An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London

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Received 1 July 2020; accepted 22 October 2020

Objectives: To describe the prevalence and nature of bacterial co-infections in COVID-19 patients within 48 hours of hospital admission and assess the appropriateness of empirical antibiotic treatment they received.

Methods: In this retrospective observational cohort study, we included all adult non-pregnant patients who were admitted to two acute hospitals in North West London in March and April 2020 and confirmed to have COVID-19 infection within 2 days of admission. Results of microbiological specimens taken within 48 hours of admission were reviewed and their clinical significance was assessed. Empirical antibiotic treatment of representative patients was reviewed. Patient age, gender, co-morbidities, inflammatory markers at admission, admission to ICU and 30 day all-cause in-hospital mortality were collected and compared between patients with and without bacterial co-infections.

Results: Of the 1396 COVID-19 patients included, 37 patients (2.7%) had clinically important bacterial co-infection within 48 hours of admission. The majority of patients (36/37 in those with co-infection and 98/100 in selected patients without co-infection) received empirical antibiotic treatment. There was no significant difference in age, gender, pre-existing illnesses, ICU admission or 30 day all-cause mortality in those with and without bacterial co-infection. However, white cell count, neutrophil count and CRP on admission were significantly higher in patients with bacterial co-infections.

Conclusions: We found that bacterial co-infection was infrequent in hospitalized COVID-19 patients within 48 hours of admission. These results suggest that empirical antimicrobial treatment may not be necessary in all patients presenting with COVID-19 infection, although the decision could be guided by high inflammatory markers.

Introduction

COVID-19 is a newly emerged viral infectious disease caused by SARS-CoV-2. It was first identified in Wuhan, China in December 2019.1 Since it was identified, it has spread worldwide, resulting in a pandemic and bringing challenges to healthcare systems everywhere. The UK has been one of the most affected countries, with >250000 cases claiming 38000 lives by the end of May 2020.2 There have been numerous reports describing the epidemiological and clinical characteristics of COVID-19. Drugs with therapeutic efficacy are only just beginning to be identified and vaccines are still at an experimental stage.

Early reports from China showed that the vast majority of patients received antibiotic therapy: a multicentre study in Wuhan reported 95% of patients received antibiotic therapy.3 Reports from the UK also showed >80% of patients received antibiotic treatments.4 At present, the prevalence of bacterial co-infection in COVID-19 patients at time of admission is not well understood.5-8 Given the importance of antimicrobial stewardship in preventing the emergence of antimicrobial resistance, it is important to evaluate the prevalence and nature of bacterial co-infection to guide appropriate empirical antibiotic treatment at the time of presentation.

North West London was a focus of the COVID-19 pandemic and one of the most affected regions in the UK.9 Northwick Park Hospital (NPH) and Ealing Hospital (EH) are two acute hospitals in this area, mainly serving the boroughs of Brent, Harrow and Ealing.
The three boroughs cover a population of one million and are some of the most ethnically diverse local authorities in the UK. Black, Asian and other minority ethnicity (BAME) constitutes 51% of population in Ealing, 57.8% population in Harrow and 63.7% population in Brent. There are areas of significant deprivation in the three boroughs as well.\(^\text{10}\)

The pandemic in North West London started at the beginning of March. Admission to NPH and EH peaked in early April (up to 65 patients a day) and fell to <3 patients per day by the end of April.\(^\text{13}\) Many patients with suspected COVID-19 infection admitted to these hospitals were investigated for the presence of bacterial infections as they presented with septic features. The overwhelming majority were prescribed empirical antimicrobial treatment, despite little evidence of a bacterial cause of infection. A description of the prevalence and nature of bacterial co-infections and appropriateness of empirical antibiotic treatment is likely to provide important information regarding the need for and choice of the antibiotics. This will be particularly useful for antimicrobial stewardship and conservation of resources.

We have therefore performed a retrospective analysis of the prevalence and characteristics of bacterial co-infection in patients with confirmed COVID-19 infection who presented to our hospital in March and April 2020.

**Patients and methods**

**Study design**

This retrospective observational cohort study was conducted in Northwick Park Hospital (NPH) and Ealing Hospital (EH) in North West London.

**Subjects**

We included patients admitted to NPH and EH in the period between 1 March and 30 April 2020 who were confirmed to have COVID-19 infection within 48 h of admission. Patients younger than 18 years of age and pregnant women were excluded from the study.

