REVIEW ARTICLE

Co-Infections and Secondary Infections with Multidrug-Resistant Bacteria in COVID-19 Infected Individuals: A Review

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ABSTRACT

Bacterial co-infections and secondary infections are common in respiratory viral infections. Since COVID -19 is a respiratory viral infection proportion of the bacterial infections are high which leads to significant mortality. If these organisms were Multidrug resistance (MDR) the situation become worse. In this mini-review, we analyze the bacterial co-infections& secondary infections, and MDR status in COVID-19 individuals

Method: **This mini-review was reviewed from articles published in PubMed, Scopus, and Google scholar indexed journals between January 2021 to January 2022. The keywords used for the search were "secondary bacterial infections in COVID-19 individuals", "MDR resistant bacteria in COVID-19", and "case reports on MDR infections in COVID-19 patients"**

Results: **the proportion of bacterial co-infections and secondary infections are varied from region to region as low as 2.5% to 95% reported. MDR strains are high.**

Conclusion: **Unnecessary use of antibiotics, prolonged hospital stay, and overburden on the health care system are the main reasons for increasing MDR strains**

KEY WORDS

COVID-19 disease, co-infections and secondary infections, multidrug-resistant bacteria (MDR)

BACKGROUND

After hospital admissions with severe COVID-19 infections, some patients have been reported to have acquired bacterial infections. Methicillin-resistant Staphylococcus aureus is one of the antibiotic-resistant bacteria known to cause healthcare-associated infections (HAIs) in COVID-19 patients, according to New Delhi. Carbapenem-resistant *Enterobacteriaceae* such as *Klebsiella pneumonia*, extended-spectrum-lactamase, *Escherichia coli*, MDR *Enterobacter* spp. There were cases of carbapenem-resistant *Acinetobacter baumannii*; MBL Pseudomonas aerogenosa.Some studies have reported a decreased in *Methicillin-resistant S. Aureus (MRSA)* and *Vancomycin-resistant Enterococcus* cases, which has been attributed to enhanced infection prevention and control practices introduced to minimize the intra-hospital spread of COVID-19. The clinical signs of COVID-19 are diverse.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, and human-to-human transmission of the infection has led to the spread of the virus to other areas of Hubei Province, China. Subsequently, the disease spread across the country and then to other nations in the world[1,4]. On February 11, 2020, the World Health Organization (WHO) suggested the name of the disease Coronavirus disease 2019 (COVID-19)[1]. By April 2022, 493million cases and about6.1million deaths had been reported worldwide[1,2].The high mortality and morbidity of COVID19infections aredue to age factors, comorbidities, co-infections, and secondary bacterial infections[2].

Co-infections are defined as an infection present along with primary infection at the time of hospital admission, whereas secondary infections appear after 48 hours of hospital admission, indicating that most secondary infections are due to prolonged admission in ICUs.

Drug resistance is one of the best defense mechanisms expressed by the bacteria to protect from antibiotic drugs and it is a natural process or it can be acquired through one of the following mechanisms Permeability changes in the bacterial cell wall which restricts antimicrobial access to target sites, b) Active efflux of the antibiotic from the microbial cell, c) Enzymatic modification of the antibiotic, d) Degradation of the antimicrobial agent, e) Acquisition of alternative metabolic pathways to those inhibited by the drug, f) Modification of antibiotic targets, g) Overproduction of the target enzyme[3].

The microorganisms are categorized based on the expression of resistance.

MDR was defined as acquired resistance to at least one antimicrobial agent in three or more categories.XDR (Extensive Drug Resistance) was defined as Resistant to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories).**PDR** (Pan Drug Resistance) was defined as Resistant to all agents in all antimicrobial categories[4]. XDR and PDR are expressed by a few organisms i.e Mycobacterium tuberculosis but MDR was expressed by almost all the clinical important microorganisms.According to O'Neill, 2016 estimated that 10 million people will die and about $100 trillion dollar's economy will lost by 2050 due to antibiotic resistance[5].

This estimation was done before the COVID-19 pandemic it needs to be revised; during the COVID-19 pandemic, antibiotic resistance was significantly raised. In a study conducted by *Tiri*, *Beatrice et al*. report-

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ed that the incidence of carbapenem-resistant Enterobacteriaceae colonization increases from 6.7%(2019) to 50% by 2020[6].To quote the former director of the Centres for Disease Control and Prevention (CDC), Tom Frieden, "If we use antibiotics when not needed, we may not have them when they are most needed, this quote is correct in this COVID 19 pandemic era.

METHODS & MATERIALS

This mini-review was reviewed from articles published in PubMed, Scopus, and Google scholar indexed journals between January 2021 to January 2022. The keywords used for the search were "secondary bacterial infections in COVID-19 individuals", "MDR resistant bacteria in COVID-19", and "case reports on MDR infections in COVID-19 patients" "Antibiotic Resistance in COVID-19 patients" and "Mechanism of co-infections".

