Concurrent Respiratory Viruses and Kawasaki Disease
Jessica L. Turnier, MD, Marsha S. Anderson, MD, Heather R. Heizer, PA, Pei-Ni Jone, MD, Mary P. Glodé, MD, Samuel R. Dominguez, MD, PhD

BACKGROUND: The diagnosis of Kawasaki disease (KD) remains challenging without a definitive diagnostic test and currently is guided by using clinical patient characteristics and supported by laboratory data. The role of respiratory viruses in the pathogenesis of KD is not fully understood.

METHODS: Charts of patients with KD admitted to Children's Hospital Colorado from January 2009 to May 2013 were retrospectively reviewed. Patients with KD who had a nasopharyngeal wash submitted for multiplex polymerase chain reaction (PCR) viral testing were included. Clinical characteristics, laboratory data, and outcomes of patients with and without positive respiratory viral PCR results were compared.

RESULTS: Of 222 patients with KD admitted to the hospital, 192 (86%) had a respiratory viral PCR test performed on or shortly after admission. Ninety-three (41.9%) of the 192 patients with KD had a positive respiratory viral PCR, and the majority were positive for rhinovirus/enterovirus. No statistically significant differences were found in the clinical characteristics and laboratory values between the groups with and without positive respiratory viral PCR findings. Both groups had the same frequency of upper respiratory and gastrointestinal symptoms and had the same incidence of admission to the PICU, intravenous immunoglobulin–resistant disease, and coronary artery lesions.

CONCLUSIONS: No differences in clinical presentations or outcomes in children with KD stratified according to positive or negative respiratory viral PCR testing were observed. A positive respiratory viral PCR or presence of respiratory symptoms at the time of presentation should not be used to exclude a diagnosis of KD.

WHAT'S KNOWN ON THIS SUBJECT: Making a diagnosis of Kawasaki disease (KD) is often a diagnostic dilemma. This dilemma is confounded when children present with symptoms consistent with known, common respiratory viruses and/or with KD symptoms that could potentially be attributed to a respiratory virus.

WHAT THIS STUDY ADDS: Patients with KD commonly have a concurrent respiratory viral infection. Clinicians should not dismiss the diagnosis of KD based on the presence of respiratory symptoms. Furthermore, a positive respiratory virus test result should not be used to exclude the diagnosis of KD.
Although Kawasaki disease (KD) is the leading cause of acquired heart disease in children in the developed world, its etiology remains unknown. An infectious cause of KD has been favored due to the clinical features of the disease, its age distribution, and seasonality. Previous studies have investigated several potential viral causes of KD, including herpesviruses, paroviruses, adenoviruses, retroviruses, and coronaviruses, without finding support for a specific viral etiology. Making a diagnosis of KD is often difficult. This diagnostic dilemma is confounded when children present with symptoms consistent with known, common respiratory viruses and/or KD symptoms that could potentially be attributed to a respiratory virus. Few studies have looked at the effect of viral coinfection on patient outcomes. These previous studies primarily used serologic testing, direct fluorescent antibody–based assays, and/or culture for viral diagnostics. The clinical presentation and outcomes of children with KD and viral infections, however, have not been explored with the use of more sensitive polymerase chain reaction (PCR)-based respiratory viral diagnostics. The goals of the present study were to evaluate the frequency of respiratory viral coinfections in a large cohort of patients with KD and to determine if viral coinfections were associated with differences in the clinical features of the disease or cardiac outcomes.

**METHODS**

The medical records of all patients with a discharge diagnosis of KD admitted to the Children’s Hospital Colorado (CHCO) from January 2009 to May 2013 were retrospectively reviewed. The infectious disease team at CHCO is consulted on all patients with suspected KD and has an ongoing database of all new patient diagnoses. Medical records were retrospectively reviewed by using a standardized form to collect demographic data, clinical information, echocardiogram findings, and laboratory test results. Coronary artery lesions were defined as a z score ≥2.5 in the right coronary artery or the left anterior descending coronary artery or the presence of ectasia or aneurysms. Day 1 of illness was defined as the first day of fever. Intravenous immunoglobulin (IVIG) resistance was defined as persistence or recrudescence of fever ≥36 hours after completion of IVIG infusion. Fever was defined as a single temperature ≥38.3°C. KD cases were classified as complete or incomplete on the basis of published standard clinical criteria. Study data were collected and managed by using Research Electronic Data Capture tools hosted at the University of Colorado School of Medicine. Collection of clinical data were approved by the Colorado Multiple Institutional Review Board.

