JAMDA

Original Study

Combining Procalcitonin and Rapid Multiplex Respiratory Virus Testing for Antibiotic Stewardship in Older Adult Patients With Severe Acute Respiratory Infection

Chien-Chang Lee MD, ScD [a], Julia Chia-Yu Chang MD [b], Xiao-Wei Mao MS, PhD [c], Wan-Ting Hsu MS [d], Shey-Ying Chen MD [a], Yee-Chun Chen MD, PhD [e], Chorng-Kuang How MD, PhD [b],*

[a] Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] Department of Emergency Medicine, Taipei Veterans General Hospital and Department of Emergency Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Department of Medical Technology, National Taiwan University Hospital, Taipei, Taiwan
[d] Department of Epidemiology, TH Chan Harvard School of Public Health, Boston, MA
[e] Division of Infectious Disease, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

A B S T R A C T

Keywords:
Older adults
severe acute respiratory infections
coronavirus
influenza
human rhinovirus
point-of-care test
rapid PCR respiratory panel
viral panel
procalcitonin
antibiotic stewardship

Objectives: Virus infection is underevaluated in older adults with severe acute respiratory infections (SARIs). We aimed to evaluate the clinical impact of combining point-of-care molecular viral test and serum procalcitonin (PCT) level for antibiotic stewardship in the emergency department (ED).
Design: A prospective twin-center cohort study was conducted between January 2017 and March 2018.
Setting and Participants: Older adult patients who presented to the ED with SARIs received a rapid molecular test for 17 respiratory viruses and a PCT test.
Measures: To evaluate the clinical impact, we compared the outcomes of SARI patients between the experimental cohort and a propensity score–matched historical cohort. The primary outcome was the proportion of antibiotics discontinuation or de-escalation in the ED. The secondary outcomes included duration of intravenous antibiotics, length of hospital stay, and mortality.
Results: A total of 676 patients were included, of which 169 patients were in the experimental group and 507 patients were in the control group. More than one-fourth (27.9%) of the patients in the experimental group tested positive for virus. Compared with controls, the experimental group had a significantly higher proportion of antibiotics discontinuation or de-escalation in the ED (26.0% vs 16.1%, $P = .007$), neuraminidase inhibitor uses (8.9% vs 0.6%, $P < .001$), and shorter duration of intravenous antibiotics (10.0 vs 14.5 days, $P < .001$).
Conclusions and Implications: Combining rapid viral surveillance and PCT test is a useful strategy for early detection of potential viral epidemics and antibiotic stewardship. Clustered viral respiratory infections in a nursing home is common. Patients transferred from nursing homes to ED may benefit from this approach.

© 2019 AMDA – The Society for Post-Acute and Long-Term Care Medicine.

Community-acquired respiratory tract infections are among the most common reasons for emergency department (ED) visits and can be caused by both viral and bacterial pathogens. Identification of the pathogen causing symptoms is critical for rapid institution of adequate antiviral or antibiotic therapy. Because of the challenges in differentiating between viral and bacterial pathogens, patients with viral respiratory infections are usually underdetected, and unnecessary antibacterial agents are more likely to be administered. Therefore, laboratory tests providing accurate and timely determination of the infectious agents associated with viral respiratory diseases are important. A broad array of tests is available to detect viral respiratory agents. Rapid antigen tests are available for influenza A and B and respiratory syncytial virus (RSV), but these tests have low sensitivity and specificity.[1,2]

Molecular diagnostic tests using the polymerase chain reaction (PCR) method to detect the RNA or DNA of the infectious agents show high sensitivity and specificity, but they are technically challenging and time consuming. The advent of sensitive point-of-care (POC) molecular detection methods has made rapid diagnosis of respiratory virus infections possible. The FilmArray system (bioFire Diagnostics, Inc, Salt Lake City, UT) is a desktop automated real-time PCR system that integrates sample preparation, amplification, detection, and analysis into 1 complete process that delivers results in 1 hour. The respiratory panel can detect 17 respiratory viruses and 3 bacterial targets in a single reaction.[3] Initial studies demonstrated that such POC multiplex PCR systems identified previously under-evaluated viral or atypical infections in ED dyspneic patients, and the additional information on rapid respiratory infection testing may also change the physician's antibiotic-prescribing behavior, enabling more timely and appropriate treatment.[4−6] The hospital length of stay and direct medical cost for patients with the identified respiratory pathogens decreased.[7−16]

