Article published online: 2024-10-29

Original Article

Frequency and Clinical Outcomes of Respiratory Infections in Children with Cancer Presenting with Febrile Illness

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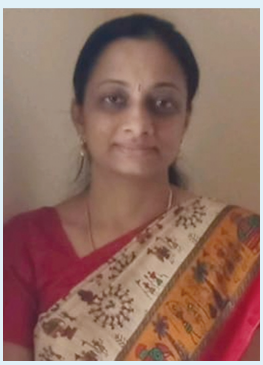
South Asian J Cancer

Abstract



Arathi Srinivasan

Objectives Fever is a known complication in pediatric cancer patients when on chemotherapy for which prompt initiation of empiric antibiotics is the single most important life-saving intervention. Nearly two-thirds of all children are treated without identifying the source of fever. Molecular diagnostics can improve management of febrile episodes and reduce unnecessary antibiotic use. The purpose of our study was to evaluate the pathogenic etiology of febrile episodes and analyze their clinical characteristics.

Materials and Methods We conducted a prospective observational study at our tertiary care institution from January 2019 to March 2020, to identify the etiology of febrile episodes with or without neutropenia in pediatric cancer patients and to study their clinical outcomes.

Results Forty febrile episodes were observed among 27 patients over a period of 15 months. The mean age group was 5 years. In 28 febrile episodes without a focus (70%), a respiratory organism (virus, bacteria, or coinfection) was detected. Rhinovirus was the most common single respiratory isolate (47.36%), followed by *Streptococcus pneumoniae* (21.05%) and six episodes had multiple viral isolates (21.42%). There was no prolonged hospitalization, need for intensive care unit or oxygen requirement, or mortality. The most common antibiotic used in empiric management was piperacillin–tazobactam. Aminoglycosides were added when there was a clinical suspicion of resistant organism.

Conclusion Around 70% of febrile episodes without a focus or documented infection in cancer children had a respiratory pathogen identified in nasopharyngeal swab. Molecular diagnostics greatly enhances diagnostic sensitivity and thereby individualizes the management of febrile illness in these children.

Keywords

- pediatric cancer
- febrile illness
- neutropenia
- respiratory virus
- bacterial infection

DOI https://doi.org/10.1055/s-0044-1791970 ISSN 2278-330X

How to cite this article: Srinivasan A, Ramya MS, Chandy S, et al. Frequency and Clinical Outcomes of Respiratory Infections in Children with Cancer Presenting with Febrile Illness. South Asian J Cancer 2024;00(00):00–00

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Key message

Molecular diagnostics can improve diagnostic sensitivity of febrile episodes in children with cancer and help rationalize the management.

Introduction

Most cases of fever in children with cancer are treated empirically with antibiotics[1] and nearly three-fifths of febrile episodes without a focus or documented infection have a respiratory pathogen identified in nasopharyngeal (NP) swab. For this reason, the present study was performed which focuses on molecular identification of the respiratory pathogens in samples collected from pediatric cancer patients presenting with fever with or without respiratory illness.

Methodology

This is a prospective observational study to identify pathogenic etiology of febrile episodes in pediatric cancer patients when on chemotherapy and study their clinical outcomes.

Materials and Methods

Children under 18 years of age with malignancies on chemotherapy admitted as inpatients with fever and either with a respiratory focus or no focus of infection during January 2019 to March 2020 were included in the study.

Those children with malignancies on chemotherapy admitted as inpatients with fever but have microbiologically documented bacterial infection/focus were excluded. Each new episode of fever in a child was considered a new episode of infection. A thorough clinical evaluation by detailed history and physical examination was done in all admitted patients at the onset of fever.

Laboratory tests included a complete blood cell count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin. At least two sets of blood cultures were done simultaneously, with one set collected from lumen of an existing central venous catheter, if present, and another from a peripheral vein site; two blood culture sets from separate venipunctures were sent if no central catheter is present.

