Received: 28 August 2020 | Revised: 28 October 2020 | Accepted: 16 November 2020

DOI: 10.1111/jcpt.13326

REVIEW ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Utility of the respiratory viral panel as an antimicrobial stewardship tool

Kelly Covert PharmD[1] | Elizabeth Bashore PharmD Candidate[1] | McKenzie Edds PharmD Candidate[1] | Paul O Lewis PharmD[2]

[1]East Tennessee State University Bill Gatton College of Pharmacy, Johnson City, TN, USA

[2]Johnson City Medical Center, Johnson City, TN, USA

Correspondence
Kelly Covert, East Tennessee State University Bill Gatton College of Pharmacy, Johnson City, TN, USA.
Email: kelly.covert@outlook.com

Abstract

What is Known and Objective: The development of rapid diagnostics has revolutionized antimicrobial stewardship with efforts targeting earlier de-escalation or discontinuation of antibiotics. The respiratory viral panel (RVP) is one tool quickly able to detect common viral and bacterial pathogens using polymerase chain reaction technology. Utility may be further enhanced in conjunction with procalcitonin (PCT). However, the optimal use of the RVP to the clinical pharmacist in the treatment of community-acquired respiratory infections remains unclear.

Methods: The purpose of this guide is to review the available literature regarding the impact of the RVP with and without procalcitonin on antimicrobial stewardship efforts and to provide guidance on how to use each of these tools.

Results and Discussion: In total, 13 studies were included, 5 of which utilized PCT in conjunction with RVP and 8 of which did not use PCT. The majority of studies were retrospective in nature, and the most common outcomes evaluated were antibiotic days of therapy (DOT) and time to antibiotic discontinuation.

What is New and Conclusion: After review, RVP alone has limited value to antimicrobial stewardship; however, when used in conjunction with procalcitonin, RVP has the potential to reduce antibiotic use and duration.

KEYWORDS

antibiotics, clinical pharmacy, drug utilisation, guidelines, intervention

1 | WHAT IS KNOWN AND OBJECTIVE

In 2014, a Presidential Executive Order was issued to combat antibiotic-resistant bacteria based on morbidity and mortality data from The Centers for Disease Control and Prevention (CDC). This document outlined the public health and economic impact of antibiotic resistance and emphasized combating antibiotic-resistant bacteria as a national security priority. The report also detailed antibiotic stewardship (ASP) tools, with a particular emphasis on surveillance efforts and rapid diagnostic technologies.[1]

While progress has been made in efforts to decrease the inappropriate use of antibiotics in the United States, more action is needed to combat the growing numbers of antibiotic-resistant infections. It is estimated that antibiotic-resistant bacteria and fungi cause an estimated 2,868,700 infections and 35,900 deaths annually. Additionally, antibiotics are associated with adverse effects, such as *Clostridioides difficile* infections, antibiotic-associated diarrhoea and cardiac abnormalities. The most recent CDC Antibiotic Resistance Threats reported an annual rate of 223,900 cases and 12,800 deaths from *Clostridioides difficile* in the United States.[2]

The CDC released an updated version of the core elements to hospital ASPs in 2019. This report highlighted community-acquired pneumonia as one of the top 3 disease states with the greatest opportunities to improve prescribing. Specific interventions include

improving diagnostic accuracy, tailoring therapy to culture results and optimizing duration of treatment. Upper and lower respiratory infections have historically been a major challenge for ASPs due to the complexity of comorbidities that are often associated with these infections. Chronic obstructive pulmonary disease (COPD) exacerbations and acute decompensated heart failure exacerbations can mimic pneumonia on chest X-ray (CXR). Viral diagnostics and/or procalcitonin (PCT) are specifically referenced by the CDC as tools to be utilized to identify patients for whom antibiotics can be stopped. The respiratory viral panel (RVP) is a multiplex polymerase chain reaction test that can quickly identify multiple viruses, including influenza, parainfluenza, coronavirus, adenovirus, human metapneumovirus, human rhinovirus/enterovirus and respiratory syncytial virus. Additionally, the RVP can detect 4 bacteria, including *Bordetella pertussis*, *Bordetella parapertussis*, *Chlamydophila pneumoniae* and Mycoplasma pneumoniae. The panel is set up to provide timely information to guide clinician decision-making in both the inpatient and outpatient settings when used with or without PCT.[3] Of note at the time of this writing, the coronavirus identified by the RVP is not the 2019 novel coronavirus (COVID-19). As such, the aim of this review is to discuss the literature regarding ASP and RVP and to make recommendations on optimal use.

2 | METHOD

A PubMed and Google Scholar search from 2014 to May 2020 was conducted using the following keywords or search terms: respiratory AND viral AND panel AND stewardship, polymerase chain reaction, and respiratory viral panel. The start date for article selection of 2014 was selected based on the 2014 Presidential Executive Order which was issued highlighting the need for antimicrobial stewardship given the rise of antibiotic-resistant bacteria and the emphasis on utility of rapid diagnostics to curb inappropriate antimicrobial use. Additional references were identified from a review of references of initially included articles to ensure thorough and complete inclusion of relevant articles. After articles were identified by the investigators, they were vetted by the investigator team collaboratively to ensure agreement on article inclusion. Articles evaluating exclusively paediatric patients were excluded. Given the volume of data recovered, case reports and case series were also excluded from the review.