Despite the availability of highly accurate viral testing results, the discontinuation or the de-escalation of antibiotics still raises concerns because mixed virus-bacteria coinfection, especially influenza with pneumococcus, is common in older adults.[17] In this study, we proposed a diagnostic approach that combines the multiplex PCR respiratory panel with procalcitonin (PCT) tests to better guide the antibiotic treatment. PCT is a precursor of calcitonin that is constitutively secreted by C cells of the thyroid gland and K cells of the lungs. In healthy individuals, PCT is normally undetectable (<0.01 ng/mL). When stimulated by endotoxin, PCT is rapidly produced by parenchymal tissue throughout the body. Unlike C-reactive protein, PCT does not respond to sterile inflammation or viral infection.[18] This distinctive characteristic makes PCT a valuable diagnostic marker. Multiple randomized controlled trials have demonstrated that PCT levels of <0.25 μg/L can guide the decision to withhold antibiotics or stop therapy early.[19,20]

Since the approval of FilmArray respiratory panel tests, only a few studies have evaluated the clinical impact after implementation of the multiplex PCR respiratory panel on patients with less severe acute reparatory illness.[8,13−15] To date, no study has focused on older adults with severe acute respiratory illness. Older adults are more vulnerable to respiratory virus infection. Because of undifferentiated clinical manifestation between bacterial and viral infection, antibiotic overuse in this population is common. In this study, we aimed to assess the impact of implementing a diagnostic algorithm that combines rapid respiratory viral surveillance and PCT tests on older patients presenting to the ED with severe acute respiratory illness. We conducted a prospective cohort study in the ED of 2 urban medical centers. Clinical impact was evaluated through a comparison of the experimental cohort with a propensity score (PS)−matched historical cohort.

Methods

Study Design and Settings

We conducted a prospective, multicenter, observational study of a sample of ED patients presenting with acute severe respiratory illness. The EDs of 2 urban medical centers participated in this project. The annual ED census is around 100,000 for one medical center and 80,000 for the other. The study period included January 2017 through March 2018. We defined the pre−respiratory panel system implementation period as January 2016 through December 2016 (12 months) and the post−respiratory panel system implementation period as January 2017 through March 2018. We had 200 multiplex PCR kits, of which 22 were used for rapid PCR respiratory panel system calibration; the remaining 178 kits were aimed for use among the study patients. However, at the planned end date of the study, we could not reach the target sample size. Therefore, a 3-month extension in the experimental group was made to collect sufficient samples. The trial was approved by the Institutional Review Board for Human Research at each participating center.

Patient Population

Patients aged 65 years or older presenting to the ED with acute severe respiratory illness were eligible for inclusion. We defined a case of severe acute respiratory illness according to the World Health Organization's case definition. We defined severe acute respiratory illness in adults as physician-diagnosed lower respiratory tract infection with a pulse oxygen saturation (SpO$_2$) on presentation of less than 90% or a respiratory rate >20 breaths/min or the requirement of intubation and mechanical ventilation. Basic demographic and clinical information and specimens were collected on the day of admission. An episode of lower respiratory tract infection was defined as acute pulmonary disease with or without acute respiratory failure, including pneumonia, influenza-like illness, or an acute exacerbation of a chronic respiratory illness (including an exacerbation of chronic obstructive pulmonary disease, asthma, or bronchiectasis). The exclusion criteria included if the patient was receiving palliative care or declined nasopharyngeal swabbing. All participants provided written informed consent.

Respiratory Sample Collection and Measurement of PCT

The FilmArray respiratory panel (bioFire Diagnostics, Inc) detects 17 viruses (RSV, influenza A H1, H1-2009, H3, influenza B, adenovirus, parainfluenza virus 1−4, rhinovirus/enterovirus, human metapneumovirus, human coronavirus OC43, 229E, NL63, and HKU1), and 3 atypical bacteria (*Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*). We collected a nasopharyngeal swab using a nylon flocked swab that was immediately placed in universal transport media (UTM). The study nurse collected all samples and specimens in UTM, and they were tested according to the manufacturer's instructions. Blood samples were collected within 24 hours of admission. PCT concentrations were measured using an immunoluminometric assay with a detection limit of 0.06 ng/mL (BRAHMS PCT-sensitive Kryptor, Thermo Fisher Scientific, BRAHMS GmbH). Respiratory swab and blood samples were tested as soon as they were received in the laboratory.

