Journal of Life Sciences & Biomedicine, vol. 2(75), No 2, p. 68-75 (2020)

Co-infections in COVID-19 patients and the importance of microbial diagnosis for disease management

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Received 12 October 2020; Received in revised form 25 November 2020; Accepted 26 November 2020

Patients infected with respiratory viral infections especially new coronavirus disease (COVID-19) are most susceptible to co-infections which in turn, increases the severity of disease and mortalities. Therefore, antibiotic agents should be applied for the treatment of bacterial co-infection and super-infections. On the other side, all guidelines for COVID-19 clearly mention that improper use of antibiotics, especially the combination of broad-spectrum antibiotic agents, should be avoided. Because the use of broad-spectrum antibiotics for a long time and in the combination of several other agents not only shows no effect on the recovery of the disease but also may lead to potentially fatal secondary superinfections and induce resistance in the normal bacterial population. Currently, due to the unavoidable use of antibiotics among patients with COVID-19 who are admitted to intensive care units, cultivation-based methods for isolating and detecting bacteria are less sensitive in the management of the disease. Hence, the use of culture-independent methods that can detect a wide range of potential pathogens and antimicrobial resistance is important, especially for screening and treatment follow-ups. So, culture-independent techniques such as whole-genome metagenomics can be used to identify monomicrobial or mixed infections without selecting the previous target. Whole-genome metagenomics can provide valuable and useful information about pathogens that cause co-infections and antimicrobial resistance in hospital settings, especially in the intensive care units. Therefore, these studies can have a valuable aid in the management of antibiotic administration and subsequent targeted treatment of infections.

Keywords: *COVID-19, bacterial infection, antimicrobial, whole-genome metagenomics*

INTRODUCTION

Viral infections of the respirstory system makes patients vulnearable to coinfections and superinfections and leading to high levels of mortalities and severity of disease (Cornbleet et al., 2002). Poor treatment outcomes of 2009 H1N1 influenzae pandemic was also attributed to the opportunistic coinfections (Ardron et al., 1994). Zhou et al., showed that 50% of Covid-19 patients who die have an additional bacterial superinfections (Zhou et al., 2020). Emerging Covid-19 pandemy has shown that health and diagnostic laboratory infrastructures needs to be revised in many of countries all over the world, especially in the context of rapid identification of organisms and management of antibiotics applications, as well as the control and management of additional bacterial or fungal infections in critical infectious conditins (Cox et al., 2020; MacIntyre et al., 2018). In fact, various studies have reported low bacterial or fungal infections in Covid-19 patients (Phlan et al., 2020; Zhou et al., 2020; Yu et al., 2020;

doi.org/10.29228/jlsb.63

Available online 25 December 2020

Huang et al., 2020; Arentz et al., 2020; Chen et al., 2020; Goyal et al., 2020; Chen et al., 2020), but in other studies, high opportunistic microbial infections such as bacterial pneumonia, and respiratory viruses have been reported in critically ill Covid-19 patients, which attributed to the samplig methods and number of samplings (Bachmann et al., 2018; Gautret et al., 2020). However, in other studies, the rate of coinfection with different pathogens were reported to be from 50 to 94% of patients, and bacteria including *S. pneumonia*, *K.pneumoniae* and *H.influenzae* were reported as dominant coinfectious agents in Covid-19 patients (Bates et al., 1992; De et al., 2016). But, in general, there is still no comprehensive information about the coinfections associated with Covid-19 infections and the types of pathogens involved in the pulmonary system, as well as their impact on disease severity and treatment outcome (De et al., 2016). Therefore, it is necessary for laboratory specialists with the help of clinicians in such cases to cooperate in order to accurately identify the organisms responsible for superinfection or coinfections. In this context, a combination of phenotypic routine, or new molecular and early biomarkers were suggested in the literature. Certainly, according to the treatment results obtained for Covid-19 disease, antibiotic treatments have caused many complications and side effects for patients due to their empirical nature and the use of a wide range of drugs.

Do Covid-19 patients have microbial coinfections, or is it acquired as a superinfection in the hospital?

