Received: 28 October 2023 | Accepted: 27 March 2024

DOI: 10.1097/LVT.0000000000000381

REVIEW

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Efficiency of machine perfusion in pediatric liver transplantation

Alessandro Parente[1,2] | **Mureo Kasahara**[3] | **Vincent E. De Meijer**[4] | **Koji Hashimoto**[5] | **Andrea Schlegel**[5,6]

[1]Department of Surgery, Division of Transplantation, University of Alberta, Edmonton, Alberta, Canada

[2]HPB and Transplant Unit, Department of Surgical Science, University of Rome Tor Vergata, Rome, Italy

[3]Department of Surgery, Transplantation Center, National Center for Child Health and Development, Tokyo, Japan

[4]Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[5]Department of Surgery, Transplantation Center, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio, USA

[6]Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence
Andrea Schlegel, Transplantation Center, Digestive Disease and Surgery Institute and Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA.
Email: schlega4@ccf.org

Abstract

Liver transplantation is the only life-saving procedure for children with end-stage liver disease. The field is however heterogenic with various graft types, recipient age, weight, and underlying diseases. Despite recently improved overall outcomes and the expanded use of living donors, waiting list mortality remains unacceptable, particularly in small children and infants. Based on the known negative effects of elevated donor age, higher body mass index, and prolonged cold ischemia time, the number of available donors for pediatric recipients is limited. Machine perfusion has regained significant interest in the adult liver transplant population during the last decade. Ten randomized controlled trials are published with an overall advantage of machine perfusion techniques over cold storage regarding postoperative outcomes, including graft survival. The concept of hypothermic oxygenated perfusion (HOPE) was the first and only perfusion technique used for pediatric liver transplantation today. In 2018 the first pediatric candidate received a full-size graft donated after circulatory death with cold storage and HOPE, followed by a few split liver transplants after HOPE with an overall limited case number until today. One series of split procedures during HOPE was recently presented by colleagues from France with excellent results, reduced complications, and better graft survival. Such early experience paves the way for more systematic use of machine perfusion techniques for different graft types for pediatric recipients. Clinical reports of pediatric liver transplants with other perfusion techniques are awaited. Strong collaborative efforts are needed to explore the effect of perfusion techniques in this vulnerable population impacting not only the immediate posttransplant outcome but the development and success of an entire life.

Abbreviations: CIT, cold ischemia time; DCD, donation after circulatory death; DWIT, donor warm ischemia time; ERL, extended right lobe; HOPE, hypothermic oxygenated perfusion; IRI, ischemia-reperfusion injury; LDLT, living donor liver transplantation; LLS, left lateral segment; LT, liver transplantation; MP, machine perfusion; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PLT, pediatric liver transplantation; RCT, randomized controlled trial; SCS, static cold storage; SLT, split liver transplantation.

HIGHLIGHTS

- Pediatric liver transplantation is a heterogeneous field with various challenges to address including a remaining waiting list mortality due to a limited number of suitable donors.
- Graft-recipient size mismatch, prolonged cold ischemia for split grafts, smaller vessel calibers together with a risk for elevated ischemia-reperfusion injury limit the graft options further.
- Machine perfusion is increasingly implemented in routine clinical practice of adult liver transplantation. There is growing evidence for the benefit of machine perfusion in the pediatric field.
- Hypothermic oxygenated perfusion (HOPE) was successfully introduced in pediatric liver transplantation in 2018. Since then, recipients were transplanted with different graft types, including left lateral segments, mono-segments, full left/right lobes, and reduced and whole livers from standard and extended criteria DBD and DCD donors.
- HOPE treatment was performed after prolonged static cold storage, during or after ex situ liver split. Outcomes in a recent case series with ex situ splits demonstrated excellent results with reduced complications and better graft survival compared to cold storage controls.
- Experimental studies demonstrated the feasibility of split procedures during normothermic machine perfusion. Clinical evidence is awaited.

INTRODUCTION

Liver transplantation (LT) is considered a life-saving treatment for children with a variety of diseases, including acute and end-stage liver disease, metabolic and genetic disorders, and unresectable hepatic tumors.[1] In addition to the need for a "good liver quality" to ideally serve the entire lifespan of young recipients, the available number of grafts is often compromised by the graft-recipient size mismatch, which is particularly important in small children. In 2021, the OPTN/SRTR of the United States reported a stable pretransplant pediatric mortality of 5.6 deaths/100 patient-years, with the highest mortality for the smallest candidates of <1 year of age.[2–4]

Different surgical techniques were developed to modulate the graft size, including splits, graft reduction, and living donor liver transplantation (LDLT), to serve children of all ages and weights.[5] The wider LDLT adoption resulted in an improved survival of very small candidates <1 year.[6]

