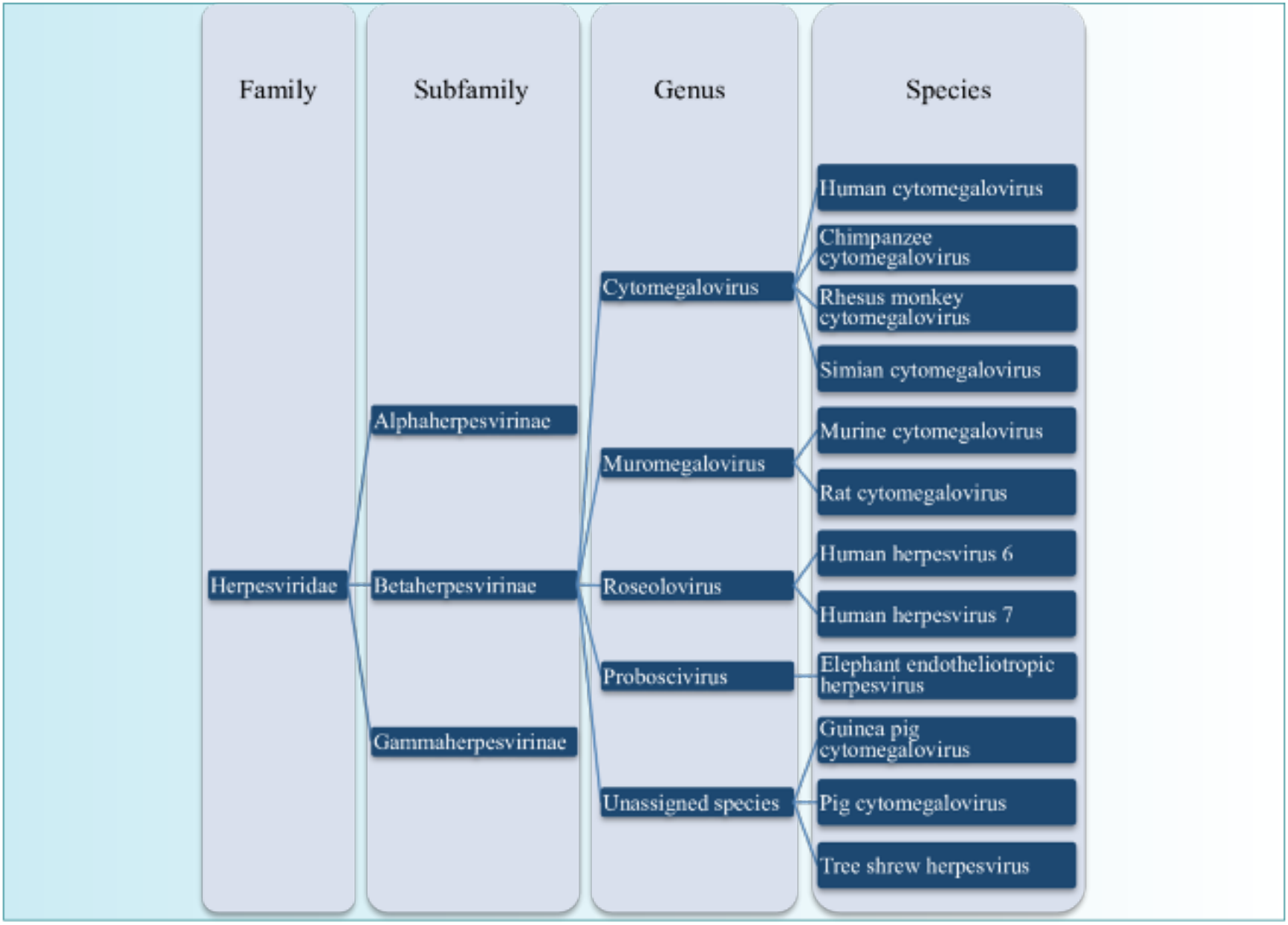
Sorunlu Viral Enfeksiyonlar

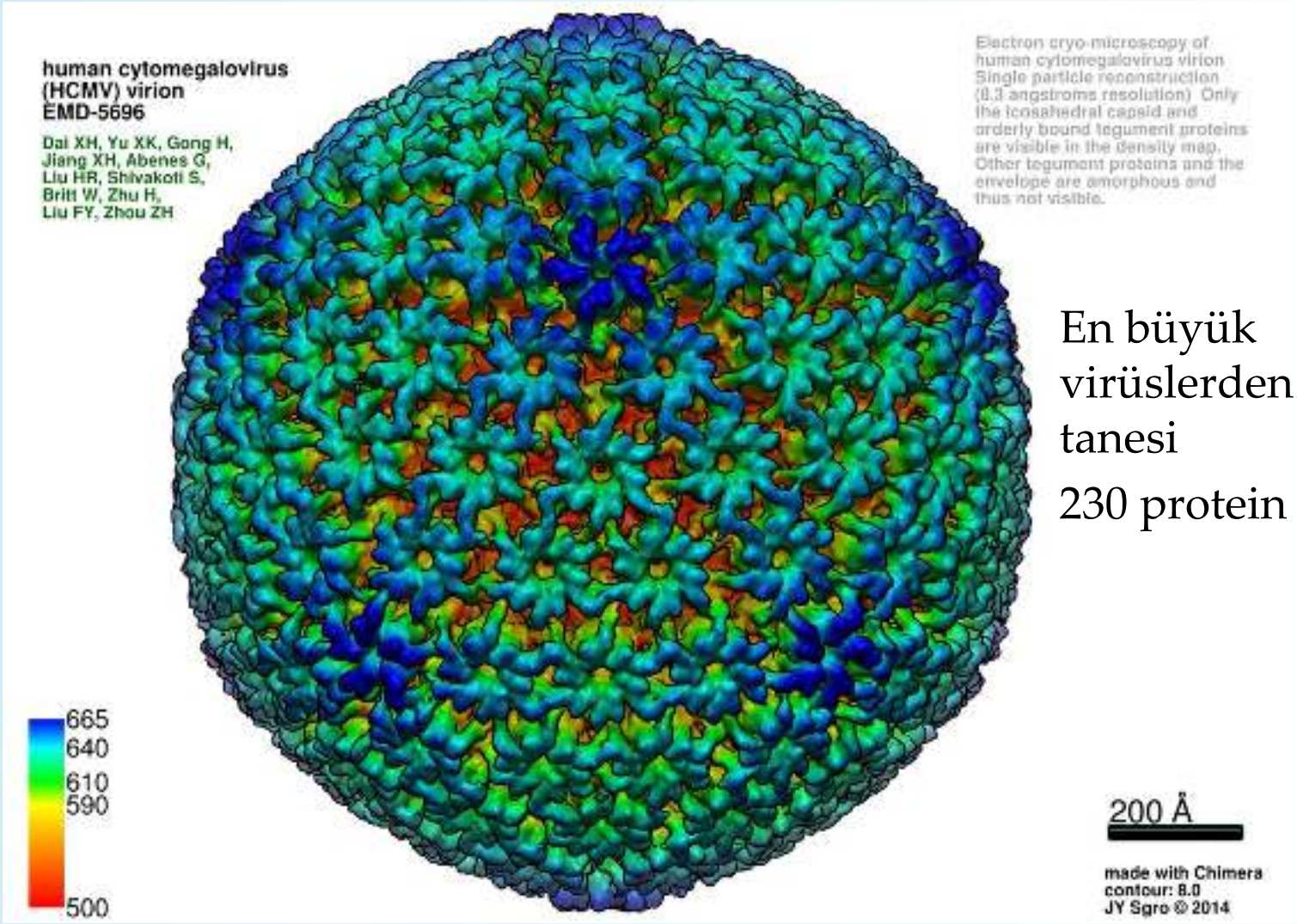
6. Türkiye EKMUD Bilimsel Platformu

Sitomegalovirüs

Dr. Cemal Bulut

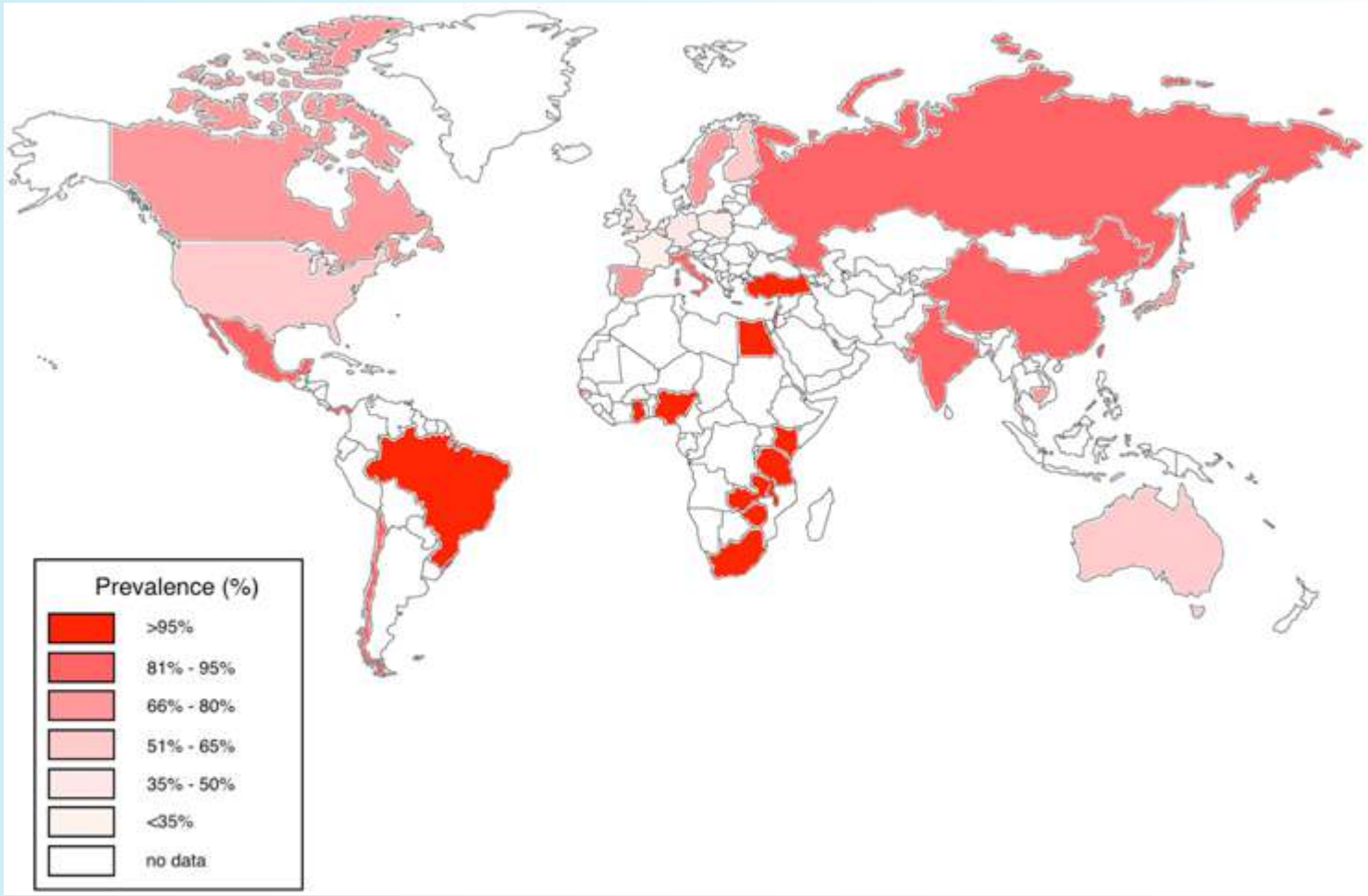
KIRIKKALE ÜNİVERSİTESİ


Family
Subfamily
Genus
Species
Herpesviridae
Alphaherpesvirinae
Betaherpesvirinae
Gammaherpesvirinae
Cytomegalovirus
Muromegalovirus
Roseolovirus
Proboscivirus
Unassigned species
Human cytomegalovirus
Chimpanzee cytomegalovirus
Rhesus monkey cytomegalovirus
Simian cytomegalovirus
Murine cytomegalovirus
Rat cytomegalovirus
Human herpesvirus 6
Human herpesvirus 7
Elephant endotheliotropic herpesvirus
Guinea pig cytomegalovirus
Pig cytomegalovirus
Tree shrew herpesvirus



En büyük virüslerden bir tanesi

230 protein kodlar



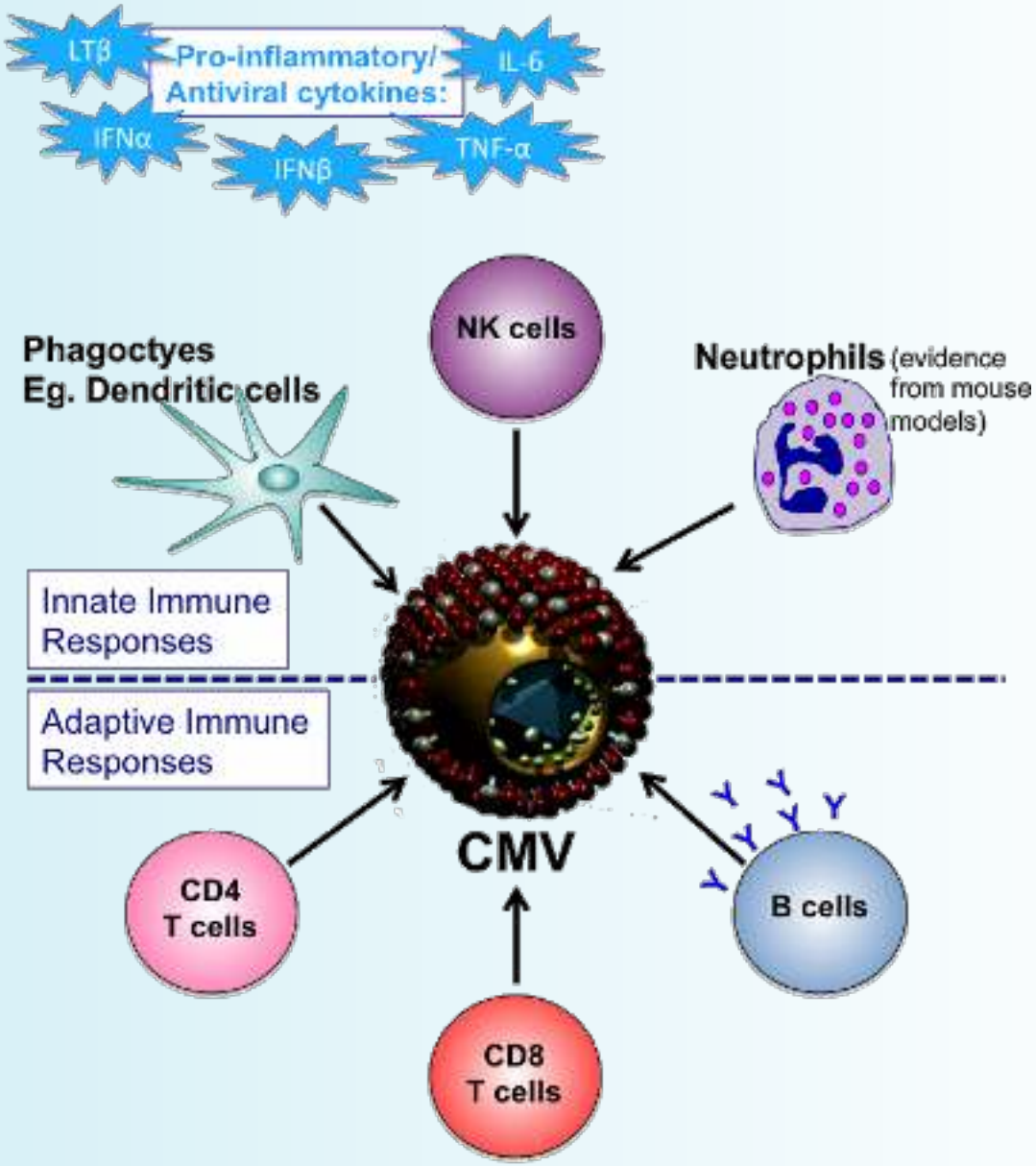
URL=http://journal.frontiersin.org/article/10.3389/fmicb.2015.01016

- Bulaş yolu:
- Yakın temas
- Cinsel temas
- Transfüzyon
- Transplantasyon
- Konjenital

Patogenez ve İmmünite

- Litik enfeksiyon yerine persistan kalmayı ve latent enfeksiyonlar yapmayı seçen mükemmel bir parazittir
- Vücutta enfekte lökosit ve lenfositler vasıtasıyla yayılır
- İmmünsüpresyon varlığında reaktive olur
