

LIVER LISTING & ALLOCATION FORUM

REPORT AND RECOMMENDATIONS

May 26-27, 2016

FAIRMONT HOTEL VANCOUVER



Canadian Society of Transplantation
Société canadienne de transplantation

LEADERSHIP IN CANADIAN TRANSPLANTATION | LEADERSHIP EN TRANSPLANTATION AU CANADA

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Introduction

The inter-provincial donation and transplantation of organs in Canada is complex; provincial and territorial governments and Canadian Blood Services each deliver programs within their respective jurisdictions. While funding for the direct delivery of healthcare to patients lies with the provinces and territories, Canadian Blood Services works collaboratively with provincial programs to provide interprovincial programs and services to advance the practice of organ donation and transplantation. Professional societies provide support and focused education for health-care professionals. A variety of organizations and institutions provide direction through legislation, regulation and accreditation, and contribute to research efforts to improve the system.

The Liver Listing & Allocation Forum was an important step in the collaborative work of the Canadian Liver Transplant Network (CLTN), the Canadian Society for Transplantation (CST), and Canadian Blood Services. The purpose of the Forum was to identify, review, and build on current listing and allocation strategies for liver transplant with a view to developing interprovincial/territorial policies for Canada. The ultimate goal was to achieve consensus to ensure fair and transparent access based on the identification of leading practices,¹ leading to improved system performance.

The objectives of the Forum were to: (a) identify, review, and advance strategies and practices related to the Model for End-Stage Liver Disease (MELD) scoring system within the Canadian landscape, (b) achieve consensus on allocation strategies for pediatric recipients, and (c) explore national approaches for eligibility and listing for patients with hepatocellular cancer. At the Forum, participants reached consensus on key decision points and identified issues for future discussion, as well as suggesting research opportunities. The need to address system deficiencies in national patient level data capture and reporting was emphasized repeatedly.

We acknowledge and thank all those who contributed to the success of the Forum, including the dedicated members of the Steering Committee and specialty Working Groups. Their significant efforts provided the Forum's foundation. We are grateful to the representatives of the liver transplant community and other experts who participated. Their expertise led to robust and insightful recommendations that will shape liver listing and allocation practices across the country.

We are pleased to provide you with this summary report presenting the consensus recommendations of the Forum participants and look forward to continued collaboration among the CLTN, the CST, and Canadian Blood Services to further advance this important work.

Ian Alwayn
Chair, Liver Listing & Allocation Forum

Kimberly Young,
Director, Donation & Transplantation
Canadian Blood Services

¹ Leading practices are developed through a rigorous evidence-based process that includes literature reviews, environmental scans, evidence synthesis and evaluation, and then discussion and recommendations among subject matter experts.

Executive Summary including Recommendations

Background

Canadian Blood Services, in collaboration with the Canadian Liver Transplant Network and the Canadian Society for Transplantation, hosted a gathering of about 40 experts in Vancouver on May 26-27 2016 to identify, review, and build on current listing and allocation strategies for transplants of livers from deceased donors. The ultimate aim was to develop recommendations for Canadian transplant programs to ensure fair access to livers for patients on transplant waitlists.

Approach

The Forum process began with comprehensive planning, including scoping and initial development of challenge questions,² and then moved to knowledge assembly that culminated in an on-site expert meeting focussed on building consensus. Background documents on liver transplant were provided to Forum participants beforehand including:

- Two draft policies developed by the MELD-PELD Liver Forum Working Group: (a) MELD-Na for liver transplant allocation, and (b) allocation of livers to pediatric recipients according to the Canadian Pediatric Allocation of Livers System (CPALS).
- Three literature reviews on (a) MELD-Na and 5vMELD versus MELD, (b) pediatric scoring models, and (c) scoring systems for hepatocellular carcinoma (HCC), based on reviews of the international literature.
- An environmental scan of HCC practices in Canada and internationally, including within it a list of selected publications from Canadian universities that were related to HCC and liver transplant.

Topic areas were addressed during the Forum using a consistent process: (a) presentations by experts were followed by question-and-answer sessions; (b) discussions among experts addressed key clinical “challenge questions” both in plenary and in small groups; (c) a Forum Recommendations Group convened to review and refine the outcomes of the plenary discussions and to finalize recommendations and key discussion points related to the questions. Areas for further research were also identified throughout the Forum.

² “Challenge questions” are used to structure expert discussions in order to address policy and practice issues. The goal is to achieve consensus recommendations. To the extent practical, challenge questions are accompanied by information to inform discussions such as available evidence and environmental scans.

Forum Recommendations

The main Forum output was 21 consensus-based recommendations for Canadian liver transplant programs, including key discussion points related to the questions asked (as the basis for each recommendation), and areas for further research.

The recommendations were developed in six areas:

- A. General Principles
 - B. Policy: Adult Scoring System
 - C. Policy: Pediatric Scoring System
 - D. HCC Eligibility Criteria
 - E. HCC Management: Bridging Therapy
 - F. HCC Management: Downstaging
-

A. General Principles

1. **It is recommended that** liver transplant programs offer livers from deceased donors first to patients at the highest risk of death, or drop-out for cause.
2. **It is recommended that** programs strive for similar rates of deaths and drop-outs for all indications for patients on the waitlist, based on exception points where required.
3. **It is recommended that** recording and sharing of outcomes data for waitlisted and transplanted patients be mandatory.
4. **It is recommended that** the minimum acceptable estimated 5-year patient survival rate be 60% for allocating a deceased donor liver for transplant.
5. **It is recommended that** the liver transplant community support Canadian programs to generate new knowledge by exploring novel approaches to liver transplant (for HCC) if (a) outcomes are expected to match or exceed the minimum 60% 5-year survival benchmark, and (b) results are reported and shared.

B. Policy: Adult Scoring System

6. **It is recommended that** the proposed MELD-Na policy be implemented by Canadian liver transplant programs (as amended in Recommendation 6).
7. **It is recommended that** a new laboratory testing frequency guideline based on MELD-Na scores be adopted: for MELD-Na ≥ 30 , lab results must be captured at least every 7 days;

for MELD-Na 21-29, lab results must be captured at least every 30 days; and for MELD-Na ≤ 20 , lab results must be captured at least every 90 days. Non-adherence to this schedule will result in reversion to a patient's previous lower MELD-Na score. There are two steps in the implications for non-adherence: (a) Beyond the deadline (with 3 days grace for MELD-Na > 30) the program will receive a warning and the patient will revert to the most recent lower MELD (if there is only one MELD score on record, the patient will drop to the median of the next lower category, e.g., > 30 drops to 25); (b) Beyond the deadline by 7 days (this includes 14 days for MELD-Na > 30), the patient will be inactivated on the waitlist.

8. **It is recommended that** programs monitor the frequency of patient non-adherence with required laboratory testing to identify opportunities for performance improvement.

C. Policy: Pediatric Scoring System

9. **It is recommended that** a Canadian pediatric allocation policy (CPALS) (Appendix 3) be implemented by pediatric liver transplant programs (including the detail contained in Recommendation 9).
10. **It is recommended that** patients listed as pediatric maintain their MELD exception points beyond their 18th birthdays until liver transplant occurs.

D. HCC Eligibility Criteria

11. **It is recommended that** programs use the TTV/AFP criteria ($TTV \leq 115 \text{ cm}^3$ and $AFP \leq 400 \text{ ng/mL}$) for eligibility rather than using the Milan Criteria.
12. **It is recommended that** programs follow the standardized diagnostic guidelines developed by the American Association for the Study of Liver Diseases (AASLD).
13. **It is recommended that** patients who are not eligible for liver transplant because they are beyond the HCC listing guidelines at evaluation should not subsequently be determined to be eligible based on deterioration of medical status.
14. **It is recommended that** patients should not be offered a liver transplant when a curative intent can be achieved by other means.
15. **It is recommended that** salvage transplant³ be offered only to patients who meet liver transplant listing criteria prior to resection.

³ Salvage transplant is where liver resection was employed as first-line treatment of patients with small HCCs and good liver function, with secondary liver transplant used in cases of tumour recurrence.

D. HCC Allocation – Exception Points

16. **It is recommended that** LTAC develop common approaches for liver transplant for HCC to ensure transparency and accountability.
17. **It is recommended that** LTAC explore a national system for awarding exception points for liver transplant for HCC, taking into consideration regional variations, e.g., differences in live and deceased donor rates, median MELD score at time of transplant, and patient populations.

