

Lung Transplantation



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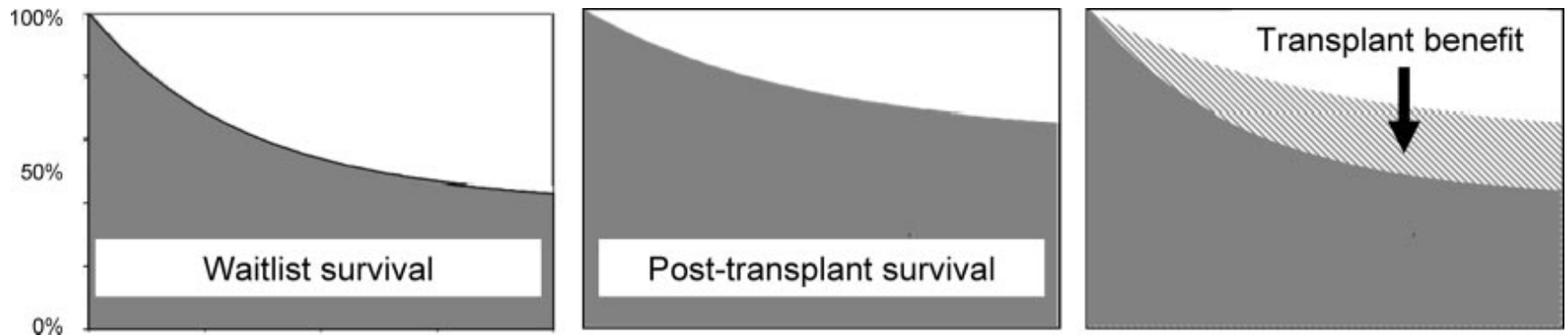
A Brief Overview

- General concepts
- Recipient selection
- Donor selection and management
- Post-transplantation complications

Lung Transplant General Concepts



Lung Transplantation – Why Do It?



