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SHORT COMMUNICATION

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Stewardship opportunities in viral pneumonia: Why not the immunocompromised?

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Abstract

Antimicrobial management of viral pneumonia has proven to be a challenge in hospitalized immunocompromised patients. A host of factors contribute to the dilemma, such as diagnostic uncertainty, lack of organism identification, and clinical status of the patient. Respiratory virus panel (RVP) use was compared between 131 immunocompromised patients who received send-out (n = 56) vs in-house (n = 75) testing. Antimicrobial optimization interventions consisted of antiviral addition/discontinuation, antibiotic discontinuation/de-escalation, or modification of immunosuppressive regimen. After implementation of an in-house test with audit and feedback, turnaround time of the RVP was reduced from 46.7 to 5.5 hours ($P < .001$) and time to intervention was reduced from 52.1 to 13.9 hours ($P < .001$), yet the frequency of antimicrobial optimization interventions was unchanged (30.7% vs 35.7%). Differences were not observed in duration of empiric antibiotic therapy or length of stay. The overall discontinuation rate for patients tested with a RVP was low (4.6%), and those with positive RVP (n = 43) had antibiotics stopped in 14% of cases. Bacterial pneumonia coinfection was confirmed in 2 patients. Further systematic efforts should be taken to reduce antibiotic use in viral pneumonia and identify the major barriers in the immunocompromised population.

KEYWORDS
immunocompromised, rapid diagnostic, respiratory virus panel, stewardship, viral pneumonia

1 | INTRODUCTION

Successful antimicrobial stewardship (AMS) faces numerous barriers in transplant and immunocompromised patients.[1] Antimicrobial use for respiratory viruses, the most common pathogens associated with community acquired pneumonia, presents an opportunity of interest for stewardship efforts.[2] Prolonged antibiotic therapy in the setting of viral pneumonia in this population is associated with increased lengths of stay and development of multi-drug resistant organisms.[3] Use of rapid diagnostics, and particularly respiratory virus panels (RVP), is a recommended AMS initiative to reduce inappropriate antibiotic therapy by effectively ruling-in/out common respiratory viruses.[4] Respiratory virus polymerase chain reaction (PCR) testing has laboratory advantages of high sensitivity (up to 100%) and fast turnaround time (as little as 1 hour). These components make a more attractive tool for AMS, in comparison to standard respiratory cultures.[5] However, there is conflicting evidence for beneficial impact on clinical outcomes and resource utilization such as decreased antibiotic duration of therapy and hospital length of stay.[5–7] The purpose of this study was to evaluate the impact on antimicrobial utilization following implementation of an in-house RVP, coupled with AMS audit and feedback, in immunocompromised patients.

2 | MATERIALS AND METHODS

In an IRB-approved single-center quasi-experimental study, interventions in immunocompromised patients tested with a RVP were

observed over 2 respiratory virus seasons (RVS). Send-out RVP testing was utilized in RVS1 (October 2014—April 2015) without AMS audit. The following year (RVS2, October 2015—April 2016), an in-house RVP that detected 20 respiratory pathogens (BioFire FilmArray RP®, Salt Lake City, UT, USA) was implemented with concurrent weekday AMS calls to providers. Multidisciplinary education for the use of the in-house RVP was presented and distributed prior to RVS2, and a prospective audit and feedback of RVP results was piloted with rounding pharmacists and the AMS service. The RVP was analyzed in-house from 7 AM to 11 PM daily. All transplant patients and patients with immunocompromising conditions in the ICU with respiratory tract infections, tested with a RVP, were included. Pneumonia diagnosis was at the discretion of the critical care or transplant team, as per documentation in progress and discharge summaries. "Immunocompromised" was defined as those with solid organ transplant (SOT), hematopoietic stem cell transplant (HSCT), ANC < 1000 cells/cc, CD4 count < 200 cells/cc, or receiving other immunosuppressive/cytotoxic therapy (alkylating agents, anthracyclines, mTOR and calcineurin inhibitors, thymoglobulin, TNF-alpha inhibitors, CTLA-4 agonists, and corticosteroids equivalent to at least 2 weeks of prednisone 20 mg daily). Patients < 18 years of age, and those who were pregnant or had death or discharge prior to the result of the RVP, were excluded. Time from specimen collection to final result in the electronic medical record was defined as turnaround time. The study was powered to an effect size of 0.5 in turnaround time between RVS1 and RVS2 with a 2-sided alpha of 0.05 and power of 0.80, which yielded a sample size of 176 patients.[5] Outcomes of interest were empiric antimicrobial duration of therapy, hospital length of stay, time to an intervention. Interventions consisted of antimicrobial optimization via de-escalation/discontinuation of antibiotic, initiation/discontinuation of antiviral, or modification of immunosuppressive regimen, beginning from collection of specimen and up to 48 hours following the RVP result. Empiric duration of therapy was defined as antibiotic therapy for pneumonia prior to RVP result and/or targeted therapy interventions. Chi-square was used for categorical variables and Mann–Whitney-*U* was used for continuous non-parametric variables. Factors associated with antimicrobial optimization were examined in a bivariate analysis. SPSS Version 22® was used for statistical analyses.

