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Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing

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

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

Results. 1007 abstracts were identified. Eighteen full texts reporting bacterial/fungal coinfection were included. Most studies did not identify or report bacterial/fungal coinfection (85/140; 61%). Nine of 18 (50%) studies reported on COVID-19, 5/18 (28%) on SARS-1, 1/18 (6%) on MERS, and 3/18 (17%) on other coronaviruses. For COVID-19, 62/806 (8%) patients were reported as experiencing bacterial/fungal coinfection 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 coinfection 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 coinfection. Generation of prospective evidence to support development of antimicrobial policy and appropriate stewardship interventions specific for the COVID-19 pandemic is urgently required.

Keywords. SARS-CoV-2; antimicrobial stewardship; antimicrobial resistance.

The emergence of 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 coronavirus disease 2019 (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 coinfection. This may be empiric or targeted in patients presenting to the 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 coinfections, not linked to their respiratory presentation—for example, urinary tract or blood stream infection.

In terms of antimicrobial prescribing for bacterial/fungal coinfection of the respiratory tract, some patients presenting to the 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

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cough, associated with bilateral chest X-ray changes [1, 2, 8]. Therefore, it is not unreasonable to treat unwell patients empirically with antimicrobials for bacterial/fungal pneumonia. Some national guidelines and cases series have suggested the use of broad-spectrum antibiotics [9, 10] or of the benefit of "cover for atypical bacteria" [7].

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 [7, 9, 10], this is important to prevent unintended consequences of antimicrobial therapy including toxicity (such as QT prolongation) [11], antibiotic-associated diarrhea, and the propagation of antimicrobial resistance through increased usage of antimicrobials within healthcare systems [12].

We performed a review of the medical literature to explore commonly reported bacterial/fungal coinfections in patients admitted to the hospital with coronavirus lower respiratory tract infections. Given the lack of data surrounding SARS-CoV-2 we also opted to include other coronavirus infections. While 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 [13] using an online tool for evidence synthesis (Covidence; Australia). The review was conducted to identify common bacterial/fungal coinfections reported in patients diagnosed with coronavirus infections since January 2000. The MEDLINE and EMBASE databases were searched from 1 January 2000 to 18 April 2020 using a combination of broad-based (and wildcard) search criteria, including coronavirus, COVID-19, SARS-1, MERS, bacterial, coinfection. 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 summarizes data extraction. Two authors (T. M. R. and L. S. P. M.) independently screened study titles and abstracts against inclusion and exclusion criteria. Any article presenting clinical data for patients (adult or pediatric) diagnosed with coronavirus infection (defined as SARS-1, MERS, SARS-CoV-2, and other coronavirus) and reported in English, Mandarin (reviewed by N. Z.), or Italian (reviewed by G. S.) was included for full-text review. Abstracts without full text were excluded at this point.

Full texts in English were analyzed by 2 authors (T. M. R. and L. S. P. M.) independently of each other. Full texts in Mandarin and Italian were analyzed by 1 individual (N. Z. and G. S., respectively). Studies not reporting identification of any coinfection were excluded at this point for 2 reasons. First, the primary aim of this study was to identify commonly reported coinfections. Second, we did not set out to define absolute rates of coinfection 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 coinfection, coinfecting organisms, organism sensitivity profiles, reported treatments, and 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 coinfection 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 864 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 coinfection or did not identify any. The remaining 37 of 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, 14–28].

Synthesis of Results

Table 1 summarizes the current evidence of bacterial/fungal coinfection in patients admitted to the hospital with coronavirus.

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

Studies reporting on COVID-19 [2, 16–18, 20, 21, 24, 25, 29] reported 62 of 806 (8%) cases of bacterial/fungal coinfection. Most studies failed to differentiate the setting where sampling

