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Microorganisms associated with respiratory syncytial virus pneumonia in the adult population

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Abstract

Respiratory syncytial virus (RSV) has been recognized as responsible for severe respiratory illness in adults, especially in the elderly. While pneumonia is commonly observed during RSV infection, the burden and epidemiology of bacterial superinfection is poorly understood. The aim of this study was to identify microorganisms associated with RSV-positive pneumonia in adults. A retrospective study was conducted during three consecutive winters (October to April 2013–2016) in the University Hospital of Lyon, France. During RSV circulation periods, a systematic RSV screening was performed by reverse-transcription PCR on all respiratory samples collected from adults. Records of RSV-positive patients were subsequently analyzed to identify radiologically confirmed pneumonia cases. Bacteria were identified by standard bacteriology cultures or urinary antigen screening and classified as potentially causative of pneumonia if quantification was above the specific threshold as defined by the European Manual of Clinical Microbiology. Overall, 14,792 adult respiratory samples were screened for RSV detection by PCR. In total, 292 had a positive RSV detection (2.0%) among which 89 presented with pneumonia including 27 bacterial superinfections (9.3%) with *Streptococcus pneumonia*, *Haemophilus influenza*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Moraxella catarrhalis*. Most patients were elderly (55.6%) and patients with comorbidities (77.8%). A more severe outcome was observed for RSV-bacteria-associated pneumonia compared with RSV pneumonia: length of stay was significantly longer (16 days vs 10 days) and ICU hospitalization more frequent (66.7% vs 21.0%) ($p < 0.05$). In conclusion, we did not observe major differences in the epidemiology of bacterial superinfections in RSV-positive pneumonia compared to reports on post-influenza pneumonia.

Keywords RSV · Bacterial coinfection · Superinfection · Pneumonia · Adults

Introduction

Respiratory syncytial virus (RSV) is now recognized as an important cause of respiratory illness in adults, especially in the elderly [1]. Secondary bacterial pneumonia after or during an RSV infection is among the more severe complications reported in this population [2].

Few studies have described superinfection or coinfection with bacteria among adults with RSV-positive pneumonia in inpatient setting [3, 4]. Diagnostic testing for RSV is usually not routinely performed in this population. However burden and epidemiology of RSV-positive pneumonia in adults is important to assess in regards of the current antibiotic therapy recommendations [5].

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The aim of our study was to gain insights in the epidemiology of bacterial superinfections associated with RSV pneumonia in adults.

Materials and methods

Patient selection

We conducted a retrospective, monocenter, and observational study on three successive winter periods (October to April, 2013–2016). In the University Hospital of Lyon (Hospices Civils de Lyon, France), upper and lower respiratory tract samples from patients with respiratory symptoms are systematically screened for RSV and metapneumovirus (HMPV) using a reverse transcriptase polymerase chain reaction (RT-PCR). We included all adult patients (≥ 18 years old) positive for RSV with radiologically confirmed pneumonia as diagnosed in the medical chart. Hospital-acquired pneumonia (HAP) was defined as radiologically confirmed pneumonia that manifests ≥ 48 h after the patient's admission to the hospital, and not present at the time of intubation.

Data collection

Data collected included laboratory results, demographics (age, sex), underlying conditions (cardiovascular disease, pulmonary disease, diabetes mellitus, and immunodeficiency), as well as clinical outcomes (length of stay, acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, in-hospital death).

Biological samples and laboratory testing

For virus detection, clinical specimens comprised nasopharyngeal swabs, endotracheal aspirates, and broncho-alveolar lavages. Respiratory specimens were extracted using Easymag (Biomerieux, Marcy L'étoile, France). RSV detection was performed using a RT-PCR (ABI 7500; Thermofisher, Illkirch, France), or duplex RT-PCR detecting RSV and HMPV (R-gene detection kit, bioMérieux-Argene, France) as previously described [6].

For bacteria detection, pathogens were classified as potentially causative of pneumonia if identified in pleural fluid or blood, or if identified within a sputum specimen, endotracheal aspirate, and broncho-alveolar lavage with good-quality criteria and if quantification was above the appropriate EMCM decision threshold. Semi-quantitative bacterial culture process and interpretation was performed following the European Manual of Clinical Microbiology (EMCM) guidelines [7]. MALDI-TOF (Vitek-MS) was used for species identification.

