SYSTEMATIC REVIEW

A rapid review of the overuse of antibiotics during the COVID-19 pandemic: lessons learned and recommendations for the future [version 1; peer review: 2 approved with reservations]

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has had severe implications on healthcare systems and the patients affected by this infectious disease. To improve outcomes for patients with COVID-19 and limit future antimicrobial resistance, there is continued urgency to improve our understanding of the rates and causative agents of secondary bacterial infections in patients with COVID-19, and recognise whether antibiotics are being overused in patients prior to and following COVID-19 diagnosis.

This article presents the results of a rapid review comparing reported rates of secondary bacterial infections with rates of antibiotic use in patients with COVID-19 predominantly in a hospital setting, within the context of treatment guidelines and recommendations.

The review revealed rates of antibiotic use in patients with COVID-19 of 37–100%, far outweighing rates of secondary bacterial infections which were typically below 20%. There was a lack of consistent reporting of causative microorganisms of secondary infections, and the distinction between bacterially- and virally-induced sepsis was rarely made.

Early in the pandemic, healthcare agencies published treatment guidelines recognising the importance of antimicrobial stewardship. However, many are yet to provide updated guidance detailing the most appropriate antibiotics to treat patients with concurrent COVID-19 and secondary bacterial infections in a way which limits the emergence of drug-resistant infections and does not negatively impact patient outcomes.

Without significant improvements to the testing and reporting of causative organisms and corresponding updates to antimicrobial treatment guidelines, there is a risk of worsened clinical outcomes and increased burden on healthcare systems from antimicrobial resistance during the remainder of the COVID-19 pandemic and beyond.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

antibiotic resistance, COVID-19, secondary bacterial infection

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Plain language summary

This article presents the results of a rapid literature review comparing reported rates of secondary bacterial infections with rates of antibiotic use in patients with COVID-19 predominantly in a hospital setting, within the context of treatment guidelines and recommendations. The review showed rates of antibiotic use in patients with COVID-19 far outweighing the rates of secondary bacterial infections in these patients. There was a lack of consistent reporting of what bacteria caused the infection and what treatment options were used, and the distinction between bacterially- and virally-induced sepsis was rarely made. More research into the development of rapid diagnostics is required to help effectively evidence bacteria causing secondary bacterial infections during the remainder of the COVID-19 pandemic and beyond, and to inform guidance on which antibiotics should and should not be used in patients with COVID-19.

Introduction

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there have so far been more than 150 million confirmed cases and over 3 million deaths worldwide; at the time of writing, cases and deaths continue to increase rapidly¹. Clinical outcomes from previous viral pandemics, such as the 1918–1919 influenza, 2003 SARS and the 2009 influenza A[H1N1]pdm09 pandemics, have shown that viral respiratory infections can often lead to secondary bacterial infections that significantly affect morbidity and mortality^{2–6}. With evidence from previous pandemics demonstrating a link between viral infections and secondary bacterial infections, there was concern at the beginning of the COVID-19 pandemic over our lack of understanding of whether patients infected with SARS-CoV-2 could also be at increased risk of developing life-threatening secondary bacterial infections⁷.

For the purposes of antibiotic stewardship, there is a need to better understand the true rates of secondary bacterial infections and bacterial sepsis in patients with COVID-19 to guide appropriate antibiotic treatment. The overuse of antibiotics in previous viral pandemics has led to increases in antibiotic resistance⁵; with drug-resistant bacterial infections currently causing around 700,000 deaths globally per year, and predictions suggesting that this figure will increase to around 10 million deaths per year by 2050⁸, antibiotic stewardship during the remainder of the COVID-19 pandemic (and in future pandemics) is of paramount importance.

Here, we report the findings of a rapid literature review investigating the prevalence of secondary bacterial infections and rates of antibiotic use in patients with COVID-19. In addition, we detail how guidance regarding antibiotic treatment for patients with COVID-19 has changed over the course of the pandemic. In light of our findings, we recommend changes to health policy and treatment guidelines to improve the clinical outcomes of patients with severe COVID-19 and to reduce the emergence of antimicrobial resistance.

Methods

A rapid literature review was conducted to determine the relationship between reported rates of secondary bacterial infections,

antibiotic usage and sepsis in patients with COVID-19. The review was initially conducted in August 2020, and updated in February 2021 due to the volume of COVID-19 research published in recent months.

Information sources and search strategy

During the initial review and the update, Embase and MEDLINE were searched simultaneously via OvidSP using a mixture of text words and subject headings relating to COVID-19/SARS-CoV-2 and sepsis or secondary bacterial infections (initial search conducted on 12 August 2020). In the review update (conducted on 26 February 2021) the search terms were narrowed to exclude sepsis owing to the high volume of published literature between the first and second searches. Full search terms can be found in [Table 1](#). All study and literature types were considered, including online pre-prints. Included studies could be from any geographic region, provided the publication was available open access in English and reported data in humans.

Selection process

Two authors (WC, MB) screened the abstracts to determine their relevance. The first 50 abstracts were screened by both authors to align on acceptance and rejection criteria, before the remainder of the abstracts were each screened by a single author. The same two authors then screened full texts to prioritise the sources, before key features of each included study were extracted.

Supplementary hand searches and searches of the reference lists of included articles were used to identify further relevant articles. Hand searches of key grey literature were used to identify resources providing clinical guidance for antibiotic treatment in patients with COVID-19. The grey literature was initially searched in August 2020, and a second search was conducted in January 2021 to identify notable updates to these resources.

