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Impact of Respiratory Viral Panel Testing on Length of Stay in Pediatric Cancer Patients Admitted with Fever and Neutropenia¹

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Abstract

Background: Polymerase chain reaction (PCR) respiratory viral panel (RVP) testing is often used in evaluation of pediatric cancer patients with febrile neutropenia (FN), but correlation with adverse outcomes has not been well characterized.

Procedure: A retrospective cohort of all children ages 0–21 with cancer admitted to Children's Healthcare of Atlanta for FN from January 2013 to June 2016 was identified. Patient demographic and clinical variables such as age, RVP results, length of stay (LOS), and deaths were abstracted. Relationship between RVP testing and positivity and LOS, highest temperature (Tmax), hypotension and ICU admission were compared using Wilcoxon rank sums, Chi-square, or Fisher's exact tests adjusting for age, sex, bacteremia, and diagnosis.

Results: The 404 patients identified had 787 total FN admissions. RVPs were sent in 38% of admissions and were positive in 59%. Patients with RVPs sent were younger (median 5.5 vs. 8.0 years, $p<0.0001$) with higher Tmax (39.2° vs. 39.1°, $p=0.016$). The most common virus identified was Rhinovirus/Enterovirus (61%). There were no significant differences in highest temperature or lowest blood pressure based on RVP positivity. Patients admitted to the ICU were more likely to have RVPs sent (OR=3.19, $p<0.002$), however neither having RVP testing nor RVP positivity were significantly associated with increased LOS or death. Coinfection with bacteremia and a respiratory virus was identified in 9.1% of patients.

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Conclusions: These data raise the question of the utility of sending potentially costly RVP testing as RVP positivity during febrile neutropenia does not impact LOS, degree of hypotension, or ICU admission.

Keywords

oncology; febrile neutropenia; respiratory viral infection

Introduction

Febrile neutropenia (FN) is one of the most common complications of pediatric cancer therapy. With widespread use of broad-spectrum antibiotics, mortality due to FN has dramatically declined. However, FN impacts patient quality of life and financial burden due to prolonged hospitalization¹. The majority of research to date on FN in children has focused on invasive bacterial and fungal disease^{2–6}. The clinical implication of systemic viral infection, however, has not been well characterized. The most recent clinical practice guidelines published by international experts on pediatric FN suggest that further research is needed on the clinical implications for management of systemic viral infections⁷.

Historically, testing for respiratory viruses was a lengthy process. With the advent of polymerase chain reaction (PCR) testing, respiratory viral panel (RVP) results are now rapid and validated in immunocompromised patients^{8,9}. Though an RVP is often sent during evaluation of FN, the clinical significance of having the results of this testing is not well characterized. Several studies have demonstrated that respiratory viral infections (RVIs) are prevalent in children with FN, ranging from 38–76%^{10–13}. Despite the prevalence of RVIs, only a few of the validated risk stratification scoring systems for pediatric patients with FN includes clinical signs of viral infection^{14,15}.

This study sought to characterize the prevalence of RVIs in pediatric patients with cancer and FN at a single institution. In addition, this study aimed to explore whether RVP positivity was associated with clinically relevant adverse outcomes, including prolonged length of stay (LOS), Intensive Care Unit (ICU) admission, or death. We hypothesized that those patients with a positive RVP would have a less severe disease course as measured by fewer ICU transfers, positive blood cultures, and hypotensive episodes.

Materials and Methods

Cohort

A retrospective cohort of children ages 0–21 with cancer admitted to Children's Healthcare of Atlanta (CHOA) for febrile neutropenia from January 2013 to June 2016 was identified using International Classification of Diseases (ICD) codes for oncologic diagnoses and patients having had a blood culture. Institutional Review Board approval was obtained. Fever was defined as a single recorded temperature $>38.3^{\circ}\text{C}$ or fever $>38^{\circ}\text{C}$ for more than one hour. Patients with a reported fever at home were included if they were treated by the clinical team as having a true fever. Each admission for febrile neutropenia was considered a separate episode. For each febrile episode, the degree of neutropenia at admission was