At the time of the study, it was our standard practice to collect a nasopharyngeal wash for viral diagnostics as part of the evaluation of patients with suspected KD. Nasopharyngeal washes were evaluated by using the xTag Respiratory Virus Panel (Luminex Molecular Diagnostics, Austin, TX), which detects 16 respiratory viruses and subtypes. These viruses and subtypes included the following: influenza A (seasonal subtypes H1 and H3); influenza B viruses; human parainfluenza virus types 1 through 4; adenovirus; respiratory syncytial virus types A and B; human metapneumovirus; human coronaviruses 229E, OC43, HKU1, and NL63; and human rhinovirus/enterovirus. The monthly distribution of virus-positive and virus-negative patients was evaluated. The incidence of each virus within the virus-positive KD patient group was compared with the viruses recorded in all samples submitted to the clinical microbiology laboratory for viral testing at CHCO during the time frame studied.

Only patients who had respiratory viral PCR results documented were included in the study. Patients were included in the study if they had a nasopharyngeal wash for viral diagnostics as part of the evaluation of patients with suspected KD. Nasopharyngeal washes were evaluated by using the xTag Respiratory Virus Panel (Luminex Molecular Diagnostics, Austin, TX), which detects 16 respiratory viruses and subtypes. These viruses and subtypes included the following: influenza A (seasonal subtypes H1 and H3); influenza B viruses; human parainfluenza virus types 1 through 4; adenovirus; respiratory syncytial virus types A and B; human metapneumovirus; human coronaviruses 229E, OC43, HKU1, and NL63; and human rhinovirus/enterovirus. The monthly distribution of virus-positive and virus-negative patients was evaluated. The incidence of each virus within the virus-positive KD patient group was compared with the viruses recorded in all samples submitted to the clinical microbiology laboratory for viral testing at CHCO during the time frame studied.

Only patients who had respiratory viral PCR results documented were included in the study. Patients were included in the study if they had a nasopharyngeal wash for viral diagnostics as part of the evaluation of patients with suspected KD. Nasopharyngeal washes were evaluated by using the xTag Respiratory Virus Panel (Luminex Molecular Diagnostics, Austin, TX), which detects 16 respiratory viruses and subtypes. These viruses and subtypes included the following: influenza A (seasonal subtypes H1 and H3); influenza B viruses; human parainfluenza virus types 1 through 4; adenovirus; respiratory syncytial virus types A and B; human metapneumovirus; human coronaviruses 229E, OC43, HKU1, and NL63; and human rhinovirus/enterovirus. The monthly distribution of virus-positive and virus-negative patients was evaluated. The incidence of each virus within the virus-positive KD patient group was compared with the viruses recorded in all samples submitted to the clinical microbiology laboratory for viral testing at CHCO during the time frame studied.

### TABLE 1 Viruses Detected in Patients With KD and Comparison With Viruses Found in All Samples Submitted to the CHCO Microbiology Laboratory for Viral Testing During the Same Time Frame

<table>
<thead>
<tr>
<th>Virus</th>
<th>Patients With KD (n = 192)</th>
<th>All CHCO Samples (n = 16415)</th>
<th>P (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Positive</td>
<td>% Positive</td>
<td>Total Positive</td>
<td>% Positive</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>9</td>
<td>700</td>
<td>4.3</td>
</tr>
<tr>
<td>Coronavirus 229E</td>
<td>2</td>
<td>77</td>
<td>0.5</td>
</tr>
<tr>
<td>Coronavirus HKU1</td>
<td>0</td>
<td>76</td>
<td>0.5</td>
</tr>
<tr>
<td>Coronavirus NL63</td>
<td>3</td>
<td>127</td>
<td>0.8</td>
</tr>
<tr>
<td>Coronavirus OC43</td>
<td>2</td>
<td>232</td>
<td>1.4</td>
</tr>
<tr>
<td>HMPV</td>
<td>9</td>
<td>498</td>
<td>3.0</td>
</tr>
<tr>
<td>Influenza A</td>
<td>6</td>
<td>912</td>
<td>5.6</td>
</tr>
<tr>
<td>Influenza B</td>
<td>3</td>
<td>251</td>
<td>1.5</td>
</tr>
<tr>
<td>Parainfluenza 1</td>
<td>2</td>
<td>245</td>
<td>1.5</td>
</tr>
<tr>
<td>Parainfluenza 2</td>
<td>6</td>
<td>227</td>
<td>1.4</td>
</tr>
<tr>
<td>Parainfluenza 3</td>
<td>2</td>
<td>369</td>
<td>2.2</td>
</tr>
<tr>
<td>Parainfluenza 4</td>
<td>7</td>
<td>330</td>
<td>2.0</td>
</tr>
<tr>
<td>RSV</td>
<td>9</td>
<td>1692</td>
<td>10.2</td>
</tr>
<tr>
<td>Rhinovirus/enterovirus</td>
<td>54</td>
<td>5566</td>
<td>33.9</td>
</tr>
<tr>
<td>All viruses</td>
<td>114</td>
<td>11290</td>
<td>68.8</td>
</tr>
<tr>
<td>Patients with positive RVP</td>
<td>95</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patients positive for 2 viruses</td>
<td>18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patients positive for 3 viruses</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