Data collection

Data extraction was performed by a single author for each individual study (WC, MB). The extracted information was independently verified by a second individual to check for accuracy of data extraction (WC, MB). The data extracted included the following, where available: characteristics of the included studies, such as study design, geographic region and population size; reported rates of sepsis/septic shock, bacterial infection and/or antimicrobial treatment; identified microorganisms; details of antimicrobials prescribed; and/or clinical guidance related to antibiotic treatment in patients with COVID-19. Extracted data were collated by hand into [Table 2](#) and [Table 3](#).

Results

A total of 488 abstracts were identified in the initial database search. Of these, 46 were categorised into three groups for full text screening: literature reporting concomitant COVID-19 and secondary bacterial infections; COVID-19 and sepsis; and COVID-19, secondary bacterial infections and sepsis. Records in the 'COVID-19 and secondary bacterial infections' and 'COVID-19, secondary bacterial infections and sepsis' were

Table 1. Full search terms for Embase and MEDLINE.

Term Group	No.	Searches	Results
Initial search (12 August 2020)			
COVID	1	SARS-CoV-2.ti,ab.	20316
	2	(Covid-19 or Covid19).ti,ab.	70995
	3	nCoV.ti,ab.	1689
	4	or/1-3	77375
Sepsis or secondary bacterial infections	5	sepsis/	216257
	6	(sepsis or septic?emi* or urosepsis).ti,ab.	288295
	7	(septic adj2 shock).ti,ab	57859
	8	(secondary bacteria* or secondary infection*).ti,ab.	15412
	9	bacter?emia*.ti,ab.	70369
	10	or/5-9	459550
Combined	11	4 and 10	786
	12	Remove duplicates from 11	488
Update (26 February 2021)			
COVID	1	SARS-CoV-2.ti,ab.	56674
	2	(Covid-19 or Covid19).ti,ab.	180576
	3	nCoV.ti,ab.	2570
	4	or/1-3	196214
Secondary bacterial infections	5	(secondary bacteria* or secondary infection*).ti,ab.	16311
	6	bacter?emia*.ti,ab.	72892
	7	or/5-6	88950
Combined	8	4 and 7	514
	9	remove duplicates from 8	316

prioritised for the review. Six texts were not open access and were excluded. Overall, thirteen key references were included from the initial review. Five additional records were included from hand searches of grey literature sources, and ten references were included from reference list searches (Figure 1).

In the review update, an additional 215 abstracts were identified after de-duplication of any articles identified during the initial review. Four texts were not open access and were excluded. 80 remaining texts were assessed for full text screening, of which 19 were included in the final review. Of the five grey literature sources identified in the initial round of review, updates to two documents were identified and included. Two additional references were included from reference list searches (Figure 2).

Secondary bacterial infections, sepsis and antimicrobial use

Reported rates of bacterial infections associated with COVID-19 varied in the literature depending on patient subgroup and geographical location. Whilst most cited an incidence below 20% (3.6%⁹, 3.2–6.1%¹⁰, 4.7%¹¹, 6.8%¹², 6.9%⁷, 8%¹³, 9.3%¹⁴, 10%¹⁵, 12.5%¹⁶, 15%¹⁷ and 19.5%¹¹), higher rates were occasionally reported (21.4%¹⁸ and 28.1%¹⁹), especially in critically ill/intensive care unit (ICU) patients (17%²⁰, 26.7%¹², 34.5%⁵, 65%²¹ and 83.3%²²). Rates of secondary bacterial infections were occasionally reported for additional patient subgroups, including patients receiving ventilator support (31%¹⁵, 48.9%²³ and 53.8%²⁴), and those receiving tocilizumab (34%²⁵ and 48.1%¹⁹) (Table 2 and Table 3). Nosocomial infections were more common than community-acquired infections^{26,27}.

Table 2. Sepsis, secondary bacterial infection and antimicrobial treatment in patients with COVID-19 (initial review).

Article	Reported rates of sepsis/septic shock	Reported rates of bacterial infection	Identified microorganisms	Reported rates of antimicrobial treatment	Details of antimicrobials prescribed	Notes
Amit et al. 2020	Sepsis: 21/156 (13%) Septic shock: 29/156 (19%)	Secondary bacterial infection: 27/156 (17%)	NR	131/156 (84%)	NR	Israel; 156 ICU patients; 5 March–27 April 2020
Antinori et al. 2020	Septic shock: 4–33.1% of patients	NR	NR	71–100% received antibacterial treatments	NR	Review article
Hantoushzadeh et al. 2020	Sepsis: •Deceased (100%) •Survived (42%) Septic shock: •Deceased (70%) •Survived (0%)	NR	NR	Up to 95% of patients received antibiotic therapy	NR	Opinion article
Hughes et al. 2020	NR	Early confirmed: 27/836 (3.2%) Throughout admission: 51/836 (6.1%)	Blood culture: <i>Enterobacteriales</i> , <i>Enterococcus</i> spp., <i>P. aeruginosa</i> , coagulase-negative staphylococci, <i>Streptococcus</i> spp., <i>S. aureus</i> , <i>P. aeruginosa</i> Respiratory culture: <i>S. aureus</i> , <i>Pseudomonas</i> spp., <i>Enterobacter</i> spp., <i>Klebsiella</i> spp., <i>Serratia</i> spp Other pathogens: <i>H. influenzae</i> , <i>Hafnia</i> spp., <i>Morganella</i> spp., <i>Providencia</i> spp., <i>S. maltophilia</i>	NR	NR	Two NHS hospitals in England; all admitted patients with COVID-19; 20 February–20 April 2020
Istituto Superiore di Sanità (ISS) Report 2020	NR	NR	NR	86.0% received antibiotics	NR	Italy; 34,142 deceased patients; up to 22 July 2020; report produced by SARS-CoV-2 Surveillance Group
Langford et al. 2020	NR	6.9% (3.5% coinfection, 14.3% secondary infection)	Most commonly reported: <i>Mycoplasma</i> spp., <i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i>	71.9%	Generally broad in spectrum with fluoroquinolones and third-generation cephalosporins comprising 74% of the antibiotics prescribed	Meta-analysis of 24 studies; found that 11/24 studies (45.8%) reported specific species of bacterial co-pathogens; 14/24 (58%) studies reported antibiotic use
Lansbury et al. 2020	NR	Bacterial coinfection: •Overall (7%) •ICU patients (14%) •Mixed ward/ICU (4%)	Most commonly reported: <i>Mycoplasma pneumoniae</i> , <i>Pseudomonas aeruginosa</i> and <i>Haemophilus influenzae</i>	NR	NR	Systematic review article

