SickKids | Transplant & Regenerative Medicine Centre

Long-Term Management of the Post-Liver Transplant Patient

Something for Everyone to Care About

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NASPGHAN 2015 Annual Meeting
Washington DC – Saturday, October 10, 2015

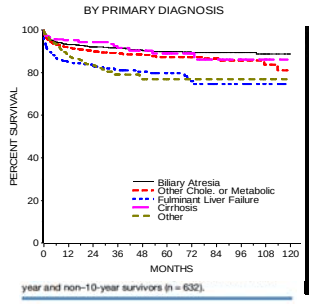
Disclosures

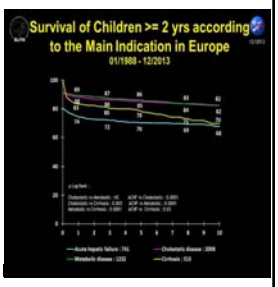
- I have no financial relationships with a commercial entity to disclose

Learning Objectives

- To provide a 2015 update on survival and health status achievable by pediatric liver transplantation
- To understand that long-term management of this patient population involves combined and integrated efforts
- To consider key gap opportunities available for focused strategies and new discoveries

Kaplan-Meier Probability of Patient Survival after Pediatric Liver Transplantation



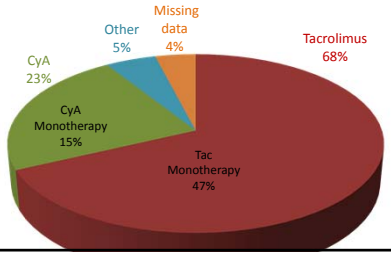


ORIGINAL ARTICLES

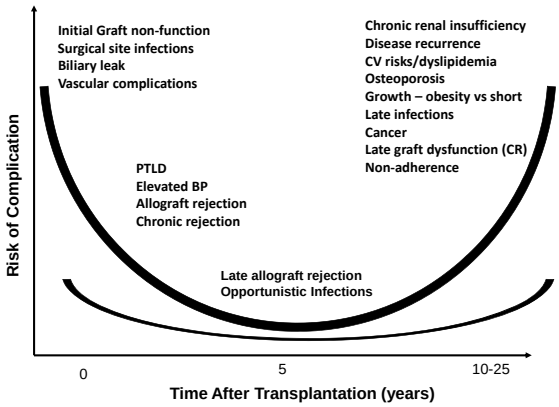
www.jpeds.com • The Journal of Pediatrics

Health Status of Children Alive 10 Years after Pediatric Liver Transplantation Performed in the US and Canada: Report of the Studies of Pediatric Liver Transplantation Experience

Vicky L. Ng, MD, FRCP(C)[1], Estella M. Alonso, MD[2], John C. Bucuvalas, MD[3], Geoff Cohen, PhD[4], Christine A. Limbers, PhD[5], James W. Varni, PhD[5], George Mazariegos, MD[7], John Magee, MD[8], Susan V. McDiarmid, MD[9], and Ravinder Anand, PhD[4], for the Studies of Pediatric Liver Transplantation (SPLIT) Research Group*



More Than Just About the Liver



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Medical Complications

- Renal insufficiency in 9.3%
- PTLD in 5%
- Overweight in 10%
- Hgt <10th percentile in 23%
- Hyperlipidemia in 25%
- Requiring insulin/anti-hyperglycemic medication in 10%

- PedsQL Total Scale Score >2 SD below mean score for healthy population in 14%

Case #1

11 year old female underwent living donor (Dad) liver transplantation at age 11 months for BA. Her post transplant course was remarkable for prolonged antibiotics for fever and ascites NYD, early allograft rejection, and challenges with feeding. She presently has excellent functional health, growing beautifully, AST, ALT and GGT <20 while on tacrolimus monotherapy with FK levels 2-3 ng/mL.

Patient and parents have zero concerns.
*Is she the **"ideal"** patient?*

"Ideal" Outcome Feasible or Futile?



"IDEAL" is defined as….