Nasopharyngeal or lower respiratory tract specimens were used to confirm the presence of SARS-CoV-2 infection. These specimens were tested using RT-PCR assay for SARS-CoV-2 using National Health Service England (NHSE) approved standard operating procedures.\(^\text{12}\) Specimens were sent to Public Health England (Colindale, UK) before 13 March 2020 and to The Doctors Laboratory (London, UK) from 13 March onwards.

**Data collection and analysis**

A list of patients who had SARS-CoV-2 tests during the study period was obtained from the laboratory information management system Winpath (CliniSys, UK). Patients with positive tests within 48 h of admission were selected for further analysis.

Relevant clinical information of these patients was retrieved from their medical records. Clinical information collected included patient age, gender, co-morbidities, inflammatory markers at the time of admission, admission to ICU and 30-day all-cause in-hospital mortality. Mortality data was not collected for those patients transferred to other hospitals.

Results of microbiological specimens taken within 48 h of admission were reviewed. These specimens included blood, lower respiratory tract, urine and other specimens for microscopy, culture and antimicrobial susceptibility testing. All specimens were processed using laboratory standard operation procedures based on the UK Standards for Microbiology Investigations.\(^\text{11}\) In addition, results of urinary antigen tests for Legionella and pneumococcus were also reviewed. Legionella pneumophila serogroup 1 antigen and Streptococcus pneumoniae antigen were detected using BinaxNOW assays (Abbott, Illinios), as per the manufacturer’s instructions. Two senior consultant microbiologists reviewed the clinical significance of these test results together and reached unanimous decisions. The criteria used to assess the clinical significance included clinical information available from medical records and the likelihood of contamination or colonization based on the nature of the isolated organisms. Inflammatory markers were not taken into consideration in assessing the significance to avoid bias. Empirical antibiotic treatment at the time of admission was recorded for those with clinically significant bacterial growth and compared with the susceptibility of the bacteria identified. Appropriateness of antibiotic use was based on the antimicrobial susceptibility of bacterial isolates and clinical presentation. Clinical notes of randomly selected patients were also reviewed to assess the adherence to hospital empirical antibiotic guidelines.

Data were analysed using SPSS version 26.0. Demographic characteristics, comorbidities and inflammatory markers at the time of admission in COVID-19 patients with bacterial co-infection were compared with those without bacterial co-infection. Clinical outcomes including admission to intensive care facilities and 30-day all-cause in-hospital mortality rate was also compared. Mann-Whitney U test was used in comparing continuous data that did not follow a normal distribution. Categorical data was compared using Chi-square test. P value <0.05 was taken as level of significance. Receiver operating characteristic curves were used to examine the ability of inflammatory markers to predict bacterial co-infection.

This study was approved by the Research and Development department of North West London University NHS Trust (Register: SE20/008). Ethics approval was not necessary as it was considered as service evaluation of the treatment and care already provided. Furthermore, patients were not identified following initial data collection. All data are presented in anonymized format.

**Results**

In the study period, 2114 unique patients tested positive for SARS-CoV-2 infection. Of these, 1396 patients were included in this analysis. A total of 718 patients were excluded (295 patients did not require hospital admission, 397 patients were tested >2 days after admission, 26 patients were either <18 years old or were pregnant women).

The age of patients included in the study ranged from 19–103 years, the mean±SD age was 67.4±16.2 years. Of the 1396 patients, 64.7% were male.

Overall, 37 patients (37/1396, 2.7%) were identified to have clinically significant bacterial co-infection. Of these 37 patients, 11 had bacterial co-infection with a respiratory focus (8 patients had sputum cultures with clinically significant bacterial pathogens and 3 patients had S. pneumoniae co-infection detected by presence of urinary antigen). The remaining 26 patients had co-infections secondary to urinary tract infection, skin and soft tissue infection (included wound site infection and abscess), line-associated infection or unspecified source. A list of the bacterial pathogens and empirical antibiotics received by patients on admission is shown in Table 1.

