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Original Article

The importance of viruses in ventilator-associated pneumonia

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Abstract

Objective: Ventilator-associated pneumonia (VAP) remains a challenge. The importance of viruses in VAP is not established. We sought to determine the prevalence of viruses in VAP and the outcomes of viral VAP.

Design: Retrospective study of VAP over 3 years. The frequency of a viral process represented the primary endpoint. Clinical outcomes served as secondary endpoints. We identified variables independently associated with a virus and conducted sensitivity analyses to assess the interaction between type of infection and patient characteristics.

Setting: Tertiary-care referral center.

Patients: The final cohort consisted of 710 patients and a virus was isolated in 5.1%.

Interventions: None.

Results: The most common viruses included: rhinovirus, influenza A, and cytomegalovirus. Baseline characteristics were similar between those with and without viral infections. In logistic regression, immunosuppression (adjusted odds ratio [aOR], 2.97; 95% confidence interval [CI], 1.44–6.14) and stem-cell transplantation (SCT, aOR, 3.58; 95% CI, 1.17–10.99) were independently associated with a virus. The presence of either variable performed poorly as a screening test for a virus. In-hospital (22.4% vs 21.6%; $P = .869$) and 30-day (32.8% vs 27.9%; $P = .448$) mortality rates were similar between the cohorts, respectively. Sensitivity analyses restricted to patients without a mixed viral and bacterial infection or those who were immunocompetent yielded similar results.

Conclusion: Although infrequent, a range of viruses may cause VAP. Viruses more often complicate SCT and immunosuppression, but one can isolate viruses in immunocompetent subjects. Viral VAP produces severe infection and results in high mortality rates. Clinical features do not differentiate viral from nonviral VAP.

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Ventilator-associated pneumonia (VAP) represents a leading nosocomial infection and remains associated with significant morbidity and mortality.[1] Given its impact on the patient's duration of mechanical ventilation (MV), the costs associated with VAP are substantial. Becuase antibiotic resistant bacteria often cause VAP, physicians initially treat suspected cases empirically with broad spectrum antimicrobials. Because of inconsistent adherence to de-escalation, overly broad VAP treatment potentially promotes further antibiotic resistance. Thus, VAP serves as a target for preventive care in the intensive care unit (ICU) but also represents a target for efforts to enhance antimicrobial stewardship.

In community-acquired pneumonia (CAP), careful epidemiologic studies that employ newer diagnostic techniques document the importance of viruses as etiologic agents.[2,3] Unfortunately, these analyses reveal that one cannot easily distinguish pneumonia caused by a virus from a pulmonary infection due to a bacterial organism. For example, in a report of over of 2000 subjects with CAP, Jain and co-workers reported that both rhinovirus and influenza were isolated in CAP more often than *Streptococcus pneumoniae*.[2] For nosocomial pneumonia (NP), generally, and VAP, specifically, the significance of viral agents is much less clear. Although in both solid organ (SOT) and stem cell transplant (SCT) patients, many recognize the potential for viruses to cause NP, in nonimmunosuppressed subjects the prevalence of viruses as the etiology for VAP is less well appreciated.[4,5] Hong et al[6] explored this question for cases of severe hospital-acquired pneumonia (HAP) and estimated that one in 5 cases of HAP arose due to a viral pathogen. However, they did not focus on VAP. Likewise, Shorr et al[7] reported that viruses were isolated in 22.4% of persons suffering from non-ventilated HAP. Neither of these reports, though, provide insight on the burden of viruses in VAP.

A better appreciation of the import of viruses in VAP could facilitate attempts to prevent antibiotic overuse. Precepts of antibiotic de-escalation, for instance, dictate the discontinuation of these agents when a non-bacterial etiology is found. Furthermore, understanding the role viruses play in VAP and their associated morbidity would also help foster the development of novel antiviral agents to treat these infections.

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Therefore, we conducted a retrospective analysis of patients with VAP (1) to assess the prevalence of viruses in VAP and (2) to describe outcomes for patients with VAP caused by a virus. Additionally, we sought to determine whether patient characteristics to successfully identify patients with VAP due to a virus as opposed to a bacterium.