3 | RESULTS AND DISCUSSION

There were 13 studies included, 5 of which utilized PCT in conjunction with RVP and 8 of which did not use PCT. The majority of studies were retrospective in nature, and the most common outcomes evaluated were antibiotic days of therapy (DOT) and time to antibiotic discontinuation.

3.1 | Studies without procalcitonin

Table 1 provides a summary of studies evaluating the utility of RVP on ASP efforts without the concomitant use of PCT.

In 2016, Yee and colleagues published their retrospective cohort study evaluating the impact of a positive RVP on patients presenting to the emergency department during the 2013–2014 influenza season. Patients were divided into one of three categories: influenza-positive, influenza-negative RVP-positive and RVP-negative. There were no significant differences in the baseline characteristics between group, and the majority of patients had at least one comorbid condition and were diagnosed with a community-acquired infection. The authors noted that a negative RVP resulted in empiric oseltamivir discontinuation in 66% of patients. Furthermore, antibiotics were empirically initiated in 66.1% of patients with a negative RVP, in 70% of patients with a non-influenza-positive RVP, and in 70.6% of patients with an influenza-positive RVP. Upon obtaining RVP results, antibiotics were continued in 84.5% of RVP-negative hospitalized patients and in 75% of RVP-positive patients. This study showed positive results for antiviral management as a result of RVP results but did not show favourable results for ASP. The small study, lack of bacterial culture data, lack of specific comorbidity data, lack of a non-RVP control group and lack of statistical or power analysis of outcomes limit the applicability of this study to broader practice.[4]

Choi and colleagues evaluated the effects of transitioning from RVP utilizing PCR technology to a rapid respiratory viral panel (rapid RP) on duration of antibiotic use and length of stay (LOS) in 140 adult hospitalized patients in a retrospective chart review. The main differences between the two tests include a higher sensitivity and faster turnaround time with the rapid RP test. Patients who received antibiotics within 30 days prior to study initiation and those who had not completed antibiotics by the end of the study period were excluded. Baseline characteristics were well-balanced with the exception of significantly more immunocompromised patients in the RVP group than the rapid RP group (35.7% vs 18.6%, $p = 0.036$). Neither the duration of antibiotics nor total hospital LOS were significantly different between groups [(4 days vs 5 days, $p = 0.8$), (4.5 days vs 5 days, $p = 0.78$)]. The lack of significant difference in days of antibiotic therapy persisted in a subgroup analysis of patients with positive test results (5 days vs 2 days, $p = 0.13$). Ultimately, this study did not demonstrate a significant difference in antibiotic prescribing or duration between groups; however, the study was not designed to evaluate the benefit or drawback to adding rapid diagnostic testing at a healthcare system. Additionally, a power calculation was not completed by the authors, but the study was likely underpowered to detect a significant difference between groups.[5]

Lowe and colleagues performed a quasi-experimental study to assess the impact of a targeted ASP intervention for viral RTIs pre- and post-intervention. The authors implemented a prospective audit and feedback intervention in adult inpatients with a positive respiratory PCR admitted in two acute tertiary care hospitals, and a historic comparator group was used as the control. There were no significant differences in the baseline characteristics between groups, and the majority of patients in both cohorts had a CURB-65 score of 0-1. The prospective cohort had, on average, 1.3 fewer days of antibiotics (2.8 days vs 4.1 days, $p < 0.01$). Furthermore, an accepted ASP recommendation within the prospective cohort was associated with 3.6 fewer antibiotic days (5.6 days vs 2.0 days, 95% CI 2.1–5.2, $p < 0.001$).

