Photopheresis in lung transplant rejection

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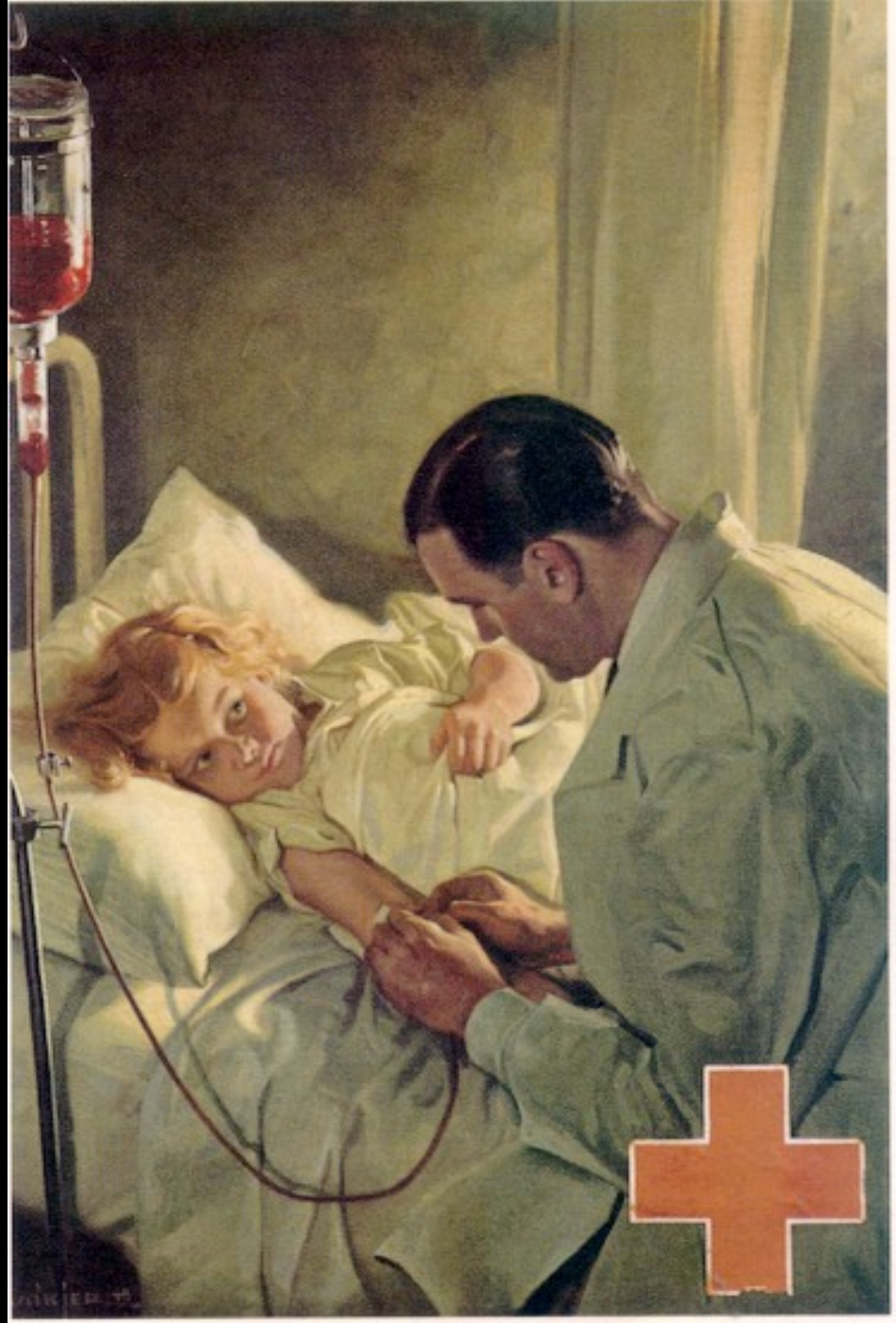


"Blood Saves Lives," by Jes Schlaikjer, 1948.

Introduction

- Bronchiolitis Obliterans Syndrome (BOS) in lung transplant
- Photopheresis in BOS
- PDH hospital experience
  - Apheresis procedures
  - Clinical results

Bronchiolitis Obliterans Syndrome (BOS)

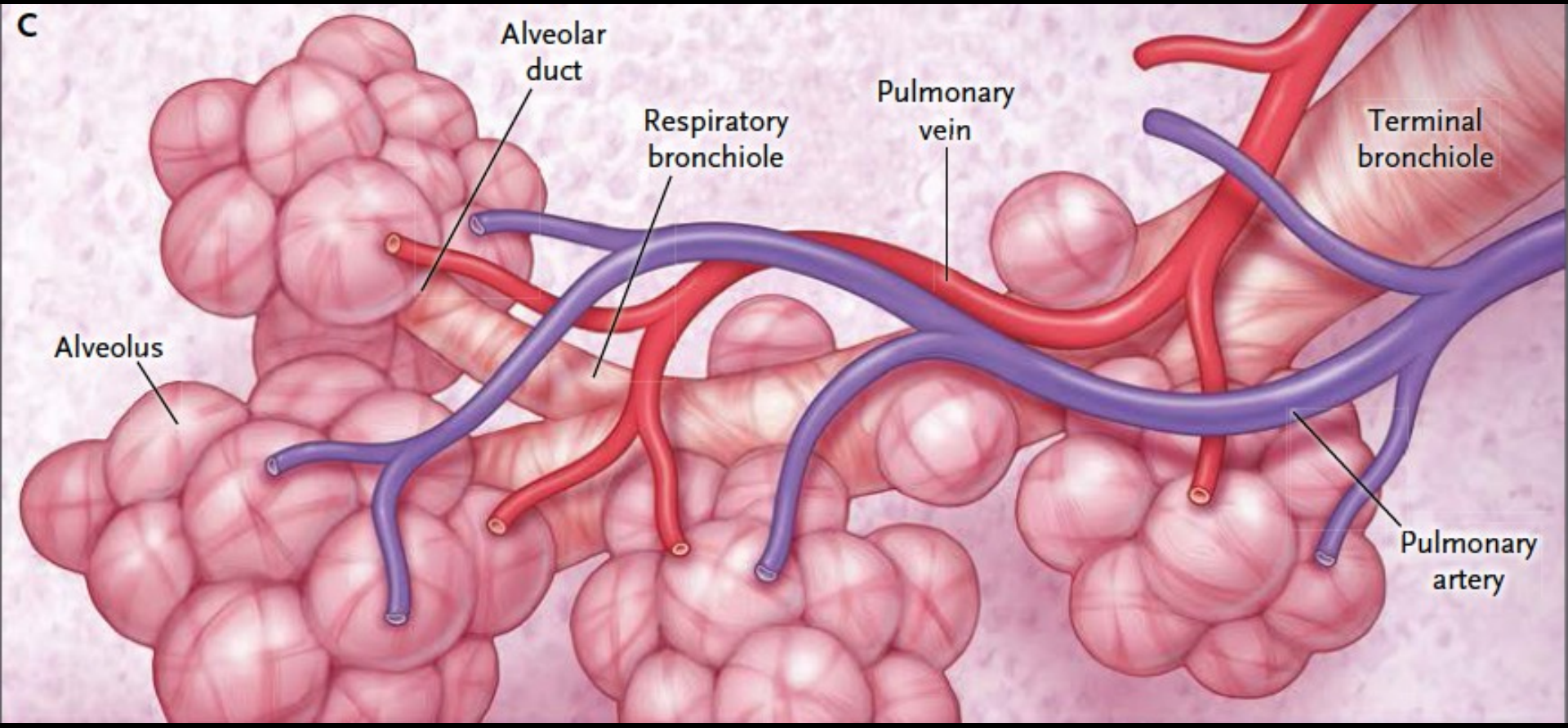
- Chronic graft rejection in lung transplant
- 60% of LT patients develope BOS in the 5 first years after transplant
- Increased risk of death and re-transplant
  - Leading cause of death after the 1st year after transplant
  - Causes 20-30% deaths
- BOS Survival median 3-4 years (range 0-9 years)

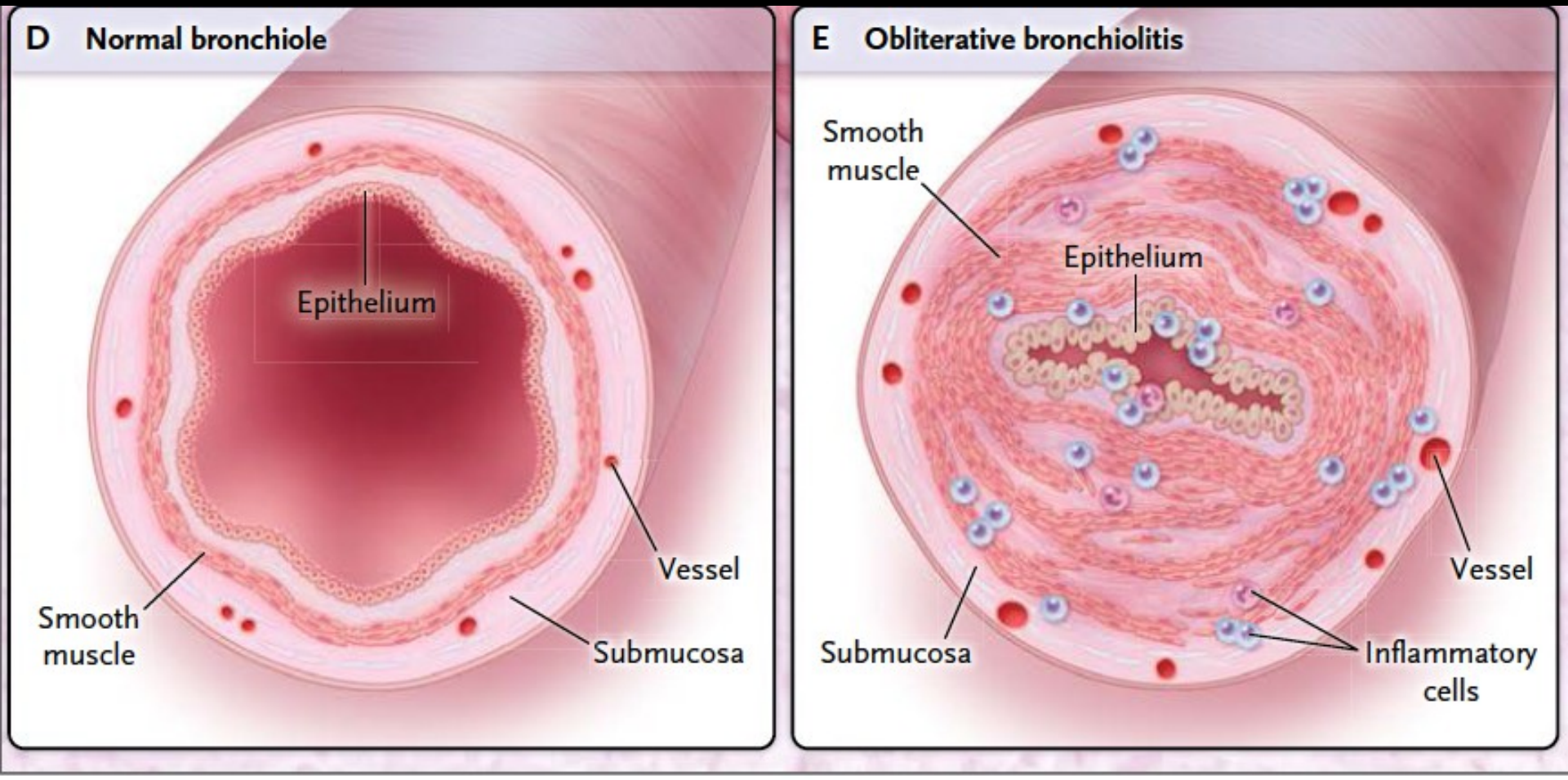
Bronchiolitis Obliterans Syndrome (BOS)