3 | RESULTS

One hundred thirty-one immunocompromised patients tested with a RVP were analyzed (RVS1, n = 51; RVS2, n = 75). The median age was 60 years and 46.6% of the total population was female. There were no differences in baseline characteristics between RVS1 (send-out testing) and RVS2 (in-house testing) with the exceptions of positive RVP, chronic obstructive pulmonary disease/asthma, and congestive heart failure (Table 1). Among 131 patients with immunocompromising factors, renal (18.3%), liver (16.8%), and lung (13%) were the most common types of SOT, while 33 (24.8%) had metastatic cancer, 16 (12%) were on immunosuppressive medications not related to SOT, 7 (5.3%) with HSCT, and 5 (4.5%) had CD4 < 200 cells/cc. Pneumonia was diagnosed in 80 (61.1%) patients, of which 22 (27.5%) had microbiologic confirmation of bacterial pneumonia via respiratory culture. Twenty-two patients with bacterial respiratory pathogens were observed; the most common were *Staphylococcus aureus* (22.8%), followed by *Streptococcus pneumoniae* (13.6%) and beta-hemolytic *Streptococcus* species (13.6%). Of the 43 positive RVPs, most prevalent pathogens isolated were influenza A (30.2%), coronaviruses (25.6%), and rhinovirus/enterovirus (18.6%). Two patients had confirmed coinfection with viral and bacterial pneumonia.

The primary outcome, turnaround time, was reduced from 46.7 to 5.5 hours ($P < .001$). Time-to-intervention was reduced from 52.1 hours

TABLE 1 Baseline characteristics

	RVS1 (n = 56)	RVS2 (n = 75)	*P*
Age, median (IQR)	61 (54.0—68.0)	60 (46.5—66.5)	.315
Male, n (%)	29 (54.0)	41 (55.0)	.901
Transplant type, n (%)			
Renal	7 (12.5)	17 (22.7)	.137
Liver	10 (17.9)	12 (16.0)	.778
Heart	4 (7.1)	7 (9.3)	.758
Intestine	2 (3.6)	5 (6.7)	.698
Lung	11 (19.6)	6 (8.0)	.050
Pancreas	1 (1.8)	3 (4.0)	.635
Multi-visceral	1 (1.8)	4 (5.3)	.392
Hematopoietic stem cell	2 (3.6)	5 (6.7)	.698
Any immunosuppressive therapy	47 (83.9)	63 (84.0)	.991
ICU, n (%)	36 (64.3)	44 (58.7)	.514
Metastatic disease or ANC < 1000 cells/cc	15 (26.8)	18 (24.0)	.839
CD4 < 200 cells/cc	1 (1.8)	5 (6.7)	.238
Other immunosuppressive therapy[a]	5 (8.9)	11 (14.7)	.321
Mechanical ventilation	16 (28.6)	15 (20)	.253
Any supplemental oxygen in ICU	32 (57.1)	38 (50.1)	.504
Pneumonia, n (%)	34 (60.7)	46 (61.3)	.943
Microbiologic confirmation	13 (23.2)	9 (12.0)	.089
Upper respiratory tract infection, n (%)	16 (28.6)	17 (22.7)	.441
Positive RVP, n (%)	11 (19.6)	32 (42.7)	.005
Lung cancer, n (%)	8 (14.3)	8 (10.7)	.531
COPD/asthma, n (%)	20 (35.7)	15 (20.0)	.044
Congestive heart failure, n (%)	4 (7.1)	19 (25.3)	.007
Pulmonary fibrosis, n (%)	6 (10.7)	8 (10.7)	.993

[a]Not related to transplantation or metastatic disease.

to 13.9 hours ($P < .001$). The in-house RVP did not significantly impact frequency of antimicrobial optimization interventions (30.7% vs 35.7%), but did reduce the time-to-intervention from specimen collection from 52.1 to 13.9 hours ($P < .001$). There were also no differences between groups for types of intervention (de-escalations, discontinuations, additions), length of stay, or empiric antibiotic duration of therapy. Most interventions were discontinuation of oseltamivir (27/43), followed by addition of antiviral agent (10/43). Antibiotics were discontinued in 5.3% of all in-house RVP results (n = 131), and in 14.0% of positive RVPs (n = 43). The subset of patients with positive RVP testing had a shorter length of stay (4.0 vs 9.0 days, $P < .05$) and was more likely to have a diagnosis of upper respiratory tract infection (URTI), (44.2% vs 15.9%, $P < .05$). Characteristics associated with prescribing inertia were positive bacterial respiratory cultures and renal transplantation, while isolation of respiratory virus (mostly driven by influenza A) was associated with antimicrobial optimization (Table 2).

