The Silent Pandemic by Super Pathogens during the COVID-19 Pandemic

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Abstract

Post-COVID-19 bacterial infections are a significant threat to global health, mainly due to the overuse and misuse of antibiotics. The review highlights the importance of using antibiotics judiciously and following appropriate guidelines and recommendations. The article also examines the potential indirect contribution of steroids to antibiotic resistance through immune suppression in severe cases of COVID-19. Anti-Microbial Resistance (AMR) is one of the leading causes of death worldwide that continues as a silent pandemic caused by the major AMR superbug includes Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB), Methicillin-Resistant *Staphylococcus Aureus* (MRSA), Carbapenem-Resistant *Enterobacterales* (CRE), Extended-spectrum Beta Lactamase producing *Enterobacterales*

Misuse and overuse of steroids

Dexamethasone is a steroid used globally to treat severe cases of carbapenem-resistant bacteria are , , and , which can cause infections in healthcare settings [3-5]. Multi-drug resistant was reported from healthcare facilities with resistance to 3rd and 4th generation cephalosporins, aminoglycosides, beta-lactam, carbapenem, and fluoroquinolones [2-5].

A study network to investigate Carbapenem-Resistant found that CRAB remains a significant threat to hospitalized patients in the USA, affecting the most vulnerable patients, and resulting in a major cause of mortality (6). The data released by the CDC reports 500 (8.3%) and 700 (9.3%) CRAB-associated mortality rates in the USA during 2019 and 2023 respectively. The Lancet's report estimates that worldwide, 452,000 deaths from AMR infections, encompassing pneumonia, bloodstream infections, soft tissue infections, and UTIs, can be attributed to resistance rather than just associated deaths. Notably, among isolates, 40,000 showed fluoroquinolone resistance, and 132,000 isolates were resistant to one or more drugs [3,4].

In a COVID-19 study from a chain of hospitals in North India by Budhiraja et al., reports 9.8% of secondary bacterial infections out of 19,852 COVID-19 patients, including bloodstream infections, UTIs, soft tissue infections, and pneumonia. was isolated in 215 cases, with 68% being CRAB, contributing to a 40.3% mortality rate associated with co-bacterial infections in COVID-19 cases [7]. Examining a tertiary care hospital in North India, a comparison of carbapenem resistance rates between August-October 2019 and early 2021 revealed an overall increase from 23% (pre-COVID) to 41% (COVID period) in bacteria like , , , and [7].

A review focused on China disclosed that 74% of hospitalized COVID-19 patients received antibiotics, predominantly Fluoroquinolones (56.8%), followed by Ceftriaxone (39.5%), and azithromycin (29.1%) [8,9]. Among these treatments, 7.6% addressed confirmed bacterial coinfections and secondary infections, including bacterial pneumonia, bacteremia, and infections caused by , species, , and [8,9]. A Turkish hospital study confirms 8.7% of patients had respiratory or circulatory tract infections identified through microbial culture, with Staphylococci species, , and , displaying resistance to all antibiotics except colistin [2].

Kinross et al., findings indicate a +57% surge in *A. baumannii* blood infections between 2020-2021 compared to 2018-2019 in EU/EEC countries with a higher incidence in Bulgaria and Spain, with 80.6% (2020) and 88.3% (2021) CRAB cases [8]. This study reports in other EU/EEC countries including Austria to Sweden, with 2.3% CRAB cases (2020 and 2021); and Czechia, Portugal, and Slovenia, with 22.7% (2020) and 49.8% (2021) CRAB cases [8].

Methicillin-Resistant *Staphylococcus Aureus* (MRSA): *Staphylococcus Aureus* exhibited high levels of resistance to several antibiotics, including carbapenems and fluoroquinolones. A study published in 2021 found that, among COVID-19 patients in a hospital in Turkey, the most isolated bacteria were *Staphylococcus Aureus* and *Klebsiella pneumonia*. Both bacterial strains are known to have high rates of resistance to cephalosporin antibiotics [5]. Another study published in 2021 reported that the most identified bacteria in COVID-19 patients with secondary bacterial infections were Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Carbapenem-Resistant (CRAB) [5].

The data released by the CDC reports 10,200 (3.3%) cases of mortality in association with MRSA or MSSA in the USA with COVID-19 [6]. Lopez et al., report 25.4% of MRSA or MSSA in Spain in association with COVID-19 hospitalized patients [8]. Lancet's study estimates that out of 13.7 million global deaths in 2019, 7.7 million death was associated with bacterial infections with the highest infection of MRSA. MRSA infections include pneumonia, bloodstream infections, soft tissue infections, UTI, meningitis, and peritoneal and cardiac infections which lead to deaths [3,4]. 121,000 deaths attributable to resistance were only calculated which did not include deaths associated with resistance. 15,900 isolates of *S. aureus* were resistant to fluoroquinolones, 19,600 isolates were resistant to Macrolides, 3120 isolates were resistant to vancomycin and 178,000 isolates were resistant to one or more drugs [3,4].

