AST T3 Webinar
Updates on the International CMV Consensus Guidelines and the AST ID Guidelines Third Edition– Additional Q&A

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1. Great presentation. Please clarify for me the BK guideline regarding indication for renal allograft biopsy. You appear to imply that all cases with BKV viremia should have one. Are you referring to only those with renal allograft dysfunction?
Answer: As shown in figure 1 of the BK guidelines, they recommend and allograft biopsy when the Plasma BKV load is >4 log10 cp/mL or equivalent. By the time there is renal allograft dysfunction, it may be too late to see an effective response by reduction of immunosuppression, thus it is important to do an earlier biopsy. When there is renal allograft dysfunction, a biopsy is imperative in order to sort out whether it is from rejection (requiring more immunosuppression) or BK nephropathy (requiring less immunosuppression), even in the setting of BK viremia or viuria.

2. Hi, can you please tell us what are your recommendations for BK screening? Do you recommend checking for urine BK or should we use only serum BK?
Answer: I believe that many programs are screening as shown in figure 1 of the BK guidelines, with screening every 1 to 3 months, or with allograft dysfunction or allograft biopsy. The guidelines specifically state "Screening for BKV replication should be performed at least every 3 months during the first 2 years posttransplant, and then annually until the fifth year posttransplant." The recommended testing options include urine cytology for decoy cells, urine electron microscopy for polyomavirus aggregates, urine BK viral load, or plasma BK viral load. In general, urine is more likely to be positive before blood. I do not know of data supporting the best test to send of the options listed, and at this point it would depend on what is cost-effective, easy to do, and appropriate at your individual transplant center.

3. This is an opinion based question regarding pneumonia vaccine. In the general population the recommendation is once above age 65 and then no more. For our older transplant recipient on immunosuppression, should we continue to immunize them with the vaccine every 5 years even after age 65?
Answer: This is an excellent and relatively unstudied question. There has been concern about hyporesponsiveness with multiple repeat vaccines. There is data in Hammitt LL et al, "Repeat revaccination with 23-valent pneumococcal polysaccharide vaccine among adults aged 55-74 years living in Alaska: no evidence of hyporesponsiveness", published in Vaccine (29(12):2287-95) March 2011, that repeat revaccination with PPV23 in normal hosts, administered 6 or more years after the prior dose, was immunogenic and generally well tolerated. My personal practice has been to revaccinate transplant recipients with the Pneumovax approximately every five years. Based on the new recommendations for including PCV 13 (below), I have added that to the vaccine program.

ACIP Recommendations for PCV13 and PPSV23 Use from MMWR Vol. 61 / No. 40, Oct 2012 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm). Adults with specified immunocompromising conditions who are eligible for pneumococcal vaccine should be vaccinated with PCV13 during their next pneumococcal vaccination opportunity:

Pneumococcal vaccine-naïve persons. ACIP recommends that adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, and who have not previously received PCV13 or PPSV23, should receive a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later (Table). Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk. Specifically, a second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia and for persons with immunocompromising conditions. Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose.

Previous vaccination with PPSV23. Adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, who previously have received ≥1 doses of PPSV23 should be given a PCV13 dose ≥1 year after the last PPSV23 dose was received. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.

4. Is there a summary of ALL possible screening to do for living donors, with recommendations? If yes, where?
Answer: I would recommend looking at table 2 in the guidelines by Drs. Fischer and Lu, "Screening of Donor and Recipient in Solid Organ Transplantation", *American Journal of Transplantation 2013; 13: 9–21,* as copied below, since this is a very comprehensive list. If you are specifically interested in issues of tuberculosis, I would ask you to refer to our recent publication: Morris MI et al, "Diagnosis and management of tuberculosis in transplant donors: a donor derived infection consensus conference report", Am J Transplant. 2012 Sep;12(9):2288-300

Table 2: Frequency utilized serologic tests for screening of donor and recipient prior to transplantation
Tests commonly obtained in both donor and recipient
Human immunodeficiency virus (HIV) antibody
HSV (herpes simplex) IgG antibody (at some centers)
Cytomegalovirus (CMV) IgG antibody
Hepatitis C (HCV) antibody
Hepatitis B (HBV) surface antigen (HBsAg)
Hepatitis B core antibody (HBcAb IgM and IgG, or total core antibody)
Hepatitis B surface antibody (HBsAb)
Rapid plasma reagin (RPR)
Toxoplasma antibody (especially in heart recipients)
Epstein–Barr virus (EBV) antibody (EBV VCA IgG, IgM)
Varicella-zoster virus (VZV) antibody
Other screening measures for infectious diseases
Purified Protein Derivative (PPD) or interferon gamma release assay (IGRA) for latent TB infection in recipients
Strongyloides serology (for recipients from endemic areas)
Coccidioides serology (for recipients from endemic areas)
Trypanosoma cruzi serology (for donors and recipients from endemic areas)
Serologies for tetanus, diphtheria, measles, mumps and pneumococcal titers as an aid to pretransplant immunization (at some centers)
Optional screening measures
West Nile virus serology or NAT
HHV-8 serology
BK serology (kidney donor and recipients)
Nucleic acid amplification testing (NAT) for HIV, HCV, HBV, particularly in donors with high-risk social histories

