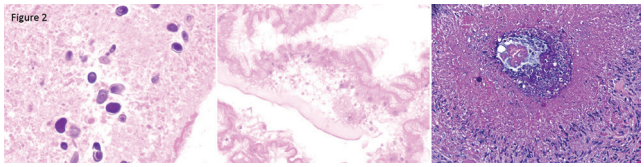

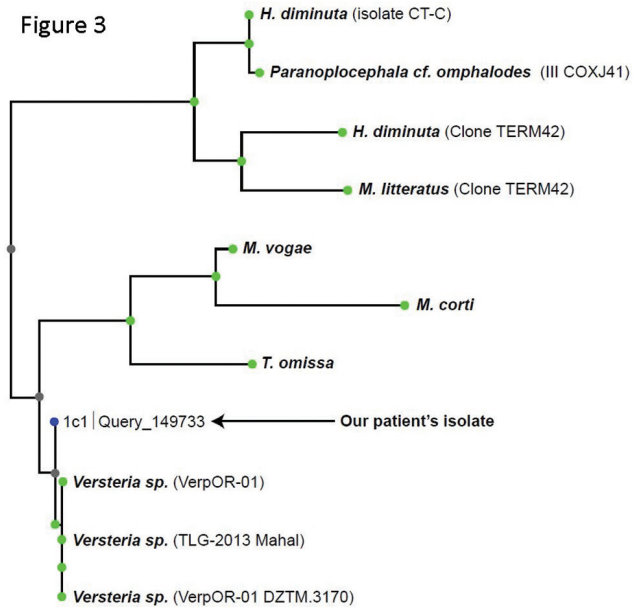

Disclosures. **All authors:** No reported disclosures.

1732. Adenovirus Load Dynamics Are Consistently Correlated With Risk of Mortality in Pediatric Allogeneic Hematopoietic Cell Transplant Recipients: Findings From the Landmark AdVance Study

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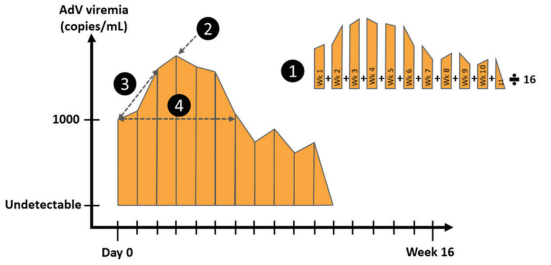
Background. Adenovirus (AdV) infection is an important cause of mortality among allogeneic hematopoietic cell transplant (allo-HCT) recipients. Current European Conference of Infections in Leukemia (ECIL-4) guidelines support weekly AdV screening for those at-risk and pre-emptive antiviral treatment with off-label cidofovir when adenoviremia is detected. However, there is limited understanding of the relative prognostic strength of different dynamic AdV viral load measures. We examined the association between adenovirus viral load dynamics and mortality in pediatric allo-HCT recipients managed under the current standard of care.

Methods. AdVance was a multinational, multicenter study characterizing the current screening and treatment practices for AdV infection in allo-HCT recipients between January 2013 and September 2015. This analysis focused on pediatric (<18 years) patients who experienced AdV viremia ≥1,000 copies/mL within 6 months of HCT. Multivariate Cox Proportional Hazard models, controlling for factors including immune reconstitution, were used to examine the relationship between AdV viral load dynamics (Figure 1) and all-cause mortality in the 6 months after first AdV viremia ≥1,000 copies/mL.

Results. A total of 241 pediatric allo-HCT recipients had AdV viremia ≥1,000 copies/mL in the 6 months following allo-HCT. Among these, 43/241 (18%) died within 6 months of first AdV ≥1,000 copies/mL. AdV viral load dynamics; whether measured by AdV $AAUC_{0-16}$, peak viremia, 2-week change in viremia, or days of viremia >1,000 copies/mL, were consistently correlated with all-cause mortality (Figure 2; hazard ratio [HR] range: 1.3–2.3). Most notably, patients with AdV $AAUC_{0-16}$ in the highest quartile had an HR of 11.6 relative to those in the lowest (confidence interval: 4.7–24.0; Figure 3).

Conclusion. AdV infection is a significant risk for allo-HCT recipients. The AdVance study has identified several dynamic measures of AdV viral load that correlate with the risk of mortality in pediatric allo-HCT recipients. Results show for the first time, that AdV $AAUC_{0-16}$ provides the optimal correlation with mortality in this population and serves as a clinically useful indicator of outcome in patients with AdV infection.

