The Unnecessary Uses of Antibiotics During COVID-19 Fulfill Antibiotic Resistance

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ABSTRACT

Coronavirus disease-19 (COVID-19) is a critical health challenge in all countries and according to united nation report, one of the most common problems during COVID -19 is the bacterial resistance to antimicrobial drugs that face the health issues which is due to antibiotics misuses during the pandemic disease as a protective to expected secondary bacterial infections after a viral infection. Subsequently COVID-19 early phase courage or enhance this massive antibiotic use in several countries all over the world. The purpose of this review to cover the prevalence and reasons behind these antibiotics misuse and analyze most common antibiotics uses during early-phase COVID-19 pandemic.

Kewords: Antibiotic, Covid-19, Pandamic, SARS.

1. Introduction

SARS-CoV-2 or severe acute respiratory syndrome coronavirus 2 is the virus which make the World Health Organization (WHO) announced an emergency state over all the world in May 31st, 2021, the virus which causes COVID-19 pandemic disease.

Spreading of the disease is occur primarily by either in contact to infected people drops by coughing, sneezing, or by touching [1, 2].

Therefore, one of the important preventive strategies is to inform people how they can be boosting function of their immune system in order to either prevent SARS-CoV-2 infection or control progression of the disease.

Globally all countries around the world in a continuous racing seeking to get a novel & effective treatment for COVID-19 with less side effects & more hopeful controlling, subsequently every day there are many research published in an attempt to solve this critical issue. Similarly, most common drugs which is used in COVID-19 treatment remdesivir, vitamin D, aspirin, paracetamol, zinc, dexamethasone, chloroquine & antibiotics [3].

Most of the patients of COVID-19 classified according to their signs & symptoms into early phase (stage 1 & 2) which is the majority of the patients suffering from cough, fever, sore throat, loss of appetite, myalgia, loss of taste and smell, & breathing problems, & the developed stage which require hospitalization due to presence of pneumonia & secondary respiratory infections [4].

Diagnosing COVID-19 infection is done by either computed tomography (CT) scan; immunoglobulin G (IgG); immunoglobulin M (IgM). Or by common laboratory tests: complete blood count (CBC); C-reactive protein (CRP);

erythrocyte sedimentation rate (ESR); lactate dehydrogenase (LDH); Ferritin & D- Dimer, serum liver function tests (LFT); serum Kidney function tests (KFT) [5].

In general, the aim of this review dose not claim the laboratory or other diagnostic tests but rather cover the previous researches about COVID-19 and how affects mortality rates among population & review of the most common antibiotics which lead to resistance with the prevalence of this resistance among population around the world, although how to decrease or prevent this resistance .

Despite that China National Health Commission (**CNHC**) guidelines for Covid-19 declared that ''blind or inappropriate use of antibiotic drugs should be avoided, especially broad-spectrum antibiotics.''

At the beginning most hospital admitted patients treated following pneumonia guidelines, subsequently more often to cover atypical pneumonia pathogens [7].

According to the International Severe Acute Respiratory Infection antibiotics treatment decision reported in about 72% in hospitalized patients, taking into consideration that there were higher rates of antibiotic uses. [8]

Guidelines of **NICE** stated that "Do not use antibiotics for preventing or treating COVID-19 patients and it should be used only when there is strong clinical suspicion of bacterial infection," while the **National Institutes of Health** treatment guideline declared that "in patients with COVID-19 and severe or critical illness, there are insufficient data to recommend broad- spectrum antimicrobial therapy in the absence of other indications. If antimicrobials are initiated, their use should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy." [9, 10]

As we know the COVID-19 was viral infection rather than bacterial which was uncommon, so "there are no data to support the safety or efficacy of antibiotic chemoprophylaxis to prevent bacterial complications." Subsequently, helpful therapy for COVID-19 mainly focus on the antiviral & the immune basics in the body. Also in the early phase of COVID-19 the incidence of bacterial infection was not prevalent, Although the antibiotics uses was very popular & common despite ''there are no data to support the safety or efficacy of antibiotic chemoprophylaxis to prevent bacterial complications." Which was one of the leading causes to antimicrobial resistance [11].

