Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

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Summary: Current evidence does not support a high rate of bacterial respiratory co-infections in patients with SARS-COV-2 infection. Broad spectrum antibiotics are commonly prescribed. Nosocomial infections are reported during previous coronavirus outbreaks with SARS-1.

Abstract

Background: To explore and describe the current literature surrounding bacterial/fungal co-infection in patients with coronavirus infection.

Methods: MEDLINE, EMBASE, and Web of Science were searched using broad based search criteria relating to coronavirus and bacterial co-infection. Articles presenting clinical data for patients with coronavirus infection (defined as SARS-1, MERS, SARS-COV-2, and other coronavirus) and bacterial/fungal co-infection reported in English, Mandarin, or Italian were included. Data describing bacterial/fungal co-infections, treatments, and outcomes were extracted. Secondary analysis of studies reporting antimicrobial prescribing in SARS-COV-2 even in the absence of co-infection was performed.

Results: 1007 abstracts were identified. Eighteen full texts reported bacterial/fungal co-infection were included. Most studies did not identify or report bacterial/fungal coinfection (85/140;61%). 9/18 (50%) studies reported on COVID-19, 5/18 (28%) SARS-1, 1/18 (6%) MERS, and 3/18 (17%) other coronavirus.

For COVID-19, 62/806 (8%) patients were reported as experiencing bacterial/fungal co-infection during hospital admission. Secondary analysis demonstrated wide use of broad-spectrum antibacterials, despite a paucity of evidence for bacterial coinfection. On secondary analysis, 1450/2010 (72%) of patients reported received antimicrobial therapy. No antimicrobial stewardship interventions were described.

For non-COVID-19 cases bacterial/fungal co-infection was reported in 89/815 (11%) of patients. Broad-spectrum antibiotic use was reported.

Conclusions: Despite frequent prescription of broad-spectrum empirical antimicrobials in patients with coronavirus associated respiratory infections, there is a paucity of data to support the association with respiratory bacterial/fungal co-infection. Generation of prospective evidence to support development of antimicrobial policy and appropriate stewardship interventions specific for the COVID-19 pandemic are urgently required.

Keywords: SARS-COV-2, antimicrobial stewardship, antimicrobial resistance

Introduction

The emergence and subsequent pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) virus has required major adjustments to healthcare systems and frameworks.[1–3] As part of the response, infection control and antimicrobial stewardship programs have had to rapidly adapt in real-time in the face of an evolving body of evidence.[4–6]

Antimicrobials have several potential roles in the management of COVID-19. Experimental therapies for the treatment of SARS-COV-2 are being explored, for example hydroxychloroquine and azithromycin.[7] Antimicrobial therapy has a role in the treatment of suspected or confirmed bacterial or fungal (bacterial/fungal) respiratory co-infection. This may be empiric or targeted in patients presenting to hospital or for the management of nosocomial infection acquired during admission to hospital, such as hospital acquired pneumonia or ventilator associated pneumonia. Patients may also be suffering from secondary co-infections, not linked to their respiratory presentation, for example urinary tract or blood stream infection.

In terms of antimicrobial prescribing bacterial/fungal co-infection of the respiratory tract; some patients presenting to hospital with SARS-COV-2 infection have a clinical phenotype that is not dissimilar from atypical bacterial pneumonia.[1,2,8] Furthermore, SARS-COV-2 infection may also be difficult to distinguish from hospital acquired and ventilator associated pneumonia in hospital inpatients.[1,2,8] Patients often present febrile with respiratory symptoms, such as a dry cough, associated with bilateral chest x-ray changes.[1,2,8] Therefore, it is not unreasonable to treat empirically with antimicrobials for bacterial/fungal pneumonia in unwell patients.