Reasons for MDR raised in the COVID-19 pandemic

There are various reasons to raise the MDR strains few of them are

1) Uncontrolled/Misuse of antibiotics
2) Unnecessary prescription of antibiotics
3) Prolonged hospitalization
4) Overburden on the healthcare system
5) Self-medication/online treatment
6) Uncertainty in the treatment regimen
7) Bacterial co-infections and secondary infections

1) Uncontrolled/Misuse of antibiotics:

In developed countries like the United States and England, the usage of antibiotics during pandemicsplunged. In developing countries like India, the consumption of antibiotics during the pandemic was increased, already India is the highest antibiotic consumption county this pandemic even raise the problem.2000-2015 the usage of antibiotics quantity was double and it increased gradually every year. A study conducted by *Georgia*, *et al*. showed a total of 16.29 billion doses of antibiotics were sold in India in 2020. Increased from 72.6 % in 2018 and 72.5% in 2019 to 76.8 % in 20207). Unlike in developed countries in India, antibiotics can available to buy easily, most antibiotics can access without a prescription. In India, almost all positive COVID-19 patients consume antibiotics irrespective of symptoms. There is no mechanism to control the misuse of antibiotics in India.

2) Unnecessary prescription of antibiotics:

Unlike developed countries In India, an unregulated private sector accounts for 75% of healthcare and 90% of antibiotic sales, allowing for antibiotic overprescription[7]. In a study published on hospitalized COVID-19 patients identified that 72% of patients received antibiotics, only 8%[8] demonstrated superimposed bacterial or fungal co-infections. Another study reported 71.5% of patients received antibiotics that did not require any antibiotics, leading to an escalation of multidrug resistance another study from china reported usage of 100% antibiotics in ICU, only 10% of confirmed secondary bacterial infections[9].

3) Prolonged hospitalization

Hospitalized patients during the COVID-19 pandemic were increased. A minimum of 7 to 14 days of hospital admission is required for symptomatic patients, in severe cases, it may long prolonged, during this period antibiotics have been given to prevent secondary bacterial infections. Patients who are admitted to the ICUs are more prone to bacterial co-infection and secondary infections subsequently MDR strains. Studies show most of the MDR strains are isolated from ICUs. Equipment like mechanical ventilators acts as a barrier to the transfer of antibiotic resistance genes. In a cohort study conducted by *Rouzé*, *Anahita*, *et al*. 50.5% of developed Ventilator-associated lower respiratory tract infections in COVID-19 patients as compared to influenza patients 30.3%, patients with no viral infection 25.3%[10]

4) Overburden on the healthcare system

The COVID-19 pandemic affects all sectors of the world. In the health sector diagnosis of another disease, the high burden on the functioning of the existing medical system, neglect of patients with other diseases and health problems, overload on doctors and other healthcare professionals, who are at very high risk, and overloading of medical shops directly. COVID-19 pandemic explores the gaps in the health care system in terms of infrastructure, manpower, lacking experts to diagnose and treat all over the world, in fact, no country in the world to ready to tackle the pandemic. In India very few real-time PCR labs were available to analyze the sample, laboratories and hospitals were more focused on RT-PCR tests, rest of the diagnostic tests were neglected including hospital infection control programs and antibiotic stewardship programs.

5) Self-medication and online treatment:

The World Health Organization (WHO) defines self-medication (SM) as the selection and utilization of medicines to treat self-recognized symptoms or ailments without consulting a physician. (WHO)[11,12].

It also includes the usage or re-usage of previously prescribed or unused drugs, direct purchasing of prescription drugs without consultation, and irrational use of over the counter (OTC) drugs. Self-medication was the problem of developed and developing countries with a prevalence of 32.5-81.5% worldwide. Till date COVID-19 had no definitive treatment this encourages the using self-medication was increased and it also increased by the influence of social media regarding misinformation about medications leading to public confusion and panic and increased use of SM, including home remedies, without established safety and efficacy[11,12]

6) Uncertainty in treatment regimen:

Since COVID-19 had no definitive treatment in many countries, azithromycin and Hydroxychloroquine (HCQ) are reportedly being used for prophylactic and therapeutic. In India, azithromycin is used for respiratory tract infections, bacterial dysentery, and enteric fever. This microcline antibiotic was repurposed for the treatment of COVID-19 based on its hypothetical anti-inflammatory and immunomodulatory properties. On the other hand, HCQ in India is mainly utilized for the treatment of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, and post-viral infectious arthritis, such as chikungunya arthritis, and is not part of national malaria treatment guidelines. It has been suggested that HCQ could have antiviral activity as well as indirect anti-inflammatory properties through the activation of CD8+ T cells and the reduction of pro-inflammatory cytokine response, thus leading to its widespread use in the management of COVID-19 as well as in pre-and post-exposure prophylaxis. However, an increasing number of studies have observed no beneficial effects from the use of azithromycin and/or HCQ, and several safety concerns have also been raised this uncertainty of treatment regimens contributes to antibiotic resistance[11,12]