E. HCC Management: Bridging Therapy

18. **It is recommended that** access to bridging therapy while on the waitlist be considered a standard of care.
19. **It is recommended that** access to bridging therapy within 4-6 weeks of the decision to bridge is desirable, given the potential for rapid progression of HCC.

F. HCC Management: Downstaging

20. **It is recommended that** downstaging for patients with HCC be accepted as reasonable treatment.
21. **It is recommended that** macrovascular invasion and extrahepatic metastases be considered contraindications for downstaging.

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1.0 Welcome from Canadian Blood Services

Kimberly Young, Director of Donation and Transplantation at Canadian Blood Services, welcomed participants to the Liver Listing and Allocation Forum in Vancouver. She described the role of Canadian Blood Services in organ donation and transplantation, starting almost a decade ago.

With respect to program policy and funding, the Canadian Organ Donation and Transplantation Network (under Canadian Blood Services) is a collaboration that functions at the level of the federal/provincial/territorial ministries of health.

For the organizations involved in the Forum collaboration, development of leading practices is of particular interest. In organ and tissue donation this includes deceased donation, living donation, allocation, data collection, and tissue donation.

A “Forum Process” to develop leading practices is often used (Figure 1).

FIGURE 1: Development of Leading Practices using a Forum Process



2.0 Objectives and Core Assumptions

2.1 Objectives of the Forum

In collaboration with the Canadian Liver Transplant Network (CLTN) and the Canadian Society for Transplantation (CST), Canadian Blood Services co-hosted a forum in Vancouver in May 2016. Its purpose was to identify, review, and build on current listing and allocation strategies for liver transplant with a view to developing interprovincial/territorial policies for Canada. The ultimate aim was to ensure fair access to available donated livers for patients on the liver transplant waitlist.

Forum objectives were to:

- Identify and review current liver listing and allocation practices and policies in Canada and internationally to understand the needs of the country with respect to MELD-Na for adults, allocation of livers for children, and issues related to liver transplants for patients with hepatocellular carcinoma (HCC).
- Develop agreement on evidence-based criteria to inform listing and allocation policies for liver transplants.
- Launch the Liver Transplant Advisory Committee as (LTAC) an advisory body to (a) developing liver listing and allocation processes among Canadian jurisdictions, (b) facilitate collaborative work on relevant policy and practice issues, and (c) advance the outcomes of the Forum.
- Produce a meeting report identifying agreements reached by meeting participants and suggesting areas for future research.

2.2 Core Assumptions

The following core assumptions were the agreed-upon “givens” that provided a common starting point for participant reflection, discussion, and decision-making.

1. The following principles guide optimal policy evolution for organ donation:
 - a) Medical need – access to ensure health and life
 - b) Utility – optimal use of a limited resource
 - c) Fair access – equitable access to a limited resource
 - d) Balance of competing principles
 - e) Transparency
 - f) Accountability
2. Live donation is out of scope.

3. With respect to access to deceased donor livers, children are prioritized over adults.
4. The patient need for deceased donor livers outstrips the supply so decisions must be made about which patient(s) among those waiting will receive liver transplants.
5. Developing an organ listing and allocation model for deceased donation does not dictate medical practice but provides a framework for operations. Individual physicians will continue to make decisions regarding individual patients.
6. Policies and approaches that are specific to Canadian health care systems are necessary for accountability.
7. Discussions will be informed by available information based on national and international experience and current practice.
8. Liver transplantation should align with guidelines for combined organ transplants.
9. While patients are on the wait-list they should be provided with the best possible standard of care.
10. Ethical considerations are important in relation to liver listing and allocation and are one of many factors that will influence leading practice.

3.0 The Forum

3.1 Leadership & Governance

Forum leadership included a broad cross-section of experts from the liver transplant community (medical and surgical), working collaboratively in committees and working groups, i.e., Forum Steering Committee, Working Group on MELD and Pediatrics, Working Group on HCC, and Forum Recommendations Group (FRG)

3.1.1 Forum Steering Committee

Dr. Ian Alwayn chaired the CLTN in 2014 when planning for the 2016 Forum began. Many of the Forum's Steering Committee members had already served on the Steering Committee for CLTN's 9th Annual Forum in the fall of 2014. Additional members were recruited to ensure representation of key areas of expertise, including pediatric liver transplant and donation, as well as a regional balance. One of their roles was to develop challenge questions for the Forum through a comprehensive iterative process. Forum Steering Committee members are shown in Table 1.

TABLE 1: Forum Steering Committee Members

Member	Affiliation
<i>CHAIR</i>	
Dr. Ian Alwayn (Chair)	Surgical Lead, Multi Organ Transplant Program; QEII Health Sciences Centre; Halifax, NS
<i>MEDICAL EXPERTS</i>	
Dr. Fernando Alvarez	Chief, Division of Gastroenterology, Hepatology and Nutrition; Director, Hepatic Transplantation Program; CHU Sainte-Justine Hospital; Montreal, QC
Dr. Vince Bain	Medical Director, Liver Transplant Program, U of Alberta Hospital; Edmonton, AB
Dr. Kelly Burak	Director, University of Calgary Liver Unit; Director, Southern Alberta Liver Transplant Clinic; Calgary, Alberta
Dr. Prosanto Chaudhury	Hepatobiliary and Transplant Surgery; MUHC Royal Victoria Hospital; Montreal, QC
Dr. Stephen Chung (alternate for Dr. Scudamore)	Head, Hepatobiliary & Pancreatic Surgery; Scientific Director, BC Transplant Society; Vancouver, BC
Dr. David Grant	Surgical Director, Multi-Organ Transplant Service; Surgical Head of GI Transplantation; Hospital for Sick Children; Toronto, ON
Dr. Roberto Hernandez Alejandro	HPB Surgery, Surgical Director of Liver Transplantation; London Health Science Centre; London, ON
Dr. Norman Kneteman	Zone Section Chief, Transplantation; Alberta Health Services; Edmonton, AB
Dr. Denis Marleau	Gastroenterologist; CHUM Saint Luc Hospital; Montreal, QC
Dr. Paul Marotta	Medical Director, Liver Transplant Program; London Health Science Centre; London, Ontario
Dr. Peter Metrakos	Medical Director, Liver Transplant Program; MUHC Royal Victoria Hospital; Montreal, QC
Dr. Charles Scudamore	Section Head, Hepatobiliary and Pancreatic; Vancouver General Hospital; Vancouver, BC
Dr. Nazia Selzner	Multi Organ Transplant Program; UHN Toronto General Hospital; Toronto, ON
Dr. Jason Yap	Pediatric Gastroenterologist; University of Alberta, Edmonton Clinic Health Academy; Edmonton, Alberta
<i>CANADIAN BLOOD SERVICES</i>	
Mr. Sean Delaney	Associate Director, Listing and Allocation; Edmonton, AB
Ms. JoAnne Lussier-True	Senior Program Manager, Listing & Allocation; Ottawa, ON
Ms. Tara Phillips	Program Manager; Ottawa, ON
Dr. Kathryn Tinckam	Medical Advisor, Transplantation; Toronto, ON
Ms. Kimberly Young	Director, Donation and Transplantation; Edmonton, AB
<i>CONSULTANTS</i>	
Dr. Vicki Foerster	Medical / technical writer; Oxford Station, ON
Ms. Dorothy Strachan	Process Consultant, Strachan-Tomlinson; Ottawa, ON

3.1.2 Forum Working Groups: MELD-Pediatrics and HCC

In July 2015, a need was identified for two working groups as sub-groups to the broader Forum Steering Committee. Their role was to focus on and oversee background work and preparation for the Forum in the key subject areas of MELD, pediatric allocation, and HCC.

- *MELD-Pediatrics Working Group*: Kelly Burak (Lead), Fernando Alvarez, Ian Alwayn, Charles Scudamore, Nazia Selzner, Jason Yap.
- *HCC Working Group*: David Grant (Lead), Ian Alwayn, Roberto Hernandez, Norman Kneteman, Denis Marleau, Paul Marotta, Peter Metrakos.

3.1.3 Forum Recommendations Group (FRG)

A cross-section of expert Forum leaders made up the facilitated FRG. These individuals were responsible for: (a) reflecting on issues and concerns emerging from Forum plenary discussions, (b) reviewing proposed final recommendations for each challenge question, and (c) presenting the final recommendations in plenary for discussion and confirmation by participants.

