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Microbiological findings and prescribing trends in SARS-CoV-2 positive patients in two United Kingdom Hospitals

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SUMMARY

Objective: To describe antibiotic prescribing and microbiological findings in patients admitted to two London hospitals with COVID-19.

Methods: This is a retrospective review of confirmed SARS-CoV-2 infected adults admitted between 9th February and 10th May 2020. Demographics, critical care unit (CCU) admission, antibiotic prescribing and microbiology results within 10 days of COVID-19 diagnosis were analysed.

Results: 1155 patients were identified. 32.9% (380) died. 12.4% (143) had positive microbiology. After excluding likely contaminants, 6.9% (80) had clinically significant microbiology. The most common organisms isolated from blood cultures were *Escherichia coli* 9.5% (7), *Klebsiella pneumoniae* 4.0% (3), and *Staphylococcus aureus* 2.7% (2). A high percentage of blood cultures yielded coagulase negative staphylococci (51/74, 68.9%) and likely represented contamination. Organisms isolated from lower respiratory tract samples included *Candida albicans* 44.4% (12), *Staphylococcus aureus* 22.2% (6), *Klebsiella* species 11.0% (3), *Pseudomonas aeruginosa* 11.0% (3), and Citrobacter species 11% (3). Legionella and pneumococcal urinary antigen tests were positive in 0/117 and 2/71 (2.8%) samples. 91% (1051) of patients received antibiotics. Clarithromycin (24.2% total antibiotic use) and amoxicillin (21%) were most frequently used, followed by piperacillin-tazobactam (12.6%), gentamicin (10.6%), co-amoxiclav (9.3%) and meropenem (3.2%). Piperacillin-tazobactam or meropenem use was associated with a higher length of stay and mortality.

Conclusions: Positive microbiology in COVID-19 patients is uncommon. Antibiotic use was widespread, despite lack of microbiological evidence of co-infection. When present, positive microbiology was more likely due to gram negative bacteria. Current local clinical and antimicrobial guidelines have incorporated these findings and recommend against routine antibiotic use in COVID-19 patients.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterised by fever and respiratory symptoms. The clinical signs

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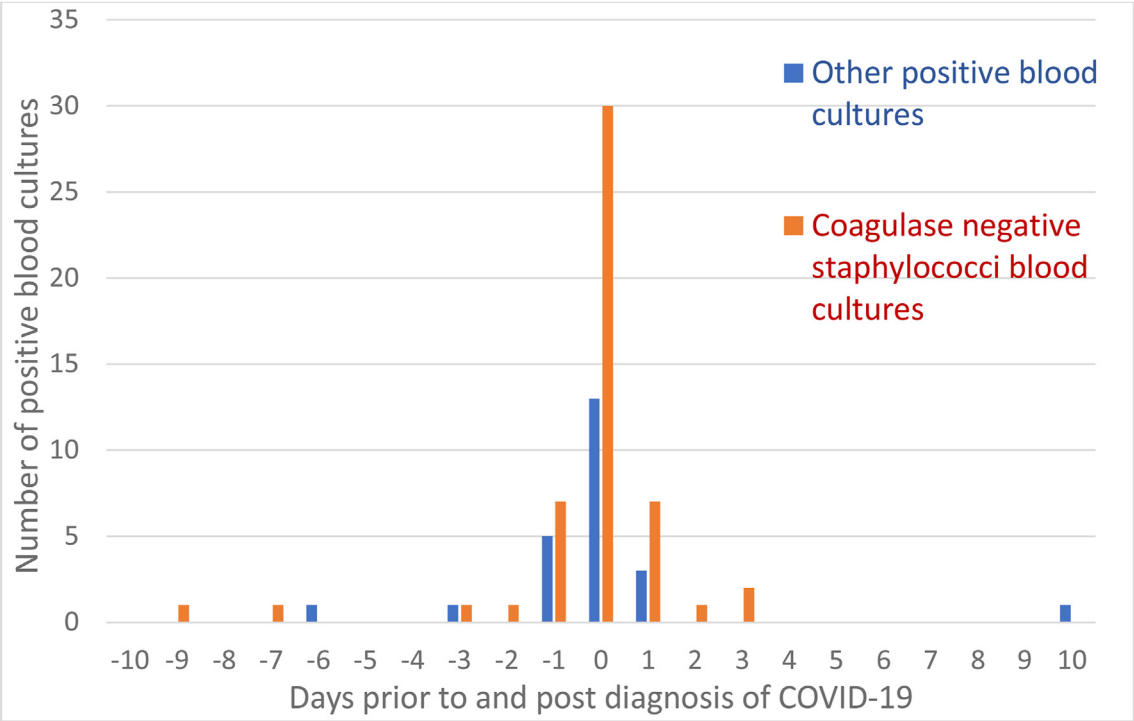

