

# Bacterial co-infections and antibiotic prescribing practice in adults with COVID-19: experience from a single hospital cluster

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## Abstract:

**Background:** Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of individuals since December 2019, resulting in significant morbidity and mortality globally. During the 1918 Influenza Pandemic, it was observed that influenza was associated with bacterial co-infections. However, empirical or prophylactic antibiotic use during viral pandemics should be balanced against the associated adverse drug events.

**Methods:** In this retrospective cohort study, we investigated bacterial co-infections in adults with COVID-19 in Hong Kong. Notably, at the time of writing this report, patients with varying disease severities were isolated in hospitals until confirmatory evidence of virological clearance or immunity was available. The study included adults with laboratory-confirmed COVID-19 admitted to a single hospital cluster between 8 January 2020 and 1 May 2020. We obtained data regarding patient demographics, clinical presentations, blood test results, treatment, and outcomes. Bacteriological profiles and risk factors for co-infections were investigated. Antibiotic prescription practices were also reviewed.

**Results:** Of the 147 patients recruited, clinical disease was suspected in 42% ( $n=62$ ) of patients who underwent testing for other respiratory infections. Notably, 35% ( $n=52$ ) of the patients were prescribed empirical antibiotics, predominantly penicillins or cephalosporins. Of these, 35% ( $n=18$ ) received more than one class of antibiotics and 37% ( $n=19$ ) received empirical antibiotics for over 1 week. Overall, 8.2% ( $n=12$ ) of patients developed bacterial co-infections since the detection of COVID-19 until discharge. Methicillin-susceptible *Staphylococcus aureus* was the most common causative pathogen identified. Although 8.2% ( $n=12$ ) of patients developed hypoxia and required oxygen therapy, no mortality was observed. Multivariate analysis showed that pneumonic changes on chest radiography at the time of admission predicted bacterial co-infections.

**Conclusion:** These findings emphasise the importance of judicious administration of antibiotics throughout the disease course of COVID-19 and highlight the role of antimicrobial stewardship during a pandemic.

**Keywords:** antibiotics, antimicrobial stewardship, bacterial co-infection, COVID-19, SARS-CoV-2

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## Introduction

### Background

A novel strain of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of a cluster

of viral pneumonia cases in December 2019 in Wuhan in Hubei Province of China. The disease was later named coronavirus disease 2019 (COVID-19). SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus that belongs to the same family as the severe acute respiratory

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syndrome-related coronavirus and the Middle East respiratory syndrome coronavirus, which caused large outbreaks in Hong Kong in 2003 and in South Korea in 2015, respectively. To date, COVID-19 has affected millions of individuals globally, and mortality rates continue to increase. The 1918 Influenza Pandemic was the most severe pandemic in recent history that similarly swept the globe. At that time, it was observed that influenza infections were associated with bacterial co-infections,<sup>1,2</sup> and several studies performed during the pandemic (H1N1) 2009 and seasonal influenza episodes corroborated these findings.<sup>3–5</sup> Secondary bacterial infections often complicate the course of a viral infection, leading to a further increase in morbidity and mortality.<sup>1,6</sup>

Currently, specific antiviral therapeutic agents against COVID-19 remain investigational. Remdesivir is approved only for emergency use, and its distribution is controlled. In contrast, antibiotics are readily available for treatment of secondary bacterial infections. Nevertheless, empirical or prophylactic use of antibiotics should be balanced with adverse drug events at all times. These adverse drug events such as *Clostridioides difficile* infections and selection of drug-resistant organisms complicate the control of the pandemic. Limited information is available regarding secondary bacterial co-infections in COVID-19; most existing literature focuses on patients with severe disease. The ongoing COVID-19 pandemic necessitates treatment based on the principles of antimicrobial stewardship. This study provides useful data on bacterial co-infections and antibiotic prescription practices across a spectrum of disease severity in patients with COVID-19.