**Blood cultures**

There were 969 patients (69.4%) who had blood cultures taken within 2 days of admission. Of those 969 patients, 892 (92.1%) patients had negative blood cultures. Of 77 patients with positive blood cultures, 65 (65/969, 6.7%) were likely due to contamination and only 12 (12/969, 1.2%) were suggestive of clinically significant
Table 1. Organisms isolated and susceptibility to empirical treatment received

| Patient number | Type of sample | Organisms isolated | Antibiotics received on admission | Susceptibility of isolates to empirical antibiotics received |
|----------------|----------------|--------------------|-----------------------------------|-------------------------------------------------------------|
| 1              | Blood culture  | *Escherichia coli*  | Teicoplanin and clarithromycin⁴   | No                                                          |
| 2              | Blood culture  | *Escherichia coli*  | Ceftriaxone and clarithromycin    | No                                                          |
| 3              | Blood culture  | *Klebsiella pneumoniae* | Not received (patient on palliative pathway) | Not applicable                                              |
| 4              | Blood culture⁵ | *Klebsiella variicola* | Ciprofloxacin                     | Yes                                                         |
| 5              | Blood culture  | *Proteus mirabilis* | Ceftriaxone and clarithromycin    | Yes                                                         |
| 6              | Blood culture  | *Proteus mirabilis* | Ceftriaxone and clarithromycin    | Yes                                                         |
| 7              | Blood culture  | *Proteus mirabilis* | Ceftriaxone and amikacin          | Yes                                                         |
| 8              | Blood culture  | *Proteus mirabilis* | Ciprofloxacin and amikacin        | Yes                                                         |
| 9              | Blood culture  | *Pseudomonas aeruginosa* | Co-amoxiclav and amikacin        | Yes                                                         |
| 10             | Blood culture  | *MRSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 11             | Blood culture  | *MSSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 12             | Blood culture (central line) | *Staphylococcus epidermidis* | Ceftriaxone and clarithromycin | No                                                          |
| 13             | Sputum         | *Escherichia coli (ESBL)*, *Candida albicans* | Teicoplanin and clarithromycin⁴ | Yes                                                         |
| 14             | Sputum         | *Group A Streptococcus* | Cefuroxime                        | Yes                                                         |
| 15             | Sputum         | *Haemophilus influenzae* | Cefuroxime and clarithromycin    | No                                                          |
| 16             | Sputum         | *Pseudomonas aeruginosa* | Cefuroxime and clarithromycin    | No                                                          |
| 17             | Sputum         | *MSSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 18             | Sputum         | *MSSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 19             | Sputum         | *MSSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 20             | Sputum         | *MSSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 21             | Urine (catheter) | *Caliform, Candida species* | Cefuroxime and clarithromycin    | Yes                                                         |
| 22             | Urine          | *Escherichia coli* | Co-amoxiclav and clarithromycin    | Yes                                                         |
| 23             | Urine (catheter) | *Escherichia coli* | Co-amoxiclav and clarithromycin    | Yes                                                         |
| 24             | Urine (catheter) | *Escherichia coli* | Ceftriaxone and clarithromycin    | Yes                                                         |
| 25             | Urine          | *Escherichia coli* | Piperacillin/tazobactam and gentamicin | Yes                                                         |
| 26             | Urine (catheter) | *Escherichia coli (ESBL)*, *Enterococcus faecalis* | Ceftriaxone and amikacin        | Yes                                                         |
| 27             | Urine          | *Enterococcus faecalis* | Ceftriaxone and amikacin        | Yes                                                         |
| 28             | Urine          | *Klebsiella pneumoniae* | Piperacillin/tazobactam and teicoplanin (neutropenic sepsis) | No                                                          |
| 29             | Urine          | *Klebsiella pneumoniae* | Ciprofloxacin                     | Yes                                                         |
| 30             | Urinary pneumococcal antigen test | *Streptococcus pneumoniae* | Piperacillin/tazobactam and clarithromycin | Yes                                                         |
| 31             | Urinary pneumococcal antigen test | *Streptococcus pneumoniae* | Teicoplanin and clarithromycin⁴ | Yes                                                         |
| 32             | Urinary pneumococcal antigen test | *Streptococcus pneumoniae* | Ceftriaxone and clarithromycin    | Yes                                                         |
| 33             | Eye swab       | *MSSA*              | Ceftriaxone and clarithromycin    | Yes                                                         |
| 34             | Foot ulcer swab | *Serratia species* | Benzylpenicillin, flucloxacillin and gentamicin | Yes                                                         |
| 35             | Foot ulcer swab | *MSSA*              | Ceftriaxone, clarithromycin and doxycycline | Yes                                                         |
| 36             | Psoas abscess drainage | Specimen 1: *Escherichia coli (ESBL)*, *Klebsiella oxytoca, Streptococcus anginosus, Candida species,* *Bacteroides ovatus* Specimen 2: *Granulicatella adiacens, Escherichia coli (ESBL)*, *Escherichia coli,* *anaerobe* | Piperacillin/tazobactam and clarithromycin | Yes                                                         |
| 37             | Surgical wound swab | Specimen 1: *Group A Streptococcus* Specimen 2: *Staphylococcus aureus* | Co-amoxiclav                     | Yes                                                         |