7) Bacterial co-infections and secondary infections

Bacterial co-infections and secondary infections are common in viral disease which leads to significant morbidity and mortality. Co-infection is defined as simultaneous infection of a host by multiple pathogens. Secondary infection defined as Infection occurs during or after treatment for another infection. Historically In the 1918 influenza pandemic, most deaths occurred due to co-infections than the actual influenza infection, in 2009 the H1N1 influenza pandemic was complicated by bacterial pneumonia in 4-33% of hospitalized patients. Bacterial co-infection is not restricted to influenza and is caused by other respiratory viruses such as parainfluenza virus, respiratory syncytial virus, adenovirus, rhinovirus, and human metapneumovirus. Present COVID-19 pandemic, the proportion of bacterial co-infections and secondary infections were reported varies in different countries. It may be depending on the severity of disease, immunity, period of hospitalization, and hospital infection control strategies. Most of the co-infection and secondary infections are identified in patients admitted to ICUs further those patients showed a high percentage of MDR bacterial strains. The proportion of co-infections is lesser than secondary infections.

Prevalence of Bacterial co infection & secondary infection and MDR in COVID 19 individuals

Overall bacterial co-infection in COVID 19 patients reported from 3.5% to 96%[6-8,30,31]. In a review conducted by Langford BJ *et al*. About 3.5 % bacterial co-infection and 14.3% of patients had secondary infections, the overall proportion of COVID-19 patients with bacterial infections was 6.9%[13]. Nori P *et.al*. from New York reported 3.6% bacterial co-infections and 15% MDR strains identified[14]. *Feng*, *Yan*, *et al*. reported 34.5% Bacterial co-infections in critically ill patients in his study patients were divided into 3 groups (moderately ill, severely ill, and critically ill). The critically ill patients had the highest percentage of bacterial coinfection (34.5%) compared to patients in the moderately ill and severely ill groups (3.9% and 8.3%, respectively[15]. *Baskaran et al*. in their study showed bacterial co-infections 5.5% within 48 hours with *Streptococcus pneumonia* and *Staphylococcus aureus* and co-infection/ co-colonization rate > 48 h after admission in ICU stay consisting largely of Gram-negative bacteria, particularly *Klebsiella pneumoniae* and *Escherichia coli*[16].

Zhu, *Xiaojuan et al* from china reported 96.2% bacterial co-infection it is the highest proportion of co-infection in present literature[17].

In India studies are very limited, in existing literature bacteria co/ secondary infections are high compared to developed countries. Sharma, Bhawna et al.reported 26% bacterial co-infections 74% of secondary bacterial infections, ovaral17.9% bacterial infection are reportedmost common isolated organisms are *Acinetobacter species* (35.6%), followed by *Klebsiella pneumoniae* (18.1%). The majority 50.7% of the pathogenic organisms reported were multidrug resistant[18]. *S. Khurana et al*. reported 13% of patients had secondary infections, and most of them infected within the first 14 days of hospital admission with predominant pathogens *Klebsiella pneumoniae* (33.3%), *Acinetobacter baumannii* (27.1%) *Escherichia coli* (16.7%), and *Pseudomonas aerogenosa* (11.5%) and 9-84% of resistance was reported[19]. *Palanisamy N et al*. reported 8.5% of secondary bacterial infections in the blood culture of COVID 19 patients further 57.8% of MDR organisms identified, predominantly *Acitanobacter baumanii* (32.8%), followed by *Klebsiella pneumonia* (21.9%) were isolated from ICU[20].

Karruli A et al. reported 50% bacterial co-infectionsand 50% of patients developed MDR in ICU after 8 days of admission carbapenem-resistant Klebsiella pneumoniae was the predominant organism followed by *Acinetobacter baumannii*. Most of the co-infections and secondary infections are identified in patients admitted tohospitals, especially in intensive care units (ICUs)[21]. Temperoni, *Chiara et al*. reported *A.baumannii* 75% carbapenem-resistant, 100% *P. aeruginosa* were MDR, including 4 carbapenem-resistant strains, 50% of *K. pneumoniae* isolates were MDR, 31% of *E. coli* isolates are MDR. *S. aureus* and *E. faecalis* were the most common species: MRSA 27.5% *E. Faecium* 71.4% all most all the studies show similar results[22]

Predominant isolated organism's were *Acinetobacter baumanii*, followed by *Klebsiella pneumonia*, *Pseudomonas aerogenosa*, *Staphylococci* (*Coagulase-negative species*), *Staphylococcus aureus*, Streptococcus pneumonia, *Escherichia coli*. The bacterial co-infections and secondary infections in COVID-19 are variable from country to country even from hospital to hospital. The occurrence of these infections depends on the host immune system and the severity of the infection[13-22].