TABLE 1 Studies not utilizing procalcitonin

Citation	Study Design	Study Population	Intervention	Outcome
Yee, 2016[4]	Retrospective cohort	Adult patients presenting to the ED with influenza-like illness who received RVP testing Positive influenza ($n = 61$) Positive non-influenza ($n = 32$) Negative RVP ($n = 93$)	Administration of RVP	• Negative RVP resulted in empiric oseltamivir discontinuation in 66% of patients. • Antibiotics empirically initiated in: ○ 66.1% of patients with a negative RVP ○ 70% of patients with a non-influenza-positive RVP ○ 70.6% of patients with an influenza-positive RVP • RVP results lead to antibiotic discontinuation in ○ 15.5% of RVP-negative hospitalized patients ○ 25% of RVP-positive hospitalized patients
Choi, 2017[5]	Retrospective chart review	Adult patients with a BioFire FilmArray and Luminex xTAG RVP who received empiric antibiotic therapy for a respiratory indication Pregnant patients and patients who received antibiotics 30 days prior to admission were excluded	Rapid Respiratory Panel by BioFire FilmArray ($n = 70$) Respiratory Viral Panel by Luminex xTAG ($n = 70$)	• No difference in median length of stay between groups (4.5 days vs 5 days, $p = 0.78$) • No difference in median duration of antibiotic use between groups (4 days vs 5 days, $p = 0.8$)
Lowe, 2017[6]	Quasi-experimental	Adult inpatients, positive RVP from upper or lower respiratory samples, absence of positive bacterial cultures or CXR suggestive of pneumonia Paediatric patients and CF patients were excluded	Retrospective ASP Consult ($n = 98$) Prospective ASP Consult ($n = 70$)	• 1.3 fewer antibiotic days with the prospective cohort after RVP results (2.8 days vs 4.1 days, 95% CI 0.3–2.3) • Accepted ASP recommendations within the prospective cohort was associated with 3.6 fewer antibiotic days (2 days vs 5.6 days, 95% CI 2.1–5.2) • Prospective review was associated with a significant reduction in mortality within 30 days (1% vs 9%, $p = 0.04$) • No difference in appropriate empiric oseltamivir discontinuation within 24 of influenza-negative RVP results (88% vs 89%, $p = 0.91$)
Semret, 2017[7]	Prospective secondary analysis of influenza surveillance data	RVP-tested patients hospitalized for at least 24 h admitted for an acute RTI, COPD or asthma exacerbation, unexplained sepsis, or influenza-like symptoms Patients with a RVP done >7 days after symptom onset, hospital-acquired infection, or non-respiratory indication for antibiotics were excluded@Influenza-positive ($n = 425$) Other virus-positive ($n = 69$) Virus-negative ($n = 306$)	Administration of RVP	• In influenza-positive patients, antibiotics were discontinued after RVP results in: ○ 37% of patients with CXR suggestive of pneumonia ○ 47% of patients with an unremarkable CXR, • In non-influenza virus-positive patients, antibiotics were discontinued after RVP results in: ○ 20% of patients with CXR suggestive of pneumonia ○ 57% of patients with an unremarkable CXR • Influenza virus-positive RVP was significantly associated with oseltamivir use (OR 9.38, 95% CI 4.48–19.61) • Influenza-positive RVP was not associated with a significant discontinuation rate of antibiotics (OR 1.38, 95% CI 0.89–2.16) • CXR suggestive of pneumonia was an independent risk factor for lack of antibiotic discontinuation (OR 0.61, 95% CI 0.41–0.93).

(Continues)

TABLE 1 (Continued)

Citation	Study Design	Study Population	Intervention	Outcome
May, 2019[8]	Prospective, pilot RCT	ED patients >/= 1 years old being evaluated for influenza-like illness or URI Patients on antibiotics at time of ED presentation, not English- or Spanish-speaking, cognitively impaired with no legal representative, or expected to leave before multiplex test results were available were excluded	Intervention group: Rapid near POC RVP plus clinician-directed usual care ($n = 93$) Control group: Usual care alone ($n = 98$)	• No significant difference in antibiotic prescribing in the intervention group (22% vs 34%, $p = 0.06$) • No difference in antiviral prescribing between groups (10% vs 7%, $p = 0.53$)
Srinivas, 2019[9]	Retrospective, quasi-experimental	Adult patients with a positive RVP Patients with a documented bacterial infection were excluded	Pre-ASP intervention ($n = 77$) Post-ASP intervention ($n = 86$)	• No significant difference in time to antibiotic de-escalation between groups (2.7 days vs 2.33 days, $p = 0.88$) • Median time to initiation of oseltamivir was significantly shorter in the post-intervention group (3.6 days vs 11.3 days, $p = 0.02$)
Weiss, 2019[10]	Retrospective cohort	Adult patients, ICD-10 code for lower respiratory symptoms, RVP or RPP collected within 48-h of presentation Patients with outpatient or indicated antibiotic use were excluded	RVP-positive ($n = 110$)[a] RPP-positive ($n = 234$)[a]	• Lower antibiotic prescribing in patients with negative CXR in RPP-positive patients (44.5% vs 68.9%, $p = 0.013$) • Fewer patients received antibiotics prior to test results in RPP-positive patients ○ Unremarkable CXR: (54.7% vs 96.8%, $p = 0.0007$) ○ Remarkable CXR: (81.6% vs 100%, $p < 0.001$)

ASP, antimicrobial stewardship programme; CI, confidence interval; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CXR, chest X-ray; ED, emergency department; ICD-10, International Classification of Diseases, 10th edition; POC, point of care; RPP, respiratory pathogen panel; RTI, respiratory tract infection; RVP, respiratory viral panel; URI, upper respiratory infection.

[a]Time to results (RVP, 12-72 h vs RPP, ≤4 h).

