Why so few Pediatric PH patients referred for Lung Transplantation?

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Overview

- Setting the Stage
  - PAH survival and quality of life 2019
  - Death risk for PH and Prevalence of Lung Txp
- Pediatric PH as a substrate for Lung Transplantation
- Assessing Individual Patient with PH
- Consideration for early referral
- Know your Transplant Centers
- Transparency and Eschewing Paternalism

The Dimension of Pediatric PH deaths

- Pulm Circ 2015; 10792 *PH hospitalizations* in US Children's Hospitals in 2009 with 4.5% mortality or 485 deaths with diagnosis of PH
- Pulm Circ 2017; 14880 hospitalizations of PH patients *admitted to PICUs* in 153 hospitals over seven years with mortality of 6.8% = 144 deaths per year; 10% with idiopathic PAH
- These databases underestimate national totals
- PH diagnosis as % of pediatric hospital admissions increasing over time

Increasing Prevalence of Pediatric PH – Hospital Admissions

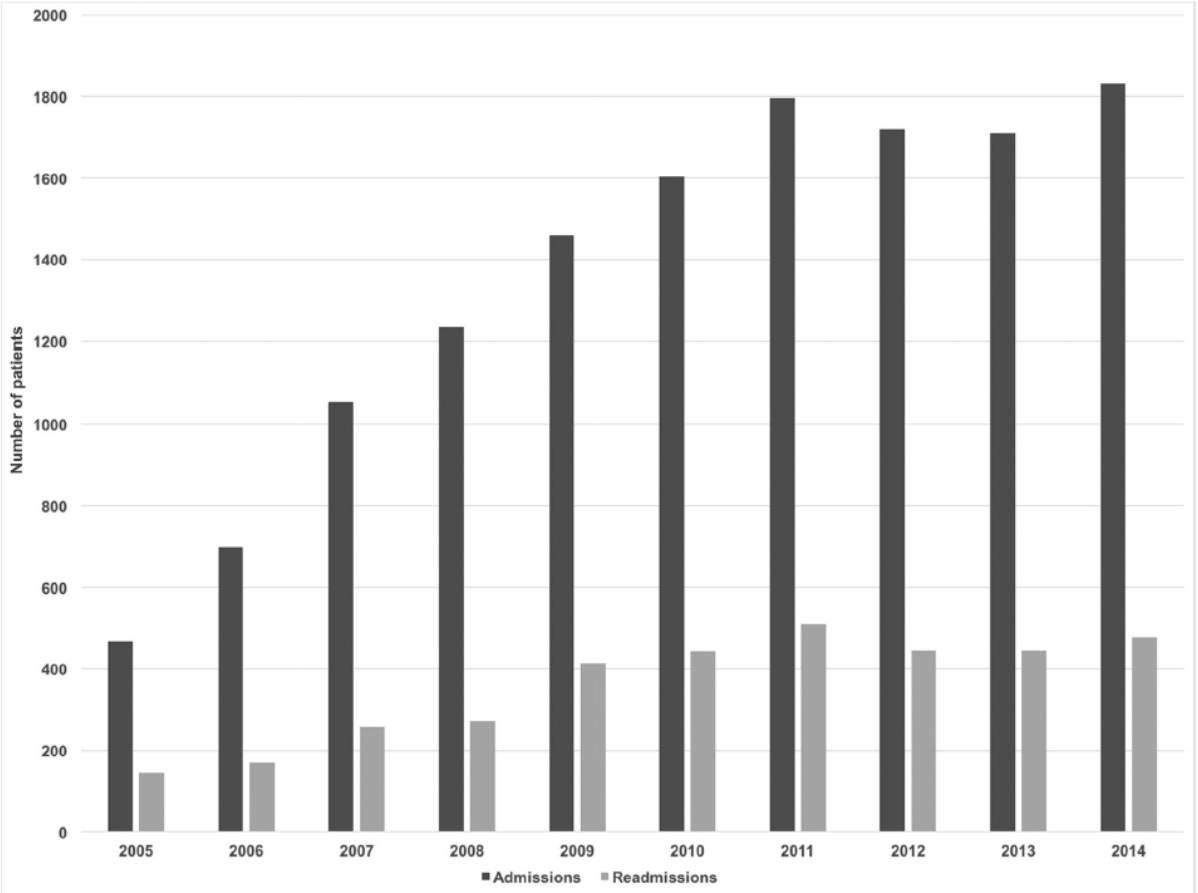

Figure 3. Total hospital admissions and readmissions.

