

Pediatric Heart Transplantation

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Disclosures

No financial disclosure

Will not discuss off label use of medical devices

Will discuss off label use of medications

Any patient pictures shown are done with
permission

Objectives

- 1 Review indications and contraindications for heart transplantation
- 2 Be familiar with evaluation process for transplantation
- 3 Be aware of new developments in transplantation





AM

- Presented with PVCs in infancy
- Progressed to intractable ventricular tachycardia unresponsive to medical or surgical therapy
- Referred for heart transplant evaluation at 18 months of age

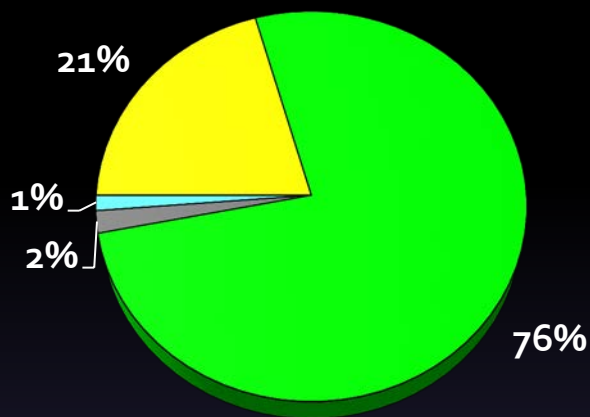
Selection for Pediatric Heart Transplant

- Dilated Cardiomyopathy –symptomatic on maximal medical therapy
- Restrictive Cardiomyopathy
- Intractable arrhythmias
- Graft failure

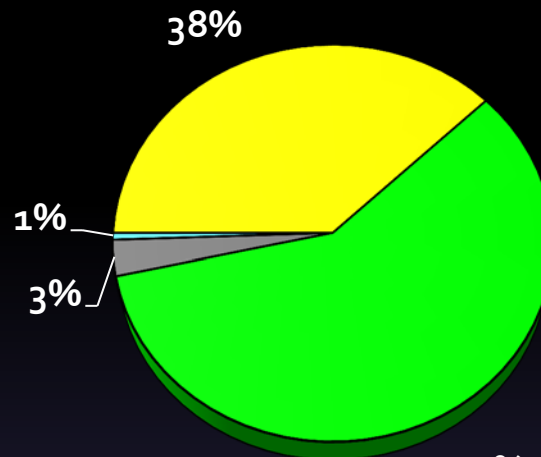
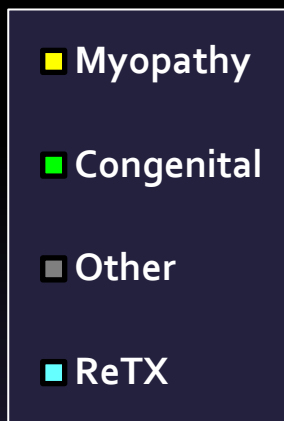
Selection for Pediatric Heart Transplant

- End stage congenital heart disease not amenable to surgical or medical therapy
 - Ross Classification III-IV
 - Failure to thrive
 - Protein losing enteropathy
 - Intractable arrhythmias
 - Plastic bronchitis

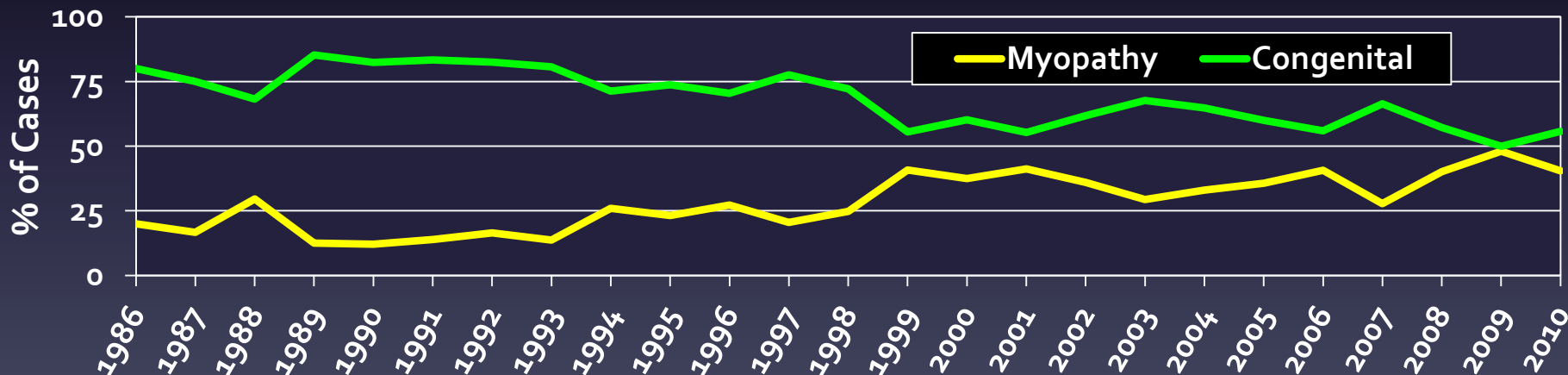
DIAGNOSIS IN PEDIATRIC HEART TRANSPLANT RECIPIENTS (Age: < 1 Year)



1988-1999



2000-6/2011

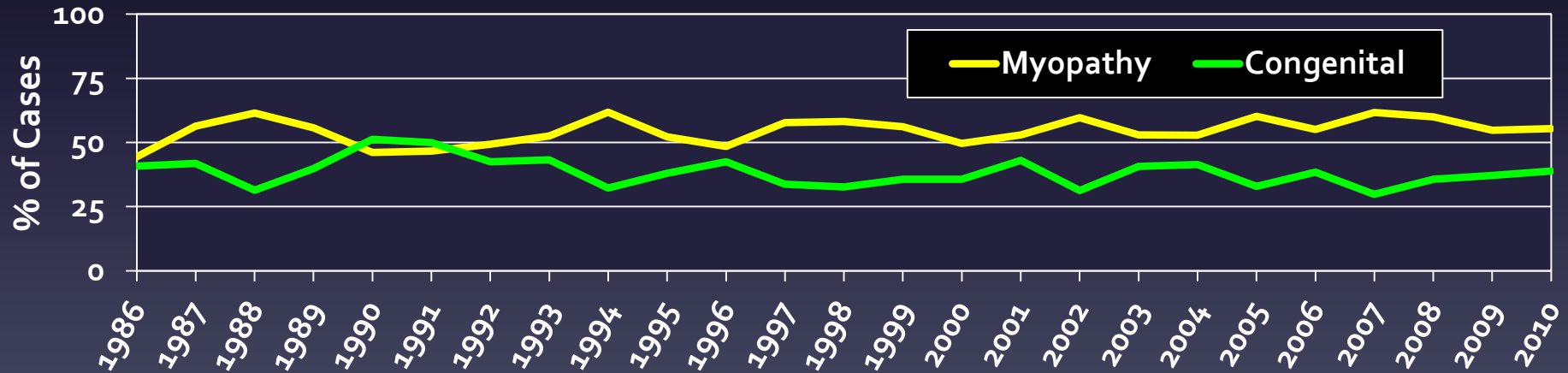
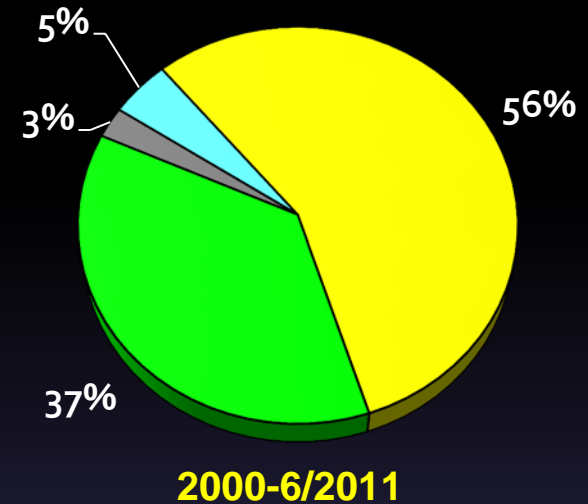
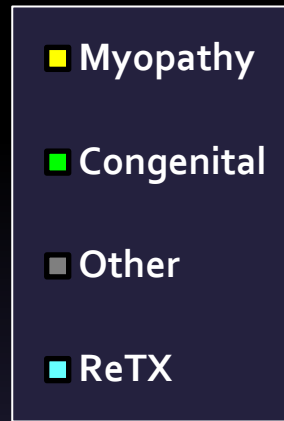
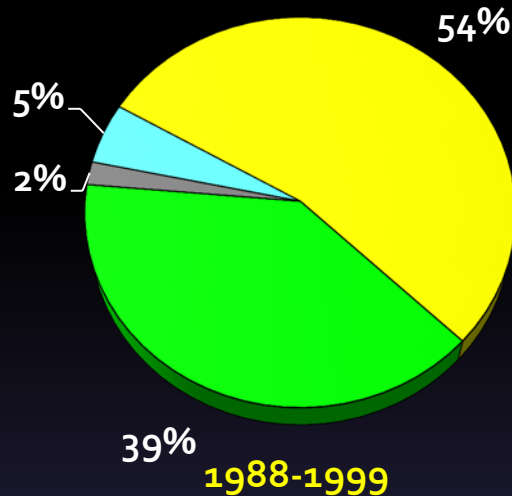


ISHLT

2012

J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

DIAGNOSIS IN PEDIATRIC HEART TRANSPLANT RECIPIENTS (Age: 1-10 Years)

