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Emerging Antibiotic Resistance in Post-COVID-19 Co-infections

Keywords: Antibiotic Resistance; Post-COVID-19 infections; Bacterial Pneumonia

Abstract

There is emerging evidence of antibiotic resistance, particularly for antibiotics commonly used to treat secondary bacterial infections in COVID-19 patients. The overuse of antibiotics in COVID-19 patients has contributed to the development of antibiotic-resistant bacterial strains against amoxicillin, azithromycin, cephalosporins, ciprofloxacin, and carbapenem. The most resistant bacteria isolated from COVID-19 patients include *Klebsiella pneumonia, Acinetobacter baumannii,* and *Pseudomonas aeruginosa,* which showed multiple antibiotic resistance. The increasing rates of antibiotic resistance are labeled as a "silent pandemic" as post covid-19 bacterial infections caused by deadly pathogens are the most significant threats to global health.

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Introduction

Antibiotics have been extensively used to treat secondary bacterial infections and as a preventative measure in COVID-19 patients. However, the widespread use of antibiotics, particularly prophylaxis use, has contributed to the emergence of new, antibiotic-resistant bacterial strains, posing a threat to post-COVID-19 patients with weakened immune systems [1-4]. Studies have shown that patients with severe COVID-19 symptoms are more prone to developing secondary bacterial infections. The overuse and misuse of antibiotics in COVID-19 patients have also contributed to the development and spread of antibiotic-resistant bacteria. It raises concerns about the potential emergence of antibiotic-resistant bacteria that could further complicate the treatment of COVID-19 patients and other infections. Antibiotic resistance occurs when bacteria evolve to resist the effects of antibiotics, making it more challenging to treat infections. This review article will explore the potential impact of the COVID-19 pandemic on antibiotic resistance and discuss the strategies to mitigate this emerging threat.

Post-COVID-19 Bacterial Pneumonia

The COVID-19 pandemic can lead to the development of bacterial pneumonia in individuals. Due to a weakened immune system, a person with COVID-19 is more vulnerable to developing a secondary bacterial infection in their lungs. The bacteria associated with COVID-19 pneumonia with bacterial co-infection include *Mycoplasma pneumonia, Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* [3-6]. The most isolated bacteria in COVID-19 patients were *Streptococcus pneumoniae* while *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Staphylococcus aureus* were isolated in those who require hospitalization or ventilator support [2-5].

Post-COVID-19 bacterial pneumonia is a potential complication that may arise after a person has recovered from COVID-19. COVID-19 weakens the immune system, which could make a person more susceptible to secondary bacterial infections, including pneumonia. Symptoms of bacterial pneumonia include cough, fever, chest pain, shortness of breath, fatigue, and in severe cases, coughing up blood [3-5]. If a person develops bacterial pneumonia after recovering from COVID-19, they may require antibiotics to treat the infection. Treatment may also involve oxygen therapy, bronchodilators, and other supportive measures to help with breathing and other symptoms [7,8].

Secondary bacterial infections and co-infections can occur in individuals already infected with a virus, such as influenza or COVID-19. This type of infection can be more severe and difficult to treat than infections caused by a single pathogen. A secondary bacterial infection could occur when bacteria infect an individual already infected with a virus or another pathogen. It can occur because the virus weakens the immune system, making it easier for bacteria to cause an infection. In severe cases, the virus may also damage the respiratory tract, making it easier for bacteria to infect the lungs. A global study from 204 countries and territories found that 13.6% of all global deaths were associated with 33 pathogens, and over 50% of deaths were caused by five pathogens, including *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [9].

Pneumonia caused by *Mycoplasma pneumonia*

Mycoplasma pneumonia is a type of bacteria without a cell wall that can cause pneumonia and bronchitis, and it was one of the common co-infections found in patients with COVID-19. Beta-Lactam, such as Amoxycillin and cephalosporins are ineffective against *Mycoplasma pneumoniae* as these antibiotics target to block bacterial cell wall biosynthesis. Azithromycin and clarithromycin are the antibiotics used to treat Mycoplasma infections as it works by inhibiting bacterial protein synthesis [7-11]. They bind to the 50S subunit of bacterial ribosomes, preventing the elongation of

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nascent peptides and inhibiting the translation of bacterial proteins. Fluoroquinolones such as ciprofloxacin, moxifloxacin, levofloxacin, and ofloxacin are another option for Mycoplasma treatment as they interface with bacterial DNA replication and transcription [7-11].

