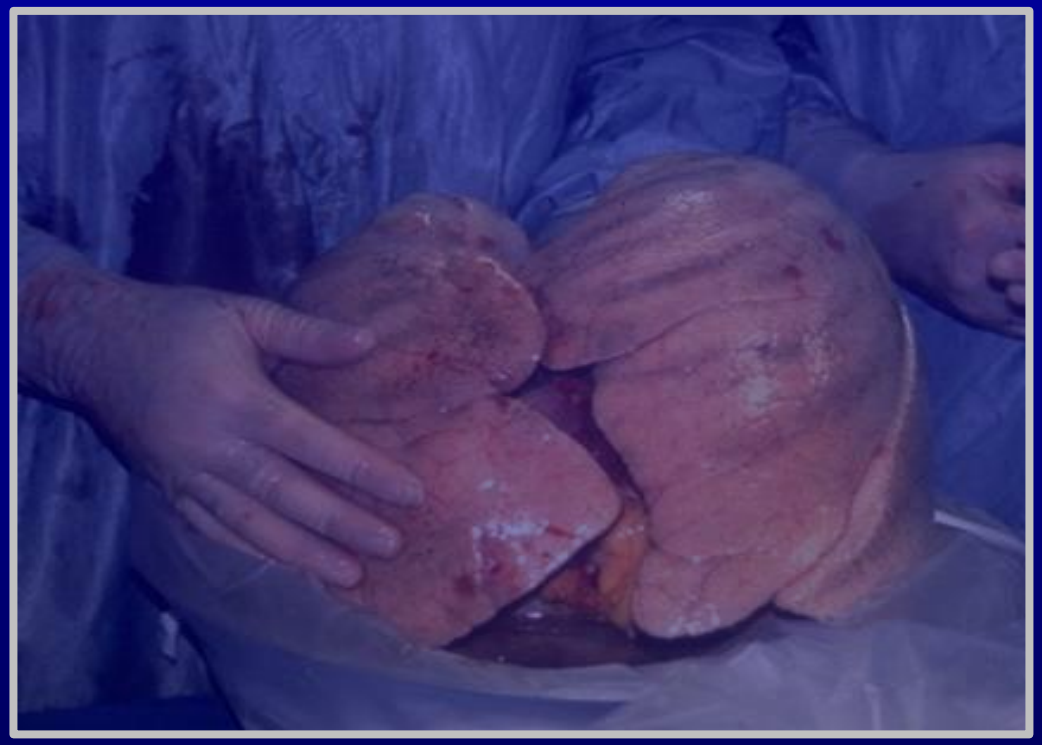


Lung Transplantation For the Internist

Tony N Hodges MD FCCP FACP

Discussion Focus

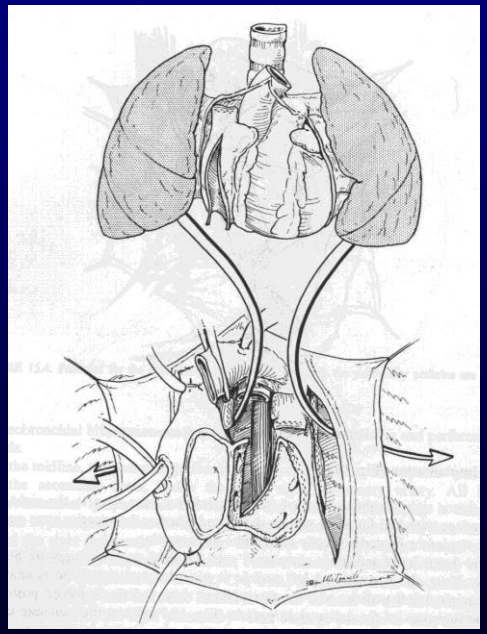
- Historical Background
- Indications/Contraindications
- Timing of Referral
- Surgical Technique
- Postoperative Management and Complications
- Survival and Functional Outcomes
- Future Directions

Historical Perspective

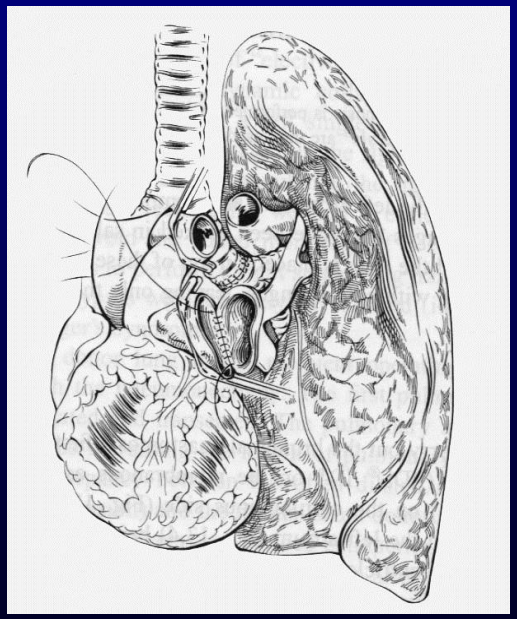
1963 - James Hardy performed first lung transplant
1976 - Cyclosporine introduced
1981 - Stanford performs first heart-lung transplant
1983 - Toronto performs first single lung transplant
1986 - Toronto performs first double lung transplant
1987 - Wash U/Barnes first single lung transplant in US
1992 - USC performed first living lobar lung transplant
2005 - Lung Allocation Score Introduced

