Προφυλακτική αγωγή ανοσοκατεσταλμένου ασθενούς «Αντιϊκή προφύλαξη: Ενδείξεις και αποτελεσματικότητα»

ΣΤΕΛΙΟΣ ΑΣΗΜΑΚΟΠΟΥΛΟΣ

ΠΑΘΟΛΟΓΟΣ - ΛΟΙΜΩΞΙΟΛΟΓΟΣ

ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ

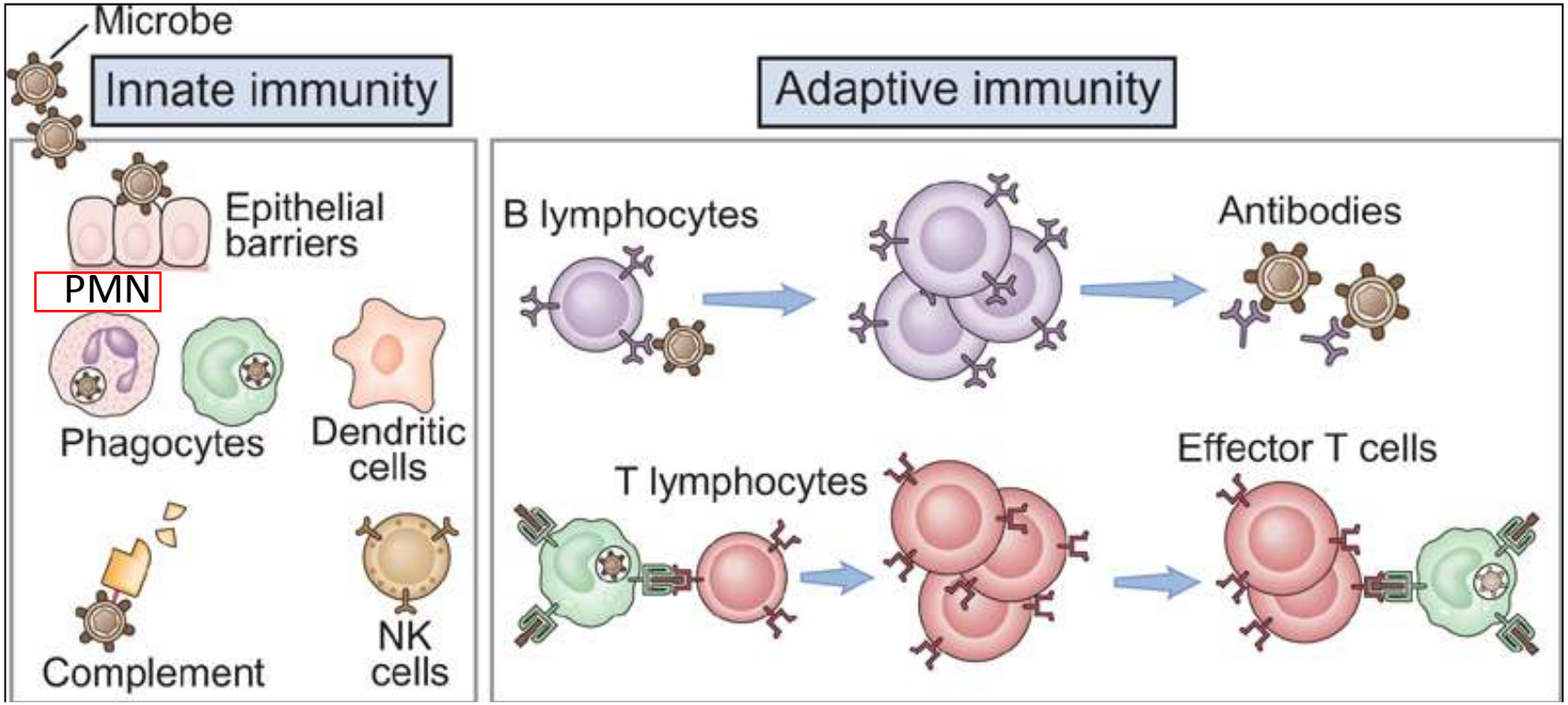
ΠΑΘΟΛΟΓΙΑΣ

ΙΑΤΡΙΚΟ ΤΜΗΜΑ ΠΑΝ/ΜΙΟΥ ΠΑΤΡΩΝ

Σύγκρουση συμφερόντων

- Honoraria για ομιλίες: *Pfizer, Gilead Sciences, MSD, Angelini*
- Honoraria για συμβουλευτικές υπηρεσίες: *Pfizer, GSK, Angelini*
- Research Grants: *Pfizer, Gilead*

Μηχανισμοί άμυνας στις λοιμώξεις



Λοιμώξεις αναλόγως του σκέλους που πάσχει

Φυσική ανοσία

- Κοινά βακτήρια (Gram +, Gram -)
- Μύκητες (Candida, Aspergillus)

Β–κυτταρική ανοσία

- Κόκκοι και βακτήρια με κάψα

Strep. Pneumoniae
Haemophilus infl.
N. Meningitidis

Τ-κυτταρική ανοσία

- Ενδοκυττάρια βακτήρια (Listeria, Nocardia)
- Ιοί (HSV, VZV, CMV, RSV)
- Μύκητες (Cryptococcus)
- Παράσιτα (Pneumocystis jirovecii, Toxoplasma)
- Μυκοβακτήρια (TB, άτυπα)

Καταστάσεις με διαταραχή κυτταρικής ανοσίας

- Τ-λεμφοκύτταρα (CD4 / CD8)
- Κυτταροκίνες

Συγγενή σύνδρομα

Διαταραχή κυτταρικής ανοσίας

Reticular dysgenesis
Lymphocyte enzymopathies
Severe combined immunodeficiency
DiGeorge syndrome
Wiscott-Aldrich syndrome
Αταξία τηλαγγειεκτασία

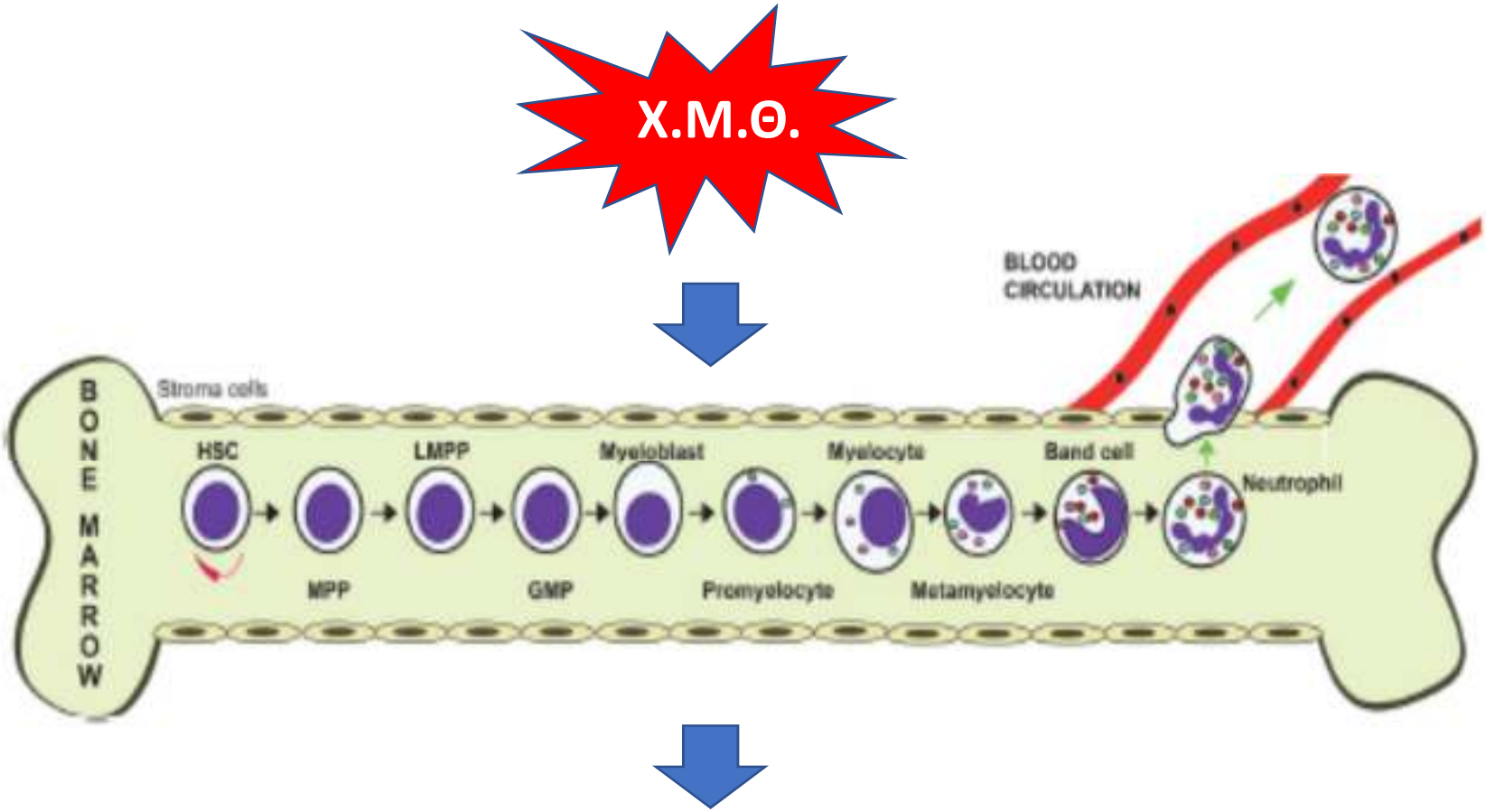
Διαταραχή Χυμικής και κυτταρικής ανοσίας

Σοβαρή συνδυασμένη ανοσοανεπάρκεια (SCID)

Επίκτητα σύνδρομα

AIDS
Αιματολογικές κακοήθειες
Ανοσοκατασταλτικά
Κορτικοειδή
ΣΕΛ
Σαρκοείδωση
Σοβαρή συστηματική νόσος
Συμφορητική καρδιακή ανεπάρκεια
Απόφραξη λεμφικής κυκλοφορίας
Χημειοθεραπεία
Βιολογικοί παράγοντες

