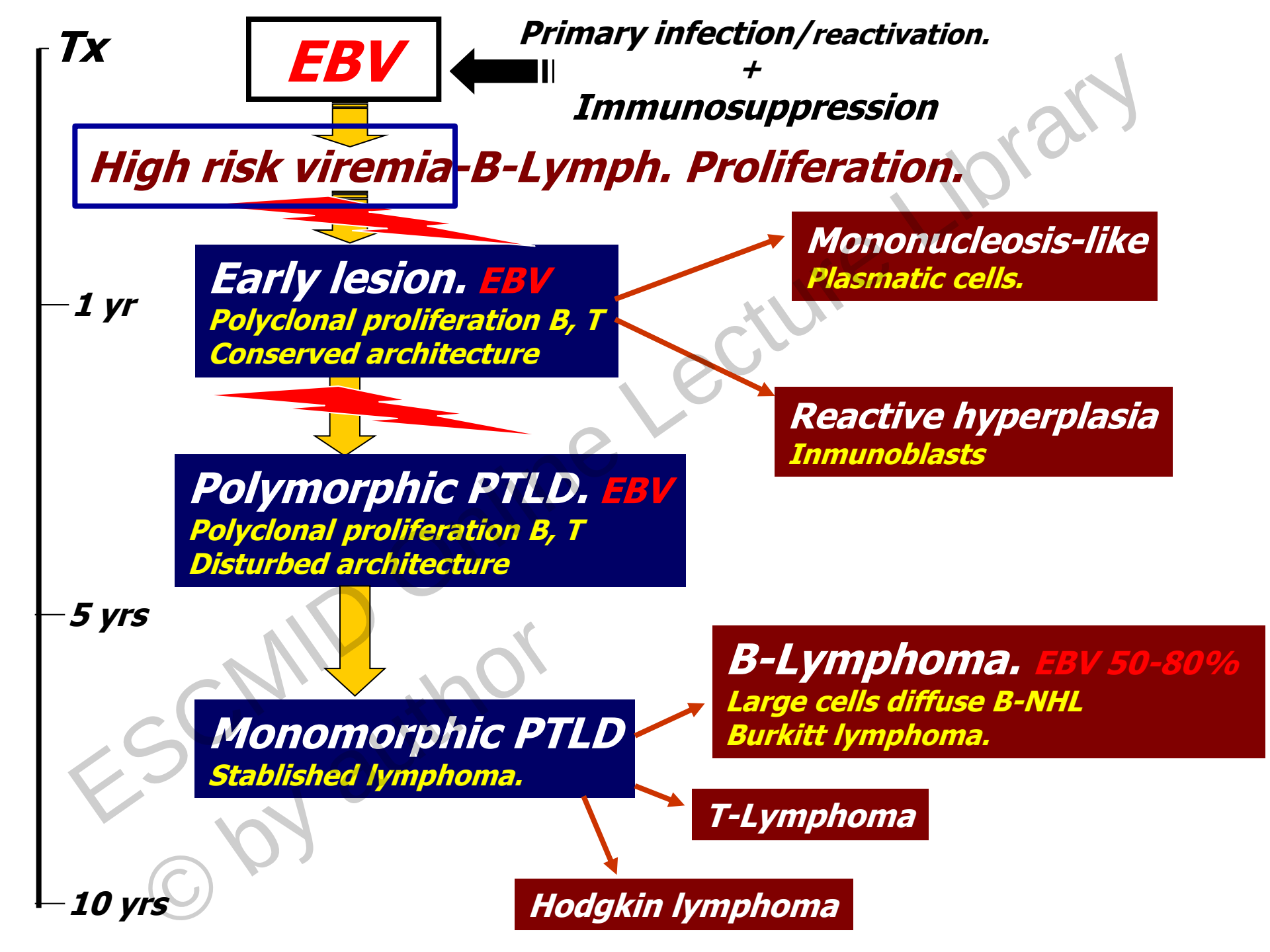
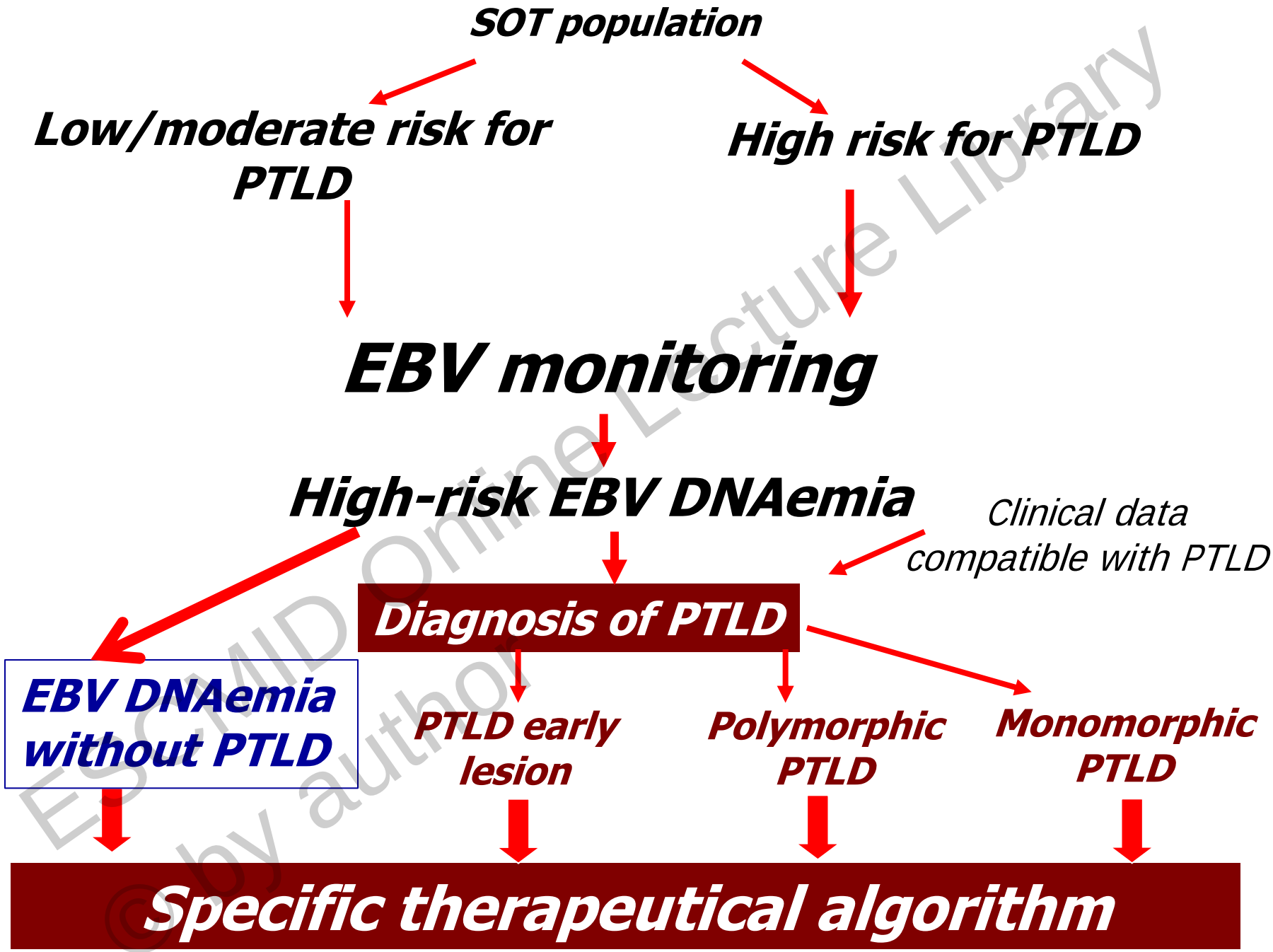
Educational WorkShop: How to prevent the consequences of EBV infection in transplant recipients?

