Journal of Infectious Diseases & Therapy

Das S, et al., J Infect Dis Ther 2023, 11:S5

Review Article Open Access

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

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Received: 25-Sep-2023, Manuscript No. JIDT-23-116270; **Editor assigned:** 28-Sep-2023, Pre QC No. JIDT-23-116270 (PQ); **Reviewed:** 13-Oct-2023, QC No. JIDT-23-116270; **Revised:** 20-Oct-2023, Manuscript No. JIDT-23-116270 (R); **Published:** 27-Oct-2023, DOI:10.4173/2332-0877.23.S5.003.

Citation: Das S, Gladston VJ, Silvanse C (2023) The Silent Pandemic by Super Pathogens during the COVID-19 Pandemic. J infect Dis Ther S5:003.

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* (ESBL) which is resistant to cephalosporin and Multidrug-Resistant (MDR) *Pseudomonas aeruginosa.* Ongoing surveillance and monitoring of antibiotic use and resistance helped to minimize the risk of antibiotic resistance and shrink it from pandemic to endemic.

Keywords: Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB); Methicillin-Resistant *Staphylococcus Aureus* (MRSA); Carbapenem-Resistant *Enterobacterales* (CRE), Extended-Spectrum Beta Lactamase producing *Enterobacterales* (ESBL); Multidrug-esistant (MDR) *Pseudomonas aeruginosa*

Introduction

Antibiotic Resistance was one of the post-COVID-19 pandemics concerning issues that had been looming during and after the pandemic, and bacterial infections are becoming more resistant, making them harder to treat. Increasing rates of antibiotic resistance have been labeled a "silent pandemic" due to its potential to cause immense harm and a lack of awareness among the public which added to high mortality during and after the COVID-19 pandemic. The overuse and misuse of antibiotics, particularly during the COVID-19 pandemic, have accelerated the development of antibiotic resistance [1,2].

This review article aims to explore the potential impact of antibiotic resistance in the post-COVID-19 era, including delving into the causes, consequences, and possible solutions to address this growing public health threat. Since the COVID-19 pandemic has worsened the antibiotic resistance crisis, the manuscript discusses the actions that must be taken to mitigate its effects. Additionally, this article aims to raise awareness and prompt action toward addressing the silent pandemic of antibiotic resistance and discussing the effective methods to combat bacterial infections in the coming years.

Literature Review

Post-COVID-19 complications may lead to antibiotic resistance due to misuse and overuse of antibiotics, and steroids. Antibiotics are over-prescribed to COVID-19 patients who did not have bacterial co-infections during the COVID-19 pandemic. This overuse of antibiotics can contribute to the development of antibiotic-resistant bacteria, as bacteria become exposed to antibiotics more frequently and can evolve to resist them. Additionally, Hospital-Associated Infections (HAIs) are added to the burden of antibiotic-resistant mortality. Post-COVID-19 review studies by Das et al., summarize the antibiotics used to treat COVID-19-associated bacterial co-infections which are listed in Table 1, and discuss the major causes of AMR [1,2].

Misuse and overuse of antibiotics

COVID-19 can weaken the immune system of infected individuals, making them more vulnerable to bacterial infections. COVID-19 has disrupted healthcare systems worldwide, leading to delays in diagnoses and treatments for bacterial infections. The COVID-19 pandemic has highlighted the misuse of antibiotics, both during and after the pandemic. During the pandemic, antibiotics were often prescribed unnecessarily for patients with COVID-19, and this overuse of antibiotics can contribute to the development of antibiotic-resistant bacteria, which can be difficult to treat and pose a serious threat to public health [1,2]. Additionally, the pandemic has disrupted routine healthcare services, leading to delays in routine medical care and increased use of telemedicine. This can lead to the inappropriate prescribing of antibiotics without proper diagnosis or appropriate follow-up, contributing to the development of antibiotic-resistant bacteria. After the pandemic, there may be a surge in the use of antibiotics as patients seek to catch up on routine medical care that was postponed during the pandemic. This increased use of antibiotics can contribute to the development of antibiotic-resistant bacteria and increase the risk of healthcare-associated infections.