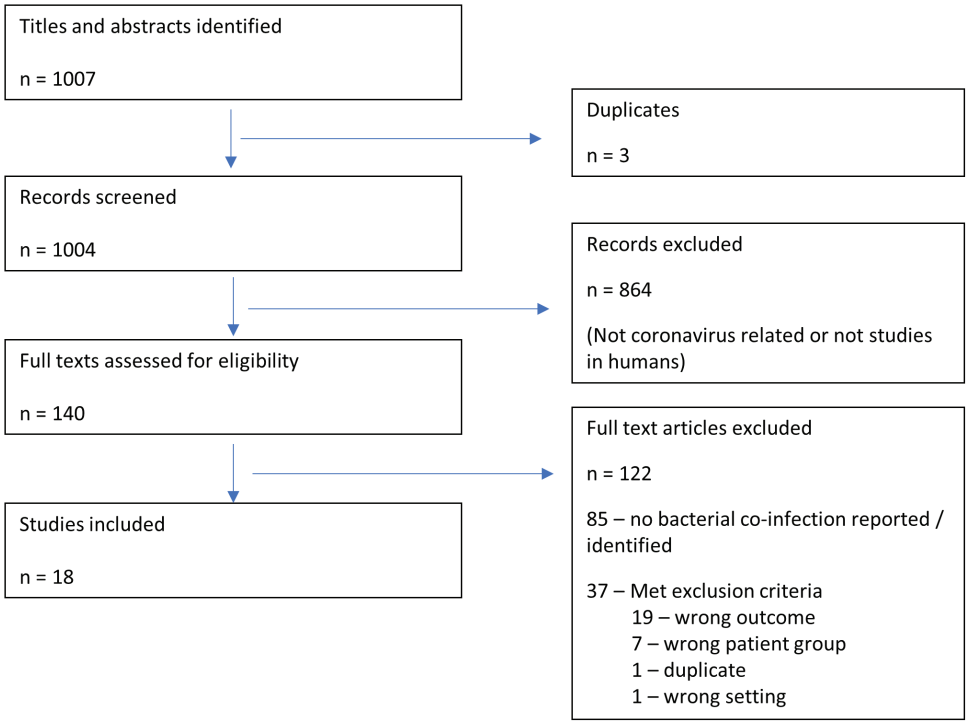

Figure 1. PRISMA flow diagram outlining study selection. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

was performed (critical vs noncritical care). The largest series reporting bacterial/fungal coinfection was reported by Goyal and colleagues [21] in the United States. In this study, the authors reported 19 of 338 (6%) cases of bacteremia during hospital admission. It is not clear whether these patients were in critical or noncritical care and whether these were nosocomial in nature [21]. Zhou and colleagues [2] reported observation of secondary bacterial infection in 28 of 191 (15%) patients admitted to hospitals in China. Of these patients with secondary bacterial infection, 27 of 28 died [2]. No further details 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 [24] reported 2 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. Prior healthcare exposure and underlying respiratory conditions predisposing 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 [30]. Wang and colleagues [8] reported 29 of 69 patients undergoing sputum culture on admission to the hospital to identify respiratory bacterial/fungal coinfection. Of these, 5 of 69 (7%) had positive microbiology, including *C. albicans* (2/5, 40%), *Enterobacter cloacae* (2/5, 50%), and *A. baumannii* (1/5, 20%). Of all studies reporting bacterial/fungal coinfection in COVID-19, very few atypical organisms were identified, with *Legionella pneumophila* identified in 1 obstetric patient admitted in China with COVID-19 [16].

Table 2 summarizes the secondary analysis of 17 full texts that reported microbiological sampling with no observed coinfections and/or antimicrobial prescribing [2, 8, 16, 17, 20, 24, 25, 29, 31–39]. Kim and colleagues [34] report 116 individual patients undergoing respiratory pathogen sampling for atypical organisms, including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. The authors report no atypical bacterial coinfection identified within this cohort. Similar findings were reported by Wu and colleagues [36] from China, where 148 of 201 patients underwent sputum culture for bacteria/fungi. No significant growth was reported.