A recent survey on the current worldwide practice of pediatric liver transplantation (PLT) included a total number of 108 pediatric transplant centers from 38 countries with 10,619 PLTs.[1] Most PLTs were accomplished in Asia with the highest volume of single centers in China and LDLT, including mono-segmental grafts, being the major source of livers.[1,7–13] In addition to the candidate's size and body weight, strict selection criteria limit the number of available livers of acceptable quality for children. Split liver transplantation (SLT) involves transection of a whole deceased donor liver into a left lateral segment (LLS), transplanted into a child, and the remaining extended right lobe (ERL), typically used for an adult or a larger child.[14] SLT has been demonstrated to expand the donor pool and reduce waitlist times.[15–20] Next to ischemia-reperfusion injury (IRI) observed in every transplantation, the act of liver transection together with an often prolonged cold ischemia time (CIT) increases the overall risk in SLT (Figure 1). In situ splits appear attractive to limit additional injury conveyed by prolonged CIT. Strict acceptance criteria are in place (split-policy) to balance the increased donor risk.[15,18] Between 2010 and 2015, only 6.3% of transplanted livers were utilized as split grafts in the United States.[3] Another potential source to enhance the number of usable grafts for pediatric recipients appears with donation after circulatory death (DCD) donors. While DCD livers are increasingly utilized in the adult population, such grafts are rarely accepted for children. In the United States, no pediatric patient received a DCD graft in 2021, compared to only 0.6% in 2011.[2] In Europe, 0.1% of all PLTs were performed with a DCD graft.[10] So far, <100 PLTs have been reported from DCD donors worldwide, a cohort of strictly selected donors for age, donor warm ischemia time (DWIT), and additional risk factors.[21,22] Next to advanced donor age, the combination of DWIT and prolonged CIT is of particular concern to trigger IRI-associated inflammation, graft stiffness with liver dysfunction, vascular, and biliary complications.[22] The liver transection and reduction add more inflammation to the overall process (Figure 1).[23] Dynamic organ preservation techniques appear therefore highly attractive to increase the number of available organs through modulation of graft quality with reduced CIT.[24] Additional benefit is expected with the use of viability criteria to predict posttransplant outcomes during machine perfusion (MP). Mainly established in adult liver recipients, 10 randomized controlled trials (RCTs)[25–35] and an ever-increasing number of "real-world" cohort studies are currently available.[24,36–38] While there is a better understanding of the underlying mechanisms of MP, the application of this technology in pediatric grafts remains limited.[39–41] This review discusses the current literature on PLT and MP with a focus on special needs and challenges in children. Regional variances and the impact of MP on different graft types are critically analyzed.

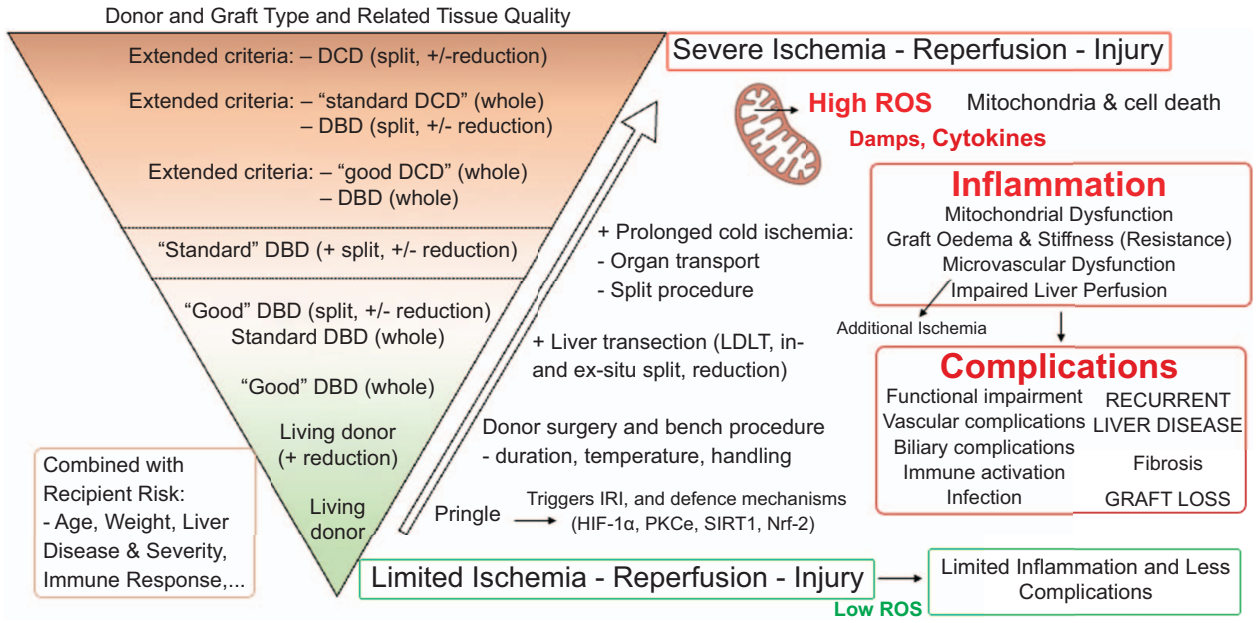

FIGURE 1 Different levels of reperfusion injury and complications with different graft types and quality: donor risk and graft quality depend on various not always objective risk factors. The main contributors are donor age, BMI, and warm and cold ischemia time. With the need to modulate graft size to the recipient size and weight, pediatric liver transplantation comes with an additional risk for elevated ischemia-reperfusion injury (IRI) through required liver transection to achieve a split or reduced graft. The accumulation of risk based on donor parameters, parenchymal transection, and cold ischemia time leads to an elevated overall risk for impaired outcomes in combination with a smaller vessel diameter and sick recipients. Abbreviation: BMI, body mass index.

