization of surgical approaches and further improvement of results [40]. As before, pediatric recipients were the main beneficiaries, since split transplantation allowed optimal use of a single donor organ to save two lives – most often an adult and a child, or two children.

At the same time, advances in precision parenchymal transection, including the use of ultrasonic dissectors, argon plasma coagulation, and other innovative technologies, as well as a deeper understanding of the variability of biliary and vascular anatomy, made it possible not only to refine transplantation of left-sided liver fragments (the left lateral segment or left lobe) – pioneered in the late 1980s by S. Raia and R. Strong – but also to take the next, even bolder step.

After carefully analyzing the not entirely successful but innovative attempt by Japanese surgeon Y. Yamaoka in 1994 to transplant the right lobe of the liver from a living related donor to an adult patient [41], as well as the controversial experience of Lo Chung Mau in Hong Kong [42], several countries began intensive preparations for introducing this fundamentally new and technically demanding variant of partial LT, living donor right lobe transplantation.

This operation required surgeons to possess not only extensive expertise in liver resection but also the utmost precision and responsibility, as the risks to healthy donors undergoing right-sided hemihepatectomy were considerably higher than in left-lobe donation.

In 1997, within just a few months of each other, the first successful living donor right lobe liver transplants were carried out: in Moscow by a team led by Sergey Gautier at Petrovsky National Research Centre of Surgery, and shortly thereafter in Denver (USA) by a team under Michael Wachs. Paradoxically, history repeated itself here as well – the recipient in the Moscow pair was a minor teenager with autoimmune hepatitis [43, 44]. In Europe, the technique of transplanting the right lobe from a living donor began to be actively used around 1998, largely due to the efforts of Professor Christoph Broelsch and his team, who, after returning to Essen (Germany), continued their pioneering work [46].

In addition to revolutionary surgical innovations, the 1990s also marked a turning point in immunosuppressive therapy. A new, highly potent calcineurin inhibitor – tacrolimus (FK506), developed by Japanese researchers – was increasingly and confidently integrated into clinical practice. Multiple studies demonstrated its superiority over cyclosporine in preventing and treating rejection, and today tacrolimus remains the cornerstone of most modern LT protocols [47, 48].

Tacrolimus provided more reliable and selective control of the rejection response, which in many cases allowed for a reduction in glucocorticosteroid dosages or even their complete withdrawal. This was particularly important for pediatric patients, as it significantly reduced the risk of steroid-associated complications that could impair growth and development [49].

Equally transformative was the introduction, in the mid-1990s, of a new class of immunosuppressants – mycophenolic acid derivatives, especially mycophenolate mofetil, approved by the FDA in 1995. When combined with calcineurin inhibitors, these agents enhanced efficacy while enabling the almost complete elimination of older, more toxic cytostatics such as azathioprine from immunosuppression regimens [50, 51].

In addition, the 1990s witnessed major progress in the prevention and management of infectious complications, which had long remained one of the leading causes of morbidity and mortality after LT. Of particular importance was the development and implementation of effective strategies for the prevention and early treatment of cytomegalovirus (CMV) infection. These strategies relied on regular monitoring of viral load – using either pp65 antigenemia assays or CMV DNA detection by PCR – followed by the timely initiation of antiviral therapy with ganciclovir or foscarnet once viral replication was detected [52, 53]. This approach significantly reduced the incidence of CMV disease and improved transplant outcomes, especially in seronegative recipients receiving grafts from seropositive donors.

Thus, the 1990s became not only a period of consolidation of the achievements of the preceding decades but also an era of remarkable innovation, which firmly established LT as a standard, highly effective therapeutic option. Once again, pediatric transplantology played a key role, driving the search for and implementation of the most advanced technologies and approaches.

THE MODERN ERA: FROM THE 2000s TO THE PRESENT DAY

Pediatric LT entered the modern era as a highly effective therapeutic method with broad clinical applications. Yet, despite these successes, by the beginning of the 21st century a number of pressing challenges had accumulated. These ranged from the limited availability of care, concentrated in a relatively small number of highly specialized centers, to the absence of clear and equitable policies for allocation of deceased donor organs. The shortage of suitable grafts became increasingly acute as the number of children requiring transplantation steadily grew [56].

