MANAGING OF CMV AND EBV IN SOT PATIENTS

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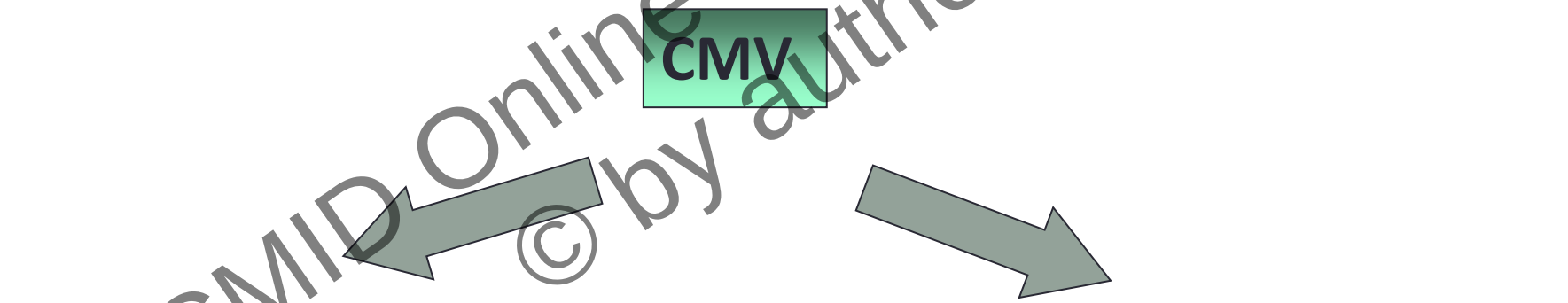
CMV infection in SOT recipients

- CMV is one of the most important pathogens affecting SOT recipients.



Direct effects

Classicaly first three months
CMV disease:
- **Viral syndrome**
- **CMV invasive disease:**
  - **Gastrointestinal disease**

Indirect effects

Immunomodulatory effect
- **Infections**
- **Graft rejection**

56 years old man

- No toxic habits
- End stage renal disease: policystic kidney disease
- Non-living kidney tranplantation

- Immunosuppression: MMF+tacrolimus+steroids
- Pretransplant CMV serology: D+/R-, PPD negative, EBV D+R+

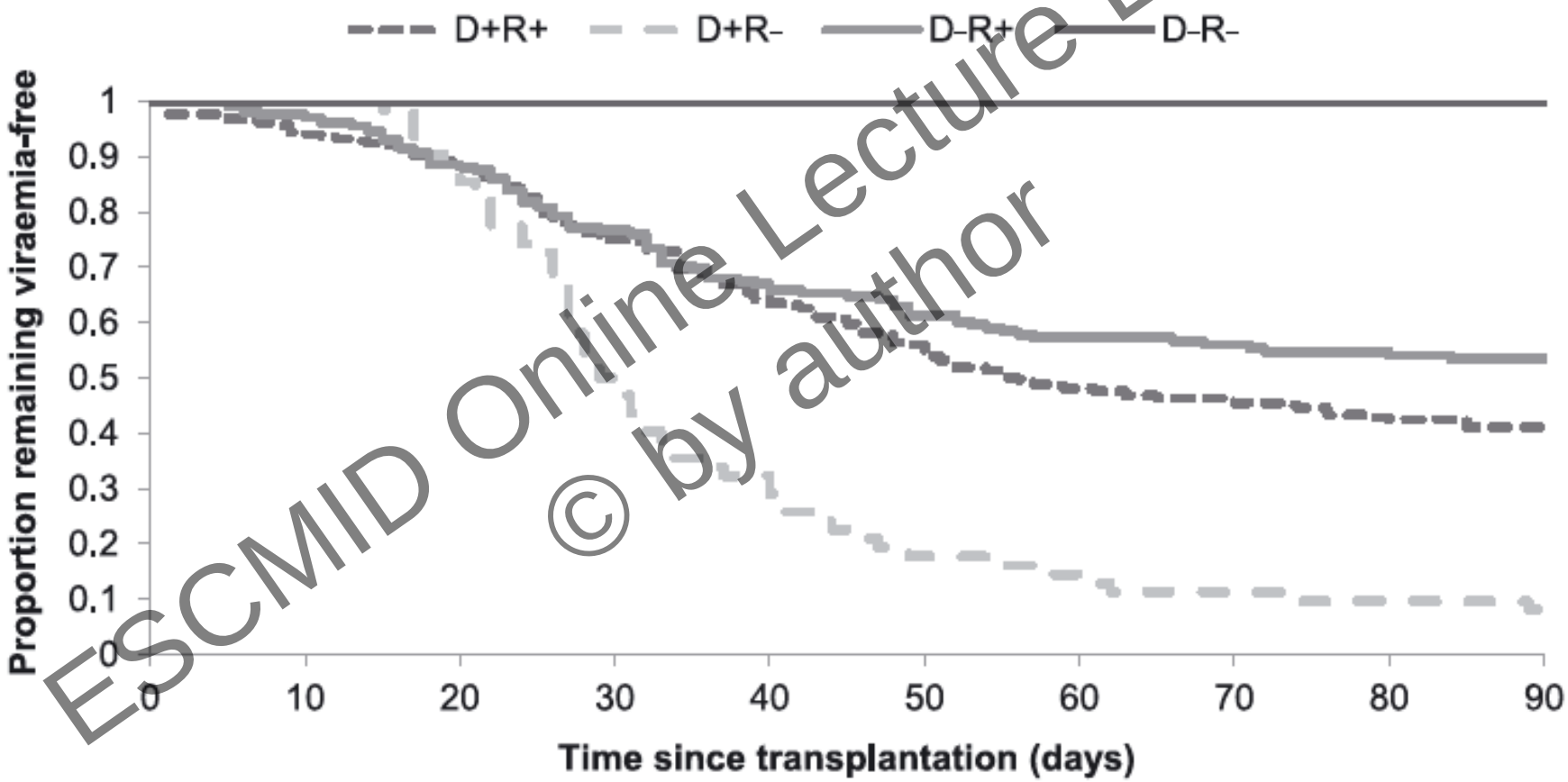
Should I recommend CMV prophylaxis?

a. No. It is R-, therefore, a reactivation of the infection is unlikely and prophylaxis is not needed
b. No. It is a CMV disease low- risk patient, monitorization of CMV viral load is not needed
c. Yes. It is a CMV high risk patient therefore a prevention strategy is needed
d. Answers 1 and 2 are true

CMV risk factors

Protector factors	Risk factors
Antiviral prophylaxis	Organ - Lung - Intestine - Pancreas
R-/D-	**R-/D+**
mTOR Inhibitor	Immunosuppressive net-state
Tcell immune response	Viral load

Atabani et al.



Atabani Am J Transplant 2012

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What should I recommend in terms of CMV prophylaxis?