Methods

Study overview

We conducted a retrospective analysis of all patients diagnosed with VAP at a single center between January 2016 and December 2019. We included adult patients (aged >18 years) who required MV for at least 48 hours. We excluded subjects transferred from other acute healthcare facilities, persons who were on MV support for <48 hours, and those who died within 48 hours of admission. If patients suffered multiple episodes of VAP, we only examined the first instance. As this study was retrospective, the hospital's institutional review board waived any need for informed consent (IRB no. 2018801189). Select aspects of this population have been described previously.[8]

Definitions and end points

The isolation of a viral pathogen in patients with a clinical diagnosis of VAP served as our primary end point. Secondary end points included patient characteristics along with clinical outcomes. We identified cases of VAP in accordance with the American Thoracic Society/Infectious Disease Society of America position statement on NP.[9] Initially, we screened cases based on the presence of either an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) discharge diagnosis code for pneumonia or respiratory failure. Thereafter, we determined which individuals required MV. Following this, records were reviewed for evidence of VAP based on the ordering of respiratory cultures after an initial 48 hours of MV and the administration of antibiotics. Subsequently, chest imaging for a randomly selected cohort of potential cases was reviewed by one investigator (M.H.K.) blinded to infection cause to ensure that there was a new or progressive infiltrate consistent with VAP. In addition to radiographic results, cases had to fulfill clinical criteria for VAP. Specifically, to ensure the presence of pneumonia, patients were required to meet at least 1 of the following criteria: fever (>38°C), hypothermia, and/or leukocytosis.

Patients were categorized as either having a virus identified on diagnostic testing or not. Thus, patients with bacterial pathogens or in whom cultures were negative were grouped together to facilitate comparisons. We recorded results from all forms of respiratory cultures such as endotracheal aspirates, traditional bronchoalveolar lavages (BALs), and nonbronchoscopic BALs. We further assessed the results of blood cultures and any urinary antigens ordered. We additionally explored the findings from a variety of viral diagnostic techniques to include qualitative nucleic acid tests for respiratory viruses and select bacterial pathogens (BioFire Respiratory 2.1 Panel, BioFire Diagnostics, Salt Lake City, UT). The hospital laboratory has validated the BioFire Resp 2.1 panel on LRT specimens. During the study period, the diagnostic protocol in place relied upon obtaining lower airway cultures and viral washings routinely in cases of suspected VAP. However, the specific ordering of cultures and viral testing was at the discretion of the primary treatment team. We classified respiratory samples for which only yeast, fungal structural elements, and/or clinically insignificant flora were recovered as culture negative.

We recorded demographic variables and information regarding multiple co-morbid conditions. Specifically, we noted if patients suffered from coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular disease (CVA), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and diabetes mellitus (DM). Given the nexus between immune status and the risk for viral infection, we also noted if the patient had undergone either a stem-cell transplant (SCT) or a solid-organ transplant (SOT). We additionally determined if the patient was immunocompromised based on medications given in the last 30 days (See the Supplementary Material for a list of relevant medications). We calculated a Charlson comorbidity score to assess each patient's burden of chronic illnesses.[10] For acute severity of illness, we noted if the patient was in shock (based on need for vasopressors) at the time of diagnosis of VAP and computed an Acute Physiology and Chronic Health Evaluation (APACHE) II score.[11]

Relevant clinical outcomes of interest comprised short-term in-hospital mortality and mortality rates at 30 and 90 days following a diagnosis of VAP. We assessed the duration of MV after the onset of VAP, as well as the total intensive care unit (ICU) length of stay (LOS) and hospital LOS. Need for any new renal replacement therapy (RRT) and all-cause readmission at 30 days following discharge alive represented additional measures of resource utilization.

Sensitivity analyses

Prior to examining results, we conducted 2 sensitivity analyses to limit certain forms of bias. In one sensitivity analysis, we compared patients in whom a virus was the only recovered pathogen to all remaining patients, placing those with a bacterial coinfection into the comparator group. Because immune suppression is known to be a strong predictor of a viral infection, and because we were interested in examining other potential factors associated with viral pneumonia, in the second sensitivity analysis we excluded all subjects who were immunosuppressed (see definition presented above).