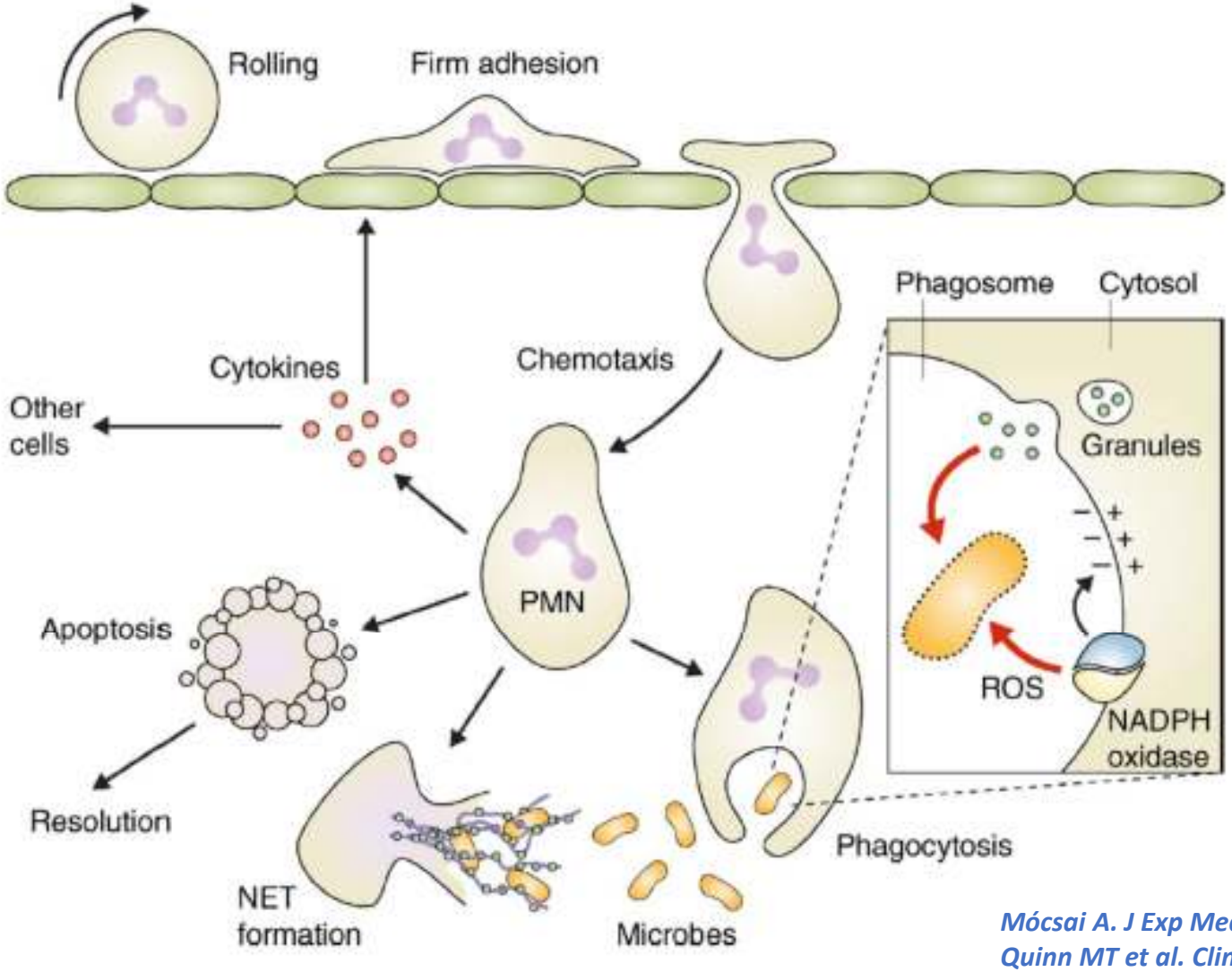
Χημειοθεραπεία και λοιμώξεις



ουδετεροπενία

Το ουδετερόφιλο πολυμορφοπύρηνο στη λοίμωξη

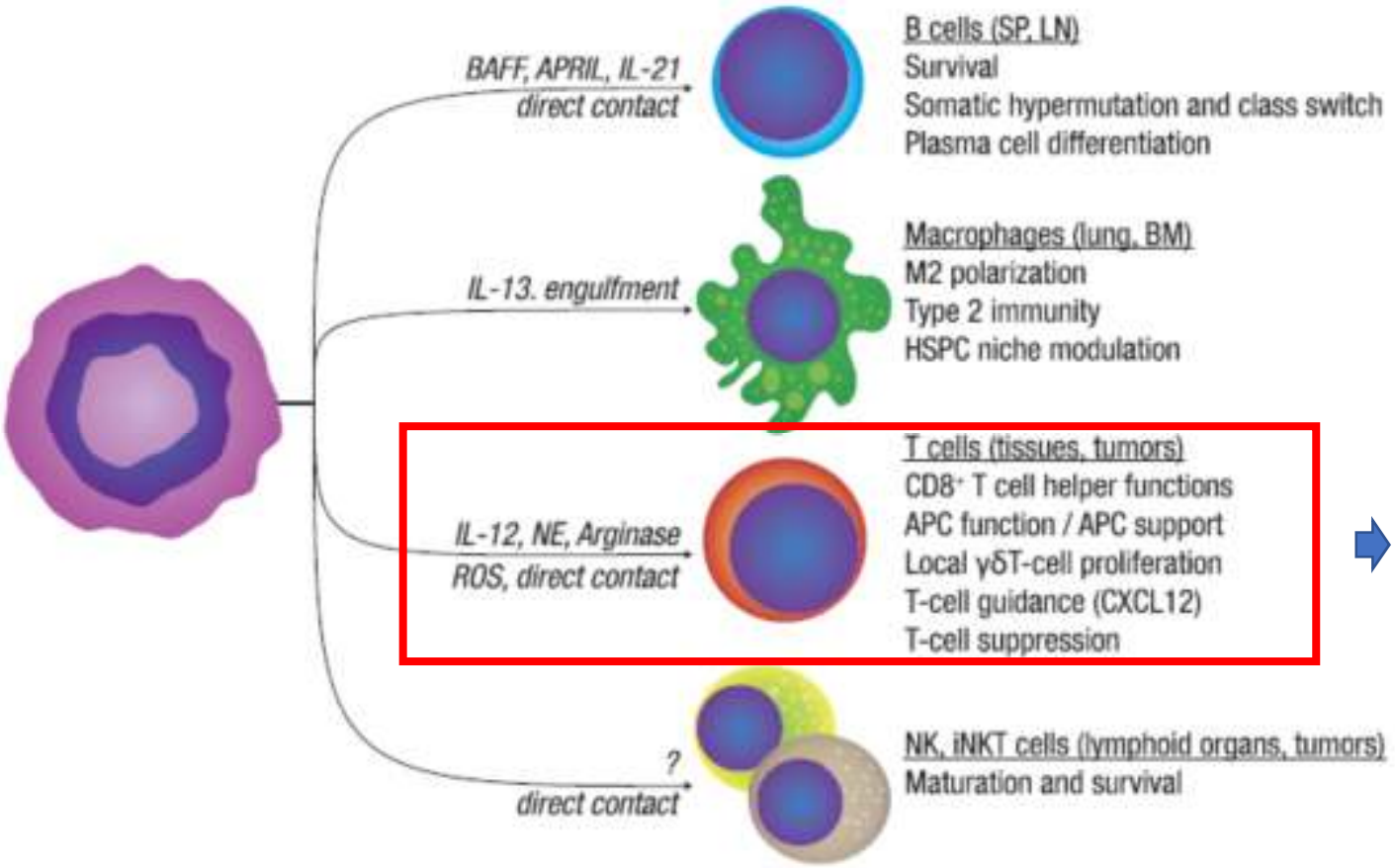
- *τα ουδετερόφιλα κινητοποιούνται και συναθροίζονται γρήγορα στην εστία της λοίμωξης, προσελκυόμενα από τις κυτοκίνες που εκφράζονται από το ενεργοποιημένο ενδοθήλιο, τα μαστοκύτταρα και τα μακροφάγα*



Mócsai A. J Exp Med. 2013
Quinn MT et al. Clin Sci 2006

Το ουδετερόφιλο πολυμορφοπύρηνο στη λοίμωξη

Although classically considered endpoint effector cells, neutrophils have the capacity to modulate other immune cells



Viral infections

Mócsai A. J Exp Med. 2013
Quinn MT et al. Clin Sci 2006

Ιογενείς λοιμώξεις σε ανοσοκατασταλμένους

Ερπητοϊοί

- CMV
- HSV
- VZV
- EBV
- HHV-6
- HHV-7
- HHV-8

Άλλοι ιοί

- Ιοί αναπνευστικού (αδενοϊοί, RSV, influenza, parainfluenza, metapneumovirus)
- Ιοί polyoma (BK, JC, MCC)
- HBV
- HPV

ανάλογα με τον τύπο ανοσοκαταστολής επιρρέπεια λοιμώξεων από διαφορετικούς ιούς..

Ο μεταμοσχευμένος ασθενής

Ιογενείς λοιμώξεις και επιπτώσεις σε μεταμόσχευση

- **Άμεσες επιπτώσεις**

- Ιαιμία, πυρετός, ουδετεροπενία, ηπατίτιδα
- Κολίτιδα, αμφιβληστροειδίτιδα, νεφρίτιδα, παγκρεατίτιδα

- **Έμμεσες επιπτώσεις ή ανοσοτροποποιητικές**

- Ανοσοκαταστολή → ευκαιριακές λοιμώξεις
- Απόρριψη μοσχεύματος, GVHD
- Κατάργηση της ανοσοανοχής

- **Ογκογένεση/ Κυτταρικός πολλαπλασιασμός**

-**HBV:** ηπατοκυτταρικό καρκίνωμα
-**EBV:** μεταμοσχευτική λεμφοϋπερπλαστική νόσος, PTLD
-**HCV:** σπληνικό λέμφωμα, non-Hodgkin's lymphoma
-**Papillomavirus:** ακανθοκυτταρικός καρκίνος και πρωκτογεννητικός
- HHV8: Kaposi's σάρκωμα, effusion lymphoma
- Επιταχυνόμενη αθηρογένεση σε μεταμόσχευση καρδιάς, αποφρακτική βρογχιολίτιδα σε μεταμόσχευση πνεύμονα, BK-ουρητηρική απόφραξη

Ανοσολογικό profile μεταμοσχευμένων ασθενών (αλλογενή μεταμόσχευση)

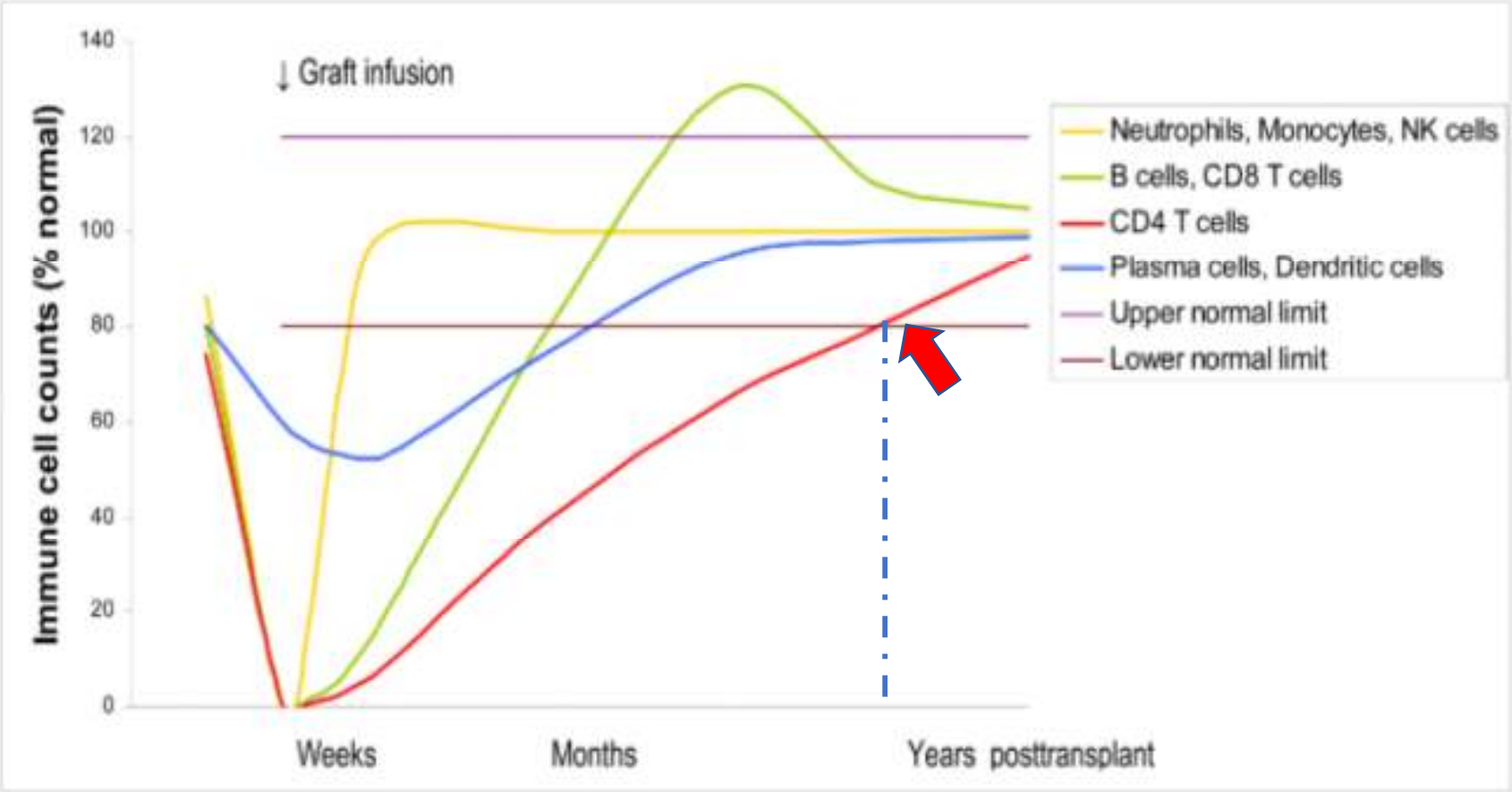
- **Ανοσοανεπάρκεια** λόγω της υποκείμενης **βασικής νόσου**
- Ανοσοκαταστολή εκ των **προηγηθεισών συμβατικών χημειοθεραπειών**
- Ανοσοκαταστολή εκ του **σχήματος προετοιμασίας** της μεταμόσχευσης
- Ανοσοκαταστολή από την **προφύλαξη για το οξύ GVHD**
- Μεγάλη **Τ- και CD4-λεμφοπενία**
- Αριθμητική και λειτουργική **υστέρηση των δενδριτικών κυττάρων**
- **Ανυπαρξία ανοσολογικής ρύθμισης** και προσπάθεια οργάνωσης του ανοσοποιητικού συστήματος με Τ-λεμφοκύτταρα δότη και αντιγόνα ιστοσυμβατότητος του λήπτη
- **Ουδετεροπενία** τις πρώτες 2-3 εβδομάδες μετά τη μεταμόσχευση

Ανοσολογική αποκατάσταση μετά τη μεταμόσχευση

Εξαρτάται από:

- **Η σχέση και ο βαθμός HLA-ασυμβατότητας δότη/λήπτη**
  - Απλοταυτόσημη > mismatched unrelated > matched unrelated > > related > syngeneic > autologous SCT
- **Το είδος του μοσχεύματος**
  - Επιλεγμένα CD34+ κύτταρα > ομφαλοπλακούντια > ολικά κινητοποιημένα αιματικά μοσχεύματα > ολικά μυελικά
- **Το είδος του σχήματος προετοιμασίας**
  - Μυελοαφανιστικό ή μη μυελοαφανιστικό
  - Περιεχόμενη ολοσωματική ακτινοθεραπεία και δόση της
  - Είδος / δόση αντιλεμφοκυτταρικών φαρμάκων (ATG, Campath, Fludara κλπ)
- **Η χορήγηση post-infusion ανοσοκαταστολής (Endoxan κλπ)**
- **Το είδος της GVHD προφύλαξης**
- **Η εμφάνιση οξέος GVHD**

Ανοσολογική αποκατάσταση μετά τη μεταμόσχευση



Biol Blood Marrow Transplant 15:1143-1238, 2009

Ανοσολογικό profile μετά από αυτόλογη μεταμόσχευση και ιογενείς λοιμώξεις

- **Μικρή περίοδος CD4 λεμφοπενίας**
- όχι σημαντικές διαταραχές ρυθμιστικών Τ- και δενδριτικών κυττάρων
- **ελάττωση μνημονικών Τ-λεμφοκυττάρων** / απώλεια ειδικής κυτταρικής ανοσίας

- **ασυνήθιστες / όχι βαριές ιογενείς λοιμώξεις** κυρίως για **1-3 μήνες** μετά την ASCT
- **Συνηθέστερα HSV-1, VZV, HBV και ιοί γρίπης**
- **Σπανιότερα CMV** επανενεργοποίηση και λοιμώξεις από **HHV6** και **RSV**
- **Σχεδόν ποτέ** λοιμώξεις από **JCV / BK Polyoma, ParvoB19**

