2648. Terminating the Troll of Transplantation: Letermovir for Cytomegalovirus Prophylaxis

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Background: Letermovir is a novel antiviral that was approved for cytomegalovirus (CMV) prophylaxis after allogeneic hematopoietic stem cell transplant (allo-HSCT). The objective was to assess the real-world outcomes of CMV prophylaxis with letermovir compared with preemptive therapy (PT) alone.

Methods: This retrospective pre- and post-study evaluated the clinical impact of using letermovir prophylaxis in CMV-seropositive allo-HSCT recipients at our institution. The electronic medical record was used to identify patients that received PT alone from July 2016 to November 2017 and letermovir prophylaxis from November 2017 to March 2019. The primary endpoint was the proportion of patients with CMV infection requiring PT through week 24 after transplant. Secondary endpoints included the proportion of patients with CMV infection requiring PT through week 14 after transplant, time to CMV infection requiring PT, incidence of CMV disease, CMV-related hospitalization and all-cause mortality through week 14 and 24 after transplant. Safety data included incidence and time to engraftment and adverse effects due to letermovir. Chi-squared and *t*-test were utilized for categorical and continuous data respectively.

Results: The baseline characteristics were similar (Table 1) and 78.7% of patients were high risk for CMV. Fewer patients in the letermovir group (n = 50) than in the historic control group (n = 100) had CMV infection requiring PT through week 24 after transplant (9 [18%] vs. 63 [63%], $P < 0.001$). The mean time to CMV infection requiring PT through week 24 after transplant was 93.4 days (28–161) in the letermovir group vs. 37.4 days (11–126) in the historic control group ($P < 0.001$). The all-cause mortality and incidence of CMV-related hospitalization were not statistically different between the two groups through week 24 after transplant (Table 2). The incidence and time to engraftment were not statistically different between the two groups (Table 3).

Conclusion: Letermovir prophylaxis in the real-world setting resulted in less CMV infection requiring PT when compared with a historic control of patients receiving PT alone. The majority of patients in the letermovir group experienced delayed-onset CMV reactivation. Letermovir was well-tolerated with no apparent myelosuppressive toxicities.

Table 1: Baseline Characteristics

Baseline Characteristics	Letermovir Group (n = 50)	Historical Control Group (n = 100)
Age – mean (range), years	56 (21 - 77)	59 (24 - 76)
Male sex – n (%)	29 (58)	57 (57)
Prior transplantation – n (%)	4 (8)	13 (13)
Allogeneic – n (%)	2 (50)	11 (85)
Autologous – n (%)	2 (50)	2 (15)
Indication for allo-HSCT – n (%)		
Acute myeloid leukemia	21 (42)	38 (38)
Myelodysplastic syndrome	8 (16)	12 (12)
Non-Hodgkin's lymphoma	5 (10)	8 (8)
Acute lymphoblastic leukemia	7 (14)	15 (15)
Other	9 (18)	27 (27)
Stem cell source – n (%)		
Peripheral blood	35 (70)	75 (75)
Bone marrow	15 (30)	25 (25)
Cord blood	0 (0)	0 (0)
HLA matching donor type – n (%)		
Matched related	9 (18)	23 (23)
Matched unrelated	26 (52)	38 (38)
Mismatched related	13 (26)	38 (38)
Mismatched unrelated	2 (4)	1 (1)
Haploidentical related donor – n (%)	12 (24)	37 (37)
CMV-seropositive donor – n (%)	21 (42)	53 (53)
Myeloablative conditioning regimen – n (%)	41 (82)	81 (81)
Antithymocyte globulin use – n (%)	26 (52)	41 (41)
Alemtuzumab use – n (%)	0 (0)	0 (0)
Immunosuppressant regimen – n (%)		
Tacrolimus/methotrexate	35 (70)	64 (64)
Tacrolimus/mycophenolate mofetil/cyclophosphamide	13 (26)	35 (35)
Other	2 (4)	1 (1)
Time to transplant from admission – mean (range), days	8 (4 - 92)	6 (0 - 29)
Time to initiation of letermovir – mean (range), days	2 (-6 - 24)	N/A
CMV >137 IU/mL detected at transplant – n (%)	1 (2)	4 (4)
Risk of CMV disease – n (%)		
High risk	39 (78)	79 (79)
Low risk	11 (22)	21 (21)