Lung Transplant – What To Expect

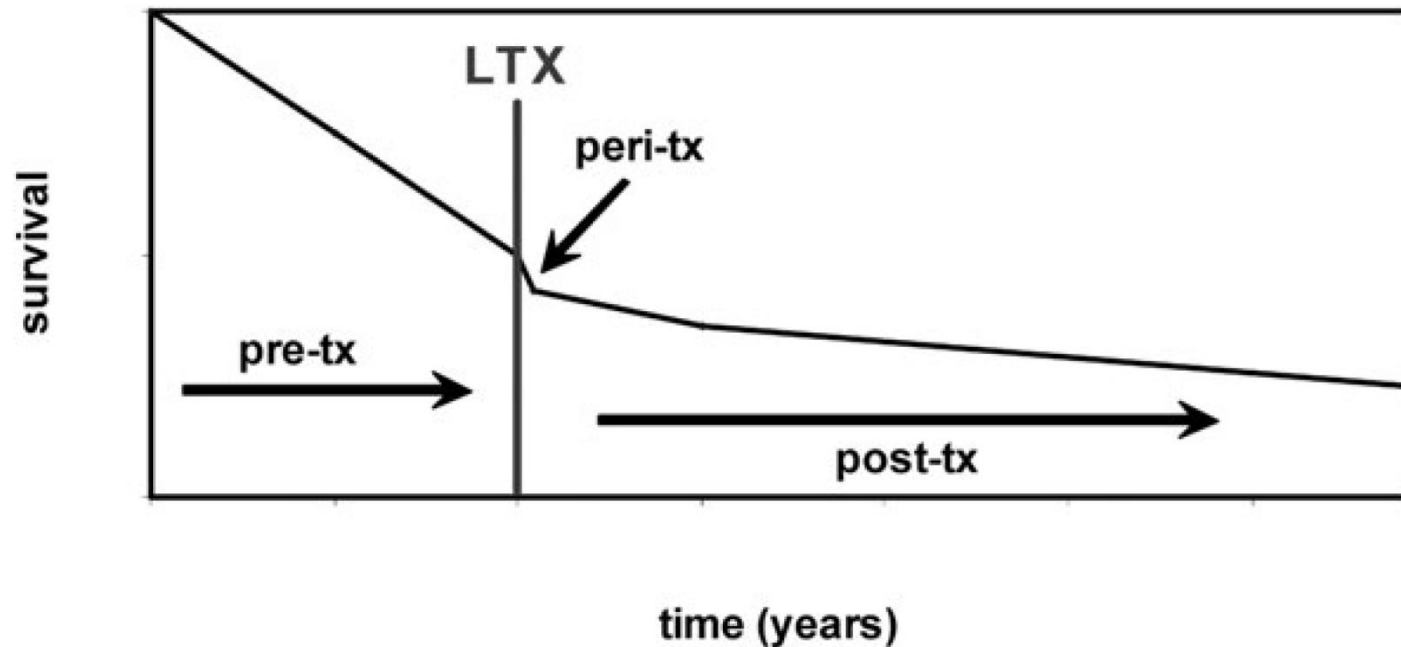


Figure LU 49: Total lung transplants by diagnosis

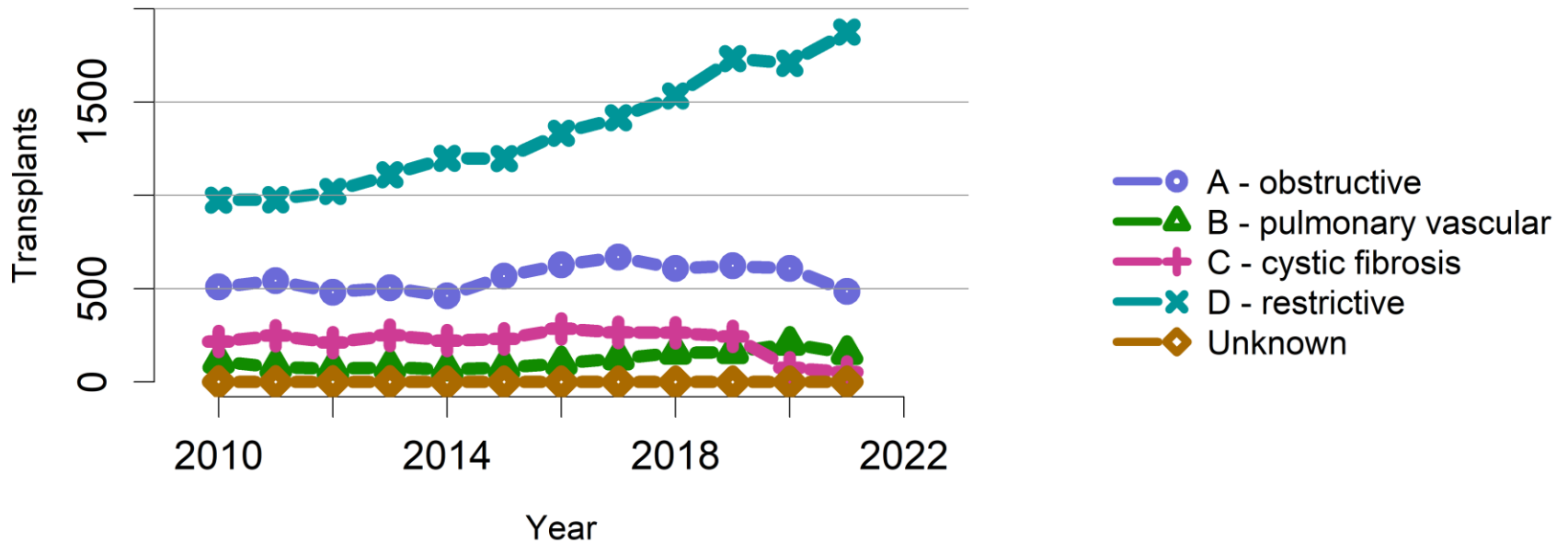


Figure LU 48: Total lung transplants by race

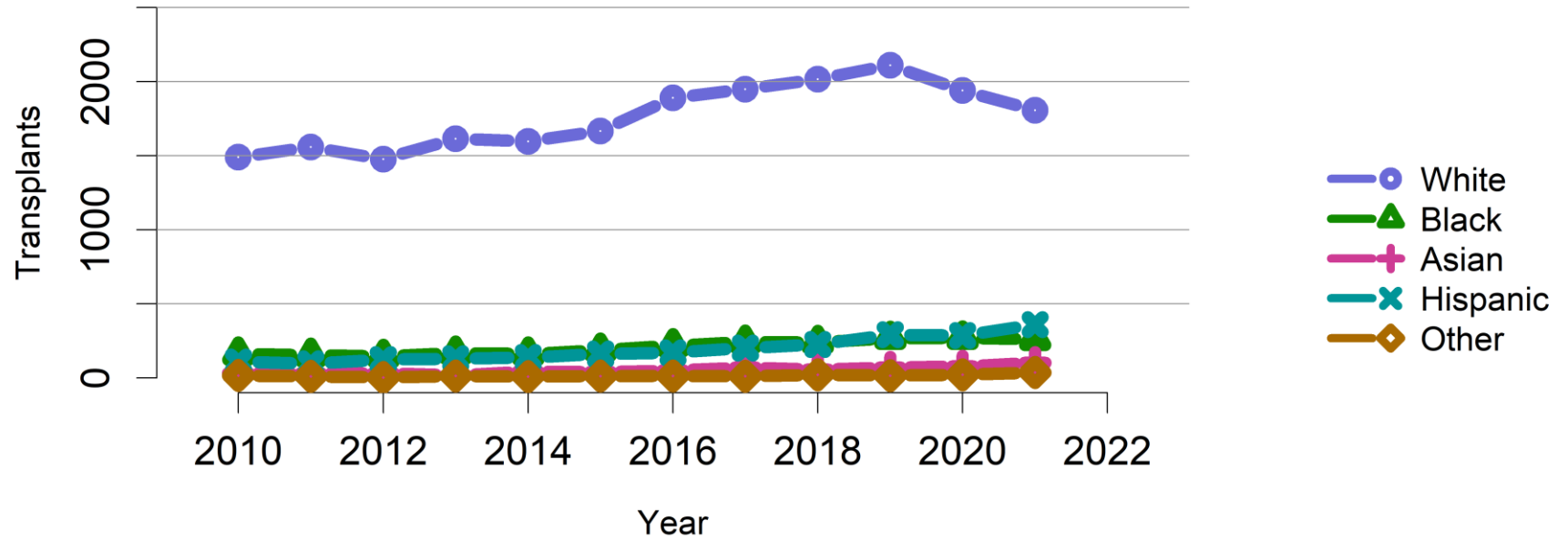


Figure LU 47: Total lung transplants by sex

