ARTICLE IN PRESS

Trends in
Microbiology

 CellPress

Review

Bacterial coinfections in coronavirus disease 2019

Lars F. Westblade,[1,2] Matthew S. Simon,[2] and Michael J. Satlin[1,2,*]

Bacterial coinfections increase the severity of respiratory viral infections and were frequent causes of mortality in influenza pandemics but have not been well characterized in patients with coronavirus disease 2019 (COVID-19). The aim of this review was to identify the frequency and microbial etiologies of bacterial coinfections that are present upon admission to the hospital and that occur during hospitalization for COVID-19. We found that bacterial coinfections were present in <4% of patients upon admission and the yield of routine diagnostic tests for pneumonia was low. When bacterial coinfections did occur, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* were the most common pathogens and atypical bacteria were rare. Although uncommon upon admission, bacterial infections frequently occurred in patients with prolonged hospitalization, and *Pseudomonas aeruginosa*, *Klebsiella* spp., and *S. aureus* were common pathogens. Antibacterial therapy and diagnostic testing for bacterial infections are unnecessary upon admission in most patients hospitalized with COVID-19, but clinicians should be vigilant for nosocomial bacterial infections.

The threat of bacterial coinfections in COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a devastating pandemic of COVID-19 and has led to more than 100 million cases and 2 million deaths globally in a span of 12 months[i]. Pandemics have plagued humans throughout history but are now becoming increasingly common. Influenza was responsible for the 1918 pandemic that resulted in ~50 million deaths worldwide, and more recently pandemics in 1957, 1968, and 2009 [1]. In 2003, a near-pandemic of severe acute respiratory syndrome coronavirus (SARS-CoV) occurred, closely followed by the emergence of another lethal coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), in 2012 [2].

Bacterial coinfection is a common complication of many viral respiratory tract infections and leads to significantly increased morbidity and mortality [3]. During the 1918 pandemic, bacterial coinfection was a significant contributor in nearly all influenza deaths, with common upper respiratory tract bacteria such as *S. pneumoniae*, β-hemolytic streptococci, *H. influenzae,* and *S. aureus* being the most common pathogens [4]. Bacterial coinfection was also common in the 2009 influenza pandemic, occurring in 18–30% of cases admitted to the intensive care unit (ICU) and up to 55% of published autopsy series [5–7]. Bacterial coinfections were associated with increased risk of shock and respiratory failure, prolonged ICU length of stay, and mortality [5,6]. The frequency of bacterial coinfection with coronaviruses SARS-CoV and MERS-CoV is not clearly defined because of the relatively small numbers of cases, but a multicenter study of patients admitted to ICUs in Saudi Arabia identified that 19% of patients with MERS had bacterial coinfection [8]. The high frequency and clinical significance of bacterial coinfections in influenza and other novel coronaviruses raises concern that bacterial coinfection could be an important complication of SARS-CoV-2 infection.

Highlights

Bacterial coinfections occur in <4% of patients who are hospitalized with COVID-19 and are usually caused by *S. aureus*, *S. pneumoniae*, and *H. influenzae*.

Empirical antibacterial therapy and diagnostic testing for bacterial pathogens in patients hospitalized with COVID-19 are indicated only in those patients with critical illness, severe immunosuppression, radiographic findings suggestive of a bacterial pneumonia, or multiple laboratory parameters compatible with bacterial infection.

Hospital-acquired infections are common among patients with prolonged hospitalization for COVID-19, and hospital-acquired pneumonia is most commonly caused by *P. aeruginosa*, *Klebsiella* spp., and *S. aureus*.

Carbapenem-resistant Gram-negative infections are being increasingly reported in patients with COVID-19 requiring intensive care.

[1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, USA
[2]Division of Infectious Diseases, Department of Medicine, Weill Cornell Medicine, New York, NY, USA

*Correspondence:
mjs9012@med.cornell.edu (M.J. Satlin).

Although initial reports described the clinical presentations and outcomes of patients hospitalized with COVID-19 [9,10], few reports have focused on the frequency and microbiological etiologies of bacterial coinfections. Furthermore, these reports did not distinguish secondary infections that were present upon admission from those that were acquired in the hospital. Thus, initial reviews on secondary infections complicating COVID-19 relied on limited data [11,12]. However, since those initial reports, numerous studies have reported on secondary infections in COVID-19 patients, and thus our understanding of bacterial coinfections has evolved. Therefore, the focus of this review is to highlight the frequency, risk factors, etiologies, and outcomes of bacterial coinfections in COVID-19, separating those that are present on admission from those that are acquired in the hospital, evaluate the yield of diagnostics, assess the emergence of multidrug-resistant (MDR) bacterial infections, and provide practical guidance to clinicians.

Bacterial coinfections at the time of initial presentation to the hospital
Frequency of bacterial coinfection and associated risk factors
We reviewed publications in which the primary objective of the study was to evaluate bacterial coinfections upon hospital admission in patients with COVID-19. We identified ten studies that evaluated a minimum of 100 patients (Table 1), and in nearly all of these studies fewer than 4% of hospitalized patients with COVID-19 had a documented bacterial coinfection [13–21].

Despite the low prevalence of bacterial coinfection, the majority of patients in these studies received empirical antibacterial therapy. For example, of 1705 patients with COVID-19 presenting to 38 Michigan hospitals, 57% received empirical antibacterial therapy for a median of 3 days (interquartile range: 2–6 days); however, only 3.5% were found to have a bacterial infection upon admission [13]. Furthermore, 15% of patients received agents targeting methicillin-resistant *Staphylococcus aureus* (MRSA) and 15% received agents targeting *P. aeruginosa*.