- existing only in the imagination; desirable or perfect but not likely to become a reality
  - synonyms: unattainable, unachievable, impracticable
- "satisfying one's conception of what is perfect; most suitable"
  - synonyms: perfect, best possible, excellent, flawless, faultless, exemplary, model, ultimate quintessential, picture-perfect
- exactly right for a particular situation or person

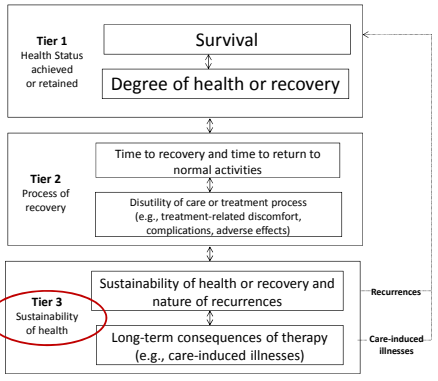
Oxford Advanced Learner's Dictionary (Language Matters) AND Merriam-Webster dictionary

"Ideal" life post transplant: How could/do we measure it?

- **Value**- defined as health outcomes per $ spent
  - not synonym for cost reduction
  - should reflect full cycle of care
  - requires tracking patient outcomes and costs longitudinally

From What is Value in Health Care? Michael E. Porter, MD NEJM 363:26 December 23, 2010

Outcome Measures Hierarchy



Q. What is the applicability in the pediatric LT patient population?

Potter NEJM 2010

Paradigm Shift: Composite Analysis Strategy Approach

Has evidence of a stable allograft

	Medical Variable (result at 10 yr visit)	#pts in which data available	Answering YES n(%) patients	Data missing n(%) pts
1	No Retransplantation	167	147(88%)	0
2	Chronic rejection-free	167	152 (91%)	0
3	Normal ALT	166	148(89%)	1(1%)
4	Normal TB	165	161 (98%)	2 (2%)
5	Normal Alb	162	160 (99%)	5 (3%)
6	Normal GGT	149	126 (85%)	18 (11%)

Has avoided Immunosuppression-Induced Co-Morbid Conditions AND avoided additional treatments

7	No PTLD	167	158 (94%)	0
8	No renal dysfunction	118	107 (91%)	49 (29%)
9	Normal growth (<-2SD)	121	112 (93%)	46 (27%)
10	No Diabetes	167	165 (99%)	0
11	No Prednisone use	167	135 (81%)	0
12	No anti-HT agent use	167	146 (87%)	0
13	No use of anti-Sz meds	167	167 (100%)	0

32% of SPLIT 10 y Survivors = IDEAL

OUTCOMES
10 years post LT

↓

COMORBIDITIES

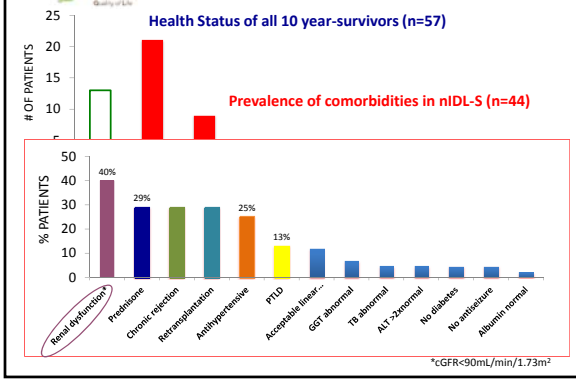
< 1/3 of the n=167 ten-year survivors enrolled in the SPLIT Registry met the requisition composite definition of "**Ideal 10-year survivor of pediatric LT**"

"Ideal 10-year Survivor after Pediatric Liver Transplantation"

1. No Retransplantation
2. No Chronic Rejection
3. Normal ALT
4. Normal Total Bilirubin
5. Normal Albumin
6. Normal GGT
7. No PTLD
8. No renal dysfunction
9. Linear growth ≥-2SD
10. No diabetes
10. No ongoing use of prednisone
11. No antihypertensive
12. No antiseizure

Ng et al. J Peds 2012

23% PeLTQL subjects = Ideal



*cGFR<90mL/min/1.73m²

Case #1

A patient who has achieved an "ideal outcome" – normal allograft health as defined by liver tests, absence of biliary or vascular changes (and normal histology) without immune or non-immune complications of IS medications with excellent functional health and effective self-management – achievable in 25-32% of patients.

