

A Perspective on the Emergence of Antimicrobial Resistance During COVID-19 Pandemic

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Abstract

As microorganisms accumulate genetic changes in their susceptibility to currently available antimicrobial drugs over time, they eventually cease to respond to them, which makes diseases more difficult to treat and increases the risk of infection spreading to other people. This phenomenon is known as Antimicrobial Resistance (AMR). Around 7 million people die each year due to AMR globally, and if immediate action is not taken to stop the spread of drug-resistant microbes, this figure is predicted to rise to 10 million by the year 2050. Around 70 percent of hospital admissions and 80 to 100 percent of COVID-19-related emergency room stays involve the usage of antibiotics, which adds to the burden of AMR globally. This article offers insight into the underlying causes of AMR during the ongoing COVID-19 pandemic and a critical viewpoint on how the coexistence of COVID-19 disease and AMR occurs and their interaction with one another. In general, four major factors contributed to the rapid emergence of AMR during the COVID-19 pandemic: nosocomial and secondary bacterial, fungal, and fungus infections or co-infections; excessive use of antimicrobial drugs and steroids, and biocides; and compromised healthcare services due to periodic increases in COVID-19 cases. The current article reiterates the urgent need for multifaceted interventions because AMR will continue to be a problem after the COVID-19 pandemic. These interventions should be designed to lessen the synergistic interactions between the primary SARS-CoV-2 infection and co-occurring microorganisms, to enable cross-management of the twin diseases, and to move society towards sustainable development growth.

Introduction

Antimicrobial Resistance (AMR) [1,2] was one of the top concerns for global public health before the COVID-19 pandemic broke out in late 2019. AMR occurs when bacteria, viruses, fungi and parasites acquire genetic changes in their susceptibility to currently available antimicrobial drugs over time and eventually no longer respond to them, making diseases harder to treat and increasing the spread of infections to other people [3]. Antibiotics are given in between 80 and 100 percent of COVID-19-related intensive care unit hospitalizations and around 70 percent of hospital admissions, increasing the burden of AMR globally. The increasing global expansion of “superbugs,” [4] or multi- and pan-resistant bacteria, which cause diseases that cannot be treated with current antimicrobial drugs like antibiotics, is particularly concerning. There are about 7 million deaths/year globally due to AMR and this number is expected to increase to 10 million deaths/year by the year 2050, unless urgent measures are taken to combat the spread of drug-resistant organisms [5]. The COVID-19 pandemic exacerbates this, placing an extra weight on the already overburdened global healthcare infrastructure, and making a prior, hidden AMR pandemic more apparent.

In addition to lengthening hospital stays and necessitating the use of costly antimicrobial medications, a prolonged illness brought on by AMR also increases the risk of mortality and disability and places a financial burden on the patients [6,7]. Therefore, it is essential to create newer global viewpoints in order to build well-orchestrated population surveillance and lay more emphasis on enhancing our preparedness and developing effective remedies to two intersecting public health issues, including AMR and COVID-19 disease. More importantly,

preventing the transmission of COVID-19 infections may also lessen the incidence of AMR in the general population, and vice versa [8,9]. Therefore, having a complete understanding of how COVID-19 affects the trajectory of AMR can help public health policy makers create effective policies, to more effectively manage AMR in the global community. Given this context, the current study provides insight into the fundamental causes of AMR during the ongoing COVID-19 pandemic as well as a critical perspective on how the co-existence of COVID-19 sickness and AMR occurs and their interaction with one another.

Methods

The epidemiological assessments of AMR-COVID-19 cases during the ongoing COVID-19 pandemic were carefully reviewed in the relevant literature, on which the current article is based. It is also based on information from other trustworthy sources, including preprints posted to servers like medRxiv and bioRxiv as well as government (state and federal) websites, public databases like Coverage, the Centers for Disease Control and Prevention in the United States, the European Centre for Disease Prevention and Control COVID-19 tracking, the European Monitoring of Excess Mortality for Public Health (Euro MOMO), etc.

