Evolution of Antimicrobial Resistance in the era of COVID-19

ABSTRACT

Antimicrobial resistance is slow growing phenomenon that could even be a reason for a future pandemic. Due to inappropriate diagnosis and consumption of antibiotics the bacteria have become resistant to the antibiotics used. In the era of COVID-19 this blind consumption of antibiotic has rapidly increased due to the period of quarantine and fear of disease. As many patients due to the fear of the pandemic especially in rural areas avoid going to hospital and consume antibiotics without any prescription. Various retrospective studies have shown relation between bacterial co-infection and AMR which is found to be increased in the era of COVID-19. Also, the secondary bacterial infections associated to the pandemic of COVID-19 has added to the risk of the antimicrobial resistance. The viral effect on the respiratory system is evident to be favourable for the bacterial infection as in case of COVID-19 affecting the respiratory tract that is followed by co-bacterial infection in some cases.COVID-19 has affected AMR in many aspects. Proper antibiotic resistance tests should be performed before prescribing any antibiotic to the patient to reduce the chances of AMR especially in such an obnoxious situation of COVID-19.This crucially calls for brand new and effective plan of action to attenuate the influence of the pandemic on antimicrobial resistance. Statistics of various countries in matter of antimicrobial resistance have shown that there is an increase in AMR due to all the concentration of health workers, researchers and population on the pandemic associated with COVID-19. This calls for necessity to aware the population worldwide about antimicrobial resistance and how it could be a hidden menace in future and could probably prove to be a matter of concern as it would worsen the condition of patient in a particular disease and would decrease the various possible aspects of the treatment especially in case of treatment based on antibiotics.

KEY WORDS: Antimicrobial resistance, Antibiotics, Co-bacterial infection, COVID-19.

INTRODUCTION

Antimicrobial resistance(AMR) is seen to be emerging as a threat to effective prevention and treatment in the 21st century[1].AMR can be explained in regards to antibiotic resistance developed over decades in the bacteria causing infections resulting to the ineffectiveness of any new antibiotic in the market on the resistant bacteria[1]. Accurate secondary bacterial infection characterisation is critical in the clinical management of the most severe COVID-19 cases, might save lives, and will enhance patient outcomes a commitment to antimicrobial stewardship across the pandemic's progress [2].In patients of covid 19,bacterial co-infections associated with COVID-19 have been reported which will ultimately add up to the possibility of increased antimicrobial resistance[3].

The obnoxious situation that we are hit with, the COVID-19 is reported to be contributing to the risk of antimicrobial resistance through medical management (i.e. by reported cases of bacterial co-infections) although the reported cases of secondary bacterial infections associated to COVID-19 are less as compared to the reports of usage of the antibiotics when treating COVID -19 patient[4].Bacterial and fungal infections of various types have been reported in patients of COVID-19 along with resistance to antimicrobials leading to worse outcomes and even death[5].

Retrospective studies, Facts and Findings about bacterial co-infection and AMR in different countries.

According to a retrospective study done at Wuhan Union Hospital, it was found that the bacterial co-infections were associated with the severity in case of patients hospitalised. It is also evident that the gram-negative bacteria most commonly A. baumannii and K. pneumoniae were found to be the cause of bacterial co-infections and were also found to be highly resistant to antimicrobials[6]. A retrospective cohort analysis conducted at a Barcelona hospital proved to be crucial in determining the role of empiric antimicrobial therapy and stewardship efforts[7].Another retrospective case series of confirmed COVID positive patients at UK during first wave of COVID-19 reports low levels of secondary bacterial infection in case of preliminary COVID-19 hospital presentations[8].

At least 2 million people in U.S. every year have been reported with serious bacterial infections to which they are resistant to. Among these, an unignorable figure of 23,000 patients die due to antibiotic resistance infections and this figure increases when further complications are added to the picture[9].Approx. 400,000 infections and 25,000 deaths were estimated on an yearly basis in Europe the reason being the multi-resistant bacteria like S. aureus, Escherichia coli, Enterococcus faecium, Streptococcus pneumoniae, Klebsiella pneumoniae and Pseudomonas aeruginosa(10).A study survey among the European citizens reported that the percentage of the participants in the survey involved in usage of antibiotics in the treatment of flu-like symptoms and known with the fact that antibiotics do not act against viral infections, was found to be 20%. On the other hand, 14% of the participants admitted that they took antibiotics to serve as a treatment of acute rhinitis or cold(11). A study survey in UK amidst the adults reported that the percentage of participants of the survey that didn't know about the fact that antibiotics do not act against cold and cough was found to be 38%(12). In Sweden, according to a survey it was reported that the comprehension of antibiotics as well as the possibility of AMR is good and homogenous. Only one fifth of the participants were assured with the myth that antibiotic treat common cold more effectively(12).