Misuse and overuse of steroids

Dexamethasone is a steroid used globally to treat severe cases of COVID-19, particularly in patients with respiratory distress syndrome. However, the overuse and misuse of steroids may indirectly contribute to antibiotic resistance by suppressing the immune system, making patients more susceptible to bacterial and fungal infections. Steroids can reduce the effectiveness of antibiotics by interfering with the body's natural defense mechanisms by suppressing the production of white blood cells, which are crucial for fighting infections [2]. This can result in a longer recovery time and increased use of antibiotics, increasing the risk of antibiotic resistance.

Hospital infections and antibiotic resistance

Healthcare-Associated Infections (HAIs) can lead to antibiotic resistance as patients with HAIs are often exposed to multiple rounds of antibiotics, increasing the risk of developing antibiotic-resistant bacteria. In addition, healthcare facilities can serve as a reservoir for antibiotic-resistant bacteria, making it easier for these bacteria to spread from patient to patient.

Some common types of HAIs that can lead to antibiotic resistance include: Urinary tract infections are a common type of HAI and are often caused by antibiotic-resistant bacteria such as *Escherichia coli*. Methicillin-Resistant *Staphylococcus Aureus* (MRSA) infections and other antibiotic-resistant strain infections can occur in surgical sites. Ventilator-associated pneumonia can develop in patients who require mechanical ventilation and can be caused by antibiotic-resistant bacteria such as *Pseudomonas aeruginosa*.

Preventing HAIs and antibiotic resistance in healthcare facilities requires a multi-faceted approach, including appropriate use of antibiotics, strict adherence to infection prevention and control practices, and ongoing monitoring and surveillance of antibiotic use and resistance. Healthcare facilities must also have robust antibiotic stewardship programs to ensure that antibiotics are used judiciously and appropriately to minimize the risk of antibiotic resistance.

The ICU of a hospital is often the most vulnerable to AMR bacteria. CRAB poses a serious risk to hospitalized patients and can cause severe diseases including pneumonia, UTI, bacteremia, meningitis, and soft tissue infections which can be very difficult to treat due to the bacteria's multidrug resistance. An ICU study from the UK reports that out of 35 CRAB-positive patients, 14 of them contracted it during their ICU stay [3-6]. CRAB is one of the major antibiotic-resistant strains that doctors are encountering all over the world. Hospital sewage is another reservoir of antibiotic-resistant bacteria, and any leak or spill can circulate back to common facilities. Antibiotic residues in wastewater and wastewater treatment plants may serve as hot spots for the development of antibiotic resistance and pose a potential threat to human health through exposure to different sources of water.

Developing resistance mechanisms of bacteria

Bacteria can develop resistance to antibiotics through various mechanisms including mutation, horizontal gene transfer, and enzymatic degradation. A review study by Das et al., uncovers the resistance mechanism of bacteria, and the major mechanisms are summarized in this manuscript [2].

Mutations: Bacteria can undergo spontaneous mutations that allow them to resist the effects of antibiotics. These mutations may affect the bacterial target site for the antibiotic or the drug's ability to penetrate the bacterial cell.

Horizontal gene transfer: Bacteria can exchange genetic material with other bacteria in their environment, allowing them to acquire resistance genes from other bacteria. This process can occur through mechanisms such as conjugation, transformation, and transduction.

Efflux pumps: Some bacteria have efflux pumps that can actively pump out antibiotics from the cell, reducing the drug's concentration inside the cell and making it less effective.

Modification of drug target sites: Bacteria can modify the target sites for antibiotics, making them less susceptible to the drug's effects.

Biofilm formation: Bacteria can form biofilms, which are complex communities of bacteria surrounded by a protective matrix. Biofilms can protect bacteria from antibiotics and make them more resistant to drugs.

Enzymatic degradation: Bacteria can produce enzymes that break down antibiotics, rendering them ineffective. Beta-lactamase is an enzyme produced by many bacteria and can inactivate beta-lactam antibiotics such as penicillin, cephalosporins, and carbapenems.