Awerbach et al, J Pediatrics 2018

Pediatric PH Clinical Care in 2013

- Challenge of timely diagnosis
- Clinical experience and published guidelines inform but cannot reliably prognosticate
- Therapeutic options have led to understandable clinical optimism
- Life rescuing therapies – Potts Shunt and Lung Transplantation – not urgently available therapies

Challenges of Pediatric PH for TXP

- Van Loon and Berger, 2009: commonly associated with co-morbidities and syndromes
- Beghetti, 2011: CHD-associated PH carries anatomic issues and previous surgery
- Lammers 2011: functional class is a huge challenge across childhood; comparability across age ranges?

Experience with Lung Txp for Pediatric PH

- 23 recipients from 25 centers between 1996 and 2006
- 19/23 on epoprostenol, 14 in WHO FC IV, 6 in WHO FC III, 2 on ECMO
- Median time on vent 9 days, time in ICU 11 days, hospital 30 days
- 91% survival at 6 mos
- Median survival was 45 months

Schaellibaum, Pediatr Pulmonol, 2011

Pediatric Lung Transplants

Diagnosis by Age Group (Transplants: 2000 - 2017

Diagnosis	< 1		1-5		6-10		11-17	
Cystic Fibrosis	0		4	3.4%	125	51.0%	859	66.3%
Non CF-bronchiectasis	0		0		2	0.8%	25	1.9%
ILD	5	7.9%	8	6.8%	6	2.4%	39	3.0%
ILD Other Specify Cause	7	11.1%	9	7.7%	22	9.0%	50	3.9%
IPAH	9	14.3%	33	28.2%	25	10.2%	111	8.6%
PH-not IPAH	15	23.8%	26	22.2%	10	4.1%	27	2.1%
Obliterative Bronchiolitis (non-Retransplant)	0		10	8.5%	26	10.6%	64	4.9%
Bronchopulmonary Dysplasia	4	6.3%	4	3.4%	3	1.2%	3	0.2%
ABCA3 Transporter Mutation	5	7.9%	5	4.3%	2	0.8%	1	0.1%
Surfactant Protein B Deficiency	13	20.6%	4	3.4%	1	0.4%	0	
Surfactant Protein C Mutation	0		1	0.9%	0		1	0.1%
Retransplant (Obliterative Bronchiolitis)	0		4	3.4%	8	3.3%	40	3.1%
Retransplant (not Obliterative Bronchiolitis)	0		5	4.3%	7	2.9%	45	3.5%
COPD, with or without A1ATD	2	3.2%	1	0.9%	3	1.2%	11	0.8%
				2.6%	5	2.0%	20	1.5%

Analysis includes deceased and living donor transplants.

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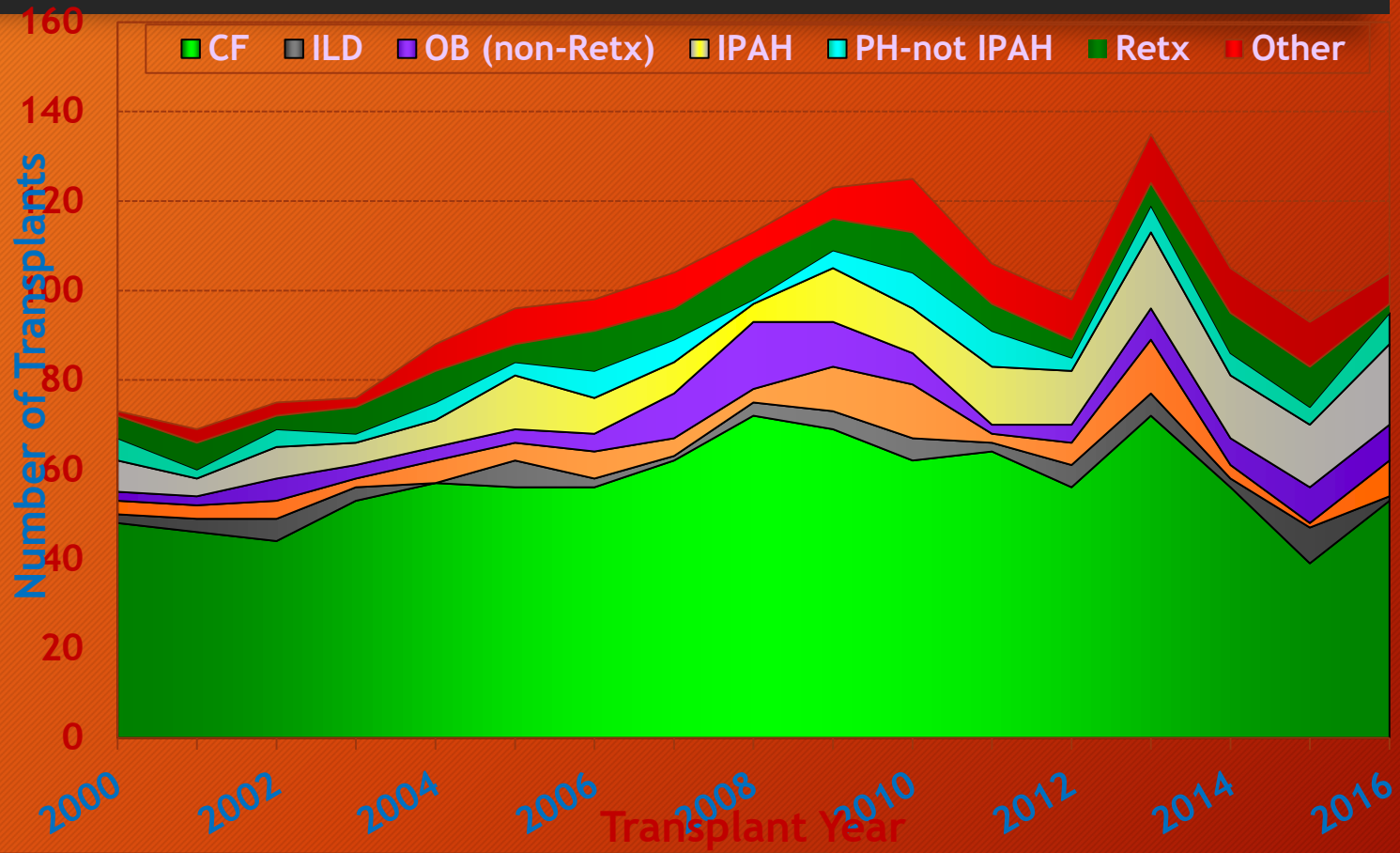
Pediatric Lung Transplants Diagnosis by Year



