Predisposition of COVID-19 patients to secondary infections: set in stone or subject to change?

Madhuri M. Sopirala[a,b]

Purpose of review
There likely are several predisposing factors to secondary infections in patients with Coronavirus disease 2019 (COVID-19), some of which may be preventable. The aim of this review is to explore the literature, summarize potential predisposing factors to secondary infections and their incidence. It also summarizes a variety of healthcare scenarios in which different kinds of secondary infections occur.

Recent findings
Apart from immune dysregulation, severe resource limitations in healthcare settings have made COVID-19 units conducive to a variety of secondary infections. Long-term effect of excess antibiotic use in COVID-19 patients is yet to be studied. Very few studies have assessed secondary infections as the primary outcome measure making it difficult to know the true incidence. Mortality attributable to secondary infections in COVID-19 patients is also unclear.

Summary
Incidence of secondary infections in COVID-19 patients is likely higher than what is reported in the literature. Well designed studies are needed to understand the incidence and impact of secondary infections in this patient population. Many of these may be preventable especially now, as personal protective equipment and other healthcare resources are recovering. Infection prevention and control (IPC) and antimicrobial stewardship programmes (ASP) must reassess current situation to correct any breaches that could potentially cause more harm in these already vulnerable patients as we brace for a future surge with another pandemic wave.

Keywords
antibiotic use in CoVID-19, antimicrobial resistance during COVID-19, bacterial infections in COVID-19, co-infections in COVID-19, fungal infections in COVID-19, secondary infections in COVID-19

INTRODUCTION

Although the coronavirus disease 2019 (COVID-19) pandemic raged, much of the discussion rightfully focused on secondary infections in patients infected with SARS-CoV-2. Majority of deaths during the 1918–1919 influenza pandemic resulted directly from secondary bacterial pneumonia [1,2]. 'If grippe condemns, the secondary infections execute' [1, p. 448]. This quote by Louis Cruveilhier in the year 1919 highlights the magnitude of concern for secondary infections during 1918–1919 pandemic influenza [1]. This experience supplemented by similar data from the subsequent 1957 and 1968 pandemics likely primed clinicians to expect bacterial superinfections to play a significant role during the current pandemic. In addition, clinically discriminating COVID-19 patients with and without secondary bacterial infections could be challenging. This may have led to increased antibiotic use in COVID-19 patients.

Despite warnings of public health threats posed by potential pandemics [3], the world was stunned by the arrival of COVID-19 and was caught in a resource-limited state, which led to changes in standard of care (SOC) including adjustments to evidence-based infection control safeguards. Thus, the pandemic affected both IPC and ASP in significant ways.

Within the long list of unknowns in this pandemic world is the question of the future of COVID-19. In general, researchers agree that COVID-19 is

[a]Division of Infectious Diseases and Geographic Medicine, University of Texas Southwestern Medical Center and [b]VA North Texas Healthcare System, Dallas, Texas, USA

Correspondence to Madhuri M. Sopirala, MD, MPH, Y07214, 5323 Harry Hines Blvd., Dallas, TX 75390, USA. Tel: +1 214 648 8268; e-mail: msopirala@gmail.com, Madhuri.sopirala@UTSouthwestern.edu

Curr Opin Infect Dis 2021, 33:000–000
DOI:10.1097/QCO.0000000000000736

KEY POINTS

- Immune dysregulation plays an important role in secondary infections in COVID-18 patients, but there may be healthcare-related predisposition that is avoidable.
- Severe resource limitations and excess antibiotic use may have resulted in a variety of healthcare acquired infections including those caused by multidrug-resistant organisms.
- True incidence and attributable mortality of secondary infections is yet to be determined.

here to stay. In a recent survey of more than 100 immunologists, infectious disease researchers and virologists working on SARS-CoV-2, 89% thought that SARS-CoV-2 will become an endemic virus [4]. A mathematical model integrating viral, environmental and immunologic factors predicted a range of potential postpandemic scenarios spanning from SARS-CoV-2 entering into regular circulation after the initial pandemic wave, to a prolonged single-peak pandemic, to an apparent elimination of the virus followed by resurgence after a few years [5▪]. Regardless of which scenario plays out, we can reasonably predict that clinicians will be caring for patients with COVID-19 and its secondary infections leading well into the foreseeable future. As we move forward, understanding the factors that predispose COVID-19 patients to secondary infections and the frequency with which secondary infections occur will have clinical, IPC and ASP implications. The aim of this literature review is to explore and summarize potential predisposing factors to secondary infections and their incidence.

PREDISPOSITION TO SECONDARY INFECTIONS

A great deal of how secondary infections occur in patients infected with SARS-CoV-2 is yet to be understood. It may be multifactorial stemming from virus and host interaction leading to immune dysregulation or treatment-related predisposition or that related to healthcare interactions (Fig. 1).