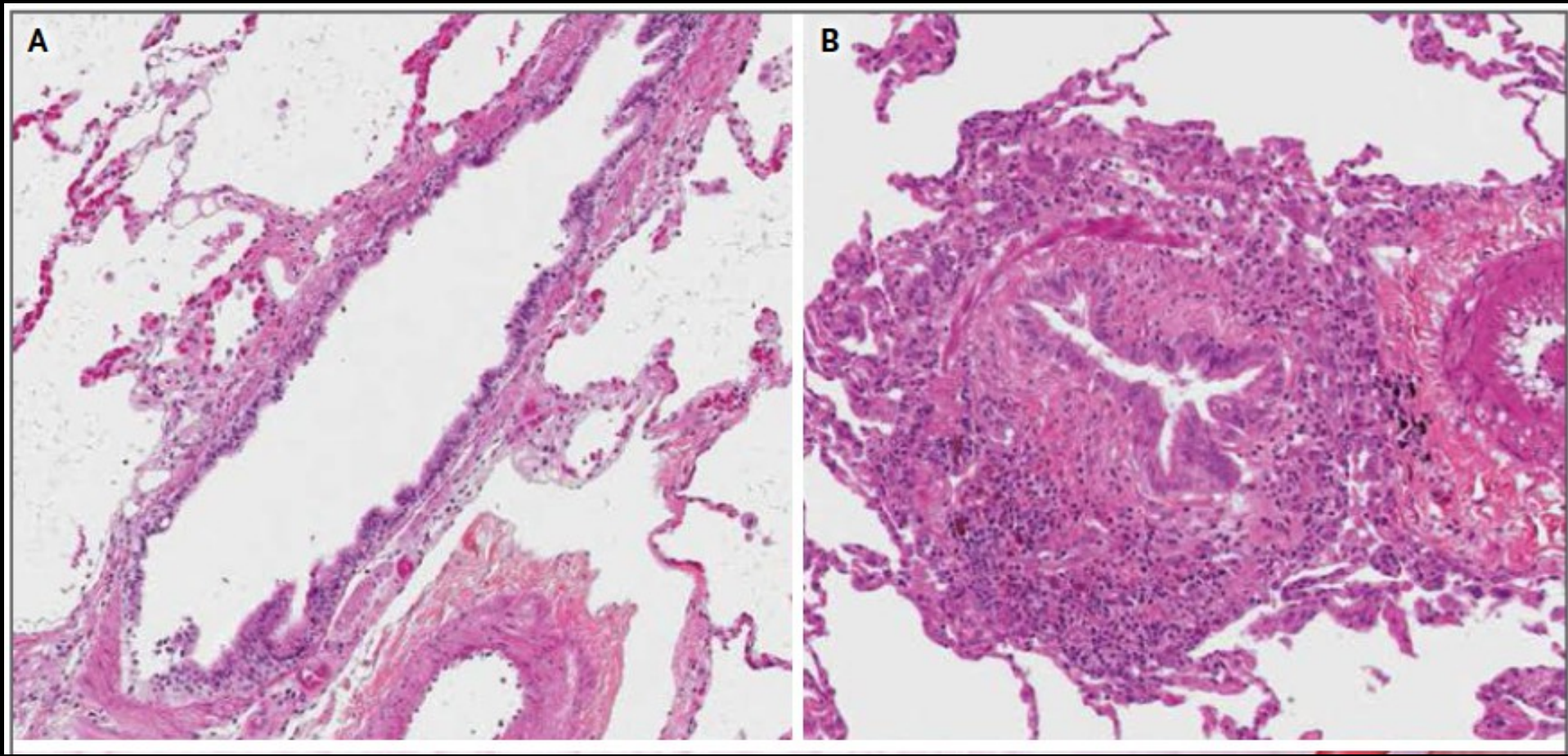
- Subepithelial inflammatory and fibrotic narrowing of the bronchioles

- After HSCT or solid organ transplantation, autoinmune disorders, viral respiratory infection, chronic GERD, air pollutants (final common pathway).

- Alloimmune reaction: direct T-cell-mediated injury of graft structures, circulating antibodies to donor HLA molecules


C
Alveolar duct
Respiratory bronchiole
Pulmonary vein
Terminal bronchiole
Alveolus
Pulmonary artery

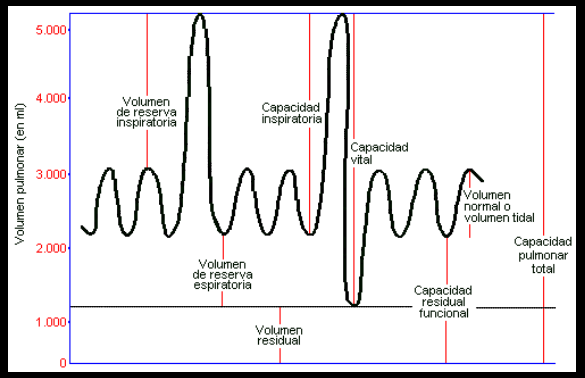

D Normal bronchiole
Epithelium
Vessel
Smooth muscle
Submucosa
E Obliterative bronchiolitis
Smooth muscle
Epithelium
Vessel
Submucosa
Inflammatory cells


A
B

Bronchiolitis Obliterans Syndrome (BOS)

- Progressive Dyspnea
- Non-productive Cough

- Persistent airflow obstruction
- Declining Forced espiratory
- volumen in 1 second (FEV-1)



Introduction

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Photoapheresis

- Second-line treatment after failure inmunosupressive treatment in the treatment of BOS
  - High-dose Methyl-prednisolone
  - Methotrexate
  - ATG
  - Alemtuzumab

TABLE I. ASFA Indications for Extracorporeal Photopheresis (ECP) [4]

Condition	Grade of Recommendation
Category I[a]	
Cutaneous T-cell lymphoma; mycosis fungoides, Sezary syndrome (erythrodermic)	1B—strong recommendation, moderate quality evidence
Category II[b]	
Cardiac transplant (cellular or recurrent rejection)	1B—strong recommendation, moderate quality evidence
Chronic graft-versus-host-disease (GVHD), skin	
Acute GVHD, skin	1C—strong recommendation, low quality evidence
Lung allograft rejection: bronchiolitis obliterans syndrome (BOS)	
Cardiac transplant (rejection prophylaxis)	2A—weak recommendation, high quality evidence
Category III[c]	
Psoriasis	2B—weak recommendation, moderate quality evidence
Scleroderma (progressive systemic sclerosis)	
Crohn's disease (CD)	2C—weak recommendation, low quality evidence
Cutaneous T-cell lymphoma (nonerythrodermic)	
Nephrogenic systemic fibrosis	
Pemphigus vulgaris	

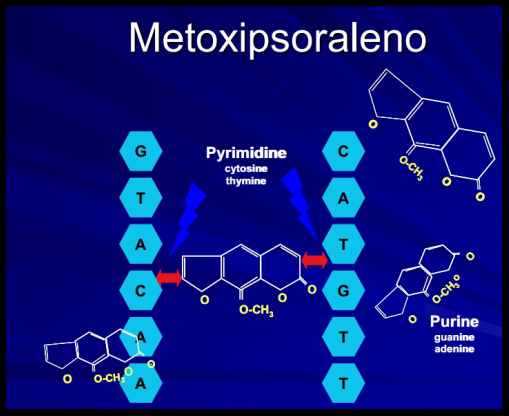
[a]Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.

[b]Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

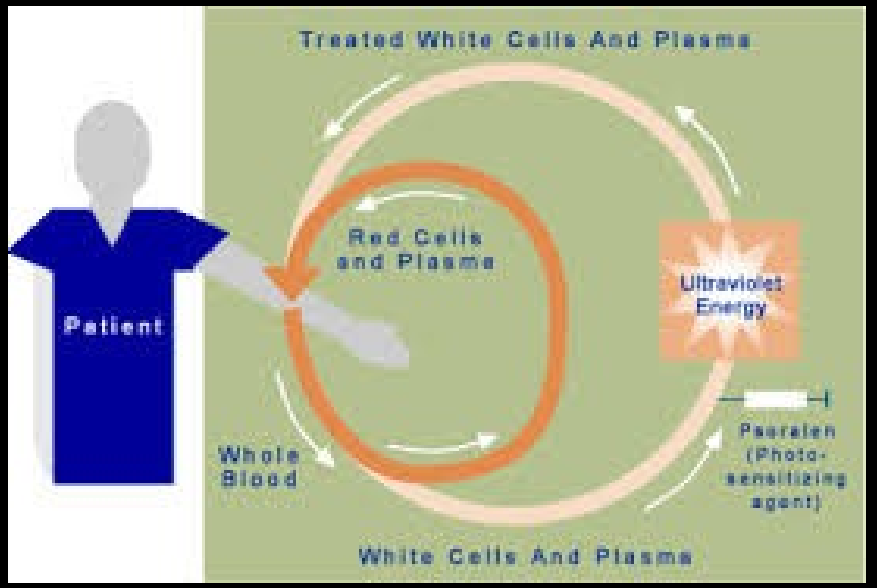
[c]Optimum role of apheresis therapy is not established. Decision making should be individualized.

