Open Forum Infectious Diseases

MAJOR ARTICLE

Antimicrobial Management of Respiratory Infections in Severe Acute Respiratory Syndrome Coronavirus 2 Patients: Clinical and Antimicrobial Stewardship Programs Conundrums

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The role of empirical and even directed antimicrobial management of patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is problematic; antibiotics are used frequently among these patients to treat confirmed or suspected coinfection or just the symptoms. In the rapidly changing clinical landscape of SARS-CoV-2, there is minimal guidance for selecting appropriate treatment versus non-antimicrobial treatment, and clinicians are pressed to make daily decisions under the stress of absence of data while watching patients deteriorate. We review current data and patterns of antimicrobial use and the potential approach for antimicrobial stewardship in the context of SARS-CoV-2.

Keywords. antimicrobial stewardship; COVID-19; fluoroquinolones; pneumonia.

The role of empirical and even directed antimicrobial management of patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) infection is problematic. The number of published research papers on "coronavirus pneumonia" has exceeded 10 000 references on PubMed (as of August 3, 2020) and on "COVID 19 SARS 2" exceeds 79 200 on Google Scholar (as of August 3, 2020). A variety of experimental regimens are being investigated including some agents that may have the dual purpose of providing anti-inflammatory and antimicrobial activities. There is scant guidance for selecting appropriate treatment, and clinicians are forced to make daily decisions under the stress of absence of data and watching patients deteriorate.

Based on diagnostic criteria used in community-acquired bacterial pneumonia (CABP) guidelines [1], it is difficult to distinguish bacterial infection from SARS-CoV-2 infection. A recent publication [2] supported the supposition that bacterial pathogens isolated from the respiratory tract in patients with coronavirus disease 2019 (COVID-19) pneumonia were the same as in CABP. An early surge in the empirical use of the macrolide azithromycin serves as a singular example of an agent with both antibacterial and anti-inflammatory effects that failed to provide a clear role in therapy [3, 4]. Of concern was the frequent use of antibiotics despite the lack of isolating a bacterial or fungal pathogen. A review of 806 patients hospitalized with COVID-19 showed 8% had a bacterial or fungal coinfection, although 72% received antimicrobial therapy, compared with 11% of non-COVID-19 cases [5]. The concern for antibiotic stewardship efforts is clear: increases in unnecessary antimicrobial use poses direct risks to the patient including the potential collateral damage such as side effects and adverse drug reactions, in addition to potentiating the risk of antimicrobial resistance through selective pressure [6].

The Basis for Use of Antibiotics in Severe Acute Respiratory Coronavirus 2 Infections

Most antibiotic use in patients with confirmed SAR-CoV-2 pneumonia has been empirical, whereas the lung damage may be a result of severe immune dysfunction linked to tissue invasion by the virus. This can create a cycle in which hypercytokinemia predisposes to lung damage that then predisposes to superinfection [7].

Insight into the extent of antibiotic use and the poor correlation with culture data can be deduced from several reports. In a case series of 41 hospitalized COVID-19 patients [8], all patients received empirical antibiotics, whereas only 4 (10%) were confirmed as having a bacterial infection. Patients with more severe infections were more often prescribed antibiotics. A larger single-center study of 52 critically ill patients [9] reported that 13.5% had documented bacterial infections, yet 94% (49 of 52) received antibiotic therapy. Infections were

Received 1 June 2020; editorial decision 19 October 2020; accepted 23 October 2020.

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Open Forum Infectious Diseases®2020

DOI: 10.1093/ofid/ofaa517

found in 1 (2%) patient who had a carbapenem-resistant *Klebsiella pneumoniae* pulmonary and blood stream infection (BSI). Hospital-acquired pneumonia occurred in 11.5% of patients and were due to either *Aspergillus flavus, Aspergillus fumigatus*, extended-spectrum β-lactamase (ESBL)-positive *K pneumoniae*, ESBL-positive *Pseudomonas aeruginosa*, or ESBL-negative *Serratia marcescens* (1 patient each). *Candida albicans* was identified in the urine culture of 1 patient.

In a parallel study, Chen et al [10] included 99 patients, 71% of whom received antibiotic therapy (25% with a single agent; 45% as combination) and 15% received antifungal therapy. However, only 1 patient had a culture-confirmed bacterial coinfection and 4 patients had fungal coinfections. The duration of antibiotic treatment was 3–17 days (median 5 days; interquartile range [IQR], 3–7]) regardless of empiric or culture-confirmed diagnosis.