1. Kidney recipients are at high risk of CMV infection so universal prophylaxis is needed
2. Foscarnet during 90 days
3. Valganciclovir prophylaxis should be used in all SOT recipients
4. In high risk patients antiviral prophylaxis is generally used

Prevention strategies

- **Prophylaxis**
- **Preemptive therapy**

Prevention strategies of CMV disease: Concepts

Universal prophylaxis :

- In patients at risk
- No clinical evidence of disease
- Without microbiological evidence of infection

Preemptive therapy:

In asymptomatic patients

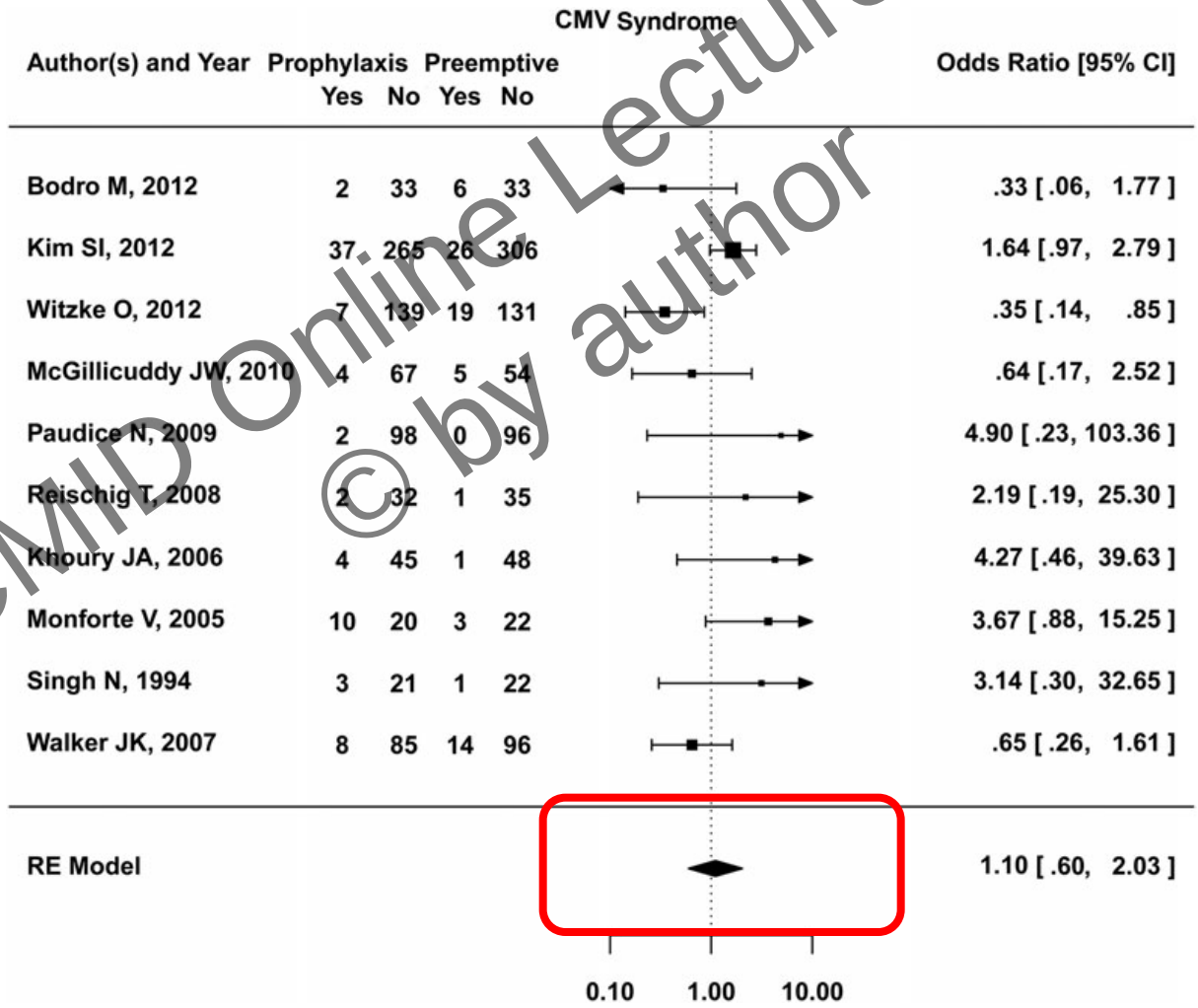
If viral replication

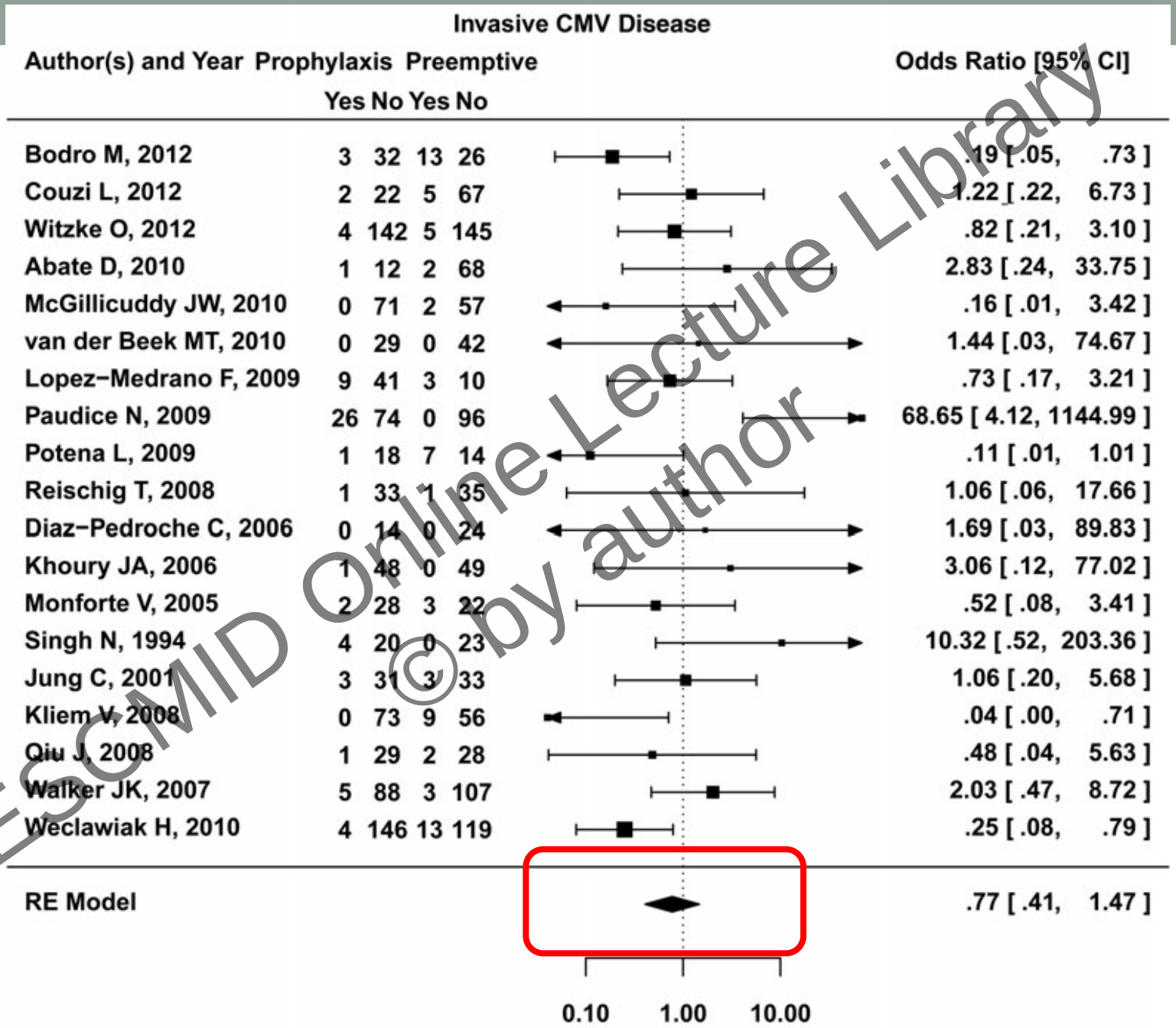
By regularly monitoring blood DNA (PCR) or antigenemia