Results & Discussion

The rapid emergence of AMR during the COVID-19 pandemic is primarily due to four major reasons: (1) nosocomial and secondary bacterial, and fungal infection or co-infection [10,11] (2) unnecessary or inappropriate prescription and use of antimicrobial drugs and steroids [12,13] (3) extensive use of biocides [14,15] (4) compromised and disrupted healthcare services due to unanticipated, periodic upsurge in COVID-19 cases [16,17]. The management of large numbers of critically ill COVID-19 patients in hospital settings in the midst of overburdened healthcare systems, along with longer duration of mechanical ventilation/critical care admission that increases the likelihood of nosocomial difficult-to-treat infections, leaves a significant knowledge gap regarding whether bacterial and fungal infections in COVID-19 patients are the direct consequences of SARS-CoV-2 infections or merely opportunistic or accidental co-infections [18,19]. Interestingly, lower respiratory tract infection with influenza is believed to be causing the release of virulence factors that predispose the host to secondary infection with bacteria, such as *Streptococcus pneumoniae* [20,21].

To date, the precise underlying mechanisms that result in secondary microbial infections during a viral infection are not completely understood. From a mechanistic standpoint, disruption of upper and lower airway epithelium, and its barrier function, as a result of viral-induced immune damage and subsequent dysregulation of the innate and adaptive immune responses are believed to promote the effective colonization of various bacteria and other microorganisms [22,23] and these immune alterations typically last for a long time. These immune alterations, known as “trained immunity,” “innate imprinting,” or “immune paralysis,” modify immune cells’ inflammatory response [24]. It is also possible

that virus-mediated immunosuppression [25,26], alterations of immune responses towards a specific pathogen (SARS-CoV-2, in this case) and increased susceptibility of host cells infected with virus to bacterial attachment and/or biofilm formation [27,28] are some of the potential causes that likely to contribute to the development of secondary microbial infections in individuals with viral disease.

For instance, one of the more significant aspects appears to be the immunosuppression of the host’s innate immune response brought on by the viral infection, which makes it easier for opportunistic bacteria like streptococcus to infect the host. Whether these general mechanisms play major roles in the increased susceptibility of SARS-CoV-2-infected patients towards co-infection or secondary infections with other microorganisms, remain to be elucidated, which may eventually provide more insights into the precision intervention of AMR in COVID-19 patients. In fact, compared to individuals with influenza, one study found that secondary bacterial infection in COVID-19 patients is a higher predictor of death [29].

Furthermore, patients with COVID-19 who are critically ill frequently experienced severe clinical problems, placing them at risk for contracting nosocomial bacterial and/or fungal pathogen infections and necessitating the prescription of numerous antimicrobial medicines, which in turn promotes the emergence of AMR. Also, they may be inappropriately used in milder cases of COVID-19 disease that further adds up to the overall AMR cases in patients treated in outpatient departments, and in people who frequently use over-the-counter antibiotics without clinical consultations [30]. The increased incidence of infections by microorganisms resistant to the most recently developed antibiotics, such as the carbapenems [31] or to ‘last resort’ antimicrobial agents like colistin is a serious concern in the biomedical community during the COVID-19 pandemic. Also, there has been a significant decline in the availability of newly developed antimicrobial agents in the market due to low production, arising primarily from the massive supply chain disruptions over the long pandemic. Additionally, during the COVID-19 pandemic, the usage of anti-parasite, antiviral, and anti-inflammatory drugs, particularly steroids for preventing secondary infections in COVID-19 patients, will probably worsen the prevalence of AMR over time. Interestingly, COVID-19 patients can present with non-specific clinical symptoms [32], such as fever and/or persistent cough, and they may be mistaken for other diseases like malaria or Tuberculosis (TB) and vice versa. These overlapping symptoms among diseases may result in inappropriate prescribing of antimicrobial drugs, and misdiagnosis in large number of patients, especially in symptoms-based screening of patients. This type of bystander selection resulted in widespread use of azithromycin for COVID-19 in the early phase of the pandemic, since it was initially mistakenly considered as potential therapy for COVID-19 disease [33,34].