Article	Reported rates of sepsis/septic shock	Reported rates of bacterial infection	Identified microorganisms	Reported rates of antimicrobial treatment	Details of antimicrobials prescribed	Notes
Nori et al. 2020	NR	152/4,267 (3.6%); bacterial and fungal coinfection)	Respiratory coinfections: <i>S. aureus</i> (44%), <i>P. aeruginosa</i> (16%), <i>Klebsiella</i> spp. (10%), <i>Enterobacter</i> spp. (8%), <i>E. Coli</i> (4%) Bloodstream coinfections: <i>S. aureus</i> (30%), <i>S. epidermidis</i> (12%), <i>Streptococcus</i> spp. (10%), <i>Enterococcus</i> spp. (7%), <i>E. coli</i> (7%), <i>Pseudomonas aeruginosa</i> (6%), <i>Candida</i> spp. (5%), <i>Klebsiella</i> spp. (3%), <i>Enterobacter</i> spp. (3%)	71% of all admitted patients received antibiotics (4130/5853; March 1–May 31, 2020)	Doxycycline, azithromycin, levofloxacin, ciprofloxacin, ceftriaxone, cefepime, intravenous vancomycin, piperacillin/tazobactam	New York City, NY, USA; all admitted patients 1 March–18 April 2020
Novy et al. 2020	No patients in study presented with septic shock	1/20 patients with confirmed bacterial pneumonia	<i>S. pneumoniae</i> , <i>S. aureus</i>	100%	Cefotaxime, 13/20 (63%); Cefepime, 3/20 (16%); Piperacillin/tazobactam, 4/20 (21%)	Report of ICU patients all taking beta-lactam antibiotics
Ren et al. 2020	ICU mortality rates: •Bacterial sepsis (34.8%) •Viral sepsis (4.8%)	NR	NR	NR	NR	China; 235 ICU patients (with/without COVID-19); up to May 13, 2020
Sepulveda et al. 2020	NR	Rates of bacteraemia for COVID-19 patients: 1.6%	<i>E. Coli</i> (16.7%), <i>S. aureus</i> (13.3%), <i>Klebsiella pneumoniae</i> (10.0%), <i>Enterobacter cloacae</i> (8.3%)	NR	NR	New York City, NY, USA; 88,201 blood cultures from 28,011 patients (with/without COVID-19); 1 January–31 March 2020
Vaillancourt et al. 2020	NR	34.5% (critically ill patients), 8.3% (severely ill patients) 3.9% (moderately ill patients)	NR	92.9% (critically ill patients), 83.3% (severely ill patients), 59.4% (moderately ill patients)	NR	Review article
Zhang et al. 2020	67% (shock, not specific as septic shock)	Secondary infection: 88/136 (65%)	NR	NR	NR	China; 136 ICU patients; 28 January–21 February 2020

HCAI: healthcare acquired infection; ICU: intensive care unit; NR: not reported.

Table 3. Secondary bacterial infection and antimicrobial treatment in patients with COVID-19 (review update).