TABLE 1.

Percentage of patients receiving antibiotics and percentage of confirmed secondary infections.

%Covid-19 patients treated with antibiotics	Confirmed secondary bacterial infection	Infecting agent	Geographical location
41/41 (100%)	4/41 (10%)	-	Wuhan, China
49/52 (94%)	1/94 (1%)	K. pneumoniae	Wuhan, China
26/53 (49%)	16/53 (30%)	A.Baumannii,Haemophilusinfluenza,P.aeruginosa, S.aureus,S.pneumoniae	Milan,Italy

39/92 (42%)	26/92 (28%)	A.baumannii,H.influenza, Moraxella catarrhalis, P.aeruginosa, S.aureus, S.pneumoniae	France
181/191 (95%)	28/191 (15%)	-	Wuhan, China
143/150 (95%)	12/150 (8%)	-	Wuhan, China
42/48 (88%)	6/48 (13%)	E.faecium, H.influenza, P.aeruginosa	Vitoria, Spain
37/298 (12%)	30/298 (10%)	-	Shenzhen City,China
319/476 (67%)	35/410 (9%)	-	Wuhan,Shanghai, and Anhui (China)
49/49 (100%)	2/49 (4%)	Serratia sp., Enterobacter sp.	Hong Kong,China
6/11 (55%)	6/11 (55%)	H. influenza, K. pneumoniae	Bangkok,Thailand
	3/28 (11%)	A. baumannii, Enterobacter cloacae	Wuhan, China
66/67 (99%)			

Antimicrobial resistant organisms

Staphylococcus aureus

MRSA is the name given to the strains of the of Staphylococcus aureus that are resistant to anti-staphylococcal penicillin[13].

In U.S. ,in 2011, there was estimation of about 80,000 MRSA cases. Only 14,000 cases out of these were reported in hospital[14,15].

Between 2010 and 2013, there was a considerable decline in the rate and ratio of MRSA from presumptuous infections in Europe.[16]

NTS- Non-typhoidal salmonella

In usage of antimicrobial agents such as ampicillin, chloramphenicol, sulphonamides, and tetracycline the cases of multi-drug resistance are frequent in Non-typhoidal Salmonella[17,18].

Klebsiella pneumoniae

ESBLs i.e., extended spectrum beta lactamases mediated resistance includes all penicillin, cephalosporins and aztreonam[19].

Various aspects in which COVID-19 impacts AMR

Secondary bacterial infections have long been thought to be a major cause of illness and death in viral infections, and they have also been documented in COVID-19 patients, but only a small percentage [20].It is evident that antibiotics are used inappropriately during the pandemic to self-limit the upper respiratory tract infection in non-hospitalised settings[21,22]. AMR is expected to cause 1,30,000 more fatalities by the end of 2020 owing to the present state of the COVID-19 epidemic [20].

Due to lack of beds in hospital in addition to weakened immune system of the COVID infected patients, they are more prone to secondary bacterial infections or co-infections[23,24,25].Multidrug resistance is reported as the result of using inappropriate antibiotic in cases of COVID-19 patients[23,26]).

Despite antibiotic prescribing practises differ by region, enlarged work pressure and psychological stress on medical practitioners make adhering to community hospital antimicrobial stewardship policies more difficult . Despite the reality that empiric antibiotics have a negative impact on later clinical output, the research suggests that secondary bacterial infections influence only a small chunk of COVID-19 victims[27]. Finally, the increased hospital utilisation antibiotics in case of COVID-19 victims throughout the preliminary phases of the COVID-19 pandemic may impact the total of antimicrobial resistance , influencing the load of diseases for later generations. Moreover, the pandemic of COVID-19 has created a serious and extensive global economic crisis, with the potential to fuel a substantial increase in global poverty levels . Lower- and middle-income countries (LMICs) are projected to agonize disproportionately, with a lot of people who are already poor being driven further into poverty[27].