Study Protocol and Clinical Impact Evaluation

During the study period, the study nurse identified eligible patients and explained the study protocol to the treating physicians and patients. Eligible patients received a rapid molecular test with 17 respiratory viruses and a PCT test. The results of the respiratory panel or PCT tests were communicated to the treating physicians directly by the study nurse as soon as they were available and were kept in the medical records. The study nurse reminded the treating physician of the recommendation of antibiotic treatment based on different viral and PCT testing results. The detection of influenza initiates isolation or neuraminidase inhibitor use. The detection of a virus with an elevated serum PCT level (≥0.25 ng/mL) may indicate the possibility of a superimposed bacterial infection and justify the continual use of antibacterial treatment in patients with non−influenza virus infection and combined antiviral and antibacterial treatment in patients with influenza infection. A positive result for respiratory virus with a low serum PCT level and stable clinical manifestation may allow early discontinuation or de-escalation of empiric antibiotics. De-escalation was defined as changing to a narrower-spectrum antibiotic or shifting the intravenous antibiotics to oral form. A negative respiratory

virus test result with a low serum level of PCT (<0.25 ng/mL) would prompt clinicians to consider noninfectious causes of respiratory distress, such as acute exacerbation of obstructive airway disease, acute decompensated heart failure, or fluid overload.

Information regarding laboratory tests, antibiotic or antiviral therapy administration, duration of intravenous antibiotic treatment, length of intensive care unit stays, length of hospital stay, and 30-day mortality was obtained from electronic health records. We compared the outcome and duration of intravenous antibiotic use with a historical cohort with similar baseline characteristics and clinical presentations. The clinical impact was measured via the proportion of stopping or de-escalating antibiotics, neuraminidase inhibitor uses in the ED, duration of intravenous antibiotics treatment, length of hospital stay, length of intensive care unit stays, 30-day mortality, and overall all-cause mortality.

Comparison With a Historical Cohort

To evaluate the clinical impact of combining the respiratory panel and PCT testing on the outcomes of patients with severe acute respiratory illness, we established a historical cohort, including all patients presenting to the ED with severe acute respiratory illness from January 1, 2016 to December 31, 2016. The database included the following: demographics, clinical presentations, presenting viral signs, laboratory data, image results, ED and admission, medications used in the ED and hospitalization course, and discharge status. We then used a PS-matching technique to select a group of patients with similar demographics, comorbidities, diagnoses, vital signs, and laboratory results to the experimental cohort that received the respiratory panel and PCT test. To increase the statistical power for analysis, we performed a 1-to-3 matching. The final cohort includes 169 older adult severe acute respiratory illness patients who received the respiratory panel and PCT test and 507 PS-matched control patients. This composite cohort was used to assess the clinical impact of the rapid respiratory viral surveillance and PCT tests.

Statistical Analysis

Baseline characteristics were summarized using appropriate descriptive statistics. The categorical variables were presented as frequency and percentage and compared using the chi-squared test. The continuous variables were presented by median with interquartile range and compared by nonparametric Mann-Whitney *U* tests. The numbers of different respiratory viral isolates and mean serum level of PCT for different viral infections were shown by bar graph. To select control patients, we built a PS for matching. PS was defined as the conditional probability of being tested with respiratory panel and PCT, which was derived from the logistic regression model that included the following potential predictors: demographics, comorbidity, presenting vital signs, laboratory results, and admission diagnoses. To verify the balancing of baseline covariates after PS matching, we made a standardized difference plot to ensure minimum differences in the baseline covariates between 2 groups of patients (Supplementary Figure 1). In the PS-matched cohort, we compared the outcome between the current cohort and the PS-matched historical cohort using the logistic regression model, adjusting for the residual difference in the baseline covariates. All statistical analyses were performed by SAS 9.4 (SAS Inc, Cary, NC), and a *P* value of < .05 was deemed significant.

Results

A total of 178 patients enrolled in the study, of which 9 were excluded because of missing data or loss of follow-up. Finally, 169 older adult patients with severe acute respiratory illness were included in the study analysis, of which 36 (21.3%) patients tested positive for respiratory virus. These patients were sick, so they were all hospitalized.

Characteristics of the Study Cohort

The demographics, presenting vital signs, laboratory test results, and underlying comorbidity of the experimental and control cohorts are shown in Table 1. In the experimental cohort, the mean age was 81.2 years and 69.8% were males. Diabetes, cancer, and chronic pulmonary disease were the leading 3 comorbidities, and pneumonia, chronic obstructive pulmonary disease with acute exacerbation, and acute respiratory failure were the most prevalent diagnoses. The control cohort had a comparable distribution on the aforementioned characteristics, except for including fewer patients with dementia or chronic liver disease.

