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Research Brief

Molecular and epidemiologic investigation of a rhinovirus outbreak in a neonatal intensive care unit

Kenza Rahmouni El Idrissi[1], Sandra Isabel MD, PhD[2], Julie Carbonneau MSc[3], Martine Lafond RN[4], Caroline Quach MD, MSc[5], Chelsea Caya MScPH[6], Patricia S. Fontela MD, PhD[6,7,8], Marc Beltempo MD, MSc[6,7], Guy Boivin MD, MSc[3], Marie-Astrid Lefebvre MD, MSc[4,7] and Jesse Papenburg MD, MSc[6,7,8]

[1]Faculty of Medicine, McGill University, Montreal, Quebec, Canada, [2]Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada, [3]Infectious Diseases Research Centre, CHU Quebec and Laval University, Quebec City, Quebec, Canada, [4]Infection Prevention and Control, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada, [5]Department of Microbiology, Infectious Diseases & Immunology, University of Montreal, Quebec, Canada, [6]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada, [7]Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada and [8]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

Abstract

We performed a molecular and epidemiologic study of a healthcare-associated rhinovirus outbreak to better understand transmission in neonatal intensive care settings. Sequencing of the 7 outbreak strains revealed 4 distinct clades, indicating multiple sources. A single clade infected 3 patients in adjacent rooms, suggesting horizontal transmission. We observed 1 rhinovirus-associated death.

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Molecular-based multiplex testing for respiratory viruses detects formerly underdiagnosed healthcare-associated infections (HAIs), including human rhinovirus (HRV).[1,2] In neonates, HRV infections may be associated with upper and lower respiratory symptoms and apnea.[2] Even though HRV is a frequent cause of pediatric viral respiratory HAIs,[2] little is currently known about HRV nosocomial transmission in neonatal intensive care units (NICU).[3–5]

We performed a molecular and epidemiologic investigation of an HRV outbreak at the Montreal Children's Hospital (MCH) NICU. Our objective was to evaluate transmission of HRV within the NICU through contact investigation and viral nucleic acid sequencing.

Methods

We describe a case series of laboratory-confirmed HRV HAI in the MCH NICU during August and September 2017. This tertiary- and quaternary-care NICU comprises 43 single rooms, and 4 twin or triplet rooms.

An HRV infection was considered an HAI if symptom onset occurred >48 hours after admission.[2] Cases were defined as laboratory-confirmed HRV infection with >1 associated clinical symptom.[6]

We extracted clinical data from patient charts and performed HRV nucleic acid sequencing for all 7 outbreak cases and 15 community-acquired control strains randomly selected among contemporaneous HRV-positive specimens tested locally. Polymerase chain reaction (PCR) amplification and nucleic acid sequencing of a 540-nucleotide fragment of the HRV VP4/VP2 capsid genes were performed directly on clinical specimens. Relatedness of outbreak and community strains (GenBank accession nos. MH603569–MH603590) was assessed by phylogenetic analyses using MEGA7 version 7.0.21 software.[7] Further details of molecular analyses are provided in the supplementary material online.

The MCH Research Ethics Board deemed this investigation exempted from review.

Results

In total, 7 NICU patients tested positive for HRV during the outbreak (August–September 2017). Demographic and baseline clinical characteristics are presented in the Supplementary Material.

Overall, 5 patients presented with apneic episodes, and 1 patient required escalation of care from no respiratory support to invasive mechanical ventilation. This baby had an underlying severe progressive hypertrophic cardiomyopathy of unknown etiology and died 15 days after onset of the HRV infection symptoms. Nosocomial HRV species C (HRV-C) bronchiolitis is thought to have contributed to this death.

