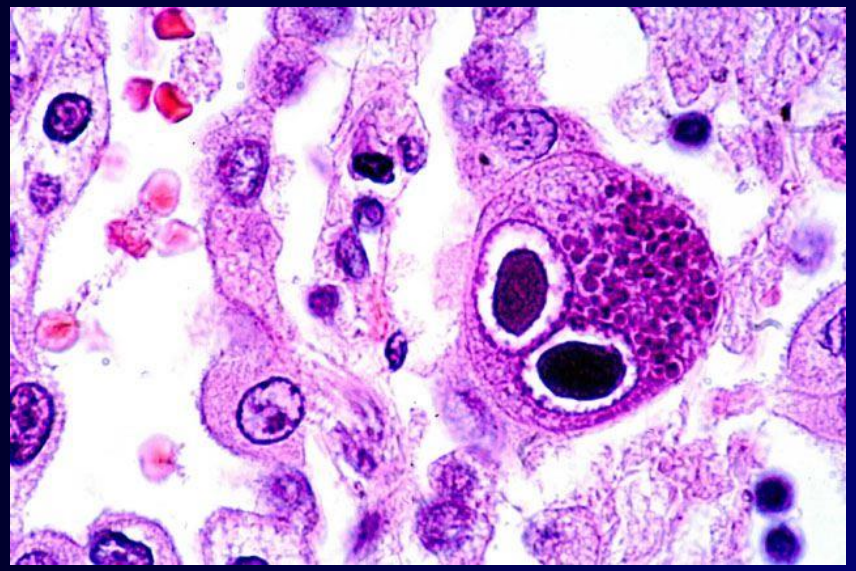
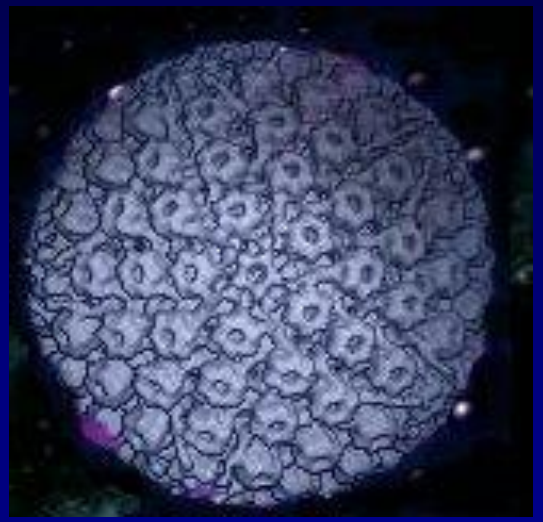
CMV definitions for clinical trials
Update the current documents





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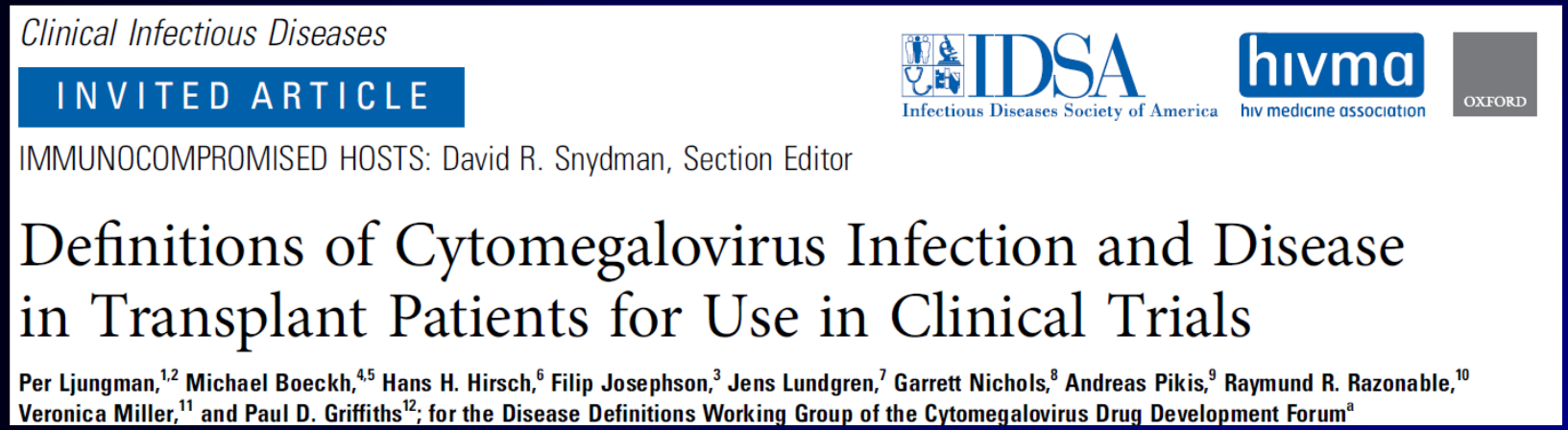
What are in the current documents?