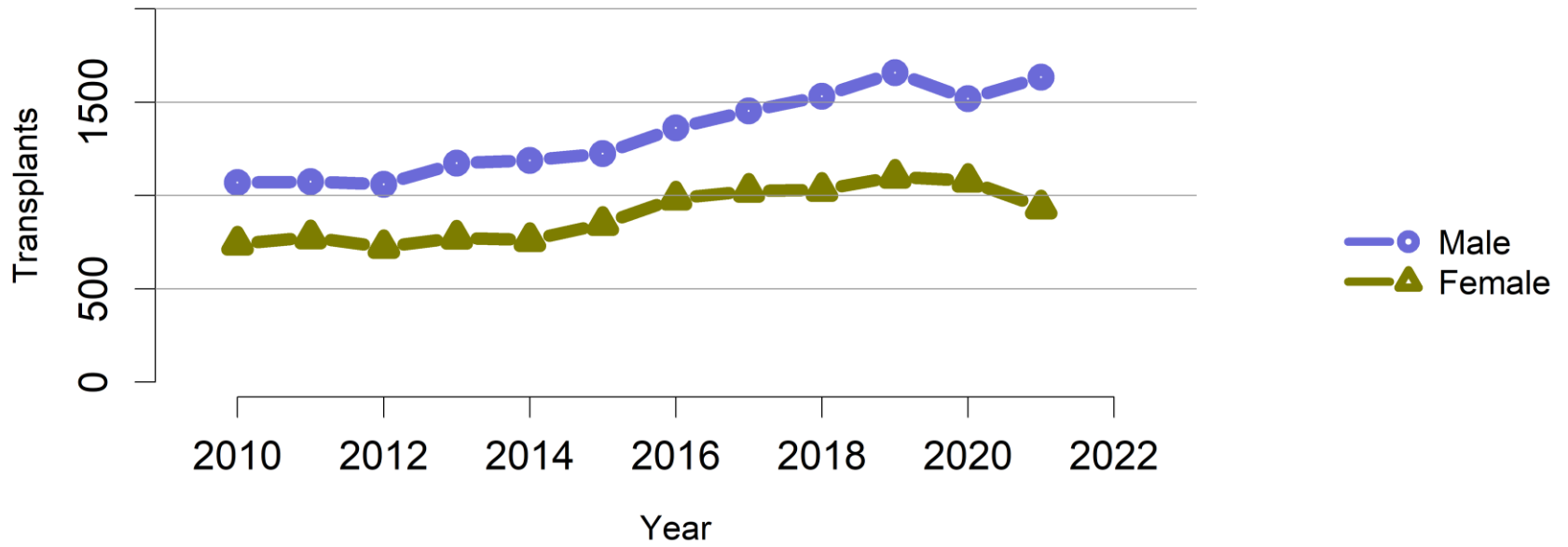
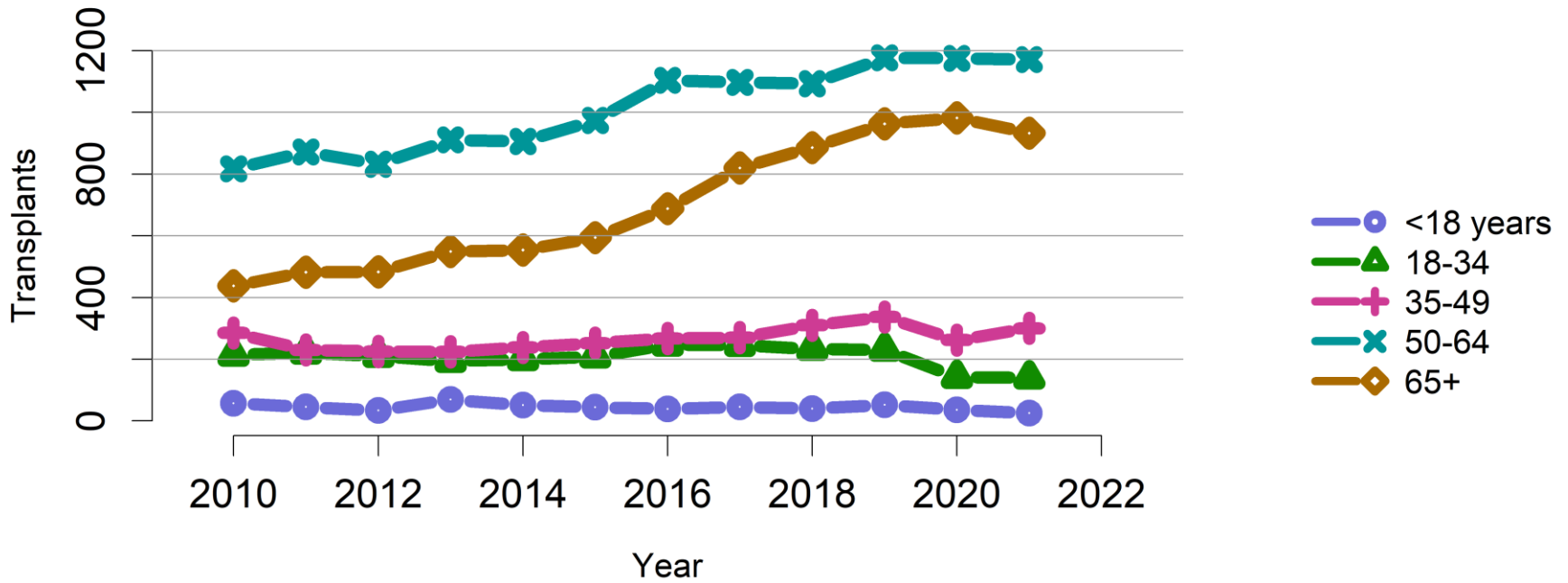


Figure LU 46: Total lung transplants by age



Recipient Selection



Recipient Selection Criteria

- ❑ Medical urgency
- ❑ Avoidance of futile transplants
- ❑ Minimize waiting times