- Hastalığın kontrolünde hücresel immünite gereklidir
- Pek çok yolla hücresel immüniteden kurtulabilir

İmmün sistemden kurtulma

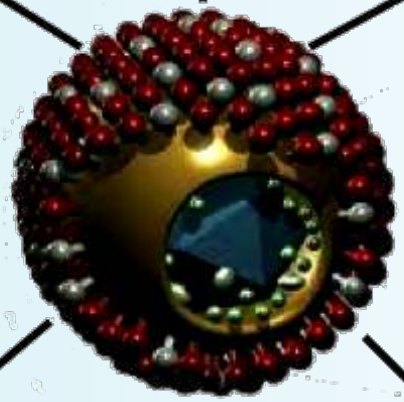


NK CELL EVASION MECHANISMS

- **UL18** – MHC class I homologue
- **UL16/UL142/miRUL112** – Prevent surface expression of NKG2D (an NK activating receptor)
- **UL141** – Prevents surface expression of CD155 (ligand for the activating receptor CD226)
- **UL83** – Binds to the NK activating receptor NKp30 to prevent NK cell activation
- **US18/US20** – promote degradation of MICA (a stress protein)

VIRAL HOMOLOGUES

- **UL111A** – Cellular IL-10 homologue
- **UL146** – CXCL1 homologue
- **US28** – Chemokine receptor homologue
- **UL144** – TNF receptor homologue



HCMV

MHC CLASS I and CLASS II INHIBITION

- **US2, US3, US6, US10** and **US11** inhibit MHC class I-restricted antigen presentation
- **US2** and **US3** inhibit MHC class II presentation of antigen

BLOCKING OF APOPTOSIS

- **IE1, IE2, UL36, UL37** and **β2.7**

INTERFERENCE OF IFN SIGNALLING

- **IE1** and **IE2**

Hamilelik ve cmv

CMV is the most common cause of birth defects in the UK yet remains unheard of

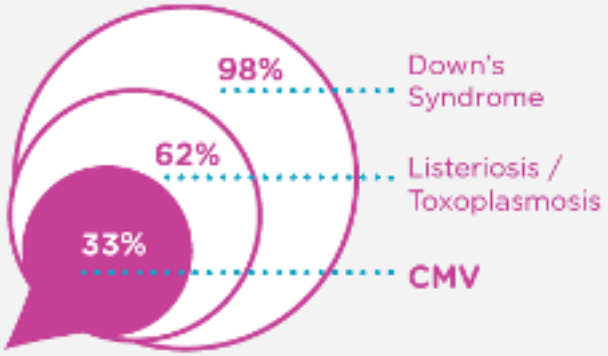
CMV 900 born / year (1 in 1000)