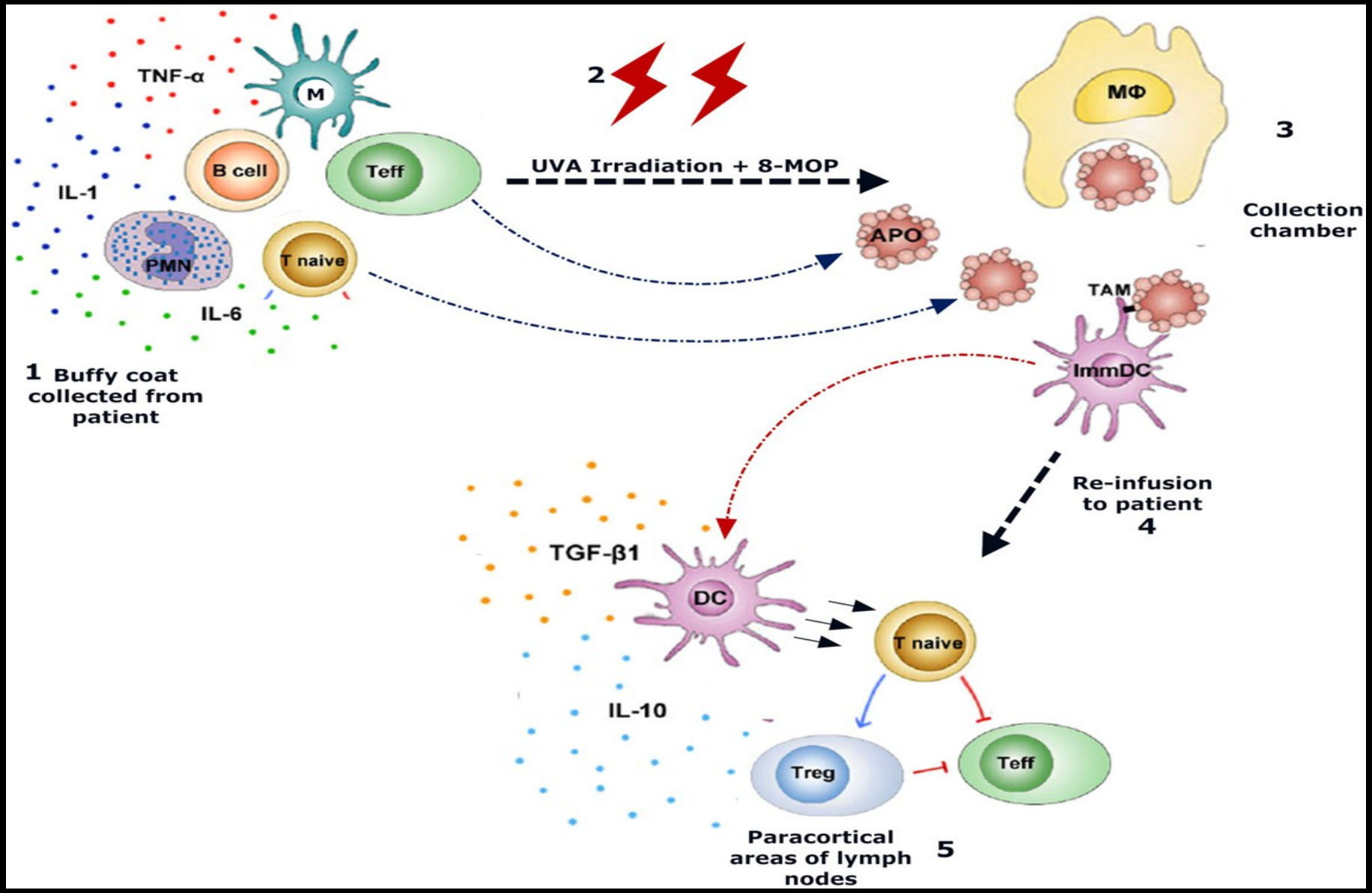
Marisa B. Marques* and Jill Adamski. Extracorporeal Photopheresis: Technique, Established and Novel Indications. Journal of Clinical Apheresis 2014 May; 00:1–7

Photoapheresis



- Lymphocytes treated with a photosensitizing agent
  - 8-Methoxypsoralen
- Irradiation with UVA light
- Nucleated cells apoptosis
- Reinfusion to the patient
- Inmunomodulation





Evgenios Goussetis a, Ioanna Varelaa, Panagiotis Tsirigotis b. Update on the mechanism of action and on clinical efficacy of extracorporeal photopheresis in the treatment of acute and chronic graft versus host disease in children. Transfusion and Apheresis Science, 2011: 1-7.

Introduction

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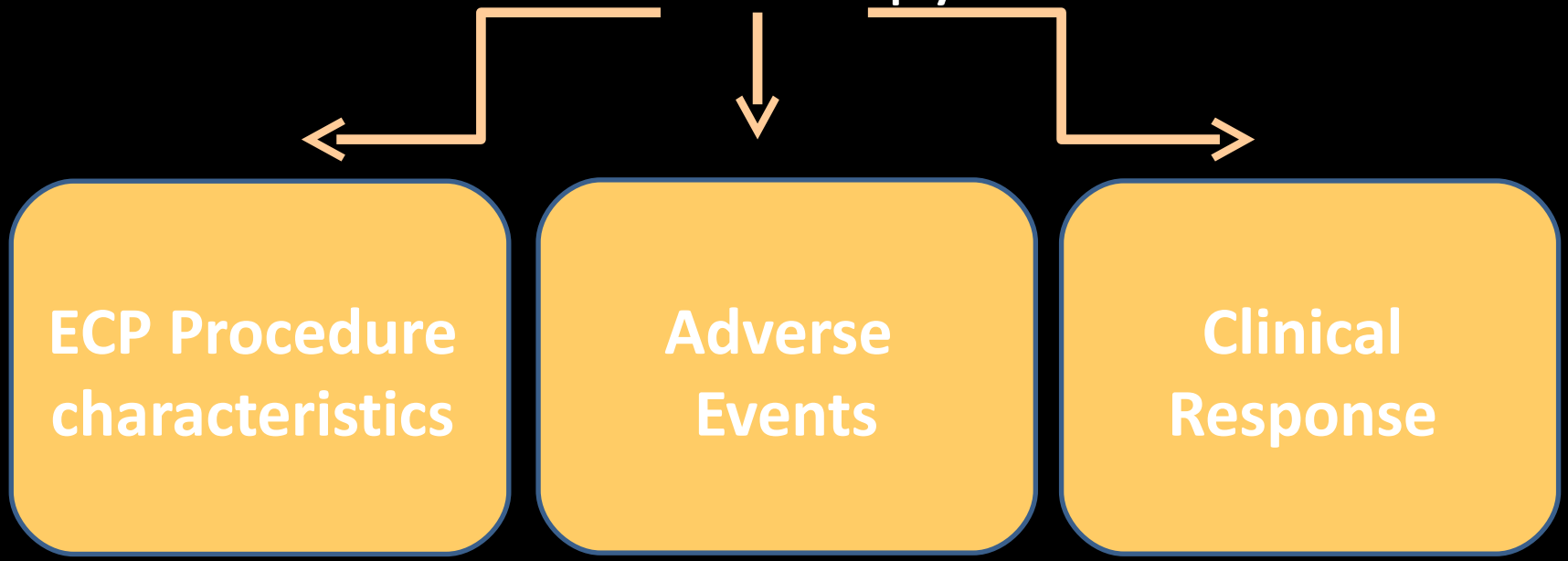
Objectives

Evaluate ECP procedures in lung transplantation patients with obliterative bronchilitis refractory to IS therapy.

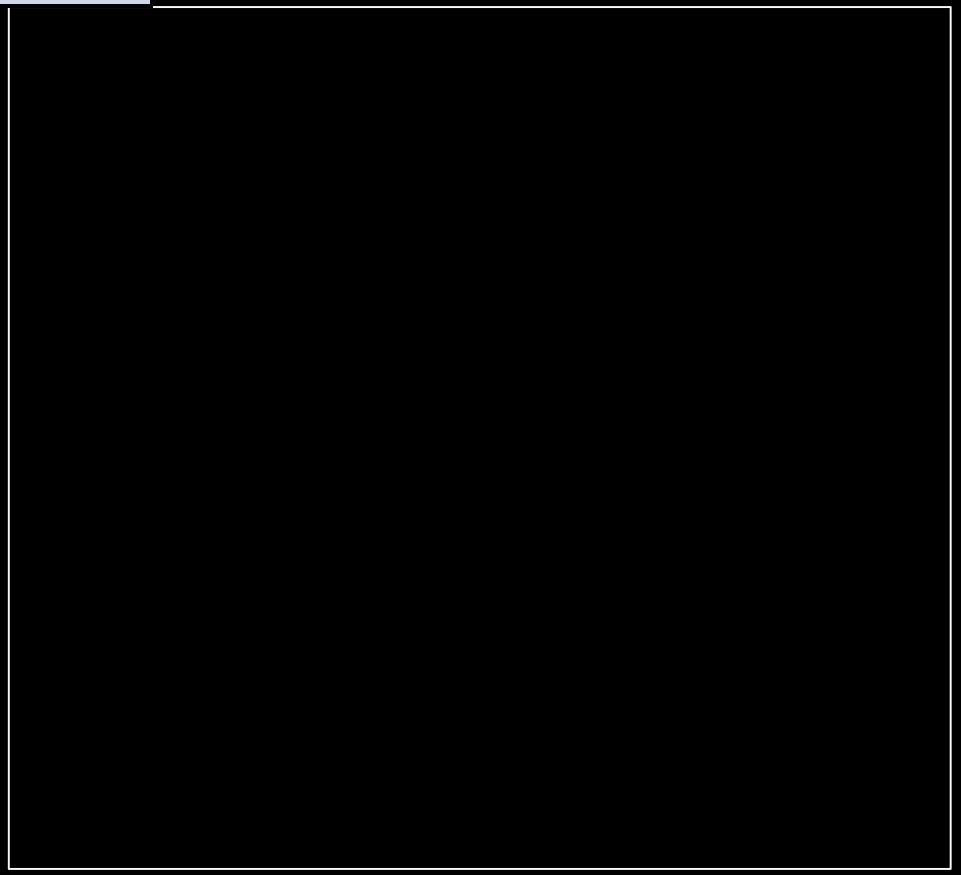


Patients and procedures

- March 2012 to Nov 2014 32 months
- Patients 16
- Procedures 302

Patients

	N= 16
Age (median)	**42,8 (19,4- 64,1)** years



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Lymphocyte collection

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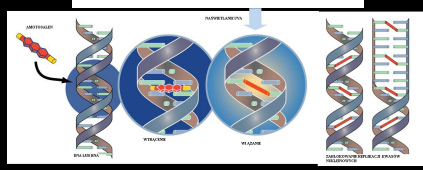