Phylogenetic analysis of the HRV outbreak strains revealed 4 distinct clades (Fig. 1). HRV-A clades 1 and 2 (color-coded red and green, respectively) comprised a single strain each. HRV-C

Author for correspondence: Jesse Papenburg MD, MSc, Montreal Children's Hospital 1001 Décarie Blvd, Room E05 1905, Montreal, QC, H4A 3J1. E-mail: Jesse.papenburg@mcgill.ca

PREVIOUS PRESENTATION: These study results were presented during a poster session at the Pediatric Academic Societies Meeting on May 6, 2018, in Toronto, Canada.

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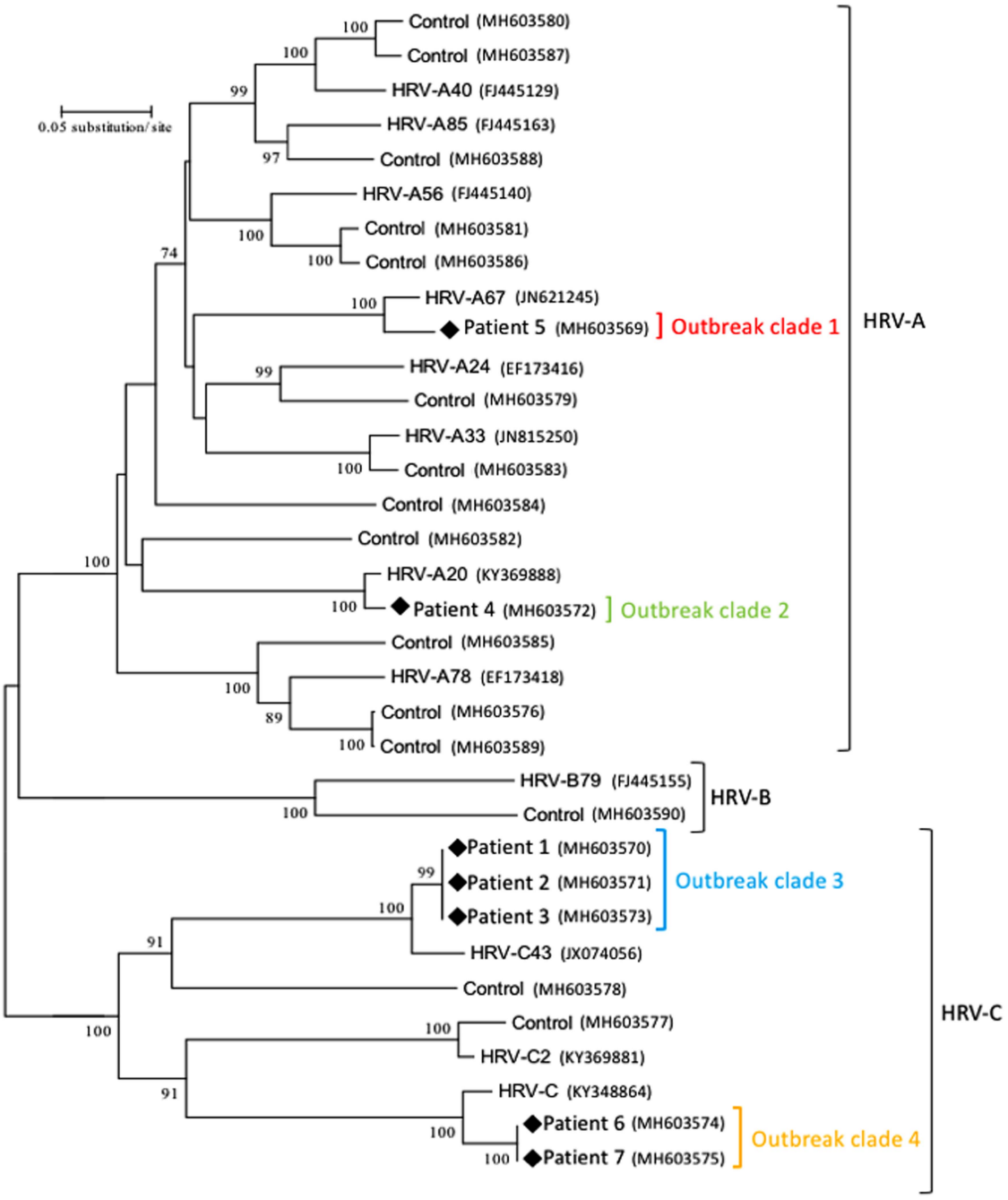