5. Hi, thank you for the summary. I had a patient who had west nile encephalitis in 2010. Now this year she got second transplant 1 month ago. She is on lower dose cellcept due to risk of reoccurrence. What are your thoughts about it.
Answer: I don't know of any true reports of recurrent West Nile encephalitis years after the initial infection, nor could I find any in my PubMed search. This topic does not seem to be covered in the recent guidelines I discussed during the webinar. I do not think she is at risk for recurrent infection from the initial infection in 2010, as I do not believe there is latency of this viral infection. Certainly, transplant patients are at risk for persistent and prolonged infection (Penn et al, Persistent neuroinvasive West Nile virus infection in an immunocompromised patient. Clinical Infectious Disease, 2006 Mar 1;42(5):680-3.) She is potentially at risk for de novo infection (in other words, from a new mosquito bite, contact with blood products or an infected organ, etc.). Personally, I would run her immunosuppression as you would usually do, and not make decisions based on this history of West Nile disease. As an infectious disease specialist, I always prefer lower dose immunosuppression, although if that were to result in a higher risk of rejection with concomitant pulse steroids or cytolytic therapy, that may be even more dangerous. In addition, if she developed an encephalitis type picture it would be important to determine the etiology, as it might not be West Nile virus. It could be a new infection, or it could be a post-infectious encephalitis, sometimes triggered by autoimmune mechanisms requiring immunosuppressive therapy. These unusual postinfectious encephalitides can be recurrent rather than monophasic. (For an excellent review on this, consider reading Greenlee JE, Encephalitis and postinfectious encephalitis, Continuum (Minneapolis, Minn) 2012 Dec;18(6 Infectious Disease):1271-89. doi: 10.1212/01.CON.0000423847.40147.06.)

For prevention, the ID COP WEST Nile virus guidelines state the following:

"In the posttransplant population, prevention of WNV infection focuses on avoidance of mosquito bites, specifically with the use of long sleeves and long pants, and application of topical insecticides on exposed skin, such as DEET, picardin, oil of lemon eucalyptus or IR3535 in concentrations between 10% and 50%. As mosquitoes are most active in the evenings, they should be advised to avoid outdoor activities from dusk to dawn whenever possible. A brochure specifically designed for transplant patients can be downloaded through the CDC website (82)."

6. Is there any role of ivig in viral encephalitis
Answer: Given the very limited antiviral medications available for viral encephalitis, passive transfer of immunity by the use of IVIG is often done. I do not know of large-scale trials in immunocompromised patients showing efficacy, although I do think this practice is done at many transplant centers.

7. So do you recommend doing boh serum and urine at the same time or urine first?
Answer: I believe this question refers to BK screening, and I would recommend picking either urine or plasma for screening, but not both (primarily due to cost issues).

8. Do you think there is a role for screening for CMV viremia DURING prophylaxis to screen for resistance or breakthrough? If so, how often do you think screening should be done?
Answer: No, there is no clear role for routine screening for CMV viremia during prophylaxis. Such testing should only be done if there is concern for active disease, or potentially when low dose antiviral prophylaxis is used (which should be avoided anyway, according to the guidelines.) The CMV guidelines (Kotton et al, Transplantation, August 2013) specifically state:
"Routine viral load monitoring (without symptoms) in patients receiving antiviral prophylaxis or at the conclusion of antiviral prophylaxis has not been shown to be of benefit."
And
"Periodic viral load monitoring may sometimes be performed during secondary prophylaxis (weak, moderate); the correct time interval for monitoring is not known, but more frequent monitoring should be done in those at high risk for breakthrough disease."