Oseltamivir discontinuation upon receipt of an influenza-negative RVP results was consistent between groups (89% vs 88%, $p = 0.91$). The prospective cohort had significantly more oseltamivir initiation upon influenza-positive RVP result (95% vs 72%, $p = 0.03$). This study showed positive results in ASP and antiviral management. Limitations to this study include its small sample size and low proportion of medically ill patients, as evidenced by the low CURB-65 score.[6]

Semret and colleagues completed a secondary analysis of data collected for influenza surveillance of patients who had been hospitalized for at least 24 h and on whom an RVP was collected. Additional eligibility criteria included acute respiratory tract infection, exacerbation of COPD or asthma, unexplained sepsis, and influenza-like symptoms. Patients were excluded if the RVP was collected >7 days after symptom onset, if the infection was hospital-acquired, or if the patient was admitted secondary to a non-respiratory tract infection. The primary was a change in antimicrobial administration after RVP results. Cox proportional hazards model was employed to adjust for RVP findings, Charlson comorbidity index, and suspicion of pneumonia. Enrolled patients were broken up into three analysis groups: influenza virus-positive, other virus-positive and virus-negative. In patients who received empiric antibiotics with and without suspicion of pneumonia, antibiotics were discontinued in 37% and 47%, respectively, once RVP testing was completed and influenza was isolated. In non-influenza virus-positive patients, antibiotics were discontinued in 20% of patients with pneumonia and in 57% of patients without pneumonia, based on RVP results. Unsurprisingly, influenza virus-positive RVP was significantly associated with oseltamivir use (OR 9.38, 95% CI: 4.48–19.61). After adjustment for confounders, the presence of an influenza-positive RVP was not associated with a significant discontinuation rate of antibiotics (OR 1.38, 95% CI: 0.89–2.16). In patients with a CXR suggestive of pneumonia, antibiotics were significantly less likely to be discontinued upon receipt of a positive RVP (OR 0.61, 95% CI: 0.41–0.93). This study strongly implicates the utility of an RVP for antiviral initiation and stewardship; however, its association with ASP is less clear. Limitations of this study include its non-randomized design, lack of microbiologic data and focus on immediate (within 48 h) antimicrobial change.[7]

May and colleagues completed a prospective, pilot randomized trial in 194 patients designed to assess the impact of the RVP on ASP efforts. Patients >12 years old with symptoms of an URI or influenza-like illness who were not already on antibiotics prior to enrolment were included. Patients who were receiving antibiotics at the time of enrolment or who were expected to leave before multiplex test results were available were excluded in the study. While the RVP numerically reduced antimicrobial prescribing (22% vs 34%, $p = 0.06$), this result did not reach statistical significance. However, the authors were unable to enrol the necessary 304 patients required to achieve 80% power, and, as such, type II error may be present in this study.[8]

Srinivas and colleagues published their retrospective quasi-experimental study in 163 adult patients detailing the stewardship impact of the RVP pre- and post-ASP intervention. Patients with a documented bacterial infection were excluded from the analysis, and included patients were matched based on age and type of respiratory virus identified. ASP alerts were generated based on the presence of a positive RVP plus meropenem, piperacillin/ tazobactam, aztreonam, ampicillin, ampicillin/ sulbactam, levofloxacin, azithromycin, ceftriaxone, cefepime or doxycycline being on the patient profile. The post-intervention group was significantly older than the pre-intervention group (67.4–13 vs 61.7–4, $P = 0.008$), while the pre-intervention group had significant more infectious disease consults during the admission (29% vs 14%, $p = 0.02$). Ultimately, there was no significant difference in time to antibiotic de-escalation between groups (2.7 days vs 2.33 days, $p = 0.88$); however, the median time to initiation of oseltamivir was significantly shorter in the post-intervention group (3.6 days vs 11.3 days, $p = 0.02$). Limitations of this study include its retrospective nature and small sample size. While this study does not support the use of RVP as an ASP tool, it does support the panel's antiviral utilization impact.[9]

Weiss and colleagues completed a retrospective cohort study in adult patients with International Statistical Classification of Disease and Related Health Problems, 10th edition (ICD-10) codes for lower respiratory tract infections (LRTI) who received either an RVP or respiratory pathogen panel (RPP). The primary difference between the two tests used in this study is the time to results (RVP, 12–72 h vs RPP, ≤4 h) and a higher number of atypical bacteria detected in the RPP. Importantly, there were differences between groups as there were more patients with asthma in the RPP group (23.1% vs 12.7%, $p = 0.027$) and more intensive care unit (ICU) patients in the RVP group (27.3% vs 17.5%, $p = 0.039$). In patients with an unremarkable CXR, antibiotic prescribing was lower in the RPP-positive group than in the RVP-positive group (44.5% vs 68.9%, $p = 0.013$) but there was no difference between groups in patients with an abnormal CXR (95.4% vs 89.6%, $p = 0.187$). Additionally, in patients with both unremarkable and remarkable CXRs, fewer patients received antibiotics prior to test results in the RPP-positive group [(54.7% vs 96.8%, $p = 0.0007$), (81.6% vs 100%, $p < 0.001$)]. The total duration of antibiotic days was not significantly different between groups, regardless of CXR status. This study highlights the significant impact of rapidity of test results with ASP. Limitations of the study include lack of a negative control group, provider preference on when to order RVP or RPP, and no third-party evaluation of CXRs. Ultimately, this study further advocates for rapid test results as an important ASP tool.[10]