Identification of respiratory viruses or bacteria (a panel total of 33 respiratory pathogens) was done by multiplex real-time polymerase chain reaction (RT-PCR) from NP swab. RT-PCR was done using Fast Track Diagnostics (FTD) kit, respiratory pathogen 21 plus kit (FTD Jung Linster, Luxembourg), which is a multiplex RT-PCR and can detect 20 viral and five bacterial pathogens.

Statistical Analysis

Statistical analysis was performed by the statistical software STATA 11.0. Continuous variables were represented as "mean (standard deviation)," and categorical variables were represented as "frequency (percentage)." Chi-square test or Fisher's exact tests were used to assess differences in categorical data. Kruskal–Wallis tests were used to find the difference in means of more than two independent data. The *p*-value of <0.05 is considered as significant.

Results

There were 40 episodes of febrile illness during the 15 months among 27 patients on therapy for cancer. There was no gender predilection (male:female 14:13). The age group ranged from 1 year 6 months to 11 years 4 months (mean and median age group of 5 years). Majority of the patients had hematological malignancy (95%) as their primary diagnosis. Half of the febrile episodes were observed in children less than 5 years.

NP swab was positive in 28 out of 40 episodes (70%) but in 12 episodes (30%) no pathogen was identified. Seasonal predilection to monsoon and winter season for admission in the hospital was evident in those with positive NP swab. There were 26 out of 28 episodes admitted from September to March (92.85%) (inclusive of both years—2019 and 2020; ►Fig. 1).

Respiratory symptoms were present in 19 out of 28 episodes with positive NP swab (67.86%), but only in 6 out of 12 episodes with negative NP swab (50%; ►Table 1). The duration of hospitalization was comparatively lesser in NP-swab–positive isolates than in negative swabs though not statistically significant. More than 50% (16/28) had absolute neutrophil count (ANC) $<1,000$ and there were six episodes with ANC <100 in positive the NP swab category (21.42%). Whereas only 2/12 (16.66%) and 5/12 (41.7%) in the negative NP swab category had ANC <100 and ANC $<1,000$, respectively. The duration of antibiotics was more or less the same in both NP-swab–positive and negative episodes (range: 7.53 ± 2.79 in positive and 8.75 ± 3.57 days in negative episodes). None of the episodes were severe enough for intensive care unit (ICU) admission or oxygen requirement. One episode of negative NP swab required ICU admission 10 days after hospitalization in view of persisting fever and manifestation of central nervous system symptoms. All the above categories of comparison like the respiratory symptoms, duration of hospitalization, duration of antibiotics, and need for ICU admissions or oxygen requirements were statistically not significant.

Among episodes with positive NP swab, the organisms identified were single respiratory virus in 15/28 (53.57%), multiple viruses in 6/28 (21.42%), respiratory bacteria in 4/28 episodes (14.28%), and co-infection of both respiratory virus and bacteria in 3/28 (10.71%). Majority of viral episodes were symptomatic (18/28, 64.29%), irrespective of whether