Predisposition due to immune dysregulation

SARS-CoV-2 inhibits IFNβ production, thereby attenuating IFN-1 innate immune response [6,7]. Inhibition of IFN-1 induced signalling may lead to impaired bacterial recognition. In addition, severe COVID-19 is associated with exhaustion of $CD4^+$ and $CD8^+$ T cells [8], which may be a result of deficient IFN-I production [6,8]. Extrapolating from influenza virus infection, alteration of TLR4 and TLR5 pathways after viral infection results in impaired neutrophil migration which in turn leads to increased bacterial adherence to respiratory epithelial cells [9]. High levels of complement component C5a, a key driver of neutrophil impairment in critical illness, have been reported in COVID-19 [10]. SARS-CoV-2 infection leads to sustained production of tumour necrosis factor- α (TNF- α) and inter-leukin-6 (IL-6) resulting in hyper-inflammation [11]. Sustained production of proinflammatory

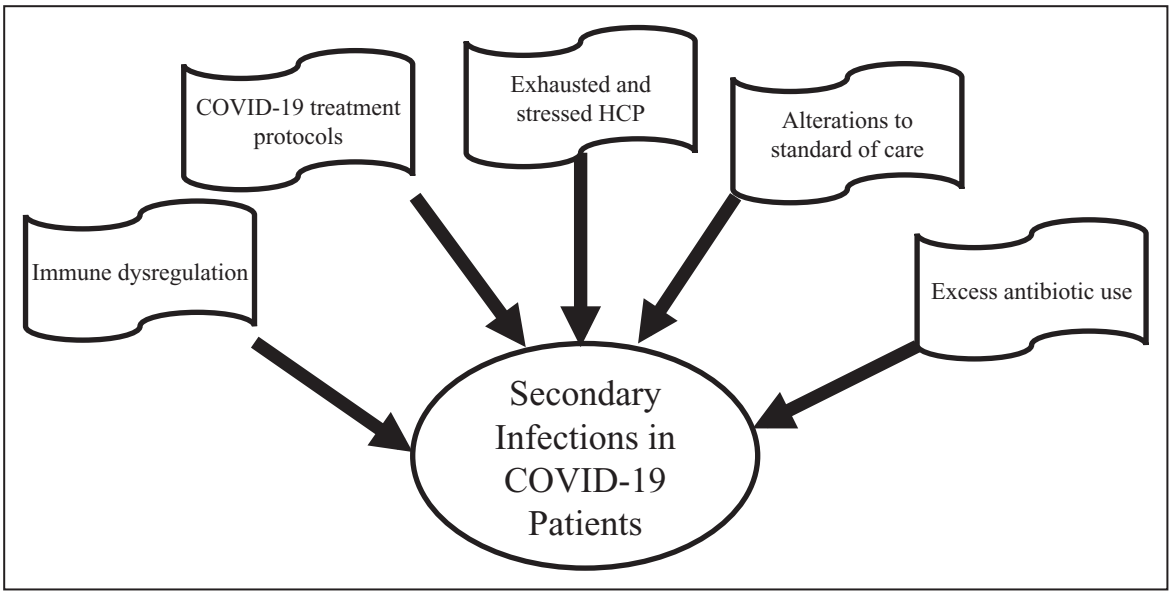

FIGURE 1. Predisposing factors to secondary infections in patients with COVID-19.

cytokines could be detrimental to host cells [12]. Macrophages become overwhelmed by the increased burden of apoptotic cells and therefore become limited in pathogen clearance [13–16]. Cytokine release syndrome and immune exhaustion combined with lung damage may predispose host to secondary infections [17]. Dysbiosis (imbalance of microbial community) occurring in the respiratory and gastrointestinal tract in association with acute respiratory viral infections may alter immunity or promote proliferation of pathogens [18]. The dynamics of how immune response predisposes host to secondary infections is still under study.

Treatment-related predisposition to secondary infections

Although it has been long known that immunomodulatory agents could predispose patients to infections, literature reveals discrepant results with some studies showing low incidence in the setting of tocilizumab use [19–21] and others showing high incidence [22,23]. IPC practices along with differences in study designs might explain these inconsistencies. Corticosteroids either alone or in combination with tocilizumab were shown to increase the risk of secondary infections [24▪,25▪].

Nonpharmacologic treatment methods for COVID-19 such as placement of patients with severe ARDS in prone position to improve oxygenation can lead to complications such as dislodgement or pulling of tubes and lines [26,27], decreased visualization of the insertion site and dependent oedema compromising dressing integrity thereby increasing the risk of secondary infections [28].