Lymphocytes Photo-inactivativation

Photo-inactivated lymphocytes infusion

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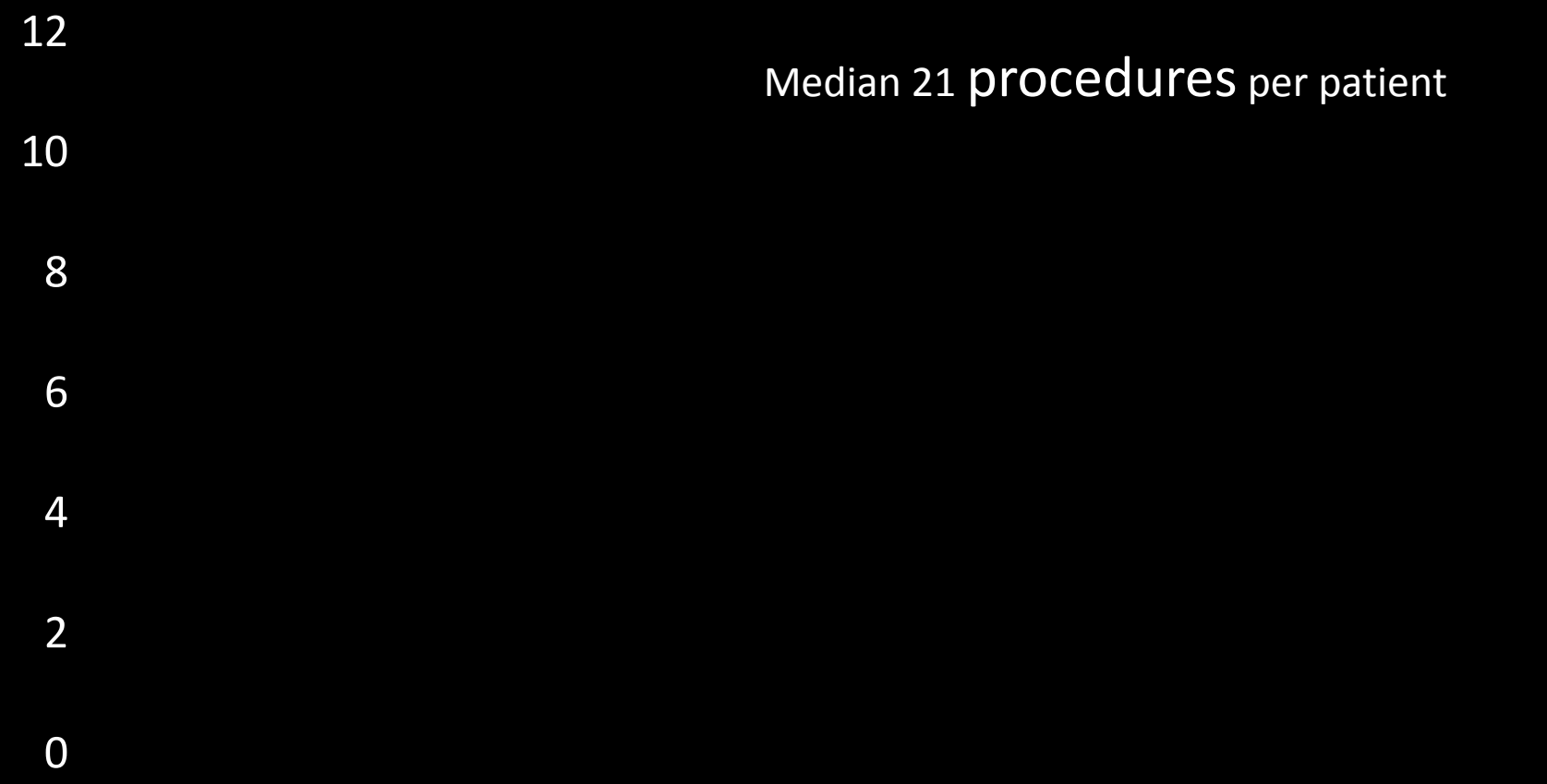
Lymphocyte collection

* Two per week for the first month
* Two every two weeks for 3 months
* Two per month

Number of photopheresis procedures per patient



Machines for lymphopheresis

Venous access

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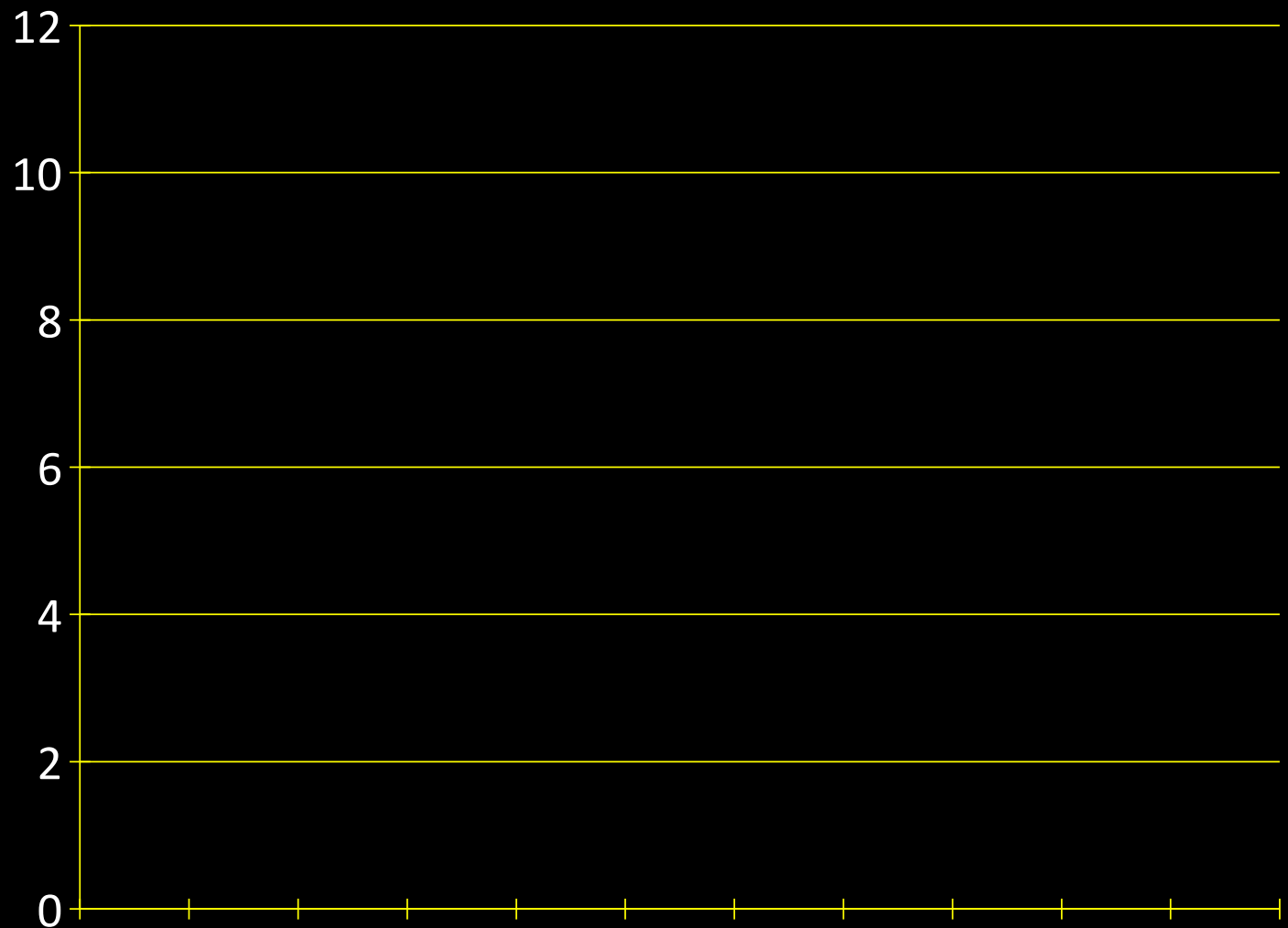
Lymphocyte collection

