Background: Norovirus can cause chronic infections with serious morbidity and mortality in immunocompromised patients. While there are no FDA-approved medications for these infections, 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 antiviral model of genotype G1 human norovirus RNA expression, respectively. However, these drugs have not been evaluated in in vivo 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 1:13,000) 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 stem cell derived enteroids 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 mM, with no increase in 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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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, effective diagnostic 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 for HA-VI in children with 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 semistructured interviews with caregivers to identify potential exposures beginning 4 days prior to HA-VI identification date. We also measured length of antibiotic 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 = 0.02, Fisher exact test). During the exposure period, patients also had a significantly higher number of hospital procedures performed when compared with controls (n = 320 vs. 232; X2 = 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 antibiotic 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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