Down's Syndrome 750 born / year (1 in 1100)

Listeriosis
30
born / year

Toxoplasmosis
25
born / year

% of GB women (18-44) who have heard of



It's more than **30 times** as common as toxoplasmosis (the cat poo one) or listeriosis (the blue cheese one), yet far fewer women have heard of it than these conditions

"ComRes interviewed 1,008 British women aged 18-44 online between 28th- 30th March 2014. Full data tables are available on the ComRes website - www.comres.co.uk"

CMV is short for cyto-megalo-virus

More about CMV

Women are not routinely screened for CMV during pregnancy

CMV vaccines are still in the research and development stage

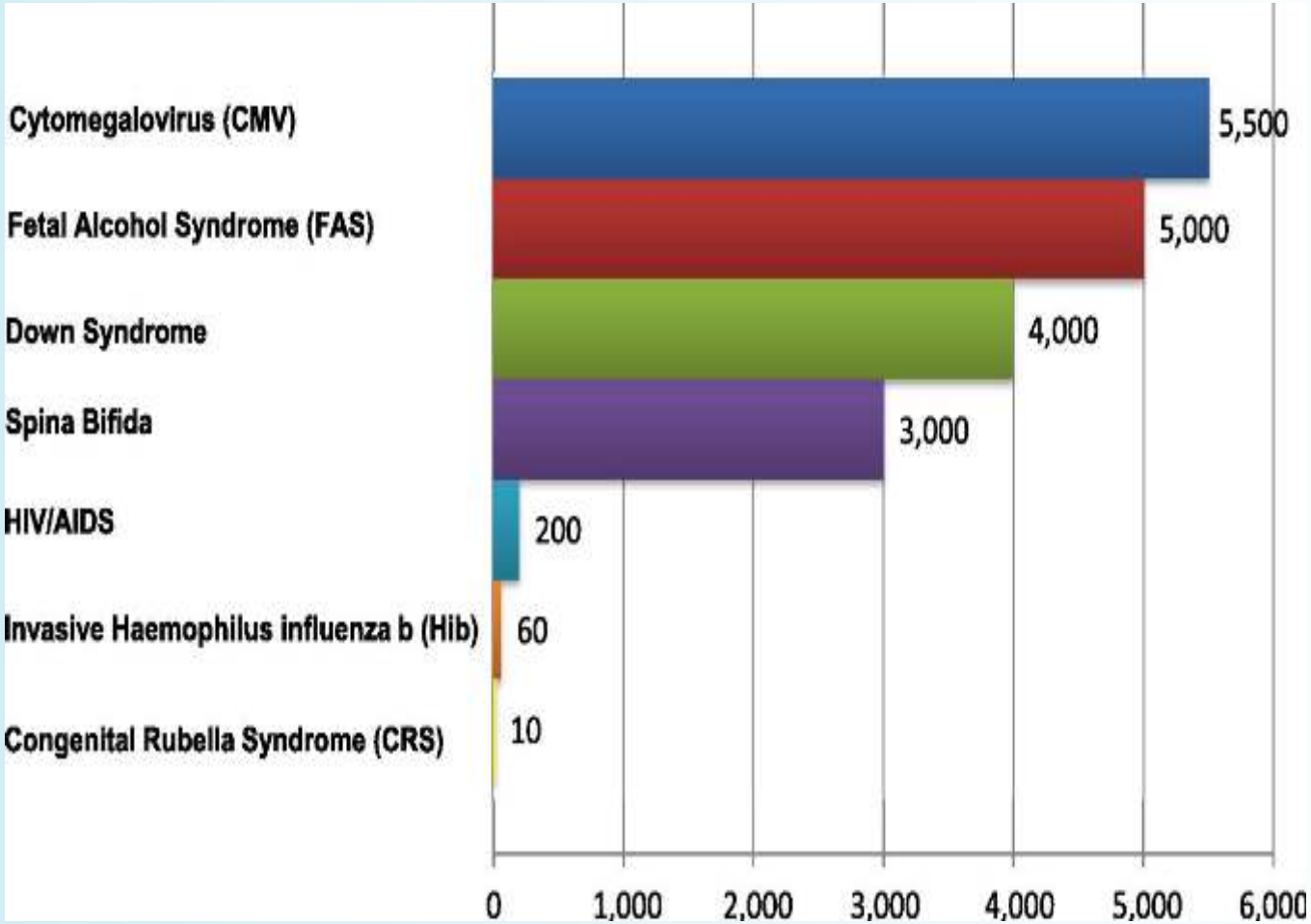
Only **9%** of women have heard of CMV

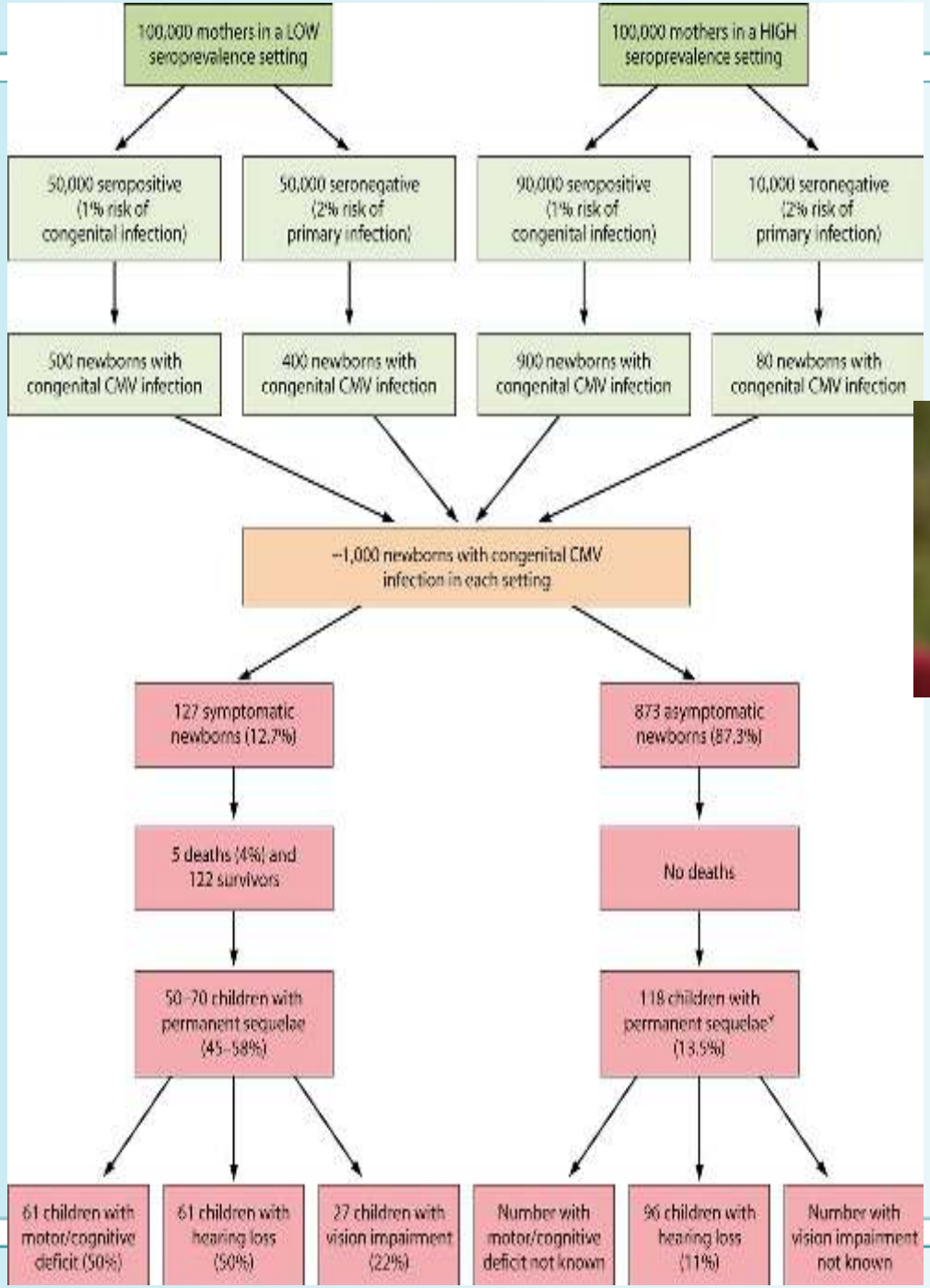
Several US states are improving CMV education through partnerships and legislation

