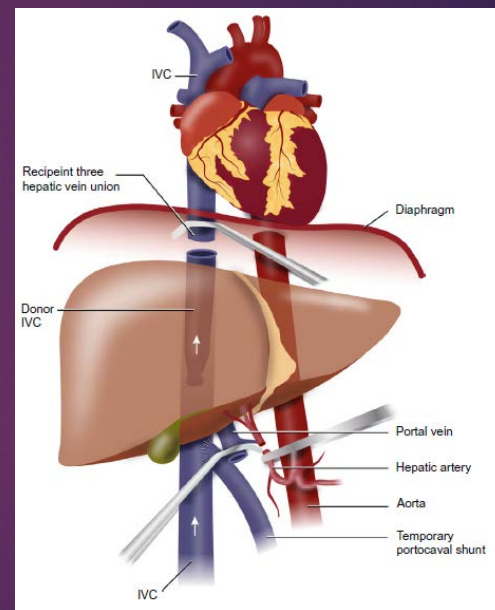


Indications for Liver Transplantation

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Medicine: Division of Gastroenterology
UNIVERSITY OF TORONTO



UHN Soham & Shaila
Ajmera Family
Transplant Centre

CanMEDS Roles Covered

X	Medical Expert (as <i>Medical Experts</i> , physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as <i>Communicators</i> , physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	Collaborator (as <i>Collaborators</i> , physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	Leader (as <i>Leaders</i> , physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	Health Advocate (as <i>Health Advocates</i> , physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	Scholar (as <i>Scholars</i> , physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	Professional (as <i>Professionals</i> , physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Conflict of Interest Disclosure

SCMD

Société canadienne des maladies digestives™

CDDW

Canadian Digestive Diseases Week™

None Relevant to this presentation

Outline: Liver Transplantation

- ▶ Background & Historical Perspective
- ▶ Canadian Landscape
- ▶ Indications and Trends in Indications
- ▶ When to Refer
- ▶ Once Listed: Organ Allocation, Dynamics on the List, and Living Donation

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Liver Transplantation

- ▶ Replacement of Diseased Liver with either a Deceased Donor or Living Donor Organ
- ▶ Life-saving intervention for ESLD, ALF and exception point indications such as HCC
- ▶ Liver has no dialysis available to replace its complex functions
- ▶ Prioritization for ESLD patients on waiting list with **MELD Na score** (INR, Bilirubin, Creatinine, Sodium)

How widespread is need for LT?

- Cirrhosis: insidious, develops over decades
- Liver is forgiving, has unique ability to regenerate
- Cirrhosis remains 12th leading cause of death for adults in U.S. (CDC)
- Death rate of nearly 9.2 cases per 100,000 persons (1.1% of total deaths)
- May grossly underestimate real impact of ESLD
- Does not include acute liver failure or other etiologies that may lead to the need for LT
- >80,000 LTs performed to date worldwide

Historical Perspective

- Initial LT techniques researched in dogs by Dr. Thomas Starzl before 1960s
- First human LT in 1963 in Denver
- First successful LT in 1967, with one-year survival
- 1970: Canada's first liver transplant occurs in Montreal
- 1976: Improved liver preservation techniques (5-8hrs)
- 1979 Development of cyclosporin
- Till then 1-year survival was 25%



History of Liver Transplantation

- 1980: Cyclosporin / prednisolone / azathioprine combination
- 1983: NIH establishes LT is to be clinically accepted as definitive treatment for ESLD (no longer experimental)
- 1987: University of Wisconsin Solution
- 1989: Development of Tacrolimus
- 1990s: Split liver transplantation
- 2000: New generation immunosuppressants (MMF)
- 2000 Live Liver donation (peds & adult recipients)

Current Outcomes of LT

- ▶ **Improved survival rates**
 - ▶ 96% at 1 year
 - ▶ 71% at 10 years
- ▶ **Success due to several advances**
 - ▶ New immunosuppressive agents
 - ▶ New preservation solutions
 - ▶ Improved surgical techniques
 - ▶ Early diagnosis and management of complications post-LT

Challenges in LT

- ▶ **Indications have expanded**
 - ▶ Growing demand for transplantable grafts
 - ▶ Dramatic organ shortage
- ▶ **Ongoing challenges**
 - ▶ Expansion of the donor pool
 - ▶ To minimize deaths on the wait list

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Trends in Canada: Liver Transplantation

Liver transplants by year, donor type, age group and re-transplants, Canada (excluding Quebec), 2009 to 2018