Despite the difficulty in distinguishing pneumoniae caused by bacterial infection from pneumoniae caused by COVID-19 infection, as well as the lack of antiviral therapy with proven efficacy, in the treatment of COVID-19 patients, particularly the critically ill, antibiotics must be utilised as part of an empirical strategy. To avoid considerably more difficult repercussions, it is critical to take antibiotics responsibly even during the pandemic. However, due to antibiotic usage and increasing percentage of antimicrobial resistance, this concept raises worries about the effects.[28]

Antibiotic selection difficulties for COVID-19 victims in LMI

If the danger of necessitating invasive mechanical ventilation justifies usage of antibiotics to cure hospital acquired bacterial coinfections , the scarcity of ventilators in LMICs reduces this probability and should thus considerably decrease unwanted usage of antimicrobial . Despite the fact that temporary peripheral venous catheters are associated to frequent number of cases of infections of bloodstream in LMICs, risk is involved in case of the rising figures of COVID-19-infected patients who are hospitalized, will result to a greater dependence on antibiotics to combat hospital acquired infections associated with catheter. Antimicrobial use, along with infection - control strategies, could assist in reducing this risk. Research findings indicate that, in case of similar pathogenic bacterias, disparities occur among HIC and LMIC in terms of communities at risk, associated symptoms, prevalence of spread of pathogenic bacteria, and drug sensitivity. The potential danger of COVID-19 may, in fact, provide chances for LMICs to enforce antimicrobial stewardship programmes in accordance with WHO guidelines, such as antimicrobial stewardship team education and training, advances in medical guidelines, resistance monitoring, and antibiotic use monitoring.[29]

Strategies to attenuate consequence of COVID-19 on AMR

The imbalance in use of antibiotics and microbial investigations need to be balanced by the health care system[30]. Assessment of the articals,reports,and studies about the enlarged possibility of AMR due to the pandemic of COVID-19 plays a very essential role in development of attenuation strategies[31].AMR should be made as an essential basic in clinical practices[32].

Diagnostics should be more appropriate in this difficult time of the pandemic od COVID-19 in terms of identifying the right organism involved as the cause of the secondary bacterial infection[30].A support system to be built to support the researchers and their confidence , encouraging them to carry on with the AMR research and monitoring[33].Formation and appearance of networks of collaborators coming up in the covid 19 era should be encouraged to help us with their motive to handle issues regarding the covid 19 pandemic[33].

International campaigns like the biennial World Antibiotic Awareness Week raise awareness of AMR and the importance of antibiotic stewardship More regularly washing hands (e.g., through Hand Hygiene Day) appears to pay off when hygiene practises are prioritised. Usage of antibiotics should be with caution and care, in case of empirical therapy in advance for occurence with a strong possibility of microbial co-infection and the statistics of resistance taken in to consideration. In reaction to microbiological discoveries, empirical prescriptions should be rapidly re-evaluated and changed.[27]

Antimicrobial stewardship programme and COVID-19

Antimicrobial stewardship denotes collaborative, integrated programmes and initiatives intended to promote selecting appropriate antimicrobial treatment regimen, which also include dose, length of therapeutic treatment, and other factors[28].Antimicrobial stewardship programmes can observe and improve compliance with the help of treatment guidelines during pandemic of respiratory virus accompanied with bacterial co-infections and diseases such as pneumonia and ARDS. Severe COVID-19 instances have been treated with broadspectrum antibiotics. Despite the complexity of distinguishing COVID-19 from bacteria associated pneumonia, the uncertainty about bacterial superinfections, the lack of precise antiviral treatment for the prevailing pandemic, and the high death rates, antibiotics should be considered to be part of the empirical therapy for the most serious suspected or confirmed COVID-19 cases (e.g., patients necessitating mechanical ventilation). Antibiotics should, however, be administered with caution and caution during such a pandemic.[28]