recorded. Neutropenia was defined as an absolute neutrophil count (ANC) of <500 thou/ μ L. Patients with an ANC ≥ 500 were not included. In addition, patient age, cancer diagnosis, highest temperature and lowest blood pressure during the hospitalization, RVP and blood culture results, LOS, and ICU admission were manually abstracted into a Research Electronic Data Capture (REDCapTM) database. RVI was determined using the host institution's standard PCR analysis panel that included: respiratory syncytial virus (RSV), rhino/enterovirus, influenza A and B, parainfluenza 1, 2, 3, and 4, coronavirus 229E, HKU1, OC43, and NL63, human metapneumovirus, adenovirus, mycoplasma pneumonia and chlamydia pneumonia. ICD-9 principal diagnosis codes were also extracted for each admission.

Analyses

Descriptive statistics were established for the cohort. The difference in age and other characteristics between those who did or did not have an RVP was tested using Wilcoxon rank sums and the remaining variables were assessed using Chi-squared or Fisher's exact tests as appropriate. All outcomes were modeled using generalized estimating equations with patient as a repeated measure and were adjusted for age, sex, and diagnosis. Highest temperature, LOS, and lowest blood pressure results were adjusted for age, sex, diagnosis, and blood culture result. Positive blood culture results were adjusted for age, sex, and diagnosis. Given the relatively low number of ICU admissions, ICU admission status during a febrile episode was adjusted for age, sex, and blood culture result only. ICD-9 codes were compared against RVP testing to assess concordance in detecting RVIs for each admission. Analyses were performed using SAS v9.4 (Cary, NC).

Results

Demographics

Overall, 404 patients met inclusion criteria of at least one episode of FN over the three and a half year study period. Median age was 7 years and 197 (48.8%) were female. Five percent of patients required ICU admission and half of all patients (51.9%) had hematologic malignancies. (Table 1)

Episode of Febrile Neutropenia

There were 787 distinct admissions for FN. (Table 2) An RVP was sent in 298 (38%) admissions, and was positive in 175 admissions (59%). Of those with an RVP ordered, the most common malignancy was acute lymphoblastic leukemia (ALL, $p=0.001$), though there was no association between malignancy and RVP positivity ($p=0.463$). RVP testing was more likely to be sent (median age 5.5 vs. 8.0, $p<0.0001$) and to be positive (median age 5.0 vs. 7.0 years, $p=0.002$) in younger patients. Sex had no association with whether a RVP was sent or was positive. (Table 3) Of the 489 admissions where a RVP was not sent, 12 (2.5%) had ICD-9 codes for RVIs. Among the 175 admissions with a positive RVP, 113 (64.6%) also had an ICD-9 code. There were 9 admissions where RVP was sent and was negative, but the admission had an ICD-9 code for RVI reported.

In those patients with a positive RVP, 157 patients (90%) had one virus, whereas 18 (10%) had two or more concurrent respiratory viral infections. The most common virus was Rhinovirus/ Enterovirus (107, 61%). Blood cultures were positive in 10% of admissions. Coinfection with bacteremia and a respiratory virus was identified 9.1% of the time. (Table 4)

Clinical Outcomes

There were no significant differences in lowest blood pressure between those with and without an RVP sent or by RVP positivity. Patients who had higher temperatures were more likely to have an RVP sent (mean 39.2° Celsius vs. 39.1°, $p=0.016$), but there was no difference in mean maximum temperature by RVP positivity.

In all patients, mean LOS was 6.5 days (SD 7.8, Range 0.5–77). There were no statistically significant differences in LOS based on if an RVP was sent ($p=0.9$) or by RVP positivity ($p=0.6$). In patients with a positive blood culture and controlling for coinfection, mean LOS was 13.5 days (SD 13.8, range 2–77); patients with a positive blood culture were more likely to have a longer LOS ($p<0.0001$). There was no significant interaction between RVP sent or its result and blood culture results on LOS. (Table 5)

Overall, ICU transfer was required in 45 (5.7%) admissions. While an RVP was more likely to be sent in patients requiring ICU transfer (OR=3.19, $p=0.002$), ICU transfer had no association with RVP positivity ($p=0.98$). There were four deaths in the cohort overall. Of these, two had a positive RVP, and both were complicated by fungal infection and respiratory failure. The other two deaths were due to disease progression.