FRG members: Ian Alwayn (Lead), Kelly Burak, Sean Delaney, Susan Gilmour, David Grant, Norm Kneteman, Peter Metrakos, Charles Scudamore and Kathryn Tinckam.

3.1.4 Future Research Group (“Listening Post”)

A small expert research group was formed to listen throughout the Forum for recommended research topics that would support continued advancement and innovation in liver listing and allocation. This group’s conclusions were presented to Forum participants for discussion on the second afternoon of the meeting.

Future Research Group members: Kathryn Tinckam (Lead), Kelly Burak, Peter Metrakos, and Kevork Peltekian.

3.1.5 Forum Participants

In addition to the Steering Committee members, Forum participants included:

Dr. Oyedele Adeyi, Dr. Yaron Avtizur, Dr. Marc Bilodeau, Ms. Rosanne Dawson, Mr. Ed Ferre, Dr. Maged (Peter) Ghali, Dr. John Gill, Dr. Susan Gilmour, Dr. Aviva Goldberg, Dr. Bashir Jiwani, Dr. Melissa Kelley, Dr. John (Jack) Lake, Dr. David Liu, Dr. Vladimir Marquez, Dr. Steven Martin, Dr. Lisa McKnight, Dr. Vicky Ng, Ms. Kim Parsons, Dr. Kevork Peltekian, Dr. David Peretz, Dr. Eberhard Renner, Dr. Gonzalo Sapisochin, Dr. Richard (Rick) Schreiber, Dr. Morris Sherman, Ms. Julie Trpkowski, Dr. William (Bill) Wall, and Dr. Mark Walsh.

3.2 Forum Speakers

Speakers were selected based on their areas of expertise, ensuring a cross-section of geographic representation.

TABLE 2: Forum Speakers

Speaker	Affiliation
Dr. Ian Alwayn	Surgical Lead, Multi Organ Transplant Program; QEII Health Sciences Centre; Halifax, NS
Dr. Vince Bain	Medical Director, Liver Transplant Program; U of Alberta Hospital; Edmonton, AB
Dr. Kelly Burak	Director, University of Calgary Liver Unit; Director, Southern Alberta Liver Transplant Clinic; Calgary, AB
Dr. Susan Gilmour	Chair, Department of Pediatrics, University of Alberta; and Zone Clinical Department Chair for Child Health, Alberta Health Services
Dr. David Grant	Surgical Director, Multi-Organ Transplant Service; Surgical Head of GI Transplantation; Hospital for Sick Children; Toronto, ON
Dr. Jack Lake	Professor of Surgery and Medicine, and Executive Medical Director for Solid Organ Transplantation; U of Minnesota Medical Center; Minneapolis, MN
Dr. David Liu	Interventional Radiologist, Clinical Associate Professor of Radiology; University of BC; Vancouver, BC
Dr. Steven Martin	Professor of Pediatrics, University of Calgary; Division Head, Gastroenterology, Hepatology & Nutrition, Alberta Children’s Hospital; Calgary, AB
Dr. Gonzalo Sapisochin	Abdominal transplant surgeon, surgical oncologist, UHN; Assistant Professor University of Toronto; Toronto, ON
Dr. Morris Sherman	Board Chair Canadian Liver Foundation, Professor of Medicine University of Toronto, staff hepatologist with the UHN; Toronto, ON

3.3 Forum Process

The Forum process began with comprehensive planning, scoping and initial development of challenge questions, and then moved to knowledge assembly that culminated in an on-site expert meeting focussed on building consensus.

Background documents on liver transplant were provided to Forum participants prior to the event:

- Two draft policies developed by the MELD-PELD Liver Forum Working Group: (a) MELD-Na for liver transplant allocation, and (b) allocation of livers to pediatric recipients according to the Canadian Pediatric Allocation of Liver System (CPALS).

- Three literature reviews on: (a) MELD-Na and 5vMELD versus MELD, (b) pediatric scoring models, and (c) scoring systems for HCC, based on international literature.
- An environmental scan of HCC practices in Canada and internationally including within it a list of selected publications related to HCC and liver transplant from Canadian universities.

Topic areas were addressed during the Forum using a consistent process:

1. Presentations by experts were followed by question-and-answer sessions.
2. Participants then either (a) discussed in plenary or (b) worked in small groups to address key challenge questions⁴ that had been pre-developed and circulated (Appendix 1).
3. After brief plenary presentations on the results of small group work, members of the FRG convened to refine the outcomes of the plenary discussions and to finalize recommendations and key discussion points related to the challenge questions. The FRG also captured key discussion points related to the recommendations.
4. Throughout the Forum discussions, areas for further research were identified.

3.4 Key Considerations

The following considerations were taken into account throughout the Forum due to their potential impact on the success of the liver listing and allocation process:

- This effort builds on existing liver listing and allocation work in the transplant community, as well as events such as the World Transplant Congress (July 2014 in San Francisco) and the 9th annual Liver Transplant Forum (October 2014 in Montreal).
- Collaboration across stakeholder groups is essential in shaping criteria that will enable all parties to support standardized liver listing and allocation across the country.
- The resulting criteria for liver listing and allocation must be responsive to jurisdictional priorities, challenges, resources, health care system capacities, and provincial/territorial ability to support pan-Canadian initiatives.
- Continued development must acknowledge and align with inter-provincial/territorial jurisdictional resource capacities and challenges. An ongoing commitment among the partners is essential to implementing liver listing and allocation criteria across the country.

⁴ “Challenge questions” are used to structure expert discussions in order to address policy and practice issues. The goal is to achieve consensus recommendations. To the extent practical, challenge questions are accompanied by information to inform discussions such as available evidence and environmental scans.

3.5 Forum Scope

The Forum Steering Committee was responsible for defining the scope of Forum discussions based on what could realistically be accomplished to advance the field.

3.5.1 In Scope:

- Listing and allocation of donor livers to adult and paediatric patients
- Scoring systems for adults (MELD-Na) and children (CPALS)
- HCC diagnosis, eligibility criteria, exception points, bridging therapy and downstaging
- Guidelines for reporting and quality control
- Discussion that informs and aligns with minimum data set recommendations.

3.5.2 Out of Scope:

- Living donation
- Modification of the minimum data set
- Emerging issues beyond criteria for listing and allocation
- Approaches for additional data collection beyond what is currently available in the Canadian Transplant Registry
- Modifications to provincial/territorial sharing algorithms.

3.6 Forum Recommendations

The process for developing the recommendations in this report took into account the need for approaches that would be acceptable, useful, and adaptable across Canada. Each Canadian jurisdiction is encouraged to implement the recommendations in a way that maximizes the use of livers from deceased donors for transplant.

3.6.1 Over-arching Principles

3.6.1.1: Deaths and drop-outs (for cause) from the waitlist

The original Model for End-Stage Liver Disease (MELD) scoring system was adopted to minimize deaths, and drop-outs for cause, on the liver transplant waitlist for patients with liver failure. When patients are listed for other reasons and assigned MELD scores the intent is to ensure that everyone has an equal risk of death while waiting for a transplant.

RECOMMENDATIONS

1. **It is recommended that** liver transplant programs offer livers from deceased donors first to patients at the highest risk of death, or drop-out for cause.
2. **It is recommended that** programs strive for similar rates of deaths and drop-outs for all indications for patients on the waitlist, based on exception points where required.

KEY DISCUSSION POINTS

- It is understood that the decision to offer organs first to patients at highest risk of death, or drop-out for cause, may lead to outcomes such as poorer post-transplant survival, greater use of resources, and dissimilar rates of transplant for different indications.
- Allocation decisions will focus on avoiding futility.
- Rate calculations are influenced by the denominator, e.g., listing practices, referral patterns.
- Comprehensive data collection is important; data by province/territory and by centre is needed in order to address access issues.
- Consider transplant access in areas without transplant programs.

3.6.1.2: Measuring post-transplant outcomes

Outcomes in the literature reviewed for the Forum included: rate of liver transplant, survival rates and death rates at various time periods such as 3 months, drop-out rates (withdrawal from the waitlist for various unfortunate reasons), and removal from the waitlist due to an improving condition. There is evidence that Canadian liver transplant programs collect data on various outcomes but there is no systematic system for data collection and reporting.

