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Control of antibiotic resistance and superinfections as a strategy to manage COVID-19 deaths

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1. Introduction

The high morbidity and mortality rates in influenza-infected patients is partly attributed to the presence of secondary bacterial infections [1]. In many instances, despite the presence of appropriate care such as hygiene, vaccine, antiviral drugs, and antibiotics, influenza-associated secondary bacterial superinfections remain a significant burden on public health [2].

By March 25, 2020, 414,179 coronavirus disease 2019 (COVID-19) cases and 18,440 deaths had been reported worldwide. The epidemic emerged in China, with a geographic focus in the town of Wuhan. Through the use of model-based analysis of 24 deaths that happened in Wuhan in combination with 165 recoveries outside of China, Verity et al. [3] estimated the average time between the start of clinical presentation and signs of COVID-19 infection to death to be 17.8 days, while the time between the start of clinical presentation of signs to hospital discharge was 24.7 days [3]. They were able to estimate a crude case fatality ratio of 3.67% in 70,117 confirmed cases. Later, after additional adjustment and considering the demography of the cases, they were able to obtain a best estimate of the case fatality ratio in China of 1.38% with noticeably higher ratios in older age groups.

Indeed, viral infections are environmental infections where the consequences rest on the infecting virus and the nearby microbiota [4]. Thus certain bacteria seem to be related to the severity of viral symptomatic appearances, such as Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus, which are known to cause
an excess of mortality in COVID-19 patients due to secondary infection. Finally, geographic location, seasonality, and climate are important cofactors, as are age, gender, and chronic pathologies. Under these conditions, and all other things being equal, COVID-19 infection cannot be described as being statistically more severe than infection with other coronaviruses in common circulation [5].

In a recent study done by Du et al. [6], out of 179 Chinese patients with COVID-19 pneumonia, 21 died. Univariate and multivariate logistic regression analysis revealed that age ≥65 years and previous concurrent cardiovascular or cerebrovascular diseases are among the risk factors. In 10 out of 21 patients, secondary bacterial lung infection was reported at late stages of the disease where the etiologic pathogen included *Klebsiella pneumoniae*, *Staphylococcus*, and *Acinetobacter baumannii* [6]. Compared to recovered patients, reduced lymphocyte levels in the deceased had been documented. Notably, the absolute numbers of CD3+ CD8+ T cells, as opposed to CD3+ CD4+ T cells, were found to be significantly reduced in deceased persons when compared with survivors. It is interesting to know that bacterial lung infections, particularly with methicillin-resistant *S. aureus* (MRSA), increase the mortality following influenza infection, but the mechanism remains unclear [7].

2. Effect of superinfections on immune response and the severity of COVID-19 infection

The principal aim for a host when being infected with a bacterial or a viral pathogen is to survive the infection and rapidly recover to a homeostatic state. This can happen in numerous ways, such as quick and powerful clearance of the infected agent, thus preventing subsequent pathogen-induced pathology, or to alleviate any damage caused by the infection. Thus the two main factors that influence the ability to survive an infection are infection clearance and host tolerance [8,9]. Infectious disease tolerance is defined as the capability of the host to overcome the effects of the pathogen and the damaging effects of the immune response. When these two processes are balanced, then infection resolution takes place. Fig. 26.1 summarizes the different mechanisms of host tolerance to infectious agents. Understanding the mechanisms behind the high fatality rate in COVID-19 lung infections and its association with community-acquired pneumonia and hospital-acquired pneumonia as common complications of COVID-19 infection that lead to increased morbidity and mortality would be of critical importance [10].

Innate immune cells, in response to signals from the infected lung epithelial cells, contribute to the control of viral replication. Natural killer (NK) cells are among the early responding cells to viral infection. These cells are necessary for viral clearance as has been shown in many infectious diseases, but they have also been involved in severe lung damage. As part of their antiviral response, NK cells produce a great amount of interferon (IFN)-γ, which contributes to acute lung injury and death [11]. Reduction of NK cell numbers or neutralization of IFN-γ can decrease morbidity and ameliorate tissue...
damage induced by NK cells during viral infections. This shows that despite the role of NK cells in the control of viral replication, they are likewise involved in lung immunopathology [12,13]. This is true for not only viral infections but also bacterial infections [14–17]. Macrophages and dendritic cells (DCs), which mediate innate immunity, are involved as essential mediators of the inflammatory reaction to pathogenic viral infection. It is well known that homeostasis of respiratory epithelial tissue is essential to conserve the constant biomechanical and cellular processes related to aerobic respiration. The respiratory epithelium is also one of the tissue types that is greatly affected during lung infection. These cells are the primary target for infection in many respiratory viral infections, among which is coronavirus [18].

