Co-infection of *Streptococcus pneumoniae* in Respiratory Infections Caused by SARS-CoV-2

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Received: 3.12.2020; Revised: 29.12.2020; Accepted: 31.12.2020; Published: 2.01.2021

Abstract: Viral respiratory infections are often associated with bacterial co-infections that often lead to increased severity and mortality of the disease. During the recent pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hospitalized patients reported developing secondary bacterial infections ranging from 0 to 40% of the cases. In the previous influenza pandemics, *Streptococcus pneumoniae* was the most isolated bacterial pathogen causing increased mortality in patients affected by viral pneumonia. Due to the difficulty to detect pneumococcal infection in SARS-CoV-2 patients by a rapid clinical test, the real prevalence of *S. pneumoniae* might be underestimated, and only a few cases have been documented so far. It has been estimated that 90% of patients admitted to the Intensive Care Unit are empirically treated with antimicrobial. The application of more rapid and sensitive diagnostic methods could help with targeted antibiotic therapy. Additionally, pneumococcal vaccination of high-risk individuals could reduce bacterial pneumonia, hospital admissions, and comorbidities associated with serious illness.

Keywords: SARS-CoV-2; *Streptococcus pneumoniae*; bacterial co-infections.

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1. Introduction

Bacterial co-infections in viral respiratory disease are clinically well-documented and can aggravate the disease’s outcome in infected patients. The ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is overwhelming the healthcare system and economy worldwide. Although more clinical data on the disease has been collected since the pandemic began to spread globally in January 2020, many aspects remain unclear on what could worsen the disease’s outcome.

SARS-CoV-2 can establish in the upper respiratory tract (URT) of the host in asymptomatic form or develop into respiratory disease with a wide degree of symptoms and severity. 80% of cases present cold symptoms up to mild pneumonia. In the remaining 20% of the cases, the infection can progress to the lower respiratory tract (LRT), causing severe pneumonia with multiorgan dysfunction that can be fatal in 5% of cases [1,2]. Incidence and prevalence of SARS-CoV-2 infection are also very variable and strongly depends on the patient’s age and health status [1].
The URT constitutes the main door of entry of the virus in the host through droplets containing infective viral particles emitted by carriers or infected people [1]. SARS-CoV-2 can penetrate the host cells by binding the receptor angiotensin-converting enzyme 2 (ACE-2) present in different organs but particularly abundant in the epithelial cells of the URT and LRT. Since SARS-CoV-2 shares different respiratory tract infection sites [3], which are in common with other respiratory bacterial pathogens, it is important to consider possible bacterial co-infections can exacerbate the fatal outcome of the disease.

Diverse viral and bacterial species can colonize the URT, coexisting being part of the normal microbiota [4]. Potential pathogenic agents can also occupy URT niches in an asymptomatic form among the microorganism community without causing damage to the host [5]. Within this complex network of microorganisms, invading pathogens compete with the commensal bacteria for adhesion receptors and nutrients present on the mucosal surface [6–8]. Changes in external environmental conditions or the weakening of the host’s immune status can be decisive for the transition to a symptomatic state leading to the onset of severe forms of the disease [5,9]. Thus, viral and bacterial respiratory pathogens can have synergistic interaction, increasing infection complications, for example, through damage to the cellular barrier [10] and dysregulation of immune responses [11].

*Streptococcus pneumoniae* is usually the primary bacterial agent causing increased morbidity and mortality in virus-associated pneumonia [12]. There is evidence supporting that the influenza virus alters the respiratory tract to enhance the adherence, invasion, and induction of disease by pneumococcus [13]. Furthermore, a viral infection appears to decrease the efficacy of the immune response and phagocytic activity by alveolar macrophages and neutrophils, leading to a reduced suppression of bacterial co-infection [14–17].

In 1918 during the Influenza pandemic, 500 million people were infected by influenza A H1N1 virus. More than 50 million died, of which 85% to 90% of fatal cases developed severe pneumonia caused by *S. pneumoniae* [18]. In the following pandemics caused by a rearranged version of the influenza virus, *S. pneumoniae* showed a lower incidence in fatal cases (approximately 25%) but was still the most common complicating organism in patients with pneumonia [19,20]. The mortality rate of viral pandemics is strongly impacted by secondary bacterial infections, with a high prevalence of fatal cases in the previous pandemics caused by secondary bacterial infections rather than the virus alone.