Two separate papers:



Clinical Infectious Diseases

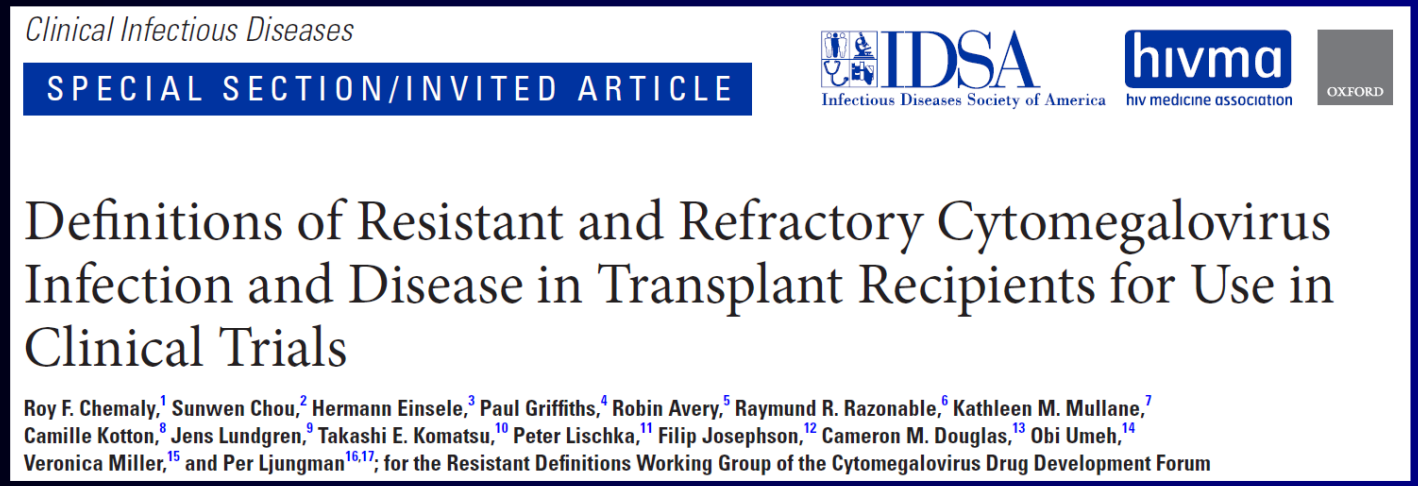
INVITED ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

IMMUNOCOMPROMISED HOSTS: David R. Snydman, Section Editor

Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials

Per Ljungman,[1,2] Michael Boeckh,[4,5] Hans H. Hirsch,[6] Filip Josephson,[3] Jens Lundgren,[7] Garrett Nichols,[8] Andreas Pikis,[9] Raymund R. Razonable,[10] Veronica Miller,[11] and Paul D. Griffiths[12]; for the Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum[a]



Clinical Infectious Diseases

SPECIAL SECTION/INVITED ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials

Roy F. Chemaly,[1] Sunwen Chou,[2] Hermann Einsele,[3] Paul Griffiths,[4] Robin Avery,[5] Raymund R. Razonable,[6] Kathleen M. Mullane,[7] Camille Kotton,[8] Jens Lundgren,[9] Takashi E. Komatsu,[10] Peter Lischka,[11] Filip Josephson,[12] Cameron M. Douglas,[13] Obi Umeh,[14] Veronica Miller,[15] and Per Ljungman[16,17]; for the Resistant Definitions Working Group of the Cytomegalovirus Drug Development Forum