#### *Coronavirus disease 2019 (COVID-19) in Hong Kong*

Since 8 January 2020, under the Prevention and Control of Disease Ordinance, the Centre for Health Protection of the Department of Health has listed COVID-19 as a statutory notifiable infectious disease to enhance surveillance of this public health threat. Several measures including early testing, health quarantine arrangements for asymptomatic inbound travellers, and hospital admission screening targeted at vulnerable groups have been implemented to minimise the risk of community outbreaks. In Hong Kong, as required by the law, individuals with COVID-19 infections are placed under isolation under the direction of the health officer until they are deemed

non-infectious. At the time of writing this report, isolation precautions are discontinued under the following circumstances: (i) 10 days after disease onset (or since collection of the first positive sample in those who were asymptomatic throughout the disease course); (ii) afebrile status with improved clinical condition and; (iii) two clinical specimens of the same test type showing negative results by real-time polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 performed at an interval of at least 24 h, or positive test results for SARS-CoV-2 antibody before discontinuation of isolation.

On 14 June 2020, 1109 confirmed cases of COVID-19 were recorded in Hong Kong. More than 50% of these were imported cases or were epidemiologically linked with imported cases. All patients were isolated in public hospitals belonging to seven hospital clusters until they met discharge criteria. Among these, four patients died. Case clusters have been observed at public venues, travel tours, and recreational premises, including large outbreaks (with 10 or more cases) observed in bars and music bands, a Buddhist worship hall, and a wedding party.

## Methods

### *Study design and patient population*

This retrospective cohort study investigated bacterial co-infections, associated risk factors, and clinical outcomes in adults with COVID-19 in Hong Kong; at the time of writing this report, patients with varying disease severities were isolated in hospitals until confirmatory evidence of virological clearance or immunity was available. Antibiotic prescription practices used in patients with a known diagnosis of COVID-19 were also investigated. The study was performed across two acute non-teaching hospitals in the Kowloon East Cluster, which includes approximately 2200 hospital beds and serves approximately 15% of the population in Hong Kong. The study was approved by the Research Ethics Committee of Kowloon Central and Kowloon East clusters (Ref.: KC/KE-20-0167/ER-2). Informed consent was waived in view of the retrospective nature of the study.

Based on data obtained from the Laboratory Information System, we recruited patients aged 18 years or over with laboratory-confirmed COVID-19 (defined as having a clinical specimen

showing positive results for the SARS-CoV-2 nucleic acid on RT-PCR testing) admitted to the United Christian Hospital and Tseung Kwan O Hospital between 8 January 2020 and 1 May 2020 and followed-up until 1 June 2020. Exclusion criteria were as follows: only radiological evidence of pneumonia or epidemiological association with a confirmed case of COVID-19 but without or inconclusive laboratory test results for the SARS-CoV-2 nucleic acid by RT-PCR assay, and unavailability of clinical data in the electronic patient record system.

### Microbiological evaluation

Nasopharyngeal, sputum, or tracheal specimens were examined for the SARS-CoV-2 nucleic acid in a local laboratory. RNA isolation from clinical specimens was performed using either NUCLISENS® easyMAG® (bioMérieux) or MagNA Pure 96 System (Roche Diagnostics GmbH) based on the manufacturer's instructions. RT-PCR amplification was performed using the LightMix Modular SARS and Wuhan CoV E-gene kit (TIB-Molbiol) based on the assay protocol with an amplification cycle of 45. Cycle threshold (Ct) values, which were inversely proportional to the viral loads, were reported. Detection of SARS-CoV-2 was confirmed by the Public Health Laboratory Centre, the centralised laboratory of Hong Kong. The following tests were included in the investigation panel for other respiratory infections: blood samples for bacterial culture, sputum for bacterial culture, urine antigen test for *Legionella pneumophila* and *Streptococcus pneumoniae*, and multiplex PCR assay (BioFire® FilmArray® respiratory panel and Pneumonia Panel) for simultaneous detection of respiratory viral and bacterial pathogens, depending on the specimen type. Sputum was not processed for culture in samples in which the number of squamous epithelial cells were >10 cells per low-power field unless the white blood cell (WBC) count was ≥25 cells per low-power field.