CURRENT STATUS OF MACHINE PERFUSION IN LT

Two main concepts, perfusion at normothermic and hypothermic temperatures, are increasingly tested in clinical studies and have been implemented in a few countries with commissioning for livers with specific risk profiles.[42] In situ normothermic regional perfusion (NRP) or ex situ normothermic machine perfusion (NMP) provides oxygen under warm conditions. The NRP technique is tied to DCDs enabling organ assessment while recirculating donor blood within the abdominal compartment.[43] Following the clinical implementation of NRP in Spain, the concept is used in different European countries and the United States. Compared to static cold storage (SCS), an early reoxygenation with NRP may appear beneficial to reduce biliary complications and improve graft survival.[37,43,44] Despite such early success, RCTs with NRP are lacking. Clinical studies from France and Spain identified limitations, particularly when DWIT is prolonged,[45,46] or when NRP is combined with $\geq$7 hours of CIT and/or retransplantation.[43] In Italy, a country with an obligatory 20-minute "standoff" period for all DCD donors, NRP is used routinely and often combined with end-ischemic MP.[47]

Ex situ NMP at 37°C has 2 applications, an upfront version, starting at the donor center with $\leq$2–3 hours of initial SCS,[25,30], or an end-ischemic approach at the recipient center.[48,49] The perfusion duration varies between 4 and 24 hours.[25,30] Four RCTs are available demonstrating feasibility with good results after NMP in mainly benchmark criteria donor livers.[25,30,33,44,50] Real-world observational data support feasibility and the use of NMP for viability assessment (Figure 2).[51] Currently mainly used clinically in the United States and Europe, the wider NMP application also depends on logistic factors and required funding. Similar complications (ie, biliary), as seen with SCS, were described by authors from the United Kingdom when NMP was initiated after 6–7 hours of SCS.[25,30] These findings are further underlined by the posttransplant results achieved with "ischemia-free-liver-transplantation" with an immediate NMP start in the donor and an overall limited NMP duration of 6 hours (avoidance of any SCS).[32,37,48] Ischemia-free liver transplantation offers relevant evidence on the contribution of SCS to IRI-associated injury during NMP, in risky livers.[32] Ischemia-free liver transplantation has been demonstrated to reduce the postreperfusion syndrome after LT, improving hemodynamic recipient stability after reperfusion.[32] Similarly, NMP was found to positively impact postreperfusion syndrome.[30,52]

Hypothermic machine perfusion was introduced first in clinical practice in 2010 by Guarrera et al.[53] Following standard organ procurement and transport in ice, the graft is perfused at 8–12°C with a highly oxygenated (pO_2: 60–100 kPa), artificial solution (ie, Belzer-MPS) for a median of 2 hours.[24,54] Two main perfusion routes are used, single portal vein (PV) or dual-hypothermic