The symptoms of *Mycoplasma pneumonia* include a non-productive cough, sore throat, headache, fatigue and weakness, fever and chills, chest pain, and shortness of breath or breathing difficulty. Diagnosis includes a physical exam, chest X-ray or CT scan, blood tests for Mycoplasma antibodies, and PCR testing for *Mycoplasma pneumoniae* in respiratory secretions. Pneumonia caused by Mycoplasma could be diagnose with its symptoms, diagnostic tests, and response to treatment. Typical bacteria like *Streptococcus pneumonia* and *Acinetobacter baumannii* pneumonia are typically associated with a productive cough and more severe symptoms. *Mycoplasma pneumonia* is associated with a non-productive cough and milder symptoms [6,8]. Additionally, *Mycoplasma pneumonia* can often be diagnosed with blood tests or PCR testing for the presence of the bacteria.

Pneumonia caused by Gram-positiveBacteria *(Streptococcus pneumonia* & *Staphylococcus aureus)*

Streptococcus pneumoniae is a common cause of bacterial pneumonia in COVID-19 patients, and some antibiotics commonly used for the treatment include Penicillin, Cephalosporins, and Macrolides [10]. The bacterial pneumonia symptoms are high fever, chest pain, and cough, which may produce phlegm or phlegm with blood, shortness of breath or breathing difficulty, fatigue and weakness, rapid heartbeat, confusion, or disorientation, especially in elderly or immune compromised patients. Diagnosis of *Streptococcus pneumoniae* infection includes a physical exam, chest X-ray or CT scan, rapid strep antigen test in throat swab, sputum culture, and sensitivity testing [4,7,8].

Staphylococcus aureus was isolated from hospitalized COVID-19 patients with co-infections of bacterial pneumonia, including methicillin-susceptible and resistant strains. Amoxycillin/clavulanate, cephalosporins, and Macrolides are the antibiotics treated in methicillin-susceptible bacterial strains. While, Vancomycin, linezolid, daptomycin, or cefazoline have been used to treat methicillin-resistant *Staphylococcus aureus* [12].

Pneumonia caused by Gram-negative Bacteria (*A. baumannii, P. aeruginosa, E. coli*, and *K. pneumonia*)

Gram-negative organisms predominantly isolated from COVID-19 cases that cause co-infections were *Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumonia* [12-14]. Pneumonia caused by typical bacteria can confirm by sputum culture and sensitivity testing (Figure 1).

B-Lactams including Amoxycillin, Amoxicillin-clavulanic acid, 2nd-generation cephalosporins such as Cefaclor, Cefuroxime and 3rd-generation cephalosporins such as Cefixime, Cefotaxime, Cefpodoxime, Ceftazidime, and Ceftizoxime used to treat as it prevents bacterial cell wall biosynthesis [12-14]. The choice of antibiotic will depend on the specific type of bacteria causing the infection and its susceptibility to different antibiotics (Figure 2).

The symptoms of *Acinetobacter baumannii* pneumonia can vary

Figure 1: The culture appearance of *Klebsiella pneumoniaon* MacConkey's agar shows mucoid, lactose fermenting pink colonies.

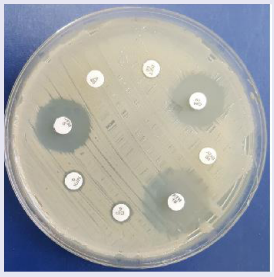

Figure 2: Antibiotic sensitivity of *Klebsiella pneumonia* showing resistance to Ciprofloxacin (CIP), Moxifloxacin (MFX), Amoxycillin (A), Amoxycillin/Clavulanate (AUG), and Doxycycline (DXT). Gentamycin (GM) and Cefuroxime (CFM) show a zone of inhibition of bacterial growth (Sensitive), while Azithromycin (ATH) shows secondary growth in the primary inhibited zone.

