Bacterial Coinfection Related to Antimicrobial Resistance in COVID-19 Patients

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Abstract

COVID-19 is a contagious disease caused by a zoonotic virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which mainly infects cells in the respiratory tract, but can also have effects on all organs. Coinfection with SARS-CoV-2 and other microorganisms such as viruses, bacteria and fungi is an important factor in the treatment of COVID-19 because this condition can improve diagnosis, treatment, prognosis and mortality rates. Bacterial coinfection can occur in hospitalized COVID-19 patients, especially in the ICU and has a worse prognosis compared to patients without bacterial infection. Gram-negative bacteria are more commonly found to cause bacterial co-infections than gram-positive bacteria.

Keywords: COVID-19 mortality, Bacterial Coinfection, antimicrobial resistance

1. Introduction

At the end of 2019 in Wuhan, China, an unknown pneumonia was discovered caused by a new zoonotic virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was later called COVID-19. The genome of this virus has a sequence homology of 96.2% and 79.5% with the RaTG13 coronovirus strain in bats. So, this virus most likely came from bats which infected humans after mutations occurred in the spike (S) and nucleocapsid (N) genes. (Rashedi et al, 2020). Compared with other human coronavirus virus genomes, SARS-CoV-2 has optimal ACE2 receptor affinity and a polybasic cleavage site at the S1/S2 junction that determines its infectivity and host range. (Ciotti et al, 2020). ACE2 is an enzyme involved in the Renin-Angiotensin Aldosterone system (RAAS). The widespread expression of ACE2 throughout the body may indicate that SARS-CoV-2 can have effects on all organs. The most common symptoms in COVID-19 sufferers are fever, cough, fatigue and shortness of breath. Death in COVID-19 patients is strongly associated with acute respiratory distress syndrome (ARDS), acute respiratory failure, coagulopathy, septic shock, and metabolic acidosis. In addition, the presence of comorbidities in the patient and the patient's age can also provide a greater risk of worse clinical outcomes. (Mukherjee and Pahan, 2021).

Bacterial coinfection is a common complication of viral infections of the respiratory tract which can trigger increased morbidity and mortality. Often bacterial infections are associated with the risk of shock and respiratory failure, prolonged ICU stay, and death. (Westblade et al, 2021). Coinfection with SARS-CoV-2 and other microorganisms such as viruses, bacteria and fungi are an important factor in the treatment of COVID-19 because this condition can improve diagnosis, treatment, prognosis and mortality rates. There are various types of infection in COVID-19, such as secondary SARS-CoV-2 after bacterial infection, mixed infection between viral and bacterial pneumonia coinfection, secondary bacterial superinfection after SARS-CoV-2 infection. (Asmarawati et al, 2021).

Antimicrobial resistance (AMR) is considered a threat to the public health system, not only in developing countries but also throughout the world. This infection causes serious illness and prolonged hospitalization, increased health care costs, higher second-line treatment costs, and can result in treatment

failure leading to death. (Dadgostar, 2019). The emergence of antimicrobial resistance is an unexpected and unavoidable consequence of the COVID-19 pandemic. There has been an increase in multidrug-resistant organisms (MDROs) during the COVID-19 pandemic. The most underlying reasons for this to occur are the high intensity of care required by patients, the vulnerability of health workers who are in contact with patients for long periods of time, and health workers who lack work experience in the intensive care unit (ICU) setting. (Lai et al, 2021).

2. Material and Method

This review was conducted by searching for the efficacy, safety indication and recommendation of using keyword "COVID-19 mortality", "bacterial coinfection" and "antimicrobial resistance" in database, PubMed (https://pubmed.ncbi.nlm.nih.gov). The inclusion criteria are full-text literature and studies conducted during COVID-19 pandemic, and the subjects were COVID-19 patients who have bacterial coinfections and received antimicrobial treatment. The exclusion criteria were review articles without an English version.