RECOMMENDATION

3. **It is recommended that** recording and sharing of outcomes data for waitlisted and transplanted patients be mandatory. Specifics:
 - a) All centres monitor and share deaths/drop-outs on the waitlist (using the Scientific Registry of Transplant Recipients [SRTR] definitions of these events).
 - b) Deaths and drop-outs are measured according to: number, percentage, rate, and time to events.
 - c) All transplant centres collect and report transplant graft and patient survival rates.
 - d) Outcomes are analyzed according to MELD-Na scores and exception point status.

KEY DISCUSSION POINTS

- Address the urgent system deficiency in data collection and tracking.
- Capture data starting from time of referral and stratify by province/territory.
- Align data with the recommendations of the Liver Data Working Group.
- Capture risk-adjusted data should assess program performance.
- Find the resources required to implement these recommendations.

3.6.1.3: Minimum acceptable estimated 5-year patient survival rate

Historically, a 5-year survival rate of at least 50% has been proposed as the minimum expectation for someone to qualify for a deceased donor liver transplant. There is an expectation that patients with HCC being considered for transplant should have outcomes comparable to those without HCC. Recently, a 5-year survival rate of 60% to 70% has been proposed as the minimum reasonable outcome, based on the improved general outcomes of transplant for all indications. The principle of equity demands that similar patients are treated in a similar fashion.

RECOMMENDATION

4. **It is recommended that** the minimum acceptable estimated 5-year patient survival rate be 60% for allocating a deceased donor liver for transplant.
5. **It is recommended that** the liver transplant community support Canadian programs to generate new knowledge by exploring novel approaches to liver transplant (for HCC) if (a) outcomes are expected to match or exceed the minimum 60% 5-year survival benchmark, and (b) results are reported and shared.

KEY DISCUSSION POINTS

- The transplant community has responsibility for stewardship of a scarce resource and must adhere to avoidance of futility.
- A 5-year survival rate is difficult to estimate for individual patients and is only one of many considerations in determining eligibility for transplant; ultimately the number is based on expert opinion.
- Programs should have transparent, fair, accountable methods to list and counsel patients and to allocate organs, including defining the criteria as to who will use the organs and the processes involved.
- No patient group should have an inferior survival rate based on listing practices.
- The opinions of patients / the public are important in this area.
- 10-year survival rates may also be worth following.

3.6.2 Policies: MELD-Na and Allocation to Pediatric Recipients

3.6.2.1: Proposed MELD-Na policy

In the United States, the MELD scoring system was adopted in February 2002 as a “sickest first” policy that de-emphasized wait time as a determinant for who is next to receive a liver transplant. Adoption in Canada began in June 2004. Since then, modifications to improve the diagnostic accuracy of MELD have been investigated. The best known and most studied of these models is the addition of sodium (Na) to MELD to result in MELD-Na.⁵ In November 2014, at the 9th Canadian Liver Transplant Forum, the CLTN reviewed the current allocation systems for liver transplant and passed two related motions:

- Canada will adopt MELD-Na (using the Scientific Registry of Transplant Recipients [SRTR] calculation) on January 1, 2015 for liver allocation for adults. (See Appendix 2)

⁵ Hyponatremia has been shown to be an independent predictor of waitlist mortality in patients awaiting transplant and the addition of sodium to the MELD improves the diagnostic accuracy of the MELD score.

- Canada will prospectively collect albumin data to determine if adding this element will improve allocation decisions.

RECOMMENDATIONS

6. **It is recommended that** the proposed MELD-Na policy (Appendix 2) be implemented by Canadian liver transplant programs (as amended in Recommendation 6).
7. **It is recommended that** a new laboratory testing⁶ frequency guideline based on a MELD-Na score be adopted: for MELD-Na ≥ 30 , lab results must be captured at least every 7 days; for MELD-Na 21-29, lab results must be captured at least every 30 days; and for MELD-Na ≤ 20 , lab results must be captured at least every 90 days. Non-adherence to this schedule will result in reversion to a patient's previous lower MELD-Na score. There are two steps in the implications for non-adherence: (a) Beyond the deadline (with 3 days grace for MELD-Na > 30) the program receives a warning and the patient reverts to the most recent lower MELD (if there is only one MELD score on record, the patient drops to the median of the next lower category, e.g., > 30 drops to >25); (b) Beyond the deadline by 7 days (this includes 14 days for MELD-Na > 30), the patient is inactivated on the waitlist.
8. **It is recommended that** programs monitor the frequency of patient non-adherence with required laboratory testing to identify opportunities for performance improvement.

KEY DISCUSSION POINTS

- Data collection is required to monitor use of MELD-Na by Canadian programs.
- Responsibility for patient compliance with laboratory testing involves the transplant program, i.e., the intent is not to punish the patients.

3.6.2.2: Proposed pediatric allocation policy (CPALS)

Liver transplant is a life-saving procedure for a child. A rising demand for scarce donor livers means a wait list system is necessary, including a scoring system to prioritize listed patients. The urgency-based Pediatric End-stage Liver Disease (PELD) scoring system was adopted as the standard in the United States in 2002. Although the PELD system has its proponents, the PELD score may not be

⁶ The term "laboratory testing" refers to the four elements used to calculate MELD-Na, plus albumin.

prioritizing children in an optimal fashion (it can underestimate death rates and PELD scoring is often bypassed through use of exceptions). A version of the PELD score was developed in Ontario for children in 2012, based on a model used by EuroTransplant with a starting PELD score that increases with time plus exception points based on disease characteristics. In late 2014 via a consensus process this system (the Canadian Pediatric Allocation for Liver System or CPALS) was accepted by all pediatric centres doing liver transplants in Canada.⁷ The details are in Appendix 3.

RECOMMENDATIONS

9. **It is recommended that** a Canadian pediatric allocation policy (CPALS) be implemented by pediatric liver transplant programs (including the detail contained in Recommendation 9).
10. **It is recommended that** patients listed as pediatric maintain their MELD exception points beyond their 18th birthdays until liver transplant occurs.

KEY DISCUSSION POINTS

- There is a high mortality rate for patients < 1 year (or weight < 6 kg).
- The policy recommendations for pediatrics are made in the context of high live donation rates (resulting in a reduction in impact on others on the deceased donor waitlist).

3.6.3 Hepatocellular Carcinoma (HCC)

3.6.3.1: HCC Eligibility Criteria – General (Milan Criteria or other?)

To select the patients with HCC who are most likely to have good long term outcomes with liver transplant (that is, low rates of cancer recurrence and high rates of survival), the “Milan Criteria” were developed in Italy in 1996 and then adopted in the USA and elsewhere. The Milan Criteria are based on the size and number of liver tumours present, i.e., a single tumour ≤ 5 cm, or three tumours, each not > 3 cm. Although the Milan Criteria have successfully identified groups of patients with HCC who have done well at 5 years, experts increasingly realize that patients “beyond Milan” with slightly larger tumours or more tumours may also do well, yet they are currently not transplant candidates in some jurisdictions. It has also been recognized that it may be possible to identify subgroups of patients within Milan criteria (e.g., those with high AFP) who do not do as well with liver transplant. This has spurred a search for modifications or alternatives to Milan in an

⁷ Prior to the Forum, the MELD/PELD Working Group and representatives from pediatric liver transplant centres in Canada agreed to minor modifications to CPALS so that all children would receive MELD-Na exceptions according to four levels of priority.

effort to increase the numbers of patients who can access this life-saving treatment without decreasing survival rates.

In the literature review, four proposed systems were explored including alpha fetoprotein (AFP), total tumour volume-AFP (TTV/AFP), University of California at San Francisco (UCSF), and “UpTo7” (with 7 being the sum of the size and number of tumors for any given HCC). The environmental scan showed that practices related to listing and eligibility vary across Canada. Four of seven programs reported using maximum listing criteria of TTV/AFP (TTV ≥ 115 cm³ and AFP ≤ 400 ng/mL). Two Canadian centres reported using the Milan Criteria and one centre reported using extended Milan Criteria, approximating the UCSF criteria.

RECOMMENDATIONS

11. **It is recommended that** programs use the TTV/AFP criteria (TTV ≤ 115 cm³ and AFP ≤ 400 ng/mL) for eligibility rather than using the Milan Criteria.
12. **It is recommended that** programs follow the standardized diagnostic guidelines developed by the American Association for the Study of Liver Diseases (AASLD).