Results of the Multiplex PCR Respiratory Panel and PCT Test

In the experimental group, 36 patients tested positive for respiratory virus, including 13 influenza A or B virus (7.7%), 9 RSV (5.3%), 9 human rhinovirus/enterovirus (5.3%), 2 coronavirus (1.2%), 2 parainfluenza virus type 3 (1.2%), and 1 human metapneumovirus (0.6%). In the control group, 20 patients (3.3%) were diagnosed with influenza, which was significantly lower than in the experimental group (*P* = .049) (Table 2). Of the 36 patients who tested positive for virus, 14 (38.9%) had a PCT level lower than 0.25 ng/mL. Coronavirus, influenza A, and human rhinovirus/enterovirus infections had higher serum levels of PCT (Figure 1).

Table 1
Comparison of Characteristics Between Multiplex PCR Respiratory Panel and PCT Implementation Cohort and PS-Matched Historical Cohort

	FilmArray RP Plus PCT (n = 169)	Control (n = 507)	P Value
Demographics			
Age, y, mean ± SD	82.8 ± 8.9	81.2 ± 9.0	.06
Gender, male	118 (69.8)	333 (65.7)	.37
Presenting vital signs, mean ± SD			
Body temperature	37.8 ± 1.2	37.5 ± 1.1	.07
Spo₂	94.4 ± 8.7	93.8 ± 6.8	.31
Systolic blood pressure	134.7 ± 29.6	137.8 ± 30.1	.24
Laboratory results, mean ± SD			
WBC, 1000/mm³	11.7 ± 5.8	11.1 ± 5.5	.26
Hemoglobin, mg/dL	11.2 ± 2.5	11.5 ± 2.5	.31
Creatinine, mg/dL	1.6 ± 1.5	1.7 ± 1.9	.71
Alanine transaminase, U/mL	32.6 ± 68.6	36.3 ± 146.2	.75
C-reactive protein, mg/L	9.5 ± 13.5	8.5 ± 5.3	.17
Comorbidity			
Diabetes mellitus	49 (29.0)	126 (24.9)	.34
Chronic liver disease	15 (8.9)	20 (3.9)	.02
Myocardial infarction	8 (4.7)	46 (9.1)	.10
Congestive heart failure	34 (20.1)	91 (17.9)	.61
Chronic kidney disease	28 (16.6)	95 (18.7)	.60
Chronic pulmonary disease	36 (21.3)	118 (23.3)	.67
Dementia	32 (18.9)	60 (11.8)	.03
Cancer	44 (26.0)	115 (22.7)	.43
Diagnosis			
Pneumonia	133 (78.7)	370 (73.0)	.17
COPD with acute exacerbation	24 (14.2)	109 (21.5)	.05
Acute respiratory failure	21 (12.4)	84 (16.6)	.24

COPD, chronic obstructive pulmonary disease; RP, respiratory panel; WBC, white blood cell.
Unless otherwise noted, values are n (%).

Table 2
Outcome Comparison Between Experimental Cohort and a 1-to-3 PS-Matched Cohort

	Multiplex PCR Respiratory Panel Plus PCT (n = 169)	Control (n = 507)	*P* Value
Diagnosis of viral infection			
Influenza A or B	13 (7.7)	20 (3.3)	.049
Respiratory syncytial virus	9 (5.3)	0	NA
Human rhinovirus/ enterovirus	9 (5.3)	0	NA
Coronavirus	2 (1.2)	0	NA
Parainfluenza virus type 3	2 (1.2)	0	NA
Human metapneumovirus	1 (0.6)	0	NA
Antibiotics treatment			
Proportion of de-escalating antibiotics	37 (21.9)	67 (13.2)	.006
Proportion of stopping antibiotics	7 (4.1)	10 (2.0)	.12
Proportion of stopping or de-escalating antibiotics	44 (26.0)	84 (16.1)	.007
Neuraminidase inhibitor use in ED	15 (8.9)	3 (0.6)	<.001
Duration of intravenous antibiotics, median (interquartile range)	10.0 (5.3-14.6)	14.5 (7.2-22.0)	<.001
Outcome			
Length of hospital stay, median (interquartile range)	14.0 (5.0-20.5)	16.1 (6.0-24.5)	.030
30-d mortality	17 (10.1)	63 (16.2)	.05
In-hospital mortality	23 (13.8)	98 (19.3)	.09

Unless otherwise noted, values are n (%).