Χρονοδιάγραμμα λοιμώξεων σε HSCT

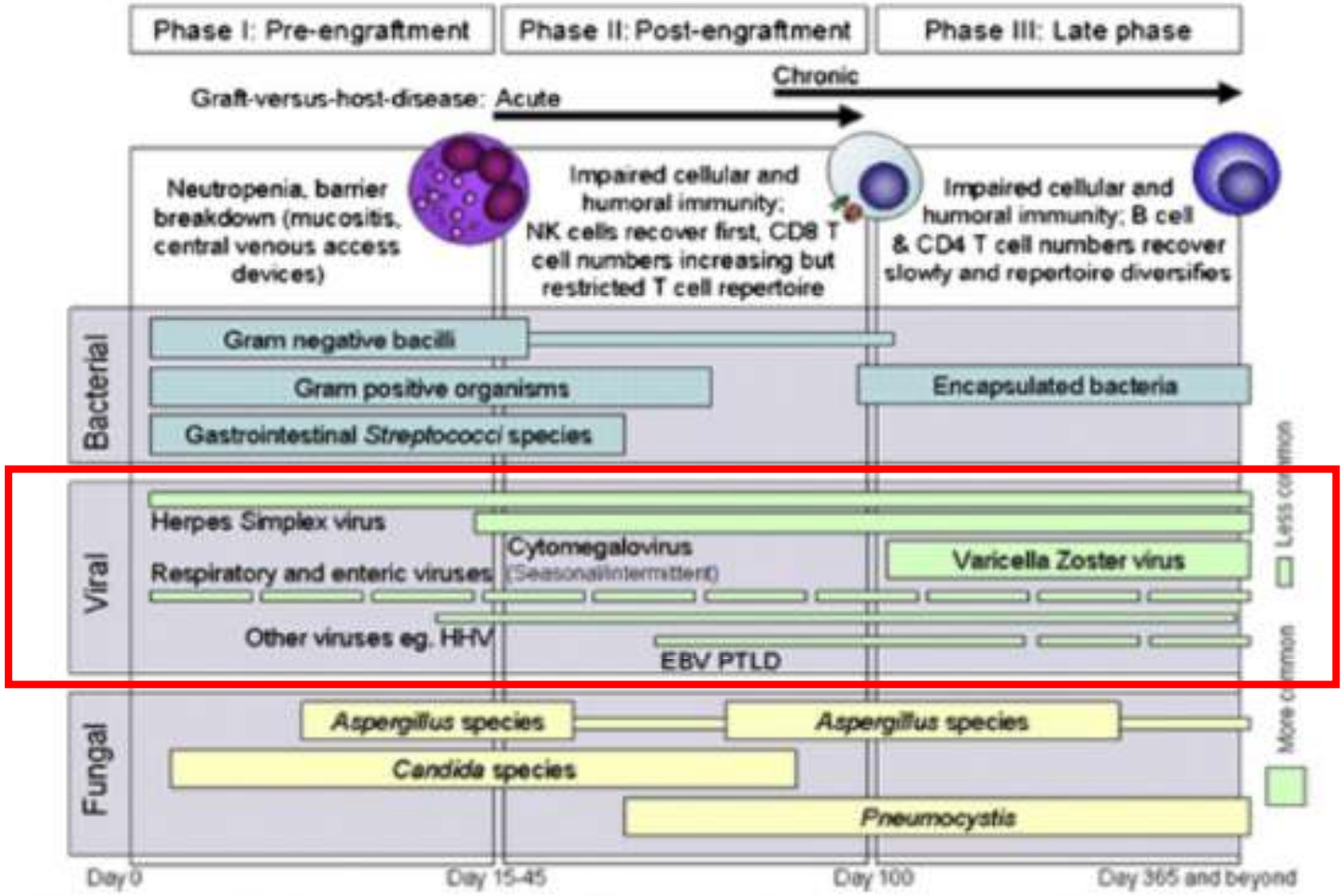
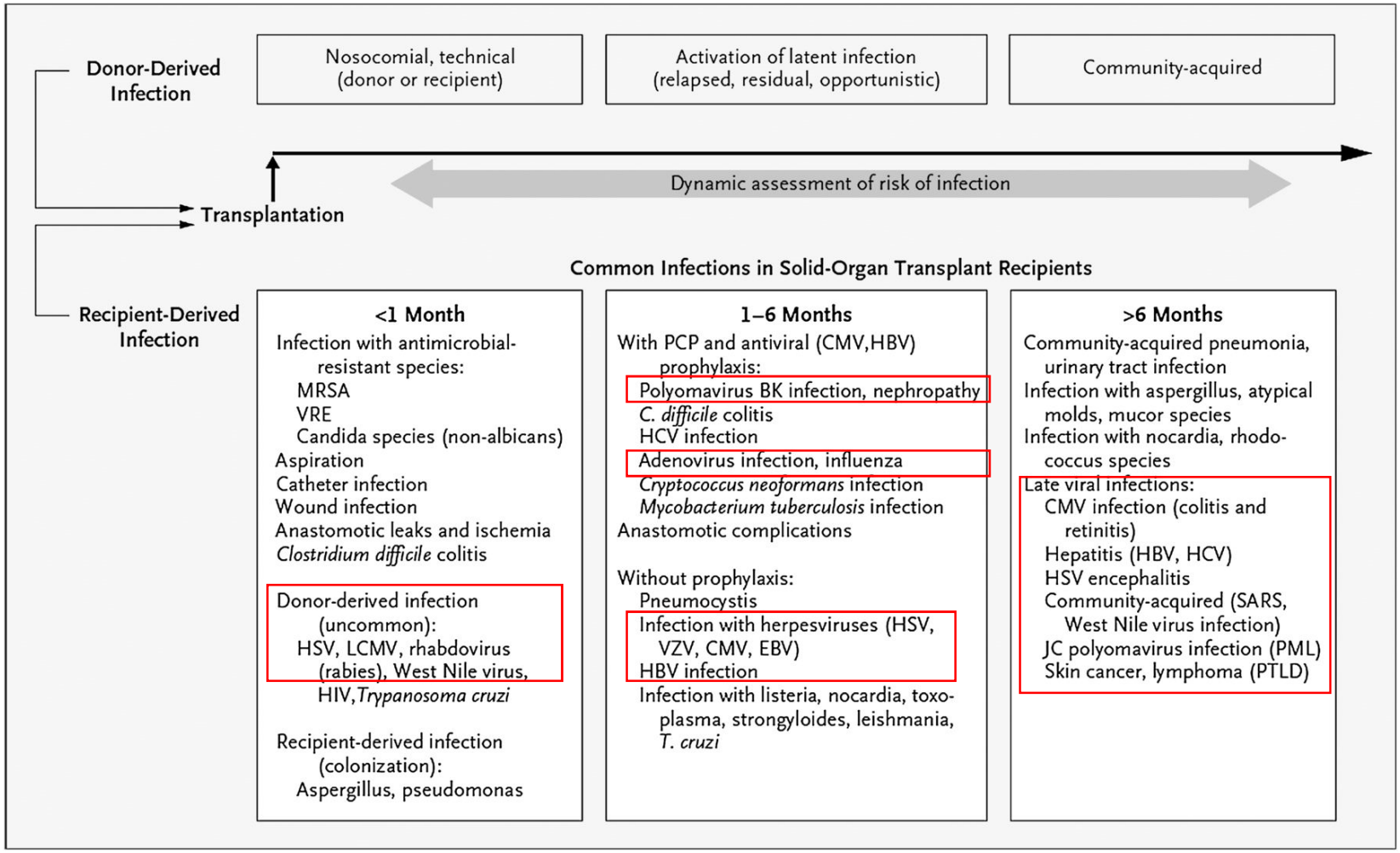


Figure 2. Phases of opportunistic infections among allogeneic HCT recipients. Abbreviations: EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; PTLD, posttransplant lymphoproliferative disease.

Biol Blood Marrow Transplant 15:1143-1238, 2009

Χρονοδιάγραμμα λοιμώξεων σε μεταμόσχευση συμπαγών οργάνων



Shamila Karuthu, and Emily A. Blumberg CJASN 2012;7:2058-2070

Ιογενείς λοιμώξεις σε μεταμοσχευμένους ασθενείς: συχνότητα εμφάνισης

- Common
  - CMV, HSV, VZV
- Less common
  - Adenovirus, influenza A, para-influenza, RSV, Rhinovirus
- Rare
  - Rotavirus, Coxsackie, polyoma virus

Prevention of HSV/VZV: allogenic HSCT

Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016

Ann Hematol (2016) 95:1435–1455
DOI 10.1007/s00277-016-2711-1

Table 3 Antiviral prophylaxis

Intention	Intervention	SoR	QoE	Comments
HSV				
Prevent HSV disease	Acyclovir 400 mg tid/day	A	II	Up to 30 days post allo-HCT (various dosages)
	Valacyclovir 500 mg bid /day	A	II	
	Acyclovir any dosage	D	III	Beyond 30 days if patient is also VZV seronegative
VZV				
VZV disease prevention in VZV seropositive recipients	Acyclovir 800 mg bid	A	I	Up to 1 year after allo-HCT
	Acyclovir 400 mg/day	B	II	
	Valacyclovir 500 mg bid	B	II	
	Acyclovir 200 mg/day	B	II	More than 365 days if continued on immunosuppressive therapy
Prevent VZV in seronegative patients	No prophylaxis	C	III	
Prevent VZV in seronegative patients if exposed	Passive immunization	C	II_t	Within 96 h post exposure, optional
	Acyclovir or other VZV-active antiviral	C	III	If patient is not on acyclovir (or any other VZV active antiviral), a short duration of therapy is an option.
Prevent VZV disease after exposure	Vaccination	–	–	No data to provide recommendation

Prevention of HSV/VZV: autologous HSCT and SOT

- **Autologous HSCT:** Acyclovir 800 mg x 2 (or valacyclovir 500 x 2)

during **neutropenia and 30 d post HCT**
(starting an antiviral agent when the conditioning regimen is started and continuing it until engraftment or until mucositis resolves)

- **Solid Organ transplantation:** Acyclovir 400-800 mg x 2 (or valacyclovir 500 x 2)

Duration:

- During the **first month post transplant** if HSV seropositive and not on CMV prophylaxis
- Consider restarting prophylaxis in periods of intensified immunosuppression

Am J Transplant 2013;S4:121
Biol Blood Marrow Transplant 15:1143-1238, 2009

Γενικές αρχές εμβολιασμών στο μεταμοσχευμένο ασθενή

- Επιθυμητή η **ολοκλήρωση των εμβολιασμών πριν την μεταμόσχευση** (≥ 2 εβδομάδες για αδρανοποιημένα, ≥ 4 εβδομάδες για ζώντα εξασθενημένα εμβόλια πχ Zostavax)

- **Επανάληψη πλήρους εμβολιασμού μετά** τη μεταμόσχευση
  - Μετά την day 100 για το εμβόλιο Influenza
  - 6 μήνες μετά για αδρανοποιημένα
  - MMR και Varicella 24 μήνες μετά και εφόσον δεν συνεχίζεται ανοσοκατασταλτική αγωγή, δεν υπάρχει GVHD
    - **Προηγείται τίτλος αντισωμάτων**. Εμβολιασμός μόνο σε ασθενείς με μη προστατευτικούς τίτλους

CID 2014

Allogeneic and autologous HSCT: vaccinations

Table 5 Vaccination recommendations for allo-HCT recipients

Intention	Intervention (timing of 1st application after allo-HCT)				SoR	QoE
Vaccine		after day +100	after 6–12 months	after 24 months		
Provide immunity	*Pneumococcus* (combination of conjugate and polysaccharide vaccines)	X			A	II_1
	Pneumococcus (polysaccharide vaccine) 23-valent (PPV23)		(X)		D	II
	Influenza	X			A	II
	Bordatella pertussis (acellular)[b]		X		A	III
	Diphtheria and tetanus toxoid[a, b]		X		A	II
	TBE[a] (Tick-borne encephalitis)		X		B	II_1
	Poliovirus[a, b]		X		A	II
	Haemophilus influenza (HI)[a, b]		X		B	II
	Meningococcal conjugate vaccine against serogroups A, C, W135, Y and Meningococcal vaccine for serogroup B		X		B	II_1
	Hepatitis A and B (HAV and HBV)[a, b]		X		B	II_1
	MMR (mumps, measles, and rubella; life attenuated vaccine)[a, b]			X	B	II
	VZV (varizella zoster virus, life attenuated vaccine)[a]			X	B	II

Ann Hematol Guidelines 2016

Biol Blood Marrow Transplant 15:1143-1238, 2009

Παθητική ανοσοποίηση στο μεταμοσχευμένο ασθενή

Νόσος	Ένδειξη	Δόση
Ιλαρά	in **seronegative** allo-HSCT recipients in case of exposure	400 mg/kg όχι αργότερα από **6 ημέρες** από έκθεση Μειώνει την πιθανότητα νόσησης /και την βαρύτητα της νόσου
Ανεμευλογιά	VZV-**seronegative** patients with chronic GVHD are exposed to varicella (primary or postvaccination illness), VZV Ig should be given within 96 hours	400 mg/kg ιδανικά **96 ώρες** και **μέχρι 10 ημέρες** από την έκθεση. Μειώνει την πιθανότητα νόσησης/ και την βαρύτητα της νόσου + Θεραπεία

Biology of Blood and Marrow Transplantation
Volume 12, Issue 4, Pages 375-396 (April 2006)

CMV και μεταμόσχευση αρχέγονων αιμοποιητικών κυττάρων

Παράγοντες κινδύνου για CMV αναζωπύρωση σε μεταμόσχευση αιμοποιητικών κυττάρων

Risk Factor	High Risk	Low Risk
CMV serostatus	▪ **Seropositive recipient**	▪ Seronegative recipient
GVHD	▪ Grade 2-4	▪ Absent
Donor type	▪ Cord blood ▪ Haploidenticαl ▪ Allogeneic mismatch	▪ Matched allogeneic
Transplant conditioning	▪ T-cell depleted (nonmyeloablative)	▪ Traditional
Medications	▪ Alemtuzumab (anti-CD52) ▪ ATG ▪ Prednisone (equivalent) dosed > 1 mg/kg (especially for aGVHD)	
Age	▪ Advanced age	

Ariza-Heredia EJ, et al. Cancer Lett. 2014;342:1-8. Emery V, et al. Br J Haematol. 2013;162:25-39. Boeckh M, et al. Blood. 2009;113:5711–5719.

Ο ρόλος της επιλογής του δότη σε μεταμόσχευση αιμοποιητικών κυττάρων

- **CMV seronegative recipient**
  - A CMV **seronegative donor** should be chosen (AI)

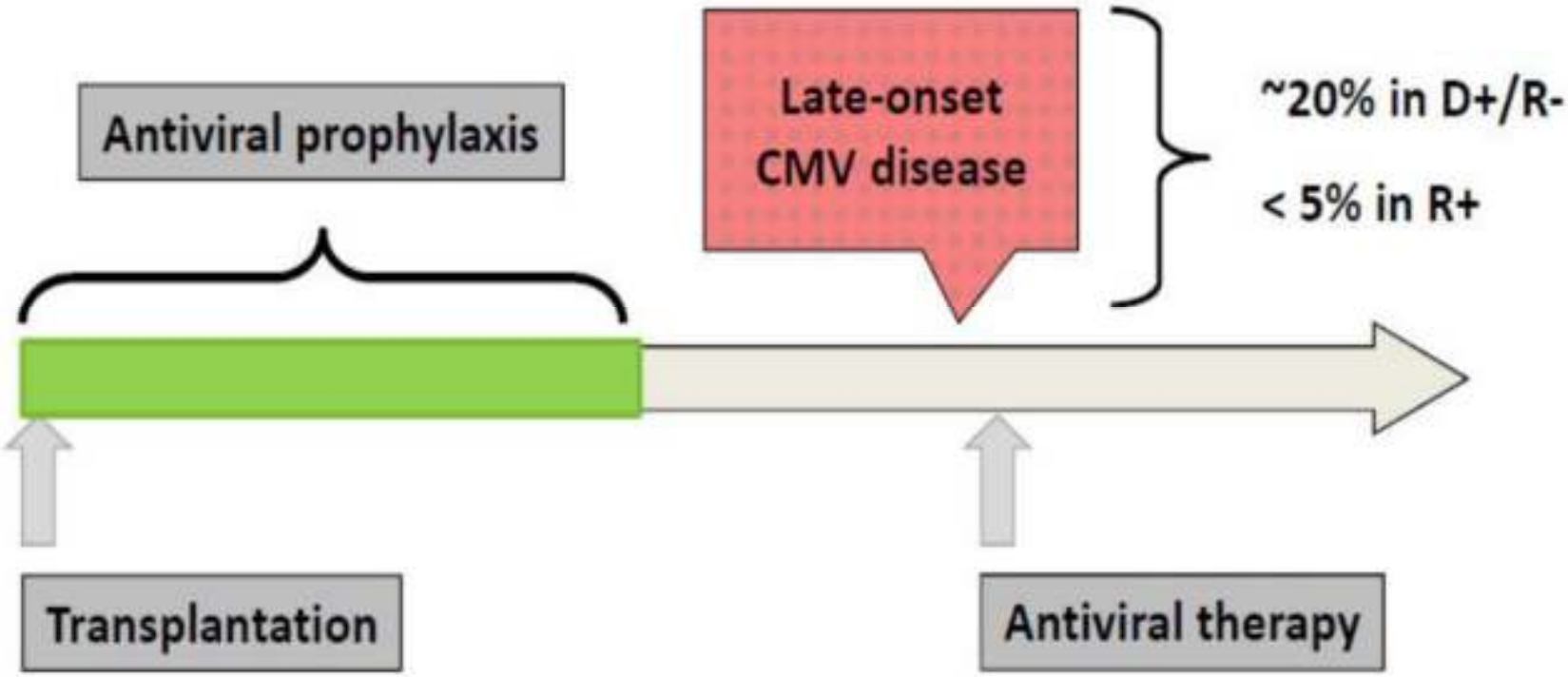
- **CMV seropositive recipient**
  - A CMV **seropositive donor** should be chosen when possible in the setting of unrelated Allo-HSCT with myeloablative conditioning (BII)