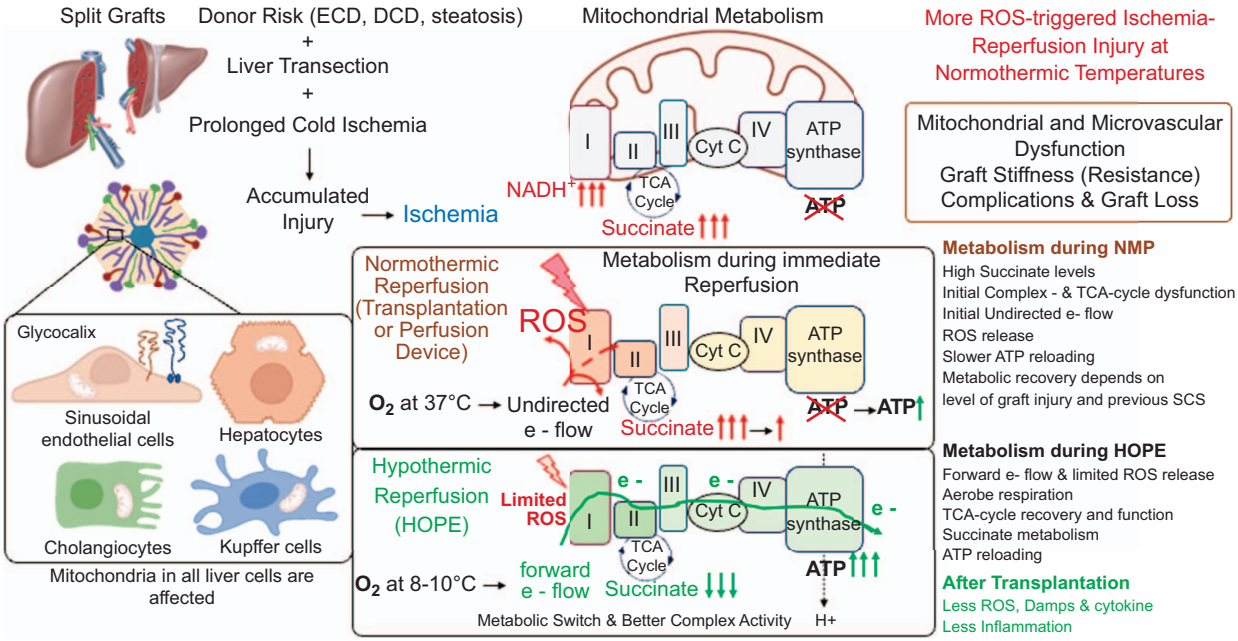

FIGURE 2 Mechanism of protection and injury during machine perfusion in liver transplantation: Mitochondria are the key compounds for successful transplantation. Following relevant ischemia, respiratory chain proteins suffer dysfunction and release ROS upon reintroduction of oxygen. The level of ROS and downstream IRI injury depend on the initial donor and graft quality (with subsequent succinate accumulation during ischemia), additional cold, and warm ischemia but also on the temperature when oxygen is reintroduced. At the time of reperfusion when oxygen is reintroduced, such succinate provokes an undirected and retrograde electron flow triggering the release of ROS from mitochondrial complex I. Under warm conditions, mitochondria release relevantly more ROS compared to cold temperatures. Cells with severe mitochondrial dysfunction suffer relevant ROS release and die, thereby releasing further proinflammatory molecules, including danger-associated molecular patterns, mitochondrial DNA, and cytokines. The danger-associated molecular patterns-release links the initial IRI-activation to an ongoing downstream inflammation triggering toll-like-receptor-activation on macrophages with subsequent pronounced secretion of proinflammatory cytokines. This ongoing sterile inflammation further activates complement proteins, supporting the recruitment of circulating recipient neutrophils and platelets after transplantation. Such cells, in turn, migrate directly into the newly implanted liver, amplifying the downstream activation of the innate immune system with further impaired liver dysfunction. An increased sinusoidal inflammation comes with elevated organ stiffness, peripheral hypo-perfusion, and a subsequent second episode of hypoxia. The modulation of the mitochondrial metabolism is therefore highly relevant to limiting inflammation and maintaining a viable microvascular environment. While NMP with the "near physiologic environment" at 37°C using a blood-based perfusate may provide an advantage over SCS for the assessment of liver injury, NMP triggers IRI with severity based on the individual metabolic profile due to donor risk factors, donor management, liver procurement, and preservation. In contrast to NMP, the reintroduction of oxygen under cold conditions leads to a steady succinate metabolism with less detrimental effects at later normothermic reperfusion at implantation. ROS release is very limited, complex proteins recover their function and the cells have uploaded ATP at the end of HOPE. Based on this lower IRI inflammation, HOPE treatment improves liver function, reduces complications, and improves graft survival as recently demonstrated by metanalyses of RCTs. Abbreviations: HOPE, hypothermic oxygenated perfusion; IRI, ischemia-reperfusion injury; NMP, normothermic machine perfusion; ROS, reactive oxygen species; SCS, static cold storage.

oxygenated perfusion (D-HOPE) with simultaneous perfusion through PV and hepatic artery.[26]

Recent RCTs have shown that both NMP and HOPE are associated with better outcomes compared to SCS, reducing allograft dysfunction (early allograft dysfunction) and peak transaminases.[25–30] Several meta-analyses of currently available RCTs demonstrated the superiority of HOPE over SCS and NMP. The reduction of major posttransplant complications, nonanastomotic strictures, graft loss, and retransplantation by HOPE was demonstrated.[24,55] Based on earlier studies, where underlying mechanisms are described, the role of HOPE with its mitochondrial protection is key in downregulating the innate immune response with lower acute cellular rejection rates, as underlined by recent meta-analyses.[56]

Considering the positive results demonstrated with MP in adults, this technology could convey many benefits for the pediatric population, which are discussed below.

CURRENT EVIDENCE OF MACHINE PERFUSION IN PLT

Despite the routine use in adults, the current evidence of MP in PLT includes case series and small cohort studies with a total number of 23 PLT with HOPE. Large cohort studies or RCTs are lacking.[57–60] The first clinical case was performed in Groningen.[60] The authors used a DCD liver from a 13-year-old female donor. The whole graft was procured (weight: 1509 g)

TABLE 1 Overview on pediatric liver transplantation with the use of machine perfusion

Author, country, reference	Study design	Donor and graft type	Study groups and number	Cold storage before HOPE	Perfusion technique and device	Perfusion route and split technique	Perfusion duration	Recipient parameter	Main findings	Discussion
Muller et al, 2023, France[61]	Case series[a]	DBD, LLS grafts	HOPE (n = 14 recipients); SCS (n = 17 recipients), LDLT (n = 15)	473 min (7.9 h)	HOPE, 8–10°C; pressure: pv: 3-5 mm Hg; flow: 150–300 ml/min; pO_2: NA (fully oxygenated); VitaSmart	Common PV, combined perfusion of eRL and LLS; split during HOPE	100 min	NA (abstract)	Lower rates of mild to severe IRI (grade ≥2). Sign. Less infiltrating neutrophils, no postreperfusion syndrome in HOPE livers, comparable IRI after HOPE split and LDLT	Largest case series published as abstract. HOPE split transplants with similar results as with living donor transplantations
Muller et al, 2023, France[62]	Case report	DBD, reduced whole liver (S6/7)	HOPE (n = 1)	390 min (6.5 h)	HOPE, 8–10°C; pressure: pv: 3–5 mm Hg; pO_2: NA (fully oxygenated) VitaSmart	Common PV; 50 min transection of S6 and 7 during HOPE	180 min (3 h)	Age: adolescent; Weight: 50 kg (GRWR reduction from 4 to 3.1%);	ICU stay: 3 d; hospital stay: 15 d, Biliary anastomotic stenosis, no other major complications	Case report, feasibility of right lobe reduction during HOPE
Rossignol et al, 2022, France[57]	Case series[a]	DBD, LLS grafts	HOPE (n = 8 recipients); SCS (n = 12 recipients)	8.2 h (7.8– 8.6 h)	HOPE, 8–10°C; pressure: PV: 3–5 mm Hg; flow: 150–300 ml/min; pO_2: NA (fully oxygenated); VitaSmart	Common PV, combined perfusion of eRL and LLS; split during HOPE	95 min = 1.6 h (86–– 126 min)	Median age: 3.5 y (2–5.4 y); Median weight: 15.5 kg (11–17.8); Median PELD: 17 (13–21); Recipient disease: Biliary atresia: 2/8; retransplantation (NAS): 2/8; Acute failure: 1/8; PSC: 1/8	Less PNF (0% vs. 8%), shorter LOS (6 d vs. 12 d), less NAS (0% vs. 8%), less HAT (0% vs. 8%), lower CCI (53p vs. 69p), better graft survival with HOPE (100% vs. 92%)	First case series, 25% retransplantation as indication; median HOPE treatment only 95 min
Oldhafer et al, 2022, Germany[63]	Case report	6y DBD, eRL graft	HOPE (n = 1)	16 h 23 min	HOPE, 8–10°C; pressure: pv: 3 mm Hg; flow max: 175 ml/min; pO_2: NA (fully oxygenated), VitaSmart	Common PV; eRL HOPE after ex situ split	200 min (> 3 h)	Age 9 y, familiar intrahepatic cholestasis type 2	ICU stay: 1 d; hospital stay: 21 d; mild ACR after 5 wk, no other complications	Case report, feasibility of HOPE after split and long SCS (> 16 h)
Rossignol et al, 2022, France[58]	Case report	12y ECD-DBD (DRI 2.25), LL (pediatric) and RL	HOPE (n = 1)	LL: 453 min (7.6 h); + 30 min after D-HOPE for second transport	T: 8–12°C; pressure: pv: 4 mm Hg; flow: 150 ml/min; pO_2: NA (fully oxygenated); VitaSmart	Common PV; split during HOPE, 60 min transection	LL: 85 min	LL: 4-y-old pediatric recipient, weight 15 kg, retransplantation for HAT with biliary strictures and sepsis (RL: 38 y adult)	Full immediate function, relaparotomy for infected hematoma; anastomotic biliary stricture, at 6-month normal functioning graft	Case report, feasibility of full left/right split during HOPE in ECD-DBD graft, second cold storage after HOPE