Over time, additional studies have appeared regarding antibiotic use in laboratory-confirmed COVID-19 patients. A retrospective study by Guan et al [11] of 1099 patients in 552 hospitals in 30 Chinese provinces revealed that 58% of all patients received parenteral antibiotics, including 80% of severely ill patients. Most of the patients carried a diagnosis of pneumonia accounting for the use of antibiotics. The investigators provided no specific data on diagnosis of secondary bacterial or fungal infections other than to note that culturing of sputum had overwhelmed the medical resources available for such assessments. An earlier study by Chen et al [12] of 21 moderate-to-severe patients with confirmed COVID-19 infection showed secondary infections in 27.3% of severely ill patients, all of whom received either moxifloxacin and/or cephalosporins.

Zhou et al [13] studied the clinical course and mortality of 191 adult hospitalized patients at 2 medical centers in Wuhan, China. In this study, 95% of patients received antibiotics, including 98% of nonsurvivors and 93% of survivors. Secondary infections were diagnosed in 15% of all patients—50% of nonsurvivors and 1% of survivors. Ventilator-associated pneumonia (VAP) occurred in 31% of patients who required invasive mechanical ventilation (IMV). The median time from illness onset to secondary infection was similar between nonsurvivors and survivors (17% and 14%, respectively). Time from IMV to occurrence of VAP was 8.0 days (IQR, 2.0–9.0). Specific coinfecting pathogens were not discussed.

A retrospective analysis [14] of 113 deceased patients from a cohort of 799 moderate-to-severely ill COVID-19 patients reported that 105 (93%) deceased patients and 144 (89%) survivors received empirical antibacterial therapy (moxifloxacin, cefoperazone, or azithromycin). The authors noted that 36% of the deceased patients and 2% of those who recovered had procalcitonin levels above 0.5 ng/mL, suggesting that a large proportion of deceased patients might have had secondary bacterial infection. However, no microbiologic analysis was provided.

A recent review of 16 publications by Clancy and Nguyen [15] reported that of 3302 hospitalized patients' IMV ranged from 1% in Zhejiang province to >40% in 2 Wuhan hospital sites, whereas in 3 US reports, IMV ranged from 20% to 75%. Antibiotic use was very common (~90%), whereas antifungals were prescribed in approximately 15%. Up to 17% developed superinfections, but this varied considerably with some sites not reporting any superinfections. Gram-negative bacilli were frequently reported, including *Acinetobacter* species, *K pneumoniae*, and *P aeruginosa*. The wide discrepancies in reporting superinfections may have been due to different definitions and variable ability to differentiate infection from colonization at the different sites.

In a retrospective, observational study at a Bronx, New York hospital center, Nori et al [16] noted a 71% mismatch between empirical antimicrobial therapy and a 3.6% coinfection rate. These investigators noted the top 5 respiratory isolates to be *Staphylococcus aureus* (equally dispersed between methicillin-susceptible and methicillin-resistant strains), *P aeruginosa*, *K pneumoniae*, *Enterobacter* spp, and *Escherichia coli.* Multidrug-resistant organisms (MDROs) were observed in 9% and 19% of BSIs and respiratory infections, respectively. The investigators noted that 79% of COVID-19 patients received antibiotics in the previous 30 days, and 98% received antibiotics during hospitalization. Moreover, >70% received 3 or more classes of antibiotics despite a 17% incidence of multidrug-resistant Gram-negative organisms. The median duration of antibiotic therapy was 8.5 days.

Community-Acquired Versus Nosocomial

The physician's decision to select an empirical antibiotic that covers CABP pathogens or to escalate to one that covers nosocomial pathogens is equally problematic. In the previously cited studies, the selection of antibiotics in the current pandemic environment lacked clear criteria.

Most viral respiratory infections originate in the community, eg, influenza, COVID-19, and adenovirus. It seems reasonable to assume that early associated bacterial pneumonias are due to conventional pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical species. In the past, a majority of deaths during the 1918 Spanish influenza pandemic likely resulted directly from secondary bacterial pneumonia caused by common upper respiratory tract bacteria [17]. More recently, both methicillin-susceptible and methicillin-resistant *S aureus* have occasionally been associated with postinfluenza infections. A study by Kim et al [18] reported coinfection with SARS CoV-2 and other pathogens, but their methodology was specific to a respiratory pathogen panel that included only viral and atypical pathogens such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*; bacterial pathogens were not included. It is interesting to note that, among their 116 COVID-19 patients, none showed coinfection by atypical pathogens.