Figure 1. Timing and identity of positive blood cultures taken within 10 days of COVID-19 diagnosis. Timing is relative to the first positive SARS-CoV-2 PCR test represented as day 0. PCR; polymerase chain reaction.

and laboratory results of COVID-19 are difficult to distinguish from bacterial pneumonia, often leading to antimicrobial use.

A systematic review conducted by Rawson *et al*. found 72% of patients with COVID-19 were prescribed antimicrobials. [1] Despite widespread antimicrobial use, there is limited data on microbiological findings at presentation with COVID-19, or potential culprit organisms. Early data from critical care unit (CCU) patients in China found bacteraemia in 2% of patients and hospital-acquired pneumonia diagnosed by respiratory tract secretions, in 11.5%. [2] Rawson *et al*. found bacterial and/or fungal co-infection in 8% of COVID-19 patients included in their review. [1].

A systematic review conducted in the first half of 2020 found *Mycoplasma pneumonia*, *Pseudomonas aeruginosa* and *Haemophilus influenzae* to be the most commonly isolated bacteria in COVID-19 patients. [3] Cohort data from the United Kingdom's (UK) first epidemic wave found *Staphylococcus aureus*, *Haemophilus influenzae* and Enterobacteriaceae to be the most common causes of respiratory infections and *E. coli* and *S. aureus* the most frequent cause of bacteraemia. [4].

There is a need to describe the microbiological findings in early COVID-19 to understand the benefits and risks of antimicrobial use. Microbiological findings and antimicrobial prescribing trends among hospitalised patients in two UK hospitals is described.

Methods

We conducted a retrospective review of patients hospitalised with COVID-19 across two London hospitals. All positive SARS-CoV-2 polymerase chain reaction (PCR) tests between 9th February 2020 and 10th May 2020 were screened for inclusion. Patients aged $\geq$ 18 years who were admitted and remained in hospital to discharge were included in the analysis. Those transferred to other hospitals, discharged from the emergency department, and who received testing as outpatients were excluded.

The microbiology laboratory database (Winpath 5.32; CliniSys, Chertsey, UK) was searched to identify patients with positive SARS-CoV-2 PCR tests. The electronic patient record (Millennium; Cerner, Missouri, USA) was used to extract demographic, clinical and microbiological data 10 days before and after a positive PCR was analysed. All data was reviewed against inclusion criteria by two authors independently prior to analysis. Day 0 was the date the first positive SARS-CoV-2 PCR sample was taken. T-tests were performed on normally distributed data and Mann Witney U tests were performed for non-parametric data. Data was anonymised and analysed using Microsoft Excel® Office 2019 and IBM® SPSS Statistics version 26.

This study was registered with the Lewisham and Greenwich NHS Trust Clinical audit team. Ethical approval was not sought for this retrospective, anonymised, non-interventional study, as per National Health Service Health Research Authority guidance.

Results

A total of 1396 patients were screened for inclusion. After exclusions, 1155 patients were analysed (Figure 1). The median age was 72 (IQR 57–83), 44.2% female (n=511), 8.9% required CCU (n=103) and 32.9% mortality (n=380). Average length of stay to discharge or death was 13.9 days.