but are typically similar to other bacterial pneumonia that produces phlegm or phlegm with blood. The diagnosis included a physical exam, chest X-ray or CT scan, and collection of a sputum sample for culture and sensitivity testing. Pneumonia caused by *Acinetobacter baumannii* could be a severe problem due to its ability to develop resistance to multiple antibiotics, making it difficult to treat. Pneumonia caused by *Acinetobacter baumannii* has been treated with antibiotics belonging to carbapenems such as Imipenem, Meropenem, Ertapenem, and Doripenem [12-19]. It may involve a combination of antibiotics in a hospital setting to monitor the patient's condition and provide supportive care. Empiric antibiotic therapy was initiated while waiting for the confirmation of antibiotic sensitivity. The symptoms of pneumonia caused by Gram-negative bacteria were similar to other bacterial infections. Table 1 summarizes the common antibiotics used in COVID-19 patients with co-infections of bacterial pneumonia [20].

Global overview of Antibiotic use in COVID-19 patients

Antibiotic therapy was given to COVID-19 patients as prophylaxis to prevent secondary infections in moderate or severe COVID-19 patients or treat co infections and secondary infections caused by bacteria. A review study focused on China found that 74% of hospitalized COVID-19 patients had antibiotic treatment, and 36.9% had treatment with Glucocorticoids [12,14,16,18]. Fluoroquinolones were most used in 56.8% of patients, followed by Ceftriaxone in 39.5% of patients, then azithromycin in 29.1% of patients [12,14]. This treatment included 7.6% of confirmed bacterial coinfection and secondary infections, mainly bacterial pneumonia, bacteremia, and

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Table 1: Most used antibiotics to treat co-bacterial infections and secondary bacterial infections in association with COVID-19. (Sibi Das et al, Genesis Journal of Medicine and surgery 2023).

Bacteria		Antibiotic Treatment
Mycoplasma pneumonia		Macrolides such as Azithromycin and Clarithromycin
Acinetobacter baumannii		Carbapenems such as Imipenem, Meropenem, Ertapenem, Doripenem.
Streptococcus pneumoniae		Amoxicillin/clavulanate, ceftriaxone, cefotaxime, azithromycin, clarithromycin
Staphylococcus aureus		Oxacillin or Nafcillin, or cephalosporins such as Cefazolin.
Staphylococcus aureus (MRSA)		Vancomycin, linezolid, daptomycin, or cefazoline.
Escherichia coli		Ciprofloxacin, Trimethoprim/sulfamethoxazole, Cefepime, Meropenem, Piperacillin/tazobactam
Klebsiella pneumonia		Ceftriaxone, Levofloxacin
Pseudomonas aeruginosa		Piperacillin-tazobactam, Ceftazidime, Cefepime,Imipenem, Meropenem

other coinfection caused by *Acinetobacter baumannii*, *Staphylococcus species*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [12,14,16,18]. Antibiotics were used in severe COVID-19 patients to prevent secondary infection as the COVID-19 virus weakens the immune system. Many studies from China reported the use of antibiotics in severe COVID-19 patients was 80% to 100%, and in non-severe patients was 45% to 54%, while other studies from China report 75.4% of patients received empiric antibiotics despite severe disease. All these studies reported higher antibiotic use in COVID-19 patients [12,14,16,18].

Antibiotics were prescribed to 75% of COVID-19 patients, while confirmed bacterial co infection rates are less than 10%. On the above background, a meta-study of Global antibiotic use during the COVID-19 pandemic analyzed through the pharmaceutical sales data from 71 countries found a monthly 10% increase in antibiotic use-associated cases across continents including Africa, Asia, Europe, North America, and South America, which includes Cephalosporins, Macrolides, Penicillin, and Tetracyclines [21]. Another study from Turkey reported 61.8% of antibiotic use in COVID-19 patients and it includes a combination of beta-lactams, and macrolides or fluoroquinolones, and in patients in the ICU, piperacillin/tazobactam was the most prescribed antibiotic [22]. A study from the USA found that 50% of hospitalized COVID-19 patients had *Mycoplasma pneumonia* co-infection which is significantly higher than other bacterial infections [23].