Over the past 25 years, the global volume of pediatric LT has risen substantially. While the United States and Western European countries have retained their roles as traditional leaders, several new regions have emerged on the world stage, demonstrating impressive results. China, Russia, Turkey, Japan, South Korea, Iran, and India have established large transplant programs, including dedicated pediatric centers, which are now performing LT at a high international standard [57, 58].

Of particular note is the pediatric liver transplant program at Shumakov National Medical Research Center of Transplantology and Artificial Organs in Moscow, developed under the leadership of Sergey Gautier. Today, the center performs more than 110 pediatric liver transplants annually, accounting for up to 95% of all liver transplants in minor recipients nationwide. With this volume and expertise, the clinic has secured its place among the world leaders in pediatric LT.

Improving the allocation of donor organs

One of the most important directions in optimizing the use of scarce donor organs in the early 2000s was the development of objective, standardized systems for assessing disease severity in patients on the waiting list and for determining transplant priority. In the United States, the Model for End-Stage Liver Disease (MELD) was introduced in 2002 in response to rising mortality among patients awaiting transplantation and the urgent need for a more equitable system of organ distribution [59, 60]. This score was calculated from objective laboratory values – bilirubin, INR, and creatinine.

Almost simultaneously, an adapted version, the Pediatric End-Stage Liver Disease (PELD) score, was developed for children under 12 years of age. In addition to laboratory parameters, PELD incorporated factors particularly relevant to the pediatric population, such as growth failure, serum albumin levels, and age [61].

The introduction of the MELD/PELD allocation system had an immediate positive impact: in the United States, mortality among children on the waiting list declined significantly, especially among the youngest and most vulnerable patients for whom delays were most critical [62, 63]. Following this success, MELD- and PELD-based allocation principles – or national modifications thereof – were subsequently adopted in many other countries and regions. This global trend has contributed to greater transparency and medical objectivity in the allocation of liver grafts [59].

In parallel with the introduction of objective scoring systems for assessing the severity of conditions, specific organizational measures were adopted to prioritize pediatric patients on waiting lists. Many national and regional allocation frameworks incorporated special rules or quotas ensuring that donor organs of suitable size and optimal quality were first offered to children [64, 65]. This approach was grounded in the recognition that alternative treatment options for young patients are often absent, and delays in transplantation carry a particularly high risk of irreversible complications or death. Pediatric candidates often receive additional points to their calculated MELD/PELD score or have priority access to organs from young donors.

Another important aspect of optimizing the donor pool has been the wider adoption of split-LT. In response to the severe shortage of suitable organs, several countries have introduced policies mandating consideration of splitting a donor liver for two recipients whenever possible. For example, in Italy, regulations require split transplantation if the donor is under 60 years of age and the organ is of adequate quality.

Thanks to this targeted policy and the active involvement of transplant centers, Italy has accumulated one of the world's largest experiences: between 1993 and 2019, more than 1,700 split procedures were performed. Analysis of these cases has shown steady improvement in outcomes for both adult and pediatric recipients as clinical experience expanded and surgical techniques were refined [66, 67]. This experience clearly demonstrates that the systematic use of split technology, particularly *in situ* splitting, is an effective way to expand the donor pool for children.

Ways to expand the donor pool

In addition to improving allocation systems and actively implementing split transplantation, a crucial strategy that has significantly shaped the landscape of modern pediatric LT has been the development of living-donor liver transplantation (LDLT) programs. This approach has become especially prominent in Asia and the Middle East, where the majority of pediatric liver transplants are now performed using living related donors [68, 69].

