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Brief Communication

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Co-Infection in COVID-19 Pneumonia: Discussion Continues

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ABSTRACT

Sixty-six patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 and pneumonia on chest computer tomography were prospectively recruited. A combined respiratory swab for polymerase chain reaction (PCR), urine sample for pneumococcal and Legionella antigen, and sputum or endotracheal aspirate were collected. Urinary antigen and blood culture tests were negative in all cases as well as the PCR tests for other respiratory viruses and atypical bacterial pathogens. In total, 5 patients (7.5%) had co-infection. By PCR a high prevalence of colonization with bacterial pathogens was found. In conclusion, co-infection is rare in coronavirus disease 2019 patients, and additional examination to identify other pathogens should be performed only in selected cases.

Keywords: COVID-19; SARS-CoV-2; Co-infection; Pneumonia; Antibiotics

An outbreak of a new coronavirus disease 2019 (COVID-19) caused an international healthcare crisis, leading to more than 6 million deaths [1]. According to reports, a bacterial co-infection in COVID-19 appears to be less common than in previous viral pandemics [2-4]. Although, frequent prescription of antibiotics in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported [4, 5].

Our study was conducted in three primary care hospitals in Moscow, Russia, aiming to study the frequency of co-infection in adults with COVID-19 pneumonia.

Patients with laboratory-confirmed SARS-CoV-2 infection and pneumonia on chest computer tomography (CT), with no history of recent use of AB, were prospectively recruited into the study in May-June 2020, June-July, and November 2021, and February 2022. For each patient demographic data, concomitant diseases, chest CT findings, laboratory tests, and in-hospital mortality were recorded.

Upon admission (first 48 hours of hospitalization), a combined respiratory swab and urine sample was collected from all patients. RNA/DNA of respiratory viruses (SARS-CoV-2,

ic Infection & Chemotherapy

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Ethics statement
This study was approved by the Local Ethical Committees of City Clinical Hospital named after S. S. Yudin (Ethics Approval Letter Nº1; dated: 11.01.2021), City Clinical Hospital named after V. V. Vinogradov (Ethics Approval Letter Nº3; dated: 09.07.2020), and Hospital for war veterans Nº3 (Ethics Approval Letter Nº2; dated: 24.06.2021), Moscow, Russia. Informed consent was obtained from the patients.

Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: SR, DS. Data curation: AK, DC, TC, NR, NA, DS. Formal analysis: SR, DS. Investigation: SR, SYa, DS. Methodology: SR. Supervision: SR. Writing - Original draft: DS. Writing - review & editing: DS, SR, AK, SY, DC, TC, NR, NA.

influenza viruses A and B, human respiratory syncytial virus, human adenovirus, human metapneumovirus, human coronaviruses (229E, HKUI, OC43, NL63), human parainfluenza virus 1-4, human rhinovirus, human bocavirus), *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Streptococcus pyogenes* were detected by real-time PCR kits (AmpliSens®, CRIE, Moscow, Russia). *Legionella pneumophila*, serogroup 1, and *S. pneumoniae* urine soluble antigens were detected using Health & Research (Vegal Farmaceutica S.L., Madrid, Spain) and BinaxNOW™ (Abbott, Abbott Park, IL, USA) kits. In patients admitted directly to intensive care unit (ICU) two sets of blood were taken for culture. If available, sputum or endotracheal aspirate (ETA) was obtained for culture, transported to a microbiology laboratory, and processed following standard methods and procedures [6]. Data were analyzed using descriptive statistics.

In total, 66 patients were recruited. The main characteristics, laboratory and instrumental data of patients are shown in **Table 1**. Urinary antigen and blood culture tests were negative in all cases as well as the PCR tests for other respiratory viruses and atypical bacterial pathogens. Two patients with severe COVID-19 were admitted to the ICU and intubated on Day 1. Mixed bacterial co-infection (*K. pneumoniae* + *A. baumannii)* was identified by culture (2 ETA) from these patients.

