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Viruses are prevalent in non-ventilated hospital-acquired pneumonia

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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

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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 $\geq$ 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 co-morbid 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