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# A Retrospective Study of Coinfection of SARS-CoV-2 and *Streptococcus pneumoniae* in 11 Hospitalized Patients with Severe COVID-19 Pneumonia at a Single Center

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**Background:** A lethal synergism between the influenza virus and *Streptococcus pneumoniae* has been identified. However, bacterial coinfection is considered relatively infrequent in hospitalized patients with COVID-19, and the prevalence of *Streptococcus pneumoniae* is low.

**Material/Methods:** We retrospectively analyzed the clinical characteristics and outcomes of patients subsequently admitted to AMITA Health Saint Francis Hospital between March 1 and June 30, 2020, with documented SARS-CoV-2 and *S. pneumoniae* coinfection.





**Results:** We identified 11 patients with *S. pneumoniae* coinfection. The median age was 77 years (interquartile range [IQR], 74–82 years), 45.5% (5/11) were males, 54.5% (6/11) were white, and 90.9% (10/11) were long-term care facility (LTCF) residents. The median length of stay was 7 days (IQR, 6–8 days). Among 11 patients, 4 were discharged in stable condition and 7 had died, resulting in an inpatient mortality rate of 64%.

**Conclusions:** At our center, 11 patients with COVID-19 pneumonia who had confirmed infection with SARS-CoV-2 were diagnosed with *Streptococcus pneumoniae* infection while in hospital. All patients had pneumonia confirmed on imaging and a nonspecific increase in markers of inflammation. The in-hospital mortality rate of 64% (7 patients) was higher in this group than in previous reports. This study highlights the importance of monitoring bacterial coinfection in patients with viral lung infection due to SARS-CoV-2.

**MeSH Keywords:** **COVID-19 • Pneumonia • SARS Virus • *Streptococcus pneumoniae***

**Abbreviations:** **COVID-19** – Coronavirus Disease 2019; **ICU** – Intensive Care Unit; **IMV** – invasive mechanical ventilation; **IQR** – interquartile range; **IV** – intravenous; **LTCF** – long-term care facility; **U.S.** – United States

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## Background

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus had caused over 3 million cases of coronavirus disease 2019 (COVID-19) and more than 150 000 deaths in the U.S. [1]. As the pandemic evolves, the scientific and medical community accumulates more evidence of the disease's clinical characteristics; however, information regarding bacterial coinfections is still minimal and sometimes overlooked [2].

Between 1918 and 1919, the "Spanish" influenza pandemic caused around 50 million deaths worldwide [3]. Preserved lung tissue sections and autopsy analyses have shown that most of these deaths likely resulted directly from secondary bacterial pneumonia by common upper-respiratory tract bacteria, with *Streptococcus pneumoniae* playing a significant role [4]. This lethal synergism between the influenza virus and *S. pneumoniae* is not limited to pandemic strains; during the seasonal influenza period, 41% of bacterial coinfections are attributed to *S. pneumoniae* [5].

In contrast, bacterial coinfection is considered relatively infrequent in hospitalized patients with COVID-19, and the co-prevalence of *S. pneumoniae* is even lower [6–10]. Lin et al. documented for the first time the coinfection of the SARS-CoV-2 with multiple common viral respiratory pathogens taking place in the community [6]. Subsequent cohort studies documented bacterial coinfections, with only a few studies reporting *S. pneumoniae* coinfection [7,10], generally with good outcomes. Therefore, this retrospective study aimed to describe 11 hospitalized patients with a coinfection of SARS-CoV-2 and *S. pneumoniae* diagnosed with severe COVID-19 pneumonia at a single center.

## Material and Methods

We retrospectively analyzed clinical characteristics and outcomes of the patients subsequently admitted to AMITA Health Saint Francis Hospital between March 1 and June 30, 2020, with documented SARS-CoV-2 infection by RT-PCR or isothermal nucleic acid amplification performed on nasopharyngeal throat swab specimens (Abbott™ RealTime™ SARS-CoV-2 assay and Abbott™ ID NOW COVID-19™ assay) and hospitalized with symptomatic COVID-19 illness.