Effect on Intravenous Antibiotic Use and Outcome

Compared with the control group, the patients in the experimental group had more antibiotics de-escalation (21.9% vs 13.2%, *P* = .007), received more neuraminidase inhibitor in the ED (8.9% vs 0.6%, *P* < .001), had a shorter duration of intravenous antibiotics use (median 10.0 days [interquartile range 5.3, 14.6] vs 14.5 [7.2, 22.0], *P* < .001), and had a shorter length of hospital stay (14.0 [5.0-20.5] vs 16.1 [6.0-24.5] days, *P* = .030). Although the patients in the experimental group had a trend of more antibiotic discontinuation, the small number of patients prevents meaningful comparison. Neither 30-day nor in-hospital mortality was significantly different between the 2 groups. To further account for the residual covariate difference after PS matching, we performed logistic or linear regression adjusting for age,

Table 3
Adjusted Odds Ratio for Different Outcomes

Dichotomous Outcomes	OR (95% CI)	*P* Value
Stopping or de-escalating antibiotics	1.97 (1.28, 3.02)	.002
Neuraminidase inhibitor use in ED	17.9 (5.02, 63.98)	<.001
30-d mortality	0.57 (0.32, 1.05)	.06
In-hospital mortality	0.66 (0.40, 1.09)	.106

Continuous outcomes	Beta (95% CI)	*P* Value
Duration of intravenous antibiotics	−4.44 (−2.08, −6.79)	<.001
Length of hospital stay	−2.85 (−5.79, 0.1)	.57

Effect estimates for dichotomous outcomes were calculated by logistic regression whereas those for continuous outcomes were calculated using quantile regression. Both models were adjusted for covariates not balanced after PS matching, including age, temperature, chronic liver disease, dementia, and chronic obstructive pulmonary disease with acute exacerbation.

temperature, chronic liver disease, and dementia. The results revealed that rapid PCR respiratory panel and PCT testing were associated with increased odds of discontinuing or de-escalating antibiotics [odds ratio (OR) 1.97, 95% confidence interval (CI) 1.28, 3.02], increased odds of neuraminidase inhibitor prescription (OR 17.9, 95% CI 5.02, 63.98), and shorter duration of intravenous antibiotics (-−4.44, 95% CI −2.08, −2.79). There was no difference in length of hospital stay and 30-day mortality (Table 3).

Discussion

This prospective cohort study reports the clinical impact of rapid molecular diagnosis of respiratory pathogens in conjunction with PCT testing on older adult patients presenting to the ED with severe acute respiratory illness. The results showed 21.3% of older adult severe acute respiratory illness patients to be having respiratory virus infection, with influenza, RSV, and human rhinovirus/enterovirus being the 3 leading pathogens. We demonstrated that the new diagnostic approach was associated with increased discontinuation or de-escalation of antibiotics, reduced length of intravenous antibiotics treatment, and improved influenza detection and antiviral use.

These findings are consistent with those of previous studies. Brendish et al[8] showed that patients receiving respiratory panel testing were more likely to undergo single doses or brief courses of antibiotics treatment. Respiratory panel testing was also associated with a reduced length of stay and improved influenza detection and antiviral use. However, they did not find that routine use of respiratory panel testing could reduce the proportion of patients treated with antibiotics, which they ascribed to the initiation of antibiotics before the results of PCT in many patients. A pre-post study showed that the use of the respiratory panel decreased the time to diagnosis of respiratory viruses, hospital admission rate, length of stay, number of chest radiographs, and duration of antimicrobial use.[13] Gelfer et al[21] combined the respiratory panel and PCT tests, but found no significant differences in overall antibiotic exposure between the experimental and standard-of-care groups. Nevertheless, they found significantly fewer patients discharged on antibiotics and a shorter duration of therapy in a subgroup of patients with positive viral and negative PCT testing results. They stressed the importance of proactive communication between the antibiotics stewardship team and physicians.