3.2 | Studies utilizing procalcitonin

Timbrook and colleagues published a retrospective single-centre study in 2031 adult patients with a respiratory infection and either RVP or PCT within the first 72 h of presentation to the hospital. Patients with cystic fibrosis (CF), a positive bacterial culture, or COPD were excluded. The primary objective of this study was to determine the frequency of change to empiric antimicrobial therapy once the results of RVP and PCT were known. Patients were divided into three groups for analyses: PCT <0.25 mcg/L, positive RVP, PCT <0.25 mcg/L and positive RVP. There were no significant differences in the baseline characteristics between groups, and the

TABLE 2 Studies utilizing procalcitonin

Citation	Study Design	Study Population	Intervention	Outcome
Timbrook, 2015[11]	Retrospective single-centre study	Adult patients with a respiratory infection and either RVP or PCT within the first 72 h of presentation to the hospital Patients with CF, a positive bacterial culture, or COPD were excluded	PCT < 0.25 mcg/L ($n = 156$) Positive RVP ($n = 170$) PCT < 0.25 mcg/L and positive RVP ($n = 31$)	• 789 patients (38.8%) had stewardship opportunities available within the first 72 h of result availability • Of the 307 patients who were prescribed antibiotics, 60 (19.5%) had antibiotics discontinued upon result availability
Keske, 2018[12]	Retrospective chart review	Patients (inpatient and outpatient) with a RVP drawn and a diagnosis of influenza-like illness	Outpatient RVP ($n = 388$) Inpatient RVP ($n = 359$) 16 years old ($n = 258$) >/= 16 years old ($n = 101$)	• Antibiotics were deemed inappropriate in 160/359 (45%) of inpatients • The use of RVP reduced inappropriate antibiotic use in the inpatient setting after implementation (51.3% vs 39.3%, $p = 0.024$) ○ Inpatient children (44.5% vs 28.8%, $p = 0.009$) ○ Inpatient adults (72% vs 63%, $p = 0.36$). • Mean duration of inappropriate antibiotic use was significantly reduced by RVP in the inpatient setting ○ Children (6.5 days vs 2 days, $p < 0.001$ ○ Adults (7.3 days vs 3.7 days, $p = 0.007$)
Moradi, 2019[13]	Multi-site pre-, post-, quasi-experimental study	Adult patients with PCT < 0.25 ng/ml, positive RVP within 48 h of each other, and receiving 1 + more systemic respiratory antibiotics Paediatric patients and patients on antibiotics for non-respiratory indications were excluded	Post-BPA assessment ($n = 226$) Pre-BPA assessment ($n = 161$)	• BPA assessment resulted in: ○ 2.2 day reduction in antibiotic days (5.8 days vs 8.0 days, $p < 0.001$) ○ A reduction in mean days of antibiotic therapy (4.5 days vs 6.3 days: ○ Higher rates of antibiotic discontinuation after 24 h (37.8% vs 18.6% $p < 0.001$) ○ Fewer patients discharged on antibiotics (20.0% vs. 47.8% $p < 0.001$) ○ A reduction in antibiotic duration post-discharge (0.9 ± 2.1 days vs 2.4 ± 3.3 days $p < 0.001$)
Lee, 2020[14]	Prospective twin-centre cohort study	Adult patients who presented to the emergency department with SARIs	RVP plus PCT ($n = 169$) Historical control ($n = 507$)	• Antibiotic discontinuation or de-escalation was significantly higher in the RVP plus PCT group (26% vs 16.1%, $p = 0.007$) • IV antibiotic duration was significantly shorter in the RVP plus PCT group (10.0 days vs 14.6 days p < 0.001) • Hospital LOS was significantly shorter in the RVP plus PCT group (14.0 vs 16.1 days, $p = 0.030$) • In-hospital mortality was not different between groups (13.8% vs 19.3%, $p = 0.09$) • 30-day mortality was no different between groups (10.1% v 16.2%, $p = 0.05$)

BPA, Best Practice Alert; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; LOS, length of stay; PCT, procalcitonin; RVP, respiratory viral panel; SARIs, severe acute respiratory infection.

authors found that 789 patients (38.8%) had stewardship opportunities available within the first 72 h of result availability. Of the 307 patients who were prescribed antibiotics, 60 (19.5%) had antibiotics discontinued upon result availability. While this study certainly suggests the potential utility of RVP in conjunction of PCT as a stewardship tool, comparative statistics were not utilized, which does limit the utility of the study results. Additionally, the exclusion criteria make this study less generalizable to patients with COPD, a patient population that is commonly prescribed respiratory antibacterial agents. Finally, timing of antibiotic administration in relation to the time of RVP or PCT results was not evaluated.[11]