Japan provides the clearest example: over 98% of pediatric LT are performed with grafts from living donors. This dominance reflects both cultural attitudes toward organ donation and long-standing legal restrictions on the removal of organs from deceased children – until 2010, Japanese law prohibited postmortem organ donation from individuals under 15 years of age [70]. A similar pattern is observed in South Korea, where the scarcity of deceased donor organs has been successfully offset by widespread reliance on living donors. As a result, South Korea reports some of the best outcomes worldwide for both waitlist survival and post-transplant outcomes [68].

In contrast, in North America and Western Europe, transplantation still relies primarily on deceased donor organs. This is possible due to the existence of robust organizational networks such as Eurotransplant and UNOS, combined with a high level of public trust in postmortem organ donation programs [68, 71]. Nevertheless, even in these regions, LDLT remains an important and much-in-demand resource, particularly for children. In the United States, for example, several hundred pediatric LDLTs are performed annually, usually in emergency situations or when no suitable deceased donor is available [71].

Legislative differences between countries also have a significant impact on the availability of donor organs. In most European nations, the prevailing model is the opt-out system, under which every citizen is regarded as a potential organ donor after death unless they have formally registered their refusal. This approach has consistently been shown to increase the number of postmortem donors [72]. By contrast, many Asian countries as well as the United States adhere to an opt-in system, where explicit consent from the donor during their lifetime – or, in many cases, from the family after death – is required. This reliance on voluntary consent, combined with cultural and religious barriers, often limits the effectiveness of postmortem donation programs [72].

To mitigate organ shortages in certain European Union countries, efforts have gone beyond national measures such as the mandatory consideration of split transplantation. An important complementary strategy has been the establishment of international organ exchange systems, notably Eurotransplant and Scandiatransplant These mechanisms are particularly valuable in urgent cases, such as acute liver failure or transplantation for highly sensitized patients [72, 73].

ABO-incompatible liver transplantation

Overcoming the immunological barrier posed by ABO blood group incompatibility has become another significant achievement in modern transplantology, particularly in pediatric practice, where identifying a donor who is both size- and blood group–compatible can be extremely challenging. In its early stages, ABO-incompatible liver transplantation (ABOi LT) was regarded as an exceptionally high-risk procedure. The incidence of hyperacute antibody-mediated rejection, along with increased rate of vascular complications (hepatic artery thrombosis) and biliary complications, led to discouraging outcomes [74, 75].

A turning point came in the 2000s with the introduction of desensitization protocols that significantly improved ABOi LT results. These strategies included plasmapheresis to remove circulating anti-ABO antibodies, use of rituximab (a monoclonal antibody against CD20-positive B cells), immunoadsorption of specific antibodies, and intravenous administration of high doses of human immunoglobulin (IVIG), with splenectomy applied selectively in some cases [76, 77]. Together, these interventions allowed for effective reduction of isoagglutinin titers to safe levels, thereby minimizing the risk of antibody-mediated rejection. As a result, ABOi LT has become a clinically viable and effective option, particularly under conditions of acute donor organ shortage or when urgent transplantation is necessary [78].

Current protocols for ABOi LT differ between transplant centers and are often tailored to the recipient's baseline anti-ABO antibody titers. Nevertheless, they share a common principle: the simultaneous use of strategies to (1) reduce circulating isoagglutinins, (2) suppress their further production, and (3) modulate the B-cell response. One example is the titer-dependent approach described by Gelbart et al. (2018) for pediatric recipients. In patients with high baseline isoagglutinin titers (≥1:32), enhanced immunosuppressive was used, consisting of pre- and post-transplant plasmapheresis, rituximab (375 mg/m^2), and IVIG (1 g/kg) [79].

Extensive clinical experience has also been accumulated in Russia, particularly at Shumakov National Medical Research Center of Transplantology and Artificial Organs, where a proprietary protocol was developed. In this protocol, an anti-ABO antibody titer of 1:8 is considered borderline. Key interventions include transfusion of AB(IV) fresh frozen plasma (which lacks anti-A and anti-B antibodies), administration of rituximab, and plasmapheresis sessions [80]. Importantly, outcomes with this protocol have been comparable to those of ABO-compatible transplantation, including similar rates of vascular and biliary complications.