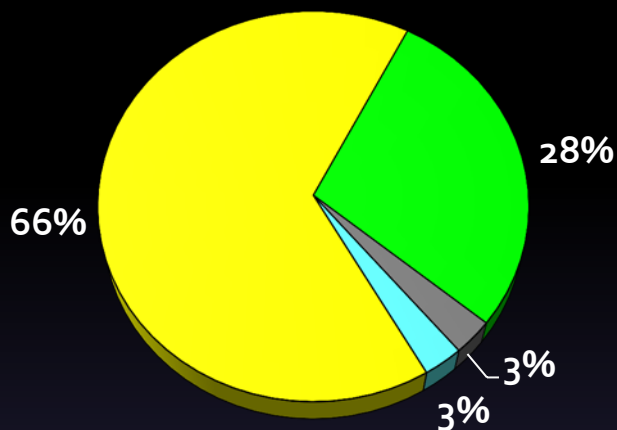


ISHLT

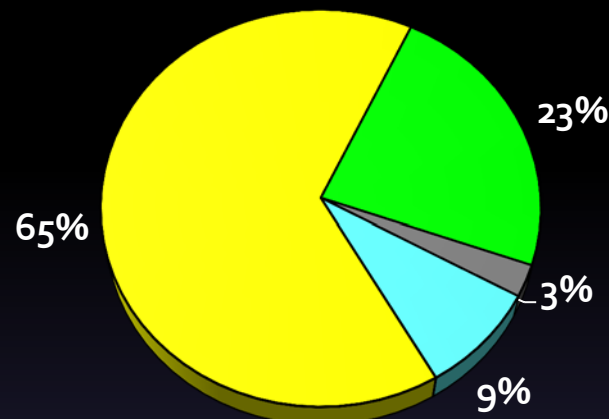
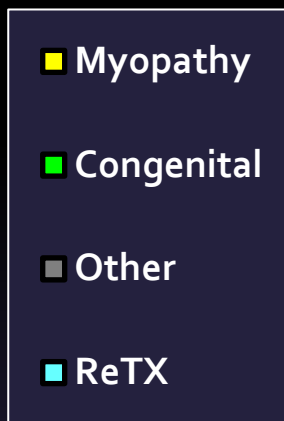
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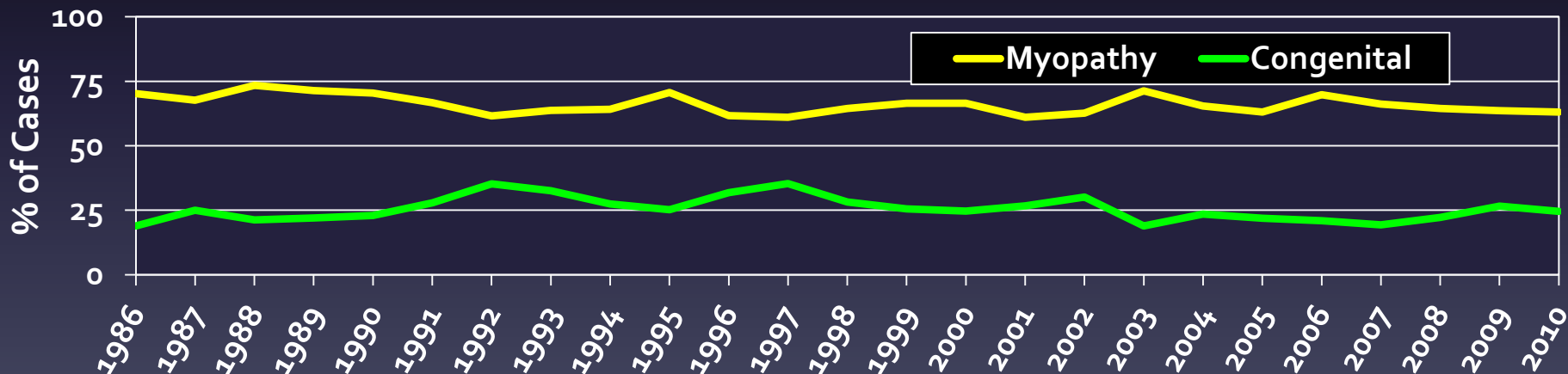
DIAGNOSIS IN PEDIATRIC HEART TRANSPLANT RECIPIENTS (Age: 11-17 Years)



1988-1999



2000-6/2011



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2012

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Exclusion Criteria

- Pulmonary Hypertension (>5-6 woods units)
 - Unresponsive to oxygen or pulmonary vasodilators
 - Transpulmonary gradient > 15mmHg
- Pulmonary vein stenosis
- Active infection
- Active malignancy

Exclusion Criteria

- Genetic syndrome with poor long term prognosis
- Neurologic abnormalities with poor long term prognosis
- Irreversible end-organ damage
- Socio-economic factors leading to poor long term compliance

Pre-transplant Evaluation

- Cardiac catheterization-resistance and anatomy
- End organ function
- Tissue typing
- Financial evaluation
- Blood work (heme, chem, viral)
- Psycho-social evaluation

National Organ Transplant Act 1984

- Established the US Organ and Procurement and Transplantation Network
- Administered by UNOS under contract with HRSA and HHS

NOTA

- Assure equitable access
- Identify barriers to donation especially to pediatric patients

CMS 2007

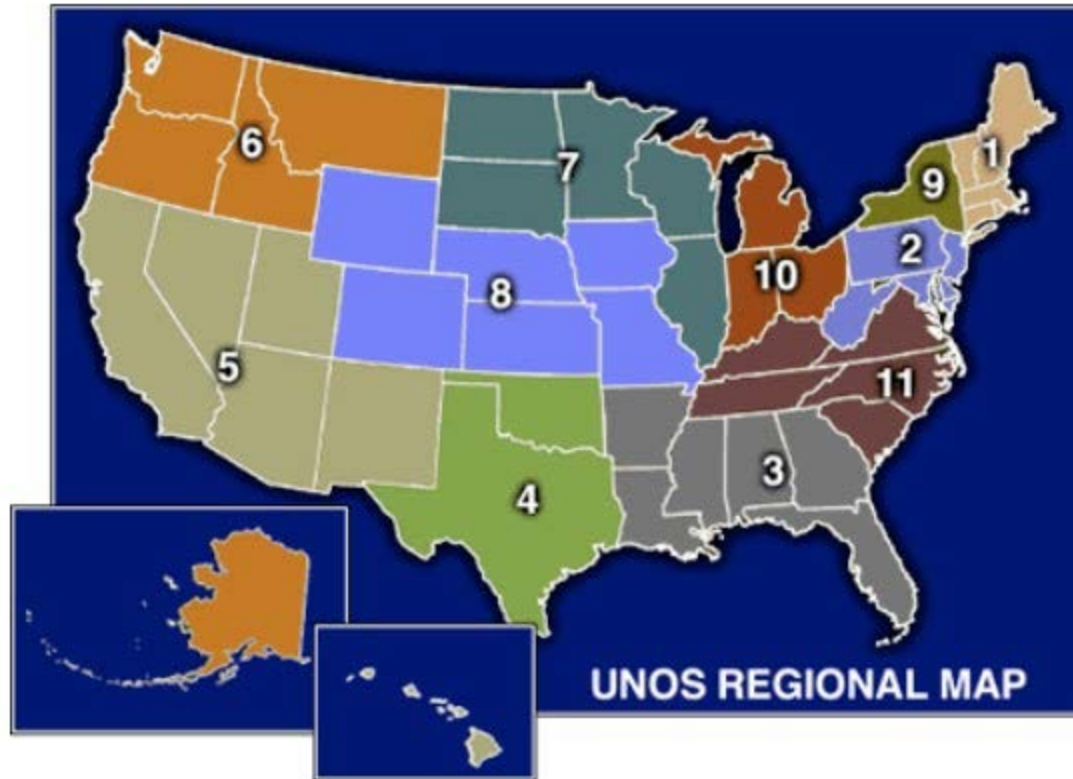
- Patient Selection
 - Fair, non-discriminatory
 - Psychosocial evaluation if possible
 - Written documentation
 - Grievance process



Allocation

- Donors <18 years of age go to pediatric candidates first
- Offered first in region then by zones

UNOS Regions



Listing

- Status
- Weight range
- Gender
- Unacceptable antigens
- High risk
- ABO compatible or incompatible

Status 1A

- Ventilator dependent
- Mechanical circulatory support
- <6 months old with reactive pulmonary hypertension < 50% systemic
- High dose inotropes (milrinone 0.5 mcg/kg/min , dobutamine 7.5 mcg/kg/min)
- Multiple inotropes (addition of dopamine 5mcg kg /min)
- Life expectancy < 14 days

Status 1B

- Low dose inotropes
- <6 months of age not meeting 1A criteria
- Growth failure (5% height and weight or loss of $1\frac{1}{2}$ standard deviations on growth curve)

A promotional poster for the TV show Grey's Anatomy. The main visual is a close-up of a man's face, specifically his eyes and nose, which are framed by a heart shape made of blue fabric. The background is dark.

Who puts you
back together?

