RESEARCH ARTICLE

One-third of Children with Febrile Neutropenia and Upper Respiratory Tract Infection Have an Identifiable Viral Isolate in Nasopharyngeal Aspirate: A Prospective Observational Study

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Abstract

Background: Upper respiratory tract infections (URTI) are common during episodes of febrile neutropenia (FN) in children receiving chemotherapy. Identification of viral organisms in children with FN and URTI may aid in reducing the duration of antibiotics.

Materials and methods: The prospective study was conducted over 1½ years (July 2012–December 2013). Nasopharyngeal aspirates (NPA) of children (age ≤14 years) with acute leukemia or non-Hodgkin lymphoma with FN and symptoms of URTI (rhinorrhea with/without cough) were obtained. Reverse transcription polymerase chain reaction (RT-PCR) was utilized to identify respiratory syncytial virus (RSV), human parainfluenza virus 3 (HPIV-3), and human metapneumovirus (HMPV). Real-time PCR was performed for the detection of influenza A and B.

Results: A total of 57 patients with a mean age of 6 years (range: 0.5–14) were included. The majority (89.5%) had acute lymphoblastic leukemia (ALL). About 21 viral isolates were identified in 19 (33%) patients. Influenza A and B (62%) topped the list, followed by RSV and HPIV-3 (14% each) and HMPV (10%). Blood cultures returned sterile from all. All patients recovered uneventfully from the episode of FN. Age ($p = 0.35$), absolute neutrophil count (ANC) ($p = 0.68$), or phase of chemotherapy ($p = 0.36$) were not identified as risk factors for the identification of the viral etiology. A higher proportion of samples collected during winter/spring were PCR-positive as compared to summer/autumn (56.7% vs 14.8%; $p = 0.036$).

Conclusion: One-third of children with FN and URTI had an identifiable viral etiology. Future trials may be conducted to explore if antibiotics can be stopped early in patients with low-risk FN and URTI with an identifiable viral etiology.

Clinical significance: The study contributes to data for antibiotic stewardship for managing children with low-risk FN and URTI.

Keywords: Acute lymphoblastic leukemia, Immunocompromised, Leukemia, Polymerase chain reaction, Treatment, Virus.

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Introduction

Viral respiratory illnesses are common in early childhood and in children receiving treatment for cancer as well. Fever in a child receiving anticancer chemotherapy with neutropenia is an oncologic emergency that merits prompt medical attention. Initiation of broad-spectrum antimicrobials is the norm for managing patients with FN. However, a bacterial pathogen can be identified in a limited proportion of episodes of FN.[1] Symptoms of URTI are not uncommon during episodes of FN in children, particularly during winter and spring. The frequently reported viruses include RSV, influenza A/B, HPIV, human rhinovirus (HRV), and adenovirus.[2] Despite the common occurrence, the virological profile in neutropenic children with URTI has not been well explored. Identification of the etiology of viral URTI in children with FN may help curtail the duration of antibiotics, reduce diagnostic tests and minimize the duration of hospitalization.[2]

This study was conducted to explore the spectrum of respiratory viruses in children with hematolymphoid malignancies and FN with symptoms of URTI from a single center in north India.

Materials and Methods

Patients

The prospective, observational study was performed over 1½ years (July 2012–December 2013). The study was conducted in the Pediatric Hematology-Oncology Unit of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Children and young adolescents (age: 0–14 years) on treatment for ALL, acute myeloid leukemia (AML), or non-Hodgkin lymphoma with FN and symptoms of URTI were enrolled. URTI was defined as the presence of rhinorrhea with or without cough. FN was defined as per the standard criteria.[3] A complete blood count, NPA, and blood culture (BACTEC™) were obtained. In addition, a chest radiograph was performed when clinically indicated. Children with signs of lower respiratory tract infection (LRTI) or a history of epistaxis in

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the past 72 hours were excluded. The study was approved by the institutional ethics committee. Informed consent was obtained.

