"Antibiotic Misuse during COVID-19 Pandemic: Review Study"

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Abstract

The beginning of the year 2019 has changed the face of the world as it was noticeable emergence of Corona Virus disease (COVID-19). This virus has spread to cover almost all the nations of the world as well as, and has paralyzed every sector even detailed life of people whom have been required compulsory to stay at home in incarceration. There have been a lot of studies that have required to investigate the effect of this pandemic from different standpoints, and to analyze the medications being applied especially the misuse of antibiotics of different categories, and which have been although many studies found that weak managing of the antibiotic and misusing it has resulted into catastrophic results ,as ensured many researchers throughout the world. Thus the WHO has informed the governments that misuse of the antibiotic might be like "pouring the oil on the fire" ,and there is a prerequisite to get antibiotic use to be managed well according to the results that this review has reached by studying several reports and studies carried out by distinguished researchers throughout the globe, and to investigate how using antibiotic to effectively be governed. However, this study will pay attention to how the antibiotic has been misused during the pandemic in many countries. The objective of this review is to learn more about researches carried out on the misuse of antibiotic during the COVID-19 pandemic.

Keywords: *antibiotic, severity, misuse, prescribed, Covid-19.*

Introduction

During the sudden break out of COVID- 19 ,the world`s nations has been gone through critical situations at all levels : economically, socially culturally and medically which has resulted in random search for immediate cure for the pandemic of COVID -19 virus that harvested millions of people around the world ,and spread panic globally as well. Thus, most of the countries have begun to intensively use the available drugs to stop the amplification of the pandemic. Therefore, the use of antibiotics as thought to be a sole solution to increase the immunity systems and strengthening the defensive shields of the infected people. However, the results have been vis versa and catastrophic due to the misuse of the antibiotics that their use has increased the health problems causing extreme deaths amongst hundreds of thousands of people. The WHO has issued lots of reports stating that due to the critical challenge in the health systems, most countries misuse of antibiotics for treating the "secondary bacterial infections", and this resulted in deaths of over" seven hundred thousand deaths worldwide annually (1). Similarly, A report issued in 2018, by the American Infectious Diseases Society of, which argued that there have been no actual "data to support the safety or efficacy of antibiotic chemoprophylaxis to prevent bacterial complications (2). In addition, the Chinese National Health Commission (CNHC) declared, in its guidelines which issued during the break out of the Covid-19 pandemic, that "inappropriate or blind use of antibiotic drugs should be avoided, in particular broad- spectrum antibiotics (2, 3). However, in this review the researchers intend to report studies` outcomes as well as information concerning the hazardous misuse of antibiotics in treating and dealing with complications of COVID-19pandemic.

The widespread use of antibiotics in treatment since there has been a believe that Covid-19 can accelerate the secondary bacterial infections, and so the intervention of antibiotics is necessary in this stage (4). For example, lots of hospitals in the USA as a study revealed that, over "56.6%" patients were prescribed early empiric antibacterial therapy, of which only 3.5% were designated to have bacterial infection (3). Two systematic studies found that among the patients included in the study report, 71% received antibiotic treatment and 14.3% had secondary bacterial infections (5). In the target study, the number of COVID-19 patients with co-infection or secondary infection is relatively small, which is reliable compared with the results of other studies. For example, in Italy, of the 16,650 patients who died of COVID-19, only 11% were told to have a secondary bacterial infection (6).

Overall, the pandemic could accelerate the threat of antimicrobial resistance due to increased use of antibiotics, increased disclosure in hospitals and the insidious methods used to treat COVID-19, while evidence of benefits of antimicrobial use in these patients is limited. Many antimicrobial resistance specialists have raised concerns about the safety of antibiotic use in COVID-19 patients and have called for intensified antimicrobial stewardship (AMS) programs around the time of COVID-19. For example, increasing the use of experiential antibiotic therapy increases the risk of "Clostridioides difficile infection in COVID19 patients and emergence of multidrug resistant organisms" (7).