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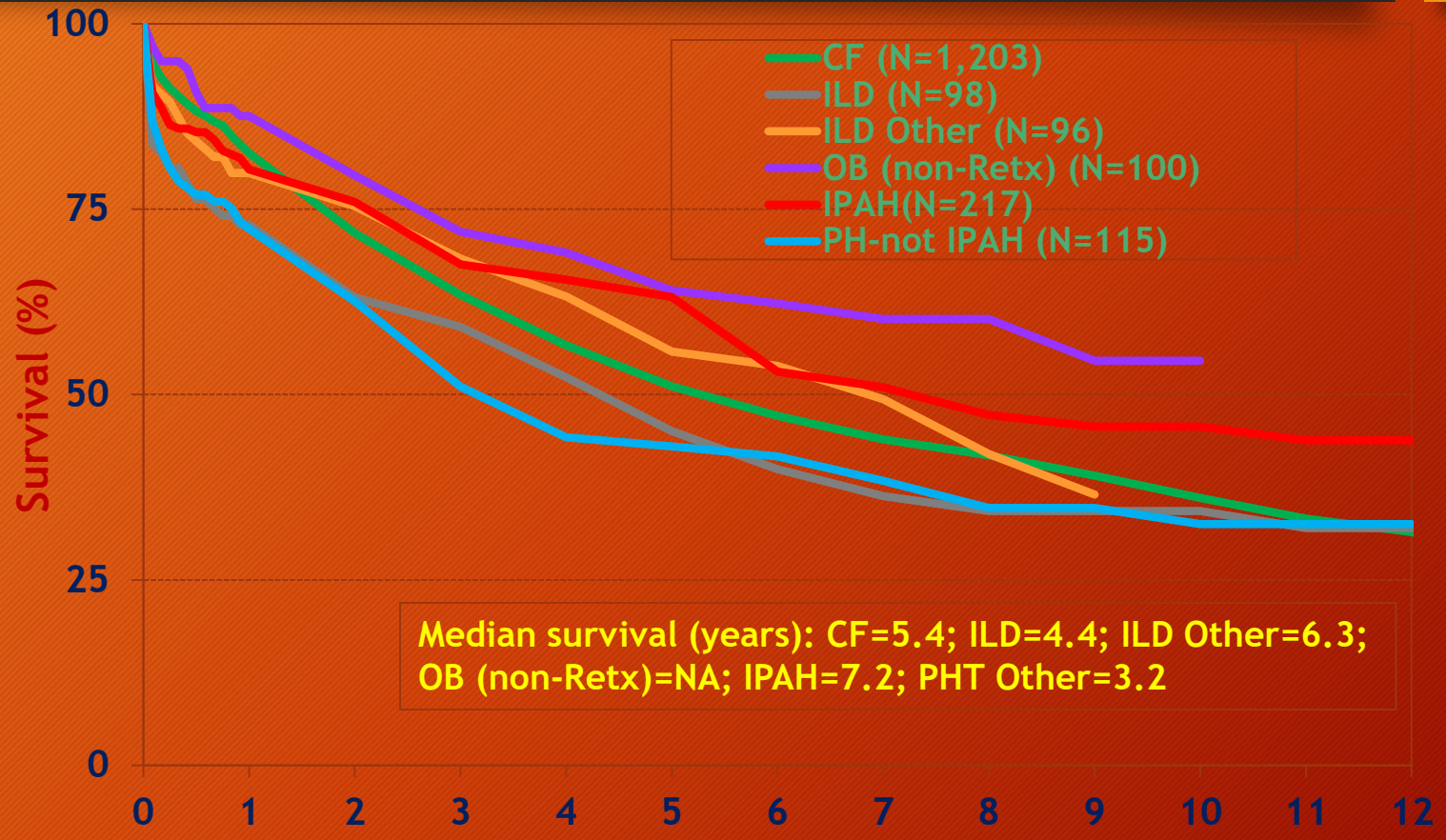
Pediatric Lung Transplants Survival by Diagnosis