Table 2: Primary and Secondary Endpoints

Outcome	Letermovir Group (n = 50)	Historical Control Group (n = 100)	P-Value
Endpoints through week 14 after transplant			
Proportion of patients with CMV infection requiring PT – n (%)	4 (8)	62 (62)	<0.001
Time to CMV infection requiring PT – mean (range), days	38.3 (28 - 62)	36 (11 - 80)	0.769
CMV disease (biopsy proven) – n (%)	1 (2)	0 (0)	0.156
CMV related hospitalization – n (%)	0 (0)	2 (4)	0.315
All-cause mortality – n (%)	6 (12)	7 (7)	0.306
Endpoints through week 24 after transplant			
Proportion of patients with CMV infection requiring PT – n (%)	9 (18)	63 (63)	<0.001
Time to CMV infection requiring PT – mean (range), days	93.4 (28 - 161)	37.4 (11 - 123)	<0.001
CMV disease (biopsy proven) – n (%)	1 (2)	0 (0)	0.156
CMV related hospitalization – n (%)	0 (0)	2 (4)	0.315
All-cause mortality – n (%)	7 (14)	12 (12)	0.728

Table 3: Safety Endpoints

Outcome	Letermovir Group (n = 50)	Historical Control Group (n = 100)	P-Value
Endpoints through week 24 after transplant			
Incidence of engraftment – n (%)	48 (96)	97 (97)	0.748
Time to engraftment – mean, days	15.4	15.8	0.691
Adverse effects due to letermovir – n (%)			
Gastrointestinal symptoms	8 (16)	N/A	N/A

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2649. Measles-Containing Vaccination Resulted in a Balanced Cytokine Profile Without Evidence of Immunosuppression in Healthy 12-Month-Old Children

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Background: Measles virus infection results in immune activation, viral clearance and lifelong immunity. In addition, there is an immunosuppressive state defined by type 2 skewing of $CD4^+$ T-cell cytokine production and induction of regulatory T cells with reduced dendritic cell (DC) activation in the recovery phase. Studies following measles immunization show conflicting immune profiles. To more robustly interrogate and define specific functional cytokine profiles, this study evaluated cytokine profiles in 12-month old infants before and after primary MMR vaccination.

Methods: Cytokine profiles using luminex assay (62-plex; eBioscience) were measured in 65 infants before and 42 days after MMR vaccination administered at 12 months of age as part of a randomized clinical trial. Mean cytokine percentages of children with increased or decreased concentrations of each cytokine in the post sample compared with the levels in the pre sample were evaluated using Student's t-test. Cytokines were arranged into dominant CD4+ T-cell type, Th1, Th2, and T regulatory (T_{reg}) and those produced by DC.

Results: No dominant cytokine pattern emerged following measles immunization, with a balanced profile. The mean percentage of children with increased and decreased concentrations (pg/mL) of signature CD 4+ T-cell Th1 (tumor necrosis factor alpha [TNFa], interferon gamma [IFNg]), Th2 (Interleukin [IL] IL5, IL4, IL13), T_{reg} (IL10, transforming growth factor-β TCFb) and DC (IL12P40 and IL12P70) cytokines were equivalent when measured at 42 days after MMR vaccine compared with levels before vaccine (Table 1) ($P \geq 0.05$ for all comparisons).

Conclusion: In contrast to data demonstrating an immune suppression profile following measles disease, measles-containing vaccine did not suppress Th1 CD4+ T-cell and DC cytokines or promote Th2 and T_{reg} CD4+ T-cell cytokines measured 42 days after vaccination. The cytokine profile represents one of balance and homeostasis. This study supports the data that show measles vaccine does not cause immunosuppression in healthy infants.

Table 1. Cytokine Profile Following Measles-containing Vaccination in 12-month-old Infants.

Cell Phenotype	*Cytokine*	*Decreased (mean %)**	*Increased (mean %)**
Th1 CD4+ T cell	IFNγ	43	57
	TNFα	43	57
Th2 CD4+ T cell	IL5	41	59
	IL4	49	51
	IL13	49	51
Treg CD4+ T cell	IL10	43	57
	TGFβ	49	51
Dendritic Cell	IL12P40	39	61
	IL12P70	41	60

*Mean concentration (pg/ml) of cytokine determined as post-vaccine concentration compared with prevaccine concentration.