Sample Collection and Identification of Viral Species

Nasopharyngeal aspirate was collected from the posterior nasopharynx with a suction catheter inserted through the nostril. The aspirates were transported to the laboratory in a viral transport media (HiMedia), maintaining the cold chain. All the samples were stored in a deep freezer at –70°C till processing.

Real-time PCR was utilized to identify viral pathogens, given its higher sensitivity and ability to detect a broader spectrum of viral species than the conventional cell culture or antigen detection methods.[4,5] Viral nucleic acids were extracted from the postcentrifugation supernatant of the NPA samples using the QIAamp viral mini kit (Qiagen, Germany). The Centers for Disease Control and Prevention and human influenza real-time RT-PCR diagnostic panel was utilized to detect the human Influenza A and B viral genomes. TaqMan one-step real-time PCR kit and Applied Biosystems (ABI) 7500 real-time PCR system were employed, using ribonuclease P as an internal control. Samples with a cycle threshold value ≤35 were considered positive. Extracted ribonucleic acid samples were reverse transcribed using Moloney murine leukemia virus reverse transcriptase [Fermentas, United States of America (USA)]. Virus-specific nucleoprotein gene-targeted singleplex reverse transcriptase PCR protocols were used to detect RSV, HMPV, and HPIV-3.[6,7] The amplified DNA fragments were identified on a 2% agarose gel with ethidium bromide and visualized with UV light. For confirmation, the PCR-amplified products were purified and sequenced bidirectionally using BigDye Terminator v3.1 cycle sequencing kit (ABI, Foster, California, USA) with ABI prism 377 analyzers and further checked by basic local alignment search tool.

The Chi-square test and independent Student's *t*-test were applied to test the statistical significance. The statistical tests were performed at a significance level of 0.05. Analysis was performed using the statistical software Statistical Package for the Social Sciences Statistics (version 1.0.0.1347, Armonk, New York, USA).

Results

A NPA sample was obtained successfully in 65 episodes of FN and URTI. Eight samples were spilled during storage. Results were available in the remaining 57. Subsequent discussion will be restricted to the 57 episodes in 57 patients. The mean age of the patients was 6 ± 3 years (range: 0.5–14). The male-to-female ratio was 8.5:1. The underlying malignancies included ALL (89.5%), AML (7%), lymphoblastic lymphoma (1.7%), and Burkitt lymphoma (1.7%). At admission, the duration of fever ranged from 1 to 10 days, with a mean of 2.3 ± 1.3 days. The phases of chemotherapy included induction (31%), consolidation (16%), delayed intensification (20%), or maintenance (33%). The ANC was below 0.2×10^9/L in the majority (89.5%) and $0.2–0.5 \times 10^9$/L in the remaining patients. The platelet count was below 20×10^9/L and ranged from 20 to 50×10^9/L in 41% and 26% of patients, respectively.

A viral pathogen was identified in 19 (33%) patients. Two patients had coinfection with HMPV and influenza virus. Influenza A was the most frequent isolate (33%), followed by influenza B (29%), RSV (14%), HPIV-3 (14%), and HMPV (10%). The distribution of viral isolates across age-groups is illustrated in Table 1. Age was not a risk factor for the identification of viral pathogens ($p = 0.35$). In addition, ANC ($p = 0.68$) or phase of chemotherapy ($p = 0.36$) did not influence the viral positivity. The distribution of viral isolates across the various seasons is listed in Table 2. The proportion of viral isolates was the maximum in spring (62.5%), followed by winter (54.5%) as compared to the remaining year (14.8%) ($p = 0.036$).

The duration of hospitalization ($p = 0.73$) and the duration of fever ($p = 0.44$) were not different among the PCR-positive and negative patients. The procedure of collection of NPA was well tolerated. Adverse effects noticed included transient nasal discomfort (81%), self-limiting epistaxis (44%), or cough (14%). No patient developed complications, including LRTI, septic shock, or fungal infections. There were no deaths.