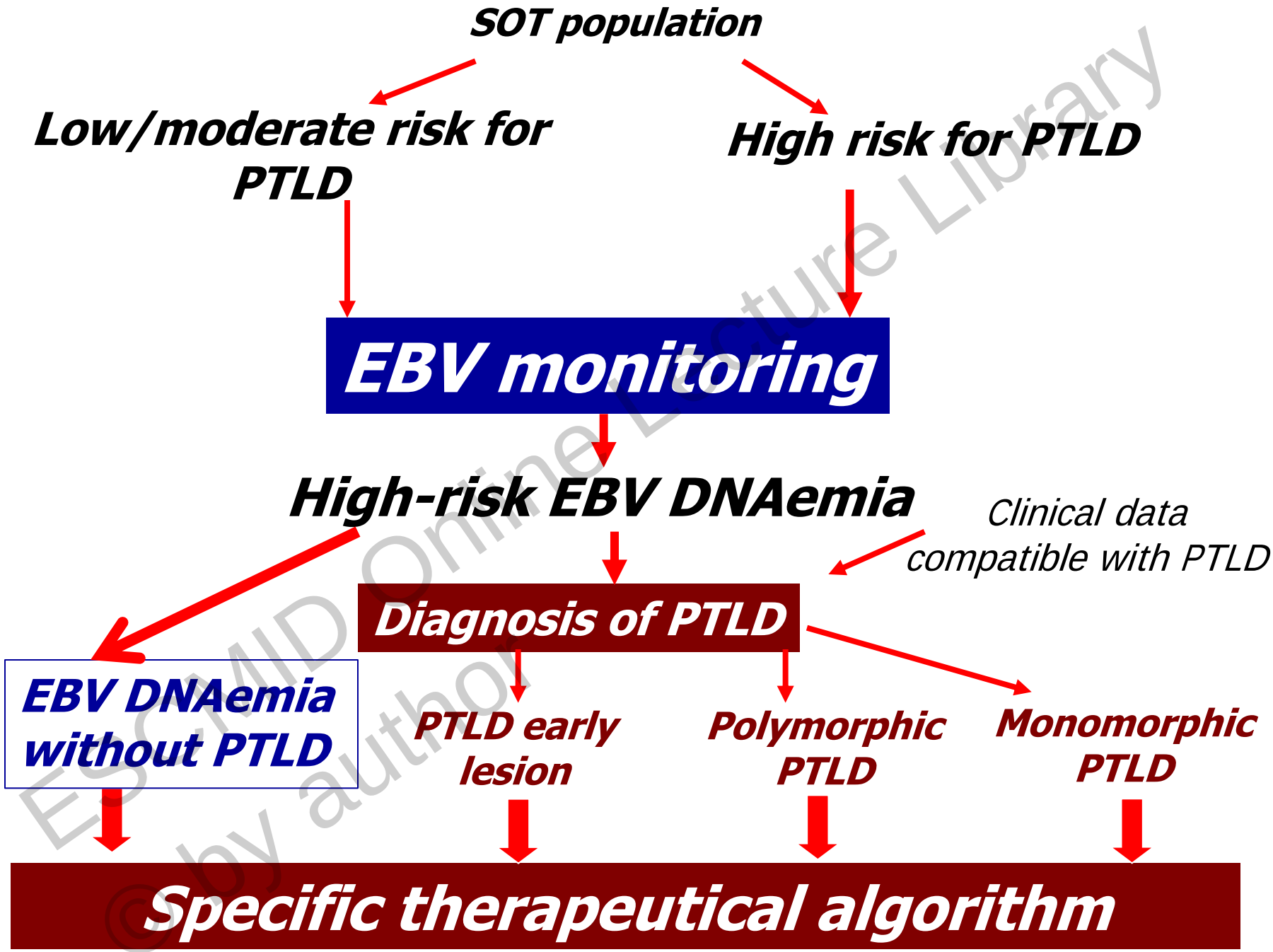
Monitoring EBV in SOT. Which population should be monitored?

Dr. Rafael San Juan.
Unit of Infectious Diseases.
Hospital U. 12 Octubre. I + 12.
Madrid. Spain.

24th ECCMID Barcelona, Spain 10-13 May 2014 | ESCMID European Society of Clinical Microbiology and Infectious Diseases







ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESGICH SURVEY.

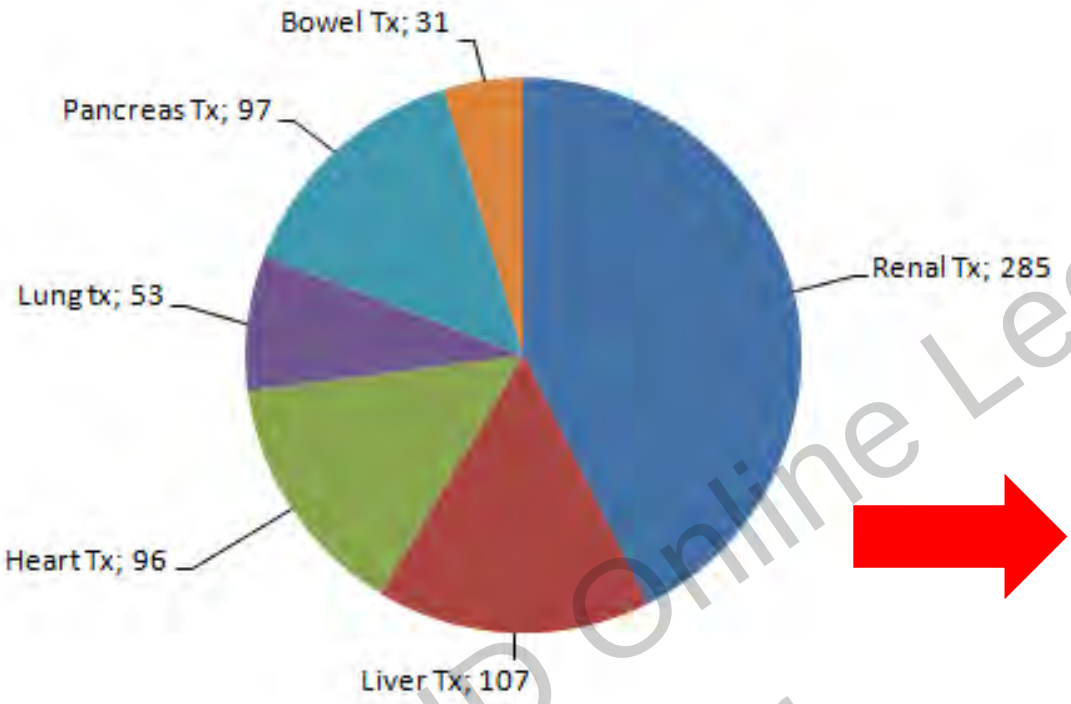
"Monitoring, prevention and management of EBV-related Post Transplant Lymphoprolipherative Disorder (PTLD) in solid organ transplant (SOT) recipients".

ESGICH Survey: EBV-related PTLD. Methods.

1. *Recopilation of European SOT groups.*

- ✓ ESGICH database.
- ✓ European liver transplantation registry.
- ✓ European liver and intestine transplant association.
- ✓ ISHLT International Registry for Heart and Lung Transplantation.
- ✓ United Kindom organ donation website.
- ✓ European society of organ transplantation registry.
- ✓ Intestinal transplant registry (Intestinal transplant association).
- ✓ Collaborative Transplant Study, University of Heideberg.
- ✓ Centro Nationale di Trapianti Italia.
- ✓ Organización nacional de trasplantes. España.

ESGICH Survey: EBV-related PTLD. Methods.



*Invitation to **339** SOT groups from **32** European countries through e-mail.*

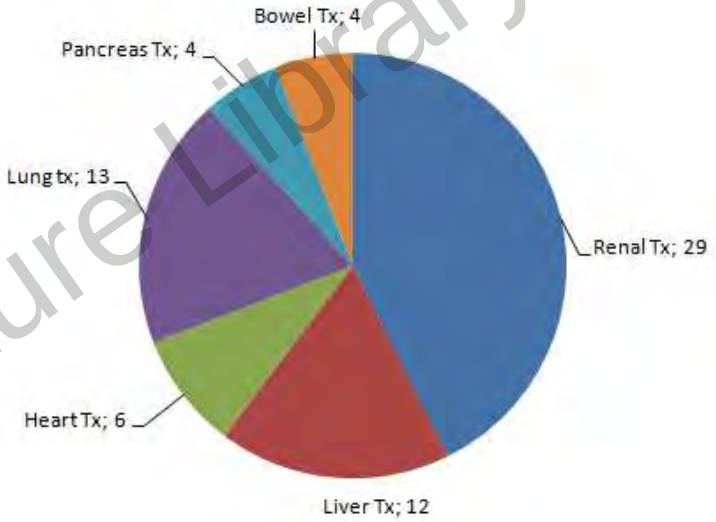
March-April, 2013.

SurveyMonkey®

Online survey. May-June, 2013

ESGICH Survey: EBV-related PTLD. Participation.

Tx centers by Country	Contacted with survey proposal	Accepted participation	% participation
Slovenia	3	3	100,0%
Switzerland	7	3	42,9%
Italy	54	22	40,7%
Spain	42	17	40,5%
Czech Republic	5	2	40,0%
Belgium	10	2	20,0%
France	60	7	11,7%
Germany	48	4	8,3%
United Kingdom	42	2	4,8%
Other	63	6	9,5%



68 groups of SOT. Representation of 15/32 European countries.

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESGICH

Received Date : 03-Nov-2013
Revised Date : 29-Dec-2013
Accepted Date : 30-Dec-2013
Article Type: Supplement Article

TITLE:

EBV-related Post Transplant Lymphoproliferative Disorder (PTLD) in solid organ transplant (SOT) recipients.