### Data collection and definition

Medical records from the date of admission to discharge were obtained from the electronic patient record system. Demographic and clinical data were analysed. The Charlson comorbidity index (CCI) was calculated for stratification of the comorbidity burden. Chest radiographs obtained on admission, showing pneumonic changes (based on the attending physician's

interpretation) were independently evaluated by another physician. Chest radiographs were meticulously evaluated for pneumonic features, including pulmonary infiltrates, bronchopneumonia, and consolidation. Chest radiographs considered to have pneumonic changes by both physicians were deemed abnormal to minimise inter-observer variation. We obtained Ct values of the respiratory specimens that initially showed positive results for SARS-CoV-2 upon admission. Only the specimen showing the lowest Ct value was considered for analysis in patients who showed positive test results for more than one type of respiratory specimen.

We recorded details regarding bacterial co-infections, defined as laboratory-confirmed evidence of bacteria with persistent clinically compatible symptoms at the time of positive specimen collection. The collection time and bacteriological profiles of the specimens showing positive results were recorded wherever available. Early co-infections referred to co-infections detected within 48 h of admission, whereas late co-infections were defined as those with co-infections detected 48 h or more after admission. Haematological and biochemical parameters associated with infection, including the WBC count and differential, the neutrophil-to-lymphocyte ratio, and serum C-reactive protein (CRP) levels were recorded. Serum lactate dehydrogenase (LDH) and creatine kinase (CK) levels, which reflect organ injury, were also measured. We evaluated empirical antibiotic prescriptions for patients with a confirmed diagnosis of COVID-19 during hospitalisation. Information was also obtained regarding investigational therapies for COVID-19. Clinical outcomes, length of hospitalisation, and the need for intensive care admission were also recorded.

### Study outcomes

The primary outcome was bacterial co-infections throughout the disease course of COVID-19 in adults, defined as laboratory-confirmed evidence of bacteria along with clinically compatible symptoms of respiratory infections at the time of specimen collection. The secondary outcomes were the bacteriological profiles and predictors of co-infections at presentation in adults with COVID-19. We also evaluated empirical antibiotic prescription practices among adults with a known diagnosis of COVID-19 during hospitalisation.

### Statistical analysis

Categorical variables were expressed as frequencies and percentages and analysed using the chi-square or the Fisher's exact test as appropriate. Continuous variables were presented as means, medians, and interquartile ranges (IQR) and compared using Mann–Whitney *U* test. A logistic regression model was used to analyse the risk factors associated with bacterial co-infections in patients with COVID-19 at the time of presentation. Variables showing *p*-values <0.2 on univariate analyses were subjected to multivariate logistic regression analysis. All statistical analyses were performed using the IBM® SPSS® Statistics for Windows software, version 22.0 (SPSS, Chicago, Illinois, USA). Two-sided *p*-values <0.05 were considered statistically significant.

## Results

### Demographics and clinical characteristics

We investigated 147 adults with laboratory-confirmed COVID-19. Table 1 lists the baseline patient demographics and clinical characteristics. The study included over 50% men, and most patients (76%) were Chinese. The median patient age was 36 years (IQR 24–54 years, range 18–71 years). Approximately 80% of the patients had a low comorbidity burden (CCI score 0–1: 79%; score 2–4: 18%; score ≥5: 3%). Approximately half of the patients (48%) presented with fever, similar to the incidence of cough and shortness of breath (47%). Diarrhoea was observed in 15% of patients on admission. Oxygen therapy was administered to 12 patients (8%) for hypoxia during hospitalisation. Chest radiography performed at the time of admission revealed pneumonic changes in approximately 25% of patients.

With regard to laboratory findings, the median Ct value of respiratory specimens that initially showed positive results for SARS-CoV-2 was 25.9 (IQR 20.7–32.6) across the hospitals included in the study. Routine blood tests results showed a normal WBC count (median  $5.6 \times 10^9/\text{L}$ , IQR  $4.4\text{--}7.0 \times 10^9/\text{L}$ ) and absolute neutrophil count (median  $3.8 \times 10^9/\text{L}$ , IQR  $2.5\text{--}5.0 \times 10^9/\text{L}$ ) in most patients. The median absolute lymphocyte count was  $1.3 \times 10^9/\text{L}$  (IQR  $0.9\text{--}1.8 \times 10^9/\text{L}$ ). The neutrophil-to-lymphocyte ratio, a biomarker that indicates the level of immune response to systemic inflammation,

showed a median value of 2.7 (IQR 1.8–4.1). Other inflammatory biomarkers, including CRP, LDH, and CK are shown in Table 1. Most patients had relatively normal readings.

