

## Contemporary Review

# A Narrative Review of Pharmacologic Treatments for COVID-19: Safety Considerations and Ototoxicity

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**Objective/Hypothesis:** The purpose of this review is to summarize evidence-based data regarding the ototoxic effects of potential COVID-19 therapeutics to treat patients suffering from SARS-CoV-2.

**Methods:** Medications under investigation as novel therapeutics to treat COVID-19 were identified using the search term *coronavirus therapeutics*, *COVID therapeutics*, and *SARS-CoV-2 therapeutics* on ClinicalTrials.gov and the PubMed Database. A literature review was performed using the PubMed Database for each proposed COVID-19 therapeutic to identify relevant articles. Search criteria included Medical Subject Headings (MeSH) and key word search terms for *ototoxicity*, *vestibulotoxicity*, *hearing disorders*, and *vertigo*.

**Results:** Six proposed COVID-19 therapeutics were identified as possessing ototoxic side effects including chloroquine and hydroxychloroquine, azithromycin, lopinavir-ritonavir, interferon, ribavirin, and ivermectin.

**Conclusions:** Available evidence suggests that ototoxic effects may be improved or mitigated by stopping the offending agent. Recognition of hearing loss, tinnitus, or imbalance/vertigo is therefore crucial to facilitate early intervention and prevent long-term damage. Hospitals should consider the inclusion of audiologic monitoring protocols for patients receiving COVID-19 therapeutics with known ototoxicity, especially in high-risk patient groups such as the elderly and hearing impaired.

**Key Words:** COVID-19, ototoxicity, SSNHL, vertigo, tinnitus.

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## INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly evolved into a global pandemic. Although the first cases of Coronavirus Disease 2019 (COVID-19) emerged in late December of 2019, there still remains no widely established standard of care for the pharmacological treatment of these patients. More than 300 clinical trials are currently underway, many of which seek to reposition existing immunomodulatory medications, corticosteroids, and antiviral agents as novel therapeutics to treat COVID-19 patients.

Multiple off-label drugs, such as hydroxychloroquine and azithromycin, gained early enthusiasm and were widely prescribed to COVID-19 patients despite a lack of comprehensive clinical evidence to support their use. Results from a large, randomized clinical trial (RCT) have since found that hydroxychloroquine has no effect on

mortality or recovery in SARS-CoV-2 infection.<sup>1</sup> However, this medication remains in use in many centers worldwide.

Many previously or currently used COVID-19 therapeutics have known ototoxicity including antimalarials, macrolide antibiotics, immunomodulatory agents, and antiviral therapies.<sup>2,3</sup> Ototoxicity refers to drugs that cause functional impairment or cellular damage to tissues of the inner ear including both the cochlear and vestibular system, often manifesting as hearing loss, tinnitus or disequilibrium.<sup>2</sup> When unrecognized, ototoxic effects may be permanent, leading to significant long-term disability. Hearing loss has widespread impact on communication, impacting quality of life, productivity, cognitive function, and health care cost.<sup>4</sup> Tinnitus is associated with increased rates of depression, anxiety, and reduced cognitive functioning.<sup>5,6</sup> Imbalance and falls have widespread implications for physical injury, social isolation, and reduced quality of life.<sup>7,8</sup> Understanding and recognizing potential ototoxic side effects are the key to risk mitigation and limiting long-term damage. The purpose of this contemporary narrative review is to summarize the evidence-based data regarding the ototoxic effects of current and previously used COVID-19 therapeutics.

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## SEARCH METHODOLOGY

The authors first sought to identify medications under investigation as novel COVID-19 therapeutics by

searching ClinicalTrials.gov and the PubMed Database using the search terms *coronavirus therapeutics*, *COVID therapeutics* and *SARS-CoV-2 therapeutics*. Medications were limited to those in active or completed clinical trials, as well as those approved for use in COVID-19 patients under the Emergency Use Authorization by the Food and Drug Administration prior to July 1st, 2020. A comprehensive list of drugs was compiled including antivirals, immunomodulatory agents, and antibiotics (Table I).

Subsequently, a literature search for all relevant publications related to ototoxicity published through July 1st, 2020 was performed within the PubMed Database for each COVID-19 therapeutic (Fig. 1). Search criteria included Medical Subject Headings (MeSH) and key word search terms for *ototoxicity*, *vestibulotoxicity*, *hearing disorders*, and *vertigo*. Additional papers were identified by hand search of bibliographies. Numerous levels of evidence including clinical trials, cohort studies, animal trials, and in vitro studies were included. Studies were excluded if they reported intratympanic administration of medications in humans, lacked sufficient data, or used multiple drug combinations.

## RESULTS

Of the original list of COVID-19 therapeutics, six medications were identified as possessing potential ototoxic effects (Table I).