Lung Allocation Score (LAS) was developed out of need to address these issues

A New World Order: LAS

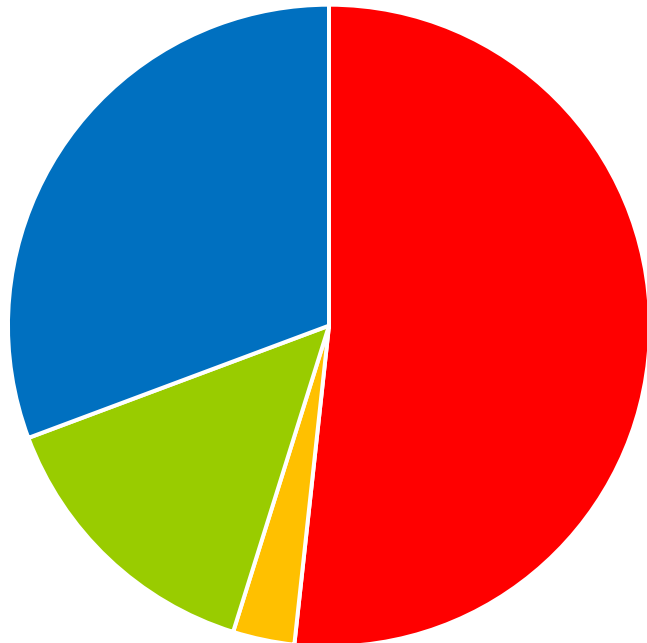
- Modeled a bit after MELD score
- Estimate the risk of death on waiting list
- Estimate the risk of death after transplant
- A total of 17 variables considered:
 - Age
 - BMI
 - Underlying diagnosis
 - Pulmonary HTN
 - 6MWD
 - Renal function

A New World Order: LAS

- Introduced in the USA in 2005
- Reduced mortality on waitlist by 20-40%
- Sicker patients get transplanted
- Adopted by many in Europe
 - Germany 2011
 - Netherlands 2014
 - Italy 2016
 - USA-LAS update 2015
 - ~ 60 % Worldwide use LAS

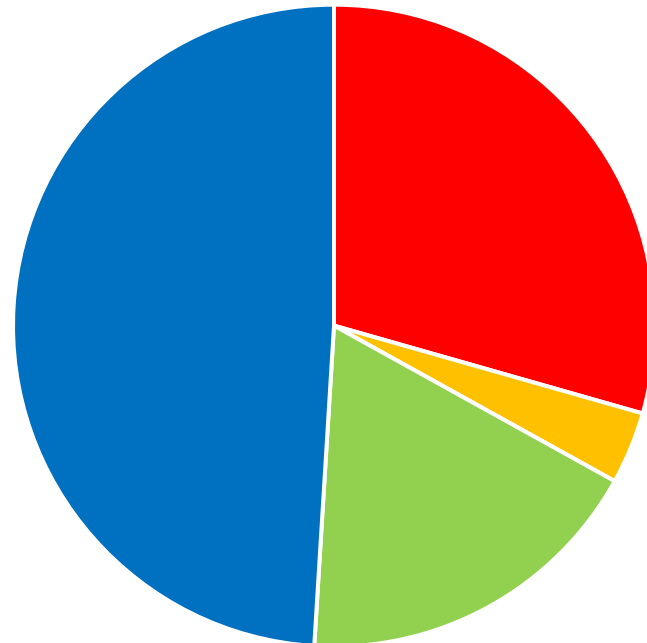
Lung Transplant Allocation

Pre-LAS



■ COPD ■ PPH ■ CF ■ IPF

LAS 2005



■ COPD ■ PPH ■ CF ■ IPF

Patient Selection – General Criteria

- High risk of death from lung disease (50%) without transplant
- High likelihood (80%) of surviving 90 days post transplant
- High likelihood (80%) of survival from the general medical perspective 5 years post-transplant

Patient Selection - Contraindications

- ❑ Malignancy
- ❑ Other major organ failure
- ❑ Severe atherosclerosis
- ❑ Acute unstable medical condition
- ❑ Uncontrollable bleeding
- ❑ Chronic infection with virulent/MDR bugs
- ❑ Chest wall/spinal deformity
- ❑ Extremis of weight
- ❑ Poor social support
- ❑ Substance abuse/dependence

Relative Contraindications

- Age
- Mild obesity (BMI 30-35)
- Malnutrition
- Osteoporosis
- Prior thoracic surgery
- Extracorporeal life support ***
- Hep B/C, HIV infection ***
- Colonization with virulent/MDR bugs
- Manageable atherosclerosis
- Other medical conditions without organ damage

ILD/IPF

□ Indications for Referral:

- FVC < 80% or DLCO < 40% predicted
- Any functional disability due to lung disease
- Any oxygen requirement
- Failure to improve after medical therapy

□ Indications for Listing:

- Decline in FVC > 10% in 6 months
- Decline in DLCO > 15% in 6 months
- 6MWD < 250m or decline > 50m in 6 months
- Pulmonary HTN
- Hospitalization related to exacerbation

COPD

□ Indications for Referral:

- Progressive disease
- Not a candidate for lung reduction surgery
- BODE index 5-6
- $PCO_2 > 50$, and/or $PO_2 < 60$
- $FEV_1 < 25\%$ predicted

□ Indications for Listing:

- BODE index > 7
- $FEV_1 < 20\%$ predicted
- One severe exacerbation with resp failure
- Moderate to severe pulmonary HTN

Pulmonary HTN

□ Indications for Referral:

- NYHA Functional Class III or IV
- Rapidly progressive disease
- Use of IV meds

□ Indications for Listing

- Cardiac index < 2
- mRAP > 15 mm Hg
- 6MWD < 350
- Hemoptysis, pericardial effusion, progressive R heart failure

Cystic Fibrosis

□ Indications for Referral:

- FEV1 < 30%
- 6MWD < 400m
- Pulmonary HTN
- Clinical decline w/frequent exacerbations