Despite low rates of bacterial/fungal coinfection 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 noncritical care settings. For example, Cao and colleagues [39] report on 102 patients from critical and noncritical care in China. Of these, 101 (99%) received antibacterial therapy [39]. The reported 87 of 102 (85%) patients received quinolone therapy, 34 of 101 (33%) received cephalosporins, and 25 of 102 (25%) received carbapenems. No bacterial/fungal coinfection was reported

Table 1. Summary of Papers Describing Hospital Patients With Coronavirus and Bacterial or Fungal Infections

Study	Coronavirus	Population	Region	Number of Coinfected Patients	Identified Organisms	Sensitivity Profiles	Reported Treatments in Coinfected Patients	Reported Outcomes for Coinfected Patients
Chen et al. 2020 [24]	COVID-19	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 [8]	COVID-19	29/69 Adult patients undergoing sputum culture	China	5/29 Patients	*Candida albicans* (2/5 patients), *Enterobacter cloacae* (2/5 patients), *Acinetobacter baumannii* (1/5 patients)	NR	Moxifloxacin empirically	NR
Dong et al. 2020 [25]	COVID-19	11 Adult cases	China	1/11 Patients	On admission: gram-positive and gram-negative organisms seen in sputum (no identification provided)	NR	Broad-spectrum antibiotics and caspofungin– agent in coinfected NR	NR
Yu et al. 2020 [16]	COVID-19	7 Obstetric patients admitted to hospital	China	1/7 Patients	*Legionella pneumophilia* (1 patient)	NR	NR for individual patient (cephalosporins, quinolones, macrolides prescribed in general)	Good outcomes, no ICU admission
Chen et al. 2020 [20]	COVID-19	29 Patients admitted to hospital	China	1/29 Patients	1 patient with bacterial coinfection, organism NR	NR	Antibiotics prescribed, agents NR	1 Patient with bacterial coinfection died
Goyal et al. 2020 [21]	COVID-19	338 Patients admitted to hospital	USA	19/338 Patients with bacteremia during admission	19 patients with bacteremia during admission—organism NR	NR	NR	NR
Huang et al. 2020 [17]	COVID-19	41 Patients admitted to hospital	China	4/41 Developed secondary bacterial infections in ICU	NR; 3/4 patients had elevated procalcitonin >0.5 ng/mL	NR	Antibacterial agent prescribed—agent NR	NR
Arentz et al. 2020 [18]	COVID-19	21 Adults admitted to critical care	USA	1/21 Reported to have evidence of bacterial coinfection	NR	NR	NR	NR
Zhou et al. 2020 [2]	COVID-19	191 Adults admitted to hospital	China	28/191 Reported to have developed secondary infection	NR	NR	NR specifically for secondary infection; 181/191 overall received antibacterials	27/28 with secondary infection died
Kozak et al. 2020 [19]	Coronavirus (other)	266 Adults admitted to hospital: OC43, 50%; 299E, 22.3%; HKU1, 13.9%; NL63, 13.7%	Canada	17/266 Patients with bacterial coinfection	*Capnocytophagia* spp. (1/17 patients), coagulase-negative *Staphylococci* (4/17 patients), *Escherichia coli* (2/17 patients), *Haemophilus influenzae* (2/17 patients), *Moraxella* spp. (3/17 patients), *Streptococcus pneumoniae* (3/17 patients), *Klebsiella pneumoniae* (1/17 patients), *Pseudomonas aeruginosa* (1/17 patients)	NR	NR	NR
Arabi et al. 2019 [26]	MERS	349 Critically ill adults with MERS	Saudi Arabia	5/349 Patients with identified atypical coinfection	Coinfection on admission: Legionella (1/5 patients), Chlamydia (1/5 patients), Mycoplasma (3/5 patients)	NR	Macrolides did not alter outcome in patients with MERS	

Table 1. Continued

Study	Coronavirus	Population	Region	Number of Coinfected Patients	Identified Organisms	Sensitivity Profiles	Reported Treatments in Coinfected Patients	Reported Outcomes for Coinfected Patients
Zheng et al. 2019 [10]	Coronavirus (other)	21/287 Coronavirus infection cases from patients hospitalized with acute respiratory infection admitted from 2015–2017	China	7/21 Patients with clinical isolates	7 Clinical isolates from 7 cases: *Klebsiella pneumoniae* (3/7 patients), *Staphylococcus aureus* (2/7 patients), *Streptococcus pneumoniae* (1/7 patients), *Pseudomonas aeruginosa* (1/7 patients)	NR	NR	NR
Jung et al. 2017 [22]	Coronavirus (other)	233/5298 Patients 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 patients), *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 [23]	SARS-1	10 Adult surgical patients	Singapore	8/10 Patients 15 organisms identified	Blood/line: *Escherichia coli* (1/15 identified organisms), MRSA (2/15), *Klebsiella pneumoniae* (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 [28]	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: eg, quinolone use increased from <100 to >250 DDD/1000 patient-days; carbapenem use increased from <100 to >180 DDD/1000 patient-days	NR
Jang et al. 2004 [27]	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

