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Update on pleiotropic immunologic and potential antiviral effects of antibiotics and their clinical impact

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SUMMARY

While antibiotics are widely used as antimicrobial agents for treating a variety of bacterial infections, it has been reported that a majority of them also exert antiviral, anti-inflammatory, immunomodulatory, and antioxidant activities that may a significant role in alleviating many clinical disorders such as severe acute respiratory syndrome coronavirus 2 (SAR-SCoV-2). Interestingly, literature mentioned that macrolide antibiotics (e.g., azithromycin) significantly reduce viral replication, downregulate the inflammatory cascade and excessive cytokine production, and decrease mortality. In the same line, fluoroquinolones as moxifloxacin and ciprofloxacin suppress COVID-19 replication, overproduction of nitric oxide in the lungs besides inhibiting inflammatory cell responses. Similarly, various antibiotics, such as doxycycline, clarithromycin, ceftriaxone, amoxicillin, amoxicillin-clavulanic acid, ampicillin, gentamicin, benzylpenicillin, piperacillin/tazobactam, ciprofloxacin, ceftazidime, cefepime, vancomycin, meropenem, and cefuroxime among others, were recommended for use in the management of COVID-19 owing to their pleiotropic activities. The current review illustrates the potential immunologic activities beyond the antibacterial effect of different antibiotics in clinical practice from the pharmacological point of view.

Keywords: Antibiotic; Macrolides; COVID-19; Pleiotropic data

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INTRODUCTION

Antibiotics are now widely prescribed in various protocols for treating COVID-19 infections, especially in severe cases. The data in the literature about the antiviral role of these antibiotics are greatly contradictory. Despite their known adverse effects on patients' health, physicians usually take into consideration the benefits versus risks ratio and insist on using them in therapeutic protocols during viral infections. Piperacillin/tazobactam, meropenem, and co-amoxiclav drugs were used mainly in critical care units for COVID patients [1-3]. there should be good management while using antibiotics to prevent superinfection and resistance [4]. Moreover, physicians should always consider that a virus may be a superinfection [5]. Despite the use of doxycycline as an antiviral drug, there are some contraindications between published researches on whether or not this drug is causing serious side effects such as esophagitis, ulceration, and resistance to the drug [6]. Azithromycin was found to be effective against COVID-19 due to its antiviral and immunomodulating properties, such as decreasing the viral load and release, as well as preventing lung fibrosis so it is helpful in the treatment journey [7-9]. Many virally ill patients are taking cefepime for the claims that it has antiviral effects although when influenza A study was conducted, it proved otherwise, so more researches are needed for this drug [10]. Ceftazidime shows antiviral activity against COVID-19 so it should be considered as the first drug of choice according to Chang Dong et al [11]. Although fluoroquinolones have antiviral effects and showed effectiveness against CMV, VZV, HSV-1, HSV-2, HCV, and HIV, their side effects are wild and serious since they affect the nervous system, tendons, and joints [12-13]. However, other researchers state that some types of them are the best antibiotics to be used for COVID due to their pharmacokinetic profile [12]. A study aimed to measure the changes and patterns of national antimicrobial use for one year preceding and one year during the COVID-19 pandemic in Jordan reported that there was an increase in the use of several antibiotics during 2020 compared with 2019. Third-generation cephalosporins, carbapenems, macrolides, and lincosamides are the most frequently used drug and cephalosporins the least. In 2020 there was a marked reduction in amoxicillin and on the other hand, the use of azithromycin highly increased. Moreover, there was an increase in using hydroxychloroquine in 2020 compared with 2019 [14]. Based on the aforementioned

data, it is obvious that most available antibiotics have significant activities notably potential antiviral effects. The current review highlights the different possible antiviral mechanisms that lead to their potential clinical use in COVID-19 outbreaks and focuses on the current status protocols used in Jordan compared with those worldwide.