Mabrut et al, 2021, France[64]	Case report	2 DBD, LLS (2 pediatric recipients)	HOPE (n = 2)	LLS: 352 min and 353 min (5.8 h)	T: 10°C; pressure: pv: 4 mm Hg; flow: 150 ml/min; pO_2: NA (fully oxygenated); Liver Assist	Common PV; split during HOPE, 675 min and 62 min transection	NA	LLS: age 36 mo and 5 mo, weight: 15 kg and 5 kg, recipient disease: 1 retransplant for HAT/ITBL due to alagille syndrome (36 mo)	Full recovery (36 mo with retransplant required two relaparotomies).	Overall graft improvement with HOPE for challenging recipients requiring retransplantation with LLS grafts
Thorne et al, 2021, The Netherlands[65]	Case report	51 y, DBD, eRL, LLS grafts	D-HOPE (n = 1)	299 min (5 h) before D-HOPE and split; eRL: + 294 min (4.9 h) after D-HOPE; LLS: + 31 min after D-HOPE)	HOPE, 8–10°C; pressure: pv: 3 mm Hg, HA: 25 mm Hg; flow: pv: 80–120 mL/min; HA: 50-60 mL/min, pO_2: > 106 kPa; Liver Assist;	Common PV and celiac trunk; eRL and LLS, split during D-HOPE, 110 min split duration	LLS: 125 min (2 hrs); (eRL: 152 min)	LLS for pediatric recipient at splitting center ERL for adult recipient at receiving center	eRL: good graft function, but severe pancreatitis with jejunum perforation; LLS: good graft function, relaparotomy for hematoma evacuation; both recipients: 1 episode of ACR; at 6 mo 2 fully functioning grafts	Case report, second cold storage after D-HOPE; D-HOPE reduced the overall cold storage to <8 h
Spada et al, 2020, Italy[59]	Case report	19 y DBD, eRL and S2 graft	D-HOPE; 1 donor liver, 2 pediatric recipients;	eRL: 6 h S2 graft: 6 h	T: 8–10°C; pressure: pv: 6 mm Hg, HA: 25 mm Hg; flow: pv: 200–300 mL/min; HA: 50–80 mL/min, pO_2: 500–600 mm Hg; Liver Assist;	Common PV and celiac trunk, eRL & LLS with anatomical S3 resection (hyper-reduction to a S2 graft, 141 grams) during D-HOPE	eRL: 8hrs S2 graft: 5 h	eRL: 9-y-old, biliary atresia S2-graft: 29-day-old neonate; weight: 3.7 kg, acute liver failure, GRWR: 3.8	eRL: no complications at 14 mo S2-recipient: pv thrombosis on POD14 with retransplantation	Case report, feasibility of split and hyper-reduction during D-HOPE for two pediatric recipients and monosegmental grafts
Werner et al, 2019, The Netherlands[60]	Case report	13-y-old DCD, whole graft (tDWIT 34 min, 19 min agonal phase)	D-HOPE (n = 1)	384 min (6.4 h)	T: 10°C; pressure: pv: 4 mm Hg, HA: 18 mm Hg; flow: pv: 210 mL/min; HA: 63 mL/min, pO_2: > 70 kPa; Liver Assist	HOPE through common PV and celiac trunk, whole DCD graft	2 hrs (128 min)	Age: 16 y, weight: 42 kg; progressive familial intrahepatic cholestasis type 2	Full function, hospital stay 18 d; Healthy recipient with functioning graft and normal histology after 1 y	First case report of D-HOPE for pediatric recipient and using a DCD graft

Note: Figures are number (percentage), median (interquartile range) or mean (SD) or range as described.

[a]The French case series from 2022 is included in the recent case series published in 2023, at the time of review preparation this publication is an abstract only.