3. Result and Discussion

Bacterial infections overall are less common in patients hospitalized with COVID-19, bacterial infections are common in patients treated in the ICU. This may be related to blood culture examinations which are more frequently performed on patients in the ICU. (Westblade et al, 2021). The incidence of bacterial infections that are resistant to antibiotics increases from year to year, and it is estimated that 10 million people will die by 2050 due to antibiotic resistance. However, the COVID-19 pandemic has had a worse impact on this estimate, namely there is a possibility that this increase will occur more quickly. (Mirzaei et al, 2020). Giving antibiotics to patients in hospitals is carried out for various reasons. The clinical manifestations shown by each patient with a bacterial infection, whether bacterial co-infection or secondary infection, are taken into consideration when administering antibiotics. (Asmarawati et al, 2021). At the start of the COVID-19 pandemic, data regarding bacterial co-infections in COVID-19 patients was still lacking, resulting in an increase in antibiotic prescriptions, following pneumonia treatment with cefotaxime, ceftriaxone, and amoxicillin clavulanic acid. (Ruiz-garbajosa & Canton, 2021).

The following are several studies that discuss bacteria that are often found in COVID-19 patients with bacterial infections.

Table 1. List of Articles

Location	References	Bacterial Coinfection	Infection
Wuhan Union Hospital, China	Li et al, 2020	Acinetobacter baumannii, Klebsiella pneumonia, Stapylococcus maltophia	Lung infection, bloodstream infection, mixed lung-bloodstream infection
Shanghai Public Health Clinical Center, Tongji Hospital, Tongji Medical College, China	Zhang et al, 2020	Enterococcu faecium, Acinetobacter baumanni, Klebsiella pneumonia	Respiratory infection, Bloodstrean infection, urinary infection
RS. Universitas Airlangga, Surabaya, Indonesia	Asmarawati et al, 2021	Acinetobacter baumannii, Candida spp, Klebsiella pneumonia	Respiratory tract infection, bloodstream infection, urinary tract infection
Medical Center Philadelphia, Philadelphi pennsylvania	Neto et al, 2021	Escherichia coli, Enterobacter cloacae	Genitourinary infection, skin infection, respiratory infection
Tertiary Care hospita;, North India	Sahu et al, 2022	Escherichia coli, Pseudomonas	Bacteremia, respiratory infection, urinary infection

		aeruginosa, Klebsiella spp.	

Acinetobacter baumanni is a bacteria that causes respiratory tract infections that is most often found, especially in patients treated in ICUs that use mechanical ventilation. Apart from that, environmental contamination and length of hospitalization also influence the occurrence of bacterial co-infections. (Asmarawati et al, 2021). On average, 31 out of 32 patients with COVID-19 who used mechanical ventilation were declared dead on the 14th day. None of the patients who used extracorporeal membrane oxygenation survived. (Zhou et al, 2020).

In research conducted by Li et al. (202), it was found that there were more gram negative bacteria than gram positive bacteria. However, if we look at the bacteria that infect the bloodstream alone, gram-positive bacteria are more dominant. The use of central venous catheter implantation during hospital treatment is associated with the occurrence of gram-positive bloodstream infections. Providing invasive procedures to patients in the ICU, such as tracheotomy and other procedures associated with skin colonization during surgery, provides a more dominant proportion of gram-positive bacteria. (Zhang et al, 2020). Other research suggests that gram-negative bacteria are the most common cause of bacterial coinfection in COVID-19 patients. The increase in the prevalence of gram-negative bacteria and gram-positive bacteria in research conducted by Sahu et al (2022) was associated with immune dysregulation and intestinal dysbiosis in COVID-19 patients. Inflammatory mediators disrupt intestinal permeability which causes leakage of intestinal microbes and related metabolites into the circulation so that they migrate to organs including the lungs and cause bacteremia, urinary tract infections, and various other infections.