A Direct and Indirect Comparison Meta-Analysis on the Efficacy of Cytomegalovirus Preventive Strategies in Solid Organ Transplant

Diana F. Florescu,[1,2] Fang Qiu,[3] Cynthia M. Schmidt,[4] and Andre C. Kalil[1]

Clinical Infectious Diseases 2014;58(6):785–803





Florescu Clin Infect Dis 2014

- No differences in:
  - Mortality
  - Other infections
  - Graft rejection
- In R-/D+
  - Higher risk for CMV viremia and CMV disease with preemptive therapy
  - Higher risk for late-onset disease

Prophylaxis vs. Preemptive therapy in kidney recipients.

- 4 clinical trials
  - Different results according to the type monitoring frequency and drugs used
- If strict control weekly for 4 months:
  - Similar reduction rates of CMV disease , CMV infection
  - Long-term survival equal or better with preemptive therapy
- If monitoring is less rigorous or spaced
  - Prophylaxis better long-term survival and lower CMV disease

Reischig Am J Tranaplant 2008, Kliem Am J Transplant 2008, Witzke Transplantation 2012, Spinner Transplantation 2010, Asberg Am J Transplant 2009, Reishig J Am Soc Neprhrol 2012

Prevention strategies of CMV disease.

- **Universal prophylaxis**

Advantages:

- Other herpes virus prevention
- Prevention of CMV indirect effects
- Avoid posttransplant virological control

Drawbacks :

- Increased toxicity and resistance to treatment
- Late CMV disease

Preemptive therapy

Advantages:

- Lower cost
- Lower toxicity and resistance

Drawbacks :

-It requires frequent virological control (PCR / antigenemia)

Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation

Camille N. Kotton,[1,8] Deepali Kumar,[2] Angela M. Caliendo,[3] Anders Åsberg,[4] Sunwen Chou,[5] Lara Danziger-Isakov,[6] and Atul Humar,[7] on behalf of The Transplantation Society International CMV Consensus Group

For seropositive recipients after kidney, liver, and heart transplantation, either strategy is acceptable. Preemptive

For D+/R-, the majority of consensus conference participants endorsed the use of either prophylaxis or preemptive therapy after kidney and liver transplantation (strong, high). For centers or patients unable to meet the stringent logistic requirements required with a preemptive therapy strategy, prophylaxis is preferred.

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(*Transplantation* 2013;96: 333–360)

Prophylaxis may be preferred in other high-risk patients, including those on recent antilymphocyte therapy, potent immunosuppression including desensitization or ABO-incompatible protocols (including those on rituximab, bortezomib, eculizumab, and plasmapheresis/immuno-

What should I recommend in terms of CMV prophylaxis?

1. Kidney recipient are at high risk of CMV infection so universal prophylaxis is needed
2. Foscarnet during 90 days
3. Valganciclovir prophylaxis should be used in all SOT recipients
4. **In high risk patients antiviral prophylaxis is generally used**

Let's continue with our patient

- Patient received valganciclovir 900 mg/24h for 90 days
- + 125 days
  - Diarrhea and epigastric pain (10 days)
  - Low grade fever
- Blood tests:
  - Hemoglobin: 142 g/L
  - Leucocyte cells count: 8.43 x10e9/L
  - Neutrophil cells count: 4.2 x10e9/L
  - Platelets: 213 x10e9/L
  - Creatinine: 1.51 mg/dl
  - CCr 85 ml/m
- X ray: normal

¿What do you think it is the most probable?

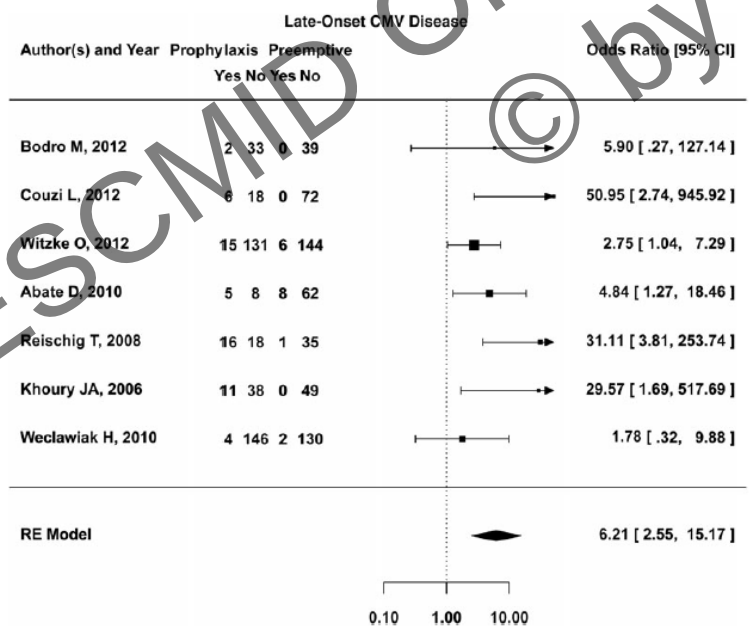
- 1. *Salmonella* infection
- 2. Drug toxicity
- 3. CMV disease
- 4. *Clostridium difficile* infection

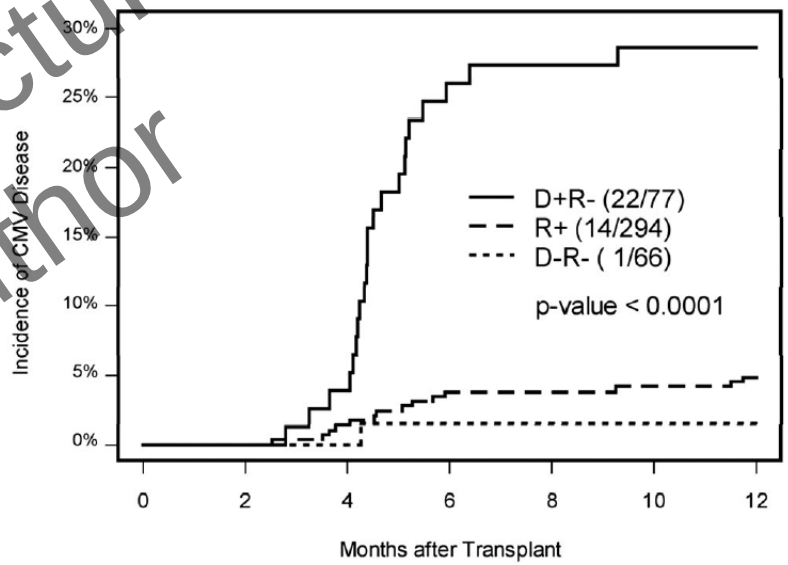
What is your diferential diagnosis?