Statistics

Statistical analyses were performed using GraphPad Prism software (version 5.0, GraphPad Software, La Jolla, CA, USA). Univariate analysis was used to compare RSV-bacteria-associated pneumonia and RSV-positive pneumonia. Quantitative variables (age and length of stay) were expressed as median and interquartile range (IQR). Difference between the age groups was assessed by Student's t test. Difference between lengths of stay was assessed by non-parametric Mann-Whitney test. Qualitative variables were expressed as number and percentage. A Fisher's exact test was used for univariate comparisons. A p value < 0.05 was considered significant.

Results

Characteristics of the patients with RSV-positive sample

During the study period, viral RT-PCR was performed on 14,792 respiratory samples collected from adult patients. Influenza was detected in 1441 patients (9.7% of all respiratory samples), rhinovirus in 438 patients (3.0% of all respiratory samples), RSV in 292 patients (2.0% of all respiratory samples), and HMPV in 114 patients (0.8%). The median age of patients tested positive for RSV was 68 years (interquartile range 54 to 82), with a sex ratio of 1 (51.9% were men). Among RSV-positive patients, 95.5% of case records were retrieved ($n = 279/292$). Primary discharge diagnoses in patients without respiratory symptoms were as follows: 10.0% ($n = 28/279$) of systematic sampling without acute respiratory infection in immunosuppressed patients, 6.5% ($n = 18/279$) of acute heart failure, 2.5% ($n = 7/279$) of sepsis, and 1.4% ($n = 4/279$) of neurological disorders. 79.6% ($n = 222/279$) patients presented with respiratory disorders, including 19.4% ($n = 54/279$) of respiratory failure, 15.8% ($n = 44/279$) of acute respiratory infection, 12.5% ($n = 35/279$) of acute respiratory distress syndrome, and 31.9% ($n = 89/279$) radiologically confirmed pneumonia.

Characteristics of patients with an RSV-positive sample and a radiologically confirmed pneumonia

Among these 89 pneumonia, 27 cases were associated with bacteria classified as potentially causative (RSV-bacteria-associated pneumonia) and 62 cases had no bacterial documentation (RSV-positive pneumonia). Among these 62 RSV-positive pneumonia, 5 cases were associated with another virus (2 RSV and influenza coinfections, 1 RSV and picornavirus coinfection, 1 RSV and bocavirus coinfection, and 1 RSV and CMV coinfection).

Among the 27 RSV-bacteria associated pneumonia, hospital-acquired pneumonia (HAP) was observed mostly in adults ≥ 65 years old ($n = 8/10$) whereas community-acquired pneumonia (CAP) occurred mostly in 18 to 64-year-old adults ($n = 10/17$).

Most of the patients presenting a pneumonia were elderly (median age 74 years (interquartile range 58 to 85)) and had underlying conditions (77.8%) (Table 1). Only 11.1% were resident of nursing homes. Demographic characteristics did not differ between patients with an RSV-bacteria-associated pneumonia and patients with an RSV-positive pneumonia.

Management and outcome of patients with an RSV-positive sample and a radiologically confirmed pneumonia

Among these 89 pneumonia, 31 patients received an empiric antibiotic treatment and 3 immunosuppressed patients received an antiviral treatment: 1 patient received ribavirin, 1 patient received polyvalent immunoglobulins, and 1 patient received ribavirin and polyvalent immunoglobulins.

In total, 22 patients presented an ARDS, 31 patients were admitted to ICUs and in-hospital mortality occurred in 18 adults of which all were ≥ 65 years old ($n = 14/18$) or immunosuppressed ($n = 4/18$). RSV and bacteria coinfection was statistically associated with a more severe outcome than RSV-positive pneumonia as length of stay was significantly longer (16 days vs 10 days) and ICU hospitalization more frequent (66.7% vs 21.0%) ($p < 0.05$). However no significant difference was observed regarding in-hospital mortality (Table 1).