These mechanisms can occur individually or in combination, leading to the development of multidrug-resistant bacteria. It is crucial to use antibiotics judiciously and only when necessary to minimize the development of antibiotic-resistant bacteria. Additionally, research into new antibiotics and alternative treatments is essential to combat the growing threat of antibiotic resistance.

Post-COVID-19 antibiotic resistance and super-pathogens

Antibiotics are commonly used to treat bacterial infections, but they can also kill beneficial bacteria in the gut microbiome, leading to dysbiosis. When the normal flora is disrupted, potentially harmful bacteria can overgrow, and these bacteria may acquire antibiotic-resistance genes through horizontal gene transfer. This can lead to the emergence of antibiotic-resistant strains of bacteria, which are increasingly difficult to treat with standard antibiotics. Major antibiotic-resistant strains that evolved during the COVID-19 pandemic include Carbapenem-resistant *Acinetobacter baumannii* (CRAB), Methicillin-resistant *Staphylococcus Aureus* (MRSA), Extended-spectrum Beta Lactamase-producing *Enterobacterales* (ESBL), Beta-Lactam resistant *Streptococcus pneumonia* and Multidrug-resistant (MDR) *Pseudomonas aeruginosa* [2-6].

A global study published by Lancet in 2022, estimated 7.7 million deaths associated with bacterial pathogens in 2019, and 54.9% of death was by five pathogens including *Staphylococcus Aureus*, *Streptococcus pneumonia*, *E. coli*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* [3,4]. Later, *Acinetobacter baumannii* was added to the superpathogen class as the mortality associated with this pathogen increased rapidly in COVID-19-infected patients [3,4]. The Lancet study in 2019 accounted for 73.4% of AMR-related deaths in Saharan Africa due to six super pathogens. AMR is reported globally, with a high incidence of mortality and there is emerging evidence of antibiotic resistance, particularly for antibiotics most used to treat secondary bacterial infections in COVID-19 patients [3,4].

Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB): Carbapenems are a class of antibiotics that are often used as a last resort for treating serious bacterial infections, but some strains of bacteria have developed resistance to these drugs. The most reported

carbapenem-resistant bacteria are *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, which can cause infections in healthcare settings [3-5]. Multi-drug resistant *Acinetobacter baumannii* 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 *Acinetobacter* 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 *A. baumannii* 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. *Acinetobacter baumannii* 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 *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* [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 *Acinetobacter baumannii*, *Staphylococcus* species, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* [8,9]. A Turkish hospital study confirms 8.7% of patients had respiratory or circulatory tract infections identified through microbial culture, with Staphylococci species, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, 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 *Acinetobacter Baumannii* (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 *S. pneumoniae* ranged from less than 5% in some countries to over 50% in others [2]. In addition, some strains of *S. pneumoniae* have also developed resistance to macrolide antibiotics, which are often used to treat respiratory tract infections. A cohort study was performed in Spain, describing the outcomes of bacterial coinfections diagnosed in COVID-19 patients mainly due to *S. pneumoniae* and *S. aureus*, and the resistance reported by *S. pneumonia* includes 3rd generation of cephalosporins, beta-lactam, and fluoroquinolones [2].

A study by Lancet estimated out of 13.7 million global deaths and 829,000 drug-resistant *S. pneumonia* infections included pneumonia, bloodstream infections, and cardiac infections. 41,900 deaths were attributable to resistance which did not include deaths associated with resistance. 41,900 isolates of *streptococcus pneumonia* was resistant to carbapenem, 11,200 isolates were resistant to fluoroquinolones, 12,500 isolates were resistant to Macrolides, and 122,000 isolates were resistant to one or more drugs [3,4]. Lopez et al., report 53.3% *Strep. Pneumonia* cases in association with COVID-19 hospitalization from Spain [10].

Extended-Spectrum Beta Lactamase producing *Enterobacterales* (ESBL): Cephalosporin-resistant *Escherichia coli* & *Klebsiella pneumonia*.