### *Chloroquine and Hydroxychloroquine*

Chloroquine and hydroxychloroquine, which have long been used in the treatment of malaria and autoimmune diseases, exert antiviral properties in several ways, including inhibition of endosome mediated viral entry, viral uncoating, and proteolytic processing.<sup>46</sup> Early clinical data suggested COVID-19 patients treated with chloroquine or hydroxychloroquine exhibited improved radiologic findings, faster time to recovery, and a reduction in viral load.<sup>47–49</sup> However, this benefit has since questioned by a series of studies, including a large RCT, that showed no benefit to standard of care.<sup>1,50,51</sup> There are currently over 25 RCTs underway to fully assess the clinical benefit of chloroquine and hydroxychloroquine in treating COVID-19 patients.

TABLE I.  
List of Identified COVID-19 Therapeutics and Their Association with Ototoxic Effects.

COVID-19 Therapeutic	Evidence of Ototoxicity	Outcome of Toxicity		References
		Reversible with Disuse of Toxic Agent	Improvement with Steroid Therapy	
<b>Antivirals</b>				
Lopinavir-ritonavir	Known SE <sup>+,†</sup>	Reversible	Not assessed	9,10
Ribavirin	Known SE <sup>*</sup>	Sometimes reversible	Yes	11–21
Ivermectin	Known SE <sup>*</sup>	Reversible	Not assessed	22–24
Remdesivir	Not investigated	-	-	
Favipiravir	Not investigated	-	-	
Darunavir-cobicistat	Not investigated	-	-	
Camostat mesilate	Not investigated	-	-	
<b>Immunomodulators</b>				
HCCQ/CQ <sup>‡</sup>	Known SE <sup>+,†</sup>	Sometimes reversible	Yes	25–30
Interferon <sup>‡</sup>	Known SE <sup>+,†</sup>	Reversible	Not assessed	31–35
Colchicine	Unclear <sup>†</sup>	-	-	
Tocilizumab	Not investigated	-	-	
Sarilumab	Not investigated	-	-	
Aviptadil	Not investigated	-	-	
Eculizumab	Not investigated	-	-	
Bevacizumab	Known not toxic <sup>§</sup>	-	-	36,37
Anakinra	Known not toxic <sup>§</sup>	-	-	38,39
<b>Corticosteroids</b>				
Methylprednisolone	Known not toxic <sup>§</sup>	-	-	40
Prednisone	Known not toxic <sup>§</sup>	-	-	40
Dexamethasone	Known not toxic <sup>§</sup>	-	-	40
<b>Other</b>				
Azithromycin	Known SE <sup>+,†</sup>	Sometimes reversible	Yes	41–45
Famotidine	Not investigated	-	-	

<sup>\*</sup>In vivo clinical evidence to support toxicity.

<sup>†</sup>In vitro or animal studies to support toxicity.

<sup>‡</sup>HCCQ/CQ denotes hydroxychloroquine/chloroquine; interferon includes IFN- $\alpha$ , IFN- $\beta$  and PEG-IFN.

<sup>§</sup>In vivo, clinical evidence to support lack of toxicity.

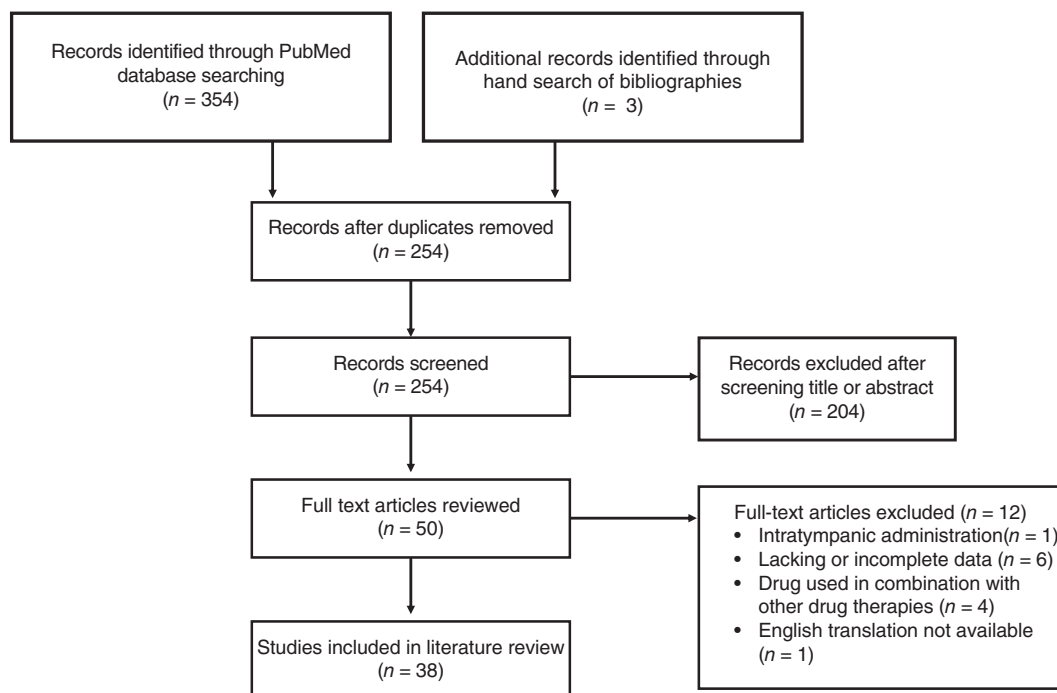


Fig. 1. Search flow diagram of the study selection process investigating the association of proposed COVID-19 therapeutics with ototoxicity.