Beta Lactam-resistant *Streptococcus pneumonia*: Azithromycin and Clarithromycin are commonly prescribed antibiotics for COVID-19 patients, particularly those with severe symptoms and several studies have shown that clarithromycin resistance is becoming an increasing concern, particularly in the treatment of respiratory tract infections such as pneumonia [1,2]. Clarithromycin resistance in *S. pneumoniae* increased from 11% in 2011 to 17.8% in 2018 and it increased rapidly during the COVID-19 period [1,2]. A report by the European Centre for Disease Prevention and Control (ECDC) in 2020 found that the prevalence of penicillin-resistant

15.4%, and 30.3% of the isolates, respectively and these rates varied among individual countries. Eastern Europe and the USA showed similar findings of ESBL genotype with 15.9% and 15.8% respectively. The most isolated ESBL gene was CTX-M from all the regions [11]. The emergence of high-level resistance to carbapenems in Enterobacteriaceae was reported in HAIs and in patients with antibiotic-resistant septicemia caused by Enterobacteriaceae [11].

In a study from North India, out of 19,852 COVID-19 patients, secondary bacterial infections were diagnosed in 1940 (9.8%) cases with bloodstream infections, UTI, soft tissue infection, and pneumonia; and 319 isolates were E. coli and 396 isolates were *Klebsiella pneumonia*. Among the overall bacterial isolates, 76.9% were ESBL and 47.1% CRE with an overall mortality of 40.3% [7]. Another study published in 2021 found that among COVID-19 patients who developed bacterial infections, over 70% of the bacteria were multidrug-resistant. These included bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [12]. *Klebsiella pneumonia* and *Escherichia coli* are the most isolated ESBL or CRE resistant to 3rd cephalosporins, aminoglycosides, beta-lactam, carbapenem, and fluoroquinolones. The data released by the CDC reports 9,300 (4.7%) cases of mortality in 2020 associated with CRE/ ESBL in the USA associated with COVID-19 [6].

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patients without COVID-19. It is likely that there will continue to be ongoing studies evaluating the effectiveness of antibiotics and the emergence of antibiotic resistance in the coming years, and these studies will provide valuable insights into the management of infections in the post-COVID-19 period. Thus, bacterial isolates and antibiotic susceptibility testing must be incorporated with infectious cases to avoid further complications for the patient and resistance to antibiotics.

Discussion

Antibiotic stewardship and treatment modalities

Antibiotic resistance is a complex issue that requires a multifaceted approach. It's important to note that treating infections caused by multidrug-resistant bacteria can be challenging, and success rates may vary depending on the specific circumstances of the patient and infection. In some cases, it may not be possible to completely eradicate the infection, and the focus may shift to managing symptoms and preventing further complications. Antibiotics are necessary to treat bacterial infections, but they can also disrupt the balance of normal flora in the gut. Thus, probiotics play an important role in restoring balance to the gut microbiome.

On a public health level, the emergence of antibiotic-resistant bacteria is a growing concern. The spread of these bacteria can lead to outbreaks of infections that are difficult to treat, with potentially serious consequences for large populations. In addition, the increasing prevalence of antibiotic resistance can lead to the development of "superbugs" that are resistant to multiple types of antibiotics, making treatment even more challenging.

There are several solutions to address the issue of antibiotic resistance and the misuse of antibiotics during and after the COVID-19 pandemic.

Reducing the unnecessary use of antibiotics: One of the main drivers of antibiotic resistance is the overuse and misuse of antibiotics.

Antibiotic stewardship: Healthcare facilities can implement antibiotic stewardship programs to ensure that antibiotics are used judiciously and appropriately. These programs can include guidelines for prescribing antibiotics, ongoing monitoring of antibiotic use and resistance, and education and awareness campaigns for healthcare providers and patients.

Infection prevention and control: Proper infection prevention and control measures can help to reduce the incidence of healthcare-associated infections, which are a major contributor to antibiotic resistance. This includes measures such as hand hygiene, appropriate use of personal protective equipment, ICU disinfection, Ventilator sanitization, and hospital waste incineration. Hospital sewage is another source of resistant pathogens which must be treated with disinfectant and ensure the absence of resistant pathogens.

Public education and awareness: Educating the public about the appropriate use of antibiotics and the risks associated with overuse can help to reduce unnecessary use of antibiotics. This can include educational campaigns in schools, community outreach programs, and public awareness campaigns through social media and other channels.

Development of new antibiotics: There is a need for the development of new antibiotics to combat antibiotic-resistant bacteria. Governments and private organizations can provide funding and support for the research and development of new antibiotics.

Monitor the use of antibiotics in veterinary and agricultural practice: AMR super pathogens can be transmitted between pets, pet owners, and livestock. Thus, the use of antibiotics and resistance patterns in veterinary must be monitored and documented. This approach can help to promote the responsible use of antibiotics in both human and animal healthcare, as well as in agriculture and the environment.

International collaboration: Antibiotic resistance is a global problem that requires international collaboration to address. Governments, healthcare organizations, and public health agencies can collaborate to develop and implement policies and guidelines for the

Conclusion

Post-COVID-19 studies recorded bacterial strains resistant to beta-lactams including amoxicillin, cephalosporins, and carbapenem. The wide use of macrolides such as azithromycin and clarithromycin developed resistant strains in certain geographical areas. Bacterial strains resistant to fluoroquinolones such as Ciprofloxacin and Levofloxacin were developed in patients with co-infections. The overuse or misuse of these antibiotics in COVID-19 patients has contributed to the development of new, antibiotic-resistant bacterial strains including *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Escherichia coli*, and *Pseudomonas aeruginosa* which showed multiple antibiotic resistance. Overuse of steroids was another reason for post-COVID-19 bacterial pneumonia and its resistance to antibiotics. This review uncovers the post-COVID-19 silent pandemic by super pathogens, a new battle to fight.

Conflict of Interest

The authors have no conflicts of interest to declare.

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