Predisposition due to alterations in standard of care

There was a critical global shortage of PPE through most of the year 2020 [29▪,30,31], which led to alterations in healthcare practices to conserve PPE. There were reports of unconventional solutions for PPE, such as plastic garbage bags and plastic water bottle cutouts for gowns and eye protection, respectively [32]. In March 2020, the *Journal of the American Medical Association* (JAMA) issued a call for ideas on how to address the impending PPE shortage [29▪], which was met within a week with more than 100 000 views and more than 250 comments from readers [30]. Suggestions to reduce patient contact such as utilizing mobile and out-of-room monitoring and device controls, batching medications or self-administration and barrier visits, were among the responses sent by the readers [30]. Operating with minimal resources, anxiety and fear were rampant among healthcare personnel (HCP) [33]. Fear might have resulted in bypassing SOC and evidence-based practices, which in turn might have led to an increased risk of transmission of hospital pathogens and healthcare-acquired infections (HAIs) [33].

Batching tasks could put pressure on HCP to complete all tasks in a limited amount of time while trying to minimize contact, rushing the tasks that need attention to detail [34]. This could lead to missed opportunities for the five moments of hand hygiene and breaches in device insertion and maintenance among others. Many hospitals moved medication pumps and dialysis machinery out of the patient care room into the hallways. This practice could result in tubing laying on the floor increasing the risk of contamination [34]. Support staff reassigned from noncritical care areas to meet the demand in patient surges in critical care areas may not be as well trained in the care of critical care devices and may feel reluctant to remove unnecessary devices [34]. Staff that were locums or parachuting in from elsewhere may be unfamiliar with the hospital, the equipment and the policies. Use of ventilator circuits and suctioning catheters for individual patients were extended by some, only replacing if they were visibly soiled or malfunctioning, a major deviation from prepandemic SOC when those were changed at scheduled intervals or when malfunctioning or visibly soiled [35▪]. These changes to SOC could have increased the risk of secondary infections.

Some hospitals had protocols to wear multiple layers of gowns and gloves during care of COVID-19 patients [35▪,36▪]. An N95 respirator, a bouffant cap and shoe covers with a gown and a pair of gloves were worn on entry to the COVID-19 unit. These were donned during the entire shift (referred by some as PPE skin). A second gown and another pair of gloves were worn before entering individual patient rooms. The outer layer of gown and gloves were discarded after exiting patients' rooms. Hand hygiene was to be performed after removing the outer layer of PPE. The inner layer of gown and gloves along with all other PPE was discarded before exiting the unit. Some hospitals used a single set of PPE with all patients and throughout the shift [37]. Gloves and gowns in these emergent situations were utilized more for personal protection of HCP from COVID-19 than as tools to protect patients from HAIs [38]. Some hospitals allowed extra PPE layers because of the fear and the perception of increased protection for HCP [36▪] from SARS-CoV-2 when in fact they might increase the risk of self-contamination during doffing and transmission of other pathogens among patients [36▪]. Such alterations

Table 1. Multidrug-resistant organism outbreaks in COVID-19 patients

Author	Geographic location	Outbreak time period	Organism/s	Changes to infection control standard of care
Patel *et al.* [40]	Maryland, USA	May–June 2020	MDR *Escherichia coli* *Pseudomonas aeruginosa* *Acinetobacter baumannii*	Possible contamination: two layers of gown and gloves Remove outer layers before moving to another patient. Inner layer stays Team nursing model Tight spaces and close proximity in double occupancy
Perez *et al.* [35▪]	New Jersey, USA	February–July 2020	Carbapenem-resistant *Acinetobacter baumannii*	Extended use of ventilator circuits and suctioning catheters only replacing when visibly soiled or malfunctioning
Tiri *et al.* [41]	Terni, Italy	March–June 2020	Carbapenem-resistant *Klebsiella pneumoniae*	Four to five healthcare workers turning the patient to prone position None other reported
Nori *et al.* [42]	Bronx, NY, USA	March–April 2020	New Delhi Metallo-betalactamase (NDM) producing carbaenem-resistant *Enterobacterales*	Reuse of PPE Lapses of standard of care for device maintenance Patient cohorting in surge ICU
Porretta *et al.* [43]	Tuscany, Italy	March–May 2020	NDM producing carbapenem-resistant *Enterobacterales*	NR
Kampmeier *et al.* [44]	Münster, Germany	March–April, 2020	Vancomycin-resistant enterococci	Hand hygiene Environmental hygiene
Prestel *et al.* [36▪]	Florida, USA	July-August 2020-	*Candida auris*	Contamination due to multiple layers of gown and gloves. One inner gown and one pair of gloves are worn the entire shift
Chaudhary *et al.* [39]	New Delhi, India	April–July 2020	*Candida auris (67%)* *Other Candida spp.*	NR

PPE, personal protective equipment.

in SOC resulted in multiple outbreaks of multidrug-resistant organisms (MDRO) in COVID-19 patients [35▪,36▪,37–44], no doubt only a fraction of those reported in the literature (Table 1).