Learning Objective #2

- To provide a 2015 update on survival and health status achievable by pediatric liver transplantation
- To understand that long-term management of this patient population involves combined and integrated efforts
- To consider key gap opportunities available for focused strategies and new discoveries

LIVER TRANSPLANTATION 19:798-825, 2013

SPECIAL ARTICLE

Long-Term Medical Management of the Pediatric Patient After Liver Transplantation: 2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

Routine Monitoring & Management *– Growth & Nutrition, Endocrine (bones), Psychosocial, Neurocognitive (and HRQOL) monitoring, Adherence*
Graft surveillance *– late surgical complications (HAT, PVT, IVC/HV), late biliary strictures, protocol liver biopsies*
General *– skin cancer surveillance, safe living*
Immunosuppression *– ACR, CR, A/E's, iWITH*
Disease - specific issues *– recurrent ds, CFLD*
Late infections *– viral, PCP, PTLD*
Adolescent Health *– STD, menstrual anomalies, OCP, Pregnancy, non-adherence, risk behaviours*
Transition *– self-management components*

Case #2

6 year old boy with missed BA, s/p DD (whole) LT age 8 months.

- IS treatment with CyA, prednisone and azathioprine. Early post-operative course was complicated by persistent elevated LFTs, concerns with HA flow, no rejection or infection.
- Age 4 years - switched to Tacrolimus for AST, ALT, GGT in mid 100-200's. CB 0, INR normal, Alb normal. Plts > 300. Told to remain on steroids.
- Age 5 years – clinical onset of pruritus and jaundice → U/S and diagnostic PTC revealed multiple intrahepatic duct dilatations, and anastomotic stricture. IR intervention – guidewire unsuccessful, external drain left in – lots of admissions, refractory pruritus.
- Age 6 years - referred for 2nd opinion.

Case #2

- Meds – FK 0.6 mg BID, Pred 5 mg po QD, amlodipine multi-vitamin, iron, ASA.
- O/E – wgt and hgt .both <<3rd percentile, BMI 18 (50th). Non-jaundiced but pale. BP 120/80. Pruritic. Abdo exam – firm liver with palpable spleen 3 cm. No ascites.
- Labs – AST 354, ALT 288, GGT 362, plts 268. CB, Alb, INR normal. Hb 92, MCV 62?

Q. Parents ask about - growth, anemia, BP, biliary complications, graft life, QOL after liver transplant, graft life?

American Journal of Transplantation 2009; 9: 1389–1397
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02634.x

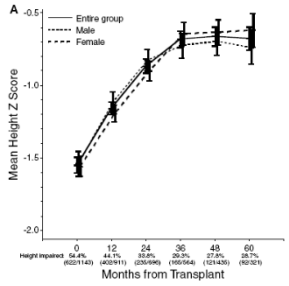
Linear Growth Patterns in Prepubertal Children Following Liver Transplantation

1143 pts

E. M. Alonso[a,*], R. Shepherd[b], K. L. Martz[c], W. Yin[c], R. Anand[c] and the SPLIT Research Group

Catch-up growth patterns of children who undergo LT is incomplete

MVA suggests that some risk factors are modifiable – including pre-LT nutritional status, duration of steroid use post-LT, graft function (lower TB and GGT levels at 12 months post LT)



ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

Long-Term Linear Growth and Puberty in Pediatric Liver Transplant Recipients

892 pts

Saeed Mohammad, MD[1], Adda Grimberg, MD[2], Elizabeth Rand, MD[2], Ravinder Anand, PhD[3], Wanrong Yin, MS[3], and Estella M. Alonso, MD[1], on behalf of the Studies of Pediatric Liver Transplantation (SPLIT) Research Consortium*

- Linear growth impairment (20%)
- Delayed puberty (39% girls, 42% boys ages 16-18 years were not yet Tanner 5)
- Independent predictors of growth impairment included:
  - impaired growth at time of LTx (OR 11.53, p<=0.001), re-transplantation (OR 4.37, p=0.991), non-white race and primary diagnosis other than BA.

Pediatr Transplantation 2012: 16: 137–141

Pediatric Transplantation

Risk factors for chronic anemia in pediatric orthotopic liver transplantation: Analysis of data from the SPLIT registry

1026 pts

Liem RI, Anand R, Yin W, Alonso EM. Risk factors for chronic anemia in pediatric orthotopic liver transplantation: Analysis of data from the SPLIT registry. Pediatr Transplantation 2012: 16: 137–143. © 2011 John Wiley & Sons A/S.