□ Indications for Listing

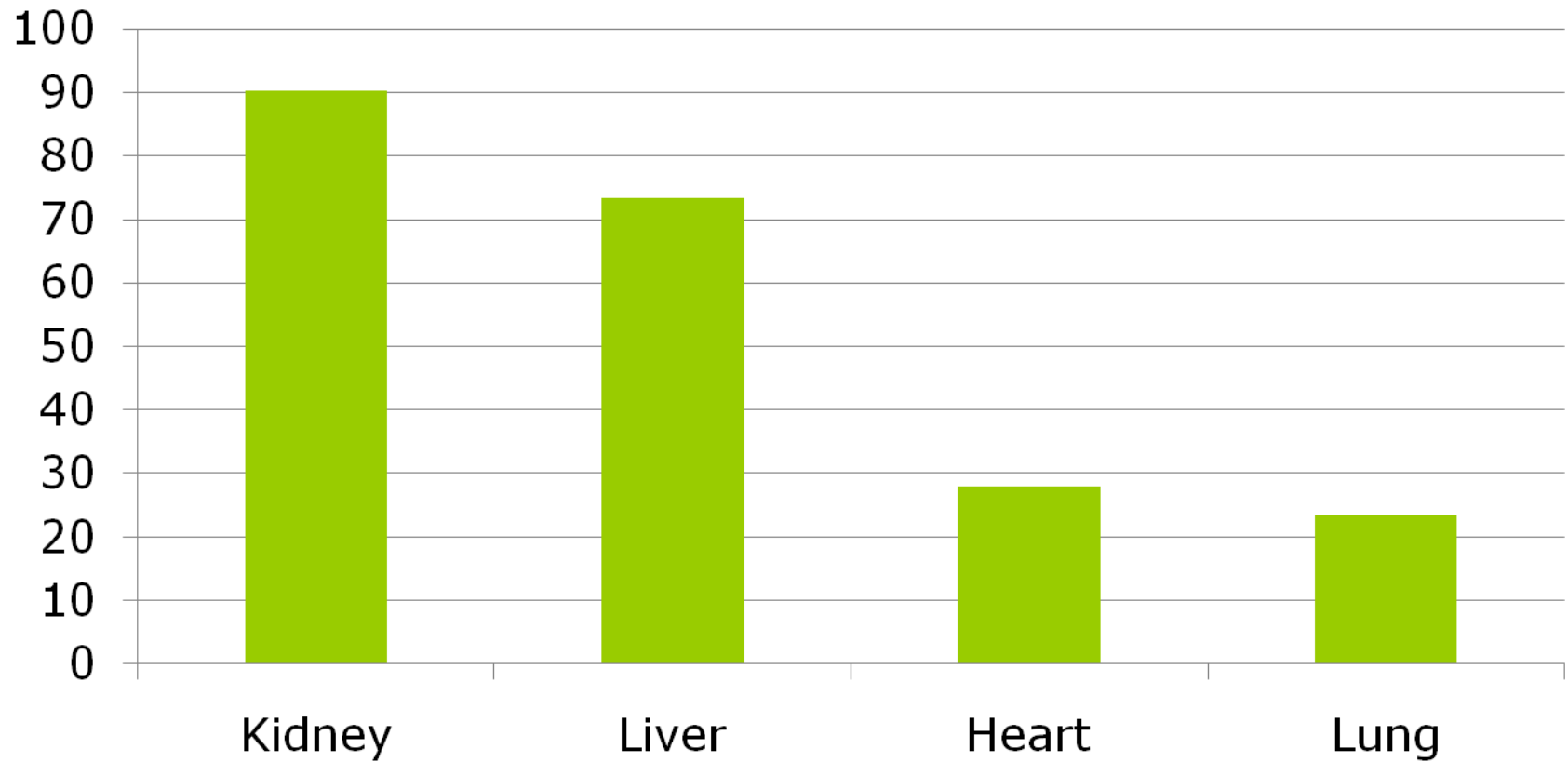
- Chronic respiratory failure
- Long term NIPPV use
- Rapid lung function decline
- WHO functional class IV

Donor Management



Lung Recovery Rates

% Suitable donors



Donor Selection: 'Ideal' Donors

TABLE 1. STANDARD ("IDEAL") LUNG DONOR CRITERIA

Age < 55 yr
Clear serial chest X-ray
Normal gas exchange ($\text{Pa}_{\text{O}_2} > 300$ mm Hg on $\text{Fi}_{\text{O}_2} = 1.0$, PEEP 5 cm H_2O)
Absence of chest trauma
No evidence of aspiration or sepsis
Absence of purulent secretions at bronchoscopy
Absence of organisms on sputum gram stain
No history of primary pulmonary disease or active pulmonary infection
Tobacco history < 20 pack-years
ABO compatibility
No prior cardiopulmonary surgery
Appropriate size match with prospective recipient