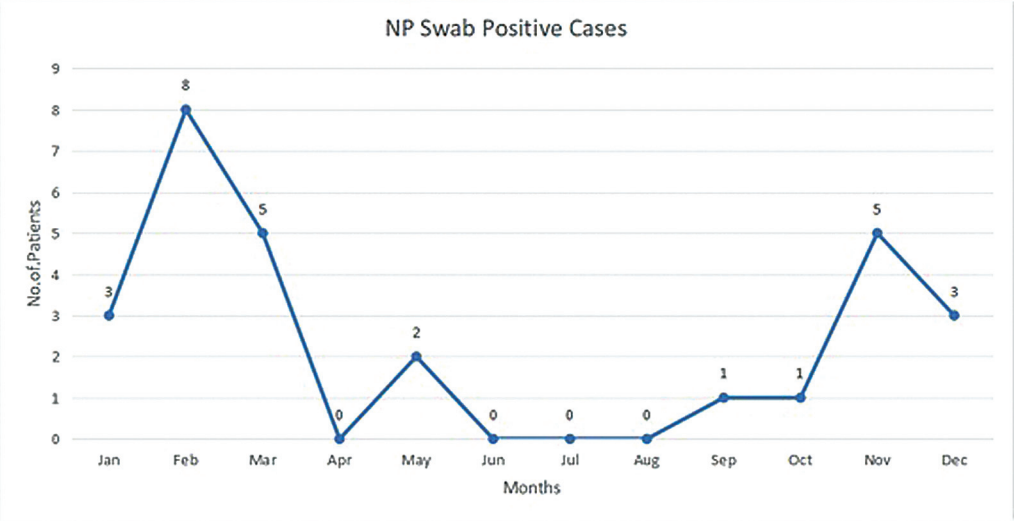


Fig. 1 Seasonal distribution of respiratory pathogens.

the NP swab showed a single virus (12/15, 80%), multiple viruses (4/6, 66.67%), or viral co-infection with bacteria (2/3, 66.67%). In contrast, isolated bacterial NP swabs were largely without respiratory symptoms (1/4, i.e., only 25% with symptoms).

Out of the single organisms isolated through NP swab (virus: 15 and bacteria: 4), the most common was Rhinovirus (RV; $n = 9/19$; 47.36%). Next in the prevalence was *Streptococcus pneumoniae* ($n = 4/19$; 21.05%) followed by human parainfluenza virus 3 (HPIV3; $n = 3/19$; 15.78%). Among the multiple organisms isolated, there were six episodes with multiple viruses and three with combination of virus and bacteria (►**Table 2**).

On comparing the three most prevalent organisms identified in our study, we found that RV and HPIV3 were prevalent in wider age groups starting from 1 year 5 months to 8 years, whereas *S. pneumoniae* was prevalent among 4-to-6-year age groups (►**Table 3**). Of all the variables, respiratory symptoms seem to be significant for viruses (RV and HPIV3) than bacterial isolate (*S. pneumoniae*). None of the three organisms required prolonged hospitalization or oxygen therapy or ICU admission. The most commonly used antibiotic as an empiric management as per febrile neutropenia institutional protocol was piperacillin–tazobactam and aminoglycoside was added when there was a clinical suspicion of resistant organism.

Table 1 Comparison between NP-swab-positive and -negative episodes

	Nasopharyngeal swab		
	Positive	**Negative**	***p*-Value**
Respiratory symptoms			0.285
Yes	19 (67.86%)	6 (50%)	
No	9 (32.14%)	6 (50%)	
Duration of hospitalization	4.32 ± 1.51	6.5 ± 5.35	0.1874
Absolute neutrophil count			0.369
< 1,000	16 (57.14%)	5 (41.67%)	
> 1,000	12 (42.86%)	7 (58.33%)	
Duration of antibiotics	7.53 ± 2.79	8.75 ± 3.57	0.4934
ICU/oxygen required			0.300
Yes	0 (0%)	1 (8.33%)	
No	28 (100%)	11 (91.67%)	
Type of malignancy			0.480
Hematological malignancy	26 (92.8)	12 (100)	
Solid tumors	2 (7.1)	0	

Abbreviation: NP, nasopharyngeal.

Table 2 Respiratory viruses and bacteria in episodes with positive nasopharyngeal swab: single respiratory viral infection (bold) and co-infection

	RV	Flu A	Flu B	H1N1	HPIV3	COR43	COR63	HRSV A	HRSV B	EV	SPN
RV	**9**					1					1
Flu A		**1**		1							1
Flu B			**1**								
H1N1		1									
HPIV 3					**3**						
COR 43						**1**					
COR63		1									
HRSV A									1		
HRSV B											
EV	1										
SPN											**4**

Abbreviations: COR 43, corona 43; COR 63, corona 63; EV, enterovirus; Flu A, influenza A; Flu B, influenza B; HPIV3, human parainfluenza virus 3; HRSV A & B, human respiratory syncytial viruses A and B; RV, rhinovirus; SPN, *Streptococcus pneumoniae*.
Note: There was one more episode of febrile neutropenia with four respiratory organisms isolated not included in this table: RV + HRSV A + HRSV B + SPN.