KEY DISCUSSION POINTS

- It is difficult to address the question of expanding the criteria without solving the issues related to lack of availability of organs.
- Programs may choose to explore different eligibility criteria provided outcomes are tracked and shared, continuing Canada’s history of innovation in this area.
- Consider the role of bridging therapies in managing HCC.
- Aspects of tumour biology may ultimately be incorporated.
- Programs are encouraged to participate in the online tracking system (PROLIT).

3.6.3.2: HCC Eligibility Criteria – where a satisfactory outcome is achievable by treatment other than transplant, e.g., RFA, resection

The management of HCC has been described as a complex multidisciplinary process. Although resection and liver transplant have been the cornerstones of curative surgical treatments, ablative techniques have recently emerged as alternatives for select patients. Treatment plans must be individualized, depending on patient- and tumour-related factors, with resection being an option

for solitary tumours with preserved liver function and ablative techniques for low volume tumours in patients unfit for resection.⁸

RECOMMENDATIONS

13. **It is recommended that** patients who are not eligible for liver transplant because they are beyond the HCC listing guidelines at evaluation should not subsequently be determined to be eligible based on deterioration of medical status.
14. **It is recommended that** patients should not be offered a liver transplant when a curative intent can be achieved by other means.
15. **It is recommended that** salvage transplantation⁹ be offered only to patients who met liver transplant listing criteria prior to resection.

KEY DISCUSSION POINTS

- Patients must be informed clearly about eligibility or ineligibility for liver transplant as needed if they experience complications post-resection of the liver.

3.6.3.3: HCC Allocation – Exception Points

All patients awaiting liver transplant are prioritized on the waitlist via the MELD scoring system; this includes assignment of “MELD exception points” to patients with HCC. Until recently in the USA, those with HCC received 22 MELD exception points with an automatic increase every 3 months (if their disease remained within the Milan Criteria) to adjust for HCC progression. Recognition of an unfair MELD advantage for patients with HCC led the USA Organ Procurement and Transplantation Network (OPTN) to revise its scoring system as of October 2015. Patients with HCC awaiting liver transplant who fulfill the Milan Criteria must now wait 6 months at their calculated MELD. If the tumour remains within the appropriate limits for 6 months, a MELD score of 28 is assigned. This increases every 3 months, capping at 34.

⁸ Deshpande R, O'Reilly D, Sherlock D. *Improving Outcomes with Surgical Resection and Other Ablative Therapies in HCC*. Int J Hepatol. 2011:686074.

⁹ Salvage transplant is where liver resection was employed as first-line treatment of patients with small HCCs and good liver function, with secondary liver transplant used in cases of tumour recurrence (Adam R, Azoulay D, Castaing D, et al. *Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy?* Ann Surg. 2003 Oct;238(4):508-18).

RECOMMENDATIONS

16. **It is recommended that** LTAC develop common approaches for liver transplant for HCC to provide transparency and accountability.
17. **It is recommended that** LTAC explore a national system for awarding exception points for liver transplant for HCC, taking into consideration regional variations, e.g., differences in live and deceased donor rates, median MELD score at time of transplant, and patient populations.

KEY DISCUSSION POINTS

- National sharing for HCC patients occurs only in the context of salvage liver transplant.

3.6.3.4: HCC – Bridging Therapy

Due to the significant concern related to tumour progression, patients with HCC are treated with locoregional therapies while on the waitlist for liver transplant. However, across Canada, there is no consistent practice in terms of bridging therapy for treating patients with HCC while they are on the waitlist, e.g., interventions and the triggers for those interventions. Canadian centres use radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), and/or transarterial radioembolization (TARE) but the conditions (HCC status/progression) under which these treatments are chosen vary. Internationally, there is also variation in HCC bridging therapy protocols.

RECOMMENDATIONS

18. **It is recommended that** access to bridging therapy while on the waitlist be considered to be a standard of practice.
19. **It is recommended that** access to bridging therapy within 4-6 weeks of the decision to bridge is desirable, given the potential for rapid progression of HCC.

KEY DISCUSSION POINTS

- There is a need to define standard of care in this context.

3.6.3.5: HCC – Downstaging

Some patients with HCC who are being considered for the liver transplant waitlist exceed criteria and are therefore ineligible for listing, e.g., their tumours may be too large or their AFP too high. Tumour downstaging is defined as reduction in the tumour burden using locoregional therapy (LRT) specifically to meet transplant criteria. This aims to shrink the tumour(s) and/or decrease AFP and so decrease tumor-related drop-out rates on the waitlist. A number of technologies are used for LRT, i.e., RFA, TACE, PEI, TARE, and liver resection; the largest experience is with the first two of these technologies.

Downstaging is an attractive approach because the response to downstaging can serve as a prognostic marker. It can also be a tool to select patients with more favorable tumour biology who will likely do well after transplant.

There is no consistent practice across Canada with respect to downstaging. Six of seven Canadian centres reported that downstaging is permitted in their jurisdictions and these centres all reported that the listing criteria after downstaging are the same as the regular listing criteria. In terms of the waiting period before waitlisting for transplant once a patient meets listing criteria, responses varied between immediate listing and 6 months.

RECOMMENDATIONS

20. **It is recommended that** downstaging for patients with HCC be accepted as reasonable treatment.
21. **It is recommended that** macrovascular invasion and extrahepatic metastases be considered contraindications for downstaging.

KEY DISCUSSION POINTS

- Leading practices are evolving regarding the eligibility criteria (e.g., pre- and post-treatment size, AFP and durability of response) and optimal protocols for downstaging.
- A definition of reasonable is required.¹⁰
- A method to prioritize downstaged HCC patients is required.

¹⁰ At the Forum, a definition of reasonable was provided as stated by a Canadian ethicist: “an expectation that decisions should be based on reasons (i.e., evidence, principles, values) that fair-minded people can agree are relevant to the particular circumstance...includes the credibility of those involved in the decision-making process, the process itself, as well as accountability for the same.”

3.7 Research Listening Post

Throughout the Forum, the Research Listening Post group captured a number of topics for future research (Table 3). This group also emphasized an overall clear message, i.e., there is a real need for more and better data.

TABLE 3: Research Topics for Consideration

TOPIC AREA	SPECIFIC TOPICS
Death and drop-outs	<ul style="list-style-type: none"> ○ Variability in listing practices across the country based on comorbidities and how this affects deaths, drop-outs, and post-transplant survival ○ A Canadian definition of drop-out and how to record it ○ Canadian data elements beyond those of SRTR ○ Donor rates, transplant rates, and death rates from liver disease and HCC by province ○ Spectrum of chronic liver disease
Access, referral, and listing	<ul style="list-style-type: none"> ○ How listing practices affect dropout ○ Impact of referral patterns and allocation practices on overall deaths from liver disease ○ Variability in access to transplant across Canada ○ Optimal timeframes for evaluation and listing (including recommendations) ○ Timelines from referral to listing and from listing to transplant in Canada (e.g., Does distance from a transplant centre make a difference? Rural and urban variations?) ○ Measures of disease severity at referral and listing to capture access issues
Predictions	<ul style="list-style-type: none"> ○ Calculator for predicting post-transplant survival ○ Donor Risk Index in all liver transplant patients, including regional variations ○ Literature review of post liver transplant scoring systems to predict survival (1 month, 1 year, 3 year, 5 year) with validation using Canadian data
Disadvantaged populations	<ul style="list-style-type: none"> ○ Transplant access and female sex, e.g., MELD, size ○ Strategy for high mortality in <1 year age groups ○ 12-18 year olds regarding compliance issues and other considerations such as immunologic differences and factors influencing outcomes