Recommendations for the Prevention and Management of Infections in Solid Organ Transplantation. A European Perspective

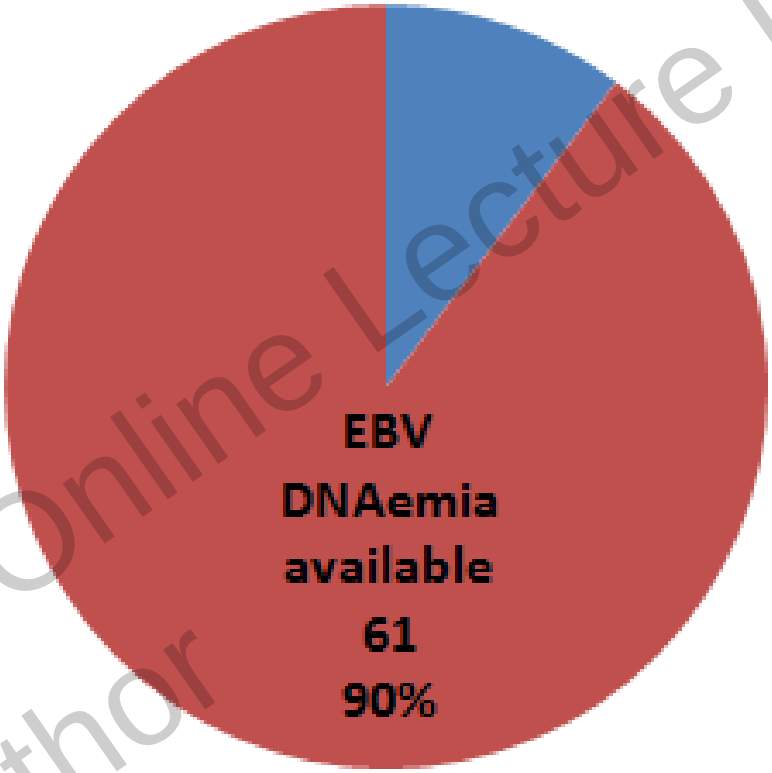
San Juan R[1], Commoli P[2], Caillard S[3], Moulin B[3], Hirsch HH[4,5], Meylan P[6] | On behalf of the ESGICH

Clinical Microbiology and Infection. 2014 Jan 29. [Epub ahead of print]

1. Is EBV-DNAemia available in clinical practice at the Microbiology Laboratory of your transplant center?

1. **Yes.**
2. **No.**

ESGICH PTLD survey. Availability of EBV DNAemia in SOT centers.

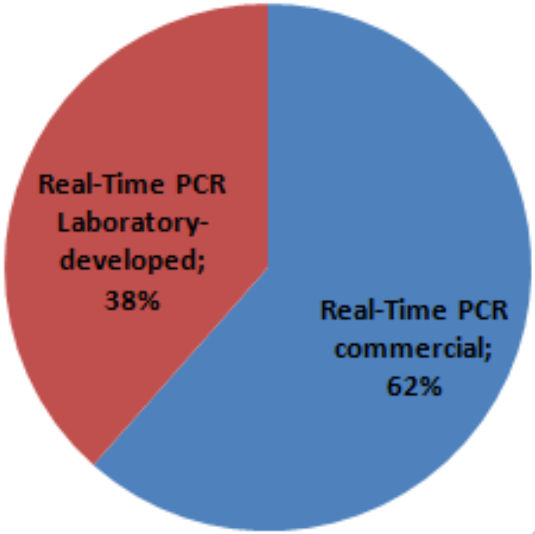


PCR techniques for EBV DNAemia determination are available in 90% of surveyed SOT centers.

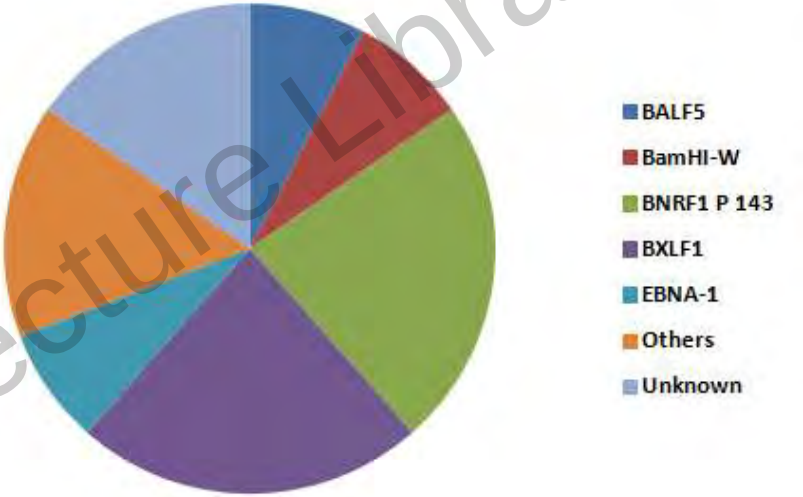
ESGICH Survey: Sample of SOT reference virology departments performing EBV DNAemia.

Country	No of Centres
France	3
Spain	3
Denmark	2
Germany	2
Finland	1
Norway	1
Switzerland	1
Overall	13

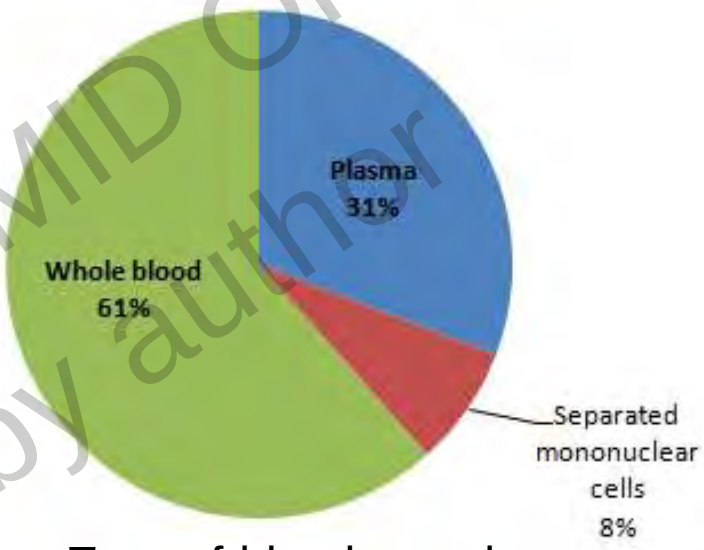
ESGICH PTLD Survey. Virology Laboratories. PCR for EBV DNAemia.



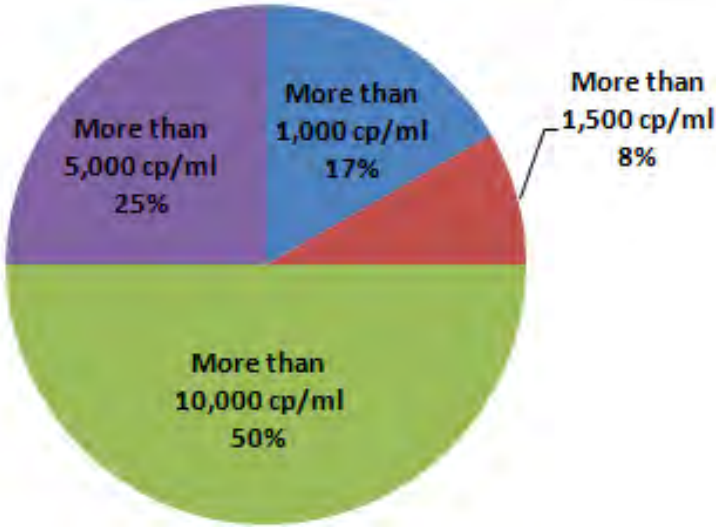
Type of PCR



EVB PCR target



Type of blood sample



"High" DNAemia

World Health Organization

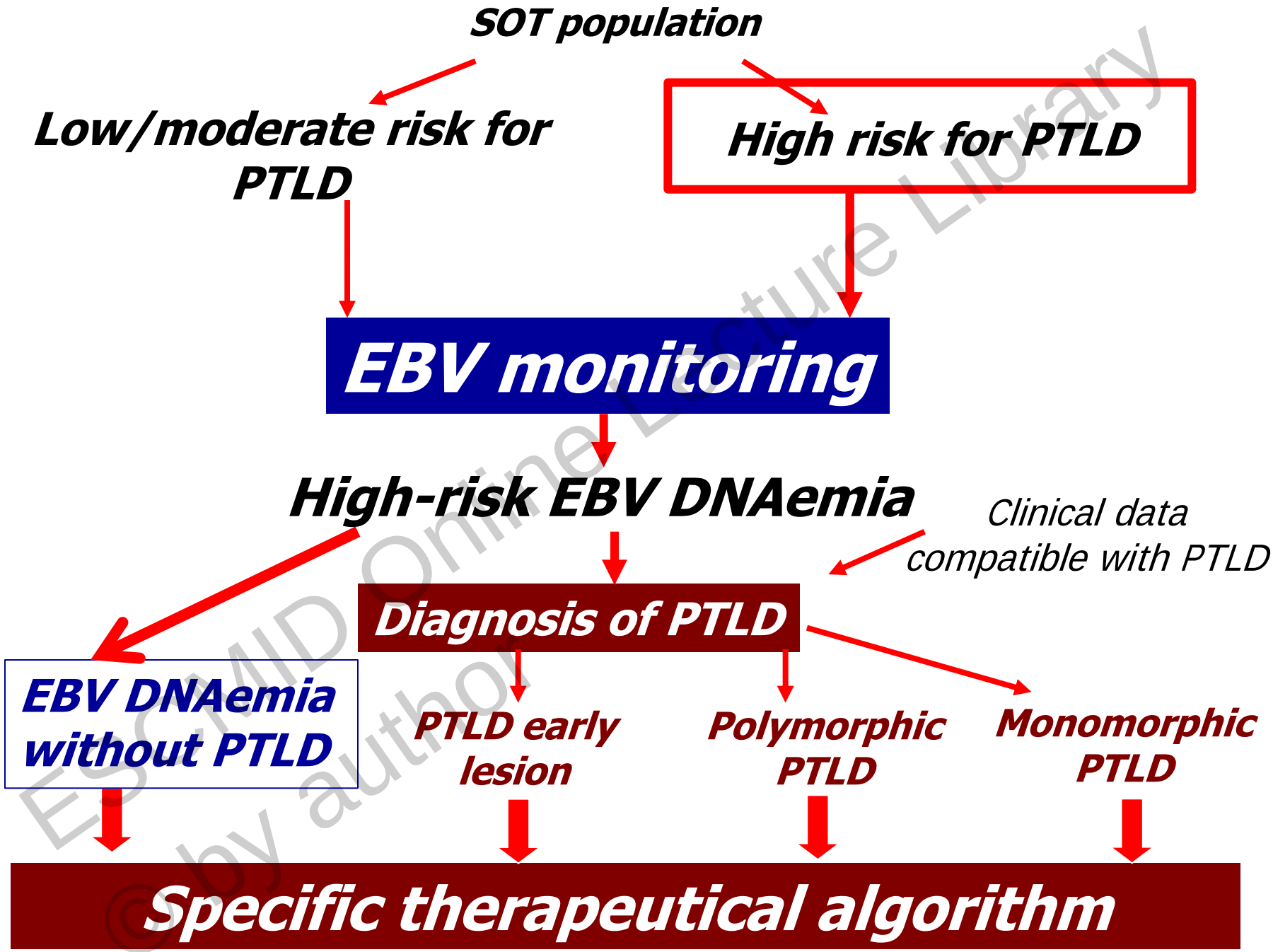
WHO/BS/2011.2172
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2011