Lung Transplant Options

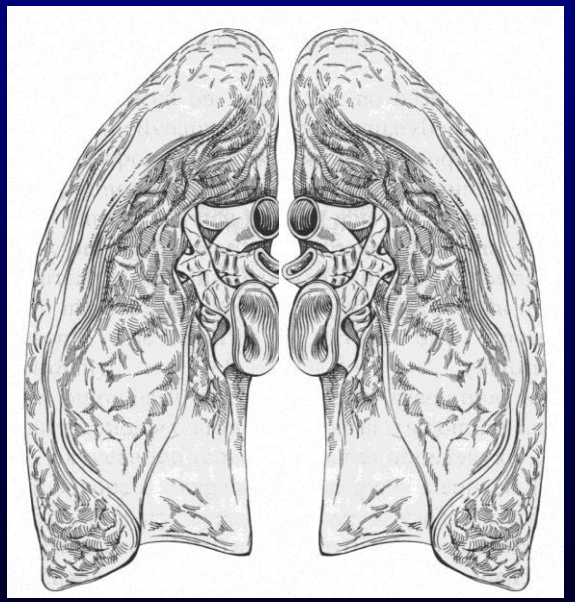
Heart-Lung TX

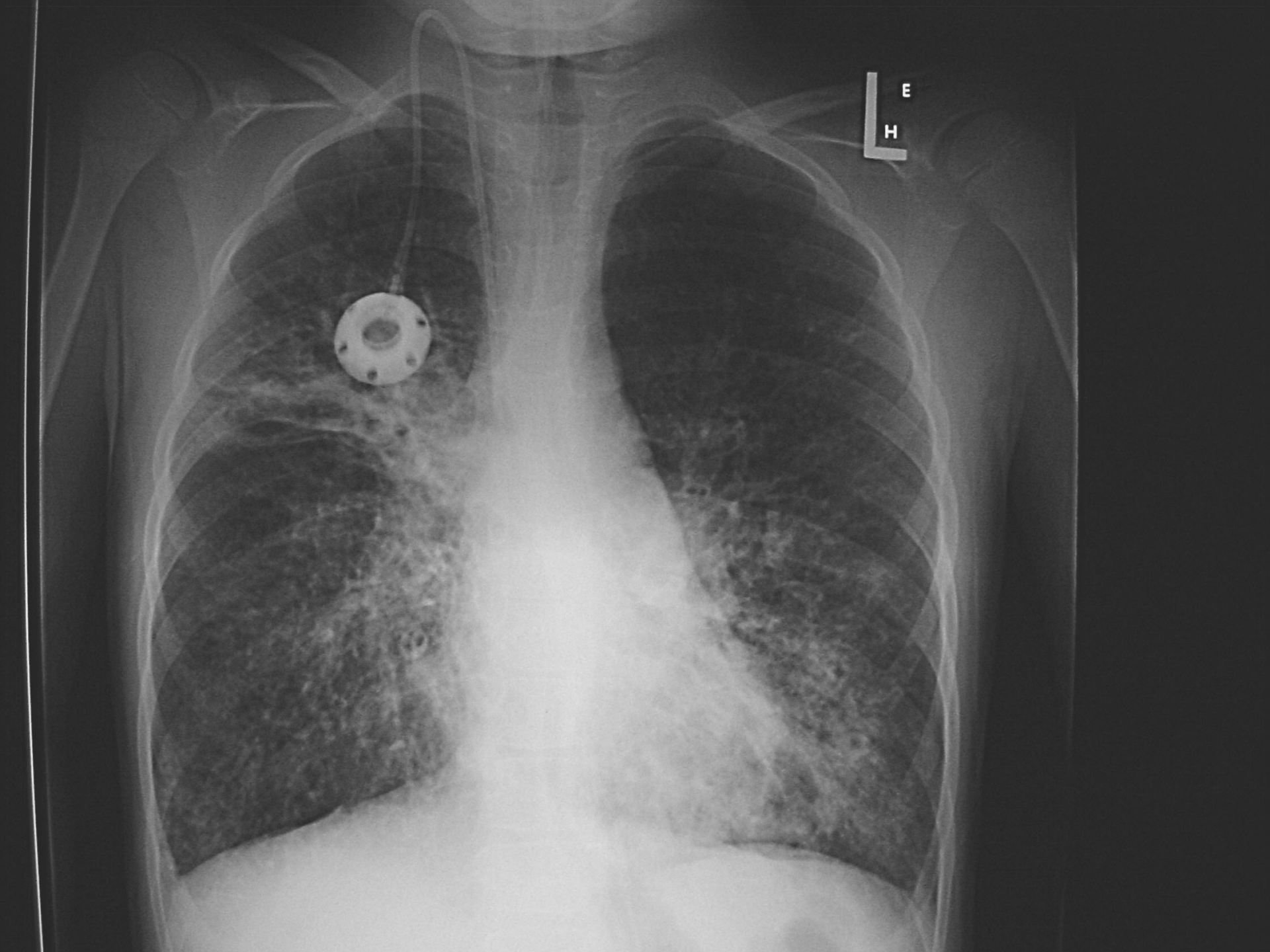


Single Lung TX



Bilateral Sequential Lung TX

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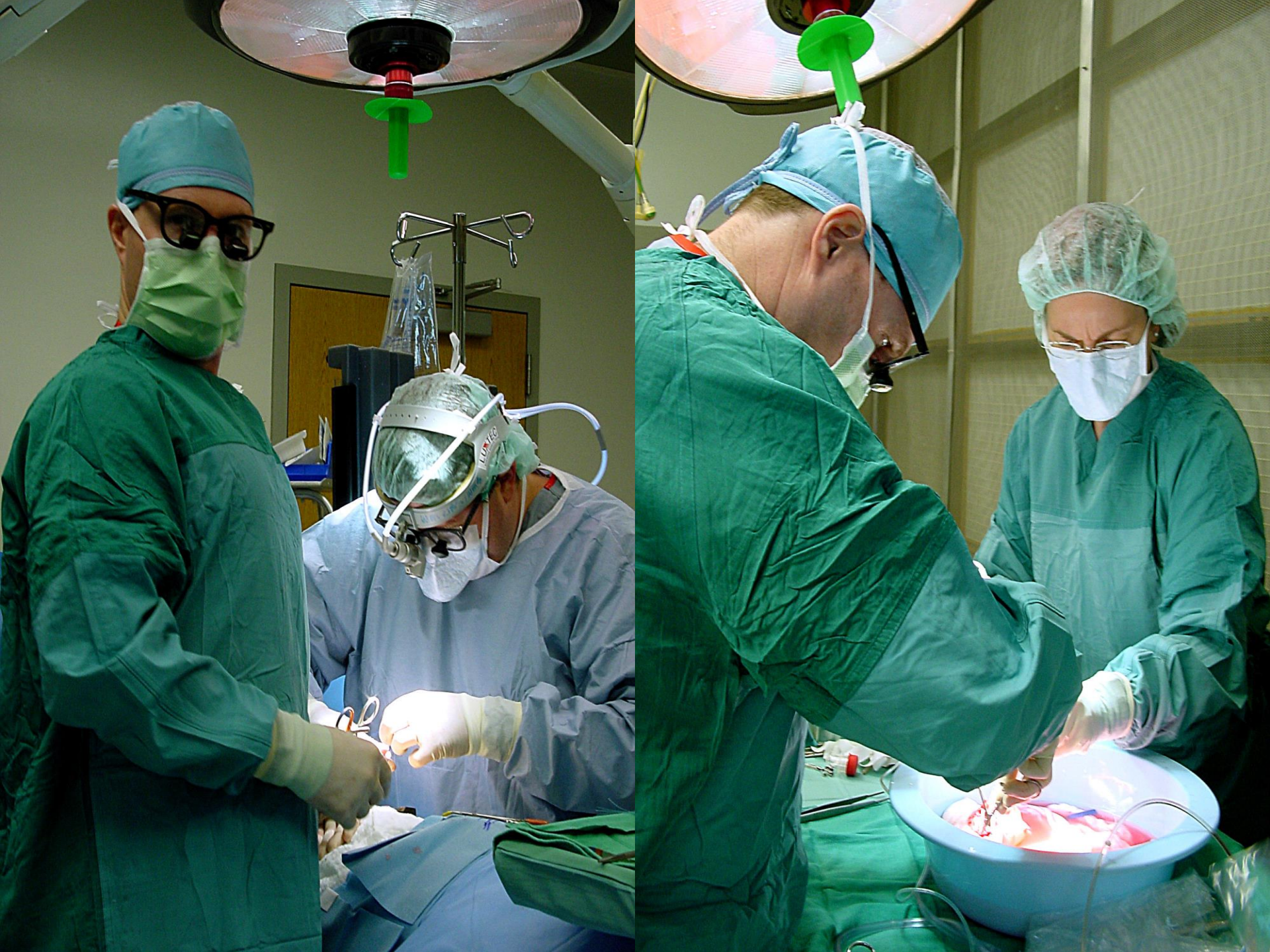
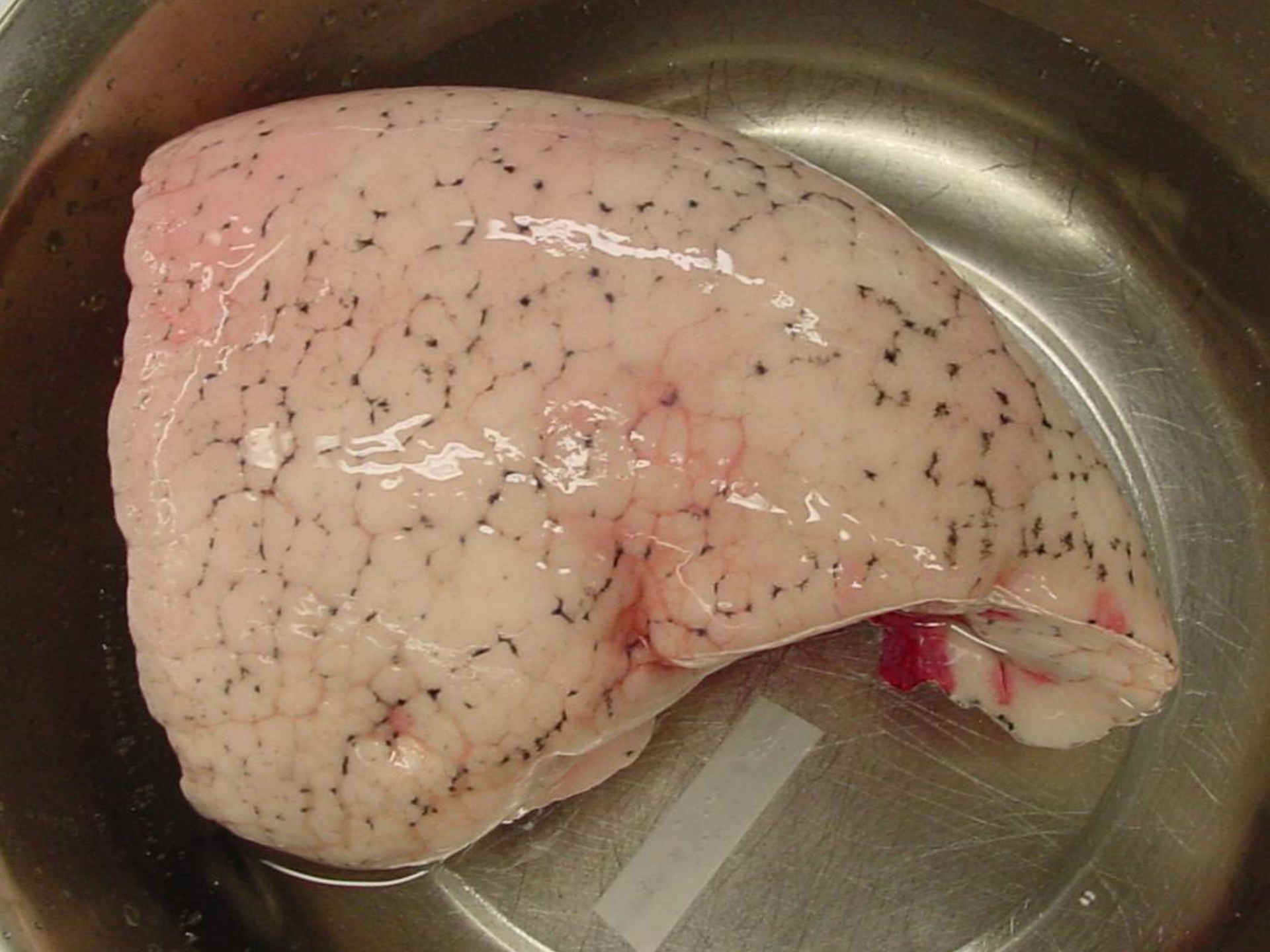
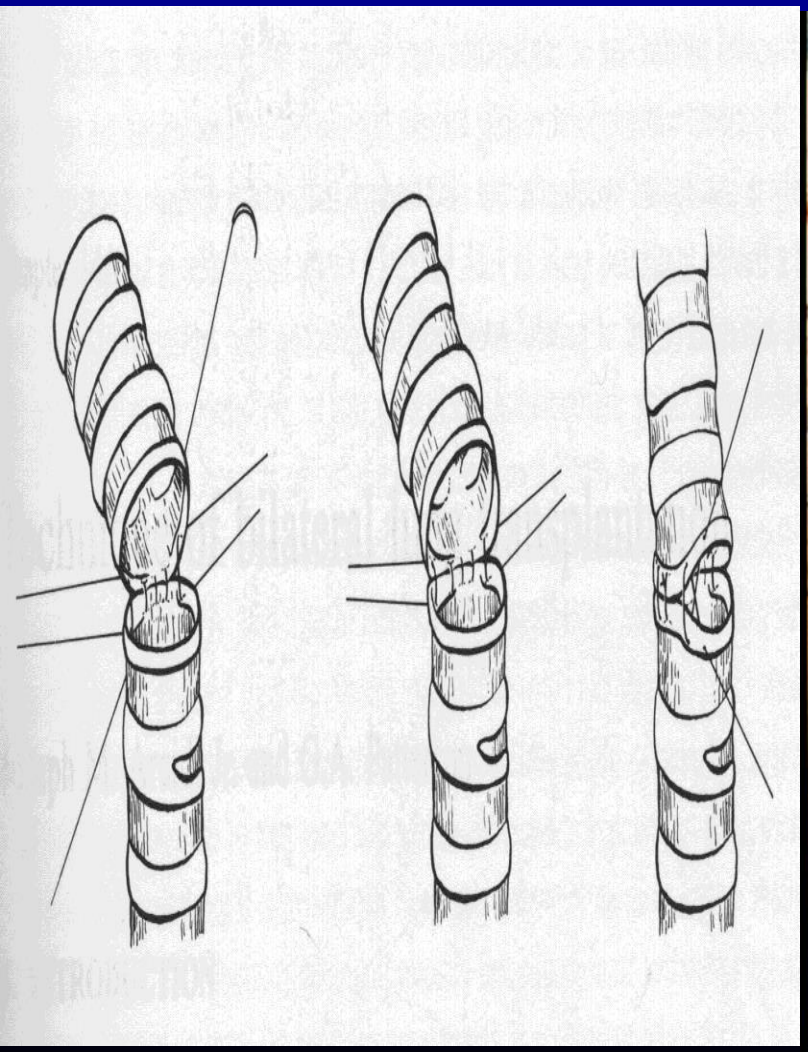
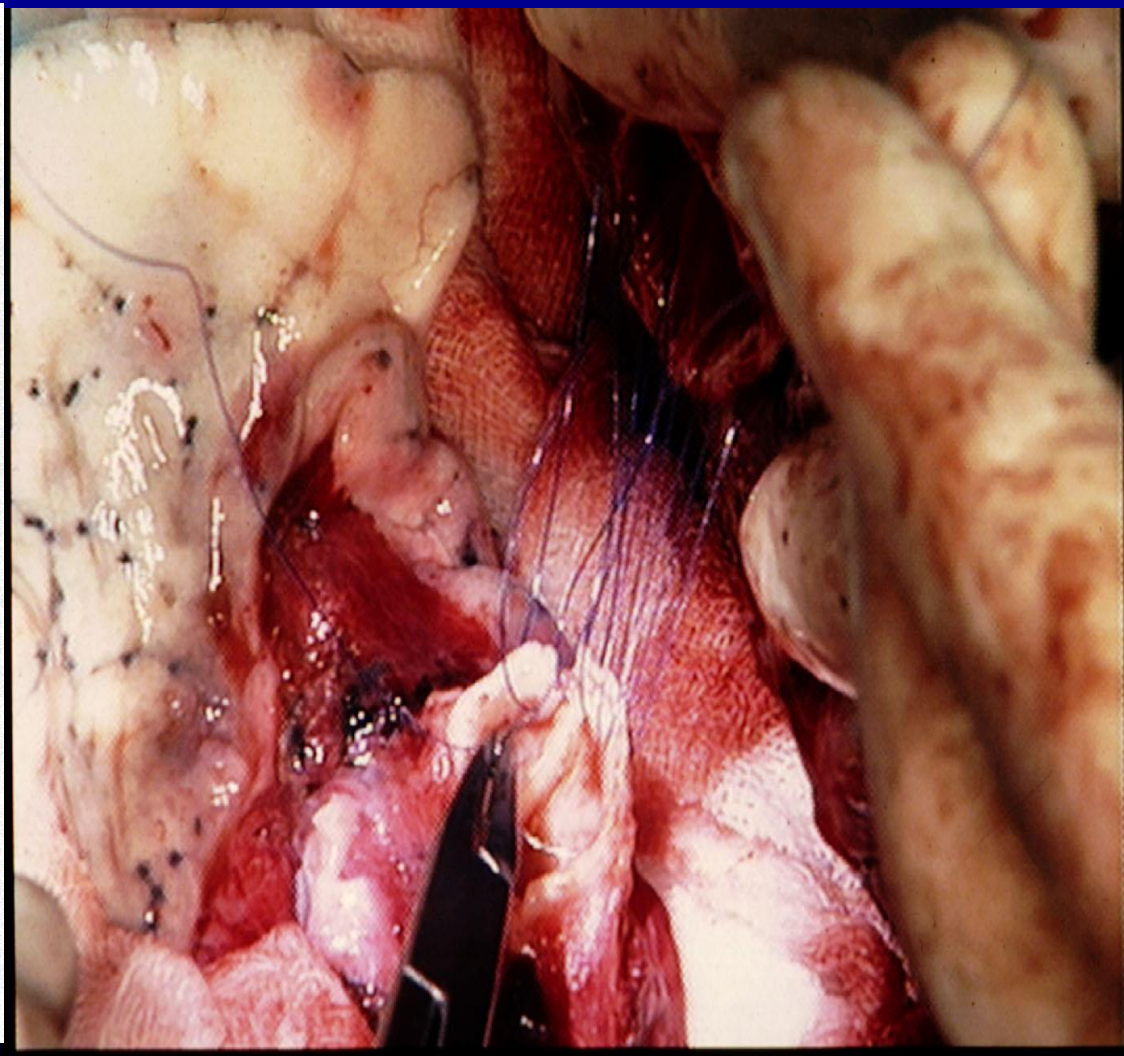
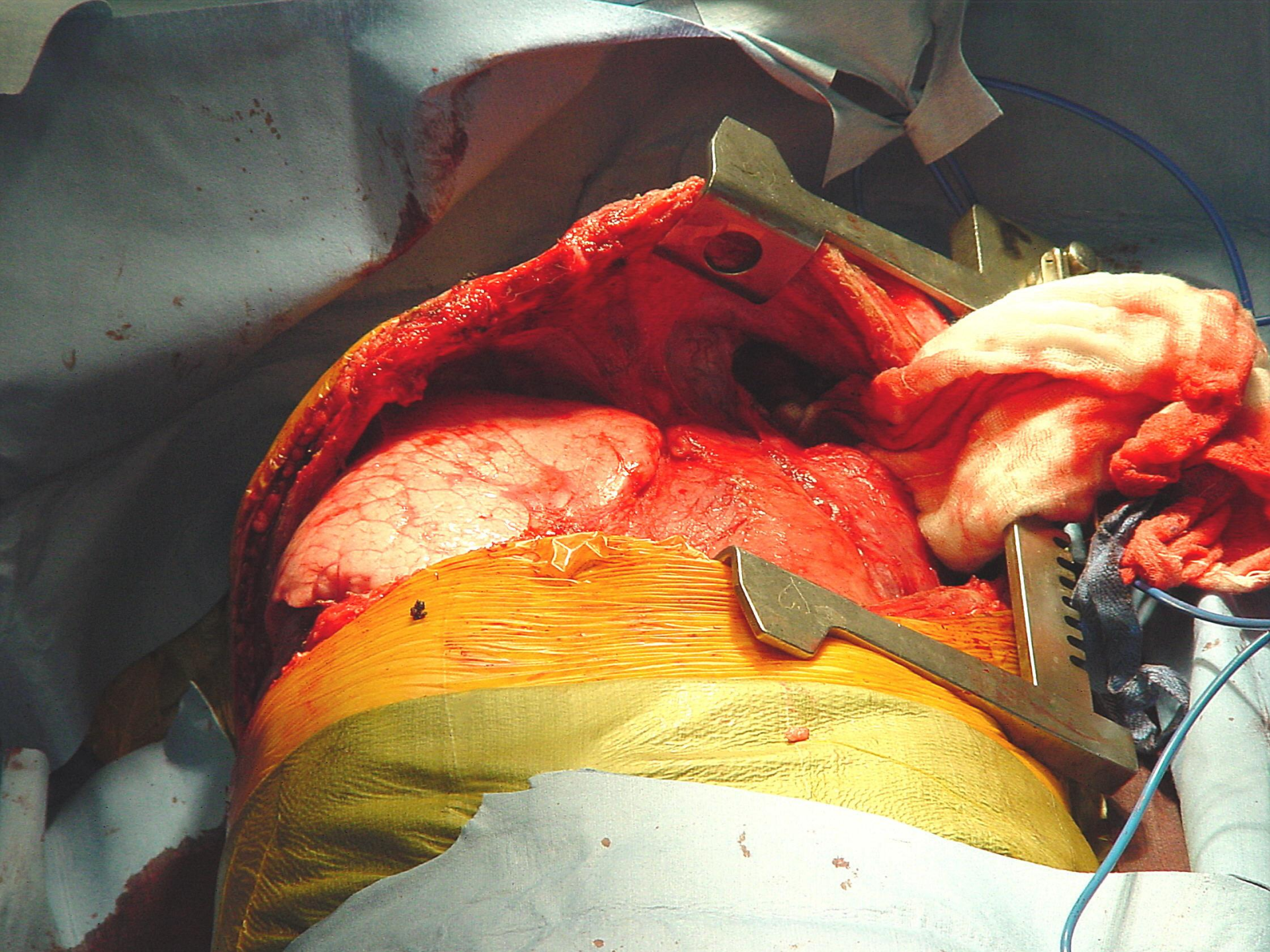


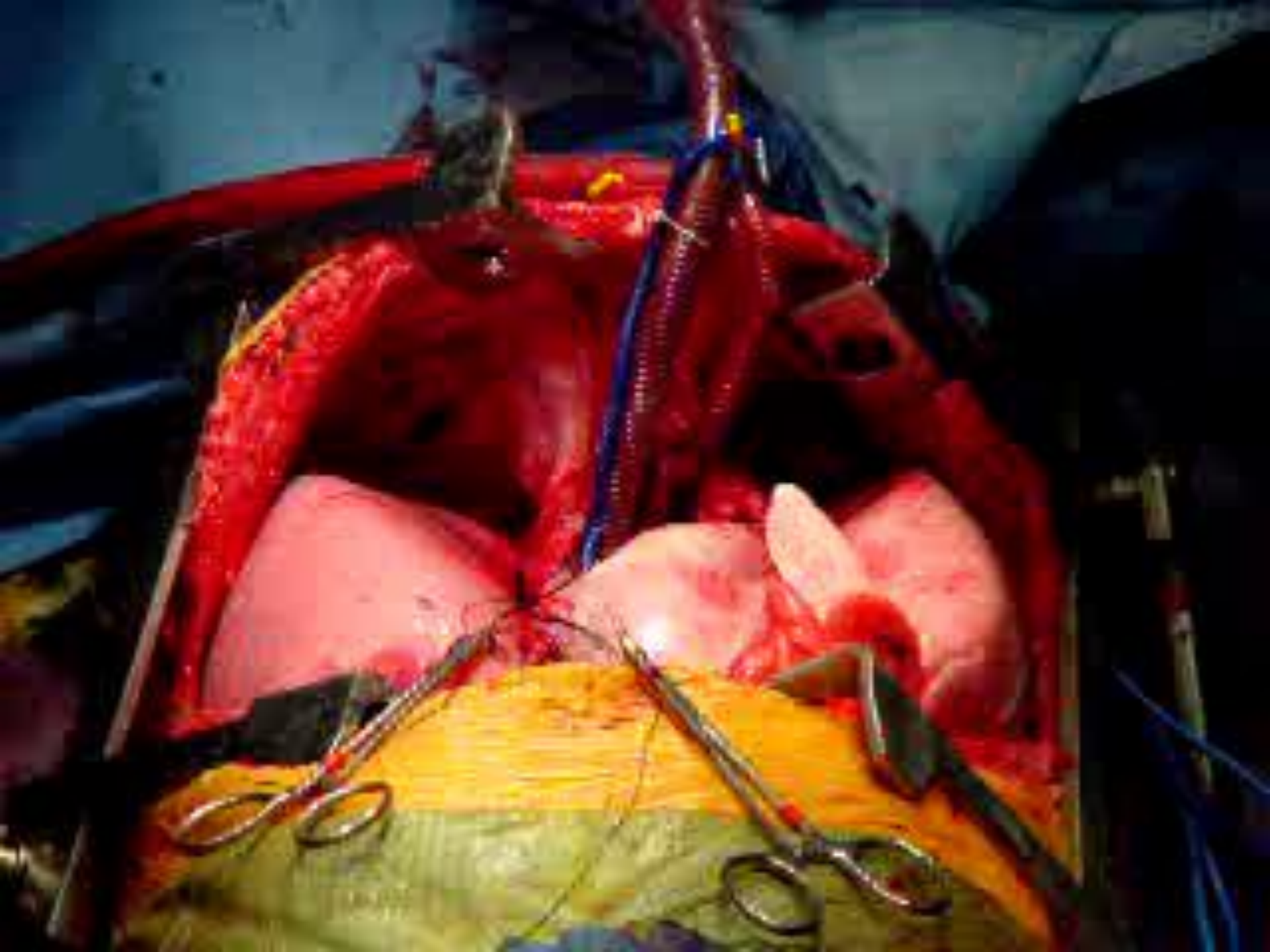


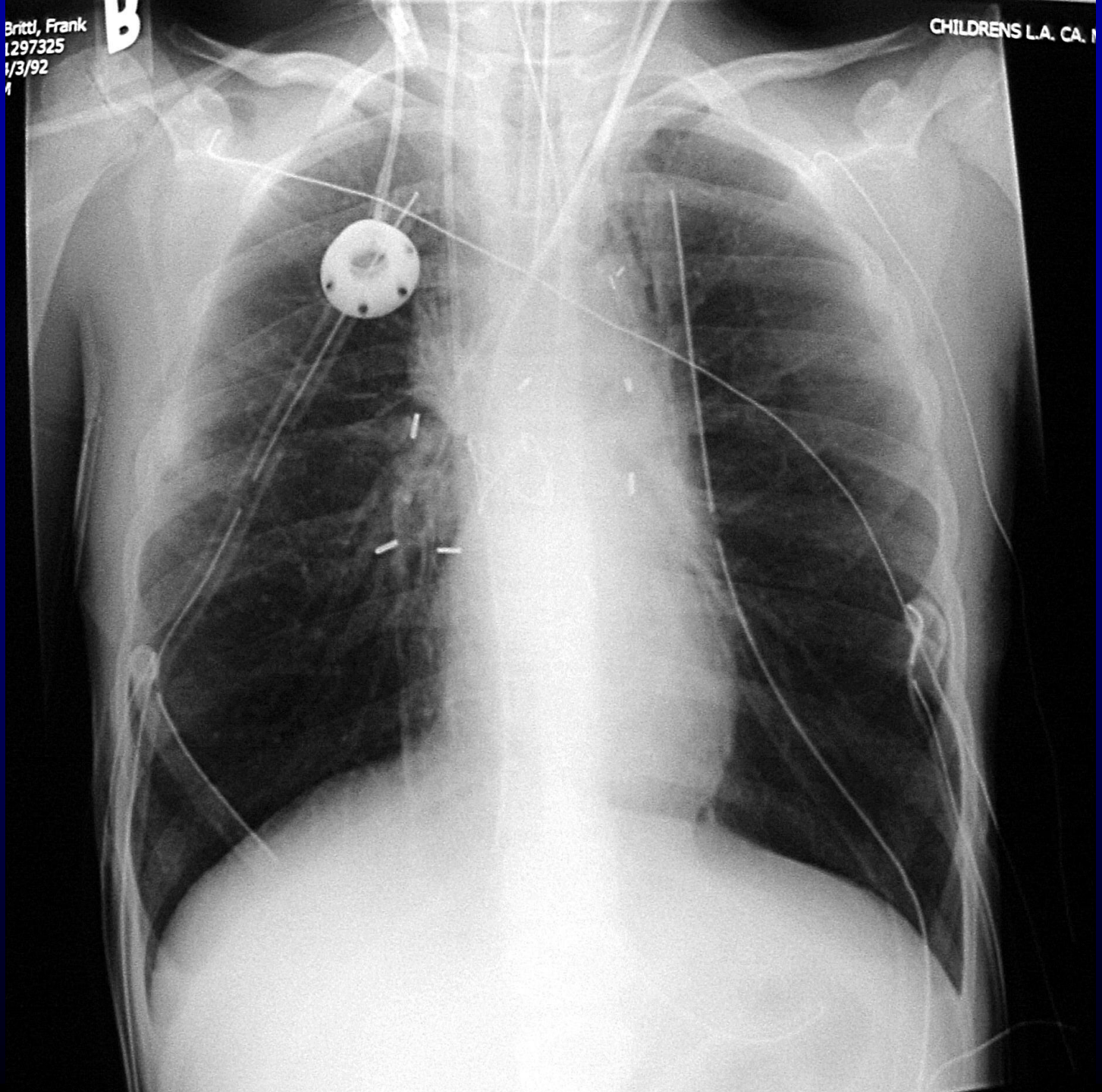
Bronchial Anastomosis for Lung Transplantation







