

Fifth Generation Quaternary Ammonium in dentistry: Effective against SARS-CoV-2?

Amonio cuaternario de quinta generación en odontología:
¿Eficaz contra el SARS-CoV-2?

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Coronaviruses are a family of lipid-enveloped, single-stranded, positive RNA viruses that may be present in vertebrates, causing respiratory, enteric, liver, and neurological diseases.¹ There are two members of this family that have previously affected humans severely, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), related to respiratory diseases.²

On December 31, 2019, several cases of pneumonia of unknown etiology detected in the city of Wuhan, Hubei province (China), were reported to the Office of the World Health Organization (WHO) in China³ where a study funded by the National Key Research and Development Program of China and the Major National Project for the Control and Prevention of Infectious Diseases reported a new coronavirus (2019-nCoV) in patients who were hospitalized, revealing that this virus belonged to the genus betacoronavirus, which was found to be present in humans, bats, and other wild animals, with zoonotic infection being possible in humans.⁴ On February 11, 2020, the International Committee on Taxonomy of Viruses announced that the new virus would be named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to its genetic relationship with the coronavirus responsible for the SARS outbreak in 2003 and the OMS announced that this entity would be called, coronavirus disease 2019 (COVID-19).⁵

Currently it is known that SARS-CoV-2 presents a phospholipid bilayer in its envelope, along with a protein S that allows it to bind and interact with cell receptors: angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), present in the cell membrane of different organs of the body such as the kidney, heart, lung among others; being especially important in the field of dentistry, the fact that a large number of these receptors have been reported in the epithelial cells of the excretory ducts of the salivary glands, which would explain the high viral load present in the saliva in individuals with COVID -19.⁶

It is important that preventive measures are adopted against this virus, reducing the salivary viral load, since the main form of contagion of this coronavirus is through the droplets of saliva expelled when sneezing or coughing (Flügge droplets). For this reason, the use of various mouthwashes that cause the lysis of the phospholipid bilayer of SARS-CoV-2, namely

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0.23% povidone iodine and 0.5% hydrogen peroxide, has been proposed.⁷ On the other hand, another form of contagion is through physical contact with surfaces (fomites) contaminated with droplets of saliva, for example if an individual touches these fomites with bare hands and does not wash them properly, they could become infected when touching then their eyes, nose, or mouth.⁸

When searching for information in PubMed and Scopus, very little literature is found regarding the efficacy of mouthwashes against SARS-CoV-2. However, the few existing articles, generally reviews on the subject, highlight the possible efficacy of quaternary ammonium compounds as a promising treatment for lowering salivary viral load in COVID-19 patients.^{7,9}

Quaternary Ammonium Compound

Quaternary ammonium compounds (QAC) are cationic surfactants, made up of amphiphilic molecules that have a wide spectrum of antibacterial activity, which is why they are used as antiseptics commonly used in industrial, domestic and hospital environments. Their chemical structure is made up of four aliphatic or aromatic radicals linked to a central nitrogen atom, being effective against a variety of bacteria, fungi and viruses in very

low concentrations; and even though their antibacterial action is already broad spectrum, they demonstrate much greater activity against Gram-positive bacteria, as well as being potent antifungal agents.¹⁰

Optimal activity against Gram-positive bacteria and yeasts is achieved with chain lengths of 12 to 14 alkyls, while optimal activity against Gram-negative bacteria is achieved with chain lengths of 14 to 16 alkyls. Compounds with N-alkyl chain lengths less than 4 or greater than 18 are practically inactive.¹¹ Fifth generation QACs are currently available, whose generation changes were based mainly on the union and modification of chemical components to search for a better biocidal and virucidal effect, and which are set out. (Table 1)^{10,11}

Fifth generation QACs at a concentration of 10 to 50mg per liter, result in a higher microbicidal performance especially in difficult environmental conditions, also being non-corrosive to metals or clothing.¹¹ Even at concentrations of 1: 20,000 to 1: 50,000 weight/volume, they can be used to disinfect dental root canals without causing periapical inflammation.¹²

Due to their amphiphilic nature, QACs have an antimicrobial mechanism of action similar to detergents. The positively charged "head" of the QAC, interacts

Figure 1. Similarity of the phospholipid bilayer present in bacteria, influenza viruses and SARS-CoV-2, and the mechanism of action of quaternary ammonium against the phospholipid bilayer. Source: Adapted from Schrank *et al.*¹¹

