Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Viruses are prevalent in non-ventilated hospital-acquired pneumonia

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ARTICLE INFO

ABSTRACT

Background: Hospital-acquired pneumonia arising in non-ventilated patients (NVHAP) is traditionally thought to be caused by bacteria, and little is known about viral etiologies in this syndrome. We sought to describe the prevalence of viruses causing NVHAP and to determine factors independently associated with the isolation of a virus.
Methods: We identified patients with NVHAP over one year and reviewed their cultures to determine etiologies. Patients with a viral process were compared to those with either negative cultures or a bacterial infection to determine variables independently associated with the recovery of a virus.
Results: Among 174 cases, cultures were positive in 46.0%, with viruses identified in 22.4%. Bacterial pathogens arose 23.6% of subjects. The most common viruses included rhinovirus, influenza, and parainfluenza. We noted no seasonality in the isolation of viral organisms, and most cases of viral NVHAP developed after more than a week length of stay (LOS). Outcomes in viral NVHAP were similar to those with bacterial NVHAP. Patients with viral and bacterial NVHAP were generally similar. Two variables were independently associated with isolation of a virus: a history of coronary artery disease (adjusted odds ratio: 5.16, 95% CI: 1.14–22.44) and a LOS of greater than 10 days prior to NVHAP diagnosis (adjusted odds ratio: 2.97, 95% CI: 1.35–6.51). As a screening test for a virus, neither had a good sensitivity or specificity.
Conclusions: Viruses represent a common cause of NVHAP. Clinicians should consider viral diagnostic testing in NVHAP, as this may represent a means to enhance antimicrobial stewardship.

1. Introduction

Nosocomial pneumonia (NP) remains an important hospital-acquired complication resulting in substantial morbidity and mortality [1]. Comprising both ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) arising in the non-ventilated subject, NP is the focus of multiple quality efforts in hospitals across the globe [1–3]. The majority of research into NP has dealt with VAP, mainly because patients at risk for VAP are easy to identify given their location in an intensive care unit (ICU). As such, less is known about HAP arising in non-ventilated patient (NVHAP). Thus, conclusions based on studies conducted in VAP are often generalized to NVHAP [1]. However, the pool of persons at

risk for NVHAP is substantially larger than the cohort of those at risk for VAP. Only the relatively small proportion of hospitalized patients undergoing mechanical ventilation (MV) may develop VAP, while the vast majority of subjects in the hospital never require MV. Therefore, there is a need for more information regarding NVHAP, particularly as it relates to the microbiology and outcomes in NVHAP.

Traditionally, most cases of pneumonia in the hospital, whether they be community-acquired pneumonia (CAP), HAP, or VAP are thought to be caused by bacterial pathogens. The role of viral organisms in pneumonia historically was felt to be mainly an issue in the immunosuppressed and transplant populations. More recent analyses, though, have underscored the significance of viruses as important causes of pneumonia. For example, Jain and colleagues in a multicenter observational study of hospitalized CAP noted that viruses were a more prevalent cause of the infection than were bacteria [4]. Similarly, investigators have implicated viral organisms as a major cause of VAP. Hong et al. isolated viruses in more

than 20% of VAP cases [5].

Despite the growing appreciation and significance of viruses in various forms of pneumonia, no study has yet described the role of viruses in NVHAP. Appreciating the importance of viruses in NVHAP could prove important in facilitating the development of tools that might foster antibiotic stewardship. For example, principles of antibiotic de-escalation would demand the discontinuation of antibacterials if a non-bacterial pathogen were identified as the etiologic agent [6].

Therefore, we conducted a retrospective analysis of patients with NVHAP to determine both the prevalence of viruses in this syndrome and to describe the characteristics of persons with such viral infections. Additionally, we sought to determine if one could identify patients likely to have a viral etiology (as opposed to a bacterial one) based on patient characteristics.

2. Methods

2.1. Study overview

This study was a retrospective analysis of all persons diagnosed with NVHAP during a single year at a single center. Prior aspects of this analysis have been described elsewhere [7]. Briefly, the study was conducted between 1 January 2014 and 31 December 2014. We included only adults (age ≥ 18 years) admitted to the hospital for at least 48 h. We excluded subjects transferred from other healthcare facilities and persons who required MV (and were subsequently extuabted) in the 48 h prior to the onset of their new pneumonia. In other words we excluded both VAP and processes that likely evolved while the patient was on MV. Subjects needing MV as support for their NVHAP were enrolled. If patients suffered multiple episodes of NVHAP, only the first instance was included. As this study was retrospective, the hospital's institutional review board waived any need for informed consent (IRB# 201409001).