Abbreviations: ACR, acute cellular rejection; DBD, donation after brain death; DCD, donation after cardiac death; DRI, donor risk index; ECD, extended criteria donor; eRL, extended right lobe; HA, hepatic artery; HAT, hepatic artery thrombosis; HOPE, hypothermic oxygenated perfusion; LLS, left lateral segment; NA, not available (not presented in the paper); NAS, nonanastomotic stricture; PV, portal vein; RCT, randomized controlled trial; RPS, right posterior sectionectomy; SCS, static cold storage.

after a total DWIT of 34 minutes (withdrawal of life support to cold flush).[60] Following transport and 6 hours 24 minutes SCS, the liver underwent 2 hours D-HOPE before transplantation in a 16-year-old girl with progressive familial-intrahepatic-cholestasis type-2 (Table 1). The recipient's posttransplant follow-up was uneventful with normal liver histology after 1 year.[60] This female recipient remains the only child until today transplanted with a machine-perfused DCD liver. Of interest is also that this liver was obtained from a pediatric donor, a graft type often used for adult recipients. Only 86 selected whole grafts from DCD donors were used for pediatric recipients, with a 5-year graft survival of 93%.[21] The results were satisfactory with highly selected donors; however, it needs to be underlined that DCD livers for pediatric recipients are rarely used and the minimization of additional risk factors is key. Given the small number of reported cases, a robust recommendation for a more routine use of such organs cannot be provided. However, based on the limited availability of LDLT and elevated waitlist mortality, DCD livers could be increasingly utilized for children with routine use of MP in the future, particularly when current viability criteria are better defined and widely practiced.[38]

Looking at available large cohort studies with DCD LT for adult recipients, MP has various benefits protecting hepatocytes and cholangiocytes through the described modulation of the mitochondrial metabolism.[39,66] A recent RCT demonstrated the reduction of the number and severity of nonanastomotic biliary strictures with HOPE treatment.[26] In large cohort studies with extended criteria, DBD and DCD donors paralleled such findings demonstrating excellent outcomes after transplantation with prior HOPE.[36] Particularly with the concern of combining advanced donor age and DWIT, the HOPE procedure is expected to convey multiple benefits for children.

Machine perfusion also reduces CIT, which is of particular importance and may enable the use of "good quality" DCD livers as split grafts in the future.[62] Based on the expected high cumulative risk with donor warm and prolonged CIT combined with elevated inflammation due to the split procedure, the use of DCD livers remains limited.

Liver transection, done for the split but also during hepatectomies for cancer surgery, leads to different levels of inflammation in the patient based on liver tissue quality and previous injury through ischemia or chemotherapy.[67] The use of MP targets also the elevated injury in the context of SLT to safely increase the utilization of livers for pediatric recipients (Figure 3). Several European centers have described a few pediatric SLTs after HOPE. In 2020, authors from Italy presented a case of liver splitting during D-HOPE. The DBD donor was hemodynamically unstable precluding the performance of in situ split. Spada and colleagues reported here the first LLS-ERL split procedure during perfusion with additional LLS-reduction to a monosegment 2. Both grafts were transplanted after a total preservation time of 11 and 14 hours with satisfactory outcomes.[59]

These 2 cases were further paralleled by similar reports from The Netherlands and France. Thorne et al and Mabrut et al described another 3 cases of LLS and extended right lobe liver splits during continuous D-HOPE and HOPE, respectively.[64,65] All grafts were successfully transplanted, and the authors concluded that liver splitting during continuous HOPE is feasible and has the potential to substantially shorten CIT optimizing transplant logistics.[64,65] One of the cases was a retransplantation for hepatic artery thrombosis and related biliary complications in a 36-month-old with Alagille syndrome (Table 1). All recipients showed satisfactory immediate allograft function and recovery. Most case reports and a recent case series were presented by the group from Lyon, who proposed a standard technique for liver splitting during HOPE to obtain LLS and ERL grafts.[64] Such livers were perfused through the common PV, facilitating the procedure, and reducing the risk of injuring arterial branches during graft handling and split.[64] Other groups may prefer dual HOPE. Additional perfusion through the HA may facilitate the identification of arterial branches during transection. Subsequently, the same group from France performed a full left/full right split procedure during HOPE. The 2 grafts were transplanted in a 4-year-old pediatric and 38-year-old adult recipient.[58] Both grafts showed immediate function and low transaminase release. At 6 months, both recipients were alive with normal liver function. HOPE treatment was started after 7.6 hours of CIT.[58]

Rossignol and colleagues described 8 PLTs with a split during HOPE. The results were compared to 12 pediatric recipients transplanted with standard, cold-stored ex situ split grafts. All HOPE splits were successfully transplanted, and no graft loss or recipient death was observed during the 7.5-month follow-up. The HOPE-split procedure was started after 8.2 hours of cold ischemia.[57] In addition, HOPE-split grafts were perfused for a median of 125 minutes, which significantly shortened the CIT (472 vs. 544 min; $p = 0.001$). Reduced neutrophil infiltration was found in postreperfusion biopsies.[57] Recently, the same authors published an updated series of 14 partial grafts from deceased donors, split during HOPE, and compared to 17 cold-stored splits and 15 living donor transplantations.[61] HOPE-split grafts had lower IRI rates and a significantly reduced number of infiltrating neutrophils with a reduction of postreperfusion syndrome and lower recipient transaminase levels compared to SCS controls. Despite prolonged SCS before HOPE and split (7.9 vs. 2 h, $p < 0.001$), posttransplant results after HOPE split were comparable to LDLT grafts including levels of IRI, postreperfusion syndrome, and surgical complications within 3 months.