ESBL enzymes are mediated by genes, commonly CTX-M, TEM, and SHV, which are harbored by self-transmissible conjugative plasmids that are horizontally shared within the same and different species of bacteria. CTX-M-type ESBLs exhibit powerful activity against cefotaxime and ceftriaxone but generally not against ceftazidime. ESBL includes both Carbapenem-Resistant (CRE) and non-carbapenem-resistant *Enterobacterales* [11].

A study by Mariano et al., found that among 15449 non-CRE *E. coli* and *K. pneumoniae* clinical isolates collected in Europe, Asia-Pacific, and Latin America, an ESBL gene was detected among 8.2%,

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].

A global study by Lancet study estimates 13.7 million global deaths in 2019, 7.7 million death was associated with bacterial infections. *E. coli* isolates were resistant to 3rd generation cephalosporins and fluoroquinolones were isolated in association with pneumonia, bloodstream infections, soft tissue infections, UTI, meningitis, and peritoneal and cardiac infections which lead to deaths. 29,500 isolates of *E. coli* were resistant to carbapenem, 21,300 isolates were resistant to Beta-Lactam, 56,000 isolates were resistant to fluoroquinolones, 59,900 isolates were resistant to 3rd generation cephalosporins, and 219,000 isolates resistance to one or more drug [3,4]. 55,700 isolates of *Klebsiella pneumonia* were resistant to carbapenem, 7,930 isolates were resistant to Beta-Lactam, 29,000 isolates were resistant to fluoroquinolones, 50,100 isolates were resistant to 3rd generation cephalosporins, and 193,000 isolates resistance to one or more drug [3,4].

Multi Drug Resistant (MDR) *Pseudomonas aeruginosa*: *Pseudomonas aeruginosa* and *E. coli* are the microorganisms most frequently involved in ICU-acquired infections, with special importance in ventilator-associated pneumonia [12]. A study published in June 2021 found that among COVID-19 patients, there was a high prevalence of ciprofloxacin-resistant bacteria, with 44% of the isolates showing resistance to ciprofloxacin [12]. MDR *Pseudomonas aeruginosa* showed resistance to 3rd generation cephalosporins, 4th cephalosporins, aminoglycosides, beta-lactam, carbapenem, and fluoroquinolones; and the resistance was more common in COVID-19 patients with severe disease compared to those with mild or moderate disease [12].

A study by Budhiraja et al., reports out of 19,852 COVID-19 patients, secondary bacterial infections were diagnosed in 1940 (9.8%) cases (bloodstream infections, UTI, soft tissue infection, and pneumonia) with 207 isolates of *Pseudomonas aeruginosa* with 43%resistant to Carbapenem with an overall mortality of 40.3% [7]. Another study by Yuan et al., reports 22.4% of co-infections of *Pseudomonas aeruginosa* in COVID-19 cases from China [9]. Lopez et al., found 40.2% co-infections associated with COVID-19 from hospitalized patients in Spain [10].

Pseudomonas aeruginosa was isolated in association with pneumonia, bloodstream infections, soft tissue infections, UTI, and peritoneal and cardiac infections which lead to deaths [3]. Lancet study found that 38,100 isolates of P. aeruginosa were resistant to carbapenem, 18,300 isolates were resistant to fluoroquinolones, and 84,600 isolates were resistant to one or more drugs [4].

A study published in 2021 found that over 80% of COVID-19 patients received antibiotics, and 70% of those patients received broad-spectrum antibiotics such as cephalosporins and fluoroquinolones. This study also reports that 70% of the bacteria isolated from COVID-19 patients were resistant to at least one antibiotic, and over 15% were multidrug-resistant bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [11].

Global view on high-risk regions with super pathogens

AMR is a leading cause of death in all regions and a study report published in 2022 estimated the mortality with pneumonia caused by AMR super pathogens which had the greatest impact, causing more than 400,000 deaths and associated with more than 1.5 million deaths [3]. Additionally, it also estimated that mortality with sepsis caused 370,000 deaths and was associated with 1.5 million deaths. The direct mortality in African countries by AMR super pathogens was estimated at 24 deaths per 100,000 population, to be the highest, at 22 deaths per 100,000 populations in South Asia, and 13 deaths per 100,000 in high-income countries. AMR-associated mortality was 99 per 100,000 in African countries, 77 deaths per 100,000 in South Asia, and 56 deaths per 100,000 in high-income countries [3,4].

