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Original article

Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting

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ABSTRACT

Objectives: To investigate the incidence of bacterial and fungal coinfection of hospitalized patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this retrospective observational study across two London hospitals during the first UK wave of coronavirus disease 2019 (COVID-19).

Methods: A retrospective case series of hospitalized patients with confirmed SARS-CoV-2 by PCR was analysed across two acute NHS hospitals (20 February–20 April 2020; each isolate reviewed independently in parallel). This was contrasted to a control group of influenza-positive patients admitted during the 2019–2020 flu season. Patient demographics, microbiology and clinical outcomes were analysed.

Results: A total of 836 patients with confirmed SARS-CoV-2 were included; 27 (3.2%) of 836 had early confirmed bacterial isolates identified (0–5 days after admission), rising to 51 (6.1%) of 836 throughout admission. Blood cultures, respiratory samples, pneumococcal or *Legionella* urinary antigens and respiratory viral PCR panels were obtained from 643 (77%), 110 (13%), 249 (30%), 246 (29%) and 250 (30%) COVID-19 patients, respectively. A positive blood culture was identified in 60 patients (7.1%), of which 39 were classified as contaminants. Bacteraemia resulting from respiratory infection was confirmed in two cases (one each community-acquired *Klebsiella pneumoniae* and ventilator-associated *Enterobacter cloacae*). Line-related bacteraemia was identified in six patients (three *Candida*, two *Enterococcus* spp. and one *Pseudomonas aeruginosa*). All other community-acquired bacteraemias ($n = 16$) were attributed to nonrespiratory infection. Zero concomitant pneumococcal, *Legionella* or influenza infection was detected. A low yield of positive respiratory cultures was identified; *Staphylococcus aureus* was the most common respiratory pathogen isolated in community-acquired coinfection (4/24; 16.7%), with *Pseudomonas* and yeast identified in late-onset infection. Invasive fungal infections ($n = 3$) were attributed to line-related infections. Comparable rates of positive coinfection were identified in the control group of confirmed influenza infection; clinically relevant bacteraemias (2/141; 1.4%), respiratory cultures (10/38; 26.3%) and pneumococcal-positive antigens (1/19; 5.3%) were low.

Conclusions: We found a low frequency of bacterial coinfection in early COVID-19 hospital presentation, and no evidence of concomitant fungal infection, at least in the early phase of COVID-19. **S. Hughes, Clin Microbiol Infect 2020;26:1395**

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Introduction

Bacterial and fungal coinfection in hospitalized adults with coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is poorly understood. Clinically, differentiating between isolated COVID-19-related viral infection and possible superadded bacterial or

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fungal infection is challenging. Secondary bacterial infections from COVID-19 cases in Wuhan were reported in 15% of hospitalized patients [1], and higher among the nonsurvivor group than survivors (50% versus 1%). In the wider COVID-19 data, there remains a paucity of information on the frequency, nature and susceptibility profiles of secondarily infecting pathogens [2,3].

Among other viral (influenza) pneumonitis epidemics and pandemics, there have been increased secondary bacterial and fungal infections [4–7], particularly with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Aspergillus* spp., which are frequently associated with poor patient outcomes [6]. National Institute for Health and Care Excellence (NICE) COVID-19 guidance recommends the consideration of antibacterials in patients where infection is likely bacterial, if the source of infection is unclear and the symptoms are concerning, or for patients with comorbidities who are at high risk of complications from untreated bacterial infection [8].

Relevant to the NICE COVID-19 guidance and the doxycycline and amoxicillin advocated, there is an urgent need to characterize the frequency, nature and susceptibility profiles of secondarily infecting pathogens in the United Kingdom. To investigate this, we undertook a retrospective observational analysis of patients admitted with confirmed SARS-CoV-2. A control group of patients with confirmed influenza was used as a comparator to derive relative rates of secondary infections between these two viral pneumonitis presentations and explore any variation in causative organisms.

Methods

Study setting and design

A retrospective observational analysis was undertaken of all hospitalized patients with COVID-19 across a multicentre NHS acute trust, the Chelsea and Westminster NHS Foundation Trust (London, UK). All patients with confirmed SARS-CoV-2 between 20 February 2020 and 30 April 2020 were included. Electronic patient records (Millennium; Cerner, North Kansas City, MO, USA; and ICNet, Baxter, UK [9]) and microbiology laboratory data (Sunquest 8.3; Sunquest, Tucson, AZ, USA) were used to identify patients, clinical data and outcomes. Patient demographics gender, age, level of care (critical care vs. standard ward), microbiology data (including culture of blood, sputum and bronchoalveolar lavage (BAL), as well as urinary pneumococcal and *Legionella* antigens and respiratory viral panels looking for non-SARS-CoV-2 pathogens) and in hospital mortality were extracted.

