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Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study

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ABSTRACT

Background: Data on the frequency and role of respiratory viruses (RVs) in hospital-acquired pneumonia (HAP) are still scarce.
Objectives: We assessed the proportion of RVs and their impact on the outcome of hospital-acquired pneumonia (HAP) in the intensive care unit (ICU).
Study design: Cases of HAP were retrospectively selected among patients who underwent screening for RVs by multiplex PCR (mPCR) in the ICU of a French tertiary care hospital from May 2014 to April 2016. ICU length of stay and in-hospital mortality were compared between four groups defined according to the identified pathogens: virus only (V), virus/bacteria (V/B), bacteria only (B) and no pathogen (Neg). When available, previous mPCR was retrieved in order to assess possible chronic viral carriage.
Results: Overall, 95/999 (10%) ICU patients who underwent mPCR had HAP (V(17,18%), V/B(13,14%), B (60,63%), Neg(5,5%)). Median age was 61 years and 45 (47%) were immunocompromised. Influenza (27%) and rhinovirus (27%) were the most common RVs. V/B group had higher mortality rate than B and V groups (62% vs. 40% and 35%, $p = 0.3$) and a significantly longer length of stay (31 days (18–48)) than V group (5 days (3–11), $p = 0.0002$)) and B group (14.5 days (5.5–25.5), $p = 0.007$)). Among the 15 patients with available mPCR tests before viral HAP, seven were negative and eight were positive corresponding to long-term carriage of community-acquired viruses.
Discussion: RVs were detected in 32% of HAP patients who underwent mPCR. Two situations were encountered: (i) acute acquired viral infection; (ii) long-term viral carriage (mostly rhinovirus) especially in immunocompromised patients complicated by a virus/bacteria coinfection. The latter was associated with a longer length of stay and a trend toward a higher mortality.

1. Background

Respiratory viruses (RVs) are known to constitute a large burden in community-acquired respiratory infections [1–4]. With regards to nosocomial infections, RVs (excluding herpes simplex virus (HSV) and cytomegalovirus (CMV)) have traditionally been paid little attention, except in hematopoietic stem cell or solid organ transplant recipients [5,6]. Although hospital-acquired pneumonia (HAP) is the second most common nosocomial infection in the developed countries and is associated with high mortality and morbidity [7,8], it has always been seen to be driven by bacteria, with no role of RVs [9]. However, in a recent South Korean study 22.5% of cases of HAP were related to viral infections, and 59.5% to bacterial infections. This finding, showing a non-negligible role of viruses, can be explained by recent improvements in detection methods and needs to be explored further. Indeed, improvements in the sensitivity of detection techniques such as multiplex polymerase chain reaction (mPCR) have greatly enhanced the ability to detect RVs [10,11]. However, data on the frequency and role of RVs in HAPs and especially their outcome are still scarce. Apart from influenza and respiratory syncytial virus (RSV), other viruses are not

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usually investigated because of weak evidence of their pathogenicity, lack of available treatment, and the high cost of mPCR tests. Furthermore, the role of viral-bacterial coinfection is still unclear in pneumonia and all of the few investigations using mPCR were conducted on community-acquired pneumonia presenting viral-bacterial coinfection and yielded divergent data on pathogenicity and prognosis [2,12–14].

2. Objectives

We retrospectively reviewed all cases of HAP who underwent screening for RVs in patients admitted to or in an intensive care unit (ICU) between 2014 and 2016 in order to estimate the proportion of HAP associated with RVs, bacteria or viral-bacterial coinfection and to compare their impact on prognosis.

3. Study design

3.1. Study population and data collection

The study was conducted at the medical ICU of the Bichat-Claude Bernard Hospital, a teaching tertiary referral hospital in Paris, France. All medical records of patients who underwent mPCR assay for RVs during an ICU stay from May 1, 2014 to April 31, 2016 were retrospectively reviewed. Patients with community-acquired pneumonia or with a diagnosis other than pneumonia were excluded. Only adult patients diagnosed with HAP who underwent screening for RVs at the time of suspected pneumonia were included in the study. When multiple episodes of HAP occurred in the same patient, only the first episode was taken into consideration. Patients included were classified in one of the following four groups according to the microorganisms identified from specimens collected within 72 h after the diagnosis of pneumonia: virus only, bacteria only, virus/bacteria and no pathogens. Of note, the use of mPCR for respiratory virus screening in the ICU of the Bichat-Claude Bernard Hospital is not systematic and is left at physician's discretion. Its use that started in 2013 and was at first limited to immunocompromised patients has progressively expanded over the years. We compared characteristics of those who did not undergo screening for RVs to those who underwent and were included in the study. For this we identified the total number of HAP that occurred during the study period in the ICU using the primary diagnosis coded according to the Tenth Revision of the International Classification of Diseases (ICD10).

