Review

Approach to post COVID-19 persistent cough: A narrative review

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ABSTRACT

A large proportion of patients who completely recovered from acute coronavirus disease 2019 (COVID-19) infection later continued to experience symptoms even after recovery, irrespective of the severity of the disease. Various terms with varying duration were used for those who had persistent symptoms, of which cough was the most common. We systematically searched the published literature concerning post-COVID-19 cough, its prevalence, and the potential ways to reduce it in clinical practice. The aim of this review was to provide an overview of existing literature concerning post-COVID-19 cough. Literature shows that augmented cough reflex sensitivity is responsible for persistent cough after acute viral upper respiratory infection (URI). Overall, the heightened cough reflex associated with SARSCoV2 induces neurotropism, neuroinflammation, and neuroimmunomodulation via the vagal sensory nerves. Therapies for post-COVID-19 cough aim at the suppression of cough reflex. For a patient who does not respond to early symptomatic treatment, Inhaled corticosteroids can be given a trial to suppress airway inflammation. More trials of novel cough therapies in patients with post-COVID-19 cough using various outcome measures need to be studied in future research. Several agents are currently available for symptomatic relief. However, non-response or refractory cough continues to preclude adequate symptom relief.

KEY WORDS: Cough, inhaled steroids, post-COVID

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INTRODUCTION

A large proportion of patients acute coronavirus disease 2019 (COVID-19) infection later continued to experience symptoms even after recovery, irrespective of the severity of the disease. All the symptoms that occur during acute or follow-up and persist beyond four weeks of COVID-19 diagnosis were labelled by many authors as 'long COVID'.[1] This term has been used in multiple ways in literature and is further classified according to National Institute for Health and Care Excellence (NICE) guidelines as 'Ongoing symptomatic COVID-19' with signs and symptoms persisting from four weeks to twelve weeks and 'Post-COVID-19 syndrome' with signs and symptoms developing during or after acute COVID-19 infection persisting more than 12 weeks and not explained by any alternative diagnosis.[2] Greenhalgh *et al*.[3] used the terms 'post-acute COVID-19' (from 3 to 12 weeks) and 'chronic COVID-19' for symptoms extending beyond 12 weeks. However, one of the most common persisting symptoms after COVID-19 infection is cough.[4] Over time, this cough can develop into a vicious cycle, where excessive coughing leads to irritation and inflammation and further worsens

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the cough. Here, we systematically searched the published literature concerning post-COVID-19 cough, its prevalence and the potential ways to reduce it in clinical practice.

MATERIALS AND METHODS

Due to the rapidity of the new research during the COVID-19 pandemic, many systematic reviews conducted in the earlier phase soon became redundant.

Here, we did a literature search on the PubMed database using the following keywords (POST SARS-CoV-2 or POST COVID-19 or LONG COVID) and (COUGH), and included all the studies published in 2021. Peer-reviewed studies were considered eligible if the sample size of at least 100 with laboratory-confirmed and/or clinically diagnosed COVID-19. A total of 209 articles were searched, and 176 free full texts were retrieved by our search strategy. We screened the titles and abstracts to identify relevant studies, and all the references that did not fit into the inclusion criteria were eliminated. A few more articles were identified through manual searching, bringing the total number of included articles to 22.

PREVALENCE

The aim of this review was to provide an overview of existing literature concerning post-COVID-19 cough. Previously published long COVID disability 2020 reports showed that 10%–20% of COVID-19 patients do experience some symptoms, including cough, for months.[5] Further, cough categorisation has been done as acute (lasting less than three weeks), subacute (lasting between three and eight weeks) and chronic (persisting for more than eight weeks).[6] The prevalence of chronic cough after SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) varies across studies found in literature ranging from 2.1%[7] to as high as 73%[8] [Table 1].