Some national guidelines and cases series have suggested the use of broad-spectrum antibiotics[9,10] or the benefit of atypical antibiotic cover.[11]

It is anticipated that during the epidemic an increased number of patients will require commencement on empirical antimicrobial therapy. Therefore, it is important that antimicrobial stewardship programs focus on supporting the optimal selection of empirical therapies and the rapid de-escalation of treatment once SARS-COV-2 infection is confirmed. Given the suggested use of broad-spectrum agents and macrolides;[9–11] this is important to prevent unintended consequences of antimicrobial therapy including toxicity (such as QT prolongation),[12] antibiotic associated diarrhoea, and the propagation of antimicrobial resistance through increased usage of antimicrobials within healthcare systems.[13]

We performed a review of the medical literature to explore commonly reported bacterial/fungal co-infections in patients admitted to hospital with coronavirus lower respiratory tract infections. Given the lack of data surrounding SARS-COV-2 we also opted to include other coronavirus infections. Whilst acknowledging that evidence may differ between coronavirus infections, we wanted to explore whether similar observations have been made between these infections. We opted to include, Severe Acute Respiratory Syndrome (SARS-1), Middle Eastern Respiratory Syndrome (MERS), and other coronavirus infections.

Method

Search methods

This review was performed following PRISMA guidelines[14] using an online tool for evidence synthesis (Covidence; Australia). The review was conducted to identify common bacterial/fungal co-infections reported in patients diagnosed with coronavirus infections since January 2000. The MEDLINE and EMBASE databases were searched form 1st January 2000 to 18th April 2020 using a combination of broad-based (and wildcard) search criteria including, *coronavirus*, *COVID-19*, *SARS-1*, *MERS*, *bacterial*, *co-infection*. Given the rapidly evolving nature of the literature on SARS-COV-2, journal advanced articles in leading infection journals and bibliographies of relevant articles were also reviewed. Articles in English, Mandarin, and Italian were included.

Study selection and data extraction

Figure 1 summarises data extraction. Two authors (TMR and LSPM) independently screened study titles and abstracts against inclusion and exclusion criteria. Any article presenting clinical data for patients (adult or paediatric) diagnosed with coronavirus infection (defined as SARS-1, MERS, SARS-COV-2, and other coronavirus) and reported in English, Mandarin (reviewed by NZ), or Italian (reviewed by GS) was included for full text review. Abstracts without full text were excluded at this point.

Full texts in English were analysed by two authors (TMR and LSPM) independently of each other. Full texts in Mandarin and Italian were analysed by one individual (NZ and GS, respectively). Studies not reporting identification of any co-infection were

excluded at this point for two reasons. Firstly, the primary aim of this study was to identify commonly reported co-infections. Secondly, we did not set out to define absolute rates of co-infection within the population given the expected variation in methods of screening and reporting expected within the literature in the field. Data extracted included journal and publication details, coronavirus class, the population described, region, number of patients with reported coronavirus and bacterial or fungal co-infection, co-infecting organisms, organism sensitivity profiles, reported treatments, reported outcomes for patients. As part of a secondary analysis, studies that were identified as part of the literature search reporting antimicrobial prescribing but not necessarily reporting bacterial/fungal co-infection in COVID-19 cases were reviewed. Data reporting antibiotic prescribing, microbiological sampling undertaken, and reported complications of antimicrobial therapy were extracted.

Results

Study selection

In total, 1007 abstracts were identified for consideration. Three duplicates were excluded and 1004 abstracts were deemed irrelevant at the screening phase. Of the 140 texts that were reviewed for eligibility, a further 122 were excluded. Eighty-five full text articles excluded (85/122; 70%) either did not report on bacterial co-infection or did not identify any. The remaining 37/122 (30%) articles were excluded as they did not meet inclusion criteria on full text review. Eighteen full texts were included in the final report.[2,8,10,15–29]

Synthesis of results

Table 1 summarises the current evidence of bacterial/fungal co-infection in patients admitted to hospital with coronavirus.

Nine of eighteen (50%) studies reported COVID-19, 5/18 (28%) SARS-1, 3/18 (17%), 1/18 (6%) MERS. Of the COVID-19 studies, 7/9 (78%) reports were from China with 2/9 (22%) from the USA. Of non-COVID-19 studies, 2/9 (22%) were from China, 2/9 (22%) Hong Kong, 1/9 (11%) Taiwan, 1/9 (11%) Singapore, 1/9 (11%) Saudi Arabia, 1/9 (11%) Canada, and 1/9 (11%) South Korea.