### Treatment and clinical outcome

Management of patients with COVID-19 in Hong Kong is in accordance with the recommendation of the Hospital Authority Task Force, which is based on evidence extrapolated from the relevant coronavirus research, expert opinions, and local availability of therapeutic options. Interferon beta-1b, lopinavir–ritonavir, and ribavirin were the recommended drugs of choice with early initiation advocated by the hospitals included in this study. Approximately 48% of patients received interferon-based antiviral therapy and 33% received dual antiviral therapy comprising a combination of lopinavir–ritonavir and ribavirin.

With regard to antibiotic use, 35% ( $n=52$ ) of patients were administered antibiotics despite a confirmed diagnosis of COVID-19, commonly the penicillins or the cephalosporins. Approximately 35% of these patients received more than one class of antibiotics. Antibiotics were administered for more than a week to 19 patients (37%), despite negative culture test results during antibiotic treatment. No antibiotic-associated adverse events were observed.

The median length of hospitalisation was 21 days (IQR 13–29 days). Favourable clinical outcome was observed in most cases; only three patients (2%) required intensive care admission, and no mortality was observed.

### Bacterial co-infections

Of the 147 patients investigated, 62 patients (42%) showed clinically suspected infection and underwent subsequently investigation panel tests for respiratory bacterial co-infections. Among these, bacterial pathogens were detected in 12 patients (8.2% of the study population). Table 2 shows data of bacterial co-infections. Notably, 67% of patients showed positive test results for bacterial pathogens late during hospitalisation (i.e. ≥48 h after admission). Methicillin-susceptible *S. aureus* was the most common causative bacteria pathogen ( $n=8$ , 67%), followed by *Haemophilus influenzae* ( $n=3$ , 25%); both *H.*

**Table 1.** Baseline demographics and clinical characteristics of the study patients.

Characteristics	Value ( <i>n</i> = 147)
<b>Demographics</b>	
Male sex, <i>n</i> (%)	85 (58)
Ethnicity, <i>n</i> (%)	
Chinese	112 (76)
Non-Chinese	35 (24)
Age, year, median (IQR)	36 (24–54)
<b>Charlson Comorbidity Index, <i>n</i> (%)</b>	
0–1	117 (79)
2–4	26 (18)
≥5	4 (3)
<b>Symptoms at presentation, <i>n</i> (%)</b>	
Fever	70 (48)
Cough/shortness of breath	69 (47)
Diarrhoea	22 (15)
<b>Oxygen therapy required, <i>n</i> (%)</b>	12 (8)
<b>Pneumonic changes on chest radiography, <i>n</i> (%)</b>	37 (25)
<b>Laboratory findings</b>	
Ct value of respiratory specimens first tested positive for SARS-CoV-2, median (IQR)	25.9 (20.7–32.6)
Baseline blood test, median (IQR) <sup>†</sup>	
White blood cells ( $\times 10^9/L$ )	5.6 (4.4–7.0)
Absolute neutrophil count ( $\times 10^9/L$ )	3.8 (2.5–5.0)
Absolute lymphocyte count ( $\times 10^9/L$ )	1.3 (0.9–1.8)
Neutrophil-to-lymphocyte ratio	2.7 (1.8–4.1)
C-reactive protein (mg/L)	1.9 (0.4–7.6)
Lactate dehydrogenase (IU/L)	169 (151–213)
Creatine kinase (IU/L)	84 (57–120)
Investigated for other respiratory infections, <i>n</i> (%)	62 (42)
Tested positive for bacterial pathogens	12 (8)
<b>Treatment</b>	
Investigational therapies for COVID-19, <i>n</i> (%)	
No	16 (11)
Lopinavir–ritonavir	12 (8)
Lopinavir–ritonavir + Ribavirin	48 (33)
Interferon-based therapy	71 (48)

(Continued)



