INTRODUCTION

Successful antimicrobial stewardship (AMS) faces numerous barriers in transplant and immunocompromised patients. Antimicrobial use for respiratory viruses, the most common pathogens associated with community acquired pneumonia, presents an opportunity of interest for stewardship efforts. 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. 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. 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. 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. 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.

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, 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 addition 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 infection, n (%)

| 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 | 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 |

*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. 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. 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. 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

| 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*, n (%)                              | 20 (46.5)                   | 23 (26.1)                     | 2.46       | 1.14–5.28 |
| Influenza 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*                              | 3 (7.0)                     | 19 (21.6)                     | 0.27       | 0.08–0.98 |
| Renal transplant*, 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.

*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.

ACKNOWLEDGEMENTS
We thank Arin Jantz, PharmD and Zachary Smith, PharmD for their contributions to this study.

CONFLICTS OF INTEREST
None.

ORCID
S.L. Davis [http://orcid.org/0000-0001-7521-9486]

REFERENCES
1. So M, Yang DY, Morris HA, Husain S. Solid organ transplant patients: are there opportunities for antimicrobial stewardship? Clin Transplant. 2016;30:659-668.
2. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415-427.
3. Crotty M, Meyers S, Hampton N, et al. Impact of antibacterials on subsequent resistance and clinical outcomes in adult patients with viral pneumonia: an opportunity for stewardship. Crit Care. 2015;19:404.
4. Barlam T, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Inf Dis. 2016;62:51-77.
5. 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.
6. Rodgers BB, Shankar P, Jerris RC, et al. Impact of a rapid respiratory panel test on patient outcomes. Arch Pathol Lab Med. 2015;5:636-641.
7. Barenfanger J, Drake C, Leon N, Troutt T. Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. J Clin Microbiol. 2000;38:2824-2828.
8. Charani E, Edwards R, Sevdalis N, et al. Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. Clin Infect Dis. 2011;53:651-662.

How to cite this article: Mercuro NJ, Kenney RM, Samuel L, Tibbetts RJ, Alangaden GJ, Davis SL. Stewardship opportunities in viral pneumonia: Why not the immunocompromised? Transpl Infect Dis. 2018;20:e12854. https://doi.org/10.1111/tid.12854.