Studies reporting on COVID-19[2,17–19,21,22,25,26,30] reported 62/806 (8%) of bacterial/fungal co-infection. Most studies failed to differentiate the setting where sampling was performed (critical versus non-critical care). The largest series reporting bacterial/fungal co-infection was reported by Goyal and colleagues in the USA.[22] In this study, the authors report 19/338 (6%) rate of bacteraemia during hospital admission. It is not clear whether these patients were in critical or non-

critical care and whether these were nosocomial in nature.[22] Zhou and colleagues reported observation of secondary bacterial infection in 28/191 (15%) of patients admitted to hospitals in China.[2] Of these patients with secondary bacterial infection, 27/28 died.[2] No further detail on the type of infection, methods of identification, and healthcare setting were provided. In a report of 99 patients all undergoing respiratory sampling on admission in China, Chen and colleagues report two patients with significant growth in their sputa. One individual had a polymicrobial infection with *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Aspergillus fumigatus* isolated from either sputum or tracheal aspirate.[25] Prior healthcare exposure and underlying respiratory conditions pre-disposing this individual are not described. The second individual with significant microbiology grew a *Candida albicans*. This organism is not normally regarded as a pathological organism when identified in culture from sputum.[31] Wang and colleagues, reported 29 of 69 patients undergoing sputum culture on admission to hospital to identify respiratory bacterial/fungal co-infection.[8] Of these, 5/69 (7%) had positive microbiology, including *Candida albicans* (2/5, 40%), *Enterobacter cloacae* (2/5, 50%), and *Acinetobacter baumannii* (1/5, 20%). Of all studies reporting bacterial/fungal co-infection in COVID-19, very few atypical organisms were identified with *Legionella pneumophila* identified in one obstetric patient admitted in China with COVID-19.[17]

Table 2 summarises the secondary analysis of 17 of full texts that reported microbiological sampling with no observed co-infections and or antimicrobial prescribing. [2,8,34–40,17,18,21,25,26,30,32,33] Kim and colleagues report 116 individual patients undergoing respiratory pathogen sampling for atypical organisms including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae.*[35] The authors report no atypical bacterial co-infection identified within this cohort. Similar findings

were reported by Wu and colleagues from China, where 148/201 patients underwent sputum culture for bacteria/fungi. No significant growth was reported.[37]

Despite low rates of bacterial/fungal co-infection reported in patients with COVID-19, high rates of antimicrobial prescribing are reported. Of 2010 patients reported within these studies, 1450 (72%) received antibacterial therapy. Where reported, selected agents tended to be broad-spectrum and empiric, being prescribed across critical and non-critical care settings. For example, Cao and colleagues report on 102 patients from critical and non-critical care in China.[40] Of these 101 (99%) received antibacterial therapy.[40] The report 87/102 (85%) receiving quinolone therapy, 34/101 (33%) cephalosporins, and 25/102 (25%) carbapenems. No bacterial/fungal co-infection was reported in this study.[40] Guan and colleagues report on 1099 patients admitted to critical and non-critical care settings in China.[33] Of these 637/1099 (58%) received antibacterial and 31/1099 (3%) antifungal therapy. No microbiology was reported in this study.[33] Complications of antimicrobial therapy were not reported in any study.