Silver is the official color of CMV awareness

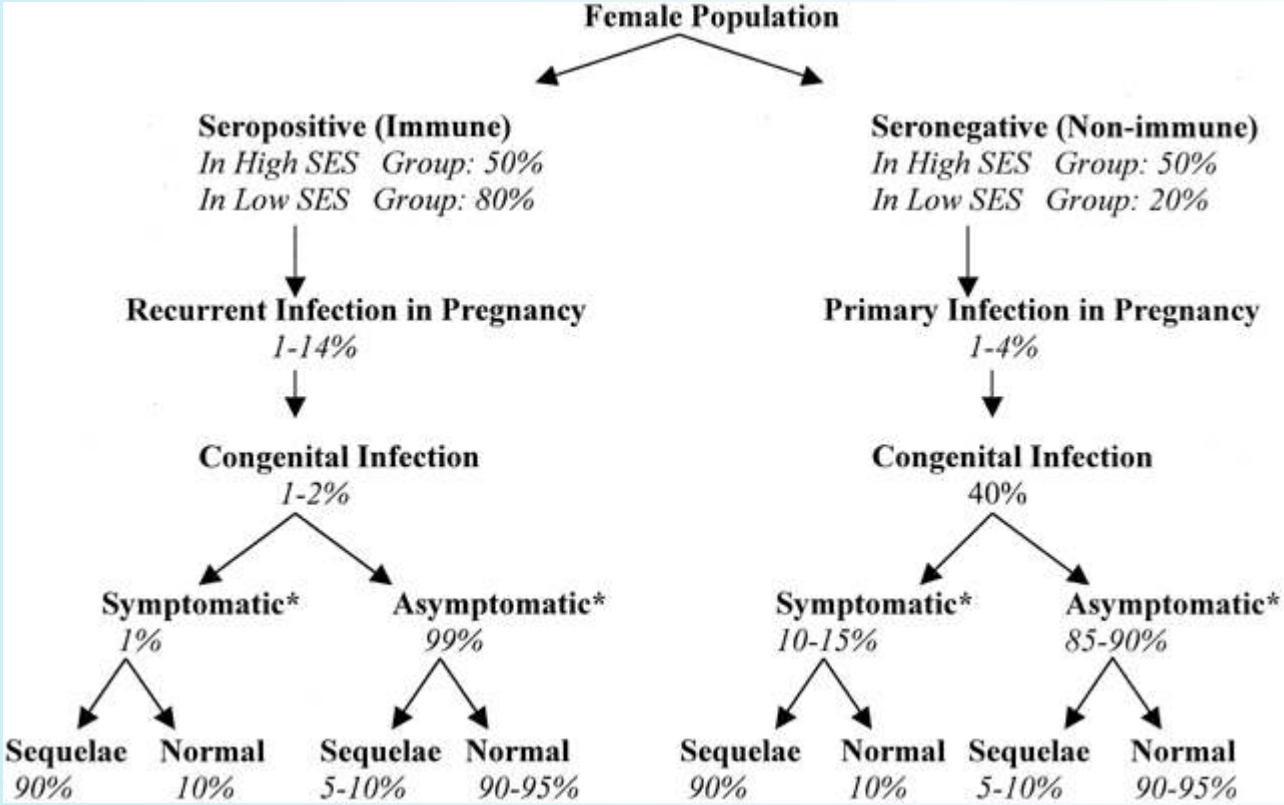
June is National CMV Awareness Month

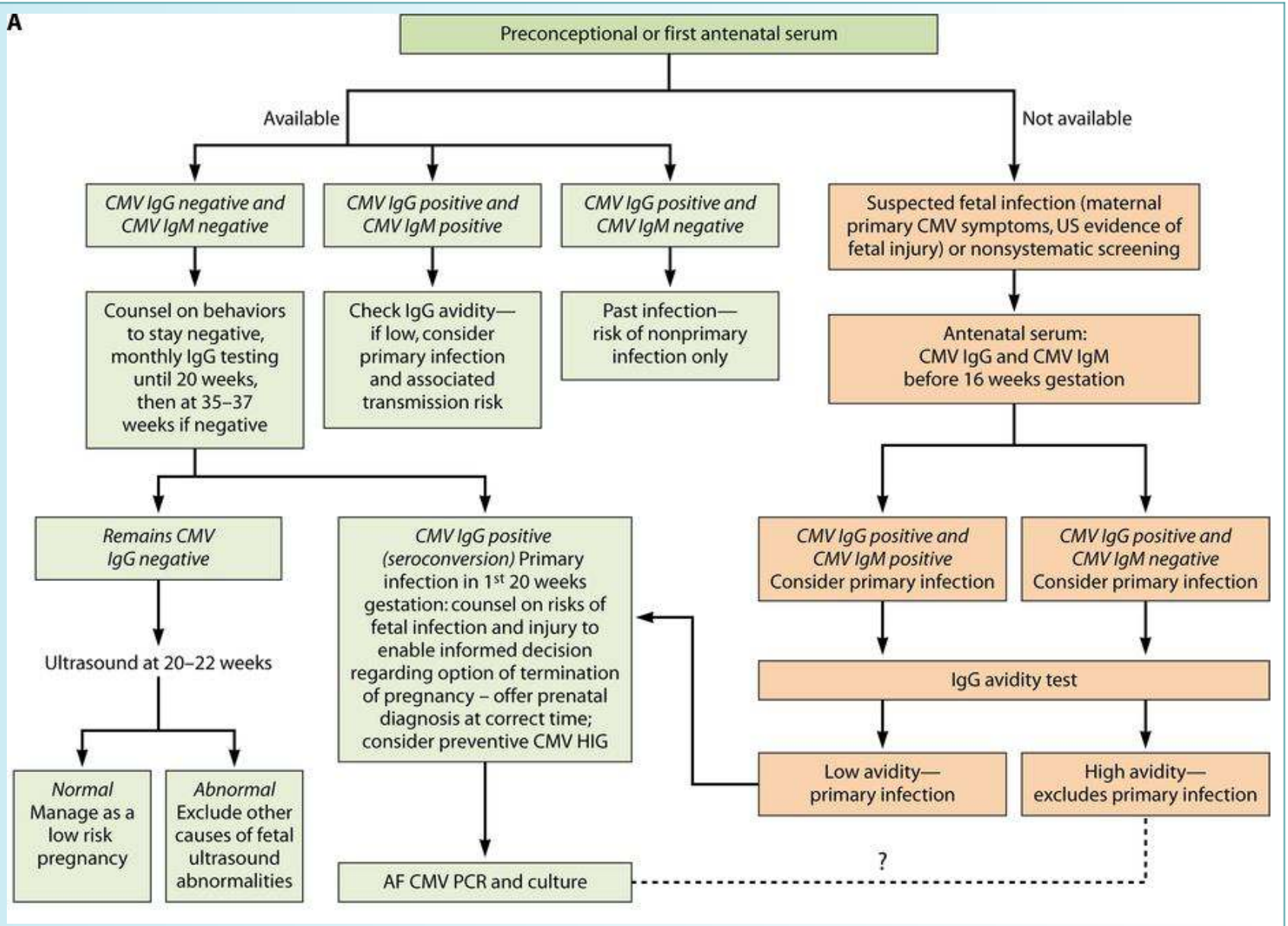
NATIONAL CMV FOUNDATION


Cytomegalovirus (CMV)
5,500
Fetal Alcohol Syndrome (FAS)
5,000
Down Syndrome
4,000
Spina Bifida
3,000
HIV/AIDS
200
Invasive Haemophilus influenza b (Hib)
60
Congenital Rubella Syndrome (CRS)
10
0
1,000
2,000
3,000
4,000
5,000
6,000

