

# Advances in Cystic Fibrosis Lung Transplantation

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# Cystic Fibrosis

Multisystem disease

Causes of death

End stage lung disease 79%

Lung transplantation 12%

Other causes 9%

GI/Liver disease, suicide, accidents

# Lung Transplantation

Most aggressive therapy for end-stage lung disease

No prospective trials

CF patients in the United States

- 3<sup>rd</sup> most frequent recipients

- Most frequent pediatric recipients

- Best studied recipients of lung transplantation

# Lung Transplants in CF

US reported 219 transplants in 2006

ISHLT reported 46 European transplants 2005

Requires transplant of both lungs to avoid complications from old airway infections

# Surgical Choices

Heart-Lung

Bilateral Sequential Single Lung

Lobar Lung

Double Lung—no longer done



All procedures use the clam-shell incision.

Photo courtesy of Marlyn Woo, MD, Children's Hospital of Los Angeles

# Heart-Lung

Heart and lungs transplanted from deceased donor to CF patient

Heart and diseased lungs are removed from CF patient

CF heart is transplanted to second recipient

Original procedure of choice

# Heart-Lung

May improve availability of heart transplants

Reduced ischemia time for heart transplant

No clear benefit for CF patient

Additional risks

- Cardiopulmonary bypass

- Cardiac allograft vasculopathy (16%)

# Bilateral Sequential Single Lung

Most common modern procedure

New lungs joined at the level of the main-stem  
bronchus

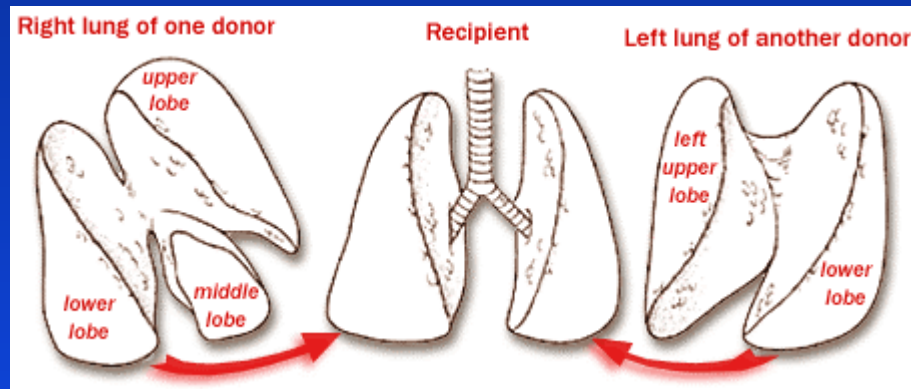
Avoids tracheal anastomosis

# Lobar

Used when there are two living donors

Right lower lobe from one donor

Left lower lobe from the other donor



Advantage: choose the time of transplant

Disadvantage: high risk for two other people

# Post Transplantation Management

Inattention can quickly lead to death

Careful follow up for potentially higher mortality for 6 months after surgery

Less intensive routine long-term follow up

Immunosuppression

Induction immunosuppression (Optional)

Three component immunosuppression regimen

# Induction Immunosuppression

Reduces acute rejection in kidney transplant

Little or no data from lung transplant

Anti-T cell monoclonal antibodies

- Thymoglobulin

- Alemtuzumab (Campath)

- Basiliximab (Simulect)

# Three Component Immunosuppression

Calcineurin inhibitor—cyclosporine A or tacrolimus

Anti-metabolite—mycophenolate mofetil (Cellcept) or  
azathioprine (Imuran)

steroid (usually prednisone)

Benefit: avoid chronic rejection

Problems: post-transplant lymphoproliferative  
disease/other B-cell lymphomas, hypertension, renal  
insufficiency, hirsutism (CyA)

# Chronic Rejection

*Bronchiolitis obliterans*

Major long term complication

Recent excitement about cyclosporine A

- New inhaled preparation

- Reduced chronic rejection

- Reduced mortality

More studies needed

# Selection Guidelines

Guiding principle is to select patients who will do better with transplantation than without.