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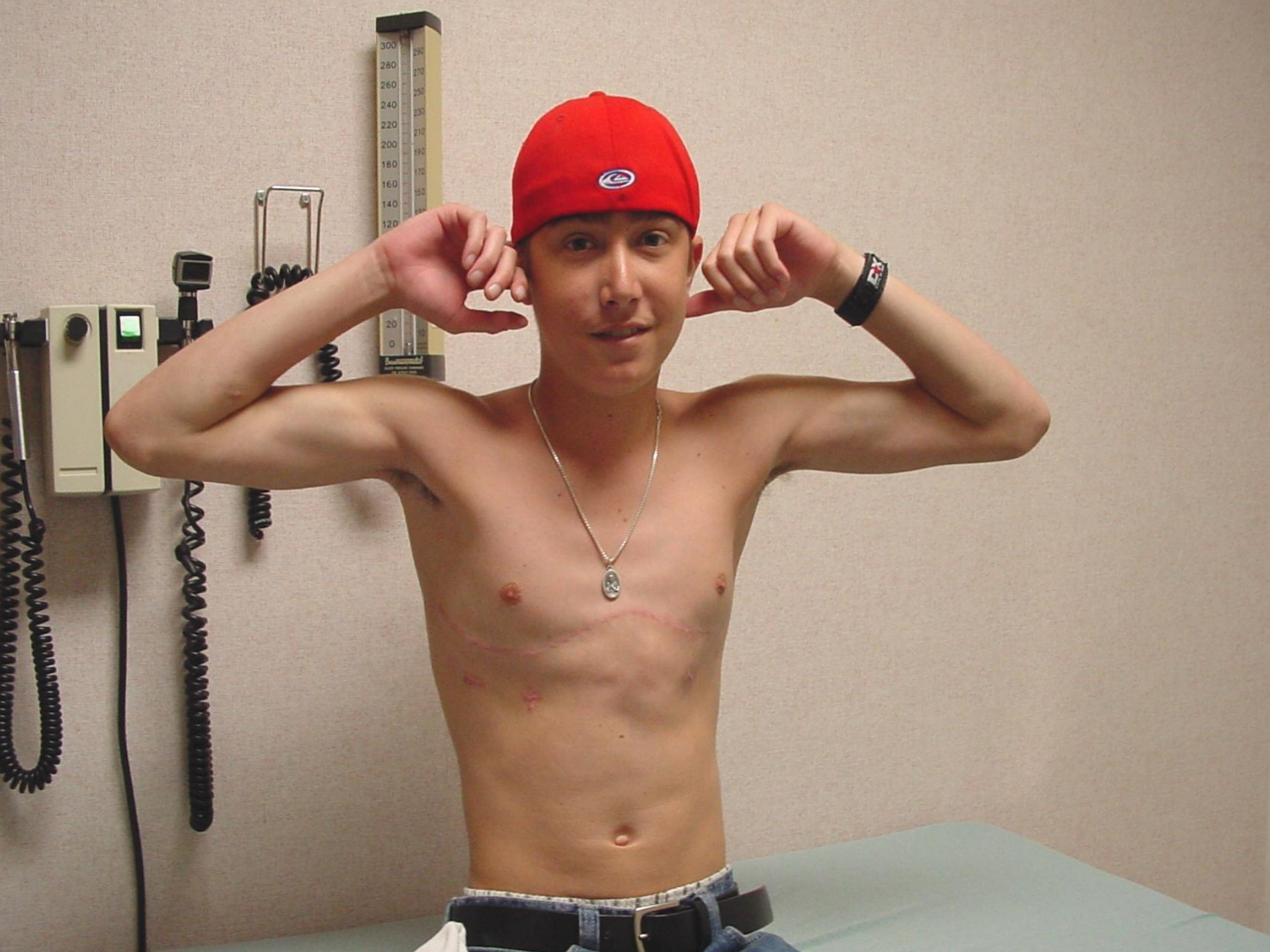


Reasons for Early Era Failures

- Poor patient selection
- Inadequate lung preservation
- Excessive immunosuppression
- No/poor infection diagnosis/prophylaxis
- No way to diagnose AMR
- Poor understanding of the physiology of the transplanted lung
- Limited donor availability

Candidate Selection

and

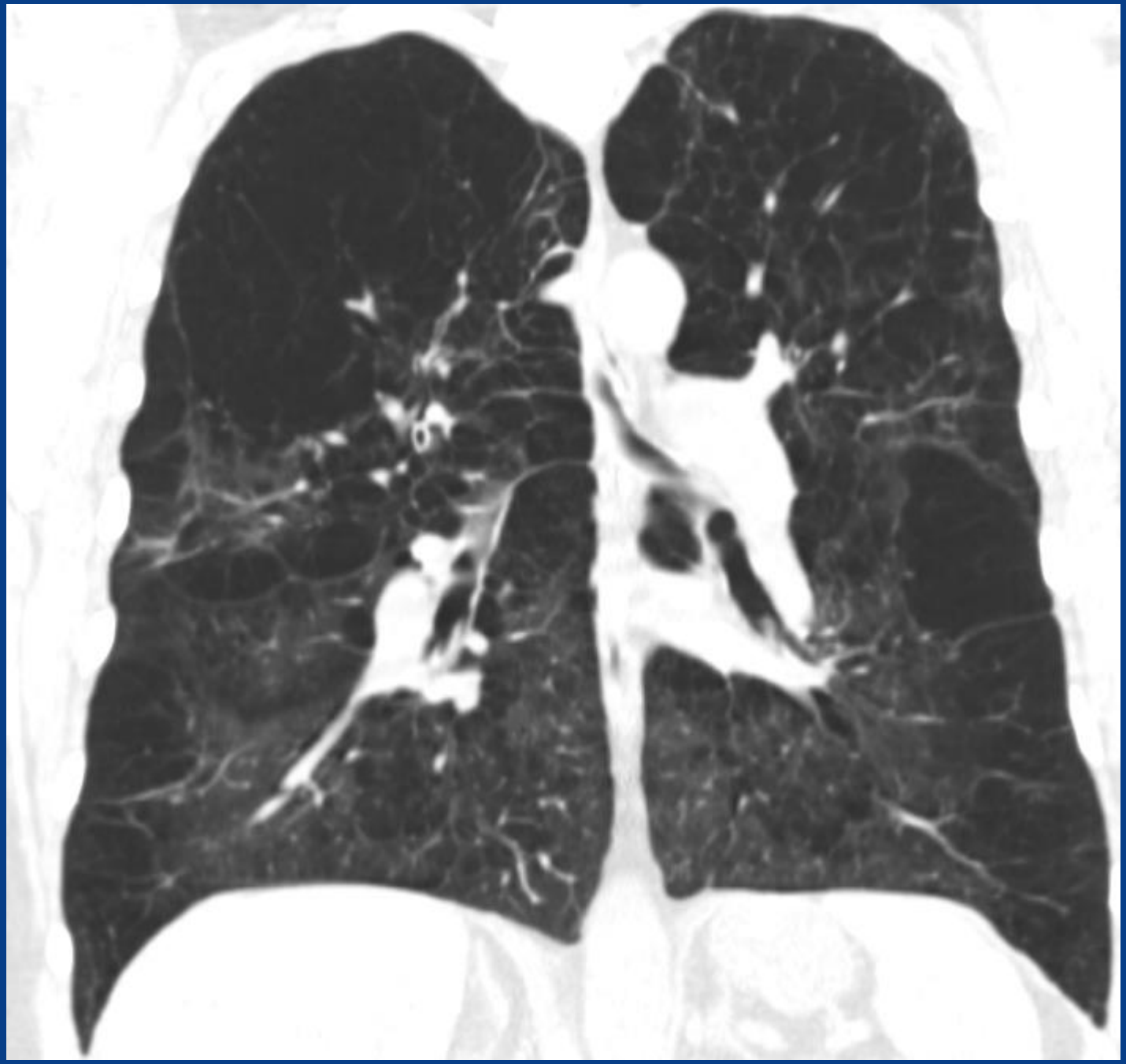
Indications

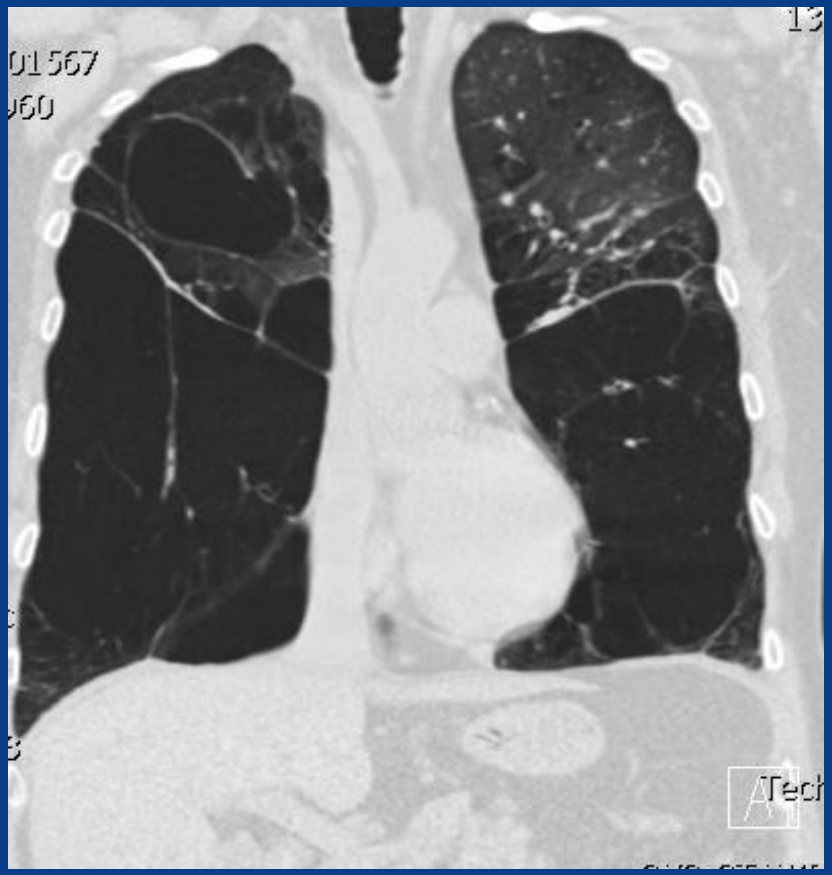
When Should Patients Be Referred ?

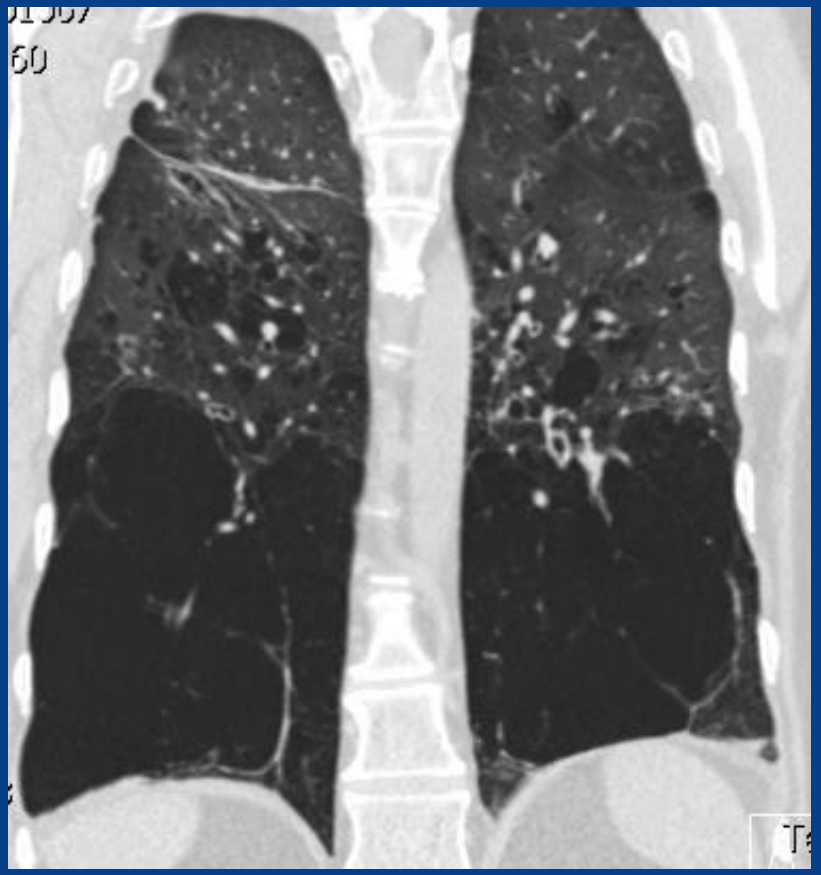
Absolute Contraindications

- ***Malignancy within prior 2 years***
- ***Acute medical instability***
- ***Untreatable dysfunction of other major organ***
- Chronic poorly controlled
- infection
- Active TB
- Severe Musculoskeletal disease
- ***Obesity (BMI>35)***
- ***Substance addiction in prior 6 months***
- ***Absence of reliable support system***
- ***Untreatable psychosocial problems***
- ***Non-compliance***

Weill D. J Heart Lung Transplant 2015







COPD

Referral to transplant center:

- **BODE index of 5**
- **FEV1 < 25% pred**
- Disease progression despite max treatment
- PCO2 > 50
- Moderate to severe pulm HTN
- 3 or more exacerbations during previous year

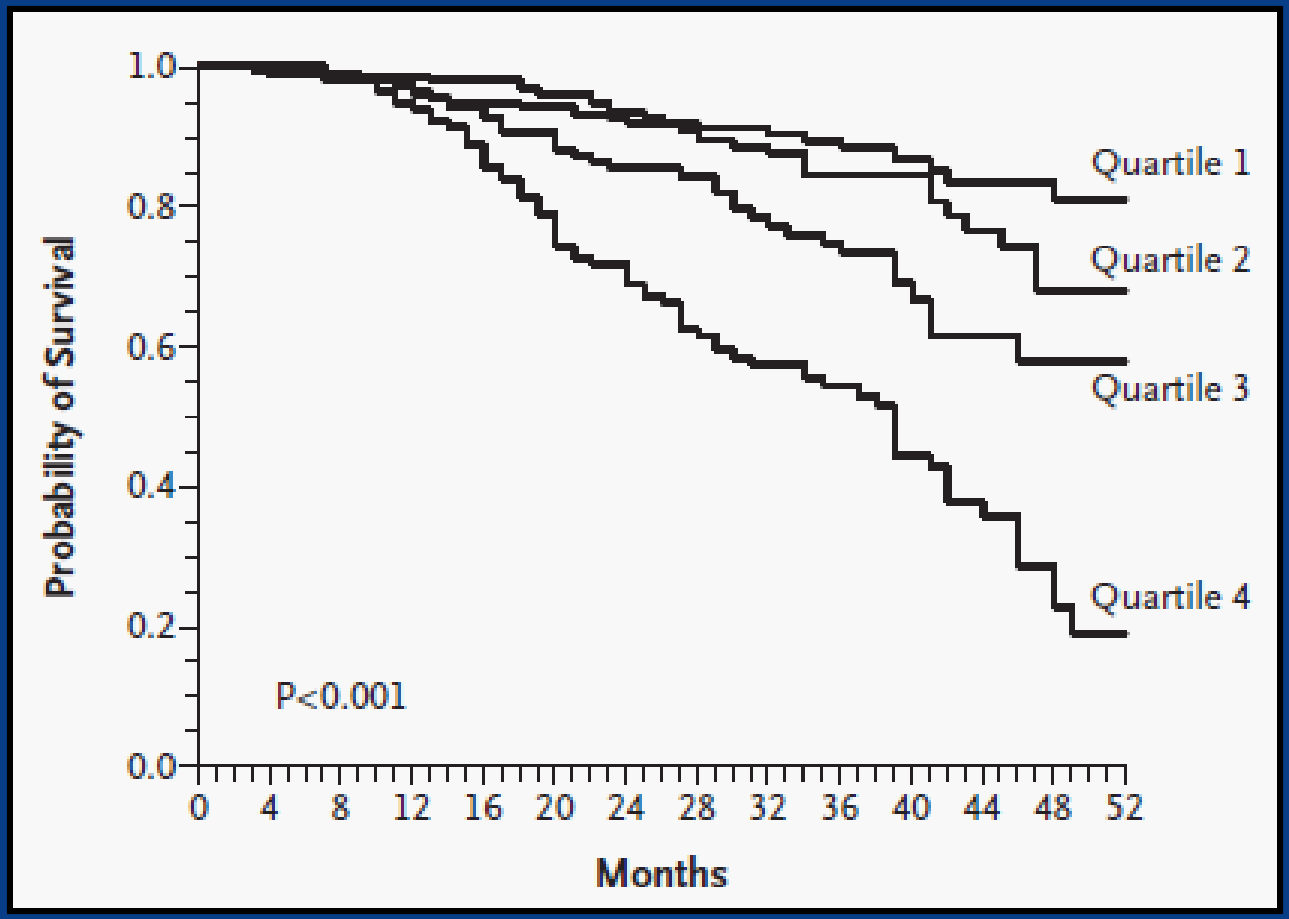
Weill D. J Heart Lung Transplant.