Article	Reported rates of bacterial infection	Identified microorganisms	Reported rates of antimicrobial treatment	Details of antimicrobials prescribed	Notes
Bhatt et al. 2020	117/375 (31.2%); sBSIs in patients with severe COVID-19	<i>S. epidermis</i> , methicillin-sensitive <i>S. aureus</i> , <i>E. faecalis</i> , <i>E. coli</i> , methicillin-resistant <i>S. aureus</i>	70.5% (no sBSI), 99.2% (sBSI)	Ceftriaxone, azithromycin, piperacillin-tazobactam	United States; includes hospitalised patients with COVID-19 in three medical centres; unclear whether rates are adjusted for contamination
Blonz et al. 2021	17 bacterial isolates in co-infection; 92/188 patients (48.9%) had ≥1 VAP	Bacterial co-infection: <i>S. aureus</i> , <i>Enterobacteriaceae</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> VAP: <i>Enterobacteriaceae</i> (49.8% of isolates), <i>P. aeruginosa</i> (15.1%), <i>S. aureus</i> (13.7%), other Gram-negative (10.2%); <i>S. maltophilia</i> , <i>Haemophilus</i> spp., <i>A. baumannii</i> , other <i>Pseudomonas</i> spp., and other Gram-positive (5.9%); <i>S. pneumoniae</i> , <i>S. agalactiae</i> , <i>Corynebacterium</i> spp., <i>E. faecium</i> and <i>E. faecalis</i> (5.4%)	169/188 (89.9%)	Third-generation cephalosporins (82.9%), spiramycin (67.5%), amoxicillin-clavulanate (12.4%), azithromycin (6.5%), piperacillin-tazobactam (5.4%)	France; includes patients with COVID-19 in an ICU and on ventilator support >48 hours
Fattorini et al. 2020	10%, 11.7%, 15% (overall); 1.3% (superinfections)	<i>M. pneumoniae</i> , <i>S. aureus</i> , <i>L. pneumophila</i> , <i>Haemophilus</i> spp., <i>Klebsiella</i> spp., <i>P. aeruginosa</i> , <i>Chlamydia</i> spp., <i>S. pneumoniae</i> , <i>A. baumannii</i> , <i>M. tuberculosis</i>	476/539 (88.3%); broad-spectrum	Third-generation cephalosporins, quinolones, carbapenems	Review article; some studies included are included separately in this review
Kimig et al. 2020	16/57 (28.1%); patients not receiving tocilizumab), 26/54 (48.1%); patients receiving tocilizumab); proven or suspected	NR	NR	NR	United States; only includes critically ill patients with COVID-19
Lardaro et al. 2021	6/542 (1.1%); true positive bloodstream infections), 15/542 (2.8%); true respiratory infections)	Blood cultures: coagulase-negative <i>Staphylococcus</i> , methicillin-resistant <i>S. epidermis</i> , <i>E. faecalis</i> , <i>Aerococcus</i> spp., <i>Globicatella</i> spp., <i>Corynebacterium striatum</i> , <i>S. pettenkoferi</i> , <i>A. radioresistance</i>	NR for overall; all patients with positive blood cultures treated	Meropenem, vancomycin, cefepime, ceftriaxone, doxycycline, ampicillin	United States; only 395/542 patients had blood cultures performed
Lee et al. 2021	30/140 (21.4%)	<i>S. pneumoniae</i> (64.5%), <i>H. influenzae</i> (48.4%), <i>Staphylococcus</i> spp. (12.9%), <i>Corynebacterium</i> spp. (6.5%), <i>E. faecium</i> (6.5%), <i>K. pneumoniae</i> (3.2%), <i>Enterobacteriaceae</i> spp. (3.2%), <i>P. aeruginosa</i> (3.2%), <i>M. pneumoniae</i> (3.2%)	NR	NR	Korea; letter to editor

Article	Reported rates of bacterial infection	Identified microorganisms	Reported rates of antimicrobial treatment	Details of antimicrobials prescribed	Notes
Li et al. 2020	102/1495 (6.8%); sBSIs: Critical patients: 26.7%; severe patients: 3.1%	<i>A. baumannii</i> (35.8%), <i>K. pneumoniae</i> (30.8%), <i>S. maltophilia</i> (6.3%)	99/102 (97.1%) before sSBI diagnosis	NR	China; 91.2% <i>A. baumannii</i> and 75.5% <i>K. pneumoniae</i> were carbapenem-resistant. All <i>S. aureus</i> and coagulase-negative <i>Staphylococci</i> were methicillin-resistant. 75% <i>E. coli</i> isolates were ESBL-producing. 1050/1495 patients had severe COVID-19, 258/1495 were critical
Mahmoudi et al. 2020	43/340 (12.5%)	<i>Klebsiella</i> spp. (25.6%), methicillin-sensitive <i>S. aureus</i> (20.9%), <i>E. coli</i> (16.3%), methicillin-resistant <i>S. aureus</i> (14.0%), <i>Enterobacter</i> spp. (11.6%), <i>P. aeruginosa</i> (9.3%), <i>S. pneumoniae</i> (9.3%)	NR	NR	Iran; 74%, 67.5%, 47.5% and 42.5% of <i>Enterobacteriaceae</i> isolates resistant to cotrimoxazole, piperacillin, ceftazidime and cefepime, respectively. <i>S. aureus</i> resistance to oxacillin, erythromycin and clindamycin over 90%
Moretti et al. 2021	21/39 (53.8%; VAP only)	<i>K. pneumoniae</i> (44%), <i>P. aeruginosa</i> (18%), <i>Enterobacter</i> spp. (11%)	17/21 (81%) before VAP onset	For VAP treatment: piperacillin-tazobactam (42%), meropenem (25%), trimethoprim-sulfamethoxazole (9%)	Belgium; all included patients on ventilators. 71.4% patients had multi-resistant VAP pathogen
Pereira et al. 2020	34% (SOT recipients treated with tocilizumab), 24% (SOT recipients not treated with tocilizumab)	NR	NR	NR	United States
Pulia et al. 2020	NR	NR	27/73 (37%)	NR	United States; 92.6% patients received antibiotics prior to COVID-19 test results. Prescribing rate 21.3% lower in patients with PCT test prior to antibiotic order
Ripa et al. 2021	68/731 (9.3%); 58/731 (7.9%) had ≥ 1 BSI, 22/731 (3.0%) had ≥ 1 pLRTI	BSIs: Gram-positives (76/106 isolates, 71.7%, including coagulase-negative <i>Staphylococci</i> [53/76, 69.7%]), Gram-negatives (23/106, 30.4%, including <i>A. baumannii</i> [7/23, 30.4%] and <i>E. coli</i> [5/23, 21.7%]) pLRTIs: Gram-negatives (14/26 isolates, 53.8%, including <i>P. aeruginosa</i> [6/14, 42.9%])	NR	NR	Italy; blood or LRT cultures performed in 298/731 (40.8%) patients