The wide disparities between the proportion of hospitalized COVID-19 patients who are treated with antibacterial agents and the proportion of patients who actually have a bacterial coinfection highlights substantial unnecessary use of antibacterial agents among COVID-19 patients. Antibiotic overuse early in the pandemic was driven by uncertainty around the course of a new

Table 1. Bacterial coinfections in patients admitted to the hospital with COVID-19

Refs	Location	No. of patients	Prevalence of bacterial coinfection	Proportion of patients who received antibacterial therapy
[13]	Michigan, USA (38 hospitals)	1705	3.5%	57% (median: 3 days)
[14]	London, England (2 hospitals)	1396	2.7%	98%[a]
[15]	Barcelona, Spain (1 hospital)	989	2.5%	NR
[16]	The Netherlands (4 hospitals)	925	0.8%	60% (median: 2 days)
[17]	London, England (2 hospitals)	836	3.2%	NR
[18]	Chicago, USA (1 hospital)	321	1.2%	69%
[19]	Liverpool, England (1 hospital)	195	2.6%	NR
[20]	Hong Kong (1 hospital)	147	2.7%	35%[b]
[21]	Hangzhou, China (1 hospital)	101	0%	NR
[22]	Paris, France (1 hospital)	101 (ICU patients only)	19.8%	58%

Abbreviations: ICU, intensive care unit; No., number; NR, not reported.
[a]The denominator for this proportion includes 37 patients with bacterial coinfection and 100 randomly selected patients without bacterial coinfection.
[b]Of the 35% of patients who received empirical antibiotics, 37% received them for more than 1 week.

infectious disease, extrapolation from experiences of bacterial coinfection with influenza [23], a surge in critically ill patients, and the lack of effective therapies for SARS-CoV-2. As our knowledge of COVID-19 grows, understanding presenting factors associated with bacterial coinfection is essential so that clinicians can target empirical antibacterial therapy to these high-risk patients. Advanced age and other comorbidities, such as chronic kidney disease, diabetes, and chronic heart disease, have been associated with bacterial coinfections in some but not in other studies [13–15]. Leukocytosis is more common in patients presenting with bacterial coinfections. In two of the largest studies, the median white blood cell (WBC) counts were higher in patients with bacterial coinfection compared to those without coinfection (median of approximately 10.0×10^9 to 11.3×10^9 cells/µl versus 7×10^9 cells/µl, respectively) [13,14]. Wang and colleagues found that the absolute neutrophil count of patients with bacterial coinfections was 9.2×10^9 cells/µl, compared to 5.5×10^9 cells/µl in patients without bacterial coinfection ($P<0.0001$) [14]. Vaughn and colleagues found that procalcitonin levels are also higher in patients with bacterial coinfection compared to those without coinfection [13]. However, leukocytosis, neutrophilia, and elevated procalcitonin levels do not have sufficient sensitivity, specificity, or positive predictive value to accurately diagnose bacterial coinfection as stand-alone tests [13,14]. For example, Vaughn *et al.* found that the positive predictive value of a procalcitonin level >0.5 ng/ml was only 9.3% [13]. Conversely, the negative predictive values of a WBC count $<8.8\times10^9$ cells/µl, absolute neutrophil count $<6.8\times10^9$ cells/µl, and procalcitonin level ≤0.5 ng/ml are ≥98%.

While bacterial coinfections are overall rare among patients who are hospitalized for COVID-19, they are more common among patients admitted to an ICU, occurring in 6–29% of these patients [13,22,24–28]. Although some of the increased frequency of bacterial coinfections in patients admitted to an ICU may be related to increasing use of blood and respiratory tract cultures to diagnose bacterial infections [17], these patients may also be more likely to have positive cultures [13,29,30].

Clinicians face a difficult challenge in deciding which hospitalized patients with COVID-19 to treat with antibacterial therapy. Figure 1 illustrates a recommended approach for diagnosing bacterial coinfection and antibiotic management upon hospital admission in patients with COVID-19. We recommend pursing microbiologic diagnostic tests and initiating empirical antibiotic therapy only in patients who are critically ill, severely immunocompromised, or have radiographic or multiple laboratory findings suggestive of bacterial coinfection. When empirical therapy is warranted, we recommend β-lactam agents and provide guidance for when coverage of *P. aeruginosa*, atypical bacteria, and/or MRSA is warranted.

Yield of diagnostic tests for bacterial pathogens in patients hospitalized for COVID-19