BODE Index

Variable	Points on BODE Index			
	0	1	2	3
FEV1 (% predicted)	≥65	50-64	36-49	≤35
6-Minute Walk Test (meters)	***≥350***	***250-349***	***150-249***	***≤149***
MMRC Dyspnea Scale	0-1	2	3	4
Body Mass Index	>21	≤21		

Celli BR. N Engl J Med. 2004;350:1005

COPD predicted survival based on BODE Index



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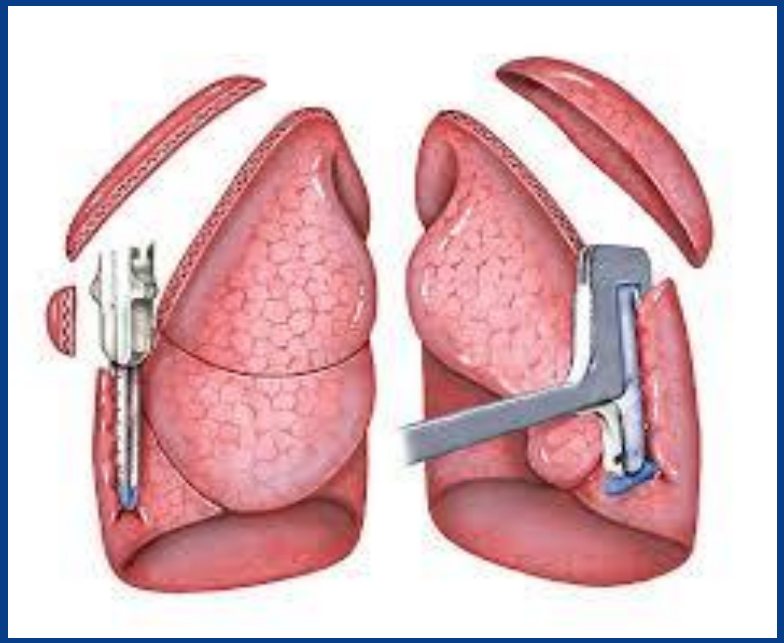
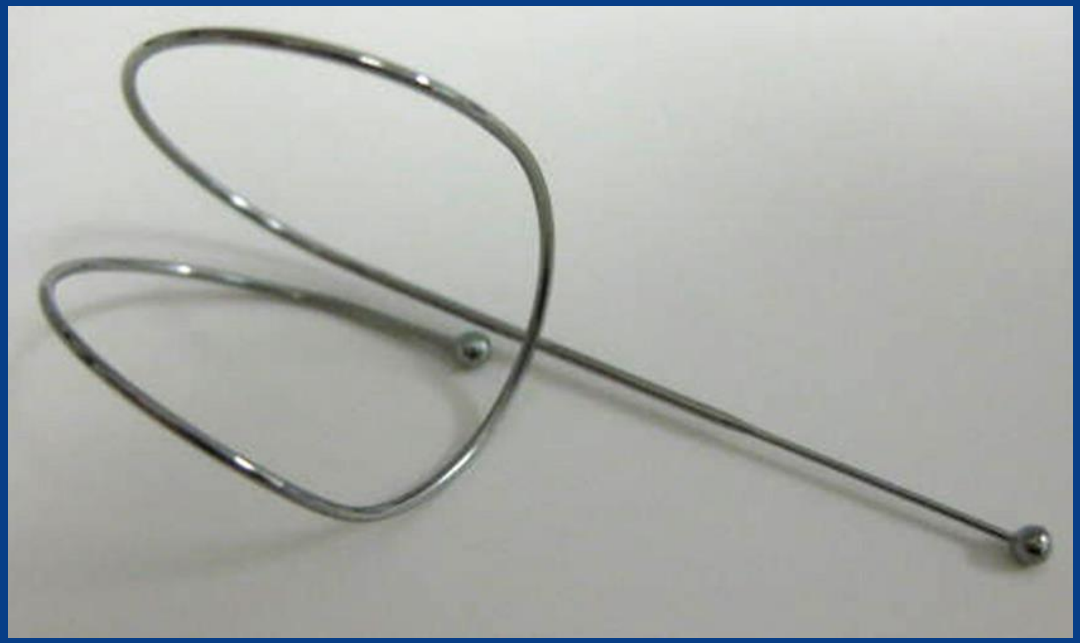
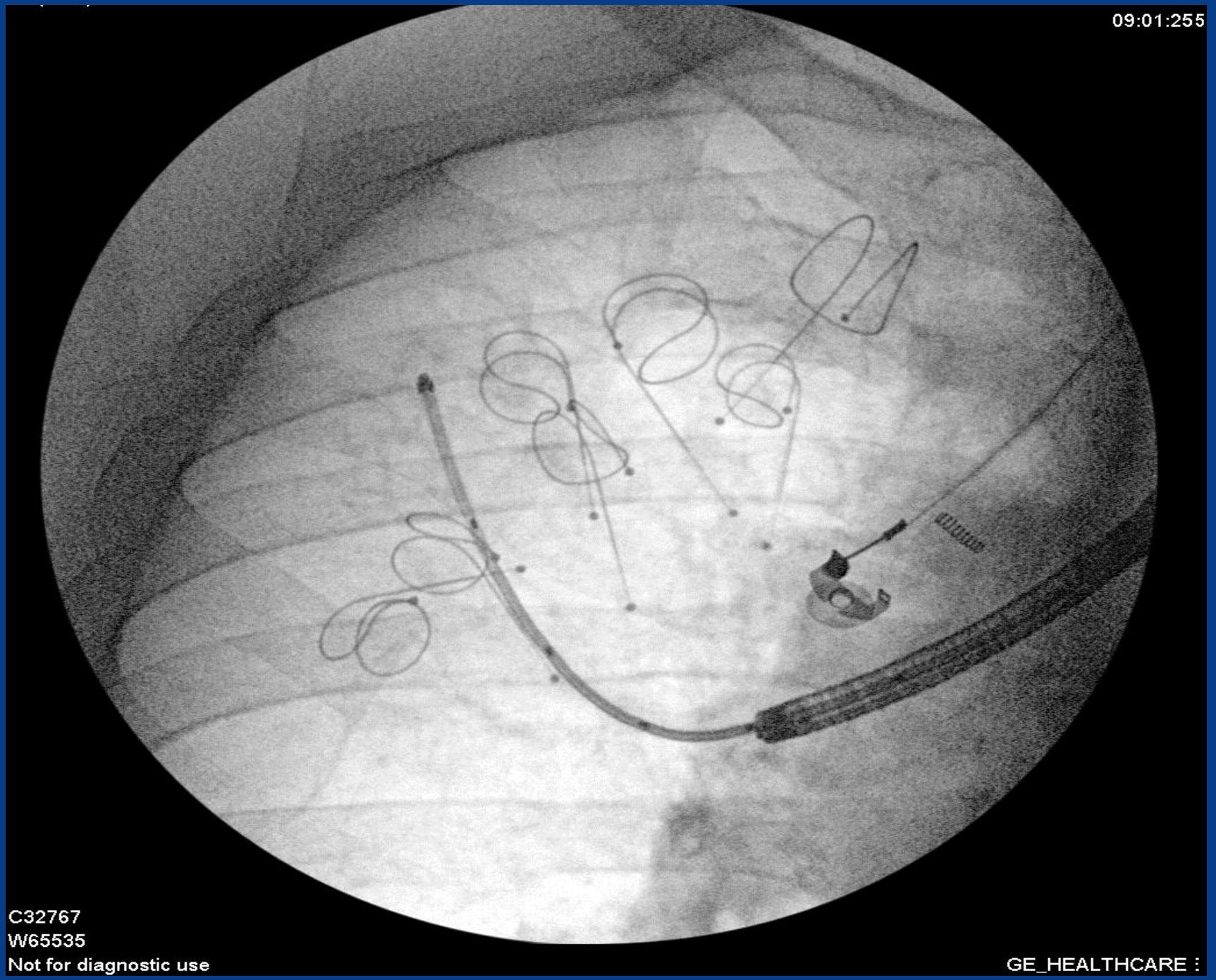
Lung Volume Reduction

- Bronchoscopic or surgical





- Does not exclude patients from future transplantation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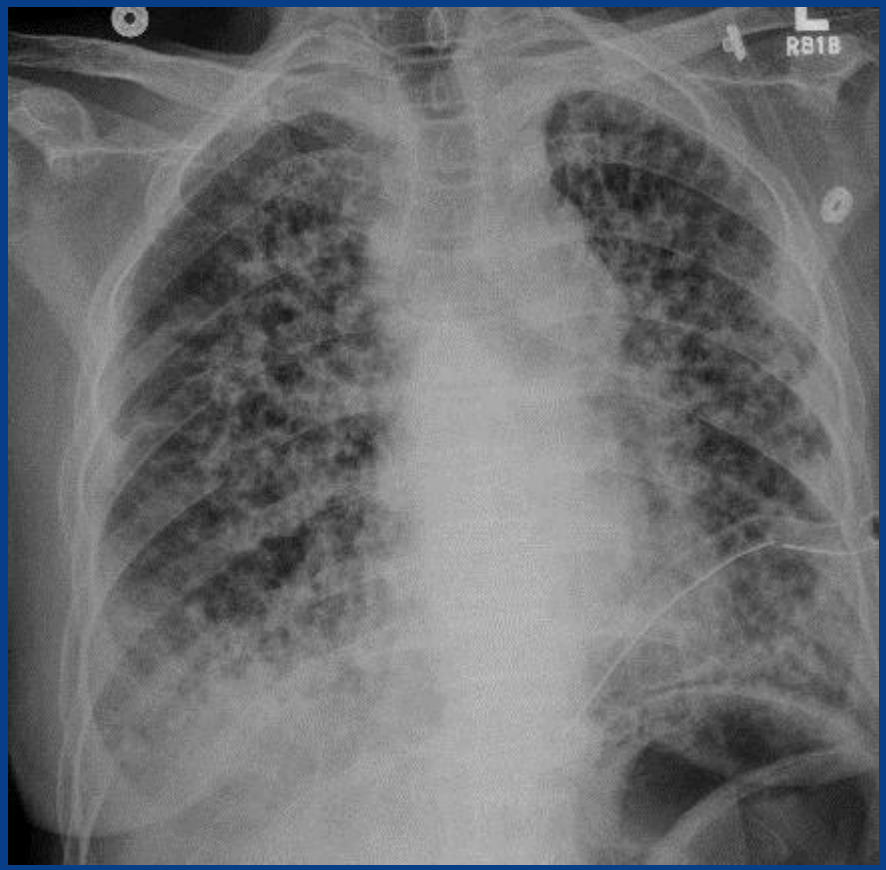
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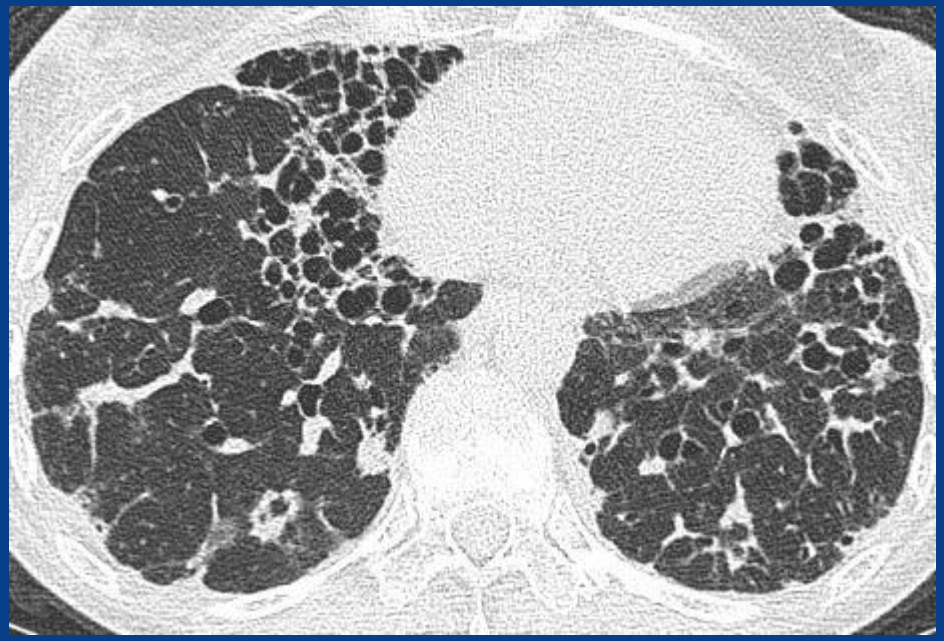
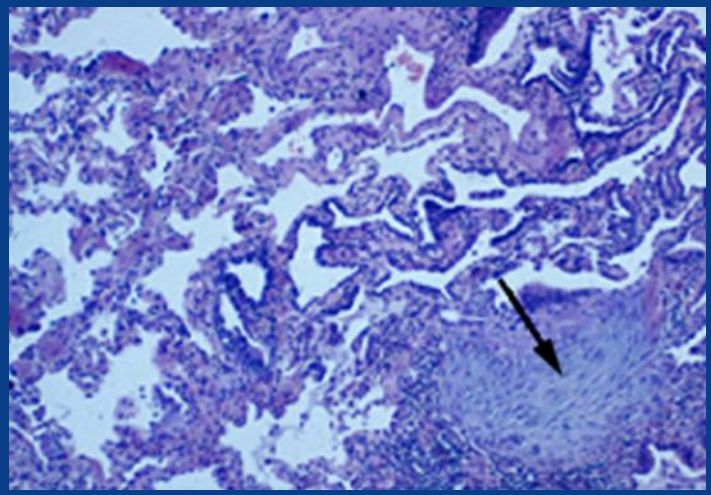


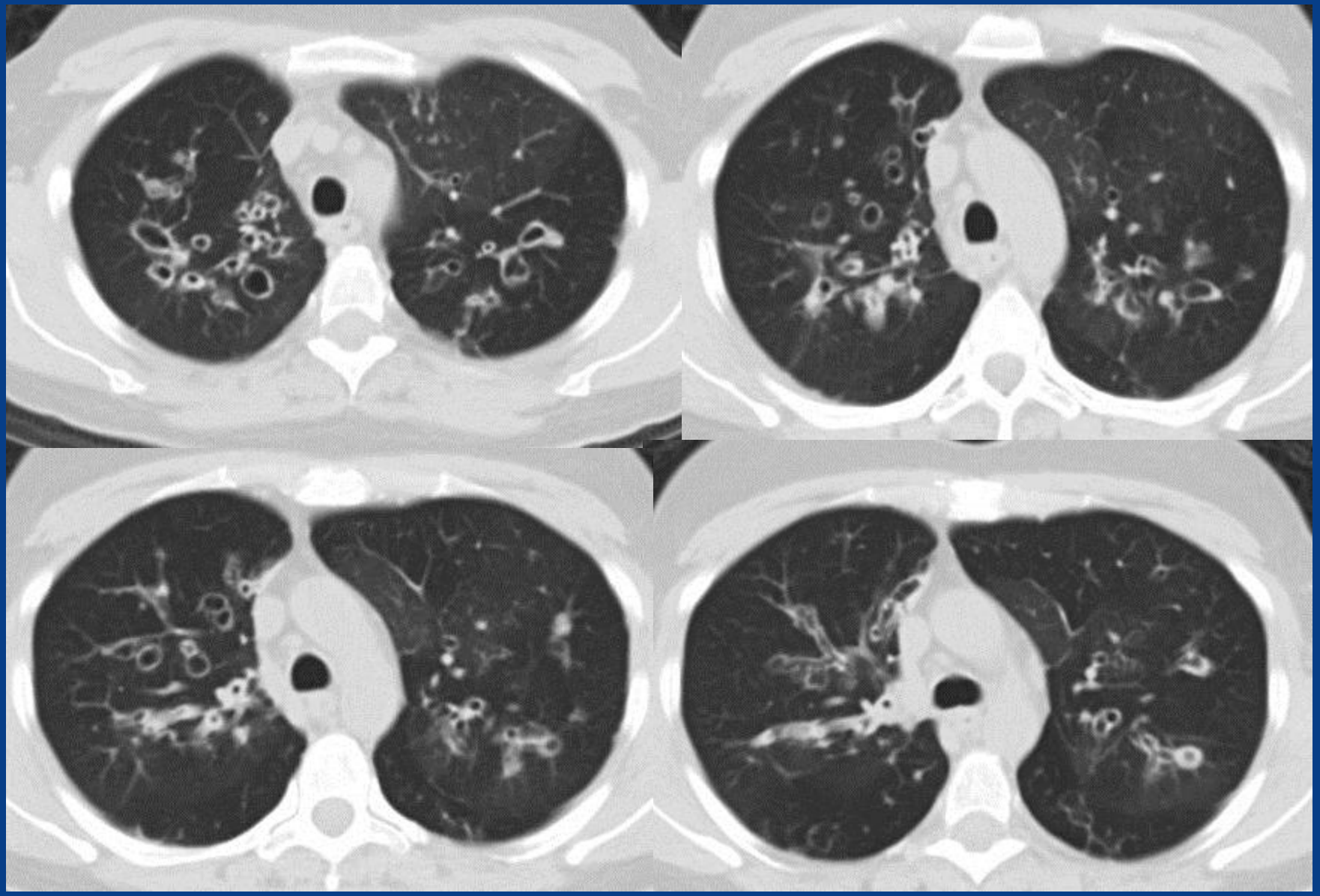


Idiopathic Pulmonary Fibrosis

Referral to transplant center

- **Histologic or radiographic evidence of UIP or fibrotic NSIP**
- FVC < 80% pred or DLCO < 40% pred
- 10% or greater decrease in FVC during 6 months of follow-up
- 15% or greater decrease in DLCO
- Desaturation < 88% during a 6MWT
- Pulm HTN on Right heart catheterization

Weill D. J Heart Lung Transplant.



