

## A review

**Bacterial infections in COVID-19 patients and their possible treatments**A'liyatur Rosyidah<sup>1\*</sup>, Mohamad Padri<sup>2</sup>, Paulus Damar Bayu Murti<sup>3</sup><sup>1</sup>Research Center for Biology, National Research and Innovation Agency (BRIN), Indonesia<sup>2</sup>School of Environment Engineering, Faculty of Engineering, Suranaree University of Technology, Thailand<sup>3</sup>Department of Food Technology, Faculty of Science and Technology, Karangturi National University, Indonesia**Abstract**

The COVID-19 pandemic, which started in the beginning of 2020 was triggered by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, severely affected various sectors, especially health. The effect of COVID-19 on patients is exacerbated by bacterial co-infections and secondary bacterial infections. There are few studies on how bacterial co-infections and secondary bacterial infections worsen COVID-19 patients, including in Indonesia. Therefore, it is necessary to update and summarize the understanding of bacterial infections characteristics to help optimize the diagnosis, prevention, and treatment decisions. Antibiotics have been used in COVID-19 patients to treat bacterial infections to date, which could contribute to antimicrobial resistance in the future. The review's objective is to summarize bacterial infections in COVID-19 patients and several possible treatments, including antibiotics, phage therapy, probiotics/prebiotics, and nanomedicine for antimicrobial peptides (AMPs) delivery.

Keywords: antibiotics, bacterial infections, COVID-19, nanomedicine, phage therapy, probiotics, SARS-Cov-2

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**Introduction**

Coronavirus disease 2019 (COVID-19) is an illness caused by the infections of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was initially found in Wuhan in December 2019, and became a global pandemic worldwide in early 2020 (Xie and Chen, 2020). Coronaviruses can cause various problems, including respiratory, gastrointestinal (GI), and neurological. The common symptoms of SAR-CoV-2 infections include fever, breathlessness, muscle ache, dry cough, tiredness, headache, sneezing, sore throat, anosmia, and pneumonia. Several uncommon symptoms were reported, such as abdominal pain, diarrhea, nausea, and vomiting (Jiang et al., 2020; Zu et al., 2020). COVID-19 may cause a shift in the lung microbiome community, influencing the GI tract microbiota and causes GI problems. The SARS-CoV-2 primary host receptor is angiotensin-converting enzyme 2 (ACE2), which was presented in the lung and intestines. Therefore, the colonization of ACE2 receptors in the intestine caused by the entry of the virus through ingestion might be the cause for GI tract symptoms. Another possibility for COVID-19-related GI symptoms is intestinal apoptotic pathway failure caused by a respiratory infections (Kumar et al., 2020; Perrone et al., 2012).

Generally, bacterial infections (both bacterial co-infections and secondary infections), are common infections identified in the viral respiratory tract infections, including COVID-19. The frequency and features of infections of bacteria on COVID-19 patients

are poorly understood. To date, only a few studies investigated bacterial infections related to COVID-19. Typically, bacterial infections has been linked to the most severe illness, increased healthcare costs, and increased patient death in patients with acute viral respiratory. According to the meta-analysis of COVID-19 patients conducted by Langford and co-workers, bacterial infections were found in 6.9% of patients that commonly come from critically ill patients (Langford et al., 2020). Some of the literature suggested that secondary bacterial infections were more common than bacterial co-infections (Feldman & Anderson, 2021; Vaillancourt & Jorth, 2020). Broad-spectrum antibiotics such as third-generation cephalosporin and fluoroquinolones have been given to more than 90% of COVID-19 patients with bacterial infections. However, identifying bacterial infections in COVID-19 patients is essential to justify initial antibiotics treatment and avoid misuse or overuse of antibiotics, ultimately leading to the development of antimicrobial resistance (Bengoechea & Bamford, 2020; Feldman & Anderson, 2021).

Nowadays, most studies and healthcare focus on the SARS-CoV-2 infection treatment, while only few prioritize bacterial infections and their treatments. This review therefore highlights the bacterial infections in COVID-19 patients and their potential treatments, including antibiotics and non-antibiotic treatment. This review is sourced from published articles regarding COVID-19, especially on the bacterial infections, to help health workers worldwide manage bacterial infections.