HMPV, human metapneumovirus; RSV, respiratory syncytial virus; RVP, respiratory virus panel. * χ² with Yates correction.
RESULTS

A total of 222 patients with KD were admitted during the study period, of whom 192 (86%) had respiratory viral PCR results. Ninety-three patients (41.9%) had a positive respiratory viral PCR. The most commonly detected viruses were rhinovirus/enteroviruses, with 54 patients (28.1%) testing positive. The next most frequently encountered viruses were adenovirus, human metapneumovirus, and respiratory syncytial virus, each detected in 9 patients (4.7%). Table 1 displays the full spectrum of viruses detected in patients admitted with KD.

The clinical characteristics of children with KD who were virus-positive compared with those who were virus-negative are shown in Table 2. The median age of patients was 2.9 years in the virus-positive group and 3.5 years in the virus-negative group (P = .07). There were no significant differences in the major clinical manifestation of KD noted in patients between the virus-positive and virus-negative groups. Overall, 63% of virus-positive KD patients and 56% of virus-negative KD patients presented with current or a recent history of upper respiratory tract infection (URTI) symptoms as part of the acute illness. Similarly, 57% of virus-positive KD patients and 67% of virus-negative KD patients presented with current of a recent history of gastrointestinal symptoms as part of the acute illness. The median day of illness at admission did not differ between patient groups. More patients in the virus-positive group were admitted to the PICU (10.9% vs 6.1%), but this difference was not statistically significant (P = .23). Twenty-five percent of patients in the virus-negative group were diagnosed with incomplete KD compared with 31.2% of patients in the viral-positive group.

No differences were found in laboratory parameters between the virus-positive and virus-negative KD patients (Table 2). Interestingly, no differences were noted between groups in median white blood cell count, hematocrit, highest erythrocyte sedimentation rate, or highest C-reactive protein level. There were no differences in the frequency of coronary artery lesions between the 2 groups. Sixteen percent of the virus-positive group and 18% of the virus-negative group had coronary artery lesions. In addition, no differences were noted between the 2 groups in terms of day of illness the patient was treated with IVIG, percentage of patients who were IVIG resistant, and length of hospital stay.

More patients with KD were virus-positive in the winter and spring months compared with in the summer and fall months (Fig 1). With the exception of respiratory syncytial virus, which was more prevalent in the virus-positive group, there were no significant differences in the overall distribution of types of viruses detected in the KD patient group was similar to those detected in all CHCO patients.
patients admitted from January 2009 to May 2013 (Table 1).

Adenovirus is the most commonly detected, regularly circulating virus that produces clinical and laboratory values in children which are most similar to those seen in children with KD. We therefore separately examined our 9 patients with KD who were also positive for adenovirus. All 9 (100%) of the adenovirus-positive patients had conjunctivitis, 8 (89%) had a rash, and 8 (89%) had mucous membrane involvement. Four (44%) presented with concurrent URTI symptoms. Three (33%) developed coronary artery lesions, 2 of whom had concurrent URTI symptoms, suggesting that KD and adenovirus infection, similar to other viruses, can present at the same time.