Cystic Fibrosis

Referral to transplant center

- **FEV1 < 30% predicted or a rapid decline in FEV1**
- **Increasing frequency of exacerbations**
- **Chronic Respiratory Failure**
- 6MWT < 400 meters
- Development of pulmonary hypertension
- Recurrent hemoptysis not controlled by embolization

Weill D. J Heart Lung Transplant.

Recipient Criteria
Special Issues

Cystic Fibrosis

- Pulmonary Infections
  - Pan-resistant pseudomonas aeruginosa
  - Burkholderia cepacia (esp. genomovar III)
  - MRSA
  - Mycobacterium abcessus
  - Aspergillus sp
- GI/Hepatic Disease
- Narcotic dependence

Recipient Criteria
Timing of Evaluation

PPH

- NYHA III or IV
- Failed epoprostenol therapy
- Hemodynamics: RAP > 15

  CI < 2.0

  Mean PAP > 60

Where does it begin for the potential recipient?

Transplant Evaluation

- Referral to the Transplant Center
- Initial clinic visit:
  - Review of medical records
  - History and physical exam
  - Education about transplant
  - What do we do now?
    - Transplant evaluation?

Transplant Evaluation

- Evaluation Week
  - 4-5 full days of testing
  - Consultations with the entire team

Pre-transplant Evaluation

- PFTs
- 6 minute walk test
- EKG
- Echocardiogram
- Cardiac cath
- HRCT
- Chemistries
- LFTs
- Serologies- CMV, HIV, Hepatitis, EBV
- V/Q scan
- Dexa scan
- GERD

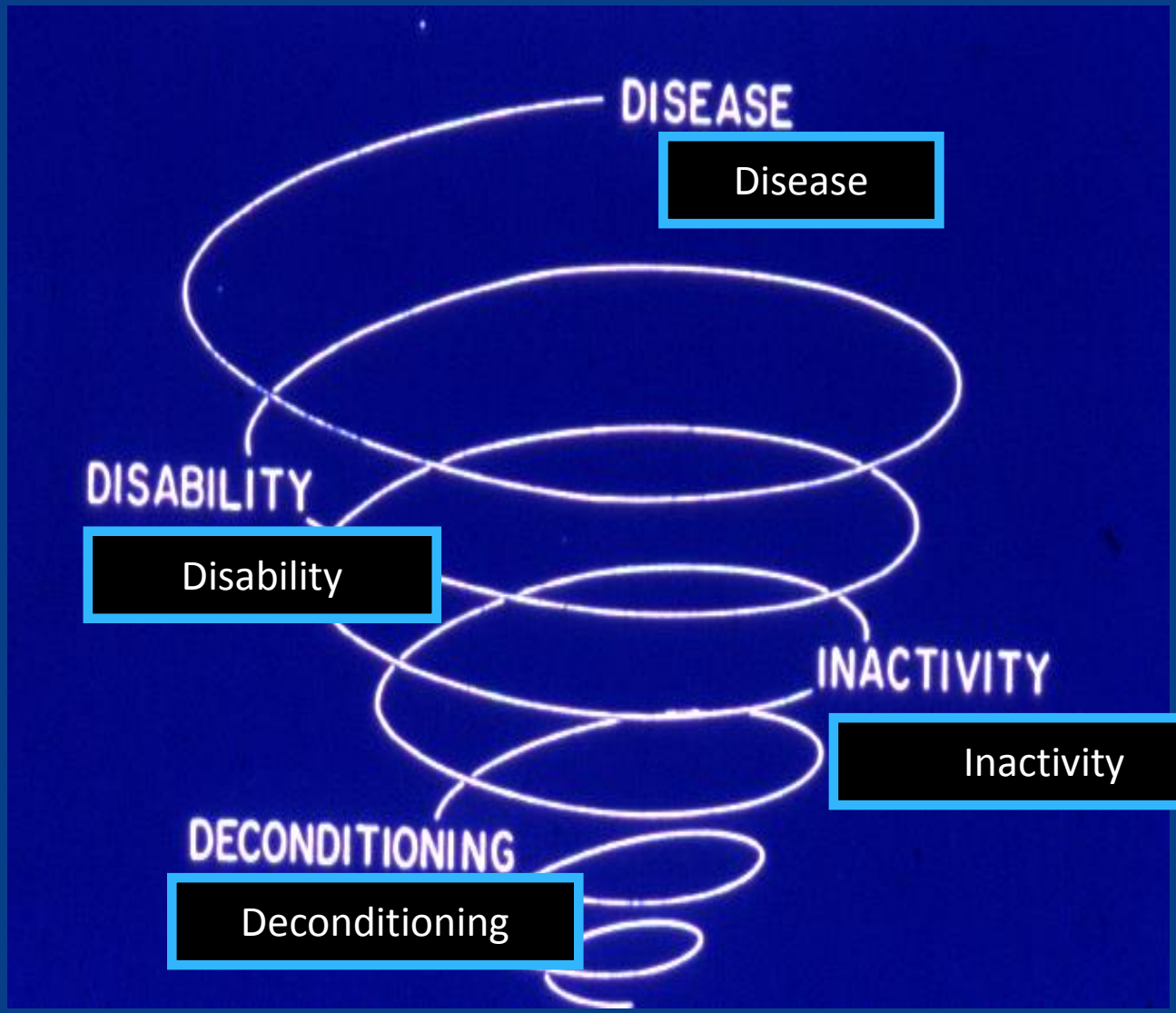
Selection Committee

- Entire Transplant Team Participates
  - All data reviewed
  - Decision:
    - List
    - Further work to do
    - Not a candidate
- Communication with Candidate

Getting ready for transplant takes time

- **Cancer screening with up to date health maintenance**
- Weight Loss
- Finances
- Pulmonary Rehabilitation

Deconditioning Spiral



Donor recipient matching

- ABO compatibility
- size matching
- absence of recipient preformed antibodies that react against the donor

Postoperative Care

and

Complications

Early Postoperative Management

- Ventilator Management
- Hemodynamic Stability
- Immunosuppressive Regimen
- Infectious Disease Prophylaxis

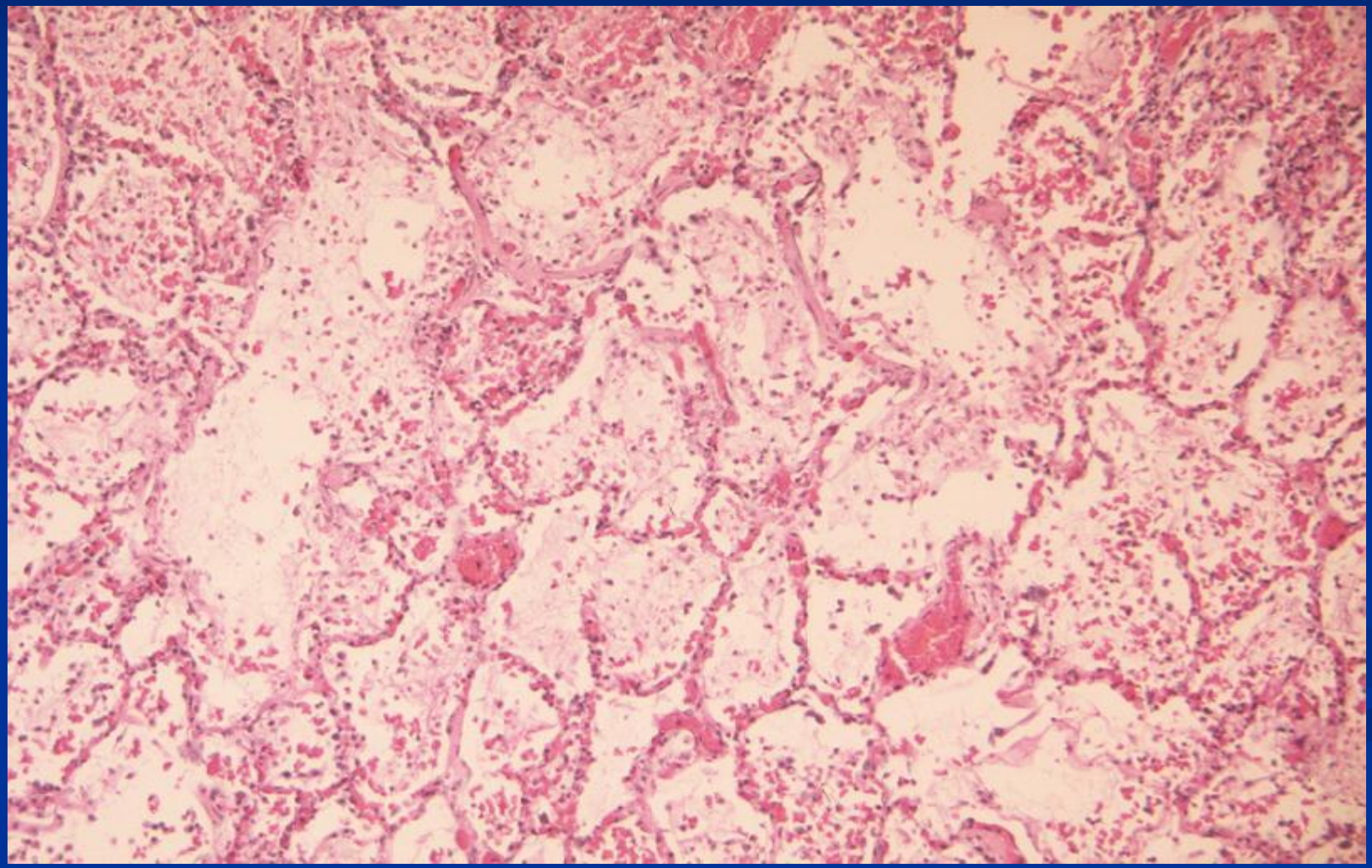
Postoperative Oxygenation and Ventilation

- Extubate as soon as possible
- Chest physiotherapy
- Minimize fluids +/- diuresis
- PEEP only in patients without COPD
  - In COPD, avoid native lung hyperinflation in those receiving a SLT by allowing maximal expiratory time

Reimplantation Response
Treatment

- Support with Mechanical Ventilation (avoid barotrauma)
- Independent Lung Ventilation if a SLT
- Diurese
- Nitric Oxide
- ECMO

Reimplantation Response Histology



Immunosuppression

and

Rejection

Immunosuppression

- Preoperative
  - Tacrolimus
  - Mycophenolate mofetil
- Intraoperative
  - Solumedrol 500mg
- Postoperative
  - Tacrolimus 2 mg/24 hrs, then adjusted for trough blood levels
  - Mycophenolate mofetil
  - Solumedrol 125 mg q12 hr x 3 doses, then 0.6 mg/kg, tapering eventually to 0.1 mg/kg

Cyclosporine (Neoral, Gengraf)

- Target trough levels = 200 – 400 ng/ml
- Primary toxicities
  - Renal
  - CNS
  - Gingival hyperplasia
  - Hirsutism

Tacrolimus (Prograf)

- Target trough level = 7 to 15 ng/ml
- Primary toxicities
  - Renal
  - Diabetes
  - CNS
  - Type 4 RTA

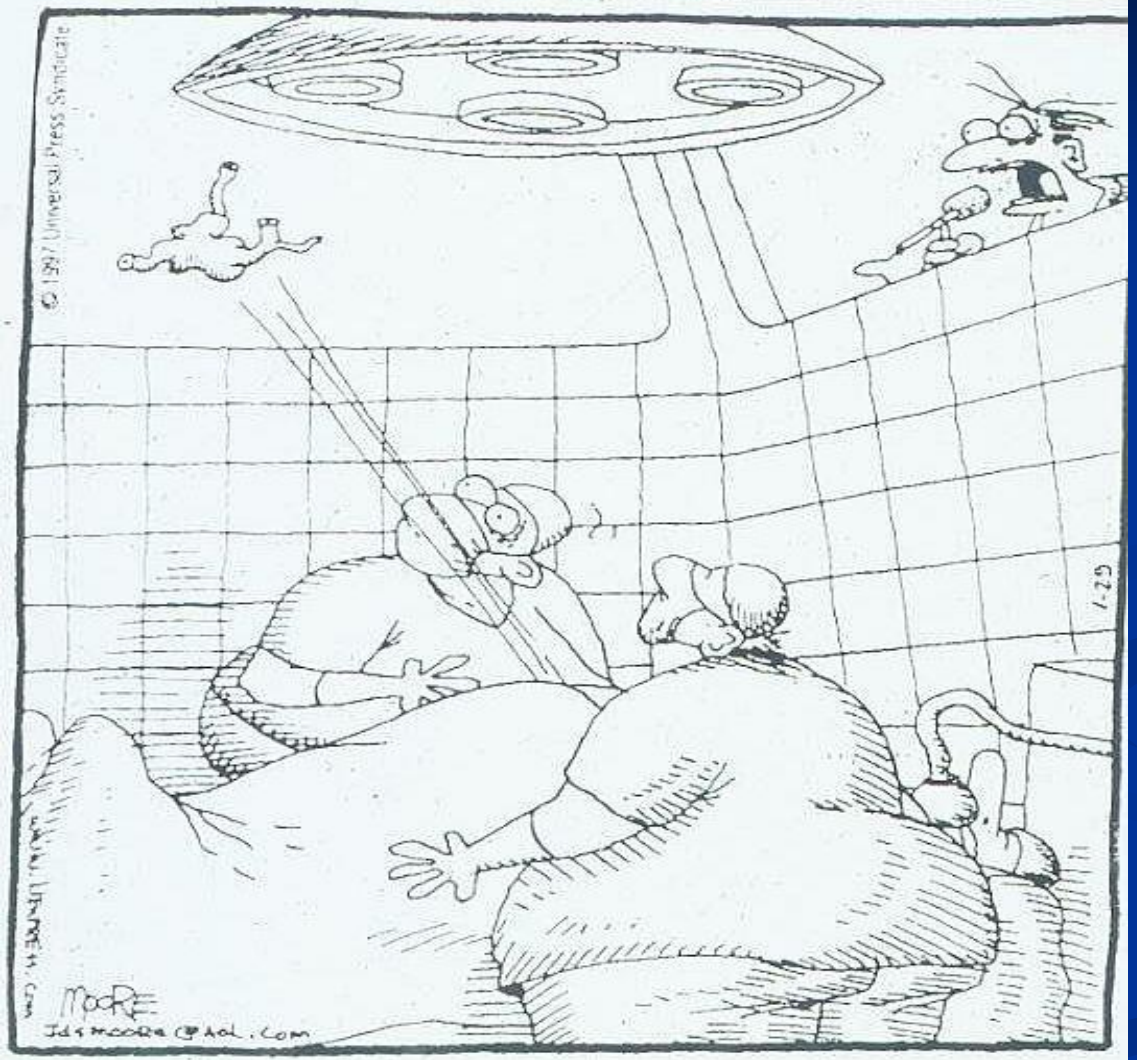
Mycophenolate Mofetil (Cellcept)

- Mycophenolic acid target levels = 1-3 (I think)
- Primary toxicities
  - GI (diarrhea, N/V)
  - Leukopenia
  - Thrombocytopenia
  - ? Increase risk of viral diseases

Sirolimus /Everolimus

- Target trough levels (5 – 7 ng/ml) or combined level with tacrolimus of ~ 10
- Primary toxicities
  - Organizing Pneumonia
  - Pleural effusions
  - Hyperlipidemia. check lipids monthly
  - Pancreatitis
  - Renal