The ototoxic effects of chloroquine use are well documented and include symptoms of reversible and irreversible sensorineural hearing loss (SNHL), tinnitus, and vertigo. An observational study ( $n = 74$ ) receiving chloroquine therapy reported abnormal brain stem audiometry (ABR) in 13 patients, although there was no change in hearing by pure tone audiogram.<sup>25</sup> Likewise, a prospective observational study ( $n = 30$ ) abnormal ABR findings in two patients, both of whom also exhibited bilateral SNHL by pure tone audiometry.<sup>26</sup> In both studies, symptoms resolved after discontinuation of chloroquine treatment. A recent systematic review found evidence of abnormal ABR or SNHL in 10 patients across 6 case reports after chloroquine therapy.<sup>27</sup> Severe permanent bilateral SNHL was reported in two of these patients, the first occurring within hours of chloroquine administration and the later after prolonged chloroquine therapy. Three out of the 10 patients additionally reported vertigo or imbalance occurring concurrently with hearing loss. Reports of tinnitus after chloroquine therapy are much less common, although it has been described in a small percentage of patients.<sup>28,29</sup>

Hydroxychloroquine has likewise been associated both reversible and irreversible hearing loss in a number of case reports in the clinical literature. A systematic review found evidence of mild to severe SNHL occurring in seven patients across six case reports after hydroxychloroquine therapy, with two of these patients experiencing tinnitus concurrent with hearing loss.

Although the mechanism by which chloroquine and hydroxychloroquine induce ototoxicity is not fully understood, chloroquine has been shown to accumulate in melanocytes resulting in damage to cochlear sensory hair

cells.<sup>29</sup> Evidence from the literature suggests that SNHL is more common with prolonged use and high doses of chloroquine and hydroxychloroquine.<sup>30</sup> Importantly, the suggested dose in COVID-19 patients is significantly higher than the recommended dose for malaria treatment and there is currently no data assessing the ototoxic effects of chloroquine at these increased doses in the literature.<sup>27</sup>

### ***Azithromycin***

Azithromycin is a macrolide antibiotic commonly used to treat a wide variety of gram positive and atypical bacterial infections; it also possesses anti-inflammatory properties and inhibits viral replication of human influenza virus H1N1 in vivo.<sup>52,53</sup> A recent study demonstrated that azithromycin may have therapeutic effects against SARS-CoV-2 through modulation of the pH of endosomes in the trans-Golgi network of respiratory epithelial cells.<sup>54</sup> A single arm, non-RCT reported azithromycin combined with hydroxychloroquine was significantly more effective at reducing viral load than hydroxychloroquine alone in COVID-19 patients, suggesting possible synergistic effects.<sup>49</sup> There are currently over 30 active clinical trials assessing the effects of azithromycin in COVID-19 patients, many of which use a combination therapy of azithromycin with chloroquine or hydroxychloroquine.

Several studies report ototoxicity associated with azithromycin use, including SNHL, tinnitus, and imbalance. Ototoxicity typically manifests as bilateral hearing loss within a week of treatment initiation and increases with dose and blood serum levels.<sup>2</sup> An RCT ( $n = 1,146$ ) of

long-term azithromycin in chronic obstructive pulmonary disease (COPD) found that patients treated with azithromycin had a 25% higher rate of SNHL compared to the placebo control group.<sup>41</sup> A systematic review investigating macrolide associated hearing loss concluded that SNHL was significantly associated with azithromycin use, even at standard oral doses of 250 mg.<sup>42</sup> The severity of SNHL ranged from mild to severe and was often reversible, although a small subset of patients suffered from permanent hearing loss. A retrospective study investigating azithromycin use in HIV-related infections (n = 41) reported similar findings, with eight patients experiencing severe ototoxic adverse events including bilateral SNHL, tinnitus, and vertigo.<sup>43</sup> Symptoms were found to resolve in an average of 5 weeks after discontinuation of treatment.