Statistics

Categorical variables were compared with Fisher's exact test and continuous variables with either the Student *t* test or the Mann-Whitney *U* test, as appropriate. All tests were 2 tailed and a *P* value of <.05 was considered to represent statistical significance.

To determine factors independently associated with recovery of a viral pathogen, we employed logistic regression. The regression was a stepwise, backwards approach and all variables significant at the 0.15 level in univariate analysis were entered into the model. Variables were assessed for colinearity. We assessed goodness of fit with the Hosmer-Lemeshow (HL) test and R^2 values. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are presented where appropriate. Statistical analyses were completed with SPSS version 28.0 software (IBM, Armonk, NY).

We utilized the findings from our logistic regression in the entire population to calculate a risk score for the presence of a viral etiology. The AORs for variables significant in the logistic regression were converted to points based on the presence of that factor in an individual patient. Then, for each patient, a total score was computed. To measure the utility of the score as a screening test

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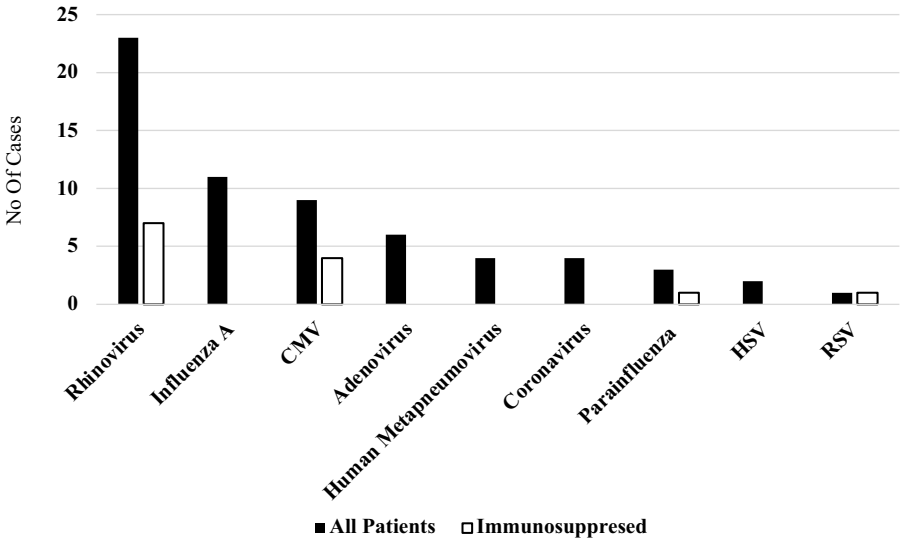

Fig. 1. Distribution of viruses in all patients and those who were immunosuppressed. See text for abbreviations.

for the recovery of a virus in VAP, we determined the area under the receiver operating curve (AUROC) for the scoring metric.

Results

The final cohort included 710 patients with VAP (mean age 57.3+16.1 years, 59.0% male). The mean APACHE II score equaled 15.4+5.5 and 21.9% of cases died while hospitalized. Viral panels were obtained in 78.9 % of cases. Figure 1 reveals that the most common viruses recovered were: rhinovirus (n = 23), influenza A (n = 11), cytomegalovirus (CMV) (n = 9), and adenovirus (n = 6). With the exception of influenza, of which there was none, the viruses isolated among the immunosuppressed population were generally similar (Fig. 1). A virus was the only agent identified in 5.1% of the cohort.

With few exceptions, subjects in whom a virus was isolated were generally similar to patients with a nonviral etiology (Table 1). COPD occurred more often, though, in persons with a viral VAP (29.3% vs 17.8%; $P = .036$). Immune suppression was present in >20% of cases of VAP associated with a virus as compared to <10% of persons in whom there was no evidence of a viral infection ($P = .001$). This distinction was mostly due to the greater prevalence of SCT in the viral infection cohort. SCT was noted 4.64 times (95% CI, 1.59–13.50) more often among those with viral pathogen. We did not detect differences in severity of illness as measured by either the development of shock or the APACHE II score. Furthermore, in each group, the diagnosis of VAP was, on average, made after 5 days of hospitalization.

With respect to outcomes (Table 2), mortality rates at all time points did not differ based on recovery of a virus. The duration of MV after the onset of VAP was generally high but did not vary based on VAP etiology (~5 days in each group). We also noted similar rates of readmission and need for RRT.