IN THE BLEACHERS



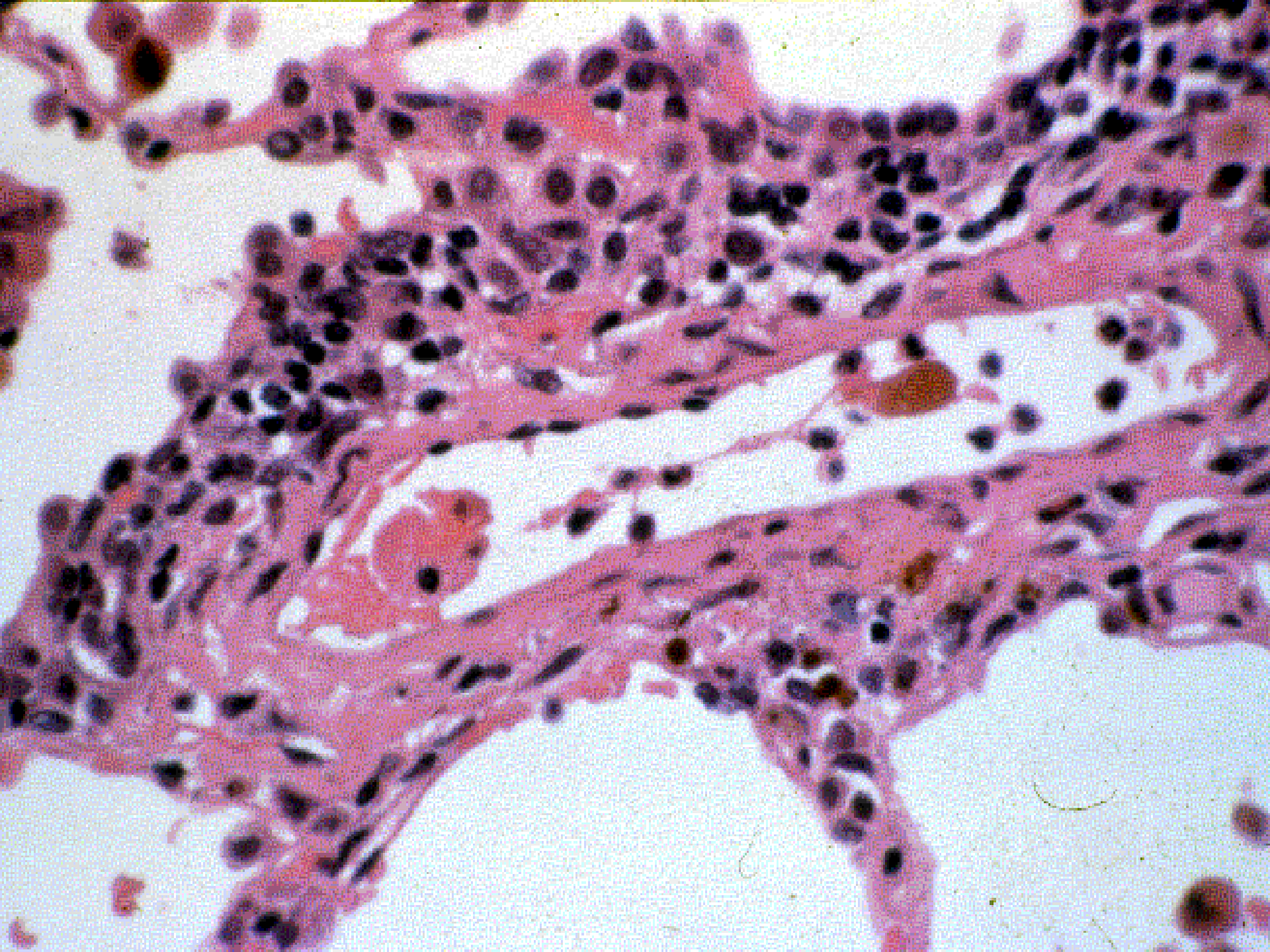
"The surgeon looks to the left, pivots to the right, transplants the organ and ... whoa! Rejected!"

Acute lung rejection

- sudden deterioration over 6 to 8 hours
- malaise
- shortness of breath
- low grade fever
- hypoxemia
- CXR - perihilar diffuse infiltrate

Diagnosis of acute rejection

- typical symptoms and signs
- CXR appearance
- response to increased immunosuppression
- BAL and transbronchial lung biopsy



Acute Rejection

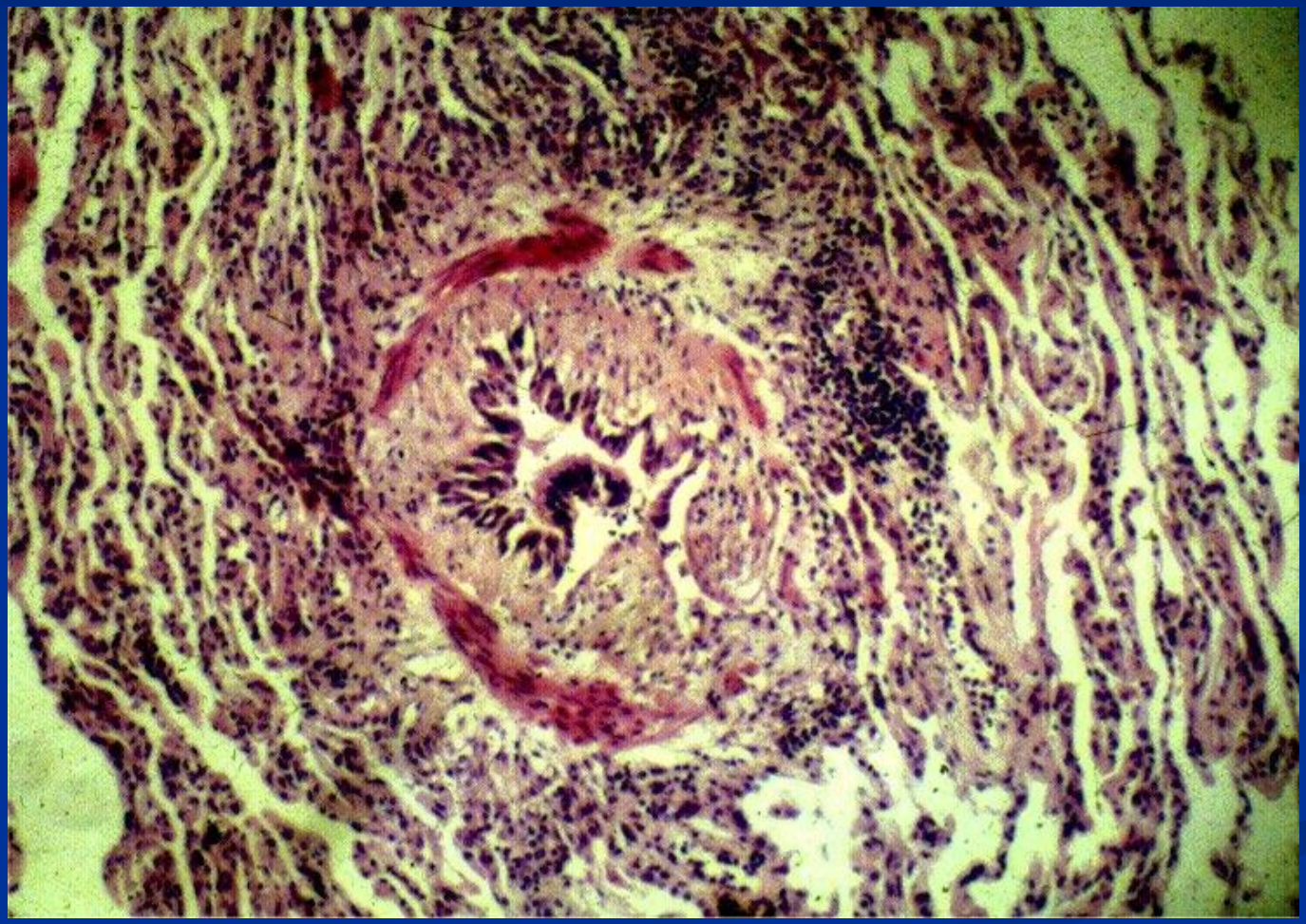
- Treatment
  - Solumedrol 10mg/kg for 3 days
  - Refractory cases: thymoglubulin, TLI, photopheresis
- Significance
  - Majority respond clinically to treatment
  - Majority do not regain lost lung function
  - Multiple early episodes predispose to chronic rejection

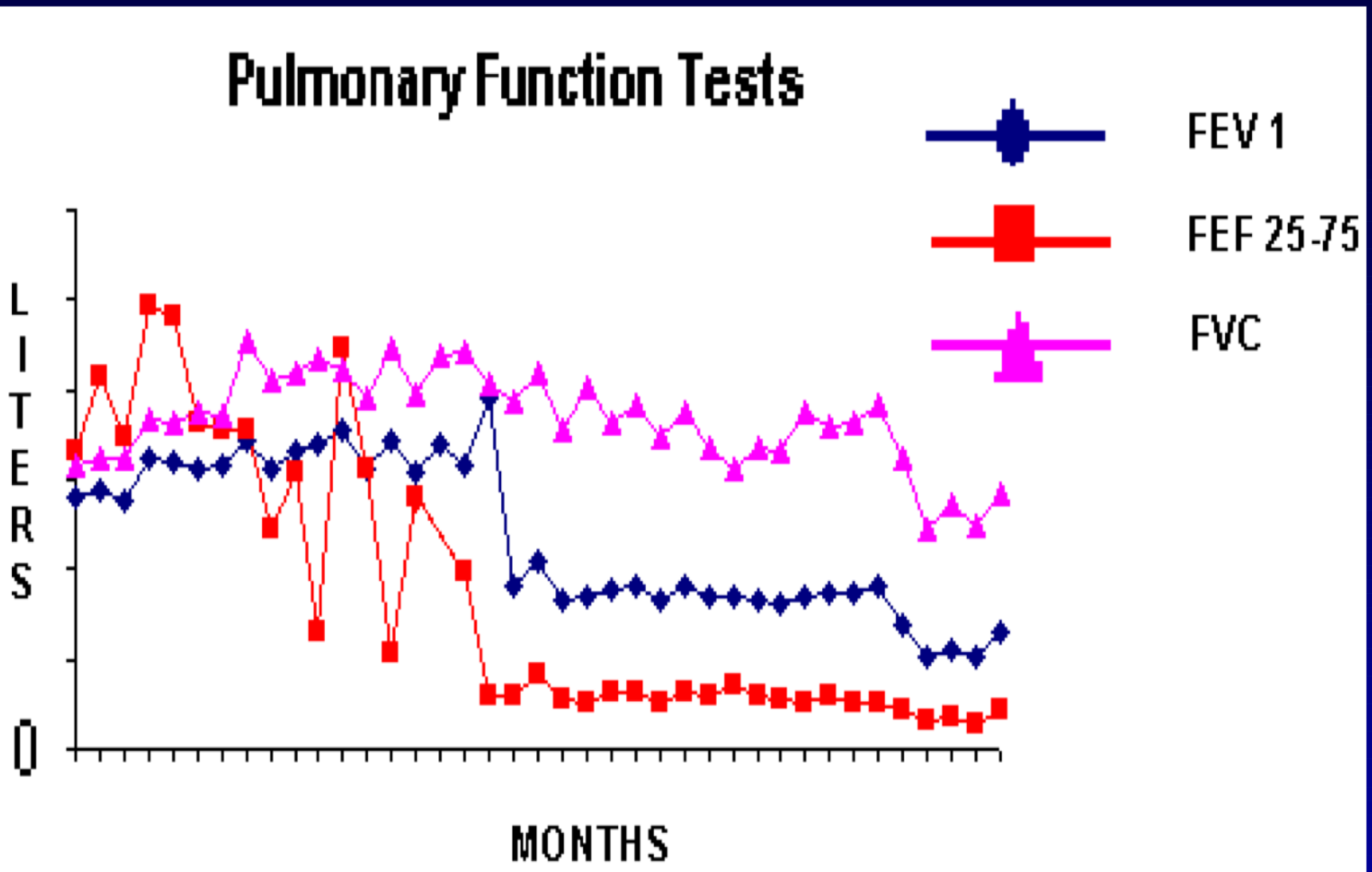
Bronchiolitis Obliterans Syndrome

Definition (=chronic rejection)

Inflammatory disorder of the small airways of unknown etiology leading to their obstruction and destruction and eventually progressing to impairment of the large airways

Bronchiolitis Obliterans Histology

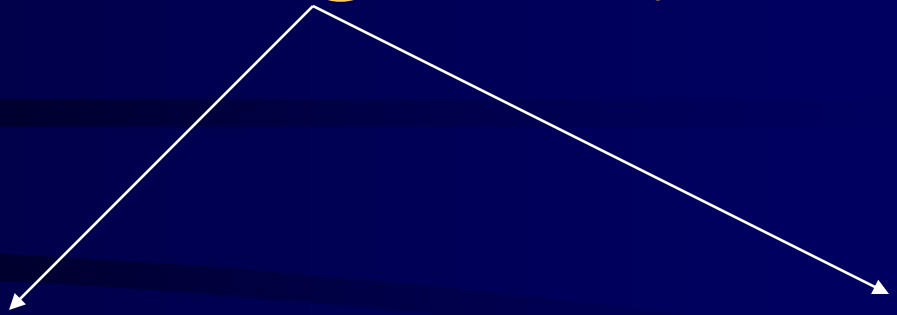



Pulmonary Function Tests
FEV 1
FEF 25-75
FVC
LITERS
0
MONTHS

Bronchiolitis Obliterans Syndrome

- Classification
  - Stage 0 – FEV1 > 80% baseline
  - Stage I – FEV1= 66-80% baseline
  - Stage II – FEV1= 51-65% baseline
  - Stage III – FEV1< 50% baseline