B-LACTAMS: BEYOND ANTIBACTERIAL EFFECTS

Antibiotics may be prescribed for patients with COVID-19 due to confirmed superinfection with bacteria. Among patients in the intensive care unit (ICU), Piperacillin/tazobactam was the most commonly used antibiotic [1]. Many antibiotics are recommended for COVID-19 management, such as piperacillin/tazobactam. However, there should be wisdom while using antibiotics to prevent their evolution in having antimicrobial properties and thereby becoming inefficient [4]. A case report talked about an old man diagnosed with end-stage renal disease (ESRD) on hemodialysis, influenza A and COVID-19 as a co-infection. He was experiencing worsening flu-like symptoms, including fever of up to 38.6°C, non-productive cough, generalized abdominal pain, nausea, vomiting, and liquid green diarrhea. He started taking oseltamivir for influenza and vancomycin/cefepime for the probable bacterial cause of his pneumonia and diarrhea. This patient had a superinfection of COVID-19, so the probability of the patient having COVID should not fail to be noticed by the physicians, even when other viruses are causing the symptoms like influenza in this case [5]. Liu C, et al. [2] made a comparison between the suspected bacterial infection patients and patients without bacterial infection but with COVID-19, the risk factors of mortality and the incidence of acute organ injury were analyzed. The suspected bacterial infection group had more severely ill patients, more deaths, and more acute organ injuries. The death rate increased in suspected bacterial infection patients taking intravenous moxifloxacin and meropenem, while oral antibiotics reduced mortality in this group. In addition to that, the mortality of the patients without bacterial infection also increased due to penicillin and meropenem. Suspected bacterial infection patients had negative clinical outcomes compared to patients without bacterial infection. Antibiotics were associated with an increased risk for acute organ injury in hospitalized patients with COVID-19. Antibiotics were useless for most patients and correlated with an increase in deaths. The real use of antibiotics failed to give the expected results. A comprehensive antimicrobial plan and guidelines should be applied in the time of COVID-19 [2]. There is a study that included a comparison between COVID-19 positive and negative patients and patients on non-critical care and critical care units. COVID-19 has been a challenge for antibacterial stewardship due to bacterial co-infection, which caused recommendations for suspected bacterial respiratory tract infection complicating COVID-19. In non-critical care wards, amoxicillin, doxycycline, and co-amoxiclav accounted for over half of all antibiotics. Moreover, meropenem, piperacillin-tazobactam, and co-amoxiclav accounted for approximately half prescribed in critical care. Systemic antifungals were prescribed in 9.8% of critical care patients. In non-critical care units, COVID-19 hospitalized patients had a low proportion of broad-spectrum antibiotics as well as a low prevalence of antibiotic prescribing. On the other hand, in the critical care unit, broad-spectrum antibiotics and antifungal prescribing was observed indicating the importance of infection prevention and control and stewardship initiatives in this setting [3]. Amoxicillin/Clavulanic acid was prescribed for pneumonia-like lower airway symptoms and persisted for 14 days. A high-flow nasal cannula (HFNC) was initiated as respiratory supportive therapy and was instrumental in the clinical recovery of the patient after seven days, proving its efficacy as a successful treatment for respiratory support in a patient with active pneumonia from COVID-19 [15]. Even though cefepime is a proven- food and drug administration (FDA) antibacterial drug, sometimes it exhibits some antiviral activity. A study was made to explore new drugs related to the treatment of influenza A virus endonuclease protein, one of these drugs was cefepime which exhibited the best interactions with the influenza A virus endonuclease protein but eventually, the testing showed no antiviral activity because it showed no reduction in the viral plaque numbers, but further studies are needed to prove this in vitro study [10]. A case report of a 51 years old man with several diseases along with COVID-19 was administering cefepime because it can decrease secondary bacterial infections but not the COVID-19 itself so more studies are needed to discover the relation between antibiotics and COVID-19 [16]. In another case report of a 78 years old man who was diagnosed with urinary tract infection and COVID-19 along with other diseases, the patient has been told to take cefepime, but it appeared that there was no effect on the virus and it only reduced the infection of the urinary tract [17]. Research by Chang Dong, et al showed that ceftazidime is the best potential inhibitor for the COVID-19 since it mainly needs to bind to the ACE2 found on the surface of the host cell to enter and fuse with the cell. It inhibits the interaction of ACE2 with the viral spikes of COVID-19 (spike receptor-binding domain), so ceftazidime can be thought of as an antibacterial and antiviral effect and should be considered as a first-line antibiotic for COVID-19 treatment. Also, it showed negligible cytotoxicity even at high concentrations, indicating its safety for clinical usage [11].