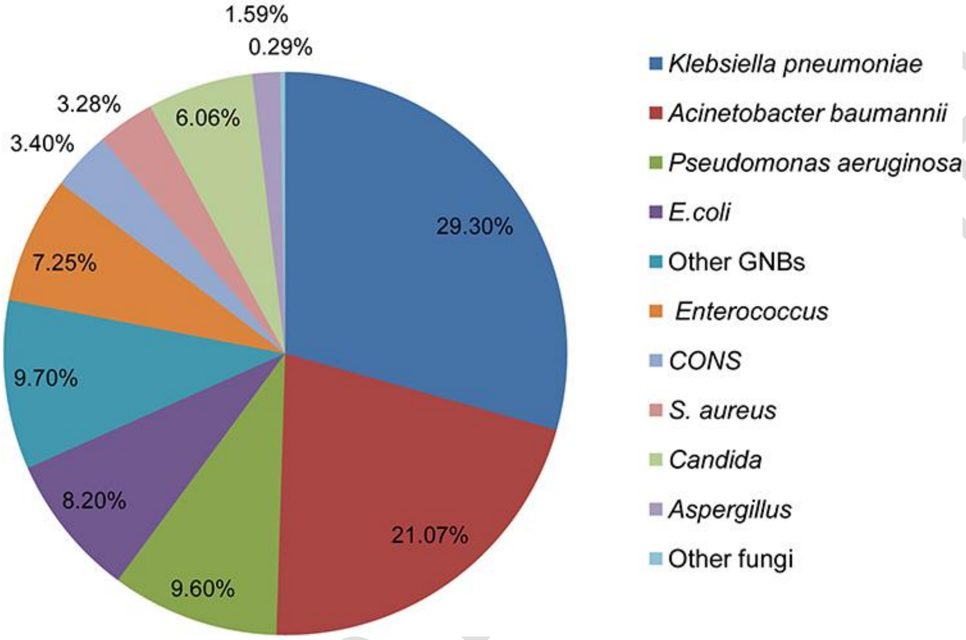

Figure 1 Isolated bacterial and fungal pathogens from Covid-19 patients with their distribution.[32]

Monitoring AMR in the era of Covid-19: A challenge

Due to lack of time and increase of burden and responsibilities on health care professionals and population the whole attention is being shifted towards working on Covid-19. This in turn has affected the participation and involvement in AMR research and has also led to the discontinuation in maintaining the accounts of and monitoring of AMR. Recently developed and implemented systems of monitoring for Covid-19 can be utilized to fortify environmental monitoring of antimicrobial resistance.[33]

Statistics and facts

- In Wuhan, antibiotics were preffered for treatment in 95% patients and antivirals were given to 21% of the patients [34].
- As per the fourth GLASS report the 2019 data collection regarding AMR by WHO estimates 3 106 602 laboratory confirmed cases of infections in 70 countries[35].
- Another data collected by GLASS in 2019 presents the percentage resistance to ciprofloxacin for UTI to be 8.4% - 92.9% with the involved bacteria as E. coli, and in case of kleibsella pneumoniae it ranges from 4.1% - 79.4%.[29]
- As a result of a study, it was found and admitted by 41% of the participants that during the treatment of COVID 19 frequently prescribed drug of choice was azithromycin.[28]
- COVID-19, due to the SARS coronavirus 2 (SARS Cov2), caused 119.2 million illnesses and 2.64 million deaths worldwide as of 14 March 2021.
  India had 11.35 million illnesses and 0.15 million fatalities as of March 14, 2021.[32]
- In 2020, AMR is expected to have killed one-third of the total people killed due to COVID-19.[33]