Our results showed that the proposed diagnostic approach could reduce intravenous antibiotics treatment duration by 4.44 days without compromising patient outcomes. Historically, it has been advised to complete the course of intravenous antibiotics treatment despite the resolution of clinical symptoms. However, there is little evidence to support this practice.[22,23] Overuse of antibiotics was associated with increased risk of *Clostridioides difficile* infection, and a prolonged course of intravenous antibiotics may increase the risk of adverse drug events, organ dysfunction, or mortality.[24] It is noteworthy that the identification of respiratory virus alone may not be sufficient to reduce antibiotic use because of the concerns regarding mixed virus-bacteria coinfection, especially influenza with pneumococcus infection.[25] Low serum level of PCT may help alleviate the concerns of mixed infection. In addition, communicating the results to the treating physicians is important.[13,16] Although we did not have a formal antibiotic stewardship team, the study nurse communicated the results to the treating physicians and promoted antibiotics stewardship. Another finding is the underdiagnosis of influenza in older adult patients. Older adult patients were less likely to undergo a provider-ordered influenza test. They usually lack the typical presentation of influenza-like illness and may present with respiratory distress or confusion.[26] A recent study showed that the diagnosis of influenza based on clinical grounds alone was associated with a suboptimal sensitivity of 36% and a specificity of 78%.[27]
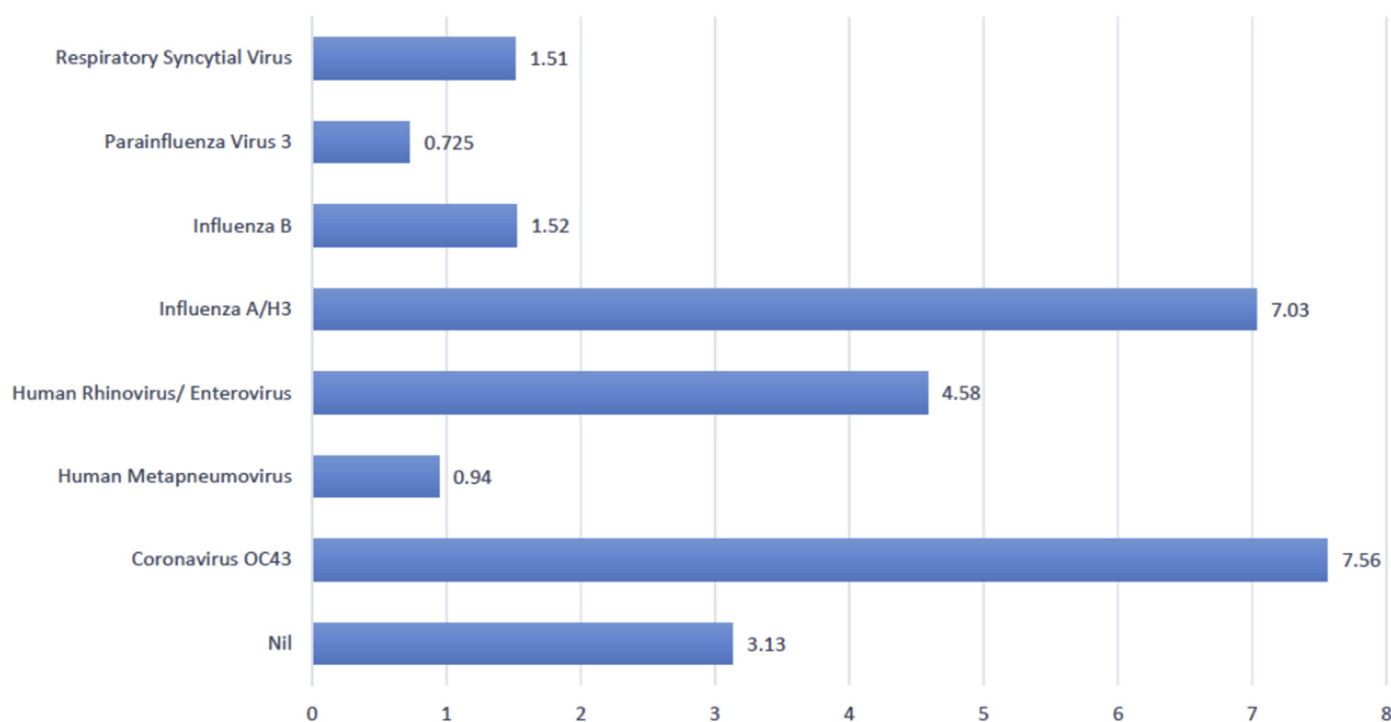
Mean Procalcitonin level (ng/mL)

Figure 1. Mean procalcitonin level among patients with different respiratory viral infections.

The proposed algorithm for respiratory virus infection diagnosis and antibiotic stewardship may also have implications for nursing home (NH) residents. Acute respiratory virus infection outbreaks are a common problem in NHs.[28,29] A recent systematic review reported a 1.21% to 85.2% annual incidence of influenza or RSV infection in long-term care facilities.[28] Other than influenza and RSV, human metapneumovirus is the third most common causative pathogen for NH respiratory infection outbreaks.[30] NHs often do not have on-site equipment to evaluate suspected infection; therefore, a lower threshold for antibiotic prescription is common. It is estimated that approximately two-thirds of NH residents received antibiotics each year, and up to 75% of the treatment is inappropriate. NHs become the reservoirs for resistant bacteria within a community.[31] Although the present protocol cannot be implemented in NHs, it can be used among severe NH patients who are transferred to the ED. In a less severe outbreak, the nasopharyngeal samples of NH residents can be collected and sent to contracted laboratories for respiratory panel testing. The early detection of acute respiratory infection enables early isolation of infected patients and early antiviral drug administration, which can prevent or contain a respiratory virus infection outbreak.