The Abbott™ RealTime™ SARS-CoV-2 assay is a dual-target real-time reverse transcription-polymerase chain reaction assay for the RdRp and N genes of the SARS-CoV-2 virus. In contrast, the Abbott™ ID NOW COVID-19™ assay is a rapid molecular *in vitro* diagnostic test that utilizes an isothermal nucleic acid amplification technology intended for the qualitative detection

of nucleic acid from the SARS-CoV-2 viral RNA. Both tests were provided an Emergency Use Authorization (EUA) by the U.S. FDA for use by authorized laboratories. *S. pneumoniae* infection was diagnosed in patients with positive blood or sputum cultures or urinary antigen. For cultures, B.D.™ Taxo™ P Discs for differentiation of pneumococci were used, with bile solubility as a confirmatory test (B.D.™ Desoxycholate™ Reagent). The urine antigen was detected with a rapid immunochromatographic test (Abbott™ BinaxNOW™ *Streptococcus pneumoniae* Antigen Card Test Kit).

The study and creation of this de-identified dataset were approved by the Institutional Review Board of AMITA Health System (2020-0128-02). The Ethics Commission waived the requirement for informed consent given this research involves no more than minimal risk to subjects. Descriptive statistics were used to summarize results. The data were analyzed using SPSS Version 23.0 (IBM Corp, Armonk, NY).

## Results

We identified 11 patients with *S. pneumoniae* coinfection: 9 patients with positive urine antigen, 1 with positive blood cultures, and 1 with positive sputum cultures. Detailed clinical characteristics and outcomes of the patients are shown in Table 1. The median age was 77 years (interquartile range [IQR], 74–82 years), 45.5% (5/11) were males, 54.5% (6/11) were white, and 90.9% (10/11) were long-term care facility (LTCF) residents. The most common comorbidity was hypertension (9/11, 81.8%), and the most common symptom on admission was shortness of breath (9/11, 81.8%). The median temperature at presentation was 38.8°C (IQR, 38.1–39.5°C), the median systolic blood pressure was 103 mmHg (IQR, 80–145 mmHg), the median respiratory rate was 28 rpm (IQR, 22–38 rpm), the median heart rate 106 bpm (IQR 98–119 bpm), and the median lowest documented oxygen saturation in the emergency department was 91% (IQR, 85–96%). Unilateral infiltrates were initially found in 45.5% (5/11) of the patients, whereas 54.5% (6/11) had bilateral infiltrates. All the patients received intravenous (IV) antibiotic therapy and only 3 patients were ultimately intubated. The median length of stay was 7 days (IQR, 6–8 days). Among 11 patients, 4 patients were discharged in stable condition, and 7 had died, resulting in an inpatient mortality rate of 64%. The Intensive Care Unit (ICU) admission rate was 36%, and the invasive mechanical ventilation (IMV) rate was 27%.

## Discussion

In this retrospective study, we describe 11 hospitalized patients with a coinfection of SARS-CoV-2 and *S. pneumoniae* who were