WHO instruction has been clearly recommended that no usage of antibiotics prophylaxis or therapy for those patients who have moderate or mild Covid-19 except in cases prove the existence of "symptoms of bacterial infections". Thus, the emergence round the usage of antimicrobials in COVID-19 patients is to be controlled effectually. Daily assessment of patients who suffer from severe Covid-19 is needed for monitoring the escalation of "antibacterial treatment" is also to be followed as recommended. The use of antibiotics is to be planned well in use and categorized not randomly, but in a way as permitted by WHO which has put an access list of medicines like for example: "co-amoxicillin" (8).

In March 2021, the National Institute for Health and Care Excellence (NICE) in the UK established hasty principles on administering COVID19 which provide the following recommendations from the agreement such as: "Do not use antibiotics to prevent or cure COVID-19; only use antibiotics if you have a strong clinical suspicion of additional

bacterial infection"(7, 8). Other rules such as those of the Dutch Antibiotics Policy Working Group and the Scottish Group on Prescribing antimicrobials both recommend avoiding routine use of antibiotics by suspecting the existence of COVID19. On the other hand, there should be further studies to offer more eligible evidences for the advantages and disadvantages of using antibiotics for patients suffer from Covid-19. Also, reassessment of types of antibiotics are required to offer more guidelines for "antimicrobial stewardships" in patients of Covid-19 (7).

Methods

In order to carry out this systematic review, the researchers carried out numerous studies and analyzed them to obtain an adequate and organized structure of the review. The bibliography was searched in Web of Science (WOS) databases, using the keywords: "COVID19" and "antibiotic abuse". The criteria that were established for the selection of the study were focusing on use of antibiotic for treatment from COVID-19, papers relating COVID-19 and antibiotic use, and studies analyzing the negative results of the misuse of antibiotic as noticed by the studies, and other related issues as well. Thus, in general the review followed the following dimensions of methods to attain the purposes of the review study.

Selection benchmarks and search study

Inclusion measures were journal articles and other clinical reporting studies on misuse treatment of Covid-19 patients with antibiotics. Case reports, non-clinical studies, reports on coronavirus other than the misuse of antibiotics in treating coronavirus-19 were excluded from the review. Besides, studies for which data about were scarce in revealing the misuse of antibiotic in treatment of the pandemic were as well excluded. The sources of information that were used in this review focused primarily on the searching through Google, in particular, Web of Science (WOS) using the terminologies:" COVID-19 Pandemic and misuse of antibiotic" and selected about 15 studies as per the including researchers standards to be engrossed in this review from different accredited scientific websites.

This research retrieved many records and studies, and this was done after the researchers had eliminated the non- journal articles from the research outcomes. A lot of studies have been reviewed to ensure their eligibility to the topic of this review, as well as to guarantee the compliance of the selected studies and articles with annexation criteria.

Studied variables

The following features were extracted from every study: country where the study was conducted, number of patients, percentage of chronic sicknesses (such as hypertension, diabetes, cardio-vascular illness, pulmonary disease, etc.) as reported in each study, proportion of severe cases, death rate, rate of antibiotic use, rate and type of secondary and co-infection, types of antibiotics used, duration of antibiotic treatment, as well as rate of use of glucocorticoids and antiviral.

Results

Amounts of Antibiotic Used

A total of over fifteen manuscripts related to the antibiotic and its impacts on patients who suffer from respiratory problems due to COVID-19, and the mismanagement as well as the misuse of the antibiotic in many countries as most of the studies found that antibiotics have been used in arbitrary and unmeasured way without any eligible evidences about the positive impacts of most antibiotics on patients. On the contrary, it has been found that most antibiotics have reversed side effects on patients causing lots of deaths round the world especially in Africa as well as India, China, Brazil, USA, Denmark.

The table below illustrated the amounts of proportions of antibiotic being used in different countries as stated by different studies. The majority of studies were gathered from Chinese professionals in medical field around 9 studies, one study from the United States of America, another study from Brazil and a study from Denmark, ten African countries Besides, the table designated the severity of disease and death levels in these countries. (Table. 1). Data gathered from the different selected studies concerning patients'

physiognomies and modality of antibiotics used in different countries.