The most common microbiology samples were blood cultures, then urine and lower respiratory tract cultures (sputum or non-directed bronchial lavage [NBL]). Other samples in

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descending order of frequency included pneumococcal and legionella urinary antigen, bacterial stool culture, skin swabs and pleural cultures. A description of these cultures is seen in Table I. 12.4% of patients had positive microbiology within our study period. After excluding coagulase negative staphylococci (CNS), interpreted as contaminants or clinically insignificant, this proportion fell to 8.0% of patients. Samples isolating only candida in respiratory samples and mixed organisms in urine

Table I
Microbiological results from patients sent within 10 days of COVID-19 diagnosis

	Total samples sent	Proportion of patients for which samples were sent, % (n)	Proportion of samples with organism identified, % (n)	Proportion of positive cultures identifying the named organism % (n) of positive samples of this type[a]
Blood cultures	874	55.3% (639)	8.5% (74)	68.9% (51) *Coagulase negative staphylococci* 9.5% (7) *Escherichia coli* 4.0% (3) *Klebsiella pneumoniae* 2.7% (2) *meticillin sensitive Staphylococcus aureus* Other: Meticillin resistant *Staphylococcus aureus*, *Acinetobacter lwoffii*, *Acinetobacter baumannii*, *Alcaligenes faecalis*, *Klebsiella aerogenes*, *Peptoniphilus indolicus*, *Pseudomonas aeruginosa*, Viridans type streptococcus, *Candida albicans*, *Streptococcus vestibularis*, *Streptococcus pneumoniae*, *Staphylococcus haemolyticus*, *Streptococcus salivarius*, (isolated once each)
Lower respiratory tract samples[b]	147	8.1% (94)	18.4% (27)	44.4% (12) *Candida albicans* 22.2% (6) *Staphylococcus aureus* 11% (3) *Klebsiella species* 11% (3) *Pseudomonas aeruginosa* 11% (3) Citrobacter species Isolated two: *Serratia marcescens* Isolated one each: *Proteus mirabilis*, *Haemophilus influenzae*
Legionella urinary antigen	117	8.7% (100)	0% (0)	N/A
Pneumococcal urinary antigen	71	6.1% (71)	2.8% (2)	N/A
Pleural cultures	2	0.2% (2)	0% (0)	N/A
Urine cultures	416	26.3% (303)	13.2% (55)	40% (22) *Escherichia coli* 20% (11) *Candida species* 5.4% (3) *Proteus species* 5.4% (3) Mixed organisms Other: coagulase negative staphylococci, Enterococcus species, *Enterobacter cloacae*, *Citrobacter species*, *Pseudomonas aeruginosa*,
Wound and skin swab cultures[c]	86	3.9% (45)	10.5% (9)	77.8% (7) *Staphylococcus aureus* Other: *Group G streptococci*, *Pseudomonas* species, *Serratia marcescens* (isolated one each)
Stool[d]	109	7.1% (82)	0% (0)	N/A

N/A; not applicable.
[a] 8 blood cultures, 4 lower respiratory tract samples and 1 wound swab isolated multiple organisms.
[b] sputum or non-directed bronchial lavage samples.
[c] wound and skin swabs.
[d] composed of bacterial culture for *Salmonella sp*, *Shigella sp*, *E. coli 0157*, *Campylobacter Jejuni*, viral PCR norovirus and *C. difficile* glutamate dehydrogenasePCR/toxin.