- Diarrhea and epigastric pain in a kidney recipient (+5th months)
  - Infections:
    - CMV. First option
    - *Clostridium difficile*
    - Other : norovirus , *Campylobacter jejuni*
  - Noninfectious etiologies
    - Toxic : mycophenolate mofetil
    - Neoplasia: post-transplant lymphoproliferative disease (PTLD)

Late onset CMV disease

- CMV disease beyond the first 3 months of the transplant.
- Incidence: 12-30% depending to the diagnostic criteria
  - 30 % in high risk patients
  - 5 % low risk.
- Always after withdrawal of prophylaxis .
- 25-50% organ invasive disease .
- 5 times increased risk of death: poor prognosis independent factor



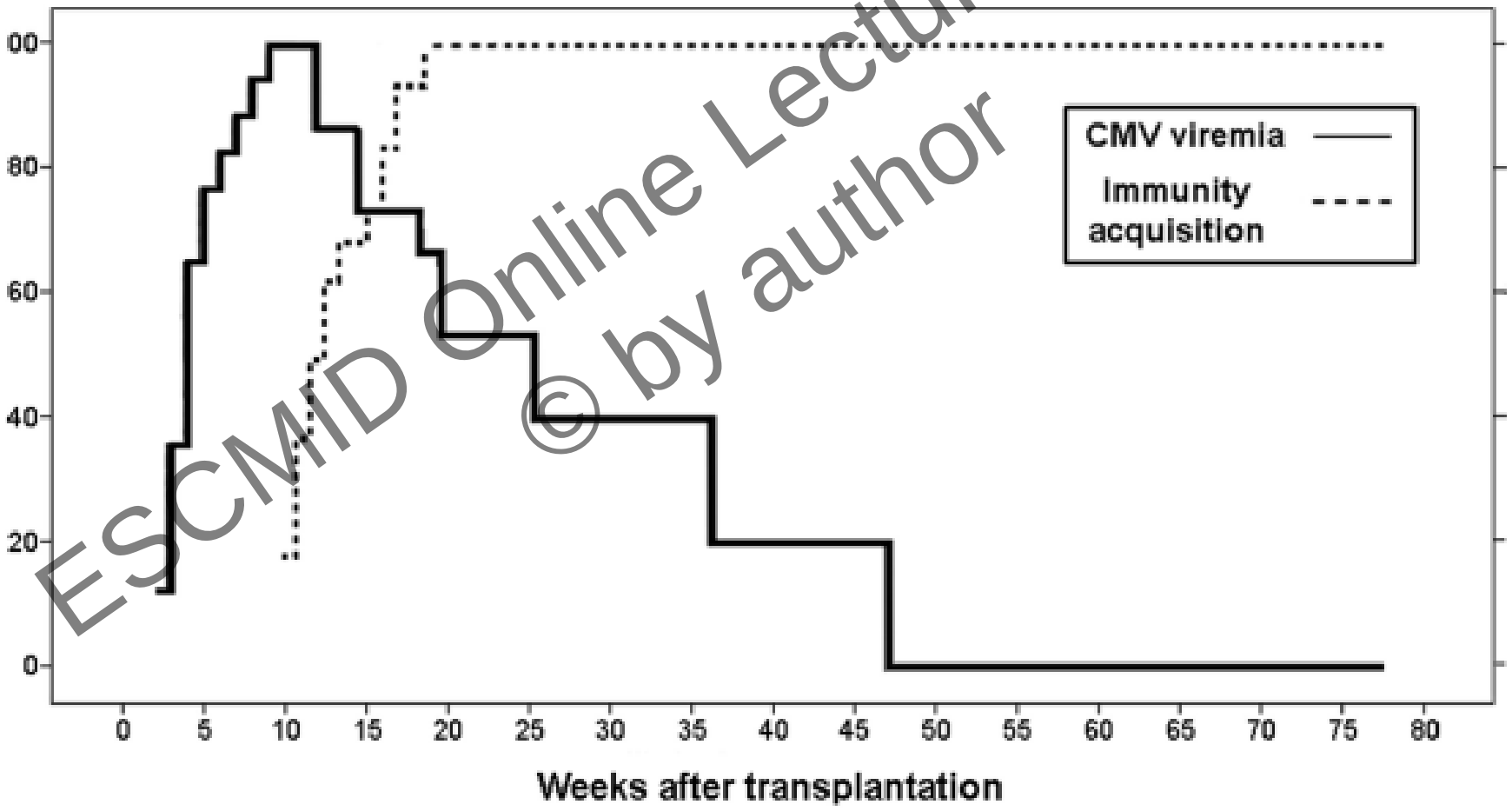


Florescu Clin Infect Dis 2014
Limaye .Transplantation 2006

Late onset CMV disease

- Rare in patients who receive preemptive therapy including R-D+
- Possible explanation :
  - Universal Prophylaxis prevents replication and acquisition of specific immune response
    - After completing prophylaxis -> uncontrolled replication and disease
  - Preemptive therapy : allows low-level replication and with it the early acquisition of specific immunity

CMV viremia in high risk patients with preemptive therapy



Benmarzouk Transplantation 2011

¿What do you think it is the most probable?

- 1. *Salmonella* infection
- 2. Drug toxicity
- 3. **CMV disease**
- 4. *Clostridium difficile* infection

What would you do next?

- 1. CMV viremia
- 2. Withold mycophenolate
- 3. Order an oral endoscopy
- 4. Initiate ganciclovir iv
- 5. All of them

PCR CMV

26/11/2012	6055	34200	EQUIVALENTES A 31122 UI/ML
08/11/2012	6055	<150	EQUIVALENTES A < 137 UI/ML (RESULTADO INFERIOR AL RANGO DE LINEARIDAD DE LA TECNICA)
24/10/2012	6055	NEG	-
03/10/2012	6055	NEG	-
19/09/2012	6055	NEG	-
07/09/2012	6055	NEG	-
28/08/2012	6055	NEG	-
21/08/2012	6055	NEG	-
14/08/2012	6055	NEG	-
09/08/2012	6055	NEG	-
02/08/2012	6055	NP	TIENE UNA DETERMINACION NEGATIVA DE AYER 01/08/2012
01/08/2012	6055	NEG	-
23/07/2012	6055	NEG	-

Admission

End of valganciclovir

Oral endoscopy findings

- Esophagus, pylorus, duodenum normal
- Stomach: Antral mucosa with rough and numerous flat lesions , ulcerated , surface and sub-centimeter lesions
- Biopsy: CMV gastritis
- CMV PCR: 32210 IU/ml

- **Diagnosis:**
  - **Gastrointestinal CMV disease**

What would you do next?

- 1. CMV viremia
- 2. Withold mycophenolate
- 3. Order an oral endoscopy
- 4. Initiate ganciclovir iv
- 5. **All of them**

Do you need any blood test control during CMV treatment?