Number of transplants	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Pediatric: First graft, age 0-17, deceased donor	21	19	27	18	16	19	14	7	11	15	167
Pediatric: First graft, age 0-17, living donor	9	12	14	15	18	29	26	27	16	19	185
Pediatric: Re-transplants, age 0-17	7	6	4	3	3	1	5	1	5	1	36
Adult: First graft, age 18+, deceased donor	231	255	275	278	264	294	305	356	360	314	2,932
Adult: First graft, age 18+, living donor	47	49	48	63	50	58	54	44	43	48	504
Adult: Re-transplants, age 18+	26	16	19	25	28	23	27	39	29	33	265
Total: All ages	341	357	387	402	379	424	431	474	464	430	4,089
Source											
Canadian Organ Replacement Register, 2019, Canadian Institute for Health Information.											

Since 2006, the national deceased donation rate has risen from 14.1 to 18.2 donors per million population (dpmp) or 29 per cent

Outline: Liver Transplantation

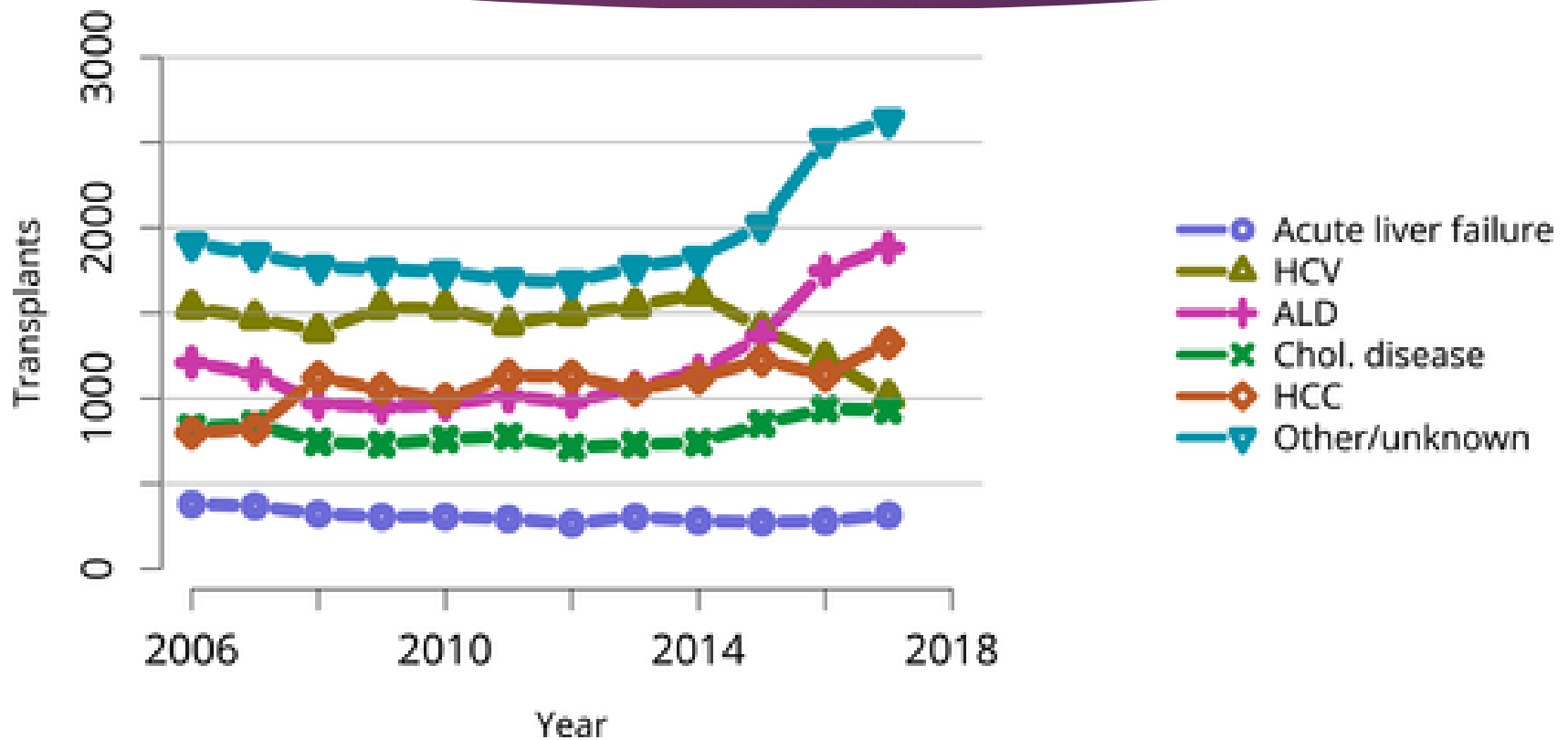
- ▶ Background & Historical Perspective
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Primary diagnosis* for LT, 2009 to 2018