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2650. Evaluating Antiviral Agents for Human Noroviruses Using a Human Intestinal Enteroid Model

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Background: Norovirus can cause chronic infections with serious morbidity and mortality in immunocompromised patients. While there are no FDA-approved medications for these infections, nitazoxanide, ribavirin, and enterally administered pooled immunoglobulin (IVIG) are used off-label on the basis of expert opinion. Nitazoxanide and ribavirin show antiviral activity in a murine norovirus infection model and an *in vitro* replicon model of genotype GI.I human norovirus RNA expression, respectively. However, these drugs have not been evaluated in *in vitro* infections with GII.4 human noroviruses, responsible for most human norovirus disease. We used the stem cell-derived nontransformed human intestinal enteroid (HIE) system, which supports GII.4 human norovirus replication, to evaluate the antiviral activities of nitazoxanide, ribavirin, and IVIG.

Methods: We inoculated HIEs with GII.4 human norovirus in the presence of half-log dilutions of nitazoxanide (3 μM to 100 μM), ribavirin (10 μM to 10 mM), or IVIG (1:100 to 1:3,000) and a media control. One and 48 hours after inoculation, we extracted and quantified GII.4 norovirus RNA from the HIEs. To demonstrate that replication inhibition was not due to cytotoxicity, we performed quantitative lactate dehydrogenase release assays on the HIEs across the therapeutic range of each compound.

Results: Nitazoxanide reduced GII.4 replication at 48 hours in a dose-dependent manner, achieving a >90% reduction in viral replication at 10 μM without cytotoxicity. These findings were confirmed in multiple HIE lines representing different intestinal segments and established from different donors. IVIG completely inhibited GII.4 replication at up to a 1:1,000 dilution and was not cytotoxic at therapeutic concentrations. Ribavirin did not reduce GII.4 replication at concentrations up to 10 mMμM, well in excess of levels achieved in human sera with standard doses.

Conclusion: Nitazoxanide and IVIG, but not ribavirin, potently inhibit GII.4 human norovirus replication in a biologically relevant in vitro model of human norovirus infection. These data highlight the use of HIEs as a new pre-clinical model for developing therapeutics for human norovirus disease.

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2651. Protection Against Human Cytomegalovirus Acquisition Is Associated with IgG Binding to Cell-Associated CMV glycoprotein B in Two Historical gB/MF59 Vaccine Cohorts

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Background: Human cytomegalovirus (CMV) is the most common congenital infection worldwide. A CMV glycoprotein B (gB) subunit vaccine with MF59 adjuvant achieved ~50% protection in phase II clinical trials in postpartum and adolescent women. Interestingly, postpartum vaccinees showed poor virus neutralization but robust antibody-dependent cellular phagocytosis (ADCP). In this study, we performed a combined humoral immune correlate of risk analysis in vaccinees to define vaccine-elicited immune responses associated with protection and targets for vaccine candidate immunogenicity.

Methods: gB/MF59 vaccinees who became infected and those who remained uninfected were 2:1 matched on race and number of vaccine doses. This study included 42 women from the adolescent (14 infected, 28 uninfected) and 33 from the postpartum cohorts (11 infected, 22 uninfected). IgG binding to whole gB, gB-neutralizing epitopes, F_CRs, and whole virions were assessed by standard or multiplex ELISA. IgG binding to gB mRNA-transfected HEK293Ts was measured by flow cytometry. Neutralization of Towne, TB40/E, and AD169-repaired-GFP strains were measured in MRC-5, BJ5Ta, and/or ARPE-19 cells. Phagocytosis was assessed by THP-1 uptake of fluorescently conjugated TB40/E and AD169-repaired-GFP virions. Multiple linear regression controlling for cohort was performed for the combined log-transformed group data (apriori significance cut-off of $P < 0.05$, Benjamin–Hochberg FDR < 0.2).

Results: Vaccine-elicited antibodies in adolescent and postpartum cohorts exhibited similar magnitude IgG binding to soluble HCMV gB protein, gB-neutralizing domains, and gB-transfected cells. Autologous Towne strain neutralization was observed in both cohorts, but heterologous strain neutralization was observed only in adolescent vaccinees ($P = 0.001$). Both cohorts exhibited robust phagocytosis of HCMV virions. Regression analyses revealed that risk of HCMV acquisition in vaccinees was associated with magnitude IgG binding to gB-transfected cells ($P = 0.006$, FDR = 0.15), not neutralization or phagocytosis responses.