(Transplants: January 1990 - June 2016)



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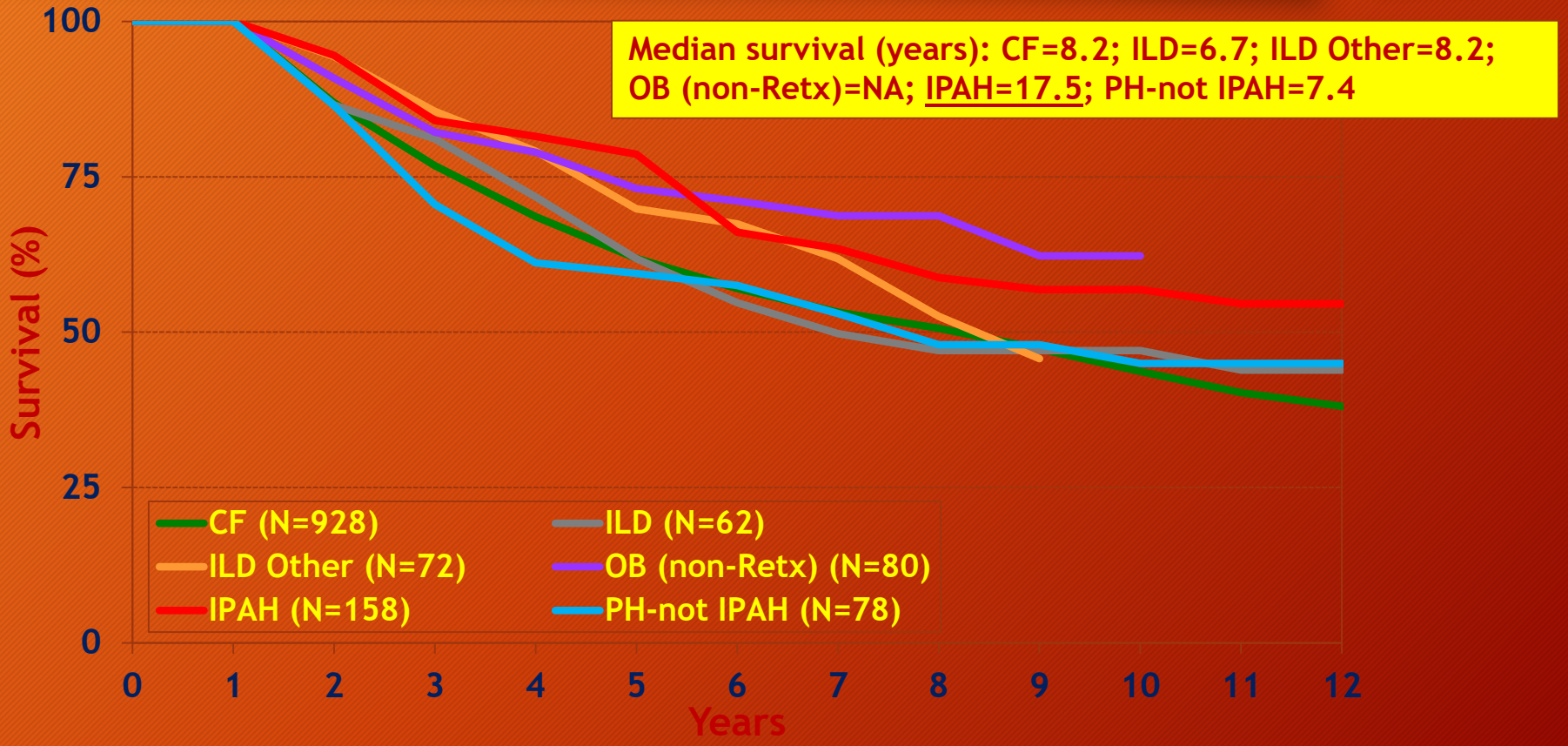
Pediatric Lung Transplants
Conditional Survival by Diagnosis
(Transplants: 1990 - 2016)



