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Poor positive predictive value of influenza-like illness criteria in adult transplant patients: a case for multiplex respiratory virus PCR testing

Claus JA, Hodowanec AC, Singh K. Poor positive predictive value of influenza-like illness criteria in adult transplant patients: a case for multiplex respiratory virus PCR testing.

Abstract: Background: Respiratory viral infections (RVIs) are a significant cause of morbidity and mortality among transplant patients. The CDC's influenza-like illness (ILI) criteria (fever ≥100°F with cough and/or sore throat) are a screening tool for influenza with unknown applicability to the transplant population.
Methods: We reviewed all respiratory virus PCR tests performed on adult patients with a history of solid organ (SOT) or stem cell transplantation (HSCT) during the 2012–2013 influenza season. The positive (PPV) and negative predictive values (NPV) of ILI criteria were calculated.
Results: Of 126 transplant patients (66 HSCT, 60 SOT), 54 (42.8%) tested positive for an RVI by PCR: 24 influenza and 30 non-influenza. Of 30 patients who met ILI criteria, 12 (40%) were positive for influenza. The PPV and NPV of ILI for influenza were 50% and 82.4%, respectively. Mortality was low (3.7%), but morbidity was high (14.8% required ICU stay) among transplant patients diagnosed with RVI.
Conclusions: Influenza and non-influenza RVIs are associated with significant morbidity among transplant patients. CDC ILI criteria correlate poorly with PCR-positive cases of influenza in transplant patients, but may be useful in excluding the diagnosis. Routine RVI PCR testing is recommended for better diagnosis and improved antiviral use in transplant patients with suspected RVI.

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Key words: ILI criteria – influenza – influenza-like illness – respiratory virus – transplantation

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Respiratory viral infections (RVI), particularly influenza, parainfluenza, adenovirus, and respiratory syncytial virus (RSV) are common causes of upper and lower respiratory tract infections among patients with a history of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT). RVIs are associated with increased morbidity and mortality in the transplant population. Influenza-associated mortality, in particular, may approach 28% among HSCT recipients and 4–8% in SOT recipients (1, 2). In addition, RVIs are associated with numerous infectious complications, such as secondary bacterial pneumonia, which has been reported in up to 49% of SOT recipients with influenza (2). Allograft dysfunction and acute rejection are additional, serious, non-infectious sequelae of RVIs among transplant patients (3, 4).

Accurately distinguishing influenza from other respiratory infections is of great interest given the availability of effective influenza treatment. The prompt initiation of antiviral therapy among patients with confirmed influenza has been shown to reduce the duration of illness and mortality (5, 6). To date, there are limited therapeutic options for the other RVIs and treatment remains supportive. Nonetheless, timely diagnosis of non-influenza RVIs is beneficial as it facilitates the implementation of appropriate infection control measures (thereby limiting person-to-person transmission) and reduces unnecessary antibiotic/antiviral exposure.

The Centers for Disease Control and Prevention (CDC) has established influenza-like illness (ILI) criteria to identify patients with possible influenza. The criteria include fever ≥100°F with either a

cough or a sore throat. These criteria were intended to be used primarily as an epidemiologic tool, but are frequently utilized as a screening tool for clinical decision-making. In the setting of an influenza epidemic, these criteria performed well among the general population; the presence of cough and fever had a positive predictive value for the diagnosis of influenza of 87% among outpatient adults and children (7). Transplant recipients frequently have atypical manifestations of influenza including an absence of fever (2). Therefore, the applicability of the CDC ILI criteria in this population is uncertain. In this study, we retrospectively characterize the respiratory virus infections observed among solid organ and bone marrow transplant recipients using a multiple respiratory virus reverse transcriptase polymerase chain reaction (PCR) and evaluate the performance of the CDC ILI criteria in this population.

Methods

This study was approved by the Institutional Review Board of Rush University Medical Center, a 646-bed tertiary academic center in Chicago. All patients who underwent respiratory viral PCR testing from December 1, 2012, through February 28, 2013, were retrospectively identified. The study period represents the peak of the 2012–2013 influenza season, with a positivity rate of 35% for any RVI among all patients tested. All respiratory virus testing was performed using the Luminex xTAG Respiratory Viral Panel (Austin, TX, USA). This is a qualitative multiplex PCR used to detect 18 different viruses and subtypes including respiratory syncytial virus (RSV) A and B, influenza A including subtypes H1 and H3, influenza B, parainfluenza viruses 1, 2, 3, and 4, coronaviruses OC43, 229E, NL63, HKU1, human metapneumovirus (hMPV), adenovirus, and rhinovirus/enterovirus. Specimens submitted for testing included nasopharyngeal swabs, sputum, and bronchoalveolar lavage fluid.