Chronic Allograft Dysfunction

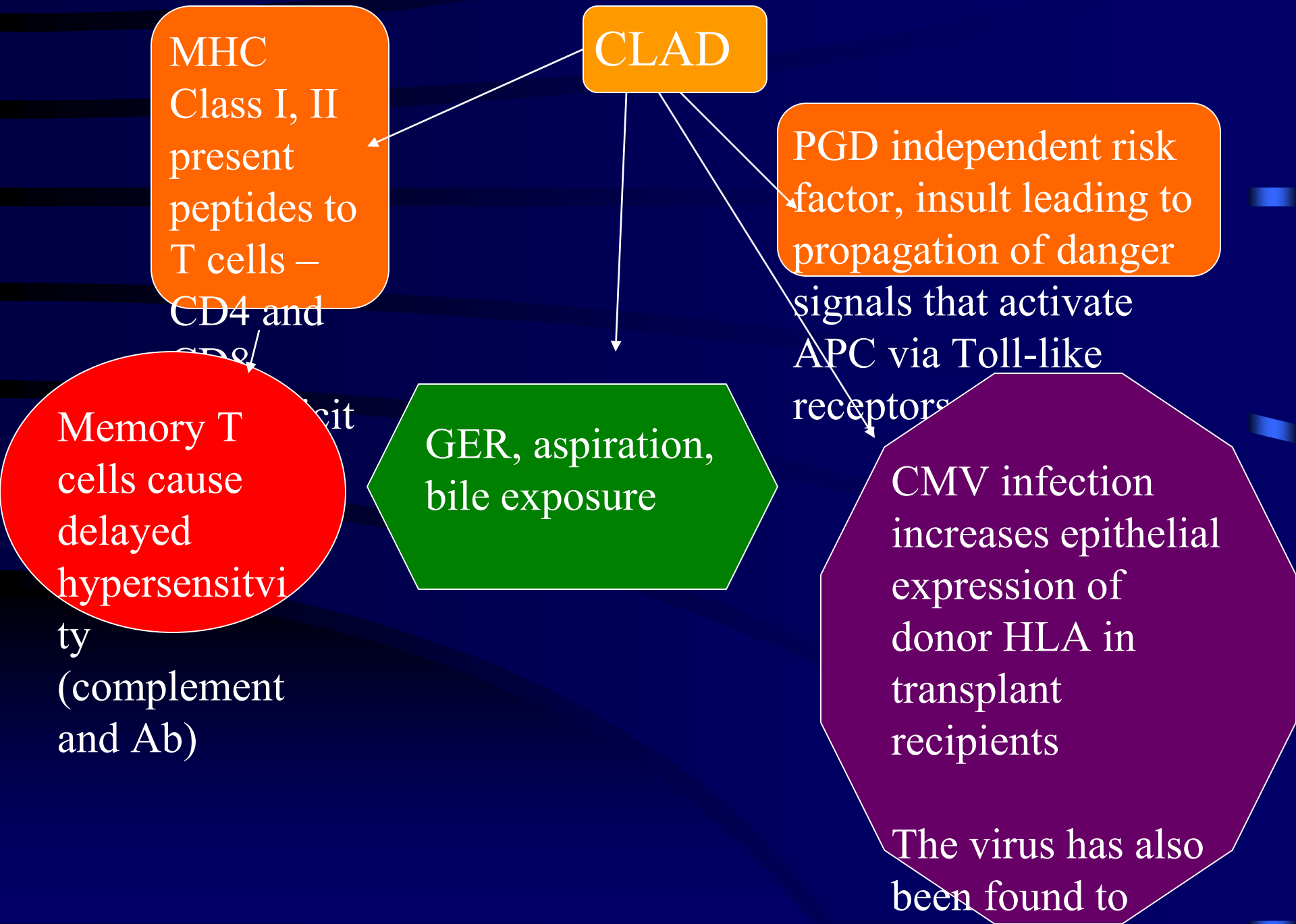


Alloimmune dependent factors

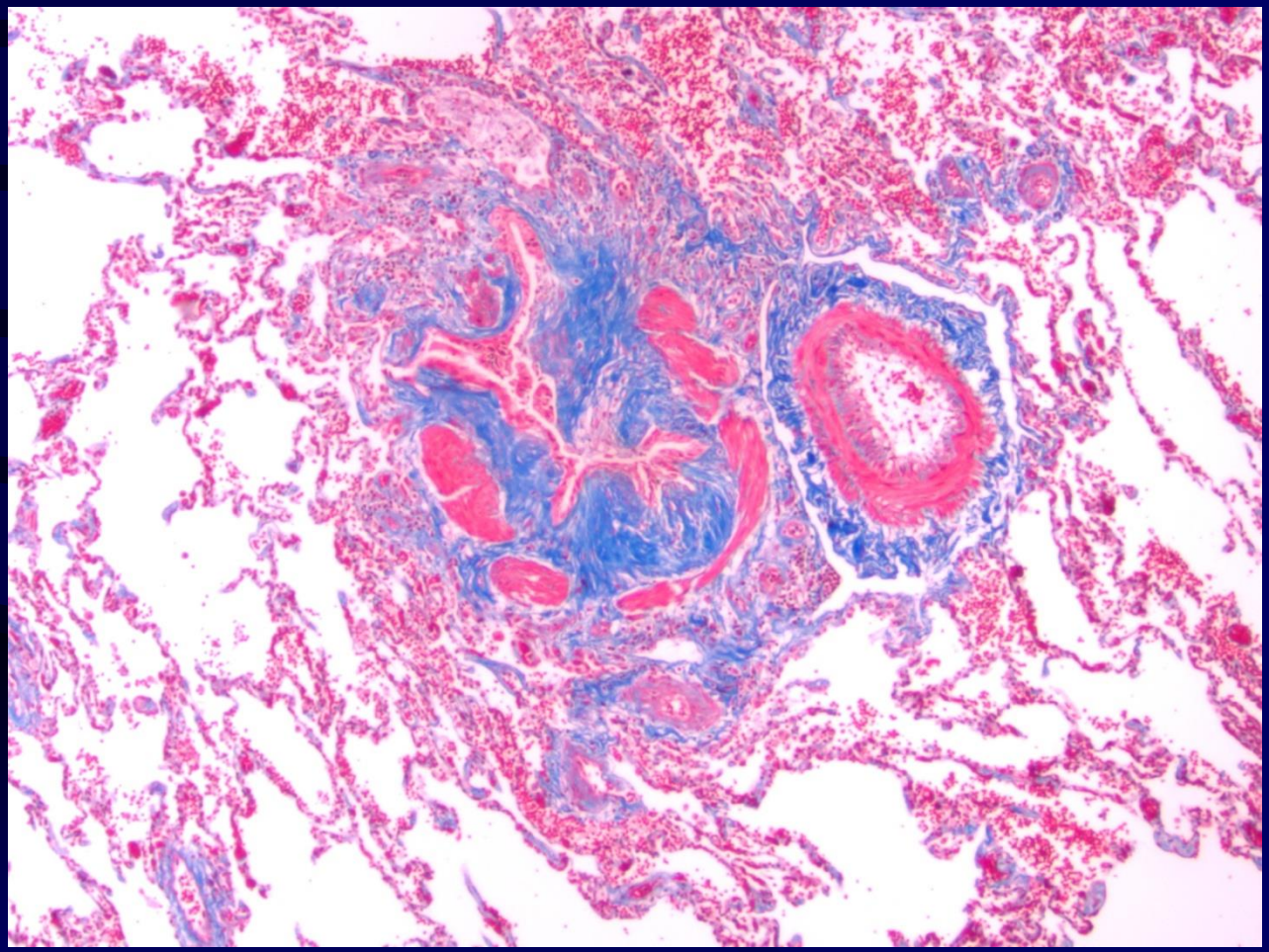
1. Acute cellular rejection
2. Lymphocytic bronchiolitis
3. Organizing pneumonia
4. HLA mismatches

Non alloimmune

1. Infections
2. GERD
3. Graft Vasculopathy
4. PGD and role in BOS


CLAD
MHC Class I, II present peptides to T cells – CD4 and
Memory T cells cause delayed hypersensitvi ty (complement and Ab)
GER, aspiration, bile exposure
PGD independent risk factor, insult leading to propagation of danger signals that activate APC via Toll-like receptors
CMV infection increases epithelial expression of donor HLA in transplant recipients
The virus has also been found to

Chronic Allograft Dysfunction



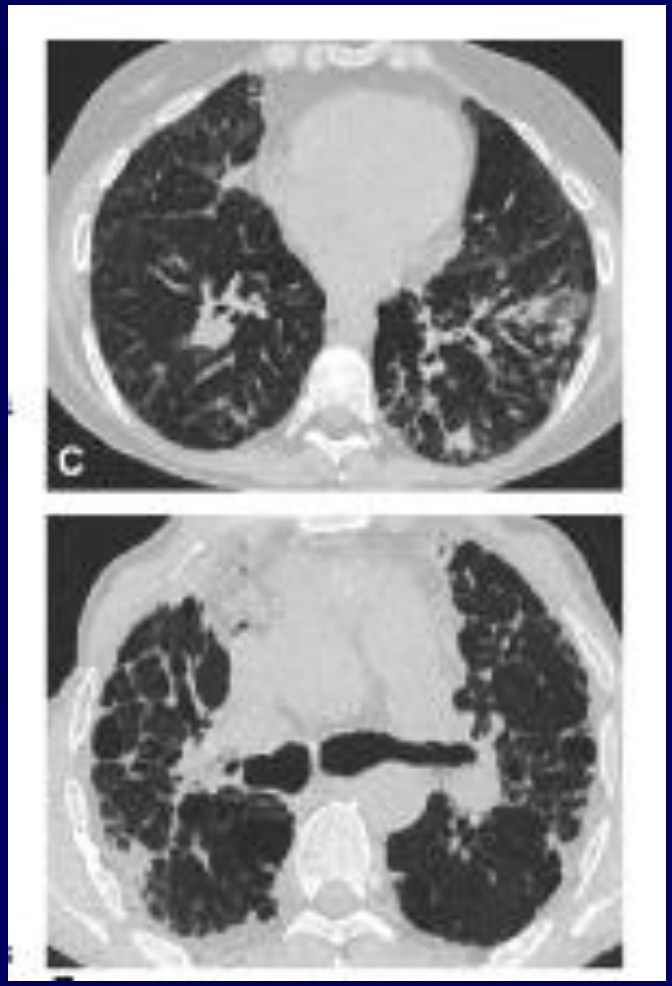
Courtesy Dr. Stone, Henry Ford Pathology: Masson Trichrome

Treatment of CLAD

- Change in IS unlikely to benefit
- Antilymphocyte or anti-thymocyte treatments(ATGAM, thymoglobulin, CAMPATH)- limited benefit
- Azithromycin (only medication proved in trials to stabilize CLAD and pre treatment BAL neutrophilia predicts response)
- ECP: Photophoresis, expensive but no increased infection risk. Benefit in early BOS
- Fundoplication

rCLAD

- Restrictive rather than an obstructive pulmonary function defect (defined as a decline in total lung capacity of at least 10%)
- Demonstrate persistent interstitial and ground-glass opacities on chest CT



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Antibody Mediated Rejection

- AMR, also known as humoral rejection, is described as the combination of four factors:

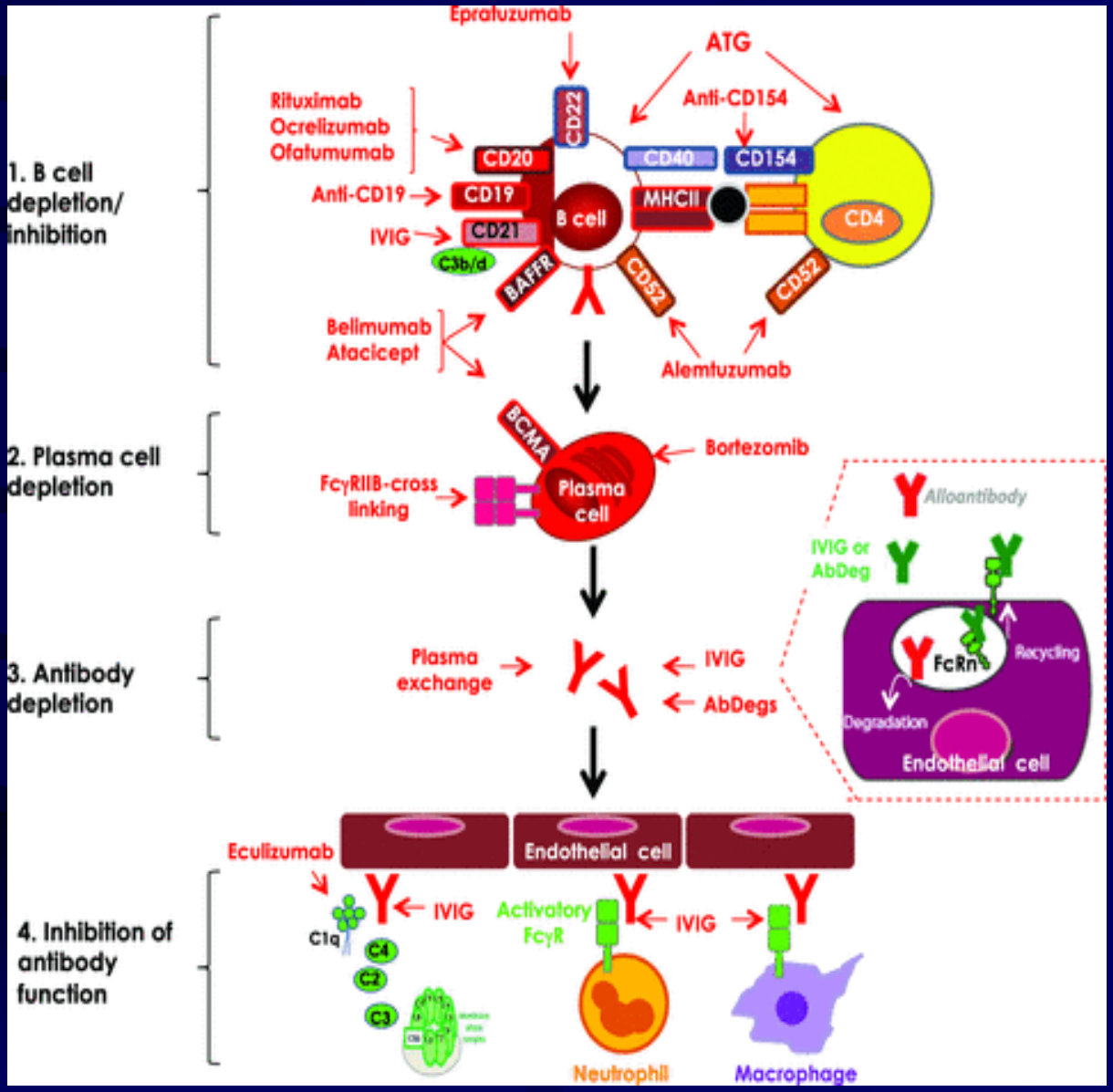
(1)donor-specific anti-HLA anti- bodies

(2)evidence of complement deposition in allograft biopsies

(3) histologic tissue injury, and

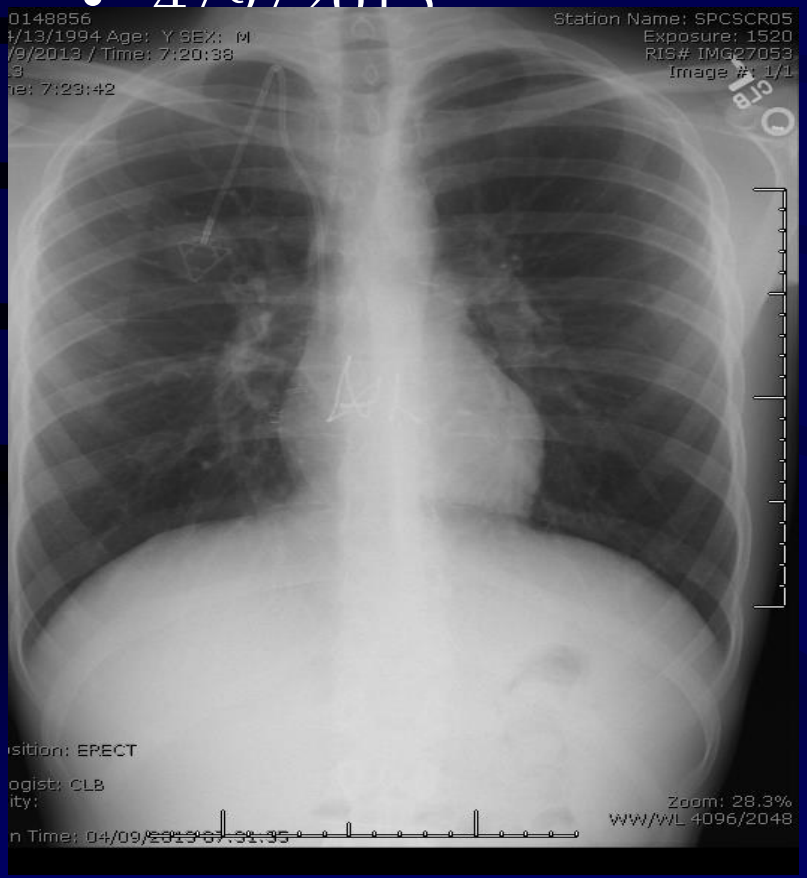
(4) clinical allograft dysfunction

Targeting B Cells and Antibody in Transplantation



American Journal of Transplantation Vol11, Issue7, pages 1359-1367

- 4/9/2013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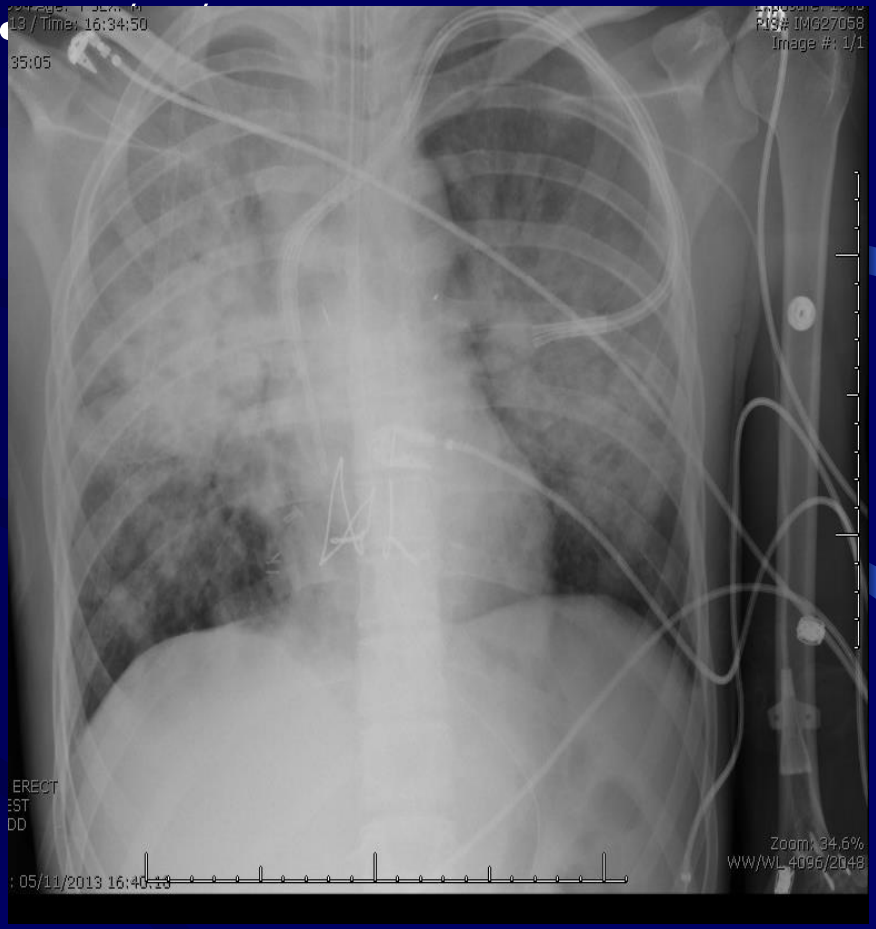
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AMR

- We are still evolving in its treatment
  - IVIG
  - Plasma exchange
  - Rituximab

Infections Following Lung Transplantation

Pathogenesis of Infections

- Immunosuppression
- Ischemic injury
- Interruption of lymphatic circulation
- Denervation of allograft

Infectious Disease Prophylaxis

- Antibacterials perioperative
- CMV / Herpes virus prophlaxis
- Antifungal prophylaxis
- PJP prophylaxis
- Nebulized antimicrobials

Infectious Complications

- Early (<14 days)
  - Bacterial
    - Donor – ventilator bugs
    - Recipient
      - depends on disease
      - Rx based on cultures
      - Empiric MRSA/MDR Pseudomonas coverage
      - Atypical coverage (Ureaplasma sp./hyperammonemia)
  - Fungal : Aspergillus, Candida