In many studies, about 6 to 8% of microbial coinfection has been reported in Covid-19 patients. In these patients, it is not clear whether these rates are related to nosocomial infections or not (Arentz et al., 2020; Chen et al., 2020; Huang et al., 2020; Phlan et al., 2020; Yu e tal., 2020; Zhou et al., 2020). But a study in China reported 15 percent of nosocomial infections in Covid-19 patients. In this study 27 out of 28 nosocomial infections was died in hospital which indicates that coinfections could complicate and affect the mortalities of patients (Phlan et al., 2020).

There is no detailed report on the type of genus and microbial species involved in the coinfection or nosocomial infection after admission of patients in hospitals based on standard identification methods. And in different studies poly or mono-microbial infections composed of *A.baumannii*, *K.pneumo-niae*, *E.cloacae*, *S.pneumoniae*, *S.aureus*, *M.pneumoniae*, *C.pneumonia*, *L.pneumophila*; *A.fumigatus* and Candida species; and viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, influenza B virus, and human immunodeficiency virus have been reported from sputum or tracheal aspirate samples (Bates et al., 1992; Chen et al., 2020; De et al., 2016; Gautret et al., 2020; Goyal et al., 2020; Wang et al., 2020). Sometimes no organism has been reported in microbial studies of patient samples (Bonadio et al., 1992; Emmanuel et al., 2020).

In a large review of 1007 abstracts, it was found that 62 out of 806 cases of Covid-19 patients had bacterial or fungal infections at the time of admission (about 8%), while subsequent studies found that most Patients (about 72%) were prescribed broad-spectrum antibiotics (Cox et al., 2020). Of course, this could be due to the fact that the majority of patients develop secondary infections after hospitalization, which can be considered for better patient management.

Empirical versus antibiogram based antibiotic prescription in Covid-19 patients

Opportunistic or coinfections are inevitable in viral pulmonary diseases, therefore, antibiotics should be used to help treating such diseases. But usually clinicians, prescribing broad-spectrum antibiotics mostly as empirically. Which may have problems for patients.

On the other hand, bacterial/fungal/viral coinfections appears to be low in Covid-19 patients. But, broad-spectrum antibiotics have been used in most studies, especially in the later stages of the disease. For example, in Cao et al. studies, 101 out of 102 (99%) patients have been treated with quinolones, cephalosporines, and carbapenems (Cao et al., 2020). In a study by Guan et al., 637(58%) and 31(3%) out of 1099 patients received antibacterial and antifungals, respectively (Guan et al., 2020).

However, coinfections appear to be less reported in studies. But, the positive effect of prescribing antibiotics in patients shows that in order to prevent the side effects of drugs, opportunistic infectious organisms should be well identified in the laboratory

and antibiogram tests should be performed to determine the correct antibiotic for treatments (Ardron et al., 1994; Kuppermann et al., 1999).

Neccessity on the microbial identification in the Covid-19 patients

Based on the explanations given and the results of various studies, it is clear that coinfections, both as a actual concomitantly microbial or as a hospital-acquired superinfections, are seen in high rates in Covid-19 and other coronavirus patients (Bates et al., 1992; Cornbleet et al., 2002; Touzard et al., 2013; De et al., 2016; Chih-Chang Lai et al., 2020). On the other hand, the widespread use of broad-spectrum antibiotics in the treatment of these infections suggests that patients are forcibly infected by other opportunistic organisms (Timpthy et al., 2020; Zhou et al., 2020). In order to increase the success of treatment, concomitant bacterial/fungal infectious agents must be identified accurately to the genus and even species levels.

However, coinfections in some reported cases, such as *M.pneumoniae* with Covid-19, has not been associated with disease severity. But, at the same time the outcome of the complications of coinfections or superinfections with the virus is still unknown (Gautret et al., 2020). And as a fact, accumulating data shows that respiratory microbial coinfections incresing the risk of disease severity in humans (De et al., 2016).

In fact, the main problem in downplaying the role of identifying organisms in the treatment of Covid-19 patients is that physicians generally prefer emprical treatment with broad-spectrum antibiotics using clinical signs. Therefore, in some cases, after empirical treatments, death occures in the patients as a result.For this reason, in order to help properly manage the treatment of Covid-19 patients, it is suggested that microbial agents of coinfections or superinfections, should be detected to genus level in the patient samples, and effective and selective antibiotics should be determined for proper treatment of patients by standard antibiogram tests.