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Assessing the Individual Pediatric Patient with PAH for Lung TXP

- Prognostication from the onset
  - Pulmonary vein stenosis when progressive poor prognosis; note sutureless technique complicates lung transplant surgery
  - Pulmonary veno-occlusive disease
  - Severe RV failure at diagnosis
- The family of every newly diagnosed child with IPAH should know therapeutic options –pharmacotherapy, Potts Shunt and lung transplantation

Initial Education of Child and Family with PH

- Indication for lung transplantation = worsening disease despite maximal medical therapy; QOL is key factor
- Potts shunt ameliorates, does not cure PH but can be scheduled (in theory)
- Lung transplant cures, cannot be scheduled
- Contraindications: HLA sensitization with RV conduit, homografts and blood transfusions, pulmonary atresia with MAPCAs
- Adequate familial resources, including insurance

Severe RV Failure at diagnosis

- High mortality
- Role of VA ECMO – usually a contraindication to TXP in most programs, destination therapy to rest right ventricle and institute therapy??
- Pulseless extracorporeal device with central cannulation
  - Pulmonary circulation largely circumvented
  - Patient can be ambulatory
  - Inherent danger of hemorrhage
- Consideration of VV ECMO with surgical ASD if RV improves with Rx

The PH Lung Transplant Candidate

- Medical therapy optimized = most patients on parenteral prostanoid and at least one oral agent with ongoing RV failure
- No other major co-morbidities
- Viable surgical approach
- Committed family support system
- A record of adherence to complex regimen

Child with Progressive PAH: The Trajectory of Disease

- Assessing RV function serially – multiple modalities
- Growth and development
- Exercise capacity
- Quality of life

Assessing Pediatric Lung Transplant Centers

- Patient volume, waiting list size and duration of wait, patients transplanted per year, deaths on the wait list, trustworthy PH clinicians caring for patient on the list, post-operative survival – much of this data publicly available in US
- Look at age range for recent center experience – most US centers avoid infant lung transplantation
- Encourage patient and family to consider conference call with transplant center

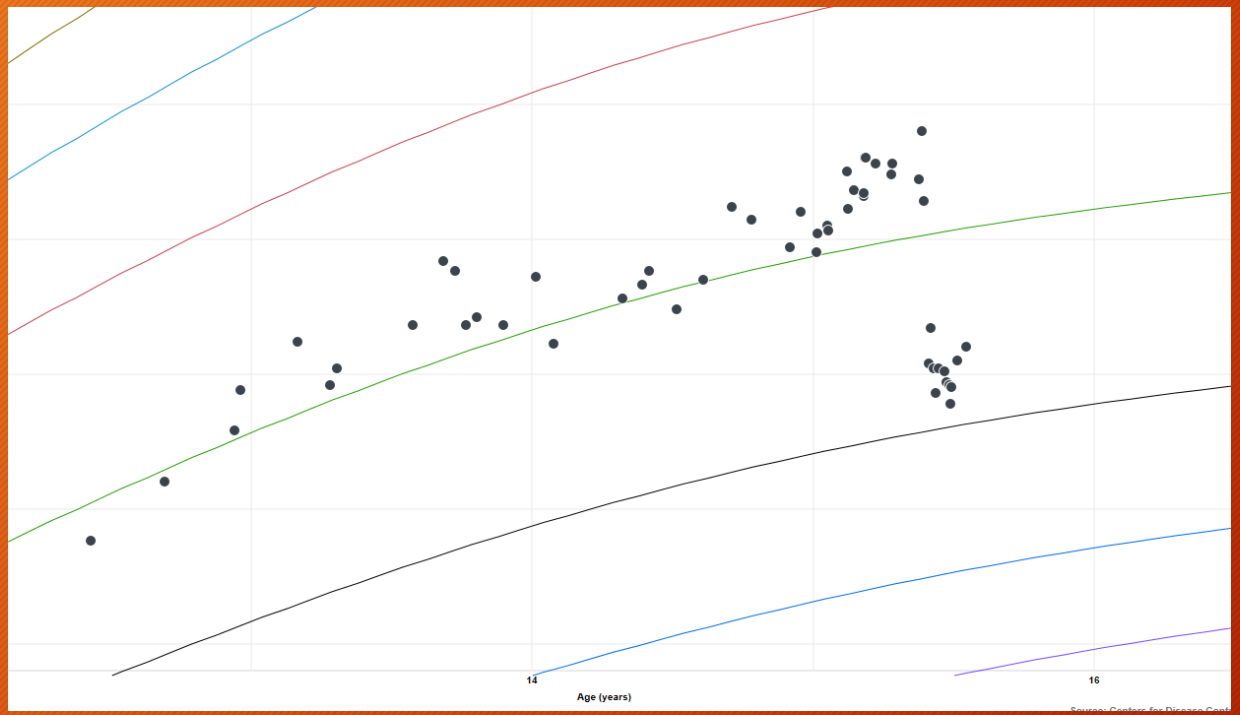
The Spectrum of Pediatric Lung Transplant Centers in USA