To better understand the role of influenza viral infection during viral/bacteria coinfection, it was shown that viral infection usually induces a decrease in the synthesis of interleukin (IL)-17 and IL-22. IL-17 is important in the clearance of *S. aureus* by neutrophils [19], while IL-22 contributes to directing the formation of antibacterial peptides as well as staphylococcal ligand expression [20,21]. Additionally, influenza viral infections positively affect the colonization of *S. aureus* via the induction of III-IFN.
expression, which alters the IL-22 responses impairing host production of antimicrobial peptides [22]. Several synergistic mechanisms have been suggested between viral and bacterial coinfection. Multiple studies reported remarkable elevation of viral load during bacterial coinfection. This can be attributed to the decline of viral clearance, which might explain the high fatality rate of COVID-19. It is still, uncertain whether this is due to bacterial and viral mutual interaction or just from bacteria deteriorating the immune response of the host resulting in the reduction of viral clearance. Therefore additional research is necessary to clarify the nature of the interaction between bacteria and viruses during coinfections [23,24].

Many respiratory pathogens have developed their own strategies to stop epithelial homeostasis and tissue repair mechanisms in order to maintain a favorable environment for their replication [25–27]. In 2009, transcriptomics analysis of the pandemic influenza A virus infection with S. pneumoniae coinfection demonstrated the synergistic interaction between the two pathogens that significantly downregulated tissue restoration, epithelial cell proliferation, and cytoprotective transcriptional pathways [28]. The lung is host to numerous microbiota, and their roles in human health and disease are being documented [29]. Many studies have examined the link between gut microbiota and pulmonary health through the gut-lung cross talk [30,31].

Among the mechanisms that contribute to host tolerance of infections is the diversity of the commensal lung microbiota. Although their role is not yet fully understood, studies are beginning to investigate the alterations that occur in the lung microbial milieu during viral and bacterial infection, which may clarify their role in tissue homeostasis [32,33]. It is well documented that opportunistic bacteria, or pathobionts, are among the most common secondary bacterial infections following viral infections of the respiratory tract. It is fairly accepted that the onset of acute viral respiratory infections early in life was associated with the transient appearance of Streptococcus, Moraxella, or Haemophilus species [34]. The composition of the microbiome is considered a contributing factor to the spread of viral infection to the lower respiratory system with concomitant development of inflammation or asthma [34].

The composition of the respiratory tract microbiome is not only restricted to bacterial species, but intensive-care unit (ICU) patients indicated the presence of an overgrowth of Candida species that was independent on the form of pneumonia or whether the patient had been treated with antibiotics [35].

Monitoring the constitution of the lung microbiota in patients with viral and bacterial coinfections has been an area of research interest. For example, serially drawn bronchoalveolar lavage fluid samples from an H7N9 influenza-infected patient were examined, and it was found that A. baumannii increasingly dominated the microbiota and eventually became multidrug resistant and led to secondary bacterial infection [36]. This transition was accompanied by increased inflammation, raising the possibility that there could be an associated increase in lung immunopathology and further dysbiosis in case of secondary infection [37,38]. It is potentially possible to use commensal microbes to improve host defenses against pathogens, provided the changes that occur in the airway as a result of pulmonary infections are precisely elucidated.
Based on the function of DCs in immune surveillance, readying, and easiness, it was proposed that DCs have an important role in the immunopathology of coronavirus infection. DCs are specialized antigen-presenting cells that connect innate and adaptive immunity. Immature DCs reside in the respiratory tract for immune surveillance, and they respond vigorously to local tissue inflammation in the airways and the lung. They express a group of c-type lectin receptors and toll-like receptors for the recognition of conserved viral antigen as well as the induction of later immune reactions [39]. In an attempt to understand the reason behind the increase in mortality in S. aureus-infected patients, it was found that S. aureus targets and kills DCs through the production of virulence factors known as leukocidins [40-42]. Berends et al. [41] reported that through direct killing and lowering the levels of antigen-presenting molecules on the surface of DCs, activation of CD4 T lymphocytes can be negatively affected, which in turn can increase the mortality in influenza-infected patients in general and COVID-19 patients in particular.