Overuse of steroids has given rise to a parallel epidemic of thousands of cases of “black fungus” infections. *Mucor* mycosis [35], the fungal infections affect patients-initially in the nose, but

the fungus can then spread into the brain-causing life-threatening complications in the patients. Since the beginning of COVID-19 pandemic, the use of steroids [36,37] were rampant based on a large WHO (World Health Organization) initial study that showed steroids reduced the mortality of COVID-19 patients who received oxygen or required mechanical ventilation. Even though the actual cause(s) of the high prevalence of mucor mycosis have not yet been identified, the working theory holds that excessive steroid treatment, which is immunosuppressive in nature, given to COVID-19 patients directly responsible for black fungus infections.

During the COVID-19 pandemic, chemical disinfectants are ubiquitously and routinely used in community environments, especially on common touch surfaces in public settings to control the SARS-CoV-2 transmission. In case of COVID-19, the most frequently used disinfecting agents are quaternary ammonium hydroxide, hydrogen peroxide, sodium hypochlorite, and ethanol, which account for two-thirds of the active ingredients in current EPA (Environmental Protection Agency, USA) [38]. Consequently, the emergence of biocide-tolerant microorganisms in the environment may offer significant hazards of direct human infection, particularly in heavily populated urban areas [39]. Additionally, the COVID-19 pandemic's widespread tendency to use excessive amounts of antimicrobial compounds in a variety of settings necessitates increased antimicrobial production, which is likely to result in abrupt changes in antimicrobial concentrations in the environment, which may then cause selective pressures for AMR development in water and soil systems [40], further leading to selection for AMR in animals, and possibly increasing the prevalence of Antibiotic-Resistance Organisms (ARO) within the animal-based food supply chain [41,42].

Taken together, accumulating evidence suggests that even though there is strong likelihood for COVID-19-induced AMR cases worldwide, we cannot completely rule out the possibility that secondary microbial infections that affect COVID-19 patients may be sporadic. This is because the very low incidence of co-infections found and their resemblance to organisms acquired from the community appear to imply that these co-occurring secondary microbial infections may emerge sporadically in hospitalized COVID-19 patients. In this context, it should be noted that the most concerning group of MDR (Multi-Drug Resistant) bacteria linked to AMR are those that pose a specific threat to hospitals and nursing homes. These pathogens are referred to as "ESKAPE" pathogens [43] by IDSA (The Infectious Diseases Society of America), and they include *Enterococcus faecium* (E), *Staphylococcus aureus* (S), *Klebsiella pneumoniae* (K), *Acinetobacter baumannii* (A), *Pseudomonas aeruginosa* (P) and *Enterobacter species* (E).

Conclusion

In conclusion, AMR will continue to be a problem even after the COVID-19 pandemic is over. The current article therefore reiterates the urgent need for multifaceted interventions, such as the development of novel antibiotics, Monoclonal Antibodies (mAbs) and antibody-antibiotic conjugates, microbiome therapy,

antibacterial oligonucleotides, CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9) and phage therapy, either as a stand-alone treatment or in combination with antibiotics, may offer a valuable alternative for treating secondary bacterial infections. This may lessen the synergy dialogues between the primary SARS-CoV-2 infection and co-occurring microbes, resulting in the disruption of the AMR and COVID-19 disease nexus, leading to cross-management of the twin disease, and put society on a path of sustainable development growth, by reducing the emergence, transmission, and burden of AMR in the population. Lastly, there are still some critical questions that need to be addressed, such as the following: What proportion of COVID-19-associated bacterial infections in hospitalized patients is acquired in the community as opposed to acquired in a hospital? Do rates of COVID-19-associated bacterial infection differ by demographics, comorbidities, and/or geographic location? And what is the prevalence of COVID-19-associated bacterial infection in non-hospitalized populations? Besides, more fundamental studies are also necessary to ascertain the precise underlying mechanisms by which SARS-CoV-2 causes secondary microbial infections, and to further determine whether SARS-CoV-2 directly imparts antibiotic resistance to co-infecting bacteria through yet-to-be-identified mechanisms.

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