Laboratory technique

Nasopharyngeal and oral swabs were used to sample all patients with suspected COVID-19 and tested at a central hub laboratory using real-time reverse transcriptase PCR (proprietary Public Health England Assay until 10 March 2020, then commercial AusDiagnostics, Australia, assay thereafter). The hospital network's 'COVID-19 anti-infectives policy' advises the responsible clinicians to request clinical samples (as above) if there was (i) clinical deterioration in acute physiology (e.g. persistent fever, increasing oxygen requirements), (ii) an upwards trend in inflammatory markers (white blood cell count and/or C-reactive protein) or (iii) new infiltrates on chest radiography. These samples were cultured in line with the national UK Standards for Microbiology Investigations from Public Health England [10] on the relevant media, atmospheres and duration noted in the relevant standard operating procedure. Isolate speciation was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (BioTyper; Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibilities were

determined by European Committee on Antimicrobial Susceptibility Testing disc diffusion criteria [11] Where concomitant viral infections were considered (i.e. from 20 February 2020 to 6 April 2020, when the national incidence of influenza-like illness was above 10/10 000), patients tested for SARS-CoV-2 also had contemporaneous testing for influenza A/B and respiratory syncytial virus (RSV) using GeneXpert (Cepheid, Sunnyvale, CA, USA).

Definitions

Each microbiology isolates was reviewed by two members of the antimicrobial team (SH and OT) to determine the clinical significance; pathogens identified but not warranting targeted therapy were defined as commensal and nonsignificant infective pathogens. The time from SARS-CoV-2 detection and initial presentation to time of culture was used to assess likely community-associated (CA) infection (less than 120 hours from admission) or HA infection (more than 120 hours from admission). This time point correlates with locally defined definition for HA pneumonia (≥ 5 days from admission) and was agreed by the study team to define HA-associated pathogens in this study.

Comparison with postinfluenza secondary infections

A control group of influenza-positive (influenza A or B detected from respiratory virus testing undertaken on either (i) laboratory AusDiagnostics, Australia, or (ii) near-patient GeneXpert) patients admitted to the same study sites between September 2019 and April 2020 was analysed. The same microbiology culture methods and data extraction as above were used.

Data analysis

All data were anonymized and collated on Excel 2017 (Microsoft, Redmond, WA, USA). Descriptive statistics only were derived by GraphPad 8 (2018; GraphPad Software, La Jolla, CA, USA). The chi-square or Fisher exact test was used for analysis of categorical data, and the Mann-Whitney *U* test was used for nonparametric continuous variables.

Ethical approval

The Chelsea and Westminster NHS Trust research committee waived the need for patient consent, agreeing that ethical approval for the collection, analysis and publication of retrospective anonymized data for this noninterventional study was not needed, in line with NHS Health Research Authority guidance (2020). The project was registered as a service evaluation with the Chelsea & Westminster NHS Foundation Trust Antimicrobial Stewardship Committee.

Results

A total of 836 patients with confirmed SARS-CoV-2 were identified during the study period (20 February 2020 to 30 April 2020) with a median follow-up of 6 days (range, 1–47 days). The median age of patients was 69.5 years (interquartile range, 55–81 years) with 518 male (62%). A total of 216 patients with confirmed influenza were included in the comparator study period (1 September 2019 to 30 April 2020); median age was 36 years (interquartile range, 22–65 years) with 42% male (Table 1). There was high sampling rate for blood culture in both the SARS-CoV-2 cohort (643/836) and among the comparator influenza patients (141/216), but similarly, both groups had only low frequency of respiratory (sputum or bronchiolar lavage) sample culture (Table 1). The SARS-

Table 1
Characteristics and microbiologic investigations on SARS-CoV-2 cohort and comparator influenza A/B cohort, London 2020

Characteristic	SARS-CoV-2 (n = 836)	Influenza A/B (n = 216)	p
Date range of study	25/2/20–30/4/20	1/9/19–30/4/20	
Age (years), median (interquartile range)	69 (55–81)	36 (22–65)	<0.0001
Gender			
Male	519 (62)	91 (42)	<0.0001
Female	317 (38)	125 (58)	<0.0001
Microbiologic investigations undertaken			
Blood culture	643 (77)	141 (65)	0.0006
Respiratory (sputum)	110 (13)	38 (18)	0.1185
Respiratory (BAL)	13 (2)	—	0.1340
Pneumococcal urinary antigen	249 (30)	19 (9)	<0.0001
Legionella urinary antigen	246 (29)	21 (10)	<0.0001
Respiratory viruses (influenza A/B, RSV)	250 (30) ^a	—	NA

Data are presented as n (%) unless otherwise indicated.