3. Antibiotic resistance as a challenge in the COVID-19 pandemic

Development of bacteria that are resistant to most of the exciting classes of antibiotics, or what is often called “superbugs,” is considered a serious global environmental threat [43]. The causes of “the global resistome” or antibiotic microbial resistance include unnecessary use of antibiotics, antibiotics sold without prescription, increased global tourism, reduced sanitation/hygiene, and release of nonmetabolized antibiotics or their excesses into the environment [44,45]. Several efforts have been made to characterize the multifaceted aspects of antibiotic resistance as well as explore the potential remedies to deal with this global challenge [46] (Fig. 26.2).

S. aureus, Staphylococcus epidermidis, and S. pneumoniae are among the recorded superbugs. S. aureus is a nasal commensal of humans and can cause common skin infections. At present, MRSA with increased acquired virulence has emerged as a major public health distress [47,48].

3.1 Therapeutic strategies to combat antibiotic resistance

Considerable efforts toward finding effective strategies to combat infections are a microbiologic research priority that is continuously addressed. However, the production of novel small molecules that are usually an extension of the present drug classes takes the lead over the production of biotherapeutics such as antibiotics, unique combination treatments, and drug delivery techniques [49].

Control of microbial resistance might be better than the development of new antibiotics. The role of biologics in the control of bacterial infection is in its infancy; however, its potential to combat multidrug resistance (MDR) cannot be ignored. Among the therapeutic approaches to control MDR are the combination of conventional antibiotics,
novel adjuvants, and viable limited delivery strategies. Advanced bioinformatics to determine effective combinations, delivery methods, and new targets will possibly bring significant benefits [50].

In the face of rising antibiotic resistance, antibiotic efficacy seems to be progressively diminishing, so alternative approaches to antibiotics are highly recommended. The use of nanotechnology in medicine is developing rapidly, and it is not surprising to see these technologies being practically used to overcome the antibiotic resistance threat. Nanoparticles (NPs) can be employed for the therapeutic control of bacterial infections by different means. They can be joined with existing antimicrobial agents for improvement of their physiochemical effects against antibiotic-resistant superbugs. Moreover, the colloidal forms of zinc, silver, copper, and titanium can itself be used as antimicrobial agents. Although the principal targets of antibiotics include the inhibition or disruption of bacterial cell wall, inhibition of proteins, and inhibition of nucleic acid

FIGURE 26.2 Suggested explanation of the role of secondary bacterial pneumonia in the increase of COVID-19 deaths. IFN, interferon; IL, interleukin.
synthesis, NPs are reported to affect the respiration system and in that way produce reactive oxygen species that eventually lead to bacterial death. NPs also target the bacterial cell wall; therefore silver NPs can be coupled with the relevant antibiotics to enhance their antibacterial action through synergy [51,52].

Interestingly, many researchers are directed toward traditional plant-based medicines as an alternative drug that might aid in solving the problem of antibiotic resistance, as will be discussed in detail later in this chapter.

4. Alternative treatment strategies to overcome antibiotic resistance as a contributor to COVID-19 deaths

4.1 Antibacterial effects of medicinal plants and nanomaterials

Bacterial infections are a major contributor to the development of chronic infectious diseases and death. They are commonly treated by antibiotics; nevertheless, the extensive use of antibiotics has given rise to the development of MDR bacterial strains. The most popular groups of antibiotics that are presently in use have three bacterial targets: cell wall synthesis, DNA replication machinery, and translational machinery. Antibiotic resistance mechanisms include the production of enzymes such as β-lactamases and aminoglycosides that alter or breakdown antibiotics [53], expression of efflux pumps, and modification of cell components, such as ribosomes in tetracycline resistance and the cell wall in vancomycin resistance [53], which give resistance against many antibiotics [54]. Most of antibiotic resistance mechanisms are unrelated to NPs because NPs act by direct contact with the bacterial cell wall and do not need to penetrate the cell; this explains why NPs are less prone to promoting resistance in bacteria than antibiotics [55]. In general, the mechanism of action of NPs against microorganisms follows one of three models: metal ion release [56], oxidative stress induction [57], or nonoxidative mechanisms [58]. In effect, many types of NPs have been investigated for their antibacterial efficacy.