Collection time (average, SD)	**206(29) min**
Blood volume average (SD) ml	**4205(788)**
Blood-volume processed average (SD)ml	**8074 (2161)**
Number of Patien blood volume processed. Median (range)	**1.95 (0.2-3.1)**
ACD used ml (average (SD)	**753 (194)**
Average flow ml/min average (SD)	**47 (25)**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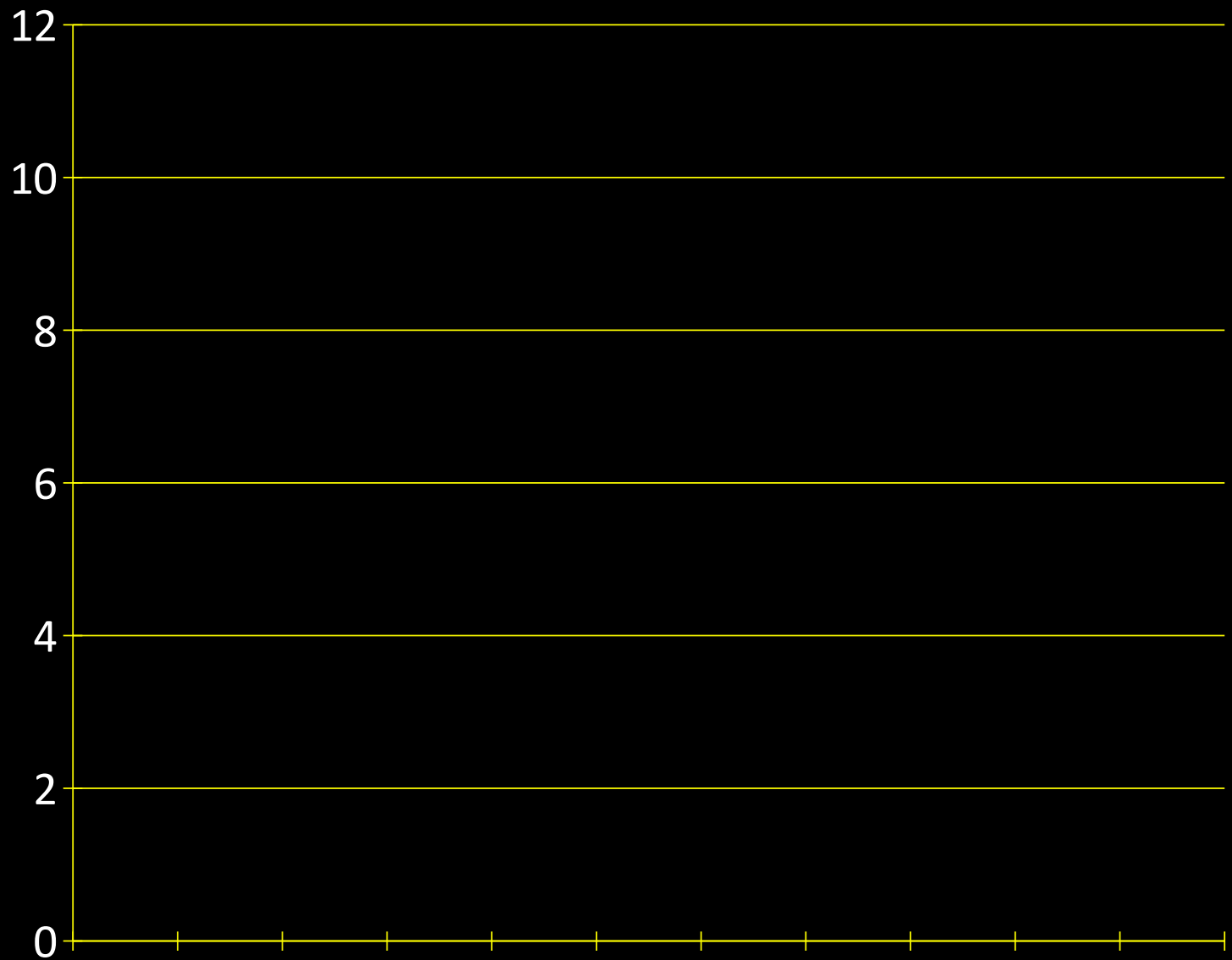
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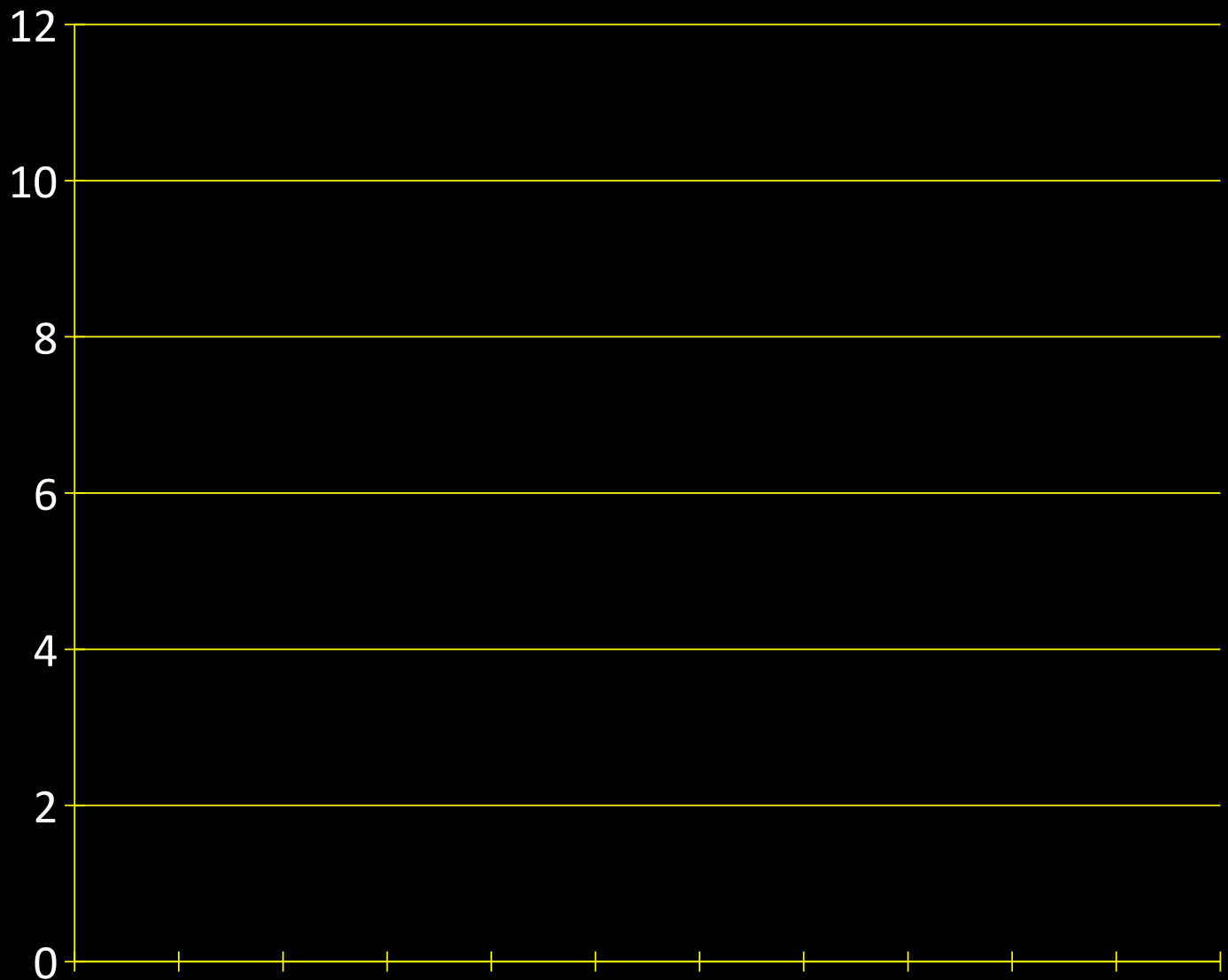