Discussion

The study was conducted prospectively on a focused cohort of children receiving chemotherapy with FN and URTI. Patients with LRTI were excluded. Viral URTI top the list of common childhood conditions, particularly during the fall and winter months. The global data on the etiologic spectrum of respiratory viruses in children with URTI during the episodes of FN is limited. The probable reasons include (1) a lack of interest of the treating physicians given the unavailability of specific antiviral therapy, (2) a trivial, self-limiting course in the majority of episodes of URTI, and (3) a lack of expertise or availability of virological laboratory. Nevertheless, gathering accurate information on the burden of viral URTI and the epidemiology of respiratory viruses can help develop recommendations for prioritizing drug and vaccine development.[7] Selected reports of viral acute respiratory infection (ARI) in children receiving chemotherapy are summarized in Table 3.[8–14]

The yield of respiratory viruses is dependent on the method of collection of respiratory specimens. The options for collecting upper respiratory samples are multiple and include a swab from the respiratory passage (nasal, throat, mid-turbinate, nose–throat, oropharyngeal, or nasopharyngeal), nasal/NPA, nasal or nasopharyngeal wash, nasal brush, or saliva. Dissenting evidence exists regarding choosing the best respiratory sample, and robust

Table 1: Distribution of viral isolates in NPA across age-groups

Age (years)	*Number of positive cases*	*p-value*
0–5	8/25 (32%)	0.35
5–10	10/25 (40%)	
10–14	3/7 (43%)	

Table 2: Distribution of viral isolates in relation to seasons

	Patients enrolled	*Number of positive viral isolates*					
Season	*n = 57 (%)*	*Influenza A*	*Influenza B*	*RSV*	*HPIV-3*	*HMPV*	*Total*
Winter (Nov–Feb)	22 (38.6%)	5	4	1	0	2	12 (54.5%)
Spring (Mar–Apr)	8 (14%)	2	2	1	0	0	5 (62.5%)
Summer (May–Aug)	20 (35%)	0	0	0	2	0	2 (10%)
Autumn (Sept–Oct)	7 (12.3%)	0	0	1	1	0	2 (28.6%)

Table 3: Selected reports of viral ARI in children with cancer

S. No.	*City, country, and year of publication*	*Patient number, age, and diagnosis*	*Clinical profile*	*Methodology*	*Prevalence and common viral agents*	*Comment*
1.	Atlanta, USA, 2020[9]	404; median age: 7 years, and leukemia and solid malignancies	298 episodes of FN	PCR	59%; HRV/ enterovirus (61%), RSV (11.4%), and HCoV (9.7%)	Identification of respiratory virus had no impact on the length of hospital stay or death
2.	New Delhi, India, 2019[1]	81; median age: 4.5 years (IQR, 3.2–8), and leukemia and solid malignancies	81 episodes of FN with ARI (URTI: 56.5% and LRTI: 43.5%)	NPA; RT-PCR	76.5%; HRV (36.8%) and RSV (13.6%)	Respiratory viral infections associated with prolonged fever and duration of antibiotics
3.	Beirut, Lebanon, 2019[8]	67; median age: 4.5 years (IQR 3–8) and hematologic and solid malignancies	89 febrile episodes with symptoms of URTI	Nasopharyngeal swab; RT-PCR	86.5%; RSV (45.45%), HPIV (26%), influenza type B (26%), HMPV (24.6%), and HCoV (24.6%)	Significant association of RSV infection with LRTI, bronchitis, and bacteremia observed
4.	Istanbul, Turkey, 2018[10]	48; median age: 8 years (range: 0.6–18) and hematologic and solid malignancies	72 ARI episodes (URTI: 80.6% and LRTI:19.4%)	Nasal swab; multiplex RT-PCR	56.9%; Rhinovirus (36.5%), RSV (19.5%), and HCoV (19.5%)	-
5.	Izmir, Turkey, 2018[11]	108; mean age 76.8 ± 59.3 months and hematologic and solid malignancies	138 febrile episodes and 44% episodes had neutropenia. Respiratory symptoms in 50% patients	Nasal swab; RT-PCR, viral culture, and immunofluorescent assay	44%; HRV (22%) and RSV (11%)	33.3% patients had a delay in cancer treatment owing to viral respiratory infection
6.	Memphis, USA, 2016[12]	160; median age: 5.4 years (range: 1.0–20.6) and ALL	269 episodes of ARI (URTI: 81.9% and LRTI: 18.1%)	Nasopharyngeal swab or wash, tracheal aspirate and BAL. Viral culture, direct fluorescent antibody immunoassay, and PCR	49.4%; influenza (38%) and RSV (33%)	19% of the patients with URTI had complications including otitis media, sinusitis, and parotitis
7.	Stockholm, Sweden; 2016[13]	54; median age: 7 years (range: 0.5–17.7) and hematologic and solid malignancies	87 episodes of FN and respiratory symptoms in 70% of patients	NPA; RT-PCR	45%; HRV (22%), HCoV (8%), and influenza (5%)	Authors postulate that the finding could lead to a decrease in the duration of both hospitalization and treatment with broad-spectrum antibiotics
8.	Santiago, Chile, 2012[14]	193; median age: 7 years (IQR: 4–12) and hematologic and solid malignancies	331 episodes of FN	Nasopharyngeal swab; PCR and low-density microarray	57%; RSV (31%), HRV (23%), parainfluenza virus (12%), and influenza A (11%)	Viral isolation associated with a lower probability of hypotension and admission to PICU ($p < 0.05$)
9.	Current study	57; mean age: 6 years (range: 0.5–14) and leukemia and non-Hodgkin lymphoma	57 episodes of FN with URTI	Nasopharyngeal swab; PCR	33%; influenza A and B (62%), RSV (14%), and HPIV-3 (14%)	Identification of respiratory virus had no impact on clinical outcome