- **CMV seropositive recipient undergoing non-T-Cell-Depleted aplo-HSCT with Post Transplant Cyclofosfamide**
  - Either a CMV seropositive or seronegative donor is suitable (BII)

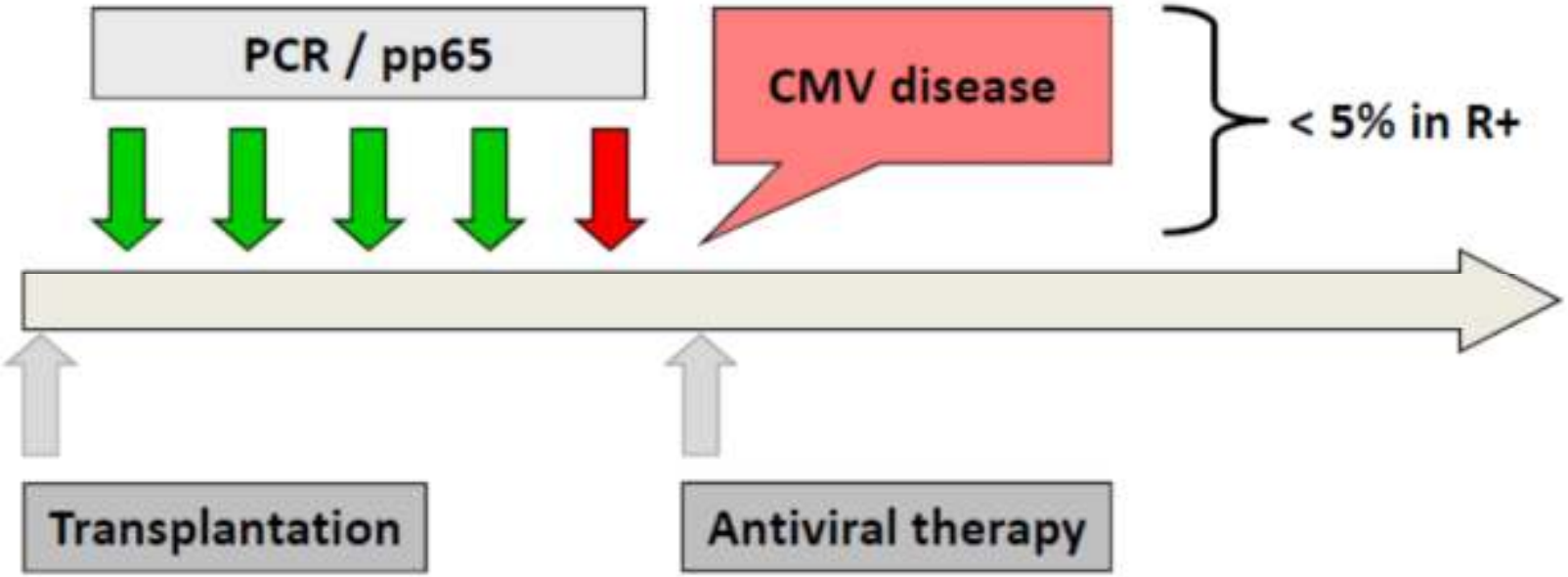
ECIL: CMV UpDate, September 2017

CMV
Στρατηγικές πρόληψης και αποτελεσματικότητα

Στρατηγικές πρόληψης: (1) antiviral prophylaxis



Στρατηγικές πρόληψης: (2) preemptive therapy



Antiviral prophylaxis vs. preemptive therapy

	Prophylaxis	Preemptive Therapy
Description	▪ Antivirals for all pts at risk prior to the onset of CMV infection	▪ Routine monitoring for CMV infection ▪ Treatment **upon detection of asymptomatic CMV infection**
Pros	▪ Can prevent direct and indirect effects ▪ **VL monitoring not required** (if agent is effective) ▪ CMV disease may occur without detectable CMV DNA ▪ protection from infections caused by **other herpes viruses** (HSV, VZV, EBV, HHV-6)	▪ Targets pts at highest risk ▪ **Minimizes overtreatment and toxicity** ▪ May improve CMV-specific immune reconstitution (exposure to low level CMV viremia)
Cons	▪ Potential for **overtreatment/**added cost ▪ Potential for unnecessary exposure to **drug toxicity** (reduced with letermovir; GCV: hematologic; foscarnet: renal) ▪ May delay CMV-specific immune reconstitution	▪ Potential to **miss cases of CMV** disease **not preceded by DNAemia or antigenemia** ▪ Relies on **availability** of CMV testing ▪ Concern for **drug resistance**

Slide credit: clinicaloptions.com

Antiviral prophylaxis vs. preemptive therapy

Σε μεταμόσχευση συμπαγών οργάνων

- meta-analysis of 17 universal prophylaxis trials and 9 preemption trials demonstrated that both prophylaxis strategies were equally effective in reducing the incidence of CMV disease.
- However, **only universal prophylaxis** **affected patient survival** and **reduced graft rejection** and reduced the incidence of **posttransplant opportunistic infections** and **posttransplant lymphoproliferative disorder (PTLD)**
- Prophylaxis **not associated with higher resistance** (one study showed the opposite)
- **Ganciclovir, Valganciclovir**

Σε αλλογενή μεταμόσχευση αιμοποιητικών κυττάρων

- Both approaches have been associated with a survival benefit
- **Preemptive therapy** has been the **preferred strategy** over the past decade
- Which Pre-emptive test??
  - **PP65 limited clinical utility in leucopenic patients**
  - **Quantitative real time PCR** is preferred (higher sensitivity – ECIL 2017)

Σε αυτόλογη μεταμόσχευση αιμοποιητικών κυττάρων

- The risk of CMV infection is 2 to 5 times **lower** than after allogeneic HSCT
- For standard autologous HSCT monitoring and **pre-emptive therapy not recommended**
- **High-risk autologous HSCT pts** such as pts with autoimmune disease with CD34 selection or receiving ATG may benefit from **pre-emptive strategy**

CMV αντιϊκοί παράγοντες

FDA-Approved Agents			
Agent	**MoA**	**Dosing**	**Considerations**
Ganciclovir* Valganciclovir*	▪ Target CMV polymerase	IV Oral	▪ Recommended for **first-line preemptive** therapy
Foscarnet* Cidofovir*	▪ Target CMV polymerase	IV IV	▪ Recommended when ganciclovir/valganciclovir **resistance/intolerance**
Val/acyclovir	▪ Target CMV polymerase	IV/oral	▪ Limited activity against CMV disease
Letermovir	▪ CMV UL56-binding agent	oral	▪ **Approved for CMV prophylaxis**
Late-Phase Investigational Agents/Approaches			
Brincidofovir	▪ Lipid conjugate of cidofovir	Oral	▪ Phase III studies
Maribavir	▪ CMV UL97-binding agent	Oral	▪ Phase III studies
CMV CTLs	▪ Varied	IV	▪ Phase II/III studies
CMV vaccines	▪ Varied	IV	▪ Phase II/III studies

clinicaloptions.com

CMV prophylaxis

Prophylaxis in Solid Organ Transplantation

- **Primary Regimens:** Valganciclovir 900 mg po x1
- **Alternative:** Letermovir 480 mg IV/po x1 or 240 mg if on cyclosporine
  Ganciclovir 5 mg/kg x1
  Valacyclovir 2gm x4 (kidney only)

Drug	D+/R-	R+	D-/R-
Kidney	6 moths	3 months	No
Pancreas and Kidney/pancreas	3-6 months	3 months	No
Liver	3-6 months	3 months	No
Heart	3-6 months	3 months	No
Lung and Heart/lung	≥12 months	6-12 months	No
Small intestine	3-6 months	3-6 months	No

Am J Transplantation 2010;10:1228, Ann Intern Med 2010;152:761

Prophylaxis in allogenic HSCT - grading

Drug	Grading	References	Comment
Letermovir	**AI (provisional)**	Ljungman, EBMT 2017	
Valaciclovir	BI	Ljungman, Blood 2002 Winston, CID2003 Milano, Blood 2011	Association with preemptive strategy
Ganciclovir / valganciclovir	CI CII	Winston, Ann Intern Med 1993 Goodrich, Ann Intern Med 1993 Montesinos BBMT 2009	 Cord blood HSCT
Aciclovir	CI	Prentice, Lancet 1994 Milano, Blood 2011	Less efficient than valaciclovir
Foscarnet	DII	Ordemann, Ann Hematol 2000 Bregante, BMT 2000	
Ig	DI	Cordonnier, Ann Intern Med 2003 Winston, BMT 2003	
Specific anti CMV Ig	DI	Zikos, Hematologica 1998 Raanani, JCO 2009	
CMV vaccines	No recommendation		In development

ECIL 7, 2017

Letermovir FDA Approved for CMV Prophylaxis

- **Letermovir:** inhibits **CMV terminase complex via UL56 binding**; terminase complex important in CMV DNA cleavage and packaging
- **Indication: prophylaxis** of CMV infection and disease in adult **CMV-seropositive recipients** of an **allo- HCT (not active against HSV or VZV → other agent)**

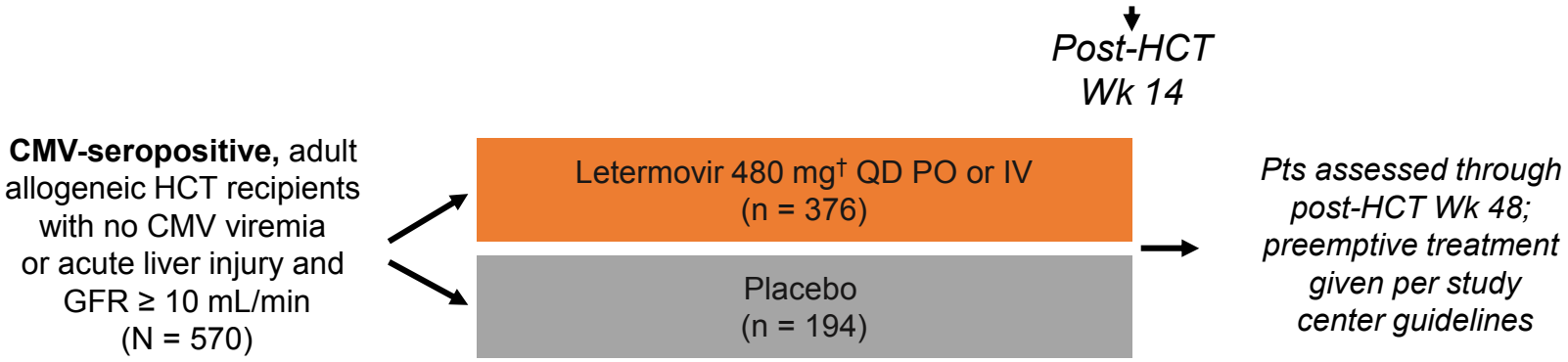
Section	Recommendation
Dosing	▪ Forms: tablet or injection ▪ 480 mg QD (1 tablet PO or IV infusion over 1 hr) ▪ **Initiate between Days 0 and 28 post transplantation (before or after engraftment); continue through Day 100 post transplantation**
Dose adjustments	▪ If coadministered with **cyclosporine, reduce letermovir to 240 mg QD**
Contraindications	▪ Pimozide ▪ Ergot alkaloids ▪ Pitavastatin/simvastatin (coadministered with cyclosporine)
Monitoring for CMV reactivation	▪ Recommended following completion of prophylaxis

- **Letermovir was safe, without any signs of hematologic, liver, or renal toxicity even when administered pre-engraftment**
- this **lack of toxicity** was predicted, as the target of letermovir (CMV terminase) does not have any human analogue

Slide credit: clinicaloptions.com

MK-8228-001: Letermovir for Post-HCT CMV Prophylaxis

- Randomized, multicenter, double-blind, placebo-controlled phase III trial[1]
  - **Letermovir:** inhibits CMV terminase complex via UL56 binding; terminase complex important in CMV DNA cleavage and packaging
  - randomized 2:1 to receive either oral or intravenously administered letermovir at a dose of 480 mg vs placebo through Week 14 after stem cell transplant
  - begin treatment before post-HCT Day 28.
  - **Primary endpoint:** pts with clinically significant CMV infection (**CMV disease or a CMV viremia—requiring preemptive therapy**) through post-HCT Wk 24



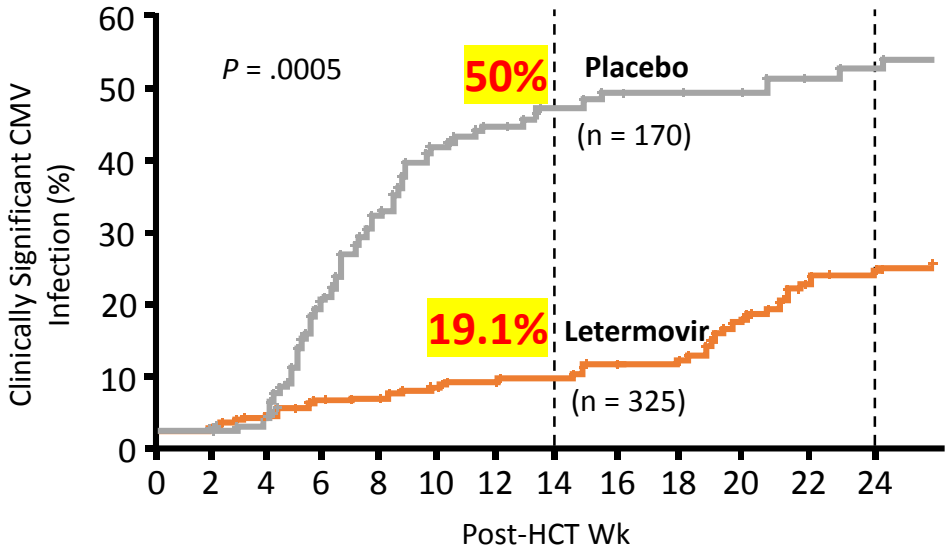
Marty FM, et al. BMT Tandem 2017. Abstract LBA2.