**SARS-CoV-2 and COVID-19**

Coronaviruses (CoV) are viruses that have a crown-like structure in their surfaces. Firstly, Human coronaviruses was discovered in 1960, and there are currently seven varieties of CoV that are known to cause disease. SARS coronaviruses are included in the family

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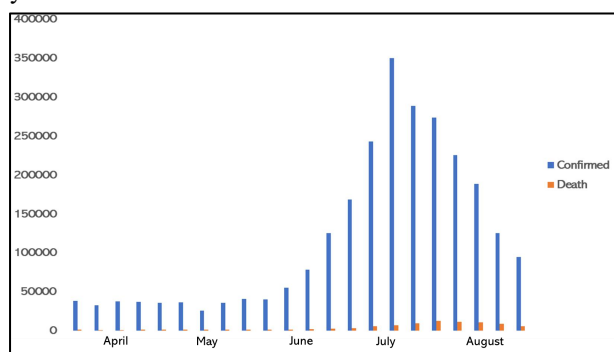
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of the zoonotic beta-coronavirus, and SARS-CoV-2 is a novel coronavirus that generates COVID-19 disease in humans, which was initially found in the end of 2019 in Wuhan, China. Most of the initial cases were attributed to the Huanan seafood market, which sold seafood and live animals (Chowdhury & Oommen, 2020). Several findings indicate that the initial host of COVID-19 was bats and subsequently spread to humans via wild animals. However, further virus spread occurs through human-to-human transmission (Olaimat et al., 2020; Xie & Chen, 2020; Zu et al., 2020).

Infection with SARS-CoV-2 can lead to various symptoms in the respiratory, digestive, and nervous systems. In addition, SARS-CoV-2 is highly harmful and rapidly transmitted, and thus the number of affected people has risen over the world. The infection rate of SARS-CoV-2 in China, United States, and India is very high, and the disease is gradually spreading to Indonesia. Until the time of writing this manuscript confirmed there were 222,637,937 cases globally (Dong et al., 2020) and has now been declared as a pandemic by World Health Organization (WHO). In Indonesia, the first case of COVID-19 with 2 patients was reported on March 2020 (Kemenkes RI, 2021). As of September 9, 2021, there are more than 4,147,365 confirmed COVID-19 cases with 137,782 (3.3%) reported deaths (Dong et al., 2020). The confirmed COVID-19 cases data in Indonesia was sourced from the Center for System Science and Engineering (CSSE) at John Hopkins University and is presented in Figure 1. Indonesia observed its highest peak of COVID-19 cases in mid-July and has subsequently seen a decrease in confirmed cases. However, the total number of confirmed cases remains comparatively higher than those observed earlier in this year.



**Figure 1.** Weekly cumulative confirmed case and death in Indonesia from April 4 to August 29, 2021.

The clinical symptoms of COVID-19 are diverse, ranging from asymptomatic to several prevalent symptoms, such as fever, breathlessness, dry cough, muscle pain, and tiredness. In addition, sneezing, headaches, sore throat, anosmia, pneumonia, abdominal pain, nausea, diarrhea, and vomiting were also reported as symptoms of COVID-19 (Jiang et al., 2020; Kumar et al., 2020; Olaimat et al., 2020; Zu et al., 2020). COVID-19 patients are divided into four categories based on their clinical manifestations: mild, moderate, severe, and critical disease. Mild patients were categorized by fever < 38 °C, and without symptom of pneumonia imaging

findings. The moderate patients were identified by fever (>38 °C) with respiratory symptoms, followed by pneumonia imaging findings. In contrast, the severe patients were categorized by respiratory disorder with a respiratory rate of more than 30 times per minute and more than 93% oxygen saturation at rest. In comparison, the critical patients were classified by respiratory failure, which needs mechanical assistance, extrapulmonary organ failure, and needed an intensive care unit (ICU) facility (Zu et al., 2020).

The Angiotensin-converting enzyme 2 (ACE2), presented in the lungs and gut, is a primary receptor of SARS-CoV-2. The first step of viral infection begins with the virus entrance into the host cells by attaching a virus's spike glycoprotein to the ACE2 receptor. Briefly, the virus's Spike protein (S-protein) adheres to the ACE2 receptor, especially on the tip of subdomain I. This interaction leads to the activation of the virus-host membrane fusion. Then, the virus's RNA is released into the cytoplasm, resulting in infection. The division of the furin-like cleavage site by proprotein convertase furin, which is found at the envelope glycoprotein of the virus, improves the virus's fusion with the host cell membrane. Several transmembrane proteinases have been implicated in this interaction, including transmembrane protease serine 2 (TMPRSS2), a disintegrin and metalloproteinase domain 17 (ADAM17), and a TNF-converting enzyme (Cheng et al., 2020; Jiang et al., 2020; Li et al., 2003; Ni et al., 2020; Song et al., 2018; Xie & Chen, 2020).