⁴History of penicillin allergy.
⁵Specimens from the same patients.
bacterial co-infections. These blood cultures were positive for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella variicola*, *Proteus mirabilis*, MRSA, MSSA and *Staphylococcus epidermidis* (Table 1). Based on clinical information and further microbiology investigations, the sources of bacteraemia were determined to be urinary tract infection for six patients and central venous access associated infection in one patient. The sources of bacteraemia in the other five patients were unclear as there was insufficient information from the clinical records and other investigations to confidently ascribe a source.

**Lower respiratory tract specimens**

Only 48 patients (3.4% of the 1396 patients) had sputum specimens analysed, 8 of which were suggestive of bacterial co-infection. The bacterial growth including *E. coli* (ESBL-producing), group A streptococcus, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (MSSA). Notably, four patients had growth of *S. aureus* and they were all deemed clinically significant based on parameters including documentation of clinical signs and radiological appearances. There were 16 additional patients with sputum culture growing *Candida* species. However, following careful review, none of the *Candida* species isolated was clinically significant. None of the patients had bronchoalveolar lavage specimens sent within 2 days of admission.

**Urine cultures**

Of the 463 patients who had their urine specimens analysed, 420 (90.7%) were negative, 27 were likely due to colonization or contamination (5.8%) and 16 (3.5%) were indicative of bacterial co-infection. The commonest bacterial co-infections were due to *E. coli* (n=6). Details of significant culture results are shown in Table 1.

**Urinary antigens**

A total of 308 patients were tested for urinary *Legionella* antigen and none was positive. Of the 296 patients who were tested for pneumococcal urinary antigens, 3 were positive and clinical features were consistent with *S. pneumoniae* co-infection. However, it is worth noting that 226 additional samples were sent for urinary atypical antigen testing (116 for *Legionella* and 110 for pneumococcal antigen testing) in mid-April but were not processed due to test reagent supply shortage.

**Specimens from other body sites**

Of the 12 patients with positive specimens sent from other body sites, 5 were of clinical significance. Two patients had significant growth from diabetic foot swabs, one patient had drainage of psoas abscess which grew a mixture of bacterial and *Candida* species, one patient with an eye swab indicative of bacterial conjunctivitis and one patient had surgical site wound swabs which grew Group A streptococcus and *S. aureus* (Table 1).

**Empirical antibiotic therapy**

Empirical antibiotic treatment guidelines for community-acquired pneumonia used in our hospitals during the study period were guided by local prevalence of antimicrobial resistance and the availability of antibiotics (Table 2).

Empirical antibiotics received by patients with bacterial co-infection are listed in Table 1. All patients with bacterial co-infection received antibiotics except for one patient who was on the end-of-life-care pathway. Twenty-one (56.8%) patients received empirical antibiotics as per guidelines while the rest had either escalated antibiotics (e.g. piperacillin/tazobactam in critically ill patients) or targeted antibiotics due to concerns regarding other sources of infection.

We randomly selected 100 patients from those without bacterial co-infection and recorded their empirical antibiotic prescriptions. We found that nearly all patients (98%) received antibiotics at time of admission. Out of the 100 patients, 73 received antibiotics as per guidelines. A further 10 patients received cefoxime/ceftriaxone only as the treating team was not concerned about atypical causes of pneumonia. Five patients received co-amoxiclav. The remaining patients received coverage for suspected other infection sources or had escalated therapy as the patients were critically unwell.

**Comparison of characteristics of COVID-19 patients with and without bacterial co-infection**

A comparison between COVID-19 patients with and without bacterial co-infection is shown in Table 3.