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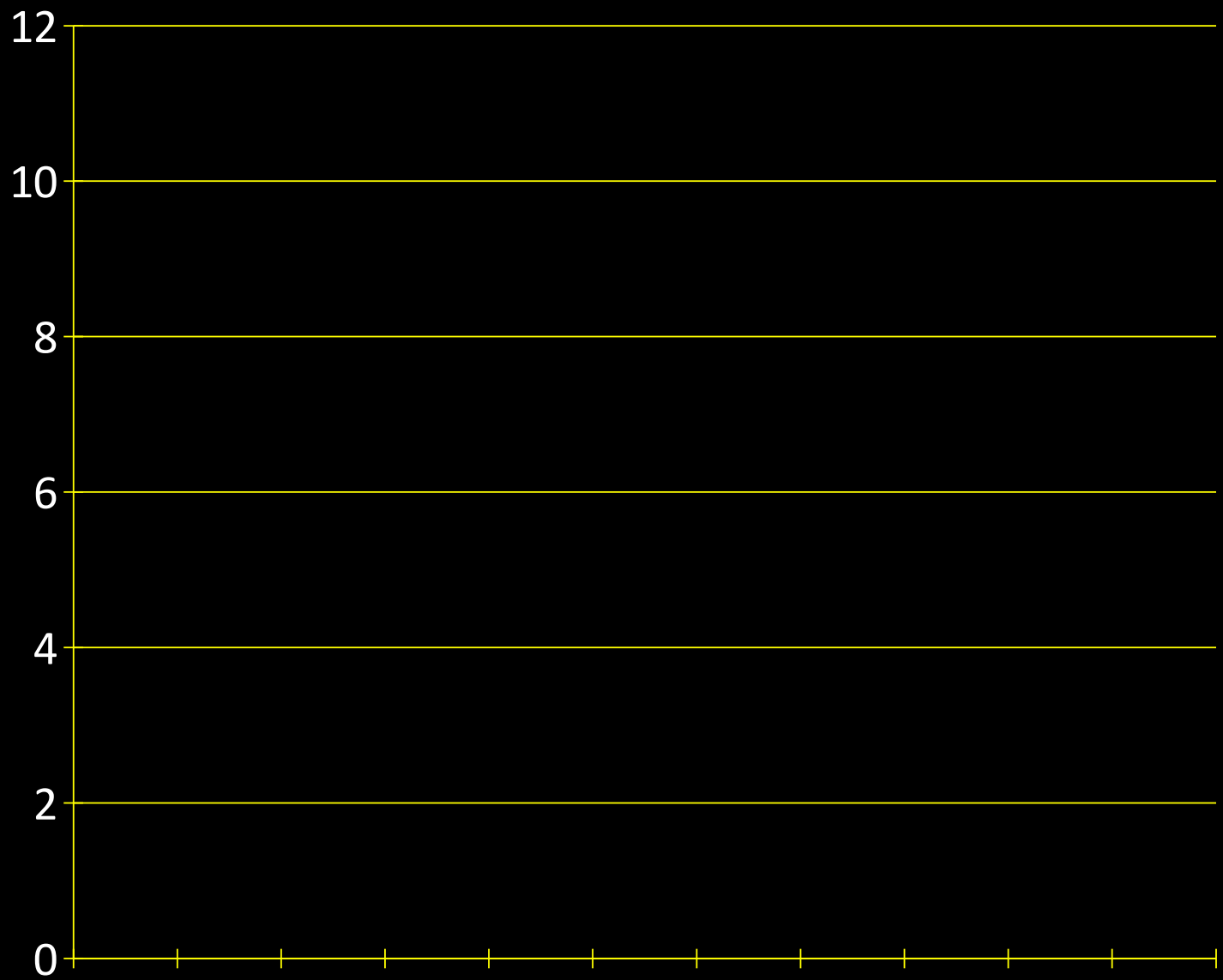
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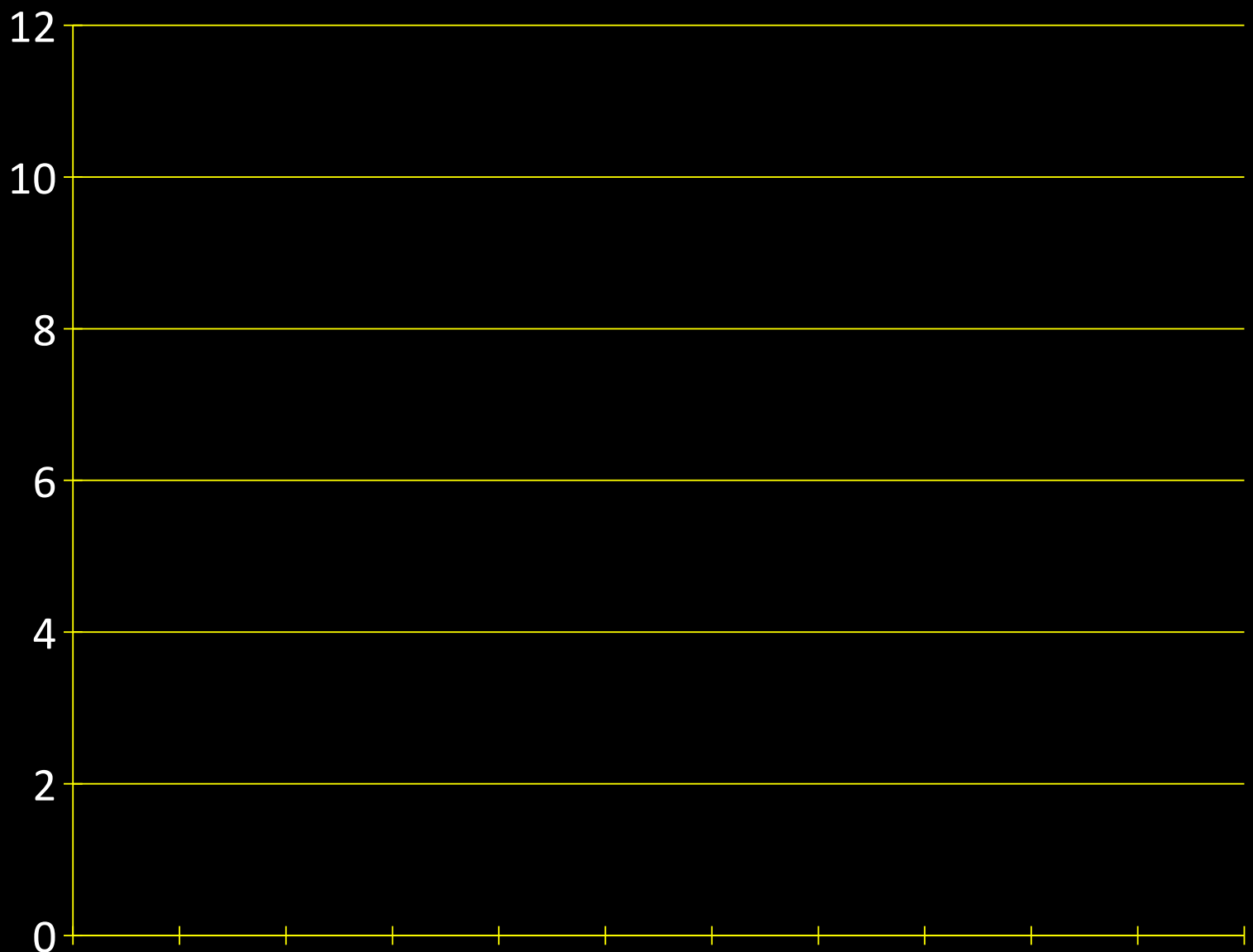
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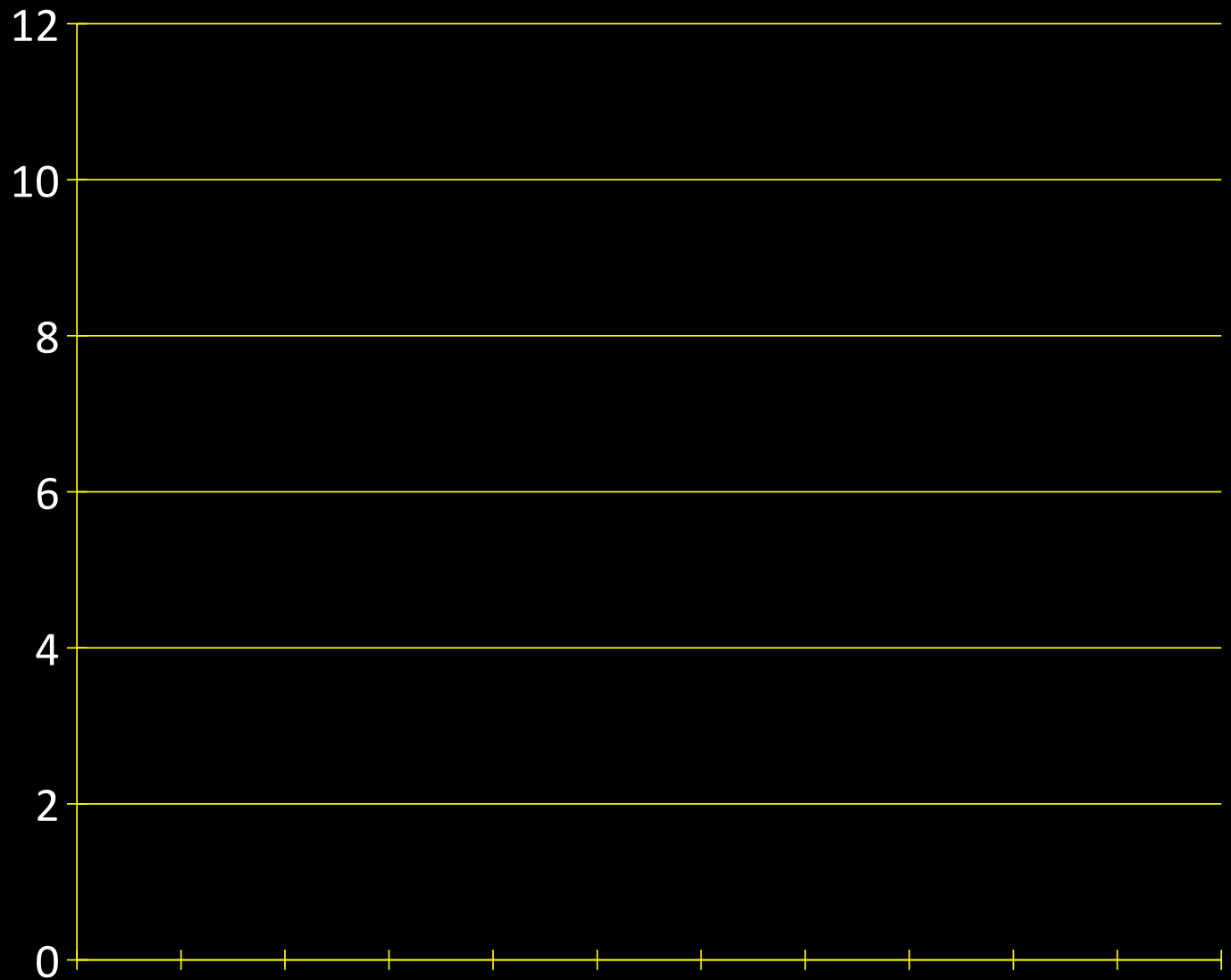
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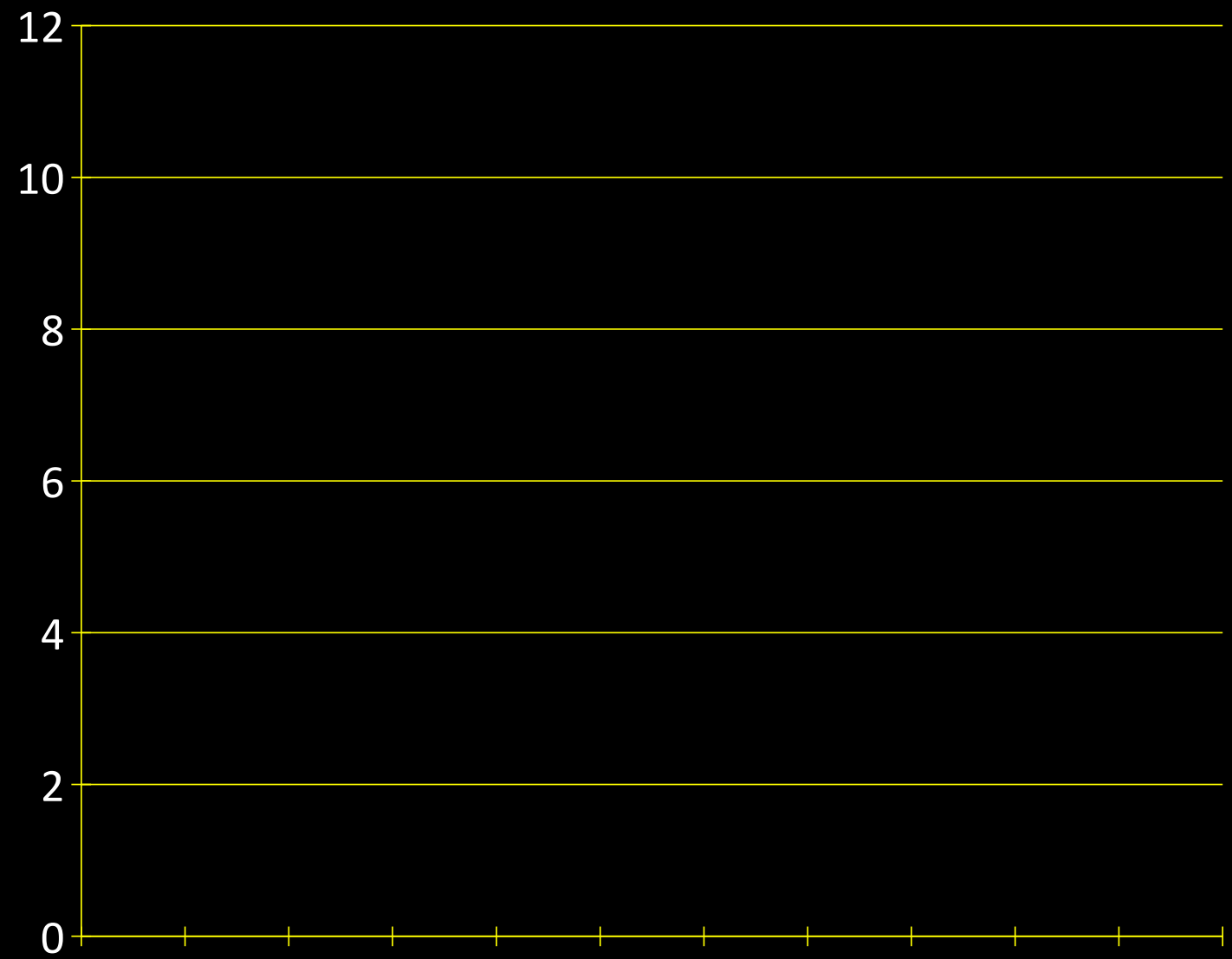
12
10
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6
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2
0