Subsequently, the incidence of bacterial infections with COVID- 19 is very low & the clinical studies that search the uses of antibiotics during COVID- 19 not approve the empirical antibiotics uses during pandemic. Currently, with regard that about only 3.5% of COVID- 19 cases diagnosed with bacterial infection & the 2ndry infections estimated in only 15.5%, despite bout 71.3% cases was treated with antibiotics. Although there was little difference between COVID-19 & other upper respiratory tract infections, therefore antibiotics uses increases even with a simple infection because the panic of development of respiratory failure & hypoxia [12].

Study by Goyal et al, showed that only about 5.6% patients having bacterial infections without antibiotics uses in New York & major bacterial infections occur in ventilator patients (about 8%). Besides, low incidence of bacterial infections in non-hospitalized patients [13].

However, there is a myth "antibiotics are effective in preventing and treating new coronavirus." Furthermore, COVID-19 is a viral rather than bacterial. So, given antibiotics is useless with the absence of clinical evidence. [14]

Although one of the serious warning of COVID-19 which was one of the clinical warning is the higher level of IL-6 with the cytokines and chemokines that is leading cause to self-healing possibility [15].

One of the most important reasons which lead to this huge antibiotics misuse was the self-medication & the easy access to the antibiotics especially the OTC (over the counter) due to panic during the pandemic which as a result end in a massive bacterial resistant & increase 2ndry bacterial infections which result in antimicrobial efficacy reduction with the thread of higher mortality rates [16].

Taking into account the sub-optimal use of the drugs or unjustified drug course, such as incorrect dose, missing a dose, error in the duration or stopping drug course and history of other chronic disease which result in lack of medication adherence [17, 18].

Keeping in mind that prescribing antibiotics by physician depend on many factors such as age, history of other disease, severity of signs and symptoms, dyspnea with the need for ventilator and the laboratory tests with CT scan. On the other hand, there was increase in the antimicrobial drug resistance due to massive antibiotic misuse by the patients especially in the early phase of the disease. Beside the steroids administration which mask the signs & symptoms & worsen the presence of other bacterial co-infections [19].

A study by Langford B et al, revealed that this misuse of antibiotics differ according to the world region, were the

highest rate reported in the east & south east except china (> 80%) & lower rate seen in west and Europe (= 60%). Other study stated that patients with weak immune system associated with more deterioration in the COVID-19 disease & increase mortality rates [20].

According to study done by Abu-Rub LI et al, one of the most common used antibiotics with a higher ratio during early COVID-19 pandemic was macrolides (azithromycin) with β-lactamase inhibitors (amoxicillin/clavulanate) to cover any suspected secondary bacterial infections despite it was uncommon [21]. Although there was higher rate of ICU admission & mortality due to respiratory failure progression, at that point antibiotics with more broad-spectrum properties such as ceftriaxone, cefepime, meropenem, moxifloxacin, & piperacillin/ tazobactam used to cover secondary bacterial infections [22].

According to Langford et al, a review which is estimate the wide uses of antibiotics during COVID- 19, stated that the antibiotics which is widely used in COVID- 19 patients were the broad-spectrum, & mainly the 3rd generation cephalosporin, azithromycin, & fluoroquinolones in majority of the patients [23].

Other study stated that beta-lactams was the number one used antibiotic during COVID- 19, followed by macrolides by the second degree & lastly fluoroquinolones according to EU (European Union), while in the beginning of pandemic the most commonly used empiric pattern by hospitals was 3rd generation cephalosporins plus azithromycin. Nonetheless, despite that this study concluded that the non-need uses of antibiotics used empirically in the majority of patients (about 90%) admitted to hospital even without diagnostic tests & the most common antibiotics was beta-lactam, macrolide, & fluoroquinolones, although the fact that COVID- 19 was a viral infection with little incidence of bacterial infections [24].

Beovic et al, found that dispensing antibiotics in COVID-19 patients takes place after developing signs & symptoms of pneumonia (fever, productive cough, dyspnea), accompanied with laboratory & radiological tests [25].

A Study by Grigoryan L et al revealed that the most common obstacles in the pharmacist daily practices was high claim or easy access of the OTC drugs without prescription or cultural of bacteria which result in antibiotics resistance & as a result this broad- spectrum antibiotic misuse lead to elevated bacterial co-infections & upward in the mortality level [26].