The mechanism by which azithromycin-induced ototoxicity occurs is not well understood. Topical azithromycin induces significant inner and outer sensory hair cell loss in guinea pigs.<sup>44</sup> A study carried out in erythromycin, a related macrolide antibiotic, found that erythromycin-induced SNHL was associated with the absence of serial-evoked auditory brainstem potentials in waves I to III, suggesting hearing loss may be related to dysfunction in the peripheral auditory system.<sup>45</sup>

### **Lopinavir-ritonavir**

Lopinavir-ritonavir is an orally administered antiretroviral therapy (ART) approved for the treatment of human immunodeficiency virus (HIV) type I. Lopinavir is an aspartate protease inhibitor administered in combination with the pharmacokinetic booster ritonavir to increase plasma half-life through inhibition of cytochrome P450. Lopinavir has shown effectiveness against both middle east respiratory syndrome coronavirus (MERS-CoV) and acute respiratory syndrome (SARS), caused by the related SARS-CoV coronaviruses, with significantly reduced rates of acute respiratory distress syndrome (ARDS) and mortality.<sup>55–57</sup> Clinical data for the use of lopinavir-ritonavir in COVID-19 patients remain limited and RCTs are ongoing. Lopinavir-ritonavir therapy was shown to promote recovery rates in a case series of 10 patients hospitalized with severe COVID-19.<sup>58</sup> However, a large RCT assessing lopinavir-ritonavir treatment in severe COVID-19 found no benefit compared with standard of care.<sup>59</sup>

Data from the research literature have confirmed that ritonavir possesses ototoxic effects in vitro. Ritonavir was shown to significantly reduce the viability of auditory HEI-OC1 cells, with toxicity increasing with length of exposure.<sup>9</sup> However, clinical data are limited. Moderate, bilateral hearing loss was confirmed by audiologic testing in a patient 4 weeks after initiation of lopinavir-ritonavir therapy. Hearing loss was reported to resolve shortly after discontinuation of lopinavir-ritonavir treatment and audiologic testing revealed borderline normal auditory acuity by 20 weeks after discontinuation.<sup>10</sup>

### **Interferon**

Interferons (IFNs) are a group of naturally occurring signaling proteins released by numerous cell types in response to inflammation or infection. Type I IFNs, which include interferon- $\alpha$  (IFN- $\alpha$ ) and interferon- $\beta$  (IFN- $\beta$ ), are known to possess robust antiviral and immunomodulatory capabilities.<sup>60</sup> IFN- $\alpha$  and IFN- $\beta$  have been studied in previous coronavirus outbreaks, with both demonstrating activity against SARS-CoV in vitro.<sup>61</sup> Recent clinical trials in COVID-19 patients reported that IFN- $\alpha$  therapy significantly reduced rates of viral shedding and levels of inflammatory markers, whereas IFN- $\beta$  therapy improved virologic clearance.<sup>62,63</sup> However, both had small sample sizes and lacked a control group. Over 15 clinical trials are ongoing to assess the efficacy of IFN- $\alpha$  or IFN- $\beta$  in COVID-19 patients. Importantly, many of these trials utilize IFNs in combination with other therapeutics discussed in this review, including chloroquine, hydroxychloroquine, lopinavir-ritonavir, and ribavirin.

Ototoxic effects of interferon therapy have been documented both in vitro and in vivo. A prospective cohort study (n = 49) receiving either IFN- $\alpha$  or IFN- $\beta$  therapy confirmed SNHL in 18 (35%) patients and tinnitus in 14 (29%) patients.<sup>31</sup> IFN- $\beta$  therapy was associated with both unilateral and bilateral hearing loss, whereas treatment with IFN- $\alpha$  resulted exclusively in unilateral hearing loss. A prospective cohort study (n = 77) documented 37% SNHL, with no difference between patients receiving IFN- $\alpha$  or IFN- $\beta$ .<sup>32</sup> Across all studies, IFN-induced hearing loss was generally reversible and returned to normal within 14 days of discontinuing therapy. Importantly, a case-controlled study demonstrated a higher incidence of hearing loss in elderly and male patients.<sup>33</sup> Increased age and male gender have been identified as independent risk factors for increased severity of COVID-19 disease, raising concern for increased risk of IFN-induced ototoxicity in these already vulnerable patient populations.<sup>34</sup>

Although the mechanism behind IFN-induced ototoxicity is not fully understood, animal models suggest cochlear damage. Mice receiving intraperitoneal injections of IFN- $\alpha$  exhibited an elevated ABR threshold and prominent histologic changes in the cochlea compared to the control group.<sup>35</sup> Loss of hair cells was not observed.

### **Ribavirin**

The antiretroviral agent ribavirin has been used to treat several viral infections including respiratory syncytial virus (RSV), hepatitis C, and some viral hemorrhagic fevers. Ribavirin is a guanosine analog that interferes with viral replication through inhibition of viral mRNA synthesis. A recent open label RCT found that triple therapy of ribavirin, lopinavir-ritonavir, and IFN- $\beta$ 1b in COVID-19 patients shortened hospital stay and decreased viral shedding compared with lopinavir-ritonavir therapy alone.<sup>64</sup> Additional clinical trials evaluating efficacy of ribavirin alone, and in combination with ivermectin and nitazoxanide, for SARS-CoV-2 are ongoing.