Individual viral type had no statistically significant association with LOS (Table 5). Coronavirus infection was associated with increased odds of ICU admission (OR: 4.5, CI: 1.4–14.3, p -value 0.01).

Discussion

Though RVP testing is often sent during the initial workup of a patient with FN, it is not clear if having a documented positive RVP impacts care or hospitalization course. This study presents the first assessment to our knowledge of the predictors of RVP testing and the outcomes of positive RVP results in a large pediatric cancer cohort. Specifically, we demonstrate no influence of having an RVP sent or having an RVP that is positive on the duration of hospitalization in patients with FN and note that there is a 9.1% rate of coinfection with a bacterial pathogen in those with a positive RVP.

Prior research has shown that respiratory viral infections (RVI) are associated with treatment delays and increased frequency of hospitalization in patients with Acute Lymphoblastic Leukemia.¹⁶ In addition, prior studies demonstrated that fever of unknown origin is more common in pediatric patients with cancer and neutropenia than in adults, particularly in young children.^{11,17} It was suspected and later confirmed by Torres et al that the high prevalence of febrile RVIs was contributing to the increased rate of FN in pediatric patients with cancer.¹¹ Our study found that, consistent with prior research^{5–8}, the prevalence of

diagnosed RVI was high, with 58% of patients who had RVP testing having positive results. Further, the high prevalence of Rhinovirus/Enterovirus is also consistent with prior research, although the epidemiology of respiratory virus type varies by setting and time of year^{10,13,18,19}.

Despite a high prevalence of RVI, the current study found that neither sending an RVP nor the result of the RVP impacted LOS in the setting of FN or bacteremia, as there was no significant difference in LOS based on RVP for all patients or for those with bacteremia. In addition, there was no association between the result of the RVP on the degree of hypotension the patient experienced or if the patient required ICU admission. This is contrary to Torres et al., who found that pediatric patients admitted for FN with diagnosed RVIs in Chile had shorter LOS, fewer hypotensive episodes, and fewer ICU admissions than those with bacterial infections or mixed bacterial-viral infections¹¹. This difference may in part be attributed to difference in study design, where all patients in the prior study had RVPs sent, regardless of clinical respiratory symptoms, and in our study RVPs were only sent when the clinical team had decided to send them. Thus, it is likely that the percentage of diagnosed RVIs in the Chilean cohort was higher than in ours, and it is possible that it included more otherwise well-appearing children. In addition, Torres et al compared clinical outcomes between patients with diagnosed RVIs and patients with diagnosed bacterial infections. In contrast, our study primarily compared patients diagnosed with RVIs by RVP versus the cohort of all patients as a whole admitted with FN. In addition, Mueller et al. found in a retrospective study using the Kids' Inpatient Database including all pediatric patients diagnosed with cancer and admitted with FN in 2009 that a diagnosed upper respiratory tract infection by ICD-9 code was associated with shortened LOS¹. The results of this study may be different, as respiratory infection status was determined by ICD-9 code rather than RVP results. Our study showed that only 64.6% of patients in our cohort with a positive RVP had an ICD-9 code for RVI, and there were also patients with RVI ICD-9 codes for whom RVP testing was not sent or was negative. Patients in the Mueller study with symptoms of a respiratory tract infection who were otherwise well appearing may have been classified as having via an RVI by ICD code. Such patients in our study may not have had an RVP sent, and therefore were not classified as having an RVI. If such well-appearing patients were discharged home quickly, in the Mueller study they would have been classified as RVI positive, while in our study they would be in the cohort who did not have an RVP sent. Further, the Mueller study may have missed patients with a RVI by using ICD-9 codes alone. This could impact the determination of the relationship between RVI and LOS. Further, there may be practice variation at different hospitals regarding when RVP testing is sent. Associations between RVP positivity and ICU admissions may be affected if a hospital sends testing on all patients who are admitted to the ICU regardless of severity of clinical concern for respiratory infection as the need for ICU admission.