R. I. Liem[1], R. Anand[2], W. Yin[2] and E. M. Alonso[1]

[1]Division of Hematology, Oncology & Stem Cell Transplant, Children's Memorial Hospital, Department of Pediatrics, Northwestern University

- **Chronic anemia was common in children following LT → 242/1026 (24%)**
- **MVA identified use of cyclosporine, steroid use, GI bleeding, presence of leukopenia, and renal insufficiency (cGFR<90 mL/min/1.73 m2) = independent risk factors associated with chronic anemia**
- **Screening and attention to chronic anemia important – impact on growth and development, overall graft health, as well as important outcome measures including QOL and physical function**

Accepted for publication 1 November 2011

American Journal of Transplantation 2012; 12: 193–199
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03772.x

Blood Pressure Elevation in Long-Term Survivors of Pediatric Liver Transplantation

815 pts

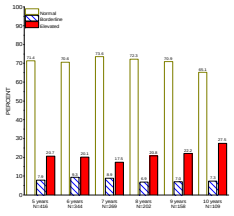
V. A. McLin[a,b,*], R. Anand[c], S. R. Daniels[d], W. Yin[e], E. M. Alonso[e] and the SPLIT Research Group

Pediatric liver transplantation (LT) has transformed the prognosis of children with acute or chronic liver disease. It is now the therapeutic modality of choice in children with end-stage liver disease and excellent long-term survival

The prevalence of elevated BP measurements in 5-10 yr LTx survivors - 17% to 28%

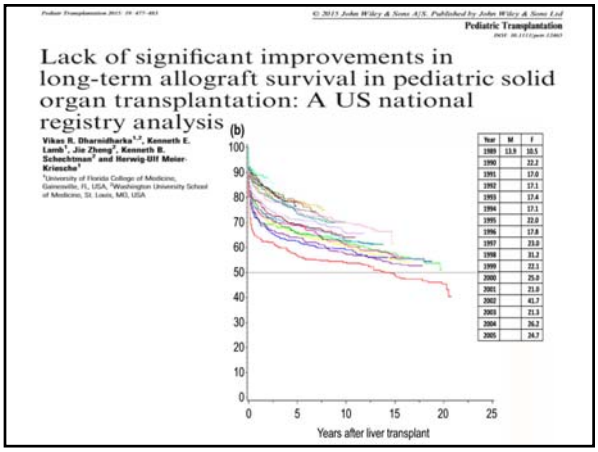
How can Pediatric Health Care Teams Help?

- **Check BP with any encounter**
- **Evaluate for cardiovascular risk factors**



Biliary complications

	Country	Year	N	# (%) BC	Graft type	Risk factors
Laurence 2015	Toronto	2001-2011	173	29(17%)	75 LRD, 98 DD	Duct-to-duct
Darius 2014	Belgium	1993-2010	429	98 (23%)	203 LRD, 226 DD	HAT ACR
Feier 2014	Brazil	1995-2012	489	71 (15%)	All DD	
Luthold 2014	Geneva	1990-2011	116	29 (24%)	All DD	OR duration, early HAT, D2D, donor age



Mental Health Issues – Focus Moving Forward

		nIDL-S	n	IDL-S	n	p value
DEPRESSION	CDI-S[1] score	2.2 ± 3.3	44	3 ± 4.3	13	0.62
	score ≥ cut off for depression (n, %)	5 (11%)		2 (15%)		>0.9

[1]Children Depression Inventory Short Form (10 items)

ANXIETY	SCARED[2] score	17.2 ± 13.4	44	25.1 ± 13.8	12	0.11
	score ≥ cut off for anxiety (n, %)	12 (27%)		6 (50%)		0.3

[2]Screen for Child Anxiety Related Disorders (41 items)

5

c/w 5-17% incidence of **anxiety** in general population

Slide 27

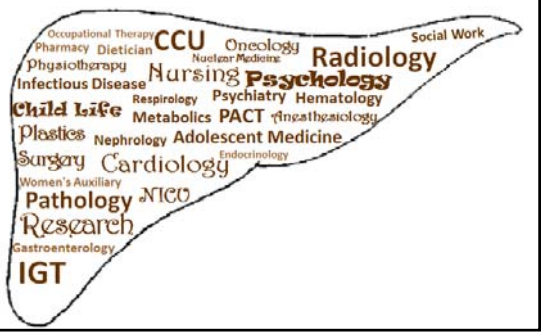
5 ASk Amy for analysis
Mar Miserachs, 4/28/2015