Across all protocols, regular monitoring of antibody titers before and after transplantation remains a cornerstone of patient management, enabling timely adjustments to therapy in response to changes in the immune response [77, 79].

Once again, it was the urgent need to save the lives of children in a critical situation for whom no ABO-compatible donor could be found that catalyzed the development and refinement of these complex and resource-intensive technologies.

Surgical aspects and modern challenges

Despite remarkable progress, pediatric LT entered the 21st century with several unresolved surgical problems and new challenges. One of the most pressing issues, particularly in infants under one year of age, is large-for-size syndrome. This condition, essentially a variant of abdominal compartment syndrome, can have severe consequences, including respiratory failure due to elevation of the diaphragm, reduced graft perfusion caused by vascular compression, and impaired visceral blood flow in general [81, 82]. To prevent and manage this syndrome, various surgical strategies have been proposed. Among them are the use of monosegmental grafts (e.g., isolated segment II or III) and hyper-reduced grafts, in which additional resection of a standard left lateral section is performed. However, this approach presents major limitations. The technical difficulty of creating adequate vascular and biliary anastomoses in very small grafts remains a challenge, as does the significantly increased wound surface area, which predisposes to bleeding and infectious complications [83].

Portal vein hypoplasia, commonly found in children with biliary atresia (the leading indication for pediatric LT), represents another major surgical challenge. Successful reconstruction of portal blood flow is crucial for both graft function and long-term patient survival.

To address this problem, transplant surgeons have developed a range of complex reconstructive techniques. Hwang et al. (2013) described a successful method involving the use of a vascular interposition graft, such as a segment of the donor's iliac vein, in an infant with severe portal vein hypoplasia [84]. Later, Namgoong et al. (2021) proposed several alternative strategies, including venous homograft interposition with an inverted T- or Y-shaped incision to create a wider anastomosis; longitudinal incision of the recipient's native portal vein to increase the diameter of the anastomosis; or the use of the recipient's portal vein branches to create a vascular "patch" (patch plasty), compensating for the size discrepancy between donor and recipient vessels [85].

All of these approaches aim to ensure adequate laminar blood flow into the graft and to minimize the risk of portal vein thrombosis, which remains a serious complication in pediatric transplantation, with reported incidence rates of up to 9% [85].

Retransplantation poses another major surgical challenge, particularly when performed long after the initial LT. Indications for repeat transplantation include irreversible chronic graft dysfunction resulting from chronic rejection, unresolvable vascular or biliary complications, or recurrence of the underlying disease in the graft. These procedures are technically demanding for several reasons: severe adhesions within the abdominal cavity, distorted vascular and biliary anatomy, and frequently the absence of clear anatomical planes for safe dissection.

All this is associated with a high risk of massive intraoperative blood loss, injury to surrounding organs and structures, and a greater incidence of postoperative complications [86, 87].

PROMISING TECHNOLOGIES AND FUTURE DIRECTIONS

By the late 2010s and early 2020s, several promising technologies initially tested in experimental settings began entering clinical practice, including pediatric LT. A key development has been the rapid advancement of dynamic *ex vivo* organ perfusion techniques. MacConmara et al. (2020) demonstrated that normothermic machine perfusion (NMP) can improve the viability of grafts obtained from "suboptimal" donors – such as those with expanded criteria or following circulatory death – and enables safe *ex situ* liver splitting while maintaining high functional activity in both grafts [88]. Similarly, Boteon et al. (2022) reported that NMP not only increases the utilization of marginal organs, including those from donors after circulatory death, but also facilitates split transplantation with consistently high-quality outcomes for pediatric recipients [89].

An additional advantage of NMP-assisted splitting is its ability to combine the benefits of *in situ* and *ex situ* approaches: precise identification of vascular and biliary structures in a perfused organ, safer and more controlled parenchymal division under optimal visualization, and elimination of bleeding risks in the donor. However, the high costs of equipment and disposables, the risk of biliary complications – particularly when using marginal grafts – and a range of organizational and institutional barriers currently limit the widespread adoption of this promising technology, requiring further research and experience [90].