In combined respiratory swabs analyzed by PCR, a high prevalence of colonization with bacterial pathogens was revealed. DNA of *S. pneumoniae*, *P. aeruginosa*, *S. aureus*, *A. baumannii*, *K. pneumonia*, and *H. influenzae* was detected in 20, 19, 16, 15, 14, and 7 out of 66 cases, respectively. Summing up the PCR results, 22 patients had mixed bacterial colonization, 28 had only one pathogen found, and in 16 of 66 patients, no other pathogen's DNA or RNA except for SARS-CoV-2 was detected. Three patients (one also had positive ETA, described earlier) had neutrophil leukocytosis upon admission, and one patient developed it up to 16.3 10^9/L on Day 2. In these cases, we evaluated a positive PCR as a co-infection. In total, 5 of 66 patients (7.5%) had co-infection, their characteristics are described in **Table 2**.

To our knowledge, this is the first prospective Russian study of co-infection in adults with COVID-19, where a detailed examination, including urinary antigen testing and respiratory PCR panel, was performed. Our small cohort, collected during different periods of the pandemic, coincides with larger studies where the low frequency of co-infection in patients with COVID-19 pneumonia was revealed. The patients in our study were relatively old (median age of 67 [59 - 75]), had multiple comorbidities, and nearly a quarter required admission or transfer to the ICU. Both microbiological data and clinical criteria were applied to detect coinfections.

In a systematic search by Langford et al., a bacterial co-infection on presentation was identified in 3.5% of hospitalized patients, and a secondary bacterial infection was seen in 14.3% of cases [2]. Although in a more recent meta-analysis a higher proportion of co-infection was found: 21.0% for bacterial, 12.6% for viral, and 12.6% for fungal pathogens [7]. We suppose that it is not due to the actual changes, but due to the studies selection. More studies, where a positive PCR of respiratory specimens was a confirmative test for co-infection, were included. Also, there were a lot of studies with mixed co-infection and superinfection data. Large cohort studies show a lower incidence of co-infection [8, 9]. In a Spanish study by Garcia-Vidal et al., diagnosis of community-acquired bacterial co-infection was confirmed by urinary antigen test, good-quality sputum, or blood culture. They reported 3.1% (31/989) of community-acquired co-infection, mainly caused by *S. pneumoniae* and *S.*

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Table 1. Patients' characteristics

Characteristics	Value[a]
Demographic characteristics	
Age, years	67 [59 – 75]
Female, n	42 (63.6%)
On admission	
Days after symptoms onset prior sample collecting, n	7 [5 – 9]
On-air SpO_2 on admission, %	94 [91 – 96]
On-air SpO_2 on admission ≤94%, n	38 (57.6%)
Comorbidities	
Arterial hypertension, n	56 (84.8%)
Diabetes mellitus, n	21 (31.8%)
Chronic kidney disease, n	14 (21.2%)
Atrial fibrillation, n	10 (15.2%)
Ischemic heart disease, n	9 (13.6%)
Maximal respiratory support during hospitalization	
No respiratory support, n	19 (28.7%)
Low-flow oxygenation, n	32 (48.5%)
High-flow oxygenation, n	1 (1.5%)
Noninvasive ventilation, n	4 (6.1%)
Invasive mechanical ventilation, n	10 (15.2%)
Outcomes	
ICU admission or transfer, n	16 (24.2%)
Discharge, n	54 (81.8%)
Transfer to another hospital, n	6 (9.1%)
Death, n	6 (9.1%)
Chest CT	
CT-1[b], n (%)	19 (28.7%)
CT-2[b], n (%)	30 (45.5%)
CT-3[b], n (%)	14 (21.2%)
CT-4[b], n (%)	3 (4.5%)
Laboratory data	
Hemoglobin, g/L	137 [126 – 145]
Anemia, n	14 (21.2%)
WBC level × 10^9/mm^3	5.75 [4.6 – 7.8]
Leukocytosis, n (%)	3 (4.5%)
Leukopenia, n (%)	10 (15.2%)
Lymphocytes level × 10^9/L	1.2 [0.9 – 1.6]
Lymphopenia, n (%)	36 (54.5%)
Platelets level × 10^9/L	184 [144 – 231]
Thrombocytopenia, n (%)	31 (47.0%)
Serum CRP, mg/L	58 [37 – 112]
Creatinine, μmol/L	94 [79 – 120]
D-dimer, ng/mL	259 [164 – 485]