Table 3 Comparison table of the three most common respiratory pathogens

Single organism isolated through NP swab ($n = 19$)	Rhinovirus ($n = 9$; 47.36%)	*S. pneumoniae* ($n = 4$; 21.05%)	HPIV3 ($n = 3$; 15.78%)	*p*-Value
Age				0.6524
Mean	3.85 (1.53)	5.19 (0.43)	4.09 (3.41)	
Median	3.48	5.15	2.5	
Range	1.53–6.09	4.72–5.77	1.76–8.01	
Gender				0.545
Male	5 (55.5)	1 (25)	1 (33.33)	
Female	4 (44.4)	3 (75)	2 (66.67)	
Type of malignancy				
Hematological malignancy	9 (100)	4 (100)	3 (100)	
Solid tumor	0	0	0	
Respiratory symptoms				0.072
Yes	7 (77.77)	1 (25)	3 (100)	
No	2 (22.22)	3 (75)	0	
Absolute neutrophil count				0.906
$< 1{,}000$	5 (55.5)	2 (50)	2 (66.67)	
$> 1{,}000$	4 (44.4)	2 (50)	1 (33.33)	
Duration of hospitalization	3–7 days	2–5 days	3–4 days	0.6824

Abbreviations: HPIV3, human parainfluenza virus 3; NP, nasopharyngeal.

Discussion

Fever in children with cancer during chemotherapy is quite common owing to their immunocompromised status.[2,3] This is one of the main causes of morbidity, delay in chemotherapy schedule, and sometimes mortality.[4] These patients often are initiated on broad-spectrum antibiotics to cover serious bacterial diseases.[5] Decision on discontinuation of antibiotics is also subjective[6] and hence adds up to indiscriminate use of antibiotics[1] and potential emergence of antibiotic resistance.[5]

The respiratory tract of immunocompromised patients becomes a vulnerable target for microorganisms, pathogenic or opportunistic, as it is directly connected with the environment.[6] In healthy children, respiratory viruses are usually confined to the upper respiratory tract; in

immunocompromised patients, owing to defects in innate and adaptive immunity and frequent visits to hospital, respiratory infections can rapidly disseminate[6] and progress to the lower respiratory tract leading to respiratory distress and pulmonary compromise.[5]

Routine chest X-ray is not recommended in the initial assessment of pediatric febrile neutropenia[2] in the absence of respiratory symptoms. In recent years, significant progress has been implemented in molecular techniques for the detection of respiratory pathogens as compared with conventional methods of cell culture or antigen detection.[5] Although there are several studies on respiratory organisms in children with cancer, there are limited reported studies on their detection by multiplex molecular amplification assays (RT-PCR) in India.[1,7] Our study analyzed the RT-PCR positivity and correlated it with the respiratory illness of patients with febrile episodes with or without neutropenia.

Our study could identify pathogens (either single virus or bacteria or multiple viruses or co-infection) among 70% subjects through this technique, whereas it was 46% in Torres et al[8] and 52% in Suryadevara et al's[9] studies. The reason for higher percentage in our study could be because we tested for a larger panel of 33 respiratory pathogens unlike other studies. In our study, half of the febrile episodes were observed in children less than 5 years, which is almost similar to the study done by Soudani et al.[5]

RV was the most commonly identified pathogen in our study, similar to few other studies.[1,8–10] The next common organism was *S. pneumoniae* in contrast to other studies that had RSV as the second most common virus isolate.[8,10] The reason could be that these studies had only viruses in the respiratory panel unlike our study which included bacteria also in the respiratory panel. We could also find that there was co-presence of respiratory organism (either single virus or a co-infection) detected in more than half of the febrile episodes with culture-positive bacteremia. Since we needed to exclude the patients who had a microbiologically documented infection or focus, we did not take them into our analysis.