Slide credit: clinicaloptions.com

MK-8228-001: Clinically Significant CMV Infection and Mortality Through Wk 24

FAILURES

Clinically Significant CMV Infection, Full Analysis Set



Outcome at Wk 24,* %	Letermovir (n = 325)	Placebo (n = 170)
Failure of therapy	37.5	60.6
Clinically significant CMV	17.5†	41.8
▪ Started preemptive therapy	16.0	37.6
▪ CMV diagnosis	1.5	1.8
All-cause mortality	9.8‡	15.9
Nonrelapse mortality	6.5	10.6

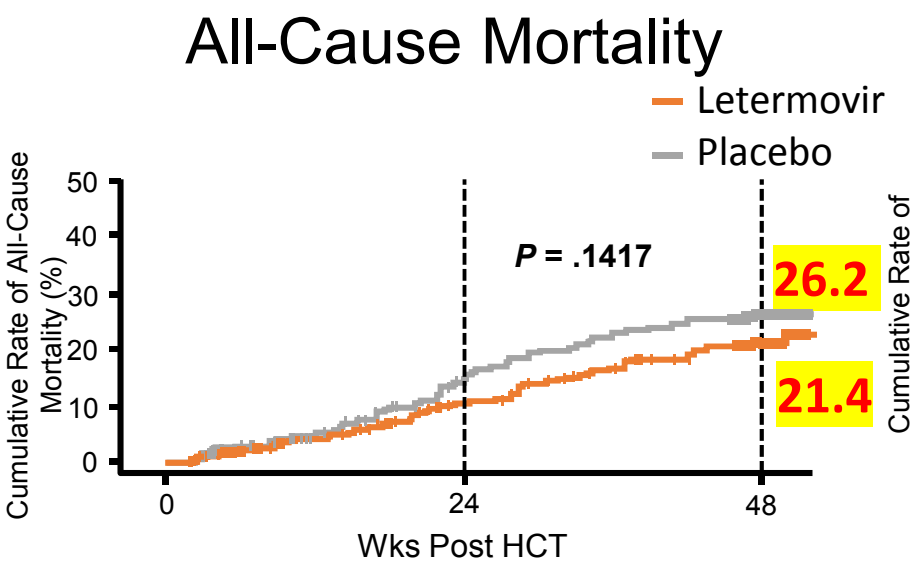
*Full analysis set. †Adjusted treatment difference: -23.5% (95% CI: -32.5% to -14.6%; $P < .0001$). ‡$P = .0317$ vs placebo.

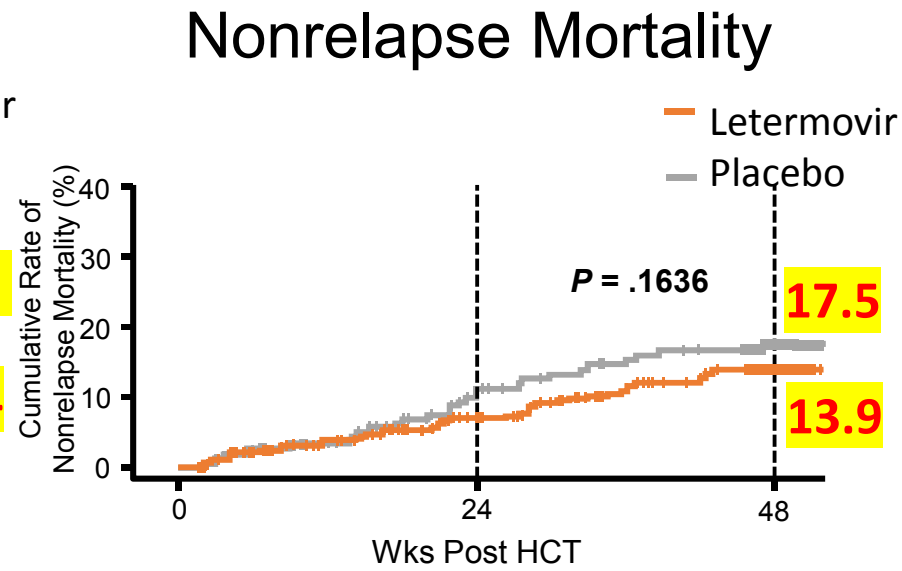
- Failure of therapy at Wk 14 (end of treatment): letermovir, 19.1%; placebo, 50% ($P < .0001$)

Marty FM, et al. BMT Tandem 2017. Abstract LBA2.

Slide credit: clinicaloptions.com

MK-8228-001: Mortality Through Wk 48





Deaths, n/N (%)	Letermovir (n = 373)	Placebo (n = 192)
Pts with clinically significant CMV infection	14/79 (17.7)	26/88 (29.5)
Pts without clinically significant CMV infection	58/294 (19.7)	19/104 (18.3)

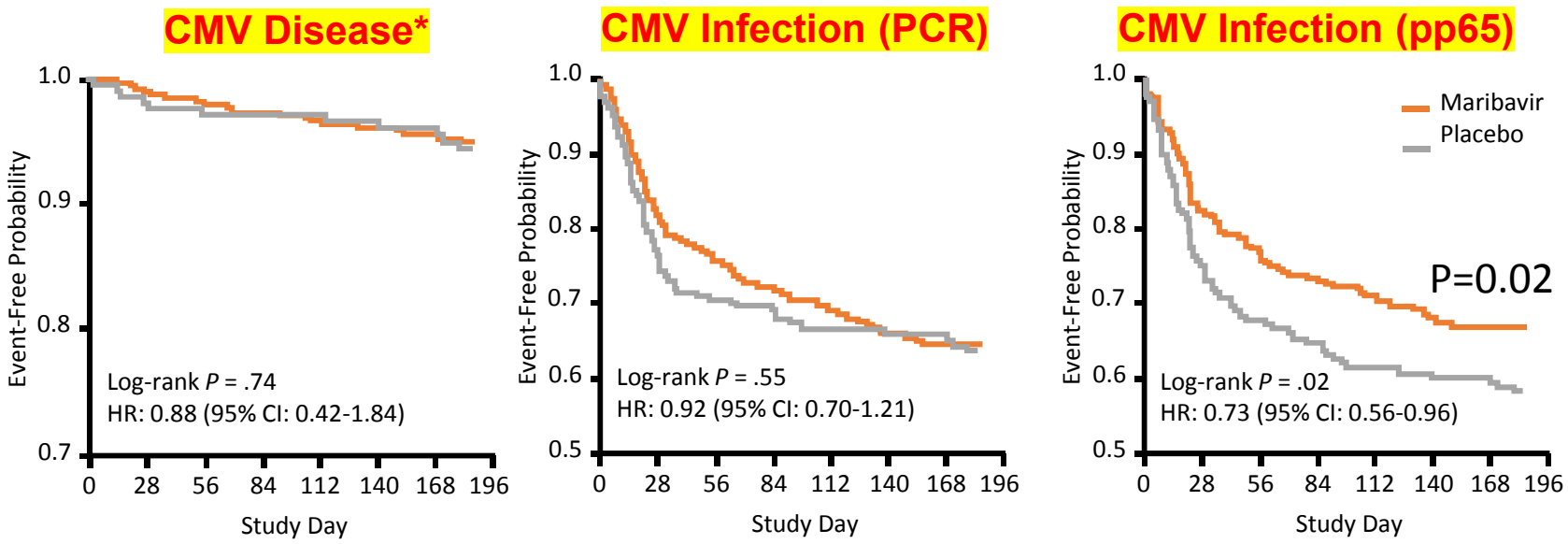
Maertens J, et al. IDWeek 2017. Abstract 1029.

Slide credit: clinicaloptions.com

Maribavir for CMV Prophylaxis: failed

Maribavir: binds **CMV kinase UL97**, inhibiting viral encapsidation and cell exit

Randomized, double-blind phase III trial of **maribavir 100 mg PO BID** prophylaxis vs placebo for allogeneic HCT pts (recipient or donor CMV seropositive) (N = 681)



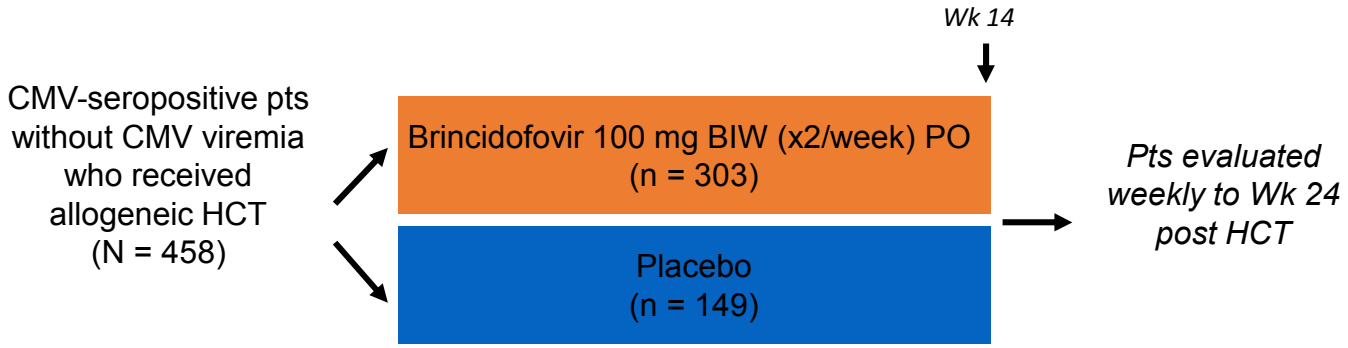
Comment: too low dose for maribavir to prevent toxicities like dysgeusia

Marty FM, et al. Lancet Infect Dis. 2011;11:284-292.

Slide credit: clinicaloptions.com

Brincidofovir for CMV Prophylaxis: SUPPRESS

- Randomized, double-blind, placebo-controlled phase III trial
  - Brincidofovir (CMX001): **lipid conjugate of cidofovir** (viral DNA polymerase inhibitor); active **against herpes viruses, adenovirus, and BK polyomavirus**
  - **x 400 more potent** than cidofovir in vitro against CMV
  - unlike cidofovir, brincidofovir is not concentrated in the renal proximal tubules and is therefore **not nephrotoxic**
  - Primary endpoint: **prevention of clinically significant CMV infection (viremia)* at Wk 24**



- Protocol included a symptom-driven diarrhea management plan

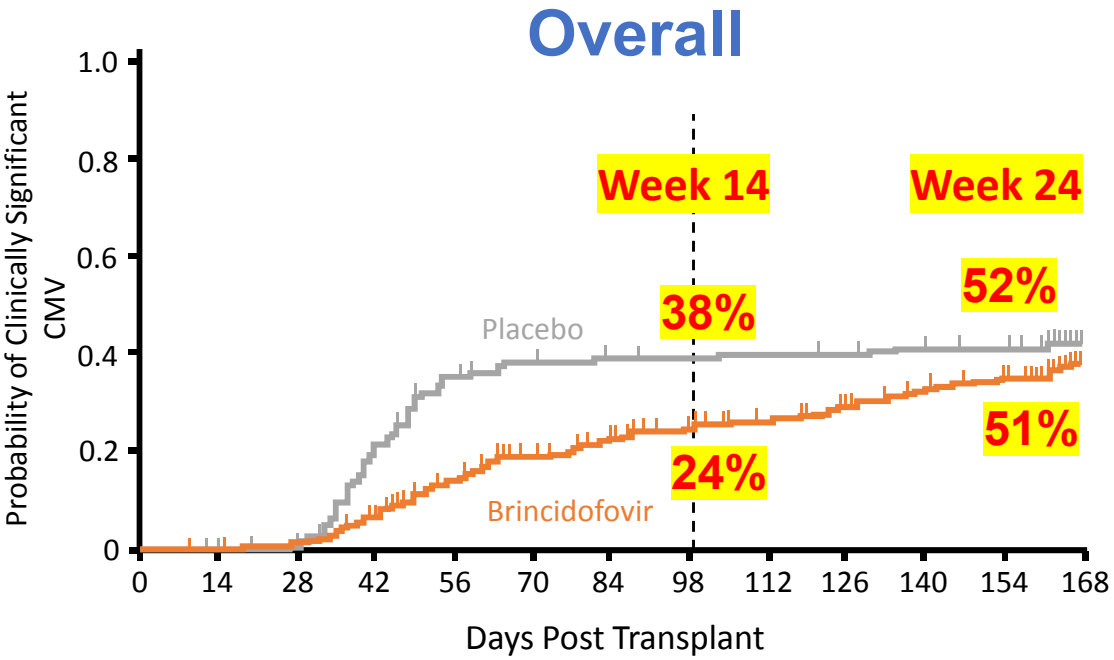
*Onset of CMV disease, initiation of preemptive CMV treatment due to viremia, or missing data at Wk 24.

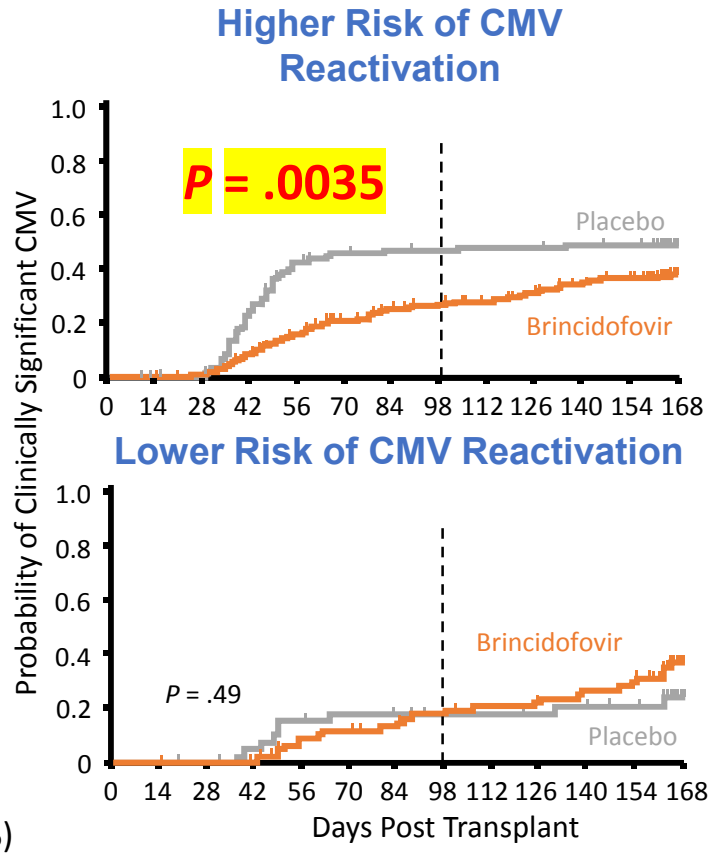
Marty FM, et al. BMT Tandem 2016. Abstract 5. ClinicalTrials.gov. NCT01769170.

