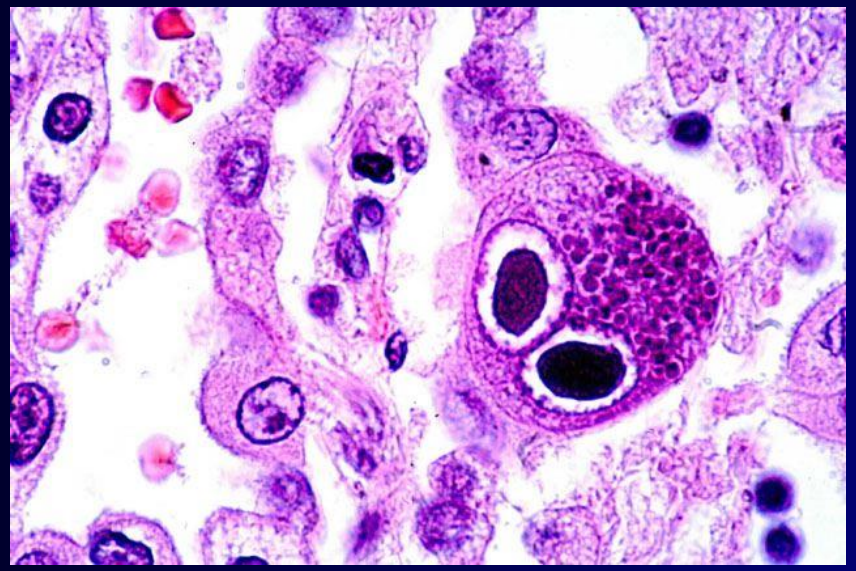
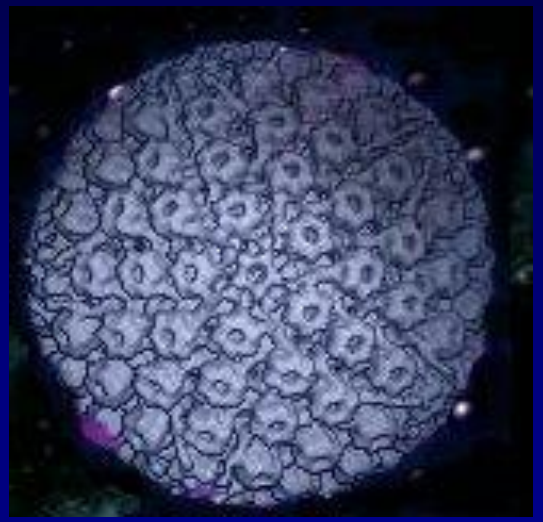
CMV definitions for clinical trials
Update the current documents





Professor (em) Per Ljungman

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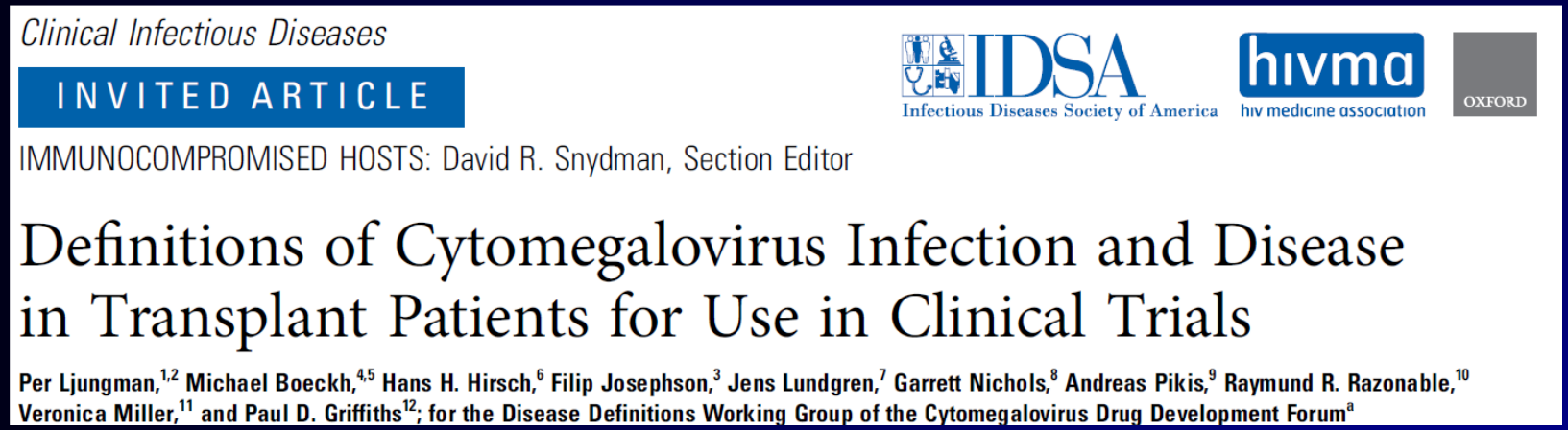
What are in the current documents?