- Marked variation in recipient volume, waiting time, deaths on waiting list and interest in young transplant recipients
- +/- availabilty of local PH expertise
- Insurers may try to narrow family choice
- Geographic concerns may also narrow choice
- Variations in bridges to transplantation

Survival after Lung Transplant

- Survival has improved over time but remains significantly below achievements in other organs
- Early mortality largely related to LV and RV dysfunction, dynamic RVOT obstruction, fluid balance and cardiotonic medications
- Biology of the transplanted lung remains daunting in terms of rejection and infection
- Easy for physicians to underestimate parental valuation of the dream of conquering a child's disease and the value of a few years of health

Dramatic weight loss after Transplantation in an adolescent with PH



No clinical edema at time of TXP, transient interference with nutritional intake. Loss of >8.2 Kg

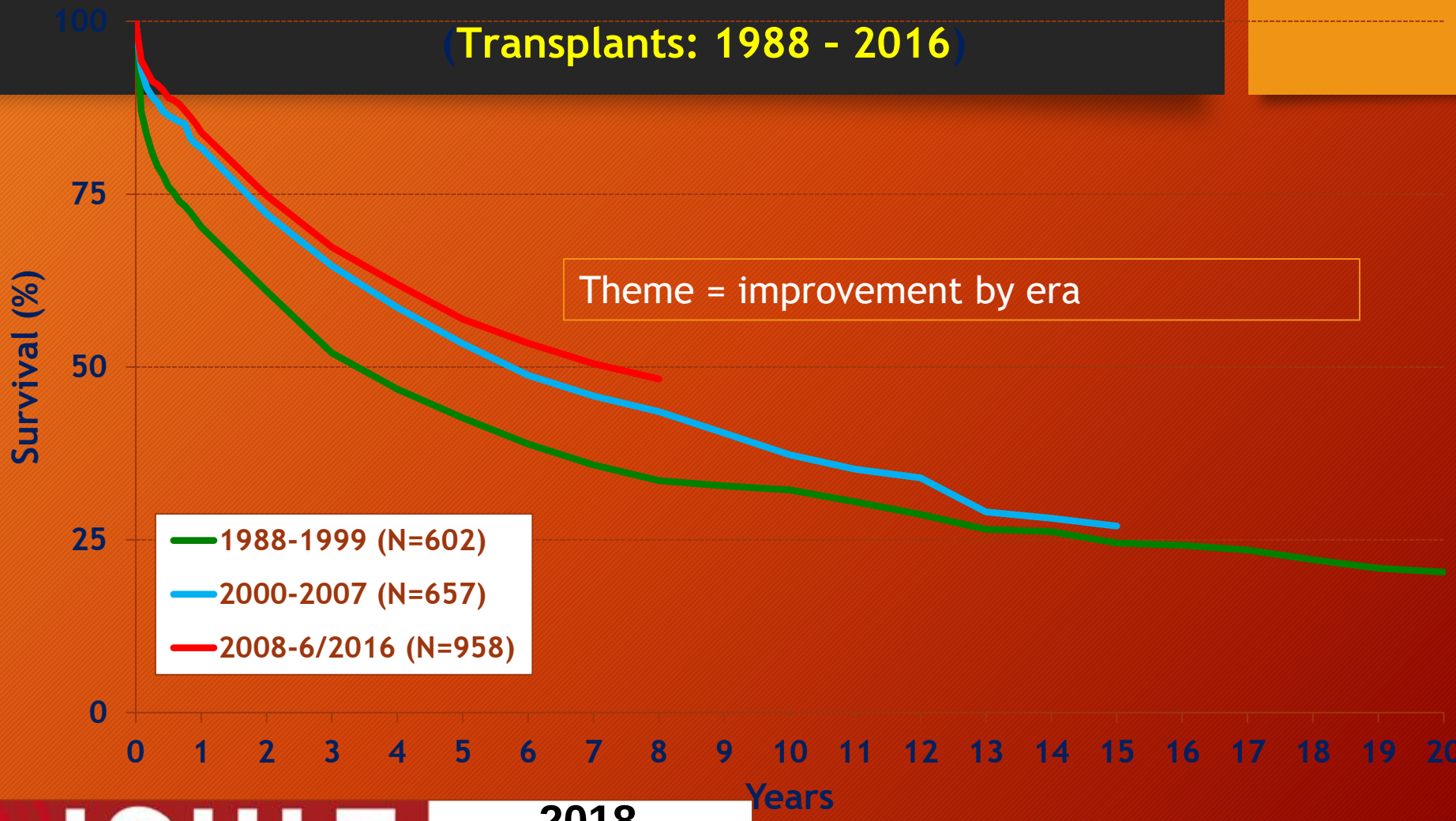
Underlying diagnoses: congenital diaphragmatic hernia with progressive PH; time in hospital 17 days; time between weight at TXP and nadir = 37 days.

