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Impact of Bacterial Infections and Antibiotic Use on Hospitalized COVID-19 Patients: An Emerging Infections Network Survey

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Abstract: The SARS-CoV-2 pandemic has had a significant impact on the United States healthcare system. This is exacerbated by antimicrobial-resistant bacterial pathogens endemic to healthcare settings. Respiratory viral infections are known to predispose patients to bacterial infections, which were a major contributor to mortality in previous pandemics. This study's goal was to gain an understanding of bacterial infections in hospitalized COVID-19 patients. A case form for COVID-19 patients with bacterial infections was developed and sent to clinicians on the Emerging Infections Network listserv. The case form included 22 questions on patient demographics, COVID-19 and bacterial infection and treatment, and patient outcome. One hundred and nine patient cases were collected and analyzed. The majority of patients (59.6%) were critically ill, and 66.9% of patients were diagnosed with sepsis. Empiric and directed antibiotics were administered to 81.6% and 94.5% of patients, respectively. Thirty-one infections were not resolved with antibiotics, and of those patients, 74.2% died. Unresolved bacterial infections were found to be a significant contributor to mortality in this case series. These bacterial infections can most likely be attributed to long hospital stays and exposure to nosocomial pathogens. Thus, unresolved nosocomial bacterial infections warrant additional attention during future events where there is a strain on the US healthcare system.

Keywords: COVID-19; antimicrobial resistance; secondary infection; co-infection; sepsis; pandemic; empiric antibiotic therapy

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1. Introduction

The SARS-CoV-2 pandemic has significantly affected the healthcare system in the United States, inflicting a heavy emotional and physical toll on both healthcare workers and society-at-large, as well as straining resources, which often rely on just-in-time supply chains. Adding to these challenges is the persistence of antimicrobial-resistant (AMR) bacterial pathogens endemic to community and healthcare settings. The association of bacterial secondary infections and the prognosis of COVID-19 patients has not yet been well studied. However, respiratory viral infections are known to predispose patients to opportunistic bacterial co-infections (community-acquired) and secondary infections (healthcare associated), and these bacterial infections are a common complication during viral pandemics and a major contributor to morbidity and mortality in these patients [1,2].

During the 2009 H1N1 pandemic, co/secondary bacterial pneumonia was associated with up to 50% of mortalities [3–6], due, in part, to the ability of influenza virus and bacterial pathogens to enhance each other's infectivity of host cells and tissues [7–10].

Early and aggressive treatment with effective antibiotics could prevent these co/secondary infections and save most patients [3]. Thus, the Infectious Diseases Society of America (IDSA) recommends empiric antibiotic therapy in patients with confirmed or suspected influenza who present with severe disease, deteriorate upon initial improvement, or fail to improve after three to five days of antiviral therapy [11]. Consistent with this guidance, antibiotics were an integral component of patient therapy during the initial COVID-19 response. Early retrospective studies in Wuhan, China, established that 91% to 95% of all COVID-19 positive patients with severe COVID-19 received antibiotics [12–14]. A survey of clinicians in 23 countries in April 2020 found that 70% had prescribed antibiotics to their COVID-19 patients [15]. This is consistent among US hospitals in which 56% to 72% of COVID-19 patients were prescribed antibiotics on admission [16–18].

Conversely, in some of these same studies, the rate of confirmed bacterial infection is very low. Two studies out of China noted secondary bacterial infections in 13.5% and 15% of patients despite antibiotics being used in 95% of all patients [13,14]. Studies of US hospitals have found the incidence of bacterial co-infection in COVID-19 patients to range from 3.5–7% while the percentage of patients receiving empiric therapy was 56% or more [17,18]. A meta-analysis of the literature worldwide has found that the overall percentage of COVID-19 patients with a bacterial infection is 8% (https://www.tarrn.org/covid (accessed on 16 November 2020) [19]).