PLEIOTROPIC EFFECTS OF MACROLIDE ANTIBIOTICS

Macrolides have anti-inflammatory and immunomodulating actions in addition to their antibacterial effects, so these properties may ensure the efficacy of macrolides in respiratory viral infections especially there is much data showed that the macrolides reduced the receptors of viruses, excessive cytokines production, and virus replication as well as downregulated the inflammatory cascade **(Fig.1)**. Additionally, they

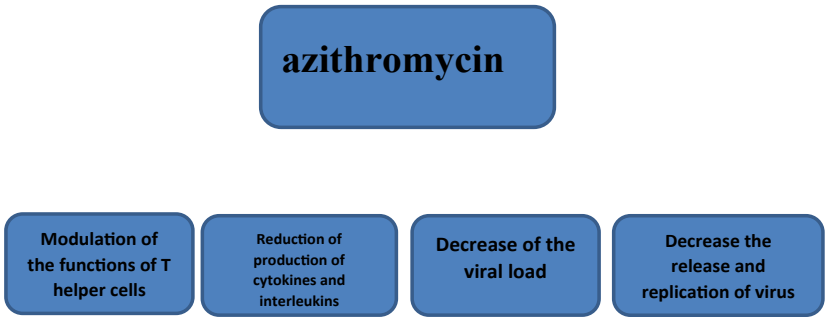

Fig. 1. Macrolides immunologic and antiviral effects.

may reduce the exacerbation of the virus [18]. There are different types of macrolides such as azithromycin which has been proposed as a potential treatment due to immunomodulating and antiviral properties as there are vitro studies have demonstrated the capacity of azithromycin in reducing the production of pro-inflammatory cytokines such as interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis factor α (TNF α), reducing the oxidative stress and modulating the functions of T helper cells [7]. CD147 is a receptor of COVID-19 on host cells and it is a novel route for COVID-19 invasion, but the azithromycin may be beneficial in reducing the viral load of hospitalized patients by interfering with ligand/CD147 receptor interactions, may decrease the expression of some metalloproteinases which are downstream to CD147 and may decrease the viral replication and release [8]. Azithromycin maintains epithelial cell integrity or prevents lung fibrosis so it can be beneficial in COVID-19 treatment [9]. Azithromycin prevents COVID-19 infection by raising the levels of interferons and interferon-stimulated proteins which helps in reducing the replication and releasing of the virus [19]. Perhaps, azithromycin antiviral effects result from interfering with receptor-mediated binding, viral lysosomal escape, intracellular cell-signaling pathways, and enhancing type I, III interferon expression [20]. It is proposed as a medication for COVID-19 in association with hydroxychloroquine or chloroquine [21]. A multi-center retrospective observational study in the United States of consecutive patients hospitalized with a COVID-19 has reported that the treatment with hydroxychloroquine alone significantly decreased the mortality, and hydroxychloroquine in combination with azithromycin exhibited a highly significant decrease in mortality [22].

A French study has reported that 100% of patients treated with a combination of hydroxychloroquine and azithromycin were virologically cured compared to 57.1% of patients treated with hydroxychloroquine only, and 12.5% in the control group at day 6 post-inclusion [23]. On the other hand, there must be caution in using the combination of azithromycin and hydroxychloroquine due to the potential cardiac harm, especially in more fragile patients such as those with cardiovascular disease or prolonged QTc [7]. More recent evidence has raised serious safety concerns on the use the azithromycin with hydroxychloroquine or chloroquine in COVID-19 treatment because all these drugs have a role in arrhythmia [21]. Recent evidence suggests that this toxicity may be related to hydroxychloroquine [9]. Egyptian randomized trial of patients with mild COVID-19 aims to testify whether adding azithromycin or clarithromycin to a standard of care regimen was superior to standard of supportive care alone in those patients who received only symptomatic treatment for control of cough and fever. The results of this trial have shown a signifcant early improvement of symptoms (fever, dyspnea, and cough) as well as significant early conversion of COVID-19 polymerase chain reaction (PCR) to negative in patients who treated with either azithromycin or clarithromycin compared who standardly cured. Using azithromycin and clarithromycin in mild COVID-19 could be effective in early control of fever and PCR negative conversion, but the safety and efficacy of macrolides and their conjunction with other therapy modalities need more research [24]. The empirical practice of azithromycin in COVID-19 treatment did not show good quality in clinical data.