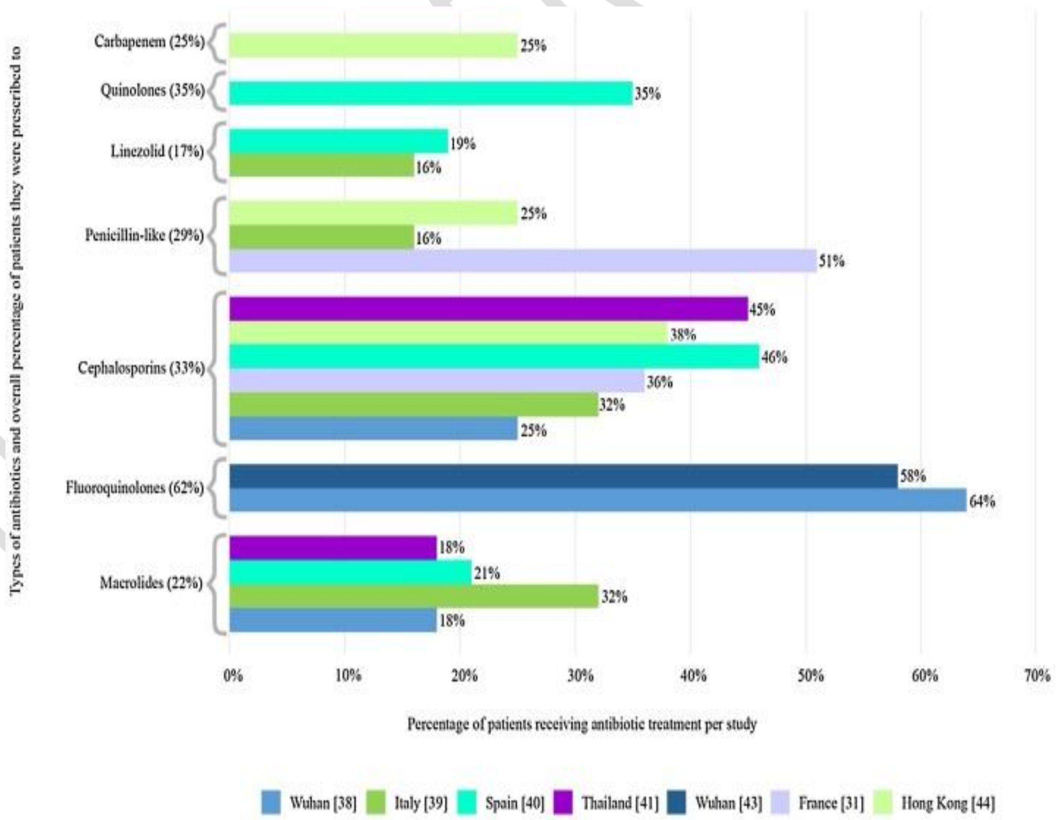

Figure 2. Rate of patients with particular antibiotics received and Rate of patients with prescribed antibiotics.[28]

COMBINED EFFECTS OF BACTERIAL AND VIRAL PATHOGENS

It is evident that viral infection like COVID-19 effecting the respiratory tract also promotes bacterial growth by altering function of the innate immune system[29].It is also evident that due to the impact of immune response throughout a viral infection like covid there is modification in anatomy of respiratory tract which has been known to sabotage the defenses of the immune system against the pathogenic virus or bacteria[29].In case of an infected SARS-CoV-2 subjects the pulmonary alveoli filled with puss and fluid favours and provides the suitable medium for the growth of P. aeruginosa and S. aureus like bacteria[29].

Bacterial coinfection and subsequent infections predictors (clinical, biomarkers)

There is a need for more research into the predictive ability of various investigations be it clinical or laboratory during hospitalisation of the patient for coinfections. Across randomised trials , studies and in varied patient profiles, full data collection must be harmonised, along with adequate microbiological investigations[20]. Clinicians have employed biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) to aid in the diagnosis of infections associated with bacteria. In severe cases, it may be high. COVID-19 patients have a limited lifespan due to the virus. Use in determining how long and how often antibiotics should be given[36].

Access of antimicrobials

COVID-19 has impacted antibiotic availability by altering supply chains and worldwide antimicrobial manufacture, resulting in modifications in consumption levels.

The vulnerability of network of antibiotics was emphasised not so long ago when a single Chinese manufacturer was shut down, resulting in a worldwide scarcity of piperacillin-tazobactam. Fears of scarcity have prompted the European Medicines Agency to take "urgent and synchronized measure to stop and reduce medicine deficits inside the EU".As a result of COVID-19, nations that produce and trade antibiotics are increasingly facing domestic demand, which could lead to a drop in shipments, as observed in India . This may result to a request for expanded antibiotic production beyond the production hubs of India and China. COVID-19 is supposed to be leading to modifications in antibiotic use, which would have a parallel impact on supply chain shortfalls; eleven producers have claimed azithromycin scarcity to the United States Food And drug, possibly due to its use for COVID-19 medication.[33]

Antimicrobial use in COVID-19 patients

Antimicrobials are administered to up to 70% of COVID-19 patients in either an inpatient facility or outpatient care setting which in turn will support AMR[33]. Antimicrobials are being used because they are thought to have a detrimental influence on SARS-CoV-2. This could lead to the development of resistance in pathogenic microbes that co-infect or co-colonize[37]. Cheap, quick diagnostics in community settings may detect infections like SARS-CoV-2 earlier particularly in the face of imprecise symptomatology, and hence reduce the use of antibiotic . This will be especially relevant in low- and middle-income countries where antibiotics are available without a prescription and testing is emphasized, whereas vaccinations may take more time to become more widely utilised[33-45].

CONCLUSION

This review demonstrates effect of covid 19 pandemic on antimicrobial resistance and vice-versa. AMR which has been a hidden menace is discussed in relation to covid 19 with a motive to create awareness regarding future risks with AMR. Importance of correct diagnosis in relation with the secondary bacterial infections is mentioned, as it was found to be out of focus in covid 19 era due to the burden on health care professionals. Realising the fact that covid 19 has piqued our curiosity leading to unbalanced monitoring of the AMR which will now be encouraged. An account of bacterial and fungal co-infection in covid 19 patients along with retrospective studies from different countries are discussed in this review to draw knowledge about the link between AMR and covid 19.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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