### Bacterial infections in COVID-19

Bacterial infections, particularly those caused by multidrug-resistant bacteria (MDR), continue to be a significant public health concern worldwide, so antibiotics treatment becomes less effective. Each year, the number of patients infected with antibiotic-resistant bacteria grows, leading to the death of patients caused by resistant bacterial infections (Michael et al., 2014; Thongkrachang et al., 2016). Bacterial co-infections are commonly identified in viral respiratory infections and lead to the severe disease and mortality, as seen in influenza and H1N1 outbreak in 1918 and 2009, respectively (Feldman & Anderson, 2021; Nasir et al., 2021; Rice et al., 2012; Taubenberger & Morens, 2020). In addition, these infections able to suppress the host's immune system, raise antibiotics treatment sensitivity, and worsen the disease severity (Xin-Xu & Xiao-Nong, 2013).

The Centres for Disease Controls and Prevention (US) interpret the co-infection as an infection that arises simultaneously alongside the primary infection. In contrast, secondary infection refers to an infection that develops after a primary infection, most commonly caused by bacteria that are resistant to the antibiotics used previously (Feldman & Anderson, 2021). In the COVID-19 case, 20% of the patients that developed acute respiratory syndrome were taken to the ICU. Bacterial infections, particularly ventilator-related pneumonia and bloodstream infections are substantially associated with ICU admission. Nosocomial infections are the most described hospital-acquired infections within 48 to 72 h after admission that are mainly trans-

mitted through human contact and medical devices (Agaba et al., 2017; d'Humieres et al., 2021; Sharifipour et al., 2020). Mucociliary clearance can be compromised if ciliated cells are damaged due to viral respiratory infections, increasing the bacterial adhesion to the mucins and enhancing the colonization of bacteria (Manohar et al., 2020; Wilson et al., 1996). Moreover, the viral infections might induce acute inflammatory reactions and pulmonary tissue damage. This condition might enhance the susceptibility to bacterial infections after viral infections, called superinfection or secondary infections (Lucien et al., 2021; Paget & Trottein, 2019).

The bacterial co-infections in COVID-19 patients were predominantly identified over viral and fungal infections. The rate of bacterial co-infections on COVID-19 patients varies between 3 to 30%. There are around 91.8% bacterial infections compared to fungal (23.3%) and viral (31.5%) infections (Langford et al., 2020; Vaillancourt & Jorth, 2020). The exact mechanism of bacterial co-infections worsening COVID-19 patients remains unclear. However, the historical data of seasonal flu and the first SARS-CoV outbreak indicates that bacterial co-infections can exacerbate viral infections. In 2003, the bacterial infections were diagnosed from 30% of first SARS-CoV patients in Prince of Wales Hospital, Hong Kong, and positively associated with the disease severity (Lee et al., 2003). In influenza itself, bacterial co-infections constitute a leading source of morbidity and mortality. The highest severe complication rate of the influenza infection was observed among children under 2 years old and adults over 65 years old, and also patients with chronic medical conditions. From 2004-2007, there were 166 influenza-associated pediatric deaths reported in the United States during the influenza season. *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus* (MRSA) are the most common bacteria identified in patients. Children with *S. aureus* infection were reported having a higher frequency of acute respiratory distress syndrome and pneumonia than children without any bacterial infections. This condition was followed by an increase in child mortality rate (Finelli et al., 2008). The majority of deaths during the 1918 influenza pandemic were due to bacterial infections rather than direct impacts of the virus, according to data from lung tissue samples obtained during the pandemic. Bacterial co-infections increased by 65% during the seasonal influenza cases and were largely associated with mortality and morbidity (Chertow & Memoli, 2013; Klein et al., 2016; Zahariadis et al., 2006). It is currently unknown if bacterial co-infections in the COVID-19 patients is increasing, and thus further investigations into this phenomenon is urgently needed since the COVID-19 also relates to viral respiratory infections.