Cost is an important consideration for the large-scale clinical implementation of rapid multiplex PCR testing. Previous analyses showed that rapid multiplex PCR testing was the most cost-effective testing strategy for the detection of influenza in children.[12,32] The cost-effectiveness of respiratory panel testing is highly influenced by the prevalence of influenza and the proportion of patients treated with antivirals. The significant improvement in influenza diagnosis and antiviral treatment in our study suggests that a combination of respiratory panel and PCT testing may be cost-effective in our study setting. Such speculation, however, requires future validation.

Our results have to be interpreted in light of several limitations. First, PCT tests were not used in the comparison cohort. We cannot determine the impact of the viral panel and PCT tests separately. Second, the study nurse only enrolled patients during working hours of weekdays. Selection or spectrum bias is less likely because we did not find significant difference in the outcomes of patients presenting to the ED on different time shifts. Third, the postdischarge follow-up data of the historical comparison cohort cannot be retrieved. We therefore could not compare the duration of oral antibiotics between the 2 cohorts. The reduction of intravenous antibiotic duration alone is important because it has been shown to be a strong risk factor for the development of resistant bacteria strains. Fourth, the generalization of the results to other settings should be taken into consideration. The long hospitalization duration in our study was due to old age, severe illness, and low hospitalization cost.[33,34] Lastly, the incidence of various respiratory viruses may have varied across the 2 seasons of the study period. The strengths of our study include the older adult population, the twin-center prospective cohort design, the simple antibiotic stewardship algorithm, and the comparison to a PS-matched cohort.

Conclusions and Implications

The findings of our study support the use of rapid multiplex PCR respiratory panels in conjunction with the PCT test for early diagnosis of respiratory viral infection and to inform optimizing antibiotic use in older adult patients presenting to the ED with severe acute respiratory illness. Respiratory viral infection outbreak is common in nursing homes. Performing the proposed diagnostic approach on patients transferred from NHs may enable early detection of the causative pathogens and early isolation of infected patients. As the cost per test is still high, institutions should develop a protocol to prevent indiscriminate testing with multiplex PCR and provide proactive real-time feedback to treating physicians for antimicrobial stewardship. Further

studies are needed to assess the incremental value of multiplex PCR viral testing compared with PCT testing alone in the management of patients with severe acute respiratory infection in the ED.