A. No, ganciclovir is a very safe drug
B. Yes, CMV viral load, weekly
C. Yes, hemogram and creatinin levels weekly
D. b and c are correct

Clinical impact of neutropenia related with the preemptive therapy of CMV infection in solid organ transplant recipients

Journal of Infection (2014) 69, 500–506

Cecilia Martín-Gandul [a,b], Pilar Pérez-Romero [a,b], Francisco M. González-Roncero [c], Soledad Berdaguer [d], Miguel A. Gómez [e], Ernesto Lage [f], Magdalena Sánchez [a,b], José M. Cisneros [a,b], Elisa Cordero [a,b,*], The Spanish Network for Research in Infectious Diseases (REIPI)

- Hematological toxicity 27 (31%) of the CMV replication episodes treated with valganciclovir
  - 28.7% neutropenia
  - 21% severe neutropenia

Do you need any blood test control during CMV treatment?

A. No, ganciclovir is a very safe drug
B. Yes, CMV viral load, weekly
C. Yes, hemogram and creatinin levels weekly
D. **b and c are correct**

Evolution

- Asymptomatic after 5 days of antiviral therapy
- CMV PCR negative after 14 days of therapy
- We continued monitoring CMV PCR weekly for 4 weeks after the end of therapy

Ideas to take home

- Consider CMV any time a SOT recipient has fever without other associated symptoms and in case of diarrhea or epigastric pain

- CMV must be monitorized after transplantation. The interval must be narrower (weekly) in case of high-risk patients

Ideas to take home

- Once valganciclovir /ganciclovir is started, hematological toxicity and CMV response must be monitorized
- Although CMV infection usually occurrs within the first 3 months of the transplant, late onset disease must be considered, especiallly after withdrawing prophylaxis in high- risk patients
-

LIVER TRANSPLANT RECIPIENTS WITH INTESTINAL SUBOCLUSION

67 years male

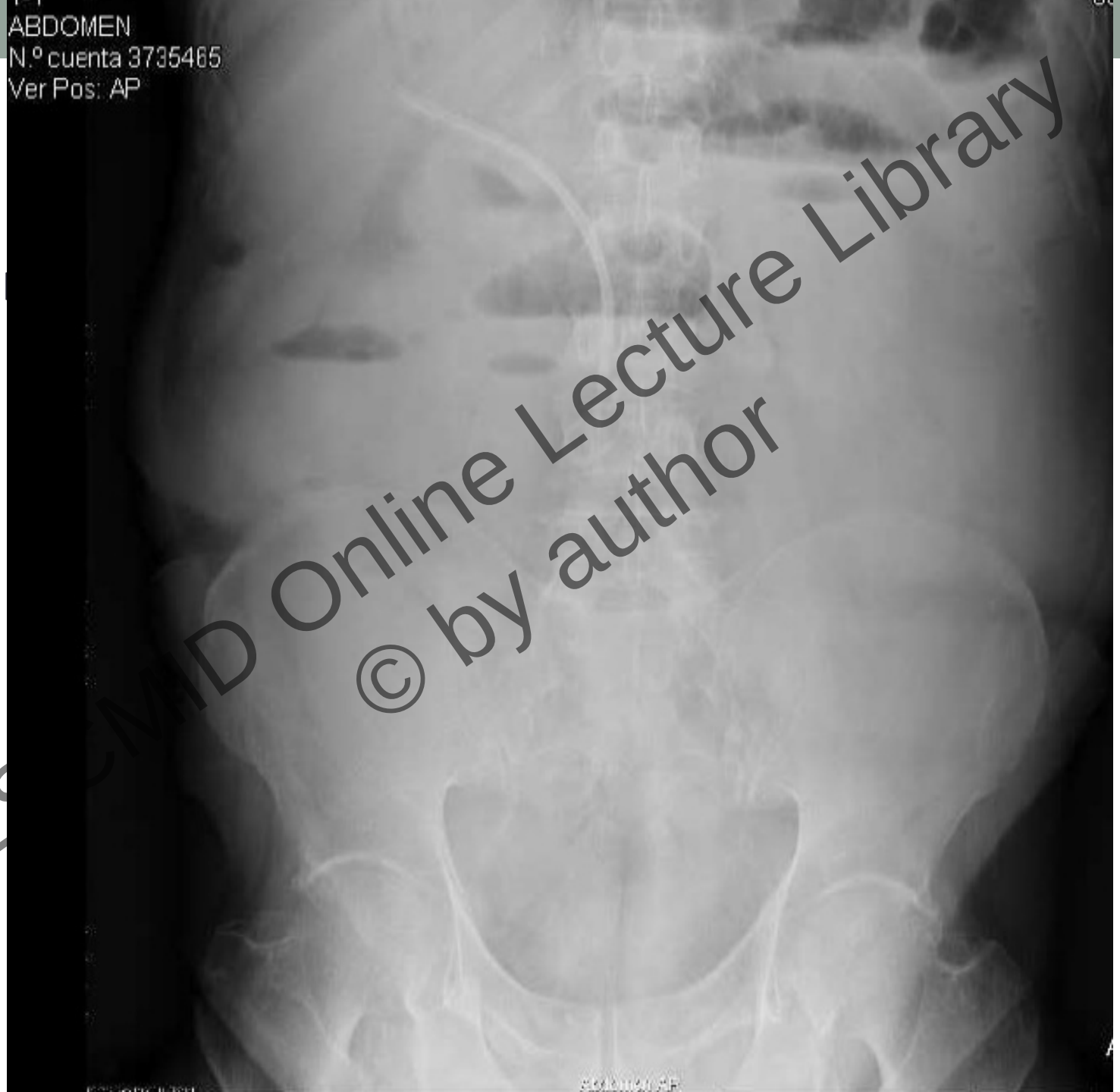
- No allergies
- Smoker, alcohol >80g/day one year ago.
- Hypertension, diabetes , renal tuberculosis 19 years ago.
- Liver cirrhosis and hepatocellular carcinoma
- Liver transplantation (+8 months)
  - Serology CMV R + / D +, VEB R- / D +
- Postransplant events
  - Herpes simplex virus gastritis (+4 month)
  - Biliary fistula
  - Immunosuppressant drugs: tacrolimus + mycophenolate