Blood stream infections, central line associated blood stream infections, catheter-related blood stream infections, catheter-associated urinary tract infections and ventilator-associated pneumonias

The scant number of studies that reported the incidence of catheter-related blood stream infections (CRBSI), central line associated blood stream infections (CLABSI) or catheter-associated urinary tract infections (CAUTI) (Table 2) are before and after comparisons that do not control for the multiple changes in practices noted above. Therefore, no conclusions can be made from these studies. In addition to the excess risk posed by the myriad of pandemic-imposed changes to healthcare practice that were implemented to manage these patients, BSI may occur as a direct result of the damage incurred by SARS-CoV-2 itself. Bacterial translocation may be an early event related to intestinal damage due to tissue infection, systemic inflammation-induced dysfunction and IL-6 mediated diffuse vascular damage [45] and due to ischemic enteritis and mesenteric infarctions [46,47]. Some studies reported either a high frequency of *Enterococcus*-related BSI or had an unknown source [48,49,50] supporting the idea that BSI may be the result of bacterial translocation from gastrointestinal tract. In a retrospective cohort study, Knepper *et al.* [51] reported that CAUTI rates were 83% higher, and CLABSI rates were 65% higher in COVID-19 areas than in non-COVID-19 areas. In a retrospective study of CLABSIs and CAUTIs, Fakih *et al.* found that the proportion of COVID-19 patients with CLABSI events was five times greater than that for non–COVID-19 patients with CLABSI with significantly higher mortality [52]. There was no significant change in CAUTI incidence.

High incidence of VAPs ranging from 29 to 86% has been reported in patients with COVID-19 [53–

Table 2. Incidence, mortality and antibiotic use in COVID-19 patients with BSI, CLABSI, CAUTI and VAP

Type of infection	Author	Study Design	Incidence	Predominant organisms	Mortality	Antibiotic Use
BSI	Buetti *et al.* [49]	Matched case-cohort	15%	CoNS Enterococci	NR	79%
	Bhatt *et al.* [50]	Multicentre case–control (BSI vs. no BSI)	34%	*Staphylococcus epidermidis,* Methicillin susceptible *Staphylococcus aureus, Enterococcus fecalis*	53%	80%
	Bonazzetti *et al.*[48]	Retrospective observational	67%	*Enterococcus* species, CoNS, *S. aureus*	NR	NR
CLABSI	Knepper *et al.* [51]	Retrospective cohort	65% higher in COVID-19 areas	NR	NR	NR
	Fakih *et al.* [52]	Retrospective observational	Five times greater in COVID-19 patients	CoNS, *Candida* spp.	53.8%	NR
CAUTI	Knepper *et al.* [51]	Retrospective cohort	83% higher in COVID-19 areas	NR	NR	NR
	Fakih *et al.* [52]	Retrospective observational	No significant change from prepandemic timeframe	NR	NR	NR
VAP	Maes[a] *et al.* [53]	Retrospective observational	48%	Enterobacteriaceae, *Hemophilus influenza, P. aeruginosa*	38%	94%
	Rouze *et al.* [54]	Multicentre retrospective cohort	51%	*P. aeruginosa, Enterobacter spp., Klebsiella spp.*	29%	95%
	COVID-ICU Group [55]	Multicentre prospective cohort	58%	NR	31%	NR
	Luyt *et al.* [56]	Retrospective cohort	86%	Enterobacteriaceae (40% Amp-C cephalosporinase producers) *P. aeruginosa*	34%	100%
	Zhou *et al.* [57]	Retrospective multicentre cohort	31%	NR	NR	95%
	Giacobbe *et al.* [58]	Multicentre retrospective observational	29%	*P. aeruginosa*	46%	95%

BSI, blood stream infections; CLABSI, central line associated blood stream infection; CAUTI, catheter-associated urinary tract infection; CoNS, coagulase-negative Staphylococcal spp.; NR, not reported; VAP, ventilator-associated pneumonia.
[a]Reported three cases of *Aspergillus fumigatus*.

58]. Giacobbe *et al.* [58] reported a high 30-day case-fatality of 46% (78 of 171 COVID-19 patients with VAP); it most likely reflects the prognostic implications of the underlying viral infection and the superimposing secondary bacterial infection.

Predisposition due to empiric broad-spectrum antimicrobial treatment

It is challenging to distinguish the clinical picture of COVID-19 from atypical bacterial pneumonia during early presentation, and VAP and hospital-acquired pneumonia during severe COVID-19 [57,59]. Resulting widespread antimicrobial use especially in the setting of corticosteroids, immunomodulators such as interferon, tocilizumab and other mAbs could potentially lead to changes in microbiome and antimicrobial resistance, and likely to an increased risk of fungal infections.