Studies of hospitalized patients with COVID-19 have demonstrated that blood cultures upon admission are positive for pathogens in 1.2–4.2% of cases (Table 2) [13,14,17,19,30]. Furthermore, at least half of positive blood cultures in hospitalized patients with COVID-19 represent skin contaminants [14,17,30–32], perhaps in part due to technical challenges for healthcare personnel collecting blood cultures while wearing personal protective equipment (PPE) required for SARS-CoV-2. Hospitals in New York City (NYC) noted a surge in blood culture utilization during the peak of the pandemic, with 35% more cultures analyzed than the same time during the previous year, that at times overwhelmed the capacity of blood culture instruments [31]. Moreover, the rate of positive blood cultures in patients with COVID-19 has been shown to be significantly lower than in patients without COVID-19 [32]. As with the initiation of empirical antibacterial therapy, blood cultures should not be routinely ordered in hospitalized patients with COVID-19. Instead, they should be selectively ordered in patients with a suspicion for bacterial coinfection, which would include patients for whom empirical antibacterial therapy is being initiated.
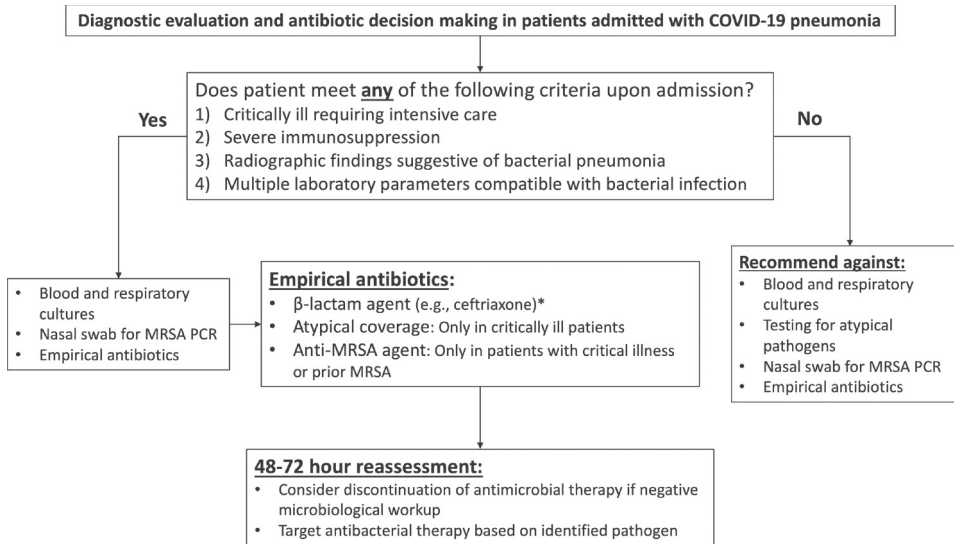
Figure 1. Algorithm to guide diagnostic evaluations and antibiotic decision making in patients who are admitted to the hospital with COVID-19 pneumonia. This flow diagram provides criteria for clinicians to help identify patients for whom a diagnostic work-up should be pursued and for whom empirical antibiotic therapy is warranted. It also provides guidance for the selection of antibiotics. *Consider anti-pseudomonal β-lactam agents in patients with prior *Pseudomonas aeruginosa*, bronchiectasis, or recent use of parenteral antibiotics. MRSA, methicillin-resistant *Staphylococcus aureus*.

Most patients who present to the hospital with COVID-19 do not have a productive cough and thus are not able to produce sputum for culture [13,33]. Studies report that respiratory tract cultures yielded a pathogen in 3–19% of the general population of hospitalized patients with COVID-19 and in 10–21% of patients admitted to ICUs (Table 2) [13,14,18,19,26,29,30]. Based on these data, we recommend the use of respiratory-tract cultures only in the minority of patients who have a productive cough and for whom empirical antibacterial therapy is being considered or in patients who are admitted to the ICU and intubated for respiratory failure.

Only 11 (0.9%) out of 1237 patients had a positive urine pneumococcal antigen test result (Table 2) [14,16–19,26,27,30]. Thus, we do not recommend routine use of urine pneumococcal antigens in patients hospitalized with COVID-19. However, this test may be considered in patients with severe disease for whom antibacterial therapy is being considered, which is in line with guidelines of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) for community-acquired pneumonia (CAP) [34]. The yield of urine legionella antigen tests is even lower, with only one (0.08%) positive test in 1263 patients (Table 2) [14,16–19,26,27,30]. None of the samples that were sent for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* PCR were positive (Table 2) [18,27,29,35–37]. Thus, we do not recommend the routine use of urine legionella antigens or atypical pneumonia PCR panels in patients with COVID-19.

Etiologies of bacterial coinfection on admission, and implications for empirical antibacterial therapy

The most common bacterial respiratory and bloodstream pathogens that caused coinfection upon admission with COVID-19 are outlined in Figure 2. Of 132 total bacterial respiratory and bloodstream pathogens, the most common were *S. aureus* (*n* = 41, 31%), *S. pneumoniae* (*n* = 31, 23%), and *H. influenzae* (*n* = 15, 11%). Thus, for patients hospitalized with COVID-19

Table 2. Yield of diagnostic tests for bacterial coinfection in patients presenting to the hospital with COVID-19

Blood cultures: the yield of blood cultures is low among patients who present to the hospital with COVID-19 and many of the positive results represent skin contaminants.

Refs	Yield for pathogen	Yield for contaminant
[13]	31/1063 (2.9%)	Not reported
[14]	12/969 (1.2%)	65/969 (6.7%)
[17]	21/643 (3.2%)	39/643 (6.1%)
[19]	2/128 (1.6%)	Not reported
[30]	5/118 (4.2%)	4/118 (4.2%)

Respiratory tract cultures: the yield of respiratory-tract cultures is higher than the yield of blood cultures in patients presenting to the hospital with COVID-19; however, respiratory tract cultures are frequently not obtained because many patients do not have a productive cough.

Refs	Patient type	Yield for respiratory pathogen
[13]	All hospitalized patients	25/131 (19.1%)
[18]	All hospitalized patients	2/66 (3.0%)
[14]	All hospitalized patients	8/48 (16.7%)
[29]	Intensive care unit (ICU) patients	9/43 (20.9%)
[26]	ICU patients	3/30 (10.0%)
[30]	Mostly ICU patients	3/24 (12.5%)
[19]	All hospitalized patients	0/25 (0%)

Urine antigen tests: the yield of urine pneumococcal and urine *Legionella* antigen tests is low in patients with COVID-19. Additionally, none of the 965 patients in six different studies who had nasopharyngeal or bronchoalveolar lavage samples analyzed for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* by PCR had positive test results [18,27,29,35–37]. Thus, coinfections with atypical bacteria are extremely rare.