Silver nanoparticles (AgNPs) are prominent nano-antibacterial agents against gram-negative and gram-positive bacteria as well as antibiotic-resistant strains. Compared with their NP counterparts, AgNPs have higher surface-to-volume ratio and better contact with microorganisms [59]. In fact, it was found that a silver disinfectant continues to efficiently inhibit bacterial growth on a solid glass surface even with repeated rinsing under tap water, whereas other nonsilver disinfectants did not exhibit the same effectiveness [60]. It was shown that AgNPs can also be used successfully in humans as antidandruff, antiacne, healing, and antiscarring agents among other uses. Their safety depends on particle size and concentration [60].

In addition, chitosan nanoparticles (ChNPs) have shown a wide range of antimicrobial activities. Studies have reported antibacterial activity of ChNPs against different bacterial species such as Escherichia coli, Streptococcus mutans, S. aureus, Pseudomonas aeruginosa, Salmonella choleraesuis, and Salmonella typhimurium [61–64].
Kubacka et al. [65] studied the antibacterial activity of TiO$_2$ NPs. They found that TiO$_2$ NPs exhibited a broad spectrum of activity against gram-negative and gram-positive bacteria and fungi [65]. Similarly, ZnO NPs inhibited $S$. aureus [66].

Moreover, many bacteria exist in a biofilm form, where bacteria are adhering together within a matrix to form a resistant barrier against antibiotics. This biofilm is the cause of many systemic chronic infectious diseases [67]. Considerable research work have found that most NPs can overcome or prevent biofilm formation, including Ag-based NPs [68], Au-based NPs, NO NPs, ZnO NPs [69], Mg-based NPs [70], CuO NPs [71], and Fe$_3$O$_4$ NPs [72].

Medicinal plant extracts provide an enticing alternative for the treatment of MDR bacteria. In fact, medications that are currently used for the treatment of infectious diseases raise concerns, as drug safety issues remains a major global problem. Many synthetic pharmaceutical products are associated with side effects. To mitigate some of these problems, it is important to explore potential antimicrobial compounds from plants. In general, these medications of plant origin are less toxic; their side effects are scanty and they are cost-effective. In effect, these medications are effective in treating infectious diseases while attenuating many of the side effects often associated with synthetic antimicrobials [73].

The antibacterial activity of Abrus precatorius, Boswellia serrata, Careya arborea, Emblica officinalis, Syzygium cumini, Woodfordia fruticosa, and Sphaeranthus indicus extracts against gram-positive bacteria ($Bacillus$ cereus and $S$. aureus) and gram-negative bacteria ($E$. coli, $P$. aeruginosa, and $P$. vulgaris) has been evaluated with evidence of considerable antibacterial activity against the tested bacterial strains [74].

$Sapindus emarginatus$ appears to have strong activity against $Pseudomonas$ testosteroni and $K$. pneumoniae, which are the most resistant bacterial strains [75].

Saha et al. [76] examined the antibacterial efficacy of Parkia javanica bark extracted by different solvents against five antibiotic-resistant bacterial species, namely, $P$. aeruginosa, $Bacillus$ subtilis, $Micrococcus$ luteus, $S$. aureus, and $E$. coli. The findings demonstrated dose-dependent positive action against all bacteria except $E$. coli [76].

Methanolic extract of Thymus pubescens exhibited antibacterial activity against gram-positive bacteria ($S$. aureus, MRSA, $Streptococcus$ pyogenes, $Enterococcus$ faecalis, vancomycin-resistant $E$. faecalis, and $M$. luteus) and produced 8–16 mm diameter of inhibition zones [77].

Antibacterial efficacy of normal routine antibiotics against $K$. pneumoniae along with 23 plant extracts by the Bauer-Kirby method was investigated. It was found that this organism is resistant to erythromycin, amoxicillin, roxithromycin, cefaclor, cefadroxil, and cephalixin. On the other hand, $Punica$ granatum (bark), $Terminalia$ catappa (leaves), $Azadirachta$ indica (leaves), and $S$. cumini (bark) demonstrated potential antibacterial activity against the organism [78].