6 Should we inclupe parents results?? I am not sure we have them, need to look at PeLTQL database
Mar Miserachs, 4/28/2015

Case #2

- Patient seen by Liver Transplant multi-disciplinary team members plus various consultants.
- Re-reviewed all films
- Interventional radiology
- Currently – with internal-external drain, no longer pruritic, stools pigmented, "his eyes are whiter than mine". CB 0, GGT from 338 to 258, INR and Alb normal, plts continue to be normal.
- Parents advised will need re-LT in future

It takes a village to raise a child……..



Learning Objective #3

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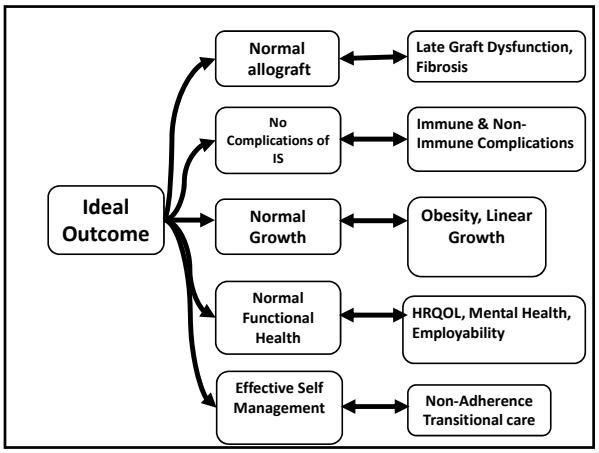

Key Drivers over the Full Cycle of Care

- Patient Selection
- Pre-Transplant Considerations
- Organ Allocation
- Donor Selection
- Peri-Transplant Challenges
- Short-Term Outcomes
- Long-Term and Longer-Term Outcomes

Current active efforts:

1) Understanding long term graft dysfunction – DSA, protocol liver biopsies
2) Biliary complications – diagnostic and treatment subgroups
3) Infectious Disease – CMV, immunization practices
4) Ideal Outcomes – heat map analyses

Summary and Take-Home Messages

- Multiple outcomes collectively define success of pediatric LT
  - Composite Outcome inclusive of sustainability of health – both for the **allograft** (maximizing longevity) AND for the **patient** (minimizing immunosuppression-induced comorbidities and its treatment effects)
  - Definition of "ideal" Tiers 1, 2 and 3 outcomes may be further refined – histopathology, clinical event and biochemical markers
- Still LOTS to do - collaborative opportunities
  - Longitudinal tracking as the cohort ages - standardization of follow-up, innovative ways (web-based etc)
  - Well-designed interventional clinical trials, Comparative Effectiveness research initiatives, etc

Standardization of follow-up

"If you hadn't done those tests to find out what's wrong with me, *I'd still be healthy!*"

"You have a rare condition called 'good health'. Frankly, I'm not sure how to treat it."

Acknowledgments

- Studies of Pediatric Liver Transplantation (SPLIT)
  - EMMES
  - All SPLIT coordinators and PIs
- Pediatric Liver Transplant Quality of Life (PeLTQL) Research Group
- Patients and families
- The “Teams”

Thank you for your attention!

QUESTIONS?

Slide 37

1 Vicky Ng, 11/15/2012

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Pediatric Transplantation

Post-transplant diabetes mellitus in pediatric liver transplantation 1611 pts

Eba Hathout[1], Estella Alonso[2], Ravinder Anand[3], Karen Martz[3], Essam Inseis[4], Joyce Johnston[1], James Lopez[5], Richard Chinnock[1], and Sue McDiarmid[6] on behalf of the SPLIT study group*

- Glucose intolerance or post-transplant diabetes was found in 214 (13%) patients, of whom 166 (78%) were diagnosed within 30 days of transplantation (early GI/PTDM)
- Multivariate analyses - age >5 yr at transplant, hospitalization at transplant, a primary diagnosis other than BA, early steroid use, and tacrolimus use are associated with increased incidence of early glucose intolerance

Routine monitoring for the development of glucose intolerance and post-transplant diabetes is indicated in the short- and long-term care of children following LTx

LIVER TRANSPLANTATION 16:1041-1048, 2010

ORIGINAL ARTICLE

School Outcomes in Children Registered in the Studies for Pediatric Liver Transplant (SPLIT) Consortium

Susan M. Gilmour,[1] Lisa G. Sorensen,[2] Ravinder Anand,[3] Wanrong Yin,[3] and Estella M. Alonso,[4] on behalf of the SPLIT Research Consortium

- Survey study – 823 SPLIT participants
- 33% of patients missed >10 days of school per year
- 34% of participants were receiving special education services
- 20% participants repeated a grade level
- Parents reported a diagnosis of learning disorder made previously in 17% of patients.