In logistic regression, two variables, SCT and immunosuppression, were independently linked with the recovery of a virus (Table 3). Although model's fit was moderately good as shown by a Hosmer-Lemeshow statistic of 0.683, its explanatory power was limited, with the R^2 value measuring only 0.06.

Based on these two variables and their relatively equal AORs, we created a score where one point each was assigned for the presence of either immunosuppression or SCT. The score, therefore, could range from zero to 2. Figure 2 reveals the relationship between the risk score and recovery of a virus. Among those with zero points, the frequency of a virus was <10% as compared to a prevalence of nearly 35% in persons with a score of 2 ($P = .001$). Despite this relationship, the score performs poorly as a screening test. For example, the AUROC is only 0.596 (95% CI, 0.512–0.680). Additionally, relying only on immune status and SCT leads to missing 42 (72.4%) of 58 cases of viral infection.

In the first sensitivity analysis where patients with only a viral pathogen (n = 36) were compared to other VAP subjects, the general findings were analogous to what was noted in the original analysis. We detected few differences between cohorts in terms of demographics and co-morbidities. A history of COPD, SCT, and recent immunosuppression all occurred more frequently in those in which the sole pathogen isolated was a virus (Table 4). We noted a trend towards more shock in persons with a pure viral VAP. Outcomes (eg, in hospital mortality, duration of MV, ICU LOS, etc) also did not differ between the two groups in this sensitivity analysis (Table 5).

In the second sensitivity analysis (n = 651), in which immunosuppressed patients were excluded, we noted a viral organism in 7.43% of VAP cases. No baseline characteristic (see Supplementary Table 1 online) differed between VAP cases categorized as viral versus nonviral. COPD was more frequent observed in those non-immunosuppressed patients with a virus (26.7% vs 15.8%), but this difference only approached statistical significance ($P = .093$). Despite removal of immunosuppressed subjects, mortality rates for those with a viral infection remained similar to persons with other causes of VAP.

Discussion

This large retrospective analysis of >700 patients with VAP indicates that a diverse range of viruses may cause this syndrome. Although viral infection more frequently complicates SCT and occurs in those who are immunosuppressed, one can isolate viruses in immunocompetent subjects with VAP. Viral VAP may produce severe infection and results in both high short and intermediate-term mortality. In general, the clinical outcomes for VAP related to a virus are similar to those noted in patients with other etiologies. Additionally, clinical characteristics alone do not allow the clinician to determine if a suspected case of VAP is related to a virus as opposed to other pathogens.

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Table 1. Baseline Characteristics

Characteristic	Virus (n=58), %[a]	Other (n=652), %[a]	*P* Value
Demographics			
Sex, male,	65.5	58.4	.331
Age, mean y +SD	55.8+15.8	57.4+16.1	.462
Race			
White	72.4	66.0	.384
African American	20.7	29.8	
Other	6.9	4.3	
Comorbidities			
COPD	29.3	17.8	.036
Congestive heart failure	37.9	42.6	.579
Myocardial infarction	24.1	26.5	.758
Stroke	17.2	24.2	.262
Chronic kidney disease	32.8	39.4	.399
Liver disease	10.3	14.7	.439
Diabetes mellitus	24.1	28.5	.544
Immune status			
Stem cell transplant	8.6	2.0	.011
Solid-organ transplant	5.2	4.9	.759
Immunosuppressed	22.4	7.1	.001
Severity of illness			
MV day of onset, median	5	5	.817
Shock	60.3	55.5	.494
APACHE II, mean+SD	15.6+5.3	15.4+5.5	.794

Note. APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; SD, standard deviation.
[a]Units unless otherwise specified.

Table 2. Clinical Outcomes

Variable	Virus (n=58)	Other (n=652)	*P* Value
Hospital mortality, %	22.4	21.6	.869
30-d mortality, %	32.8	27.9	.448
90-d mortality, %	37.9	32.4	.385
Hospital LOS after VAP, median d	18	15	.150
Total ICU LOS, median d	21	18	.099
Total hospital LOS, median d	26	22	.111
30-day readmission, %	13.8	14.5%	.382
New RRT, %	8.7	7.8	.774

Note. ICU, intensive care unit; LOS, length of stay; RRT, renal replacement therapy; VAP, ventilator-associated pneumonia.