There was no significant difference between patients with or without bacterial co-infection in gender, age or presence of underlying comorbidities (Table 3). Patients with bacterial co-infections had significantly higher white cell count, neutrophil count and CRP (Table 4). However, lymphocyte count was not significantly

**Table 2. Empirical antibiotic treatment guidelines used in the study hospitals**

| Infection severity<sup>a</sup> | First line empirical treatment | Alternative treatment in low risk penicillin allergy | Alternative treatment in high risk penicillin allergy |
|-------------------------------|-------------------------------|---------------------------------------------|---------------------------------------------|
| Low (CURB 65=0 to 1)          | Amoxicillin                    | Doxycycline/clarithromycin                  | Doxycycline/clarithromycin                  |
| Moderate (CURB 65=2)          | Amoxicillin and clarithromycin | Cefuroxime and clarithromycin               | Teicoplanin and clarithromycin              |
| High (CURB 65 > 2)           | Ceftriaxone and clarithromycin | Cefuroxime and clarithromycin               | Teicoplanin and clarithromycin              |
| or cefuroxime and clarithromycin |                              |                                              |                                              |

<sup>a</sup>CURB 65 is a risk scoring system whose name is an acronym of each of the risk factors measured. Each risk factor scores one point, for a maximum score of 5: Confusion of new onset (defined as an AMTS of 8 or less); Blood Urea nitrogen greater than 7 mmol/L (19 mg/dL); Respiratory rate of 30 breaths per minute or greater; Blood pressure <90 mmHg systolic or diastolic blood pressure 60 mmHg or less; age 65 years or older.
different between the two groups. We attempted to use inflammatory marker cut-off points to exclude bacterial co-infection, however, analysis showed poor sensitivity and specificity (Table 5).

Comparison of clinical outcomes of COVID-19 patients with and without bacterial co-infection is shown in Table 6. A higher proportion of patients with bacterial co-infection were admitted to the ICU, although this was not statistically significant. There was no significant difference between the two groups in 30 day all-cause in-hospital mortality.

Discussion

This study describes the prevalence and characteristics of bacterial co-infection in COVID-19 patients at the time of hospital admission. In the patient cohort, we identified only 37 out of 1396 patients (2.7%) with diverse clinically significant bacterial co-infections within 48h of hospital admission. The prevalence of bacterial co-infection identified in our study was comparable to the 3.5% value reported in a recent review looking at bacterial co-infection rate on presentation. However, the authors of that review (Langford et al.) excluded non-respiratory tract sources of infection in their analysis, whereas our study included non-respiratory infections. The prevalence of bacterial co-infection reported in our study is also lower than the rate of 7%-7.3% reported in other reviews of COVID-19 patients. A likely explanation is that we restricted our analysis to the first 48h of hospital admission, whereas other authors have included hospital-acquired bacterial infections. Furthermore, the reviews that reported higher rates included studies that detected a wide range of respiratory pathogens using non-culture methods such as nucleic acid amplification tests (NAATs) and serology tests. The clinical relevance of positive non-culture tests is more difficult to determine.

We found that there was no significant difference in age, gender, pre-existing illnesses (hypertension, diabetes and respiratory diseases), intensive care admission or 30 day all-cause mortality in COVID-19 patients with and without bacterial co-infection on admission. In contrast, bacterial co-/secondary infections contribute significantly to morbidity and mortality in influenza pandemics. The effects of bacterial secondary infections later in the COVID-19 disease course were not studied, as our aim was to describe bacterial co-infection at the time of presentation to guide empirical antibiotic treatment.

A majority of patients included in this study (69.4%) had blood cultures analysed, as they presented with features of septicemia.

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Table 3. Comparison of demographics and co-morbidities in COVID-19 patients with and without bacterial co-infection