Article	Reported rates of bacterial infection	Identified microorganisms	Reported rates of antimicrobial treatment	Details of antimicrobials prescribed	Notes
Sharov et al. 2020	36.0% (secondary bacterial pneumonia)	<i>S. pneumoniae</i> , <i>S. aureus</i> , <i>H. influenzae</i> , <i>E. coli</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , <i>K. pneumoniae</i>	NR	NR	Russia; cites overwhelming majority of patients dying with COVID-19 also had secondary bacterial pneumonia complications. Reports that critical shortages of antibiotics experienced in March–April 2020
Sieswerda et al. 2020	3.5% (admission to hospital), 1.5% (during hospitalisation)	<i>S. aureus</i> , <i>H. influenzae</i> , <i>S. pneumoniae</i>	NR	NR	Netherlands; review and executive summary of treatment guidelines. Cites very low quality of evidence on secondary bacterial infections in patients with COVID-19
Sogaard et al. 2021	24 bacterial infections in 162 patients; bacterial/fungal infections more prevalent in ICU (36.6%) than other (1.7%) patients	Predominantly Gram-negative rods; no single species more prevalent	71/162 (43.8%); antibiotic or antifungal	Amoxicillin and clavulanic acid (36/162, 22.2%), piperacillin-tazobactam (30/162, 18.5%), ceftriaxone (14/162, 8.6%)	Switzerland; 23/71 patients treated with antimicrobials given 2–6 different antimicrobials
Thelen et al. 2021	1.0% (bacteraemia)	<i>E. coli</i> , <i>S. pneumoniae</i> (both 28.6%)	NR	NR	Netherlands; significantly lower rates of bacteraemia in patients with COVID-19 than those with Influenza A/B
Vazzana et al. 2020	4.8%–19.5%; most infections in patients with severe course/fatal outcome (89.7%)	NR	43.7%–100.0%	NR	Review of studies evaluating PCT as diagnostic marker of secondary bacterial infections
Yu et al. 2020	197/3027 (6.5%; blood culture episodes from 2240 patients)	Coagulase-negative <i>Staphylococci</i> , <i>S. aureus</i> , <i>E. coli</i>	NR	NR	Sweden; notes high rates of contamination in blood cultures in COVID-19 patients compared with control groups
Zhang et al. 2020	22/38 (57.9%; only severely or critically ill patients with COVID-19. Higher in critical [83.3%] than severe [14.3%] patients)	<i>K. pneumoniae</i> , <i>E. faecium</i> , <i>A. baumannii</i>	NR	NR	China; only includes severely and critically ill patients with COVID-19

ESBL: extended-spectrum beta-lactamase; NR: not reported; PCT: procalcitonin; pLRTI: possible lower respiratory tract infection; sBSI: secondary bloodstream infection; SOT: solid organ transplant; VAP: ventilator-associated pneumonia.

Figure 1. PRISMA flow diagram outlining initial rapid literature review. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Specific bacteria commonly cited as causative agents of secondary infections included *Staphylococcus* spp.^{9,10,14–18,20,23,27–33}, *Streptococcus* spp.^{9,10,15–18,20,23,27,29,34}, *Escherichia coli*^{9,14,16,27,28,30,31,33,34}, *Klebsiella* spp.^{9,10,12,15,16,18,22,24,27,28,31}, *Enterococcus* spp.^{9,10}, *Pseudomonas aeruginosa*^{7,9,10,31}, *Enterobacter* spp.^{9,10,16,18,23,24,28}, *Haemophilus* spp.^{7,10,15,17,18,23,27,31} and *Acinetobacter baumannii*^{12,14,15,17,22}; however this information was often not reported, especially in literature identified in the initial review (Table 2 and Table 3).

Incidence of sepsis in patients with COVID-19 varied across the literature in the initial review, ranging from 13.5% in an

ICU setting²⁰ to 100% in patients who did not survive³⁵. There was similar variation in the reported rates of septic shock^{35,36} (Table 2). Sepsis was widely recognised as a predictor of patient mortality^{20,35} and bacterial sepsis in particular was correlated with far worse ICU patient outcomes than viral sepsis³⁷. However, the literature neither commonly differentiated between bacterially- and virally-induced sepsis, nor reported causative microorganisms of sepsis in patients with COVID-19^{20,21,36}. Although sepsis was not defined in the search criteria of the review update, overall rates of bloodstream infections in patients with COVID-19 were often reported and were generally

Figure 2. PRISMA diagram outlining rapid literature review update. Duplicates removed both from within the updated search and when compared against the results from the initial search. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

lower than overall rates of secondary bacterial infections (1.0%³⁴, 1.1%³², 6.5%³³ and 7.9%¹⁴). By contrast, one paper reported that 31.2% of hospitalised patients in three medical centres in the United States had a positive secondary bloodstream infection; however, the paper did not clarify whether the rate had been adjusted for contaminants, and the study only included patients with 'severe' COVID-19³⁰.