**Table 1.** (Continued)

Characteristics	Value (n = 147)
Use of empirical antibiotics, n (%)	52 (35)
Use of more than one class of empirical antibiotics, n (%)	18 (35)
Class of empirical antibiotics, n (%)	
Penicillins & cephalosporins	46 (88)
Tetracyclines	14 (27)
Quinolones	3 (6)
Macrolides	3 (6)
Duration of empirical antibiotics	
Length of course of empirical antibiotics, days – median (IQR)	7 (5–12)
Length of course of empirical antibiotics for >7 days, n (%)	19 (37)
<b>Clinical Outcome</b>	
Length of hospitalisation, days – median (IQR)	21 (13–29)
Need for intensive care admission, n (%)	3 (2)
Death, n (%)	0 (0)
†Four patients had no white blood cell count differential performed on admission. Ct, cycle threshold; IQR, interquartile range.	

**Table 2.** Findings of the 12 patients with COVID-19 detected to have bacterial co-infections.

Characteristics	Value (n = 12)
<b>Timing of co-infection detected, n (%)</b>	
Early co-infection (within 48 h of admission)	4 (33)
Late co-infection (48 h or more after admission)	8 (67)
<b>Bacterial pathogen,<sup>†</sup> n (%)</b>	
<i>Haemophilus influenzae</i>	3 (25)
Methicillin-susceptible <i>Staphylococcus aureus</i>	8 (67)
<i>Pseudomonas aeruginosa</i>	1 (8)
<i>Streptococcus pneumoniae</i> (by urine antigen)	1 (8)

<sup>†</sup>Both *Haemophilus influenzae* and methicillin-susceptible *Staphylococcus aureus* were isolated from sputum cultures in one patient.

*influenzae* and methicillin-susceptible *S. aureus* were isolated from sputum culture in one patient. Pneumococcal antigen positivity on urine testing was observed in one patient.

### *Risk factors for bacterial co-infections*

Table 3 presents a comparison of patients with COVID-19 with and without bacterial co-infections. Bacterial co-infections occurred more commonly in men and in older patients; however, the difference was not statistically significant. Ethnicity did not appear to affect the development of bacterial co-infections. CCI  $\geq 2$  was more commonly observed in patients with bacterial co-infections (41.7% versus 18.5%). Presence of fever at presentation or the need for oxygen therapy during hospitalisation did not significantly differ between patients with and without bacterial co-infections. Patients with pneumonic changes on chest radiography showed a significantly higher probability of positive test results for bacterial pathogens on subsequent investigations for other respiratory infections.

With regard to laboratory findings, no statistically significant intergroup difference was observed in the Ct values of respiratory specimens that initially showed positive results on SARS-CoV-2 testing. Co-infected patients had comparable absolute neutrophil and lymphocyte counts.

Among all the inflammatory biomarkers evaluated in the study, the neutrophil-to-lymphocyte ratio ( $p=0.044$ ) and serum LDH ( $p=0.033$ ) levels were significantly higher in patients with bacterial co-infections.

Multivariate logistic regression analysis (Table 4) showed that pneumonic changes on chest radiography performed upon admission was the only statistically significant clinical predictor of bacterial co-infections (odds ratio 6.14, 95% confidence interval 1.15–32.65,  $p=0.03$ ).

#### *Clinical outcomes in patients with and without bacterial co-infections*

Patients with co-infections showed a significantly longer length of hospitalisation (Table 3,  $p=0.016$ ). No mortality occurred in either study group; however, we observed a significantly higher incidence of intensive care admissions in patients with bacterial co-infections, although the sample size was relatively small (1/12 *versus* 2/135) and not statistically significant ( $p=0.227$ ).

#### **Discussion**

Currently, co-infection remains an underexplored area associated with the COVID-19 pandemic. A multicentre study that reported the clinical course of adults with COVID-19 who showed definite outcomes in Wuhan, China observed secondary infections in 1% of survivors and in 50% of those who died.<sup>7</sup> Chen *et al.*<sup>8</sup> and Huang *et al.*<sup>9</sup> reported secondary infection rates of 5.1% and 9.8%, respectively, in patients with COVID-19 who presented with features of pneumonia. Another retrospective cohort study performed by Zhang *et al.*<sup>10</sup> reported bacterial co-infections in 7.7% of patients with COVID-19, which is comparable with our findings. Notably, a significantly higher rate (25%) of bacterial co-infections was observed among those with severe diseases. Based on pathogen-specific RT-PCR assays, Zhu *et al.* reported a significantly high bacterial co-infection rate of 91.8% among critical ill patients or in those with severe disease.<sup>11</sup> Patients with severe diseases were more likely to receive interventional care such as mechanical ventilation and consequently showed a higher rate of complications, including superimposed bacterial infections. We observed a bacterial co-infection rate of 8% in

our cohort of hospitalised patients with COVID-19, which included patients with varying disease severities.