Better may be determined as

Prolonged life

Improved Quality of Life

# Selection Guidelines

## “Deteriorating Chronic Respiratory Failure”

Geddes and Hodson. *J R Soc Med* 1989; 82(Suppl 16):49-53.

$FEV_1\% < 30\%$

Kerem *et al.* *NEJM* 1992; 326:1187-1191.

Elevated  $PaCO_2$  associated with early deaths

Kerem *et al.* *NEJM* 1992; 326:1187-1191.

# ISHLT Patient Selection Guidelines

$FEV_1 < 30\%$

Rapidly worsening lung disease or  $FEV_1$

Increasing hospitalizations

Massive hemoptysis (bleeding)

Severe and worsening malnutrition

Female gender

$PaCO_2 > 50$  mm Hg

# Difficulties with the ISHLT Guidelines

FEV<sub>1</sub>% < 30% may not predict mortality

Doershuk and Stern. *Chest* 1999; 115:782-787

Milla and Warwick. *Chest* 1998; 113:1230-1234

Other variables not included

Diabetes

Microbiology

Imprecise definitions

Cachexia

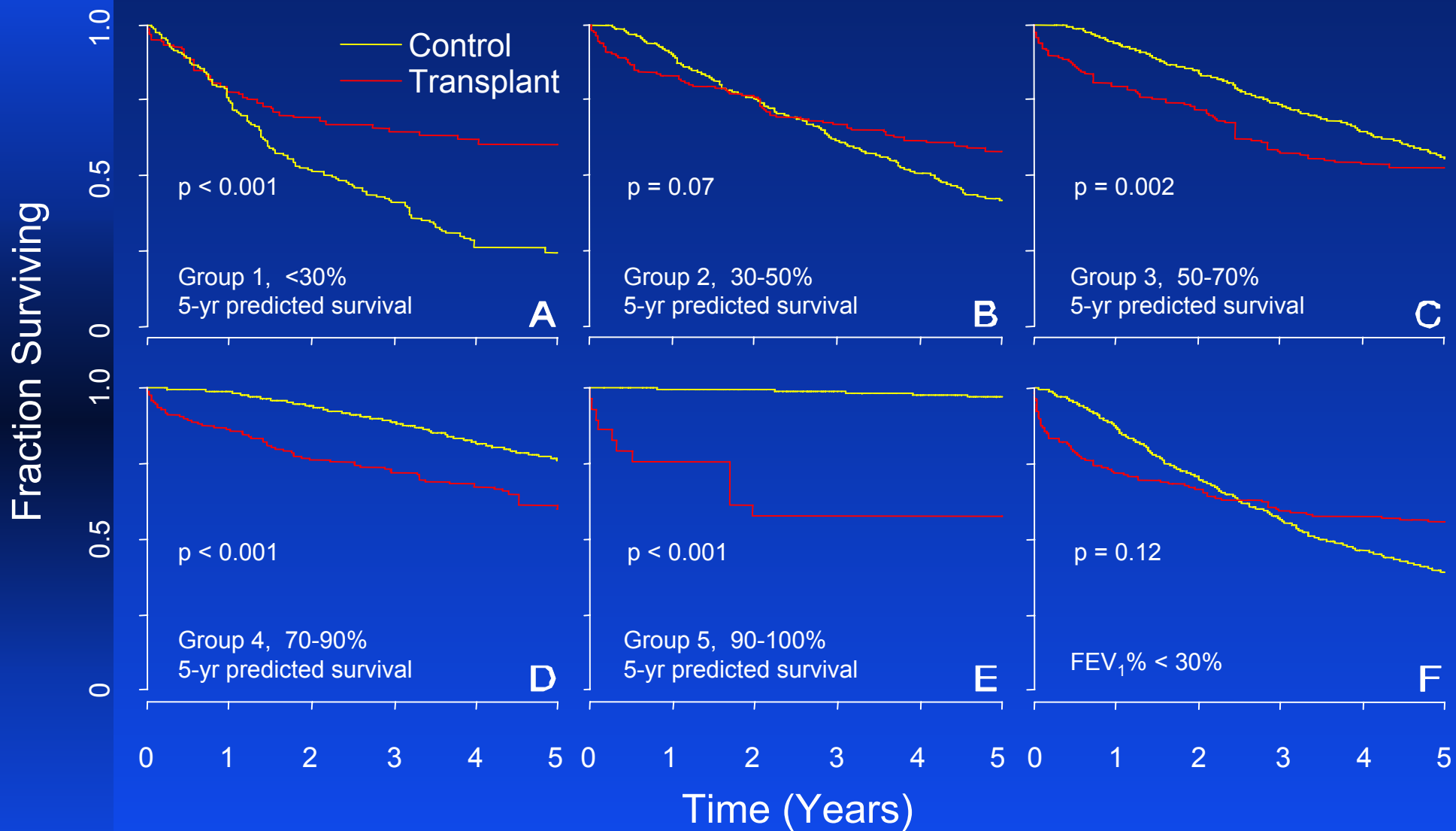
Increasing hospitalizations

Massive hemoptysis

## A Validated 5-Year Predictive Model of CF

Age (years)	-0.28	-0.7
Gender (Male=0, Female=1)	-0.23	-6
FEV <sub>1</sub> %	0.038	1
Weight-for-age z-score	0.40	10
Pancreatic Sufficiency (0 or 1)	0.45	12
Diabetes Mellitus (0 or 1)	-0.49	-13
<i>S. aureus</i> (0 or 1)	0.21	6
<i>B. cepacia</i> (0 or 1)	-1.82	-48
Acute Exacerbations (0-5)	-0.46	-12
Acute Exacerbations × <i>B. cepacia</i>	0.40	11