2.2. Endpoints and definitions

The recovery of a viral pathogen served as the primary endpoint for the study. We defined NVHAP in accordance with the American Thoracic Society position statement on NP [1]. Subjects were screened for a potential diagnosis of NVHAP based on the ordering of respiratory cultures after an initial 48 h of hospitalization. Subsequently, chest imaging for all identified potential cases was reviewed by one investigator (MHK) to ensure that 1) there was a new or progressive infiltrate and that 2) this infiltrate did, in fact, arise after 48 h of being hospitalized (eg, was not present on admission). In addition to radiographic results to ensure the presence of pneumonia, all cases were required to meet at least meet two of the following criteria: fever (greater than 38° C) or hypothermia, leukocytosis or leukopenia, and purulent respiratory secretions).

Findings from respiratory cultures were classified as revealing either a viral or bacterial organism, or as culture negative. In addition to blood cultures, potential respiratory cultures reviewed in patients not requiring MV as a result of their NVHAP included those from sputum or bronchoalveolar lavage (BAL). In subjects requiring MV after the onset of respiratory failure complicating their NVHAP, we also examined cultures from tracheal aspirates and from blind BALs – so long as they were obtained within the 24 h after the onset of MV for NVHAP. We further determined the results from a variety of viral diagnostic techniques to include qualitative nucleic acid tests for respiratory viruses and select bacterial pathogens (FilmArray® Respiratory Panel, BioFire Diagnostics, Inc, Salt Lake City, Utah). It is standard practice at the study instittuion to obtain viral panels on all patients with suspected pneumonia,

irrespective of whether they are ventilated. Furthermore, for patients unable to provide a specimen, a nasopharyngeal swab is obtained. All decisions regarding the ordering of the initial respiratory cultures were undertaken by the patient's primary clinical team and were not guided by a formal protocol.

We recorded patient demographic characteristics along with comorbid illnesses such as coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and others. We calculated a Charlson co-morbidity score for each patient to capture the global burden of chronic illness. We also noted the duration of hospitalization (LOS) prior to NVHAP onset and whether the subject required ICU care in the week prior to their NVHAP. With respect to outcomes, we determined if the patient died while hospitalized and the LOS after NVHAP diagnosis.

To determine variables independently associated with a viral etiology for NVHAP we specifically compared those with a viral pathogen to all remaining subjects with either no organism identified or with a bacterial pathogen diagnosed.

2.3. Statistics

We compared categorical variables with Fisher's exact test and continuous variables with either the Student's t-test or the Mann Whitney U test, as appropriate. Comparisons of continuous variables across the three potential cohorts (viral, bacterial, culture-negative) were analyzed via ANOVA if the data were parametrically distributed. If such data were non-parametric in nature, we employed the Kruskal-Wallis test. All tests were two tailed and a p value of <0.05 was considered to represent statistical significance.

To determine factors independently associated with recovery of a viral etiology, we relied on logistic regression. The regression was a step-wise backwards approach, and we entered all variables significant at the 0.15 level in univariate analysis into the model. Variables were assessed for co-linearity. We assessed goodness of fit with the Hosmer-Lemeshow (HL) test. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are presented where appropriate.

3. Results

The final cohort included 174 cases (mean age 57.5 ± 15.0 years, 54.6% male). Cultures were positive in 46.0% of cases, with viruses identified in 22.4% of patients. We noted bacterial pathogens in 23.6% of subjects. Crude hospital mortality was 15% and did not correlate with the type of pathogen causing the infection.

The most common viral organisms were rhinovirus (n = 19), influenza (n = 7), parainfluenza (n = 6), coronavirus (n = 5), and metapneumovirus and rhinovirus (n = 4 for each). The most frequent bacterial pathogens were *Staphylococcus aureus* (n = 17) and *Pseudomonas aeruginosa* (n = 9). Although influenza arose most often during the traditional influenza season in North America, there was no seasonality seen in the distribution of other viral organisms.

As Table 1 reveals, there were few differences between those for whom cultures were negative and patients with either viral or bacterial etiologies. Patients with viruses were more likely to have been cared for in an ICU in the week prior to NVHAP onset, but this difference only approached statistical significance. CAD was less prevalent in patients with viral infections. For other variables such as the Charlson score and the LOS prior to NVHAP there were no significant differences among subjects as a function of the results of their respiratory cultures.

Table 2 shows the results of bivariate comparisons between those with positive viral findings and others with NVHAP. As with the general comparisons across the three strata of possible culture

Table 1
Patient characteristics.