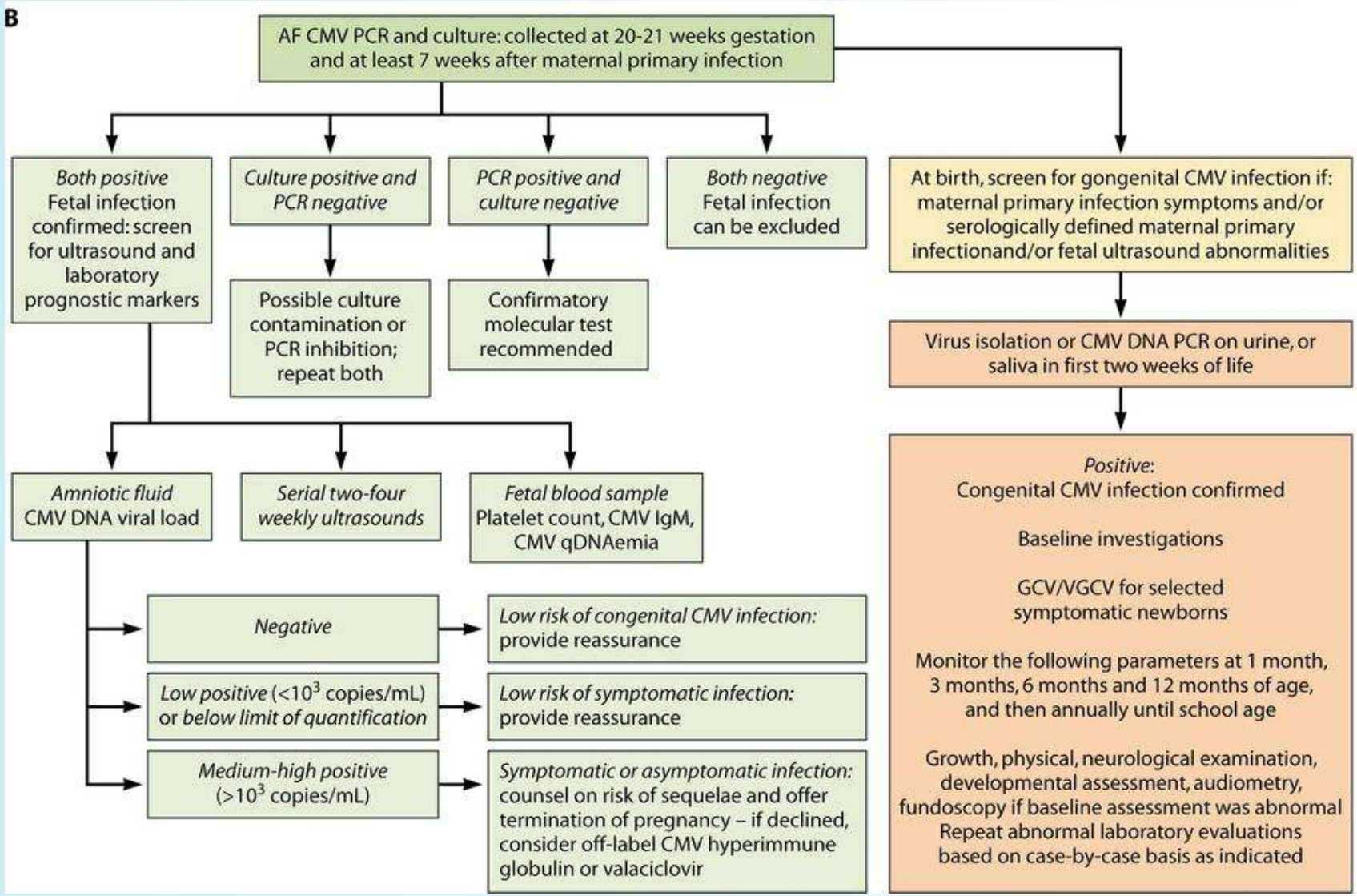


Clin. Microbiol. Rev. **2013** 26;1 **86-102**


Female Population
Seropositive (Immune)
In High SES Group: 50%
In Low SES Group: 80%
Seronegative (Non-immune)
In High SES Group: 50%
In Low SES Group: 20%
Recurrent Infection in Pregnancy
1-14%
Primary Infection in Pregnancy
1-4%
Congenital Infection
1-2%
Congenital Infection
40%
Symptomatic*
1%
Asymptomatic*
99%
Symptomatic*
10-15%
Asymptomatic*
85-90%
Sequelae
90%
Normal
10%
Sequelae
5-10%
Normal
90-95%
Sequelae
90%
Normal
10%
Sequelae
5-10%
Normal
90-95%



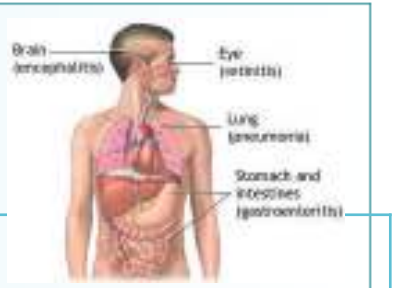
Sheetal Manicklal et al. Clin. Microbiol. Rev. 2013;26:86-102



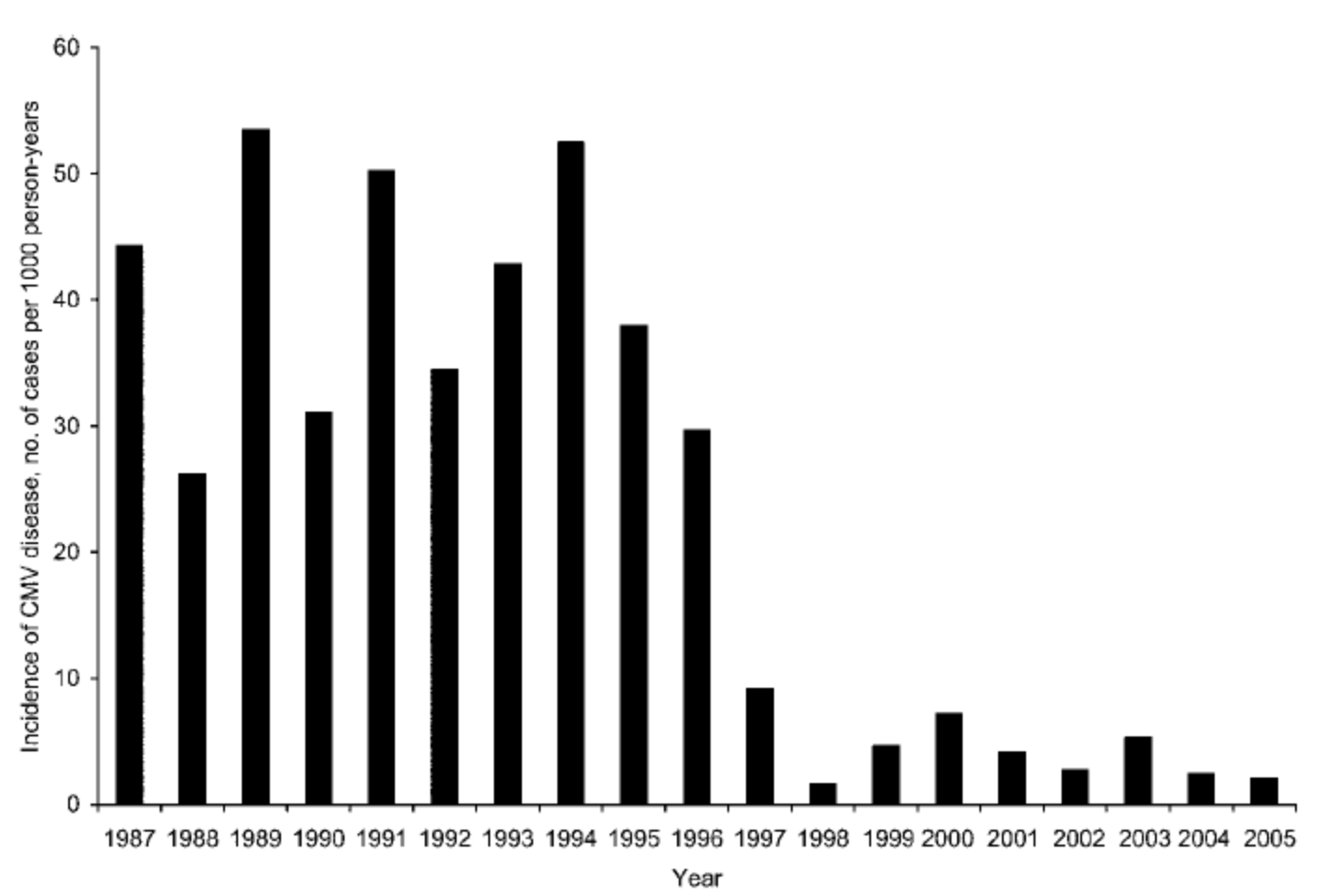
Sheetal Manicklal et al. Clin. Microbiol. Rev. 2013;26:86-102


I'm beginning to have blurred vision in my left eye.
I want to check for CMV because your CD4 count is below 100.

CMV ve Hiv



Klinik	
CMV ve Göz	•Sıklıkla CD4<50 h/mL •Retinit tek taraflı olarak başlar •Sistemk hastalığa eşlik edebilir
CMV ve GIS	•ÜST GIS: özefagial ülserler, gastrik ülserler, duodenal ülserler •ALT GIS: kolit
CMV ve Akciğer	•CMV pnömonsi nadir görülür •CMV pnömonisi sıkılıkla diğer patojenlerle birlikte etkendir
CMV ve Sinir sistemi	•Demans •Ensefalit •Poliradikülomyopatiler


Incidence of CMV disease, no. of cases per 1000 person-years
60
50
40
30
20
10
0
1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005
Year

CID 2006:42

Cmv ve transplant hastalari

- Solid organ transplant hastalarında
- Allojenik kemik iliği transplant hastalarında önemli morbidite ve mortalite nedeni

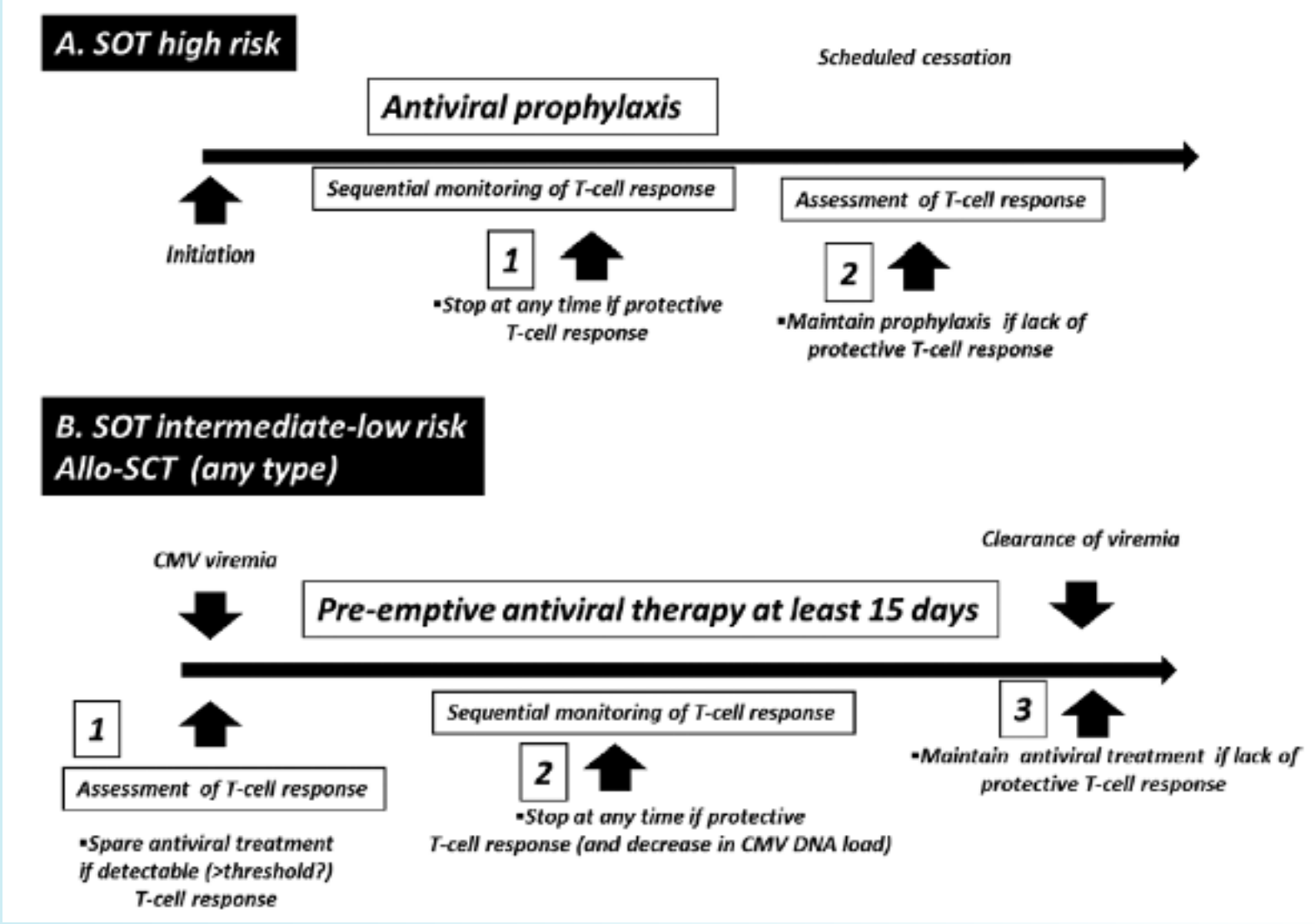
- Basit viral hastalık
  - Ateş, halsizlik, lökopeni
- İnvasif hastalıklar
  - GIS
  - Pnömoni