Culture based versus non-culture based methods

More than 24 different organisms have been reported from Covid-19 patients sputum or bronchial washing samples as coinfections and superinfections (Bates et al., 1992; De et al., 2016), which complicating the treatment and management of disease, and this emphasizes the accurate isolation and identification of microbes from patient samples. In some cases it is claimed that viruses such influenza A as a most common coinfecting viruses could cause a false-negative results in real-time RT-PCR tests in Covid-19 patients. Even it has been mentioned that laboratory and imaging results alone cannot help for differentiation of concomitant microbial infections from Covid-19 infections. So, in fact, some kind of identification of coinfections or superinfections should be used for analysis of patients samples. It is suggested that new multiplex molecular panels based on syndromic patterns with incorporation of Covid-19 virus probabely help to the early and correct detection of coinfecting organisms (Bates et al., 1992). Therefore, it seems that even routine methods of identification based on microbial culture and phenotypic tests can not be useful in differentiating the main causes of coinfections, so it is better to use new molecular methods, including diagnostic metagenomics, Whole genome sequencing (WGS), next-generation sequencing for accurate identification Infectious organisms should be used so that patients can be treated more accurately (Zarkesh et al., 2015; Paliogiannis et al., 2020; Zhihua et al., 2020).

DISCUSSION AND CONCLUSIONS

According to various studies, although primary microbial coinfection appears to be low in Covid-19 patients, the use of broad-spectrum antibiotics in the majority of patients means that like most human infections these patients are also attacked by opportunistic bacteria. But, certanly empirical therapy with broad-spectrum antibiotics is not a right and corrects method in management of patients. At present, due to the urgency of the treatment of critically ill patients, we can not give a definite opinion on the widespread use of antibiotics, or the prescription of broad-spectrum antibiotics. Meanwhile, at least we know that due to the high dose of drugs used and the severe involvement of the immune system in Covid-19 infections and phenomena such as cytokine storms, and the possibility of drug resistance induction in normal flora bacteria, many problems are possible as threatening patients under antibiotics. Therefore, the global scientific community should think of a consensus on identifying the causes of coinfection or superinfections in Covid-19 patients and highlight the role of microbiological laboratories.

On the other hand, there are no reports of side effects or complications from the hasty use of broad-spectrum antibiotics in coronavirus patients. Some drug groups, such as macrolides, also have antiviral effects, so their effect on coronavirus patients should be compared with other broad-spectrum antibiotics, to define that if their effect on disease control is different from other antibiotics (Xianjouan et al., 2019).

Early detetion biomarkers, such as calcitonin, band cells, increased mean total white blood cell (WBC) and absolute band counts (ABC), and high IL-6, interleukin-10, C-reactive protein, and D-dimer levels in critical ill patients, can also be used to differentiate between types of microbial infections(bacterial or viral) and to determine the need for antibiotics as a more non-invasive methods (Yap et al., 2004; Pallen et al., 2014; Dekker et al., 2018; Arabi et al., 2019; Cao et al., 2020; Guan et al., 2020; Kim et al., 2020; Liang et al., 2020; Wu et al., 2020). In some studies, this has been addressed in more detail. For example, one study found that lymphopenia was more severe in men than women, and that in patients with critical symptoms the tumor necrosis factor alpha was lower than the severe or mild patients. They reported about 24% coinfection with other respiratory pathogens in critical and severe cases,and suggested that coinfection, lymphocyte count and d-dimer have relation with severity of Covid-19 infections (Dekker et al., 2018). In other study, analysis indicate that bilirubin level was very higher in severe COVID-19 patients (Meier et al., 2019). This suggests that early detection criteria can also be used to differentiate between clinical status and the severity of disease, as well as treatment management.

Another important issue in the need for careful microbiological examination of samples of Covid-19 patients and identification of microbes involved in coinfections is that inappropriate and incorrect treatments can affect the outcome of the patient's recovery.

The bottom line is that, in order to reduce the side effects of broad-spectrum antibiotics in emergency patients, we must first be able to detect nosocomial infections in hospitalized patients through laboratory routine or molecular new methods. Then, in order to target antibiotic therapies, we need to use of standard antibiograms to determine the correct antibiotics for treatment.