Slide credit: clinicaloptions.com

SUPPRESS: Time to Clinically Significant CMV Infection

- 24% of brincidofovir compared to 38% of placebo patients had CMV reactivation
- By Week 24, the difference were not different
- Significant **benefit in high-risk pts:** receiving T-cell–depleted transplants, those who have had ATG or alemtuzumab, a cord or haplo-cord stem cell transplant, a MUD or a mismatched related donor, or those patients getting more than 1 mg/kg of prednisone for acute GVHD





*P = .002. †Trial did not meet primary endpoint.

- Wk 24 mortality numerically increased with BCV (15%) vs PBO (10%)

Marty FM, et al. BMT Tandem 2016. Abstract 5.

Slide credit: clinicaloptions.com

CMV preemptive

CMV antivirals for preemptive therapy

1ης γραμμής

Ganciclovir (AI)

- 5 mg/kg x2 x 2weeks -> 5mg/kg/d
- Για CMV / EBV (10X potency of acyclovir)
- Μυελοτοξικότητα, ουδετεροπενία, νεφρική ανεπάρκεια

Foscarnet (AI)

- 60 mg/ g x 2 x2 weeks -> 90 mg/kg/d
- CMV ανθεκτικό σε ganciclovir, HSV ανθεκτικού σε Acyclovir
- Νεφρική ανεπάρκεια, υπασβεστιαιμία, έμετοι, σπασμοί
- Καλή ενυδάτωση

Εναλλακτικά

Valganciclovir (AII)

900 mg x 2 x 2 weeks -> maintenance??

Φάσμα και ανεπιθύμητες ενέργειες όπως Ganciclovir

2ης ή 3ης γραμμής

Cidofovir 3-5 mg / kg ανά εβδομάδα x 2 → ανά 2η εβδομάδα

- Ερπητοιοί, αδενοιοί, Polyoma-viruses, Papilloma-viruses
- Νεφροτοξικότητα, μεταβολική οξέωση, ουδετεροπενία
- Προβενεσίδη 2 γρ 3 ώρες πριν και 1 γρ σε 2 και 8 ώρες μετά

ECIL 7, 2017

Preemptive therapy monitoring and threshold for initiation in HSCT

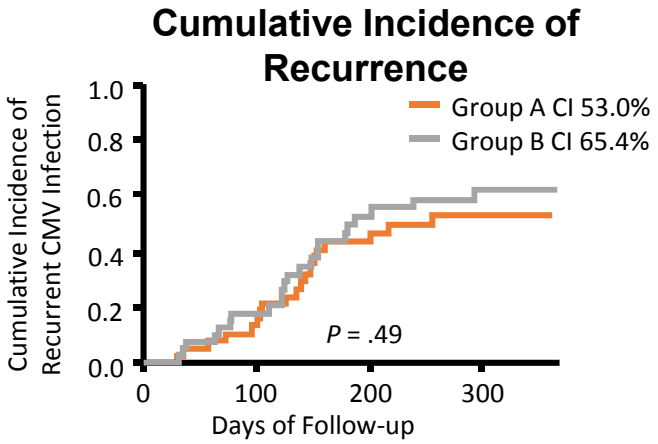
Site-Specific Recommendations	
Monitoring frequency	▪ **Early after transplant:** variably monitored 1-3 times/wk ▪ **After 30 days:** monitoring frequency reduced to 1-2 times/wk ▪ **After 100 days:** monitoring frequency reduced to every wk-every other wk ▪ **Additional:** routinely monitor pts with previous CMV reactivation, pts who present for an active acute illness or CMV syndrome, or pts who have an unexpected drop in WBC count
Threshold for PET initiation	▪ **High-risk pts** • CMV DNA > 150 IU/mL ▪ **Lower-risk pts** • CMV DNA > 500 IU/mL

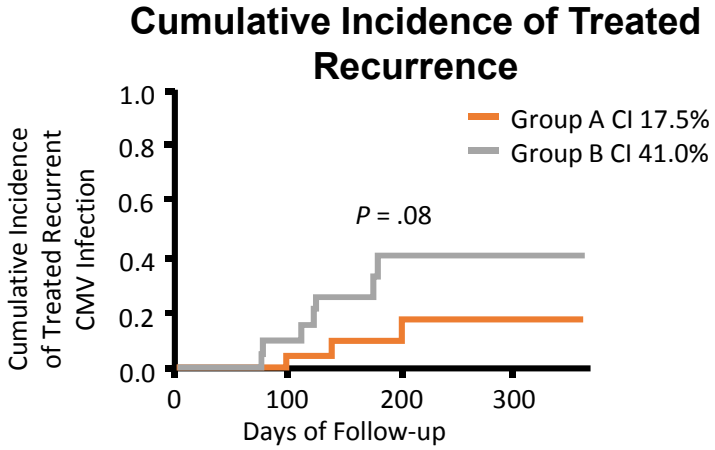
Slide credit: clinicaloptions.com

CMV Preemptive Therapy: when to stop??

- ✓ little data to support optimal time to stop CMV-specific antiviral therapy
- ✓ few randomized studies evaluating the optimal time for discontinuation
- ✓ **it is common practice to treat patients until they have 1, 2, or even 3 negative follow-up viral loads**

- **Single-center, prospective, nonrandomized study** assessing the impact of length of primary preemptive CMV therapy on incidence of recurrence in allogeneic HCT recipients
  - Group A (prospective cohort): consecutive pts who had detectable CMV DNA; preemptive therapy initiated* and d/c **after 1 negative CMV DNA PCR result** (< 31 IU/mL) (n = 38)
  - Group B (historical cohort): pts who had detectable CMV DNA; preemptive therapy initiated† and **d/c after 2 negative CMV DNA PCR results** (n = 40)





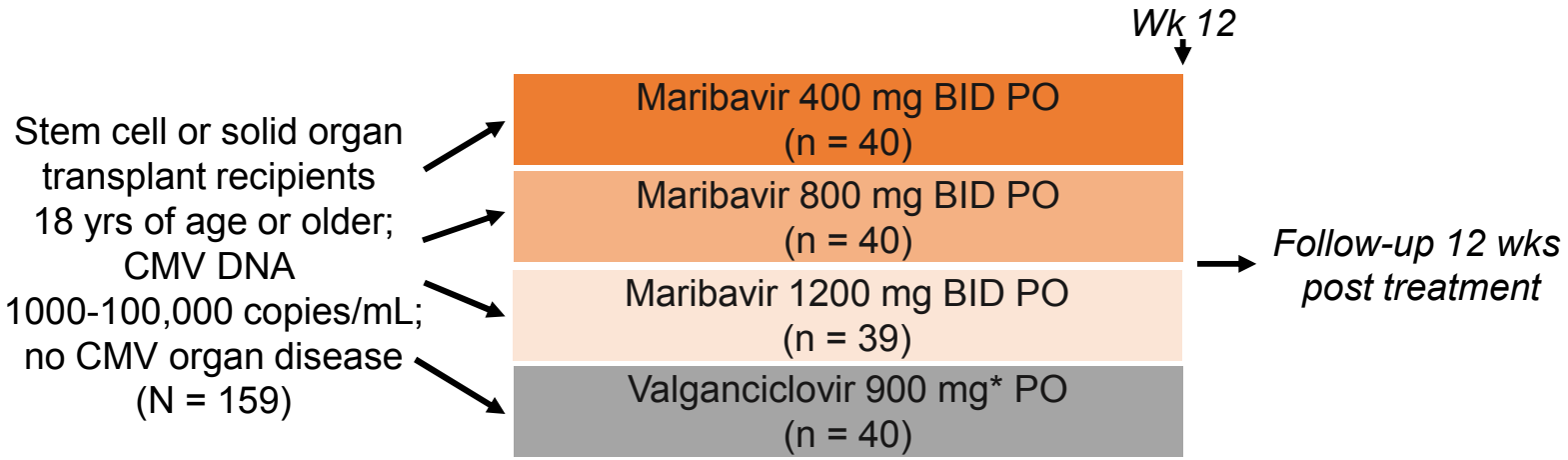
*When CMV DNA > 1500 IU/mL OR when CMV DNA doubling time of ≤ 2 days. †When CMV DNA > 1000 IU/mL.

Solano C, et al. Bone Marrow Transplant. 2017;52:1448-1451.

Slide credit: clinicaloptions.com

Maribavir for Primary Preemptive CMV Treatment in Stem Cell or Solid Organ Transplant Pts

- Randomized, multicenter, dose-ranging, active-controlled phase II study
- 52% of pts received stem cell transplant
- **Primary endpoint**: undetectable plasma CMV DNA (< 200 copies/mL) within 3 or 6 wks of treatment



Pts receiving maribavir knew they were receiving this drug but we blinded to dose; valganciclovir treatment open label.
*BID Wks 1-3, then QD; adjusted for renal function.

Maertens JA, et al. BMT Tandem 2017. Abstract 229.

Slide credit: clinicaloptions.com

Maribavir for Primary Preemptive CMV Treatment in Stem Cell or Solid Organ Transplant Pts

- **comparable rates** of patients in the maribavir and valganciclovir groups achieved **undetectable CMV DNA within 6 weeks** (65% to 83%)
- **Recurrence** occurred in numerous patients: 12.9% to 30.3% of those receiving maribavir vs 17.9% of those receiving valganciclovir
- Dysgeusia and gi toxicities

Outcome	Maribavir 400 mg (n = 40)	Maribavir 800 mg (n = 40)	Maribavir 1200 mg (n = 39)	Maribavir All Doses (n = 119)	VGC (n = 40)
Undetectable CMV DNA within 3 wks, %	65	58	59	61	55
▪ ***P* value vs VGC**	.28	.72	.64	.41	--
Undetectable CMV DNA within 6 wks, %	78	83	72	78	65
▪ ***P* value vs VGC**	.17	.06	.45	.08	--
CMV recurrence during study period, % (n/N)*	30 (10/33)	24 (8/34)	13 (4/31)	22 (22/98)	18 (5/28)
Discontinuation for AEs, %†	30/13	13/10	26/18	23/13	13/10
Serious TEAEs, %†	40/8	43/3	49/21	44/10	33/3
GI TEAEs, %	NR	NR	NR	20-23	10-15
TE dysgeusia, %	NR	NR	NR	40	3
TE neutropenia, %	NR	NR	NR	5	18

CMV Vaccines: Considerations and Strategies

- For HCT immunogenicity must **overcome immunosuppression** (previous chemotherapy, conditioning, GVHD, immunosuppressive agents)
- Must **impart both B-cell and T-cell immunity**; T-cell immunity may be most important
- Several strategies currently in development

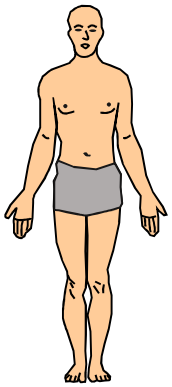
Vaccine Type	Antigen	Phase
DNA (plasmid)	pp65, gB	I-III
Vectored	pp65, gB, UL123/IE1-exon 4, UL122/IE2-exon 5	I/II
Attenuated and DISC	Vectored	I
Recombinant/subunit	gB	I/II
Peptide	pp65, T-cell fused to tetanus epitope or PADRE	I/II

CMV vaccines are in development but no recommendations can currently be made

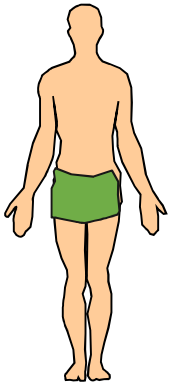
Chaer FE, et al. Blood. 2016;128:2624-2636. Schleiss MR. J Virus Eradication. 2016;2:198-207. Boeckh M, Gilbert PB. Lancet Haematol. 2016;3:e58-e59. Kharfan-Dabaja MA, et al. Lancet Infect Dis. 2012;12:290-299. Kharfan-Dabaja MA, et al. Lancet Infect Dis. 2012;12:257-259.

Slide credit: clinicaloptions.com

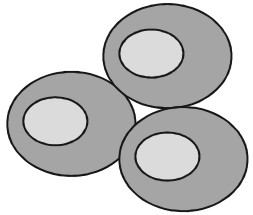
Adoptive CMV-directed T-Cell Therapy as prophylactic strategy



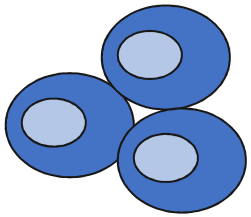
- T-cells from the blood of a CMV-seropositive stem cell donor are purified and made specific for CMV viral antigens, **such as pp65**. They are then reinfused back into the HCT patient.
- Efficacy/safety not examined in randomised trials



Blood drawn from HCT donor



T-cells harvested



CMV-specific T-cells generated/banked

CMV-specific T-cells infused into HCT recipient

Slide credit: clinicaloptions.com

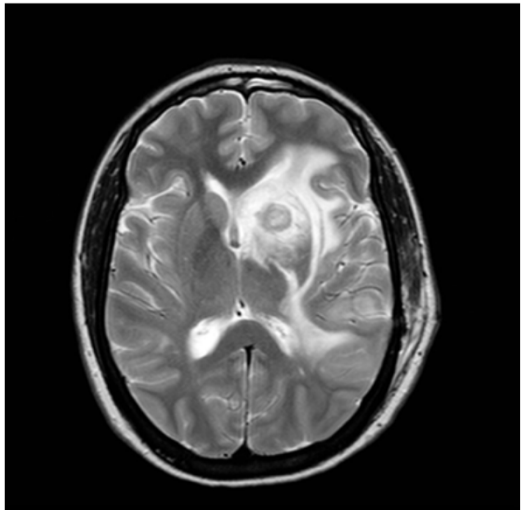
Άλλες Ιογενείς λοιμώξεις: Πρόληψη??