Reported bacterial/fungal co-infection was greater in other coronavirus studies compared to COVID-19. Overall, 90/815 (11%) of reported patients has identified bacterial/fungal co-infection. In a review of 349 critically ill patients with MERS in Saudi Arabia, Arabi and colleagues identified atypical bacterial co-infection in 5/349 (1%) instances on admission. Atypical organisms identified were Mycoplasma spp. (3/5), Legionella (1/5), and Chlamydia spp (1/5). However, only 6 to 17 patients appear to have been investigated for atypical organisms.[27] This may reflect physician screening preferences based on clinical presentation. Despite low rates of

confirmed bacterial co-infection, the use of empirical broad-spectrum antimicrobials was once again widely reported with 326/349 (93%) patients receiving antibacterial agents.[27]

Of studies reporting SARS-1 42/135 (31%) of reported cases had bacterial/fungal co-infection. During the SARS-1 outbreak in the early 2000s, Yap and colleagues reported nosocomial infection in a series of 83 patients managed within intensive care. The authors report increased rates of *Meticillin Resistance Staphylococcus aureus (MRSA)*, *Stenotrophomonas spp*., and *Acinetobacter baumannii* in an intensive care unit that cared for 83 SARS-1 patients during a three-month period.[29] This included 30 episodes of ventilator associated pneumonia and 23 cases of MRSA transmission. This period was associated with significant increases in antimicrobial usage within the intensive care unit.[29]

For other coronavirus infections, bacterial/fungal co-infection were observed in 43/331(13%) of cases.[10,20,23] These co-infections were for a range of Gram-positive (10/43, 23%), Gram-negative (23/43, 53%), and atypical bacteria (10/43, 23%). No data on antimicrobial susceptibility and prescribing was reported in these studies.

Discussion

Rates of bacterial or fungal co-infection reported in the current medical literature for patients presenting with coronavirus infections appear to be low. Of nine studies reporting bacterial co-infection in COVID-19 cases, 62/806 (8%) cases of bacterial/fungal co-infection were reported. Use of broad-spectrum antimicrobial therapy was widely reported with 72% of COVID-19 cases receiving antibacterial therapy.

Selection of empiric antimicrobial therapy for respiratory bacterial/fungal co-infection and recommendations for duration of treatment require several considerations. As the pre-test probability of SARS-COV-2 positive presentations increase, the role of empirical atypical coverage needs to be considered. There have been concerns associated with the potential of sudden cardiac arrest secondary to QT prolongation that is associated with many of the agents we use for atypical infection.[12] The mainstay of treatment for atypical organisms are the macrolides, tetracyclines, and quinolones. Some of these can prolong QT and therefore the potential benefits of such treatment must be carefully balanced against risks.[12] Macrolides have also been associated with potential antiviral effect in combination with hydroxychloroquine, but also have a potential synergistic effect on QT prolongation.[11] Current evidence reported from MERS cohorts does not suggest any added benefit from the use of macrolides in the treatment of ARDS associated with coronavirus infection.[27] Furthermore, very few atypical bacterial co-infections have been identified in reports of COVID-19 cases to date. Therefore, the potential unintended consequences of prolonged macrolide use must be weighed against potential likelihood of atypical bacterial co-infection within COVID-19 cohorts.

A further concern with the rapid expansion of critical care capacity to manage SARS-COV-2 is the potential increased rate of nosocomial infection within the hospital environment.[41] Whilst many studies reported failed to separate reporting on critical and non-critical care settings, a large proportion of reported bacterial co-infections within coronavirus literature appear to be healthcare associated, including central-line associated blood stream infections, and ventilator associated pneumonia.[8,24–26,29] With observed strain being placed on healthcare systems currently during the upstroke of the SARS-COV-2 pandemic; guidelines must focus on maintenance of good infection control, antimicrobial stewardship, and robust surveillance for HCAIs and antimicrobial resistance. Ensuring access to core antimicrobials must also be a primary goal.

Potential stewardship interventions to support reduced antimicrobial prescribing during the COVID-19 pandemic urgently require consideration.[41] Traditional markers used to support antimicrobial decisions, such as vital signs, blood tests like white cell count and C-reactive protein, and imaging tend to be abnormal in SARS-COV-2 infection.[1–3] This makes decision making surrounding the requirement for empiric antibacterial cover challenging. Furthermore, with fears surrounding prolonged patient contact and aerosol generation, the number of patients undergoing routine microbiological investigation may be reduced.[41]