However, patients with baseline comorbidities, such as chronic obstructive pulmonary disease, or those coming from long-term acute care facilities, may be at risk for coinfection with a variety of additional pathogens [19].

Hospitalized patients, especially those receiving ventilatory support, those on prior antibiotics targeting community-acquired pathogens, and those with prolonged lengths of stay, would be at increased risk for developing bacterial superinfections due to nosocomial organisms reflective of the ecology of the microbial environment of the hospital ward or intensive care unit (ICU). This would include multidrug-resistant phenotypes of *K pneumoniae*, *P aeruginosa*, *Acinetobacter* species, and *Stenotrophomonas maltophilia* [16, 20]. Empirical antibiotic selection is generally broad based to either community-acquired or hospital-acquired pathogens and should be de-escalated when identification and susceptibility results are available.

The challenges of deciding when antibiotics should be initiated, which antibiotics should be empirically prescribed to cover which appropriate pathogens during the different phases of COVID-19 disease, and the appropriate duration of therapy remain unanswered. Monotherapy with macrolides for the treatment of CABP-associated pathogens should be dependent on the local epidemiology and susceptibility patterns against *S pneumoniae*. As pneumococcal macrolide resistance exceeds 30% in many regions in the United States [1], azithromycin may offer insufficient coverage; therefore, it may be prudent to consider other classes of agents that have better antipneumococcal activity [21, 22] such as fluoroquinolones and tetracyclines in early onset of COVID-19 infections. In addition to an appropriate spectrum of activity, these 2 classes have anti-inflammatory activities. Treatment of suspected nosocomial infections should include broader antimicrobial regimens active in vitro against *P aeruginosa*, ESBL, or carbapenem-resistant *Enterobacterales*, and methicillin-resistant *S aureus*, at least empirically while awaiting definitive pathogen and susceptibility information.

The Balance Between Empiric Treatment and Antimicrobial Stewardship

There is no definitive timeline in which concerns for nosocomial infections supplants the consideration of a community-acquired secondary infection. A number of questions remain. When is antimicrobial therapy and selection of specific empiric regimens consistent with the tenets of antimicrobial stewardship of targeting likely pathogens? The threat of severe bacterial BSIs and respiratory infections increases as a result of the significant endothelial damage caused by the massive outpouring of cytokines and inflammatory products, and this could alter the microbiology in subsequent infections. It is reasonable to believe that endothelial damage could alter adherence of bacteria and play a role in pathogen selection, although this has yet to be demonstrated. Superinfections are often caused by a broader spectrum of pathogens, some of which are multidrug resistant, and antimicrobial stewardship programs (ASPs) must collect and assess the data as it accumulates, constantly modifying their practices and adjusting their education programs. Use of broad-spectrum agents, even though they provide empirical coverage, can select for collateral damages with opportunistic species such as *Clostridioides difficile* and *Candida* species. In addition, emergence of resistance and safety characteristics need to be weighed by prescribers. Local antimicrobial susceptibility patterns must dictate the formulary and be updated on an ongoing basis. All antibiotics should be reviewed on a daily basis, per ASP protocols, and as soon as appropriate stopped or de-escalated. Discussions between hospitalists, intensivists, infectious diseases consultants, and the ASP team may be strained and complicated by rapidly published preliminary data that conflicts with ongoing local observations or ASP policies.