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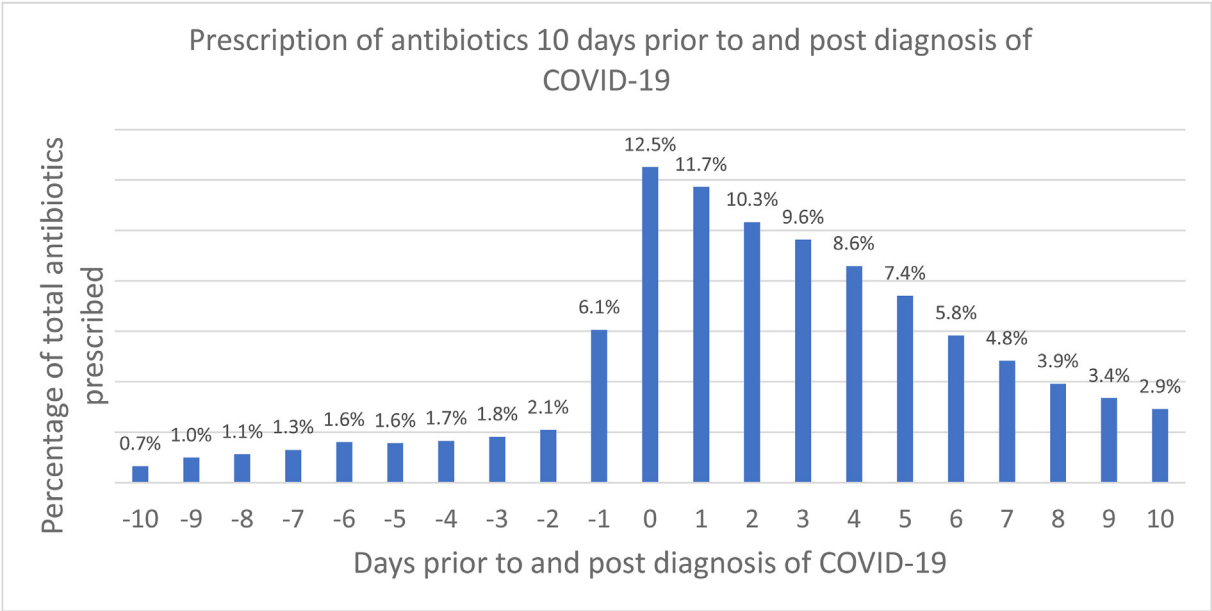

Figure 2. Percentage of total antibiotics used per day from 10 days prior to and after the first positive PCR test. Shown in days relative to the first positive SARS-CoV-2 test represented as day 0.

were interpreted as insignificant (Table I). After excluding these, the proportion with positive microbiology within 10 days of positive SARS-CoV-2 test fell to 6.9%.

Overall rate of positive microbiology across samples was 9.1%, falling to 5.5% after the exclusion of organisms interpreted as clinically insignificant. Patients requiring admission to CCU had a statistically insignificantly lower rate of positive microbiology compared to patients managed on wards (10.7% vs 13.3%, P=0.08). The converse was observed after exclusion of all likely contaminants with CCU patients having a higher rate of positive microbiology (9.1% vs 8.8%, P=0.44).

Microbiology samples

Blood and line tip cultures

874 blood cultures were taken from 639 of the 1155 (55.3%) patients. 8.4% (74/874) of blood cultures taken were positive, however most (68.9%, 51/74) isolated CNS. No line tips were sent. Only 2.6% (23/874) of blood cultures grew a clinically significant organism. *Escherichia coli* (9.5%, 7/74), *Klebsiella pneumoniae* (4.0%, 3/74), and meticillin-sensitive *Staphylococcus aureus* (2.7%, 2/74) were the most commonly cultured significant organisms (Table I). All CNS were interpreted as contaminants by the clinical team and not treated with antimicrobials. After excluding CNS, 50.0% of all the remaining positive blood cultures were taken on day 0 (Figure 1). Median time from admission to collection of positive blood culture was 1 day (inter-quartile range, IQR 0—2 days), and from date of first positive SARS-CoV-2 PCR test to positive blood culture, 0 days (-1 to 0 days).