Methicillin-susceptible *S. aureus* was the predominant co-infecting bacterial pathogen in our study, followed by *H. influenzae* and other typical respiratory pathogens; this observation was similar to the findings reported by previous studies that investigated influenza-associated bacterial pneumonia.<sup>12,13</sup> A report on a previous coronavirus outbreak in 2003 also suggested that patients were predisposed to secondary infection with *S. aureus*.<sup>14</sup> Limited data are available in the literature with regard to the microbiology of bacterial co-infection in patients with COVID-19. A French case report described a previously healthy man in his thirties with PCR-confirmed SARS-CoV-2 infection who presented with pleuropneumonia induced by Pantone–Valentine leukocidin-secreting methicillin-susceptible *S. aureus*.<sup>15</sup> A retrospective cohort study performed by Zhu *et al.* reported that *S. pneumoniae* was co-isolated in nearly 60% of patients with COVID-19, and 94.2% of patients were co-infected with more than one pathogen.<sup>11</sup> Multidrug-resistant organisms, including methicillin-resistant *S. aureus*, carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*, extended-spectrum  $\beta$ -lactamase-positive *K. pneumoniae* and *Pseudomonas aeruginosa* have also been isolated in critically ill patients with COVID-19.<sup>10,16,17</sup> Per policy guidelines, all infected patients are isolated in hospital facilities across Hong Kong regardless of disease severity; therefore, nosocomial pneumonia is a theoretical concern in view of prolonged hospitalisation. Nonetheless, bacteriological analysis revealed that most patients did not co-infect with gram-negative bacteria, which are commonly associated with hospital-acquired infections.<sup>18–20</sup> Multidrug-resistant pathogens were not isolated in any infected patient in our cohort. Resources optimisation is a priority for the authorities in Hong Kong to ensure a high standard of care to protect patients and healthcare workers as part of infection containment measures. Patients with laboratory-confirmed COVID-19 are hospitalised in isolation wards with adequate ventilation and distancing, and personnel with infection control training are designated to provide patient care in such settings. Traffic around infected patients is minimised with strict enforcement of infection control measures such as hand hygiene and the use of personal protective equipment by staff.

**Table 3.** Characteristics of patients with COVID-19 with and without bacterial co-infections.

Characteristics	Patients with no bacterial co-infection (n = 135)	Patients with bacterial co-infection (n = 12)	p-value <sup>‡</sup>
<b>Demographics</b>			
Male sex, n (%)	76 (56.3)	9 (75.0)	0.196
Ethnicity			1.000
Chinese, n (%)	103 (76.3)	9 (75.0)	
Non-Chinese, n (%)	32 (23.7)	3 (25.0)	
Age – median (IQR)	35 (24–50)	49 (30–61)	0.133
Charlson Comorbidity Index, n (%)			0.094
0–1	110 (81.5)	7 (58.3)	
2–4	21 (15.5)	5 (41.7)	
≥5	4 (3.0)	0 (0)	
<b>Symptoms at presentation, n (%)</b>			
Fever	62 (45.9)	8 (66.7)	0.166
Cough/shortness of breath	63 (46.7)	6 (50.0)	0.825
Diarrhoea	21 (15.6)	1 (8.3)	0.694
Oxygen therapy required, n (%)	9 (6.7)	3 (25.0)	0.060
Pneumonic changes on chest radiography, n (%)	29 (21.5)	8 (66.7)	0.002
<b>Laboratory Findings</b>			
Ct value of respiratory specimens first tested positive for SARS-CoV-2 – median (IQR)	26.3 (20.9–32.6)	22.92 (19.1–29.2)	0.233
Baseline blood test – median (IQR)			
White blood cells (×10 <sup>9</sup> /L)	5.50 (4.40–7.00)	6.15 (4.45–8.20)	0.398
Absolute neutrophil count (×10 <sup>9</sup> /L)	3.80 (2.40–4.90)	3.85 (3.00–6.85)	0.190
Absolute lymphocyte count (×10 <sup>9</sup> /L)	1.30 (1.00–1.80)	1.20 (0.75–1.35)	0.066
Neutrophil-to-lymphocyte ratio	2.60 (1.65–3.71)	4.01 (2.30–7.50)	0.044
C-reactive protein (mg/L)	1.80 (0.40–6.00)	14.25 (0.1–93.10)	0.126
Lactate dehydrogenase (IU/L)	168 (151–206)	212 (165.5–366.5)	0.033
Creatine kinase (IU/L)	84 (57–122)	79 (56–102)	0.871
<b>Clinical Outcomes</b>			
Length of hospitalisation, days – median (IQR)	20 (13–28)	27 (22–36)	0.016
Need for intensive care admission, n (%)	2 (1.5)	1 (8.3)	0.227
<sup>‡</sup> p-values were calculated by the chi-square test or the Fisher's exact test as appropriate for nominal data, Mann–Whitney U test for continuous data. Ct, cycle threshold; IQR, interquartile range.			