The antibiotic prescription rate in Bangladesh was evaluated in a study and found that the antibiotic prescribing rate among SARS-CoV-2 positive patients at a Bangladesh tertiary COVID-19-dedicated hospital indicate that 100% of hospitalized patients were getting at least one antibiotic which includes ceftriaxone (53.8%), meropenem (40.9%), moxifloxacin (29.5%), and doxycycline (25.4%) [24]. Another study conducted in Bangladesh found that antimicrobial drug use patterns are significantly high including cephalosporin and macrolide. Azithromycin was the most frequently used antibiotic with an estimation of 54% during the COVID-19 pandemic [25]. A study from Pakistan reported 1.4% of a secondary bacterial infection or co-infection in association with COVID-19, while antibiotics were prescribed to 85.4% of COVID-19 patients as prophylaxis. Antibiotics frequently prescribed in Pakistan include azithromycin (35.6%), ceftriaxone (32.9%), and meropenem (7.6%) [26].

In a systemic review of 36 studies, 32 studies were on the use of antibiotics in COVID-19 inpatients and 4 were on antibiotics used in COVID-19 outpatients showing the higher use of antibiotics in both cases [26]. A cohort study was performed in Spain describing the outcomes of bacterial co infections diagnosed in COVID-19 patients mainly due to *S. pneumoniae* and *S. aureus* [26]. Hospital-acquired bacterial super infections, mostly caused by *P. aeruginosa* and *E. coli,* were diagnosed in 4.3% of patients [25,27-29]. Similar findings were reported in the Netherlands in COVID-19 patients with 1.2% of bacterial co infections (75% pneumonia) [25]. An observational cohort study performed in two hospitals in London reported that among hospitalized COVID-19 patients, 2.7% had bacterial co infection and most of the patients (up to 98%) received empirical antibiotic treatment [27]. Many similar studies reported that COVID-19 patients received antibiotics at admission; while the reported rate of bacterial infections was lower [27-31]. Another retrospective observational study reported an outbreak of *A. baumannii* in COVID-19 patients and identified carbapenem-resistant strains [32].

A nation wide cross-sectional study conducted in Japan covering 25% of all acute care hospitals in the country reported that 13.21% of COVID-19 patients received antibiotics. Antibiotics were prescribed more often in inpatients (16.15%) than outpatients (10.53%) and which is significant at $p < 0.001$. The most frequently prescribed antibiotic among outpatients was cefazolin, while that among inpatients was ceftriaxone [33]. A study from Malaysia found that the prevalence of antibiotic usage was 17.1%, with 5.5% of them being prescribed two or more types of antibiotics. The most frequent antibiotics prescribed were amoxicillin/clavulanic acid (37.8%), ceftriaxone (12.3%), piperacillin/tazobactam (13.3%), azithromycin (8.3%), and meropenem (7.0%) [34].

Post covid-19 Antibiotics Resistance

There is emerging evidence of antibiotic resistance, particularly for antibiotics most used to treat secondary bacterial infections in COVID-19 patients. Overuse of these antibiotics in COVID-19 patients has contributed to developing the new, antibiotic-resistant bacterial strains against amoxicillin, azithromycin, and cephalosporins [25,35,36]. 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 [36-40]. 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 bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. 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) [41].

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Azithromycin and Clarithromycin were the antibiotics commonly prescribed for COVID-19 patients, particularly those with severe symptoms [36-40]. Many studies have shown that clarithromycin resistance is becoming an increasing concern, particularly in the treatment of respiratory tract infections such as pneumonia. Clarithromycin resistance in Streptococcus pneumoniae increased from 11% in 2011 to 17.8% in 2018 and it increases the resistance significantly after COVID-19 pandemic. [39,40].

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 [22]. The study highlights the importance of implementing infection control measures and judicious antibiotic use in COVID-19 patients to prevent the development of antibiotic-resistant bacterial infections. Another study published in 2020 found that in a hospital in China, patients with severe COVID-19 symptoms were more likely to develop secondary bacterial infections with multiple antibiotic resistance, including cephalosporins [39-40]. 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 [40].

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* and *Acinetobacter baumannii*, which can cause infections in healthcare settings [32]. A tertiary care hospital in North India compared the carbapenem resistance rates from August-October 2019 with those in early 2021. Overall carbapenem resistance increased from 23% (pre-COVID) to 41% (COVID period) in *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa* [32].

There have been reports of increased antibiotic resistance to ciprofloxacin in post-COVID-19 patients. 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. Another study published in 2021 found that ciprofloxacin resistance was more common in COVID-19 patients with severe disease compared to those with mild or moderate disease [25]. A study from Turkey confirms 8.7% of patients were confirmed for respiratory or circulatory tract infections via microbial culture results with *Staphylococci* species and *Acinetobacter baumannii*, and *Klebsiella pneumonia. A. baumannii*, were resistant to all antibiotics other than colistin [22].