Adverse events in photopheresis

March 2012 to Nov 2014
299 procedures in Lung Transplant patients

Product features (by machine)

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Lymphocyte collection

47 min

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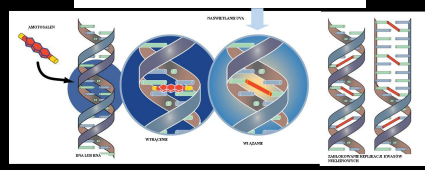

Lymphocytes Photo-inactivativation

Photo-inactivated lymphocytes infusion

Photoinactivation

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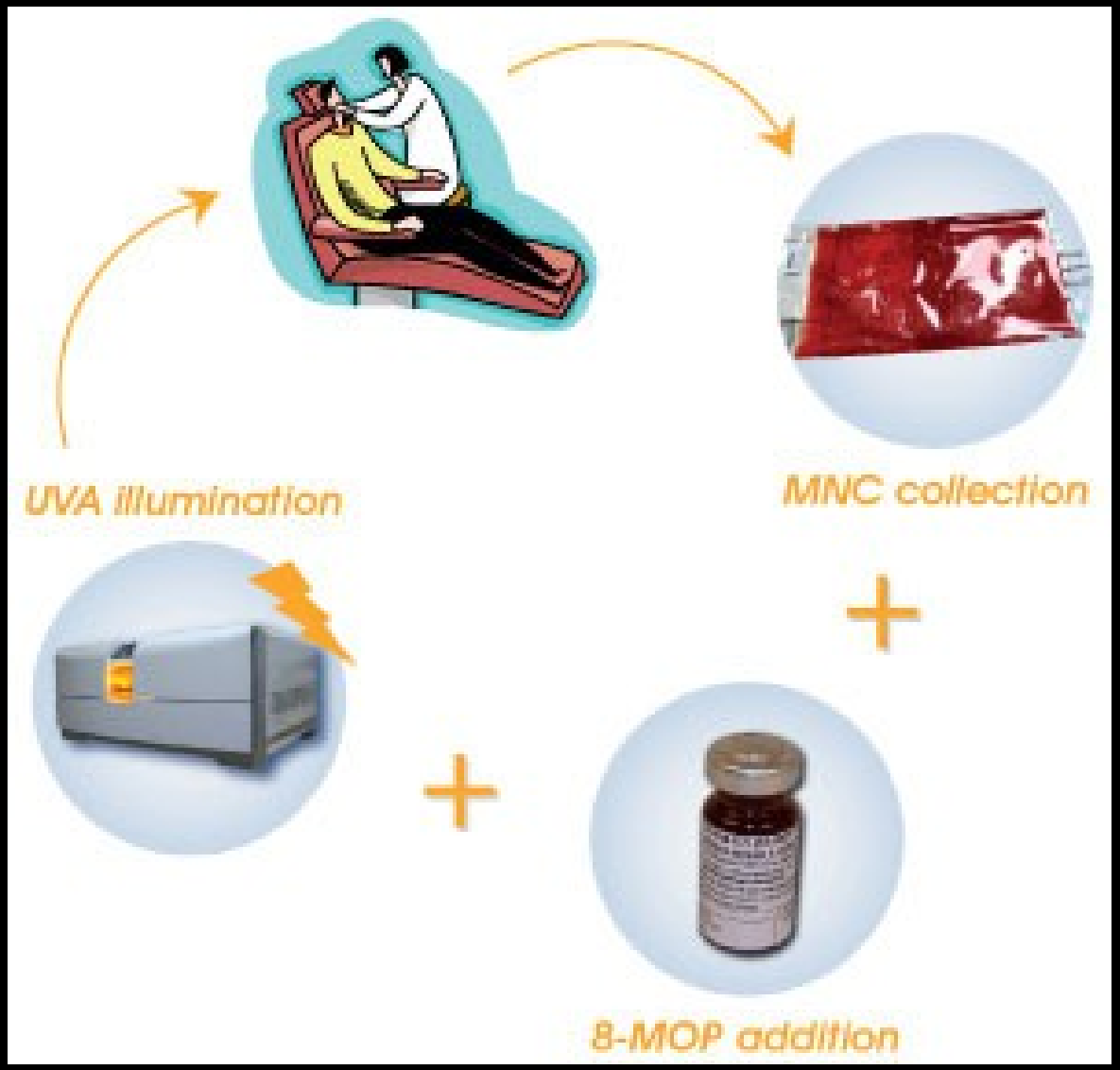

Theraflex-MacoPharma ®

8-MOP 0,2 umg/ml

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Lymphocyte collection

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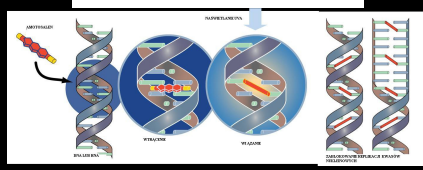


Lymphocytes Photo-inactivativation

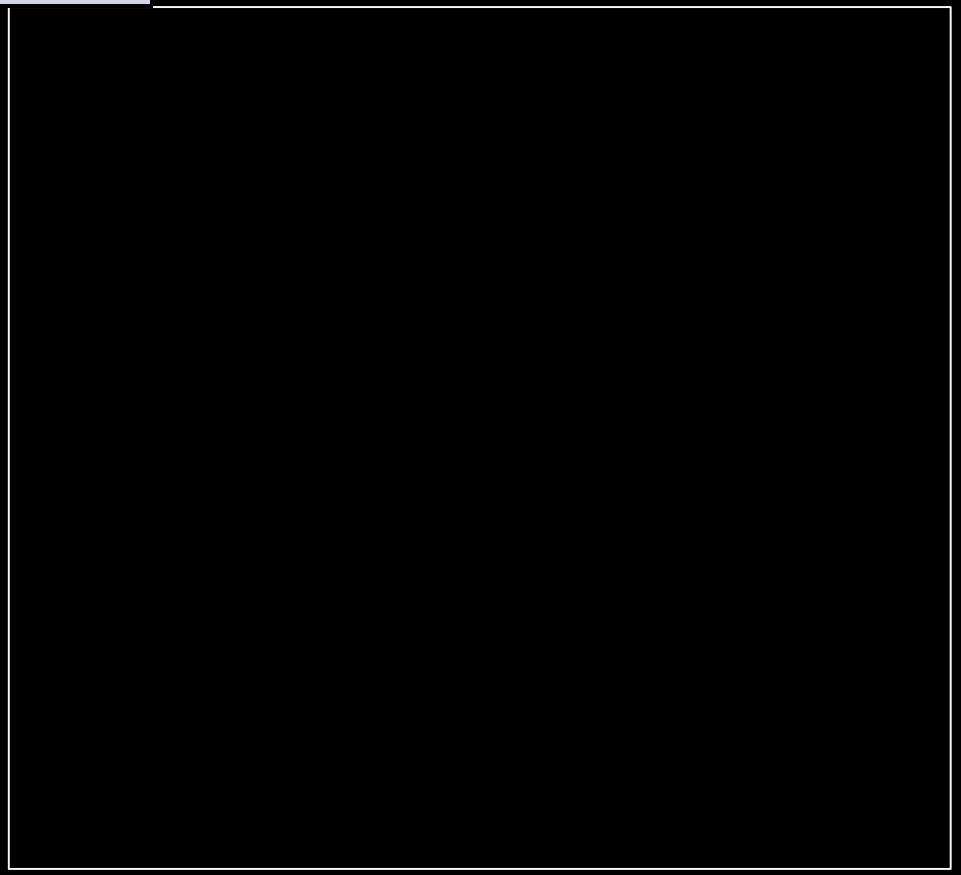
4:14 min

Photo-inactivated lymphocytes infusion

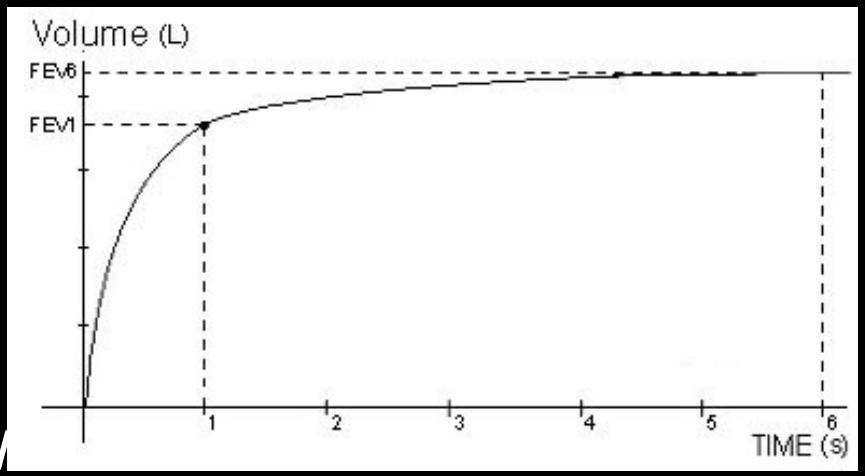
Clinical evaluation & response

Patients

	N= 16
Age (median)	**42,8 (19,4- 64,1)** years



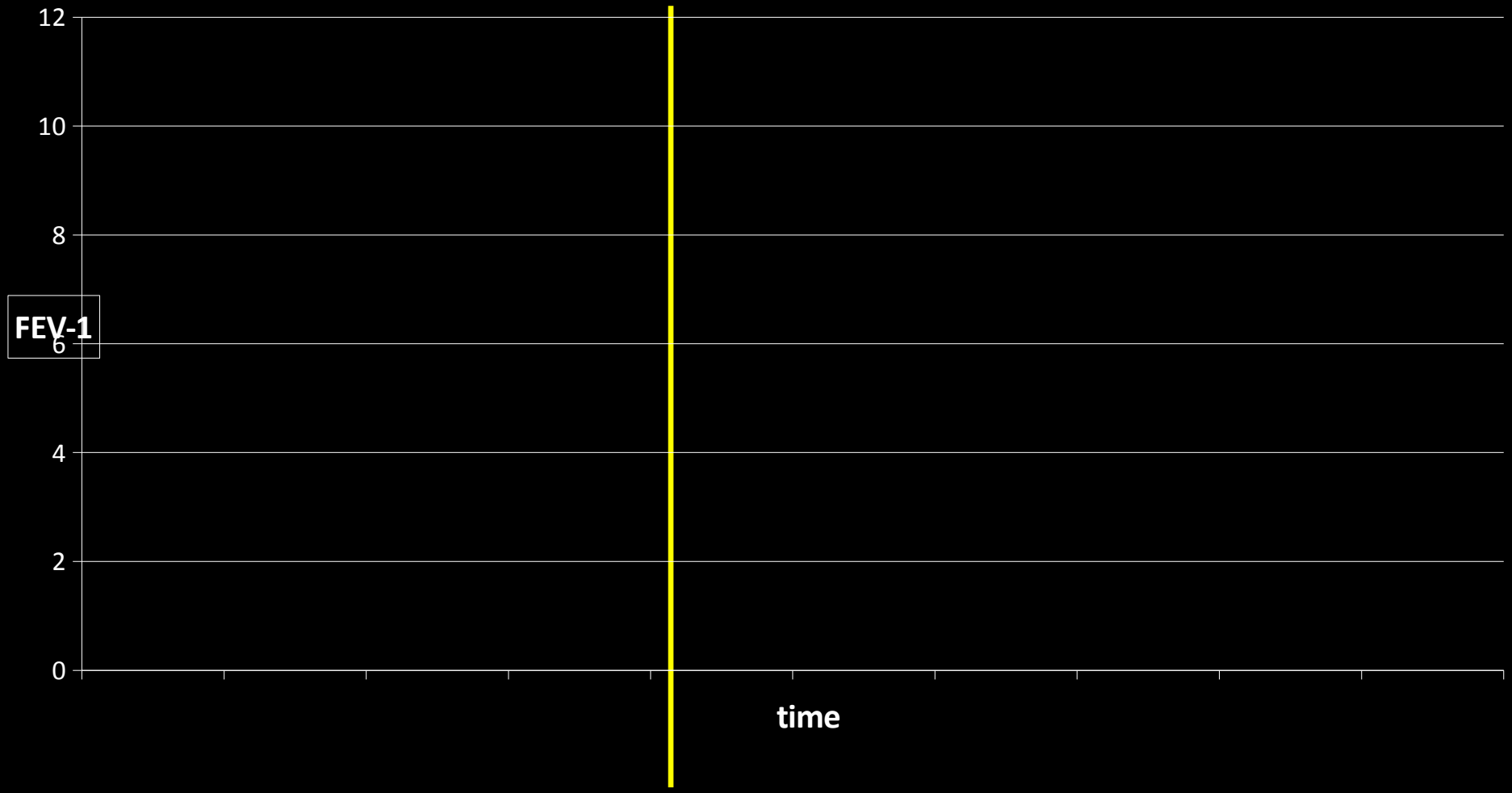
Clinical evaluation



- FEV1 measured every tw

- Response criteria were:
  - Stabilized FEV1
  - Decreased rate of FEV1 decline (compared to the previous three months)