BAL, bronchoalveolar lavage; NA, not applicable; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^a From 20 February 2020 to 6 April 2020, a total of 223 (43.7%) of 510 patients were tested for respiratory viruses; and after 7 April 2020, a total of 27 (8.3%) 326 patients were tested for respiratory viruses.

Table 2
Microbiologic culture results from SARS-CoV-2 cohort and comparator influenza A/B cohort, London, 2020

Characteristic	SARS-CoV-2 (n = 836)	Influenza A/B (n = 216)
Blood culture results, respiratory source		
Enterobacterales (CA/HCAI)	1/1	—
Streptococcus spp. ^a	—	1
Staphylococcus aureus (CA/HCAI)	—	1/0
Blood culture results, nonrespiratory source		
Coagulase-negative staphylococci	36	6
Enterobacterales (CA/HCAI)	5/1	—
Streptococcus spp. ^a	4/0	—
Staphylococcus aureus (CA/HCAI)	1/0	—
Enterococcus spp. (CA/HCAI)	1/3	—
Candida albicans (CA/HCAI)	0/3	—
Pseudomonas aeruginosa	0/1	—
Other	5 ^b	—
Blood cultures, no growth	583	133
Respiratory culture results		
No growth	64	22
S. aureus (CA/HCAI)	4/2	—
Pseudomonas spp. (CA/HCAI)	3/9	0/4
Enterobacter spp. (CA/HCAI)	2/3	—
Klebsiella spp. (CA/HCAI)	2/4	—
Serratia spp. (CA/HCAI)	1/1	1/0
Candida spp./yeast (CA/HCAI)	10/14	0/7
Aspergillus spp. (CA/HCAI)	1/2	0/1
Other pathogens		
CA (n)	Haemophilus influenzae (1)	Moraxella spp. (1), Streptococcus pneumoniae (2)
HCAI (n)	Hafnia spp. (1), Morganella spp. (1), Providencia spp. (1), Stenotrophomonas maltophilia (2)	—
Pneumococcal antigen (detected/tested)	0/249	1/19
Legionella antigen (detected/tested)	0/246	0/21
Influenza A/B, RSV (detected/tested)	0/250	—

Total number of pathogens exceeds total number of blood cultures because more than one isolate can be identified in a single culture.

CA, community acquired; HCAI, healthcare-associated infection; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^a Group A streptococci, group B streptococci, group C/G streptococci, Streptococcus oralis, S. pneumoniae.

^b Acinetobacter (contaminant), anaerobe (contaminant), Bacteroides fragilis (pelvic inflammatory disease), Sphingobacterium multivorum (contaminant).

CoV-2 group had significantly ($p < 0.0001$) higher frequency of samples sent for pneumococcal and Legionella urinary antigens (Table 1). In total, 3.2% (27/836) had early confirmed bacterial isolates identified (0–5 days after admission), which rose to 6.1% (51/836) throughout admission.

Secondary bacterial infections

There was no significant difference in sampling rates (73% vs. 80%) or positivity rates (7.5% vs. 5.1%) between the two hospitals in this study. Despite substantial numbers of blood cultures being performed for patients with viral pneumonitis, there was a low yield among both the SARS-CoV-2 (60/643; 9.3%) and influenza (8/133; 6%) cohorts (Table 2). Among patients with SARS-CoV-2, true clinical pathogens were identified in 21 (3.2%) of 643 patients, with 39 (6.1%) of 643 classified as contaminants 36 coagulase-negative staphylococci, one Acinetobacter sp. (non-A. baumannii), one Streptococcus oralis and one Sphingobacterium multivorum. Bacteraemia resulting from respiratory infection was confirmed in two cases (one each CA Klebsiella pneumoniae and ventilator-associated Enterobacter cloacae). Line-related bacteraemia was identified in three patients (2 Enterococcus spp. and 1 Pseudomonas aeruginosa). The remaining 16 clinically significant bacteraemias among SARS-CoV-2 patients were CA acquired and unrelated to their COVID-19 presentation (six urinary tract infections, three skin and soft tissue infections, and one each pelvic inflammatory disease, postpartum infection, gastrointestinal translocation and upper respiratory tract infection. Among the comparator cohort of patients with influenza, two (1.5%) true blood culture pathogens were identified (one each Streptococcus pyogenes and S. aureus) with six (4.5%) of 133 contaminants. There was no significant difference between the SARS-CoV-2 and influenza cohorts for either true bacteraemias ($p 0.285$) or contaminants ($p 0.547$).