Numerous reports support ribavirin-induced ototoxicity. A retrospective cohort study estimated that sudden hearing loss may occur in up to 1% of patients receiving pegylated (PEG)-IFN/ribavirin combination therapy.<sup>11</sup> Our review identified nine separate case reports of severe sudden hearing loss in patients receiving pegylated (PEG)-IFN/ribavirin combination therapy. Of these, unilateral SNHL was far more common, occurring in eight out of the nine patients.<sup>12–19</sup> Three cases reported temporary hearing loss that improved with cessation of pegylated (PEG)-IFN/ribavirin combination therapy.<sup>13,14,18</sup> SNHL was fully reversible in two cases (after prednisone treatment) and permanent in four cases, even after cessation of treatment.<sup>12,15–17,19,20</sup> Tinnitus occurred concurrently with hearing loss in one case.<sup>16</sup>

These reports suggest that the therapeutic use of (PEG)-IFN/ribavirin combination therapy may mimic the ototoxic effects of non-pegylated interferons alone. Ribavirin in combination with (PEG)-IFN remains the standard of care in many patients with chronic hepatitis-C infections. Minimal data exists on the ototoxic effects of ribavirin alone; therefore, it is difficult to discern whether SNHL is the sole result of IFN therapy or if ribavirin may enhance known ototoxic effects. Interestingly, whereas hearing loss induced by IFN therapy alone is usually reversible, (PEG)-IFN/ribavirin combination therapy has shown higher rates of permanent hearing loss.<sup>21</sup>

### ***Ivermectin***

Ivermectin is a broad spectrum antiparasitic drug that has been suggested as a novel COVID-19 therapeutic after it was shown to inhibit replication of the SARS-CoV-2 virus *in vitro*.<sup>65</sup> There are limited clinical data for Ivermectin in COVID-19 patients, or against prior outbreaks of SARS-CoV or MERS-CoV. Numerous RTCs of ivermectin in COVID-19 patients are ongoing, many of which combine ivermectin with previously discussed drugs, such as azithromycin, chloroquine, hydroxychloroquine, and ribavirin.

Clinical reports indicate ototoxic effects associated with ivermectin use, primarily manifesting as vestibulopathy. The results of four studies evaluating the efficacy of ivermectin in strongyloidiasis reported vertigo in 0.9% and dizziness in 2.8% of participants. However, a recent large database monitoring found rates of disequilibrium to be much higher: 7.5% of patients treated with ivermectin reported dizziness.<sup>22</sup> A study on ivermectin in gnathostomiasis (n = 20) reported similar results, with 15% participants experiencing dizziness.<sup>23</sup> Data suggest rates of disequilibrium are unrelated to ivermectin dose or duration of treatment.<sup>23,24</sup> In all cases, disequilibrium was self-limited and no long-term ototoxic effects were observed.

## **DISCUSSION**

The purpose of this narrative review was to summarize the literature regarding the ototoxic effects of COVID-19 therapeutics. Ototoxicity was found to be a shared feature among many of these proposed

therapeutics, including chloroquine and hydroxychloroquine, azithromycin, lopinavir-ritonavir, interferon, ribavirin, and ivermectin. Due to the growing number of COVID-19 patients worldwide who may be exposed to these medications, vigilance regarding symptoms of hearing loss, tinnitus, and imbalance/dizziness is a key strategy to prevent long-term disability.

Synergistic adverse audiovestibular effects may occur with the co-administration of multiple ototoxic COVID-19 therapeutics. Varying combinations have been- or are currently being-used in patients with COVID-19. Most notably, hydroxychloroquine-azithromycin combination therapy has been used clinically to treat thousands of COVID-19 patients worldwide. Additional clinical trials include hydroxychloroquine in combination with IFNs or lopinavir-ritonavir, azithromycin in combination with ivermectin, as well as a triple combination of IFNs, lopinavir-ritonavir, and ribavirin. Minimal data exist on the possible synergistic ototoxic effects of these combination therapies. Of particular concern, azithromycin and lopinavir-ritonavir may increase serum levels of hydroxychloroquine due to the inhibition of cytochrome P450 3A4 (CYP3A4), which may result in increased risk of ototoxic adverse effects.<sup>66</sup>