Based on a meta-analysis study, which sampled 3338 hospitalized COVID-19 patients, it was known that 3.5% and 14.3% of patients had bacterial co-infections and secondary bacterial infections, respectively. In COVID-19 patients, 6.9% of the total patients were found in critical patients (Langford et al., 2020; POH, 2020). Through the first wave of the COVID-19 pandemic in France, among 197 ICU-COVID-19 patients, 44.7% of them experienced bacterial infections, such as

pneumonia, bloodstream infections, and urinary tract infections. The number of infected patients with bacteria were more severe at ICU than patient non-ICU and showed a higher mortality rate in ICU. The most common bacteria isolated from bloodstream infections are Enterococci (35.5%) and Staphylococci (32.2%). On the other hand, the most frequent bacteria identified from pneumonia are *S. aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Among 37 Enterobacteriaceae, 11 and five isolated bacteria were resistant to third-generation cephalosporin and carbapenems, respectively. Bacterial infections in the bloodstream may lead to digestive or oropharyngeal translocation. Therefore, the information on the oropharyngeal and gut microbiota compositions is essential to accurately identify bloodstream infections. Moreover, patients with bacterial infections spent more time in the hospital than patients who did not have bacterial infections. (d'Humieres et al., 2021; Fontaine et al., 2020). According to Sharifipour et al. (2020), the isolated *Acinetobacter baumannii* from COVID-19 patients with secondary bacterial infections undergoing ICU hospitalization were resistant to all antibiotics tested, except colistin. They also wrote about one isolate of MRSA and resistance to all evaluated antibiotics, including penicillin, cefoxitin, erythromycin, azithromycin, gentamycin, linezolid, cotrimoxazole, and ciprofloxacin (Sharifipour et al., 2020).

Feng et al. (2020) conducted a multicenter investigations on 476 COVID-19 patients at three hospitals in Wuhan, Shanghai, and Anhui, reporting that secondary bacterial infections was linked to severity. The patients were divided into three categories in this study: moderate, severe, and critical. The percentage of bacterial infection was higher on the critical patient with the rate of 34.5%, followed by severe (8.3%) and moderate (3.9%) (Feng et al., 2020). Another study conducted by Zhu et al. (2020) in Jiangsu Province, China, discovered that 242 from 257 of COVID-19 patients were infected by one or more pathogens, containing viruses, bacteria, and fungi. The main bacteria in all COVID-19 patients was *S. aureus*, followed by *K. pneumoniae*, *Haemophilus influenzae*, and other microorganisms as seen in Figure 2. The COVID-19 patients with the highest bacterial infections rates are those aged 15 to 44 (Zhu et al., 2020). Another study mentioned that *K. pneumoniae*, *Acinetobacter* sp., *S. aureus*, *P. aeruginosa*, *E. coli*, and *Stenotrophomonas maltophilia* were identified from culture specimens of moderate and severe COVID-19 patients. In addition, several drug-resistant strains were also identified, such as multidrug-resistant (MDR) and ceftriaxone-resistant *Acinetobacter*, vancomycin-resistant *E. coli*, ceftriaxone-resistant *K. pneumoniae*, MDR *P. aeruginosa*, MRSA, and methicillin-resistant *P. aeruginosa*. Hospital acquired pneumonia, community acquired pneumonia, and the infection on bloodstream, urinary tract, skin, and soft tissue were the most common sources of infections. The mortality of the COVID-19 patients with bacterial co-infections or secondary infections was 42 and 18%,

respectively, which was greater than the mortality rate in patients without bacterial infections. The majority of the patients who died were infected with Gram-negative bacteria such as *Acinetobacter* sp. and *P. aeruginosa* (Nasir et al., 2021).

In Indonesia, the information of incidence and prevalence of bacterial infections in COVID-19 patients has not been widely reported (Prasetyoputri, 2021). However, based on a retrospective study at the Airlangga University Hospital, Surabaya conducted by Asmarawati et al. (2021), it was stated that there 19.7% of moderate

and critically ill patients had bacterial infections. Those bacterial infections impacted the increase of hospitalization length, high risk of respiratory failure, use of ventilators, and ICU admission. Of the identified bacteria, the proportion of Gram-negative bacteria infections was higher than Gram-positive bacteria, as seen in Figure 3, which is dominated by *A. baumannii*. Several resistant bacteria were also identified in this case, such as extended-spectrum beta-lactamases (ESBL) producing *E. coli* and ESBL+ producing *K. pneumoniae*