Allocation and outcomes	<ul style="list-style-type: none"> ○ Optimal ways to calculate the relative benefit of transplant between groups of patients and comparison to similar groups of non-liver-disease patients ○ Outcome data in different listed patient groups defined by disease and comorbidities ○ Acceptable post-transplant survival for different stakeholders (patients, families of deceased donors, living donors, program coordinators, non-transplant physicians and surgeons including primary care providers, and the general public) ○ Importance of public commentary on all listing and allocation systems ○ Futility threshold (defined by the expected post-transplant survival standard? What other factors should be considered?) ○ Graft and patient survival (1 month, 1 year and 3 year) in those undergoing combined liver-kidney transplant versus those undergoing liver transplant only with dialysis post-liver transplant in the first 100 days post-transplant ○ Impact of non-traditional risk factors on outcomes, e.g., frailty, sarcopenia
MELD score	<ul style="list-style-type: none"> ○ Evolution of MELD in the Canadian landscape ○ Variables in addition to albumin that could improve MELD-Na accuracy, e.g., creatinine vs eGFR, sex-based differences in MELD (can they be equalized by use of different variables or cofactors) and ways to document IV albumin administration ○ Transition to MELD in Canada (pre- and post-transition) ○ Variations in MELD-Na calculation across Canada including whether differences in laboratory methodology impact waitlist decisions
Imaging	<ul style="list-style-type: none"> ○ Standardization of imaging interpretation, especially in the community (degree of discrepancy and regional issues) ○ Potential for teleradiology ○ CT versus MRI as optimal imaging ○ Utility of the Liver Imaging Reporting and Data System (LiRADS) – a system created to standardize the reporting and data collection of CT and MR imaging for HCC ○ Data-driven imaging recommendations (including training, expertise, modalities) ○ Synoptic reporting to inform data analysis or CTR data entry ○ Imaging versus explant pathology, i.e., correlations and opportunities for improvement
Milan vs TTV AFP criteria for HCC	<ul style="list-style-type: none"> ○ Optimal AFP level (a) 400 was employed in the prospective studies, (b) best AFP cut-off to minimize HCC recurrence and inappropriate exclusion from transplant, (c) AFP cut-off for patients within and beyond Milan ○ Optimal TTV ○ Bridging therapies: (a) acceptable bridging therapies, (b) acceptable criteria post-bridging therapies, (c) use of the “modified Response Evaluation Criteria In Solid Tumors” (mRECIST) tool for tumour response in bridging therapy

HCC exception points	<ul style="list-style-type: none"> ○ Incorporation of tumour biology in the approach to HCC exceptions ○ Impact of regional variation in assignment on access to transplant for different patient groups
Additional HCC issues	<ul style="list-style-type: none"> ○ Variations in listing of HCC in the seven adult liver transplant programs ○ Use of live donation when outside deceased donation criteria ○ Consideration of AFP value, e.g., AFP level ○ Issue of excluded listing for tumour < 2.5 cm with complete ablation ○ Inter-regional study criteria for resectability – factors impacting recommendations ○ Behaviors of different types of HCC and their impact on outcomes ○ Inclusion of time (along with size, number, and AFP level) to better predict waitlist dropout and explore whether time should be measured from diagnosis ○ Acceptable HCC recurrence rate to permit retransplant ○ Characterization of remaining HCC in the explanted liver and tumour-free survival rates post-liver-transplant, plus correlations with pre-transplant interventions
Bridging therapy	<ul style="list-style-type: none"> ○ Quality of life measures in the bridge period ○ Validation of models relating to “Time to Strategy” failures ○ Cost effectiveness for depth of response (hospitalization, therapy cost, recidivism) ○ Outcome differences based upon access differences ○ Radioembolization versus TACE in a randomized controlled trial ○ Optimal time to bridging therapies to maximize benefit (perhaps assessed via a systematic review and regional difference analysis) ○ Quantifying risk benefit ratio for bridging therapy
Research ethics	<ul style="list-style-type: none"> ○ Clarity around the language of futility (interpreted variously by various people and the language of futility can, intentionally and unintentionally, be used to inappropriately suppress voices of difference) ○ Acceptable level of risk for live donors and variation according to recipient prognosis (e.g., HCC); donor relationship (e.g., parent to child); and supply of deceased donor livers ○ "Gaming" of the system, including perceptions of gaming ○ Directed donation of deceased donor livers ○ Consequences of poor maintenance of appropriate lab testing ○ Maintaining pediatric priority into adulthood for children who are listed but not transplanted as children ○ Consideration when listing of adherence rates and substance use, e.g., alcohol, smoking, marijuana ○ Hidden biases in the referral, listing, and allocation systems that disadvantage certain groups, e.g., gender, ethnicity, rural, and the system can be changed to improve justice and access

3.8 The Liver Transplantation Advisory Committee

The LTAC, chaired by Dr. Susan Gilmour of Alberta, was formally launched at the Forum. The Committee will include 10 to 12 members from medical and surgical areas, both adult and pediatric, including representation from each liver transplant program, as well as *ad hoc* members.

The LTAC will oversee knowledge mobilization and implementation of the consensus recommendations that came out of the Forum. Over the summer and fall of 2016, LTAC will begin drafting policies for listing and allocation practices and inter-provincial sharing of donated livers.

LTAC's initial focus will be to develop a basic policy on inter-provincial balancing, supported by data modelling, in order to protect local program activity while ensuring that high status patients retain maximum access to transplant in Canada. LTAC will then oversee next steps based on the recommendations resulting from the Forum and will provide leadership in addressing the liver community's long-standing concern, and the unanimous assertion of Forum participants, regarding the need for data collection and reporting. This is essential to support innovation, research, policy development, and practice improvement.

LTAC aims to provide advice on:

- Policy: Liver donation and transplant policy and practice issues, plus leading practices.
- Implementation: Coordination, implementation, and standardization of liver donation and transplant policies and practices
- Data: National liver donor data collection, data quality, system performance, and outcome measures.
- Operations: Interprovincial Liver Program operations for the purpose of evaluating listing, matching, and allocation within the Program.

3.9 Concluding Remarks

The Forum was an important step in the collaborative work of Canadian Blood Services, the CLTN, and the CST to standardize liver listing and allocation practices across Canada. The ultimate goal was consensus on patient selection criteria and prioritization to ensure fair and transparent access to transplant. To this end, the objectives of the Forum were to identify, review, and advance strategies and practices related to an adult scoring system (MELD-Na) and a pediatric scoring system (CPALS), and to agree on acceptable national approaches for awarding listing exception points for patients with HCC who are awaiting liver transplant. The assembled experts (a) reached consensus on key decision points, (b) identified issues for future discussion, and (c) suggested research opportunities.

With respect to overarching principles for liver listing and allocation across Canada, participants unanimously agreed to two goals:

- Offer livers first to patients on the waitlist who are at highest risk of death or drop-out for cause.
- Strive for similar rates of deaths and drop-out for cause for all indications while patients are on the waitlist, using exception points where required.

In addition, consensus was reached with respect to reporting of key outcomes and a target 5-year survival rate after liver transplant of 60%.

The following overall achievements of the Forum included:

- Evidence of the evolution of Canadian principles to support advancing clinical practice and science of liver transplantation.
- The reality of regional differences.
- The importance of being transparent and accountable.
- Support for innovation.
- Unanimous support of the need for comprehensive national data collection and reporting.

Appendix 1: Challenge Questions

A. Overarching Principles

1. For each of these recommendations, do you support / support with questions / not support?
 - a. All centres should monitor and share deaths / drop-outs on the waitlist
 - b. Deaths / drop-outs should be measured by number, percentage, rate, and time to events
 - c. All centres should collect and report transplant graft survival rates
 - d. Outcomes should be analyzed according to MELD-Na scores and exception point status
2. How should we specifically measure patient survival rates?
3. What is the minimum acceptable estimated 5-year patient survival rate for allocating a deceased donor liver for transplantation in patients with cancer or chronic liver disease: 70%, 60%, 50%, 40%, 30%?

B. Draft policies for MELD-Na and Pediatric Allocation

1. Do you support the proposed MELD-Na policy for implementation across Canada?
2. Do you support the proposed CPALS for implementation across Canada?

C. HCC

HCC eligibility criteria

1. Should we replace the use of the Milan Criteria with another allocation scheme? If no, why not? If yes: TTV plus AFP, UCSF plus AFP, other?
2. If a patient with HCC exceeds the deceased donor listing criteria, is this patient eligible for deceased donor transplantation due to the progress of liver failure (high natural MELD-Na score)?
3. If the patient in (2) has a live liver transplant followed by complications / graft failure, is the patient eligible for listing for a deceased donor transplant the following year?
4. What are the criteria (see below) to exclude patients from listing if a satisfactory short term (3-5 year) HCC outcome is achievable with alternative treatment?
 - a. Solitary HCC < 2.5 cm completely ablated with compensatory cirrhosis (size a factor in your decision)?
 - b. Resectable HCC (e.g., 6 cm tumour in a well-compensated cirrhotic, 15 cm tumour in a non-cirrhotic)?
 - c. Other criteria?
 - d. Liver transplants are reserved for patients who cannot achieve an acceptable outcome by other means. What is the impact, if any, if decompensation occurs post-treatment?