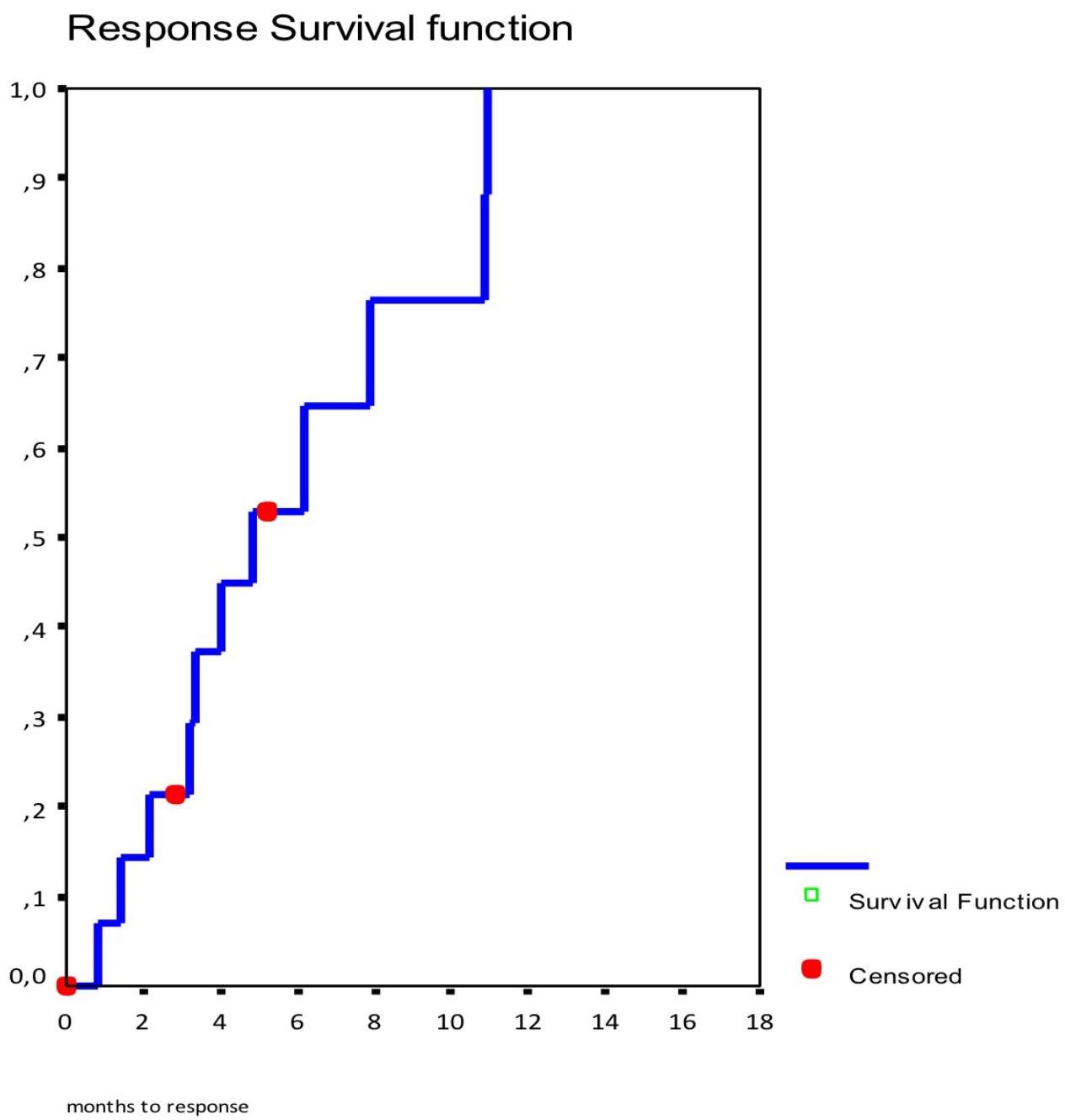
FEV-1 evolution

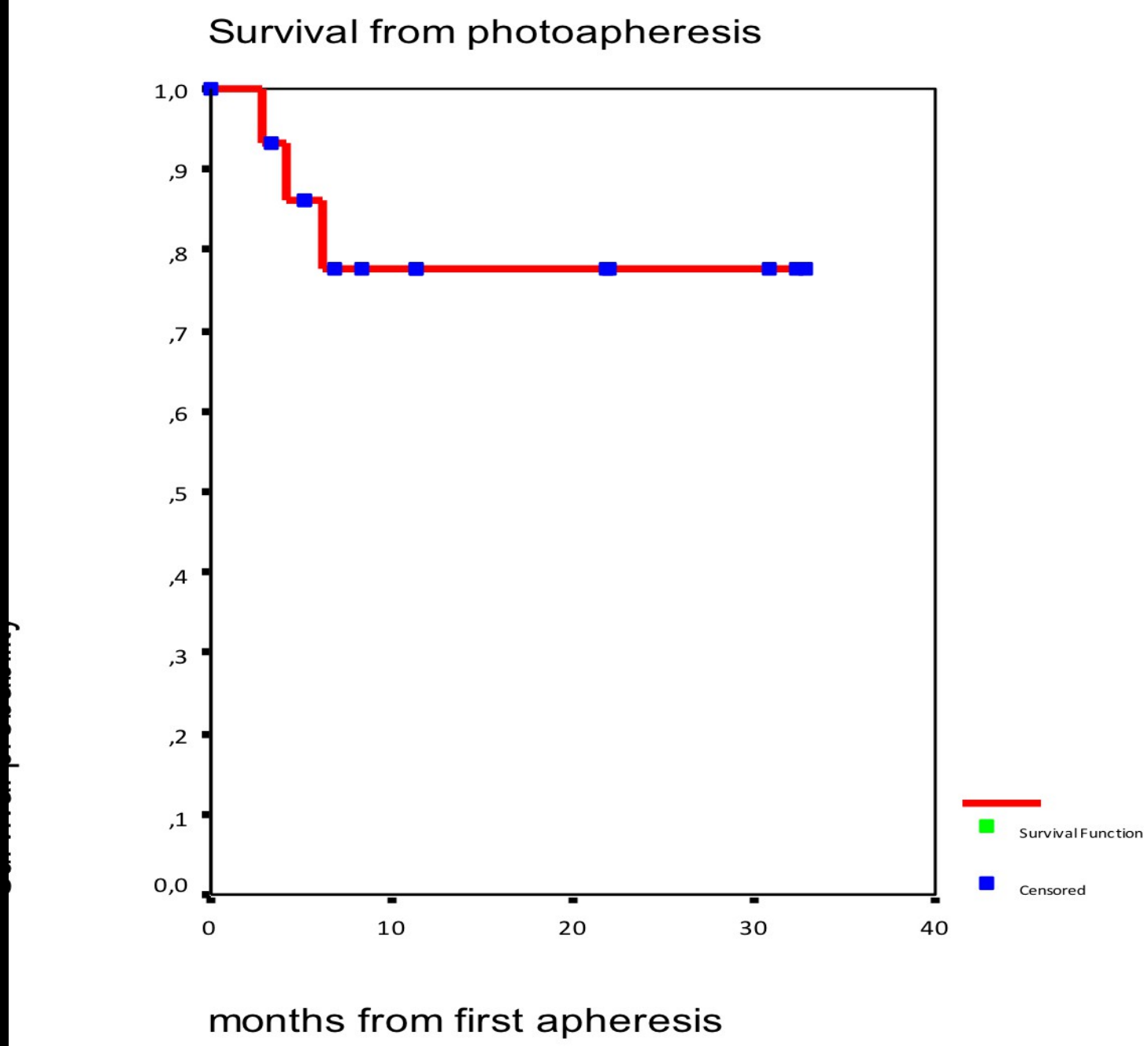


Photopheresis treatment

Clinical Response

	N=16
Time from transplant to photoapheresis treatment Months (median-range)	**58,4 (29,4-182,8)**
Time on ECP treatment Months (median-range)	**5,8 (0,1-29,8)**
Time to **clinical response** since first procedure Months (median-range)	**3,7 (0.03-10.9)**
Follow-up: Months (median-range) Clinical improvement n(%) Stable disease n(%) No response n(%)	**7,6 (0,03- 32,8)** **1 6,25%** **11 68,75 %** **4 25%**
Re-Transplantation n(%) **Deaths** n(%)	**0 (0%)** **3 (18,7%)**


Response Survival function
1,0
,9
,8
,7
,6
,5
,4
,3
,2
,1
0,0
0
2
4
6
8
10
12
14
16
18
months to response
Survival Function
Censored


Survival from photoapheresis
1,0
,9
,8
,7
,6
,5
,4
,3
,2
,1
0,0
0
10
20
30
40
Survival Function
Censored
months from first apheresis

Conclusions

Extracorporeal photopheresis :

- Is a well tolerated procedure
- It can stabilizes BOS progression and delay re-transplantation

in patients with refractory BOS to other immunosuppressive therapies.

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Bronchiolitis Obliterans Syndrome (BOS)

HRCT. “Mosaic attenuation” pattern in BOS

Bronchiolitis Obliterans Syndrome (BOS)

- Plain chest radiograph: N , hyperinflation, increased linear or reticular markings of airway wall thickening

- HRCT in expiration: “mosaic attenuation” pattern (air trapping).
- Lack of ground-glass opacities.