SARS-CoV-2 can cause immune dysregulation due to increased production and circulation of cytokines leading to hyperinflammation and impaired lymphoid function. (Son et al, 2021). The elderly patient population is more likely to be found with bacterial co-infections, they experience an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines. These age-related pathological processes include changes in ACE-2 receptor expression, excess reactive oxygen species (ROS) production, and altered autophagy. (Neto et al, 2021). The use of corticosteroids can increase patient survival, but can cause consequences in the form of secondary bacterial infections, invasive pulmonary aspergillosis, osteonecrosis of the femoral head, and delayed viral shedding in COVID-19 patients. Therefore, the use of corticosteroids is recommended only for short periods of time. (Son et al, 2021). Due to COVID-19, the need for antimicrobial use has increased compared to previous years. High levels of antibiotic administration can be a factor in the emergence of antibiotic resistance. Microbiological examination is an important strategy to confirm infection in patients and determine the choice of antibiotics appropriate to the infection. Patients who do not show signs of pathogenic bacteria after 48 hours of culture should stop giving antibiotics. (Asmarawati et al, 2021).

4. Conclusion

Koinfeksi bakteri dapat terjadi pada pasien COVID-19 yang dirawat di rumah sakit terutama pada ICU dan memiliki prognosis yang lebih buruk dibandingkan dengan pasien tanpa infeksi bakteri. Bakteri gram negative lebih banyak ditemukan sebagai penyabab koinfeksi bakteri dari pada bakteri gram positif.

Acknowledgements

References

Asmarawati, T. P., et al. 2021. The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya. F1000Research, 10, 113. https://doi.org/10.12688/f1000research.31645.2

Ciotti, M., et al.. 2020. The COVID-19 pandemic, Critical Reviews in Clinical Laboratory Sciences, 57:6. Available at: https://doi.org/10.1080/10408363.2020.1783198

Dadgostar, P. 2019. Antimicorbial Resistance: Implications and Costs. Infect Drug Resist. 12: 3903-3910. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6929930/

Lai, C., et al. 2021. Increased Antimicrobial Resistance During the COVID-19 Pandemic. International Journal of Antimicrobial Agents, 57(4). Available at: https://doi.org/10.1016/j.ijantimicag.2021.106324

Mukherjee, S., Pahan, K. 2021. Is COVID-19 Gender-sensitive?. J Neuroimmune Pharmacol 16. Available at: https://doi.org/10.1007/s11481-020-09974-z

Mirzaei, R., et al. 2020. Bacterial co-infections with SARS-CoV-2. IUBMB life, 72(10), 2097–2111. https://doi.org/10.1002/iub.2356

Neto, G., M., et al. 2021. Bacterial infections and patterns of antibiotic use in patients with COVID-19. Journal of medical virology, 93(3), 1489–1495. https://doi.org/10.1002/jmv.26441

Rashedi, J. et al. 2020 "Risk Factors for COVID-19," Le Infezioni in Medicina, 4, pp. 469–474. Available at: https://pubmed.ncbi.nlm.nih.gov/33257620/

Ruiz-Garbajosa, P., & Cantón, R. 2021. COVID-19: Impact on prescribing and antimicrobial resistance. Revista espanola de quimioterapia : publicacion oficial de la Sociedad Espanola de Quimioterapia, 34 Suppl 1(Suppl1), 63–68. https://doi.org/10.37201/req/s01.19.2021

Sahu, C., et al. 2022. Bacterial coinfections in COVID: Prevalence, antibiotic sensitivity patterns and clinical outcomes from a tertiary institute of Northern India. Journal of family medicine and primary care, 11(8), 4473–4478. https://doi.org/10.4103/jfmpc.jfmpc_41_22

Son, H. J., et al. 2021. Risk factors for isolation of multi-drug resistant organisms in coronavirus disease 2019 pneumonia: A multicenter study. American journal of infection control, 49(10), 1256–1261. https://doi.org/10.1016/j.ajic.2021.06.005

Westblade, L. F., Simon, M. S., & Satlin, M. J. 2021. Bacterial Coinfections in Coronavirus Disease 2019. Trends in microbiology, 29(10), 930–941. https://doi.org/10.1016/j.tim.2021.03.018

Zhou, F., et al. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England), 395(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3