Diagnosis	Age <1	Age 1-10	Age 11-17	Age 18-34	Age 35-59	Age 60+	Total
Primary biliary atresia	53.2	22.8	4.1	1.3	0.2	0.1	2.7
Hepatitis C	0	0	0	0.6	18.8	15.2	14.8
Hepatitis B	0	0	0	5.3	2.9	2.4	2.7
Other hepatitis	0.7	2.0	6.8	13.8	4.0	2.5	4.1
Alcoholic cirrhosis	0	0	0	3.1	17.2	15.8	14.3
Cryptogenic cirrhosis	0	0	2.7	2.5	1.9	2.0	1.9
Cancer	3.5	6.7	4.1	6.3	19.7	34.4	22.5
Metabolic disorders	9.9	22.1	13.7	7.2	2.0	1.3	3.3
Cholestatic liver disease	0.7	4.7	16.4	24.8	12.7	7.5	11.3
Unknown/missing	22.0	24.8	24.7	5.3	2.6	1.3	4.1
Other*	9.9	16.8	27.4	29.6	17.9	17.3	18.4
Total	100	100	100	100	100	100	100

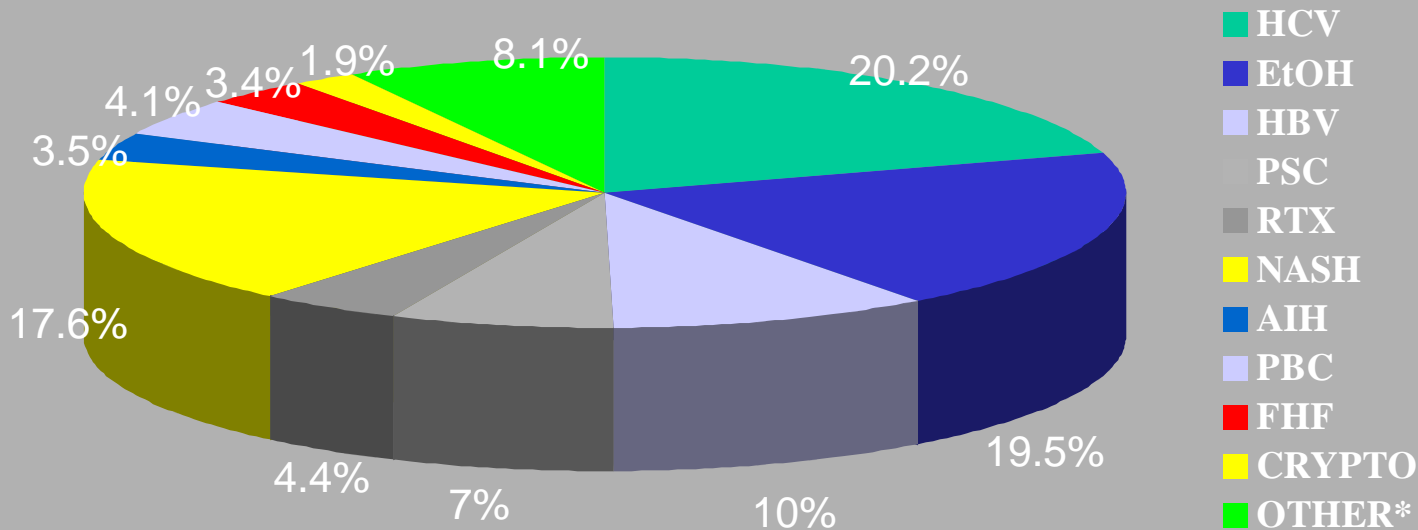
Canadian Organ Replacement Register, 2019,
Canadian Institute for Health Information.

Changing Trends in LT by diagnosis in the U.S.