9. Excellent presentation. Thank you! In recipients with CMV disease who demonstrate clearance of viremia via CMV PCR testing after treatment, do you recommend secondary prophylaxis and if so for how long and what agent?
Answer: In general, I personally don't do much secondary prophylaxis, and prefer to reduce the immunosuppression is much as possible early in the treatment of active CMV infection, as a means to gain better immunologic control of the infection. Nonetheless, in certain high-risk situations, you may wish to use secondary prophylaxis, generally with valganciclovir 900 mg once a day, renally adjusted. I have excerpted the guidelines, below.

The CMV guidelines (Kotton et al, Transplantation, August 2013) state that for active disease,
"Treatment with valganciclovir or intravenous ganciclovir every 12 hr should be continued until viral eradication is achieved on one or two assays after a minimum of 2 weeks (strong, moderate) (28, 42, 125). Risk factors indicating possible longer treatment duration are CMV IgG seronegativity at the onset of initial viremia (42), high initial viral load, high net state of immunosuppression, thoracic transplant recipients, and gastrointestinal tissue-invasive disease (42, 49, 125, 177, 180, 181). Secondary prophylaxis with valganciclovir 900 mg once daily (renally adjusted) for 1 to 3 months may be given, with the longer duration employed in high-risk patients as outlined above (weak, low)."

"Secondary prophylaxis is defined as prolonged therapy with standard prophylaxis doses (e.g., once daily) after a successful treatment course as indicated above. The use of secondary prophylaxis is variable across transplant centers, but when used the duration often ranges from 1 to 3 months (42, 125). Use and duration should reflect the likelihood of recurrent CMV infection. In cases of serious disease and in tissue-invasive disease without viremia, a longer duration of secondary prophylaxis with clinical monitoring of the specific disease manifestation may be preferred. In cases of recurrent CMV disease, secondary prophylaxis after successful retreatment may need to be prolonged (and level of immunosuppression potentially decreased). Risk factors for recurrence of CMV infection include primary CMV infection, deceased-donor transplantation, high initial viral load, slow reduction in viral load on treatment, persistent viremia when transferred to secondary prophylaxis, multiorgan disease, and treatment of rejection during treatment for CMV disease (125, 177Y179). Additional factors that influence viral decay are a high net state of immunosuppression, thoracic

organ transplantation, and gastrointestinal tissue invasive CMV disease (49, 180, 181). Knowledge of these risk factors allows for some individualization of therapy but only as a supplement to clinical and virologic monitoring."

10. If there is low grade CMV viremia on prophylaxis, is resistance a possibility??
Answer: Yes, although we don't generally recommend checking for viremia on prophylaxis (see question several above this one), if the patient is checked and found to be viremic, they are certainly at higher risk for resistance. I would switch to treatment dose in that setting. If this is something you are observing on a somewhat routine basis, I suspect that you may be under dosing the valganciclovir or intravenous ganciclovir, which ever you are using for prophylaxis.

11. What would you do for a patient who develops a herpes infection while on 450mg of valganciclovir?
Answer: That's an interesting question, and hopefully a fairly rare scenario. I would wonder whether this is a true herpes infection, since valganciclovir is quite effective prophylaxis against HSV-1 and HSV-2, and there are many things that can mimic herpes. I would also wonder what the GFR is. Realistically, antiviral resistance in herpes viruses is quite rare, although more commonly seen in immunocompromised hosts than others. If you are able to culture the virus, I would send resistance testing.

12. The newer CMV assay now reports CMV detectable but <137 at our center. Would you consider this an appropriate time to change from induction to maintenance or would you wait for it to indeed be "undetectable". When you decrease to maintenance dosing how log would you continue for R+ or the D+/R- pt.
Answer: As the new CMV viral load assays have gained insensitivity, we are seeing many results at the lower end of the spectrum, as you suggest with your results of "positive but <137". Interpretation of this would depend on the clinical scenario and also specimen type (whole blood generally being more sensitive than plasma, perhaps even overly sensitive). It is possible to detect latent virus with some of the newer assays. I do not know a good clinical trials examining this question. My personal practice has been to consider these very low results, often positive but below the lower limit of detection for determining a viral load, as negative. Once they have two such assays, I am comfortable stopping treatment dose antiviral therapy and switching to either secondary prophylaxis, or stopping completely, and either monitoring clinically or checking weekly viral loads (a post treatment hybrid approach, treatment, followed by monitoring, which I find especially useful in those at high risk for recurrent infection).

Regarding secondary prophylaxis, please see my reply to the above question on that topic. In general, I would not give secondary prophylaxis for seropositive recipients as they are at much lower risk for recurrent infection, except for those perhaps on high-dose immunosuppression, or other high risk scenarios.