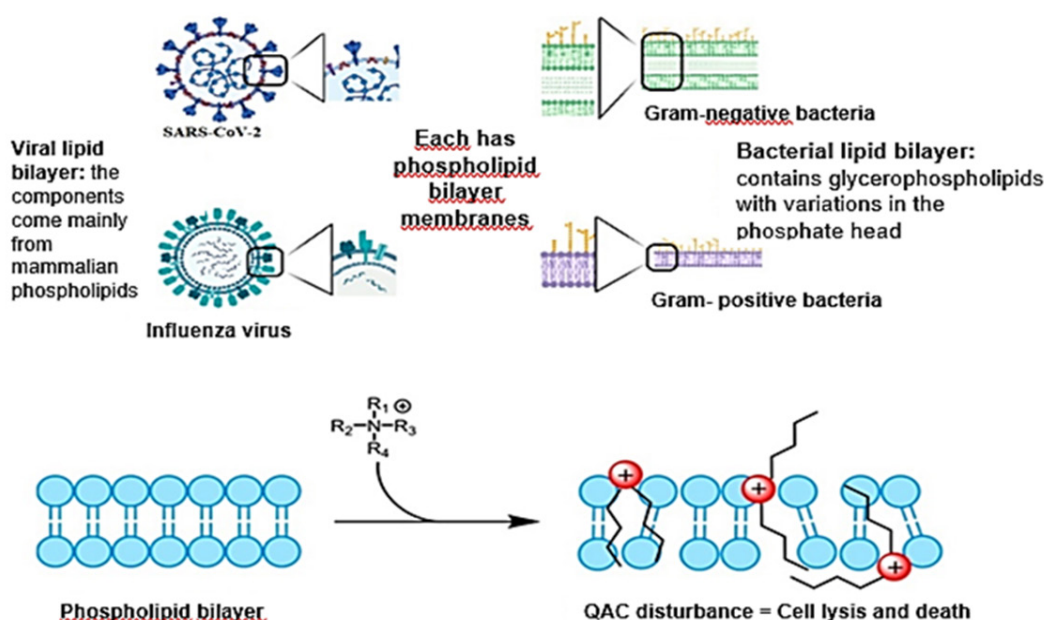


Tabla 1. Chemical components of quaternary ammonium according to their generations.^{10,11}

Quaternary ammonium generation	Chemical components	Known acronyms in English
First	Alkyl Dimethyl Benzyl Ammonium Chloride (Benzalkonium Chloride)	ADBAC
Second	Alkyl dimethyl ethylbenzyl ammonium chloride	ADEBAC
Third	Alkyl dimethyl benzyl ammonium chloride + Alkyl dimethyl ethylbenzyl ammonium chloride	ADBAC + ADEBAC
Quarter	Didecyl dimethyl ammonium chloride	DDAC
Fifth	Alkyl Dimethyl Benzyl Ammonium Chloride or Alkyl Dimethyl Ethyl Benzyl Ammonium Chloride + Didecyl Dimethyl Ammonium Chloride	(ADBAC o ADEBAC) + DDAC

electrostatically with the negative charge of the cytoplasmic membrane of bacteria and fungi,¹¹ causing the membrane to become disorganized and the leakage of low-weight intracellular material occurs; immediately afterwards, proteins and nucleic acids are degraded to later conclude with the autolysis of the cell wall. In the case of SARS-CoV-2, which causes severe respiratory syndrome (COVID-19), the disruption of their lipid envelope by the action of the QAC seems to be easier, as they do not have a cell wall.¹³

Currently the Centers for Disease Control and Prevention (CDC) indicate that although benzalkonium chloride (first generation QAC) is eligible for hand disinfection, it appears to be less reliable against SARS-CoV-2 compared to solutions with at least 60% ethanol, or 70% isopropanol.¹³

However, it seems prudent not to completely rule out the quaternary ammonium compound, since nowadays fifth generation QACs are available, the sum of the benzalkonium chloride plus didecyl dimethyl ammonium chloride, and which allows it to have increased effectiveness against Gram-positive and Gram-negative bacteria, as well as against the influenza virus,^{10,11} since its effectiveness lies in causing lysis of the phospholipid bilayer present in the cell membrane and in the viral envelope, respectively. Due to the similarity of these with the lipid envelope of SARS-CoV-2, it can be inferred that fifth generation QAC could also be very effective against this virus.¹¹

As a final consideration, we can mention that fifth generation QACs interact electrostatically with

the negative charge of the phospholipid bilayer of the enveloped viruses, causing its disorganization and subsequent destruction. For this reason, it is recommended to carry out research in the field of dentistry with randomized clinical trials applying fifth-generation QAC as a mouthwash against SARS-CoV-2, since probably the highest load of this virus in humans is found in the oral cavity, specifically in the excretory ducts of the salivary glands, since their epithelial cells contain angiotensin converting enzyme 2 and transmembrane protease serine 2 in the cell membrane, which allow the binding of the S protein of SARS-CoV -2, thus allowing its entry into the host cell and subsequent viral replication.⁶

Additionally, the efficacy of the fifth generation QAC against this coronavirus should be tested in fomites, since if its virucidal action is demonstrated in a similar or better way to solutions with at least 60% ethanol or 70% isopropanol, we would obtain multiple advantages when using it in the dental office since this compound does not generate odors, does not corrode metals, and does not inactivate as quickly in the presence of light, as it happens to 0.1% sodium hypochlorite solution.

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