Urine & lower respiratory tract cultures

416 urine cultures were taken from 303 (26.3%) patients. Fifty-five (13.6%) cultures grew an organism of which 28 were typical uropathogens. These patients were often treated with multiple antibiotics inlcuding, in descending order of frequency, amoxicillin (13 patients), gentamicin (12), clarithromycin (8), co-amoxiclav (4), piperacillin-tazobactam (2) and teicoplanin (2). Seven patients received no antibiotics. 147 lower respiratory tract cultures were taken from 94 (8.1%) patients. Twenty-seven (18.4%) cultures grew an organism of which 17 were typical pneumonia pathogens in addition to two positive pneumococcal urine antigen tests. Of these patients, 9 were admitted to CCU and treated with, in descending order of frequency, piperacillin-tazobactam (4 patients), clarithromycin (2), vancomycin (1), meropenem (1), gentamicin (1) and teicoplanin (1).

β-d-Glucan and galactomannan

Twenty-five β-d-Glucan and galactomannan blood samples were sent in 23 patients. All galactomannan tests sent were negative. There were 3 positive β-d-Glucan tests in 2 patients, one of whom had no fungal microbiology identified and was not given antifungals. The other patient, with two positive tests, was admitted to CCU and treated for invasive fungal disease with anidulafungin during their admission.

Antibiotic use

Most patients (91%, 1051/1055) included in the analysis were treated with antibiotics during their admission, with highest use on day 0 (Figure 2). Antibiotics were rarely used prior to diagnosis of COVID-19, peaked on day 0 (12.5% of total antibiotic use [287 patient days]) before reducing towards day 10 (2.9% [67 patient days]). Patients prescribed antibiotics had no significant difference in age, mortality or CCU admission compared to those not prescribed antibiotics.

The most commonly used antibiotics were clarithromycin (555 patient days, 24.2% of total antibiotic use, median duration 5 days, IQR 3—7) and amoxicillin (482 patient days, 21% total antibiotic use, median duration 5 days, IQR 3—7), followed by piperacillin-tazobactam (289 patient days, 12.6% total antibiotic use, median duration 6 days, IQR 3—6), gentamicin (244 patient days, 10.6% total antibiotic use, median duration 3 days, IQR 2—5), co-amoxiclav (213 patient days,

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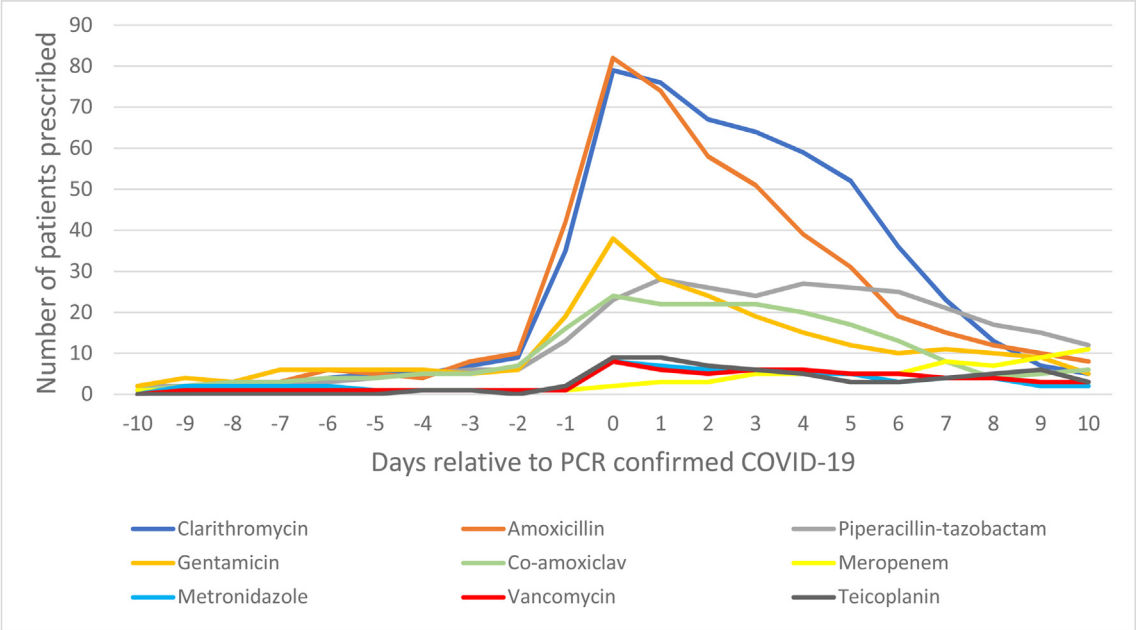

Figure 3. The total number of patients receiving the nine most used antibiotics within 10 days of diagnosis of COVID-19. Shown in days relative to the first positive SARS-CoV-2 test, represented as day 0. PCR; polymerase chain reaction.