# Transplant Outcomes by 5-Year Predicted Survival



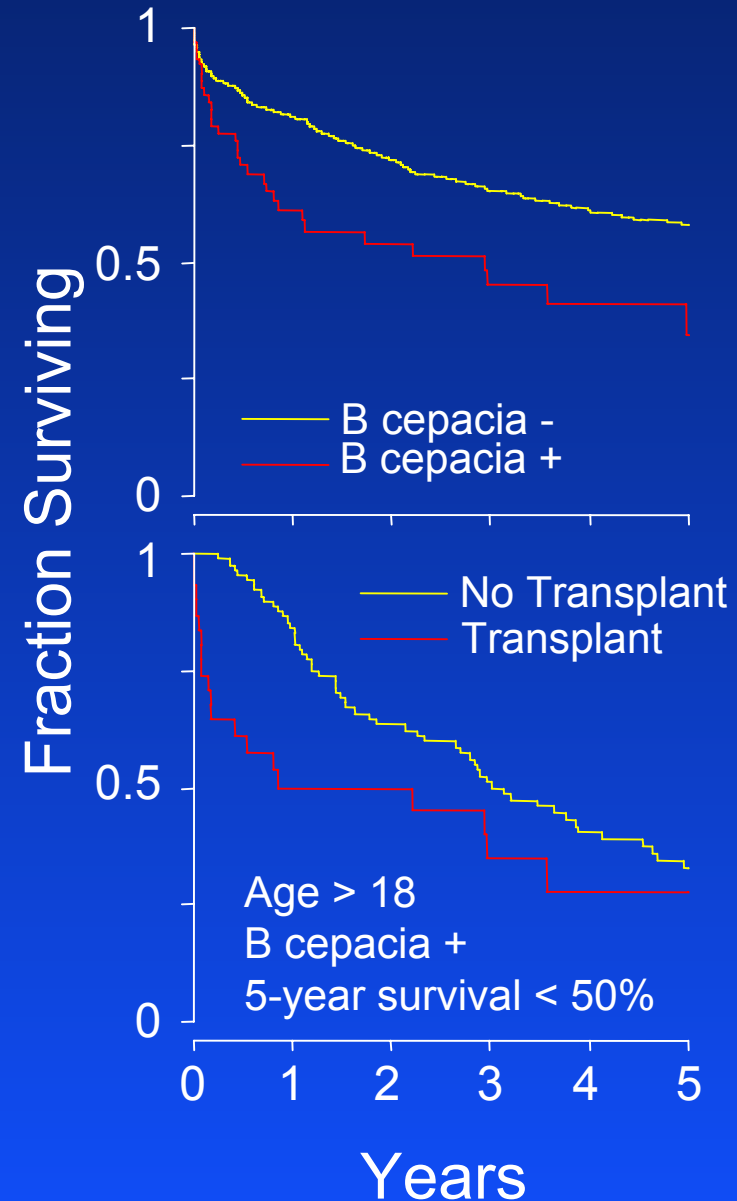
# Adults with *B cepacia*

Decreased survival post-transplantation compared to non-*B cepacia* infected recipients

Decreased survival compared to non-transplanted patients with same 5-year predicted survival

Liou *et al.* *AJRCCM* 2005; 171:1053-1059.