Collaborative Study to Evaluate the Proposed 1st WHO International Standard for Epstein-Barr Virus (EBV) for Nucleic Acid Amplification Technology (NAT)-Based Assays

Jacqueline F. Fryer [1,3], Alan B. Heath [2], Dianna E. Wilkinson [1], Philip D. Minor [1] and the Collaborative Study Group *

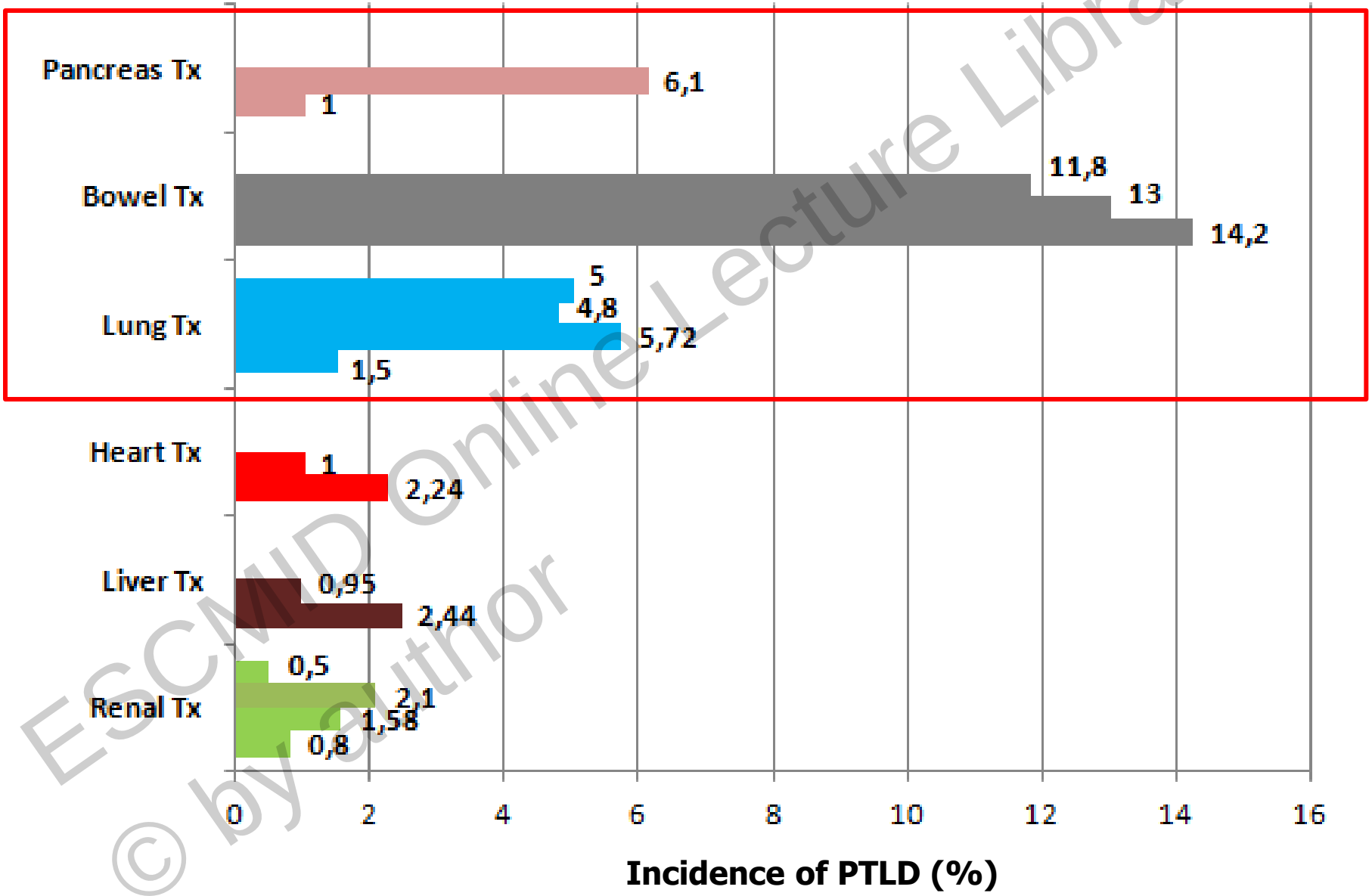
[1] Division of Virology and [2] Biostatistics
National Institute for Biological Standards and Control,
South Mimms, Potters Bar, Herts, EN6 3QG, UK



2. Which of the following groups of solid organ transplant recipients is at the highest risk for presenting PTLD?.

1. **Kidney transplant.**
2. **Bowel transplant.**
3. **Lung transplant.**
4. **Liver transplant.**

Pooled figures of PTLD incidence in different retrospective studies per transplant type.

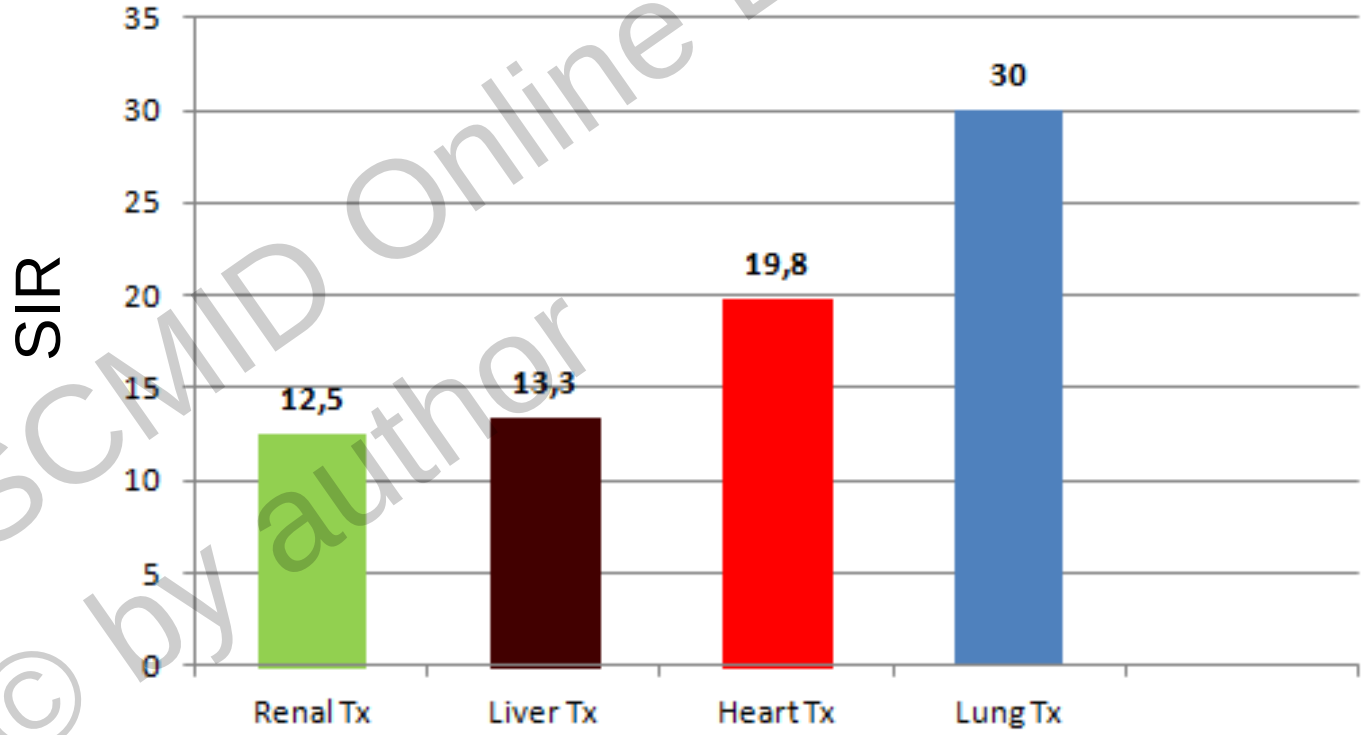


Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit

D. Collett[a], L. Mumford[a], N. R. Banner[b,c,†], J. Neuberger[d,†] and C. Watson[e]

American Journal of Transplantation 2010; 10: 1889–1896
Wiley Periodicals Inc.