Refs	Yield of pneumococcal antigen	Yield of *Legionella* antigen
[14]	3/296 (1.0%)	0/308 (0%)
[17]	0/249 (0%)	0/246 (0%)
[18]	1/236 (0.4%)	0/240 (0%)
[16]	1/189 (0.5%)	0/187 (0%)
[30]	0/107 (0%)	0/117 (0%)
[27]	1/88 (1.1%)	0/88 (0%)
[26]	2/43 (5.7%)	0/46 (0%)
[19]	3/29 (10.3%)	1/31 (3.2%)
Total	11/1237 (0.9%)	1/1263 (0.08%)

for whom empirical antibacterial therapy is indicated, coverage of these organisms is recommended (Figure 1: empirical antibiotic regimens).

Initial treatment strategies for CAP, as recommended by the ATS and IDSA, consist of combination therapy with a β-lactam and a macrolide or a respiratory fluoroquinolone [34]. These regimens will generally cover *S. aureus*, *S. pneumoniae,* and *H. influenzae*, with the exception of MRSA. The choice of whether to include anti-MRSA therapy in the empirical treatment of bacterial coinfection should be influenced by the local geographic prevalence of MRSA and/or prior isolation of MRSA from the patient (Figure 1). Furthermore, collecting a nares swab for MRSA PCR can guide the use of anti-MRSA therapies. This test has high specificity for MRSA pneumonia and a high negative predictive value for ruling out MRSA in patients with and without COVID-19 [38,39]. Thus, a reasonable strategy to pursue in critically ill patients admitted with
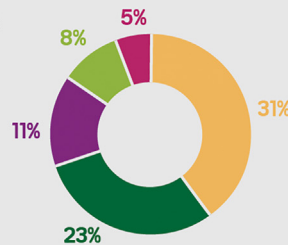
Etiologies of community-onset and hospital-acquired bacterial co-infections in patients hospitalized with COVID-19

Community-onset infection
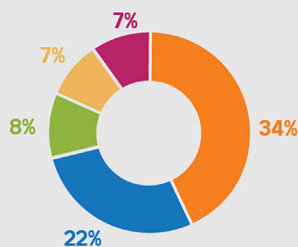
Bloodstream and respiratory infections
Total - 132
S. aureus - 41
S. pneumoniae - 31
H. influenzae - 15
P. aeruginosa - 10
Klebsiella spp. - 6
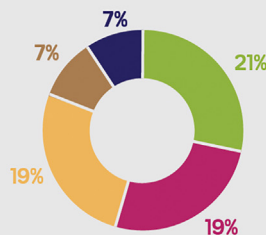

5%
8%
31%
11%
23%

Hospital-acquired infection

Bloodstream infections
Total - 335
CoNS - 113
Enterococcus spp. - 73
P. aeruginosa - 26
S. aureus - 25
Klebsiella spp. - 24

Respiratory tract infections
Total - 165
P. aeruginosa - 34
Klebsiella spp. - 31
S. aureus - 31
E. coli - 12
Enterobacter spp. - 11

7%
7%
34%
8%
22%

7%
7%
21%
19%
19%

Trends in Microbiology

(See figure legend at the bottom of the next page.)

COVID-19 pneumonia to an ICU is to begin anti-MRSA coverage, collect a nares swab for MRSA PCR, and discontinue anti-MRSA coverage if the PCR is negative.

P. aeruginosa was identified as a bacterial respiratory pathogen in 10 (8%) of the 132 coinfections outlined in Figure 2. Thus, routine empirical coverage of *P. aeruginosa* is generally unnecessary, unless the patient has had a history of infection due to this organism, a chronic lung disease associated with *P. aeruginosa* pneumonia, such as bronchiectasis [40], or recent parenteral antibiotic exposure (Figure 1). As with MRSA, if *P. aeruginosa* is not isolated from culture within 48–72 h, anti-pseudomonal therapy should be discontinued if it was started empirically.

The extremely low yield of PCR and urine antigen tests for atypical bacteria suggests that these organisms rarely cause secondary infections in patients with COVID-19, and thus the inclusion of coverage for atypical pathogens with a macrolide or fluoroquinolone may not be necessary in patients with suspected bacterial pneumonia. This conclusion contrasts with findings from a review by Lansbury *et al.* that highlighted *M. pneumoniae* as a common cause of bacterial coinfection [12]. However, this review reported studies that detected *M. pneumoniae* infection based on positive serologic IgM tests, a diagnostic test that lacks specificity for infection [41]. *Legionella pneumophila* may be more common in critically ill patients requiring ICU admission. Although only a single urine legionella antigen test was positive, *L. pneumophila* was identified by culture or PCR in 3 of 50 bacterial coinfections in studies that evaluated only those patients who were admitted to an ICU [24–28].

Although guidelines prefer combination therapy with β-lactam/macrolide antibiotics to monotherapy with just β-lactam antibiotics for CAP in hospitalized patients [34], a recent randomized trial found that the latter is not inferior when compared to the former in patients with CAP who are admitted to non-ICU wards [42]. Another randomized trial of β-lactam/macrolide combination therapy vs. β-lactam monotherapy for CAP also found similar outcomes between groups, except in patients who were infected with atypical pathogens or who were critically ill [43]. A potential benefit of including macrolides in the treatment of CAP is that they may have beneficial immunomodulatory properties [44]. However, randomized trials have not identified a clinical benefit for the use of macrolides in hospitalized patients with COVID-19 [45,46]. Based on available data, we do not recommend adding macrolides to β-lactam agents for patients being treated empirically for bacterial coinfection with COVID-19, with the exception of critically ill patients where *L. pneumophila* coinfection has been observed (Figure 1).

