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SPECIAL ARTICLE COVID-19

# Chloroquine and COVID-19: Should We Care about Ototoxicity?

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## Abstract

**Introduction** Severe acute respiratory syndrome coronavirus 2 was first described in December 2019 in China leading to a Public Health Emergency of International Concern. It was named by the World Health Organization as Coronavirus Disease 2019 (COVID-19), and it garnered unprecedented attention from public health researchers around the world, and studies analyzing chloroquine and hydroxychloroquine as a possible therapy have arisen in the last 2 months.

**Objective** To review the literature and describe updated facts about the ototoxicity of chloroquine and hydroxychloroquine, an important side effect that can be present in patients with COVID-19 treated with these drugs.

**Data Synthesis** The most typical treatment regimen is 5 days of hydroxychloroquine at daily doses of 400 to 600 mg. There is no randomized clinical trial that can prove so far the efficacy of this medication, and few studies have evaluated adverse events potentially linked to their use in patients with COVID-19. While there is no concrete evidence on the incidence of ototoxicity using chloroquine in the short term, we need to consider that, as a pandemic disease, millions of patients with COVID-19 may receive this treatment, and ototoxicity can be a possible adverse event.

**Conclusion** Despite the urgent global situation caused by the COVID-19, the risk of irreversible hearing loss may outweigh the unproven benefit of using hydroxychloroquine or chloroquine, especially in patients with mild forms of COVID-19, who may be cured with supportive treatment. The potential hearing loss that can be caused by these medications may advise against their use in COVID-19 patients.

**Keywords**

- ototoxicity
- hearing loss
- COVID-19
- hydroxychloroquine
- chloroquine

## Introduction

On December 31st, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) was identified in Wuhan, China. It was responsible for an outbreak of a severe acute respiratory syndrome that led to a Public Health Emergency of International Concern (PHEIC), and the World Health Organization (WHO) named it Coronavirus Disease 2019 (COVID-19). It is considered the third zoonotic human coronavirus of the century, since there were cases of SARS-CoV in 2002 in China and cases of Middle East Respiratory Syndrome

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(MERS-CoV) in 2012 in Saudi Arabia, and it was declared a pandemic by the WHO on March 11th, 2020.[1,2]

Since the emergency of COVID-19, many studies have been published trying to clarify some clinical questions, such as route of transmission, risk factors, natural course, outcomes, and treatment options. One of the medications that has been used in many hospitals to manage these patients is chloroquine, a 4-aminoquinoline drug currently used to treat malaria, rheumatoid arthritis, and systemic erythematosus lupus, reported as a potential broad-spectrum antiviral drug. Hydroxychloroquine has also been used, due to its clinical safety profile being better than chloroquine, which allows higher daily doses with fewer drug interactions.[3]

In his review, Juurlink (2020) has evidenced that the most typical regimen is 5 days of hydroxychloroquine at daily doses of 400 to 600 mg, which was corroborated by Mehra et al (2020), and its doses did not exceed 600 mg daily for 5 to 10 days.[4,5] On May 20th, 2020, the Brazilian Department of Health expanded the use of hydroxychloroquine or chloroquine associated with azithromycin during 5 days for patients with mild symptoms of the disease.[6] However, on the same day, the Brazilian Society of Infectious Diseases pronounced themselves against the routine use of these drugs, since until this date there are no randomized clinical trials with a control group that confirm the effectiveness of these medications in the treatment of patients diagnosed with COVID-19. According to them, these medications should only be used for scientific purposes and in a clinical trial.[7]

The most common adverse events related to the use of chloroquine and hydroxychloroquine are cardiotoxicity and retinal toxicity. However, an important side effect that is not commonly discussed is the potential ototoxicity of these medications, which is already known and has been studied for several years. Many reports have described sensorineural hearing loss after prolonged therapy with chloroquine, but there are also studies that described cochleovestibular ototoxicity with both acute and chronic use of chloroquine and hydroxychloroquine. These drugs accumulate and fix selectively in melanocytes of cochlear sensory hair cells, resulting in variable injuries that can be irreparable.[3,8] There are reports about children with systemic lupus erythematosus who developed ototoxicity soon after the therapy with hydroxychloroquine was initiated.[9] There are also cases reported in the literature, since 1968, of hearing loss in newborns of mothers who had malaria and used chloroquine during pregnancy.[10,11]

Therefore, the present paper aims to review the literature and describe updated facts about the ototoxicity of chloroquine and hydroxychloroquine, an important side effect that can be present in patients with COVID-19 treated with these drugs.