Taken together, these data suggest a high rate of antibiotic use in COVID-19 patients with a very low incidence of bacterial infections. Our goal with this study was to investigate bacterial infections in hospitalized patients with laboratory-confirmed COVID-19 and how antibiotic treatment of these infections could impact patient outcomes. To do so, we engaged healthcare providers via IDSA's Emerging Infections Network (EIN) to create a case series that evaluated the bacteria causing infections, how and what antibiotics were used for treatment, and the outcome of the patients.

2. Materials and Methods

Data on COVID-19 patients with bacterial infections were gathered by the EIN, a provider-based emerging infections sentinel network supported by a cooperative agreement between the Centers for Disease Control and Prevention (CDC) and the IDSA, and operated out of the University of Iowa [20]. EIN listserv members consist of ≈250 public health members who work in federal, state or local public health plus ≈2600 clinicians who are IDSA members primarily based in the US.

A case form (https://ein.idsociety.org/surveys/survey/128/) to collect data on COVID-19 patients with bacterial infections was developed using results from two preliminary projects: an initial 3 question query in May 2020 to listserv members asking about suspected bacterial infections in hospitalized COVID-19 patients, and a more in-depth follow-up query in June 2020 to 81 individuals who agreed to participate via the initial query. The final 22-question case form covered four areas: patient demographics, COVID-19 infection and treatment, bacterial infection and treatment, and patient outcome. A link to the survey was sent via the EIN listserv on 19 August 2020 with two follow-up reminders in August and September.

In response to the survey, 109 COVID-19 patient cases occurring between March and September 2020, with an identified bacterial infection, were submitted from 34 physicians located in 22 states within the US and Nigeria. Cases were included from all geographic regions in the US, as defined by the US Census Bureau, including regions severely impacted by the SARS-CoV-2 outbreak (Figure 1). One physician provided one patient case (0.9%) from Nigeria.

The University of Iowa Institutional Review Board (IRB) determined that the project was IRB exempt. Statistical analyses were completed using SAS v9.4 software (SAS, Cary, NC, USA) and logistic regression to model the data. This survey did not violate the Paperwork Reduction Act due to the declared public health emergency (https://aspe.hhs.gov/public-health-emergency-declaration-pra-waivers (accessed on 16 November 2020)).