Discussion

The School of Medicine and Pharmaceutical Technology in Washington University, USA (2021) stated that the antibiotics` sales have been notably showed an increase throughout the COVID wave ,and so lots of countries ,in particular in the developing countries used antibiotics intensively to cure COVID patients .However, the use of such antibiotics as it seemed was not effective as it only targeted the " bacterial infections" and not the virus itself. This resulted in misuse of antibiotics, and also to be considered as a real "threat to "drugs resistant at the global level."

Bacterial disease specialist Dr Sumath Gundra of the University of Washington said, "Excessive use of antibiotics minimizes the ability to effectively treat minor injuries in common infections such as pneumonia". Thus, such thing will provide an indication that like these situations are to be very risky as well as fatal for patients who have Covid-19 virus. Thus , it is necessary to designate that antibiotic resistance will be a real threat for the public health .Similarly, reports by WHO reported that the " drug- resistant diseases" has the ability to end the live of ABOUT 700,000 people annually ,and this as being estimated to cause devastation to the international health. Besides, the report indicated very frightening results as over 230,00 people will die due to taking "multidrug-resistant tuberculosis" (1, 8).

In India, over 70% of health care is private, and so it compels to "unregulated use of over 90% of antibiotic consumption." So, such misuse will be worrying as well as frightening since the probable impacts of Covid-19 on prescribing and administration practices. Most of people in particular, in the developing countries receive antibiotics as the false supposition in the patients as well as medical staffs who are inexperienced that Covid-19 is bacterial illness as reported School of Medicine and Pharmaceutical Technology in Washington. Besides, WHO stated that the wave of Covid-19 had resulted in India only the contribution of 216.4 million doses of the total antibiotics as well as over 38 million excess doses of azithromycin for 4

months during the zenith of the COVID-19 epidemic wave (8).

As the number of people with COVID-19 continues to rise globally, the widespread use of antibiotics to treat patients with COVID-19 and its latent consequences for AMR are of growing concern. Moreover, In their study , which aimed to carry out a quick assessment of national treatment procedures for COVID-19 in ten African countries, and examined its insinuation for antimicrobial resistance rejoinder on African countries in general, Adebisi et al., argue that in spite of the warnings released by the WHO concerns and recommendations that the therapy of antibiotic is not to be used for the patients who got moderate or mild COVID-19 except in case it is justified well, some (9).

African nations still use the antibiotics for " mild or moderate COVID-19",and this may increase the worries of anti-bacterial resistance" as it is considered a hidden "threat prowling behind the COVID-19 pandemic that has caused the deaths of thousands of Africans preceding the appearance of the worldwide outbreak ,"say the researchers. The study revealed that several types of antibiotics have been recommended to be used in the African countries where the study was conducted to manage COVID-19, and these embedded by ceftazidime, amoxicillin-clavulanic acid, azithromycin, clarithromycin, erythromycin, amoxicillin and other categories of antibiotics (9). In addition, our integrated studies make patient data available in hospitals; this was not a standard for inclusion, however none of the studies identified presented data on outpatients (eg, home care patients, patients in the community or treated on an outpatient basis).

The summary of data from the many studies included in this review shows that approximately "82.3% of hospitalized COVID-19 patients were prescribed antibiotics, while the antibiotic prescription rates of COVID-19 patients were almost 100% in the first clinical reports of COVID19 patients. Wuhan Hospitals (10) Doctors are expected to use to administer antibiotics almost around the world to treat this unidentified respiratory infection at the start of the pandemic; the use of antibiotics is expected to decrease with increasing knowledge of

the COVID-19. More surprisingly, the level of prescription of antibiotics does not differ with the severity of the disease (75.4% in critically or critically ill patients versus 75.1% in mild or moderate patients) The use of antibiotics may be reasonably accepted in the management of patients with COVID-19 suspected "bacterial co-infections and severe / critically ill patients" with an increased risk of developing bacterial co-infections due to long hospital stay or immune suppression (8, 10).