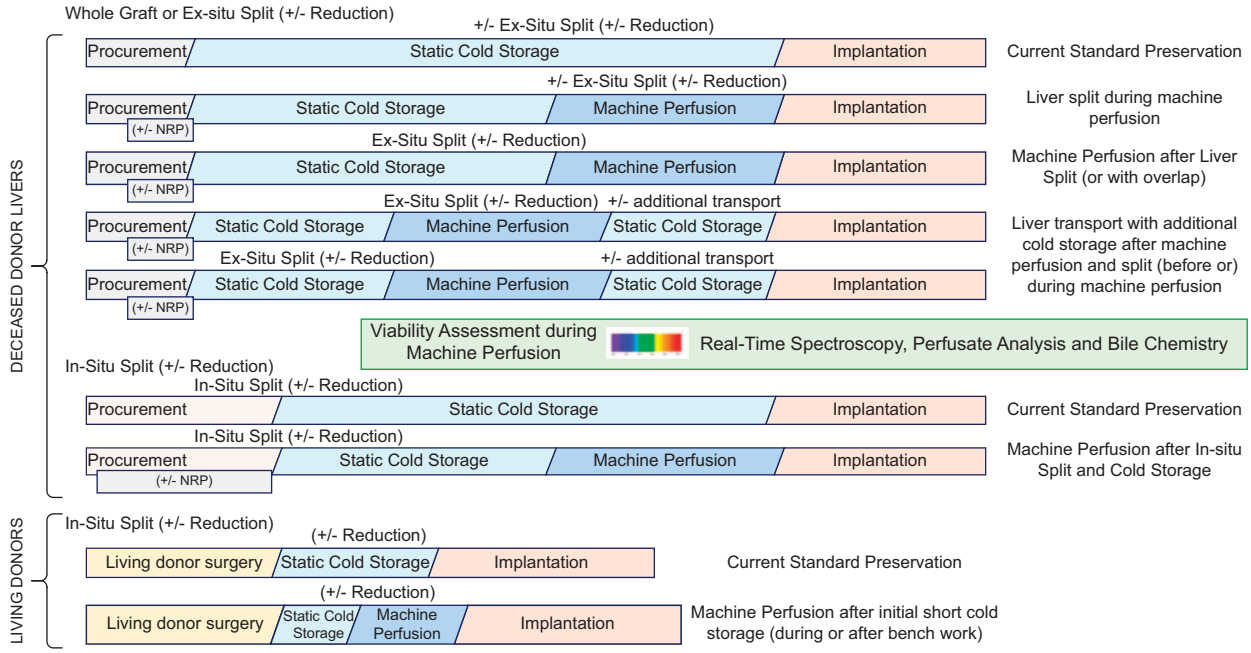

FIGURE 3 Different scenarios of liver preservation for pediatric recipients: Various liver preservation pathways were described with machine perfusion in pediatric liver transplantation. HOPE concepts were used for full-size DCD grafts and during or after ex situ split procedures. In countries where livers are preferably split in situ, machine perfusion can be performed thereafter either in the donor or recipient center. Portal vein–only perfusion techniques are beneficial enabling the perfusion through the common PV during split or easier access to small vessel calibers and short stumps. An additional benefit is conveyed through the opportunity to assess viability during perfusion before implantation. While viability testing was discussed as an exclusive benefit of NMP, mitochondrial injury and function can be assessed during HOPE using real-time spectroscopy. FMN, a vitamin B_2 derivate, is released from its pocket in mitochondrial complex I based on the metabolic liver quality. Too high-risk organs release high levels of FMN at oxygenated reperfusion under cold conditions. While most livers can be improved and recharged with HOPE, those of too high risk can be reliably identified and declined from transplantation based on viability assessment.[68] Abbreviations: DCD, donation after circulatory death; FMN, flavin-mononucleotide; HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion.

While HOPE was used for split grafts in various countries, other perfusion techniques, including NMP remain experimental. This is particularly relevant, as the main feature, IRI and graft quality dependent viability assessment is lost for this vulnerable cohort. The known criteria of liver injury (ie, perfusate pH, lactate and bile production, and biliary chemistry) are routinely measured to reduce the risk of graft loss.[69] The recent work from the Turin group demonstrated a 20% PNF rate after transplantation of steatotic livers despite NMP and the use of current viability criteria.[70] A few groups have performed splits during NMP.

Brockmann et al reported 1 standard split procedure of a discarded human DCD graft after 24 hours of NMP.[71] This case report has been paralleled by authors from Birmingham, who split 4 discarded human DCD grafts, maintaining the viability of both liver lobes during 6 hours of NMP.[72] Increased HA and PV flows were however found in both lobes with a progressive decrease in perfusate lactate and glucose levels.[73] Recently, a group from Australia published the first split procedure during prolonged NMP (>6 h) using a modified liver assist device. Graft quality however deteriorated to "non-viable" within 6 days of NMP.[74] In 2022 the same group presented another case series of prolonged NMP with split grafts for >12 days.[75] The latest series included 10 discarded human livers that underwent split during NMP to obtain LLS and ERL grafts without transplantation. One graft failed due to a technical device error and all other grafts showed functional viability, with lactate clearance, bile production, and synthesis of coagulation factors for 24 hours after split.[76]

As shown in whole livers, the group from Boston described comparable metabolic processes of 2 liver lobes during subnormothermic perfusion.[77] Eleven discarded human livers underwent subnormothermic perfusion for 3 hours after surgical split. The lobar perfusion parameters were comparable to whole livers perfused under the same conditions. Each lobe showed a decrease in arterial resistance and metabolized lactate throughout perfusion.[77]

Although these are interesting approaches, more information regarding optimal perfusion parameters for liver lobes of different sizes and weights in the context of different surgical split techniques is required. No systematic analysis of perfusion parameters, such as flow and pressures with different liver weights and quality, is available today. None of these livers were transplanted; reports are however expected within upcoming years.