Table 1. Continued

Study	Coronavirus	Population	Region	Number of Coinfected Patients	Identified Organisms	Sensitivity Profiles	Reported Treatments in Coinfected Patients	Reported Outcomes for Coinfected Patients
Nicholls et al. 2003 [14]	SARS-1	6 Adult patients undergoing post mortem examination including lung biopsy	Hong Kong	1/6 patients who had been intubated for 16 days	No significant growth while alive; *Pseudomonas aeruginosa* on post mortem biopsy	NR	Doxycycline, cefotaxime	Coinfected patient died 16 days after presentation
Wang et al. 2003 [15]	SARS-1	7 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 organisms): *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 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	NR	All 7 deceased patients had secondary bacterial infections (18 episodes in total), 5 patients with >1 episode, 2 patients had monomicrobial infection, 5 had polymicrobial infection

Abbreviations: COVID-19, novel coronavirus disease 2019; CXR, chest X-ray; GPC, gram-positive cocci; ICU, intensive care unit; MERS, Middle Eastern respiratory syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; PCR, polymerase chain reaction; SARS-1, severe acute respiratory syndrome 1; VAP, ventilator-associated pneumonia.

Table 2. Summary of coronavirus disease 2019 Studies Reporting Antimicrobial Prescribing or No Bacterial or Fungal Coinfection Identified as Part of the Literature Search

Study	Population	Region	Setting	Microbiology Samples Sent	Antimicrobials Prescribed	Complications of Therapy
Bhatraju et al. 2020 [31]	24 Adult cases in critical care	USA	Critical care	15/24 sputum sampling, 4/24 bronchoalveolar lavage, 20/24 blood cultures; no growth from all 29 samples	NR	NR
Cao et al. 2020 [39]	102 Patients admitted to hospital	China	Noncritical 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 [24]	99 Patients admitted to hospital	China	Noncritical care and critical care	Sputum and endotracheal aspirates taken during admission; 2/99 yielded significant results	70/99 received antibacterial treatment: cephalosporins, quinolones, carbapenems, tigecycline, and linezolid; 15/99 received antifungal treatment: NR	NR
Chen et al 2020 [20]	29 Adult cases admitted to hospital	China	NR	NR	29/29 Patients received antibiotic therapy: agents NR	NR
Dong et al. 2020 [25]	11 Patients treated in hospital	China	Noncritical 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 [32]	1099 Patients admitted to hospital	China	Noncritical care and critical care	NR	Antibacterial therapy: 637/1099; antifungal therapy: 31/1099	NR
Holshue et al. 2020 [33]	1 Patient admitted to hospital	USA	Noncritical care	Nasal PCR screen for MRSA, serial procalcitonin samples; no positive results	Vancomycin and cefepime	NR
Huang et al. 2020 [17]	41 Patients admitted to hospital	China	Noncritical care and critical care	Routine bacterial and fungal cultures; NR	41/41 received antibacterial therapy: agents NR	NR
Kim et al. 2020 [34]	116 Patients with confirmed SARS-CoV-2	USA	Noncritical care and critical care	116/116 respiratory pathogen PCR including *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*; no bacteria identified	NR	NR
Liu et al. 2020 [35]	2 Patients admitted to hospital	Taiwan	Noncritical care	Nasopharyngeal respiratory pathogen PCR; no positive results	1/2 received antibacterial therapy: levofloxacin (1)	NR
Paret et al. 2020 [38]	2 Febrile infants admitted to hospital	USA	Noncritical 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 [8]	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 [29]	138 Patients admitted to hospital	China	Noncritical care and critical care	NR	89/138 moxifloxacin, 34/138 ceftriaxone, 25/138 azithromycin	NR
Wu et al. 2020 [36]	201 Patients admitted to hospital	China	Noncritical 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 [37]	18 Patients admitted to hospital	Singapore	Noncritical care and critical care	NR	Empirical broad spectrum antibiotics for those with suspected CAP: number treated NR	NR
Yu et al. 2020 [16]	7 Obstetric patients admitted to hospital	China	Noncritical care	NR	7/7 Patients received antimicrobial therapy: 2/7 monotherapy, 5/7 combination therapy; cephalosporins, quinolones, macrolides prescribed	NR
Zhou et al. 2020 [2]	191 Patients admitted to hospital	China	Noncritical care and critical care	28/191 reported to have secondary bacterial infection	181/191 received antibiotic therapy	NR