In the current SARS-CoV-2 pandemic, data on the prevalence of pneumococcal co-infections are limited and irregularly reported. The only diagnosis based on the Ray-X image of lung and clinical symptoms could render it difficult to distinguish between pneumococcal and SARS-CoV-2 infection.

SARS-CoV-2 is diagnosed on nasopharyngeal swab specimens by Real-Time reverse transcriptase-polymerase chain reaction (RT-rtPCR), which is often a sensitive method used in clinical virology [21]. *S. pneumoniae* is usually detected by microbiological culture from the respiratory tract or blood and confirmed for the presence of C-polysaccharide antigen in urine. Although the microbiological method is still a valid screening, the result less sensitive and rapid compared to molecular methods [22]. Moreover, not all health care centers regularly carry out the detection of respiratory pathogens and longitudinal respiratory sampling, especially in Intensive Care Units (UNI) patients, to reduce aerosol-generating procedures.

Therefore, the real incidence of *S. pneumoniae* in severe SARS-CoV-2 pneumonia remains to be defined [23].
2. Materials and Methods

This study was performed using PubMed and Scholar databases on COVID-19 articles published before October 17 2020, and after February 2020. Separate searches were done for Streptococci respiratory infection, years 2006 to 2020.

3. Pneumococcal Co-infection in SARS-CoV-2 Patients

The current literature suggests that the prevalence of the total bacterial co-infection in SARS-CoV-2 patients could range from 0 to 40% [2,24–26]. The secondary infections seem to have a nosocomial origin with a higher incidence in UNI patients (14% - 31%) and no survivors (50%) [2,26]. The difference in prevalence in bacterial co-infection poses a strong debate for the empirical use of antibiotic therapy in SARS-CoV-2 patients prior to and after admission to UNI [27,28].

Among reports of case-cohort studies, few provided details about the pathogens involved in a secondary infection. Pneumococcal infection associated with SARS-CoV-2 pneumonia is reported only in a few studies (Table 1). The difference in incidence is greatly variable and depends on the country, the pandemic period, and the detection method utilized for the diagnosis.

Table 1. Cohort retrospective studies where the pneumococcal infection was reported.

<table>
<thead>
<tr>
<th>Biblio</th>
<th>Country</th>
<th>Period of study</th>
<th>N° of patients</th>
<th>Median age of patients (years)</th>
<th>Pneumococcal secondary infection</th>
<th>Pneumococcal infection incidence</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>[36]</td>
<td>China</td>
<td>22nd Jan - 24th Feb, 2020</td>
<td>257</td>
<td>51 (2-99)</td>
<td>153</td>
<td>59.5%</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>[37]</td>
<td>China (Suzhou)</td>
<td>8th Feb - 15th Feb, 2020</td>
<td>194</td>
<td>45 (1-88)</td>
<td>14</td>
<td>7.2%</td>
<td>qPCR</td>
</tr>
<tr>
<td>[38]</td>
<td>Spain</td>
<td>28th Feb - 23rd April, 2020</td>
<td>989</td>
<td>61 (48-74)</td>
<td>12</td>
<td>1.2%</td>
<td>Pneumococcal urinary antigen</td>
</tr>
<tr>
<td>[25]</td>
<td>USA (Chicago)</td>
<td>1st Mar - 11th Apr, 2020</td>
<td>321</td>
<td>60 (43-77)</td>
<td>4</td>
<td>1.2%</td>
<td>Pneumococcal urinary antigen</td>
</tr>
<tr>
<td>[39]</td>
<td>France</td>
<td>16th Apr - 6th Apr, 2020</td>
<td>47</td>
<td>68 (56-74)</td>
<td>3</td>
<td>6.3%</td>
<td>Bacterial culture plus Multiplex PCR panel</td>
</tr>
<tr>
<td>[40]</td>
<td>UK</td>
<td>6th Mar - 7th Apr, 2020</td>
<td>195</td>
<td>69 (59-81)</td>
<td>5</td>
<td>2.5%</td>
<td>Bacterial culture</td>
</tr>
<tr>
<td>[41]</td>
<td>France</td>
<td>13th Mar - 16th Apr, 2020</td>
<td>92</td>
<td>61 (55-70)</td>
<td>6</td>
<td>6.5%</td>
<td>Bacterial culture plus Multiplex PCR panel</td>
</tr>
<tr>
<td>[42]</td>
<td>Italy</td>
<td>21st Jan - 7th Feb, 2020</td>
<td>56</td>
<td>35 (1-85)</td>
<td>1</td>
<td>0.8%</td>
<td>Bacterial culture plus Respiratory panel cartridge</td>
</tr>
<tr>
<td>[43]</td>
<td>Italy</td>
<td>25th Mar - 10th Apr, 2020</td>
<td>168</td>
<td>2.3 (1-17)</td>
<td>1 (infant)</td>
<td>0.5%</td>
<td>NA</td>
</tr>
</tbody>
</table>