Factors Accelerated the Emergence of Antibiotic Resistance during COVID-19 pandemic

Bacteria can acquire antibiotic resistance through mutation, horizontal gene transfer, efflux pumps, and other mechanisms which are listed in Table 2 [41-45]. These mechanisms can occur in various combinations and can lead to the emergence of antibiotic-resistant bacterial strains. The development of resistance is a complex and ongoing process, and it is important to continue to monitor and develop new strategies to combat antibiotic resistance.

The main factors which accelerated antibiotic resistance during the COVID-19 pandemic include the wide use of antibiotics as prophylaxis, prolonged and unscientific use of steroids, and overuse and misuse of antibiotics.

Antibiotic Prophylaxis and Resistance

Antibiotics were widely used during the COVID-19 pandemic as prophylaxis. Antibiotic prophylaxis, which involves the use of antibiotics to prevent infection before a medical procedure, has been associated with the development of antibiotic resistance. The overuse and misuse of antibiotics can contribute to the emergence of resistant bacterial strains, as bacteria can develop genetic mutations or acquire resistance genes through horizontal gene transfer [41]. To mitigate the risk of antibiotic resistance associated with antibiotic prophylaxis, it is important to use these drugs judiciously and only when necessary. Antibiotic use should be limited to cases in which the benefits of prophylaxis outweigh the risks, and appropriate infection prevention and control measures should also be employed to minimize the risk of infection. In addition, efforts to promote the development of new antibiotics and alternative treatments for infections can help to reduce reliance on current drugs and slow the development of resistance. Prophylaxis refers to the use of preventive measures, such as medications or procedures, to prevent the development of a disease or infection. The purpose of prophylaxis is to reduce the risk of infection or disease transmission in individuals who are at elevated risk, particularly in situations where the risk of infection or disease transmission is high.

There are several situations where prophylaxis may be necessary, including:

- Surgery: Antibiotic prophylaxis is often used before surgery to prevent infections that can occur during and after the surgery.
- Immuno compromised patients: Patients with weakened immune systems due to medical conditions, such as HIV, cancer, or organ transplantation, are at high risk of developing infections, and may require prophylactic treatment.
- Exposure to infectious agents: People who have been exposed to infectious agents, such as healthcare workers, may require prophylaxis to prevent the development of infection.
- Chronic medical conditions: People with chronic medical conditions, such as heart disease, may require prophylactic treatment to prevent complications that may arise due to their condition.

Overall, the goal of prophylaxis is to prevent the development of infections or diseases in high-risk individuals, and it is often an important part of disease management and infection control. The decision to use prophylaxis is based on individual risk factors, the severity of the disease, and the potential benefits and risks of the prophylactic treatment.

Antibiotic-resistant genes can be transferred from normal flora to pathogens which can lead to the development of antibiotic-resistant strains. Horizontal gene transfer is a mechanism by which bacteria can transfer resistant genes from one to another bacteria

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Table 2: Common antibiotic resistance mechanisms lead to resistant strains of bacteria.

Mode	Resistance Mechanisms
Mutation	Bacteria can undergo genetic mutations that enable them to resist the effects of antibiotics. This can occur through natural selection, as bacteria that are able to survive exposure to antibiotics are more likely to reproduce and pass on their resistance to their offspring.
Horizontal gene transfer	Bacteria can also get resistance genes from other bacteria through horizontal gene transfer, and it includes conjugation, transformation, and transduction.
Efflux pumps	Bacteria can use efflux pumps to expel antibiotics from their cells, reducing their effectiveness.
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.
Alteration of antibiotic targets	Bacteria can also change the targets of antibiotics, making them less susceptible to the drugs.
Biofilm formation	Bacteria can form biofilms, which can protect them from the effects of antibiotics.

through transformation, transduction, and conjugation, leading to resistance against multiple antibiotics. In contrast, bacteria can also acquire resistance to several antibiotics through the accumulation of mutations over time, which happens due to natural selection [41-45].