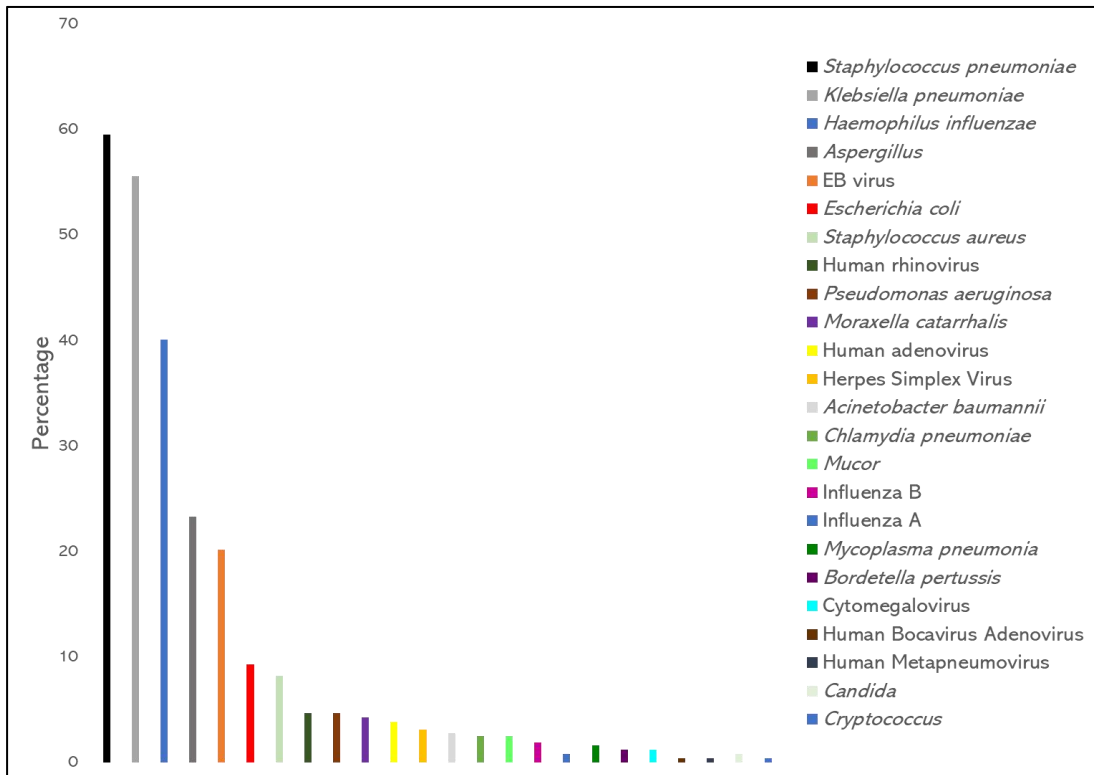


Figure 2. Distribution of respiratory pathogen in COVID-19 patients. Figure reproduced with permission from Zhu et al., 2020

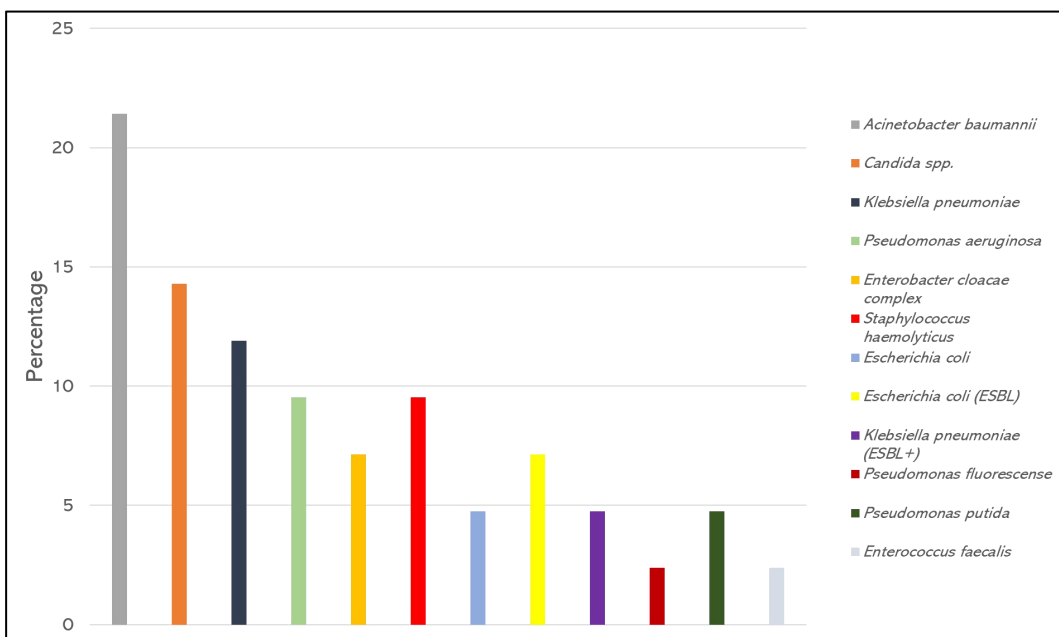
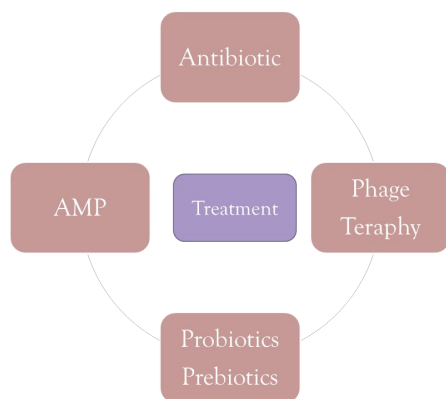