Incidence of secondary bacterial infections and antibiotic use

In a meta-analysis that included more than 3000 patients with COVID-19, bacterial coinfection (estimated on presentation) was identified in 3.5% of patients [95% confidence interval (95% CI) 0.4–6.7]

and secondary bacterial infection in 14.3% of patients (95% CI 9.6–18.9). Most patients with COVID-19 received antibiotics (71.9%, 95% CI 56.1–87.7) [60]. In another meta-analysis, 7% of hospitalized COVID-19 patients had a bacterial coinfection (95% CI 3–12, $n = 2183$) with 14% from ICU and 4% from mixed ward/ICU settings. COVID-19 patients with a coinfection were more likely to die than patients who did not have a coinfection [pooled odds ratio (OR) 5.82, 95% CI: 3.4–9.9, $n = 733$, four studies]. Antibiotic use was reported in 17 studies, with more than 90% of patients receiving empirical antibiotics in 10 studies [61]. Other studies have shown similar low incidence of secondary infections [59,62–67]. Although a few studies such as those by Karaba *et al.* [63] identify bacterial infections using criteria that include more than respiratory cultures, all of the studies are retrospective reviews of existing data with very little control over the clinical practice in terms of diagnostic tests or antimicrobial prescribing patterns; respiratory cultures were infrequently obtained.

Antimicrobial resistance

Regardless of the true incidence of secondary infections, a staggering number of patients with COVID-19 receive antibiotics potentially contributing to antimicrobial resistance. This could adversely affect the microbial landscape of secondary infections to include difficult-to-treat MDRO. A combination of excess antibiotic exposures, widespread use of immunosuppressive medications, reuse of protective equipment, lapses in standards of care for maintenance of invasive devices and patient cohorting in surge ICUs likely contributed to spread of New Delhi Metallo-beta-lactamase producing *Enterobacterales* infections in COVID-19 patients at a medical centre in the Bronx, New York, USA [42]. How COVID-19 will affect antimicrobial resistance in the long run is yet to be seen.

Secondary mould infections

Wang *et al.* [68] reported a significant association between antibiotic use and mould infections, whereas Bartoletti *et al.* did not [69]. Some studies reported high use of antibiotics [70▪]. An incidence in the range of 7.7–30% was reported for invasive mould infections in COVID-19 patients [68,69,70▪,71▪,72,73]. A few studies found the use of corticosteroids to be a risk factor for invasive mould infection [69,73]. Available literature hints to excess mortality in COVID-19 patients scourged by secondary mould infections [69,70▪]. Invasive mould infection was reported to have occurred in otherwise immunocompetent COVID-19 patients [70▪,71▪].

Candidemia in COVID-19 patients

Some studies reported a significantly higher rate of candidemia in COVID-19 patients than in non-COVID-19 patients [74,75], whereas a few others did not. [76]. Arastehfar *et al.* [77] found that the extent of COVID-19 associated candidiasis (both superficial and invasive) varies by country and region. Such variations are likely to be explained by differences in factors other than COVID-19 related immune dysfunction such as prolonged ICU stay, central venous catheters, and broad-spectrum antibiotic use [77]. Differences in IPC protocols may also be vital confounders leading to this variation. It is currently unknown whether invasive candidiasis leads to increased mortality in this population.

CONCLUSION

Innate immune response to SARS-CoV-2 infection in a host triggers an inflammatory cascade. The resultant immune exhaustion and organ damage may predispose the host to secondary infections. Pandemic-imposed failure in ASP and IPC oversight likely added insult to this injury and made the host even more susceptible to secondary infections. Incidence of secondary infections and attributable mortality has been poorly studied. Few studies had secondary infections as primary end points. Regardless, antibiotic use has been staggeringly high in COVID-19 patients. Effect of antibiotic use on antimicrobial resistance in these patients has also not been well studied. However, there are breadcrumbs throughout the literature that lead one to suspect that the incidence and impact of secondary bacterial or fungal infections is not insignificant in COVID-19 patients and that in addition to predispositions inherent to COVID-19, several other preventable factors are at play.

Future studies should be designed to specifically assess the incidence, risk factors and outcomes of secondary infections in COVID-19 patients. MDRO outbreaks are underreported in the COVID-19 literature and are likely more prevalent than what meets the eye. IPC and ASP assessments and corrections must be made widely to avoid further affronts. Although it is difficult to distinguish viral pneumonia or ARDS from secondary bacterial or fungal pneumonia, relying on findings such as lobar consolidation or evidence of necrotizing pneumonia on chest imaging, and rise in leukocyte counts, and paying close attention to fever trends watching for recrudescence of fever after initial defervescence may help clinicians in making this distinction. In addition, strict de-escalation protocols in COVID-19 patients could be helpful in reigning in the

antibiotic use. A wish list for the future, though likely far-fetched, includes widespread bedside molecular diagnostics that can quickly recognize the pathogens and help curtail empiric antibiotic use when used in combination with appropriate ASP protocols [78]. A better understanding of predisposing factors could help prevent morbidity and mortality associated with secondary infections in COVID-19 patients.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 2008; 198:962–970.
2. MacCallum WG. Pathological anatomy of pneumonia associated with influenza; 23 plates. Johns Hopkins Hosp Rep 1921; 20:149–249.
3. Osterholm MT. Preparing for the next pandemic. N Engl J Med 2005; 352:1839–1842.
4. Phillips N. The coronavirus is here to stay: here's what that means. Nature 2021; 590:382–384.
5. ■ Kissler SM, Tedijanto C, Goldstein E, *et al.* Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 2020; 368:860–868.