It is evident that extracts from medicinal plants demonstrate positive antimicrobial activity against human pathogenic bacteria. Therefore medicinal plants should be considered in the search for new antimicrobials to overcome antibiotic resistance as a contributor to COVID-19 deaths.
4.2 Antiviral effects of medicinal plants and nanomaterials

Despite the constant rise in the number of affected individuals by COVID-19, there are currently no FDA-approved drug. Treatments provided at present are predominantly symptom-based, and seriously affected individuals are given organ support therapy when necessary [79,80]. Currently, most of the drugs that are available on the market for the treatment of COVID-19, albeit not approved by the FDA for use with COVID-19, fall into five drug classification categories. The first category consists of antiviral drugs that inhibit viral replication, ion channel functioning, or serine protease activity and have been used in the treatment of herpes, hepatitis, human immunodeficiency virus (HIV), and influenza [81], in addition to Ebola, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) [82]. The second category includes antimalarial drugs that are further divided into three subgroups depending on the specific mode of action, namely, artemisinin, antifolate, and aryl amino-alcohol compounds [83]. The third category comprises anti-HIV drugs, which are characterized depending on their target mechanism. These mechanisms include retrotranscription, viral-cell fusion, reverse transcription, incorporations/interactions of proviral DNA into the host genome, and proteolytic processing [82]. The fourth category includes anti-inflammatory drugs that are effective against elevated cytokine levels and viral infection inhibition. A combination of an anti-inflammatory drug (baricitinib) with an antiviral drug (remdesivir) was suggested to produce a more potent reduction of viral infectivity, replication, and aberrant host inflammatory response [84]. The fifth category includes monoclonal antibodies. COVID-19 virus particles have been reported to bind the S protein to the angiotensin-converting enzyme 2 (ACE2) receptors, enabling their entry into host cells. Developing neutralizing antibodies has been suggested as a possible mechanism for reducing disease severity [85].

Despite the emergence of various categories of antiviral drugs, the development of drug resistance is hindering efforts to efficiently treat and cure viral infections, this is clearly manifested in the drugs that are used to treat HIV [86–89] as well as influenza [90]. Consequently, it is imperative to continue producing and developing new drugs as well as exploring novel approaches for the treatment of viral infections.

Functional NPs have the potential to function as an effective antiviral agent. They are designed with the aim of blocking or suppressing one or more of the basic steps involved in the process of viral infection, namely, attachment, penetration, replication, and budding.

Antiviral functional NPs: The most direct way to suppress viruses is to inactivate them. Some reported nanostructures have shown viral interaction and change to the capsid protein shell of a virus enclosing genetic material and this has led to a dramatic reduction in virulence. A viral infection usually starts by attachment to the host cell via target acceptor protein binding. If this initial process of attachment can be effectively inhibited by NPs, the host cell will be infection free. A series of antiviral NPs that exhibit flexible and long linkers that mimic heparan sulfate proteoglycans, a highly conserved
viral attachment ligand (VAL) target, were designed. Simulated strong and multivalent binding to repeating VAL units was reported to achieve an efficient viral prevention via successful viral association [91]. These NPs have virtually no cytotoxicity and display nanomolar irreversible activity against respiratory syncytial virus, human papilloma virus, herpes simplex virus, lentivirus, and dengue virus, in vitro [91].

An alternative method for virus suppression is by changing the structures of the cell surface membrane and proteins. This in turn blocks virus penetration and host cell entry. To this end, Donskyi et al. [92] synthesized a number of water-soluble fullerene-polyglycerol sulfates with varying fullerene and polymer weight ratios and polyglycerol sulfate branches and reported that the vesicular stomatitis viral coat glycoprotein interaction in baby hamster kidney cells were prevented [92]. Another strategy for virus inhibition is by suppressing the process of enzyme expression responsible for the completion of virus DNA/RNA replication. This is effective in cases where virus entry into host cells has already occurred. Finally, inhibiting virus budding and promoting its excretion from host cells is another method for virus suppression. Virus offspring tend to be more virulent than the parent; hence using functional NPs to prevent virus budding will significantly reduce virulence.