## Review of a Particular Subject

A bibliographic search was performed in the PubMed and Scientific Electronic Library Online (Scielo) databases for papers published up to May 21st, 2020 using the terms *coronavirus* or *COVID-19* in combination with *hydroxychloroquine* or *chloroquine*; and using *ototoxicity* in combination with *hydroxychloroquine* or *chloroquine*. There were no published studies regarding ototoxicity and COVID-19 and chloroquine or hydroxychloroquine. Moreover, we also consulted the web pages of organizations such as World Health Organization, the Brazilian Department of Health, and theBrazilian Academy of Otorhinolaryngology and Head and Neck Surgery.

## Discussion

The SARS-Cov-2 is a betacoronavirus that uses the angiotensin-converting enzyme 2 receptor for cell entry. The main mode of transmission is person-to-person, especially via respiratory droplets that can be dispersed in the air for up to two meters and stay viable in surfaces for a variable amount of time. Thus, the virus is released not only when an infected person sneezes or talks, but also when a person touches an infected surface and then touches the eyes, nose, or mouth.[12] According to Park et al (2020), who analyzed 41 epidemiological studies, the mean incubation period ranges from 4 to 6 days, which is comparable to that of SARS-CoV (4.4 days) and MERS-CoV (5.5 days worldwide).[13]

Lovato and Filippis (2020) analyzed 5 retrospective cohort studies and described that fever (85.6%), cough (68.7%), and fatigue (39.4%) were the most commonly observed symptoms. Among upper airway symptoms, pharyngodynia was present in 12.4% of patients, rhinorrhea was found in 4%, and nasal congestion in 3.7% of the patients.[2]

Moreover, some cases of smell disorders have been described in patients with COVID-19. On March 22nd, 2020, the Brazilian Academy of Otorhinolaryngology and Head and Neck Surgery warned physicians about the possibility of hyposmia and anosmia being a symptom of COVID-19.[14] The European Rhinology Society reported that up to 60% of patients appear to have some loss of smell that can be presented before other common symptoms, like fever and cough.[15] Giacomelli et al (2020) analyzed 59 hospitalized patients with COVID-19 in Milan, Italy. Of these, 20 (33.9%) reported at least one taste or olfactory disorder, and 11 (18.6%) reported both. It is known that a wide range of viral infections can lead to taste and smell disorders. According to a mice model, SARS-CoV-2 has a transneural penetration through the olfactory bulb, and the angiotensin converting enzyme 2 receptor is widely expressed on the epithelial cells of the mucosa of the oral cavity. Thereby, the mechanism of taste and smell disorders in SARS-CoV-2 infection could be explained by these findings.[16]

Hearing loss can also be a manifestation of several viral infections, and there are findings suggesting that SARS-CoV-2 might be one of these agents. The mechanisms involved in hearing loss are variable, ranging from direct damage to inner ear structures, such as hair cells and organ of Corti, and induction of inflammatory and immune-mediated responses to increasing susceptibility of bacterial and fungal infection. Typically, this type of hearing loss is sensorineural and, occasionally, hearing recovery can occur spontaneously.[17] Mustafa (2020) performed an audiological evaluation of 20 patients with COVID-19 who did not have the classic symptoms and compared with a group of 20 people who were asymptomatic

and tested negative for the disease. On the pure-tone audiometry, there was a significant difference between the groups at the frequencies of 4,000, 6,000, and 8,000 Hz ($p < 0.05$), and the transient evoked otoacoustic emissions exhibited a highly significant difference between both groups.[17]

Due to the significant global health threat of COVID-19, there is an urgent need for effective treatment that can not only reduce patient's symptoms, but also decrease the duration of virus carriage to limit the transmission in the community.[18] Perhaps, the treatment is the point that leads to more anxiety and doubts, since much has been speculated about it, but there is still controversial data about the safety and efficacy of some drugs, and it is not possible yet to define a therapeutic management that is known to be effective.[12]

Hydroxychloroquine and chloroquine are being widely prescribed for treatment of COVID-19.[5] Chloroquine can block virus infection by increasing the endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV-2 even before cell exposure to the virus, suggesting a prophylactic effect of the drug.[19] Chloroquine also has an immunomodulatory effect, which may synergistically increase its antiviral effect in vivo.[20] Despite its in vitro action, there are still no meta-analyses of multicenter, controlled, blind and randomized clinical trials to prove the benefit of this drug in the treatment of COVID-19.[6]

A recent study developed in a tertiary hospital in France showed efficiency in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients after 3 to 6 days of treatment ($p = 0.001$).[18] However, a meta-analysis by Chacko et al (2020), which included 11 studies among randomized controlled trials and observational studies with a control group, outlined that there were no statistically significant differences between patients who received hydroxychloroquine compared with the control group regarding mortality ($p = 0.28$), clinical worsening or lack of symptomatic improvement ($p = 0.76$), and viral clearance ($p = 0.87$). Furthermore, patients who received hydroxychloroquine had a significantly higher incidence of adverse events than those who did not receive the medication ($p = 0.009$).[21]