Steroid and Antibiotic Resistance

Steroids can have both beneficial and detrimental effects on the immune system, and their use has been associated with the development of antibiotic resistance in some cases. One of the ways in which steroids can contribute to antibiotic resistance is by suppressing the immune response and leads to bacterial infections. When the immune system is weakened, bacteria may be better able to replicate and evade the body's natural defenses, making infections more difficult to treat with antibiotics. In addition, steroids can also have direct effects on bacterial cells that can promote resistance. For example, some studies have suggested that steroids may increase the expression of genes that are involved in antibiotic resistance in certain bacterial species. Furthermore, because steroids are often used in combination with antibiotics to treat certain infections, the potential for resistance to develop may be increased. This is particularly true in cases where the antibiotic and steroid are not carefully selected and prescribed based on the specific infection and patient characteristics [46-50].

The use of steroids can contribute to antibiotic resistance, it is important to note that these drugs can also be very beneficial in certain circumstances. For example, they may be used to reduce inflammation and improve respiratory function in patients with severe respiratory illnesses, such as COVID-19. In some cases, bacterial infections can cause significant inflammation, and treatment with both antibiotics and steroids can be beneficial. For example, in severe cases of community-acquired pneumonia, treatment with both antibiotics and steroids may be necessary to reduce inflammation and combat the infection. In bacterial meningitis, steroids are often given in combination with antibiotics to reduce inflammation of the meninges and improve outcomes. While the combination of antibiotics and steroids can be effective in treating certain conditions, there are also potential risks and side effects associated with their use. Long-term use of steroids can suppress the immune system, and it can be leading to an opportunistic bacterial or fungal infection. Steroids may be given in combination with antibiotics in the treatment of severe or complicated cases of sinusitis, as they can reduce inflammation and improve outcomes [46-50].

Steroids have been shown to alter gene expression in bacteria, potentially leading to changes in antibiotic resistance. For example, a study found that dexamethasone, a type of steroid, increased the expression of genes associated with resistance to the antibiotic tetracycline in E. coli bacteria. Efflux pumps are transporters that can pump antibiotics out of bacterial cells, reducing their effectiveness [47-49]. Some studies suggest that steroids can induce the expression of efflux pumps, making it more difficult for antibiotics to kill the bacteria. Some steroids, such as prednisolone, have been shown to interfere with the mechanisms by which antibiotics kill bacteria, making them less effective [49]. Overuse of Dexamethasone, a type of glucocorticoid steroid could be one of the main reasons for post-COVID-19 bacterial pneumonia and fungal infections [48].

Overuse and misuse of Antibiotics

The overuse and misuse of antibiotics are one of the main factors contributing to the development of antibiotic resistance. When antibiotics are used inappropriately, such as for viral infections or for conditions that do not require antibiotics, this can contribute to the development of resistance [41]. In addition, antibiotics can disrupt the normal bacterial flora in the body, leading to an overgrowth of antibiotic-resistant bacteria or other pathogens. Therefore, it is important to use antibiotics judiciously and only when they are necessary to treat a bacterial infection.

Antibiotics target specific structures or processes unique to bacteria, such as cell walls or protein synthesis. Viruses, on the other hand, do not have these structures, and they rely on host cells to replicate. Therefore, antibiotics are not effective in treating viral infections such as the common cold, influenza, or COVID-19. However, in some cases, individuals with viral infections may also develop bacterial infections, either as a secondary infection or as a co-infection. In these cases, antibiotics may be necessary to treat the bacterial infection. The widespread use of antibiotics in humans and livestock has contributed to the development of antibiotic resistance in both animals and humans.

The incomplete course of antibiotic treatment can contribute to the development of antibiotic resistance in a few different ways. When antibiotics are not taken for the full prescribed duration, they may not eliminate the target bacteria, allowing some to survive and potentially develop resistance to the antibiotic. These surviving bacteria can then spread and cause recurrent or persistent infections that may be more difficult to treat [41].

Long-term antibiotic use can contribute to the development of antibiotic resistance in several ways. When antibiotics are used over a prolonged period, they can promote the survival and proliferation

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of bacteria that have acquired resistance mechanisms, leading to the emergence of resistant strains. Long-term antibiotic use can also disrupt the normal balance of microbial communities in the body, including the gut microbiota. This can lead to the overgrowth of opportunistic pathogens and colonization by antibiotic-resistant bacteria, which can contribute to the development of antibiotic-resistant infections. Evidence suggests that long-term antibiotic use can lead to the accumulation of resistance genes in microbial populations, which can then be transferred to other bacterial species, including potential pathogens [41-45].