Clinical, laboratory data including microbiological tests, and radiological findings at diagnosis of HAP data were retrieved from the patients' medical charts. Length of ICU stay after diagnosis of pneumonia and in-hospital mortality were collected and compared between groups. In order to differentiate hospital-acquired viruses from long-term viral shedding in patients with at least one virus found, all available mPCR tests performed during the same hospital stay before HAP diagnosis were retrieved.

All definitions are detailed in Supplemental data 1.

3.2. Laboratory data

All patients enrolled in this study underwent bronchoscopy with bronchoalveolar lavage (BAL) or endotracheal aspirate (ETA). Other microbiological evaluations were performed at the physician's discretion. These evaluations may have included one or more sets of blood culture (gram stain and culture), culture and histological examination for the diagnosis of fungus, PCR for diagnosis of cytomegalovirus (CMV) or herpes simplex virus (HSV) in ETA or BAL fluid and screening for RVs on nasopharyngeal swabs or in ETA or BAL fluid.

RVs were tested for by mPCR assay, using the AnyplexTM II RV16 Detection kit (Seegene® Inc., Seoul, Korea) [11] and allowing the detection of influenza A and B viruses, adenovirus, parainfluenza virus (types 1, 2, 3, and 4), RSV types (A and B), picornavirus (rhinoviruses, enteroviruses), human metapneumovirus, human coronaviruses (229E, NL63, OC43 and HKU1), and bocavirus.

Microorganisms identified from specimens collected within 72 h after the diagnosis of pneumonia were considered as pathogens.

3.3. Statistical analysis

Patient characteristics and outcome are reported as numbers and percentages for categorical variables and as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Data from the no pathogen group are not displayed. In-hospital and 28-day mortality and median ICU length of stay after HAP diagnosis in patients discharged alive were considered as outcome of interest and compared between the virus only, bacteria only and virus/bacteria groups. The Kruskal-Wallis test and Fisher's exact test were used, as appropriate, for univariate analysis. There were no missing data. P values less than 0.05 were considered statistically significant. All statistical analyses were conducted using STATA software (V12, ©1996–2014 StataCorp, College Station, Texas, USA).

4. Results

4.1. Patient characteristics

Among the 999 ICU patients who underwent an mPCR assay to test for RVs during the study period, 95 were considered to have HAP and were included in the study. During the same period, HAP were admitted or occurred in the ICU in 143 patients. Thus, screening for RVs was performed in 66% (95/143) of HAP patients. The characteristics of the 48 HAP patients not tested for RVs were similar to those of the 95 patients described in this study, except for immune status. Patients tested for RVs were more likely to be immunocompromised (47% vs. 19%, p = 0.001).

The patients had a median age of 61 (IQR, 52–69) years and 71 (75%) were male. Forty-five patients (47%) were considered as immunocompromised. Sixty-four patients (67%) had at least one chronic underlying disease (most frequently diabetes mellitus (37%) and structural lung disease (28%)). The median length of hospital stay prior to HAP diagnosis was 17 (9–36) days. The median SAPS II score at admission was 52 [34–61].

Baseline characteristics are listed in Table 1.

4.2. Microbiological results

At least one pathogen was identified in 90 out of 95 (95%) patients. Bacterial infection was observed in 73 patients (77%) and 60 (63%) had bacterial infections solely. Respiratory viral infection was found in 30 (32%) patients and 17 (17/95, 18%) had viral infections solely. Viral/bacterial co-infection concerned 13 (14%) cases. Among the 73 patients with bacterial infections identified in respiratory specimens, 7 (9%) had concomitant positive blood cultures. HSV was found in 7 (7%) cases and fungal infection in 3 (3%) cases (*Pneumocystis jirovecii* n = 1, *Aspergillus* species n = 2). RVs were more likely to be found in immunocompromised patients (19/45, 42% vs. 11/50, 22%, p = 0.04). Distribution of all pathogens identified is shown in Table 2.

4.2.1. Bacterial pathogens

A total of 90 bacteria were identified in 73 patients. Two and three concomitant bacteria were identified for 13 and 1 patients, respectively. Non-fermenting Gram-negative bacilli, *Enterobacteriaceae* and MSSA (methicillin-sensitive *Staphylococcus aureus*) were found in 37 (39%), 34 (36%) and 10 (11%) cases, respectively.

4.2.2. Respiratory viral pathogens

Overall, 30 RVs were identified in 30 patients (30/95, 32%). None of these patients were infected with more than one type of virus. All