Strd. inc.ratio of NHL respect to global population



JAMA The Journal of the American Medical Association

Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients

Eric A. Engels, MD, MPH

JAMA, November 2, 2011—Vol 306, No. 17

Strd. inc.ratio of NHL respect to global population

Transplanted organ	
Kidney	6.05 (5.59-6.54)
Liver	7.77 (6.99-8.61)
Heart	7.79 (6.89-8.79)
Lung	18.73 (15.59-22.32)

3. Which of the following clinical variables do you consider as the main risk factor for developing PTLD?.

1. **Seronegative EBV recipient with a seropositive EBV donor.**
2. **Use of m-tor inhibitors.**
3. **Use of anti-lymphocyte antibodies.**
4. **No specific risk factors have been reported.**

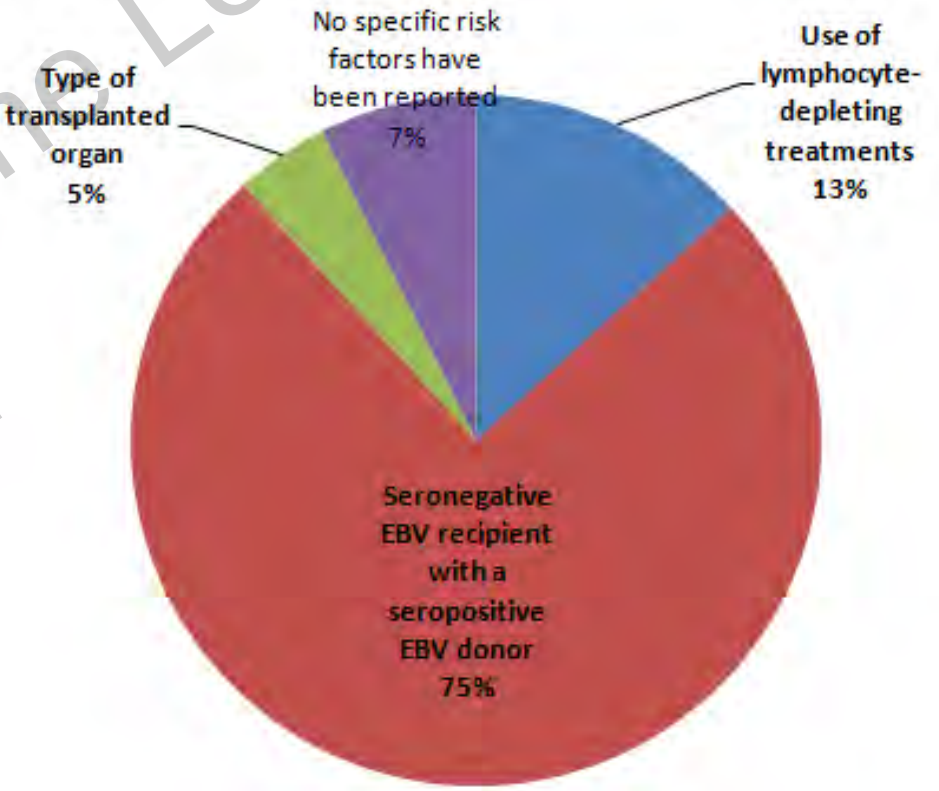
ESGICH PTLD survey. Assessment of risk factors for PTLD.

SurveyMonkey®

Q17 Edit Question ▼ Add Question Logic Move Copy Delete

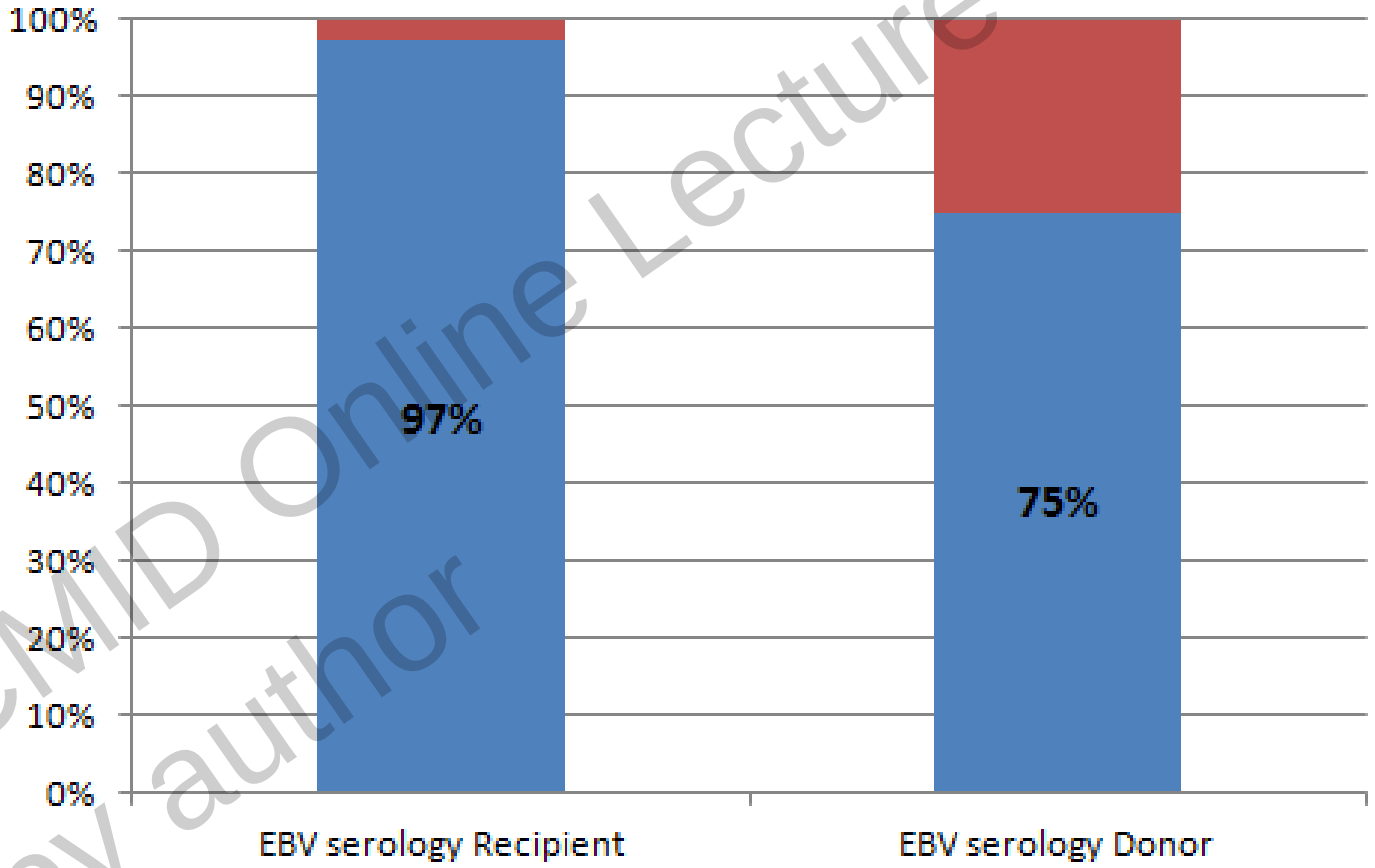
17. Which of the following clinical variables do you consider as the main risk factor for developing PTLD?.

- Seronegative EBV recipient with a seropositive EBV donor
- Type of transplanted organ
- Use of anti-lymphocyte antibodies
- No specific risk factors have been reported