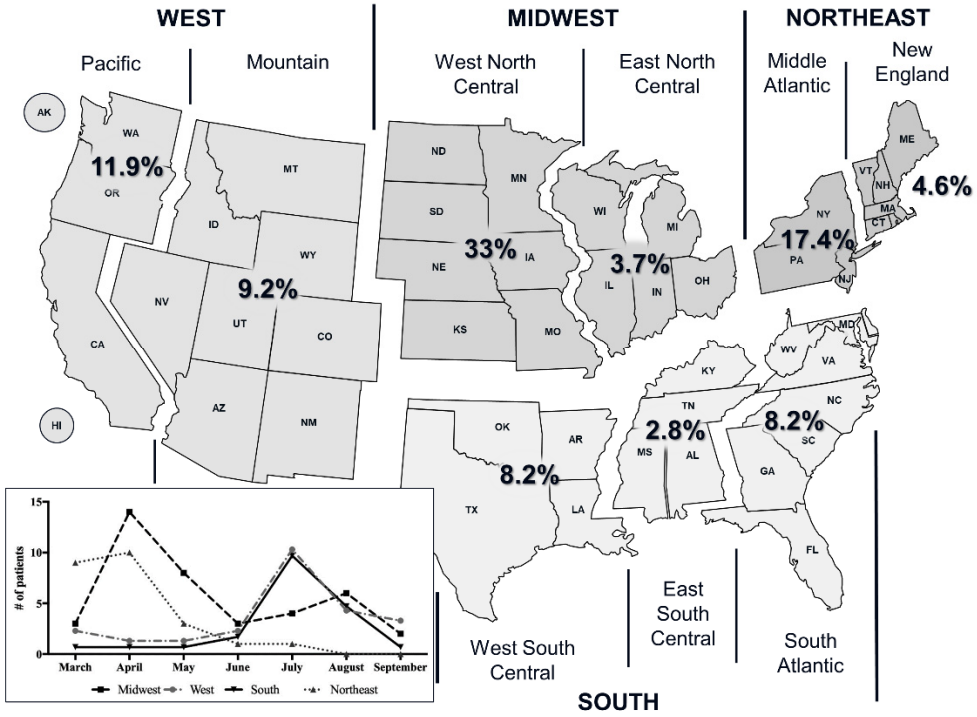

Figure 1. Geographic regions in the US where patients were located. Cases were included from 22 states from all US geographic regions, as defined by the US Census Bureau. The percentage of patients from each region is overlaid on the region of the map. Inset: Graph of the number of patients in each geographic region by month in 2020 of positive COVID-19 diagnostic test.

3. Results

3.1. Patient Characteristics

The median age range for patients was 45 to 64 years (38.5% of patients). The four most common pre-existing conditions were type 2 diabetes (44.0%), hypertension (42.2%), obesity (33.9%), and coronary artery disease (22.9%) (Table 1), with 81 (74.3%) patients with at least one comorbidity. All patients were confirmed SARS-CoV-2 positive by either a polymerase chain reaction (PCR) or antigen test. Based on the COVID-19 severity categorization parameters [21,22], 9.1% of patients had mild cases, 30.2% had severe cases, and 59.6% were listed as critical.

There were 99 (90.8%) patients in the ICU; patients were admitted to the ICU on day 1 (median) of their hospital stay. Non-invasive ventilation, such as high flow oxygen was required for 12 patients, 84 patients required invasive mechanical ventilation, and six patients received extracorporeal membrane oxygenation (ECMO) treatment. Almost all patients (91.7%) experienced complications due to the progression of COVID-19 (Table 1). The most prevalent complications were respiratory failure (87.1%), kidney failure (42.2%), and sepsis (66.9%). The median hospital day for sepsis diagnosis was day 4. Of the septic patients where the hospital day of diagnosis was included (55/73 patients), 85.4% were diagnosed with sepsis before they were diagnosed with a bacterial infection. The day of sepsis diagnosis relative to bacterial infection was not included for 18 patients.

Patients received a variety of COVID-19 treatments (Figure 2). Hydroxychloroquine use was highest in March when it was administered to 73.3% of patients, but subsequently dropped and was no longer used by July. Similarly, patients received IL-6 receptor inhibitor treatments extensively in the early months of the pandemic; however, their use also diminished by July through September. Convalescent plasma was used steadily, with an average of 48.3% of patients receiving the treatment each month during the collection period. The use of remdesivir and dexamethasone increased from 13.3% and 33.3%, respectively, to over 80% during the 7 months of the data collection period.

Table 1. Clinical Characteristics of Patients (total N = 109).

Characteristic	N (%)
Age	
0–12	4 (3.7)
13–17	3 (2.8)
18–44	17 (15.6)
45–64	42 (38.5)
65–74	22 (20.2)
75–84	16 (14.7)
>85	3 (2.8)
Pre-existing Conditions	
Asthma	10 (9.2)
Bone marrow/stem cell transplant	2 (1.8)
Cerebrovascular disease	5 (4.6)
Chronic kidney disease	13 (11.9)
Chronic obstructive pulmonary disease (COPD)	12 (11)
Coronary artery disease	25 (22.9)
Heart failure	10 (9.2)
HIV	1 (0.9)
Hypertension	46 (42.2)
Obesity (BMI > 30)	37 (33.9)
Smoking	3 (2.8)
Solid organ transplant	2 (1.8)
Type 1 diabetes	1 (0.9)
Type 2 diabetes	48 (44)
Use of corticosteroids/other immunosuppressants	5 (4.6)
Complications resulting from COVID-19 infection	
Heart failure	11 (10)
Liver failure	4 (3.7)
Kidney failure	46 (42.2)
Thrombotic events	17 (15.6)
Respiratory failure	95 (87.1)
Shock/Sepsis	73 (66.9)