Despite typically low rates of secondary bacterial infections among patients with COVID-19, the majority of hospitalised patients with COVID-19 were reported to have received

broad-spectrum antibiotics, at rates far surpassing those of secondary bacterial infections⁷. Alarming, one paper reporting antibiotic use in patients with COVID-19 in New York stated that 70% of patients who received antibiotics had been prescribed >3 different classes of antibiotic⁹. One study reported that even after a negative diagnostic test for a secondary bloodstream infection, 70.5% of patients were given antimicrobials³⁰. Another review found that empiric antibiotic use was reported in 71–100% of hospitalised patients with COVID-19³⁶. These rates were further corroborated in the literature, with rates of 43.7%¹¹, 64%³², 71%⁹, 71.8%⁷, 72%³⁸,

86%³⁹, 88.3%¹⁵, 97.1%¹² and 100%¹¹ described, often despite a lack of effective diagnostic testing to confirm the presence of bacterial infections, and with limited evidence suggesting improved outcomes for patients administered empiric antimicrobial therapy²⁸ (Table 2 and Table 3).

Notably lower rates of empiric antibiotic prescribing of 37% were reported in one study on a Midwestern US Emergency Department, possibly attributable to the use of rapid procalcitonin testing to guide antibiotic use, even before a positive COVID-19 test³⁸.

The most commonly reported antibiotics in the literature reviewed were beta-lactams, macrolides and fluoroquinolones^{7,15,23,30}, in addition to piperacillin-tazobactam^{9,23,24,26,29,30} and ceftriaxone^{9,26,29,30,32}; however, a wide range was reported (Table 2 and Table 3).

Guidance on the use of antimicrobials in patients with COVID-19

In order to address the discrepancy in the rates of secondary bacterial infections and empiric antibiotic use, clear treatment guidance and health policy is required. Despite rapid research into, and constant reassessment of, the clinical guidelines surrounding the use of antiviral drugs and immune-based therapies to treat patients with COVID-19, the guidance for antibiotic treatment has remained largely unchanged since the beginning of the pandemic.

Much of the clinical guidance continues to recommend against the widespread use of antibiotics in the treatment of COVID-19, unless a patient's symptoms are characteristic of a bacterial infection^{13,40–43}. Healthcare organisations recognise the importance of antimicrobial stewardship, and therefore have recommended that any antimicrobial treatment is reviewed regularly in light of the patient's clinical symptoms and microbiological test results, with the aim to switch to a narrow-spectrum antibiotic or initiate de-escalation protocols when appropriate^{13,40–43}.

The National Institute of Health and Care Excellence (NICE) guidance provides a protocol that encourages judicious antibiotic use during the COVID-19 pandemic^{40,41}. However, the guidance also recommends that for patients with suspected bacterial pneumonia and/or septic shock, clinical judgement is used to prescribe empiric, broad-spectrum antibiotics prior to microbiological test results^{40,41}. Guidance from the World Health Organization (WHO) also suggests immediate treatment with antimicrobials within one hour of recognition of septic shock¹³. Considering that it can be difficult to differentiate between pneumonia and sepsis caused by bacteria or COVID-19 based on the clinical presentation alone^{7,40–43}, however, it seems likely that these current guidelines could lead to the overuse of indiscriminate antimicrobials. A call in the first edition of the NICE guidance (published 1 May 2020) for research into the utility of procalcitonin testing alongside clinical judgement to guide antibiotic treatment decisions, remains unaddressed in the latest version (updated 9 October 2020), and evidence for the use of procalcitonin in the literature remains

mixed^{11,15,38}. Without the development of novel, rapid, and differential diagnostic tools such as these, healthcare professionals (HCPs) will continue to lack the information to determine the best treatment strategy for patients.

The WHO and NICE both provide some guidance for antibiotic choice in a hospital setting in the form of the Access, Watch, Reserve (AWaRe) classification tool and prescribing tables for patients with community- or hospital-acquired pneumonia, respectively^{13,40,41}. Despite this, there is no specific guidance describing which antibiotics are the most effective and/or safe to treat patients who have both COVID-19 and a secondary bacterial infection, beyond whether the patient has 'non-severe' or 'severe' pneumonia and is at a low or high 'risk of resistance'^{40,41}. In addition, a clinical guideline from the Dutch Working Party on Antibiotic Policy stated that there have yet to be any studies assessing the efficacy and safety of specific antibiotic regimens in patients who have COVID-19 with confirmed or suspected bacterial pneumonia which could help guide antibiotic choice¹⁷. This may be partly due to a lack of clarity on the bacterial infections most commonly associated with secondary infection in patients with COVID-19 as outlined above.

Although in our review the reporting of bacteria responsible for secondary infections was limited, given the high incidence of resistance to broad-spectrum antibiotics in those that were mentioned, it is concerning that the clinical guidelines recommend the empiric use of broad-spectrum antibiotics in the first instance, prior to microbiological testing results.

Discussion

The data summarised from this rapid review showed rates of antibiotic use typically far exceeded the rates of secondary bacterial infections in patients with COVID-19. The literature published more recently tended to include more detailed information on causative agents of secondary bacterial infections, antimicrobials prescribed and diagnostic tests than that published towards the beginning of the COVID-19 pandemic.