However, the elevated prescriptions of antibiotics for moderate as well as mild Covid-19 patients was estimated by around 51% of the persons given antibiotics proposes further haphazard use in the nonattendance of clinical evidence for potential bacterial co-infection. Antibiotic prescribing for mild and moderate COVID-19 patients is inconsistent with WHO Covid-19 outlines (8).

What is more, the antimicrobials that are found to have been most regularly prescribed in different studies in this review were (azithromycin, ceftriaxone, moxifloxacin, meropenem, piperacillin/tazobactam),and all of these are all being categorized as seriously imperative antimicrobials (CIA) for human medicine (2) importunate employ of these decisively vital antibiotics will incite the emergence of MDR strains and a turn down in the efficiency of these compounds (9) The effect of extensive use of ceftriaxone on advancement of resistance to third generation cephalosporins amongst clinical injuries of "Enterobacteriaceae" and other non-enteric bacteria is before now well known (11-13). If resistance to "azithromycin, ceftriaxone," and other broad-spectrum antibiotics turns out to be spread widely due to their enormous usage throughout the pandemic, there, definitely, would be a few alternative antibiotics obtainable in the market and these options antibiotics are expected to be unaffordable for the majority of patients, in particular for patients from the developing countries.

Several studies stated that most of patients who got the pandemic`s first phase was prescribed and explored the effect of documented antibiotic prescribing on treatment outcomes in COVID-19 patients. The results showed that a huge number of antibiotics were prescribed for patients with

moderate and mild Covid-19, with "41.9%" and regardless to the pandemic`s severity. However, the findings revealed that antibiotics were not beneficial to those effected by Covid-19 patients without any clinical proofs of "bacterial co-infection".

According to patient's mortality, a lot of studies have showed that most of the patients with Covid-19 whom were given antibiotics, the mortality was higher for the patients given antibiotics compared to those who were not given the antibiotics that is (26.5% vs. 2.3). WHO instructions have been clear as the organization has recommended "no antibiotic therapy or prophylaxis for patients with mild or moderate COVID-19 except indications and "symptoms of a bacterial infection exist."

A study by Alejandro et al., examined the use of antibiotics in patients admitted to the hospital due to "SARS-CoV-2 infection "(14). The method the study`s work employed was to analyse the use and efficiency of antibiotics in hospitalized patients with COVID-19 based on data from the SEMI-COVID-19 archive, an initiative to engender acquaintance about this disease by means of data from electronic medical records. The researcher's chief goal was all-cause in-hospital mortality rendering to antibiotic usage. However, the study`s secondary aim was the" effect of macrolides on mortality. "The findings of the study were astonishing as the rate of deaths among the patients who took antibiotic was about "20.7", so such result ensures that high mortality was detected with the misusage of antibiotic. According to the study the choice to start antibiotics was prejudiced by existence of augmented "provocative indicators and any thoughtful of subvert on an x-ray. "Furthermore, the results of the study revealed that the patients who received antibiotics needed respiratory care and support, and were taken to intensive care units more habitually. The researchers had concluded that the bacterial co-infection was unusual amongst COVID-19 patients, yet usage of antibiotics was in elevation. There is lacking of evidence to support prevalent use of empiric antibiotics in these patients. Most might not necessitate empiric cure and if they do, nevertheless, the researchers still argue that there is favourable signconcerning "azithromycin" as a possible COVID-19 treatment (14).

The study by Popp et al., 2020 which aimed to measure the effects of antibiotic use on people with COVID-19, and the study was conducted on different dimensions such as: people dying; whether people's COVID-19 symptoms have improved or worsened; Side effects; heart rhythm problems and quality of life. In addition, the study aimed to determine whether the use of antibiotics can reduce mortality, severity of illness and duration of infection in people with COVID-19, if they have an effect on quality of life. or cause side effects. ", no treatment, routine care, another antibiotic, or treatments for COVID-19 that are known to work to some extent, such as" remdesivir or dexamethasone " (15).