Keske and colleagues published their retrospective chart review of 1317 patients with an influenza-like illness aimed to demonstrate the impact of rapid diagnostics on antibiotic use. Adult patients with RVP were included, and PCT was included for patients with suspicion of a bacterial infection and/or who were deemed critically ill. At least one virus was detected in 747 patients (57%), and antibiotics were deemed inappropriate in 160/359 (45%) of inpatients. Ultimately, the use of a RVP did reduce inappropriate antibiotic use in the inpatient setting after implementation (51.3% vs 39.3%, $p = 0.024$); however, this impact appears to have been driven by the data collected in children (44.5% vs 28.8%, $p = 0.009$) versus by the adult population (72% Vs 63%, $p = 0.36$). Notably, mean duration of inappropriate antibiotic use was significantly reduced in both children and adults in the inpatient setting [(6.5 days vs 2 days, $p < 0.001$), (7.3 days vs 3.7 days, $p = 0.007$)]. This study highlights the impact that the RVP can have on inappropriate antibiotic use in children, but did not show significant results in the adult population. Furthermore, inconsistent PCT use and no discussion of baseline characteristic differences between groups make this study less generalizable. Finally, it was not clearly discussed in the article how antibiotics were deemed appropriate or inappropriate.[12]

Moradi and colleagues performed a quasi-experimental study at 5 hospitals analysing the impact of an electronic medical record (EMR) Best Practice Alert (BPA) for patients with a positive RVP, PCT <0.25 ng/ml within 48 h of each other, and at least one active systemic antibiotic. The BPA is designed to notify providers of potential opportunities for ASP based on RVP and PCT results and active antimicrobial orders. Paediatric patients and patients on non-respiratory antibiotics were excluded. The post-BPA cohort had a significantly higher mean Charleston comorbidity index score (4.8 vs 4.0, $p < 0.001$) and a shorter average length of ICU stay (5.0 vs 6.9 days, $p = 0.043$). Overall, days of antibiotic therapy were significantly reduced in the post-BPA group (5.8 vs 8 days, $p < 0.001$) as was mean days of therapy after BPA firing was significantly reduced (4.5 days vs 6.3 days; $p < 0.001$). Furthermore, more antibiotics were discontinued within 24 h of initiation in the post-BPA group (37.8% vs 18.6%; $p < 0.001$), and fewer patients were discharged on antibiotics (20.0% vs 47.8%; $p < 0.001$). This study highlighted the significant impact of implementing a BPA based on RVP, PCT, and antimicrobial orders on ASP. The use of PCT in conjunction with RVP identified patients who were unlikely to benefit from continued antibiotics. The limitations of this study include utilization of a single health system and potential lack of generalizability, as well as significantly different mean CCI between groups, and differences in severity of the influenza seasons between the prospective and retrospective groups.[13]

Lee and colleagues completed a prospective twin-centre cohort in 169 patients to determine the clinical impact of combining point of care (POC) RVP and PCT levels on ASP compared to a pre-POC RVP cohort. Patients ≥65 years presenting to the ED with acute respiratory illness were included in the study. The authors defined a negative PCT as <0.25 ng/ml. Baseline characteristics were well-balanced between groups with the exception of a higher incidence of chronic liver disease in the RVP/PCT group and a higher incidence of COPD in the control group. The RVP/PCT group had significantly higher rates of antibiotic de-escalation (21.9% vs 13.2%, $p = 0.007$), shorter duration of intravenous antibiotics (10.0 days vs 14.6 days, $p = <0.001$), and a shorter hospital LOS (14.0 vs 16.1 days, $p = 0.03$). Neither 30 day nor in-hospital mortality was significantly different between the groups [(10.1% vs 16.2%, $p = 0.05$), (13.8% vs 19.3%, $p = 0.09$)].[14]

4 | WHAT IS NEW AND CONCLUSION

With the expansion of ASP tools, a review of the data supporting most appropriate use of these tools is necessary. The RVP has served as a significant step forward in the rapid and accurate identification of respiratory pathogens and can guide clinicians in both antibacterial and antiviral stewardship. However, the data utilizing RVP alone are limited with minimal impact to ASP efforts. Benefits were primarily seen with improved antiviral prescribing and a small increase in de-escalation with less impact on antibiotic de-escalation or discontinuation. However, when RVP is used in conjunction with PCT, benefit in both antiviral and antibiotic was demonstrated. As such, the most appropriate method to use RVP, from a stewardship perspective, appears to be in tandem with PCT. The most commonly used cutoff for a PCT that is considered not suggestive of a bacterial pathogen is <0.25 ng/ml.[11,13,14] Based on each of these considerations, a decision-making guide is provided below (Figure 1) to guide clinical pharmacists and providers on the best use of RVP and PCT. This tool can be used in both the acute care and critical care settings but may have less utility in the community setting based on outpatient availability of rapid diagnostics in this setting.