9.3% total antibiotic use, median duration 4 days, IQR 2—6) and meropenem (73 patient days, 3.2% total antibiotic use, median duration 4 days, IQR 2—7) (Figure 3). The number of patients prescribed each of these antibiotics fell during admission, except for meropenem, the use of which increased from 2 (0.09%) patients on day 0—11 (0.5%) patients on day 10. The most commonly antibiotics used, clarithromycin and amoxicillin, are the first line community acquired pneumonia antibiotics in local guidelines whereas those treated for sepsis of likely chest source were given amoxicillin and gentamicin.

Escalation of antibiotics

Patients treated with piperacillin-tazobactam had a greater length of stay (median 12 days vs 7 days, $P<0.001$), higher rate of admission to the CCU (26.9% vs 5.0%, $P<0.001$), and higher mortality (52.9% vs 28.6%, $P<0.001$) compared to patients who did not receive piperacillin-tazobactam. Similarly, patients treated with meropenem had a greater length of stay (median 24.5 days vs 8.0 days, $P<0.001$), higher rate of admission to CCU (30.4% vs 8.5%, $P=0.003$), and higher mortality (65.2% vs 32.3%, $P=0.001$). Four patients treated with meropenem in CCU isolated *Candida albicans*, *Enterobacter cloacae* and *Escherichia coli* in lower respiratory tract cultures.

Discussion

We observed a low rate of positive bacterial and fungal microbiology consistent with the existing published literature. [1—4] After excluding contaminants and clinically insignificant results, 6.9% of patients had positive microbiology, in line with previous published data. [1,3] The low rate of positive microbiology contrasts with the finding that 91% of patients received antibiotics. This is higher than the 74.6% described in a meta-analysis of similar studies. [5] Patients admitted to CCU during their inpatient stay had comparable rates of positive microbiology compared to ward patients despite increased sample collection in CCU.

Most microbiology samples were taken at day 0, likely due to attempts to differentiate between COVID-19 and a bacterial infection. Few clinically significant organisms were identified from blood cultures, however most were gram-negative bacteria, contrasting with UK COVID-19 data and past influenza pandemics. [6—8].

Contamination of blood cultures was high, possibly due to requirements for additional personal protective equipment (PPE) worn by staff during the pandemic impacting the ability to maintain adequate sterility. Similar contamination rates were described in another UK study but remains a concerning finding considering the ongoing widespread use of PPE in treating COVID-19 patients. [9] Training on collecting blood cultures with and without PPE could reinforce culture collection technique and may help to reduce future contamination. Sustained contamination rates with the use of PPE may have wider implications on infection control procedures and would warrant further investigation.

Additionally, there was likely contamination of urine cultures. It is unclear whether organisms isolated from urine cultures represented colonisation or infection, as further data such as catheter use was not collected. They may represent perineal or urinary catheter flora.

Respiratory samples had a low yield for organisms of clinical significance. The most common isolate, *Candida albicans*, was almost always interpreted as present due to antimicrobial pressure and not treated. Similar to blood cultures, gram-negative bacteria were the most common clinically significant organisms. There was limited evidence of fungal co-infection using serum β-d-Glucan. These findings may have changed with prolonged follow up which was beyond our study's scope. Given the low proportion of COVID patients with clinically significant results (6.9%), if there is no evidence of bacterial or fungal infection, clinicians should consider stopping antibiotics.