[a]All quantitative data were expressed as median, 25 and 75 percentile.
[b]CT-1: less than 25% of lung involvement on CT, CT-2: 25 - 50% of lung involvement on CT, CT-3: 50 - 75% of lung involvement on CT, CT-4: more than 75% of lung involvement on CT.
SpO_2, oxygen saturation; ICU, intensive care unit; CT, computer tomography; WBC, white blood cell count; CRP, C-reactive protein.

aureus [8]. Hughes et al. reviewed isolates by two members of the antimicrobial team to determine the clinical significance; 27 (3.2%) of 836 patients had early confirmed bacterial isolates identified (0 - 5 days after admission) [9]. Our study also emphasizes the need for a balanced interpretation of the results of PCR tests. Despite the high prevalence of bacteria DNA in respiratory samples, it was regarded as clinically significant only in selected cases.

Overuse of systemic antibiotics in patients with COVID-19 has become a great concern as it spurs resistance among bacterial pathogens. Rawson TM, et al, identified a high rate of antibiotics usage (72.0%) despite a paucity of evidence for co-infection [4]. Meta-analysis

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Table 2. Patients with bacterial co-infections

Patients	Pathogen	Comorbidities	Chest CT	Laboratory data on admission	Antibiotics use and outcome
Patient 1, 58 y, M ETA, culture, PCR	*Klebsiella pneumoniae*, *Acinetobacter banumannii*, *Pseudomonas aeruginosa*	Hypertension, stroke, left hemiplegia	Bilateral, 75% of lung involvement	WBC 11 × 10^9/L, NEUT 9.6 × 10^9/L, LYM 0.9 × 10^9/L CRP 247 mg/L	Yes Transferred to a rehabilitation center, survived
Patient 2, 91 y, F ETA, culture	*Klebsiella pneumoniae*, *Acinetobacter banumannii*	Hypertension, myocardial infarction, atrial fibrillation	Bilateral, 90% of lung involvement	LYM 0.7 × 10^9/L, CRP 180 mg/L PCT positive	Yes Death
Patient 3, 46 y, F CRS, PCR	*Klebsiella pneumoniae*	Severe anemia	Bilateral, 75% of lung involvement	WBC 12.0 × 10^9/L, NEUT 11.0 × 10^9/L, LYM 0.7 × 10^9/L CRP 139 mg/L	Yes Discharge
Patient 4, 73 y, M CRS, PCR	*Streptococcus pneumoniae*	Hypertension, myocardial infarction, type 2 diabetes	Bilateral, 75% of lung involvement	WBC 11.2 × 10^9/L, NEUT 9.9 × 10^9/L, LYM 0.5 × 10^9/L CRP 144 mg/L	Yes Death
Patient 5, 64 y, M CRS, PCR	*Streptococcus pneumoniae*, *Acinetobacter banumannii*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*	Hypertension, morbid obesity	Bilateral, 80% of lung involvement	WBC 16.3 × 10^9/L[a]	Yes Transferred to another hospital, survived

[a]Leukocytosis developed on the 2nd day of admission.
CT, computer tomography; M, male; ETA, endotracheal aspirate; PCR, polymerase chain reaction; WBC, white blood cell count; NEUT, neutrophils; LYM, lymphocytes; CRP, C-reactive protein; F, female; PCT, procalcitonin; CRS, combined respiratory swab.

revealed an overall antimicrobial consumption of 68.0%, with a lower rate in high-income countries (58.0%) compared with lower and middle-income countries (89.0%) [10]. According to our data, antibiotics were used in 68.0% (46.0%, excluding azithromycin) in 2020, and in 29.0% of cases 2021 - 2022.

In conclusion, co-infection is relatively rare in COVID-19 patients. Additional examination to identify pathogens should not be performed routinely. In selected cases (for example, in patients with leukocytosis or elevated procalcitonin) before antibiotic initiation, sputum and blood culture should be collected, and urinary antigen testing, as well as PCR for viral and atypical bacterial pathogens, should be performed, if available.

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