When looking at the entire data set of 109 patients, the outcomes were 34 deaths (31.2%), 60 discharged as recovering (55.0%), 3 moved to hospice (2.8%), 11 ongoing (10.0%), and 1 patient was included without final outcome data (0.9%). For the 34 patients that died, the major contributing factor(s) to the patient's cause of death were: complications due to COVID-19 (6), complications due to bacterial infection (2), or a combination of complications due to COVID-19 and bacterial infection (23). For the remaining three patients, two deaths were attributed to other factors (i.e., multi-organ failure and cardiac arrest) and one death had no major contributing factors noted. The data were analyzed for single predictors of death. It was found that both coronary artery disease ($p < 0.0026$) and hypertension ($p < 0.0469$) were significant predictors of death. Type 2 diabetes approached significance ($p < 0.0642$), and obesity was not a significant contributor ($p < 0.1158$). The total number of pre-existing conditions, the age range of patients, and the severity of COVID-19 disease were not significant.

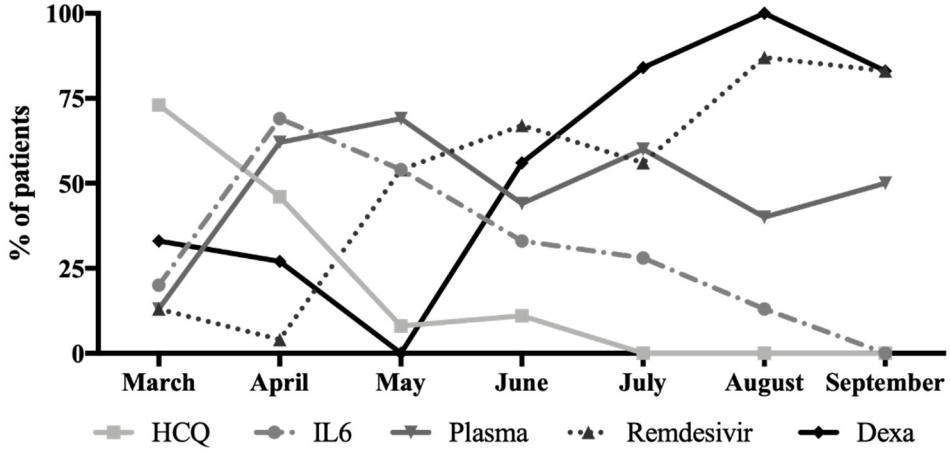

Figure 2. COVID-19 treatments administered to patients each month of the study in 2020. The preferred treatments changed over time based on the CDC/FDA recommendations. At the beginning of the pandemic, use of Hydroxychloroquine and IL-6 receptor inhibitors were high but decreased as clinical trials failed to show their efficacy. Convalescent plasma was used steadily during the pandemic. The use of remdesivir and dexamethasone increased during the 7 months of the data collection. The percentage of patients receiving each treatment each month was calculated based on the total number of patients receiving treatment each month. HCQ—hydroxychloroquine; IL6—IL-6 receptor inhibitor; Plasma—convalescent plasma; Dexa—dexamethasone.

3.2. Microbiology and Antibiotic Therapy

The time of diagnosis of a bacterial infection occurred at a median of day 8 post-admission. The infecting bacteria were identified in 95 cases (87.1%). For the 14 cases where the bacterial species were not identified, the presence of infection was detected by radiological or laboratory findings. Community-acquired bacterial pneumonia (CABP) was diagnosed in 22 patients, 14 patients were diagnosed with hospital-acquired bacterial pneumonia (HABP), and 63 patients with ventilator-associated bacterial pneumonia (VABP). The remaining 10 patients were diagnosed with other infections: bacteremia (7), empyema (1), pharyngitis (1), and scalded skin syndrome (1). The study survey also asked if patients had another infecting organism or syndrome identified; 36 patients were diagnosed with multiple bacterial infections either at the same site of infection or at multiple body sites. Whether these additional infections occurred concurrently with, or subsequent to the first instance of bacterial infection, could not be determined.