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Our data was collected in the first wave of the UK pandemic, prior to identification of the Alpha variant in November 2020 and prior to NICE guidelines advising against antibiotic use in COVID-19. [10] The high antibiotic use encountered is likely due to the difficulty clinicians experienced managing an illness that presented similarly to a bacterial respiratory infection. Signs and symptoms that could help differentiate COVID-19 from a bacterial pneumonia could be the loss of sense of smell or taste, non-lobar bilateral chest x ray changes or an absence of neutrophilia.

Beta-lactams and macrolides were the antibiotics of choice in our study, reflecting local antimicrobial guidelines and contrasting with the global preference for cephalosporins and fluoroquinolones. The higher length of stay, rate of admission to CCU, and mortality rate noted in patients who were treated with piperacillin-tazobactam or meropenem may relate to their use as escalation antibiotics for deteriorating patients.

The highest antibiotic use on day 0 was likely due to admission or clinical deterioration which would also prompt SARS-CoV-2 testing. An inflection point at day 5 in the use of clarithromycin (Figure 3) is due to a standard 5-day course duration for a bacterial pneumonia. Despite the low rate of legionella in our cohort, if atypical bacterial co-infection is suspected, there may be merit in empirical treatment with macrolides to cover for other atypical organisms causing community-acquired pneumonia that we did not collect data on, but have been described as causes of bacterial co-infections in other data sets. [3] The reduction in antibiotics over time could also be due to mortality, however the timing of mortality relative to antibiotics was not collected. Although mortality, length of stay, and CCU admission appeared to be higher in patients treated with antibiotics, this was not statistically significant, and is likely related to clinical instability of the patients. It is not possible to draw any causal or associative links between these two different groups of patients, nor was this study designed to make these conclusions.

The results of this study were limited by the narrow timeframe of data collection and a lack of longitudinal data particularly those with prolonged CCU admissions in whom CNS in blood culture may have been clinically significant. Additionally, both hospitals in this study are district hospitals in a high-income country with the ability to transfer patients to tertiary centres and therefore all findings may not be generalisable to other settings. No data was collected on atypical respiratory pathogens (e.g. *Mycoplasma* and *Chlamydia)* and the legionella urinary antigen test only tested for serogroup 1. The route and dosage of antimicrobials was not collected, precluding the use of defined daily dose analysis. Limited clinical data was collected which precluded calculating any mortality or comorbidity scores. The study was limited by the retrospective design and the inability to control for confounders and data gaps. The same type and number of microbiological samples were not collected for each patient. Although the data was collected during a time where non-evidence based treatments such as high dose steroids were being employed by some clinicians, the study was conducted before the now widespread use of immune suppressive therapeutics such as dexamethasone, [11] tocilizumab [12] and casirivimab/imdevimab [13] as a result of randomised control trials that took place during the pandemic. Hence the rate of and type of organisms observed in secondary bacterial or fungal infections may be subject to change, as noted during the second COVID-19 wave in India where high rates of superadded mucormycosis infection were described. [14] Future studies of secondary bacterial and fungal infections are of particular importance considering immunosuppressive therapies used in COVID-19 management.

Conclusion

We observed a low rate of positive microbiology in the first 10 days of COVID-19 in patients admitted to two urban UK hospitals. Antibiotic use was widespread but did not provide sufficient cover for the gram-negative bacteria identified. Antibiotic selection should consider the need to provide gram-negative cover and should limit macrolide use to suspected atypical pneumonias. Current local clinical and antimicrobial guidelines have incorporated these findings and recommend against routine antibiotic use in COVID-19 patients. Where bacterial co-infection is suspected, guidelines now advised the use of antibiotics with broader gram-negative cover. Training on the collection of blood cultures with and without PPE should be reinforced to reduce the high rate of contaminants in samples.

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Author Statement

Teoh PJ: Conceptualization, methodology, formal analysis, investigation, data curation, visualisation, writing-original draft.

Maan I: Conceptualization, methodology, formal analysis, investigation, data curation, writing-original draft, writing-review & editing.

Uwagwu J: Conceptualization, writing-review & editing, supervision.

Odedra A: Conceptualization, methodology, writing-review & editing, supervision.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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