Figure 3. Summary of pathogenic bacteria from COVID-19 patients. Figure reproduced with permission from Asmarawati et al. 2020.

### Treatments of bacterial infections

Because bacterial infections can exacerbate the COVID-19 patient's conditions, a medication to overcome it is required. Antibiotics, phage therapy, the use of probiotics/prebiotics, and AMPs encapsulated in nanomedicine are some of the possible treatments that could be used in bacterial infections (Fig. 4) will be discussed below.



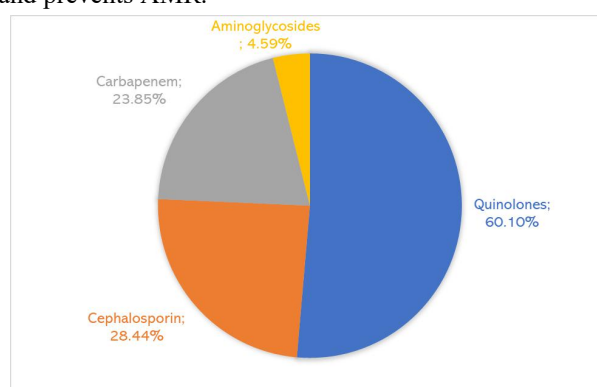
**Figure 4.** Possible treatment of bacterial infections in COVID-19 patients.

### Antibiotics

Bacterial co-infections and secondary bacterial infections are frequently the cause of death in COVID-19 patients. Thus, antibiotic use appears to be a key barrier to COVID-19 patients mortality (Sieswerda et al., 2021). The spreading of COVID-19 worldwide is accompanied by a surge in antibiotic use (Lucien et al., 2021), with the most frequently used antibiotics being fluoroquinolones, azithromycin, vancomycin, linezolid, carbapenems, and cephalosporins (Chedid et al., 2021; Clancy & Nguyen, 2020; Langford et al., 2020). In several reports, the majority of COVID-19 patients admitted to hospitals are treated with broad-spectrum antibiotics with unknown efficacy. For example, Nasir et al. (2021) reported 82% of antibiotic utilization, of which 62% were given to patients without a clear indication of bacterial infections. This phenomenon can potentially cause increased antimicrobial resistance rates (d'Humieres et al., 2021; Nasir et al., 2021; Sharifipour et al., 2020; Sieswerda et al., 2021). Asmarawati et al. (2021) conducted a retrospective study on COVID-19 patients and reported around 75.2% of the moderate to critically ill patients reported receiving antibiotics treatment (Fig. 5). The antibiotics used are quinolones (moxifloxacin and levofloxacin), cephalosporin (ceftazidime, cefotaxime, ceftriaxone, cefuroxime, and cefoperazone-sulbactam), a carbapenem (meropenem), and levofloxacin (Asmarawati et al., 2021).

The high use of antibiotics and the emergence of resistant isolates have been reported in several hospitals in Indonesia. To date, there are no guidelines for the use of antibiotics in cases of COVID-19. Therefore, the efforts to minimize the impact of COVID-19 on the emergence of resistant bacteria and policies for implementing an antibiotics stewardship program (ASP) are urgently needed (Prasetyoputri, 2021). Antibiotic

overuse has been linked to the appearance and spread of antimicrobial resistance (AMR) in numerous studies, and is one of the significant global health challenges (Lucien et al., 2021). Therefore, the China National Health Commission has advised that the misuse of antibiotics, particularly those with broad-spectrum activity, must be avoided. To date, there have been no studies proving the potency and prosperity of specific antibiotics in COVID-19 patients with suspected bacterial pneumonia. However, most committees recommend that the treatment of antibiotics should be given to a patient with radiological abnormalities and inflammatory markers associated with bacterial infections, as a good practice antibiotics use (Sieswerda et al., 2021). It means that antibiotics must be given at the correct dose, for the right amount of time, and in a way that assures the best result and prevents AMR.