The efficacy of chloroquine or hydroxychloroquine to prevent or to treat patients with COVID-19 is not well established yet. However, the potential side effects and harms of these medications, which are widely used to treat other diseases, are known. Qaseem et al (2020) plead against the use of hydroxychloroquine as both prophylaxis and treatment for COVID-19, due to known harms and absence of evidence of benefits of the medication.[22]

Furthermore, Mehra et al (2020) published an analysis made of 96,032 hospitalized patients from 671 hospitals who were diagnosed with COVID-19. Of these, 81,144 patients were in the control group and the other 14,888 patients were in the treatment groups (1,868 received chloroquine, 3,783 received chloroquine with a macrolide, 3,016 received hydroxychloroquine, and 6,221 received hydroxychloroquine with a macrolide). In this large multinational analysis, there were no benefits on in-hospital outcomes with the use of chloroquine or hydroxychloroquine (with or without a macrolide), but, instead, its use was associated with a higher risk of ventricular arrhythmias and, hence, increased the chances of in-hospital death.[5] These data were corroborated by a cohort study done by Rosenburg et al (2020) in the state of New York, which is the largest disease and mortality burden of the US. The study compared the effects of the treatment with hydroxychloroquine and/or azithromycin. They concluded that following the adjustment for illness severity, preexisting conditions, and demographics characteristics, there were no significant differences in mortality rates between the groups, but cardiac arrest was more frequent in patients who received hydroxychloroquine.[23]

The ototoxicity related to chloroquine is known, but it is not widely studied. In the literature, there have been cases reported since 1968. The oldest one described hearing loss in a child whose mother used chloroquine during pregnancy.[11] Drug ototoxicity can be defined as a transient or definitive disturbance of auditory and/or vestibular function, induced by therapeutic substances.[24] There is no current available therapy to reverse the damage that can be caused by ototoxic drugs, such as balance disorders and permanent hearing loss.[25] The patient's main symptoms are tinnitus, vertigo, and sensorineural hearing loss, which is usually irreversible, although there have been reported exceptions.[10]

A study published in 1975 demonstrated a high concentration of chloroquine in the vascular stria, modiolus, planum semilunatum, sac and utricle walls, and semicircular canals, which are inner ear tissues that contain melanin. This protein is present in highly vascularized areas in the inner ear, and the melanocytes usually are arranged around the blood vessels.[26] In this context, it is believed that the buildup of chloroquine is responsible for a vascular injury and degenerative changes in the planum semilunatum and stria vascularis.[24] Thus, the high demand for oxygen from the vascular stria and external hair cells may be responsible for their sensitivity to quinine, a natural alkaloid present in chloroquine and hydroxychloroquine.[27]

Castoldi et al (2001) described that chloroquine may induce ototoxicity by mechanisms other than the one described in the 1975 study by Dencker and Lindquist[26]. The increased glutamate concentration in the extracellular environment induced by the drug can favor neuronal excitotoxicity in the inner ear. Thus, chloroquine causes an overproduction of reactive oxygen species (ROS), which is another important mediator of toxicity on glial cells of the inner ear.[28] The authors also implied a possible therapeutic target for this drug-induced ototoxicity. Antioxidants, such as ascorbic acid, are effective against cell death induction by overproduction of ROS. Thereby, the protective effect in glial cells observed with this essential vitamin can contribute to the treatment against ototoxicity induced by the use of chloroquine.[29]

There is a predominance of adverse events related to chloroquine toxicity, but ototoxicity is also related to the use of hydroxychloroquine, which is theoretically known to be less toxic. Most of these cases are reported with chronic use of chloroquine, and it may be explained by a long-term retention and accumulation of the drug in the melanocytes in the inner ear cells, resulting in variable injuries to the cochlear sensory hair cells and decreasing neuronal

population. Nevertheless, cochleovestibular ototoxicity has also been related to acute use of the drug.[3]

Khalili et al (2014) reported the case of a 54-year-old-man with bilateral hearing loss that initiated 1 month after receiving hydroxychloroquine for treatment of rheumatoid arthritis. Pure-tone and speech audiometry presented with moderate-to-severe sensorineural hearing loss and reduced speech recognition in both ears. Hydroxychloroquine-induced hearing loss was suspected to be the cause. The drug was discontinued and, 2 months later, his audiometric findings improved, with pure-tone and speech audiometry revealing mild-to-moderate hearing loss and slightly-to-mild disability in speech recognition. As it was described before, the hearing loss is usually irreversible, but there are some exceptions reported in the literature.[30]