Indications for Liver Transplant

UHN – 2015 - 2019



HCC (n=374; 40%) listed according to underlying liver diagnosis

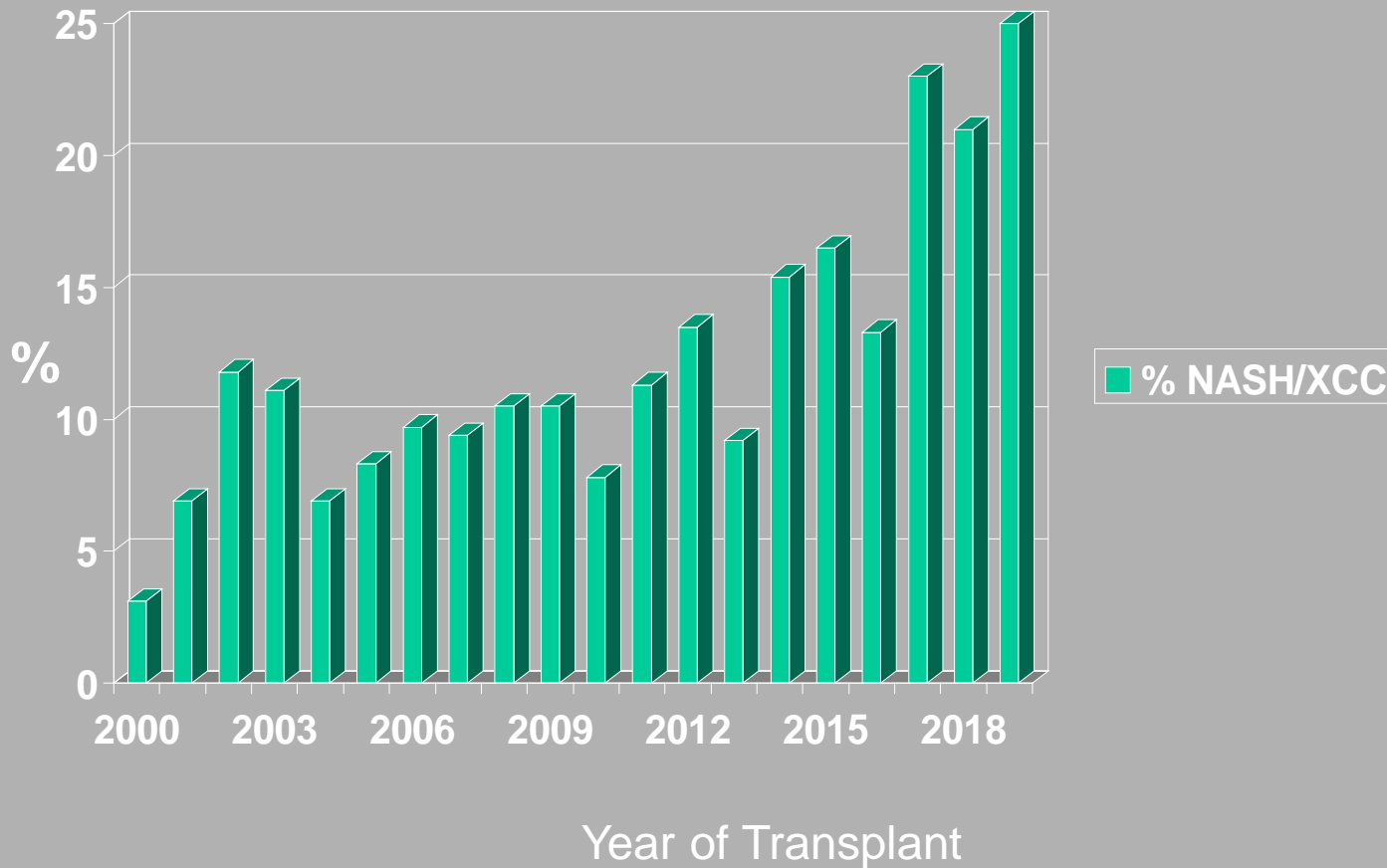
N = 931

* Other: TPN, AATD, BCS, Wilsons, PCLD, CF, Alagille, GranHep, FAP, et al.

- 288 patients waiting for LT in Ontario as of Jan 19th, 2020
- UHN 202 adult LTs in 2019, 27 pediatric