Fig. 1. Phylogenetic tree of human rhinovirus outbreak strains, community control strains and GenBank reference strains. The evolutionary distances were computed using the maximum composite likelihood method and the topology accuracy by 1,000 bootstrap replicates in MEGA7 software. The outbreak clades have been color-coded in red, green, blue, and yellow.

clade 4 (color-coded yellow) infected 2 patients (twins), whereas HRV-C clade 3 (color-coded blue) infected 3 patients occupying 3 adjacent rooms who were treated by the same medical team (Supplementary Fig. 1 online). Concurrently circulating community control strains were genetically diverse, included HRV-A, -B and -C, and were not closely related to the HA-HRV outbreak strains.

Discussion

Viral nucleic acid sequencing and phylogenetic analyses of 7 HRV NICU outbreak strains revealed 4 distinct HRV clades. Thus, multiple sources of HRV infections were contemporaneous to a genetically diverse community summer HRV outbreak. The 2 HRV-C clades infected groups of 2 and 3 patients. This points to probable common sources for these clades, possibly an infected family member (in the case of the twins), shared infected healthcare worker (HCW), improperly disinfected shared equipment, or horizontal transmission via contaminated HCW hands. Coincidentally, HCW hand hygiene audits during the outbreak period recorded suboptimal compliance of 68%. With the exception of the twins, each patient had a private room. Notably, single rooms alone did not fully prevent HAI horizontal transmission.[8]

The HRV genetic analyses of specimens obtained during NICU outbreaks have previously been used to confirm nosocomial

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transmission and to differentiate prolonged HRV shedding periods from reinfections with a different strain.[4] Marcone et al[4] reported an HRV outbreak involving 6 preterm NICU patients whose genotyping identified 4 different and 2 identical strains, pointing to nosocomial transmission of the latter.[4] Reid et al[3] described a neonatal HRV outbreak involving 8 patients. Screening of asymptomatic patients allowed them to detect 4 of these cases, which could otherwise have been unidentified sources of further transmission. These studies show a potential adjunctive role of genotyping in outbreak investigations. Nonetheless, genotyping should not override the use of a case definition combined with the epidemiologic context to establish the presence of an outbreak.

Similarly to previously described HRV outbreaks, 5 of our 7 patients presented mild respiratory symptoms.[1,3,4] However, our case of HRV-associated mortality progressed from no respiratory support to mechanical ventilation, showing the potential severity of HRV outbreaks in vulnerable populations.[9] Among outbreak cases, this patient was the only baby born at term and the only patient without active pulmonary comorbidities. However, the presence of HRV bronchiolitis in the context of underlying symptomatic progressive hypertrophic cardiomyopathy likely contributed to his evolution to respiratory failure and death.

This study has several limitations. Asymptomatic or very mild HRV infections may not have been recognized because no systematic screening was undertaken. Furthermore, we did not test symptomatic family members, visitors, and HCWs for HRV during the outbreak; thus, we could not fully determine the sources of nosocomial HRV transmission. Nonetheless, our epidemiologic and viral sequencing data demonstrate multiple distinct introductions of HRV into our NICU and possible secondary transmission. Given the observed morbidity of HRV infection in NICU patients and potential for severe outcomes, these cases underscore the importance of HCW and visitor hand hygiene and respiratory hygiene, as well as HCW compliance to additional precautions, especially during community HRV outbreaks, which may not occur during periods typically associated with high levels of respiratory virus circulation. The MCH NICU has since continued to reinforce additional measures to prevent outbreaks and to limit their extent, namely by cohorting infected infants and through sensitizing parents and HCWs.

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Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.311

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