ALL, acute lymphoblastic leukemia; ARI, acute respiratory infection; BAL, bronchoalveolar lavage; FN, febrile neutropenia; HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; HRV, human rhinovirus; IQR, interquartile range; LRTI, lower respiratory tract infection; NPA, nasopharyngeal aspirate; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; RV, respiratory virus; RT-PCR, reverse transcription polymerase chain reaction; URTI, upper respiratory tract infection; USA, United States of America

literature is yet not available to support the development of a consensus guideline.[15] In a meta-analysis comparing the diagnostic value of 16 sampling methods with 54,438 samples from 57 literature, NPA was identified as a sample with an intermediate diagnostic value (6th rank). Nasopharyngeal wash, mid-turbinate swab, and nasopharyngeal swab were the three top-ranked samples.[15] Several prospectively conducted trials have reported comparable sensitivity of NPA with other respiratory samples.[16,17] Despite being relatively invasive, the procedure of NPA is safe and largely well tolerated, as was our experience too.[18] However, with the increasing availability of highly sensitive methods of virus identification, such as PCR, relatively noninvasive procedures, such as nasal swabs or washing, may be considered a more suitable option.[16]

The conventional diagnostic armamentarium for respiratory viral pathogens includes viral culture, rapid immunoassay, or direct fluorescent antibody staining. We used a PCR-based method as it has a higher sensitivity than conventional diagnostics.[19–23] The methods of parallel detection of multiple respiratory pathogens by moderate to high-complexity multiplex panel assays, such as multiplex PCR, nucleic acid sequence-based amplification, transcription-mediated amplification, etc., are gaining momentum for the etiological diagnosis of viral respiratory infection.[24]

The yield of a viral pathogen in the current study was 36.8%. Influenza, RSV, and HPIV-3 were the most common isolates. A retrospective study from Turkey in children with cancer undergoing chemotherapy reported a 39.1% yield of viral isolation associated with episodes of ARI. The HRV was the most common agent, followed by HPIV-3 and RSV.[11] A noticeably higher frequency of viral isolation was reported from a case-control study from New Delhi.[1] The study reported a prevalence of 76.5% among children with FN and ARI; HRV and RSV were the most common viral isolates. A relatively higher frequency of viral yield, compared to our study, has been reported from several other trials as well (Table 1). The plausible reasons could be (1) noninclusion of selected respiratory viruses in the PCR panel, namely, HRV, adenovirus, bocavirus, and coronavirus, (2) exclusion of patients with LRTI, and (3) intermediate level diagnostic value of NPA.