| Variable                        | All patients (n = 1396) | Patients without bacterial co-infection (n = 1359) | Patients with bacterial co-infection (n = 37) | P value |
|---------------------------------|-------------------------|---------------------------------------------------|---------------------------------------------|---------|
| Male, n (%)                     | 903 (64.7%)             | 875 (64.4%)                                       | 28 (75.7%)                                  | 0.16 (Chi-square) |
| Age, years, median (IQR)        | 69 (56–80)              | 69 (56–80)                                        | 76 (64–82)                                  | 0.16 (Mann–Whitney U test) |
| Hypertension, n (%)             | 623 (45.8%)             | 602 (45.5%)                                       | 21 (56.8%)                                  | 0.23 (Chi-square) |
| Diabetes, n (%)                 | 511 (37.6%)             | 492 (37.2%)                                       | 19 (51.3%)                                  | 0.12 (Chi-square) |
| Asthma, n (%)                   | 149 (11.0%)             | 147 (11.1%)                                       | 2 (5.4%)                                    | 0.32 (Chi-square) |
| COPD, n (%)                     | 92 (6.8%)               | 87 (6.6%)                                         | 5 (13.5%)                                   | 0.15 (Chi-square) |
| Pre-existing respiratory illness, n (%) | 286 (21.0%)         | 279 (21.1%)                                       | 7 (18.9%)                                   | 0.60 (Chi-square) |

Co-morbidities data was only available in 1322 patients.

Table 4. Comparison of routine inflammatory markers in COVID-19 patients with and without bacterial co-infection

| Inflammatory markers on admission | All patients | Patients without bacterial co-infection | Patients with bacterial co-infection (n = 37) | P value (Mann–Whitney U test) |
|-----------------------------------|--------------|-----------------------------------------|---------------------------------------------|-------------------------------|
| White cell count (×10^9/L)        | 7.3 (5.4–10.1) | 7.3 (5.4–9.9)                             | 11.3 (6.2–15.8)                             | 0.00013 |
| Neutrophil count (×10^9/L)        | 5.5 (3.9–8.0)  | 5.5 (3.9–7.8)                             | 9.2 (4.8–13.3)                              | 0.000059 |
| Lymphocyte count (×10^9/L)        | 1.0 (0.7–1.4)  | 1.0 (0.7–1.4)                             | 0.8 (0.6–1.4)                               | 0.29 |
| C-reactive protein (mg/dL)        | 96.0 (48.5–159.8) | 95.4 (48.0–158.3)                         | 136.5 (70.0–235.7)                         | 0.0082 |

Data are presented as median (IQR).
We received only a small number of lower respiratory tract specimens and many of these were from patients who required intensive care admission. This could be due to patients commonly presenting with non-productive cough at the time of hospital admission. A recent study conducted in another London hospital also reported that 90.7% of all blood cultures taken in COVID-19 patients upon admission were negative. Given the low yield of blood culture amongst hospitalized COVID-19 patients, we suggest the practice for routine blood culture analysis in these patients should be reviewed, especially in those with typical presentation of COVID-19.

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Table 5. Diagnostic performance for the prediction of co-infection

| Cut-offa | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|----------|----------------------|----------------------|--------------|--------------|
| WCC >8.8 x 10^9/L | 67.6% (50.2–82.0) | 67.9% (65.3–70.4) | 5.5% (3.6–8.0) | 98.7% (97.8–99.3) |
| Neutrophils >6.9 x 10^9/L | 67.6% (50.2–82.0) | 66.4% (63.8–68.9) | 5.2% (3.4–7.6) | 98.7% (97.7–99.3) |
| CRP >119.8 mg/dL | 62.2% (44.8–77.5) | 61.8% (59.1–64.4) | 4.3% (2.8–6.4) | 98.3% (97.2–99.1) |

PPV, positive predictive value; NPV, negative predictive value; WCC, white cell count.

*aCut-off points were chosen to give the optimal combination of sensitivity and specificity.

Table 6. Comparison of clinical outcomes of COVID-19 patients with and without bacterial co-infection

| Outcomes | All patients (n = 1396) | Patients without bacterial co-infection (n = 1359) | Patient with bacterial co-infection (n = 37) | P value (Chi square) |
|----------|-------------------------|-----------------------------------------------|---------------------------------|-------------------|
| Intensive care admission | 226 (16.2%) | 215 (15.8%) | 11 (29.7%) | 0.075 |
| 30 day all-cause in-hospital mortality | 420 (30.1%) | 410 (30.2%) | 10 (27.0%) | 0.68 |
| Discharged at 30 day follow up | 771 (55.2%) | 756 (55.6%) | 15 (40.5%) | – |
| Remained inpatient at 30 day follow up | 55 (3.9%) | 48 (3.5%) | 7 (18.9%) | – |
| Transferred to other hospital | 150 (10.7%) | 145 (10.7%) | 5 (13.5%) | – |

But only 1.2% patients had clinically significant bacteraemia after exclusion of likely contaminants. Our findings are comparable to those reported by Sepulveda et al. who reported a bacteraemia rate of 1.6% after excluding skin contaminants amongst COVID-19 patients during hospitalization. A recent study conducted in another London hospital also reported that 90.7% of all blood cultures taken in COVID-19 patients upon admission were negative. Given the low yield of blood culture amongst hospitalized COVID-19 patients, we suggest the practice for routine blood culture analysis in these patients should be reviewed, especially in those with typical presentation of COVID-19.