Epidemiology of RSV-bacteria co-detection

Among the 27 cases of RSV-positive pneumonia with superinfection, the most frequent bacteria were *Streptococcus pneumoniae*, *Enterobacteriaceae* (*Klebsiella pneumonia*, *Enterobacter cloacae*, *Citrobacter koseri*), *Pseudomonas aeruginosa*, *Haemophilus influenza*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. In two patients, more than one bacterial pathogen was detected. In patients hospitalized for CAP, the most frequent bacteria were *S. pneumoniae*, *H. influenzae*, and *S. aureus* whereas in HAP the most frequent bacteria were *P. aeruginosa* and *Enterobacteriacae* (Table 2).

Discussion

In this study, detection rates of the screened viruses were consistent with previous reports describing the epidemiology of respiratory viruses in hospitalized adults [8–10]. RSV detection in our study was low (2.0%) compare to rates of RSV detection reported in previous studies ranging from 7% of hospitalized adult patients to 10% of hospitalization for acute respiratory illness in an elderly population [11–13]. It is probably due to the systematic testing strategy associated to a

Table 1 Demography, characteristics, and outcome of the 89 patients with an RSV-positive sample and a radiologically confirmed pneumonia

	RSV-bacteria-associated pneumonia	%	RSV-positive pneumonia	%	p value
	n = 27	%	n = 62	%	
Age, median (IQR)	70 (56; 82)		76 (59; 85)		ns
18–64	12	44.4	21	33.9	
≥ 65	15	55.6	41	66.1	
Sex					ns
male	14	51.9	34	54.8	
female	13	48.1	28	45.2	
Living situation					
Independent	24	88.9	53	85.5	ns
In nursing facility	3	11.1	9	14.5	ns
Chronic illnesses					
Cardiovascular disease	11	40.7	32	51.6	ns
Pulmonary disease	13	48.1	18	29.0	ns
Diabetes mellitus	6	22.2	10	16.1	ns
Immunodeficiency	10	37.0	28	45.2	ns
No chronic illness	6	22.2	5	8.1	ns
Clinical severity and outcomes					
Length of stay, median (IQR)*	16 (10; 23)		10 (6; 19)		$p < 0.05$
ARDS	10	37.0	12	19.4	ns
ICU admission	18	66.7	13	21.0	$p < 0.01$
In-hospital death	7	25.9	11	17.7	ns

IQR interquartile range, *ns* non-signficant

*A Mann-Whitney test was used to verify statistical significance for quantitative variable with a non-normal distribution. $p < 0.05$ was considered significant

Table 2 Bacteria associated with RSV in CAP and HAP

	Total (n = 27)	CAP (n = 17)	HAP (n = 10)
Streptococcus pneumoniae	9	8	1
Enterobacteriaceae	5	2	3
Pseudomonas aeruginosa	4	1	3
Haemophilus influenza	4	4	0
Staphylococcus aureus	4	2	2
Moraxella catarrhalis	3	2	1

Species distribution of pathogenic bacteria involved in RSV-positive pneumonia (CAP) and hospital-acquired pneumonia (HAP)

sampling bias toward influenza-like illness. Those symptoms are indeed poorly predictive of an RSV infection [14].

Among RSV infected patients, 31.9% presented a radiologically confirmed pneumonia and 9.7% had an RSV-bacteria-documented pneumonia. Despite the large number of RSV testing among the adult population, we identified only a few RSV radiologically confirmed pneumonia. Although this is a low prevalence, it is in agreement with the current literature in which 9 to 39% of RSV-bacteria co-infections were reported [3]. In our study, a higher prevalence was noted in the elderly (15/27), immunosuppressed, and patients with comorbidities (21/27). As it has been previously described, we observed that RSV-bacteria-associated pneumonia have a more severe outcome than RSV-positive pneumonia [15].

Enterobacteriaceae and *Pseudomonas aeruginosa* were the most frequently detected pathogens in HAP and did not differ from the pathogens usually responsible for HAP in ICU [16]. *S. pneumonia* and *H. influenza* were the most frequently detected pathogens in CAP. In a previous study in adults with CAP, *S. pneumonia* and *H. influenza* were also mainly reported in RSV-bacteria coinfections [4]. We did not observed major differences to influenza-bacterial coinfections [17]. Those results suggest that there is no main difference between the microbiological epidemiology of RSV-bacterial coinfections and influenza-bacterial coinfections. This observation needs to be confirmed by other studies. Further research should focus on estimating the RSV CAP burden in adult as well as understanding the underlying mechanisms of co-pathogenesis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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