Outcomes of hospitalized patients with COVID-19 who present with a bacterial coinfection

Most studies of bacterial coinfections in patients with COVID-19 did not have a sufficient number of patients to identify differences in outcomes between patients with and without bacterial coinfection. The largest study of bacterial coinfections on admission in our review, however,

Figure 2. Etiologies of community-onset and hospital-acquired bacterial coinfections in patients hospitalized with COVID-19. Community-onset bacterial infections are those that occurred within 2 days of hospital admission in 10 studies [15,16,19,20,23,25–29], and hospital-acquired bacterial infections are those that occurred after the second day of hospitalization in six studies [16,31,48–50,52]. Other bacterial etiologies of community-onset bloodstream or respiratory infections included *Escherichia coli* (*n* =5), *Proteus* spp. (*n* = 4), *Legionella pneumophila* (*n* = 4), and *Citrobacter* spp. (*n* = 2). Other hospital-onset bloodstream infections included *E. coli* (*n* = 14), *Acinetobacter* spp. (*n* = 8), *Enterobacter* spp. (*n* = 7), *Serratia marcescens* (*n* = 3), and *Stenotrophomonas maltophilia* (*n* = 3). Other respiratory tract infections included *S. maltophilia* (*n* = 9), *S. marcescens* (*n* = 8), *Acinetobacter* spp. (*n* = 7), *Citrobacter* spp. (*n* = 6), and *Proteus* spp. (*n* = 5). CoNS, coagulase-negative staphylococci; *H. influenzae*, *Haemophilus influenzae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*.

found that patients with bacterial coinfection had a longer length of hospital stay (median 7 days vs. 5 days; P = 0.003) and increased in-hospital mortality (48% vs. 18%; P <0.001) compared to patients without bacterial coinfection [13]. However, other smaller studies have not found the same association, possibly due to insufficient power or nonrespiratory sources of infection [14,15].

Hospital-acquired bacterial infections that occur in patients with COVID-19

Frequency and risk factors for hospital-acquired bacterial infections

Table 3 outlines results from nine studies in which the primary objective was to assess hospital-acquired bacterial infections in patients with COVID-19 and which evaluated a minimum of 100 patients [15,20,30,47–51]. Hospital-acquired bacterial infections occurred in 3.7–21.9% of patients admitted with COVID-19. Two studies that evaluated only patients admitted to an ICU found that 38.6% and 47.5% of patients developed a hospital-acquired bacterial infection, respectively. The median time from admission until hospital-acquired bacterial infection was typically 1–2 weeks. Pneumonia and bloodstream infections (BSIs) were the most common sources of hospital-acquired bacterial infections.

A substantial proportion of hospitalized patients with COVID-19 require mechanical ventilation [10,33]. Thus, an important clinical question is whether patients with COVID-19 have higher risks of ventilator-associated pneumonia (VAP) than other patients receiving mechanical

Table 3. Hospital-acquired bacterial infections that occur in patients with COVID-19

Refs	Setting	No. of patients	Incidence of bacterial HAI	Median days of HAI from admission	Type of infection	Risk factors for hospital-acquired infection in multivariate models	Mortality: HAI vs. no secondary infection
[47]	Georgia, USA (1 hospital)	1565	3.7% (85% bacterial)	NR	PNA 48% BSI 38% UTI 12%	Tocilizumab; corticosteroids; hydroxychloroquine AKI requiring dialysis	40.7% vs. 11.8% (P <0.001)
[15]	Barcelona, Spain (1 hospital)	989	3.8%	11	PNA 34% BSI 36% UTI 27%	NR	18.6% vs. 9.4% (P = 0.047)
[48]	Milan, Italy (1 hospital)	731	9.3%	12	BSI 72% PNA 28%	Baseline lymphopenia; hypoxia on admission; ICU admission in first 48 h	NR
[49]	Pisa, Italy (1 hospital)	315	21.9%	19	BSI 40% UTI 28% PNA 26%	CRE intestinal colonization; mechanical ventilation; IL-6 or JAK inhibitors; elevated CRP; piperacillin-tazobactam	18.8% vs. 23.2% (P = 0.45)
[50]	Huangshi, China (1 hospital)	212	14.6%	NR	PNA 39% UTI 32% BSI 23%	Urinary catheterization; leukocytosis; elevated PCT	NR
[20]	Hong Kong (2 hospitals)	147	5.4%	NR	NR	NR	NR
[30]	Munich, Germany (1 hospital)	140	7.1% (BSI only)	NR	PNA 67% BSI 33%	NR	NR
[51]	Madrid, Spain (1 hospital)	140 (ICU patients only)	38.6%	9	BSI 56% PNA 33% UTI 8%	APACHE II score	54% vs. 24% (P <0.001)
[22]	Paris, France (1 hospital)	101 (ICU patients only)	47.5%	8	NR	NR	NR

Abbreviations: AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; BSI, bloodstream infection; CRP, C-reactive protein; HAI, hospital-acquired infection; ICU, intensive care unit; IL-6, interleukin-6; JAK, Janus-associated kinase; No., number; NR, not reported; PCT, procalcitonin; PNA, pneumonia; UTI, urinary-tract infection.

ventilation. Maes and colleagues compared the incidence and etiologies of VAP between 81 mechanically ventilated patients with COVID-19 and 144 mechanically ventilated patients without COVID-19 [52]. They found that COVID-19 patients had 28 VAP events per 1000 ventilator days, compared to 13/1000 for patients without COVID-19 (P = 0.009). Although COVID-19 patients were more likely to develop VAP, the organisms causing infection were similar to patients without COVID-19. Another group compared 90 patients with COVID-19-related acute respiratory distress syndrome (ARDS) to 82 ARDS patients without COVID-19 and found that COVID-19 patients were almost twice as likely to develop VAP [53].