Respiratory samples for microbiologic culture were obtained from 112 (13.3%) of 836 SARS-CoV-2 patients, with 39 (34.8%) of 112 identifying bacterial pathogens; these were categorized as either CA or HA. Table 2 depicts these culture results, but two notable findings are firstly the preponderance of S. aureus as a CA pathogen (4/14 of early respiratory bacterial coinfections) and secondly the number of organisms not susceptible to simple β -lactams among HA bacterial secondary infections (9/25 Pseudomonas spp. and 8/25 AmpC-producing Enterobacterales). Respiratory samples were obtained from 38 (17.6%) of 216 influenza A/B patients, with similar overall significant bacterial pathogens compared to the SARS-CoV-2 cohort, with CA 10.5% (4/38) and HA 10.5% (4/38). Despite the

historical association between influenza and *S. aureus* secondary infections, we found none in our influenza cohort.

Secondary bacterial infections determined by urinary antigen testing

Among the SARS-CoV-2 cohort, 249 (29.8%) of 836 patients had samples sent to look for pneumococcal and 246 (29.4%) *Legionella* urinary antigens. None of these tests was positive. In the influenza cohort, compared to the SARS-CoV-2 patients, significantly fewer patients had pneumococcal (19/216; 8.8%; $p < 0.0001$) and *Legionella* (21/216; 9.7%; $p < 0.0001$) urinary antigens. Despite this lower testing frequency among the influenza cohort, one patient with influenza was also found to have a positive pneumococcal urinary antigen result.

Secondary fungal infections

Candida spp. and unspicated yeast isolated from respiratory samples were common (24/112; 21.4%). These isolates are likely to represent oropharyngeal thrush or normal flora rather than pulmonary candidiasis. Three patients, all requiring critical care admission, developed HA *Candida albicans* bacteraemia. All were attributed to central line-associated infections. Three culture-positive patients with *Aspergillus fumigatus* were identified; one patient was known to be colonized with this filamentous fungus that was not thought to currently represent a pathogen. The remaining two critical care patients with *A. fumigatus* were treated as possible infection but had follow-up negative galactomannan and 1,3- β -D-glucan (BDG) serum antigens, thus making invasive fungal infection less probable.

Concomitant (non-SARS-CoV-2) viral infections

Among the 836 SARS-CoV-2 patients, zero patients of 250 tested positive for influenza A/B or RSV. During flu season (until 6 April 2020), 70.5% (223/316) of patients were tested for respiratory virus. This dropped to 9.6% (26/270) from 7 April 2020.

Secondary bacterial and fungal infections and care area

Among the 836 admitted patients, 113 (13.5%) were admitted to a critical care ward during their admission. A critical care admission was associated with higher rates of BAL sampling (all 13 BAL were conducted on critical-care patients), isolation of yeast (23 of 30 all yeast respiratory isolates) and *Pseudomonas* spp. (11/13) from a clinical isolate.

Clinical outcomes

At the time of analysis among the 836 SARS-CoV-2 patients, 514, 262 and 60 patients were discharged, dead or current inpatients, respectively. Those patients who had true pathogens in their blood had an increased relative risk of death against baseline of admitted patients (relative risk 1.51, p 0.3543), but this was not reflected among those patients who had a positive culture from their sputum (relative risk 0.90, p 0.8462).

Discussion

Our observational study identified a low rate of laboratory-confirmed bacterial coinfection in patients with COVID-19. Blood culture results were available for the majority of admitted patients, but few clinically important pathogens were isolated. Two Gram-negative organisms, one CA *K. pneumoniae* and one

ventilator-associated *E. cloacae*, were attributed to respiratory-sourced infections. Central line (three *C. albicans*, two *Enterococcus* spp. and one *P. aeruginosa*) and urinary catheter (one *Escherichia coli*) sources accounted for the other HA bacteraemia. All other bacteraemias were community onset and were attributed to nonrespiratory infections. We advocate that culturing continue of blood samples taken from all COVID-19 patients, given the possibility of concomitant (either respiratory or non-respiratory) bacterial infections. A high proportion of blood culture contamination (36 coagulase-negative staphylococci and three other contaminants isolated in COVID-19 patients) was identified. This trend may be explained by unfamiliarity of additional personal protective equipment worn by healthcare workers taking blood samples from patients with suspected or confirmed COVID-19. We advocate that initial Gram-positive cocci in blood culture results be viewed in context of higher rates of contamination and escalation of empiric antimicrobials reserved unless patients are clinically deteriorating.