Antibiotic overuse in the hospital setting during COVID-19 may be driven by a combination of factors, including the high prevalence and severity of secondary bacterial infections in previous influenza pandemics (such as H1N1)^{2–6}, guidelines recommending empiric antibiotics for the treatment of patients presenting with severe pneumonia^{40–43}, and the time required to identify safe and effective antiviral and supportive therapies⁴⁴. The overuse of antibiotics may also reflect the difficulty to clinically distinguish between bacterial- and COVID-induced pneumonia^{7,40,41} and limited access to rapid diagnostic tests⁷. Furthermore, some procedures known to produce highly specific and accurate results, such as bronchoalveolar lavage, are aerosol-producing and have been avoided during the COVID-19 pandemic to prevent the spread of infection¹⁰. However, without accurate testing, our knowledge of the interaction between severe COVID-19, bacterial infections and sepsis will remain limited^{42,43}, and lives may continue to be lost as a result of indiscriminate antibiotic treatment.

Although antibiotic treatment may be clinically beneficial for some patients with concurrent COVID-19 and secondary bacterial infections, their overuse in the COVID-19 pandemic will likely facilitate a surge in drug-resistant infections⁴⁵, as was observed after the 2003 SARS epidemic⁵. Some therapeutic combinations may also have additional unintended consequences, such as the induction of cardiac side effects^{44,46–48} in patients treated simultaneously with azithromycin and hydroxychloroquine⁴⁹. Other antimicrobials, particularly those taken in the absence of a bacterial infection, may induce an inflammatory response and a cytokine storm leading to septic shock³⁵. Ceftriaxone, listed in the NICE guidelines as an option for treating severe pneumonia^{40,41}, has been suggested as one such driver of inflammatory responses³⁵. The inappropriate use of antibiotics may also increase the risk of secondary nosocomial infections, such as *Clostridioides difficile*^{7,13}.

Other articles have also highlighted the current gaps in the reporting of secondary infections and the implications of antibiotic overuse during COVID-19 and previous viral pandemics, such as one authored by Manohar *et al.*³. However, whilst the authors of this article suggest that the solution lies in developing new antibiotics and alternative antibacterial therapies, we propose that this would have little effect during the remainder of the COVID-19 pandemic, owing to the timelines associated with developing new treatments. Instead, we suggest the following changes to enhance reporting of secondary infections and refine treatment guidelines to reduce the use of broad-spectrum antibiotics and accurately advise on narrow-spectrum antibiotics that are likely to be effective.

Firstly, there is a need for rapid, accurate and accessible diagnostic tests to identify the causative microorganisms of secondary infections. Enhanced reporting of this diagnostic information will lead to a better understanding of the prevalence of secondary bacterial infections, common causative bacterial agents and antimicrobial sensitivity, and ultimately guide HCPs in more effective treatment decisions to improve patient outcomes and limit broad-spectrum antibiotic use^{50,51}.

Secondly, bacterially- and virally-induced sepsis need to be accurately reported as distinct diagnoses. This is vital to inform HCPs on the likely rates of sepsis in patients with COVID-19, and to facilitate the use of appropriate treatments that improve patient outcomes whilst limiting the emergence of antibiotic resistance.

Thirdly, the accurate reporting of the cause of death on death certificates, as either COVID-19, a secondary bacterial infection, or bacterially-induced sepsis, is needed to fully understand the increased risks associated with secondary infections to establish the urgency of treatment with antimicrobials in lieu of microbiological test results.

Finally, there is a need for clinical guidance to recommend appropriate, narrow-spectrum antibiotics to treat suspected bacterial infections in patients who also have COVID-19. This guidance should be constantly reviewed and updated as

soon as new evidence relating to the most commonly-occurring secondary bacterial infections emerges.

This review had several limitations. Firstly, the review and update conducted were rapid and pragmatic, and did not utilise exhaustive search terms or comprehensively explore potential grey literature sources. The search terms used for the review were narrowed further for the update, although this was primarily due to the high volume of published literature between the two review periods. Secondly, the overwhelming majority of literature we identified focused on patients in a hospital setting, so our findings may not reflect the rates of secondary bacterial infections and antimicrobial use in an outpatient setting.

However, this review explored a range of literature sources published throughout the course of the COVID-19 pandemic so far, and the literature identified reported data from a diverse range of countries and patient subgroups.

Conclusions

This paper reports the results of a rapid review on the reported rates of secondary bacterial infections and antibiotic use during the COVID-19 pandemic. Worryingly, the reported rates of antibiotic use greatly outweighed the reported incidence of secondary bacterial infections, and clinical guidelines regarding antibiotic treatment in patients with COVID-19 do not appear to have been updated over the course of the pandemic to recommend specific antimicrobials for the treatment of patients with COVID-19 and secondary bacterial infections.

If the gaps in understanding, testing and reporting of causative microorganisms of secondary bacterial infections highlighted here remain, and treatment guidelines and policies are not amended to be more specific, the overuse of empiric, broad-spectrum antibiotics is likely to continue. This will likely lead to patients receiving inappropriate antibiotic treatment for both the remainder of the COVID-19 pandemic and in future pandemics, and will ultimately result in further emergence of antimicrobial resistance.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Open Science Framework: PRISMA checklist for 'A rapid review of the overuse of antibiotics during the COVID-19 pandemic: lessons learned and recommendations for the future', <https://doi.org/10.17605/OSF.IO/5NBPE>⁵².

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Current Peer Review Status: ? ?