Independent risk factors for hospital-acquired bacterial infections varied across studies. Associations between COVID-19 or antibacterial therapies and risk of infection are likely confounded by the fact that sicker patients are more likely to receive these therapies. Measures of acuity of illness upon presentation were consistently identified as risk factors for hospital-acquired bacterial infection, including hypoxia upon admission, need for mechanical ventilation, and ICU admission within the first 48 h [48,49]. Baseline laboratory results were not consistently identified as risk factors, but lymphopenia, leukocytosis, elevated procalcitonin and C-reactive protein levels, acute kidney injury requiring dialysis, and Acute Physiology and Chronic Health Evaluation II score were identified as independent risk factors in individual studies [47–51].

Etiologic agents of bacteria that cause hospital-acquired bacterial infections

Figure 2 outlines the most common etiologies of hospital-acquired bacterial infections in patients with COVID-19. We reviewed data from seven studies that characterized hospital-acquired bacterial infections and identified 556 microbiologically confirmed infections [15,30,47–49,51,54]. The five most common bacterial pathogens were coagulase-negative staphylococci (n = 115, 21%), *Enterococcus* spp. (n = 86, 15%), *Klebsiella* spp. (n = 84, 15%), *P. aeruginosa* (n = 72, 13%), and *S. aureus* (n = 50, 9%). Coagulase-negative staphylococci and enterococci were primarily causes of BSIs; whereas, *P. aeruginosa*, *Klebsiella* spp., and *S. aureus* were the predominant causes of respiratory tract infections.

Outcomes of patients with COVID-19 and hospital-acquired bacterial infections

Three of the four studies that compared outcomes of patients with and without hospital-acquired bacterial infections found an increased mortality rate in the former group [15,47,49,51]. Garcia-Vidal *et al.* found that patients with hospital-acquired bacterial infections had a longer length of hospital stay (20 days vs. 9 days, P <0.001) [15]. Bhatt and colleagues found that 53.1% of patients with a secondary BSI died during the hospitalization, compared to 32.8% of controls (P = 0.0001) [54]. These findings are similar to those observed in patients hospitalized with influenza, where in one study in-hospital mortality was 45.7% in patients who developed a hospital-acquired bacterial or fungal infection and 11.8% in patients who did not develop a hospital-acquired infection [55].

Carbapenem-resistant Gram-negative infections in patients with COVID-19

Although patients with COVID-19 rarely have bacterial coinfections upon admission to the hospital, many receive antibacterial therapies, have prolonged hospitalizations that often require mechanical ventilation, and develop hospital-acquired infections. Thus, it is not surprising that MDR bacterial infections have been reported in patients with COVID-19. One NYC hospital reported 13 patients infected with carbapenemase-producing Enterobacterales, including *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* and New Delhi metallo-β-lactamase (NDM)-producing *Enterobacter cloacae*, during the height of the COVID-19 pandemic in the city [56]. All but one of these patients were receiving mechanical ventilation at the time of

infection and 5 of the 13 patients died. Genomic sequencing identified multiple lineages, suggesting that this was not an outbreak caused by a single strain. Another NYC hospital reported five patients with NDM-producing *E. cloacae* infections who did not have recent international travel history and were admitted from the community [57]. Four of these five patients died of septic shock.

A hospital in New Jersey reported a large increase in the number of patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) during a surge in COVID-19 admissions [58]. They identified 34 patients infected or colonized with CRAB, none of whom had prior CRAB infection or colonization, and most were admitted from home and were mechanically ventilated at the time the bacteria were identified. Ten of the 20 CRAB-infected patients died. Twenty-six of the isolates harbored an OXA-23 carbapenemase and three had an NDM. Upon investigation, deviations from typical infection prevention and control practices related to the COVID-19 surge were thought to be responsible for this outbreak, including discontinuation of contact precautions for certain MDR pathogens to preserve PPE, decreases in the frequency of changes of suctioning catheters, ventilator circuits, masks, and face shields, less frequent chlorhexidine bathing, suspension of typical activities to monitor the use of central venous and urinary catheters, increased patient-to-staff ratios, and use of staff without experience in an ICU setting. This report highlights how hospitals experiencing surges of patients with COVID-19 might be vulnerable to outbreaks of MDR bacteria (see Outstanding questions).

Increasing reports of carbapenem-resistant Gram-negative bacterial infections have also been reported in European hospitals during COVID-19 surges. In one Italian hospital, 19% of blood cultures were positive for KPC-producing *K. pneumoniae* in an ICU devoted to COVID-19 patients [59]. Other hospitals in Italy reported increases in transmission of KPC-producing *K. pneumoniae* that were attributed to similar factors as in the above CRAB outbreak, as well as to the large number of healthcare workers required to pronate hypoxic COVID-19 patients [60,61]. A hospital in France reported an outbreak of NDM-producing *Escherichia coli* in an ICU dedicated to COVID-19 patients that was attributed to a lack of compliance with standard and contact precautions, overworked and inexperienced ICU staff, and lack of typical screening for carriage of MDR Gram-negative pathogens [62].

Concluding remarks

Unlike in prior influenza pandemics, a relatively small proportion of patients hospitalized with COVID-19 initially presented with bacterial coinfection. Based on currently available data, we recommend that empirical antibacterial therapy and blood and respiratory tract cultures should be reserved for patients who are critically ill, severely immunocompromised, or who have multiple clinical features suggestive of bacterial pneumonia; however, additional research is needed to more accurately identify patients who present with bacterial coinfection (see Outstanding questions). When bacterial coinfections are present on admission, *S. aureus*, *S. pneumoniae*, and *H. influenzae* are the most common pathogens, and atypical bacterial infections are rare. While bacterial coinfections are rare upon admission, they are common among patients requiring prolonged hospitalization for COVID-19, particularly those who require mechanical ventilation in an ICU. In this setting, *P. aeruginosa*, *Klebsiella* spp., and *S. aureus* are the most common causative agents of hospital-acquired pneumonia. Furthermore, frequent antibiotic use and changes in infection-control practices related to COVID-19 may have also contributed to the emergence of carbapenem-resistant Gram-negative infections.