HCC exception points

1. What are the benefits and drawbacks of a common prioritization scheme (harmonization) for HCC patients listed for liver transplant across Canada?
2. Do you recommend development of a national prioritization framework? Yes/No. Please explain.

HCC bridging therapy

1. Is there consensus that bridging therapy is considered a standard of care?
2. Timely access (within one month) to which of the following treatments represents the minimum requirement to be considered an appropriate standard of care in the context of bridging therapy? Check all that apply from: (a) RFA, (b) PEI, (c) TACE, (d) TARE, (e) TAE, (f) SBRT, (g) sorafenib.

HCC downstaging

Is the practice of downstaging reasonable? If no, why not? If yes, what should the eligibility criteria for downstaging be, e.g., upper limit beyond which downstaging should not be attempted? Check all that apply from (a) any tumour confined to liver, (b) no vascular invasion, (c) TTV < 250, (d) other volume, (e) AFP upper limit, (f) Other?

Appendix 2: DRAFT POLICY: MELD-Na for Liver Transplant Allocation

Purpose

The purpose of this policy is to standardize the allocation of cadaveric organs for liver transplant in Canada according to a “sickest first” policy using an objective scoring system, which has the greatest accuracy for predicting wait-list mortality.

Background

Approximately 500 liver transplants (LT) are performed each year in Canada. Unfortunately, in our country, the demand for liver transplantation greatly exceeds the supply of cadaveric livers and this has led to a high number of deaths on the waitlist. Therefore, in an attempt to reduce waitlist mortality, a need exists to triage the sickest patients to receive organ donation first. In the USA, the Model for End-Stage Liver Disease (MELD) was adopted in February 2002 as a “sickest first” policy that de-emphasized wait time as a determinant for who is next to receive LT [1]. MELD was initially developed to predict mortality after transjugular intrahepatic portosystemic shunting (TIPS) and was subsequently validated in adult patients awaiting liver transplantation in the USA [2,3]. It is based on objective laboratory variables, namely bilirubin, international normalized ratio of prothrombin time (INR) and creatinine. In Canada, allocation for LT had been done according to a location based algorithm with patients in the intensive care unit (ICU) having priority over patients in hospital and those patients at home (Figure 1). In this system, patients with hepatocellular carcinoma (HCC) could receive priority over other patients waiting at home. Organs were shared nationally for Urgent Status patients (4F, 4, 3F); however, after a failed payback system, national organ sharing in Canada was restricted to patients with acute liver failure (ALF) or urgent repeat transplantation for primary non function (PNF) or hepatic artery thrombosis (Status 4F and 3F).

The MELD score has been validated in patients awaiting LT in Alberta, and has been shown to predict waitlist mortality better than the CanWAIT algorithm (Figure 1) [4]. Beginning in June 2004, Canadian LT programs began to adopt MELD for allocation of non-urgent status patients. According to a survey of Canadian LT centres, performed in November 2014, MELD use has not been standardized across the country with various adaptations of the original MELD score being used (Figure 2) [4]. BC and AB used both MELD and the CanWAIT status, whereas ON and PQ programs had moved to MELD-sodium (MELD-Na) [5] and the ATL program was using the refit MELD-Na [6].

Figure 1. CanWAIT Algorithm [adapted from Reference 4]

CanWAIT	Definition
4F	ALF in ICU on ventilator
4	Chronic liver disease in ICU on ventilator
3F	ALF in ICU not requiring mechanical ventilation
3	Chronic liver disease in ICU for Grade 3 or 4 encephalopathy or renal dysfunction but not requiring ventilation
2	Chronic liver disease in hospital
1T	Chronic liver disease at home with HCC
1	Chronic liver disease at home
0	On hold for liver transplantation

Note: Currently, national organ sharing is performed for Urgent Status (4F and 3F)

Figure 2. Survey of MELD use by Canadian Liver Transplant Programs [adapted from Reference 4]

	BC	AB	ON	PQ	ATL
System	MELD and CanWAIT	MELD20* and CanWAIT	MELD → MELD-Na	MELD-Na	MELD → Refit MELD-Na
Adopted	2006	JUL 2004	2006 → NOV 2012	JUL 2008	2006 → 2012

Note: MELD20 Policy in Alberta (July 2004 – December 2014) gave priority to patients waiting at home (status 1) with a MELD \geq 20; however, hospitalized patients (status 2) with a lower MELD score would still receive an organ first.

Since the inception of the MELD score, several groups have investigated modifications which may improve the diagnostic accuracy of the model. The best known, and most studied, of these models is the MELD-Na [5]. Hyponatremia has been shown to be an independent predictor of waitlist mortality in patients awaiting LT and the addition of sodium to the MELD improves the diagnostic accuracy of the MELD score [5]. It has been estimated that MELD-Na allocation could potential reduce waitlist mortality by 7% [5]. This has led the United Network for Organ Sharing (UNOS) to officially approve MELD-Na allocation [7], with implementation beginning in 2016. Similarly, in the United Kingdom organs are allocated according to the UKELD score, which is a model that includes bilirubin, INR, creatinine and sodium [8].

In November 2014, at the 9th Canadian Liver Transplant Forum (CLTF-9), the Canadian Liver Transplant Network (CLTN) reviewed the current allocation systems for LT in Canada, the USA and UK. Speakers at this meeting critically appraised liver transplant allocation based on MELD, MELD-Na, and UKELD. Additionally, we reviewed the development and validation of the five variable MELD (5vMELD), which adds albumin to the MELD-Na model [9,10]. Furthermore, issues regarding MELD exception points for HCC and non-HCC patients (e.g. hepatopulmonary syndrome) and allocation for children, including the Pediatric End-stage Liver Disease (PELD) model [11], were discussed. A critical review of the MELD-Na was presented by Dr. Ray Kim, which included an analysis of allocation models based on more recent data from waitlisted patients in the USA using the Scientific Registry for Transplant Recipients (SRTR). Based on the SRTR analysis, UNOS will adopt the MELD-Na allocation using coefficients that are different from the original MELD-Na [5] and refit MELD-Na [6] publications.

At this meeting, CLTN members voted on and passed three motions:

1. Canada will adopt MELD-Na (SRTR calculation) for liver allocation for adults on January 1, 2015.
2. Canada will prospectively collect albumin data to determine if adding this element will improve allocation decisions.
3. Once motion #1 is implemented, Canada will develop and adopt a common allocation algorithm for pediatric liver transplantation.

Subsequently, Canadian Blood Services has commissioned two extensive literature searches around MELD and PELD allocation, which were completed in May 2015.

- MELD-Na and 5vMELD versus MELD [12]. This report concluded: “Overall, the evidence base for MELD-Na was supportive, particularly the earliest studies, although more recent studies do not show MELD-Na to be consistently superior to several other related scoring systems. The evidence base for 5vMELD is smaller; however findings are positive, suggesting that this scoring system is worthy of further investigation.”
- Pediatric end-stage Liver Disease (PELD) [13]. This report concluded: “Although some evidence supports the utility of PELD, experts seem to believe that the system can be improved. This provides an opportunity to rethink the use of PELD in its current form or to develop a new scoring system.”

Policy

Guiding Principles for Adult Liver Transplant

- Sickest or highest risk first
- Urgent Status = Acute liver failure, and repeat liver transplant for primary non-function or hepatic artery thrombosis are listed as Urgent Status (4F if intubated or 3F if not requiring mechanical ventilation) and should receive first priority with national sharing of organs. Mandatory sharing occurs for status 4F and mandatory discussion around sharing occurs for status 3F.
- All other non-urgent status patients who are 18 years or older should be ranked locally

according to the MELD-Na score (SRTR formula) regardless of their location (hospital versus home).

- Exceptions can be granted for certain patients with hepatocellular carcinoma, hepatopulmonary syndrome, portopulmonary hypertension, familial amyloidosis polyneuropathy, primary hyperoxaluria, cystic fibrosis, cholangiocarcinoma, etc. A separate policy statement on MELD-Na exceptions is required that outlines which diagnosis are eligible for MELD-Na exceptions (eMELD-Na) and exactly how eMELD-Na scores will be awarded and changed over time.