In our study, urinary antigen tests identified three COVID-19 patients with S. pneumoniae co-infection and no cases of Legionella co-infection. Although we did not detect legionella co-infection, it has also been reported in COVID-19 patients. Previous studies based on the use of polymerase chain reaction (PCR) also reported respiratory bacterial co-infections with S. pneumoniae, but these were not confirmed by culture. Other respiratory bacterial co-infections previously reported in COVID-19 patients included K. pneumoniae, H. influenzae, Mycoplasma pneumoniae and Chlamydia pneumoniae, all of which were detected using non-culture methods. However, these non-culture methods are not routinely used in our hospitals. In addition to bacteraemia and respiratory infections, 16 patients had urinary tract infections and 5 patients had other sources of bacterial infections including diabetic foot ulcer, psoas abscess, eye infection and surgical wound infection.

It is worth noting that our cohort had a high rate of urine cultures processed (463/1396, 33.2%) and high number of patients with urinary bacterial co-infection (22/37, 59.5%). Many of the elderly patients presented with pyrexia or breathlessness but the focus of infection was unclear. As a result, urine cultures were requested to ascertain the source of infection. Results of these urine cultures were included in our analysis as these would have guided the choice of antibiotics.

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Based on our review of 100 random COVID-19 patients without bacterial co-infection, we estimated that over 95% of COVID-19 patients in our cohort received antibiotics upon admission. Most received a second- or third-generation cephalosporin plus clarithromycin. This broad-spectrum antibiotic regimen provided adequate antimicrobial coverage in many patients with confirmed bacterial co-infection (Table 1). However, the low rate of bacterial co-infections reported in our study suggests that many of these
antibiotics were given unnecessarily. Guidelines published in England by the National Institute for Health and Clinical Excellence (NICE) have also stated that bacterial co-infection occurs in <10% of patients with COVID-19. The guidance recommends that if there is confidence that the clinical features are typical for COVID-19, it is reasonable not to start empirical antibiotics. Our findings support these recommendations. Although we did not find a cut-off value for inflammatory markers to exclude bacterial co-infection, our findings suggested leucocytosis, neutrophilia and high CRP could be taken into consideration when deciding to start empirical antimicrobial therapy.

Limitations
We acknowledge several limitations in our study. The study is limited to two hospitals, which are included in our Trust. While this limited our patient cohort, being a single centre study allowed us to have consistency in antimicrobial policies. There was no standardized protocol for screening COVID-19 patients for bacterial co-infection. We relied on the treating physicians’ clinical judgement on requesting microbiological investigations. Therefore, it is possible that we may not have received appropriate specimens from all eligible patients. Additionally, there was a shortage of supply of the urinary antigen testing kit during the month of April, which could have resulted in underestimation of concomitant infections with Legionella or S. pneumoniae. With the exception of urinary antigen tests, we did not use non-culture tests such as NAATs or serology for detection of respiratory pathogens. In particular, we did not investigate for atypical respiratory pathogens such as Chlamydia pneumoniae and Mycoplasma pneumoniae as they are not routinely investigated in patients presenting with community-acquired pneumonia in the UK. The aim of the study was to describe the prevalence and nature of bacterial co-infections in COVID-19 patients within 48 h of hospital admission. It is conceivable that some patients incubating bacterial co-infection at time of admission could have presented after 48 h and this study did not aim to address the acquisition of infections in the hospital.

Conclusions
In this study we have found that clinically significant bacterial co-infection was infrequent in hospitalized COVID-19 patients in the first 48 h of admission. These results suggest that empirical antimicrobial treatment may not be necessary in patients presenting with high suspicion of COVID-19 infection, though the decision could be guided by high inflammatory markers. Furthermore, our findings suggest that presence of bacterial co-infection at the time of presentation does not affect the clinical outcome adversely.

Funding
This project was carried out as part of our routine work.

Transparency declarations
None to declare.

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