Current data are primarily from experiences in the first wave of the pandemic. Evaluations of bacterial coinfections during subsequent waves of the pandemic are critical, particularly given

Trends in Microbiology

CellPress

changes in the care of these patients, such as the routine use of corticosteroids [63], and the emergence of new SARS-CoV-2 variants [64] (see Outstanding questions). Optimizing antibacterial therapies in patients with COVID-19 will hopefully minimize the risks of increasing antimicrobial resistance while appropriately treating bacterial coinfections when they occur.

Resources
ihttps://covid19.who.int/

References

1. Morens, D.M. *et al.* (2020) Pandemic COVID-19 Joins History's Pandemic Legion. *mBio* 11, e00812-20
2. Memish, Z.A. *et al.* (2020) Middle East respiratory syndrome. *Lancet* 395, 1063–1077
3. Gupta, R.K. *et al.* (2008) Bacterial pneumonia and pandemic influenza planning. *Emerg. Infect. Dis.* 14, 1187–1192
4. Morens, D.M. *et al.* (2008) Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J. Infect. Dis.* 198, 962–970
5. Martín-Loeches, I. *et al.* (2011) Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A (H1N1) virus. *Chest* 139, 555–562
6. Rice, T.W. *et al.* (2012) Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Crit. Care Med.* 40, 1487–1498
7. Gill, J.R. *et al.* (2010) Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. *Arch. Pathol. Lab. Med.* 134, 235–243
8. Arabi, Y.M. *et al.* (2017) Critically ill patients with the Middle East Respiratory Syndrome: A multicenter retrospective cohort study. *Crit. Care Med.* 45, 1683–1695
9. Guan, W.J. *et al.* (2020) Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 382, 1708–1720
10. Goyal, P. *et al.* (2020) Clinical characteristics of Covid-19 in New York City. *N. Engl. J. Med.* 382, 2372–2374
11. Rawson, T.M. *et al.* (2020) Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support Covid-19 antimicrobial prescribing. *Clin. Infect. Dis.* 71, 2459–2468
12. Lansbury, L. *et al.* (2020) Co-infections in people with COVID-19: a systematic review and meta-analysis. *J. Infect.* 81, 266–275
13. Vaughn, V.M. *et al.* (2020) Empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized with COVID-19: A multi-hospital cohort study. *Clin. Infect. Dis.* Published online August 21, 2020. https://doi.org/10.1093/cid/ciaa1239
14. Wang, L. *et al.* (2021) An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. *J. Antimicrob. Chemother.* 76, 796–803
15. Garcia-Vidal, C. *et al.* (2021) Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clin. Microbiol. Infect.* 27, 83–88
16. Karami, Z. *et al.* (2021) Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands. *Infect. Dis. (Lond)* 53, 102–110
17. Hughes, S. *et al.* (2020) Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. *Clin. Microbiol. Infect.* 26, 1395–1399
18. Lehmann, C.J. *et al.* (2020) Community acquired co-infection in COVID-19: A retrospective observational experience. *Clin. Infect. Dis.* Published online July 1, 2020. https://doi.org/10.1093/cid/ciaa902
19. Adler, H. *et al.* (2020) Low rate of bacterial co-infection in patients with COVID-19. *Lancet Microbe* 1, e62
20. Cheng, L.S.-K. *et al.* (2020) Bacterial co-infections and antibiotic prescribing practice in adults with COVID-19: experience from a single hospital cluster. *Ther. Adv. Infect. Dis.* 7, 2049936120978095
21. Fu, Y. *et al.* (2020) Secondary bacterial infections in critically ill patients with coronavirus disease 2019. *Open Forum Infect. Dis.* 5, ofaa220
22. Elabbadi, A. *et al.* (2021) Bacterial coinfection in critically ill COVID-19 patients with severe pneumonia. *Infection* https://doi.org/10.1007/s15010-020-01553-x
23. Chertow, D.S. and Memoli, M.J. (2013) Bacterial coinfection in influenza: a grand rounds review. *JAMA* 309, 275–282
24. Kolenda, C. *et al.* (2020) Assessment of respiratory bacterial coinfections among severe acute respiratory syndrome coronavirus 2-positive patients hospitalized in intensive care units using conventional culture and BioFire, FilmArray Pneumonia Panel Plus Assay. *Open Forum Infect. Dis.* 7, ofaa484
25. Soriano, M.C. *et al.* (2021) Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19. *J. Infect.* 82, e20–e21
26. Stevenson, D.R. *et al.* (2020) Improving antimicrobial stewardship in critically-ill patients with COVID-19. *Clin. Infect. Dis.* Published online October 11, 2020. https://doi.org/10.1093/cid/ciaa1559
27. Contou, D. *et al.* (2020) Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. *Ann. Intensive Care* 10, 119
28. Dudoignon, E. *et al.* (2021) Bacterial pneumonia in COVID-19 critically ill patients: a case series. *Clin. Infect. Dis.* 72, 905–906
29. Caméléna, F. *et al.* (2021) Performance of multiplex polymerase chain reaction panel for identifying bacterial pathogens causing pneumonia in critically ill patients with COVID-19. *Diagn. Microbiol. Infect. Dis.* 99, 115183
30. Rothe, K. *et al.* (2020) Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship. *Eur. J. Clin. Microbiol. Infect. Dis.* 40, 859–869
31. Sepulveda, J. *et al.* (2020) Bacteremia and blood culture utilization during COVID-19 surge in New York City. *J. Clin. Microbiol.* 58, e00875-20
32. Yu, D. *et al.* (2020) Low prevalence of bloodstream infection and high blood culture contamination rates in patients with COVID-19. *PLoS One* 15, e0242533
33. Argenziano, M.G. *et al.* (2020) Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ* 369, m1996