Among all patients who underwent respiratory virus PCR testing during the study period, adult patients (≥18 yr of age) with a history of transplantation (HSCT or SOT) were included in our analysis. The incidence of RVIs among these patients was determined. The electronic medical record was reviewed to determine whether patients fulfilled the CDC ILI criteria (fever ≥100°F with either a cough or a sore throat). The sensitivity, specificity, and positive and negative predictive values of ILI criteria for laboratory confirmed influenza were calculated. Additional information collected from the medical records included patient demographics, past medical and surgical history, type of transplant, signs and symptoms at time of testing, prior influenza vaccination, and immunosuppressive regimen. Statistical analysis was performed using SPSS software (version 17.0; Chicago, IL, USA).

Results

A total of 1297 patients underwent respiratory virus PCR testing during the study period, and 126 patients were included in the analysis. Reasons for patient exclusion included age <18 yr (200 patients) and absence of prior transplantation (971 patients). The study patient characteristics are summarized in Table 1. Of the 126 transplant patients, 60 (48%) had undergone SOT and 66 (52%) had a history of HSCT. The types of solid

Table 1. Clinical characteristics of 126 adult transplant patients undergoing RVI testing

Characteristic	N (%)
Age, yr (mean, range)	52.5 (20–76)
Sex	
Male	67 (53)
Female	59 (47)
Type of transplant	
Allogeneic HSCT	34 (27)
Autologous HSCT	32 (25)
Kidney transplant	46 (37)
Liver transplant	13 (10)
Heart transplant	1 (1)
Co-morbid conditions	
Lung disease	28 (22)
Heart disease	28 (22)
Diabetes mellitus	51 (40)
Chronic kidney disease	59 (47)
Chronic liver disease	21 (17)
Immunosuppression	
None	31 (25)
Corticosteroids	65 (52)
Other (+/− corticosteroids)[a]	83 (66)
Symptoms	
Cough	87 (69)
Rhinorrhea	47 (37)
Subjective fever	50 (40)
Headache	19 (15)
Sore throat	18 (14)
Myalgias	15 (12)
Signs	
Temperature ≥100.0°F	40 (32)
CXR infiltrate	29 (23)
Hypoxia (<90% on room air)	16 (13)
ICU admission	21 (17)
Received influenza vaccine	58 (46)
Received oseltamivir	43 (34)

CXR, chest x-ray; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.
[a]Calcineurin inhibitors, mycophenolate.

organs transplanted included 46 kidneys, 13 livers, and one heart. HSCT patients were relatively equally divided between allogeneic (34) and autologous (32) transplants. Sixty-seven (53%) subjects were male, with an average age of 52.5 (range 20–76) yr. The mean time from transplantation to testing was 4.1 (range 0–23) yr. Thirty-one patients (25%) were not on any immunomodulatory medications at the time of testing. Corticosteroids were used in 65 (52%) patients, with or without additional immunosuppressive medications. Sixty-three percent of patients were tested as inpatients, 32% were tested in an outpatient clinic, and 6% were tested in the emergency department.

Fifty-four (43%) of the 126 study patients tested positive for a respiratory virus. The most commonly isolated virus was influenza, 24 cases (44.5%), of which 22 were influenza A and two were influenza B. Thirty patients had other RVIs including 11 (20%) rhinovirus/enterovirus, 9 (17%) RSV, 5 (9%) coronavirus, 4 (7.5%) parainfluenza viruses, and 1 (2%) hMPV. Among patients with influenza, 7 (30%) had received the 2012–13 influenza season vaccine. Of 43 patients who were started on empiric oseltamivir, only 22 patients (51%) had confirmed influenza A or B using PCR testing. No patient had more than one type of respiratory virus detected. Bacterial superinfection was rarely reported; only one patient with parainfluenza 3 infection developed a secondary *Streptococcus pneumoniae* bacterial pneumonia. Seven of the 126 transplant patients were tested for RVI via bronchoalveolar lavage specimen. Among these patients, testing for additional respiratory opportunistic infections (including cytomegalovirus and *Pneumocystis jirovecii*) was performed, but none were detected. Twelve (40%) patients with non-influenza RVI required hospitalization and 6 (20%) required an ICU stay. Comparatively, two of 24 (8%) influenza positive patients required ICU level of care ($p = 0.28$, Fisher's exact test). The mean length of stay for patients hospitalized with non-influenza RVI was significantly longer, 17.5 d compared to patients with influenza 4.4 d ($p = 0.004$). There were three deaths among study patients, for an overall mortality of <2%. Of the three patients who died during the study period, two tested positive for an RVI: one with influenza A, and the other with rhinovirus/enterovirus.