13. Do you consider Ideal body weight in CrCl calculation for Valcyte dosing?
Answer: In the CMV guidelines, we recommended being aware of which formula was used to evaluate renal function. Below is what we specifically that in the guidelines. Per Dr. Vineeta Kumar, transplant nephrologist at the University of Alabama at Birmingham, "There is no clear consensus on whether one uses ideal body weight or current body weight in dosing not only valganciclovir but also other weight based immunotherapy i.e IVIG, Anti-thymocyte globulin etc. However, creatinine clearance is generally is typically calculated based on current body weight and not ideal. "
From the CMV guidelines : "The pivotal trials with valganciclovir and ganciclovir for the prevention and treatment of CMV disease used the Cockcroft-Gault formula (174). Use of other methods to estimate renal function such as the Modified Diet in Renal Disease formula may lead to underdosing (175)"

14. At what level of viral load (IU) would you consider to start treatment dose?
Answer: Per the CMV guidelines (Kotton et al, Transplantation, August 2013), pertinent section copied below, it's hard to know precisely when to start treatment, as there are no clearly defined viral load levels at which to initiate therapy, given the wide variation in different test results across different platforms and specimen types. The guidelines recommend that each institution develop its own set of guidelines to initiate therapy. Hopefully we will have better input as the international standard becomes broadly applied and is used in clinical trials. In general, I would recommend treatment with any significant replication, although not necessarily with very low level replication. Determination of significant versus low level depends on the individual assay you are using.

"There is poor interinstitutional correlation of QNAT results partly due to the historical lack of an international

reference standard and variation in assay design (36). This has prevented the establishment of broadly applicable cutoffs for clinical decision-making, particularly for preemptive strategies. In October 2010, a World Health Organization (WHO) International Reference Standard became available from the National Institute of Biological Standards and Controls (United Kingdom). The standard was made from a clinical isolate (Merlin) and has a titer of 5_106 IU/mL. All commercial and laboratory developed tests should be recalibrated and show colinearity to the WHO International Standard and results should be reported as IU/mL. A recent study showed good reproducibility in viral load values across multiple laboratories when using a commercial test calibrated to the WHO standard (37). Additional sources of variability include the specific target, probe, and extraction method (38). It remains imperative that laboratories use an external quantitative standard material (independent of that provided by the manufacturer) to monitor quantification across different lots of reagents to ensure consistency of assay performance. If the laboratory changes QNAT or extraction method, there must be a comparison of the performance characteristics of the new versus old tests. Interinstitutional comparison of QNAT values requires cross-referencing via specimen exchange or common external reference material (39). Until test harmonization has been clearly demonstrated, a single test should be used for clinical trials and for monitoring patients over time."

15. Are there any recommendations frequency adjustments of the 450 mg capsule after HD in pt who don't have access to the liquid formulation
Answer: Table 7 in the CMV guidelines (Kotton et al, Transplantation, August 2013) discusses the various doses of valganciclovir and ganciclovir for patients on dialysis. The liquid formulation is available for pediatric use in the United States. In the past, we have also done compounding of the tablets so that a liquid formula could be made. It would be extremely challenging to use the 450 mg tablets as whole tablets after dialysis, and I believe it would result in overdosing. I would consider an alternative, perhaps intravenous ganciclovir, compounding, or looking for another source of the liquid product.

16. Is there a rationale to routinely test for CMV viremia under prophylaxis? (related to the question on low grade CMV viremia under prophylaxis!)
Answer: No, there is no clear role for routine screening for CMV viremia during prophylaxis. Such testing should only be done if there is concern for active disease, or potentially when low dose antiviral prophylaxis is used (which should be avoided anyway, according to the guidelines.) The CMV guidelines (Kotton et al, Transplantation, August 2013) specifically state:
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18. In patients with ganciclovir resistance who also require CytoGAM -- a worst-case scenario which does occur -- are there any good long-term maintenance strategies?
Answer: Secondary prophylaxis after treatment of ganciclovir resistant CMV is always a complicated situation. Whenever possible, it is recommended that the immunosuppression be lowered. You could certainly give CMV immunoglobulin for quite some time afterwards; this passive transfer of immunity may be helpful. Some clinicians find it helpful to switch to an mTor inhibitor such as rapamycin or everolimus. I would recommend reading the CMV guidelines, and consider the various medications that are mentioned. Use of an individual medication would depend on the individual resistance mutation noted. We have had some success using cidofovir every two weeks, always given with probenecid. I don't know of many experts who are in favor of the use of leflunomide. You are welcome to e-mail me (Camille Kotton, ckotton@partners.org) to discuss an individual case if that might be helpful to you.