Transparency

- PH clinicians must balance between over-optimism and over-pessimism
- Early education about “final options”
- Transplant centers must be transparent with referring physicians and patients/families
- Long-term survival better than most are aware
- Beware temptation of paternalism
- Refer early, especially age < 12 yrs

Pediatric Lung Transplants Survival by Era

(Transplants: 1988 - 2016)



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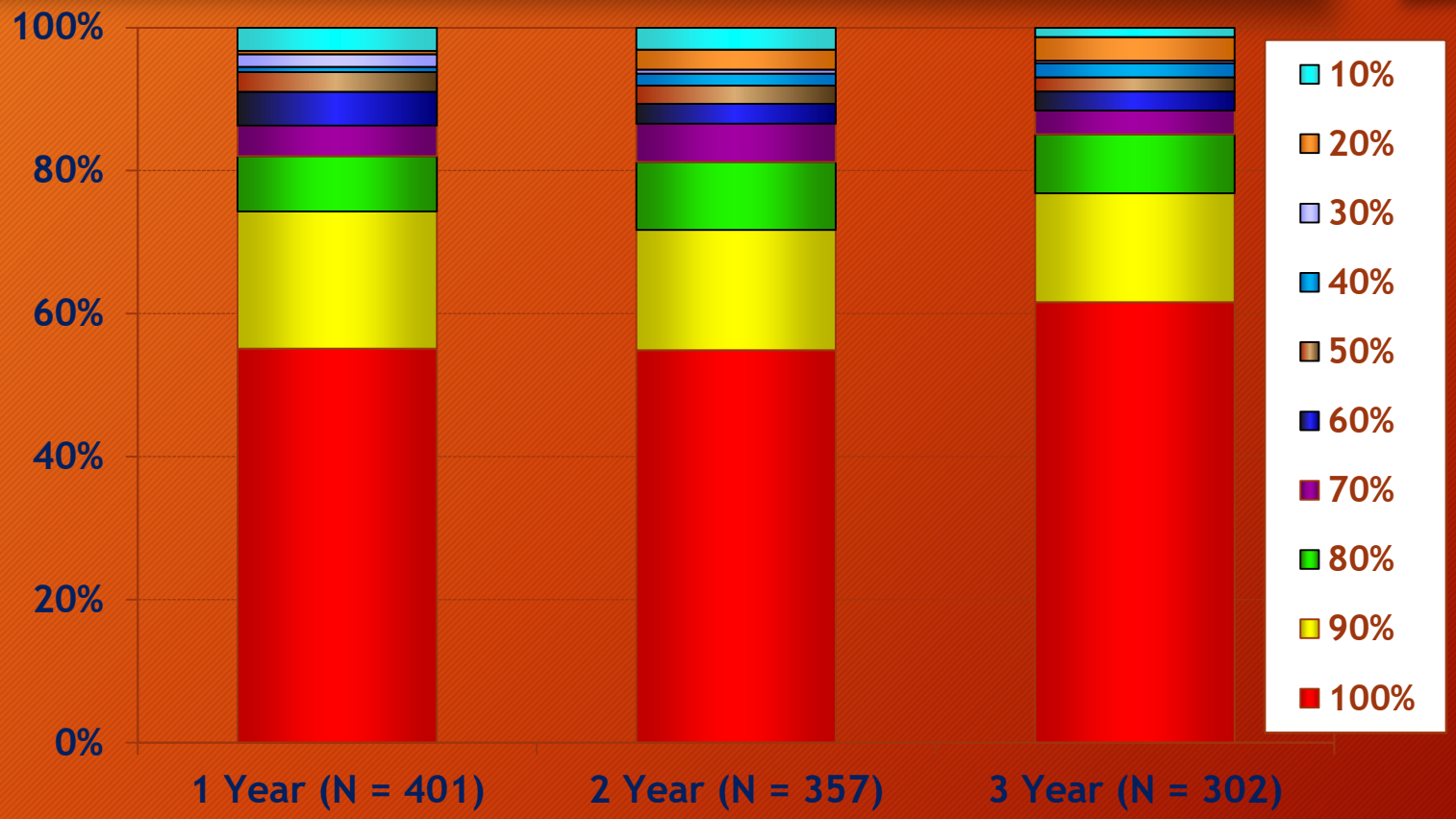
Pediatric Lung Transplants
Functional Status of Surviving Recipients
(Follow-ups: January 2008 - June 2017)