GREY'S ANATOMY

PREMIERES THURSDAY SEPT 23 9|8c

abc



Status 2

- Does not meet criteria
for 1A or 1B

Status 7

- Temporarily ineligible

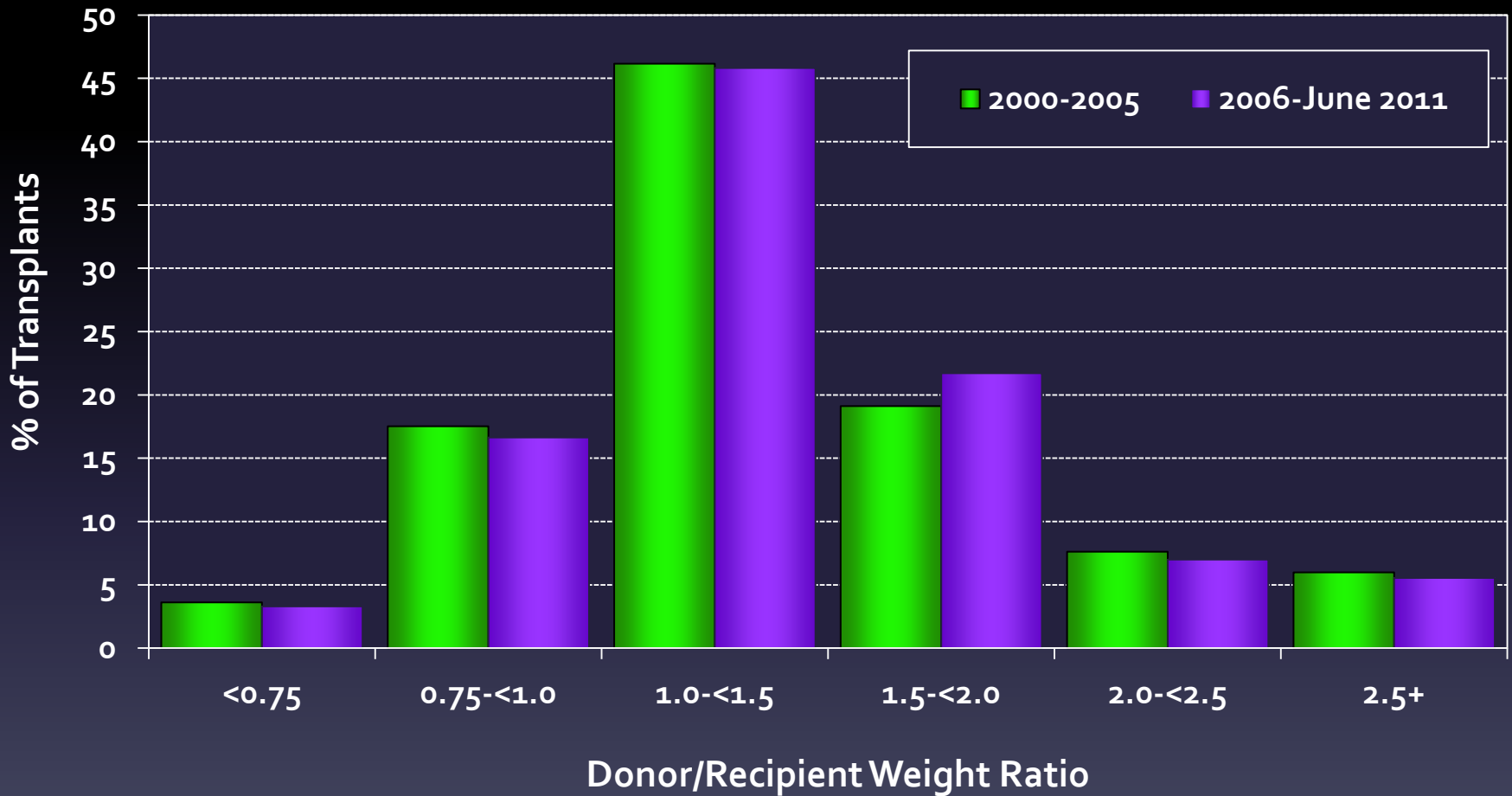
Listing

- Status
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DISTRIBUTION OF TRANSPLANTS

by Donor/Recipient Weight Ratio

(Pediatric Heart Transplants: January 1, 2000 - June 30, 2011)



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2012

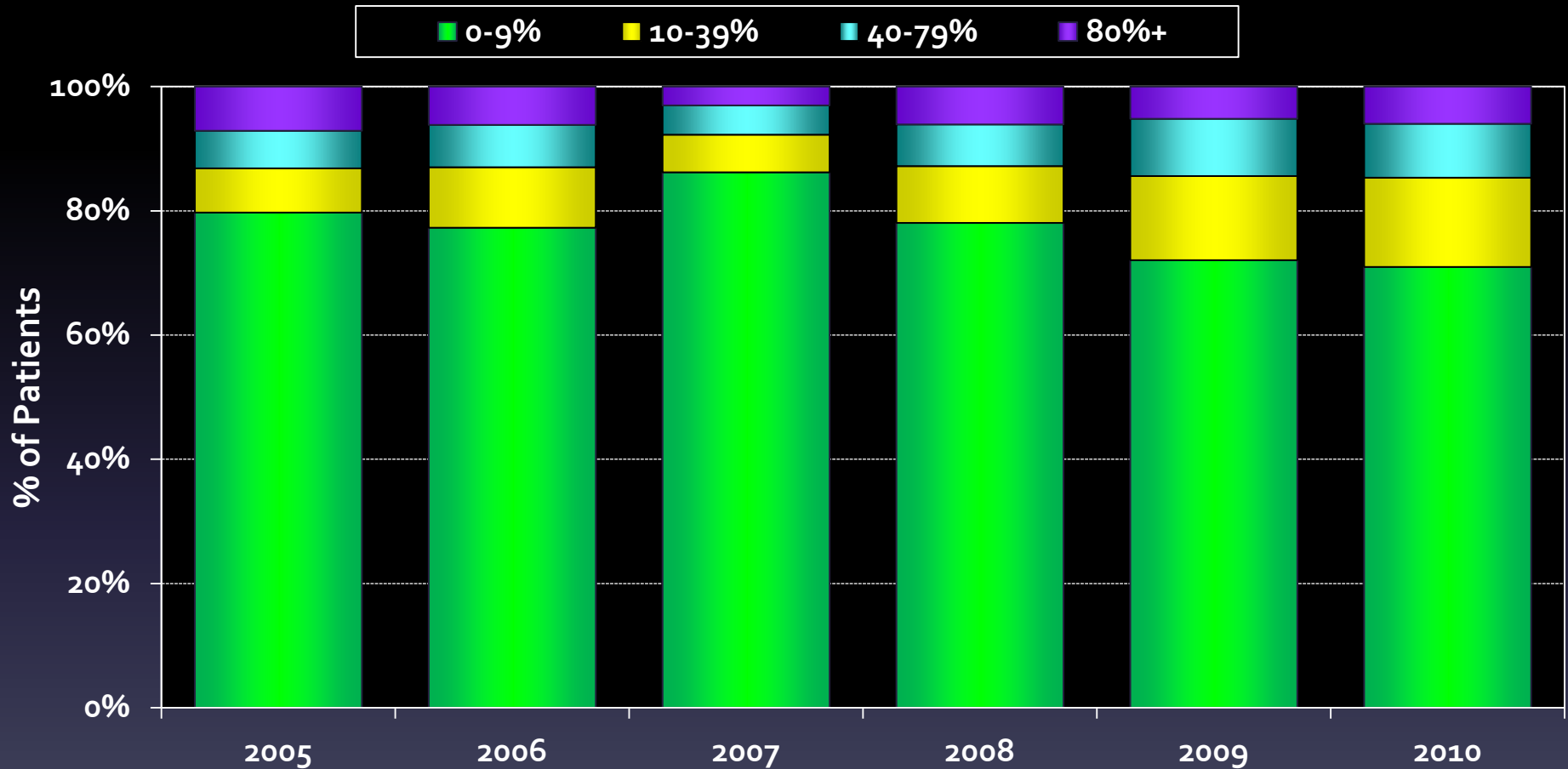
J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

Listing

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PEDIATRIC HEART RECIPIENTS

PRA Distribution by Year (Transplants: 2005 – 2010)



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Virtual Crossmatch

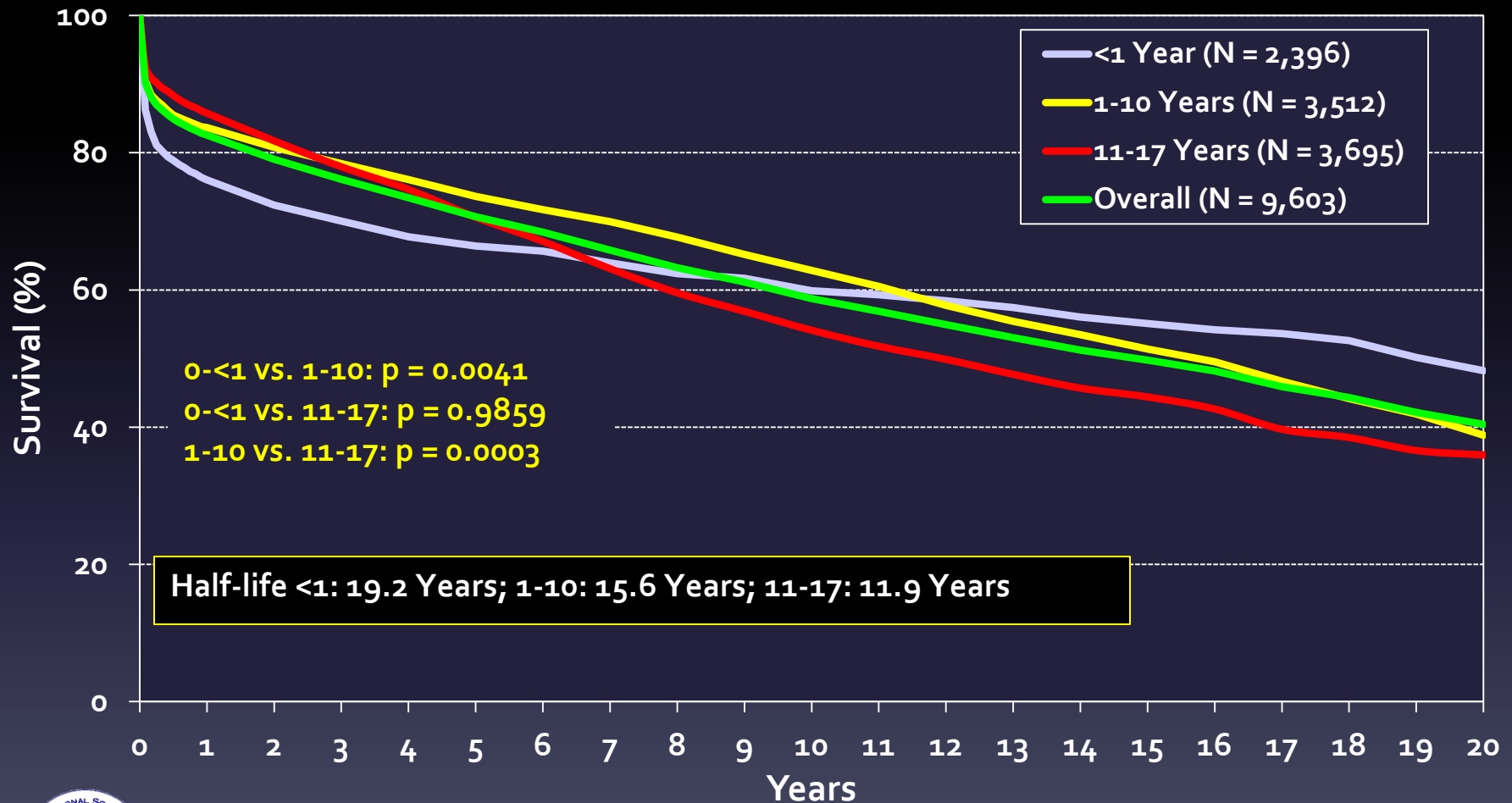
- Requires careful identification of antibodies and complete donor typing
- Immunogenetics accuracy in VXM: 96% for CDC, 98% for FCXM
- Cases where VXM can't be done reliably
 - Inadequate donor typing and strong Abs to certain Ags: DQA, DP
 - Broadly reactive sera – can't determine collective strength of all antibodies, accurately
 - Serum > 30 days old

Listing

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- Weight range
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PEDIATRIC HEART TRANSPLANTS