The higher incidence of pneumococcal infection in SARS-CoV-2 patients was reported by Zhu et al. (Table 1) [29]. In this study, 294 patients were tested by RT-PCR for 24 respiratory pathogens, of which S. pneumoniae was the most isolated bacteria in bacterial co-infection, followed by Klebsiella pneumoniae and Hemophilus influenzae. Most pathogen species were detected after 1 - 4 days from the onset. The highest rates of co-infections were found in patients aged from 15 to 44 years.

In contrast, in Europe, the prevalence of reported cases of S. pneumoniae co-infection is variable, ranging from 0% to 6%. The study conducted in a UNI in France presents a well-documented analysis of mixed co-infection detected using a broad-spectrum molecular diagnostic panel to detect the most common respiratory pathogens rapidly. In 28% of patients diagnosed with bacterial co-infection on ICU admission, S. pneumoniae was the third most detected respiratory pathogen before Staphylococcus aureus and H. influenzae.
<table>
<thead>
<tr>
<th>Bibliography</th>
<th>Country</th>
<th>Age (years, months)</th>
<th>Gender</th>
<th>Symptoms</th>
<th>Comorbidity</th>
<th>X-Ray Image</th>
<th>Diagnostic</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[44]</td>
<td>Spain</td>
<td>8 months/M</td>
<td>F</td>
<td>Fever, Cough, Dyspnea</td>
<td>None</td>
<td>Left lobe opacity, small pleural effusion</td>
<td>Blood culture</td>
<td>Meropenem Linezolid</td>
<td>discharged</td>
</tr>
<tr>
<td>[45]</td>
<td>Lebanon</td>
<td>16 months/F</td>
<td>F</td>
<td>Fever, Severe diarrhea</td>
<td>None</td>
<td>Upper lobe consolidation, bilateral lower lobe infiltrates</td>
<td>Blood culture</td>
<td>Ceftriaxone Metromidazole</td>
<td>discharged</td>
</tr>
<tr>
<td>[46]</td>
<td>Spain</td>
<td>86 years/M</td>
<td>M</td>
<td>Fever, Cough, Dyspnea</td>
<td>Ischemic Heart Disease, Aortic Stenosis, CKD</td>
<td>Unilateral consolidative infiltrate</td>
<td>Pneumococcal antigen in urine</td>
<td>Ceftriaxone Ceftaroline</td>
<td>discharged</td>
</tr>
<tr>
<td>[46]</td>
<td>Spain</td>
<td>38 years/F</td>
<td>F</td>
<td>Fever, Cough, Dyspnea</td>
<td>Arthromyalgia</td>
<td>None</td>
<td>Bilateral interstitial infiltrates</td>
<td>Pneumococcal antigen in urine</td>
<td>Ceftriaxone Cefixime</td>
</tr>
<tr>
<td>[46]</td>
<td>Spain</td>
<td>65 years/M</td>
<td>M</td>
<td>Fever, Cough, Dyspnea</td>
<td>Arthromyalgia</td>
<td>Depression</td>
<td>Bilateral interstitial infiltrates</td>
<td>Pneumococcal antigen in urine</td>
<td>Ceftriaxone Levofloxacine</td>
</tr>
<tr>
<td>[46]</td>
<td>Spain</td>
<td>79 years/F</td>
<td>F</td>
<td>Fever, Cough, Dyspnea</td>
<td>Arthromyalgia</td>
<td>CKD Chronic anemia</td>
<td>Bilateral interstitial infiltrates</td>
<td>Pneumococcal antigen in urine</td>
<td>Ceftriaxone Teicoplanin</td>
</tr>
<tr>
<td>[46]</td>
<td>Spain</td>
<td>44 years/F</td>
<td>F</td>
<td>Fever, Cough, Dyspnea</td>
<td>Arthromyalgia</td>
<td>Obesity, Asthma</td>
<td>Bilateral interstitial infiltrates</td>
<td>Pneumococcal antigen in urine</td>
<td>Ceftriaxone Cefixime</td>
</tr>
<tr>
<td>[47]</td>
<td>The UK</td>
<td>86 years/M</td>
<td>M</td>
<td>Fever, Dyspnea, Fatigue</td>
<td>Alzheimer’s disease, Hypertension</td>
<td>Abnormality in the lung</td>
<td>Blood culture</td>
<td>Amoxicillin Clarithromycin Vancomycin</td>
<td>death</td>
</tr>
<tr>
<td>[47]</td>
<td>The UK</td>
<td>82 years/F</td>
<td>F</td>
<td>Chest pain, Fever, Cough</td>
<td>Type 2 diabetes mellitus, ischemic cardiomyopathy, Hypertension, CKD</td>
<td>Abnormality in the lung</td>
<td>Blood culture</td>
<td>Amoxicillin Co-amoxiclav</td>
<td>discharged</td>
</tr>
<tr>
<td>[48]</td>
<td>Brunei</td>
<td>42/M</td>
<td></td>
<td>Fever, cough, dyspnea, rhinorrhea, and myalgia</td>
<td>None</td>
<td>Normal</td>
<td>Sputum</td>
<td>Oseltamivir Amoxicillin</td>
<td>discharged</td>
</tr>
<tr>
<td>[49]</td>
<td>USA</td>
<td>80/F</td>
<td>F</td>
<td>Respiratory Distress, Cardiac arrest</td>
<td>Diabetes mellitus hypertension, asthma, paroxysmal atrial fibrillation, and dementia</td>
<td>Bilateral interstitial and intra-alveolar infiltrates</td>
<td>Pneumococcal antigen in urine</td>
<td>Ceftriaxone, Azithromycin</td>
<td>death</td>
</tr>
</tbody>
</table>
Single case reports of pneumococcal infection have been globally described in SARS-CoV-2 infected patients (Table 2). The clinical conditions of patients often appear critical and are characterized by severe respiratory distress. Antibiotic treatment was associated with antiviral therapy to burden the infection.