There were 133 bacterial isolates identified from the 109 patients; 13 patients had multiple infecting bacterial species identified. Of the 133 isolates, 72 were Gram-negative and 61 were Gram-positive (Table 2). The most common Gram-negative species were *Pseudomonas* (29.1%) and *Klebsiella* (26.3%). The most common Gram-positive species was *Staphylococcus aureus* (57.3%), almost half of which were methicillin-resistant *S. aureus* (MRSA), followed by *Corynebacterium* (16.3%), and *Streptococcus* (14.7%). Antibiotic susceptibility testing (AST) data were collected for piperacillin/tazobactam, vancomycin, levofloxacin, azithromycin, gentamicin, meropenem, cefepime and ceftriaxone. All isolated bacteria were susceptible to at least one of these antibiotics.

Empiric antibiotic therapy was administered to 89 out of 109 patients (81.6%) before the infecting bacteria were identified. The median number of days of empiric antibiotic treatment was five days. The most common antibiotics administered empirically were vancomycin (46.1%), ceftriaxone (31.4%), cefepime (24.7%), piperacillin/tazobactam (25.8%). Out of the 89 patients that received empiric antibiotics, 28 received monotherapy and 61 received a combination of antibiotics. The most common combination was vancomycin with a broad spectrum β-lactam. For the 6 patients out of 109 that only received empiric antibiotic treatment (did not receive directed antibiotic therapy), 3 patients' infections

resolved with empiric treatment alone, 2 patients expired before direct therapy could be administered, and 1 patient's treatment was ongoing at the time the survey period closed.

Table 2. Bacterial Species Identified.

Species *	Number of Isolates
Staphylococcus aureus †	35
MSSA (15)	
MRSA (16)	
Pseudomonas (aeruginosa)	21
Klebsiella (aerogenes, pneumoniae)	19
Corynebacterium (striatum)	10
Streptococcus (viridans, pneumoniae, pyogenes)	9
Enterobacter (cloacae)	5
Escherichia coli	5
Serratia (marcescens)	4
Acinetobacter (baumannii)	3
Enterococcus (faecalis)	3
Haemophilis	3
Proteus mirabilis	3
Citrobacter koseri	2
Clostridioides difficile	2
Coagulase-negative *Staphylococcus*	2
Moraxella catarrhalis	2
Stenotrophomonas maltophilia	2
Fusobacterium	1
Morganella morganii	1
Pantoea agglomerans	1

* Some responders provided the full species name, others only included the genus; species that were identified are in parentheses after the genus. † Some of the *Staphylococcus aureus* isolates were identified as MSSA (methicillin-susceptible) or MRSA (methicillin-resistant); not all isolates were identified as one or the other, thus the total number of isolates (35) is greater than the sum of MSSA and MRSA.

Directed antibiotic therapy specific to the bacterial infection following identification was ultimately administered to 103 (94.5%) patients. Of those patients, 15 were continued on their empiric therapy antibiotic due to the sensitivity of the infecting pathogen(s) to this treatment. Another 68 patients were switched to directed therapy composed of a different or modified antibiotic regimen than what the patient received during empiric therapy. The remaining 20 out of the 103 patients (19.4%) had culture and susceptibility results that enabled directed antibiotic therapy from antibiotic initiation, precluding the use of empiric antibiotics. Out of the 103 patients who were placed on directed antibiotic therapy, 71 received monotherapy and 32 received more than one antibiotic. The median number of days of directed antibiotic therapy was eight days.

The most common antibiotic used for directed treatment depended on the infecting bacterial species. β-lactams with or without a β-lactamase inhibitor were used most often to treat patients infected with *Pseudomonas* (89.4%), *Klebsiella* (95.2%), and *Streptococcus* (77.7%). Patients infected with *S. aureus* received vancomycin (38.2%), linezolid (20.6%), or a combination of a β-lactam with or without a β-lactamase inhibitor (41.1%). Vancomycin was used to treat 100% of the *Corynebacterium*-infected patients.