A global estimation of mortality caused by six super pathogens (*E. coli*, *S. aureus*, *K. pneumonia*, *S. pneumoniae*, *A. baumannii*, and *P. aeruginosa*) led directly to 929,000 deaths and was associated with 3.57 million deaths [3]. The direct cause of death by MRSA was estimated above 100,000 in 2019 and other super pathogens each caused between 50,000 and 100,000 deaths. Among all pathogens, resistance to two classes of antibiotics is often considered the first line of defense against severe infections which are fluoroquinolones and beta-lactam antibiotics, and it is estimated more than 70% of deaths are caused by AMR [3]. The health impact of pathogens varied widely based on location, with deaths attributable to AMR in African countries most often caused by S. pneumonia (16% of deaths) or K. pneumonia (20%), while around half of the deaths attributable to AMR in high-income countries were caused by S. aureus (26%) or E. coli (23%) [3,4].

There is emerging evidence of post-COVID-19 antibiotic resistance reporting from all countries, particularly for antibiotics that are most used to treat secondary bacterial infections in COVID-19 patients. This includes antibiotics such as amoxicillin, azithromycin, and cephalosporins. The overuse of these antibiotics in COVID-19 patients has contributed to the development of new, antibiotic-resistant bacterial strains [3,4]. A study published in 2021 found that over 80% of COVID-19 patients received antibiotics, and 70% of those patients received broad-spectrum antibiotics such as cephalosporins and fluoroquinolones [12]. The study also found that 70% of the bacteria isolated from COVID-19 patients were resistant to at least one antibiotic, and over 15% were multidrug-resistant [12].

Overall, these studies suggest that there may be differences in the antibiotic susceptibility patterns of bacterial isolates obtained from patients with COVID-19 compared to historical control groups or

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 all 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 responsible use of antibiotics and share information and best practices.

It is important to note that the choice of treatment modality in AMR cases will depend on the specific type of infection, the severity of the infection, and the patient's health status. A review study by Das et al., reveals the possible modalities for patients with antibiotic-resistant strains [2].

Alternative antibiotics: MIC will provide the best option for the alternate administration of antibiotics available that are effective against resistant strains. This may involve using higher doses of the antibiotic or combining multiple antibiotics.

Antimicrobial stewardship: This involves using antibiotics in a more targeted and responsible manner to prevent the development of resistance. This may include limiting the use of antibiotics to only when they are necessary, using the appropriate dose and duration of treatment, and using narrow-spectrum antibiotics when possible.

Combination therapy: This involves using two or more antibiotics together to improve their effectiveness. This approach may be particularly useful for treating infections caused by multidrug-resistant bacteria.

Non-antibiotic therapies may include phage therapy, which uses viruses to target and kill specific bacteria, or immunotherapy, which involves using the body's immune system to fight the infection. These are naturally occurring antimicrobial peptides that have antimicrobial properties. They can be used to treat infections and have the potential to be effective against antibiotic-resistant bacteria.

Mode of administration: In cases of antibiotic-resistant infections, Intravenous (IV) administration of antibiotics may be more effective than oral administration. This is because IV antibiotics can achieve higher concentrations in the bloodstream and target the site of an infection more directly than oral antibiotics. IV administration allows the antibiotics to bypass the gastrointestinal tract, where they may be affected by factors such as pH, enzymes, and food. This can be particularly important in cases where the patient's gastrointestinal tract is compromised, such as in patients with severe infections, nausea, or vomiting.

Monitoring marker tests to evaluate response to treatment which includes total WBC count, C-Reactive Protein (CRP) and Procalcitonin (PCT).

Antimicrobial stewardship programs are crucial in the global fight against antimicrobial resistance and these programs are initiated globally to improve patient outcomes, reduce the risk of adverse effects associated with antibiotic use, and prevent the development and spread of antibiotic-resistant infections.

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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