34. Metlay, J.P. *et al.* (2020) Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am. J. Respir. Crit. Care Med.* 200, e45–e67

35. Kim, D. *et al.* (2020) Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA* 323, 2085–2086

36. Harza, A. *et al.* (2020) Coinfections with SARS-CoV-2 and other respiratory pathogens. *Infect. Control Hosp. Epidemiol.* 41, 1228–1229

37. Oster, Y. *et al.* (2020) Decreased prevalence rate of respiratory pathogens in hospitalized patients during the COVID-19 pandemic: possible role for public health containment measures? *Clin. Microbiol. Infect.* Published online December 31, 2020. https://doi.org/10.1016/j.cmi.2020.12.007

38. Parente, D.M. *et al.* (2018) The clinical utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening to rule out MRSA pneumonia: A diagnostic meta-analysis with antimicrobial stewardship implications. *Clin. Infect. Dis.* 67, 1–7

39. Punjabi, C.D. *et al.* (2020) Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in respiratory cultures and diagnostic performance of the MRSA nasal polymerase chain reaction (PCR) in patients hospitalized with coronavirus disease 2019 (COVID-19) pneumonia. *Infect. Control Hosp. Epidemiol.* Published online August 26, 2020. https://doi.org/10.1017/ice.2020.440

40. Restrepo, M.I. *et al.* (2018) Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalized patients. *Eur. Respir. J.* 9, 1701190

41. Nir-Paz, R. *et al.* (2006) Evaluation of eight commercial tests for *Mycoplasma pneumoniae* antibodies in the absence of acute infection. *Clin. Microbiol. Infect.* 12, 685–688

42. Postma, D.F. *et al.* (2015) Antibiotic treatment strategies for community-acquired pneumonia in adults. *N. Engl. J. Med.* 372, 1312–1323

43. Garin, N. *et al.* (2014) β-lactam monotherapy vs. β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern. Med.* 174, 1894–1901

44. Kanoh, S. and Rubin, B.K. (2010) Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin. Microbiol. Rev.* 23, 590–615

45. Furtado, R.H.M. *et al.* (2020) Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* 396, 959–967

46. Cavalcanti, A.B. *et al.* (2020) Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N. Engl. J. Med.* 383, 2041–2052

47. Kumar, G. *et al.* (2020) Predictors and outcomes of HAIs in COVID-19 patients. *Int. J. Infect. Dis.* 104, 287–292

48. Ripa, M. *et al.* (2021) Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. *Clin. Microbiol. Infect.* 27, 451–457

49. Falcone, M. *et al.* (2021) Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. *J. Antimicrob. Chemother.* 76, 1078–1084

50. Cheng, K. *et al.* (2020) Analysis of the risk factors for nosocomial bacterial infection in patients with COVID-19 in a tertiary care hospital. *Risk Manag. Healthc. Policy* 13, 2593–2599

51. Bardi, T. *et al.* (2021) Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. *Eur. J. Clin. Microbiol. Infect. Dis.* 40, 495–502

52. Maes, M. *et al.* (2021) Ventilator-associated pneumonia in critically ill patients with COVID-19. *Crit. Care* 25, 25

53. Razazi, K. *et al.* (2020) Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to coronavirus 19 disease. *Crit. Care* 24, 699

54. Bhatt, P.J. *et al.* (2020) Risk factors and outcomes of hospitalized patients with severe COVID-19 and secondary bloodstream infections: A multicenter, case-control study. *Clin. Infect. Dis.* Published online November 20, 2020. https://doi.org/10.1093/cid/ciaa1748

55. Zhou, F. *et al.* (2018) Risk factors for nosocomial infection among hospitalized patients with severe influenza A(H1N1) pdm09 patients. *Respir. Med.* 134, 86–91

56. Gomez-Simmonds, A. *et al.* (2021) Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital. *J. Antimicrob. Chemother.* 76, 380–384

57. Nori, P. *et al.* (2020) Emerging co-pathogens: New Delhi Metallo-beta-lactamase producing Enterobacterales infections in New York City COVID-19 patients. *Int. J. Antimicrob. Agents* 56, 106179

58. Perez, S. *et al.* (2020) 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. *Morb. Mortal. Wkly Rep.* 69, 1827–1831

59. Arcari, G. *et al.* (2021) *Klebsiella pneumoniae* infections in COVID-19 patients: a 2-month retrospective analysis in an Italian hospital. *Int. J. Antimicrob. Agents* 57, 106245

60. Tiri, B. *et al.* (2020) 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.* 25, 2744

61. Belvisi, V. *et al.* (2020) Impact of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) pandemic on carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) prevention and control program: convergent or divergent action? *J. Hosp. Infect.* 109, 29–31

62. Farfour, E. *et al.* (2020) Carbapenemase-producing Enterobacterales outbreak: Another dark side of COVID-19. *Am. J. Infect. Control* 48, 1533–1536

63. RECOVERY Collaborative Group *et al.* (2021) Dexamethasone in hospitalized patients with Covid-19. *N. Engl. J. Med.* 384, 693–704

64. Lauring, A.S. *et al.* Genetic variants of SARS-COV-2-What do they mean? *JAMA* 325, 529–531.