**Figure 5.** Statistics of antibiotic usage in the COVID-19 patients in Airlangga University Hospital. Figure reproduced with permission from Asmarawati et al. 2020.

### Phage therapy

One alternative for bacterial infections treatment is phage therapy, especially the infection caused by resistance pathogens. Phage therapy is based on the premise of using microbial viruses to destroy their hosts, ideally eliminating bacterial illnesses (Murray et al., 2021). The bacteriophage will utilize bacteria as hosts to replicate the genome, synthesize proteins, and phage assembly. The phage therapy has several advantages, including that they exhibit bacterial specificity to their host, lack of cross-resistance with antibiotics, and easy discovery (Loc-Carrillo & Abedon, 2011; Manohar et al., 2020; Singh et al., 2021). Phage therapy was found to be effective in eradicating resistant bacterial infections in a clinical study (Kutter et al., 2010). Phages have minimum toxicity because they are primarily made up of protein and DNA, which are eventually digested in the human body (Loc-Carrillo & Abedon, 2011; Manohar et al., 2020), and phage therapy has previously been helpful in medication bacterial infections in cancer patients (Weber-Dabrowska et al., 2001). Moreover, the bacteriophages have been effective as preventive agents against *Salmonella enterica* infections (Ahmadi et al., 2016). However, there is no evidence that phage therapy can be used to treat viral infections and thus, phage therapy studies must be investigated.

The engineered phage proteins for dissemination also can be used as an alternative for phage therapy. Endolysins are phage-encoded enzymes that are released into the environment at the end of the lytic cycle. This enzyme has the ability to break down the peptidoglycan layer of the bacteria (Murray et al., 2021). Furthermore, due to the enzyme specificity, the ability of endolysins to destroy the bacterial cell wall opens up the opportunity for their use as possible antimicrobial agents to eliminate pathogenic bacteria without affecting normal microbiota (Loc-Carrillo & Abedon, 2011; Murray et al., 2021). Therefore, phage-derived endolysins offer promise as a treatment for multidrug-resistant bacteria.

### Probiotics and prebiotics

According to recent studies, some COVID-19 patients experience symptoms related to the digestive system, such as nausea, diarrhea, and vomiting (Kumar et al., 2020). This virus infections might also change the host-microbiota structure since ACE2 receptor also presented in the intestine. Thus, COVID-19 can induce changes in the lung's microbiota community, which modulate the microbiota in the gastrointestinal (GI) tract and cause symptoms related to the digestive system such as diarrheal, nausea, and vomiting. The colonization of ACE2 receptor in the GI tract might be caused by the entry of the virus through ingestion or the presence of intestinal apoptotic dysfunction due to the infection of the respiratory system can cause symptoms in the GI tract linked with COVID-19 (Kumar et al., 2020; Perrone et al., 2012).

Probiotics are live bacteria that have a positive outcomes on the host if given in sufficient proportions. Probiotics proved to have a useful immune response on the health of the host by managing the bacterial community and modulating immune cells (Bustamante et al., 2020; Olaimat et al., 2020; Rao & Samak, 2013). COVID-19 infections change the equilibrium of natural microbiota in the gut. In China, SARS-CoV-2 infections cause a reduce in the amount of *Bifidobacterium* spp. and *Lactobacillus* spp. (Xu et al., 2020). Another observation was the amount of pathogens including *Actinobacteria* spp., *Corynebacterium* spp., and *Ruthenibacterium* spp. were also increased significantly (Yu et al., 2020). Because COVID-19 is a new disease, no research has been done on utilizing probiotics to treat it.

Using probiotics to treat and prevent COVID-19 could be an effective strategy (Olaimat et al., 2020), and since COVID-19 is a new disease, no research has been done on using probiotics as a treatment. In COVID-19, the immunological advantages of probiotics could be gained by stimulating IgA secretion, improving phagocytosis and macrophages capabilities, and adjusting regulatory cells. Furthermore, the impact of probiotics on improving immune activities have been observed, which may play a part in the blockage and infection management caused by SARS-CoV-2 (Jayawardena et al., 2020).