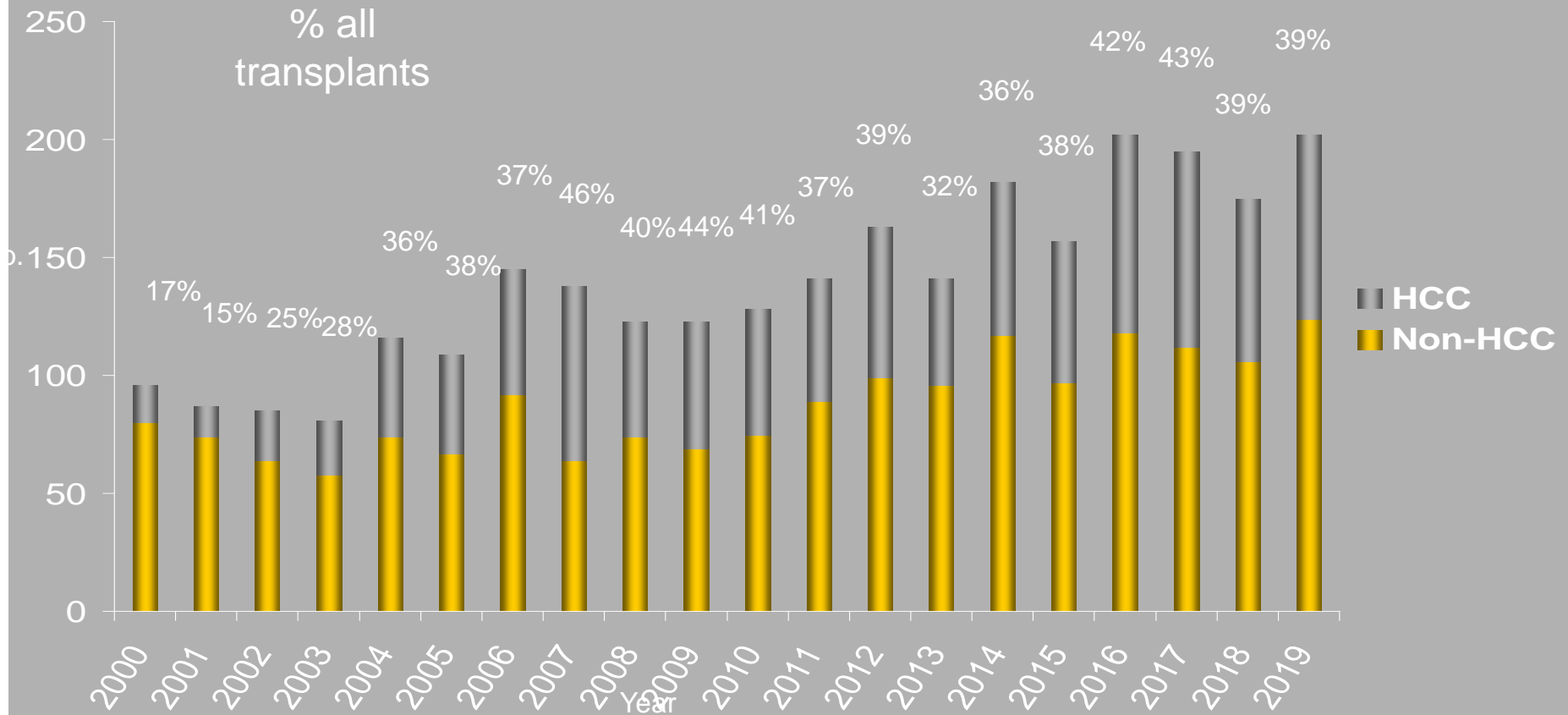
NASH has become a top indication

UHN 2000 – 2019



OLT for HCC*

UHN, 2000 – 2019



1040 transplants with HCC

*includes incidental HCC's

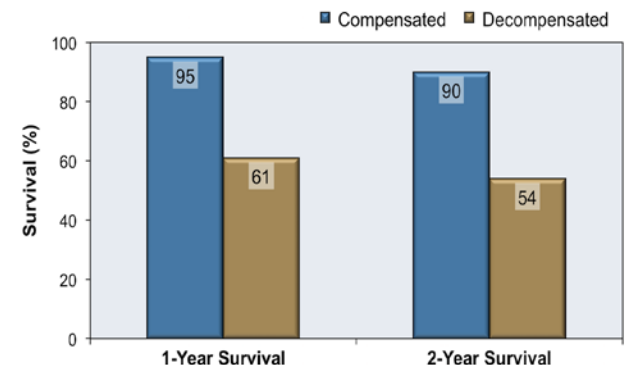
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When to Refer

- ▶ Once index complication such as ascites, hepatic encephalopathy, or variceal hemorrhage results in MELD Na Score ≥ 15
- ▶ **LT should be considered** in any patient with ESLD, in whom:
 - ▶ LT would extend life beyond that predicted by natural history of underlying liver disease
 - ▶ Expected survival without LT is ≤ 1 year
 - ▶ LT is likely to improve QoL

Survival in Patients with Compensated versus Decompensated Cirrhosis



Exception Point Indications

- ▶ MELD does not reflect the impact of all complications
 - ▶ **MELD exceptions**
 - ▶ Extra points given to prioritize for LT
 - ▶ HCC is most common