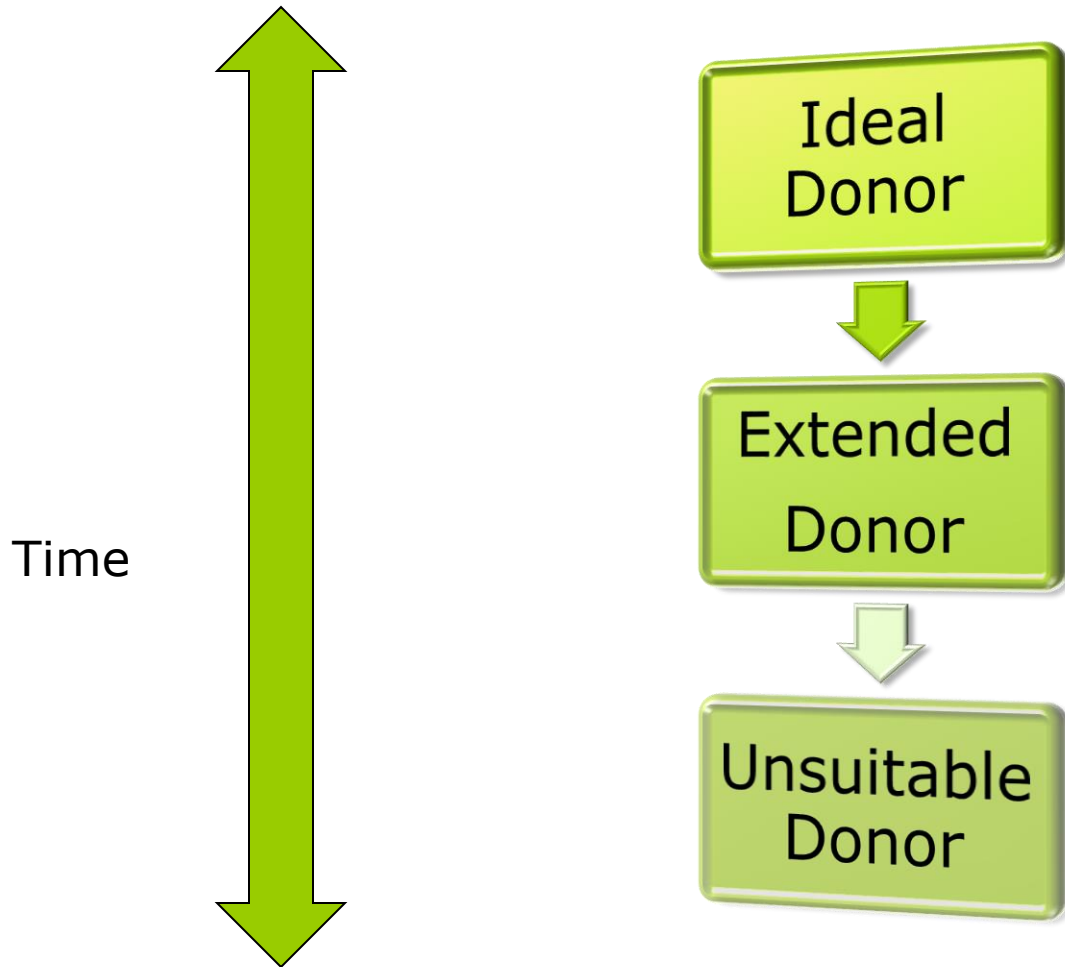
- ❑ Only 15-25% of donor pool
- ❑ Criteria not evidence-based
- ❑ Clinical judgement often substituted

Raemdonck et al; Proc ATS 2009

Non-”Ideal” Donors

- ❑ Extended criteria donors (ECD)
 - ❑ Becoming common practice
 - ❑ At least one marginal factor in majority of donors
- ❑ Donors after cardiac death
- ❑ Use of unsuitable donors after ex vivo lung perfusion (EVLP)

Donor Classification



Lung Recovery – Why So Bad?

- Resuscitation maneuvers
- Neurogenic edema
- Aspiration
- Pneumonia
- VILI
- PE

Donor Management – Brain Death

□ Autonomic crisis

- Increased SVR → LV afterload
- Increased LA filling pressures
- Redistribution of blood → increased RV output
- Hydrostatic pulmonary edema

□ Hypotension

- Fluid resuscitation
- SIRS cascade
- Cytokine-mediated pulmonary edema (ARDS)

Donor Management

- Volume management
 - Limited use of fluids for hypotension
 - Diuretics for pulmonary edema
 - β 2 agonists for alveolar fluid clearance
- Hormonal management
 - Steroids
 - Thyroids
- Lung protective strategies
 - Prevent atelectasis
 - Low tidal volumes???

What's Good For The Goose...

Table 3. End Points by Conventional and Protective Ventilatory Strategies

	Ventilatory Strategy, No. (%)		Difference of Percentage (95% CI)
	Conventional (n = 59)	Protective (n = 59)	
Met lung donor eligibility criteria			
At study inclusion	49 (83)	51 (86)	3 (-4.0 to 24.4)
6 h after randomization	32 (54) ^a	56 (95) ^b	41 (26.5 to 54.8)
Lungs harvested			
Yes	16 (27)	32 (54) ^c	27 (10.0 to 44.5)
No	16/32 (50) ^d	24/56 (43) ^d	7 (0 to 29.3)
Reasons lungs not harvested			
Functional	4 (25)	7 (29)	
Infectious	3 (19)	4 (17)	
Inspection	3 (19)	5 (21)	
Donor-receipient incompatibility	4 (25)	5 (21)	
Logistical	2 (12)	3 (12)	

Mascia et al; JAMA 2010

Post-Transplant Care



Post-Transplantation Vocabulary

- PGD – primary graft dysfunction
- CLAD – Chronic lung allograft dysfunction
 - BOS – bronchiolitis obliterans (obstructive pattern)
 - RAS – restrictive allograft syndrome
- ACR – acute cellular rejection
- AMR – antibody-mediated rejection

Complications of Lung Transplant

- Primary Graft Dysfunction
- Rejection
 - Acute
 - Chronic (CLAD, formerly BOS)
- Infection
- Miscellaneous
 - Cardiac
 - Renal
 - Metabolic

PGD

- Happens within first week of transplant
- Severe respiratory failure
 - ARDS of the graft
- Must exclude
 - Volume overload
 - Acute rejection
 - Infection
 - Surgical complications

PGD – Risk factors

□ Risk factors:

- Suboptimal recipient
- Suboptimal donor
- Suboptimal organ handling
- Molecular biology being investigated