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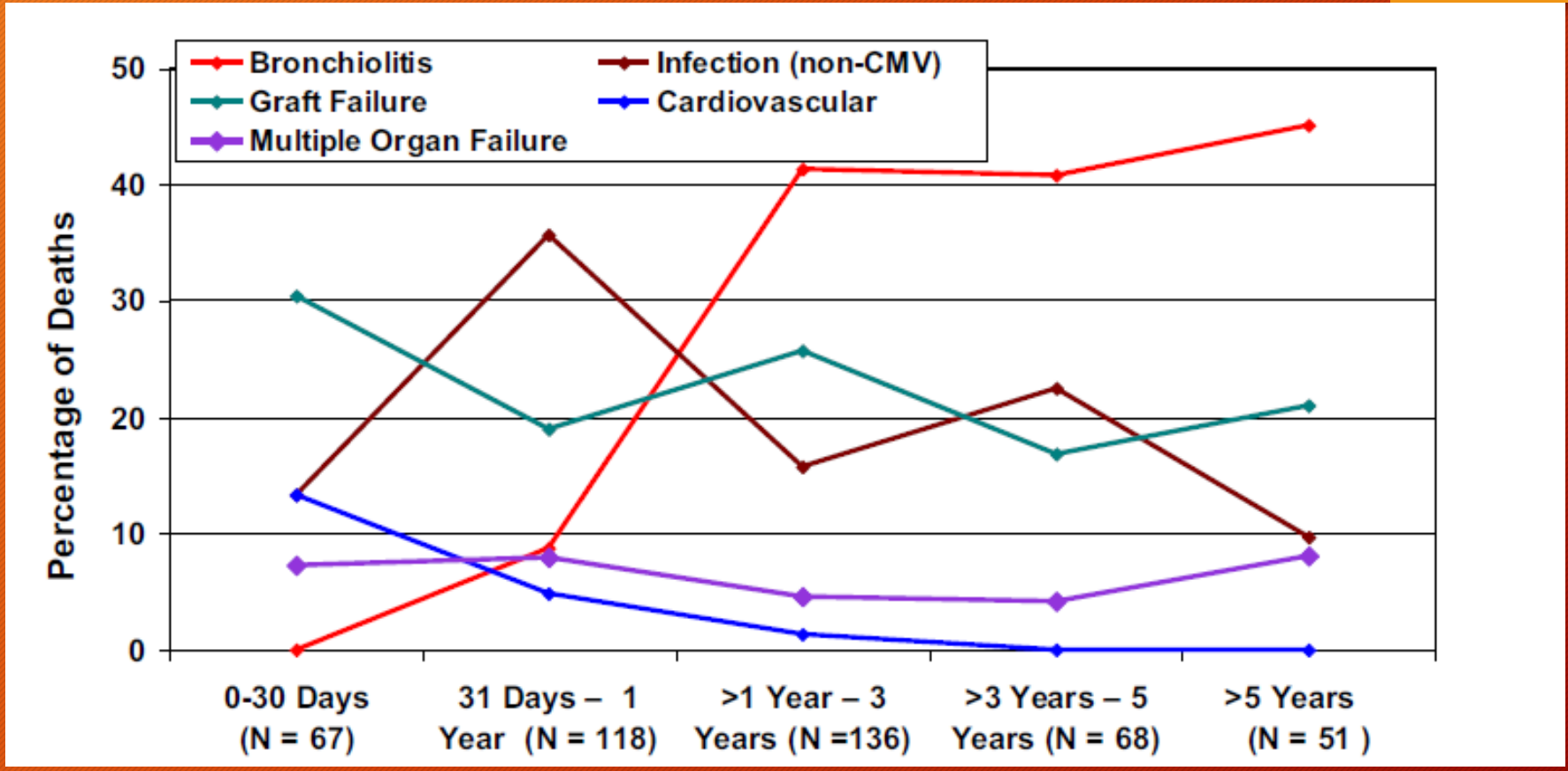
Causes of Death after Pediatric Lung Transplantation



Aurora P, J Heart Lung Transplant, 2011

Conclusions

- Despite diagnostic and therapeutic advances, pediatric PH often a lethal diagnosis in 2019
- Few pediatric lung transplant centers worldwide and marked variation in accepted indications among and between centers
- Lung Transplantation is only cure for PH
- Advances in survival are encouraging and the quality of life of most survivors is high