+9 months

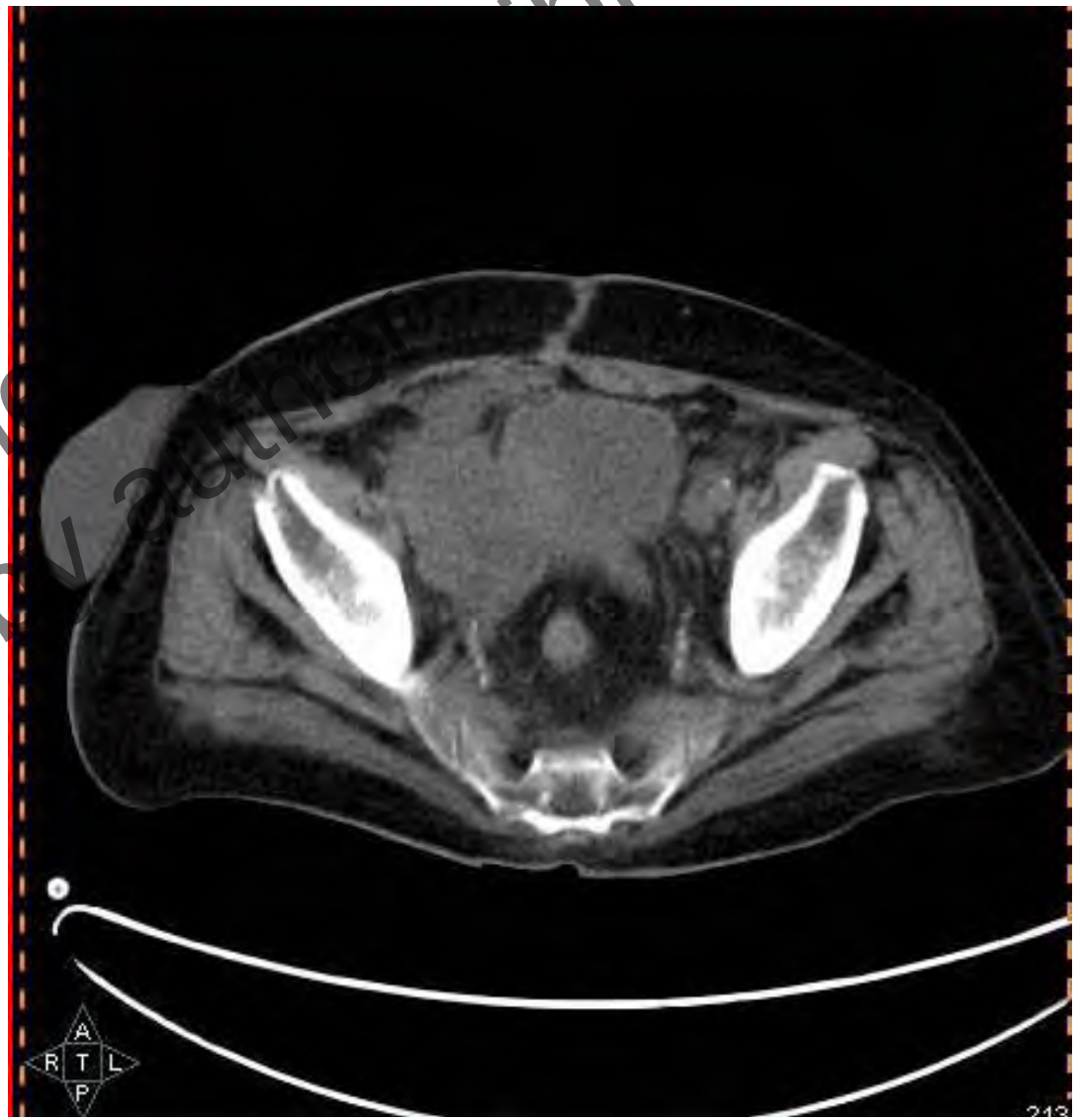
- Two days ago: Abdominal pain with nausea and vomits
- Physical examination:
  - Distended abdomen, diffusely painful, with increased peristalsis and without signs of peritonism . No palpable lymphadenopathy

Blood tests

- Leukocytes 6720/µl, PMN 5800/µl, Lymphocytes 1000/µl, Hb 9.1g/l, platelets 180000/µl
- Creatinine 1.35 mg/dl
- Alkaline phosphatase 2513 U/l, GGTP 272 IU/l, AST 69 IU/l, ALT 41 IU/l, total bilirrubin 0.3 mg/dl
- LDH 672 U/l, beta2microglobulin 18.3 mg/l



- Observation.
- No improvement.
- CT ordered.
  - Mass in right iliac fossa and small bowell dilatation.



What would you do next?

A. Wait 48 hours with total parenteral nutrition and further evaluation
B. CMV PCR test
C. Order for a colonoscopy
D. Surgical intervention

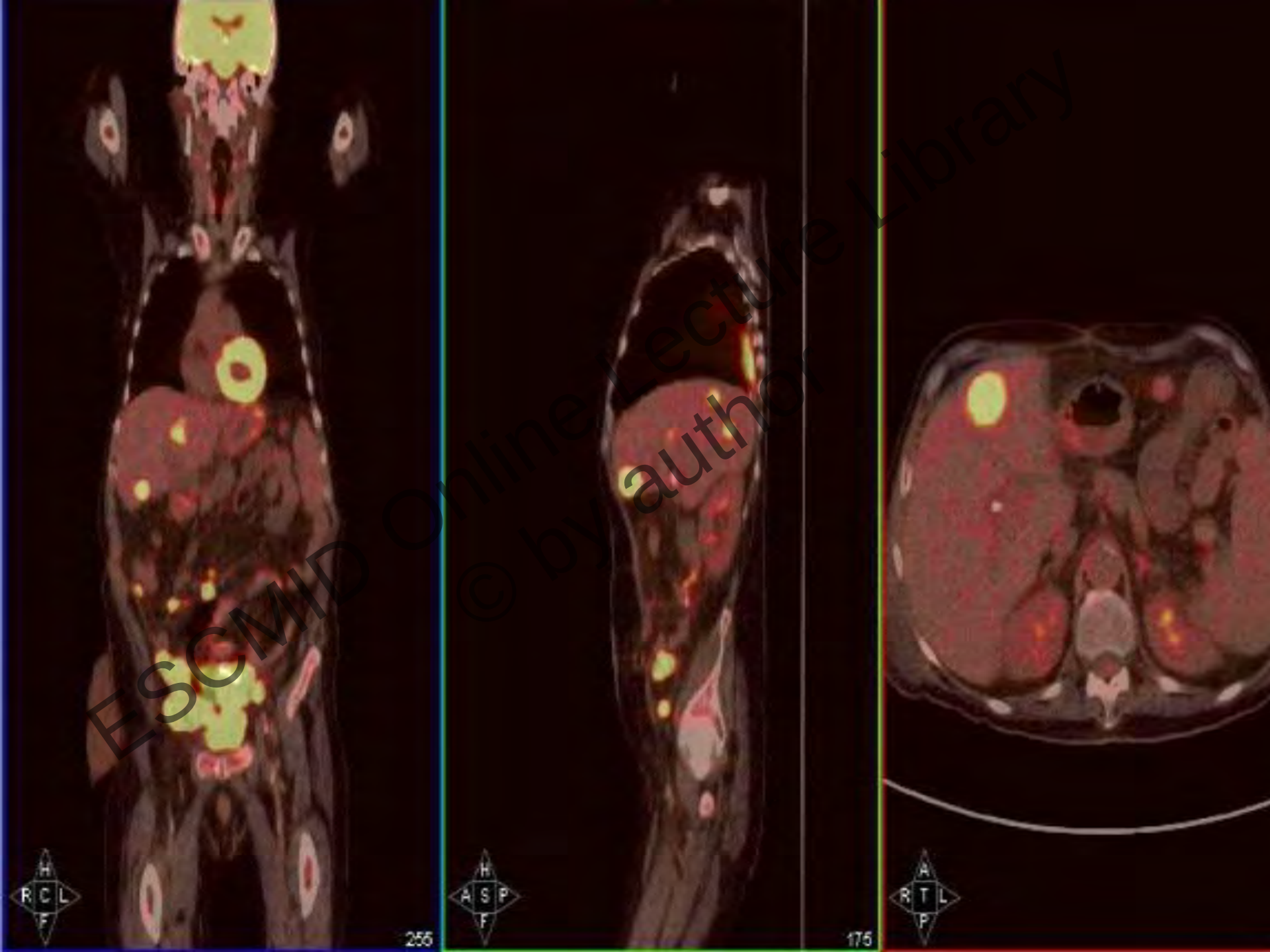
What would you do next?