This publication predicts the future of the pandemic and suggests interventions to mitigate the intensity of the current outbreak.

6. Schreiber G. The role of type I interferons in the pathogenesis and treatment of COVID-19. Front Immunol 2020; 11:595739.
7. Li JY, Liao CH, Wang Q, *et al.* The ORF6, ORF8 and nucleocapsid proteins of SARS-CoV-2 inhibit type I interferon signaling pathway. Virus Res 2020; 286:198074.
8. Diao B, Wang C, Tan Y, *et al.* Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020; 11:827.
9. Didierlaurent A, Goulding J, Patel S, *et al.* Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. J Exp Med 2008; 205:323–329.
10. Carvelli J, Demaria O, Vély F, *et al.* Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature 2020; 588:146–150.
11. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, *et al.* Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020; 27:992–1000e3.
12. Cook DN, Pisetsky DS, Schwartz DA. Toll-like receptors in the pathogenesis of human disease. Nat Immunol 2004; 5:975–979.
13. Bragonzi A, Copreni E, de Bentzmann S, *et al.* Airway epithelial cell-pathogen interactions. J Cyst Fibros 2004; 3(Suppl 2):197–201.
14. Hendaus MA, Jomha FA, Alhammadi AH. Virus-induced secondary bacterial infection: a concise review. Ther Clin Risk Manag 2015; 11:1265–1271.
15. Morgan DJ, Casulli J, Chew C, *et al.* Innate immune cell suppression and the link with secondary lung bacterial pneumonia. Front Immunol 2018; 9:2943.
16. Lucien MAB, Canarie MF, Kilgore PE, *et al.* Antibiotics and antimicrobial resistance in the COVID-19 era: perspective from resource-limited settings. Int J Infect Dis 2021; 104:250–254.
17. Clancy CJ, Nguyen MH. Coronavirus disease 2019, Superinfections, and antimicrobial development: what can we expect? Clin Infect Dis 2020; 71:2736–2743.
18. Hanada S, Pirzadeh M, Carver KY, Deng JC. Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. Front Immunol 2018; 9:2640.
19. REMAP-CAP Investigators. Gordon AC, Mouncey PR, Al-Beidh F, *et al.* Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021; 384:1491–1502.
20. Salvarani C, Dolci G, Massari M, *et al.* Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med 2021; 181:24–31.
21. Hermine O, Mariette X, Tharaux PL, *et al.* Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial [published correction appears in JAMA Intern Med. 2021 Jan 1;181(1):144]. JAMA Intern Med 2021; 181:32–40.
22. Somers EC, Eschenauer GA, Troost JP, *et al.* Tocilizumab for treatment of mechanically ventilated patients with COVID-19 [published online ahead of print, 2020 Jul 11]. Clin Infect Dis 2020; ciaa954.
23. Aziz M, Haghbin H, Abu Sitta E, *et al.* Efficacy of tocilizumab in COVID-19: a systematic review and meta-analysis. J Med Virol 2021; 93:1620–1630.
24. ■ Giacobbe DR, Battaglini D, Ball L, *et al.* Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest 2020; 50:e13319.

This publication is one of the few that showed that corticosteroid treatment with or without tocilizumab was independently associated with the development of blood stream infection.

25. ■ Kumar G, Adams A, Hererra M, *et al.* Predictors and outcomes of healthcare-associated infections in COVID-19 patients. Int J Infect Dis 2021; 104:287–292.

This study is one of the few studies with HAI as primary outcomes.

26. Petrone P, Brathwaite CEM, Joseph DK. Prone ventilation as treatment of acute respiratory distress syndrome related to COVID-19. Eur J Trauma Emerg Surg 2020; 1–6. [Epub ahead of print]
27. Phua J, Weng L, Ling L, *et al.* Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations [published correction appears in Lancet Respir Med. 2020 May;8(5):e42]. Lancet Respir Med 2020; 8:506–517.
28. McCormick J, Blackwood B. Nursing the ARDS patient in the prone position: the experience of qualified ICU nurses. Intensive Crit Care Nurs 2001; 17:331–340.
29. ■ Bauchner H, Fontanarosa PB, Livingston EH. Conserving supply of personal protective equipment: a call for ideas. JAMA 2020; 323:1911.

This is a very interesting editorial comment followed by reader suggestions on how to conserve resources during the pandemic.