USE OF TETRACYCLINE IN COVID INFECTIONS

Doxycycline works as antiviral, anti-inflammatory, immunomodulatory drug [25]. It also has a great efficacy by inhibiting matrix metalloproteinases (MMP) which was leading to damage to the base plate and increased vascular permeability and as a result used to prevent lung damage, alongside reducing pro-inflammatory cytokines in addition to interleukin-6 [26]. Although there is a study that proves that there are no side effects of doxycycline [27]. New research has emerged showing its effects and negative aspects in the long run such as a decrease in the body's ability to absorb it when it is taken with antacid and iron tablets. It also can cause esophagitis, ulceration and the reuse of doxycycline in COVID-19 is a major driver of antimicrobial resistance [6]. Another study was conducted in New York on patients who were given doxycycline in the early stage of treatment to assess fever, shortness of breath, cough, and oxygen saturation/oxidative stress, the study showed the importance of using doxycycline in patients to recover from the fever, cough, and shortness of breath also it is associated with improved clinical outcome, reduced hospitalization and decrease mortality [25]. In clinical research that was carried out in Pakistan, it is found that doxycycline is effective in reducing the symptoms of COVID-19 and increasing body desire for recovery and healing process in patients [28]. In addition to the

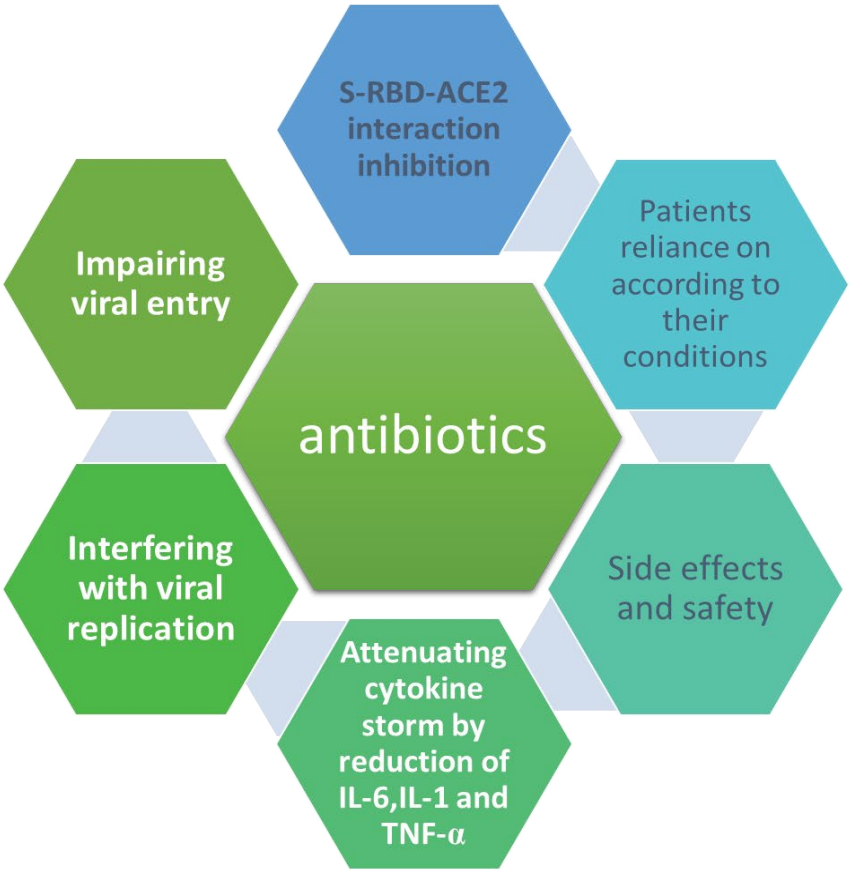

Fig. 2. Pleitropic effects of antibiotics in viral infections.