One potential solution to support antimicrobial prescribing in COVID-19 is the use of bacterial specific biomarkers, such as procalcitonin.[42] Procalcitonin has been demonstrated to support differentiation between bacterial and viral infection and supports early cessation of antibiotics in confirmed bacterial infection with no effect on patient mortality.[42,43] Procalcitonin use has been reported in the COVID-19 literature and may be an important tool to support reducing antimicrobial

use.[8,17,19,22,25,30,33] Furthermore, the use of clinical decision support systems may facilitate better use of data in supporting decision making, especially when linked with artificial intelligence.[44]

In addition, infection specialties who are normally responsible for co-ordinating stewardship programs must continue to provide support to clinical teams managing COVID-19 patients to ensure that regular review and cessation of antimicrobial therapy is considered based on the limited clinical evidence available within these patients.[41] Supporting appropriate microbiological sampling prior to commencement of antimicrobial therapy should also be encouraged within this patient cohort to ensure that the clinician has as much data as possible to support decision making.

With medication shortages, including key antimicrobials, being a concern across areas currently affected by the pandemic,[45,46] judicious use of antimicrobials will be vital to ensure access to therapy by those with confirmed bacterial infection. With a growing body of evidence supporting short-course antimicrobial therapy,[47] guidelines and stewardship programs during this time should reflect this.

Evidence also supports the safety of early oral versus intravenous antibiotics for a range of infections including bone and joint infection, infective endocarditis, and lower respiratory tract infection.[48–51] With a need to ensure that bed capacity is maintained, a focus on developing guidance on optimal pharmacokinetic-pharmacodynamic strategies for common infections requiring antimicrobial should be considered to support early oral antibiotic switch and treatment de-escalation in patients with short- and long-term infections.[52,53]

This review had several limitations that must be considered. The rapidly evolving nature of the COVID-19 pandemic means that data is continuously evolving. This study included coronavirus infections from predominantly Asia, which may limit the generalisability of the findings. Furthermore, the studies described often did not uniformly report or undertake examination for bacterial co-infection, which may have under or over-estimated the rates of respiratory bacterial co-infection. Our decision to exclude studies reporting no observed bacterial co-infections may also have over-estimated the rate of respiratory bacterial/fungal co-infection. Similarly, many studies failed to differentiate the healthcare setting and stage of COVID-19 infection where co-infection was identified. This makes differentiating community co-infection from nosocomial co-infection, such as hospital acquired pneumonia or ventilator associate pneumonia in critical care, difficult. Finally, studies presented in this manuscript were not graded for quality and potential bias, making it difficult to weight any recommendations based on currently evidence.

Conclusion

Despite the extensive reporting of broad-spectrum empirical antibiotic prescribing in patients with coronavirus respiratory infections, there is a paucity of data to support their association with bacterial/fungal co-infection. With increasing pressure on healthcare infrastructure during the COVID-19 pandemic, a general evidence-base on which to develop antimicrobial prescribing and stewardship strategies is required to support optimal treatment outcomes and prevention of the unintended consequences of antimicrobial usage on the individual and wider society. These must be supported by appropriately powered, prospective clinical studies focusing on the prescription and stewardship of antimicrobial therapy where possible.

Notes

Author contributions

TMR & AH developed the concept and methodology for the review. TMR, LSPM, NZ, and GS undertook data extraction and reviewing. All authors contributed significantly to data interpretation. TMR drafted the initial manuscript. All authors contributed significantly to the revision of the manuscript and finalisation for submission.

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Transparency declarations

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14. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist SECTION ITEM PRISMA-ScR CHECKLIST ITEM REPORTED ON PAGE # TITLE Title 1 Identify the report as a scoping review.

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Figure 1. PRISMA flow diagram outlining study selection

Table 1. Summary of papers describing hospital patients with coronavirus and bacterial or fungal infections.