30. Livingston E, Desai A, Berkwits M. Sourcing personal protective equipment during the COVID-19 pandemic. JAMA 2020; 323:1912–1914.
31. Burki T. Global shortage of personal protective equipment. Lancet Infect Dis 2020; 20:785–786.
32. Bowden E, Campanile C, Golding B. Worker at NYC hospital where nurses wear trash bags as protection dies from coronavirus. New York Post. 25 March 2020. https://nypost.com/2020/03/25/worker-at-nyc-hospital-where-nurses-wear-trash-bags-as-protection-dies-from-coronavirus/. [Accessed 7 April 2020]
33. Cawcutt KA, Starlin R, Rupp ME. Fighting fear in healthcare workers during the COVID-19 pandemic. Infect Control Hosp Epidemiol 2020; 41: 1192–1193.
34. McMullen KM, Smith BA, Rebmann T. Impact of SARS-CoV-2 on hospital acquired infection rates in the United States: predictions and early results. Am J Infect Control 2020; 48:1409–1411.
35. ■ Perez S, Innes GK, Walters MS, *et al.* Increase in hospital-acquired carbapenem-resistant *Acinetobacter baumannii* infection and colonization in an acute care hospital during a surge in COVID-19 admissions - New Jersey, February-July 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1827–1831.

One of the few publications that candidly shows how strategies to preserve continuity of care resulted in lapses in infection control during the pandemic. Investigated by CDC.

36. ■ Prestel C, Anderson E, Forsberg K, *et al. Candida auris* outbreak in a COVID-19 specialty care unit: Florida, July-August 2020. MMWR Morb Mortal Wkly Rep 2021; 70:56–57.

Lapses in infection control led to this outbreak. Investigated by CDC and was abated after improvement in orocesses.

37. Arteaga-Livias K, Pinzas-Acosta K, Perez-Abad L, *et al.* A multidrug-resistant *Klebsiella pneumoniae* outbreak in a Peruvian hospital: another threat from the COVID-19 pandemic. Infect Control Hosp Epidemiol 2021; 1-2:. [Epub ahead of print]
38. Arcari G, Raponi G, Sacco F, *et al. Klebsiella pneumoniae* infections in COVID-19 patients: a 2-month retrospective analysis in an Italian hospital. Int J Antimicrob Agents 2021; 57:106245.
39. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant *Candida auris* infections in critically ill Coronavirus disease patients, India, April-July 2020. Emerg Infect Dis 2020; 26:2694–2696.
40. Patel A, Emerick M, Cabunoc MK, *et al.* Rapid spread and control of multidrug-resistant Gram-negative bacteria in COVID-19 patient care units. Emerg Infect Dis 2021; 27:1234–1237.

41. Tiri B, Sensi E, Marsiliani V, *et al.* Antimicrobial Stewardship Program, COVID-19, and infection control: spread of carbapenem-resistant Klebsiella pneumoniae colonization in ICU COVID-19 patients. What did not work? J Clin Med 2020; 9:2744.

42. Nori P, Szymczak W, Puius Y, *et al.* Emerging co-pathogens: New Delhi Metallo-beta-lactamase producing *Enterobacterales* infections in New York City COVID-19 patients. Int J Antimicrob Agents 2020; 56:106179.

43. Porretta AD, Baggiani A, Arzilli G, *et al.* Increased risk of acquisition of New Delhi metallo-beta-lactamase-producing carbapenem-resistant *Enterobacterales* (NDM-CRE) among a cohort of COVID-19 patients in a teaching hospital in Tuscany, Italy. Pathogens 2020; 9:635.

44. Kampmeier S, Tönnies H, Correa-Martinez CL, *et al.* A nosocomial cluster of vancomycin resistant enterococci among COVID-19 patients in an intensive care unit. Antimicrob Resist Infect Control 2020; 9:154.

45. Cardinale V, Capurso G, Ianiro G, *et al.* Intestinal permeability changes with bacterial translocation as key events modulating systemic host immune response to SARS-CoV-2: a working hypothesis. Dig Liver Dis 2020; 52:1383–1389.

46. Bhayana R, Som A, Li MD, *et al.* Abdominal imaging findings in COVID-19: preliminary observations. Radiology 2020; 297:E207–E215.

47. Cheung KS, Hung IFN, Chan PPY, *et al.* Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology 2020; 159:81–95.

48. Bonazzetti C, Morena V, Giacomelli A, *et al.* Unexpectedly high frequency of enterococcal bloodstream infections in coronavirus disease 2019 patients admitted to an Italian ICU: an observational study. Crit Care Med 2021; 49:e31–e40.

49. Buetti N, Ruckly S, de Montmollin E, *et al.* COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network [published correction appears in Intensive Care Med. 2021 Mar 10;:]. Intensive Care Med 2021; 47:180–187.

50. Bhatt PJ, Shiau S, Brunetti L, *et al.* Risk factors and outcomes of hospitalized patients with severe COVID-19 and secondary bloodstream infections: a multicenter, case-control study. Clin Infect Dis 2020; ciaa1748. [Epub ahead of print]

51. Knepper BC, Wallace K, Young H. 95. CAUTI and CLABSI in hospitalized COVID-19 patients. Open Forum Infect Dis 2020; 7(Suppl 1):S178.