Other classes of nanomaterials have also been explored for their antiviral activity. For example, AgNPs have long been employed as chemical drugs due to their promising physiochemical, chemical, and biological properties. They have shown anti-inflammatory, antifungal, antibacterial, and anticancer activities, among others [37,93–95]. They are also easy to synthesize, and their biomedical therapeutic properties have been explored in wound dressings and long-term burn care products [96]. In addition, their antibacterial properties have resulted in the incorporation of AgNPs in commercially available antibacterial lotions. However, very few reports have discussed the viricidal activity of AgNP-based antiviral agents [97,98]. Antiviral activity of AgNPs against influenza A virus, hepatitis B virus, herpes simplex virus, HIV, and human parainfluenza virus has been reported [99]. A quasi-spherical AgNP with aqueous Panax ginseng root extract was synthesized via a simple and green ultrasonication method. The as-prepared AgNPs displayed excellent viricidal effect against influenza A virus [100]. In a preparation consisting of zanamivir (anti-influenza A virus drug) loaded with AgNPs to inhibit H1N1 influenza virus inhibition, it was found that although AgNPs and zanamivir separately have relatively high antiviral efficacy, the combination therapy exhibited remarkable kinetics stability and thermodynamics, alongside inactivation effect on the influenza virus [101]. The neuraminidase activity, which assesses the influenza virus effect on cells, was also regulated by the AgNPs and zanamivir hybrid via the resistance of excess reactive oxygen species production [101]. However, due to the liquid atmosphere in which most AgNP-based antiviral agents are prepared, their wide application in virus control is significantly limited. To combat this, an effective solution is to synthesize the AgNPs in hydrogels, a semisolid medium.

Polymeric nanogels comprise a cross-link of hydrogel particles with water-soluble and swellable polymer 3D networks. These have the advantage of being able to
degrade into smaller sized fragments and the ability to be removed by renal clearance, making them favorable for virus entry inhibitor experimental designs. Dey et al. [102] reported the synthesis of a broad-spectrum antiviral nanogel. The nanogel’s virus inhibitory mechanism is universal to a broad-spectrum of antivirals, preventing the virus from attaching to the heparan sulfate proteoglycan on the host cell surface. This in turn causes a series of events to prevent virus entry and allows these synthesized flexible nanogels to act as robust inhibitors against viral infections.

Polymers are effective cofactors for infectious viral diseases, in addition to being effective antiviral drugs. A copolymer was synthesized from methoxy-poly(ethylene glycol)-block poly(phenylalanine) amphiphilic copolymers encapsulating mir-323a in the core and favipiravir in the exterior layer as hydrophilic and hydrophobic antiviral agents [103]. This copolymer displayed efficient treatment against influenza A virus infectious diseases. When compared to regular naked drugs, polymer-carried drugs efficiently enhance antiviral drug solubility, prolong in vivo retention time of drugs, and improve the drug’s uptake efficiency in cells. These advantageous characteristics allow polymers to be excellent drug carriers in antiviral clinical applications, explaining the growing research in their applications in antiviral drugs and antiviral coatings.

On a similar note, gold nanoparticles (AuNPs) are effective scaffolds for the development of virus inhibitors. Studies have shown that functional AuNPs suppress herpes simplex virus, influenza virus, and HIV [104]. In addition, AuNPs functionalized with sialic acid can cause influenza virus infection inhibition via multivalent interactions [105]. Two commercially available clinical drugs used in treating diseases caused by influenza virus infection are zanamivir and oseltamivir; however, these two drugs are subject to a high incidence of influenza virus developing drug resistance because of the high intrinsic mutation rate [106]. Fortunately, the synthesized sialic acid-coated AuNPs have the potential of reducing the development of this drug resistance by their ability to prevent the attachment of the influenza virus on the host cells.

Graphene oxide (GO) and its derivatives have also been noted for their remarkable mechanical, electronic, and thermal properties, in addition to their effective antiviral properties [107]. GO is a two-dimensional carbon material with single-atom thickness and a hexagonal lattice arrangement. GO has the potential to effectively inactivate endemic gastrointestinal avian influenza A virus H9N2 [108]. The antiviral activity of the reported GO was temperature-dependent, with weak disinfection effect at room temperature (25°C), and increasingly stronger inactivation effect when the temperature was raised from 37 to 56°C. It was also reported that unlabeled and unmodified GO destroyed the virus by interaction and displayed a general virus disruption effect based on its physicochemical interactions with capsid and enveloped viruses.