The results of this study showed that the antibiotic "azithromycin" is not an effective treatment for COVID-19. Additionally, it has been found that there is undefined evidence as to whether antibiotics other than azithromycin are effective treatments for COVID-19, as there is not enough research to prove their effectiveness.

According to Brian Godman who is a professor at Strathcylde Insitute of Pharmacy and Biomedical Sciences in United Kingdom, who argued that it is essential to restrain   unfortunate utilize of antibiotics for viral infections that extremely is to augment   the rates of bodily resistance   and resulting in larger loss of life in the future, as he said:" This is especially important in the community, as the inadequate prescribing and distribution of antimicrobials for predominantly viral infections is their biggest problem veruse".

Also, he stated that pharmacists who are well trained need importantly to lead patients directly to proper treatments which are more effectual in offering relief of symptoms and inexpensive as well. Also, it should be a precedence in fighting the symptoms of COVID-19 as such antibiotics have the ability to rise resistance rates of antimicrobial diseases. Analogous trends are probable to have taken place in other low- and middle-income countries where antibiotics are often overused, the study stated. The medium- and long-term results for bacterial resistance prototypes are "highly concerning", the study added, stressing the require for vital antibiotic stewardship determines such as

evading the use of antibiotics if there is no thought of bacterial contagion, and preventing the period of antibiotic conduct for co-infections.

India's method of antibiotic use during COVID-19 pandemic was more of a 'stimulating' response than a well-deliberated plan, says Diptendra Sarkar, COVID-19 strategist, public health analyst and professor at the Institute of Education and Research postgraduate medical school, Calcutta, India. "Although the evolving evidence does not favour the use of antibiotics, there was little governance over community use of antibiotics. Self-medication has also played a major role in the escalation of antibiotic use. which are not based on evidence ". Also, according to Sarkar, it is likely that there will be greater community resistance to antibiotics prevalent in India in the wake of the pandemic. "This could lead to the evolution of 'superbugs' in hospital practice," he said.

Frequently Prescribed Antibiotics

We extracted details of prescribed antibiotics from all included studies where this information was available. In addition, 33.9% of the incorporated studies did not report details about the antibiotics, but only cited that antibiotics or empiric antibiotics were used in the treatment.

Of the more than 12 studies that reported the category of antibiotics used in the treatment of COVID-19 patients; azithromycin (macrolides and ketolides "was the most commonly prescribed antibiotic (accounting for 28.0% of studies), followed by ceftriaxone (17.7%), moxifloxacin (14.5%), meropenem (14.5%) and piperacillin / tazobactam (12.6%). It is not possible to tabulate the prescription rates of these frequently prescribed antibiotics for the treatment of hospitalized COVID-19 patients since most studies, except for cases clinical or case series, did not report the percentage of each antibiotic prescribed in the treatment of COVID-19 patients. are all "broad spectrum antibiotics".

The low amount of antibiotic prescribed (less than 14%) for COVID-19 patients with a clinical rationalization for presumptuous the existence of bacterial infection gives more evidence that clinical sign was not the chief driver of antibiotic therapy. Generally, 40-50% of antibiotic prescribing (40.9% for

severe patients vs. 51.5% for mild or moderate patients) in the integrated studies took place without clinical proofs of bacterial infection (16).

While more is now known about COVID-19 and effective treatments, as it spreads around the world, there is no reason to consider that antibiotics are still not widely and widely available. used, mainly in low- and middle-income countries hit by imperfect resources, our results therefore continue to make sense. The revision also has several foreseeable limitations. First, the researchers drew on published online research and studies, as well as searches for articles in selected databases; this could lead to publication bias. Second, we expelled studies not available in English, which might as well lead to language bias as we were not able to take in studies from European countries which have made studies and published in local languages. Third, the severity categorizations given in the integrated papers varied between studies only that aimed the usage of antibiotics in dealing with Covid-19 virus. Our findings relating to relationships of random use of antibiotics and severity of COVID-19 on the patients` health. Finally, we did not appraise the quality of the incorporated studies and were incapable to conduct meta-analysis because of the heterogeneity of the studies under review. This may result in not as much of robust and generalized findings. Though, the insertion of a broad range of study designs aids to offer a further complete image of worldwide antibiotic stipulate prototypes throughout the COVID-19 pandemic than is accessible in the present scientific literature.