One common reason a clinician might consider sending an RVP is to assess for influenza and therefore need for anti-viral medication, particularly during winter months. Influenza was identified in 5% of patients with positive RVPs in this study. While RVP can be used for diagnosis of this infection, many hospitals have a limited panel that tests solely for Influenza A and B. At CHOA this test was quoted to be approximately one quarter of the cost of a full

RVP, and may be a cost effective test to consider, especially during periods of high influenza prevalence, to determine need for intervention with anti-viral medication.

Of note, patients with ALL were found to be more likely to have RVP testing, even when accounting for their younger average age. In other studies, children with ALL have been shown to have almost double the rate of RVIs as their healthy counterparts²⁰. This may be due to the relative lymphopenia that children with ALL experience from their treatment and clinician concern about increased risk of viral infection¹⁰. Further, El Saleeby et al. found that profound lymphopenia was a predictor of progression to lower respiratory tract infections in patients with cancer diagnosed with RSV²¹. Contrary to prior studies, we did not find a higher rate of RVP positivity in ALL patients when adjusting for age. This may be due to the requirement for an ANC less than 500 for inclusion in this cohort and therefore exclusion of a large cohort of ALL patients with mild neutropenia that patients experience during maintenance therapy. Inclusion of a broader range of neutropenic patients may have led to results that were more consistent with prior studies.

The greatest limitation of this study is that it is a single institution retrospective analysis. Due to the retrospective data collection, this study could not control for whether an RVP was not chosen to be sent by the treating team in the setting of respiratory symptoms. This could mean that the results under-represent the actual percentage of patients with a RVI. In addition, a positive RVP does not necessarily correlate with a clinically significant systemic RVI. Prior research has shown that respiratory viral shedding can occur in asymptomatic patients up to 6 weeks following a RVI²². No information about stage of treatment was collected for this study, which also plays a role in clinical management of FN.

In summary, this study demonstrates that a PCR-documented RVI is common during FN in children with cancer. However, given that having a positive RVP did not impact LOS or severity of disease, the question remains about if RVP testing adds to clinical management in this population. Given the cost of the RVP assay, which was quoted at CHOA to be approximately \$1000, and the resource utilization for viral media and testing supplies, future research should more deeply assess if RVP positivity influences physician comfort in discharging patients with febrile neutropenia or parental comfort in taking a child with FN home in order to determine if RVP testing should be performed routinely during admission for FN.

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Abbreviations:

PCR	Polymerase Chain Reaction
RVP	Respiratory Viral Panel
Tmax	Highest Temperature
LOS	Length of Stay

ICU	Intensive Care Unit
CHOA	Children's Healthcare of Atlanta
OR	Odds Ratio
FN	Febrile Neutropenia
RVI	Respiratory Viral Infection
ANC	Absolute Neutrophil Count
REDCap	Research Electronic Data Capture
RSV	Respiratory Syncytial Virus
ALL	Acute Lymphoblastic Leukemia
SD	Standard Deviation
JMML	Juvenile Myelomonocytic Leukemia
PICC	Peripherally Inserted Central Catheter
HMPV	Human Metapneumovirus

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TABLE 1

Characteristics Among Pediatric Cancer Patients Admitted with Fever and Neutropenia

Characteristics	Patients (N=404)	
	N	%
Sex		
Female	197	48.8%
Male	207	51.2%
Age[*] (years), Median (IQR)	7	9
Oncologic Diagnosis		
ALL	179	44.3%
Bone Tumor	60	14.9%
Other Solid Tumor	93	23.0%
Brain Tumor	41	10.2%
Lymphoma	29	7.18%
JMML	2	0.50%
Vital Status^{**}		
Deceased	4	1.00%
ICU Admission	21	5.20%