Abbreviations: CAP, community-acquired pneumonia; COVID-19, novel coronavirus disease 2019; CSF, cerebrospinal fluid; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 .

in this study [39]. Guan and colleagues [32] reported on 1099 patients admitted to critical and noncritical care settings in China. Of these, 637 of 1099 (58%) received antibacterial and 31 of 1099 (3%) received antifungal therapy. No microbiology was reported in this study [32]. Complications of antimicrobial therapy were not reported in any study.

Reported bacterial/fungal coinfection was greater in other coronavirus studies compared with COVID-19. Overall, 90 of 815 (11%) of reported patients had identified bacterial/fungal coinfection. In a review of 349 critically ill patients with MERS in Saudi Arabia, Arabi and colleagues [26] identified atypical bacterial coinfection in 5 of 349 (1%) instances on admission. Atypical organisms identified were *Mycoplasma* spp. (3/5), *Legionella* (1/5), and *Chlamydia* spp. (1/5). However, only 6–17 patients appear to have been investigated for atypical organisms. This may reflect physician screening preferences based on clinical presentation. Despite low rates of confirmed bacterial coinfection, the use of empirical broad-spectrum antimicrobials was once again widely reported, with 326 of 349 (93%) patients receiving antibacterial agents [26].

Of studies reporting SARS-1, 42 of 135 (31%) reported cases had bacterial/fungal coinfection. During the SARS-1 outbreak in the early 2000s, Yap and colleagues [28] reported nosocomial infection in a series of 83 patients managed within intensive care. The authors reported increased rates of methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas* spp., and *A. baumannii* in an intensive care unit that cared for 83 patients with SARS-1 during a 3-month period. 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 [28].

For other coronavirus infections, bacterial/fungal coinfections were observed in 43 of 331(13%) cases [10, 19, 22]. These coinfections were for a range of gram-positive (10/43, 23%), gram-negative (23/43, 53%), and atypical (10/43, 23%) bacteria. No data on antimicrobial susceptibility and prescribing were reported in these studies.

DISCUSSION

Rates of bacterial or fungal coinfection reported in the current medical literature for patients presenting with coronavirus infections appear to be low. Of 9 studies reporting bacterial coinfection in COVID-19 cases, 62 of 806 (8%) cases of bacterial/fungal coinfection 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 coinfection and recommendations for duration of treatment require several considerations. As the pretest probability of SARS-CoV-2–positive presentations increases, 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, which is associated with many of the agents we use for atypical infection [11]. 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 [11]. Macrolides have also been associated with potential antiviral effect in combination with hydroxychloroquine, but also have a potential synergistic effect on QT prolongation [7]. Current evidence reported from MERS cohorts does not suggest any added benefit from the use of macrolides in the treatment of acute respiratory distress syndrome associated with coronavirus infection [26]. Furthermore, very few atypical bacterial coinfections have been identified in reports of COVID-19 cases to date. Therefore, the potential unintended consequences of prolonged macrolide use must be weighed against the potential likelihood of atypical bacterial coinfection 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 [40]. While many studies reported failed to separate reporting on critical and noncritical care settings, a large proportion of reported bacterial coinfections within coronavirus literature appear to be healthcare associated, including central line–associated bloodstream infections, and ventilator-associated pneumonia [8, 23–25, 28]. 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 healthcare associated infections 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 [40]. Traditional markers used to support antimicrobial decisions, such as vital signs; blood tests, such as white blood 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 [40].