The formula for calculation of the MELD-Na (SRTR) [7] = $MELD + 1.32 * (137 - \text{sodium } \mu\text{mol/L}) - [0.033 * MELD * (137 - \text{sodium } \mu\text{mol/L})]$

- If sodium is less than 125 $\mu\text{mol/L}$ then sodium level will be 125 $\mu\text{mol/L}$
- If sodium is greater than 137 $\mu\text{mol/L}$ then sodium level will be 137 $\mu\text{mol/L}$

Where $MELD = (0.957 \times \ln(\text{creatinine mg/dL}) + 0.378 \times \ln(\text{bilirubin mg/dL}) + 1.120 \times \ln(\text{INR}) + 0.6431) * 10$

- Laboratory values less than 1.0 are set to 1.0 for the calculation of the MELD score
- If “had dialysis twice, or 24 hours of CVVHD, within a week prior to the serum creatinine test?” = YES then creatinine level will be 4.0 mg/dL
- If serum creatinine is greater than 4.0 mg/dL then serum creatinine level will be 4.0 mg/dL
- Creatinine levels in $\mu\text{mol/L}$ will be converted to mg/dL by dividing them by 88.4
- Bilirubin levels in $\mu\text{mol/L}$ will be converted to mg/dL by dividing them by 17.1

Lab Test Frequency Guideline

- MELD-Na score ≥ 30 ; Lab tests need to be collected and entered at least every 7 days
- MELD-Na score 29-21; Lab tests need to be collected and entered at least every 30 days
- MELD-Na score ≤ 20 ; Lab tests need to be collected and entered at least every 90 days

Implications for delayed lab test results: revert to the most recent MELD lower than current value.

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Appendix 3: DRAFT POLICY: Allocation of Livers to Pediatric Recipients

Purpose

The purpose of this policy is to standardize the allocation of cadaveric organs for pediatric liver transplantation in Canada according to a “sickest first” policy using an objective scoring system, which has the greatest accuracy for predicting wait-list mortality.

Background

Each year, about 600 pediatric liver transplants (LTs) are carried out in North America (approximately 50 in Canada) with 5-year survival rates of up to 90%. Acute and chronic liver disease in children can be the result of a number of conditions such as biliary atresia (between 45 and 50% all liver transplantation in pediatrics), other cholestatic diseases (10%), acute liver failure (10%), metabolic diseases including inherited diseases leading to cirrhosis (14.5%), other causes of cirrhosis mostly of autoimmune or viral origin (6%) and malignant tumours (5.4%), mainly hepatoblastoma (McDiarmid et al 2004). Toxic liver injury (1%) and rare diseases (5%) complete the pediatric indications for liver transplant. An important fact in the field of pediatric liver transplantation is the variety of etiologies, and the differences in natural history of each of those diseases. End-stage liver disease (ESLD) accounts for most pediatric LTs (Hsu et al 2015). Contraindications to LT can include non-resectable extrahepatic malignancy, concomitant end-stage organ failure that cannot be corrected by combined transplantation, uncontrolled sepsis, uncorrectable congenital anomalies affecting major organs, and irreversible serious neurological damage (Klamath & Olthoff 2010, Zucherman & Loveland 2012).

LT is a life-saving procedure for a child. A rising demand for scarce donor livers means a wait list system is necessary, including a scoring system to prioritize listed patients. Each system tries to optimize organ allocation through objectivity in order to deliver maximal benefit and minimal morbidity and mortality to those who are waiting (Shneider et al 2005). The urgency-based Pediatric End-stage Liver Disease (PELD) scoring system was adopted as the standard in the USA in 2002. The factors considered in the PELD formula are: the international normalized ratio (INR), total bilirubin, serum albumin, an adjustment for age <1 year and an adjustment for failure to thrive.

Although the PELD system has its proponents, concerns have been raised about a need for modifications, as the PELD score may not be prioritizing children in an optimal fashion. PELD underestimated death rates and was often bypassed through use of exceptions (Olthoff et al 2003, Shneider et al 2005, Shneider et al 2006, Klamath & Olthoff 2010). The paper from Shneider 2006 showed that 682 pediatric LTs were performed where the PELD score was potentially the primary determinant of liver allocation. However, in 53% of cases the actual calculated PELD score was not used and instead an exception to PELD was required in 24% of cases and children were listed as urgent (Status 1 equivalent of our 3-4F) without having acute liver failure in 29% of cases. There was considerable regional variability in use of PELD ranging from 26% to 71%. The authors concluded their

analysis by stating *“urgent reassessment of the PELD scoring system is needed to avoid morbidity and mortality in children.”*

This issue was very recently revisited by Hsu et al (2015) from Seattle who used UNOS data from 2002 to 2013 (n=3728) for children < 18 years to study PELD exception scores (used in 34% of cases and approved in 90%). They discovered a steady increase over time with patients being younger, with higher MELD/PELD calculated scores, who were more likely to be white race and to have private insurance. The authors noted that *“clinicians must be cognizant of the fact that patients who do not receive exceptions may become increasingly disadvantaged. Potential solutions need to address this disparity while alleviating the growing anxiety that, given the rising age and degree of illness of the average candidate on the adult liver waitlist across all regions, pediatric patients will not be able to compete for adult deceased donors. [Consideration may be given to] establishing minimal listing criteria and/or further giving children on the waitlist increasing priority on the waitlist.”*

Additional concerns with the utility of PELD include (a) the way it appears to stratify the degree of illness in children with similar diseases who are competing for pediatric livers, and (b) a concern that the PELD scoring system underestimates the risk of mortality and puts children at a disadvantage when they are competing for livers from adult donors (Neto et al 2010).

A pediatric Model for End-stage Disease (MELD) score (i.e., not PELD) developed for the EuroTransplant region (Eurotransplant manual: 20 April 2013) with a focus on wait time versus clinical urgency with automatic upgrading every 90 days found low wait list mortality with this tool, provided children were listed early in their disease course.

Children <12 yr	Point score corresponding to a 35% waitlist mortality Upgraded every 90 d until LT (by an additional 15% increase of 3-mo waitlist mortality)
Children ≥ 12-16 yr	Point score corresponding to a 15% waitlist mortality Upgraded every 90 d until LT (by an additional 10% increase of 3-mo waitlist mortality)

The before-and-after study assessed the impact of switching to the pediatric MELD system in 160 children who received a first LT from a deceased donor (110 in the 5 years before and 50 in the 4 years after). Results showed no negative impact of the new allocation rules on outcomes, with low wait list mortality provided children were listed early in their disease course. The authors noted that *“prompt listing is mandatory and frequent interdisciplinary discussions of transplant indications are required.”*

Additional factors for prediction of wait list death have been reported by others including hyponatremia, hyponatremia + ascites, and the EuroTransplant system based on wait time. Researchers have found hyponatremia to be an important variable in prediction of mortality on the wait list versus PELD alone. A Brazilian retrospective analysis found the presence of hyponatremia and ascites to impact risk of wait list death within 90 days (Pugliese 2014).

In Canada, almost 40% of all liver transplants in children are done from living-related donors. In addition, the ratio between pediatric/adult liver transplants remains throughout these years around 1 out of 10 in our country. These facts are showing that a liver transplant in a child does not produce a significant

<ul style="list-style-type: none"> • Confirmed shunt • No primary pulmonary cause <p>- Porto-pulmonary hypertension</p>	
<p>Inborn Errors of Metabolism</p> <p>Priority 1</p> <p>- Urea cycle defects with rapidly progressive disease</p> <p>Priority 3</p> <p>- Urea cycle defects</p> <ul style="list-style-type: none"> • Amino-acidopathies with high ammonia • Organic acidemias <p>- Crigler-Najjar type 1</p> <p>- Primary oxaluria</p>	<p>40 points</p> <p>29 points + additional 2 points every 2 months to a maximum of 39 points</p>

Future Directions

- The exception points for children in the CPALS system may need to be adjusted once the policy for MELD-Na exceptions for adults with HCC has been finalized.
- We propose that our CPALS allocation model should be reviewed every 5 years after its adoption.
- If the CPALS scoring system is not meeting the goal of eliminating wait list mortality in children then modifications or addition policies changes will need to be explored.
- One such future direction, intended to eliminate waitlist mortality in very young children, would be adopting national sharing of organs for children less than 1 year of age and/or <5kg in weight if they do not have access to living related donors. In such a system the CPALS score could be annotated with “xs” to indicate national sharing provided the "xs" recipient’s CPALS score is higher than the proposed local pediatric recipient.

How MELD-Na exception points will be awarded to children by CPALS categories

Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
P1	40															
P2	30	39														
P3	29	29	31	31	33	33	35	35	37	37	39					
P4	24	24	24	27	27	27	30	30	30	33	33	33	36	36	36	39

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