Exception Points

- ▶ Multi-organ clusters
 - ▶ Liver/heart, liver/lung, Liver/SB, liver/kidney, liver/pancreas
- ▶ Exception diseases
 - ▶ Cystic fibrosis, Failed LD/DCD (biliary or vascular complications)
 - ▶ FAP, Metabolic disorders, Polycystic liver disease
 - ▶ PSC (>2 episodes of cholangitis in 6/12)
 - ▶ Severe HPS (PaO₂<60)
 - ▶ Cholangiocarcinoma (within Mayo protocol)
- ▶ Hepatocellular carcinoma

Liver transplantation for HCC

Exception Points

- ▶ Single HCC $\geq 2\text{cm}$
- ▶ Multiple HCC $\geq 1\text{cm}$
- ▶ Single HCC $>1\text{cm}$ that cannot be treated with intent to cure therapy
- ▶ Any recurrent HCC $\geq 1\text{cm}$
- ▶ TTV $\leq 145\text{cm}^3$
- ▶ AFP < 1000
- ▶ No evidence of vascular invasion
- ▶ No cholangio features on histology

Emergency Indication: Acute Liver Failure

- **Acetaminophen-induced acute liver failure (two groups with poor px)**
- Arterial pH < 7.3 (taken by sampling of blood from an artery)
- All three of an INR of greater than 6.5, Cr greater than 300 micromoles per litre and HE (of grade III or IV).
- **Non-paracetamol acute liver failure¹**
- INR greater than 6.5; OR
- Three of the following five criteria:
 - Patient age of less than 11 or greater than 40;
 - Bilirubin greater than 300 micromoles per litre;
 - Time from onset of jaundice to coma > than 7 days;
 - INR greater than 3.5; or,
 - Drug toxicity, regardless of whether it was the cause of the acute liver failure

Transplant Evaluation Process

- ▶ All LT candidates require evaluation for comorbidities
 - ▶ Serologies
 - ▶ Echocardiogram
 - ▶ Cardiac Stress imaging
 - ▶ PFTs
 - ▶ Infections
 - ▶ Imaging for Anatomy
 - ▶ Age-appropriate Cancer Screening
 - ▶ Social assessment, psychiatric and addiction
 - ▶ Anesthesia
 - ▶ Frailty assessment
- ▶ There is no formal age limit
- ▶ LT has been performed successfully in patients >70 years
 - ▶ Increased risk of CV complications

Contraindications to LT

Severe cardiac or pulmonary disease

AIDS

Ongoing alcohol or illicit substance abuse

Hepatocellular carcinoma with metastatic spread

Uncontrolled sepsis

Anatomic abnormality that precludes liver transplantation

Intrahepatic Cholangiocarcinoma

Extrahepatic malignancy

Fulminant hepatic failure with sustained ICP >50 mm Hg or CPP <40 mm Hg*

Hemangiosarcoma

Persistent noncompliance

Lack of adequate social support system

Discussion at Listing meeting

- Multidisciplinary: hepatologists, surgeons, fellows, nurses, social worker, anesthesia, other disciplines by invitation
- Considering risks and benefits for individual patients
- Patients have increasing comorbidities (DM2, CAD, hx of stroke, hx of cancer, CKD, COPD)

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Timing of LT is crucial

- ▶ Not so early that benefits are outweighed by the risk of surgery and immunosuppression for life
- ▶ Before life-threatening complications occur such that too sick for transplant
- ▶ Frailty, particularly in Elderly patients
- ▶ Maintaining Independent ambulation and Nutrition