□ Management – supportive

- Lung-protective ventilation
- ECMO

Acute Cellular Rejection

- ❑ 1 week – 1 year post-transplant
- ❑ Non-specific signs & symptoms
- ❑ CXR/CT scan non-diagnostic
- ❑ Biopsy needed for diagnosis
 - ❑ At least 5 biopsies
 - ❑ Neutrophil-rich infiltrates on histology
- ❑ Immunosuppression (steroids) for Rx
- ❑ Major risk factor for CLAD

Antibody Mediated Rejection

- ❑ Mechanism of disease poorly understood
- ❑ Diagnosis difficult to make
- ❑ Treatment guidelines not well established
- ❑ Mortality close to 50% in 1 year post-diagnosis

CLAD – Chronic Rejection

- ❑ Leading cause of death 1 year post-transplant (20-30% of all deaths)
- ❑ Obstructive vs Restrictive vs Mixed
 - ❑ Persistent decline in FEV1 (>20%)
 - ❑ No other identifiable cause
 - ❑ Treatment: immunosuppression

CLAD – Treatment Options

- More immunosuppression
- Notable mentions
 - Azithromycin
 - Montelukast
 - Antifungal Rx
 - GERD treatment
 - Prevent aspiration

Infection

□ Bacterial

- MRSA/Pseudomonas
- Other nosocomial organisms
- Pneumococcus/chlamydia

□ Fungal

- Aspergillus
- Candida

□ Viral

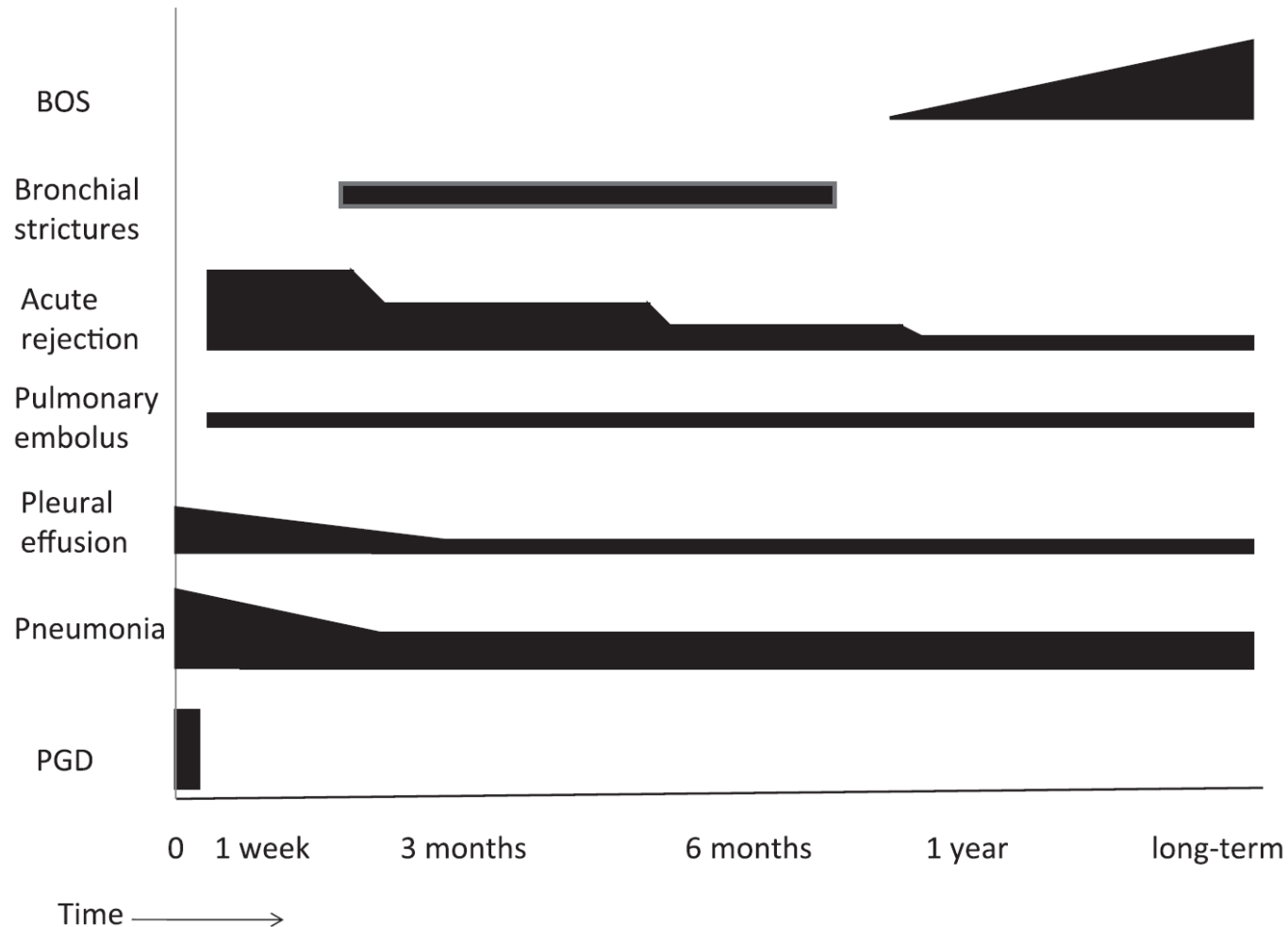
- CMV
- EBV → Post-transplant lymphoproliferative disorder