4 | DISCUSSION

Rapid diagnostic testing is quickly becoming an influential aspect of stewardship models and has been recommended in practice guidelines for initiating an AMS program.[4] We analyzed 75 immunocompromised patients who were tested with an in-house RVP after AMS implementation, which led to significant reductions in turnaround time and time-to-intervention, and increased diagnostic yield compared to 56 patients with send-out RVP testing. The broader respiratory panel PCR in RVS2 (included coronaviruses and human metapneumovirus) compared to RVS1 likely contributed to this yield. However, there was little indication that the management of these patients was significantly modified on the basis of improved diagnostic certainty with an in-house RVP, as no differences between groups for duration of therapy, length of stay, or interventions between RVS1 and RVS2 were observed. Increased diagnostic certainty may result in faster discharge, as patients with positive RVP had shorter length of stay than those with negative RVP; yet the infrequent de-escalation of antibiotics (14%) in this group was comparable to previous findings.[5] Suspected coinfection, critical status, increased oxygen requirements, specific radiographic findings, or other pending cultures may contribute to antibiotic continuation. In a recent prospective, multicenter surveillance study of community acquired pneumonia, the majority of pathogens isolated (by nasopharyngeal/oropharyngeal PCR, urinary antigen, or culture) in hospitalized patients with pneumonia are respiratory viruses, with a low (3%) incidence of bacterial-viral co-infection.[2] This population excluded immunocompromised individuals, and such a study would provide important context on current patterns in pneumonia for transplant patients and antimicrobial decision making. Only 1.5% of our population had confirmed coinfection and there were no differences in de-escalation between ICU and non-ICU populations. It is not surprising that bacterial pneumonia was a negative predictor of antimicrobial adjustment, but a similar association with

TABLE 2 Characteristics associated with AMS interventions

	AMS optimization (n = 43)	No AMS optimization (n = 88)	Odds ratio	95% CI
In-house RVP, n (%)	23 (53.5)	52 (59.1)	0.80	0.38—1.66
Positive RVP[a], n (%)	20 (46.5)	23 (26.1)	2.46	1.14—5.28
Influenza A[a], n (%)	8 (18.6)	5 (5.7)	3.80	1.16—12.41
Coronavirus, n (%)	4 (9.3)	7 (8.0)	1.19	0.33—4.30
Rhinovirus, n (%)	4 (9.3)	4 (4.5)	2.15	0.51—9.10
ICU status, n (%)	25 (58.1)	55 (62.5)	0.83	0.40—1.75
URTI, n (%)	15 (34.9)	18 (20.5)	2.08	0.93—4.70
Pneumonia, n (%)	28 (65.1)	52 (59.1)	1.29	0.61—2.76
Bacterial pneumonia[a]	3 (7.0)	19 (21.6)	0.27	0.08—0.98
Renal transplant[a], n (%)	3 (7.0)	21 (23.9)	0.24	0.07—0.85
Liver transplant, n (%)	5 (11.6)	17 (19.3)	0.55	0.19—1.61
Lung transplant, n (%)	5 (11.6)	12 (13.6)	0.83	0.27—2.54
Heart transplant, n (%)	11 (8.4)	6 (6.8)	1.80	0.52—6.26

CI, confidence interval.
[a]$P < .05$.

renal transplant patients was an unexpected finding. Appropriate antimicrobial management may be further streamlined with targeted educational efforts towards healthcare provider leaders and staff.[8]

This study is limited by its single-center retrospective nature. Methods were designed to capture appropriate RVP utility but potential opportunities may exist in patients who were not tested as well. During a select timeframe in RVS2, 251 hospitalized patients with SOT were diagnosed with a respiratory tract infection and only 27 had RVP testing. Our study sample was limited to a heterogeneous critically ill immunocompromised and/or transplant patients tested with the RVP, and did not reach the intended initial sample size within the study time frame, although an 8.5-fold difference in turnaround time was observed. Given the minimal change in prescribing behavior, however, it is unlikely that a larger sample size would have resulted in observable differences in secondary endpoints.

Seasonality presents another challenge. Most interventions were driven by the presence or absence of influenza (addition or discontinuation of oseltamivir); pathogens such as respiratory syncytial virus and adenovirus were rarely isolated. These results also suggest that, if institutionally available, a molecular influenza test can be utilized prior to RVP if there are major cost differences and similar turnaround time. Bacterial pneumonia was confirmed with inpatient diagnosis by the rounding team and culture growth of pathogen from lower respiratory samples. The in-house RVP in the present study uses nasopharyngeal samples to detect viruses in addition to *M. pneumoniae*, *C. pneumoniae*, and *B. pertussis*. While a high quality lower respiratory sample with PCR testing may provide greater confidence for presence or absence of pathogens in pneumonia, this technology is not yet widely available or practical for all patients and institutions. As RVPs gain popularity in practice, judicious use in patient populations and interpretation of respective results should be taken into higher consideration to optimize antimicrobial management and cost of care. Improved diagnostic yield and turnaround time, which may be a surrogate for ancillary testing and laboratory labor, may still justify RVP use; but will RVPs consistently be used as a de-escalation tool rather than additional academic information? Further investigation on AMS and resource utilization are warranted in critically ill immunocompromised and transplant patients.

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CONFLICTS OF INTEREST

None.

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