A. Wait 48 hours with total parenteral nutrition and further evaluation
B. CMV PCR test
C. Order for a colonoscopy
D. **Surgical intervention**

Right hemicolectomy with ilestomy and partial resection of the bladder

Histopathology

- Large cell immunoblastic B lymphoma. Monomorphic PTLD that affects ileum, cecum, cecal appendix, regional lymphadenopaties with terminal ileal perforation.
- Bladder wall biopsy: immunoblastic B lymphoma
  - CD20+, CD10-, CD30+, CD79A+, CD138+W+, EBV+ (10%)
  - Clonal rearrangement IgH.



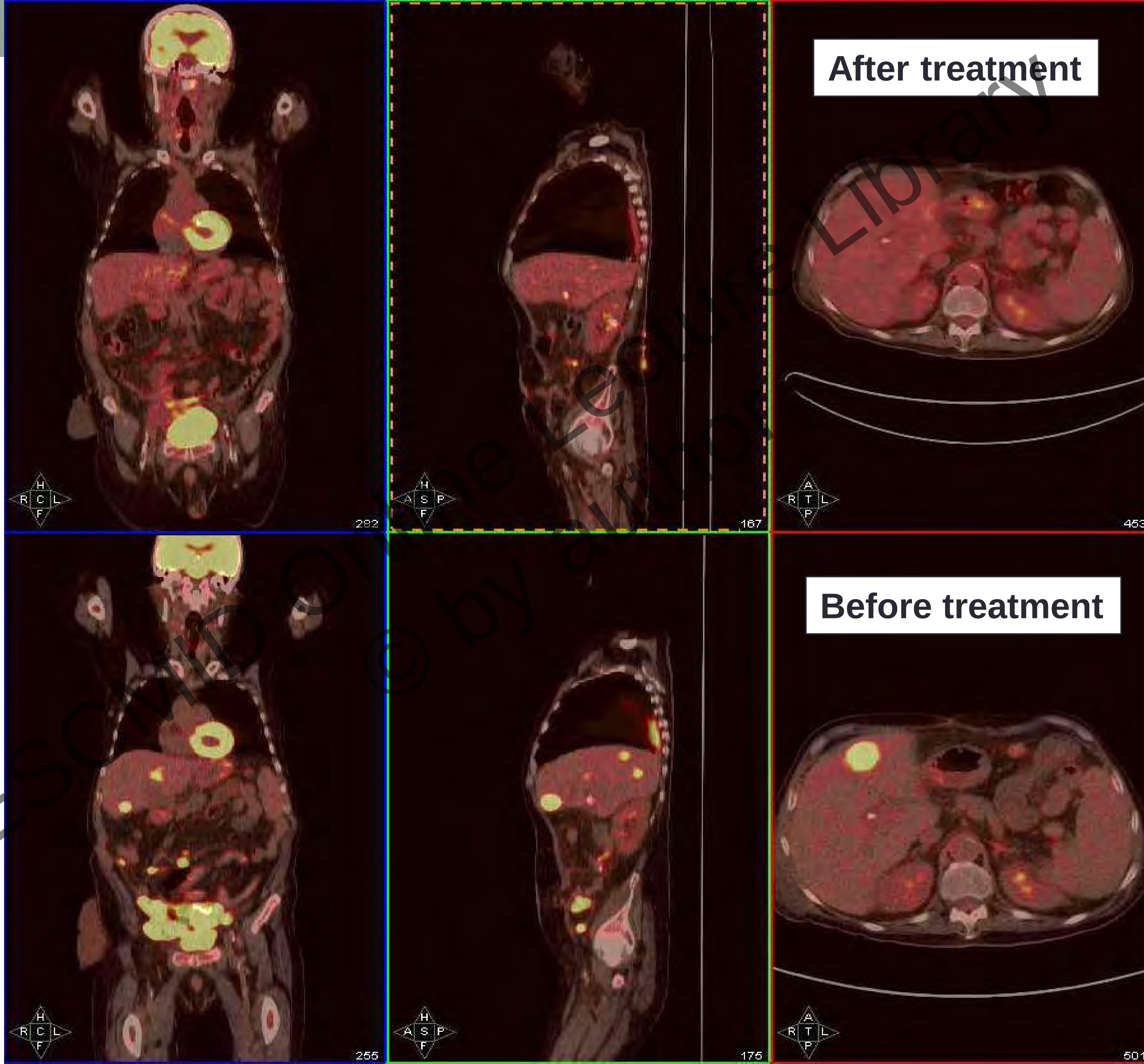
- PCR EBV viral load: 2560 copies/ml
- Bone marrow aspirate: cytology and cytometry without lymphoma infiltration

- Immunoblastic B lymphoma with abdomino-pelvic, liver ,and infradiafragmatic lymphatic extension.
  - Post-transplant lymphoproliferative disorder (PTLD).

Treatment

- Rituximab (6 doses). Partial remission after 4 doses.
  - EBV negative

The patient died 9 months after diagnosis due to an acute myocardial infarction, disease (PTLD) free.



A few questions

- Was a PTLD diagnosis expected in this patient?
- Should we have begun antiviral treatment ?
- Is the monitoring of EBV PCR useful in assessing the response to treatment ?

Was a PTLD diagnosis expected in this patient?

- A. Yes
- B. No

Was a PTLD diagnosis expected in this patient?

TABLE I. Levels of evidence of analysed risk factors for PTLD

Type of PTLD	Potential risk factor for PTLD	Level of evidence	References
Early PTLD	EBV recipient seronegativity, D+/R- serostatus	A-II	[16,21–23]
	Use of anti-lymphocyte antibodies	B-II	[16,17,20,22,25,26,30]
	Maintenance IS with tacrolimus	C-II	[17,19,20,29,30,32]
	Maintenance IS with mycophenolate	D-II	[16,27,29,33–36]
Late PTLD	Older age (>60 years)	C-III	[16,22]
	Long-term IS	C-III	[16,22]

IS, immunosuppression.

San Juan, Clin Microbiol Infect 2014

Risk factors of PTLD in SOT recipients.