There are limitations to this review that should be noted. First, while there is rationale behind the cutoff date of 2014 and for the study inclusion criteria, it is possible that studies published prior to this date may have provided valuable information and that the inclusion and exclusion criteria may have limited the number of included studies. The use of PCT alone has been thoroughly evaluated from an ASP perspective. As this review focuses primarily on the utility of RVP, evaluation of PCT alone was outside the scope. Another limitation is the lack of studies involving the use of RVP and C-reactive protein (CRP). The use of CRP in acute exacerbations of COPD reduced antibiotic prescribing from 77.4% to 57% (adjusted odds ratio

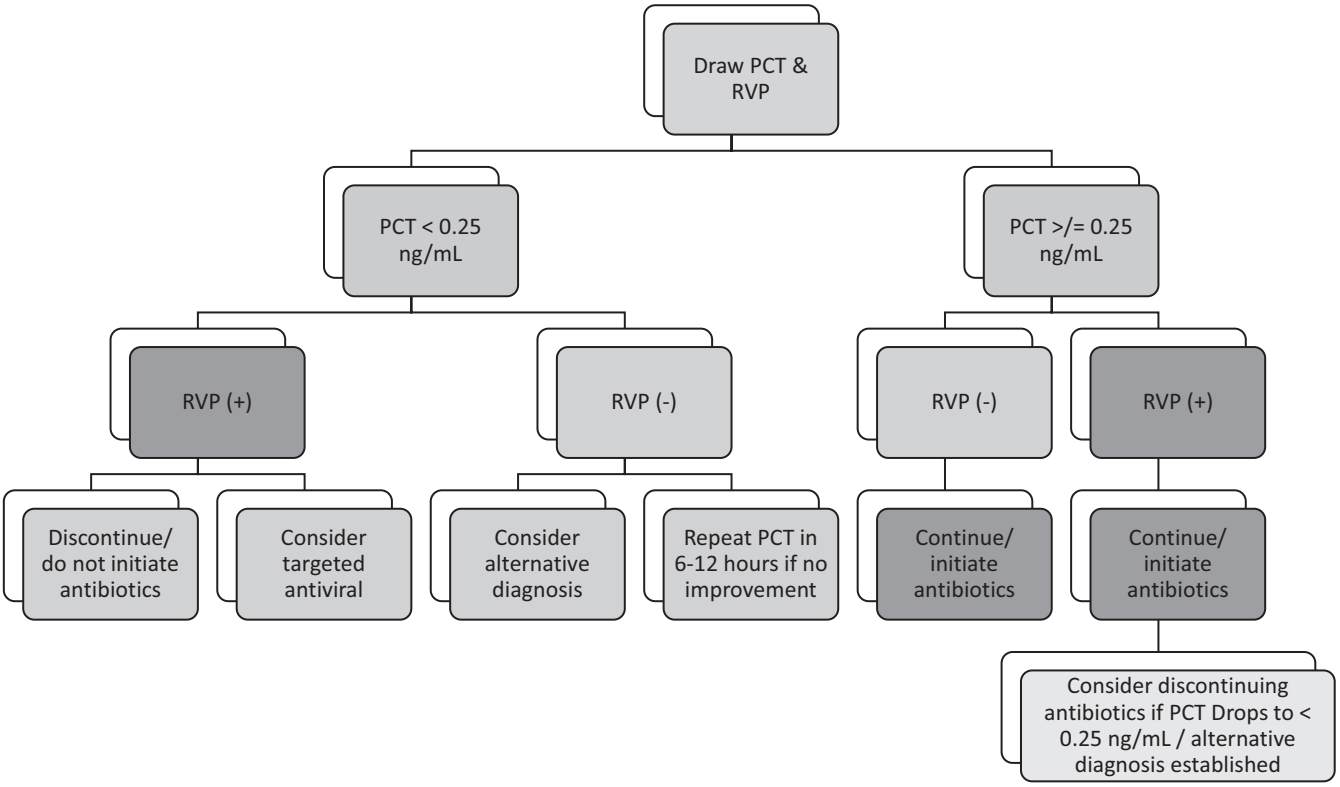

FIGURE 1 Clinician decision-making guide for RVP and PCT. PCT, procalcitonin; RVP, respiratory viral panel

0.31; 95% CI 0.2–0.47).[15] However, utility of CRP in conjunction with RVP has not been evaluated. Finally, COVID-19 has reshaped the entire approach to evaluating respiratory tract infections. Data reviewed here are specific for COVID-19-negative patients. The approach to evaluating COVID-19 patients is still evolving. Data from COVID-19-negative patients may not be extrapolatable to COVID-19 positive patients.