*But* no analysis by genomovar has been done

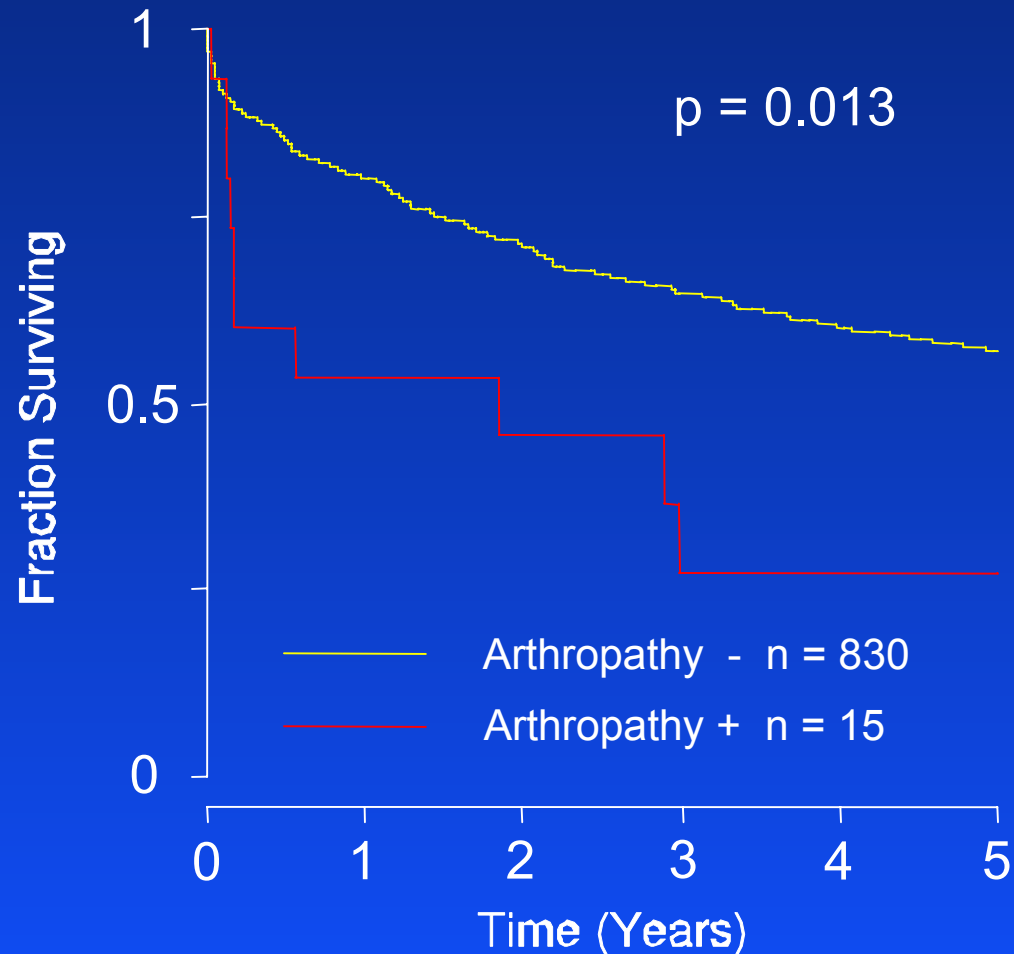


# Adults with CF Related Arthropathy

Marked decrease in survival

6 month survival <60%

Only 15 patients with arthropathy



# Critically Ill Patients on Ventilators

One year survival without transplant is poor

One year survival with transplant is only slightly less than other transplant recipients

These patients should be transplanted *if* organs can be located

Massard et al. *Ann Thorac Surg* 1993;55:1087-1092.

Sood et al. *AJRCCM* 2001;163:335-338.

Bartz et al. *J Heart Lung Transplant* 2004;22:433-438.

# Other Considerations

Multi-drug resistant *P aeruginosa* is not a problem

Aris et al. *AJRCCM* 1997;155:1699-1704

PaCO<sub>2</sub> is an unclear marker for transplant

Kerem et al. *NEJM* 1992;326:1187-1191

Belkin et al. *AJRCCM* 2006;173:659-666

Tantisira et al. *AJRCCM* 2002;165:1629-1633

Stanchina et al. *J Heart Lung Transplant* 2002;21:217-225

# Children with CF

*Aurora et al, Lancet 1999; 354:1591-93*

Proportional hazards model with time-dependent covariates

124 children with CF (47 transplanted)

Hazard factor 0.31 (0.13-0.72,  $p = 0.0007$ )