Kaplan-Meier Survival (Transplants: 1/1982-6/2010)



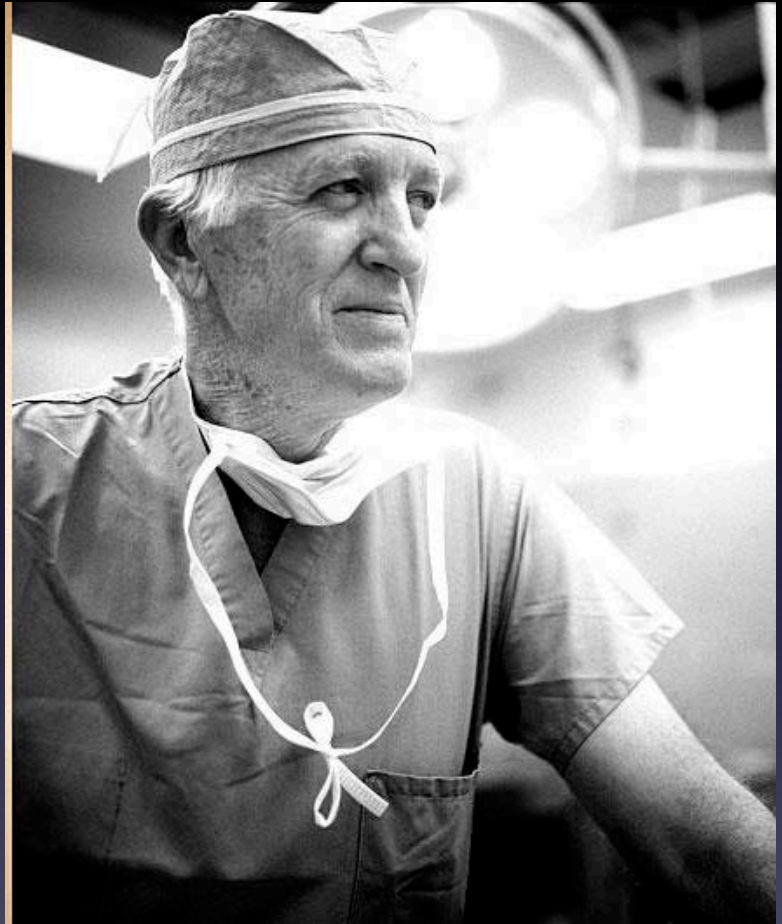
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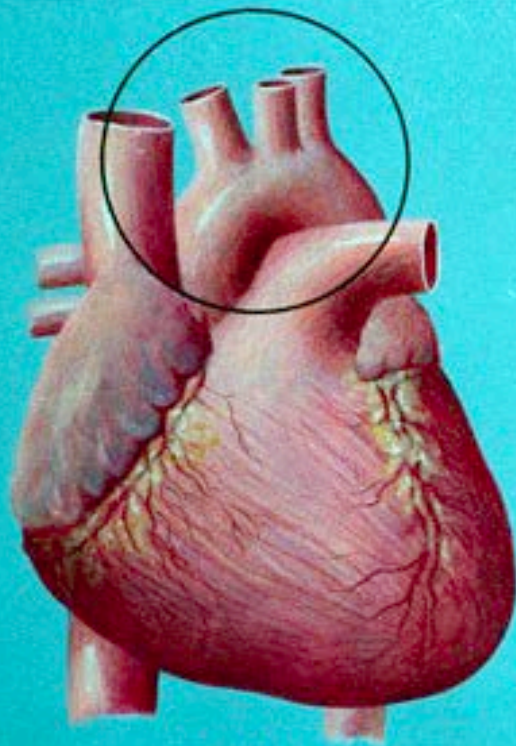
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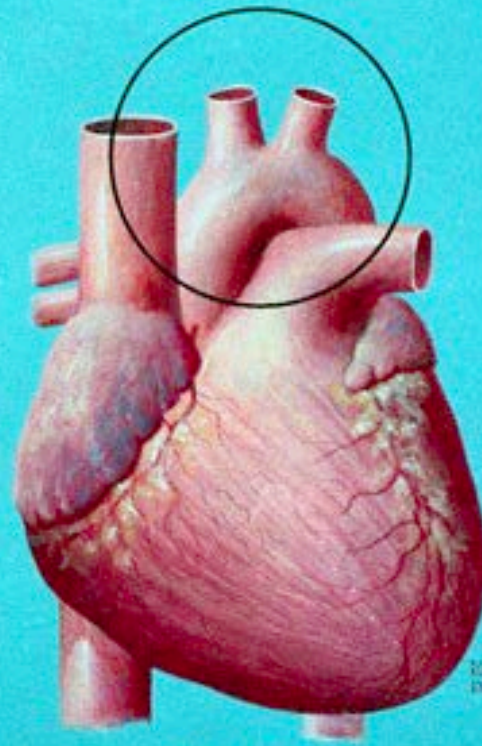
Infant Heart Transplant

- Higher conditional survival at 4 yrs (86%)
- Immunologically immature
 - Lack circulating antibodies to non-self A/B antigens for several months
- Success rates resulted in more infants being listed for transplant
- Higher mortality on waitlist for infants





HUMAN



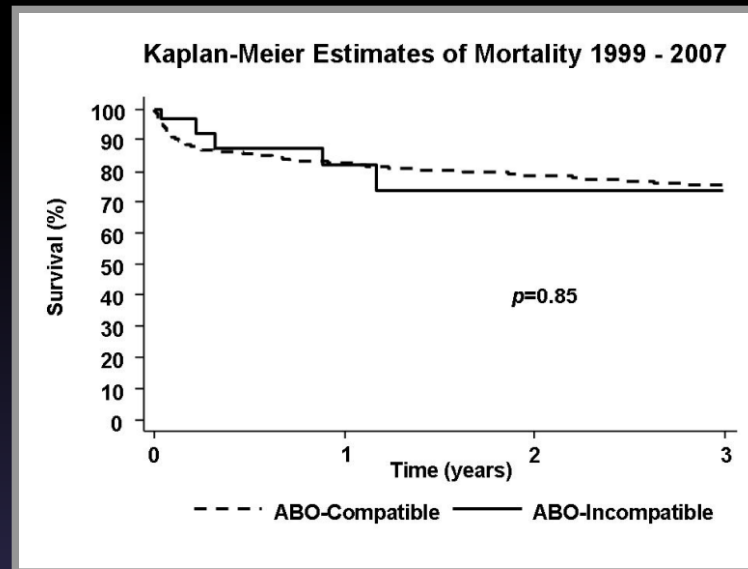
BABOON

Normal Hearts

ABO Incompatible Heart Transplant

- 2001- Cohort 10 infants
- Ages 4 days to 14 months
- 2 deaths not related to ABO incompatibility
- No hyper-acute rejection
- All infants considered for ABO incompatible hearts – mortality on waitlist dropped from 50% to less than 10%

New Directions: ABO incompatible HTx



Review of UNOS experience (1999 – 2007):

35 ABOi vs. 556 ABO compatible

No difference in acute rejection

No difference in early survival

30+ % reduction of mortality while waiting for infants

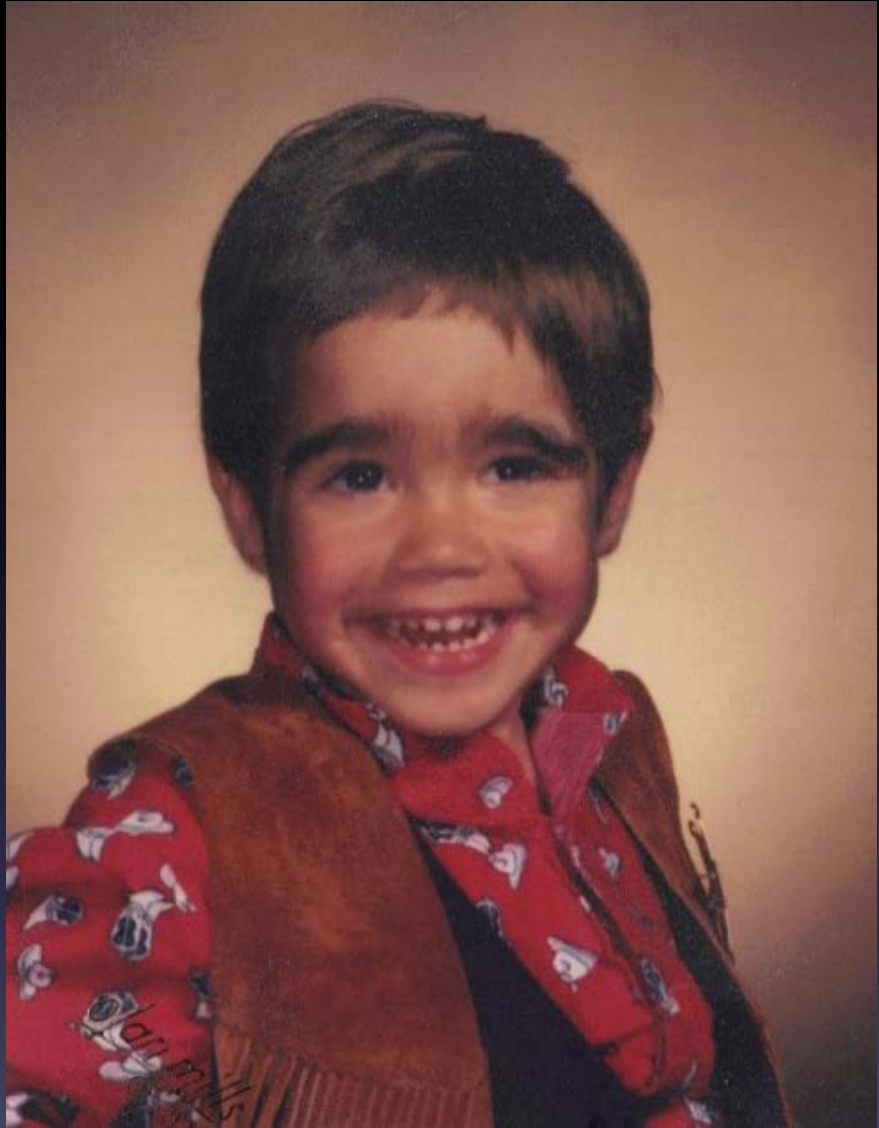
Listing

- Status
- Weight range
- Gender
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- ABO compatible or incompatible