Acknowledgments

References

1. Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: Systematic review and meta-analysis. J Clin Microbiol 2015;53:3738–3749.
2. Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: A systematic review and meta-analysis. Ann Intern Med 2017;167:394–409.
3. Babady NE. The FilmArray(R) respiratory panel: An automated, broadly multiplexed molecular test for the rapid and accurate detection of respiratory pathogens. Expert Rev Mol Diagn 2013;13:779–788.
4. Chen H, Weng H, Lin M, et al. The clinical significance of FilmArray respiratory panel in diagnosing community-acquired pneumonia. Biomed Res Int 2017; 2017:7320859.
5. Huang HS, Tsai CL, Chang J, et al. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: Systematic review and meta-analysis. Clin Microbiol Infect 2018;24:1055–1063.
6. Leber AL, Everhart K, Daly JA, et al. Multicenter evaluation of BioFire FilmArray Respiratory Panel 2 for detection of viruses and bacteria in nasopharyngeal swab samples. J Clin Microbiol 2018;56.
7. Bhavnani D, Phatinawin L, Chantra S, et al. The influence of rapid influenza diagnostic testing on antibiotic prescribing patterns in rural Thailand. Int J Infect Dis 2007;11:355–359.
8. Brendish NJ, Malachira AK, Armstrong L, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): A pragmatic, open-label, randomised controlled trial. Lancet Respir Med 2017;5:401–411.
9. Jeong HW, Heo JY, Park JS, Kim WJ. Effect of the influenza virus rapid antigen test on a physician's decision to prescribe antibiotics and on patient length of stay in the emergency department. PLoS One 2014;9:e110978.
10. Keske S, Ergonul O, Tutucu F, et al. The rapid diagnosis of viral respiratory tract infections and its impact on antimicrobial stewardship programs. Eur J Clin Microbiol Infect Dis 2018;37:779–783.
11. Mengelle C, Mansuy JM, Pierre A, et al. The use of a multiplex real-time PCR assay for diagnosing acute respiratory viral infections in children attending an emergency unit. J Clin Virol 2014;61:411–417.
12. Nicholson KG, Abrams KR, Batham S, et al. Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. Health Technol Assess 2014;18:1–274. vii-viii.
13. Rappo U, Schuetz AN, Jenkins SG, et al. Impact of early detection of respiratory viruses by multiplex PCR assay on clinical outcomes in adult patients. J Clin Microbiol 2016;54:2096–2103.
14. Rogan DT, Kochar MS, Yang S, Quinn JV. Impact of rapid molecular respiratory virus testing on real-time decision making in a pediatric emergency department. J Mol Diagn 2017;19:460–467.
15. Rogers BB, Shankar P, Jerris RC, et al. Impact of a rapid respiratory panel test on patient outcomes. Arch Pathol Lab Med 2015;139:636–641.
16. Semret M, Schiller I, Jardin BA, et al. Multiplex respiratory virus testing for antimicrobial stewardship: A prospective assessment of antimicrobial use and clinical outcomes among hospitalized adults. J Infect Dis 2017;216: 936–944.
17. Burk M, El-Kersh K, Saad M, et al. Viral infection in community-acquired pneumonia: A systematic review and meta-analysis. Eur Respir Rev 2016;25: 178–188.
18. Le Bel J, Hausfater P, Chenevier-Gobeaux C, et al. Diagnostic accuracy of C-reactive protein and procalcitonin in suspected community-acquired pneumonia adults visiting emergency department and having a systematic thoracic CT scan. Crit Care 2015;19:366.
19. Rhee C. Using procalcitonin to guide antibiotic therapy. Open Forum Infect Dis 2017;4:ofw249.
20. Schuetz P, Bretscher C, Bernasconi L, Mueller B. Overview of procalcitonin assays and procalcitonin-guided protocols for the management of patients with infections and sepsis. Expert Rev Mol Diagn 2017;17:593–601.
21. Gelfer G, Leggett J, Myers J, et al. The clinical impact of the detection of potential etiologic pathogens of community-acquired pneumonia. Diagn Microbiol Infect Dis 2015;83:400–406.
22. Del Mar C, Looke DFM. Should we abandon "finishing the course" of antimicrobials? BMJ (Clin Res Ed) 2017;358:j4170.
23. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. BMJ (Clin Res Ed) 2017;358:j3418.
24. Brown K, Valenta K, Fisman D, et al. Hospital ward antibiotic prescribing and the risks of Clostridium difficile infection. JAMA Intern Med 2015;175: 626–633.
25. Voiriot G, Visseaux B, Cohen J, et al. Viral-bacterial coinfection affects the presentation and alters the prognosis of severe community-acquired pneumonia. Crit Care 2016;20:375.
26. Hartman L, Zhu Y, Edwards KM, et al. Underdiagnosis of influenza virus infection in hospitalized older adults. J Am Geriatr Soc 2018;66:467–472.
27. Dugas AF, Valsamakis A, Atreya MR, et al. Clinical diagnosis of influenza in the ED. Am J Emerg Med 2015;33:770–775.
28. Childs A, Zullo AR, Joyce NR, et al. The burden of respiratory infections among older adults in long-term care: A systematic review. BMC Geriatr 2019; 19:210.
29. Lansbury LE, Brown CS, Nguyen-Van-Tam JS. Influenza in long-term care facilities. Influenza Other Respir Viruses 2017;11:356–366.
30. Seynaeve D, Augusseau-Riviere B, Couturier P, et al. Outbreak of human metapneumovirus in a nursing home: A clinical perspective. J Am Med Dir Assoc; May 14, 2019.
31. Pulia M, Kern M, Schwei RJ, et al. Comparing appropriateness of antibiotics for nursing home residents by setting of prescription initiation: A cross-sectional analysis. Antimicrob Resist Infect Control 2018;7:74.
32. Nelson RE, Stockmann C, Hersh AL, et al. Economic analysis of rapid and sensitive polymerase chain reaction testing in the emergency department for influenza infections in children. Pediatr Infect Dis J 2015;34:577–582.
33. Chen CC, Li HC, Liang JT, et al. Effect of a modified hospital elder life program on delirium and length of hospital stay in patients undergoing abdominal surgery: A cluster randomized clinical trial. JAMA Surg 2017;152:827–834.
34. Hung CY, Wu WT, Chang KV, et al. Predicting the length of hospital stay of post-acute care patients in Taiwan using the Chinese version of the continuity assessment record and evaluation item set. PLoS One 2017;12: e0183612.