Mortality After Lung Transplantation

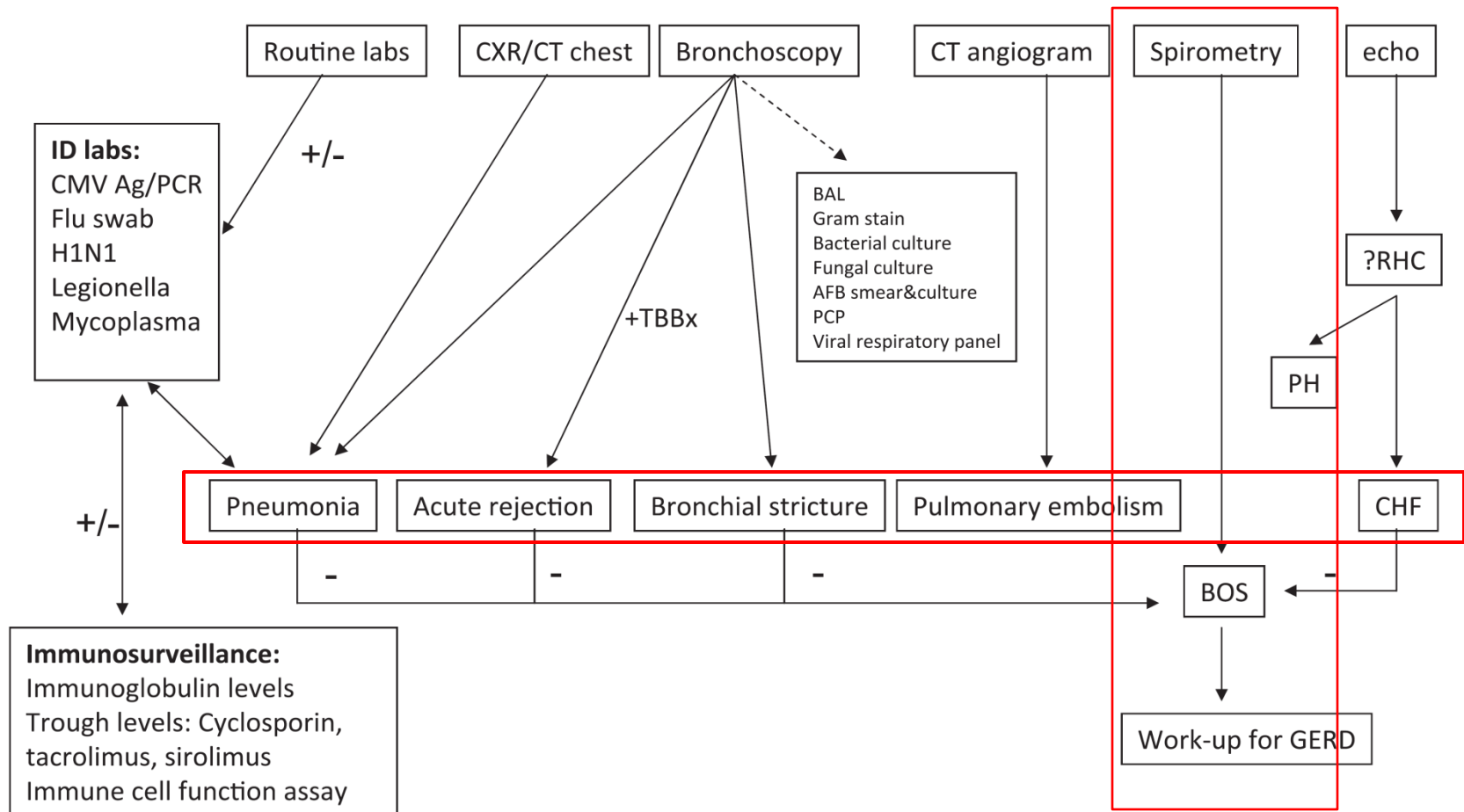
Table 2 Causes of Death After Lung Transplantation in Adult Recipients (Deaths: January 1992 to June 2009)

Cause of death	0–30 days	31 days–1 year	>1–3 years	>3–5 years	>5–10 years	>10 years
	(<i>n</i> = 1,966) No. (%)	(<i>n</i> = 3,387) No. (%)	(<i>n</i> = 3,073) No. (%)	(<i>n</i> = 1,737) No. (%)	(<i>n</i> = 2,014) No. (%)	(<i>n</i> = 483) No. (%)
Bronchiolitis	6 (0.3)	159 (4.7)	781 (25.4)	508 (29.2)	507 (25.2)	95 (19.7)
Acute rejection	74 (3.8)	61 (1.8)	48 (1.6)	10 (0.6)	15 (0.7)	1 (0.2)
Lymphoma	1 (0.1)	86 (2.5)	63 (2.1)	28 (1.6)	46 (2.3)	23 (4.8)
Other malignancy	4 (0.2)	100 (3.0)	202 (6.6)	151 (8.7)	219 (10.9)	47 (9.7)
Infection						
CMV	0	96 (2.8)	29 (0.9)	5 (0.3)	4 (0.2)	0
Non-CMV	396 (20.1)	1,205 (35.6)	710 (23.1)	329 (18.9)	363 (18.0)	81 (16.8)
Graft failure	557 (28.3)	589 (17.4)	591 (19.2)	327 (18.8)	379 (18.8)	87 (18.0)
Cardiovascular	213 (10.8)	144 (4.3)	118 (3.8)	82 (4.7)	99 (4.9)	36 (7.5)
Technical	162 (8.2)	76 (2.2)	18 (0.6)	8 (0.5)	12 (0.6)	6 (1.2)
Other	553 (28.1)	871 (25.7)	513 (16.7)	289 (16.6)	370 (18.4)	107 (22.2)

Timing of Complications



Diagnostic Algorithm



Lung Transplant - Summary

- ❑ LAS changed the landscape of lung transplant allocation
- ❑ Timing of referral depends on the nature and severity of lung disease
- ❑ Donor lung treatment very similar to routine ICU management
- ❑ Brief overview of post-transplant complications