- Pretransplant EBV serology:
  - It is the most important factor (23-50 % vs. 0.7 to 1.9 %).
  - In adults with renal transplantation, prevalence 24 times higher in R-.
- CMV infection.
  - Increased the risk in seronegative.
    - Adults liver recipients.
      - CMV infection increase the risk of PTLD 7.3.
  - Higher risk if CMV R-/D+ (4-6 times)

Allen Am J Transplant 2013, Manez R. Transplant Intern 1994, van Leeuwen MT, Blood 2009; Quinlan SC Am J Hematol 2011; Sampaio Nephrol Dial Transplant 2012

Table 2: Presenting symptoms and signs in patients with lymphoproliferative disorder

Symptoms/complaints	Signs
Swollen lymph glands	Lymphadenopathy
Weight loss	Hepatosplenomegaly
Fever or night sweats	Subcutaneous nodules
Sore throat	Tonsillar enlargement
Malaise and lethargy	Tonsillar inflammation
Chronic sinus congestion and discomfort	Signs of bowel perforation
Anorexia, nausea and vomiting	Focal neurologic signs
Abdominal pain	Mass lesions
Gastrointestinal bleeding	
Symptoms of bowel perforation	

EBV related PTLD

Benign policlonal proliferation: 55%.

- Infectious mononucleosis like.
- 2-8 weeks after the transplant.
- Normal Cytogenetics, non genetic reassortment.

- **Policlonal lymphoproliferation with evidence of early malignant transformation**: 30%.
  - Clonal cytogenetic abnormalities and genetic reassortment.
- **Monoclonal proliferation**:15%.
  - Clonal cytogenetic abnormalities and genetic reassortment.

- **Extranodal involvement** >50%.
  - Gastrointestinal.
  - Lung, skin, liver.
  - CNS: 20-25% frequently isolated.
  - Graft: 20-25%.

EBV non-related PTLD:

- Late (2324 days *vs* 546 days).
- More agressive.

Was a PTLD diagnosis expected in this patient?

- **A. Yes**
- B. No

Should we have begun antiviral treatment ?

- A. Yes
- B: No

Should we have begun antiviral treatment ?

- **There is no evidence to support the use of antiviral agents in the absence of other interventions such as decreasing immunosuppression or anti-CD20 therapy .**
- Agent of choice: **ganciclovir** (+10 times more active than acyclovir)**.**

- Included in the **early stages** of PTLD trying to control the viral infection.
  - Polyclonal disease has responded to ganciclovir in anecdotal cases .
  - Plasma cell hyperplasia and Infectious mononucleosis can respond.
  - **No evidence for use in other clinical forms.**

- Foscarnet (4 weeks) has been used in a case with complete response without reducing immunosuppression .

San Juan, Clin Microbiol Infect 2014

Should we have begun antiviral treatment ?

- A. Yes
- **B: No**

Is the monitoring of EBV PCR useful in assessing the response to treatment ?

- A Yes
- B No
- C It is not clear

Is the monitoring of EBV PCR useful in assessing the response to treatment ?

- Monitoring EBV viral load.
  - A decrease or elimination of VL is associated with clinical response after treatment
  - If rituximab is used, the decrease in viral load does not predict clinical response
- Often a rebound occurs after clinical remission:
  - Preliminary studies suggest that this increase in viral load is not a predictor of recurrent disease
  - The usefulness of monitoring viral load in patients who have survived a PTLD is unclear
  - Plasma better than cellular compatment

Young, Blood 2000. Stevens SJC, Leuk Lymphoma 2002, Oerter Ann Hematol 2006

van Esser, JW, Niesters, HG, Thijsen, SF, et al. Molecular quantification of viral load in plasma allows for fast and accurate prediction of response to therapy of Epstein-Barr virus-associated lymphoproliferative disease after allogeneic stem cell transplantation. Br J Haematol 2001; 113:814.

-14 Allogenic stem cell recipients with PTLDS

-EBV viral load and response to treatement.

- Decrease>50% after 72 h predict response to treatment.

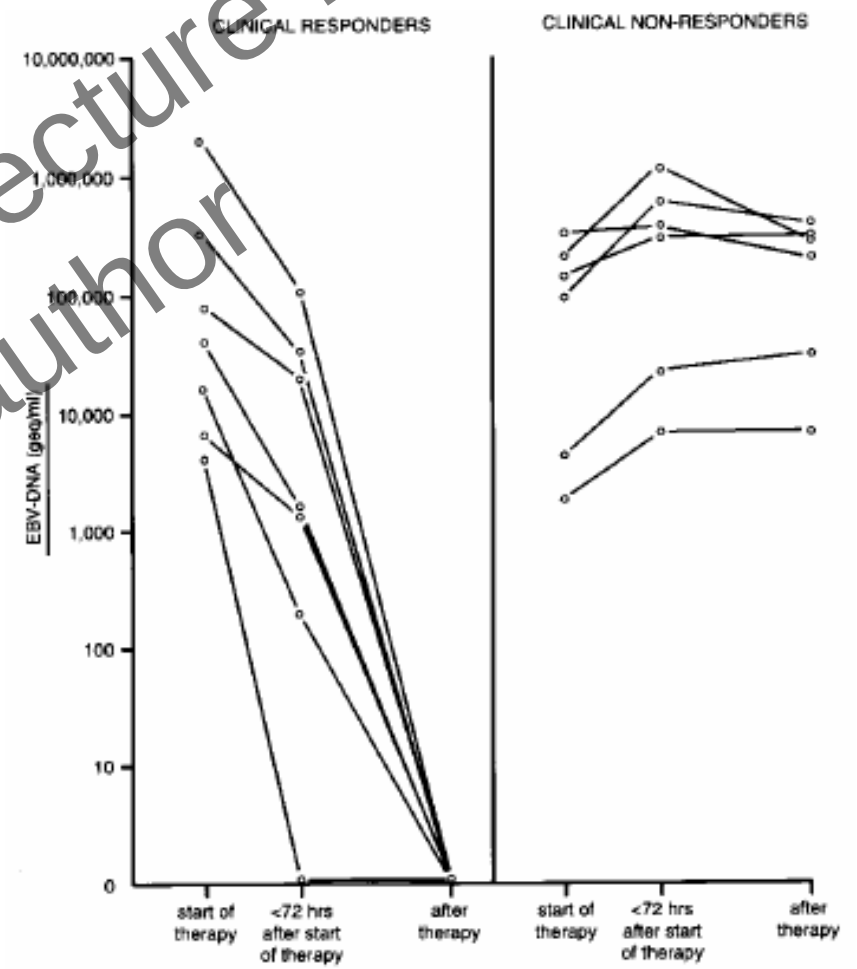


Fig 1. Individual EBV-DNA levels for clinical responders (left) and clinical non-responders (right) at the start of therapy, after 72 h and at clinical response evaluation.

Is the monitoring of EBV PCR useful in assessing the response to treatment ?

- A Yes
- B No
- C **It is not clear**

PTLD in SOT recipients. Main ideas.

- Frequently extranodal.
- Consider it in high risk patients (EBV R-D+ and antilymphocyte globulin).
- Serial monitoring of high risk with EBV viral load as part of preemptive strategies for PTLD prevention.
- Preemptive strategies in high-risk populations may lower PTLD incidence rates:
  - Reduction in immunosuppression is the best documented intervention strategy.
  - Insufficient data: antivirals, anti-CD20 antibody or adoptive immunotherapy.
- Treatment strategies:
  - First reduce immunosuppression
  - If not: AntiCD20 (rituximab)
  - If not: Chemotherapy