Author	Coronavirus	Population	Region	Number of co-infected patients	Identified organisms	Sensitivity profiles	Reported treatments in co-infected patients	Reported outcomes for co-infected patients
Chen et al. 2020	COVID19	99 adult patients	China	2/99 patients	Patient 1: Acinetobacter baumannii, Klebsiella pneumoniae, and Aspergillus flavus in respiratory samples Patient 2: Candida glabrata	Acinetobacter baumannii - highly resistant	NR	NR
Wang et al 2020	COVID19	29/69 adult patients undergoing sputum culture	China	5/29 patients	Candida albicans (2/5) Enterobacter cloacae (2/5) Acinetobacter baumannii (1/5)	NR	Moxifloxacin empirically	NR
Dong et al. 2020	COVID-19	11 adult cases	China	1/11 patient	On admission: Gram-positive and Gram-negative organisms seen in sputum (no identification provided)	NR	Broad spectrum antibiotics and caspofungin– agent in co-infected NR	NR
Yu et al. 2020	COVID-19	7 obstetric patients admitted to hospital	China	1/7 patients	Legionella pneumophillia (1)	NR	NR for individual patient (Cephalosporins, quinolones, macrolides prescribed in general)	Good outcomes, no ICU admission
Chen et al. 2020	COVID-19	29 patients admitted to hospital	China	1/29 patients	1 with bacterial coinfection, organism NR	NR	Antibiotics prescribed, agents NR	1 patient with bacterial co-infection died
Goyal et al. 2020	COVID-19	338 patients admitted to hospital	USA	19/338 patients with bacteraemia during admission	19 with bacteraemia during admission – organism NR	NR	NR	NR

Huang et al. 2020	COVID-19	41 patients admitted to hospital	China	4/41 developed secondary bacterial infections in ICU	NR 3/4 had elevated procalcitonin >0.5 ng/mL	NR	Antibacterial agent prescribed – agent NR	NR
Arentz et al. 2020	COVID-19	21 adults admitted to critical care	USA	1/21 reported to have evidence of bacterial co-infection	NR	NR	NR	NR
Zhou et al. 2020	COVID-19	191 adults admitted to hospital	China	28/191 reported to have developed	NR	NR	NR specifically for secondary infection. 181/191 overall received antibacterials	27/28 with secondary infection died
Kozak et al. 2020	Coronavirus (other)	266 adults admitted to hospital OC43 50% 299E 22.3% HKU1 13.9% NL63 13.7%	Canada	17/266 patients with bacterial co-infection	Capnocytophagia spp (1/16) Coagulase-negative Staphylococci (4/16) Escherichia coli (2/16) Haemophilus influenzae (2/16) Moraxella spp (3/16) Streptococcus pneumoniae (3/16) Klebsiella pneumoniae (1/16) Pseudomonas aeruginosa (1/16)	NR	NR	NR
Arabi et al. 2019	MERS	349 Critically ill adults with MERS	Saudi Arabia	5/349 patients with identified atypical co-infection	Coinfection on admission: Legionella (1/5) Chlamydia (1/5) Mycoplasma (3/5)	NR	Macrolides did not alter outcome in patients with MERS	
Zeng et al. 2019	Coronavirus (other)	21/287 coronavirus infection cases from patients hospitalised with acute respiratory infection admitted from 2015-2017	China	7/21 patients with clinical isolates	7 clinical isolates from 7 cases (7/287), Klebsiella pneumoniae (3/7), Staphylococcus aureus (2/7), Streptococcus pneumoniae (1/7), Pseudomonas aeruginosa (1/7)	NR	NR	NR