Antimicrobial resistance was rising gradually since the first antibiotic penicillin was discovered in 1928.COVID-19 pandemic contributed to raising even rapid. AMR rising due to the emergence, spread, and persistence of multidrug-resistant (MDR) bacteria or "superbugs". The extensive use of antibiotics to treat various microorganisms in, poor diagnosis of infection, unregulated prescriptions leading to drug overuse, and poorly regulated use of antibiotics in agriculture and animal-derived products have resulted in antibiotic resistance among various microbial strains. **MDR** was defined as acquired resistance to at least one agent in three or more antimicrobial categories. As stated by WHO, MDR bacteria is one of the leading adverse effects on humans, Some of the most frequent MDR bacteria defined by the WHO and infections they caused are listed on **table 1**[23,24].

In February 2017, WHO published a list of pathogens for which new antimicrobial development is urgently needed those are *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aerogenosa*, and *Enterobacter speciesacronym* ESKAPE pathogens given by WHO, This pathogens accountable for the majority of the infections globally and these organisms have been associated with high rates of drug resistance. There are several reports of their association with life-threatening diseases with these resistant organisms. Bacterial co-infection and secondary infection with COVID-19 are associated with these ESKAPE pathogens; these pathogens are opportunistic and associated with hospital-acquired infections[24].

Studies around the world showed that the prevalence of MDR strains increased in bacterial co-infection and secondary infection associated in COVID-19disease. MDR strains are frequently isolated from ICUs. The hospital environment, antibiotic therapy, using of steroids and ventilators in ICUs are the main triggers to increased MDR strains. The more concerning issue was carbapenem resistance detected in high proportion. Carbapenems are the last resort of drug use. Tiri, Beatrice et al. from Italy reported that *carbapenem-Resistant Enterobacteriaceae* (CRE) from 6.5% to 50% in 2019 to 202025). Li, Jie *et al* from China carbapenem-resistant in A. Baumannii, *Klebsiella pneumonia 91.5% and 75.5% respectively and Methicillin resistance was present in 100% of Staphylococcus aureus*[26,29]

Jaclyn A *et al*. reported in their case series of 42 patients hospitalized for COVID-19 with secondary S. aureus bacteremia, of these patients, 23 (54.8%) and 28 (66.7%) died at 14 days and 30 days, respectively, from their first positive blood culture Paola et al. mentioned about Mycobacterium tuberculosis COVID-19 coinfections[27,28]

Hirabayashi, A *et al*. have shown that the surveillance of antimicrobial resistance had been affected during the pandemic[30]

CONCLUSION

Antibiotic resistance is a silent pandemic, and all resistant strains have appeared worldwide. The consumption of antibiotics is high during COVID 19 pandemic where only 25-30% is required, which leads to increased antimicrobial resistance. However, the proportion of co-infection and secondary infections was less in COVID 19 patients, and the proportion of MDR organisms was very high ranging from 50 to 85%.In hospitalised COVID-19 patients with an antibiotic-resistant illness, poorer outcomes have been documented. The factors contributing to the high prevalence of MDR strains in the COVID 19 pandemic are the unnecessary use of antibacterial drugs, telemedicine, lack of antibacterial stewardship, over-prescription of antibiotic drugs, and overburdening of the health sector. Organizations such as WHO and CDC suggested that asymptomatic and mildly symptomatic patients are not required to take any antibiotics, but no one followed this guideline, which may be due to the fear of COVID 19. As we have seen in India during the first and second wave of the corvid 19 pandemics there are big queues in front of medical stores to buy antibiotics, most of which are without prescription. Such practices increase bacterial resistance. On the other hand, overburden on the health sector and shortage of technical experts to implement hospital infection control co-factors to increase MDR strains in the COVID- 19 pandemic. Multivariate analysis identified in most cases of hospital-associated infections was mostly ≥ 4 days from the date of admission. The Multidrug-resistant gram-negative bacteria were mostly responsible for morbidity and mortality in patients affected with Covid-19. Strict implementation of testing of specific antibiotic resistance patterns, regular surveillance, implementation of antibiotic stewardship programs, staff training on hospital infection control, prevention of unnecessary use of antibiotics, and prevention of self-medication presently all these programs are conducted by the organizations but over the burden of COVID-19, these programs may be hindered.

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