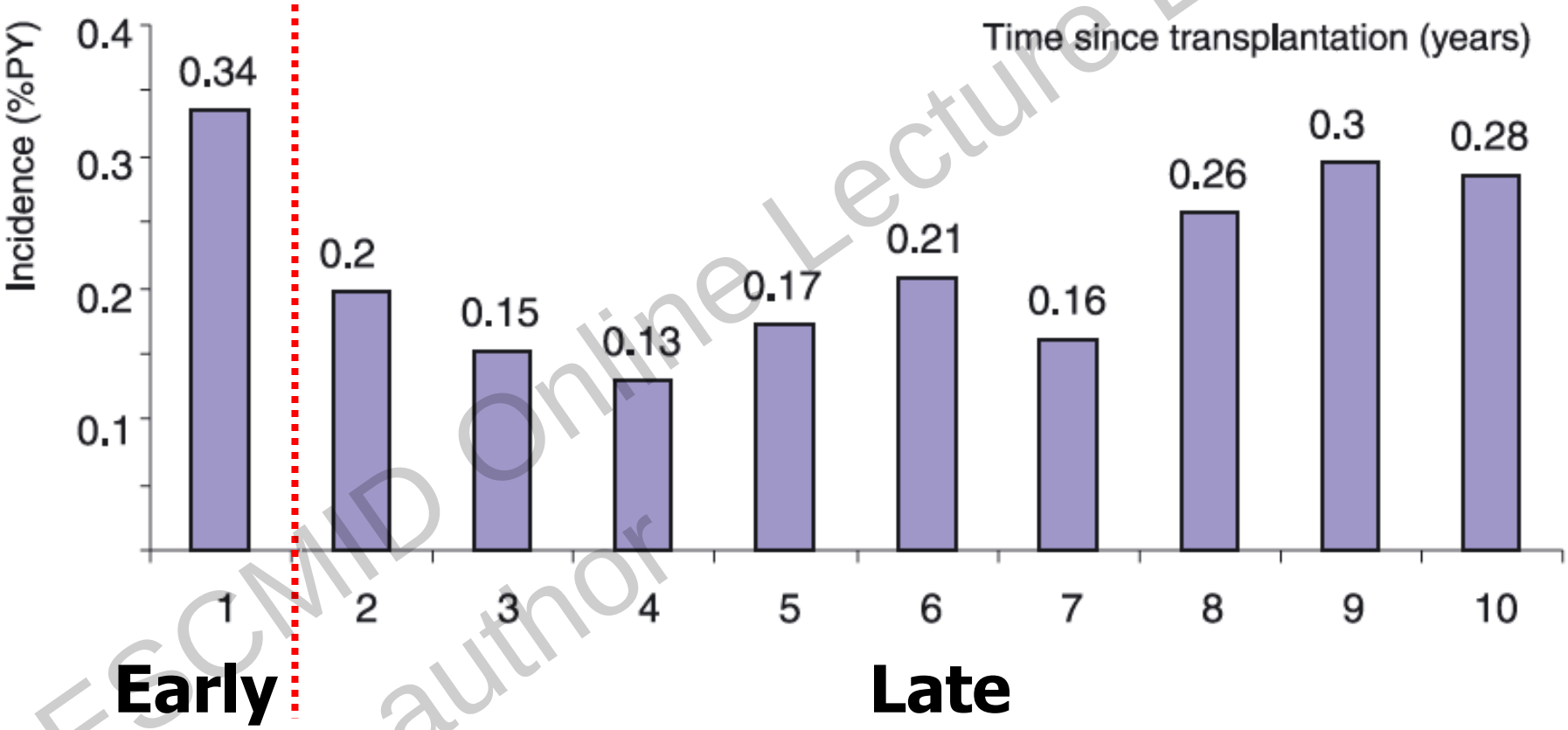
ESGICH PTLD survey

ESGICH PTLD survey. Assessment of EBV serology in recipients and donors.



ESGICH PTLD survey

French Incidence of PTLD in Renal Tx 1998-2007.



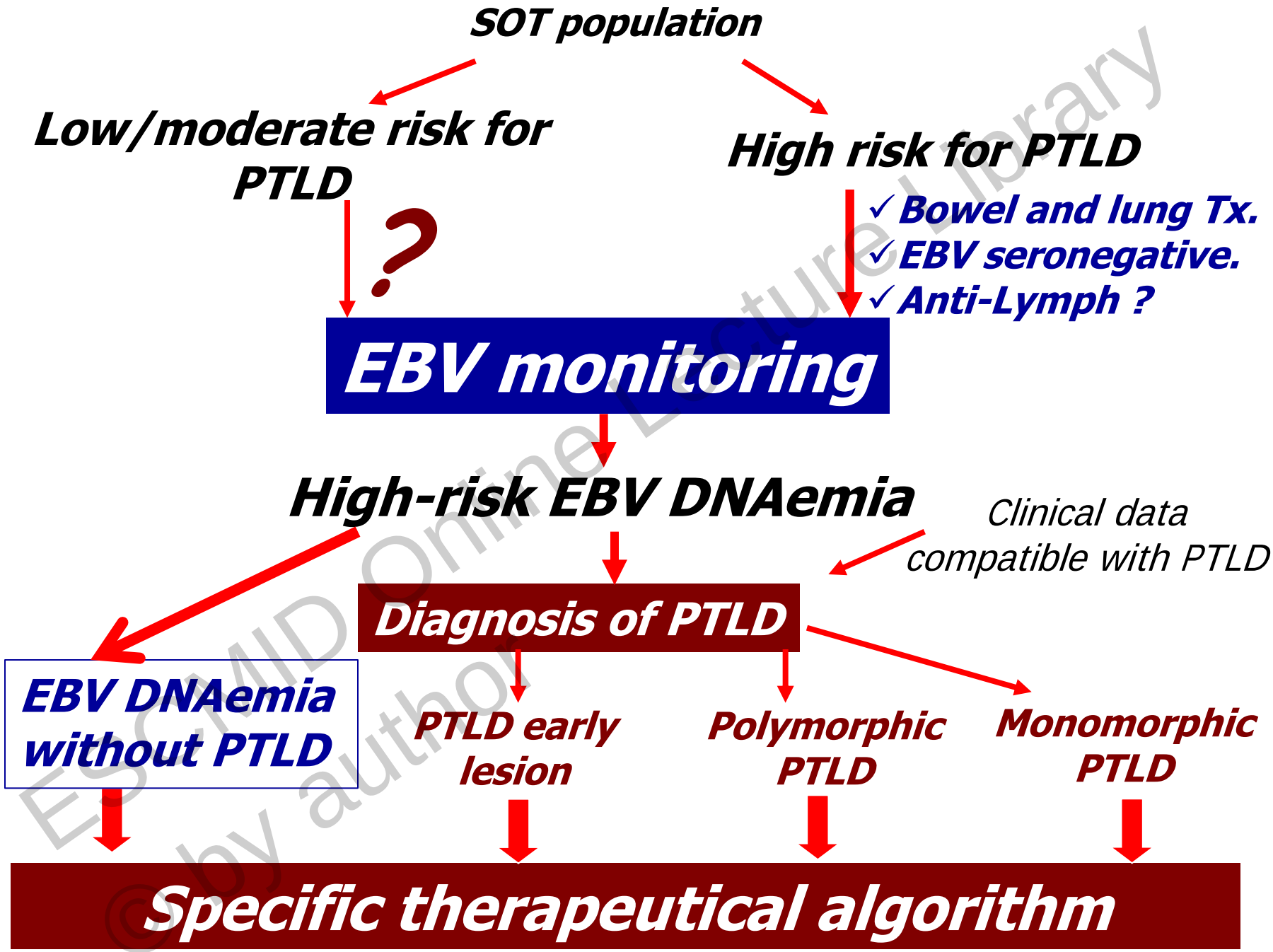
Caillard, S. et al. (2012). Am J Trans (12): 682-93..

Analysed Risk factors for PTLD in SOT.

Type of PTLD	Potential risk factor for PTLD	Level of evidence	References
Early PTLD	EBV recipient seronegativity, D+/R- seroestatus.	A-II	[1-4]
	Use of anti-lymphocyte antibodies	B-II	[1, 3, 5-9]
	Maintenance IS with tacrolimus	C-II	[5, 6, 9-12]
	Maintenance IS with mycophenolate	D-II	[1, 10, 13-17]
Late PTLD	Older age (>60 ys).	C-III	[1, 3]
	Long term IS.	C-III	[1, 3]

1. Caillard S, Am J Transplant. 2012; 12: 682-693.
2. Sampaio MS, Nephrol Dial Transplant. 2012; 27: 2971-2979.
3. van Leeuwen MT, Blood. 2009; 114: 630-637.
4. Quinlan SC, Am J Hematol. 2011; 86: 206-209.
5. Opelz G, Am J Transplant. 2004; 4: 222-230.
6. Fernberg P, Am J Transplant. 2011; 11: 2472-2482.
7. Duvoux C, Transplantation. 2002; 74: 1103-1109.
8. Bakker NA, Transplantation. 2005; 80: 595-599.
9. Caillard S, Transplantation. 2005; 80: 1233-1243.
10. Bustami RT, Am J Transplant. 2004; 4: 87-93.
11. Younes BS, Transplantation. 2000; 70: 94-99.
12. Dharnidharka VR, Transplantation. 2001; 71: 1065-1068.
13. Cherikh WS, Transplantation. 2003; 76: 1289-1293.
14. Dharnidharka VR, 2002; 6: 396-399.
15. Sampaio MS, Transplantation. 2012; 93: 73-81.
16. Robson R, Am J Transplant. 2005; 5: 2954-2960.
17. Funch DP, Transplantation. 2005; 80: 1174-1180.