Significant technological breakthroughs have also transformed the field of LDLT. In 2002, Professor Daniel Cherqui and his team in France performed the first fully laparoscopic left lateral sectorectomy from a living donor for transplantation into a child [91]. Since then, the adoption of minimally invasive donor hepatectomy has gradually expanded – initially approached with great caution, but by the early 2020s already widely and confidently implemented in many centers. Both purely laparoscopic and robot-assisted procedures are now performed with increasing frequency [92, 93, 94].

The introduction of minimally invasive approaches has been associated with substantial benefits for donors, including reduced intraoperative blood loss, less postoperative pain, shorter hospitalization, and faster recovery. With growing experience, operative times have approached those of traditional open surgery, without increasing the incidence of donor-specific complications [95].

Moreover, to date, several leading transplant programs worldwide have pushed the boundaries further by performing fully robot-assisted and even fully laparoscopic recipient operations, including pediatric cases. Early reports from these pioneering procedures have already been published [96, 97].

This fully minimally invasive transplant strategy remains confined to a few highly specialized centers. It is associated with significant challenges, such as high costs for equipment and consumables, and a significant amount of time to perform the surgical intervention itself and the need for dedicated training for the entire surgical team [98].

CONCLUSION AND HISTORICAL LESSONS

Pediatric LT has undergone an extraordinary evolution, transforming from an experimental intervention with unpredictable results into a standardized, highly effective therapy for life-threatening liver diseases in children. A unique feature of this trajectory is that pediatric transplantation has not only adopted advances from the broader field of medicine but has consistently served as a driver of innovation, propelling the discipline of transplantology forward.

The very first attempts at clinical LT in humans – including the earliest relatively successful procedure, which extended a child's life by several months – were performed in pediatric patients [4, 14]. The introduction and widespread adoption of reduced-size and split-LT were motivated primarily by the urgent needs of children facing a critical shortage of donor organs [23, 38]. Similarly, the development of LDLT, including technically demanding right-lobe grafting, was driven by the need to save children for whom no other treatment options were available [29, 43].

Overcoming the barrier of ABO incompatibility, once considered insurmountable, was likewise pioneered in pediatric populations, expanding the boundaries of what was possible for children previously deemed untreatable [77, 79]. Even the most recent advances, such as minimally invasive donor hepatectomy and recipient surgery, are increasingly being applied and refined within the pediatric setting [91, 96].

This pattern is particularly striking when compared with most other areas of surgery and transplantation, where innovations are typically developed, validated, and implemented first in adults, and only later adapted for pediatric use once safety and efficacy are established.

The modern era can by no means be considered a stage in which the challenges of pediatric LT have been definitively resolved. On the contrary, as experience accumulates and the method becomes more widely adopted for the treatment of terminally ill children, new problems and unresolved questions continue to emerge. The most obvious and pressing among them is the ongoing search for strategies to further improve not only short-term but, more importantly, long-term transplant outcomes. The steadily growing cohort of patients who have successfully passed the threshold of the second and even third decade after surgery has shifted the focus of clinicians and researchers beyond simple measures of graft and patient survival to broader issues such as quality of life, cognitive development, and full social and professional integration of former recipients [99, 100].

Today, the development and implementation of personalized immunosuppression protocols, guided by individual biomarkers and designed to minimize side effects while ensuring reliable protection against rejection, are already shaping a new standard of care. Parallel efforts are directed toward targeted prevention and treatment of specific post-transplant complications, particularly vascular and biliary disorders. The issue of infectious safety has become especially urgent in the context of continuously evolving pathogenic microorganisms and the rapid global spread of pan-resistant flora. At the same time, reducing the long-term cumulative risks of chronic immunosuppressive therapy – including nephrotoxicity, arterial hypertension, diabetes mellitus, dyslipidemia, and the increased likelihood of malignant neoplasms – remains a serious clinical challenge, one that demands a multidisciplinary approach and the development of innovative therapeutic strategies.

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