Committed adherence to these complementary measures has contributed, at least to some extent, as an important protective factor against the risk of hospital-acquired pneumonia and multidrug-resistant organisms in patients with COVID-19.

It is well known that isolation of microorganisms from respiratory specimens may not essentially reflect infection; differentiating between colonisation and co-infection is challenging. Clinical correlation is important in decision-making regarding the initiation of and the choice of antibiotics. Serum procalcitonin level serves as a useful adjunct to guide the initiation of antibiotic therapy in patients with lower respiratory tract infections.<sup>21–23</sup> However, data regarding serum procalcitonin levels were not available in our study population. A meta-analysis of patients with COVID-19 reported that high serum procalcitonin levels were associated with greater severity of disease;<sup>24</sup> however, details regarding the association between serum procalcitonin levels and the detection of bacterial co-pathogens were unavailable in the study.

In our study, pneumonic changes on chest radiography were significant predictors of bacterial co-infections among patients with COVID-19. This finding was consistent with the recommendations of the National Institute for Health and Care Excellence guidelines, which emphasise the role of chest imaging, specifically the importance of localised chest findings, in decision-making for empirical antibiotic administration.<sup>25</sup> The World Health Organization guidelines also suggest that in addition to clinical symptoms, chest imaging is useful for the identification of pulmonary complications and for monitoring the disease course in patients with COVID-19.<sup>26</sup>

In our cohort, only 25% of the patients showed abnormality on chest radiography, and 8% of these patients developed hypoxia; however, a significantly larger percentage of patients were treated with empirical antibiotics, even after the diagnostic confirmation of COVID-19. Driven by a fear of the unknown, physicians are often compelled to prescribe antibiotics based on an optimistic presumption that this approach could alter the course of this viral disease. A hospital in New York reported empirical antibiotics use among 79% of patients hospitalised for COVID-19,<sup>27</sup> and early studies from China have reported that over 90% of patients received empirical antibiotics.<sup>7,28,29</sup> Injudicious

**Table 4.** Multivariate logistic regression analysis for bacterial co-infections in patients with COVID-19.

Variable	Odds ratio	95% CI	p-value
Male sex	2.23	0.46–10.75	0.32
Age	1.01	0.93–1.09	0.90
Charlson Comorbidity Index	0.77	0.31–1.92	0.77
Fever at presentation	1.74	0.43–7.06	0.44
Oxygen therapy required	0.55	0.04–5.78	0.55
Pneumonic changes on chest radiography	6.14	1.15–32.65	0.03
Absolute neutrophil count	1.15	0.54–2.43	0.71
Absolute lymphocyte count	0.60	0.06–6.45	0.68
C-reactive protein	1.00	0.99–1.02	0.69
Neutrophil-to-lymphocyte ratio	0.92	0.48–1.77	0.80
Lactate dehydrogenase	1.00	1.00–1.01	0.41