EBV and Post Transplant Lymphoproliferative Disease

EBV infection

in HCT recipients is **very common**

- 100% in the EBV seronegative recipient who receives a seropositive BM
- the incidence of disease is rather low
- The **median time to onset is <u>3 -5 months</u>**



PTLD

- **Ευκαιριακοί όγκοι** λόγω **Τ-κυτταρικής ανοσοκαταστολής → πολ/σμος Β-λεμφοκυττάρων μολυσμένα με τον EBV (of donor)** με υψηλή έκφραση latent γονιδίων, αρχικά πολυκλωνική έκφραση → μονοκλωνική
- The **incidence of PTLD** varies from
  - **<1 % of matched** related allogeneic HCT recipients
  - **18 percent among high-risk** patients
- Καλή ανταπόκριση στο Rituximab

<u>Prevention??</u>

- Primary or secondary prophylactic use of antiviral agents is not effective against EBV and therefore **not recommended** (DII)

- Close EBV viral load monitoring and rituximab application can be considered as a **preemptive therapeutic approach** for the prevention of EBV-associated PTLD after allo-HCT **in special high-risk patients (CIII): selective T-cell depletion graft, HLA mismatched, alemtuzumab, ATG in conditioning**

Other viruses

HHV-6

- **reactivation in 40 - 60 %** of HCT recipients
- Usually **three weeks** after transplantation
- typically **not associated with disease manifestations (<1 %)**
- The most significant manifestation of HHV-6 is encephalitis
- **Prophylaxis not recommended**
- Prophylaxis with Acyclovir not active → Ganciclovir, foscarnet , cidofovir (toxicity)

Polyoma Viruses (JC and BK)

- 60-80% of humans infected in childhood
- JC causes PML (υποξεία μηνιγγοεγκεφαλίτιδα και εστιακή εκφύλιση της λευκής ουσίας, ενώ ο εγκεφαλικός φλοιός δεν προσβάλλετα
- BK → hemorrhagic cystitis (Decoy cells in Urine), nephropathy (in renal transplantation)
- **Prophylaxis not recommended**
- Treatment (?) cidofovir, mirtazapine, mefloquine, decrease immunosuppression

Community-Acquired Respiratory Virus Infections

- Community-acquired respiratory viruses have a significant impact on the morbidity and mortality of the haematological patient

Spectrum of diseases

- self-limited upper respiratory tract illnesses
- life-threatening lower respiratory tract infection
- disseminated disease

Community-Acquired Respiratory Virus Infections: emerging pathogens

- 175 HSCT patients, Korea, 2007 to 2010.
- Viruses: 89 clinical episodes in 58 patients:

- Rhinovirus 25 (28.1%)
- RSV 23 (25.8%)
- PIV-3 16 (18.0%)
- Adenovirus 12 (13.5%)
- hCoV 10 (11.2%)
- hMPV

Duration of viral shedding in HSCT

Duration	Infection
up to 4 months	influenza
up to 2 years	adenovirus
up to 22 days	RSV

Choi JH, et al. J Korean Med Sci 2013; 28: 36-41

Respiratory Syncytial virus (RSV)

- Major cause of morbidity in neonates and infants
- In adults accounts for 10.6% of hospitalizations for pneumonia and 11.4% for COPD exacerbations

- In **HSCT pts** progresses to lower respiratory tract infection in 17% to 84%
- **respiratory failure**, ICU admission
- RSV-associated **mortality: 7% to 83%**

Risk factors for progression to LRI

- GVHD
- pre-engraftment or early post-transplant status
- lymphopenia
- greater age
- transplant from a mismatched, unrelated donor

J Antimicrob Chemother 68(8): 1872–1880, 2013
NEJM 352:1747, 2005

RSV prevention

Chemoprophylaxis in susceptible patients may be **considered, in outbreak situations**

- Intravenous polyclonal **immunoglobulins**
- Intravenous RSV immunoglobulin (RSV-IVIG)
- **Palivizumab** (PVZ) (in high risk infants born ≤29 weeks): monoclonal antibody against F glycoproptein on surface of virus
  IM, once monthly, 15 mg/kg → November-April
- **Motavizumab**

- Currently, there is no commercially available vaccine for RSV infection
- Treatment with systemic and /or **aerolized ribavirin (high cost)**
- New antiviral **Lumicitabine in phase II trial**

J Antimicrob Chemother 68(8): 1872–1880, 2013
NEJM 352:1747, 2005

Adenoviruses in HSCT

- **Primary Infection**
  Case reports document **fatal primary infection**

- **Re-infection**
  Nosocomial transmission documented
  Altered susceptibility to re-infection?

- **Reactivation**
  Reactivation has been implicated in the majority of disease

Species	Tissue tropism	Serotypes
A	Gastrointestinal tract	12, 18, 31
B	Urinary tract, lung	3, 7, 11, 14, 16, 21, 34, 35, 50
C	Respiratory tract	1, 2, 5, 6
D	Eye, gastrointestinal tract	8-10, 13, 15, 17, 19, 20 22-30, 32, 33, 36-39, 42-49, 51
E	Respiratory tract	4
F	Gastrointestinal tract	40,41
	Immunocompromised adults	5, 11, 34 & 35

Adenoviruses in HSCT

- Adenovirus infections common in HSCT (5-29% but underestimated)
- Higher incidence in children and earlier diagnosis (<30 d vs. > 90 d)
- 40% of infected → disease
- **Mortality rates up to 60%**

- Risk factors for infection:
  - younger age
  - total body irradiation
  - adenovirus positive donor
  - use of Campath or ATG
  - matched unrelated donor or mismatched donor

Chakrabarti S, et al. Blood 2002;100:1619-27
Clin Infect Dis 43:331, 2006

Prevention of Adenovirus infection in HSCT

- Available antiviral treatment options have a **considerable toxicity**, which makes important to identify patients at risk of AdV disease

- Rapidly **increasing or sustained adenoviremia** **associated with the occurrence of severe disease** both in children and in adults

Preemptive strategy

- Weekly quantitative PCRs
  - AdV
  - CMV
  - EBV
  - HHV-6

Contact and droplet precautions to prevent nosocomial transmission → prolonged shedding

Pre-emptive treatment based on post-transplant surveillance:

- Reduction of immunosuppression if possible
- Antiviral therapy
  - **Cidofovir** 1 mg/kg x 3 weekly (with hydration and provenecid)
  - **Brincidofovir** has shown good activity in phase II study of HSCT pts with adenovirus viremia
  - **Adenovirus specific T cells** (Cytovir) under development

Community-Acquired Respiratory Virus Infections - Prevention

Strict **infection control** precautions:

- **Respiratory isolation** of infected patients
- **Hand-washing** before and after contact with patients
- Educational efforts targeting
  - healthcare workers
  - family members

- HCWs and visitors with URI symptoms should be restricted from contact with HSCT recipients and candidates under-going conditioning therapy (AIII).
- Visitors with URI symptoms should be asked to defer their visit to the HSCT center until their URI symptoms resolve (BIII).
- All HCWs with URI symptoms should be restricted from patient contact and reassigned to non-patient care duties until their symptoms resolve (BIII).

Ann Hematol (2016) 95:1435–1455

Influenza prevention (chemoprophylaxis)

Who??

- **consider** antiviral chemoprophylaxis for the duration of the **influenza season** for adults and children aged ≥3 months who are at **very high risk of developing complications** from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (eg, persons who are **severely immunocompromised**) ***(C-II)***
- **consider** antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥3 months who have the highest risk of influenza-associated complications, such as **recipients of hematopoietic stem cell transplant** in the **first 6–12 months posttransplant** and **lung transplant recipients** ***(B-II)***

How – duration??

- Administer preexposure antiviral chemoprophylaxis for adults at risk (HSCT) for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, **as soon as influenza activity is detected in the community and continued for the duration of community influenza activity** ***(A-II)***

- Clinicians should test for influenza and **switch to antiviral treatment** dosing in persons receiving preexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated *(A-II)*

IDSA Influenza Guidelines Updated 2018

Άλλες ομάδες ανοσοκατασταλμένων ασθενών

Προφύλαξη ιογενών λοιμώξεων σε ασθενείς με αιματολογικές κακοήθειες ή συμπαγείς όγκος υπό ΧΜΘ

Prophylaxis against	Conventionally dosed chemotherapy	Severely immunosuppressive chemo-immunotherapy	
		Purine analogs (Fludara)	**Alemtuzumab**
Influenza	Pre-seasonal vaccination	Pre-seasonal vaccination	
CMV	No prophylaxis	No prophylaxis (AII)	No prophylaxis (BII)
HSV / VZV	No prophylaxis	Acyclovir 400x3 or Valacyclovir 500x2-3	

<u>If additional risk factors:</u>
a. Second-line chemotherapy
b. Treatment with corticosteroids
c. CD4 cell count <50/ll
d. Age >65 years
e. Prolonged grade III or IV neutropenia

Annals of Oncology 17: 1051–1059, 2006

Γενικές αρχές εμβολιασμών στον αιματο-ογκολογικό ασθενή υπό ΧΜΘ

- ✓ Προτιμότερη η χορήγηση ενδεικνυόμενων εμβολιασμών πριν την προγραμματισμένη ανοσοκατασταλτική θεραπεία, ΑΚΘ ή σπληνεκτομή εάν είναι δυνατόν (> 2 εβδομάδες για αδρανοποιημένα , > 4 εβδομάδες για ζώντα εξασθενημένα)
- ✓ Τα αδρανοποιημένα εμβόλια πρέπει να χορηγούνται 3 μήνες τουλάχιστον μετά την ολοκλήρωση της ΧΜΘ και 6 μήνες τουλάχιστον μετά χορήγηση μονοκλωνικών αντισωμάτων έναντι Β ή Τ- κυττάρων (rituximab, alemtuzumab)

- ✓ Το αδρανοποιημένο εμβόλιο της γρίπης χορηγείται ακόμη και σε περίοδο ΧΜΘ
- ✓ Εμβολιασμός έναντι γρίπης των οικείων
- ✓ Εμβολιασμός κατά τη διάρκεια ΧΜΘ έχει **μικρότερα αποτελέσματα σε αιματολογικούς ασθενείς (19-27% σε Π.Μ.), έναντι ασθενών με συμπαγείς όγκους (78% σε Ca πνεύμονα ή μαστού)**

Annals of Oncology 17: 1051–1059, 2006

CMV prophylaxis in pts receiving Alemtuzumab

Alemtuzumab (Campath): anti CD52, lymphocyte(T and B cell) depleting agent indicated in **Chronic Leucocytic Leukemia**

- A **CMV management strategy** must be put in place in pts receiving alemtuzumab for hematologic malignancies (BIII)
- Monitor and antiviral treatment in pts having a positive test for CMV and compatible symptoms is one management option (BII)
- **Regular monitoring with PP65 or PCR is recommended during the period of maximum immunosuppression (during treatment and until 2 months after end) (BII)**
- **Treating asymptomatic pts is not obligatory** but **careful clinical observation** of pts with documented CMV reactivation is necessary (BII)
- **Withholding alemtuzumab is not considered necessary**, unless there are persisting symptoms (BII)

ECIL 7, 2017

Προφύλαξη ιογενών λοιμώξεων σε ασθενείς που λαμβάνουν αναστολείς κινασών (αιματολογικοί)

- **Αναστολείς bcr-abl τυροσινικής κινάσης** –→ θεραπεία ΧΜΛ- ΟΛΛ (***Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib***)

- **Αναστολείς BRAF and MEK kinase**: → All agents: unresectable or metastatic melanoma, Dabrafenib, trametinib: NSCLC, Selumetinib: thyroid carcinoma *(**vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib and encorafenib**)*

- **Αναστολείς Janus- κινάσης** → θεραπεία μυελοΐνωσης - πολυερυθραιμίας - (cGVHD) (***Ruxolitinib, Pacritinib, Momelotinib***)

- **Αναστολείς τυροσινικής κινάσης Bruton's** –→ θεραπεία ΧΛΛ-Λεμφώματος μανδύα- Μακροσφαιριναιμίας Waldenström's *(**Ibrutinib**)*

- **Αναστολείς φωσφατιδυλο-ινοσιτόλη-3-κινάσης δέλτα (PI3kδ)** → θεραπεία ΧΛΛ, οζώδους λεμφώματος *(**Idelalisib**)*

Μηχανισμοί ανοσοανεπάρκειας σε θεραπεία με αναστολείς κινασών

- Λευκοπενία-ουδετεροπενία
- Αναστολή πολλ/σμού CD4+-CD8+ Τ-λεμφοκυττάρων (Imatinib)
- Αναστολή πολλ/σμού και δραστικότητας Τ-λεμφοκυττάρων (Nilotinib-Dasatinib)
- Επίδραση και στην χυμική ανοσία, μέσω αναστολής κινασών απαραίτητων για την ενεργοποίηση των Β-λεμφοκυττάρων
- Όσο ευρύτερη η γκάμα των off-target κινασών που αναστέλλονται, τόσο σημαντικότερη η επίδραση στην ανοσία (Dasatinib: ο ισχυρότερος αναστολέας)

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journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

Table 2
Summary of infection risks and suggested recommendations and management strategies

Agent	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	Modest	IFI, HZ, tuberculosis, CMV (particularly with dasatinib)	No	Yes
Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib selumetinib,	None	No	No	No
Ibrutinib, acalabrutinib	Modest	PCP, IFI, PML	Yes (particularly in presence of additional risk factors)	No
Idelalisib, buparlisib, rigosertib, duvelisib	Major	IFI, PCP, CMV	Yes	No
Venetoclax	None	No	No	No
Ruxolitinib, tofacitinib, baricitinib	Major	PCP, HZ, tuberculosis, CMV EBV, PML	Yes (particularly in presence of additional risk factors)	Yes
Sirolimus, everolimus temsirolimus,	Major	HZ, tuberculosis	No	Yes

Πρόληψη ιογενών λοιμώξεων σε ασθενείς που λαμβάνουν αναστολείς κινασών

- **Αναστολείς bcr-abl τυροσινικής κινάσης** → θεραπεία ΧΜΛ- ΟΛΛ (*Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib*)

Dasatinib treatment appears to be associated with a higher rate of infectious complications, particularly **CMV infection and HBV reactivation** among HSCT recipients

- Antiviral prophylaxis while on therapy should be offered to hepatitis B surface antigen (HBsAg)-positive patients for preventing HBV reactivation
- monitoring for HBV virus load among hepatitis B core antibody (anti-HBc)-positive, HBsAg-negative patients

- **Αναστολείς BRAF and MEK kinase**

In view of available data, therapy with BRAF and MEK kinase inhibitors **does not increase the risk of infection**

- **Αναστολείς Janus- κινάσης** → θεραπεία μυελοΐνωσης - πολυερυθραιμίας - (cGVHD) (*Ruxolitinib, Pacritinib, Momelotinib)*

- Increased risk for **HBV reactivation, HZ infection**, especially if additional risk factors (i.e. prior or concomitant corticosteroid therapy, low lymphocyte counts or high-dose therapy with JAK inhibitors).
- In view of (limited) available data, the administration of antiviral **prophylaxis should be individualized**

Πρόληψη ιογενών λοιμώξεων σε ασθενείς που λαμβάνουν αναστολείς κινασών

- **Αναστολείς τυροσινικής κινάσης Bruton's** --→ θεραπεία ΧΛΛ-Λεμφώματος μανδύα-Μακροσφαιριναιμίας Waldenström's *(Ibrutinib)*
- **PML** is occasionally associated with the use of **ibrutinib**
- The new onset of neurobiologic symptoms in ibrutinib-treated patients should prompt clinical suspicion and early treatment discontinuation

- **Αναστολείς φωσφατιδυλο-ινοσιτόλη-3-κινάσης δέλτα (PI3kδ)** → θεραπεία relapsed ΧΛΛ, οζώδους λεμφώματος *(Idelalisib)*
- **Idelalisib** is associated with an increased risk of **CMV infection**
- Regular monitoring for CMV infection during the course of idelalisib therapy is advisable among CMV-seropositive patients
- **Preemptive CMV therapy could be considered (ECIL 2017: CIII)**
- Idelalisib therapy must be discontinued upon occurrence of suspected pneumonitis, grade 3/4 aminotransferase elevation (>5 times the upper reference limit) or grade 3/4 diarrhoea/ colitis.