LIVER TRANSPLANTATION 19:730-740, 2013

ORIGINAL ARTICLE

Decreasing Incidence of Symptomatic Epstein-Barr Virus Disease and Posttransplant Lymphoproliferative Disorder in Pediatric Liver Transplant Recipients: Report of the Studies of Pediatric Liver Transplantation Experience 2283 pts

Michael R. Narkewicz,[1,2] Michael Green,[3,4,5] Stephen Dunn,[6,7] Michael Millis,[8] Susan McDiarmid,[9,10,11] George Mazariegos,[12,13] Ravinder Anand,[12] and Wanrong Yin,[12] for the Studies of Pediatric Liver Transplantation Research Group

PTLD developed in 2% of patients by 12 months post-transplant, and 3.6% by 5 years

Outcomes of PTLD include: Death = 8/78 (10.3%) and Graft loss = 10/78 (12.8%)

How can Pediatricians/Health care provider teams help?

- **Every visit by a LTx survivor to a primary care provider represents an opportunity for surveillance for malignancy/PTLD**
- **Know the signs and symptoms of PTLD**
  - **Common sites – lymphoid (adenotonsillar) tissues, GIT, lung and liver**
  - **Can be insidious and non-specific – ie. fever (episodic/unexplained), weight loss, fatigue etc before developing more significant symptomatology → high index of suspicion**
  - **May present as constitutional symptoms, lymphadenopathy, new onset snoring/mouth-breathing, Vx/Dx, new onset anemia or hypoalbuminemia**

ORIGINAL ARTICLE: HEPATOLOGY AND NUTRITION

Obesity After Pediatric Liver Transplantation: Prevalence and Risk Factors

1706 pts

*Shikha S. Sundaram, †Estella M. Alonso, ‡Phil Zeitler, §Wanron Yin, and §Ravinder Anand, on Behalf of the SPLIT Research Group

- Prevalence of obesity at 1 year was 19%, and at 3 years was 18%
- MVA – Hispanic ethnicity, prolonged steroid use, overweight and obesity at time of LT

How can Health Care Provider Teams help?

A need to broaden standard care to include obesity assessment and intervention in routine pre- and post-LT care

to include obesity assessment and intervention in routine pre- and posttransplant care.

Key Words: liver transplant, obesity, pediatric, risk factors

(*JPGN* 2012;55: 657–662)

United States and characterize and determine risk factors for obesity in pediatric LT recipients.

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which prospect

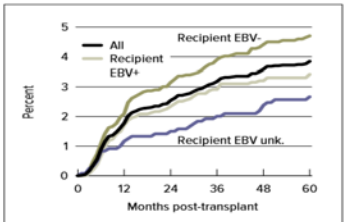
American Journal of Transplantation 2012; 12: 2301–2306
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.04204.x

Personal Viewpoint

Reducing Pediatric Liver Transplant Complications: A Potential Roadmap for Transplant Quality Improvement Initiatives Within North America

M. J. Englesbe[a,*], B. Kelly[b], J. Goss[c], A. Fecteau[d], J. Mitchell[e], W. Andrews[f], G. Krapohl[g], J. C. Magee[e], G. Mazariegos[d], S. Horslen[h] and J. Bucuvalas[i]



LI 7.14 **Incidence of PTLD among pediatric patients receiving a liver transplant, 2000–2010, by recipient Epstein-Barr virus (EBV) status at transplant**

The cumulative incidence is estimated using Kaplan-Meier competing risks methods. PTLD is identified as either a reported complication or cause of death on the Transplant Recipient Follow-up form or on the Post-transplant Malignancy form as polymorphic PTLD, monomorphic PTLD, or Hodgkin's Disease. Only the earliest date of PTLD diagnosis is considered.