AM

One episode of cellular rejection during first year

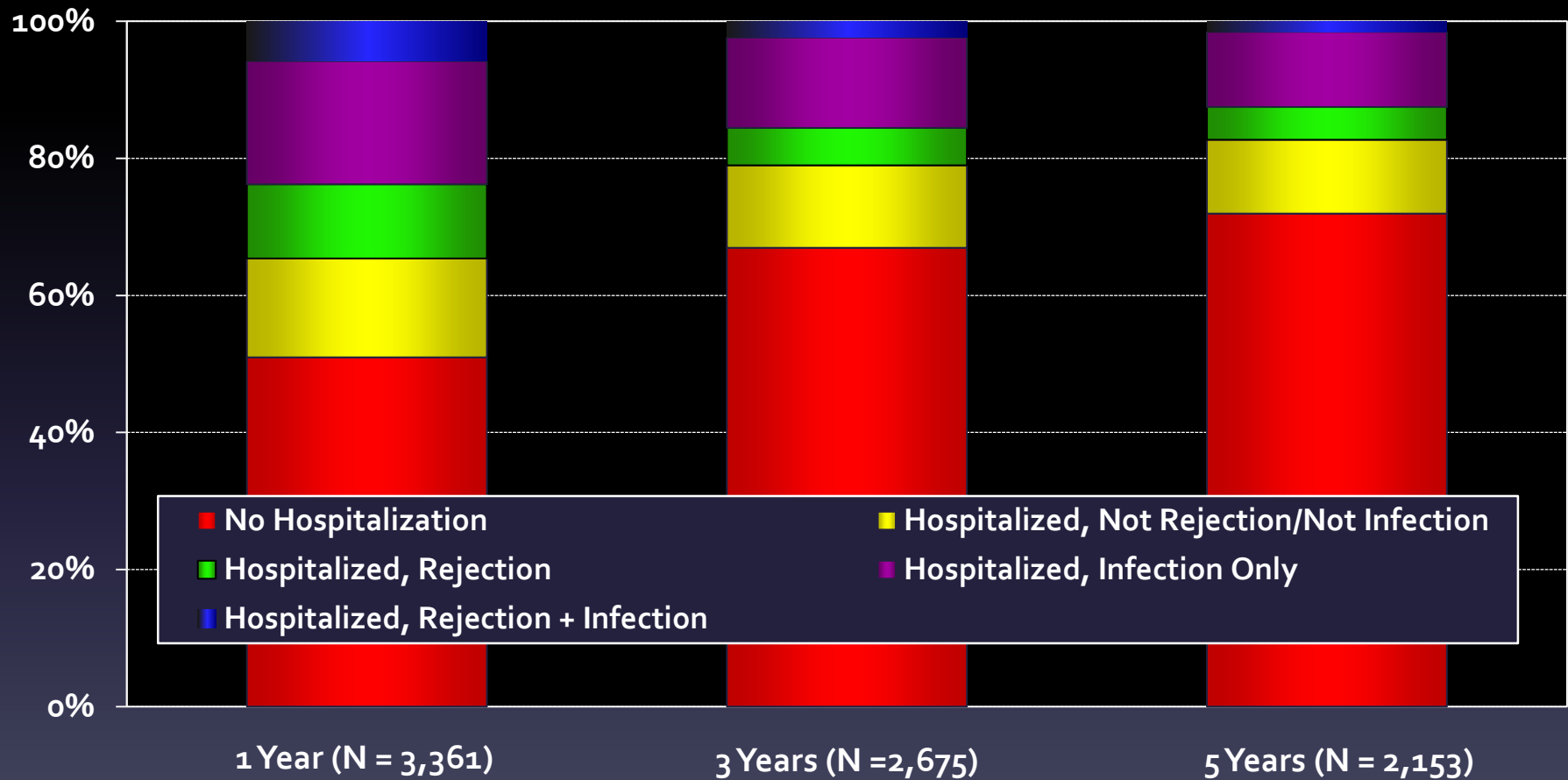
At 18 years of age developed graft dysfunction



PEDIATRIC HEART RECIPIENTS

Rehospitalization Post-transplant of Surviving Recipients

(Follow-ups: January 2000 – June 2011)



ISHLT

2012

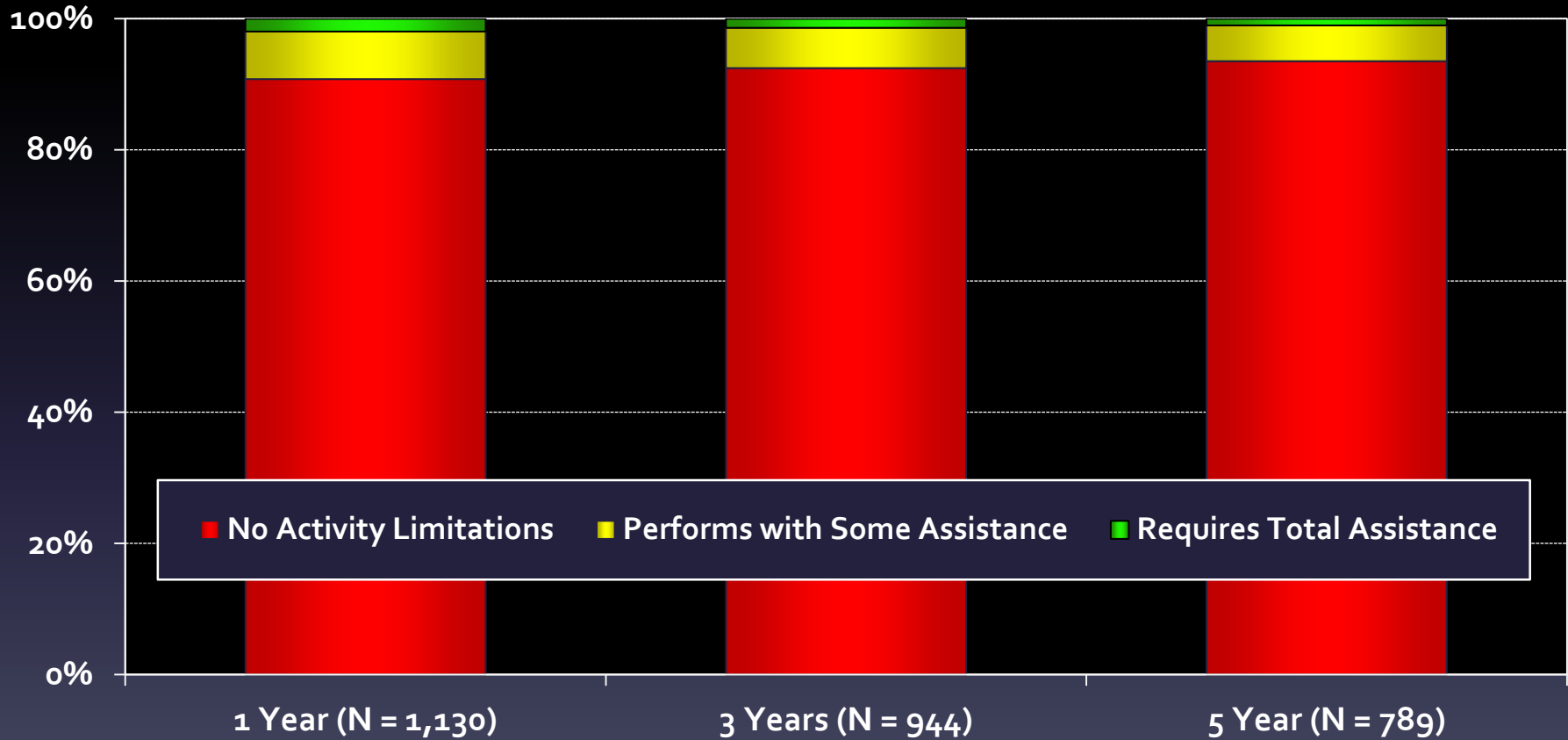
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PEDIATRIC HEART RECIPIENTS

Cross-Sectional Analysis

Functional Status of Surviving Recipients

(Follow-ups: January 2000 – June 2011)



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2012

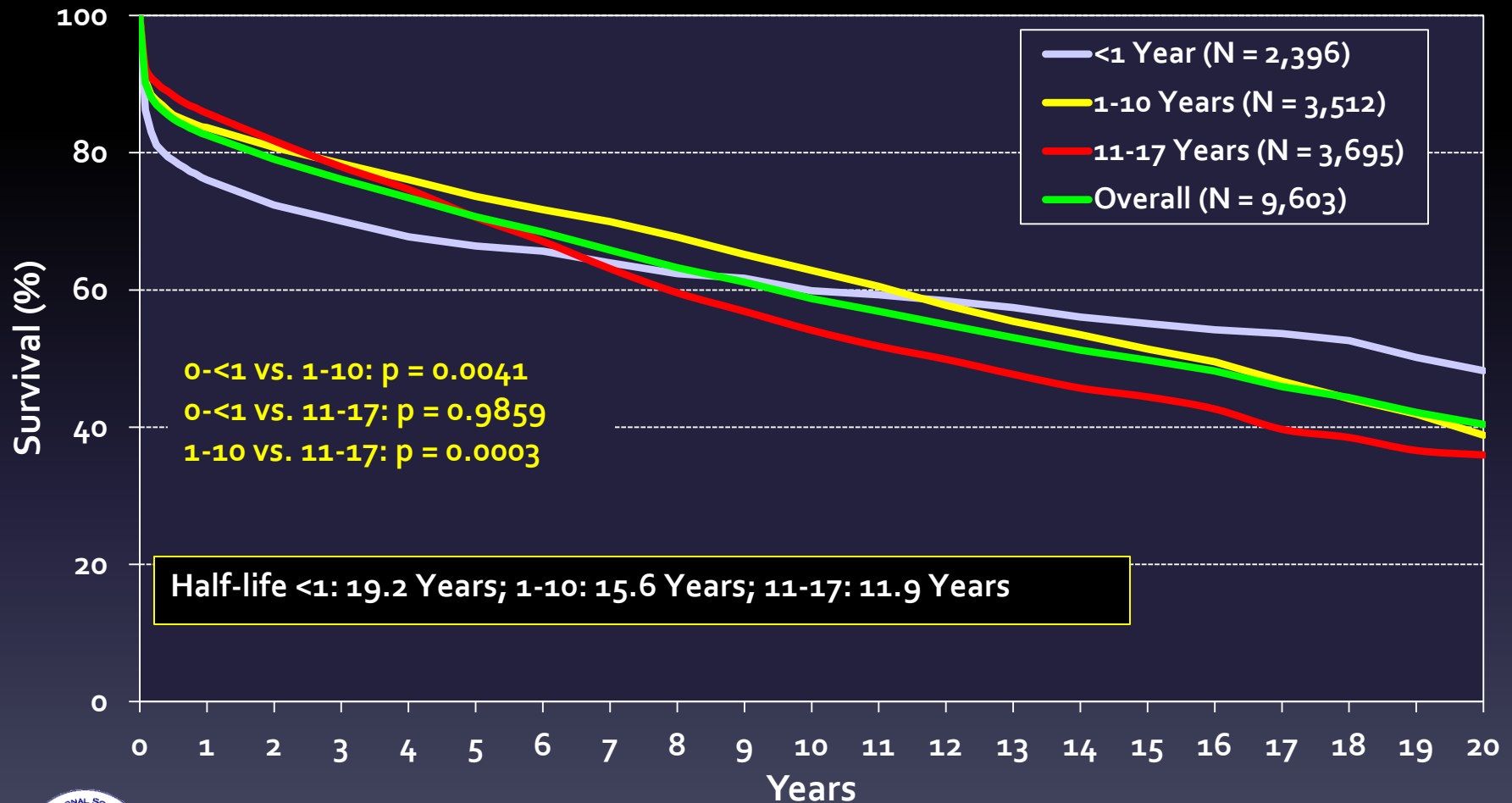
J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