**Table 1.** Characteristics of patients with SARS-CoV-2 and *Streptococcus pneumoniae* coinfection.

Patient No.	Age/Sex/ Ethnicity/Dwelling	Comorbidities	Clinical presentation	Vital signs on admission	Relevant Lab on admission
Patient 1	92 Female Black or African American Home	Hypertension, hyperlipidemia, T2D	Fever, shortness of breath, weakness, myalgia, fatigue, altered mental status	TEMP: 38.1°C SBP: 145 mmHg RR: 22 rpm HR: 116 bpm O2: 94%	WBC: 11.8 k/mm <sup>3</sup> PCT: 1.96 ng/ml LAC: 1.0 mmol/L DD: 6945 ng/mL FEU Ferritin: 451 ng/mL LDH: 514 IU/L CRP: 15.3 mg/dL
Patient 2	82 Female Caucasian LTCF	Hypertension, T2D, atrial, fibrillation, asthma, dementia	Cardiac arrest, hypoxia	TEMP: 36.2°C SBP: 85 mmHg RR: 14 rpm HR: 51 bpm O2: 96%	WBC: 34.7 k/mm <sup>3</sup> PCT: 4.41 ng/ml LAC: 9.5 mmol/L DD: 5755 ng/mL FEU Ferritin: 1301 ng/mL LDH: 2335 IU/L CRP: 0.4 mg/dL
Patient 3	75 Male Caucasian LTCF	Hyperlipidemia, OSA, seizures, CVA	Altered mental status, shortness of breath	TEMP: 39°C SBP: 140 mmHg RR: 66 rpm HR: 116 bpm O2: 90%	WBC: 9.9 k/mm <sup>3</sup> PCT: 3.37 ng/ml LAC: NA DD: 4062 ng/mL FEU Ferritin: 821 ng/mL LDH: 402 IU/L CRP: 18.4 mg/dL
Patient 4	77 Female Caucasian LTCF	Hypertension, hyperlipidemia, COPD, DVT, SVT	Shortness of breath, lethargy	TEMP: 39.5°C SBP: 69 mmHg RR: 30 rpm HR: 100 bpm O2: 75%	WBC: 6.4 k/mm <sup>3</sup> PCT: 23.98 ng/ml LAC: 2.4 mmol/L DD: 3694 ng/mL FEU Ferritin: 722 ng/mL LDH: 465 IU/L CRP: 41.90 mg/dL
Patient 5	81 Male Caucasian LTCF	COPD-asthma overlap, hyperlipidemia, T2D	Shortness of breath, cough, fever, chills	TEMP: 38.8°C SBP: 165 mmHg RR: 31 rpm HR: 119 bpm O2: 93%	WBC: 7.6 k/mm <sup>3</sup> PCT: 1.21 ng/ml LAC: 2.6 mmol/L DD: 4522 ng/mL FEU Ferritin: 175 ng/mL LDH: 180 IU/L CRP: 18.10 mg/dL
Patient 6	74 Female Hispanic LTCF	Hypertension, dementia, pre- diabetes	Shortness of breath, lethargy	TEMP: 39.5°C SBP: 80 mmHg RR: 28 rpm HR: 106 bpm O2: 91%	WBC: 14.5 k/mm <sup>3</sup> PCT: 11.47 ng/ml LAC: 7.4 mmol/L DD: 19443 ng/mL FEU Ferritin: 2126 ng/mL LDH: 405 IU/L CRP: 21.3 mg/dL
Patient 7	90 Female Hispanic LTCF	Hypertension, T2D	Fatigue	TEMP: 36.9°C SBP: 80 mmHg RR: 18 rpm HR: 93 bpm O2: 97%	WBC: 6.6 k/mm <sup>3</sup> PCT: 0.57 ng/ml LAC: NA DD: 1671 ng/mL FEU Ferritin: 1929 ng/mL LDH: 439 IU/L CRP: 7.2 mg/dL