### Nanomedicine for antimicrobial peptides (AMPs) delivery

Antimicrobial peptides (AMPs) are small peptide-based compounds that are 50-100 amino acids in length, and have been shown to inhibit bacteria, fungi, parasites, and viruses. The AMPs were developed due to the growth of antibiotic-resistant bacteria and the increasing concern about the usage of antibiotics. Until May 2021, a total of 3,257 AMPs were updated from the Antimicrobial Peptide Database (APD3) (<http://aps.unmc.edu/AP/>), which 60% (2666) of them act as antibacterial peptides (Huan et al., 2020; Teixeira et al., 2020). The AMPs have a broad spectrum of activity, with a quick initiation of killing, low levels of induced resistance, and anti-inflammatory properties (Gordon et al., 2005). As an antimicrobial agent, the AMPs form pores on the bacterial membranes, causing membrane permeability and leakage of intracellular substances, ultimately leading to cell death (Lei et al., 2019). Other AMP mechanisms of action include activating immune cells, killing, and clearing pathogenic bacteria, leading to controlled inflammation (Teixeira et al., 2020). However, AMPs showed low stability and bioavailability (Teixeira et al., 2020).

Nanotechnology offers an opportunity for the nanofunctionalization of an antimicrobial compound to restore and enhance its antimicrobial activity (Banin et al., 2017). Nanomedicine applications might provide solutions during the COVID-19 pandemic, especially in terms of treating viral and bacterial infections. By this approach, the specificity and efficiency of drug delivery could be improved by modifying the encapsulated medicine and generating a regulated release (Sharma et al., 2021). The nanomedicine approach utilizes nanomaterials which are more commonly used in diagnostic and therapeutic applications and have a substantial impact on human health (Das et al., 2017). The incorporation of AMPs into nanoparticles offers various advantages, such as improving the limitation of AMPs and the ability to control the distribution of AMPs nanomaterials inside the body or specific organ (Teixeira et al., 2020). In addition, the small size of nanomaterials will make it easy to interact and permeate several types of membranes. Nanomedicine properties can be engineered to enhance stability and reduce aggregation (Sharma et al., 2021). Rishi et al. (2015), have successfully encapsulated cryptidin-2, a Paneth cell AMP, into the chitosan nanoparticles which showed to improve their oral therapeutic potential against *Salmonella* infection (Rishi et al., 2015). Furthermore, the development of cecropin melittin-conjugated gold nanoparticles (CM-SH AuNPs) showed better antibacterial efficacy and stability in serum and the presence of proteolytic enzymes, and reduced cytotoxicity against human cells soluble cecropin melittin (Rai et al., 2016). The application of nanotechnology is not only limited to drug delivery but could also be applied for personal protective equipment (PPE) or patients suit by coating them with nanoparticles to protect both healthy and ill individuals (Sharma et al.,

2021). The fabrication of nanocutical cotton fabric enriched with non-toxic zinc oxide showed antimicrobial activity against *P. aeruginosa* as a model for SARS-CoV-2 mimic. These materials could be a candidate for further development as antibacterial or antiviral washable cloth material (Adhikari et al., 2021).

However, the use of nanomedicine for pharmacology requires several risk analyses and long-term impacts. Some researchers have difficulty interpreting the efficacy data from in-vitro and in-vivo results (Sharma et al., 2021). Therefore, the guideline for the safe use of AMPs nanomaterials needs to be developed. In addition, more accurate animal model's experiments are required to evaluate safety concerns. Nanostructure production methods should also be enhanced, and scalable studies for industrial production are critical for promoting the cost-effectiveness of these novel formulations (Teixeira et al., 2020).

## Conclusion

Combating bacterial infections in COVID-19 remains a difficult challenge. The number of bacterial co-infections cases in COVID-19 patients was lower than secondary bacterial infections cases, and despite the low number of bacterial infections, the impact of these infections needs to be considered, particularly for hospitalized patients. Antibiotics have been used in the past to treat bacterial infections in humans. The use of antibiotics for the medication of bacterial infections, in COVID-19 patients, must be considered. The appropriate use of antibiotics during the COVID-19 pandemic will help reduce the emergence of antibiotic-resistant bacteria. Several alternative therapies reduce antibiotics, such as phage therapy, probiotics and prebiotics, and nanomedicine for AMPs delivery. However, several of its applications require further investigations.

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