Allocation of Organs

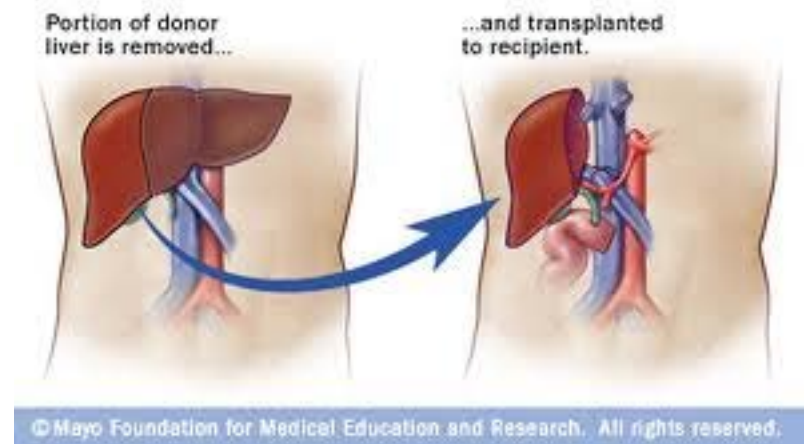
Status	Medical Criteria
4F	Imminent death; intubated and in fulminant hepatic failure (FHF): <ul style="list-style-type: none"> • meets King's College criteria for poor prognosis • includes acute M. Wilson, primary allograft failure i.e. allograft failure within 7 days of first transplant secondary to primary non function or hepatic artery thrombosis
3F	ICU admission for fulminant hepatic failure (FHF): <ul style="list-style-type: none"> • meets King's College criteria for poor prognosis • includes acute M. Wilson, primary allograft failure (i.e. allograft failure within 7 days of first transplant secondary to primary non function or hepatic artery thrombosis) OR Young paediatric candidate (current age ≤ 12) for liver bowel grafts that are hospitalized for related disease
SMC	Sodium MELD Calculation or PELD for paediatric patients (see <i>Appendix 4A</i> for formula)
Temporarily On Hold	Candidates on hold are not eligible for allocation of donor livers but accrue wait time

Allocation of Organs

- ▶ Blood Group (O to O, AB to AB etc)
- ▶ Recipient Criteria; Height, weight, BMI
- ▶ Split procedures at discretion of accepting surgeon
- ▶ **MELD-Na = MELD Score - Na - 0.025 x MELD x (140-Na) + 140**
- ▶ **MELD(i) = 0.957 × ln(Cr) + 0.378 × ln(bilirubin) + 1.120 × ln(INR) + 0.643**
- ▶ Equal SMC; patient longer on waiting list will get offer
- ▶ Exception points