Prolonged (≥21 days) viral shedding following respiratory viral infection (RVI) in immunocompromised patients is well-reported.[24–26] Hence, a positive PCR in a patient with URTI in the recent past indicates a new viral infection or persistence of the previous pathogen. In our study, patients with a history of URTI in the preceding 3 weeks were not excluded, thus leaving a window for false-positive PCR results.

The season-wise distribution curve of PCR-positivity in the respiratory samples was significantly skewed toward winter and spring. Studies conducted on a similar cohort of patients by Koskenvuo et al.,[27,28] Aydin et al.,[11] and Soudani et al.,[8] have similarly reported predilection of respiratory viral infections for winter and spring.

Polymerase chain reaction positivity did not impact the duration of hospitalization or fever in our study. A similar finding was noted in a long-term, prospective, multicenter study by Koskenvuo et al.,[28] exploring respiratory viruses in 51 children with leukemia during 138 febrile episodes. The mean duration of fever was not different between patients with [2.6 days; standard deviation (SD) 1.7] and without (2.1 days; SD 1.3) viral infection ($p = 0.44$) in our study. However, contrasting experience is reported from a case-control study from New Delhi[1]; children on anticancer therapy with FN and documented RVI had delayed defervescence (median duration of fever: 4 vs 3 days, $p = 0.005$) and required an extended period of antibiotic therapy (median duration of antibiotic treatment: 9 vs 7 days, $p = 0.046$), as compared to peers without RVI.[1]

All children with viral URTI had an uncomplicated clinical course in the current study. The finding is similar to a Brazilian study by Rondinelli et al.[29] The study was conducted retrospectively on children and adolescents on anticancer therapy with FN to identify risk factors for severe infectious complications. The study documented a lower risk of severe complications in children with FN and symptoms of URTI ($p = 0.001$).[29] In a previous study from our center on children with FN, the presence of URTI as the focus of fever was associated with a lower risk of developing complications (OR 0.29, 95% confidence interval: 0.11–0.78; $p = 0.015$); among 414 episodes of FN, mortality was observed in 43 (10.4%).[30] In the current cohort, there was no mortality. Indeed, a comparison with the historical cohort provides indirect evidence for the favorable outcome of children with FN and URTI.

A febrile illness in a neutropenic child, irrespective of the presence of URTI, is a medical emergency and obliges the treating physician to initiate antibacterial treatment. However, early discontinuation could be considered in patients with "low risk" FN and URTI as the focus of fever. In a multicentric randomized clinical trial by Santolaya et al., early discontinuation of antibiotics was found to be safe in children with FN and URTI with a documented viral respiratory pathogen.[31] In a multicentric, prospective study of children with FN, children with a respiratory virus had fewer days of hospitalization and a significantly lower probability of hemodynamic instability or admission to the intensive care unit ($p < 0.05$).[14]

All patients in our study had a favorable outcome, irrespective of viral isolation. It makes one contemplate if an early withdrawal of antibiotics could be considered in children with FN and URTI, irrespective of viral isolation. Indeed, in a study of children with FN, there was a lack of correlation of respiratory viral positivity with the clinical outcome, including the probability of hypotensive shock, length of hospital stay, and mortality.[9] Thus, the presence of symptom(s) of URTI in a child with FN may be considered a "good prognostic" marker and encourage the early withdrawal of antibiotic therapy in clinically stable patients, irrespective of the identification of a virus.

Clinical Significance

Our study contributes to data for considering a judicious approach to antibiotic therapy and antibiotic stewardship in managing children with low-risk FN and URTI.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the Institute's Ethics Committee. Written informed consent was obtained from the parents of all patients.

Consent for Publication

Consent was obtained from all the contributing authors.

Author's Contribution

Deepak Bansal and RK Ratho created the concept and design of the study. Ananata R Kancharapu collected the data, obtained NPA samples, and performed the statistical analysis. RK Ratho and Subhabrata Sarkar performed the PCR. Pritam Singha Roy drafted the manuscript and reviewed the literature. Deepak Bansal and Ananata R Kancharapu participated in the clinic. All authors read and approved the final manuscript.

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