Aim

- Documents for use when designing and carrying out clinical trials. Can also be used for registries when designing variables to be included in report forms.
- Not to be used as ”management guidelines”
- There are other documents to be used for that purpose (ECIL, AST)

These were questions discussed at the ID-week meeting

- Clinical significant CMV infection – to be included?
- Limited information about NAT based diagnosis of CMV disease in the previous document
- New data on PCR from GI tissue exists. To be included?
- Update on CMV pneumonia definitions?
- Requirement for CMV DNA from the eye to call it CMV retinitis?
- Update the CMV syndrome definition? Very difficult to use in practice.

What has happened since the last meeting?

- An agreement to merge the two sets of recommendations
- Questions to people having used the current documents for either running clinical trials or adjudicate events in trials
- One preliminary manuscript sent to several TAVI-participants to get comments
- A meeting of the working group
- Work on a second version

Issues to be discussed

- Viral load in BAL; can we find a cut-off level for pneumonia
- How to deal with possible CMV GI-disease in the absence of endoscopy?
- Is documentation of CMV from the eye necessary for diagnosis of retinitis?
- Time from start of antiviral therapy to call an infection ”refractory”.
- Is concommitant DNAemia always required for diagnosis of CMV disease?

CMV viral load from BAL – current writing

It is not possible to define a specific cut-off to be used in different patient categories. The suggested level of > 500 IU/ml in the previous publication seems to be too low and in future studies a cut-off of at least 1,000 IU/ml is recommended. The absence of CMV DNA detection in BAL, however, has a very high negative predictive value against the diagnosis of CMV pneumonia.

CMV GI disease – several different issues

- Should we include quantitation of CMV DNA from biopsy material as a part of the definition? Mostly applicable to HCT patients since endoscopies are common
- Should we accept only diarrhea + CMV DNAemia + exclusion of other causes (C.diff, norovirus other?) as possible CMV GI-disease based on that in SOT endoscopies are very rarely performed in this situation
- The other option is to include diarrhea + CMV DNAemia as a part of CMV syndrome.
- In either case, should there be a severity grading of diarrhea to be required? At least CTCAE grade II (increase of 4-6 stools/day over baseline)?

CMV retinitis

- Should we require CMV DNA from vitreous fluid to have proven retinitis?
- Should the current requirement of ”typical lesions” diagnosed by an ophthalmologist but without CMV from the eye be ”probable”?

CMV syndrome

- Has been very difficult to adjudicate in real life experience. Proposals

- Fever ≥38°C for at least 2 days of which at least one measurement is documented and without another identified cause of the fever.

- This writing: New or increased malaise (toxicity grade 2), including muscle aches or general achiness, headache, or new or increased fatigue (toxicity grade 3) (National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) has been almost impossible to document in real life experience. Can/ it be omitted?

CMV syndrome - continued

Should we ”sharpen” the LFT elevation criterion?

Now it is > 2 x ULN. We could instead say 2 x ULN if normal at baseline otherwise > 2 x baseline values

Definition of refractory CMV infection

- Refractory CMV infection is defined as CMV DNAemia (or antigenemia) that increases (i.e., >1 log10 increase in CMV DNA levels in blood or serum from the peak viral load as measured in the same laboratory with the same assay) after at least 1 week (10 days? 2 weeks) of appropriately dosed antiviral therapy OR persistent DNAemia (or antigenemia) (< 1 log increase/change? in CMV DNA levels in blood or serum) after at least 2 weeks of appropriate antiviral therapy.

- Refractory CMV disease is defined by a worsening in signs and symptoms and/or progression of end-organ disease after 1 week? 10 days? 2 weeks OR lack of improvement in signs and symptoms after at least 2 weeks of appropriately dosed antiviral therapy (CMV end organ disease is defined as per Ljungman et al

Organization - timing

- Update manuscript after today's meeting
- Circulations to co-authors
- If needed, another video working group meeting during the later part of May
- Submission in June to CID.