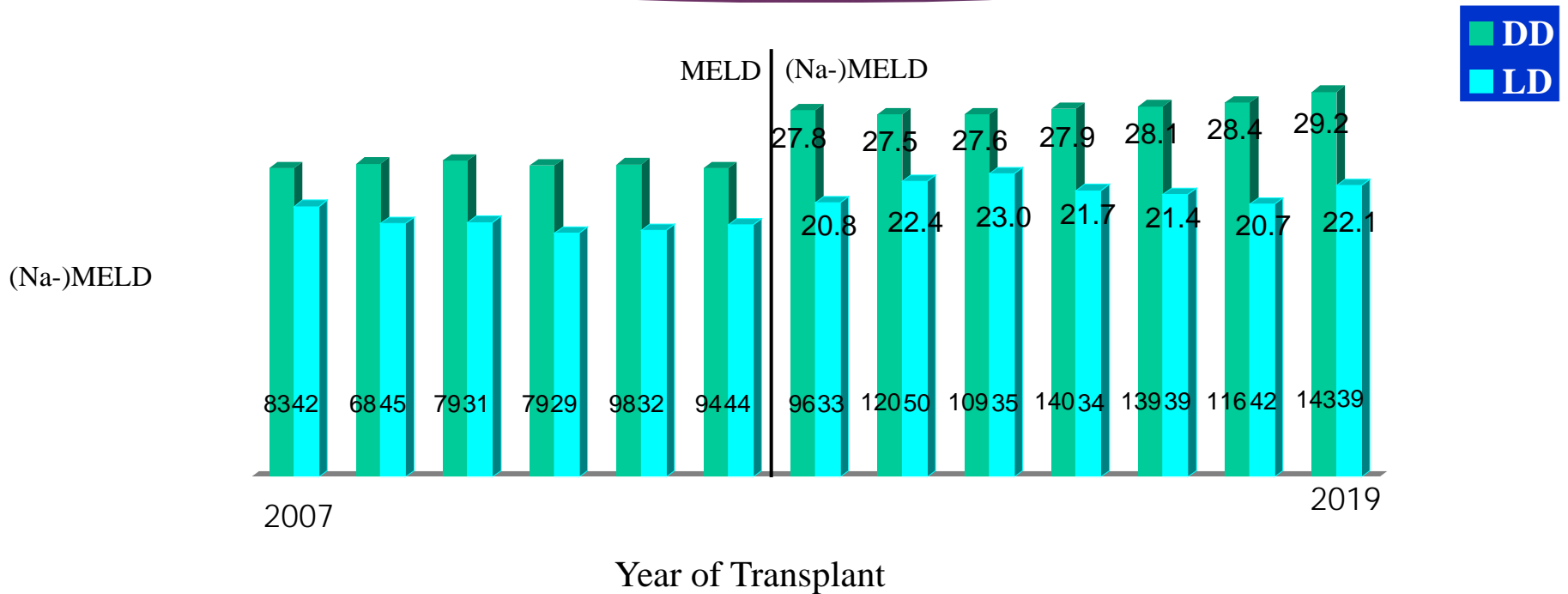
Living Donation

- ▶ Average MELD Na at which patients transplanted in Ontario: 29
- ▶ Prioritization depends on MELD Na, blood group, body habitus (height, weight)
- ▶ Living Donation discussed with all our patients in the Assessment Clinic
- ▶ Particularly helpful in groups whose disease isn't well reflected by MELD Na (women, PSC, HCC)
- ▶ Women disadvantaged due to Creatinine, height, body habitus
- ▶ Potential risks to Donor



MELD-Na Scores, LD vs DD

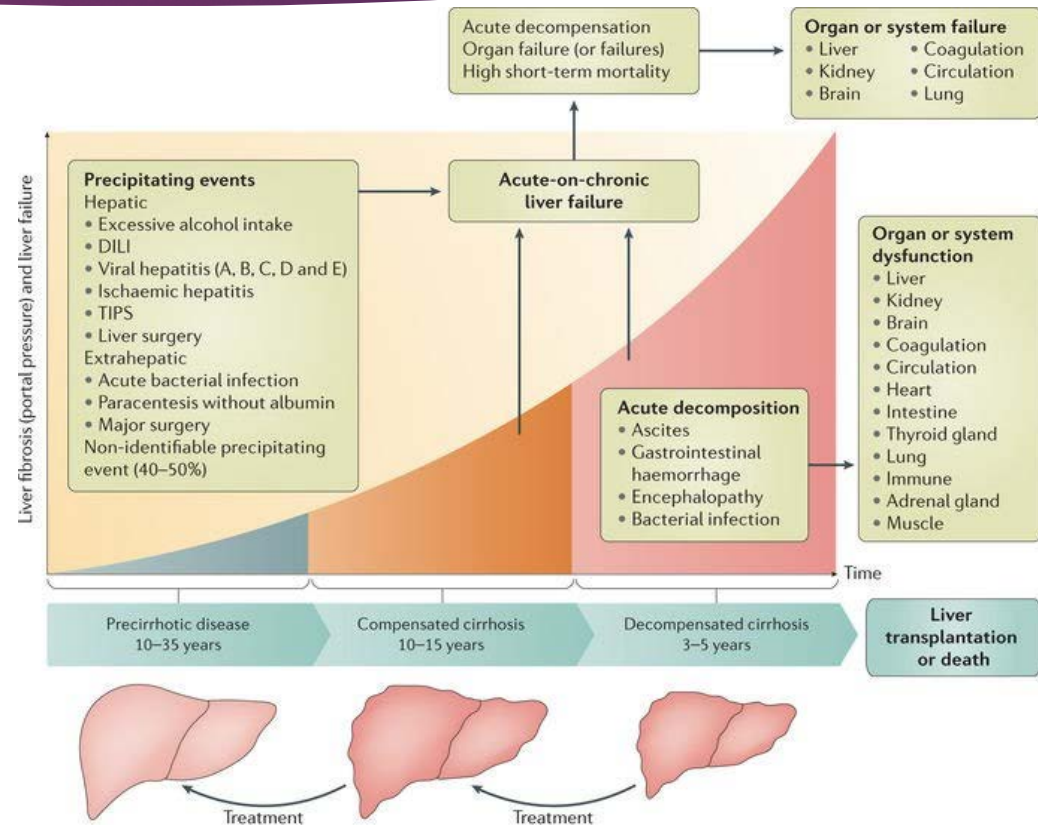
UHN 2007 – 2019*



First transplants only, no FHF, single organ only

Acute on Chronic Liver failure

- Acute decompensation of cirrhosis associated with organ failure and high short-term mortality (28-day mortality $\geq 15\%$)
- Can become “too sick for transplant”
- Tell Cirrhotic patients to present to medical attention as soon as any signs/symptoms of infection, worsened HE => treat infection early to prevent spiralling



Summary

- ▶ LT is a life-saving intervention for patients with ESLD, ALF and other indications
- ▶ Liver: the only organ for which there is no effective bridge to transplant
- ▶ NASH, ALD, HCC are top indications
- ▶ Always a question of risk versus benefit
- ▶ Significant mortality on waiting list
- ▶ Keeping patients alive on the waiting list and not too sick for LT
- ▶ Living Donation to be considered if possible, especially in women, PSC, HCC