Two separate papers:



Clinical Infectious Diseases

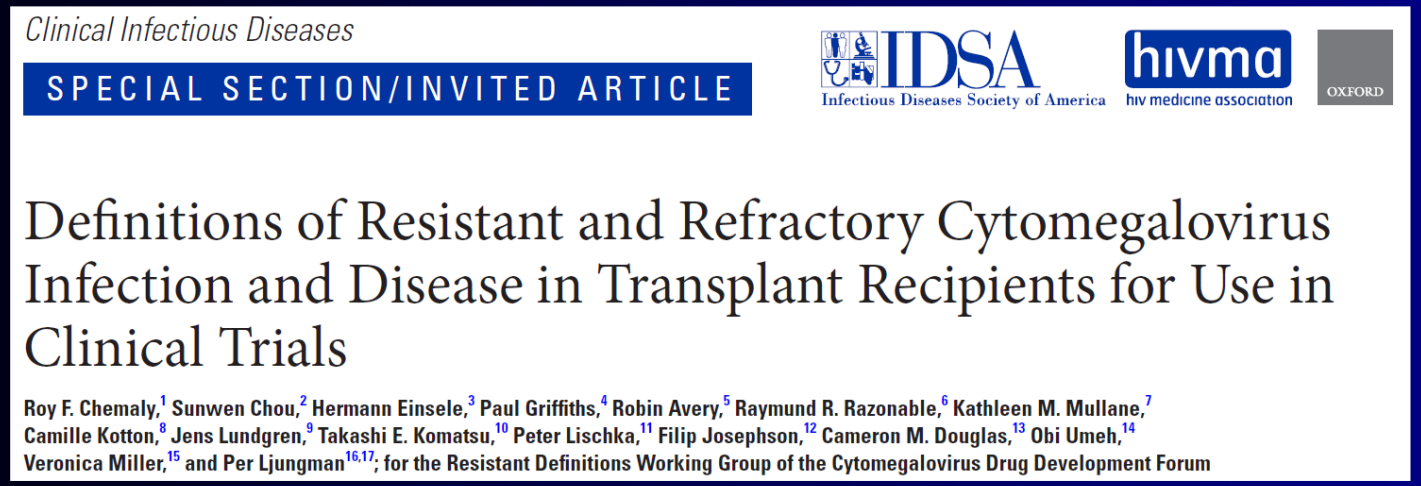
INVITED ARTICLE

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)

What has been done since the last meeting?

- A couple of video conferences
- Two new versions have been circulated to WG members
- The paper has been shortened significantly to suit the format om the most likely journals
- A specific lung tx group to address CMV pneumonia in lung tx patients

Karolinska Institutet

Thanks to all people actively participating in the discussions and providing comments to the manuscript!

Remaining issues

- Clinically significant CMV infection

- Comments regarding patient context: Prophylaxis in HCT patients only. Can the definition be used for other patient groups? Studies of other interventions?
- CMV disase is of course today an extremely rare outcom at least in HCT

- Varying thresholds for giving preemptive therapy. Can these be unified? Recommendation regarding central laboratory to be used in adjudication??

Remaining issues

- CMV pneumonia – probably disease
- Discussions have resulted in keeping it despite flaws in the HCT and non-lung tx patients.
- Regarding lung tx patients, Camille has checked the situation at different transplant centers
- The recommendation is to only accept proven disease (biopsy)

Table on probable CMV pneumonia

Patient category	Probable	Unlikely
Allo HCT patients	> 10^3	< 5 x 10^2
Auto HCT patients; CAR T treated patients	Cannot be defined	< 5 x 10^2
SOT patients except lung transplant patients isolated or combined	> 10^3	< 5 x 10^2
Lung transplant patients	Cannot be defined	Cannot be defined

Remaining issues

- How to deal with opportunistic infections in patients with pneumonia?
- This is a document for clinical trails and it is not possible to define co-pathogens that should be ”in our out”. Thus, it has to be handled on an individual basis by an endpoint committee or an adjudication committee.
- However, it could be also handled in inclusion/exclusion criteria for a study

Remaining issues

- **Probable GI disease in SOT patients:** The same definition applies as in HCT recipients. However, a frequent scenario in SOT recipients is the presence of high or increasing CMV viral load in blood together with clinically significant diarrhea and/or other gastrointestinal symptoms of an intensity as CTCAE ≥ grade 2; (National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0) in the absence of other likely causes

- Should treatment response be included in the definition?
- What about co-pathogens

Organization - timing

- Update manuscript after today's meeting
- Circulations to co-authors for sign off
- Submission ASAP
- We are getting there!