- CMV seronegatif hastalar, (CMV seropozitif allograft alıcıları)
- CMV seropozitif SOT alıcıları
  - T hücre etkili ilaçlar
    - Alemtuzumab
  - Anti rejeksiyon ilaç kullanımı

- Allograft rejeksiyonu
- Graft kaybı
- Akut/krıbik GvHD
- Bakteriyel/fungal enfeksiyon,
- Mortalite

İki strateji

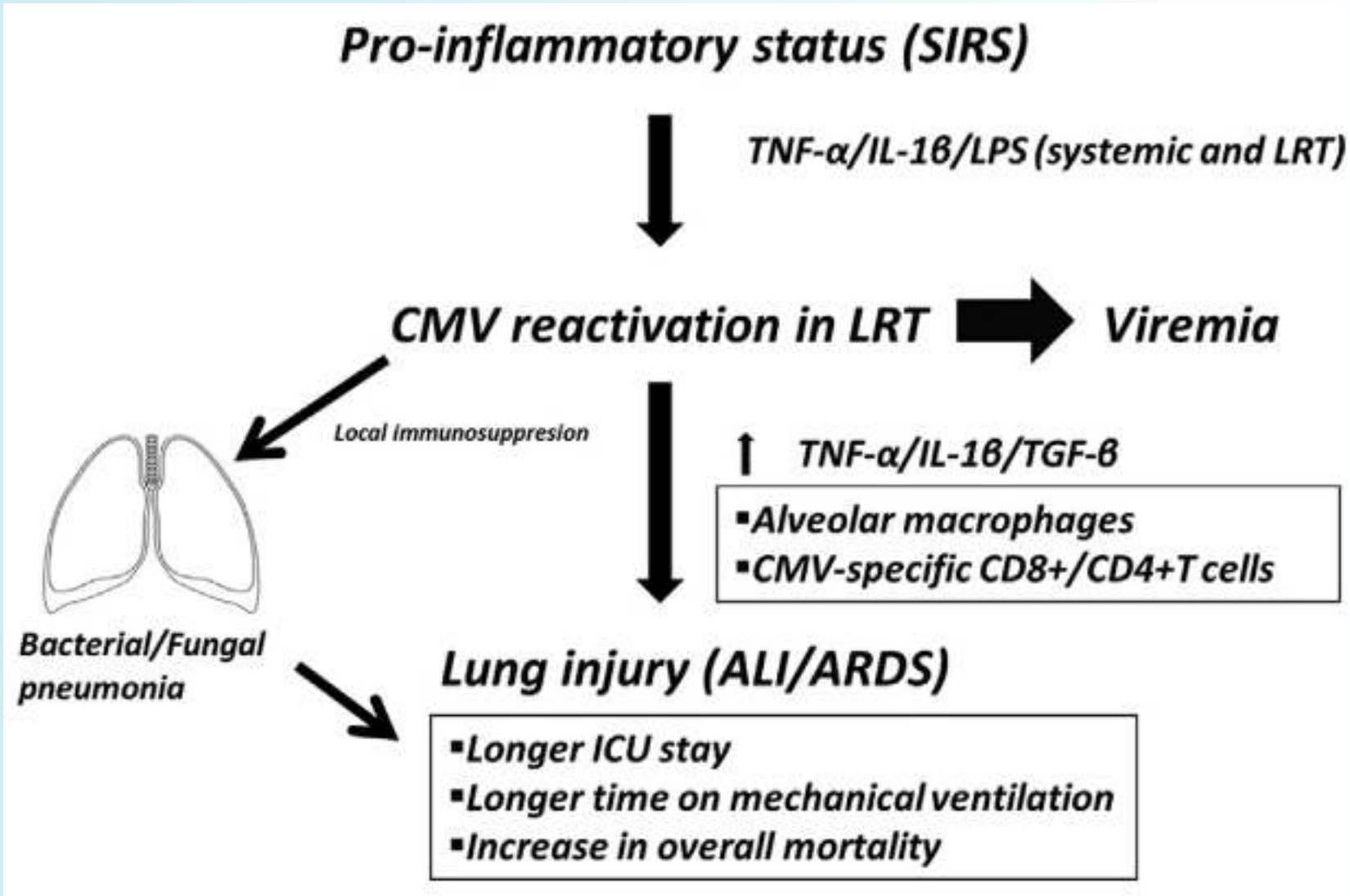
1. Üniversal profilaksi
2. Preemptif antiviral tedavi


A. SOT high risk
Scheduled cessation
Antiviral prophylaxis
Sequential monitoring of T-cell response
Assessment of T-cell response
Initiation
1
2
▪Stop at any time if protective T-cell response
▪Maintain prophylaxis if lack of protective T-cell response
B. SOT intermediate-low risk
Allo-SCT (any type)
CMV viremia
Clearance of viremia
Pre-emptive antiviral therapy at least 15 days
1
Assessment of T-cell response
▪Spare antiviral treatment if detectable (>threshold?) T-cell response
Sequential monitoring of T-cell response
2
▪Stop at any time if protective T-cell response (and decrease in CMV DNA load)
3
▪Maintain antiviral treatment if lack of protective T-cell response

CMV ve YBÜ hastalari

- Yanık, sepsis ve septik şok hastalrında CMV reaktivasyonu olmaktadır
- Sıklığı %0-71
  - Yönteme
  - Örneğe
  - Altta yatan hastalık
  - Takip süresi
- YBÜ hastalarının en az 1/3'ünde reaktivasyon gelişmekte
- 7-38 gün arasında değişmekte

Chilet et al. 2010


Pro-inflammatory status (SIRS)
TNF-α/IL-1β/LPS (systemic and LRT)
CMV reactivation in LRT
Viremia
Local Immunosuppresion
TNF-α/IL-1β/TGF-β
▪Alveolar macrophages
▪CMV-specific CD8+/CD4+T cells
Bacterial/Fungal pneumonia
Lung injury (ALI/ARDS)
▪Longer ICU stay
▪Longer time on mechanical ventilation
▪Increase in overall mortality

- Profilaksi gerekli mi?
- Tedavi gerekli mi?
  - Akcğerlerde infiltrasyon varsa
  - Hasta yüksek riskliyse
  - CMV-DNA>10.000 kopya/ml
- Patojen mi? Refakatçi mi?

Forel et al. 2014, Papazian et al. 2016

CMV ve Maligniteler

- CMV onkoenikok bir virüs olarak kabul edilmez
- Viral DNA'lar mRNA'lar ve/veya proteinler bazı tümörlerde saptanabilmektedir
  - Glioblastoma
  - Medulloblastomalar
  - Prostat kanserleri
  - Meme kanserleri
  - Olon kanserleri
  - Tükrük bezlerinin mukoepidermoid karsinomaları