MIC Studies on Bacterial isolates from COVID-19 Patients

A study published in the Journal of Global Antimicrobial Resistance in June 2021 evaluated the susceptibility patterns of bacteria isolated from patients with COVID-19 in a hospital in India. The study found that the most common bacterial pathogens were *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* and that they showed high levels of resistance to several antibiotics, including carbapenems, 3rd generation cephalosporins, and fluoroquinolones [32,51]. The study highlights the importance of antibiotic stewardship programs to prevent the emergence of antibiotic resistance.

Another study published in the Journal of Medical Microbiology in July 2021 evaluated the MIC values of antibiotics against bacterial pathogens isolated from COVID-19 patients in a hospital in Poland. The study found that the most common pathogens were *Klebsiella pneumoniae* and *Staphylococcus aureus* and that they exhibited high levels of resistance to several antibiotics, including carbapenems and fluoroquinolones [44]. The study also found that the MIC values for several antibiotics increased during the pandemic, highlighting the need for surveillance, and monitoring of antibiotic resistance during this time. A study published in the journal Lancet Infectious Diseases in January 2022 reported the emergence of high-level resistance to carbapenems in *Enterobacterales* bacteria in a hospital in China [18]. Another study published in the journal Clinical Infectious Diseases in March 2022 found that prolonged courses of antibiotics were associated with increased rates of antibiotic resistance in patients with bloodstream infections caused by *Enterobacterales* [19].

A comparative study on MIC (minimum inhibitory concentration) values for antibiotics in the pre-COVID-19 and post-COVID-19 periods published in the Journal of Global Antimicrobial Resistance in August 2021 evaluated the antibiotic susceptibility patterns of bacterial isolates from patients with COVID-19 in Pakistan and compared them to a historical control group of bacterial isolates obtained from patients without COVID-19 in the same hospital. The study found that the isolates from patients with COVID-19 had higher rates of resistance to multiple antibiotics, including azithromycin, ceftriaxone, and meropenem, compared to the control group [39].

Figure 3: An automated MIC analyzer (Vitek 2, bioMerieux), used for the *in-vitro* studies of antibiotics.

Another study published in the Journal of Medical Microbiology in December 2021 evaluated the antibiotic susceptibility patterns of bacterial isolates from patients with COVID-19 in the United Kingdom and compared them to isolates obtained from patients without COVID-19 at the same time. The study found that the isolates from patients with COVID-19 had similar rates of antibiotic resistance to the control group. Still, there were differences in the distribution of resistance patterns, with higher rates of resistance to certain antibiotics such as ceftriaxone and azithromycin in the COVID-19 group [52]. 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. However, the specific patterns of resistance may vary depending on the geographic region, patient population, and other factors. There are various automated MIC analyzers available that provide most of the results within 12-18 hours, and a preliminary results can obtained after 4 hours of incoculation (Figure 3).

Antibiotic resistance is a growing concern in modern medicine, and the treatment of patients with antibiotic-resistant strains requires a careful and individualized approach. The choice of modality will depend on the severity of the infection, the patient's overall health, and the specific characteristics of the antibiotic-resistant strain. In general, the first step in treating a patient with an antibiotic-resistant strain is to obtain a culture and sensitivity or MIC test to determine the specific type of bacteria causing the infection and the most effective antibiotics to treat it. Once this information is available, the healthcare provider can decide on the best modality for treatment.

Possible modalities for patients with antibiotic-resistant strains may include:

- Alternative antibiotics: MIC will provide the best option of the alternate administration of antibiotics available that are effective against the resistant strain. 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: This includes non-antibiotic therapies used to treat infections caused by antibiotic-resistant strains. These may include phage therapy, which uses

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viruses to target and kill specific bacteria, or immunotherapy, which involves using the body's immune system to fight the infection.

- 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: The response to treatment should evaluate with total WBC count, C-Reactive Protein (CRP): and Procalcitonin (PCT).

The choice of modality will depend on the specific circumstances of the patient's infection and the characteristics of the antibiotic-resistant strain. Preventing hospital-associated infections and antibiotic resistance in healthcare facilities requires 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.

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.

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