IQR, interquartile range; ALL, acute lymphoblastic leukemia; JMML, juvenile myelomonocytic leukemia; ICU, intensive care unit

^{*} Age at time of first febrile neutropenia admission^{**} At time of last febrile neutropenia admission

TABLE 2

Admission-level Cohort Characteristics Among Pediatric Cancer Patients Admitted with Fever and Neutropenia

Admissions (N=787)		
Characteristics	N	%
Sex		
Female	381	48.4%
Male	406	51.6%
Type of Line		
Port	620	80.6%
Tunneled Catheter	98	12.7%
PICC	24	3.1%
Multiple Lines	27	3.5%
Oncologic Diagnosis		
ALL	323	41.0%
Bone Tumor	134	17.0%
Other Solid Tumor	208	26.8%
Brain Tumor	66	8.4%
Lymphoma	50	6.4%
JMML	3	0.4%

PICC, peripherally inserted central catheter; ALL, acute lymphoblastic leukemia; JMML, juvenile myelomonocytic leukemia;

TABLE 3

Admission Characteristics by Rapid Virus Panel (RVP) Testing and Positivity

Characteristics	RVP Testing (N=787)					RVP Positivity (N=298)				
	RVP Sent (n=298)		No RVP Sent (n=489)		P-Value	RVP Positive (n=175)		RVP Negative (n=123)		P-Value
	n	%	n	%		n	%	n	%	
Sex										
Female	150	50.3%	231	47.2%	0.4165	82	46.9%	68	55.3%	0.4092
Male	148	49.7%	258	52.8%		93	53.1%	55	44.7%	
Diagnosis										
ALL	157	52.7%	166	34.0%	0.0009	101	57.7%	56	45.5%	0.4625
Bone Tumor	27	9.1%	107	21.9%		7	4.0%	20	16.3%	
Brain Tumor	17	5.7%	49	10.0%		7	4.0%	10	8.1%	
JMML	2	0.7%	1	0.2%		1	0.6%	1	0.8%	
Lymphoma	20	6.7%	30	6.1%		9	5.1%	11	8.9%	
Other Solid Tumor	75	25.2%	136	27.8%		50	28.6%	25	20.3%	
Age* (years), Median (IQR)	5.5	7.0	8.0	9.0	<0.0001	5.0	5.0	7.0	9.0	0.0016

ALL, acute lymphoblastic leukemia; JMML, juvenile myelomonocytic leukemia; IQR, interquartile range

* Age at time of febrile neutropenia admission

TABLE 4

Respiratory Viral Panel Positivity and Length of Stay (LOS) Among Pediatric Cancer Patients Admitted with Fever and Neutropenia

RVP Positive (N=175)				
	n	%	Median LOS (Days)	(Q1,Q3)
Type of Respiratory Virus				
Rhinovirus/Enterovirus	107	61%	3	(2,6)
Coronavirus	17	9.7%	4	(2,9)
RSV	20	11.4%	4	(2,6)
Parainfluenza	13	7.4%	3	(3,9)
Influenza	10	5.7%	4	(3,5)
HMPV	6	3.4%	5	(2,8)
Adenovirus	2	1.1%	-	-
Bacterial/Viral Co-infection	16	9.1%	10	SD: 21.4
Admissions (N=787)				
	N	%	Median LOS (Days)	SD
Bacteremia	79	10.0%	8	13.8

RSV, respiratory syncytial virus; HMPV, human metapneumovirus; SD, standard deviation

TABLE 5

Admission-level Median Length of Stay By RVP and Blood Culture Result

Group	N	Mean	Median	SD	P-value*
Overall	787	6.45	4	7.82	-
RVP Negative	123	7.06	4	8.26	-
RVP Positive	175	7.5	4	11.6	0.5983
Blood Culture Negative	708	5.67	4	6.39	-
Blood Culture Positive	79	13.5	8	13.8	<0.0001

* Adjusted for age, sex, diagnosis, RVP result, and blood culture result

RVP, rapid virus panel; SD, standard deviation