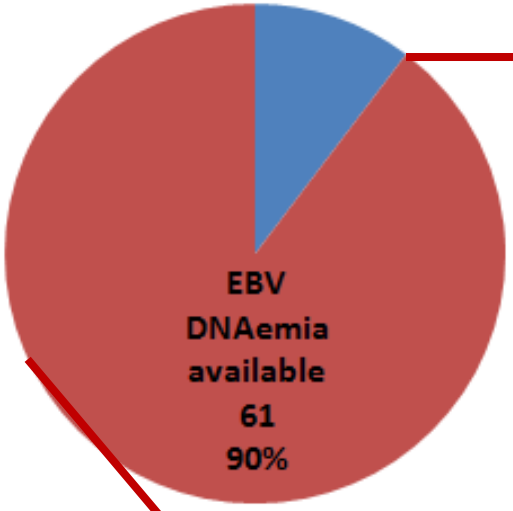
Clinical Microbiology and Infection. 2014 Jan 29. [Epub ahead of print]



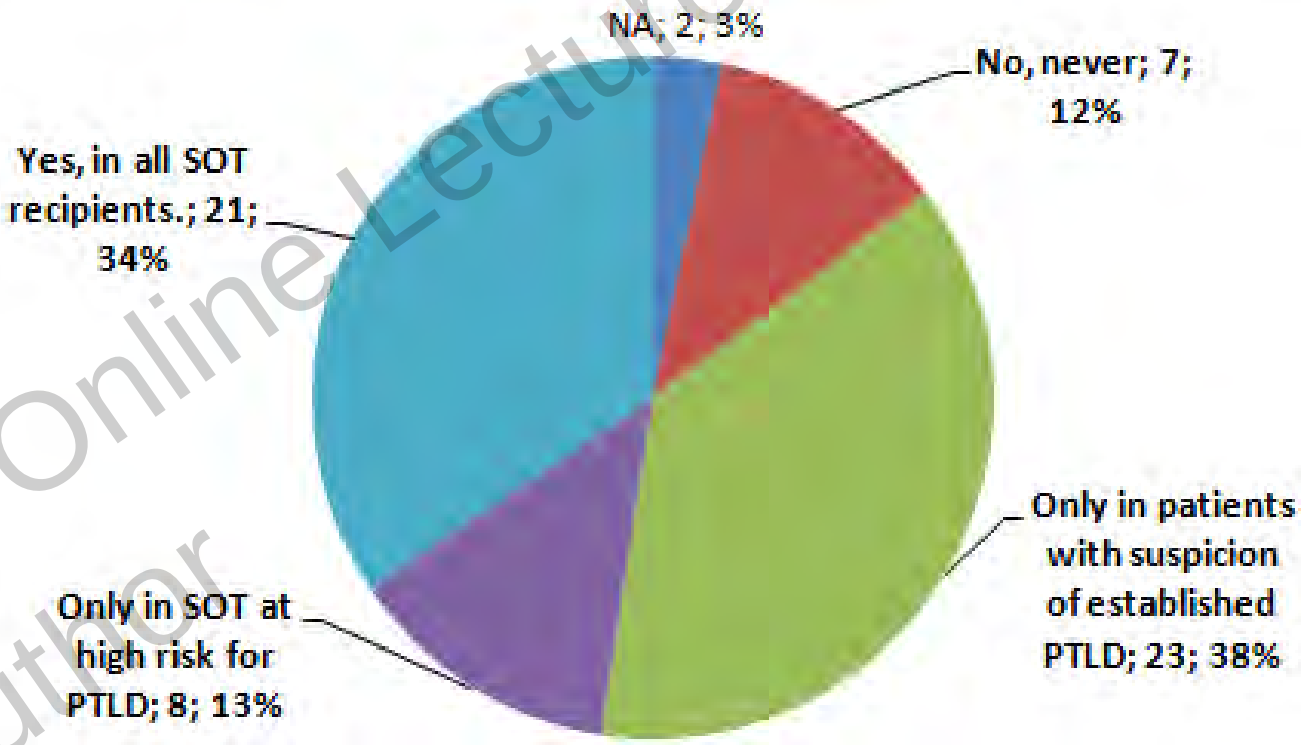
4. Do you perform any kind of monitoring of EBV DNAemia in SOT recipients?

1. No, never
2. Only in patients with suspicion of established PTLD.
3. Only in SOT at high risk for PTLD.
4. Yes, in all SOT recipients.

ESGICH PTLD survey. Monitoring of EBV DNAemia.



24. Do you perform any kind of monitoring of EBV DNAemia in SOT recipients?



In 52 centres (76%) some kind of EBV DNAemia monitoring is performed

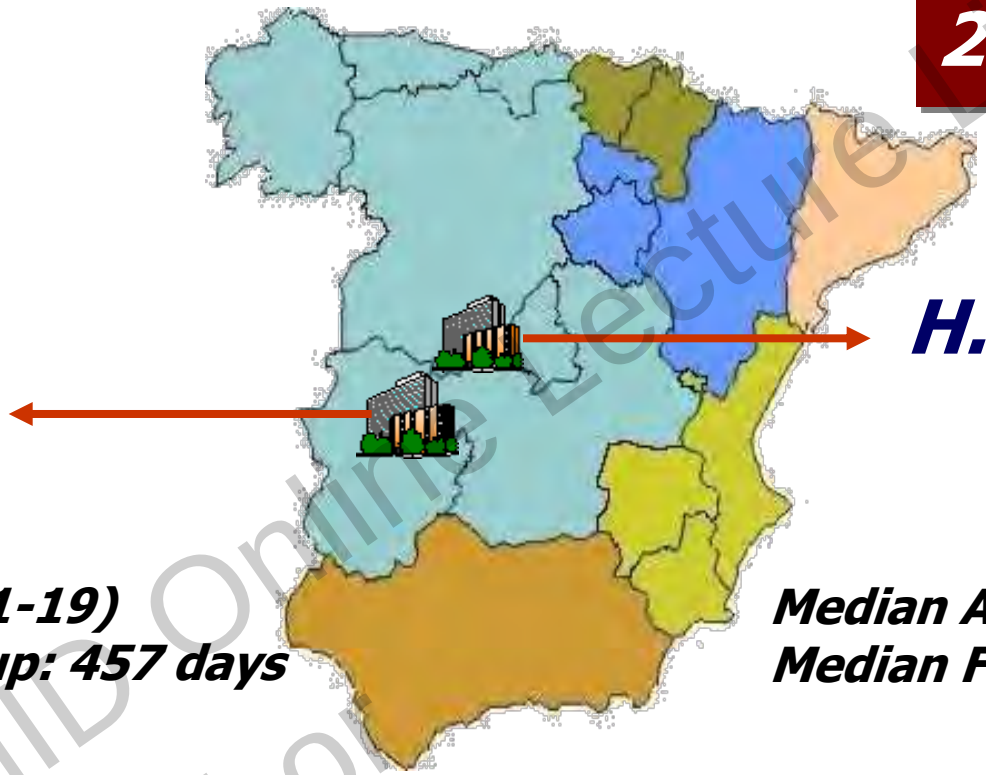
Experience in prospective EBV monitoring in SOT for preemptive interventions.

Study	Target of monitoring	Schedule of prospective monitoring	Preemptive Intervention.	Conclusions.
Bakker et al. 2007. [1]	Lung Tx (n=75)	Twice a year. Twice a month in HVL.	*Two rising EBV DNAemia >1^{4}Cp:*Red IS.	PTLD 1.5%.
Martin et al. 2011[2]	EBV D+R- Kidney/K-pancreas Tx (n=34)	6 mo: twice a mo. 6 mo: Once a mo.	Prophylaxis *Persistent DNAemia*: Rituximab.+ Red. IS	0% PTLD in Pts following protocol. Pts not followed by protocol >incidence of PTLD
Choquet et al. 2014 [3]	Heart Tx Tymoglobulin (n=299)	1st year. In each hospital follow up	*Primary infection*: Red. IS *Persistent DNAemia> 10^{6}*: Rituximab.	Only one case of PTLD (out of protocol). Less PTLD than historical cohort.

1. Choquet S, et al. Am J Transplant. 2014; 14: 857-866.
2. Martin SI, et al. Am J Transplant. 2011; 2011: 1600-6143.
3. Bakker NA, et al. Transplantation. 2007; 83: 433-438.

Infection in intestinal Tx. Spanish experience.

2004-2009



H. La Paz
40 ITx
Children

Median age: 3 (1-19)
Median Follow-up: 457 days

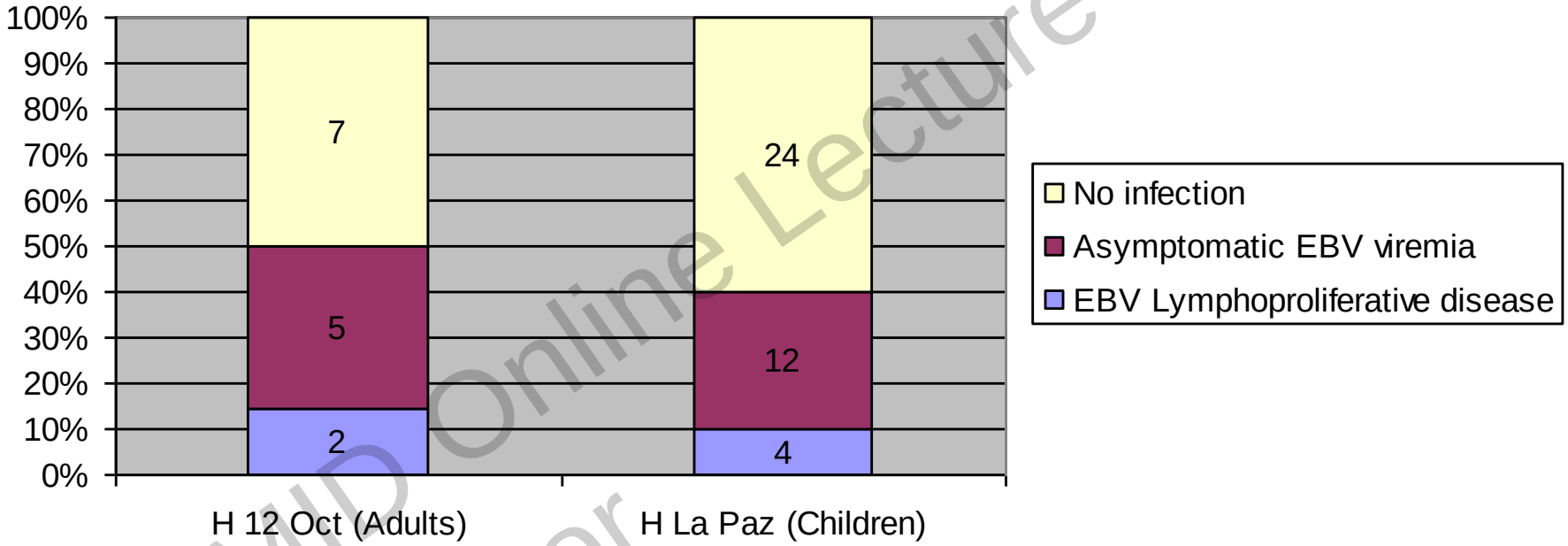
H. 12 Octubre
14 ITx
Adults

Median Age: 38 (30-64)
Median Follow-up: 250 days

Infection over follow-up:
Incidence.
Etiology.
Outcome.

