Clinical Applications of CMV Viral Load Assays in Transplantation

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Potential Impact of Reclassification of CMV VL assays: Assumptions & Concerns

• Reduced barrier to FDA-approved assays
  – more commercial assays available (particularly if LDT’s are limited)
  – greater variability [Preiksaitis Clin Infect Dis 2016]

• Potential for increased negative impact of CMV transplantation (unless appropriate special controls in place)

• Current situation:
  – multiple LDT’s in widespread use
  – variably evaluated
CMV in Transplantation: BACKGROUND

• CMV has a major negative impact on transplantation
  – Direct morbidity & mortality (closely linked to viral load)
    • HCT: end-organ disease (GI, hepatitis, pneumonia, retinitis, etc.)
    • SOT: CMV syndrome, CMV end-organ disease (GI, hepatitis, pneumonia, retinitis, etc.)
  – Cellular biological effects (less well-established link to viral load)

• Risk factors for CMV disease generally well-defined
  – HCT: R+ > D+R-, stem cell source (haplo, cord), donor type (mismatched, unrelated > other), intensity of immunosuppression
  – SOT: donor/recipient CMV serostatus pre-transplant (D+R- > R+ > D-R-), type of organ transplant (lung/heart > other), intensity of immunosuppression (lymphocyte-depletion therapy)
CMV VL Assays in Clinical Transplantation

• Widely used
• Incorporated into major transplant guidelines [KDIGO, AST ID COP, CMV International Consensus]
• Indications are expanding (site-specific testing: BAL, CSF, biopsies, etc.)
• A few built-in safeguards:
  – Used in conjunction with other clinical/lab data
  – Serial testing (trends)
Principles Underlying Use of CMV VL Assays in Transplantation

• Absolute viral load in blood predicts disease risk (static)
• Rate of increase in blood viral load predicts disease risk (dynamic/kinetic)
• Threshold concept of CMV pathogenesis
  [Griffiths & Emery Clinical Virology: Cytomegalovirus, 2002]

Reviewed in Razonable & Hayden Clin Microbiol Rev 2013
Major Indications for CMV Viral Load Testing in Transplantation

1. Diagnosis of CMV syndrome (unique to SOTx)
2. Adjunct to diagnosis of end-organ disease (de-emphasized in recent guidelines [Ljungman Clin Infect Dis 2016])
3. Marker to guide preemptive therapy (PET)
4. Monitoring response to therapy
What aspects of CMV VL assays matter to clinicians?

- Sensitivity/Lower limit of detection
- Ability to assess a “true change” in viral load across a broad range of viral loads
- Clinically significant VL threshold
Diagnosis of CMV Syndrome

Current definitions [Ljungman Clin Infect Dis 2016]

– Proven—NOT DEFINED (impossible to exclude other causes)
– Possible: NOT DEFINED
– Probable: CMV in blood + clinical and/or lab abnormalities
– Issues/Challenges:
  • no specific viral load threshold for “clinical significance” (probably varies by specific patient population)
  • significant variability in sensitivity among assays
  • do all assays measure the same thing (intact virions, “free” DNA fragments, etc.)
  • multiple viral etiologies for “CMV syndrome”
Adjunct to Diagnosis of End-organ CMV Disease

• Detection of CMV in blood is no longer part of definition for end organ disease of any type [Ljungman CID 2016]

• Definition:
  – Proven/Probable: clinical symptoms AND demonstration of CMV in biopsy specimen (viral culture, histopathology)
  – Possible category: qPCR on biopsy (and other clinical criteria)
Adjunct to Diagnosis of End-organ CMV Disease (2)

Limitations/issues:

• Biologic:
  – “compartmentalization”/local reactivation not reflected in blood VL (GI disease, retinitis, CNS disease, CMV pneumonia in lung transplant)
  – lack of specific threshold with 100% sensitivity or specificity for all CMV disease in all populations

• Non-Biologic (assay-related--Cook)
  – Inter-assay variability
  – Specimen type (WB vs Plasma vs PBMC)
  – Inability to directly compare VL across labs/assays:
    • Individual patient care (transplant center vs local lab)
    • Interpretation of data across centers
Marker to guide Preemptive Therapy (PET)

- 2 major strategies for CMV prevention:
  - Prophylaxis
  - PET
- Both strategies are recommended for most transplant settings
Importance of Specific Assay Characteristics for Guiding PET

Initiation of preemptive therapy in HCT recipients based on:

- Absolute VL thresholds based on patient risk strata (sensitivity)
- Viral kinetics

**Boeckh & Ljungman *Blood* 2009**
Monitoring response to therapy

• Expected response to therapy [Asberg Am J Transplant 2007]
  – Clinical—improvement/resolution of symptoms by 2 weeks
  – Virologic—reduction in VL within 2 weeks
    • Resistance predicted by virologic failure (trigger for resistance testing)

• Viremia at end of treatment is independently associated with risk for recurrence [Razonable Clin Microbiol Rev 2013]
  – Differences in assay sensitivity ➔ impact therapy duration [Lisboa Transplantation 2011]
cont. Monitoring response to therapy

- Ganciclovir resistance is an important concern
- Alternatives to ganciclovir are highly toxic
- Limitations of current assays (direct detection of genotypic resistance):
  - Slow TAT
  - Variable interpretation/reporting [Limaye ICAAC 2012]
  - Relatively expensive
- Accurate changes in VL ➔ important to guide:
  - Need for CMV resistance testing
  - Risk/benefit of empiric change to more toxic therapy [Avery Transplantation 2016]
Emerging uses of CMV VL assays: Blood & Beyond

• Site-specific testing:
  – CSF—CNS disease (encephalitis, ventriculitis)
  – BAL—pneumonia
  – GI or other biopsy specimens

• Yet an additional variable & layer of complexity...
CMV VL Assays in Transplantation: Current Status

• Major issues with across lab assay comparisons:
  – Generally known among transplant physicians
  – Complicates post-transplant care (decentralized care)
  – Approach: try to have all assays performed at same lab (difficult)

• Clinicians have little input into laboratory assays
  – “quality” of assay is presumed
  – little or no data to end-users:
    • assay performance
    • clinical correlation
Potential outcomes of reclassification of CMV VL Assays—The Good

• barriers to commercialization decreased ➔ more available assays ➔ less expensive?
• greater availability for local/on-site testing ➔ shorter TAT
• might facilitate greater use of PET (access to frequent testing with short TAT required)
Potential outcomes of reclassification of CMV VL Assays: Concerns

- more assays $\rightarrow$ greater variability $\rightarrow$ greater difficulty in interpretation

- “lower quality” assays $\rightarrow$ negative clinical impact
  - inadequate/variable sensitivity:
    - breakthrough disease when using PET
    - inadequate duration of therapy (higher risk of recurrence)
  - inadequate quantitation:
    - over or under-diagnosis of resistance
    - inappropriate duration of antiviral therapy