Variable	Culture negative (n = 94)	Virus isolated (n = 39)	Bacteria isolated (n = 41)	P between all groups
Demographics				
Age (yrs), mean ± SD	59.9 ± 14.5	54.5 ± 14.4	56.3 ± 15.9	0.234
Male, %	57.6%	43.6%	58.1%	0.187
Race				
-Caucasian, %	70.2%	79.5%	65.9%	0.390
-Black, %	21.3%	17.1%	25.6%	
-Other, %	9.5%	2.4%	7.0%	
Hospitalization characteristics				
Length of stay prior to onset (days), median	4.5 days	6.0 days	5.2 days	0.146
ICU care in 1 week prior to onset, %	3.3%	10.3%	7.3%	0.097
Co-morbidities				
Surgical Pt, %	57.4%	43.6%	58.5%	0.194
CAD, %	20.2%	5.1%	17.1%	0.040
CHF, %	29.8%	17.9%	26.8%	0.174
COPD, %	52.1%	41.0%	58.5%	0.366
DM, %	31.9%	28.2%	39.0%	0.846
Chronic Kidney Disease, %	19.0%	26.8%	28.2%	0.214
Liver disease, %	24.5%	15.4%	19.5%	0.229
Collage Vascular Disease, %	14.1%	5.1%	9.3%	0.120
Dementia, %	1.1%	0%	2.4%	0.454
Metastatic malignancy, %	7.4%	15.4%	12.2%	0.153
HIV, %	1.1%	0%	2.4%	0.449
Charlson score, median	6.0	5.0	4.0	0.092
Outcomes				
Hospital Mortality, %	16.0%	15.4%	14.6%	0.905
Length of stay after NVHAP, median, days	8.2 days	7.5 days	10.9 days	0.123
Re-admission at 30 days, %	20.2%	19.5%	16.3%	0.236

Abbreviations: CAD — coronary artery disease, CHF — congestive hear failure, COPD — chronic obstructive pulmonary disease,, HIV — human immunodeficiency virus, ICU — intensive care unit, NVHAP — non-ventilated hospital-acquired pneumonia, SD — standard deviation.

Table 2
Comparison between patients with viral pathogens as opposed to others.

Variable	Non-viral (n = 133)	Virus isolated (n = 39)	P
Demographics			
Age (yrs), mean ± SD	58.8 ± 14.9	54.5 ± 14.4	0.132
Male, %	57.8%	43.6%	0.145
Race			
-Caucasian, %	78.9%	79.5%	0.232
-Black, %	18.0%	17.1%	
-Other, %	3.1%	2.4%	
Hospitalization characteristics			
Length of stay prior to onset (days), median	4.5 days	6.0 days	0.135
ICU care in 1 week prior to onset, %	20.7%	41.0%	0.020
Co-morbidities			
Surgical Pt, %	42.2%	43.6%	0.715
CAD, %	19.3%	5.1%	0.045
CHF, %	28.9%	17.9%	0.218
COPD, %	54.1%	41.0%	0.203
DM, %	34.1%	28.2%	0.564
Chronic Kidney Disease, %	21.5%	26.8%	0.393
Liver disease, %	23.0%	15.4%	0.379
Collage Vascular Disease, %	6.7%	5.1%	0.460
Dementia, %	2.2%	0%	0.999
Metastatic malignancy, %	8.9%	15.4%	0.243
HIV, %	1.5%	0%	0.999
Charlson score, median	5.0	5.0	0.423
Outcomes			
Hospital Mortality, %	15.8%	15.4%	0.999
Length of Stay after NVHAP, median, days	8.7 days	7.5 days	0.702
Re-admission at 30 days, %	20.0%	30.8%	0.191

Abbreviations-See Table 1.

results, there were few differences. Again, CAD was less prevalent in those with a viral etiology for NVHAP. Neither the distribution of other co-morbidities nor the Charlson score varied based on culture findings. There also was no difference based on whether the patient had undergone surgery while hospitalized or had required ICU care prior to pneumonia diagnosis. Those with a virus identified as responsible for their infection were hospitalized longer than those without such an etiology (6.0 days vs 4.5 days), but this difference only approached statistical significance. However, persons with a viral NVHAP were twice as likely to have required a prolonged hospitalization (eg > 10 days) before NVHAP development (41.0% vs 20.7%, p = 0.020). There were no differences in outcomes (eg,

hospital mortality, LOS after NVHAP, 30-day readmission) based on whether a virus was or was not recovered.

Only two variables were independently associated with isolation of a virus based on logistic regression. Persons with a history of CAD were approximately 5 times more likely to have a viral etiology, (AOR 5.16, 95% CI: 1.14–22.44, p = 0.003). Although CAD occurred infrequently among those with viral pathogens, this variable remained associated with viral infection as many other variables entered into the model were co-linear with each other and so CAD became significant as part of the step-wise elimination process. Additionally, a LOS of greater than 10 days prior to NVHAP diagnosis correlated with the recovery of a virus (AOR 2.97, 95% CI: 1.35–6.51). The final model had a good fit based on a HL p value of 0.30. As a screening test for the isolation of a virus in NVHAP, neither of the above factors, nor their combination, had good sensitivity or specificity at predicting the eventual results of cultures.