**Table 1 continued.** Characteristics of patients with SARS-CoV-2 and *Streptococcus pneumoniae* coinfection.

Patient No.	Age/Sex/ Ethnicity/Dwelling	Comorbidity	Clinical presentation	Vital signs on admission	Relevant Lab on admission		
Patient 8	74 Male Caucasian LTCF	Hypertension, Parkinson disease, hypothyroidism	Fever, altered mental status, shortness of breath, fatigue	TEMP: 39.1°C SBP: 114 mmHg RR: 38 rpm HR: 121 bpm O2: 77%	WBC: 3.7 k/mm <sup>3</sup> PCT: 38.74 ng/ml LAC: 3.8 mmol/L DD: 2589 ng/mL FEU Ferritin: 1225 ng/mL LDH: 516 IU/L CRP: 46.8 mg/dL		
Patient 9	72 Female Hispanic LTCF	Hypertension, COPD, dementia	Shortness of breath, fever, lethargy	TEMP: 38.3°C SBP: 102 mmHg RR: 45 rpm HR: 103 bpm O2: 88%	WBC: 20.3 k/mm <sup>3</sup> PCT: 0.47 ng/ml LAC: 2.2 mmol/L DD: 2177 ng/mL FEU Ferritin: 328 ng/mL LDH: 256 IU/L CRP: 15.1 mg/dL		
Patient 10	82 Male Black or African American LTCF	Hypertension, dementia	Altered mental status, anorexia	TEMP: 40°C SBP: 89 mmHg RR: 24 rpm HR: 123 bpm O2: 98%	WBC: 12.7 k/mm <sup>3</sup> PCT: NA LAC: 3.2 mmol/L DD: NA Ferritin: NA LDH: NA CRP: NA		
Patient 11	74 Male Caucasian LTCF	Hypertension, T2D, COPD-asthma, overlap, CVA, dementia	Shortness of breath, cough, fever	TEMP: 38.8°C SBP: 71 mmHg RR: 22 rpm HR: 98 bpm O2: 85%	WBC: 3.5 k/mm <sup>3</sup> PCT: 0.84 ng/ml LAC: 1.8 mmol/L DD: 825 ng/mL FEU Ferritin: 350 ng/mL LDH: 119 IU/L CRP: 9.7 mg/dL		
Patient No.	Chest X-rays on admission	Respiratory support in the ED	Therapy	ICU admission	IMV vaso pressors	Death	Length of stay (says)
Patient 1	Unilateral infiltrates	None	Hydroxychloroquine Prophylactic heparin Ceftriaxone/Doxycycline	No	No/No	No	5
Patient 2	Bilateral infiltrates	Invasive mechanical ventilation	Hydroxychloroquine Prophylactic heparin Cefepime/vancomycin Ceftriaxone/azithromycin	Yes	Yes/Yes	Yes	7
Patient 3	Unilateral infiltrates	Invasive mechanical ventilation	IV methylprednisolone Therapeutic enoxapirin Piperacillin-tazobactam	Yes	Yes/No	No	7
Patient 4	Bilateral infiltrates	Non rebreather mask	Piperacillin-tazobactam	No	No/No	Yes	2
Patient 5	Bilateral infiltrates	None	IV methylprednisolone Therapeutic enoxapirin Ceftriaxone/azithromycin	No	No/No	Yes	6
Patient 6	Bilateral infiltrates	Invasive mechanical ventilation	IV methylprednisolone Heparin infusion Piperacillin-tazobactam Meropenem	Yes	Yes/Yes	Yes	19

**Table 1 continued.** Characteristics of patients with SARS-CoV-2 and *Streptococcus pneumoniae* coinfection.

Patient No.	Chest X-rays on admission	Respiratory support in the ED	Therapy	ICU admission	IMV vaso pressors	Death	Length of stay (says)
Patient 7	Unilateral infiltrates	Nasal cannula	Prophylactic heparin Ceftriaxone/doxycycline Azithromycin	No	No/No	No	7
Patient 8	Bilateral infiltrates	High flow nasal cannula	Prophylactic heparin Pipperacillin-tazobactam Aztreonam Azythromycin	No	No/No	Yes	8
Patient 9	Unilateral infiltrates	Humidified high-flow nasal cannula	Prophylactic heparin Ceftriaxone/azithromycin	No	No/No	Yes	6
Patient 10	Unilateral infiltrates	Nasal cannula	Prophylactic heparin Cefepime Ceftriaxone	No	No/No	Yes	6
Patient 11	Bilateral infiltrates	Nasal cannula	Dexamethasone Prophylactic enoxaparin Cefepime/vancomycin Ceftriaxone/azithromycin Cefuroxime Remdesivir Cetepime/metronidazole	Yes	No/Yes	No	21

COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein, CVA – cerebrovascular accident; D.D. – D-dimer; H.R. – heart rate; ICU – Intensive Care Unit; IV – intravenous; IMV – invasive mechanical ventilation; LAC – lactate; LDH – lactate dehydrogenase; LTCF – long-term care facility; R.R. – respiratory rate; OSA – obstructive sleep apnea, O2 – oxygen saturation; PCT – procalcitonin; SVT – supraventricular tachycardia; SBP – systolic blood pressure; T2D – type 2 diabetes, TEMP – temperature; WBC – white blood cell count.

diagnosed with severe COVID-19 pneumonia in a community hospital located in the northern Chicago area, Illinois, U.S. The majority of patients in this series presented with acute distress, namely fever and shortness of breath, had elevated inflammatory markers, showed unilateral or bilateral infiltrates in chest X-rays, and required oxygen support. The mortality rate among this group was very high (64%). However, although all these patients carried an elevated disease burden at baseline, almost all of them were LTCF residents. All of them had 2 or more comorbidities, which has to be taken into consideration. Additionally, most patients presented with advance directives; therefore, aggressive therapy was not pursued, as demonstrated by the low critical care utilization rate.