We found that respiratory symptoms were present at admission in 67.86% of the episodes with NP swab positive for respiratory virus or bacteria, which corresponds to studies done by Torres et al[8] and Suryadevara et al.[9] We also noticed that those with positive NP swab for RV had obvious respiratory symptoms compared to those with positive NP swab for *S. pneumoniae* or HPIV3, which was a statistically significant finding in our study. Similar to the study done by Srinivasan et al,[10] we had more cases from September to March.

In our study, the duration of hospitalization was comparatively low in NP-swab–positive episodes than in NP-swab–negative episodes, though it was statistically not significant. None of the episodes had any adverse outcomes or ICU admissions. Likewise, in the study by Torres et al,[3] all children with a positive respiratory virus detection, in the absence of a positive bacterial detection, had a favorable outcome.

The increasing detection of respiratory organisms highlights the importance of optimizing molecular diagnosis as part of the workup in cancer children when admitted for febrile episodes while on chemotherapy. It, however, needs to be analyzed if the PCR positivity actually represents the direct causative agent of the neutropenic fever or not, because a positive PCR result could also represent a subclinical infection, a postinfection viral shedding, or just intracellular nonreplicating viral nucleic acid remnants. Limitations of this study were we had a small sample size and since all children admitted were invariably initiated on empirical antibiotics as per febrile neutropenia institutional protocol, we could not evaluate the clinical course of positive NP swabs in the absence of antibiotic use. Furthermore, we also did not involve any control group to conclude if the NP swab results are to be taken as an acute infection or as commensals in the throat.

Conclusion

In our study, the PCR-based diagnostics could identify around 70% of respiratory pathogen in febrile episodes without a focus or documented infection. PCR-based diagnostics for respiratory pathogens can greatly enhance the management of patients with febrile neutropenia where standard tests show no documentation of cause of the infection. In the future, application of agile and broad microbial diagnostics may provide decreased use of antibiotics and individualize infection management.

Previous Presentation

Loganathan A, Bharadwaj R, Srinivasan A, Scott JX. Cytogenetics and molecular genetics in pediatric acute lymphoblastic leukemia (ALL) and its correlation with induction outcomes. South Asian J Cancer. 2022;11(4):353–360. Published 2022 Aug 22. doi:10.1055/s-0042-1754337.

Author's Contribution

A.S. was responsible for the conception and design of the study, as well as for revising the manuscript critically for important intellectual content and approving the final version for publication. M.S.R. handled the acquisition of data, conducted the analysis and interpretation of that data, drafted the manuscript, and approved the version to be published. S.C. contributed to the analysis and interpretation of data, revised the manuscript critically for important intellectual content, and approved the final version for publication. Lastly, S.B. was involved in the conception and design of the study, revised the manuscript critically for important intellectual content, and approved the manuscript for publication.

Ethical Approval

This study was cleared by the Institutional Ethics Committee (IEC) for its scientific content and ethics (IEC-23/MAY2018-IRB min dt 30.05.2018; IRB EC Re-Registration No. ECR/676/Inst/TN/2014/RR-17).

Source(s) of Support

Study was funded by The CHILDS Trust Medical Research Foundation.

Conflict of Interest

None declared.

Acknowledgments

- Dr. Anand Manoharan, PhD, MPH, Director-Research, The CHILDS Trust Medical Research Foundation (CTMRF), Kanchi Kamakoti CHILDS Trust Hospital: for editing the final manuscript.
- Dr. Dhanalakshmi, Senior Consultant, Department of Pediatric Infectious Diseases, Kanchi Kamakoti CHILDS Trust Hospital: for clinical support.
- Dr. Julius Scott, Senior Consultant, Department of Pediatric Hemato-oncology, Kanchi Kamakoti CHILDS Trust Hospital: for clinical support.
- Mr. Robinson, The CHILDS Trust Medical Research Foundation: for providing the laboratory analysis and details.
- Dr. Gothai Nachiyar, Consultant-Data Analyst, The CHILDS Trust Medical Research Foundation: for statistical analysis.

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