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COVID-19 xəstələrində ko-infeksiyalar və xəstəliklərin idarə olunmasında mikrobioloji diaqnozun əhəmiyyəti

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Tənəffüs yoluxucu viral infeksiyalara, xüsusən də yeni koronavirus xəstəliyinə (COVID-19) yoluxmuş xəstələr ən çox yoluxucu birgə infeksiyalara həssasdırlar və bu da xəstəliklərin və ölümlərin ağırlığını artırır. Bu səbəbdən antibiotik agentləri bakterial birgə infeksiyalar və superinfeksiyaların müalicəsi üçün tətbiq olunmalıdır. Digər tərəfdən, COVID-19 üçün bütün təlimatlarda antibiotiklərin, xüsusən də geniş spektrli antibiotik agentlərinin birləşməsinin düzgün istifadə edilməməsi lazım olduğu açıq şəkildə qeyd edilir. Çünki geniş spektrli antibiotiklərin uzun müddət və bir sıra digər maddələrin birləşməsində istifadəsi nəinki xəstəliyin bərpa olunmasına təsir göstərir, həm də normal bakterial populyasiyada ölümcül potensial ikincil superinfeksiyalara və müqavimətə səbəb ola bilər. Hal-hazırda reanimasiya şöbələrinə müraciət edən COVID-19 xəstələri arasında qaçılmaz antibiotik istifadəsi səbəbindən bakteriyaların təcrid edilməsi və aşkarlanması üçün becərmə əsaslı üsullar xəstəliyin idarə edilməsində daha az həssasdır. Beləliklə, geniş bir potensial patogen və antimikrob müqavimət aşkar edə bilən kulturadan asılı olmayan metodların istifadəsi, xüsusən də müayinə və müalicə təqibləri üçün vacibdir. Beləliklə, əvvəlki hədəfi seçmədən monomikrob və ya qarışıq infeksiyaları təyin etmək üçün bütöv genom metagenomikası kimi kulturadan asılı olmayan üsullardan istifadə edilə bilər. Bütün genom metagenomikası, xüsusilə reanimasiya şöbələrində xəstəxana şəraitində birgə infeksiya və antimikrob müqavimətə səbəb olan patogenlər haqqında dəyərli və faydalı məlumatlar verə bilər. Bu səbəbdən, bu tədqiqatlar antibiotik verilməsinin və infeksiyaların sonrakı hədəflənmiş müalicəsinin idarə edilməsində dəyərli bir köməkçi ola bilər.

Açar sözlər: *COVID-19, bakterial infeksiya, antimikrob, bütün genom metagenomikası*

Сопутствующие инфекции у пациентов с COVID-19 и важность микробной диагностики для лечения заболеваний

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Пациенты, инфицированные респираторными вирусными инфекциями, особенно новым коронавирусным заболеванием (COVID-19), наиболее восприимчивы к сопутствующим инфекциям, что, в свою очередь, увеличивает тяжесть заболевания и смертность. Следовательно, для лечения бактериальной инфекции, сопутствующей суперинфекциям, следует применять антибиотики. С другой стороны, во всех рекомендациях по COVID-19 четко упоминается, что следует избегать неправильного использования антибиотиков, особенно комбинации антибиотиков широкого

спектра действия. Потому что использование антибиотиков широкого спектра действия в течение длительного времени и в сочетании с несколькими другими агентами не только не способствует выздоровлению, но и может привести к потенциально смертельным, вторичным суперинфекциям и индуцированию устойчивости у нормальной популяции бактерий. В настоящее время из-за неизбежного использования антибиотиков среди пациентов с COVID-19, которые поступают в отделения интенсивной терапии, методы выделения и обнаружения бактерий, основанные на культивировании, менее чувствительны для лечения болезни. Следовательно, важно использовать методы, не зависящие от посева, которые могут определять широкий спектр потенциальных патогенов и устойчивость к противомикробным препаратам, особенно для скрининга и последующего лечения. Таким образом, независимые от культуры методы, такие как метагеномика всего генома, могут использоваться для выявления мономикробных или смешанных инфекций без выбора предыдущей мишени. Полногеномная метагеномика может предоставить ценную и полезную информацию о патогенах, вызывающих сопутствующие инфекции и устойчивость к противомикробным препаратам в больничных условиях, особенно в отделениях интенсивной терапии. Следовательно, эти исследования могут оказать ценную помощь в управлении назначением антибиотиков и последующем целенаправленном лечении инфекций.

Ключевые слова: *COVID-19, бактериальная инфекция, противомикробный, полногеномная метагеномика*