A study Karampela I et. al., analyzed Fluoroquinolones drugs potential capacity for binding to SARS-CoV-2 protease Mpro, to block the replication of the virus as a one of COVID-19 treatment [27]. Other stated that most of the COVID-19 pneumonia was after long period admission due to hospital micro-organisms (Staphylococcus aureus) or after ICU admission which is ventilator-associated pneumonia [28].

Subsequently, there are many studies coincide the pandemic of COVID-19 done on the antimicrobial drugs, one of these antibiotics was beta-lactam (amoxicillin/ clavulanic) which tested in the sever cases of the disease although it requires additional research to get more precise results. [29]

Other study demonstrates the using of macrolide antibiotics in COVID-19 patients such as azithromycin & clarithromycin, to reveal their immunomodulatory effects in addition to their antibacterial activity, which state that azithromycin uses due to antibacterial properties have no benefit in COVID-19 infection but the immunomodulation & anti-inflammatory properties of azithromycin by cytokine production attenuation & effect on viral replication was the main reason for using azithromycin during COVID-19, but in fact till now there was no clinical evidence to approve the antiviral effects of azithromycin [30].

According to FDA-approved chemical library, azithromycin approved to have activity against SARS-CoV-2 by a study in France, due to survival rates improvement & decrease need to ventilator which in most country listed in the treatment guidelines [31, 32].

Although Pedersen et al reported in his study that in sever COVID-19 cases there was needed to add more strong antibiotics such as Piperacillin-tazobactam & when there was case deterioration meropenem or vancomycin used instead [33].

While a study by Xu et al showed that in COVID-19 patients when symptoms remain for long period more than 10 days there was high rates of antibiotic use & even with the long period fever & when the level of C-reactive protein is high [34].

According to Guan et al in sever COVID-19 patients the rates of antibiotics use was higher than in in mild cases. [35] & G. Chen et al noticed that in all cases of COVID-19 antibiotics use empirically. [36] a study by Zhou et al noticed that death in COVID-19 patients about 50% due to secondary infections [37].

Moreover, the risk of infections increased with admission to hospital and increase incidence of drug-resistant & antibiotics uses, a study by Getahun H et al showed that 70% of patients received treatments or prophylaxis & about 50% only with a suspected bacterial infection in the ICU wards, while only about 8% of these patients has bacterial or fungal infections [38, 39].

On the other hand, according to PAHO, only about 7% of covid-19 patients required treatments for the bacterial infection, despite that about 90% of these patients taking antibiotics in the Americas [40].

According to Huttner BD et al beta- lactams recommended as first line treatment during COVID-19 for S. pneumoniae coverage, also he recommended to avoid macrolide antibiotics & flouroquinolones as it has higher side effects such as cardiotoxicity. Indeed, he restrict the uses only on the basis of bacterial infections with continuous evaluation if possible because he revealed that the major organism found in the ICU awards was Pseudomonas & the Klebsiella pneumonia as minor organism & the most common organism which was resistant to treatments was P. aeruginosa [41], in contrast Karampela et al recommend starting with fluoroquinolones due to its ability to inhibit replication of SARS-CoV-2 more than antiviral drugs [21, 42].

Suleyman et al. study COVID-19 more often in females & in patients ages older than 57 years African American, & all patients with one co-morbidity either hypertension, kidney disease, or diabetes. In fact, on admission they had same symptoms which make professionals miss diagnosed & increase death rates especially in patients with cardiovascular risk factor [43].

2. Conclusion

In conclusion, during the COVID- 19 there were un-reasonable antibiotic use & about 90% of hospital admitted patients received empiric antibiotics, although this un-needed use in fact has minimal effects on the mortality rate despite the fact that pneumonia associated bacterial infections not clinically estimated, therefore further clinical studies required to estimate or approve the restriction of antibiotics uses during early phase of COVID- 19.

In this review, we concluded that the macrolide antibiotics has lower mortality rates & higher survival rates among patients (especially azithromycin) compared to other antibiotics, despite the significant mortality rates among patients received other antibiotics..

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