4. Discussion

This retrospective analysis demonstrates that viruses are as commonly isolated in NVHAP as are bacterial organisms. Viruses appear to lead to a similar degree of morbidity and mortality as compared to bacteria in this infection. Patient characteristics do not readily distinguish between persons infected with a bacterial organism as opposed to a virus.

The importance of viruses in CAP has been long established, especially during influenza season [8]. However, the significance of viruses other than influenza in CAP was recently confirmed in a large epidemiologic study of hospitalized CAP [4]. In addition to showing that viruses were more frequently recovered than bacteria, Jain et al. documented that viral pathogens other than influenza are seen in CAP [4]. We document a similarity between CAP and NVHAP in that the range of viral organisms isolated in both syndromes includes parainfluenza virus, metapneumovirus, and coronavirus.

Choi and co-workers in an analysis including both CAP and healthcare-associated pneumonia (HCAP) further established a central role for viruses in pneumonia syndromes requiring hospitalization [9]. Strikingly, more than a third of those with HCAP, a form of NP, were infected with a virus according to the findings by Choi et al. [9] These same investigators in a separate study confirmed that viral organisms could also be found in persons suffering from VAP. Among a cohort of persons with VAP, 22.5% had their infection caused by a virus [9]. The most common viruses in VAP were respiratory syncytial virus and parainfluenza virus.

Our study builds on these earlier reports by revealing that viruses are a major cause of another form of NP, in this case NVHAP. No prior work has expressly focused on the role of viruses in NVHAP. Furthermore, little information exists generally describing the microbiology of NVHAP. Therefore our findings are important in that they help to confirm that the etiologic agents of VAP are generally similar to those in NVHAP. Our results also indicate that a search for a viral etiology in NVHAP is prudent, especially if bacterial cultures are unrevealing. Although select clinical variable occur more commonly in persons with a viral cause of NVHAP, reliance on these factors to either reliably include or exclude the presence of a bacterial pathogen is imprudent. The characteristics we identified as being independently linked with isolation of virus still occur commonly in subjects with a bacterial infection. Additionally, some of the independent associations we noted between clinical features and isolation of a viral pathogen lack clear biologic plausibility to explain the potentian connection (eg the relationship between CAD and viral pathogens). Therefore these findings much be interpreted with caution. Thus, clinicians should continue to empirically treat those patients diagnosed with NVHAP with antibiotics pending the results of cultures that can guide antibiotic de-escalation. On the other hand, adding a search for a viral organism to routine cultures might facilitate antibiotic discontinuation. If a virus is eventually identified and bacterial cultures remain negative then those antibiotics can likely be discontinued. Given the prevalence of virus in NVHAP that we note, the potential to limit antibiotic prescribing may be substantial. Similarly, the relatively high frequency of virus noted in NVHAP, along with the results of the studies noted above in CAP and VAP, suggest that efforts to develop rapid diagnostic microbiology testing for respiratory infections needs to include tests for viral etiologies. Failure to do so might result in subjects remaining on antibiotics when they no longer truly will benefit from them.

Our study has a number of limitations. First, it represents a retrospective effort and thus is prone to multiple forms of bias. Specifically, the fact that viral testing was not systematically undertaken in all cases suggests that viral infections were certainly missed. Hence, we may have actually underestimated the prevalence of viral organisms in this syndrome. Second, both bacterial and viral diagnostic tests and cultures are imperfect. Patients with actual infections with either types of pathogens might have been misclassified as culture negative when they did, in fact, have their infections arise from either a virus or bacterium. Third, although the ordering of viral panels is routine for suspected pneumonia at the study hospital, the quality of the specimens obtained certainly varied. Some patients were more able to expectorate sputum that could be analyzed. This may have led to our underestimating the prevalence of select pathogens. The use of nasopharyngeal swabs in patients unable to provide sputum, however, should mitigate, to some degree, the impact of this factor. Fourth, we failed to note any mixed viral and bacterial infections or any infections in with multiple viruses. This observation, along with the point above, reinforces concern that specimens may have been inadequate in some patients for diagnostic purposes, particularly bacterial culture. Our inability to review lower airway cultures on all patients is a necessary limitation of any effort to understand pneumonia in non-ventilated patients. Fifth, our findings derive from a single large academic hospital. Thus, the generalizability of our observations is certainly limited. Taken as a hole these multiple limitations demonstrate that our results need to be viewed as hypothesis generating and in need to confirmation.

In conclusions, viruses seem to cause a substantial proportion of cases of NVAHP. The viruses involved in NVHAP are potentially as diverse as the multiple potential bacterial etiologies of this infection. Physicians should consider expanding testing for viral etiologies in patients diagnosed with NVHAP.

Conflict of interest

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