There are numerous examples of other functional NPs. For example, it was reported that zirconia (ZrO2) NPs successfully protected mice against the highly pathogenic avian influenza virus while displaying no side effects [109]. In addition, zinc oxide nanoparticle (ZnO-NP)-derived drugs were used for H1N1 influenza virus inhibition. It was reported that PEGylated ZnO-NP is an effective, novel, and promising antiviral agent [110].
Furthermore, titanium dioxide (TiO$_2$) NPs were reported to inactivate the H3N2 influenza virus by directly destroying the virus particles [111]. These examples, among others, display the superior virus targeting and inhibition capability of NPs, in addition to their reduced toxicity in vivo compared with chemical drugs.

Finally, chloroquine has been previously used to investigate NP cell uptake. It was originally derived from quinine, which is the active compound in cinchona bark. This is an antimalarial drug that possesses antiviral and immune-modulating properties. It has previously shown potential in avian influenza treatment [112] and has scored 1.13 µM at half maximal concentration against SARS-CoV-2. Additionally, chloroquine has been reported to increase the endosomal pH required for viral fusion, thereby blocking viral infection [113–116]. Chloroquine is a weak base that interferes with the acidification of membrane-closed low pH organelles by becoming entrapped within them [117]. Therefore active early stage mechanisms, prior to viral replication, can be elucidated when synthetic NP interactions with cells is performed in the presence of chloroquine. Specifically, performing nanomedicine studies of chloroquine-induced alterations can help in the understanding of cellular uptake of SARS-CoV-2, which serves to aid in the identification of new prophylactic and therapeutic candidates.

5. Mouthwashes as an early preventive strategy

Patients infected with SARS-CoV-2 mostly present with mild symptoms such as dry cough, sore throat, and fever, and the majority of cases have spontaneously resolved. On the other hand, some cases develop serious complications including organ failure, septic shock, pulmonary edema, severe pneumonia, and acute respiratory distress syndrome [118] that requires specialized management at ICUs in at least one-fifth of cases [119].

Ventilator-associated pneumonia (VAP) is the most important nosocomial infection in critical-care units that occurs at least 48 h after intubation in mechanically ventilated adult patients [120]. VAP is defined as a hospital-acquired infection caused by the aspiration of bacteria from the oropharynx into the lung and subsequent failure of the host defense system to clear the bacteria, resulting in the development of a lung infection [121,122]. The incidence of VAP was reported to range from 9% to 27% with a mortality rate that may exceed 50% for those receiving mechanical ventilation [123,124]. VAP is associated with a prolonged hospital stay, increased cost of treatment, and increased morbidity and mortality rates [125,126]. Therefore prevention of VAP is a key element for managing patients undergoing mechanical ventilation.

The first conclusive evidence linking oral microbes to pneumonia was reported by El-Solh et al. [127] who demonstrated that respiratory pathogens from the lung of institutionalized elderly patients, requiring mechanical ventilation, are often genetically indistinguishable from strains isolated from the oral cavity [127]. Furthermore, several studies have demonstrated more than 95% matching organisms in dental plaque and
bronchoalveolar lavage fluids in patients with VAP [128–130], implicating aspiration of organisms within dental plaque as the cause of the pneumonia, and therefore dental plaque is recognized as a reservoir for respiratory pathogens [131,132].

A recent investigation demonstrated that poor oral hygiene was linked to an increase in the number of obligate anaerobes located in pneumonia-affected lungs of the studied patient population [133]. Moreover, it has been reported that poor oral hygiene was among the most common risk factors of pneumonia in nursing homes [134]. Professional oral hygiene measures provided by dentists and dental hygienists decrease the number of oral bacteria [135,136], reduce the number of days of fever, inhibit the development of pneumonia [137,138], reduce the frequency of nosocomial pneumonia by about 40% [139,140], and reduce the mortality rate caused by pneumonia [137,141]. Thus, enhancing oral hygiene measures in ICU patients, to reduce dental plaque, has the ability to lessen the probability of developing VAP.