Various factors are known to increase the risk of drug-induced hearing loss, including old age, underlying hearing impairment, genetics, and reduced drug elimination.<sup>67</sup> Renal failure is of particular concern as the majority of ototoxic drugs are eliminated through the kidneys, including three of six medications discussed in this review: hydroxychloroquine, chloroquine, and ribavirin.<sup>67</sup> Acute kidney injury occurs in 20% to 40% of critically ill COVID-19 patients, potentially impacting ototoxic effects due to reduced renal elimination.<sup>68</sup> Likewise, reduced renal function puts elderly patients at an increased risk of ototoxicity, especially when combined with other medications they may take for chronic conditions.<sup>69</sup> Lastly, patients with prior SNHL are at an increased risk of additional drug-induced hearing loss.<sup>70</sup> Attention to serum levels of ototoxic therapeutics in these at-risk populations may minimize long-term effects to hearing and balance. When possible, recommendations advise avoidance or replacement with a non-ototoxic drug in older, hearing-impaired patients.<sup>67</sup>

The compounding effects of hypoxia and administration of ototoxic medications is an additional concern in COVID-19 patients. Hypoxia induces metabolic changes to electrochemical potentials in the cochlea, resulting in decreased hearing thresholds, reduced speech discrimination, and prolongation of I-V waves in ABR.<sup>71</sup> Hypoxia is a defining feature of serious COVID-19 disease and may exacerbate the ototoxic effects of COVID-19 therapeutics in these patients. Furthermore, COVID-19 infection is associated with the development of a hypercoagulable state, which may increase the risk of hearing loss due to microthrombi formation. It may therefore be difficult to separate hearing loss due to microthrombi or hypoxia from ototoxic effects of COVID-19 therapeutics.

Hospitals should consider the audiologic monitoring protocols for individuals receiving ototoxic COVID-19 therapeutics, especially high-risk patient groups such as

the elderly and hearing impaired. Ideally, patients reporting symptoms of hearing loss, tinnitus, and vertigo should be undergo audiologic evaluation. While comprehensive behavioral audiometry in a sound-proof booth remains the gold standard for establishing ototoxicity, urgent cases requiring real-time decision-making may benefit from bedside behavioral or electrophysiologic testing. High-frequency audiometry may be considered when possible, and can detect ototoxic damage at a subclinical level, allowing early intervention to minimize or prevent hearing loss.<sup>2</sup>

Guidelines from The American Speech–Language–Hearing Association (ASHA) recommend that all patients administered ototoxic medications should 1) receive routine audiologic monitoring during the treatment course to facilitate early detection of ototoxicity, 2) receive post treatment audiologic evaluations 3 months and 6 months after cessation of the ototoxic medication to detect delayed or residual effects of ototoxicity, 3) receive prompt initiation of aural rehabilitation if ototoxic effects should manifest.<sup>72</sup> For those unable to travel, telemedicine with remote audiometry applications may play a role.<sup>73,74</sup>

Available evidence suggests that ototoxic effects may be improved or mitigated by stopping of the offending agent, suggesting that vigilance regarding symptoms of hearing loss and imbalance is crucial to prevent long-term damage. Evidence suggests that steroids may limit drug-induced ototoxicity of some medications, such as hydroxychloroquine, chloroquine, azithromycin, and ribavirin, however additional data is necessary.<sup>15,16,27,42,75</sup>

## CONCLUSION

Many therapeutics used in COVID-19 have ototoxic effects, including chloroquine and hydroxychloroquine, azithromycin, lopinavir-ritonavir, interferon, ribavirin, and ivermectin. Damaging effects may be reversible if identified, therefore, recognition of hearing loss, tinnitus, or imbalance/vertigo remains the frontline of both prevention and treatment. Hospitals should consider the inclusion of audiologic monitoring protocols for patients receiving ototoxic COVID-19 therapeutics, especially in high risk patient groups such as the elderly and hearing impaired.

## BIBLIOGRAPHY

- Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multi-Centre, randomized, controlled trial. medRxiv. 2020.
- Lanvers-Kaminsky C, Zehnhoff-Dinnesen AA, Parfitt R, Ciarimboli G. Drug-induced ototoxicity: mechanisms, pharmacogenetics, and protective strategies. *Clin Pharmacol Ther* 2017;101:491–500.
- Chary MA, Barbuto AF, Izadmehr S, Hayes BD, Burns MM. COVID-19: therapeutics and their toxicities. *J Med Toxicol* 2020;16:284–294.
- Lin FR, Yaffe K, Xia J, et al. Hearing loss and cognitive decline in older adults. *JAMA Intern Med* 2013;173:293–299.
- Han KM, Ko YH, Shin C, et al. Tinnitus, depression, and suicidal ideation in adults: a nationally representative general population sample. *J Psychiatr Res* 2018;98:124–132.
- Trevis KJ, McLachlan NM, Wilson SJ. A systematic review and meta-analysis of psychological functioning in chronic tinnitus. *Clin Psychol Rev* 2018;60:62–86.
- Alyono JC. Vertigo and Dizziness: Understanding and Managing Fall Risk. *Otolaryngol Clin North Am* 2018;51:725–740.