Out of 109 cases, 73 infections were resolved with antibiotic treatment. Of those 73 patients, 10 subsequently died (13.7%). Seven out of ten were noted to have another infecting organism, which for five of these patients was listed as a major contributing factor to death; multi-organ failure and cardiac arrest were listed as the cause of death for the other two patients. Two out of the ten deaths were directly attributed to COVID-19, and the cause of the final death was not provided. The outcomes for the remainder of the 73 patients with resolved bacterial infections were: 53 discharged as recovering (72.6%), 2 discharged to hospice (2.7%), and 8 ongoing hospitalizations (11.0%). Thirty-one infections were not resolved with antibiotic treatment; none of the responding physicians noted that treatment

failure was due to a lack of antibacterial activity. Of those 31 patients, 23 died (74.2%), 5 were discharged as recovering (16.1%), 1 was discharged to hospice (3.2%), and 2 were still hospitalized (6.5%) (Figure 3). Of the 23 patients that died with an unresolved bacterial infection, at least 21 patients were still receiving antibiotic treatment at the time of their death. For 19 of these patients, death was attributed to both COVID-19 and bacterial infection. For the other four patients, death was attributed to COVID-19 only for three, and to COVID-19 and bilateral pneumothorax and pneumomediastinum for one patient. The lack of resolution of bacterial infections was found to be a significant contributor to death ($p < 0.0001$).

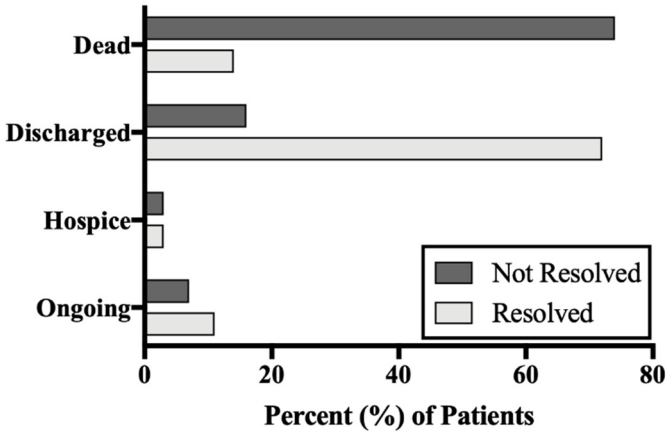

Figure 3. Patient outcome based on resolution of bacterial infection after antibiotic treatment. For patients with resolved bacterial infections, 14% died and 72% were discharged as recovering. Conversely, for patients with unresolved bacterial infections, 74% died and only 16% were discharged as recovering. At least 91% of the patients that died with an unresolved bacterial infection were still receiving antibiotic treatment at the time of their death.

4. Discussion

Healthcare providers were surveyed to understand their experience with bacterial infections and antibiotic use in hospitalized COVID-19 patients. Responses were received from 34 physicians from the EIN: one case from Nigeria and the remaining from locations across all geographic regions of the United States (Figure 1). The number of cases received correlated with the rate of COVID-19 cases in those regions during the collection period [23], and the patient characteristics observed in this study were representative of the national COVID-19 patient population based on CDC data (covid.cdc.gov (accessed on 16 November 2020)). COVID-19 therapeutic treatment for the patients in our study also closely mirrored prescribing trends across the national population: the use of hydroxychloroquine and IL-6 receptor inhibitor treatments were used extensively early in the pandemic until clinical study results reported a lack of efficacy [24–26]. Conversely, the use of remdesivir and dexamethasone increased during the data collection period after clinical trials showing these treatments shortened the time to recovery [21] and reduced mortality [27], respectively. Thus, the cases in our survey are representative of the wider US COVID-19 patient population.