Table 3. Independent Variables Associated With a Viral Pathogen

Variable	Adjusted Odds Ratio	95% CI	*P* Value
Stem-cell transplant	3.58	1.17–10.99	.026
Immunosuppression	2.97	1.44–6.14	.003
COPD	1.64	0.87–3.07	.120

Note. CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Table 4. Baseline Characteristics: Sensitivity Analysis

Characteristic	Virus (n=36)	Other (n=674)	*P* Value
Demographics			
Sex, male	61.1	58.9	.990
Age, mean y+SD	57.2+16.1	57.3+16.1	.462
Race, %			
White	75.0	66.0	.365
African American	19.4	29.5	
Other	5.6	4.5	
Comorbidities, %			
COPD	30.6	18.1	.036
Congestive heart failure	41.7	42.3	.999
Myocardial infarction	25.0	26.6	.999
Stroke	22.2	23.7	.999
Chronic kidney disease	38.9	38.9	.999
Liver disease	13.9	14.4	.999
Diabetes mellitus	30.6	28.0	.708
Charlson comorbidity score, mean+SD	5.4+3.7	5.3+3.3	.756
Immune status, %			
Stem cell transplant	11.1	2.1	.010
Solid organ transplant	5.6	4.9	.696
Immunosuppressed	22.2	7.6	.007
Severity of illness			
MV day of onset, median	4	5	.318
Shock, %	72.2	55.0	.057
APACHE II, mean+SD	15.8+5.3	15.4+5.6	.700

Note. APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; SD, standard deviation.

Prior analyses indicate that viruses may lead to NP. Hong et al, for example, reported that among a cohort of 262 persons with NP, approximately 20% had a viral organisms identified.[6] The viruses diagnosed (eg, rhinovirus, CMV) were comparable to the ones we noted. They also documented that the absence of immunosuppression did not preclude a viral cause for VAP. In a retrospective analysis of NP in a French ICU, Loubet et al[12] described the prevalence of viruses in this population. They observed a virus in >30% of cases, and 18% of cases were solely viral. Finally, Shorr et al[7] explored the epidemiology of viral NP among a cohort of persons with nonventilated NP. Consistent with the other prior reports, these authors saw that nearly 1 in 5 infections arose due to a virus.

In contrast to these earlier investigations, however, we report a far lower rate of viral infection. This disparity in the estimated prevalence of viruses in NP likely reflects select differences between earlier analyses and ours. In other studies, the rate of immunosuppression was significantly higher. The nearly 50% incidence of immunosuppression in the persons evaluated by Hong et al[6] may have confounded their observations and, therefore, limits

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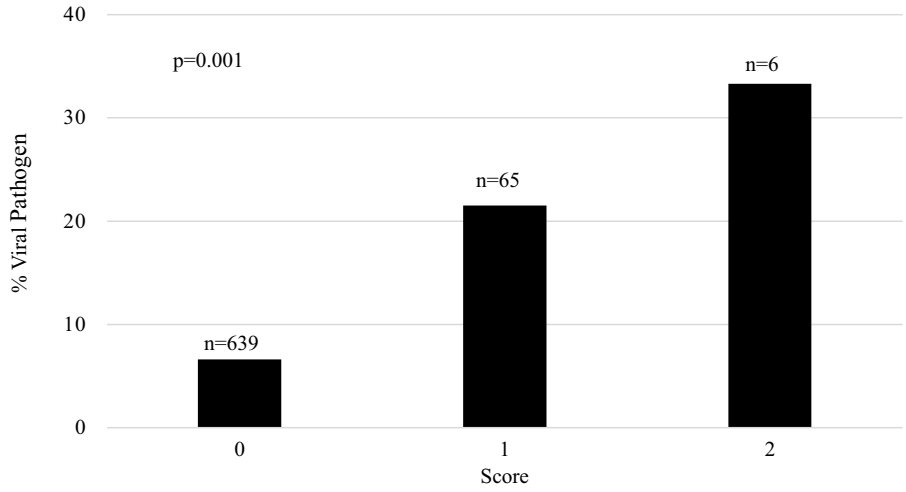
Table 5. Clinical Outcomes: Sensitivity Analysis