Conclusion: Protection against primary HCMV infection was significantly associated with vaccine-elicited IgG binding to gB-transfected cells, suggesting the importance of a native, cell-associated gB conformation in future vaccine candidates.

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2652. Cytomegalovirus Meningoencephalitis: A Comparison to Other Viral CNS Infections

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Background: Cytomegalovirus (CMV) is a rare cause of meningoencephalitis (ME) with clinical data limited to case reports.

Methods: Retrospective observational study of all viral central nervous system (CNS) infections identified in 17 hospitals in the Greater Houston area from 2000 to 2017. CMV, herpes simplex virus (HSV), varicella zoster virus (VZV), and enterovirus were all identified by a positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) and all arboviruses were identified by serology.

Results: A total of 361 patients with viral CNS infections were identified: CMV ($n = 33$), enterovirus ($n = 147$), herpes simplex virus ($n = 83$), varicella zoster virus ($n = 28$), and arbovirus ($n = 70$). CMV ME occurred more frequently in immunosuppressed patients [e.g., Acquired Immune Deficiency Syndrome (AIDS)], had more hypoglycorrhachia (59%), and had worse clinical outcomes (61%) as compared with those with HSV, enterovirus, VZV and arboviruses. Furthermore, CMV ME had more altered mental status than enterovirus and HSV and had lower CSF pleocytosis compared with HSV. Additionally, CMV ME had higher CSF protein levels than enteroviral infections and had less CSF lymphocytosis than HSV and VZV.

Conclusion: CMV meningoencephalitis is seen more frequently in immunosuppressed patients (e.g., AIDS), is associated with more hypoglycorrhachia and have worse clinical outcomes compared with other viral CNS pathogens.

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2653. Epidemiology and Risk Factors for Healthcare-Associated Viral Infections in Children

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Background: Healthcare-associated viral infections (HA-VI) are common in hospitalized children and are increasingly recognized as a cause of preventable harm. Yet, epidemiology and modifiable risk factors related to pediatric HA-VI are currently poorly understood.

Methods: We performed a prospective case–control study to identify the risk factors and outcomes associated with pediatric HA-VI at a quaternary care children's hospital between November 2016 and August 2018. Prospective surveillance for HA-VI was performed hospital-wide by certified infection preventionists using NHSN definitions. Cases were matched 1:1 to controls by age, duration of hospitalization, and hospital unit. We abstracted data from the electronic medical record and conducted semi-structured interviews with patient caregivers to identify potential exposures beginning 4 days prior to HA-VI identification date. We also measured length of antibacterial therapy (LOT) in the 7 days following enrollment.

Results: During the study period, we identified 143 eligible patients with HA-VI and enrolled 64 matched case–control pairs. In total, 79 viruses were identified among 64 case patients, of which 53 (67.1%) were respiratory viruses and 26 (32.9%) were GI. Case patients were more frequently exposed to a sick visitor, specifically either caregiver or sibling, compared with controls (18.8% vs. 9.4%; $P = 0.20$, Fisher exact test). During the exposure period, case patients also had a significantly higher number of hospital procedures performed when compared with controls ($n = 320$ vs. 232; $X^2 = 58.43$, $P < 0.001$). Case, when compared with control, patients had a greater average LOT (2.89 vs. 1.08).

Conclusion: Results of study show that exposure to a sick visitor is a potentially modifiable risk factor for pediatric HA-VI. In addition, hospitalized children with HA-VI have increased exposure to antibacterial antibiotics when compared with matched controls. Prevention of pediatric HA-VI may have implications for antibiotic stewardship. Our findings suggest that hospital policies may need to be revised, with emphasis on visitor screening and partnership with families, to reduce the incidence of pediatric HA-VI during hospitalization.

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2654. Myocarditis in Dengue: A Prospective Observational Study

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Background: Cardiac involvement in dengue fever is underdiagnosed due to low index of suspicion and overlapping clinical manifestations of capillary leak associated with dengue. The frequency of subclinical dengue myocarditis and its relative contribution to the hemodynamic instability in severe dengue needs to be explored. We studied the prevalence of myocarditis and clinical outcomes among admitted patients with dengue.

Methods: A prospective observational study was carried out in admitted patients with age between 18 and 65 years having confirmed dengue (NS1/IgM ELISA). Patients with electrolyte abnormalities or on medications affecting heat rhythm/ rate,