Jung et al. 2017	Coronavirus (other)	233 / 5298 patient identified as having mixed viral-bacterial infection	South Korea	19/44 patients with coronavirus positive PCR and evidence of pneumonia on CXR with detection of bacterial co-pathogen	< 16 years: Pseudomonas spp (1/6) Mycoplasma spp (5/6) > 16 years: Acinetobacter spp (3/13) Klebsiella spp (3/13) Pseudomonas spp (2/13) Other (5/13)	NR	NR	NR
Tan et al. 2005	SARS-1	10 adult, surgical patients	Singapore	8/10 patients 15 organisms identified	Blood/Line: Escherichia coli (1/15), MRSA (2/15), Klebsiella pneumonia (1/15) Urine: Klebsiella pneumoniae (2/15), Citrobacter spp (1/15), MRSA (1/15) Bile: Klebsiella spp (1/15), Enterococcus spp (1/15), MRSA (1/15) Wound: Pseudomonas aeruginosa (1/15), MRSA (1/15), Enterococcus spp (1/15), Other coliforms (1/15), Staphylococcus aureus (1/15)	NR	NR	2/10 with infection died of respiratory complications
Yap et al. 2004	SARS-1	83 adult admissions to ICU with SARS between March and May 2003	Hong Kong	83/83	Increased rate of nosocomial MRSA transmission with 23 cases identified 30 episodes of VAP with MRSA (47.1%), Stenotrophomonas species (29.4%), and Acinetobacter species (14.7%). Rates of Pseudomonas and Klebsiella fell during this period. Sampling was predominantly from respiratory, blood, and urine samples.	NR	Significant increase in antimicrobial usage in ICU e.g.: Quinolone use increased from < 100 to > 250 DDD / 1000 patient days Carbapenem use increased from < 100 to > 180 DDD / 1000	NR

							patient days	
Jang et al. 2004	SARS-1	29 adults with SARS in Taiwan November 2002 - March 2003	Taiwan	3/29 patients had positive microbiology	Admission: Streptococcus pneumoniae Mycoplasma pneumoniae Legionella species	NR	NR	4/29 died 2 deaths secondary to sepsis (1 confirmed blood culture) 1 secondary bacterial pneumonia
Nicholls et al. 2003	SARS-1	Six adult patients undergoing post mortem examination including lung biopsy	Hong Kong	1/6 patient who had been intubated for 16 days	No significant growth whilst alive Pseudomonas aeruginosa on post mortem biopsy	NR	Doxycycline Cefotaxime	Co-infected patient died 16 days after presentation
Wang et al. 2003	SARS-1	Seven adult patients with SARS undergoing respiratory sampling	China	7/7 patients 24/76 specimens from sputum, blood and urine 30 organisms cultured from 24 samples	Gram-positive 8/30: Staphylococcus aureus (2), Staphylococcus haemolyticus (3), Staphylococcus epidermidis (2), Enterococcus faecium (1) Gram-negative 9/30 Acinetobacter baumannii (5), Pseudomonas aeruginosa (1), Enterobacter cloacae (1), Klebsiella aerogenes (1), Pasteurella multocida (1) Fungal 13/30 Not reported	Vancomycin S 100% (GPC) Imipenem S 100% Piperacillin-Tazobactam S 44% Fluconazole S 92.4% Staphylococcus aureus 50% resistant to Trimethoprim/Sulfamethoxazole, gentamicin; 100% resistant to Amoxicillin/Clavulanic acid, Ampicillin/Sulbactam, Cefazolin, Ciprofloxacin, Clindamycin, Erythromycin, Oxacillin, Penicillin, Tetracycline, Levofloxacin. Acinetobacter baumannii 40% resistant to Tobramycin; 60% resistant to	NR	All 7 deceased patients had secondary bacterial infections (18 episodes in total), 5 patients with more than 1 episode, 2 patients had monomicrobial infection, 5 had polymicrobial

	meropenem; 80% resistant to piperacillin/tazobactam; 100% resistant to Aztreonam, Ciprofloxacin, Levofloxacin, Gentamicin, Ceftazidime, Cefepime, Cefotetan, Ampicillin, Ceftriaxone, Amikacin Pseudomonas aeruginosa 100% resistant to Imipenem, meropenem, Levofloxacin, Gentamicin, Cefotetan, Ampicillin, Ceftriaxone	infection

Legend: SARS-1 = Severe Acute Respiratory Syndrome 1; MERS = Middle Eastern Respiratory Syndrome; COVID – 19 = novel coronavirus infection 2019; NR = not reported

Table 2. Summary of COVID-19 studies reporting of antimicrobial prescribing or no bacterial or fungal co-infection identified as part of the literature search