Among study patients, cough was the most frequently reported symptom, occurring in 87 (69%) patients. Nearly one-third of patients (32%) had a measured fever (temperature ≥100°F) at time of testing. Subjective fever was present slightly more often in 40% patients. Only 18 (14%) tested patients reported a sore throat (Table 1). Of 30 patients who met the CDC ILI criteria, only 12 (40%) had PCR-confirmed influenza. Seven (23%) patients fulfilling ILI criteria had a non-influenza respiratory virus isolated, and the remaining 11 (37%) patients had no respiratory virus detected. The sensitivity of the CDC ILI criteria for the identification of patients with influenza was 40% (95% confidence interval [CI]: 23.2–59.2) and the specificity was 87.5% (CI: 78.8–93.1). The positive predictive value (PPV) of ILI for influenza was 50% (CI: 29.6–70.4), and the negative predictive value (NPV) was 82.4% (CI: 73.3–88.9). Subgroup analyses of patients on immunosuppressive medications (including corticosteroids), patients with history of HSCT, and patients with a history of SOT revealed similar performance of the ILI criteria across groups (Table 2). Among all participants, symptoms predictive of influenza over other RVIs were cough (LR 5.3, $p = 0.03$) and temperature ≥100°F (LR 4.3, $p = 0.05$). The only symptom predictive of non-influenza RVI was rhinorrhea (LR 8.5, $p = 0.003$).

Discussion

The results of our study reveal that the clinical presentation of specific respiratory viruses are largely indistinguishable from one another. Specifically, we found that the CDC ILI criteria do not reliably identify transplant recipients with influenza with a PPV of only 50%. This low PPV resulted in the overuse of oseltamivir and failure to consider non-influenza RVIs. Interestingly, we found that the NPV of ILI criteria for confirmed influenza was relatively high at 82.4% and the presence of rhinorrhea was found to predict non-influenza RVI. The combination of rhinorrhea and a failure to meet ILI criteria may be useful in identifying transplant patients with a non-influenza RVI. However, signs and symptoms of influenza and non-influenza viruses overlap greatly, and it is unrealistic to expect clinicians to distinguish them clinically even during peak influenza season.

In the past, ILI criteria were used to rapidly triage patients with possible influenza while awaiting results of viral culture, which could take 2–5 d. Although there is a prolonged turnaround time, these traditional viral culture techniques routinely allowed for identification of viruses other than influenza, including RSV, parainfluenza, and adenovirus. However, with the availability of rapid molecular diagnostics, the utility of the ILI criteria has diminished. Multiplex respiratory virus PCR testing has the ability for rapid and accurate testing for numerous respiratory viruses and has therefore largely replaced viral cultures as the diagnostic

Table 2. ILI criteria as a predictor of influenza among transplant patients

ILI performance	All transplant patients (N = 126)	Patients on immunosuppression[a] (N = 95)	Patients not on immunosuppression[a] (N = 31)	HSCT recipients (N = 66)	SOT recipients (N = 60)
Sensitivity	40.0% (95% CI: 23.2–59.2)	42.9% (95% CI: 22.6–65.6)	33.3% (95% CI: 9.0–69.0)	33.0% (95% CI: 14.4–58.8)	50.0% (95% CI: 22.3–77.7)
Specificity	87.5% (95% CI: 78.8–93.1)	89.2% (95% CI: 79.3–94.9)	81.8% (95% CI: 59.0–94.0)	81.0% (95% CI: 66.9–90.6)	93.8% (95% CI: 81.8–98.4)
NPV	82.4% (95% CI: 73.3–88.9)	84.6% (95% CI: 74.3–91.5)	75.0% (95% CI: 52.9–89.4)	76.0% (95% CI: 62.0–87.0)	88.2% (95% CI: 75.4–95.1)
PPV	50.0% (95% CI: 29.6–70.4)	52.9% (95% CI: 28.5–76.1)	42.9% (95% CI: 11.8–79.8)	40.0% (95% CI: 17.0–67.0)	66.7% (95% CI: 31.0–90.9)

HSCT, hematopoietic stem-cell transplant; ILI, influenza-like illness; NPV, negative predictive value; PPV, positive predictive value; SOT, solid organ transplant.
[a]Immunosuppression = corticosteroids +/– other immunosuppressive agents.

gold standard. Multiplex respiratory virus PCR provides discrimination between many respiratory viral pathogens with a high level of specificity and sensitivity, including determination of the specific influenza subtype (8). Unfortunately, there have been barriers to widespread implementation of multiplex PCR testing. These tests are moderate to highly complex assays which preclude near-patient testing (9). There is also increased cost associated with PCR testing. Therefore, simple, rapid antigen point-of-care tests with poor sensitivities and single targets (i.e., influenza) are frequently used in the outpatient setting, where a large portion of RVI testing occurs (32% in our study). However, in the inpatient setting, the increased cost of multiplex PCR testing is offset by the reduction in hospital length of stay associated with more sensitive and rapid molecular diagnostics (9–11).