AM

- 18 years post transplant presented with primary graft failure

PEDIATRIC HEART TRANSPLANTS

Kaplan-Meier Survival (Transplants: 1/1982-6/2010)

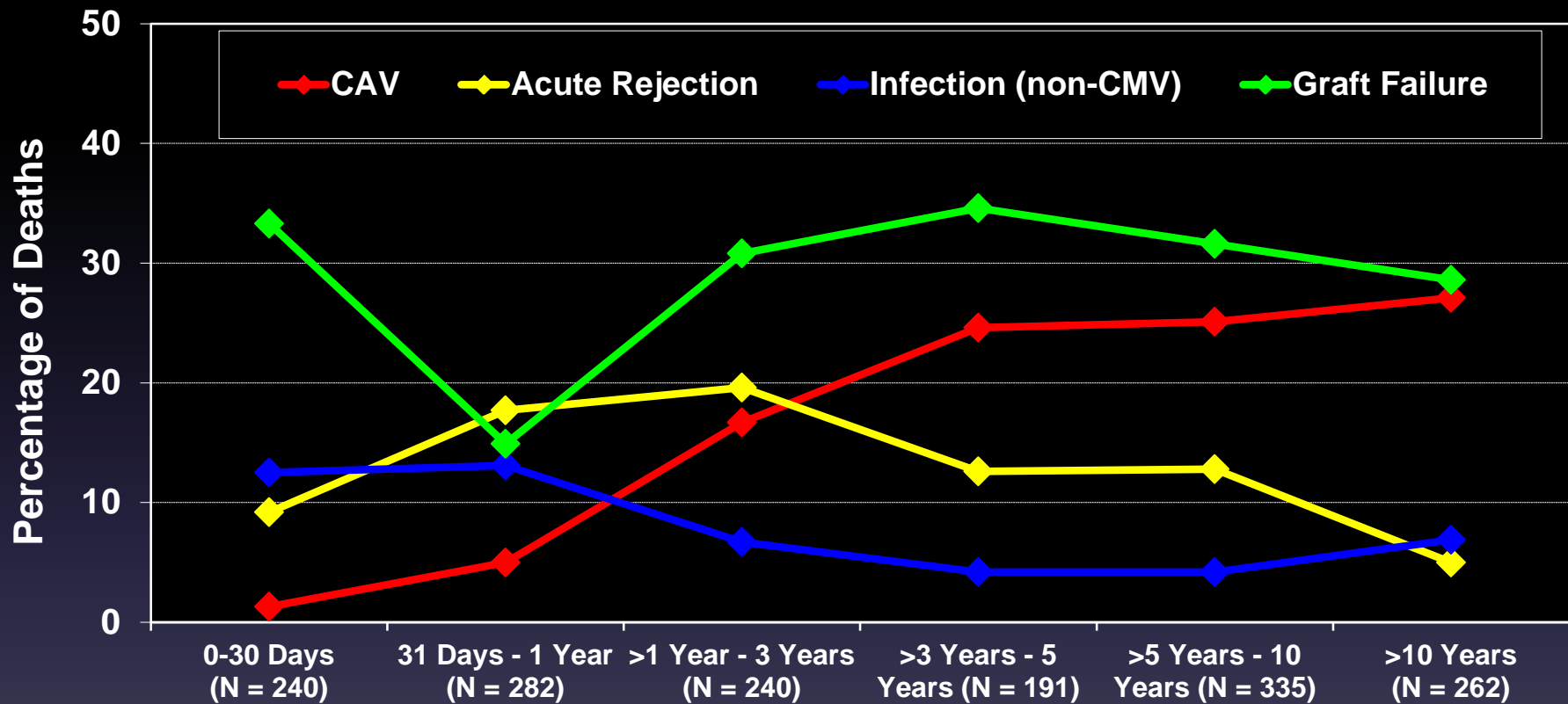


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PEDIATRIC HEART TRANSPLANT RECIPIENTS: Relative Incidence of Leading Causes of Death (Deaths: January 2000 - June 2011)



ISHLT

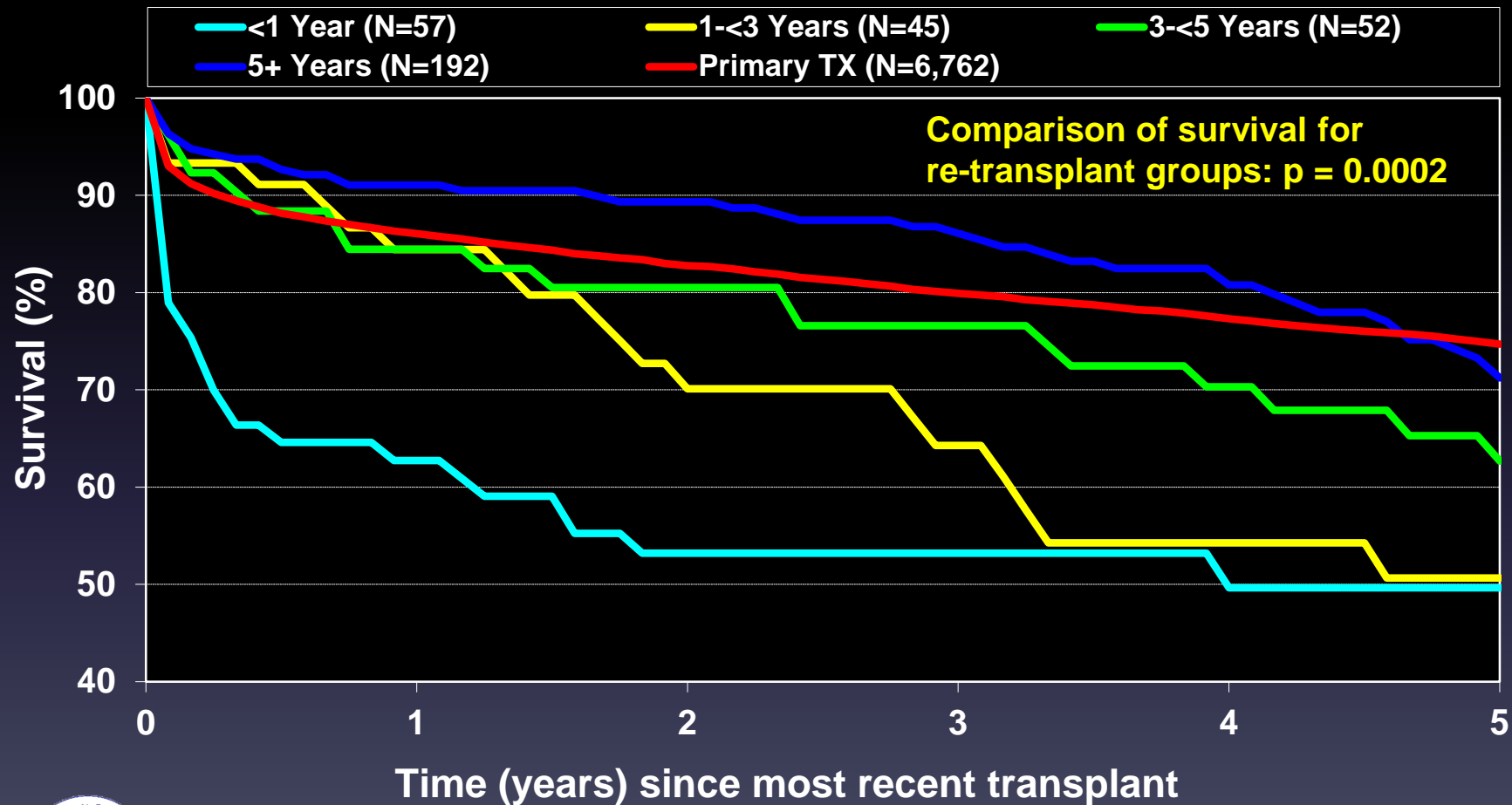
2012

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Listed for retransplantation

PEDIATRIC HEART RETRANSPLANTS

Kaplan-Meier Survival Rates Stratified by Inter-Transplant Interval
(Re-transplants: January 1994 - June 2010)



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J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

Only patients who were less than 18 years old at the time of re-transplant are included.