effectiveness and importance of doxycycline as a single drug, it has also proven its significance as a combination therapy with other agents, such as the study that was conducted on the efficacy of ivermectin with doxycycline for patients with mild to moderate COVID-19, the treatment was randomized and placebo-controlled for infected patients, the results showed that patients with COVID-19 infections who received the aforementioned combination, recovered earlier and had negative results for COVID-19 than those who received placebo treatment [29]. In another randomized trial that has been clinically tested in Indonesia, the patients who received lopinavir/ritonavir and doxycycline increased in the c-reactive protein (CRP) and IL-6 and significantly reduced IL-10 and TNF-a levels [30]. COVID-19 can cause a variety of neurological manifestations which may vary in severity, one of the symptoms that cause is meningitis and doctors managed the disease pharmacologically by using intravenous amoxicillin and ceftriaxone to treat bacterial meningitis in a 70-years old female patient [31]. An experimental study reported that imipenem is the most widely used antibiotic in the intensive care unit (ICU) for an average duration of 3 weeks [32].

EMERGING BENEFITS OF FLUOROQUINOLONES IN VIRAL INFECTIONS

Fluoroquinolones may have antiviral actions against vaccinia virus, papovavirus, CMV, VZV, HSV-1, HSV-2, HCV and HIV, ciprofloxacin and moxifloxacin may exhibit some replication inhibitory action by binding to its main protease significantly than chloroquine and nelfinavir. Noteworthy, levofloxacin and moxifloxacin are just like ceftazidime that can be thought of as first-line therapeutic agents for the management of severe community-acquired pneumonia [12]. In contrast with FDA in 2018, Irene Karampela and maria dalamaga said that fluoroquinolones, especially levofloxacin and moxifloxacin, are considered to be the best drug out of all antibiotics because of their good pharmacokinetic profile, increased concentration in the lungs, and excellent safety profile compared with other antibiotics such as b-lactams and macrolides [12]. Ciprofloxacin and moxifloxacin exert a strong capacity for binding to COVID-19 Main protease and bind to the protein active site more strongly than the native ligand. This indicates the basis for a possible new strategy of COVID-19 treatment and ciprofloxacin and moxifloxacin repositioning to treat COVID-19 infection, but more studies are needed to clarify their efficacy [33]. In a study where the potency and cellular toxicity of four fluoroquinolones (enoxacin, ciprofloxacin, levofloxacin, and moxifloxacin) were assessed in Vero cells and A549 cells engineered to overexpress ACE2, the COVID-19 entry receptor, the results showed that all four fluoroquinolones suppressed COVID-19 replication at a high micromolar concentration in both cell types. On another hand, they concluded that Fluoroquinolones are not ideal antiviral candidates for COVID-19 treatment because the potency of them while they suppressed the virus replication was low and there was minimal cellular toxicity following treatment with them [34]. A case report with moxifloxacin

treatment for COVID-19 positive-tested patient, the patient showed after 8 days of IV injection of 400 mg of moxifloxacin an obvious reduction of symptoms and recovered from COVID-19 [35]. another case report with COVID-19 showed also after treatment with the same dose of moxifloxacin with the latter case report, the patient showed a marked clinical and radiological improvement after several days of moxifloxacin treatment [36]. The side effects of fluoroquinolones make them the last choice out of all other antibiotics to treat infections or viruses which include potential or permanent disabling in tendons, joints, nerves, and central nervous system as mentioned by the FDA in 2018 [13].

DISCUSSION AND CONCLUSION

Beyond its antibacterial activities, different antibiotics elicit pleiotropic effects that have the potential to be of great benefit in the clinical treatment of viral infection e.g. COVID-19-induced pneumonia or lung injury preceding event of secondary infections by bacteria. Impairing viral entry, interfering with viral replication, attenuating cytokine storm by reduction of interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-α and other combating oxidative stress; explain the potential efficacy of antibiotics in the management of severe cases of viral infections **(Fig.2).** More experimental studies and randomized clinical trials are needed for investigating their role in reducing mortality and improving clinical outcomes

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

DATA AVAILABILITY

All data generated or analyzed during study are included in this review.

AUTHORS CONTRIBUTION

RHT, the corresponding author, has the major contribution in designing, coordinating the duties of each co-author and edited the final version the manuscript. SMMBA, searching in literature about macrolides update pleiotropic activities; HHND, help in designing figures and searching about beta lactam antibiotics; AZIB, help in searching about tetracyclines and fluoroquinolones; MRMT, help in writing manuscript; EMW, help in revising manuscript linguistically. All authors read and approved the final manuscript.

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