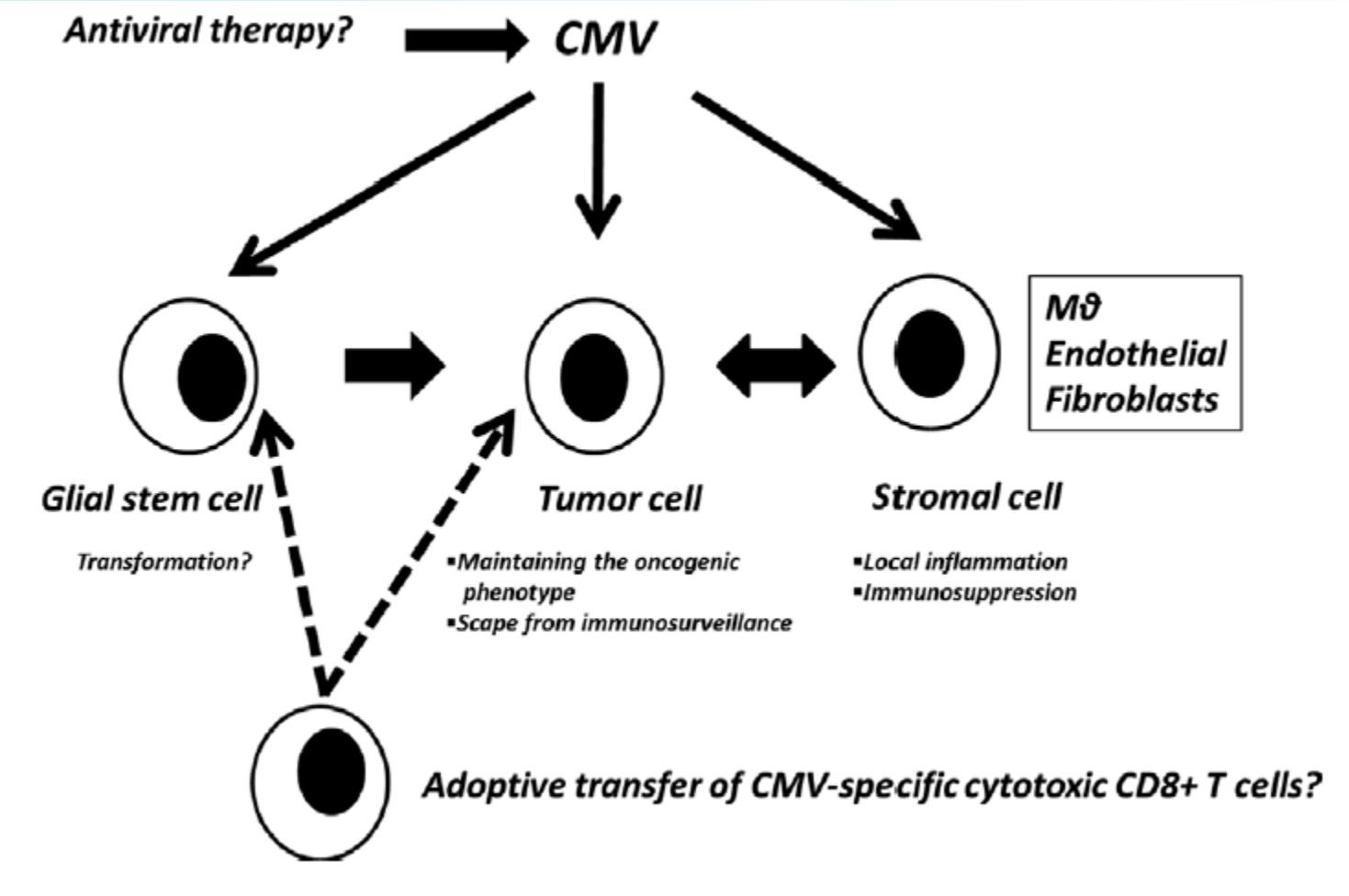
Oncotarget. 2011 Dec; 2(12): 1329–1338

- "Hit and run"
- Onkomodulatör
- Tümor hürelerinde varlığı
  1. CMV enfeksiyonunun gösterilmesi
  2. Tümörde neoplastik olamayan hücre enfeksiyonu mikroçevre için indükleyici olabilir
  3. Tümör hücrelerinin enfeksyionu onkojenik potansiyeli artırabilir

Virus Res. 2011 May; 157(2): 193–203.

- Onkojenik transformasyon
  - IE 72
  - US28
  - Apopitozu engelleyen genler
- Tümör mikroçevresinin immün sistemden kurtulabilmesi
- Kanser hücrelerinin gardiyanı
  - Nörotropik

Oncotarget. 2011 Dec; 2(12): 1329–1338



World J Exp Med 5:1–10.

Cmv ve inflamatuar barsak hastaliklari

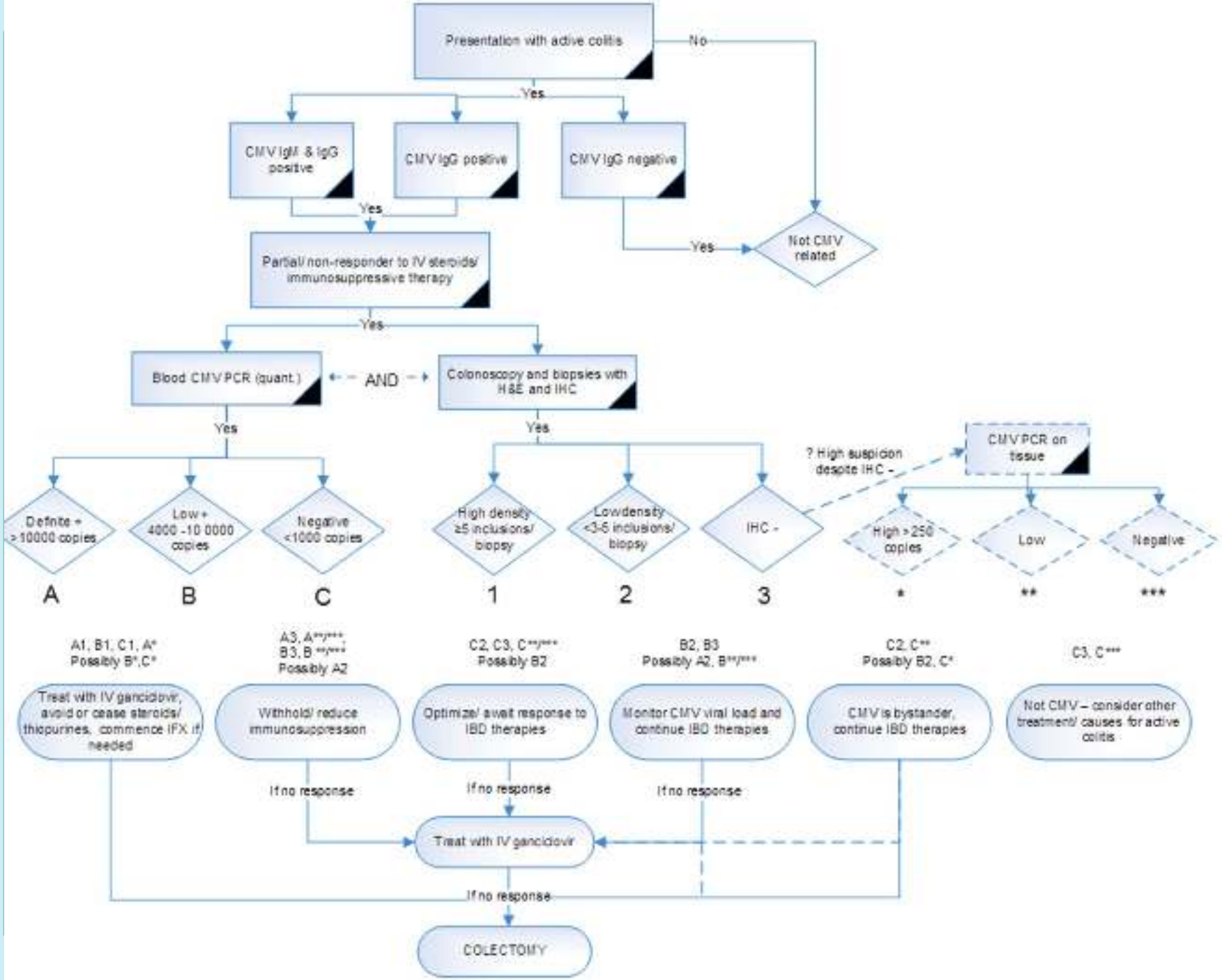
- İBH'larının doğrudan nedeni değil
- Ama
  - Kötü prognoz kriteri
  - Kolektomi ↑
  - Hastanede yatış ↑
  - Mortalite ↑
- Ülseratif kolit hastalarında daha sık

- CMV prevalansı %70
- Ülseratif kolit hastalarında daha sık
- Ağır kolitte sık
- Steoid refraktör kolit
- Akut ağır kolit

TABLE 2. Diagnostics Available for CMV Testing and Relative Utility in IBD Clinical Practice

Test for CMV	Sample Required	Indicative of GI Infection	Sensitivity, %	Specificity, %	Applicability in Clinical Practice
Serology IgM, IgG	Blood	No	100	99	− (?)
Antigenemia assay	Blood	No	60–100	83–100	+
PCR on blood	Blood	No	65–100	40–92	++
PCR on tissue	Tissue	Yes	92–97	93–99	+++
PCR on stool	Stool	Yes	29–83	86–93	−
H&E	Tissue	Yes	10–87	92–100	+++
Immunohistochemistry	Tissue	Yes	78–93	92–100	+++

Inflamm Bowel Dis 2016;22:2966–2976)


Presentation with active colitis
No
Yes
CMV IgM & IgG positive
CMV IgG positive
CMV IgG negative
Yes
Yes
Not CMV related
Partial/ non-responder to IV steroids/ immunosuppressive therapy
Yes
Blood CMV PCR (quant.)
AND
Colonoscopy and biopsies with H&E and IHC
Yes
Yes
Definite > 10000 copies
Low+ 4000 -10 0000 copies
Negative <1000 copies
A
B
C
High density ≥5 inclusions/ biopsy
Low density <3-5 inclusions/ biopsy
IHC -
1
2
3
? High suspicion despite IHC -
CMV PCR on tissue
High > 250 copies
Low
Negative
*
**
***
A1, B1, C1, A*
Possibly B*,C*
A3, A**/***;
B3, B **/***
Possibly A2
C2, C3, C**/***
Possibly B2
B2, B3
Possibly A2, B**/***
C2, C**
Possibly B2, C*
C3, C***
Treat with IV ganciclovir, avoid or cease steroids/ thiopurines, commence IFX if needed
Withhold/ reduce immunosuppression
Optimize/ await response to IBD therapies
Monitor CMV viral load and continue IBD therapies
CMV is bystander, continue IBD therapies
Not CMV – consider other treatment/ causes for active colitis
If no response
If no response
If no response
Treat with IV ganciclovir
If no response
COLECTOMY