- Lacerda CF, Silva LO, de Tavares Canto RS, Cheik NC. Effects of hearing aids in the balance, quality of life and fear to fall in elderly people with sensorineural hearing loss. *Int Arch Otorhinolaryngol* 2012;16:156–162.
- Thein P, Kalinec GM, Park C, Kalinec F. In vitro assessment of antiretroviral drugs demonstrates potential for ototoxicity. *Hear Res* 2014;310:27–35.
- Williams B. Ototoxicity may be associated with protease inhibitor therapy. *Clin Infect Dis* 2001;33:2100–2102.
- Formann E, Stauber R, Denk DM, et al. Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin. *Am J Gastroenterol* 2004;99:873–877.
- Jain S, Midha V, Sood A. Unilateral hearing loss due to pegylated interferon-alpha2b and ribavirin therapy. *Indian J Gastroenterol* 2011;30:239–240.
- Zampino R, Costa G, Barillari M, Adinolfi LE, Marrone A. Reversible sudden hearing loss in a chronic hepatitis C patient who achieved a sustained response to antiviral re-treatment. *Infez Med* 2012;20:117–119.
- Atug O, Akin H, Yilmaz Y, Sari M, Tozun N. Pegylated interferon/ribavirin-induced sudden sensorineural hearing loss in a patient with chronic hepatitis C. *J Gastrointest Liver Dis* 2009;18:256.
- Le V, Bader T, Fazili J. A case of hearing loss associated with pegylated interferon and ribavirin treatment ameliorated by prednisone. *Nat Clin Pract Gastroenterol Hepatol* 2009;6:57–60.
- Shin MK, Kim TH, Ju K, et al. A case of sudden-onset hearing loss in a patient treated with peginterferon alpha-2b and ribavirin for chronic hepatitis C. *Korean J Hepatol* 2009;15:370–374.
- Wong VK, Cheong-Lee C, Ford JA, Yoshida EM. Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. *World J Gastroenterol* 2005;11:5392–5393.
- Elloumi H, Houissa F, Hadj NB, et al. Sudden hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment. *World J Gastroenterol* 2007;13:5411–5412.
- Mendes-Correa MC, Bittar RS, Salmato N, Oiticica J. Pegylated interferon/ribavirin-associated sudden hearing loss in a patient with chronic hepatitis C in Brazil. *Braz J Infect Dis* 2011;15:87–89.
- Piekarska A, Jozefowicz-Korczynska M, Wojcik K, Berkan E. Sudden hearing loss in chronic hepatitis C patient suffering from turner syndrome, treated with pegylated interferon and ribavirin. *Int J Audiol* 2007;46:345–350.
- Szczeppek AJ. Ototoxicity: old and new foes. *Adv Clin Audiol* 2017;233–249.
- Chandler RE. Serious neurological adverse events after Ivermectin-do they occur beyond the indication of onchocerciasis? *Am J Trop Med Hyg* 2018;98:382–388.
- Bussaratid V, Krudsood S, Silachamroon U, Looareesuwan S. Tolerability of ivermectin in gnathostomiasis. *Southeast Asian J Trop Med Public Health* 2005;36:644–649.
- Henriquez-Camacho C, Gotuzzo E, Echevarria J, et al. Ivermectin versus albendazole or thiabendazole for *Strongyloides stercoralis* infection. *Cochrane Database Syst Rev* 2016;1:CD007745.
- Bernard P. Alterations of auditory evoked potentials during the course of chloroquine treatment. *Acta Otolaryngol* 1985;99:387–392.
- Subramaniam V, Vaswani R. Assessment of short term chloroquine-induced ototoxicity in malaria patients. *Global J Med Res* 2015;15:14–17.
- Prayuenyong P, Kasbekar AV, Baguley DM. Clinical implications of chloroquine and hydroxychloroquine ototoxicity for COVID-19 treatment: a mini-review. *Front Public Health* 2020;8:252.
- Dwivedi GS, Mehra YN. Ototoxicity of chloroquine phosphate. A case report. *J Laryngol Otol* 1978;92:701–703.
- Bortoli R, Santiago M. Chloroquine ototoxicity. *Clin Rheumatol* 2007;26:1809–1810.
- Hadi U, Nuwayhid N, Hasbani AS. Chloroquine ototoxicity: an idiosyncratic phenomenon. *Otolaryngol Head Neck Surg* 1996;114:491–493.
- Kanda Y, Shigeno K, Kinoshita N, Nakao K, Yano M, Matsuo H. Sudden hearing loss associated with interferon. *Lancet* 1994;343:1134–1135.
- Kanda Y, Shigeno K, Matsuo H, Yano M, Yamada N, Kumagami H. Interferon-induced sudden hearing loss. *Audiology* 1995;34:98–102.
- Sharifian MR, Kamandi S, Sima HR, Zaringhalam MA, Bakhsheae M. INF-alpha and ototoxicity. *Biomed Res Int* 2013;2013:295327.
- Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the new York City area. *JAMA* 2020;323:2052–2059.
- Akyol MU, Sarac S, Akyol G, et al. Investigation of the ototoxic effects of interferon alpha2A on the mouse cochlea. *Otolaryngol Head Neck Surg* 2001;124:107–110.
- Sverak P, Adams ME, Haines SJ, et al. Bevacizumab for hearing preservation in Neurofibromatosis type 2: emphasis on patient-reported outcomes and toxicities. *Otolaryngol Head Neck Surg* 2019;160:526–532.
- Huang V, Bergner AL, Halpin C, et al. Improvement in patient-reported hearing after treatment with bevacizumab in people with Neurofibromatosis type 2. *Otol Neurotol* 2018;39:632–638.
- Tran TA. Muckle-Wells syndrome: clinical perspectives. *Open Access Rheumatol* 2017;9:123–129.
- Marchica C, Zawawi F, Basodan D, Scuccimarri R, Daniel SJ. Resolution of unilateral sensorineural hearing loss in a pediatric patient with a severe phenotype of muckle-Wells syndrome treated with Anakinra: a case report and review of the literature. *J Otolaryngol Head Neck Surg* 2018;47:9.
- Stachler RJ, Chandrasekhar SS, Archer SM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;146:S1–35.