Among patients with confirmed SARS-CoV-2, concurrent influenza infection, invasive *Streptococcus pneumoniae* infection and legionellosis were not identified in any patients treated using the standard UK testing algorithms for CA pneumonia. In comparison, a similarly low yield was also identified among a control group of confirmed influenza patients admitted to a single site over the 2019–2020 winter season.

Sputum yield was low for true pathogens, and the significance of some culture results was unclear. CA *Enterobacter* spp. ($n = 2$), *Pseudomonas* spp. ($n = 3$) and *Serratia* spp. ($n = 1$) in this case series did not result in directed antibacterial therapy. *S. aureus* was the most commonly identified CA bacterial pathogen found in sputum, but the clinical significance remains unclear. The use of bronchoalveolar lavage was low in the COVID-19 patient group. This invasive intervention has a higher yield for identifying causative pathogens for respiratory infections but is defined as an aerosol-generating procedure, so it is contraindicated in COVID-19 patients to reduce risk of transmission [12,13].

Emerging data from North America highlight significant coinfection with rhinovirus/enterovirus (6.9%), RSV (5.2%) and non-SARS-CoV-2 *Coronaviridae* (4.3%) [14]. Our data suggest no coinfection between SARS-CoV-2 and influenza A/B and RSV, but extended virus testing was not available locally during the first wave of the COVID-19 outbreak. This may reflect the timing of the COVID-19 pandemic (March–April 2020) succeeding the traditional respiratory virus peak months of winter. PCR for atypical pathogens, such as *Mycoplasma* spp., was not available during the study period, and coinfection with nonculturable bacteria cannot be safely excluded either. The overlapping clinical presentation of COVID-19 and *Mycoplasma pneumoniae*, dry and unproductive cough, myalgia, and fever and headache make differential diagnosis challenging. Our local guidelines for hospitalized patients align with the NICE 2020 national guidance and include antibacterials to cover atypical/cell wall-deficient bacteria for all CA pulmonary infections.

The initial results of our retrospective analysis are limited to the short-term follow-up of these patients. The long-term impact of secondary fungal infections, notably among patients requiring ventilation or among any who go on to need immunomodulatory therapy, is not yet clear. This is a particular concern, given that data from influenza outbreaks of previous years suggest that late invasive fungal infection is a concern [15]. Specific to our interpretation of *Candida* spp. from respiratory tract samples as being representative of oropharyngeal candidiasis, the significance is unclear; most patients will have been receiving therapy with broad-spectrum antibacterials at the time of culture. Antigen testing for invasive fungal infections, such as BDG and galactomannan, are

advised locally for all COVID-19 patients admitted to critical care at day 7 of broad-spectrum antibacterial therapy.

Our study has several clear limitations. The retrospective design reduces control over multiple confounders and data collection. The study was limited to two hospitals in a single trust, with a short follow-up period (median, 7 days). Respiratory samples were not available for all patients; many of the patients were unable to produce sputum during their admission, and invasive respiratory sampling was restricted in order to minimize aerosol-generating procedures. Initial (empiric) antimicrobials may have selected out later (more resistant) bacterial culture results over accentuating *Pseudomonas* spp. and AmpC-producing *Enterobacterales*. The two groups differ substantially in age range infected, making direct comparisons challenging; the paediatric population had higher rates of influenza but were largely unaffected by the COVID-19 pandemic.

In conclusion, we find a low frequency of microbiologically confirmed bacterial coinfection present in confirmed SARS-CoV-2 patients admitted to secondary care in an urban UK setting. Antibacterial therapy, if indicated, should be prescribed in line with local guidelines and reviewed with clinical response at 48 to 72 hours. If no evidence of bacterial coinfection is found, then stopping antibacterial therapy should be considered. The incidence, nature and impact of late secondary bacterial and fungal infections is less clear, and further study is required.

Transparency declaration

LSPM has consulted for bioMérieux (2013–2020), DNAelectronics (2015), Dairy Crest (2017–2018), Pfizer (2018–2020) and Umovis Labs (2020); received speaker fees from Profile Pharma (2018); received research grants from the National Institute for Health Research (2013–2019), Leo Pharma (2016) and CW+Charity (2018–2019); and received educational support from Eumedica (2016–2017). NM has consulted for Pfizer (2019); and received educational support from Eumedica (2015) and Baxter (2017). SH has received educational support from Baxter (2017). All other authors report no conflicts of interest relevant to this article.

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