San Juan et al. 50th ICAAC. 2010. K-1738

Post-transplant EBV infection.



In adults EBV DNAemia was not predictive for PTLD.

Which SOT population should be monitored?

bjh guideline

© 2010 Blackwell Publishing Ltd, *British Journal of Haematology*, **149**, 675–692

Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients – BCSH and BTS Guidelines

Anne Parker,[1] (BCSH Lead) Kristin Bowles,[2] J. Andrew Bradley,[3] Vincent Emery,[4] Carrie Featherstone,[1] Girish Gupte,[5] Robert Marcus,[6] Jayan Parameshwar,[7] Alan Ramsay[8] and Charles Newstead[9] (British Transplantation Society Lead)
Writing group: On behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society

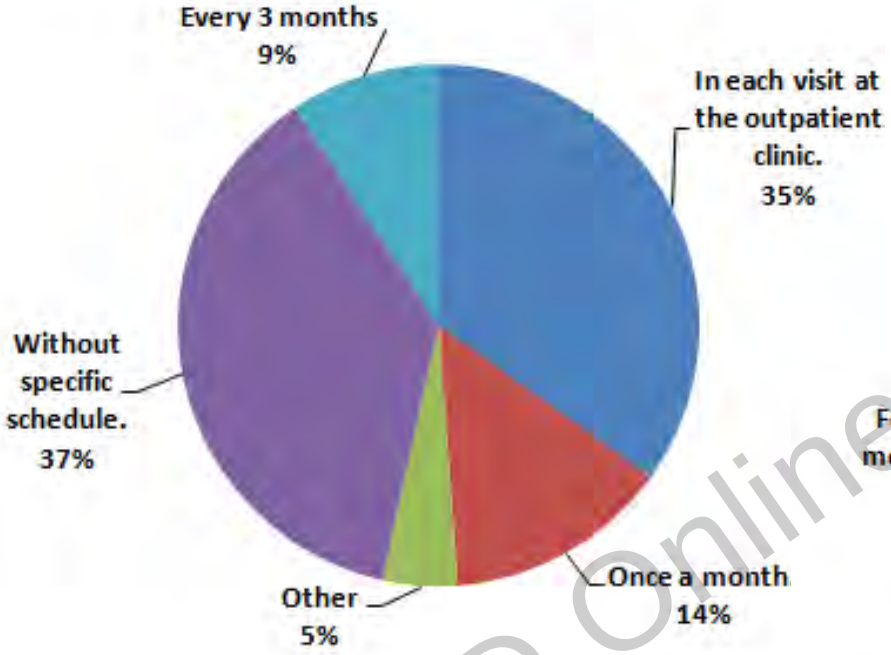
✓ ***Universal monitoring of EBV DNAemia is not recommended in SOT recipients (C-III).***

✓ ***SOT recipients at risk for primary EBV infection could benefit from post-transplant EBV monitoring, mostly over the first year (A-II).***

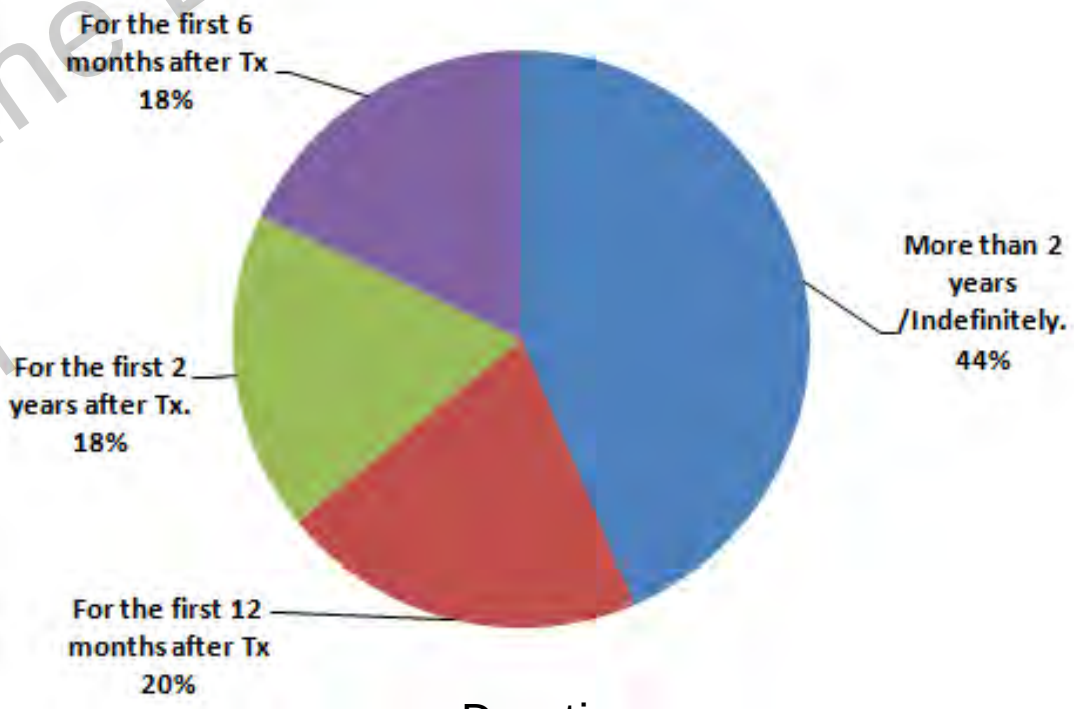
ESGICH Recommendations Document

✓ ***Monitoring of EBV DNAemia should be considered in EBV seropositive recipients of lung and intestinal transplant (B-III).***

ESGICH PTLD survey. Schedule of EBV DNAemia Monitoring.



Timing



Duration

ESGICH PTLD survey

Experience in prospective EBV monitoring in SOT for preemptive interventions.

Study	Target of monitoring	Schedule of prospective monitoring	Preemptive Intervention.	Conclusions.
Bakker et al. 2007. [1]	Lung Tx (n=75)	Twice a year. Twice a month in HVL.	*Two rising EBV DNAemia >1^{4}Cp:*Red IS.	PTLD 1.5%.
Martin et al. 2011[2]	EBV D+R- Kidney/K-pancreas Tx (n=34)	6 mo: twice a mo. 6 mo: Once a mo.	Prophylaxis *Persistent DNAemia*: Rituximab.+ Red. IS	0% PTLD in Pts following protocol. Pts not followed by protocol >incidence of PTLD
Choquet et al. 2014 [3]	Heart Tx Tymoglobulin (n=299)	1st year. In each hospital follow up	*Primary infection*: Red. IS *Persistent DNAemia> 10^{6}*: Rituximab.	Only one case of PTLD (out of protocol). Less PTLD than historical cohort.

1. Choquet S, et al. Am J Transplant. 2014; 14: 857-866.
2. Martin SI, et al. Am J Transplant. 2011; 2011: 1600-6143.
3. Bakker NA, et al. Transplantation. 2007; 83: 433-438.

Schedule of monitoring of EBV?

ESGICH Recommendations Document

✓ *Recommended time schedule of monitoring of EBV DNAemia could be: every two to four weeks in the first 3 months, monthly until 6 months post transplantation then every 3 months for the remaining first year (C-III).*

✓ *In EBV D+/R- recipients without evidence of primary EBV replication during the first year, we recommend continuing EBV load screening every three to six months until 2 or 3 years post-transplant (C-III).*

Conclusions.

- ✓ **EBV DNAemia is available in most transplant centers in Europe.**
- ✓ **Monitoring of EBV DNAemia is performed in most SOT centers in Europe.**
- ✓ **SOT at risk for primary EBV infection are clear candidates for EBV monitoring.**

Conclusions.

- ✓ **Lung and bowel transplant are the SOT with the highest risk for PTLD and could benefit from EBV monitoring.**
- ✓ **There is scarce evidence regarding the efficiency and optimal schedules of EBV monitoring protocols for PTLD preemptive treatment.**

Educational WorkShop: How to prevent the consequences of EBV infection in transplant recipients?

Monitoring EBV in SOT. Which population should be monitored?

Dr. Rafael San Juan.
Unit of Infectious Diseases.
Hospital U. 12 Octubre. I + 12.
Madrid. Spain.

24th ECCMID Barcelona, Spain 10-13 May 2014 | ESCMID European Society of Clinical Microbiology and Infectious Diseases