*S. pneumoniae* is a gram-positive diplococcus that colonizes the upper respiratory tract of up to 30% of healthy adults. It is the most frequently isolated bacterial pathogen in community-acquired pneumonia and the predominant copathogen in influenza coinfection [4,5]. Experimental models have demonstrated the lethal synergism between the influenza virus and *S. pneumoniae*, with mechanisms that include pulmonary epithelial damage associated with increased bacterial adherence, sensitization of cells to secondary infection via expression of

toll-like receptors, suppression of  $\gamma\delta$  T cell production of interleukin-17 by type I interferon favoring bacterial colonization in the lungs, functional impairment of neutrophils and macrophages (i.e., impaired phagocytosis), and worsened inflammatory disease through the release of neutrophil extracellular traps and a cytokine storm as a result of significant neutrophils influx triggered by viral and bacterial toxins [5].

Bacterial coinfection is considered uncommon in patients with COVID-19 who are newly admitted to the hospital [6–10]. Initial Chinese reports found a 5.1% to 38.9% incidence rate of secondary or hospital-acquired bacterial coinfections, and later reports in Western countries showed coinfection rates of 4.8% to 27.4% [2]. A retrospective cohort study that included 836 hospitalized patients with confirmed SARS-CoV-2 found that 27 (3.2%) patients had early confirmed bacterial isolates identified (0–5 days after admission), rising to 51 (6.1%) throughout the hospital stay. However, no patients with pneumococcal coinfection were identified [11]. Another large cohort study with 989 hospitalized patients identified a total of 88 non-COVID-19 infections in 72 patients (7.3%). Among those, 74 were bacterial, with *S. pneumoniae* being the most commonly isolated bacteria (12 cases). However, the outcomes of these

patients were not reported [7]. In contrast, Adler et al. identified 5 patients with pneumococcal coinfection among 195 patients with COVID-19, all of which survived to hospital discharge [10]. Furthermore, a meta-analysis by Lansbury et al. of 30 studies that included 3834 patients found that 7% of hospitalized patients with COVID-19 had a bacterial coinfection, increasing to 14% in studies that only included ICU patients. The most common organisms were *Mycoplasma pneumoniae* (47% of 27 confirmed bacterial isolates), *Pseudomonas aeruginosa* (12%), and *Haemophilus influenzae* (12%), with little evidence of *S. pneumoniae* having a significant role [12].

Despite the low frequency of coinfections reported in patients with COVID-19, they are associated with poor outcomes. Up to 50% of patients who have died of COVID-19 had secondary bacterial infections [8]. Furthermore, in the review mentioned above by Lansbury et al., the pooled analysis of crude odds ratios for death indicated that COVID-19 patients with a coinfection were 5.82 times more likely to die than patients who did not have a coinfection [12].

The present study has several limitations. First, this was a single-center study, and these findings may be subject to selection bias, and generalizability to larger populations of patients is limited. Second, given the situation's novelty, our institution did not have standard practices regarding testing for other respiratory pathogens. This was subject to each attending physician's discretion; hence, there may have been high microbiological sampling variability with only sicker patients being tested for other pathogens. Third, 90.9% of the patients studied were long-term care facility residents. These patients

present a higher burden of underlying conditions and low baseline functional status, which may account for the higher mortality observed compared to other cohorts. Fourth, given the study's observational nature, causality cannot be inferred from an uncontrolled observation. Whether there is a lethal synergism between SARS-CoV-2 and *S. pneumoniae* similar to that of the influenza virus needs to be explored in further basic and clinical research.

## Conclusions

At our center, 11 patients with COVID-19 pneumonia who had confirmed infection with SARS-CoV-2 were diagnosed with *Streptococcus pneumoniae* infection while in hospital. All patients had pneumonia confirmed on imaging and a nonspecific increase in markers of inflammation. The in-hospital mortality rate of 64% (7 patients) was higher in this group than in previous reports. This study highlights the importance of monitoring bacterial coinfection in patients with viral lung infection due to SARS-CoV-2.

## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Conflict of interest

None.

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