Cmv ve immünkompetan hastalar

- Bu hasta grubunda da olgular giderek artıyor
- Düşündüğümüzden fazla !!
- Tanıda gecikme
- Tedavide gecikme

- GIS (Kolit, enterit, gastrit, hepatit, pankreatit, kolanjit)
- SSS (Menenjit, ensefalit, myelit, retinit, üveit)
- SS (Pnömoni)
- Hematolojik (Hemolitik anemi, Trombositopeni, lökopeni, DIC)
- Ürolojik (nefrit, prostatit)

Cmv ve tani sorunlari

- Doğru tedavi için doğru tanı yaklışımı gerekli

- Seroloji
- Kalitatif PCR
- Kantitatif PCR
- pp65 antijeni,
- Kültür
- Histopatoloji

Tanı

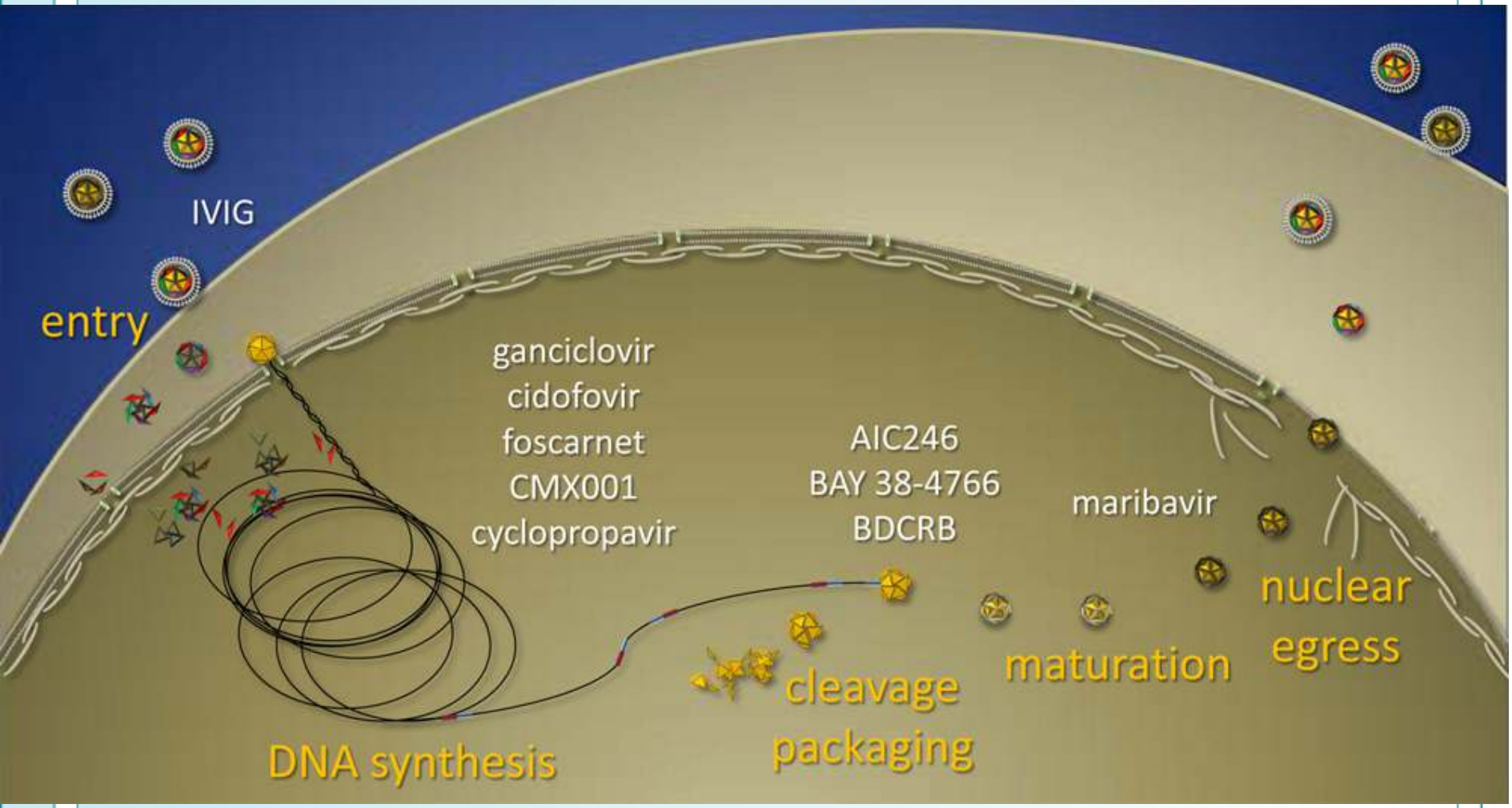
- Kullanılan yöntem
- Örnek türü
- Alıcı ve vericinin serolojik durumu
- İmmünsupresyonun türü
- Transplante edilen organ

Diagnostic method	Advantages	Disadvantages
Anti-CMV immunoglobulins	Might be used for screening for latent CMV infection	Low sensitivity and specificity for active infection
CMV PCR assays	High sensitivity and specificity and considered gold standard, quick easy to perform, gives information of viral load, can be used for wide variety of samples	Better to be performed on whole blood, qualitative might be so sensitive and detect "innocent viral shedding" quantitative might be superior
CMV antigen assays	Quick and easy to perform, has comparable sensitivity and specificity to PCR	Might be inferior to PCR in case of leukopenia
Viral culture	Highly specific, can be performed on wide variety of samples	Time-consuming, low sensitivity
Histopathology	Highly specific, confirm CMV disease and pathogenicity and invasiveness	Invasive, low sensitivity, liable to sampling error, needs skilled pathologist and so operator dependent

Cmv ve yeni ilaçlar

Agent	Mechanism of action	Common side effects
Ganciclovir	Competitively inhibits the binding of deoxyguanosine triphos phate to DNA polymerase resulting in inhibition of viral DNA synthesis	Thrombocytopenia, leukopenia, increased creatinine, fever, vomiting, diarrhea
Valganciclovir	Converted to ganciclovir in the body, much higher bioavailability of ganciclovir compared to oral ganciclovir	As ganciclovir
Foscarnet	Non-competitive inhibitor of many viral RNA and DNA polymer-ases	Electrolyte abnormalities, fever, vomiting, diarrhea, anemia, granulocytopenia, renal insufficiency, car-diotoxicity, central nervous system toxicity, hepatic toxicity
Cidofovir	Suppresses CMV replication by selective inhibition of viral DNA synthesis	Fever, alopecia, rash, ocular, renal, and gastrointestinal toxicity, cough, dyspnea

Al-Omari *et al. Ann. Intensive Care (2016) 6:110*



Virus Research 157 (2011) 212–221

CMV ve aşi

Cmv aşısı

- Antikorların hastalığı korumadaki rolü
- Hangi antikor
- Hangi antikorlar

Drugs (2016) 76:1625–1645

1. Attenuate veya disabled infectious single-cycle (DISC) aşılar
2. Recombinant gB aşılar
3. DNA temelli aşılr
4. RNA temelli aşılar
5. Viral vektör aşıları
6. Virüs benzeri partiküller
7. Peptit/subunit aşıları
8. Pentamerik kompleks aşılar

congenital

pregnancy

eye

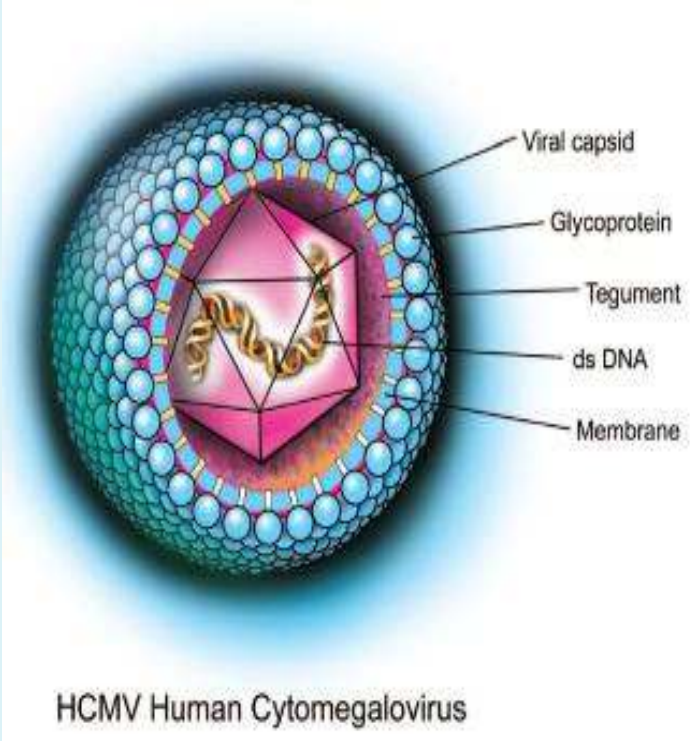
skin

mouth

lung

brain

liver



HCMV Human Cytomegalovirus

equine

guinea pig

porcine

mouse

murine

human

rash

throat

hepatitis

ocular

ulcer

retinopathy

newborn

fetus

child

patient