Treatment of bacterial infections in COVID-19 patients has involved multiple generic antibiotics [15]. In our case series, 81.6% of patients received empiric antibiotic therapy before the infecting bacterial pathogen was identified. Prescribing antibiotics empirically is supported by historical data from influenza pandemics and is recommended by the IDSA for suspected influenza cases [1–3,11]. Subsequently, 94.5% of the patients received directed antibiotic therapy following bacterial identification and AST. The antibiotics prescribed were consistent with IDSA recommendations for the treatment of CABP [28] and HABP/VABP [29].

There is limited data reported on the species of infecting bacteria isolated from COVID-19 patients; however various reports have identified antimicrobial resistant ESKAPE (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp.) pathogens [13,30–32]. The most common bacterial species identified in our case series were *Klebsiella*, *Pseudomonas*, and *S. aureus*. All of these pathogens are categorized as either urgent or serious threats by the CDC [33] and contribute to HABP or VABP [34,35]. The median day after admission for bacterial infection diagnosis was day 8, and thus over a week after SARS-CoV-2 infection was diagnosed and COVID-19 symptoms had significantly progressed (i.e., viral sepsis). These data suggest that most of these patients developed secondary nosocomial infections due to long stays in the hospital and/or invasive ventilation.

The threat of nosocomial bacterial infections in COVID-19 patients is further exacerbated during times of high patient volume or surges where lack of adequate PPE can result in IPC failures, and high demands on hospital personnel can result in lapses in proper antibiotic stewardship practices. Increases in AMR bacterial infections in COVID-19 patients have been found in healthcare centers with high rates of COVID-19 patients [36,37]. Surveillance conducted by the CDC supports these data, finding the incidence of AMR pathogens in COVID-19 patients significantly increased compared to influenza-like illness patients [38]. However, when IPC interventions were reinstated and normal hospital operations continued, the incidence of AMR outbreaks returned to baseline endemic levels.

The potential link between the diagnosed bacterial infections and COVID-19 mortality is an important consideration that has the potential to complicate an effective medical response. One often-cited study from Wuhan, China found that 50% of all non-surviving COVID-19 patients and only 1% of surviving patients had bacterial infections ($p < 0.0001$) [14]. While our study did not include COVID-19 patients without bacterial infections as a comparator, we did find that unresolved bacterial infections were a contributing factor in the deaths of patients with co/secondary bacterial infections.

Most of the patients in this study were considered critically ill (59.6%), had pre-existing conditions that were significant contributors to death (53.2%), and were diagnosed with sepsis (66.9%). Unlike bacterial co-infections reported in past influenza pandemics [1,2], the bacterial infections reported here do not appear to be SARS-CoV-2-specific, but instead are nosocomial in nature. These data highlight the fact that these patients were in very poor health, and help explain why ongoing bacterial infections, which may not be fatal on their own, contributed to death in 74.2% of patients with an unresolved infection.

The long-term impact of the COVID-19 pandemic on the US healthcare system is unknown. In the near term, however, the data from our study show that unresolved bacterial co/secondary infections in COVID-19 patients may contribute to mortality under circumstances where there is a strain on the US healthcare system. These bacterial infections are likely due to a breakdown in IPC during hospital surges and are not due to SARS-CoV-2 infection and COVID-19 disease. We hypothesize that the status of the patient did play a role, with pre-existing conditions, the severity of illness, and sepsis being contributing factors. These factors deserve additional study in preparation for future pandemics.

Our study had several limitations. The number of responding physicians (34) and patient cases (109) was relatively small. Additionally, the physicians surveyed were limited to members of the EIN, which is a self-selected sample of physicians and is not a random sample of US or worldwide health providers. This survey did not include comparator groups (e.g., COVID-19 patients without co/secondary bacterial infections or non-COVID-19 patients with bacterial infections). Lastly, this case series is based on survey data and thus only includes data requested by survey questions and may not include all pertinent patient data.

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