Because of these reported cases, we emphasize the application of rapid and broad diagnostic tests. It is estimated that more than 90% of the critically ill patients with severe SARS-CoV-2 pneumonia received an empiric antibiotic therapy upon ICU admission [25,27,30–32]. The use of a panel consisting of multiplex PCR for seasonal respiratory pathogens would support better and faster diagnosis and the choice of appropriate antimicrobial therapy.

For more in-depth information on the development of the infection, advanced molecular methods for detecting a wide range of potential pathogens and antimicrobial resistance could also be considered. For instance, the application of whole-genome metagenomics would generate information on complex mixed infections and antimicrobial resistance in a relatively short period [33,34]. Although whole-genome metagenomics does not yet have a large application in diagnostics, advanced nanopore metagenomics could have the potential to produce a rapid and accurate detection of respiratory pathogens and antibiotic-resistance genes that would help to avoid a high use of broad-spectrum antibiotics [33] and might also provide useful information on the microbiota associated to diseased patients.

4. Conclusions

These cases suggest that pneumococcal infection can occur associated with SARS-CoV-2 infection but be less frequently than in influenza [35]. However, there may be more case reports of pneumococcal pneumonia monitoring SARS-CoV-2 disease over time. The necessity of rapid, sensitive, and broad tests to detect respiratory pathogens, including S. pneumoniae, which is the most common bacteria viral-pneumonia associated, is highlighted.

The combination of seasonal influenza and the pneumococcal vaccine could help prevent a portion of secondary infections, especially in high-risk patients.

Future studies should implement standardized sampling and testing to research respiratory pathogens in SARS-CoV-2 patients and indicate which ones are more prevalent in the co-infection correlating morbidity and mortality rates.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
References