- 2nd heart transplant
- Cytotoxicity crossmatch negative
- Low level Donor HLA DQ₅
- ISHLT 2R 7 months post-transplant- AMRo
- Solumedrol pulse- ISHLT 1R, AMRo

New Heart Transplant Grading (ISHLT 2005)

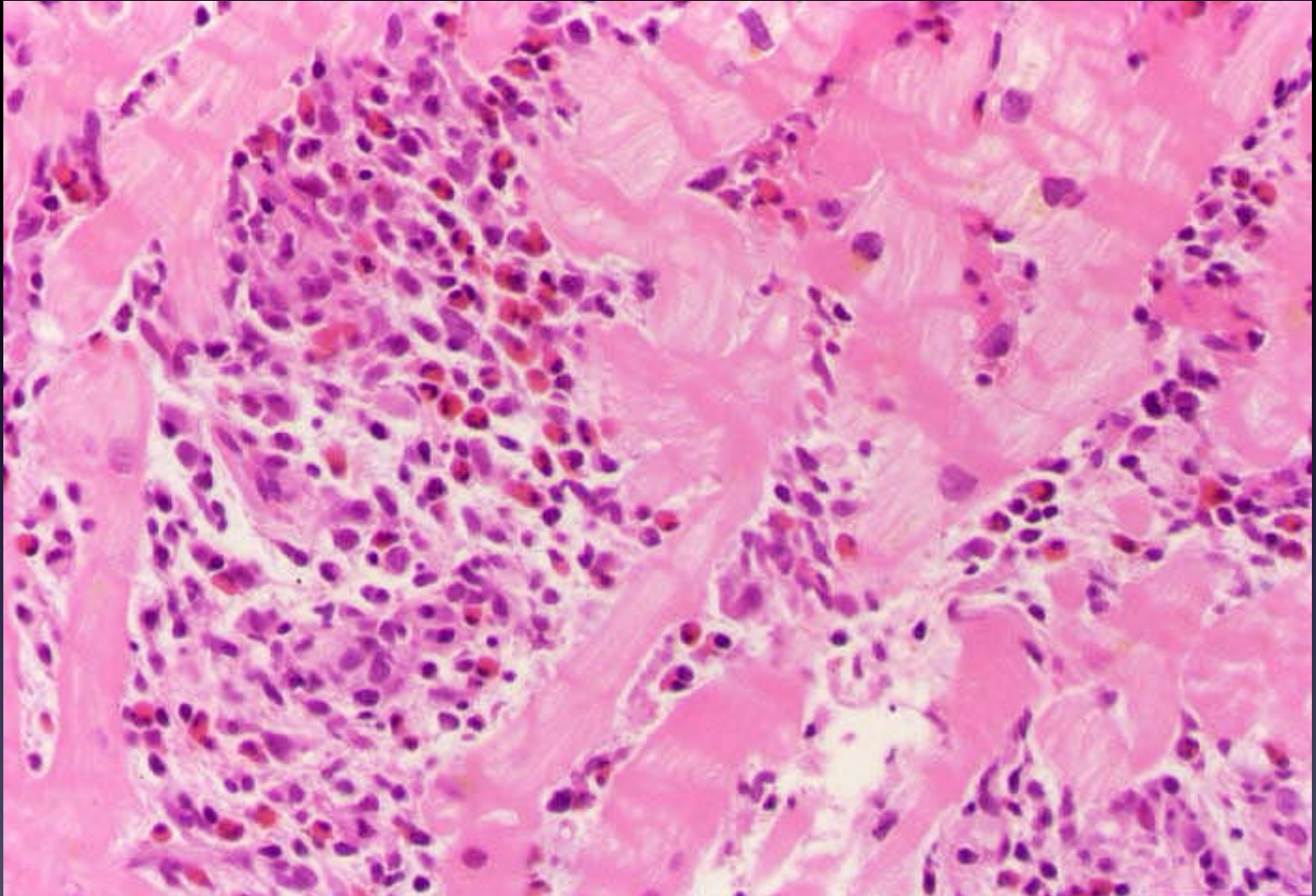
Table 1. ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection^a

2004		1990	
Grade 0 R ^a	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage	Grade 1, mild A—Focal B—Diffuse Grade 2 moderate (focal)	Focal perivascular and/or interstitial infiltrate without myocyte damage Diffuse infiltrate without myocyte damage One focus of infiltrate with associated myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate A—Focal	Multifocal infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis	B—Diffuse Grade 4, severe	Diffuse infiltrate with myocyte damage Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

^aWhere "R" denotes revised grade to avoid confusion with 1990 scheme.

^bThe presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required (see Table 3).

Grade 2R (3A)



Acute Antibody-mediated Rejection of Cardiac Transplants

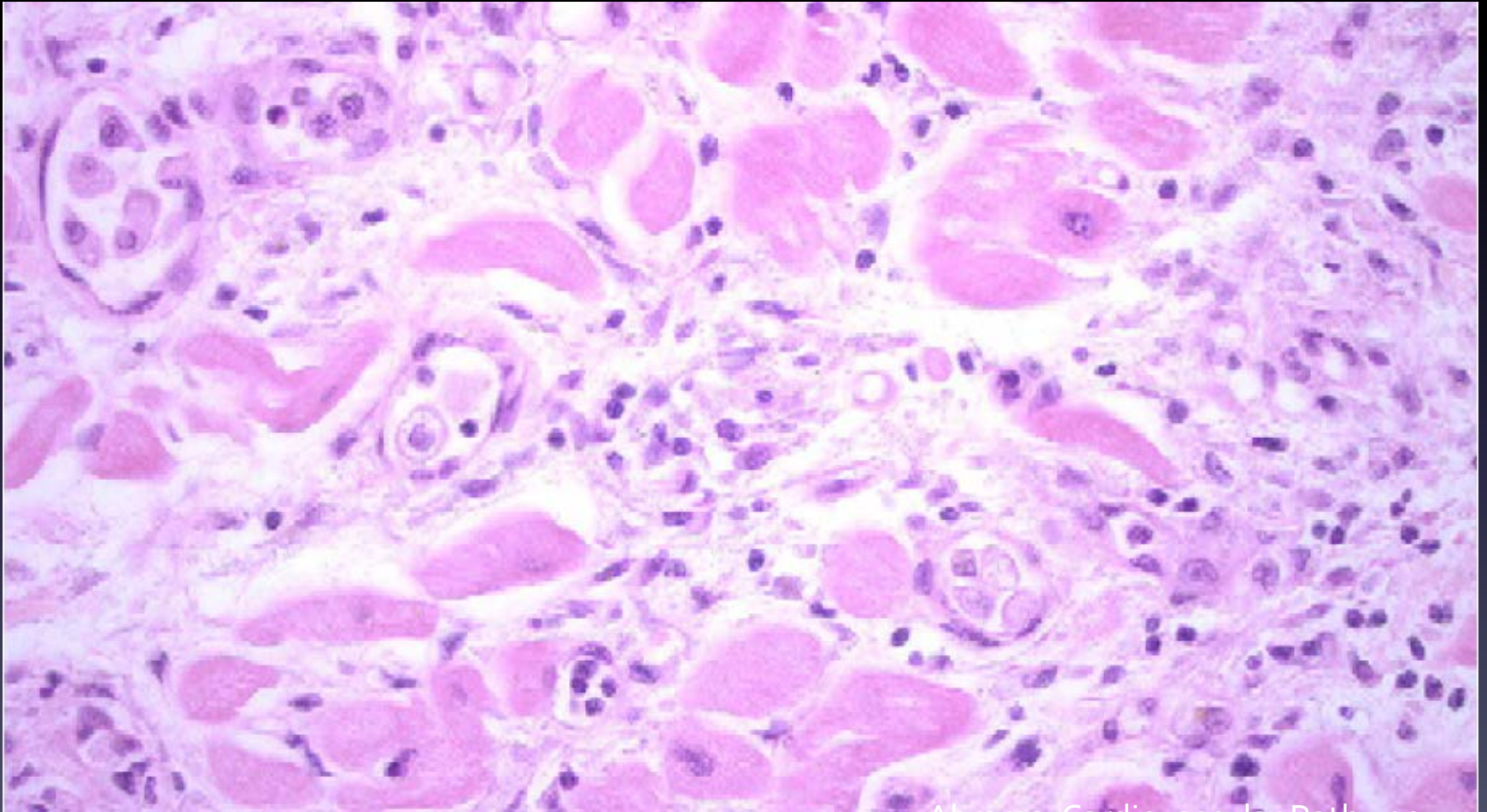
Elaine F. Reed, PhD, Anthony J. Demetris, MD, Elizabeth Hammond, MD, Silviu Itescu, MD, Jon A. Kobashigawa, MD, Nancy L. Reinsmoen, PhD, E. Rene Rodriguez, MD, Marlene Rose, PhD, Susan Stewart, FRCPath, Nicole Suci-Foca, PhD, Adriana Zeevi, PhD, and Michael C. Fishbein, MD, Chairman, for The International Society for Heart and Lung Transplantation

JHLT, 25:2, 2006

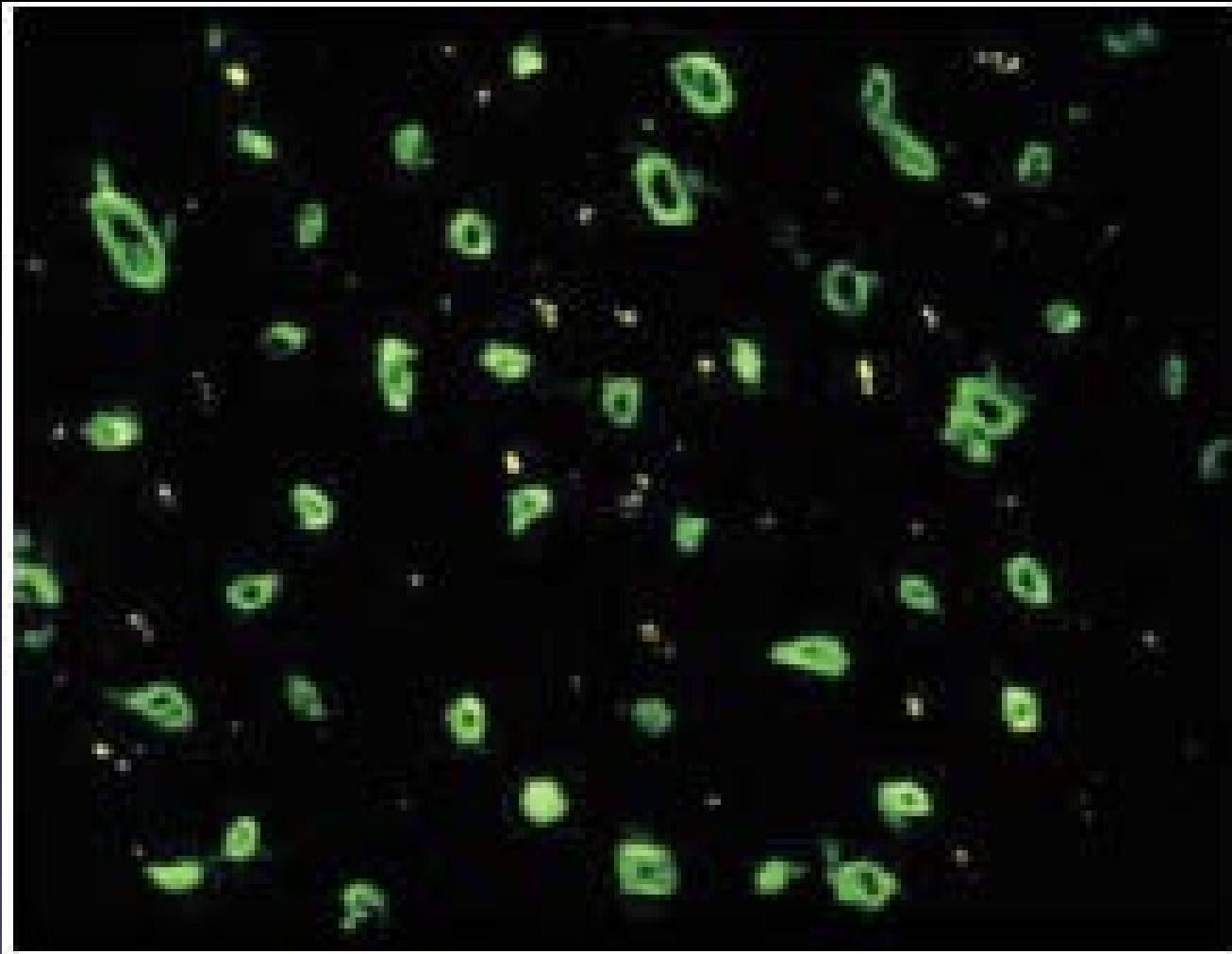
Table 1. Findings in Acute Antibody-Mediated Rejection of the Heart