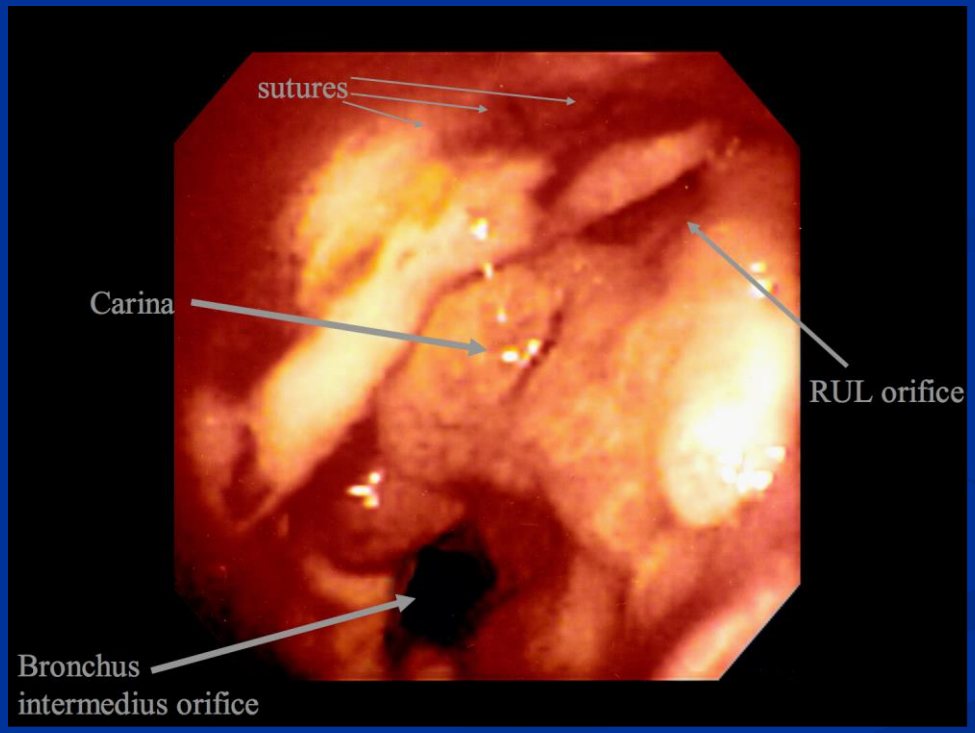
Infectious Complications

- Late (>14 days)
  - Bacterial – gram negative pneumonia
  - Fungal – Aspergillus
  - Viral – CMV, herpes

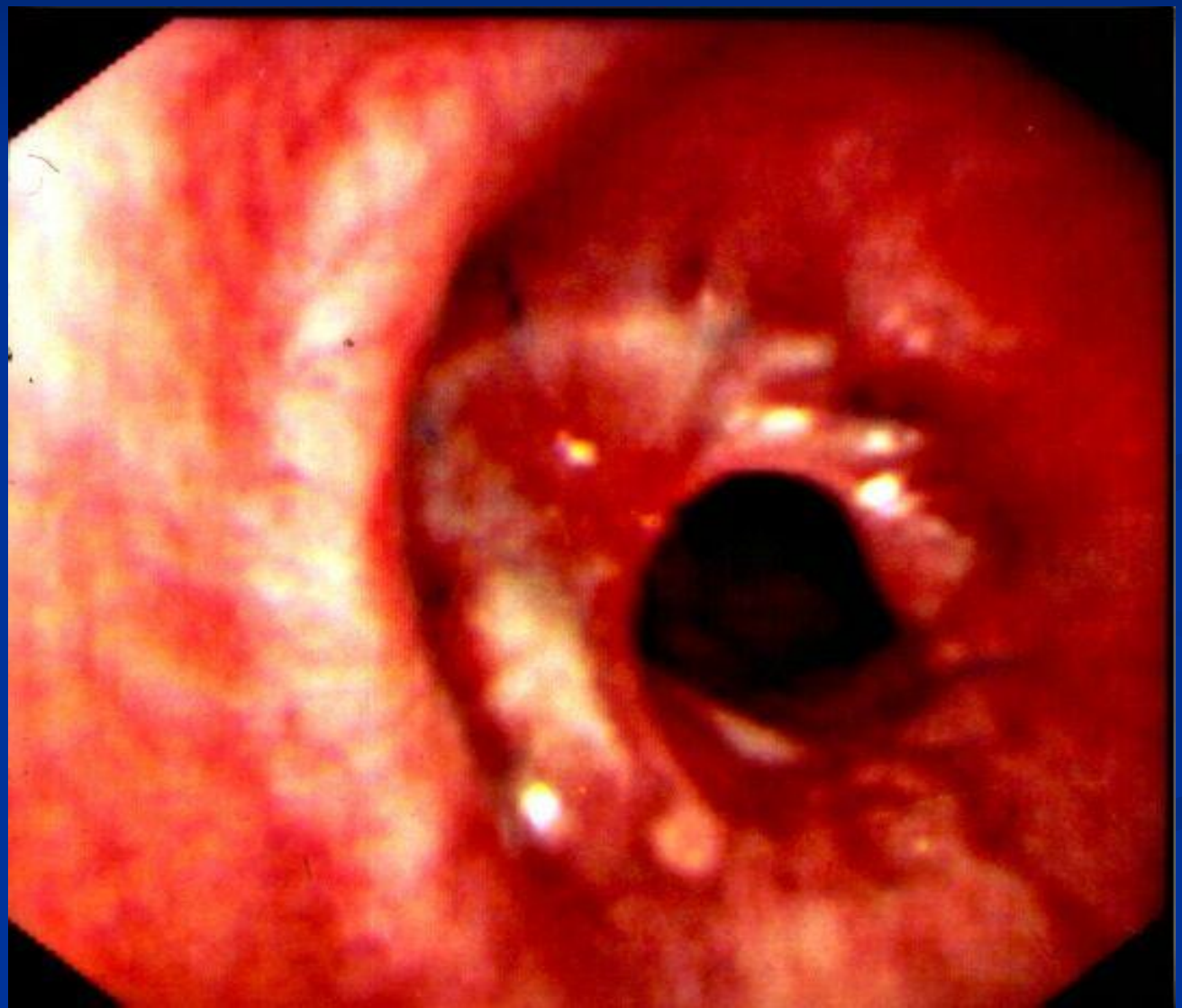
Definitions of CMV Infections

- Syndrome/Viremia
  - Fever, leukopenia, diarrhea, N/V
  - Malaise
  - CMV antigen conversion, PCR detection, or isolation from blood cultures
- Disease
  - Pneumonitis or extrapulmonary infection
  - Histopathologic evidence with compatible clinical syndrome

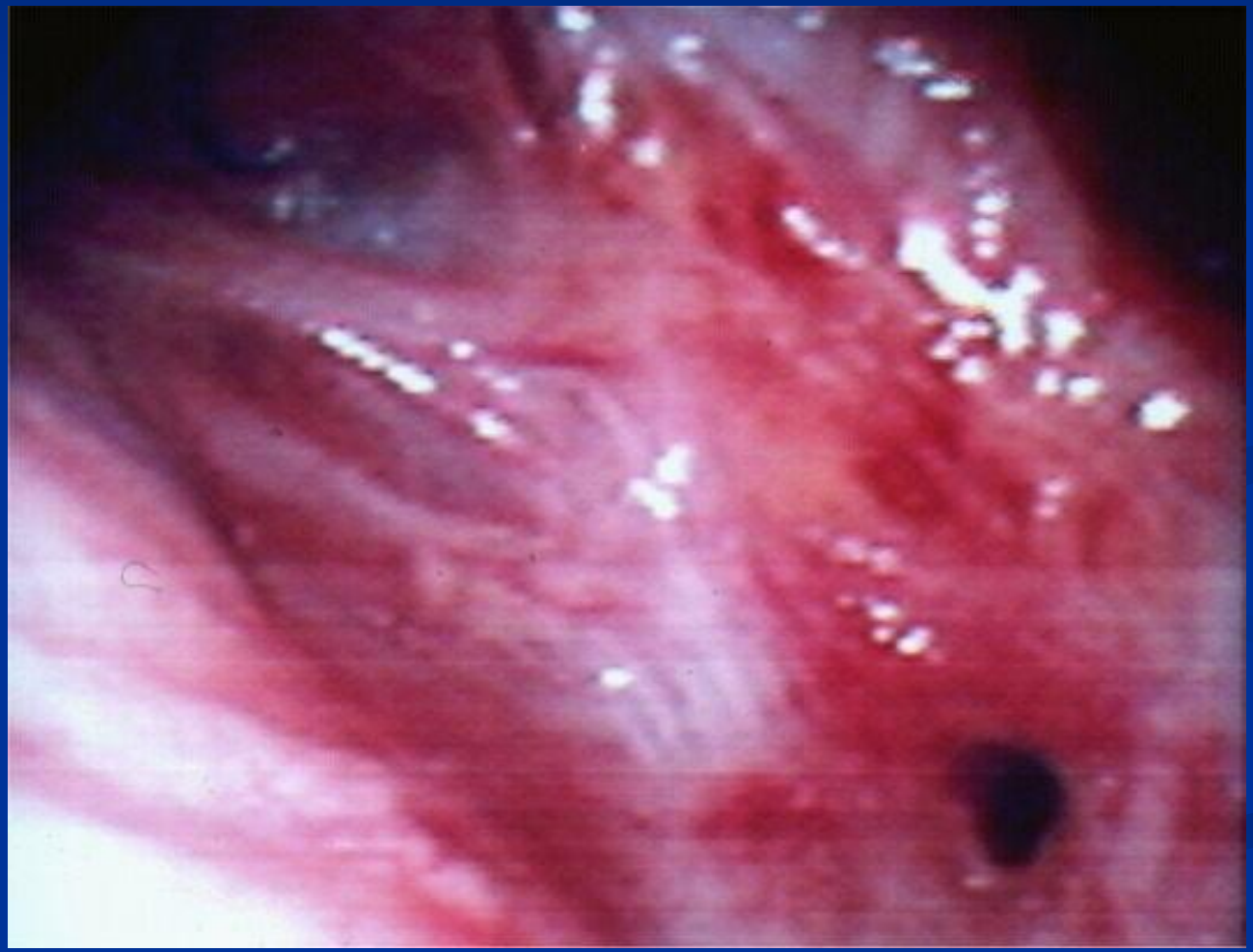
Airway Complications



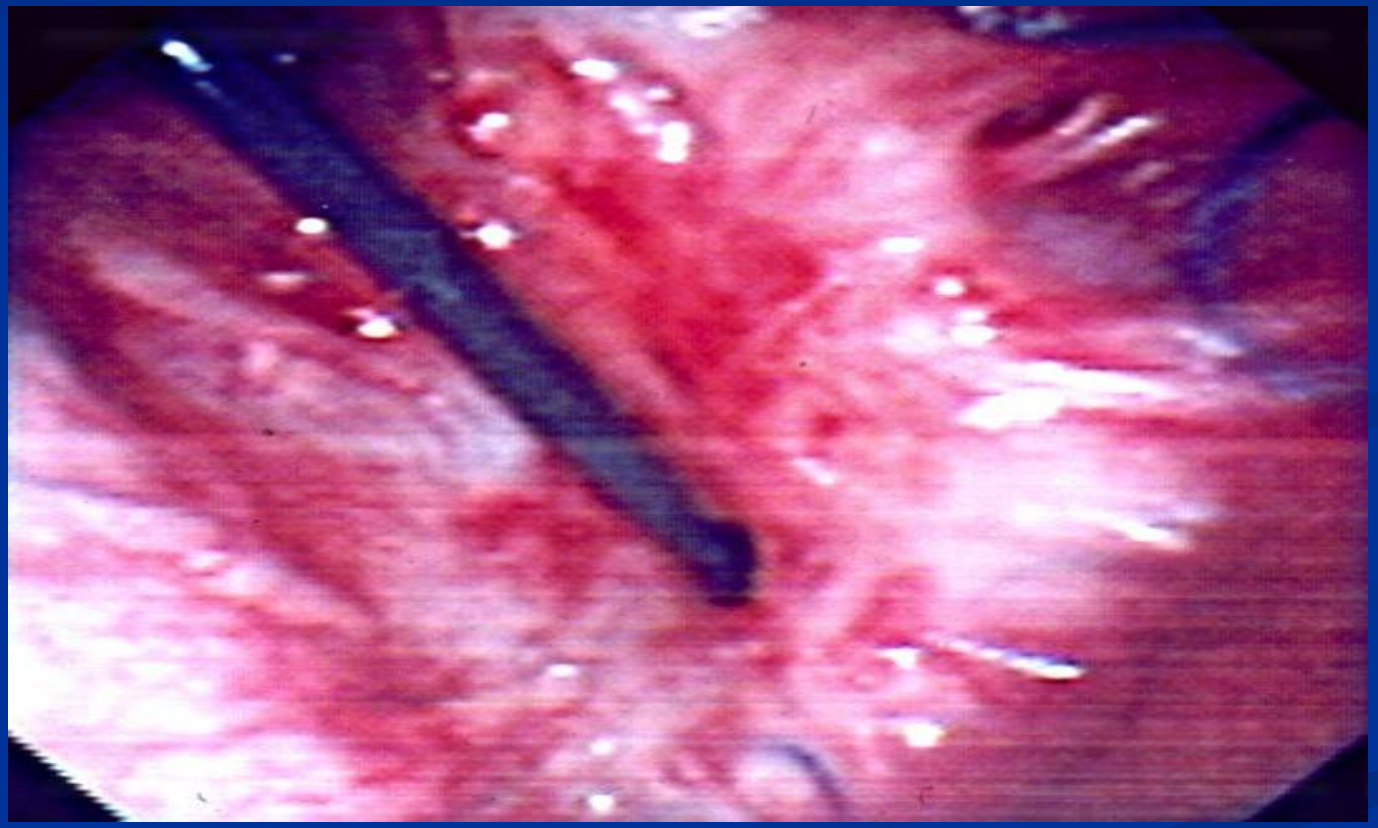
Airway Anastomosis Stricture



Airway Anastomosis Stricture

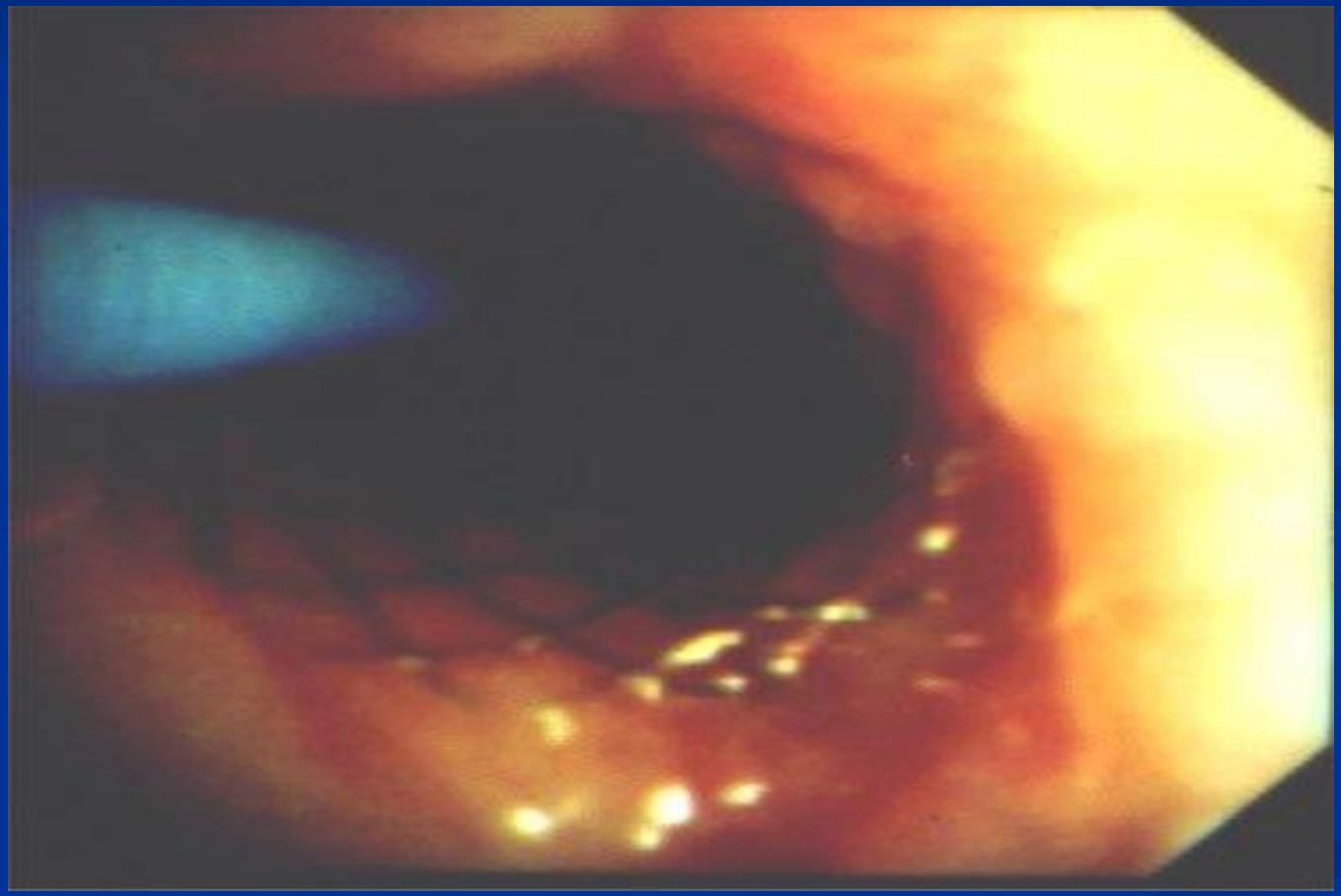


Airway Stricture
Balloon Dilatation



Airway Stricture

Stent Placement



Future Challenges
Expanding The Donor Pool

- Is xenotransplant the (an) answer?
- Should organ donation be legislated?
- Should organ donors' families be paid?
- Are we utilizing the current donor pool?