There are several limitations to the RVP when not used in conjunction with other tools. Depending on the type of test utilized, sensitivity and specific may vary. Rapid antigen detection tests typically provide rapid results, but also typically have lower sensitivity. However, assays that detect viral nucleic acids combine prompt results with high sensitivity and specificity.[16] Isolation of a respiratory virus does not eliminate the possibility of there being a bacterial superinfection or a post-viral bacterial pneumonia. If one of the commonly tested bacteria, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, or *Bordetella pertussis* are isolated, an appropriate antibiotic, most commonly azithromycin, should be added to target those microbes.[17] Additionally, a negative RVP does not eliminate the possibility of a viral infection, as there are many more possible viral causes of upper airway disorders than just what is presently on the panel. The addition of PCT to the RVP certainly reduces the likelihood of missing a bacterial coinfection. However, PCT has its limitations as well. Several conditions and medications can cause false-positive PCT values, including burns, trauma, surgery, shock, renal insufficiency, and administration of monoclonal antibodies. In contrast, false negatives can occur in patients who are early in their infectious course, those with localized infections, and those with subacute endocarditis.[18] The utility of PCT use alone in antimicrobial stewardship is outside of the scope of this review. Ultimately, the decision to change antimicrobial therapy should not be made based on any single laboratory value or marker, but in a complete evaluation of the patient's overall picture.

Respiratory viral panel in conjunction with PCT can lead to rapid de-escalation of antibiotics and initiation of targeted antiviral therapy. Limitations do exist with these tools, and decisions should be made in conjunction with the complete clinical picture. However, given the benefits observed, clinicians should consider utilization of RVP and PCT in the stewardship clinical armamentarium.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Kelly Covert https://orcid.org/0000-0003-1262-9423

REFERENCES

1. Obama B. Executive order—combating antibiotic-resistant bacteria. Released September 18, 2014. Available at https://obamawhitehouse.archives.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria. Accessed June 12, 2020.
2. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. Revised Dec. 2019. Available at

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed June 12, 2020.
3. Buchan BW, Windham S, Balada-Llasat J, et al. Practical comparison of the BioFire FilmArray Pneumonia Panel to routine diagnostic methods and potential impact on antimicrobial stewardship in hospitalized patients with lower respiratory tract infections. *J Clin Microbiol*. 2020;58(7):e00135. https://doi.org/10.1128/JCM.00.35-20
4. Yee C, Suarthana E, Dendukuri N, et al. Evaluating the impact of the multiplex respiratory virus panel polymerase chain reaction test on the clinical management of suspected respiratory viral infections in adult patients in a hospital setting. *Am J Infect Control*. 2016;44:1396-1398.
5. Choi S, Kabir R, Gautam-Goyal P, Malhotra P. Impact of respiratory viral panel polymerase chain reaction assay turnaround time on length of stay and antibiotic use in patients with respiratory viral illness. *Hosp Pharm*. 2017;52(9):640-644.
6. Lowe CF, Payne M, Puddicombe D, et al. Antimicobial stewardship for hospitalized patients with viral respiratory tract infections. *Am J Infect Control*. 2017;45:872-875.
7. 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 patients. *JID*. 2017;216:936-944.
8. May L, Tatro G, Poltavskiy E, et al. Rapid multiplex testing for upper respiratory pathogens in the emergency department: A randomized controlled trial. *OFID*. 2019;6(12):1-8.
9. Srinivas P, Rivard KR, Pallotta AM, et al. Implementation of a stewardship initiative on respiratory viral PCR-based antibiotic de-escalation. *Pharmacotherapy*. 2019;39(6):709-717.
10. Weiss ZF, Cunha CB, Chambers AB, et al. Opportunities revealed for antimicrobial stewardship and clinical practice with implementation of a rapid respiratory multiplex assay. *J Clin Microbiol*. 2019;57(10):e00861-e00919.
11. Timbrook T, Maxam M, Bosso J. Antibiotic discontinuation rates associated with positive respiratory viral panel and low procalcitonin results in proven or suspected respiratory infections. *Infect Dis Ther*. 2015;4:297-306.
12. 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*. 2018;37:779-783.
13. Moradi T, Bennett N, Shemanski S, et al. Use of procalcitonin and a respiratory polymerase chain reaction panel to reduce antibiotic use via an EMR alert. *Arch Clin Infect Dis*. 2019:1684-1689. https://doi.org/10.1093/cid/ciz1042
14. Lee C, Chang JC, Mao X, et al. Combining procalcitonin and rapid multiplex respiratory virus testing for antibiotic stewardship in older adult patients with severe acute respiratory infection. *JAMDA*. 2020;21:62-67.
15. Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med*. 2019;381(2):111-120. https://doi.org/10.1056/NEJMoa1803185
16. Brennan-Krohn T.Making sense of respiratory viral panel results. American Society for Microbiology. Last Updated March 2, 2020. Accessed on July 28, 2020. Available at https://asm.org/Articles/2020/March/Making-Sense-of-Respiratory-Viral-Panel-Results
17. Auwaerter PG, Bartlett JG.Johns Hopkins POC-IT ABX Guide. ©2000-2020 Unbound Medicine Inc.
18. Christ-Crain M, Mueller B. Procalcitonin in bacterial infections—hype, hope, more or less? *Swiss Med Wkly*. 2005;135(31–32):451-460.

How to cite this article: Covert K, Bashore E, Edds M, Lewis PO. Utility of the respiratory viral panel as an antimicrobial stewardship tool. *J Clin Pharm Ther*. 2021;46:277–285. https://doi.org/10.1111/jcpt.13326