Figure 1: Adenovirus viral load dynamics



1 $AAUC_{0-16}$:
Log_{10} of the time-averaged area under the AdV viremia curve over the 16 weeks following first AdV viremia ≥1000 copies/mL

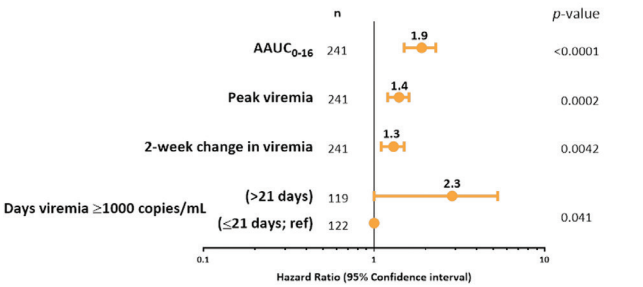
2 Peak viremia:
Peak Log_{10} AdV viremia over the 16 weeks following first AdV viremia ≥1000 copies/mL

3 2-week change in viremia:
Change in Log_{10} AdV viremia in the first 2 weeks from first AdV viremia ≥1000 copies/mL

4 Days viremia ≥1000 copies/mL:
Number of days where AdV viremia was ≥1000 copies/mL over the 16 weeks following first AdV viremia ≥1000 copies/mL

AdV, adenovirus

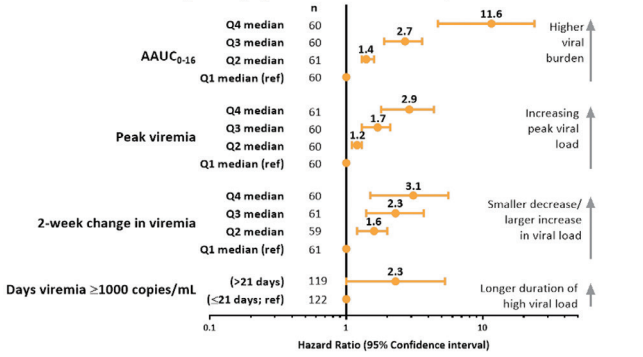
Figure 2: All adenovirus viral load dynamics were associated with a significantly higher risk of all-cause mortality in the 6 months following first adenovirus viremia ≥1000 copies/mL



$AAUC_{0-16}$, Log_{10} of the time-averaged area under the AdV viremia curve over the 16 weeks following first AdV viremia ≥1000 copies/mL; Days viremia ≥1000 copies/mL, number of days where AdV viremia was ≥1000 copies/mL over the 16 weeks following first AdV viremia ≥1000 copies/mL; Peak viremia, peak Log_{10} AdV viremia over the 16 weeks following first AdV viremia ≥1000 copies/mL; ref, reference group; 2-week change in viremia, change in Log_{10} AdV viremia in the first 2 weeks from first AdV viremia ≥1000 copies/mL (see figure 1)

Note: Other factors with $p<0.10$ in the $AAUC_{0-16}$ multivariate analysis were retained in the final multivariate models for other measures. Lymphocyte count, sex, and renal replacement therapy were significant ($p<0.05$) prognostic factors in each of the final models.

Figure 3: Pediatric allogeneic hematopoietic cell transplant recipeints with longer or more intense adenovirus infection had a significantly higher risk of all-cause mortality



$AAUC_{0-16}$, Log_{10} of the time-averaged area under the AdV viremia curve over the 16 weeks following first AdV viremia ≥1000 copies/mL; Days viremia ≥1000 copies/mL, number of days where AdV viremia was ≥1000 copies/mL over the 16 weeks following first AdV viremia ≥1000 copies/mL; Q, quartile; Peak viremia, peak Log_{10} AdV viremia over the 16 weeks following first AdV viremia ≥1000 copies/mL; ref, reference group; 2-week change in viremia, change in Log_{10} AdV viremia in the first 2 weeks from first AdV viremia ≥1000 copies/mL (see figure 1)

Note: Other factors with $p<0.10$ in the $AAUC_{0-16}$ multivariate analysis were retained in the final multivariate models for other measures. Lymphocyte count, sex, and renal replacement therapy were significant ($p<0.05$) prognostic factors in each of the final models.

Disclosures. **F. Galaverna**, Chimerix, Inc.: Investigator, Research support. **R. Wynn**, Chimerix, Inc.: Scientific Advisor, Grant recipient and Speaker honorarium. Orchard Therapeutics: Scientific Advisor and Shareholder, Consulting fee and Licensing agreement or royalty. Genzyme: Scientific Advisor, Speaker honorarium. **P. Comoli**, Chimerix, Inc.: Investigator, Research support. **A. Chandak**, Chimerix, Inc.: Research Contractor, Research support. Analytica Laser: Employee, Salary. **E. Vainorius**, Chimerix, Inc.: Employee and Shareholder, Salary. **T. Brundage**, Chimerix,

Inc.: Employee and Shareholder, Salary. **E. Mozaffari**, Chimerix, Inc.: Employee and Shareholder, Salary. **G. Nichols**, Chimerix, Inc.: Employee and Shareholder, Salary.

1733. 10 Years of DTAC Experience With Donor-Derived Cryptococcus Transmission in Solid-Organ Transplantation in the United States

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Background. Cryptococcosis is an important fungal complication of solid organ transplantation (SOT); cases occurring within 6 months posttransplant are often severe and sometimes donor derived. Morbidity can be related to delayed recognition of clinical symptoms or lack of communications among the SOT recipient centers. To better understand transmission of *Cryptococcus* (Crypto) and to identify opportunities for improved identification and communication, all potential donor-derived transmission events (PDDTE) of Crypto reported to OPTN/UNOS ad hoc Disease Transmission Advisory Committee (DTAC) over 10 years were analyzed.