One potential solution to support antimicrobial prescribing in COVID-19 is the use of bacteria-specific biomarkers, such as procalcitonin [41]. 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 [41, 42]. Procalcitonin use has been reported in the COVID-19 literature and may be an important tool to support reducing antimicrobial use [8, 16, 18, 21, 24, 29, 32]. Furthermore, the use

of clinical decision support systems may facilitate better use of data in supporting decision making, especially when linked with artificial intelligence [43].

In addition, infection specialties that are normally responsible for coordinating stewardship programs must continue to provide support to clinical teams managing patients with COVID-19 to ensure that regular review and cessation of antimicrobial therapy is considered based on the limited clinical evidence available within these patients [40]. 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 [44, 45], 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 [46], 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 [47–50]. With a need to ensure that bed capacity is maintained, a focus on developing guidance on optimal pharmacokinetic-pharmacodynamic strategies for common infections requiring antimicrobials should be considered to support early oral antibiotic switch and treatment de-escalation in patients with short- and long-term infections [51, 52].

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

Conclusions

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 coinfection. 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

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References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med **2020**; 382:727–33.
2. Zhou F, Yu T, Du R, et al. Articles Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China : a retrospective cohort study. Lancet **2020**; 6736:1–9.
3. Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. JAMA **2020**; 323:709–10.
4. Truog RD, Mitchell C, Daley GQ. The toughest triage — allocating ventilators in a pandemic. N Engl J Med **2020**:NEJMp2005689. doi:10.1056/NEJMp2005689
5. Rosenbaum L. Facing Covid-19 in Italy—ethics, logistics, and therapeutics on the epidemic's front line. N Engl J Med **2020**; 382:1873–5. doi:10.1056/NEJMp2005492
6. Hunter DJ. Covid-19 and the stiff upper lip—the pandemic response in the United Kingdom. N Engl J Med **2020**; 382:e31.
7. Gautret P, Lagier JC, Parola P, et al. Journal pre-proof hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents **2020**:105949. doi:10.1016/j.ijantimicag.2020.105949

8. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis **2020**:ciaa272. doi:10.1093/cid/ciaa272.
9. Italian Society of Infectious and tropical diseases Lombary Region Section. Vademecum per la cura delle personecon malattia da COVI-19; versione 2.0, **2020**. Available at: http://www.simit.org/medias/1569-covid19-vademecum-13-03-202.pdf. Accessed 18 April 2020.
10. Zheng Y, Chen J, Kong D, et al. Pathogenic characteristics of hospitalized severe acute respiratory infections in Shanghai, China, 2015–2017. Chinese J Endem **2019**; 40:911–6.
11. Mason JW. Antimicrobials and QT prolongation. J Antimicrob Chemother **2017**; 72:1272–4. doi:10.1093/jac/dkw591
12. Holmes AH, Moore LSP, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet **2015**; 6736.
13. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). Available at: http://www.prisma-statement.org/. Accessed 18 April 2020.
14. Nicholls JM, Poon LL, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. Lancet **2003**; 361:1773–8.
15. Wang JB, Xu N, Shi HZ, Huang XZ, Lin L. Organism distribution and drug resistance in 7 cases of severe acute respiratory syndrome death patients with secondary bacteria infection. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue **2003**; 15:523–5.
16. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis **2020**; 20:p559–564. doi:10.1016/S1473-3099(20)30176-6
17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **2020**; 395:497–506.
18. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically Ill patients with COVID-19 in Washington State. JAMA **2020**; 323:1612–4. doi:10.1001/jama.2020.4326
19. Kozak R, Prost K, Yip L, Williams V, Leis JA, Mubareka S. Severity of coronavirus respiratory tract infections in adults admitted to acute care in Toronto, Ontario. J Clin Virol **2020**; 126:104338.
20. Chen L, Liu HG, Liu W, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi **2020**; 43:E005.
21. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med **2020**:NEJMc2010419. doi:10.1056/NEJMc2010419
22. Jung HS, Kang BJ, Ra SW, et al. Elucidation of bacterial pneumonia-causing pathogens in patients with respiratory viral infection. Tuberc Respir Dis (Seoul) **2017**;80:358–67.
23. Tan FL, Loo WL, Tan SG, Wong CY, Tan YM. Severe acute respiratory syndrome in surgical patients: a diagnostic dilemma. ANZ J Surg **2005**; 75:21–6.
24. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet **2020**; 395:507–13.
25. Dong X, Cao Y, Lu X, et al. Eleven faces of coronavirus disease 2019. Allergy **2020**. doi:10.1111/all.14289
26. Arabi YM, Deeb AM, Al-Hameed F, et al; Saudi Critical Care Trials Group. Macrolides in critically ill patients with Middle East respiratory syndrome. Int J Infect Dis **2019**; 81:184–90.
27. Jang TN, Yeh DY, Shen SH, Huang CH, Jiang JS, Kao SJ. Severe acute respiratory syndrome in Taiwan: analysis of epidemiological characteristics in 29 cases. J Infect **2004**; 48:23–31.
28. Yap FH, Gomersall CD, Fung KS, et al. Increase in methicillin-resistant *Staphylococcus aureus* acquisition rate and change in pathogen pattern associated with an outbreak of severe acute respiratory syndrome. Clin Infect Dis **2004**; 39:511–6.
29. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA **2020**; 323:1061–9.
30. Shweihat Y, Perry J 3rd, Shah D. Isolated Candida infection of the lung. Respir Med Case Rep **2015**; 16:18–9.
31. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. N Engl J Med **2020**. doi:10.1056/NEJMoa2004500
32. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **2020**; 382:1708–20. doi:10.1056/NEJMoa2002032
33. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med **2020**; 382:929–6. doi:10.1056/NEJMoa2002032
34. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA **2020**. doi:10.1001/jama.2020.6266
35. Liu YC, Liao CH, Chang CF, Chou CC, Lin YR. A locally transmitted case of SARS-CoV-2 infection in Taiwan. N Engl J Med **2020**; 382:1070–2.
36. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med **2020**. doi:10.1001/jamainternmed.2020.0994
37. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA **2020**;323:1488–94. doi:10.1001/jama.2020.3204
38. Paret M, Lighter J, Pellett Madan R, Raabe VN, Shust GF, Ratner AJ. SARS-CoV-2 infection (COVID-19) in febrile infants without respiratory distress. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa452
39. Cao J, Tu WJ, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in Wuhan, China. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa243
40. Rawson TM, Moore LSP, Castro-Sánchez E, et al. COVID-19 and the potential long term impact on antimicrobial resistance. J Antimicrob Chemother **2020**.
41. Meier MA, Branche A, Neeser OL, et al. Procalcitonin-guided antibiotic treatment in patients with positive blood cultures: a patient-level meta-analysis of randomized trials. Clin Infect Dis **2019**; 69:388–96.
42. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis **2016**; 16:819–27.
43. Rawson TM, Hernandez B, Moore LSP, et al. A real-world evaluation of a Case-Based Reasoning algorithm to support antimicrobial prescribing decisions in acute care. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa383.
44. Food and Drug Adminstration. Drug shortages. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages. Accessed 18 April 2020.
45. Victoria Rees. EMA announces measures to manage drug shortages due to COVID-19. Available at: https://www.europeanpharmaceuticalreview.com/news/115123/ema-announces-measures-to-manage-drug-shortages-as-result-of-covid-19/. Accessed 18 April 2020.
46. Wald-Dickler N, Spellberg B. Short course antibiotic therapy—replacing Constantine units with "shorter is better". Clin Infect Dis **2019**; 69:1476–9.
47. Lorgelly PK, Atkinson M, Lakhanpaul M, et al. Oral versus i.v. antibiotics for community-acquired pneumonia in children: a cost-minimisation analysis. Eur Respir J **2010**; 35:858–64.
48. Chan R, Hemeryck L, O'Regan M, Clancy L, Feely J. Oral versus intravenous antibiotics for community acquired lower respiratory tract infection in a general hospital: open, randomised controlled trial. BMJ **1995**; 310:1360–2.
49. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med **2019**; 380:415–24.
50. Li HK, Rombach I, Zambellas R, et al; OVIVA Trial Collaborators. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med **2019**; 380:425–36.
51. Heffernan AJ, Sime FB, Taccone FS, Roberts JA. How to optimize antibiotic pharmacokinetic/pharmacodynamics for gram-negative infections in critically ill patients. Curr Opin Infect Dis **2018**; 31:555–65.
52. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am **2009**; 23:791–815, vii.