The Centers for Disease Control and Prevention recommends the implementation of a thorough oral hygiene program, aiming to prevent healthcare-associated pneumonia [142]. In support of this recommendation, several interventional methods have been investigated to reduce the colonization of dental plaque. Three distinct classes of agents including nonabsorbable antibiotics [143–146], antiseptics (mainly chlorhexidine gluconate [CHX]) [64,147,148], and natural antimicrobial peptides [149] have been evaluated in several studies as oral hygiene improvement measures in patients with VAP. Although using antibiotics to decontaminate the oropharynx appears to be more effective than using antiseptics, antibiotic resistance development has limited its widespread use [143]. CHX is currently recommended as part of the oral hygiene regimen for preventing VAP by lead health agencies in the ventilator care bundle [150]. Chlorhexidine is an antimicrobial agent that is less effective against gram-negative bacilli; however, it has an extended spectrum against gram-positive cocci.

There is no consensus in the literature regarding the effectiveness of CHX on the prevention or reduction of VAP incidence. In fact, some studies reported that CHX is effective in preventing or reducing VAP incidence [151–159], while other studies indicated that it is not effective [142,160–164]; AACN Practice Alert, 2017; [165–167]. This apparent variability is attributed to several factors such as the definition of the sample, diagnostic criteria for VAP, CHX concentration (0.12%–2%), method and frequency of CHX application, and the outcome measures. However, it is generally accepted that oral CHX should be used to reduce the rate of VAP in mechanically ventilated adults across all intensive-care specialties [168–171]. In addition, in a systematic review, high-quality evidence from 18 randomized controlled trials showed that CHX mouth rinse or gel, as part of oral hygiene care, reduces the risk of VAP compared with usual care or placebo [163].

The side effects of chlorhexidine reported in the literature are mild irritation of the mucosa, an unpleasant taste, staining of the teeth, and dysgeusia, which are minimal and reversible with the suspension of the use of the product [153,172–174]. In the ICU,
these effects are obviously not perceived by patients submitted to sedation. Due to the low toxicity of CHX, the benefits of using it outweighs the risks, even at higher concentrations [175].

Based on the Guideline for the Diagnosis and Treatment of Novel Coronavirus Pneumonia (the 7th edition) that was published by the National Health Commission of the People's Republic of China, 2019-nCoV is not eradicated by chlorhexidine. As 2019-nCoV is susceptible to oxidation, preoperative application of a mouth wash containing oxidative agents such as 1% hydrogen peroxide or 0.2% povidone iodine (PVP-I) is recommended to reduce the salivary load of oral microbes, including potential 2019-nCoV carriage [176].

Hydrogen peroxide has been recommended as a mouthwash for many years in ICU patients; however, its efficacy as an oral care agent has not been thoroughly evaluated in critically ill patients. Although hydrogen peroxide has antimicrobial properties as well as mechanical cleaning of debris, current evidence suggests it provokes many negative reactions, such as oral mucositis, and low acceptance by patients [177–179].

PVP-I is a disinfectant that has been used as an oral prophylactic agent against VAP. Some evidence supporting the effectiveness of PVP-I for preoperative decontamination of the oral cavity with a significant and prolonged decrease of both anaerobic and aerobic bacteria has been reported [180]. In addition, cleaning the upper airways with PVP-I, in geriatric patients, as part of a stringent infection control program significantly diminished the rates of nosocomial pneumonia [181]. Furthermore, a preliminary report compared the efficacy of PVP-I oral wash as prophylaxis against VAP with placebo and reported a trend toward benefit [182]. Although some evidence suggests the beneficial effect of using PVP-I as an oral hygiene care agent to prevent VAP, systematic reviews, of available evidence, suggest very little support to show that PVP-I is more effective than saline or placebo [163,183].

Several other oral care practices have been attempted including toothbrushing, mouthwashes with 0.5% sodium bicarbonate (NaHCO₃), 0.9% sodium chloride (NaCl), and water [184,185]. However, available evidence regarding the efficacy of these practices is still insufficient [163].

It is evident that controlling the oropharyngeal microbial flora is important to lower the frequency of developing VAP. Although oral CHX stands out as the most effective oral hygiene care practice available today to prevent VAP, it falls short of achieving the characteristics of an optimum therapeutic agent. It is recommended to use CHX oral hygiene care as a part of the regiment to manage COVID-19 patients; however, the search for a more effective therapeutic agent must be continued.

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