*Liou et al, AJRCCM 2005; 171:1053-59*

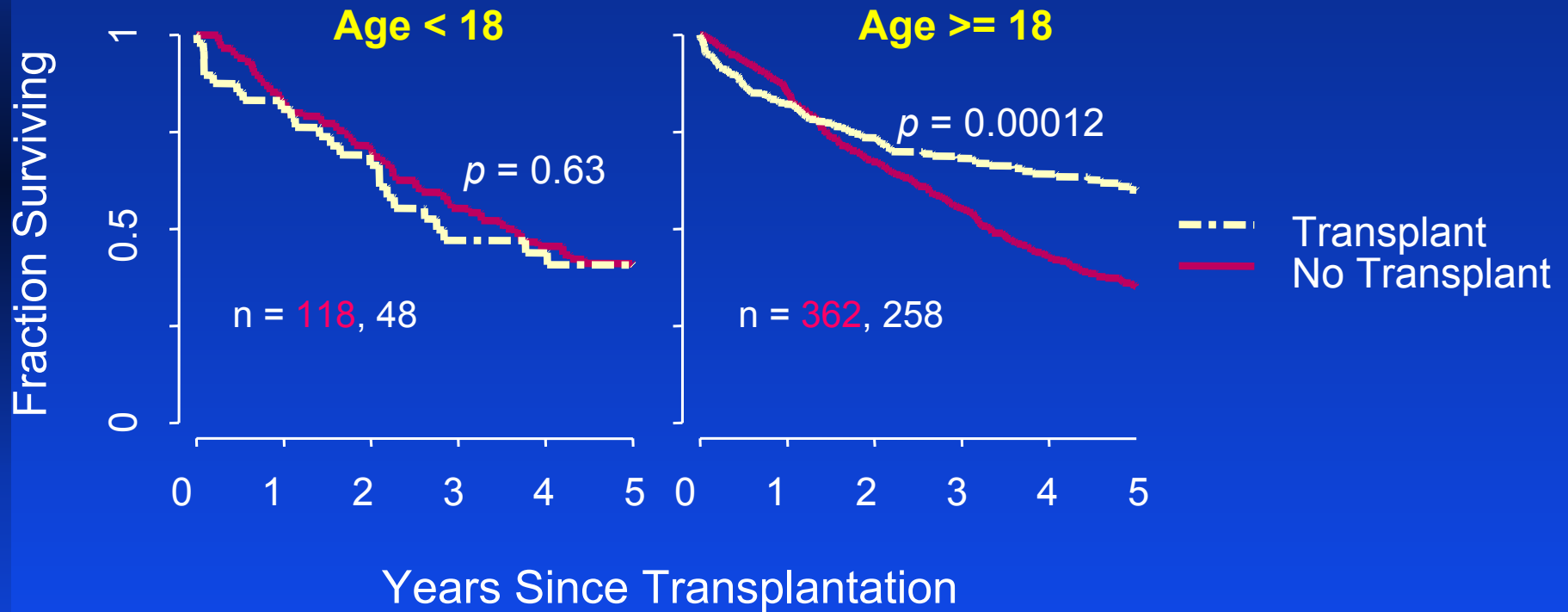
Kaplan-Meier Statistics

205 transplanted children compared to 1018 non-transplanted controls