Author	Population	Region	Setting	Microbiology samples sent	Antimicrobials prescribed	Complications of therapy
Bhatraju et al. 2020	24 adult cases in in critical care	USA	Critical care	15/24 sputum sampling 4/24 broncho-alveolar lavage 20/24 blood cultures No growth from all 29 samples	NR	NR
Cao et al. 2020	102 patients admitted to hospital	China	Non-critical care and critical care	NR	99% treated with antibacterial therapy - Quinolones (85.3%) - Cephalosporins (33.3%) - Carbapenems (24.5%) - Linezolid (4.9%)	NR
Chen et al. 2020	99 patients admitted to hospital	China	Non-critical care and critical care	Sputum & endotracheal aspirates taken during admission 2/99 yielded significant results	70/99 received anti-bacterial treatment: - Cephalosporins, quinolones, carbapenems, tigecycline, & linezolid 15/99 received antifungal treatment: - NR	NR
Chen et al 2020	29 adult cases admitted to hospital	China	NR	NR	29/29 patients received antibiotic therapy - Agents NR	NR

Dong et al. 2020	11 patients treated in hospital	China	Non-critical care and critical care	Sputum and respiratory PCR reported	3/11 antibacterials: - Moxifloxacin (2) - Cefoperazone-sulbactam (1) - “antibiotics” (1) 1/11 antifungal - Caspofungin (1)	NR
Guan et al. 2020	1099 patients admitted to hospital	China	Non-critical care and critical care	NR	Antibacterial therapy 637/1099 Antifungal therapy 31/1099	NR
Holshue et al. 2020	1 patient admitted to hospital	USA	Non-critical care	Nasal PCR screen for MRSA Serial procalcitonin samples No positive results	Vancomycin & cefepime	NR
Huang et al. 2020	41 patients admitted to hospital	China	Non-critical care and critical care	Routine bacterial and fungal cultures - NR	41/41 received antibacterial therapy - Agents NR	NR

Kim et al. 2020	116 patients with confirmed SARS-COV-2	USA	Non-critical care and critical care	116/116 respiratory pathogen PCR including: - Chlamydia pneumoniae - Mycoplasma pneumoniae No bacteria identified	NR	NR
Liu et al. 2020	2 patients admitted to hospital	Taiwan	Non-critical care	Nasopharyngeal respiratory pathogen PCR No positive results	1/2 received antibacterial therapy - Levofloxacin (1)	NR
Paret et al. 2020	2 febrile infants admitted to hospital	USA	Non-critical care	Blood, urine and respiratory tract sampling 2/2 CSF sample 1/2 No significant bacterial or fungal culture identified	Case 1: ampicillin and cefepime Case 2: ceftriaxone	NR
Wang et al. 2020	69 patients admitted to hospital	China	NR	29/69 patients underwent sputum culture 5 were positive	66/69 patients received antibacterial therapy - 39/66 moxifloxacin - Further NR 8/69 patients received antifungal therapy - NR	NR

Wang et al. 2020	138 patients admitted to hospital	China	Non-critical care and critical care	NR	89/138 moxifloxacin 34/138 ceftriaxone 25/138 azithromycin	NR
Wu et al. 2020	201 patients admitted to hospital	China	Non-critical care and critical care	148/201 underwent sputum culture for bacterial and fungal pathogens No significant growth reported	170/201 received empirical antibacterial therapy - Agents NR	NR
Young et al. 2020	18 patients admitted to hospital	Singapore	Non-critical care and critical care	NR	Empirical broad spectrum antibiotics for those with suspected CAP - Number treated NR	NR
Yu et al. 2020	7 obstetric patients admitted to hospital	China	Non-critical care	NR	7/7 patients received antimicrobial therapy: - 2/7 monotherapy - 5/7 combination therapy Cephalosporins, quinolones, macrolides prescribed	NR

Zhou et al. 2020	191 patients admitted to hospital	China	Non-critical care and critical care	28/191 reported to have secondary bacterial infection	181/191 received antibiotic therapy	NR

Legend: NR = not reported, USA = United States of America

Figure 1. PRISMA flow diagram outlining study selection