Recently, an increase in the effectiveness of antiviral drugs has been observed by taking it with zinc, especially with viruses that affect the respiratory system such as influenza H5N1, H9N2, Peste des petits ruminant's virus and SARS-Cov-2. This combination makes it difficult to adapt to the virus, which helps reduce resistance to infection (27-32).

Conclusion

After concluding the systematic review, it has been noticed that there are a lot of studies that have focused on the mismanagement and misuse of antibiotic during the pandemic ,and which resulted in catastrophic outcomes on the people who have suffered from the pandemic health problems, causing loses of lives or being admitted to the ICU at the hospitals of their countries. This review focuses on the hazards of misuse of the antibiotics of diverse categories, and aims through these results to be beneficial in the future studies that desire to enlarge the information in accordance to the evolution of the pandemic which still represent a threat to the whole world`s population.

This review and summary of the evidence suggests that in the first six months of the COVID-19 pandemic, prescribing antibiotics in hospitals was not associated with the severity of the disease. A large percentage (40-50%) of antibiotic prescriptions for COVID-19 patients had no clinical indication of bacterial co-infection; About half of COVID-19 patients with mild to moderate illness were prescribed antibiotics in the reports and studies we reviewed. Patients without clinical evidence of bacterial co-infection should not receive antibiotic treatment according to international guidelines.

Evidence reviewed suggests that any time a secondary bacterial infection is absent, prescribing antibiotics may not be beneficial for treatment outcomes for COVID-19 patients. Until more clinical data becomes available to verify these results, great caution is needed when considering antibiotic therapy in cases of COVID-19, even for critically ill and critically ill patients. Widespread use of antibiotics for COVID-19 could not only amplify the problem of antibiotic resistance globally and render currently available antibiotics ineffective, but also bring little or no benefit to COVID-19 patients. The prevalence and prescribing schedules of antibiotics for COVID-19 patients in hospitals from June 2020 to August 2021 are currently ongoing. A large percentage of antibiotic prescriptions for mild and moderate COVID-19 patients had no clinical evidence of bacterial co-infection. Antibiotics may not be advantageous for patients with COVID-19 without clinical trials of bacterial coin.

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Table 1. Data gathered from the different selected studies concerning patients' physiognomies and modality of antibiotics used in different countries.

Author(s)	Country	Proportion of Antibiotic usage	Sternness of the disease and death rate
Wang D et al., (17)	China	At least 89 (64.4%)	ICU relocation: 36 (26%); 6 (4.3%)
Wang D, et al., (17, 18)	China	85 (79.4%)	ARDS: About 28 (26.2%); 19 (17.7%)
Wang Z et al., (19)	China	66 (98.5 %)	Hypoxemia: 14 (20.3%); 5 (7.5%)
He et al., (20)	China	Prophylactic use: 49 (75.4 %)	Severe: 43 (66%); 10 (15.4 %) if incidence of a secondary infection vs 19 (7.3%) if not occurred
Zhou et al., (21)	China	180 (95%)	50% in non-survivor's vs 1% of survivors
Yang et al., (22)	China	49 (94%)	Only critically-ill patients: 2 (61.5%)
Huang et al., (23)	China	42 (100%)	Patients in ICU: 13 (33%); 6 (16%)
Chen G et al., (10)	China	20 (100%)	Moderate and severe cases: 4 (19%)
Chen N et al., (24)	China	70 (71%)	Severity criteria upon admission: 33 (33%); 11 (11%)
Aggarwal et al., (25)	USA	7 (43%)	Hypoxemia: 6 (38%); 3 (18.74%)
Pedersen et al., (26)	Denmark	15 (100%)	Intubated patients: 7 (43.75%)
Adebisi et al., (9)	Ten african countries	70 (70%)	Sternness: 23 (45%); 12 (12%)