More importantly, identifying specific non-influenza pathogens has important treatment and prognostic implications. In our study, non-influenza viruses as a whole (n = 30) were a more common cause of RVI than influenza (n = 24). In addition to the known benefits of prompt administration of antiviral therapy to patients with influenza, there are data suggesting a potential role for the use of systemic or inhaled ribavirin for the treatment of RSV infection among adult HSCT recipients (12). Studies of experimental agents for the treatment of other RVIs are also ongoing (13). Further, identification of a non-influenza RVI may allow for discontinuation of unnecessary oseltamivir and antibacterial therapy. Regarding prognosis, recent data by Campbell et al. (14) showed that infection with any respiratory virus pre-allogeneic HSCT (including rhinovirus) was associated with lower 100-d survival. Mortality was low in our transplant cohort. This may be due to the long median duration of time from transplant (median 4.1 yr, range 0–23 yr) as the mortality secondary to infection is greatest in the highly immunosuppressed early post-transplant period. We also found a low incidence of bacterial superinfection, which may represent underestimation due to failure to microbiologically confirm secondary bacterial pneumonia. However, there was significant morbidity associated with non-influenza RVI among our transplant recipients as assessed by length of hospitalization and need for ICU level of care. Additionally, the only bacterial superinfection among our cohort occurred in a patient with a non-influenza RVI.

Overall, 58 of 126 (46%) of patients tested were vaccinated against influenza. Among the 24 transplant patients who tested positive for influenza, nearly one-third (7) had received influenza

vaccination earlier in the season. There was not a significant difference in the incidence of vaccine failure between HSCT patients (4/18, 22.0%) and SOT patients (3/40, 7.5%) ($p = 0.18$). One vaccinated HSCT patient diagnosed with influenza A required ICU admission and expired. Inactivated influenza vaccines are safe for immunocompromised patients, and all transplant recipients are encouraged to receive annual influenza vaccination (2). Vaccine efficacy within the general population varies from year to year and is largely dependent upon the degree of antigenic match between the influenza strains in the vaccine and those circulating in the community (15). Unfortunately, even in the setting of a good match, vaccine efficacy may be reduced among transplant recipients, particularly in the early post-transplant period (16, 17). Because of the reduced immunogenicity of vaccines in the early post-transplant period, influenza vaccination is not recommended until 3–6 months after transplantation (18, 19). This leaves patients who are transplanted during influenza season at particularly high risk. These findings highlight the importance of good infection control practices, vaccination of transplant recipients' close contacts, and prompt diagnosis and treatment of influenza in transplant recipients regardless of vaccine history.

Our study has several limitations. Most notably, the retrospective design resulted in inconsistently available data regarding the presenting symptoms. Second, our sample size is small and the study was performed in a single tertiary medical center. Additionally, the entire influenza season was not captured. The period included in this study (December through February) represents the peak of the influenza season. This period of high influenza prevalence was thought to be the ideal time to test the accuracy of the CDC ILI criteria for PCR-confirmed influenza. However, as the PPV is dependent on the prevalence, our study may have overestimated the PPV of ILI criteria over the entire duration of influenza season. Lastly, graft dysfunction, graft loss, rejection, and graft-versus-host-disease are all important endpoints in the transplant population and were not captured in this retrospective study. Nonetheless, as described above, we were able to identify other markers of morbidity among transplant patients with RVI.

To the best of our knowledge, this is the first study evaluating the performance of ILI criteria in the transplant population. We have found that many viruses co-circulate with influenza and have indistinguishable clinical presentations. ILI criteria do not appear predictive of influenza infection among transplant patients and should not be used to guide clinical decision-making. Given the significant morbidity among transplant recipients with RVIs, prompt and routine multiplex respiratory virus PCR testing should be encouraged to allow for accurate diagnosis and appropriate therapy.

Authors' contributions

K. S. conceptualized and designed the study; performed literature search; assisted with data extraction; performed statistical analysis; and reviewed, revised, and approved the final manuscript and table as submitted. A. H. conceptualized and designed the study; performed literature search; assisted with data collection and extraction; and reviewed and revised the final manuscript and table as submitted. J. C. performed literature search; performed data collection and extraction; assisted with statistical analysis; and wrote and drafted the manuscript and table as submitted.

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