antibiotic prophylaxis or therapy should be discouraged for the management of COVID-19 associated with mild symptoms, particularly in patients without radiological evidence of pneumonia. Inappropriate antibiotic prescriptions are invariably associated with a potential increase in antimicrobial resistance, which can result in wide-ranging long-term impacts that extend way beyond the current pandemic. Therefore, effective implementation of the antibiotic stewardship programme is paramount in this time of uncertainty. Several authors had expressed this concern and support integration of an antibiotic stewardship programme into pandemic management, as well as the adoption of evidence-based practice.<sup>30–35</sup> In our study, 90% of patients received investigational therapeutic agents for the management of COVID-19; however, 35% of patients received antibiotics. The relatively low percentage of antibiotic use in our study could be partly attributed to the active participation of specialists from infectious disease and microbiology in the routine care of patients with COVID-19. These experts also oversee the antimicrobial stewardship programme previously established in the study hospitals.

Our retrospective cohort study has several limitations. All patients with COVID-19 underwent chest radiography as part of the investigations

performed upon admission; however, not all patients received microbiological investigations for bacterial pathogens. Therefore, it is possible that bacteriological analysis was not performed in patients with relatively mild symptoms. Notably, a substantial number of patients were administered empirical antibiotics, which may have resulted in inaccurate findings. The interpretation of chest radiographs was not standardised, and inter-observer inconsistency in the findings cannot be excluded. Patients' symptoms reported could have been affected by information bias; also, symptoms were significantly affected by the accuracy of patient medical records. In addition to serum procalcitonin measurement, some parameters of clinical importance, such as the date of symptom onset, were not analysed owing to data unavailability. Heterogeneity among patients is an important issue, and it may not be possible to adjust for some confounders in the multivariate analysis. Additionally, owing to the retrospective design of the study, a causal association between variables could not be established.

Our study differs from other existing epidemiologic studies on COVID-19 owing to the unique public health measures adopted in Hong Kong. Most other studies have included a significant percentage of patients who were hospitalised for severe disease. Based on the experience gained from the SARS outbreak in 2003, active SARS-CoV-2 testing and strict containment strategies along with case isolation are advocated in Hong Kong to address the issue associated with COVID-19 pandemic. Our study included patients across a wide spectrum of disease severity, and all patients were monitored in the hospital over the entire disease course until clinical recovery and a laboratory-confirmed non-infectious status. This is clear from the fact that our study cohort included a significantly lesser number of patients with severe disease, who were those diagnosed with hypoxia or required oxygen therapy, and/or intensive care admission during the disease course. No mortality was observed in the study. Our study findings serve as a valuable guide that offers a deeper understanding of the complete picture of bacterial co-infection in COVID-19 across the entire affected population and in terms of the longitudinal disease course. To our knowledge, this report is the first of its kind that describes patient trends throughout the disease course in the aforementioned containment setting.

Currently, COVID-19 remains an ongoing public health crisis, and the future of this pandemic remains largely unknown. Based on our findings, co-existing bacterial infections are uncommon in the COVID-19 infected population considered in its entirety. Routine use of empirical antibiotics should be discouraged. Pneumonic changes on chest radiography, together with clinically compatible symptoms may justify antibiotic administration as part of an antimicrobial stewardship programme for patients with COVID-19. Evidence-based care bundles and effective multidisciplinary collaborations are essential to improve disease outcomes; however, these should be guided by the fundamental principles of standard patient care. Further studies are warranted to identify the unknown facets of this unprecedented infective threat of the century. Complete and correct knowledge is crucial to contain not only the disease but also panic and irrationality associated with the pandemic.

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### Author contribution statement

This manuscript is submitted with the knowledge and on behalf of the co-authors. All the listed co-authors have made substantial contributions to the manuscript and approved the final version to be published. LS-KC conceived, performed the analysis and wrote the manuscript for submission. SK-YC designed, drafted the analysis, and critically revised the manuscript for important intellectual content. EY-KT and SW-CT contributed to acquisition of data and substantial revision of the manuscript. IY-FL participated in the collection of the data. BK-CW participated in the collection of the data and performed the data analysis. KS-CF designed and supervised the analysis.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

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### Data availability statement

Data analysed during the current study are available from the corresponding author on reasonable request.

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