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IDSA
Infectious Diseases Society of America

May 12, 2016

Jeffery E. Shuren, MD, JD
Director, Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Rm. 5442
Silver Spring, MD 20993

Dear Dr. Shuren:

The Infectious Diseases Society of America (IDSA) recognizes that the Food and Drug Administration (FDA) is committed to protecting patients. However our society remains concerned that the FDA's draft guidance to regulate laboratory developed tests (LDTs) will negatively impact the care of patients being evaluated for infectious diseases (ID). IDSA, along with the American Society for Microbiology (ASM) and the Pan-American Society for Clinical Virology (PASCV) recently published a position paper where we offer additional recommendations to help minimize the disruption of LDTs in ID patient care as the draft guidance is finalized. In the paper, we also restate that we welcome any opportunity to provide member expertise to the FDA as it works to finalize and implement the proposed regulations.

The FDA recently expressed a willingness to hold an expert panel meeting devoted to viral load testing for transplant-associated opportunistic viral infections. This meeting would likely explore the nature of these viral diseases, the intended use of their diagnostics, the impact of inaccurate results, and the risk mitigation strategies in place for these tests to ensure safe and effective use. IDSA enthusiastically supports the proposed panel meeting, having previously highlighted the critical importance of transplant-associated virus testing in ID patient care. IDSA convened a team of experts to evaluate peer-reviewed literature in order to identify evidence that can help the FDA in developing the panel meeting. Attached with this letter is literature on viral load testing for cytomegalovirus (CMV), Epstein-Barr virus (EBV), BK/JC polyomavirus, adenovirus, and human herpes virus 6 (HHV-6). In addition we also offer literature on testing for CMV anti-viral resistance. IDSA hopes this information will help inform the FDA's efforts.

IDSA also understands the importance of having knowledgeable experts attend the meeting to ensure a balanced, well informed discussion. Our society recommends the FDA consider the following subject matter experts to serve on the panel:

Barbara D. Alexander, MD, MHS, Duke University Medical Center
Emily A. Blumberg, MD, University of Pennsylvania
Angela M. Caliendo, MD, PhD, Rhode Island Hospital
Kimberly Hanson, MD, University of Utah

Randall T. Hayden, MD, St. Jude's Children's Research Hospital
Camille N. Kotton, MD, Massachusetts General Hospital
Ajit Limaye, MD, University of Washington
Raymond Razonable , MD, Mayo Clinic
Gregory A. Storch, MD, Washington University

IDSA understands that both commercial diagnostics as well as LDTs play critical roles in the care of patients suffering from infection. We firmly believe that economic incentives and appropriate regulation for both types of diagnostics can ensure that both patients and their physicians retain access to innovative testing. We again wish to reiterate that we offer the expertise of our members in assisting the FDA in developing an equitable oversight of LDTs, and hope the final FDA oversight activities will facilitate the ever-changing needs of timely ID test development.

Sincerely,

Johan S. Bakken, MD, PhD, FIDSA
IDSA President

About IDSA

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii, Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and, finally, emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Zika virus disease, and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.

IDSA expert-reviewed literature on quantitative viral load testing for transplant-associated opportunistic viral pathogens

Cytomegalovirus (including antiviral resistance)

Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. **2009**; 113(23): 5711-9.

Lurain NS, Chou S. Antiviral drug resistance of human cytomegalovirus. Clinical microbiology reviews. **2010**; 23(4): 689-712.

Kotton, CN et. al. Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. Transplantation. **2013**; 96(4): 333-60

Razonable RR, Hayden RT. Clinical utility of viral load in management of cytomegalovirus infection after solid organ transplantation. Clinical microbiology reviews. **2013**; 26(4): 703-27.

Razonable RR, Humar A. Cytomegalovirus in solid organ transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. **2013**; 13 Suppl 4: 93-106.

Epstein-Barr Virus

Meijer E, Cornelissen JJ. Epstein-Barr virus-associated lymphoproliferative disease after allogeneic haematopoietic stem cell transplantation: molecular monitoring and early treatment of high-risk patients. Current opinion in hematology. **2008**; 15(6): 576-85.

Styczynksi J, et. al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplantation. **2009**; 43: 757-770

Gulley ML, Tang W. Using Epstein-Barr viral load assays to diagnose, monitor, and prevent posttransplant lymphoproliferative disorder. Clinical microbiology reviews. **2010**; 23(2): 350-66.

Green M, Michaels MG. Epstein-Barr virus infection and posttransplant lymphoproliferative disorder. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. **2013**; 13 Suppl 3: 41-54; quiz

Chiereghin A, et al. Prospective Epstein-Barr virus-related post-transplant lymphoproliferative disorder prevention program in pediatric allogeneic hematopoietic stem cell transplant: virological monitoring and first-line treatment. Transplant Infectious Diseases. **2016**; 18(1): 44-54.

Semenova, T, et.al. Multicenter evaluation of whole-blood Epstein-Barr viral load standardization using the WHO international standard. Journal of Clinical Microbiology. **2016**; epub ahead of print.

BK/JC polyomavirus

Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. The New England journal of medicine. **2002**; 347(7): 488-96.

Drachenberg CB, et al. Polyomavirus BK versus JC replication and nephropathy in renal transplant recipients: a prospective evaluation. Transplantation. **2007**; Aug 15:84(3):323-30

Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. Bone marrow transplantation. **2008**; 41(1): 11-8.

Hirsch HH, et. al. BK Polyomavirus in Solid Organ Transplantation. American Journal of Transplantation. **2013**; 13: 177-188

Adenovirus

Lindemans CA, Leen AM, Boelens JJ. How I treat adenovirus in hematopoietic stem cell transplant recipients. Blood. **2010**; 116(25): 5476-85.

Ganzenmueller T, Heim A. Adenoviral load diagnostics by quantitative polymerase chain reaction: techniques and application. Reviews in Medical Virology. **2012**; 22(3): 194-208.

Matthes-Martin S, et. al. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECIL-4. Transplant Infectious Diseases. **2012**; 16(6): 555-563

Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. Clinical microbiology reviews. **2014**; 27(3): 441-62.

HHV-6

Le J, Gantt S. Human herpesvirus 6, 7 and 8 in solid organ transplantation. American journal of transplantation: American Society of Transplantation and the American Society of Transplant Surgeons. **2013**; 13 Suppl 4: 128-37.

Luiz CR, et al. Monitoring for **HHV-6** infection after renal transplantation: evaluation of risk factors for sustained **viral** replication. Transplantation. **2013**;95(6):842-6.

Ogata M, et al. Human Herpesvirus 6 (HHV-6) Reactivation and HHV-6 Encephalitis After Allogeneic Hematopoietic Cell Transplantation: A Multicenter, Prospective Study. Clinical Infectious Diseases. **2013**; 57(5): 671-681

Agut H, et al. Laboratory and clinical aspects of human herpesvirus 6 infections. Clinical microbiology reviews. **2015**; 28(2): 313-35.

Quintela A, et al. **HHV-6** infection after allogeneic hematopoietic stem cell **transplantation**: From chromosomal integration to viral co-infections and T-cell reconstitution patterns. Journal of Infection. **2016**;72(2):214-22.

Gautheret-Dejean A, et al. Diagnosis and practice of virological monitoring of infections by the human herpesviruses 6A and 6B. Annales de Biologie Clinque (Paris)**. 2016**;74(2):156-167.