1. Clinical evidence of acute graft dysfunction
2. Histologic evidence of acute capillary injury (*a* and *b* are required)
 - a. Capillary endothelial changes: swelling or denudation with congestion
 - b. Macrophages in capillaries
 - c. Neutrophils in capillaries (more severe cases)
 - d. Interstitial edema and/or hemorrhage (more severe cases)
3. Immunopathologic evidence for antibody mediated injury (in the absence of OKT 3 induction) *a* or *b* or *c* are required
 - a. Ig (G,M, and/or A) + C3d and/or C4d or C1q (equivalent staining diffusely in capillaries, 2–3+), demonstrated by immunofluorescence
 - b. CD68 positivity for macrophages in capillaries (identified using CD31 or CD34), and/or C4d staining of capillaries with 2–3+ intensity by paraffin immunohistochemistry
 - c. Fibrin in vessels (optional; if present, process is reported as more severe)
4. Serologic evidence of anti-HLA class I and/or class II antibodies or other anti-donor antibody (e.g., non-HLA antibody, ABO) at time of biopsy (supports clinical and/or morphologic findings)

Intravascular macrophages in humoral rejection



Humoral Rejection



C4d Immunofluorescence

- 9 months post-transplant

ISHLT 1R

Patchy perimyocytic & capillary staining

C₃d C₄d- not typical of AMR-DSA negative



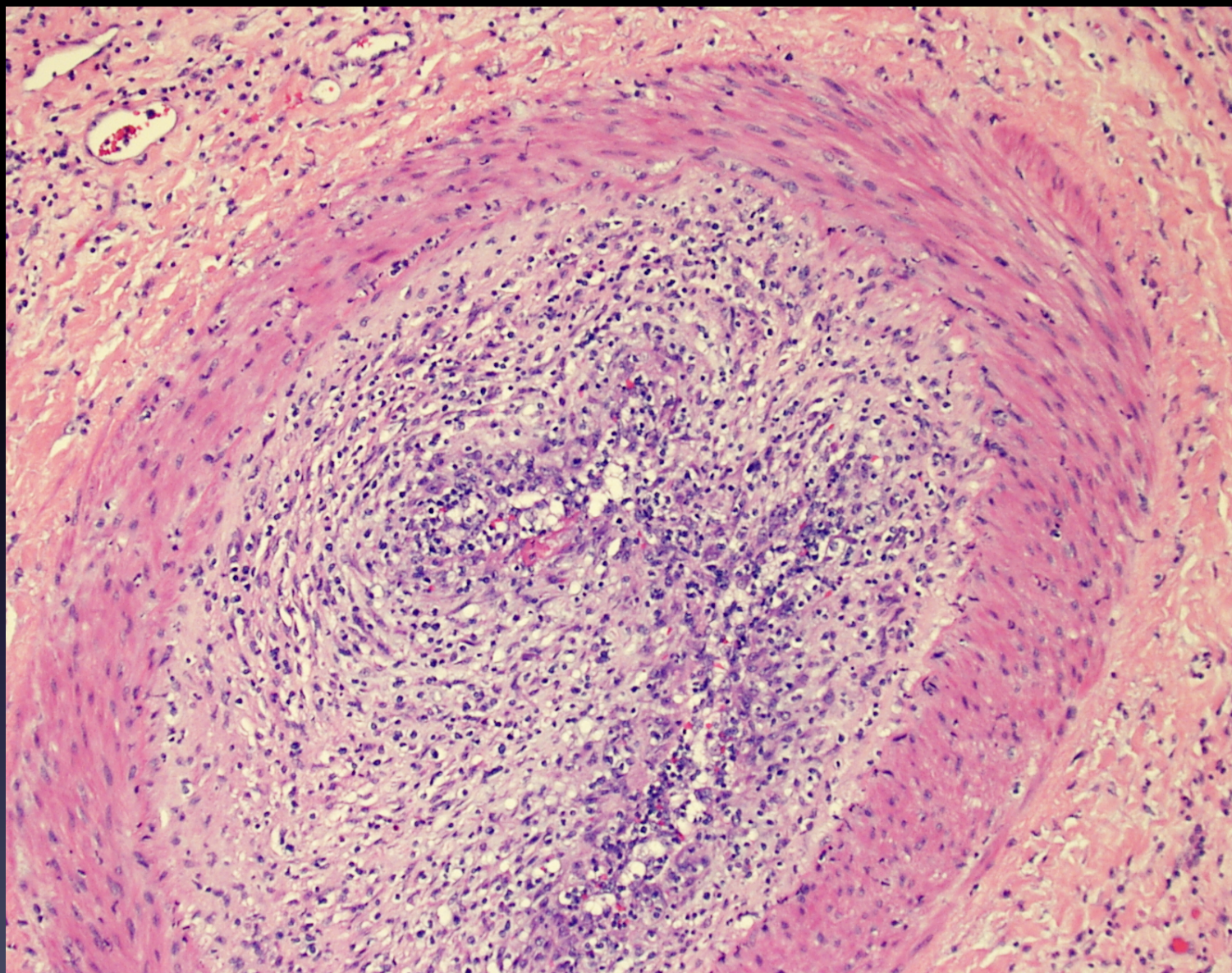
AM

- 10 months post transplant presented to OSH
- C/O chest/ abdominal pain
- Tachycardia
- Transferred home

- Diastolic dysfunction on echo
- Arrest in cath lab
- AMR o, ISHLT 1R, negative DSA
- Diffuse CAV

Heart Pathology

- Severe advanced graft atherosclerosis – some vessels >90% occluded
- Marked inflammation of the coronary vessels and endocardial endothelium
- Mild cellular rejection (1R)



Unanswered questions

Role of Non-HLA antibodies

- May occur as allo or auto antibodies
- Targets can include histocompatibility antigens, vascular receptors, adhesion molecules and intermediate filaments

AM

Non-HLA Antibodies

- EC Crossmatch IgG to two surrogate donors-
 - Strongly positive at transplant
 - Borderline/Negative at death

Non HLA Antibodies

- Vimentin IgM
 - Positive by Elisa only at transplant
 - Positive by Elisa and Luminex at death

Non-HLA Antibodies

- AT₁R IgG and IgM
 - Strongly positive at transplant
 - Strongly positive at death

Antibodies in Pediatric Heart TransplantCTOT-C

- Multicenter NIH funded prospective cohort study
- Presence of anti-HLA IgG antibodies by Luminex SA testing
- Presence of anti-MICA antibodies by Luminex TM testing
- C4d on endomyocardial biopsy
- Survival/cytoprotective genes: Bcl-xl,Bcl-2,HO-1-biopsy and EC culture

ON THE ROAD TO ADULT CARE

Dragonfly Heart And Drew's Retreat

DECEMBER 7-9, 2012



Where Children Find Strengths,
Courage and Happiness



Dragonfly
Heart Camp

Artwork by: Andrew Miller

Young Adult Transition Retreat



Educational Program led by young adult transplant recipients.

Retreat setting with scheduled training workshops to address:

- Self Advocacy
- Self Management of Care
- Life Skills





Dragonfly Triathlon



*“We make a living by what we
get, we make a life by what we
give.”*

Winston Churchill



THANK YOU!



Allo-antibodies in Pediatric Heart Transplant

CTOT-C

- Adhesion molecules: ICAM-1, VCAM-1-biopsy, EC culture
- Endothelial cell chimerism-biopsy
- Complement regulatory proteins: CD55, CD59-biopsy
- Phospho-S6 ribosomal proteins-biopsy
- Circulating precursor and mature endothelial cells-blood
- Vascular endothelial growth factor

Allo-antibodies in Pediatric Heart TransplantCTOT-C

- Vascular endothelial growth factor
- pAkt activity in circulating PBMC
- Cell-bound complement activation product levels as a potential biomarker for AMR-blood

Explanted Heart

- Severe advanced graft atherosclerosis – some vessels >90% occluded\
- Marked inflammation of the coronary vessels and endocardial endothelium
- Mild cellular rejection (1R)

*“We make a living by what we get, we
make a life by what we give.”*

Winston Churchill (Arthur Ashe)

ABO Incompatible Heart Transplant

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ABO incompatible transplant

- Recipients remain deficient in development of antibodies specific to donor A/B antigens
- Studies underway to determine if there is also tolerance to other donor antigens

ABO Incompatible Heart Transplant

- Now used in many centers
- Reports of acute cellular rejection and vasculopathy similar
- Aggressive immunosuppression not required
- Actuarial survival similar to compatible transplant
- Successfully done from ECMO and VAD