41. Albert RK, Connert J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;365:689–698.
42. Ikeda AK, Prince AA, Chen JX, Lieu JEC, Shin JJ. Macrolide-associated sensorineural hearing loss: a systematic review. *Laryngoscope* 2018;128:228–236.
43. Tseng AL, Dolovich L, Salit IE. Azithromycin-related ototoxicity in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1997;24:76–77.
44. Pawlowski KS, Si E, Wright CG, Koulich E, Hosseini K, Roland PS. Ototoxicity of topical azithromycin solutions in the Guinea pig. *Arch Otolaryngol Head Neck Surg* 2010;136:481–487.
45. Sacristan JA, Angeles De Cos M, Soto J, et al. Ototoxicity of erythromycin in man: electrophysiologic approach. *Am J Otol* 1993;14:186–188.
46. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 2003;3:722–727.
47. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14:72–73.
48. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv. 2020.
49. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;56:105949.
50. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849.
51. Geleris J, Sun Y, Platt J, et al. Observational Study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;382:2411–2418.
52. Tran DH, Sugamata R, Hirose T, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza a(H1N1)pdm09 virus infection by interfering with virus internalization process. *J Antibiot (Tokyo)* 2019;72:759–768.
53. Bermejo-Martin JF, Kelvin DJ, Eiros JM, Castrodeza J, Ortiz de Lejarazu R. Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains. *J Infect Dev Ctries* 2009;3:159–161.
54. Poschet JF, Perkett EA, Timmins GS, Deretic V. Azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells. bioRxiv. 2020.
55. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—a possible reference for coronavirus disease-19 treatment option. *J Med Virol* 2020;92:556–563.
56. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004;59:252–256.
57. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J* 2003;9:399–406.
58. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. *Int J Infect Dis* 2020;95:183–191.
59. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787–1799.
60. Lazear HM, Schoggins JW, Diamond MS. Shared and distinct functions of type I and type III interferons. *Immunity* 2019;50:907–923.
61. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006;3:e343.
62. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b treatment for COVID-19. *Front Immunol* 2020;11:1061.
63. Dastan F, Nadji SA, Saffaei A, et al. Subcutaneous administration of interferon beta-1a for COVID-19: a non-controlled prospective trial. *Int Immunopharmacol* 2020;85:106688.
64. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020;395:1695–1704.
65. Cally L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020;178:104787.
66. Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. *Eur Heart J Acute Cardiovasc Care* 2020;9:215–221.
67. Cianfrone G, Pentangelo D, Cianfrone F, et al. Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. *Eur Rev Med Pharmacol Sci* 2011;15:601–636.
68. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med* 2020;8:738–742.
69. Howarth A, Shone GR. Ageing and the auditory system. *Postgrad Med J* 2006;82:166–171.
70. Hybels RL. Drug toxicity of the inner ear. *Med Clin North Am* 1979;63:309–319.
71. Sonbay Yilmaz ND, Saka C, Oktay Arslan B, et al. The effect of hypoxia on hearing function. *Turk J Med Sci* 2019;49:1450–1454.
72. American Speech-Language-Hearing Association. Audiologic management of individuals receiving cochleotoxic drug therapy. ASHA. 1994.
73. Krumm M. Audiology telemedicine. *J Telemed Telecare* 2007;13:224–229.
74. Barczik J, Serpanos YC. Accuracy of smartphone self-hearing test applications across frequencies and earphone styles in adults. *Am J Audiol* 2018;27:570–580.
75. Hammill TL, Campbell KC. Protection for medication-induced hearing loss: the state of the science. *Int J Audiol* 2018;57:S67–S75.