Furthermore, there are reports of children with systemic erythematosus lupus who developed ototoxicity soon after the therapy with hydroxychloroquine was initialized. Lim and Tang (2011) reported an 11-year-old girl treated with hydroxychloroquine, and, 2 months later, she complained of reduced hearing in both ears. Audiological tests confirmed the complaint and outlined a bilateral sensorineural loss, predominantly affecting the low-frequency range. They also suggested in their report that ototoxicity in children might occur with low doses and in short-term use.[9] There are also case reports of hearing loss in newborns of mothers who had malaria and used chloroquine during pregnancy.[8,11] The occurrence of malaria in this period and its treatment, especially in the third trimester, can have implications for fetal or neonatal development.[31]

Ototoxicity has a high prevalence in the developing countries of Africa. Kokong (2014) analyzed 156 patients in Nigeria who had drug-induced ototoxicity over a period of 3 years, confirmed by audiometric findings. The injection of an unknown agent was the most common cause of hearing loss ($n = 55$ [35.3%]). Among the known agents, chloramphenicol was the main drug involved ($n = 25$ [16.0%]), followed by chloroquine ($n = 22$ [14.1%]) and gentamicin ($n = 20$ [12.8%]). Kokong also reports a pregnant woman that received intramuscular chloroquine and had a miscarriage 4 months after the drug use. Regarding the audiometric patterns, profound sensorineural hearing loss was identified in 155 ears (49.7%), and mixed hearing loss in 90 ears (28.8%).[25]

Considering the current scenario, COVID-19 turned out to be the major public health emergency of this century. Thus, it is plausible and essential that researchers focus unprecedented attention in analyzing the virus and understanding the disease.[18] The evidence on suppression of activity of SARS-CoV-2 and other coronavirus strains from in vitro studies increased the interest in the use of hydroxychloroquine and chloroquine with or without azithromycin for the treatment of COVID-19, raising hopes but also doubts of a possible reduction in disease morbidity and mortality.[23]

However, research has been limited by the outcomes assessed, small sample size, types of patients studied and short follow-up. There are no randomized clinical trials that can prove so far the efficacy of chloroquine or hydroxychloroquine, and few studies have evaluated adverse events potentially linked to their use in patients with COVID-19, although, as described, these drugs have known harms reported in several patients when used to treat other diseases.[23]

In the current unusual context, authorities such as the United States Food and Drug Administration and the Brazilian Department of Health recently authorized the emergency use of chloroquine and hydroxychloroquine and obscured the negative aspects of these drugs. People have been self-treating in Nigeria for apparent COVID-19, and many deaths were reported there due to chloroquine overdoses.[32] Still, it is hard not to try the use of these drugs that, despite their unclear benefits, are speculated to have potential advantage in the treatment of this pandemic disease. Thereby, with so many uncertainties, the only reliable information are that the use of chloroquine or hydroxychloroquine alone or in combination with azithromycin to prevent or treat COVID-19 is not well established, and that these 4-aminoquinolines have known side effects, especially cardiotoxicity, retinopathy, and ototoxicity, that might be irreversible.[22]

Despite the fact that there is no concrete evidence on the incidence of ototoxicity when using chloroquine in the short term, we need to consider that, as a pandemic disease, millions of patients with COVID-19 may receive this treatment. Moreover, the margin between the therapeutic and toxic dose is narrow, and chloroquine poisoning has been associated with cardiovascular disorders that can be life threatening.[33]

Since there are no convincing evidence from well-designed clinical trials that support the use of chloroquine or hydroxychloroquine with good efficacy and safety for the treatment of COVID-19, and considering their known adverse effects, especially concerning ototoxicity, we should ask ourselves: should it be used in the current scenario? Can this ototoxicity worsen the potential audiological symptoms that the disease itself may cause and turn it to be irreversible? It is important to notice that most of those infected are elderly, which already have some kind of hearing loss that can also be worsened by the use of these drugs. Future randomized and well-designed clinical trials are needed to answer these questions.

## Final Comments

Current evidence about the use of chloroquine and hydroxychloroquine in the context of COVID-19 is still uncertain and based on low-quality studies. These facts lower even more the confidence of the conclusions regarding the benefits of these drugs and understanding the balance when compared with harms. Despite the urgent global situation caused by the COVID-19 pandemic, we must endorse the individual risk of each patient. The risk of irreversible hearing loss may outweigh the unproven benefit of using hydroxychloroquine or chloroquine, especially in patients with mild forms of COVID-19, who may be cured with supportive treatment. It is a challenge in the face of a coronavirus outbreak to opt for, without convincing evidence, the use of these drugs. Considering that hearing is the sense that has the greatest impact on human communication and quality of life, the potential

hearing loss caused by these medications, along with the other serious adverse effects, may advise against its use in COVID-19 patients.

### Conflict of Interests

The authors declare that there was no conflict of interests.

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