Transplantation effect on survival,  $p = 0.63$

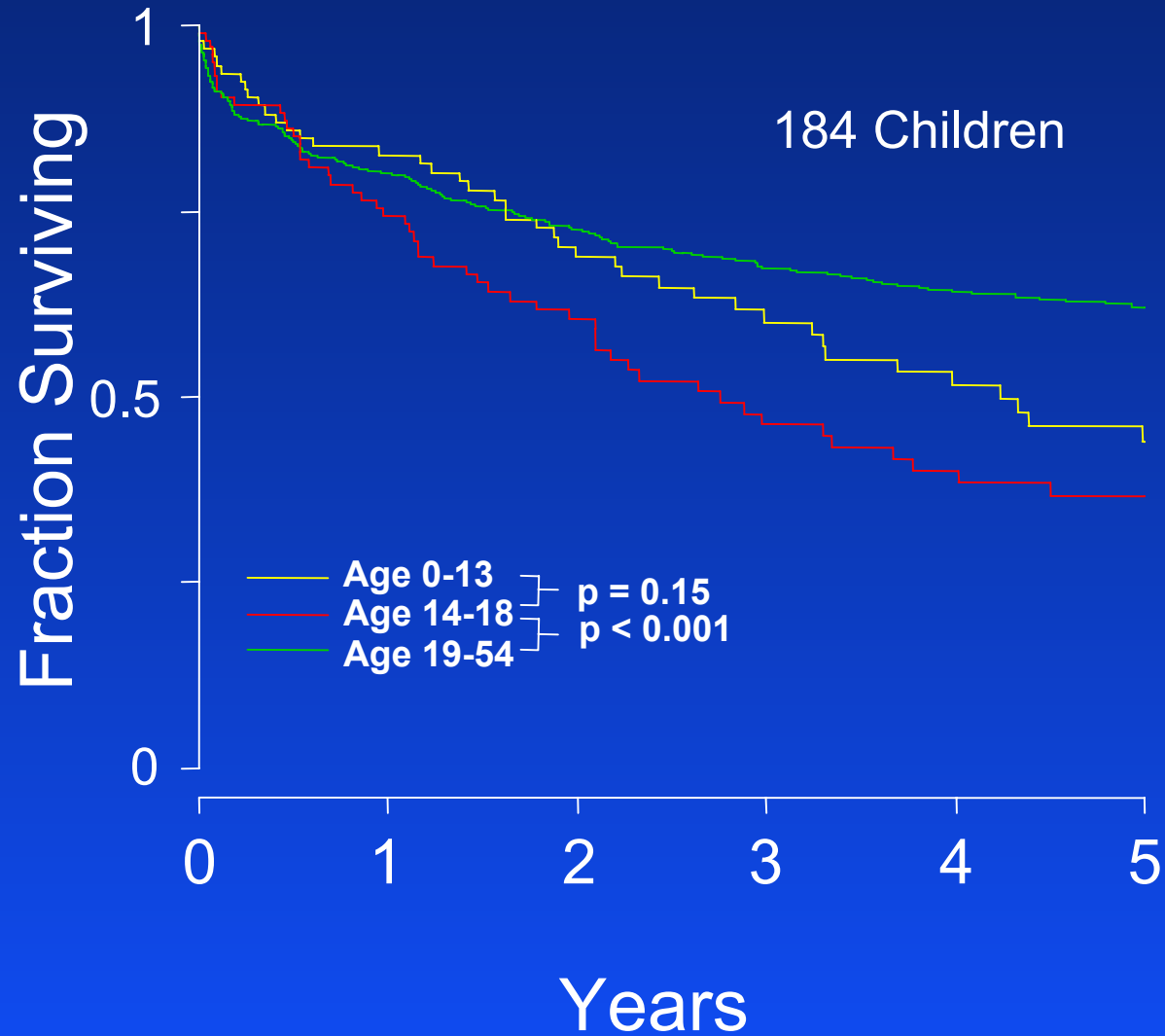
# Effect of Age on Survival Benefit of LT