Methods. All Crypto cases reported to DTAC between January 2008 and December 2017 were reviewed retrospectively as potential donor-derived transmission events (PDDTE). Likelihood of donor-derivation was adjudicated based on recipient and donor data.

Results. Fourty-six cases of Crypto were reported to DTAC during this period, involving 145 SOT recipients. Of the Proven or Probable donor-derived Crypto cases ($n = 9$), transmission occurred in 15 recipients; 2 donors each transmitted Crypto to 3 different recipients. Of the Possible cases, 9 recipients were affected. Six recipients with PDDTE Crypto died. Eight recipients received antifungal medications that would prevent transmission of Crypto (classified as intervention without disease transmission).

UNOS Region 7 had the highest number donors with 10, with 6 and 7 from Regions 2 and 3, respectively. No cases *C. gattii* were reported; however, most of the reports to DTAC did not discriminate between *C. neoformans* and *C. gattii*.

Conclusion. This DTAC case series highlights both donor and recipient-derived cryptococcal infections and their potential to have devastating clinical impact. These data also highlight important delays in recognizing Crypto in SOT and in communicating these results to other centers when a PDDTE is possible. Transplant teams should have a high level of suspicion for Crypto in SOT, particularly in those with fever of unknown etiology, pulmonary infiltrates, headaches, and mental status changes. In the future, it may be helpful for transplant center to perform specific testing to discriminate between *Cryptococcus* species to understand their differential impact in SOT.

Disclosures. **D. F. Florescu**, Astellas: Grant Investigator, Grant recipient. **C. R. Wolfe**, Merck: Scientific Advisor, Consulting fee.

1734. Cytokine Levels in Bronchoalveolar Lavage Fluid of Rhinovirus-Infected Hematopoietic Cell Transplant Recipients: Associations With Mortality

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Background. Human rhinovirus (HRV) lower respiratory tract infection (LRTI) is associated with significant mortality in hematopoietic cell transplant (HCT) recipients. The associations between specific cytokine responses and mortality after HRV LRTI are not known.

Methods. Stored frozen BALF samples from adult and pediatric HCT recipients with HRV detected in BALF were analyzed for 30 cytokines (Mesoscale, Rockville, MD). An elasticnet model with Cox regression was used to identify cytokines and other covariates most associated with overall and pulmonary mortality at 90 days, including cytopenias, baseline oxygen (O_2) use, copathogens, steroid use, viral load, and viral species. Identified variables were evaluated in multivariable models and the impact of each variable on the bootstrapped optimism corrected concordance statistic (c-statistic) was calculated. Cytokine levels as outcomes were evaluated using multivariable linear regression.

Results. BALF from 84 HCT recipients with HRV detected in BALF from 1998 to 2015 were included in the analysis. Variables identified in the elasticnet model included: baseline O_2, monocyte count, lymphocyte count, steroid use, endothelial neutrophil activator 78 (ENA-78), IL-4, IL-15, IFN-a2a, and MCP-2. Viral load and species were not associated with mortality. In the model with the highest c-statistic, baseline O_2, monocyte count, lymphocyte count, steroid use, and ENA-78 [adjusted hazard ratio (aHR) 1.19, 95% confidence interval (CI) 1.05–1.35] were significantly associated with overall mortality. For pulmonary mortality, the same clinical factors (except for steroids) and IL-4 (aHR 1.27, 95% CI 1.06–1.54) were associated with the outcome (Figure 1). Models including multiple cytokines did not improve the c-statistic. IL-4 levels were associated with viral load but not with host or clinical factors (slope 0.36, 95% CI 0.1–0.61) (Figure 2).

Conclusion. Elevated IL-4 levels in BALF of HCT recipients with HRV LRTI were associated with increased risk of day 90 pulmonary mortality and may provide unique prognostic information. Viral load and species were not associated with mortality, suggesting that host immune responses play a larger role than viral factors in disease severity. Cytokines may be possible targets for intervention.

Figure 1

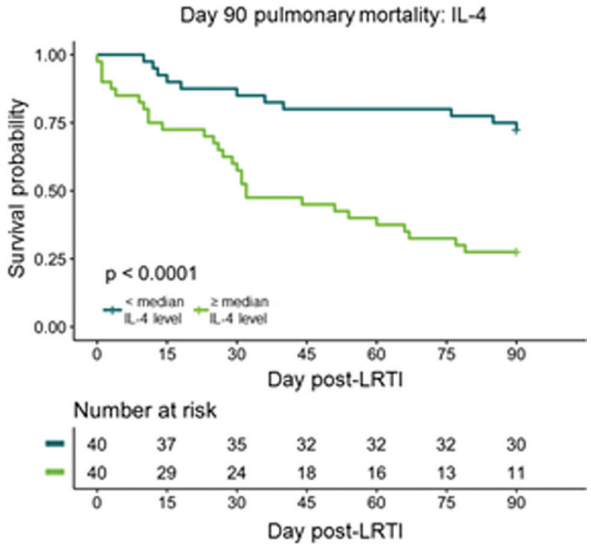

Figure 2