It may be appropriate for ASPs to consider other antibiotics that provide both antibacterial activity and anti-inflammatory properties. Two such classes include the fluoroquinolones and tetracyclines. Over 30 years ago, the fluoroquinolones were shown to modulate the host-response interaction [23] by inhibiting the synthesis of proinflammatory products by modulating phagocytosis. Studies have shown that ciprofloxacin, moxifloxacin, grepafloxacin, levofloxacin, and trovafloxacin each exert some type of immunomodulation [24–28]. These studies include in vitro and in vivo animal studies and the measurement of a plethora of cytokines [29, 30]. It is worth noting that fluoroquinolones, in particular, have been associated with a range of adverse events [31, 32]. In the setting of COVID-19 infections, cardiac effects are especially concerning, and the fluoroquinolones have demonstrated an effect on cardiac repolarization occasionally leading to torsades de pointes. In a thorough QT study, delafloxacin did not produce QTc prolongation when compared against the positive control moxifloxacin [33]. Tetracyclines have also shown multiple beneficial non-antibiotic effects that lessen the adverse impact of proinflammatory mediators in chronic diseases [34]. The non-antibiotic effects of doxycycline and minocycline have been reviewed extensively [35–37]. However, the significance of the anti-inflammatory effects of these antibiotics and classes, relative to the benefits of specific immunomodulator therapies such as interleukin-6 inhibitors and/or corticosteroids, remains unclear.

DISCUSSION

The diagnosis of secondary pneumonia is difficult in patients suffering from COVID-19-associated acute respiratory distress syndrome. Radiographic studies cannot differentiate pulmonary damage from COVID-19-induced elaboration of proinflammatory cytokines, more common in ICU patients, from damage produced by bacterial toxins. Targeted antibiotic

therapy may serve 2 complementary purposes in addressing COVID-19 infection: (1) fighting bacterial secondary infections and (2) attenuating the inflammatory effect caused by cytokines produced by T lymphocytes and by monocytes. Initially, antibiotics that exhibit these 2 characteristics might be preferred. Antimicrobial stewardship programs should consider a positive balance between efficacy and safety of these antimicrobial therapies.

Two often neglected classes of agents should be reconsidered for inclusion in the therapeutic armamentarium. The broader antimicrobial spectrum of fluoroquinolones against many Gram-negative pathogens, methicillin-resistant *S aureus* (primarily delafloxacin [32]), *S pneumoniae*, and atypicals, and their anti-inflammatory effects are characteristics that may guide the selection as empirical antibiotics. Likewise, tetracyclines such as minocycline, doxycycline, and potentially a new pleuromutilin called lefamulin [38] all combine a broad range of anti-inflammatory properties with in vitro activity against *Enterobacterales* of various phenotypes, including ESBL- and metallo-beta-lactamase-producing isolates and Gram-negative non-pseudomonal non-fermenters such as *A baumannii* and *S maltophilia*, and should also be considered as empirical agents.

We may never identify the actual contribution of bacterial copathogens, and therefore we will not understand how critical antibiotics will be or have been successful in the current pandemic. It is likely that the incidence will vary according to the institutions' MDRO profiles and infection control policies. In the meantime, many resources have been dedicated to development of antiviral therapies, vaccines, and immune modulators. Further complicating the empiric use of broad-spectrum antibiotics is the danger of emergence of antibiotic resistance.

CONCLUSIONS

Despite the current lack of early microbiological data in pneumonia patients suffering from COVID-19 infection, empirical use of antibiotics is common. Without further guidance on when to initiate antibiotic therapy and which regimens to initiate, and in light of the rapidly destructive nature of pulmonary pathogenesis, ASP efforts should focus on the selection of antibiotics with combined in vitro potency and an appropriate spectrum of activity (against early pneumonia or later hospital-acquired pneumonia), anti-inflammatory effects and immune modulation, and overall patient safety. Concomitantly, all empiric antibiotic therapies used to treat coinfections associated with SARS-CoV-2 infections must be assessed for risk of adverse drug reactions, development of *C difficile* infection, disturbance of the protective microbiome, and emergence of resistance. These considerations are important in patients who may be more prone to adverse effects of antibiotics given any multiorgan dysfunction attributable to the primary viral infection.

Acknowledgments

Author contributions. All authors had a role in study design and conceiving and writing the manuscript. According to the guidelines of the International Committee of Medical Journal Editors ([ICMJE] www.icmje.org), all authors met the criteria for authorship and no deserving authors have been omitted.

Potential conflicts of interest. E. J. C. G. is on the apeakers bereau for Allergan and Merck and the advisory board for Acrux Pharmaceuticals LLC, Bio K+, Merck, Shionogi, Inc., Isnsmed, and Kindred Hospital System. M. R. is an employee of Melinta Therapeutics Inc. G. T. has received consulting fees from Shionogi Inc., Melinta Therapeutics, Ferring, Inc., and Summit plc. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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