Version 1

Reviewer Report 10 September 2021

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Joe Standing

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Cherry and colleagues present a systematic review of rates of bacterial infection/sepsis and antibiotic use in hospitalised COVID-19 patients. The article is well written and methods easy to follow. I have some concerns about how the results are synthesised and presented, which may or may not affect inferences made from them. Therefore the authors are asked to address the following:

General comments:

1. Presentation/synthesis of results. At present authors merely provide line listings of data extracted from each study. Whilst the interested reader will find these useful and they should be retained (at least as supplementary) an opportunity to present aggregated results has been missed. For example, could a forest plot be used to show rates of bacterial infection in different studies? Could these be grouped by level of care: hospitalised, requiring oxygen, ventilated on ICU. Could antibiotic use be presented in a similar way? Is there a way to look at rates of prescribing with time?
2. Antibiotic use in the absence of a culture confirmed infection is not necessarily an incorrect/bad thing. Antibiotics are often started in a patient who may have a bacterial infection, with cultures taking 24-48 hours to come back and at the start of the pandemic virology results taking 48-72 hours sometimes. Authors should consider whether it is possible to extract the common antimicrobial stewardship metrics of DDDs or such like to really see if the volume of prescribing was high. If not possible this should be mentioned as a limitation.
3. How systematic was the review, are there really only 28 relevant papers on this topic? I don't see a clear mention of inclusion criteria. Usually systematic reviews would have a brief protocol published on e.g. PROSPERO prior to commencement of the search and report according to PRISMA criteria. Authors should clarify whether this is a systematic review aiming to synthesise new knowledge by combining/presenting results from multiple

studies, or narrative review highlighting a potential problem and providing a commentary? If a systematic review authors should mention how their work differs from the 6 similar studies on PROSPERO (search term antimicrobial stewardship AND covid-19).

Detailed comments:

Abstract 1st sentence could be snappier e.g. "disease" used twice

Introduction:

To me details on how the clinical management guidelines in terms of antimicrobial treatment is not really a finding of this study, but is highly important background information to interpret the results. Therefore I suggest the authors consider summarising the guideline changes in the introduction.

Methods:

This peer review is conducted in September 2021 whereas the literature search was last updated in February 2021. Could authors comment on the feasibility of updating the review/justify stopping in Feb?

Results:

Numerical results e.g. in section: Secondary bacterial infections, sepsis and antimicrobial use, difficult to follow in the text and provide some potentially important insights. Can these be summarised in a figure?

Discussion:

First paragraph causative "agents" re-word to "organisms"? The common use for "agents" usually refers to drugs.

Tables: At present tables are detailed summaries of the data extracted from each paper – quite difficult to follow.

General: Journal guideline states systematic reviews should follow PRISMA reporting guidelines. Authors should add a PRISMA checklist as supplementary material or clarify if this is more a narrative review.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: I serve as an unpaid member of the Antibiotics Research UK science board which is a charity. The last author, Prof Garner, founded this organisation and serves as a board

member. I do not believe this to have influenced my ability to provide an unbiased review.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 01 September 2021

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Peter Jorth

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This interesting article provides a timely update on the prevalence of secondary bacterial infections in patients with COVID-19. The authors thoroughly summarize the body of literature on this topic that was published through February 2021. Consistent with previous reports, the authors show that the rates of secondary bacterial infections are lower than the rates of prescribed antibiotics. Moreover, when data were available it appeared that antibiotic prescription was typically given empirically without specificity for the bacteria present. Finally, at the end of the manuscript the authors make recommendations to reduce the unnecessary use of antibiotics in COVID-19 patients.

There are some minor changes that could be done to help make the interpretation of the data easier.

Major comments:

The authors are very transparent in what was used for their literature search; however, the criteria that were used to exclude articles are less clear.

In some cases the number of subjects from the study is indicated, but for many studies the number of subjects is not given. If possible, it would be helpful to provide the number of subjects for each study.

Several previous review articles are cited in the table, and it would be helpful to separate these from the the primary literature. One option would be to summarize the previous reviews at the beginning of the results as a baseline for comparison to the new data presented here.

The authors also state that 7 grey literature sources were included in their analysis. It would be helpful to know which of the cited studies were grey literature, and which were peer-reviewed articles.

The authors suggest changes to improve treatment guidelines, which is a major strength of this article. However, their suggestions could be stronger if they were more specific. For example, they suggest a need for rapid, accurate and accessible diagnostic tests. However, they do not suggest specific methods that fit this description. This would clearly be very helpful for managing and treating these infections, but which diagnostic tests fit this description? Most importantly, it would be helpful to suggest such tests that might be available in many parts of the world, not just in advanced medical centers with the latest technologies.

Minor comments

The authors indicate in the discussion that "lives may continue to be lost as a result of indiscriminate antibiotic treatment." Do data actually support this? Or is this a hypothesis based on predictions that indiscriminate antibiotic usage will increase the prevalence of antibiotic resistant bacteria, which will increase infections, and in turn deaths due to infections caused by resistant bacteria? The authors may consider revising this statement to be more reflective of the data. Certainly, increased rates of resistance are a potentially troubling consequence of antibiotic misuse.

It would be helpful to know how common it is for ceftazidime to cause septic shock in the absence of an infection. It is suggested that this is a potential negative consequence, but it's not clear how often this may occur due to antibiotic misuse in COVID-19 patients.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a microbiologist who studies antibiotic resistance and chronic infections in people with cystic fibrosis. My group previously published a review at the beginning of the pandemic of the few studies at the time that had examined rates of secondary bacterial infections in people with COVID-19.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.