52. Fakih MG, Bufalino A, Sturm L, *et al.* Coronavirus disease 2019 (COVID-19) pandemic, central-line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI): the urgent need to refocus on hardwiring prevention efforts. Infect Control Hosp Epidemiol 2021; 1–6. [Epub ahead of print]

53. Maes M, Higginson E, Pereira-Dias J, *et al.* Ventilator-associated pneumonia in critically ill patients with COVID-19 [published correction appears in Crit Care. 2021 Apr 6;25(1):130]. Crit Care 2021; 25:25.

54. Rouzé A, Martin-Loeches I, Povoa P, *et al.* Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med 2021; 47:188–198.

55. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021; 47:60–73.

56. Luyt CE, Sahnoun T, Gautier M, *et al.* Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann Intensive Care 2020; 10:158.

57. Zhou F, Yu T, Du R, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet 2020; 395:1054–1062.

58. Giacobbe DR, Battaglini D, Enrile EM, *et al.* Incidence and prognosis of ventilator-associated pneumonia in critically ill patients with COVID-19: a multicenter study. J Clin Med 2021; 10:555.

59. Rawson TM, Moore LSP, Zhu N, *et al.* Bacterial and fungal coinfection in individuals with coronavirus: Aa rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020; 71:2459–2468.

60. Langford BJ, So M, Raybardhan S, *et al.* Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect 2020; 26:1622–1629.

61. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 2020; 81:266–275.

62. Garcia-Vidal C, Sanjuan G, Moreno-García E, *et al.* Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2021; 27:83–88.

63. Karaba SM, Jones G, Helsel T, *et al.* Prevalence of co-infection at the time of hospital admission in COVID-19 patients, a multicenter study. Open Forum Infect Dis 2020; 8:ofaa578.

64. Vaughn VM, Gandhi T, Petty LA, *et al.* Empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized with COVID-19: a multi-hospital cohort study. Clin Infect Dis 2020; ciaa1239. [Epub ahead of print]

65. Lehmann CJ, Pho MT, Pitrak D, *et al.* Community acquired co-infection in COVID-19: a retrospective observational experience. Clin Infect Dis 2020; ciaa902. [Epub ahead of print]

66. Townsend L, Hughes G, Kerr C, *et al.* Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection. JAC Antimicrob Resist 2020; 2:dlaa071.

67. Nori P, Cowman K, Chen V, *et al.* Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect Control Hosp Epidemiol 2021; 42:84–88.

68. Wang J, Yang Q, Zhang P, *et al.* Clinical characteristics of invasive pulmonary aspergillosis in patients with COVID-19 in Zhejiang, China: a retrospective case series. Crit Care 2020; 24:299.

69. Bartoletti M, Pascale R, Cricca M, *et al.* Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis 2020; ciaa1065. [Epub ahead of print]

70. ■ Rabagliati R, Rodríguez N, Núñez C, *et al.* COVID-19-associated mold infection in critically ill patients, Chile. Emerg Infect Dis 2021; 27:. [Epub ahead of print]

This study showed that pulmonary aspergillosis occurred in COVID-19 patients who are otherwise immunocompetent.

71. ■ Koehler P, Cornely OA, Böttiger BW, *et al.* COVID-19 associated pulmonary aspergillosis. Mycoses 2020; 63:528–534.

This study showed that pulmonary aspergillosis occurred in COVID-19 patients who are otherwise immunocompetent.

72. Alanio A, Dellière S, Fodil S, *et al.* Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. Lancet Respir Med 2020; 8:e48–e49.

73. White PL, Dhillon R, Cordey A, *et al.* A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis 2020; ciaa1298. [Epub ahead of print]

74. Mastrangelo A, Germinario BN, Ferrante M, *et al.* Candidemia in COVID-19 patients: incidence and characteristics in a prospective cohort compared to historical non-COVID-19 controls. Clin Infect Dis 2020; ciaa1594. [Epub ahead of print]

75. Macauley P, Epelbaum O. Epidemiology and Mycology of Candidaemia in nononcological medical intensive care unit patients in a tertiary center in the United States: overall analysis and comparison between non-COVID-19 and COVID-19 cases. Mycoses 2021. [Epub ahead of print]

76. White PL, Dhillon R, Healy B, *et al.* Candidaemia in COVID-19, a link to disease pathology or increased clinical pressures? Clin Infect Dis 2020; ciaa1597. [Epub ahead of print]

77. Arastehfar A, Carvalho A, Nguyen MH, *et al.* COVID-19-associated candidiasis (CAC): an underestimated complication in the absence of immunological predispositions? J Fungi (Basel) 2020; 6:211.

78. Arulkumaran N, Routledge M, Schlebusch S, *et al.* Antimicrobial-associated harm in critical care: a narrative review. Intensive Care Med 2020; 46:225–235.