- **mTOR inhibitors** (sirolimus, temsirolimus and everolimus)
- Increased risk of overall infections
- Screening **HBV infection**
- No benefit is expected from universal prophylaxis → individualize

Πρόληψη ιογενών λοιμώξεων σε ασθενείς που λαμβάνουν κορτικοειδή

Herpes Zoster (HZ)

- Several large population-based studies have found an **association between corticosteroid use and herpes zoster (HZ) infection in those with rheumatic diseases**, particularly RA, **HR 1.5.**
- In the SABER collaboration, a baseline use of **10 mg/day or more** was associated with an **increased risk of HZ** among rheumatic disease patients compared to no baseline steroid use (**HR 2.13**)

HBV

- **Reactivation** has been reported with steroid monotherapy, with one meta-analysis concluding the risk to be **at least 10% in HBsAg-positive** patients receiving **continuous systemic treatment for four weeks or more**
- High risk with doses of **≥20 mg daily of prednisolone >14 d or 600mg/month**

J Youssef, Rheum Dis Clin North Am. 2016 February ; 42(1): 157–176.

Πρόληψη ιογενών λοιμώξεων σε ασθενείς που λαμβάνουν κορτικοειδή

Disease	Prevention Strategies
Influenza	Annual vaccination in those with rheumatic diseases[88]
HZ	Vaccine in all patients with rheumatic diseases ages ≥50[75,77,78]
Pneumococcal pneumonia	In patients without prior vaccination, 1 dose of PCV13 in those on chronic steroid therapy should be given followed by PPSV23 ≥8 wk later. A second dose of PPSV23 is indicated 5 y after first dose.[88]
PJP	Treat with TMP/SMX (160 mg/800 mg) 3 times a week if on PEQ >16 mg daily for more than 8 wk.[45]
TB	Screen for latent TB using either TSTs or IGRAs[a] in those anticipated to start long-term corticosteroid therapy (10 mg for at least 1 mo) and treat for latent TB if positive.[81] If already on chronic steroid therapy, screen with IGRA and be aware of risk of false-negative results with TSTs or IGRAs.

HBV prophylaxis as already described according to EASL

Rheum Dis Clin North Am. 2016;42:157

Πρόληψη ιογενών λοιμώξεων σε ασθενείς που λαμβάνουν βιολογικούς παράγοντες

Βιολογικοί παράγοντες

ΑΝΑΣΤΟΛΕΙΣ ΚΥΤΤΑΡΟΚΙΝΩΝ

Αναστολείς TNF-α

- Etanercept
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

Αναστολείς IL-1

- Anakinra (rHuIL-1Ra)
- Canakinumab (anti-IL-1b)
- Rilonacept (anti-IL-1b)

Αναστολείς IL-6

- Tocilizumab

Αναστολείς IL-17

- Secukinumab
- Ixekizumab

Αναστολείς IL-12/23

- Ustekinumab

ΑΠΟΚΛΕΙΣΤΕΣ ΣΥΝΔΙΕΓΕΡΣΗΣ

- Abatacept

ΑΝΑΣΤΟΛΗ ΚΑΙ ΕΞΑΛΕΙΨΗ Β-ΚΥΤΤΑΡΩΝ

- Rituximab (anti-CD20)
- Belimumab (anti-B lymphocyte stimulator)

ΑΝΑΣΤΟΛΕΙΣ ΚΙΝΑΣΩΝ

- Tofacitinib (inhibitor Janus Kinases)

Βιολογικοί παράγοντες και ιογενείς λοιμώξεις

Biologic factor	Mechanism of action	Indication	Infection Risk	Pre-treatment screen-prophylaxis
Etanercept, Infliximab, Adalimumab, Certolizumab, Golimumab	**Binds TNF or Block TNF receptor**	RA IBD Psoriasis	TB, NTM Endemic mycoses HBV less common Leishmania	LTBI HBV Endemic mycoses
Abatacerpt	**Modulates T-cell activation**	RA JIA	Not well described	LTBI HBV
Alemtuzumab	**Anti-CD52 (B and T-cell depletion)**	CLL	CMV/HSV/VZV/EBV PCP Parasitic infections Fungal infections HBV Mycobacteria	CMV/HSV/VZV LTBI HBV PCP
Anakinra	**IL-1 receptor antagonist**	-RA -Cryopyrin-associated periodic syndromes -JIA -Still's disease	Bacterial infections	LTBI HBV

Βιολογικοί παράγοντες και ιογενείς λοιμώξεις

Biologic factor	Mechanism of action	Indication	Infection Risk	Pre-treatment screen-prophylaxis
Belimumab	**Reduces survival of B-cells (inhibitor of B-lymphocyte stimulator)**	SLE	HBV	HBV
Bortezomib (velcade)	**Proteasome inhibitor**	-Multiple myeloma -Mantle cell lymphoma	HSV/VZV HBV	-Consider HSV/VZV prophylaxis -HBV
Canakinumab	**Interleukin 1b inhibitor**	-Systemic JIA -Periodic Fever syndromes	-Aspergillus -Non-tuberculous mycobacteria -CMV/VZV	LTBI HBV
Eculizumab	**Terminal complement inhibitor**	-PNH -aHUS	Meningococcal	-Meningococcal vaccination -HBV

Βιολογικοί παράγοντες και ιογενείς λοιμώξεις

Biologic factor	Mechanism of action	Indication	Infection Risk	Pre-treatment screen-prophylaxis
Natalizumab (Tysabri)	**Ab against alpha-4 integrin**	-MS -Crohn	PML Meningitis Encephalitis	-JC -HBV
Ofatumumab	**Anti-CD20 (different than rituximab)**	-CLL	HBV PML	-HBV
Rituximab	**Binds CD20 depleting mature B-cells**	-RA -Psoriatic arthritis -ANCA-vasculitis -CLL -NHL	HBV PML	-HBV
Tocilizumab	**IL-6 receptor antagonist**	-RA -JIA	Peritonitis GI infection	-LTBI -HBV

Βιολογικοί παράγοντες και ιογενείς λοιμώξεις

Biologic factor	Mechanism of action	Indication	Infection Risk	Pre-treatment screen-prophylaxis
Tofacitinib	**Inhibitor of JAK3**	-RA	TBC	-LTBI -HBV
Ustekinumab	**Inhibitor of IL-12and IL-23**	-Psoriasis	HBV PML	-LTBI -HBV

Βιολογικοί παράγοντες και ιογενείς λοιμώξεις

CMV risk

- either a **prophylactic or pre-emptive approach** to prevent CMV infection is recommended for pts receiving **Alemtuzumab**

JC virus

- Risk of PML has been correlated with **Natalizumab** use
- Risk factors include serum JC virus IgG positivity and prior immunosuppression and **serological screening** is recommended (NEJM, 2012;366:1870)
- Cases have been also reported with **Rituximab and Ofatumumab** (screening not recommended)

HBV

- HBV risk has been reported with many different immunosuppressive agents
- **Rituximab** has been most closely associated with HBV reactivation
- **TNF blockers** also associated
- Screening should be performed prior to use of these agents.
- In pts on **rituximab or alemtuzumab** prophylaxis should be continued for at least **12 months after stopping therapy**
- In pts on **TNF-blockers continuation for at least 6 months after** stopping therapy is reasonable.

Natalizumab and PML

Duration of Tysabri use	No prior use of immunosuppressants				Prior use of immunosuppressants
	No index value	Index 0.9 or less	Index 0.9 to 1.5	Index more than 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

- **antibody index values ≤ 0.9** → low risk → MRI every year
- **index values ≥ 1.5**, treated with Tysabri for longer than 2 years → increased risk → frequent MRI 3-6 months
- patients who tested negative for JC virus antibodies, the PML risk estimate remains unchanged at 0.1 per 1,000 patients

EMA 2016

Εμβολιασμοί ACReumatology 2015

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]

Εμβολιασμοί ACGastroenterology 2017

Table 2. Inactivated vaccine recommendations*

Infectious agent	Target population	Check titer before immunization	Dosing regimen
Corynebacterium diphtheria, Clostridium tetani, Bordetella pertussis	All patients	No	A single dose of Tdap recommended at age 11 through 64 years; Td booster every 10 years
Hepatitis A	All patients	Yes	2 doses at 0 and 6 months
Hepatitis B	All patients	Yes	3 doses at 1, 1–2 and 4–6 months; check titers 1 month after the last dose; if no response, 3 options: revaccinate, double dose HBV vaccination or combined HAV/HBV vaccine
HPV	Female and male; 11 to 26 years of age	No	3 Doses at 0, 2, and 6 months
Influenza	All patients	No	Annual immunization with trivalent inactivated influenza vaccine; "high dose" vaccine for patients 65 and older; live attenuated intranasal influenza vaccine is contraindicated in immunosuppressed patients
Neisseria meningitidis	High risk adults	No	Two or three doses depending on vaccine
Streptococcus pneumonia	All patients	No	If no previous vaccination, PCV13 followed by a dose of PPSV23 after 2–12 months; if received 1 or more doses of PPSV23 should receive PCV13 one or more years after PPSV23; another dose of PPSV23 should be administered 5 years after the initial PPSV23 dose and at age 65 years or older if at least 5 years have elapsed since their previous PPSV23 dose

Εμβόλια με ζώντες ιούς

- **Εμβόλιο ανεμευλογιάς (Varivax):** στις οδηγίες του American College Gastroenterology 2017

<u>Αξιολόγηση για προηγούμενη έκθεση σε ανεμευλογιά</u>

- ✓ Γεννηθέντες προ 1980
- ✓ Πιστοποίηση εμβολιασμού (2 δόσεις)
- ✓ Πιστοποιημένη διάγνωση ανεμευλογιάς / ζωστήρα από γιατρό
- ✓ Αν τα ανωτέρω αρνητικά ορολογικός έλεγχος αντισωμάτων

↓

- ✓ Αν μη-άνοσος ασθενής εμβολιασμός
- ✓ 2 δόσεις με μεσοδιάστημα ≥ 4 εβδομάδες
- ✓ Ολοκλήρωση εμβολιασμού **1-3 μήνες πριν την έναρξη βιολογικού παράγοντα**

Εμβόλια με ζώντες ιούς

- **Εμβόλιο ζωστήρα (zostavax):** στις οδηγίες του American College Gastroenterology 2017 / American college of Rheumatology 2015

Ασθενείς ≥ 50 ετών

I D S A

American College Rheumatology (2015)

American College Gastroenterology (2017)

Ασθενείς ≥ 60 ετών

A C I P

Πότε?

1 dose at least **2 weeks before** starting biologic agents (ACR 2015)

1 dose at least **3 weeks before** starting biologic agents (ACG 2017)

- ✓ Zostavax licenced 2006 → recommended by ACIP for ≥ 60 years in 2008 → FDA approved for ≥ 50 in 2011 (safe)
- ✓ ACIP concerns of loss of vaccine efficacy over time with age. Immunosuppressed pts??

Εμβόλια με ζώντες ιούς

- **Εμβόλιο ζωστήρα (zostavax)**

Αν ήδη λαμβάνει ανοσοκαταστολή και πρόκειται να τεθεί σε βιολογικό παράγοντα?

According to **US CDC Guidelines**, therapy with:

- low-doses of methotrexate (≤0.4 mg/kg/week)
- Azathioprine (≤3.0 mg/kg/day)
- 6-mercaptopurine (≤1.5 mg/kg/day)

are not considered sufficiently immunosuppressive to create vaccine safety concerns and **are not regarded as contraindications** for administration of zoster vaccine

➢Shingrix™: ένα νέο εμβόλιο έναντι του ζωστήρα πήρε άδεια κυκλοφορίας στην Αμερική

CDC recommends that healthy **adults 50 years and older** get **two doses** of the shingles vaccine called Shingrix®, separated by 2 to 6 months, to prevent shingles and the complications from the disease

◦ **Recombinant, antigen/Adjuvant System**

◦ QS-21 Stimulon is an immune-potent adjuvant designed to help the body generate antibodies and T cells,

◦ **Δύο δόσεις Shingrix έχουν αποτελεσματικότητα > 90% στην πρόληψη ΕΖ και ΜΕΝ**

◦ Η προστασία διατηρείται >85% για τουλάχιστο 4 έτη μετά τον εμβολιασμό

◦ ‘Q: Can Shingrix be administered to immunocompromised individuals?

◦ A: While Shingrix **is not contraindicated in immunocompromised persons, it is not recommended by ACIP at this time**. ACIP will begin reviewing evidence for Shingrix in immunocompromised people as soon as it becomes available and will modify vaccine policy as necessary

https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/faqs.html

Εμβόλια με ζώντες ιούς

➢ **MMR?? ΝΑΙ** στις οδηγίες του American College Gastroenterology 2017

Table 3. Live vaccine recommendations[a]

Infectious agent	Target population	Check titer before immunization	Dosing Regimen	In patient already on immunosuppressive treatment	Vaccination for family contacts
Measles Mumps Rubella	If unknown vaccination history	Yes	Two doses (>28 days apart) at least 6 weeks before starting immunosuppressive therapy	Contraindicated	Yes
Varicella	If unknown vaccination history or exposure	Yes	2 doses (4–6 weeks apart) at least 1 month before starting immunosuppressive therapy	Depends on the type of immunosuppressive medications	Yes, if vaccine related rash occurs, immunosuppressed IBD patient should avoid contact
Herpes zoster	For patients aged 50 or older	No	1 dose at least 1 month before starting immunosuppressive therapy	Depends on the type of immunosuppressive medications	Yes, if vaccine related rash occurs, immunosuppressed IBD patient should avoid contact

<u>Άνοσοι στην Ιλαρά:</u>

- Οι γεννηθέντες πριν το 1970
- 2 δόσεις MMR
- Πιστοποιημένη νόσηση από επαγγελματία υγείας
- Ορολογική απόδειξη νόσησης

*όσοι έχουν **γεννηθεί μετά το 1970** και είτε δεν έχουν ιστορικό νόσου είτε δεν έχουν κάνει τη δεύτερη δόση πρέπει να εμβολιστούν (Το **1991** καθιερώθηκε η 2η δόση του MMR σε ηλικία 11-12 ετών και από το 1999 αυτή γίνεται σε ηλικία **4-6 ετών).**

Ευχαριστώ!