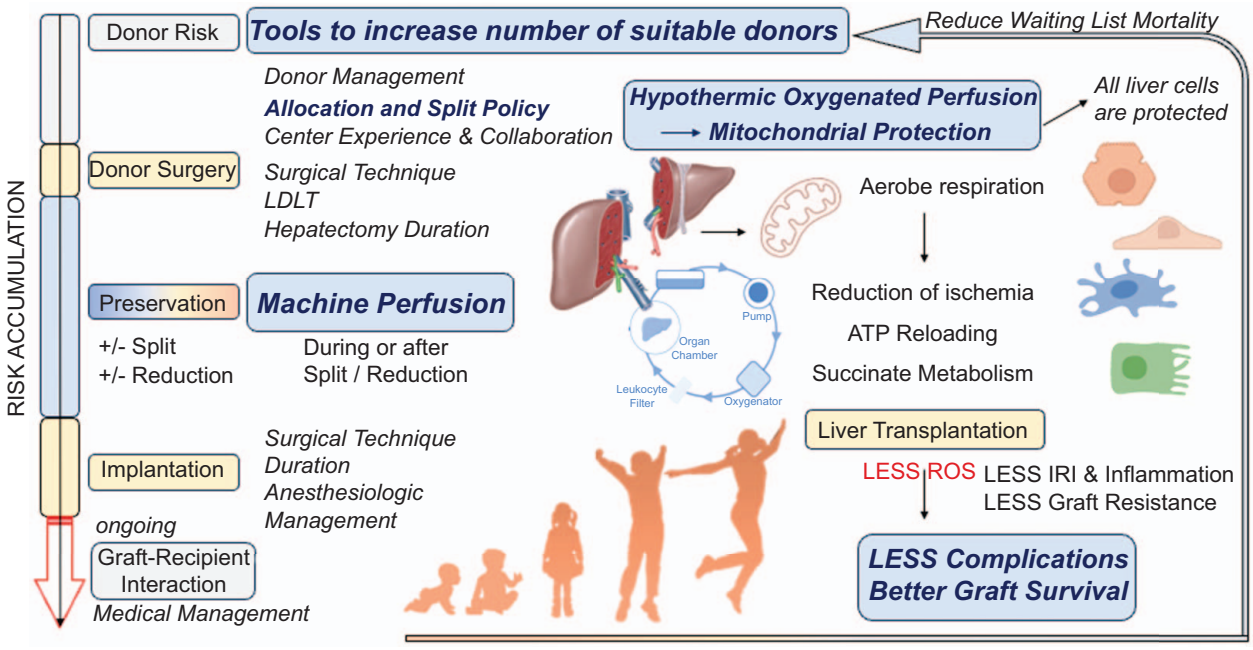

FIGURE 4 Tools to safely increase donor utilization for pediatric recipients: Improved allocation policies, living donor liver transplantation, and graft reduction have contributed to improved survival in children with liver disease. An additional benefit is seen with the use of ex situ machine perfusion offering a platform to improve graft quality and providing oxygen during or after split procedures, thereby reducing the duration of otherwise often prolonged cold ischemia. Initial experience with HOPE for pediatric recipients comes from different European countries and more larger cohort studies are awaited. Mitochondrial reconditioning with reloading of ATP levels as observed during HOPE is also of great importance for the liver to repair the IRI injury and to regenerate and regrow after split transplantation.[78] Experimental studies demonstrated better liver regeneration after HOPE with hepatocytes rapidly entering the cell cycle.[78] Hypothermic MP was found to reduce sinusoidal congestion and vacuolation with decreased hepatic enzyme release and higher proliferative activity compared to SCS alone. The expression of almost all cell cycle genes was elevated following hypothermic perfusion.[79] An enhanced liver ability to regenerate and to adapt to situations where regrowth or downsizing is needed appears highly relevant for pediatric liver transplantation. Abbreviations: HOPE, hypothermic oxygenated perfusion; IRI, ischemia-reperfusion injury; SCS, static cold storage.

SUMMARY AND ONGOING CHALLENGES

Although excellent results can be achieved with PLT, waiting list mortalities remain high.[2] Machine perfusion is a useful tool to accept donors with advanced risk and to reduce CIT. Despite promising results and wider use in adult LT, pediatric cases done with MP are limited to hypothermic techniques. Among case reports from European countries, the HOPE-split study in France is currently the only series with 14 pediatric recipients. The results with ex situ split during HOPE were excellent and comparable to LDLT, paving the way for a more systematic application of MP.[57,61] Based on the heterogeneity in PLT, demonstrating similar benefit with the use of MP as seen with adults will require time and commitment. Various graft types, recipients of all ages and weights, and underlying liver diseases may warrant the testing of different perfusion settings in a potentially high number of cases. Once implemented, MP can change the entire landscape of PLT, reducing IRI with better liver perfusion quality, regeneration, reduced graft stiffness, and subsequently less vascular and biliary complications. Through such mechanisms, MP will ultimately contribute to better graft survival. These results will possibly expand the acceptance criteria of all donor types. Future studies are therefore needed with uniform and transparent criteria and the collaboration of all stakeholders (Figure 4).

AUTHOR CONTRIBUTIONS

Alessandro Parente, Mureo Kasahara, and Andrea Schlegel designed the article; Alessandro Parente and Andrea Schlegel wrote the manuscript; Mureo Kasahara, Vincent E. De Meijer, and Koji Hashimoto revised the manuscript; Alessandro Parente and Andrea Schlegel designed the inserts of the manuscript; all authors contributed to and approved the manuscript.

CONFLICTS OF INTEREST

Andrea Schlegel consults for Bridge to Life Ltd. The remaining authors have no conflicts to report.

ORCID

Alessandro Parente https://orcid.org/0000–0001–5506–224X

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How to cite this article: Parente A, Kasahara M, De Meijer VE, Hashimoto K, Schlegel A. Efficiency of machine perfusion in pediatric liver transplantation. Liver Transpl. 2024;30:1188–1199. https://doi.org/10.1097/LVT.0000000000000381