5-Year Predicted Survival < 50%\*  
Without *B cepacia* infection



Liou et al, AJRCCM 2005; 171:1053-59  
\*Liou et al, Am J Epidemiol 2001;153:345-352.

# Effect of Age Cohort on Post Transplantation Survival



# A New Study

CFFPR 1992—2002

Data from 117 CF Centers in the US

31,394 Patients

UNOS Database 1988—2004

All US patients listed for lung transplant

21,679 Patients

Study Patients 1992—2002

3,364 patients with CF

602 patients younger than 18 years of age

# Proportional Hazards Model

Estimates covariate effects on time-to-death

Hazard factor: multiplicative change from baseline risk of death due to a covariate

Time-dependant covariate: Lung Transplant

Covariate interactions with transplant:

Reveals change in hazard with transplant

Key issue for deciding worth of transplantation

# Final Model

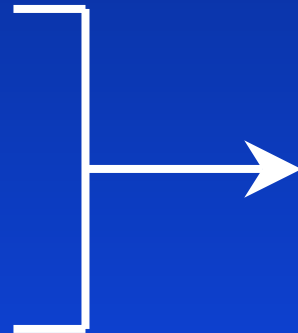
Transplantation

*B cepacia*

Age

Diabetes

*S aureus*



**Interaction with  
Transplantation**

# Results

Few children with CF have survival benefit

- Less than 12 years old with diabetes

- Less than 8 years old without *S aureus* and without diabetes

Many children do worse with transplant

- Children with *S aureus*

- Children with diabetes and *S aureus* older than 16

- Other children older than 13

*B cepacia* has no effect on lung transplant survival outcome

# Quality of Life (QOL)

No definitive study exists

Cross sectional studies conditioned on survival

QOL improves after transplant

QOL decreases with complications and rejection

Smeritschnig et al. J. Heart Lung Transplant 2005 24:474-480.

Kugler et al. J. Heart Lung Transplant 2005 24:2262-2268.

Not possible to predict which patients will have high quality of life after transplant

# US Lung Allocation Score

Manages patients with different end-stage lung disease on the wait list for transplant

Seeks to maintain equity between patients with different diseases

Seeks to maximize one year survival with transplant minus survival on the wait list

Does not really help to choose patients to list

# Summary

Several choices of surgical technique

Post surgical management requires intense management of immunosuppression

Selection of patients is difficult but there is more information for patients with CF than all other causes of end-stage lung disease

# Disclaimers

Part of the data reported here have been supplied by UNOS as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

The remaining data reported were supplied by the U.S. CF Foundation. The authors are responsible for interpretation and reporting of these data and do not express opinions or recommendations for the Foundation.