Variable	Virus (n=36)	Other (n=674)	*P* Value
Hospital mortality,%	27.8	21.4	.405
30-d mortality,%	44.4	27.4	.036
90-d mortality, %	47.2	32.0	.069
Hospital LOS after VAP, median d	18.5	16	.297
Total ICU LOS, median d	21	18	.174
Total Hospital LOS, median d	24	22	.445
30-d readmission, %	16.7	19.1	.830
New RRT, %	10.7	7.7	.474

Note. ICU, intensive care unit; LOS, length of stay; RRT, renal replacement therapy; VAP, ventilator-associated pneumonia.



*p value represents comparison for trend across all three point scores

Fig. 2. Relationship between risk score and prevalence of a viral pathogen.

the generalizability of their findings. More importantly, we restricted our population to only subjects with VAP. In the study of non-ventilated NP, no person, by definition, suffered by VAP.[7] Likewise, in the cohorts described by Loubet et al[12] and Hong et al,[6] only 60 and 250 subjects, respectively, met criteria for VAP. Thus, given our larger sample size, our estimate of the frequency of viruses in VAP is more precise. In this way, our investigation is unique and moves beyond the conclusions of others.

In addition to our large sample size, our evaluation has other strengths. First, we performed sensitivity analyses to specifically explore the interaction between immune status and detection of a virus and to assess how often one identifies solely a virus. These sensitivity analyses suggest that one should not (1) believe that viral VAP only arises in immunosuppressed subjects nor (2) conclude that viruses only occur as part of a bacterial coinfection. Second, we described several outcomes that have not previously been reported for subjects with VAP due to a virus. Specifically, we present data on measures of morbidity, such as the need for RRT and the risk for hospital readmission, and longer-term mortality. Third, our risk score approach illustrates the limited value of various factors (independently associated with isolation of a virus) as serving of markers of a viral pathogen. The poor AUROC of the risk score underscores that clinical characteristics alone fail to segregate those with viral etiologies from persons infected with alternate pathogens. Fourth, our data derive from the pre-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Multiple authors have described nosocomial spread of SARS-CoV2. Our findings are not confounded by the impact of the pandemic.[13,14]

With respect to antibiotic stewardship, our observations emphasize that viral diagnostic technologies may aid in antibiotic de-escalation. Recovery of only a virus should facilitate the discontinuation antibiotics. Considering the lower than previously reported prevalence of viruses, the cost-effectiveness of routine viral testing may be prohibitive, but it merits formal analysis. Similarly, the impact of viruses on patient outcomes accentuates the urgent need for novel antivirals. Even in our analysis restricted to the non-immunosuppressed, VAP associated with a virus results in significant morbidity and mortality. In one sense, the poor outcomes for those with a viral VAP are essentially analogous to those seen in persons who receive inappropriate initial therapy for a bacterial infection. With newer therapies, one could hopefully improve mortality rates and reduce LOS in viral VAP.

This study had several limitations. First, the retrospective nature of the analysis exposes the study to multiple forms of bias ranging from issues with case identification to selection bias. We

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attempted to address these issues by being comprehensive on our case reviews and by focusing on endpoints not prone to issues with ascertainment. Second, that our findings derive from a single center limit their generalizability. Third, the decision to test for a virus was not standardized and was at the discretion of the primary medical team. However, during the study time frame, ordering viral diagnostics was considered routine. Fourth, one could worry that the viruses isolated are not truly nosocomial in onset. Given the incubation period for various viral infections, the viral pneumonias we identified could have been acquired prior to hospitalization. This may, in fact, be the case. Nonetheless, it matters little how we classify a pneumonia relative to its onset if the patient develops a severe respiratory infection whose etiology might otherwise be missed for lack of testing. However, the median day of onset for our viral pneumonia was nearly a week after hospitalization and was similar to the time to diagnosis we observed in patients with other causes of VAP.

In conclusion, viruses may be recovered in VAP. VAP due to a virus occurs mainly in patients with intact immune systems. Viral VAP results in high rates of morbidity and mortality.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.223

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