DISCUSSION

This study showed that a positive respiratory viral PCR result does not rule out KD. Concomitant respiratory viral infections were common in the KD patient population studied. Nearly one-half of the patients with a diagnosis of KD who had a respiratory viral panel submitted were positive for at least 1 virus. No one particular virus was predominant among KD patients but rather a variety of respiratory viruses were detected by using PCR testing, mirroring the viruses that were circulating in the community. The frequencies of URTI and gastrointestinal symptoms in both virus-positive and virus-negative patients with KD were similar. Ultimately, according to PCR results, there were no clinically significant differences or outcomes in KD patients who presented with or without detectable viruses. A previous study by Jordan-Villegas et al found that patients with concurrent respiratory viral infections were more often diagnosed with incomplete KD and had a higher frequency of coronary artery dilations. Our study found no statistically significant differences in the number of patients diagnosed with incomplete KD or in the frequency of coronary artery lesions detected between the virus-positive and virus-negative groups. In the study by Jordan-Villegas et al, only 8.8% of patients with KD were found to have respiratory viral infections (compared with 42% of the patients in our study). The differences between these results are most likely due to the fact that nonmolecular-based diagnostics were used for the diagnosis of respiratory viruses in the previous study.

In contrast, a more recent study by Kim et al9 in 55 patients used a PCR-based assay and found a similar rate of respiratory virus detection (ie, 32.7%) in KD patients in Korea. In agreement with our results, they found no significant differences in clinical manifestations or coronary artery lesions between virus-positive and virus-negative patients with KD. Our study strengthens these observations by extending the findings of Kim et al to a much larger and different patient population.

Another recent study in Taiwanese children found that one-half of patients with KD were positive for a respiratory virus according to PCR, and a large proportion of KD patients presented with concurrent respiratory symptoms. Furthermore, a wide variety of viruses were detected in these patients, with rhinoviruses being the most prevalent. Our findings are in agreement with this study and further demonstrate that respiratory symptoms are a common finding in children with KD.13

Research by Rowley et al14 proposed that KD might be due to a novel RNA virus that enters via the respiratory tract. It is unclear, however, whether the respiratory symptoms we documented in our KD patient cohort are due to an unknown KD agent or due to a concomitant coinfection with respiratory viruses circulating in the community and commonly seen in this age group of children. Our study has several limitations. Because of the retrospective nature of the study, we were unable to
determine whether patients with KD had the same prevalence of respiratory virus infections as control subjects presenting on approximately the same day. Fourteen percent of the KD patients in our cohort did not have a respiratory viral PCR result documented, despite it being standard practice to obtain this specimen on patients with suspected KD at the time of the study. It is possible that some bias occurred in selecting the patients who were tested for respiratory viruses. Finally, we acknowledge that the presence of viral RNA or DNA in a respiratory specimen does not always reflect the cause of current symptoms but may be reflective of prolonged viral shedding. This issue may be particularly problematic for rhinoviruses; some early studies, without rhinovirus subtyping, have suggested that rhinovirus RNA can persist in nasal secretions up to 5 to 6 weeks. This finding may partially explain why rhinovirus and enterovirus were the most common viruses detected in our study as well as in the study by Chang et al.10

CONCLUSIONS
Overall, our study supports earlier evidence that a large number of patients with KD have respiratory symptoms and evidence of viral nucleic acid in the nasopharynx. This study showed that a large percentage of patients with KD have a concurrent or recent history of respiratory viral infections and suggests that clinicians should not dismiss the diagnosis of KD based on the presence of respiratory or gastrointestinal symptoms or solely on the results of a positive respiratory viral PCR test. Furthermore, our data support the recommendation that a positive respiratory virus test result, regardless of the virus detected, should not be used to exclude the diagnosis of KD. Continued research is needed to elucidate the etiology and/or discover a more sensitive and specific diagnostic test for this important pediatric disease.

ABBREVIATIONS
CHCO: Children’s Hospital Colorado
IVIG: intravenous immunoglobulin
KD: Kawasaki disease
PCR: polymerase chain reaction
URTI: upper respiratory tract infection

REFERENCES


Concurrent Respiratory Viruses and Kawasaki Disease
Jessica L. Turnier, Marsha S. Anderson, Heather R. Heizer, Pei-Ni Jone, Mary P. Glodé and Samuel R. Dominguez
*Pediatrics*; originally published online August 24, 2015;
DOI: 10.1542/peds.2015-0950

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
/content/early/2015/08/18/peds.2015-0950