PATHOPHYSIOLOGY

Literature shows that augmented cough reflex sensitivity is responsible for persistent cough after acute viral upper respiratory infection (URI).[31,32] However, the major question is whether SARS-CoV-2 induces a cough similar to other viral URI or has some other pathophysiology. Different hypotheses explaining the emergence of coughing due to SARS-CoV-2 infection can be found in the literature. The respiratory epithelium is the primary site of entrance for SARS-CoV-2 and the vagal sensory nerves, which tend to terminate in the epithelium and sub-epithelial mucosa of the human airways, play a key role in regulating cough.[33] For cellular entry on mucosal surfaces, SARS-CoV-2 uses the cell surface protein angiotensin-converting enzyme type 2 (ACE2),[34] which is richly expressed in upper and lower airway epithelial cells. Although this enzyme has numerous functions, one of the functions is to regulate mucosal concentrations of bradykinin (a pro-inflammatory cytokine) and hence evoke coughing.[35,36] Pneumonia and acute lung injury caused by COVID-19 infection mainly involve the most peripheral conducting airways and alveoli, compared to other viral pneumonia. Eventually, SARS-CoV-2 impacts the large conducting airways (larynx, trachea and mainstem bronchi), peripheral airways and

Table 1: Follow-up studies looked on prevalence of cough after recovery from COVID-19

Author	Country	Sample	Mean/ Median age (years)	Age Male %	Severe COVID (%)	Follow-up Period (month)	Prevalence of Cough
Reaz Mahmud *et al*.[9]	Dhaka, Bangladesh	355	39.8	58.3%	11	1	18.3%
Melina Michael *et al*.[10]	Metanalysis study (BMJ) 12 countries	5031	Not Applicable	52%	NOT REPORTED	>3	8.17%
Angelo Carfi *et al*.[11]	Rome, Italy	143	56.5	63%	53.8	2	16%
Destin Groff *et al*.[12]	Systematic Review of 57 studies	250351	54.4	56%	79	6	13.1% [5.3-22.6%]
Menges *et al*.[13]	Zurich, Switzerland	431	47	50%	NOT REPORTED	8	39%
Qu Guangbo *et al*.[14]	Multicentric, Anhui Province and Hubei Province	540	47.5	50%	9.4	3	11%
Fabio Anastasio *et al*.[15]	Italy	379	45.9	56%	60.8	4	6.1%
Rebecca F. D'Cruz *et al*.[16]	King's College Hospital, UK	119	58.7	62%	100%	2	7%
Taquet M *et al*.[17]	Oxford University Hospitals, UK	273618	46.3	44.4%	NOT REPORTED	6	12.6%
Xiong *et al*.[18]	Wuhan, China	538	52	45.5%	38.4%	3	7.1%
Arnold *et al*.[19]	Bristol, UK	110	60	56%	16.4%	3	11%
Bellan M *et al*.[20]	Northern Italy	238	61	59.7%	72%	4	6%
Dennis A *et al*.[21]	London, UK	201	44	29%	18.4%	4	73.6%
Han X *et al*.[22]	Wuhan, China	114	54	70%	21%	6	6.1%
Stavem K *et al*.[23]	Lorenskog, Norway	434	49.8	44%	Not reported, All OPD patients included	4	6%
Karaarslan *et al*.[24]	Ankara, Turkey	300	52.5	59.7%	Not mentioned	1	14
Huang *et al*.[25]	China	1733	57	52%	68%	6	4%
Moreno-Perez O *et al*.[26]	Spain	277	56	52.7%	65.7%	3.5	21.3%
Rosales Castillo *et al*.[27]	Spain	118	60.16	55.9%	7.6%	2	65.3%
Fernández-de-Las-Peñas *et al*.[28]	Multicentre study @ Spain	1950	61	53%	6.6%	11.2	2.5%
Naik S *et al*.[29]	Northern India	1234	41.6	69.4%	33%	3	2.1%
Sathyamurthi *et al*.[30]	Armonk, New York	279	71.1	63.8%	41.6%	3	4.3%

alveoli.[37,38] There is another controversy about the low incidence of persistent cough in COVID-19, especially in severe cases as compared to mild to moderate cases due to preferential involvement of lower airway and pneumonia, although more studies are required in this field. The variant of SARS-CoV-2 also has a variable prediction of the airway, as the delta variant predominantly involves the lower airway while the omicron involves the upper airway. Studies also show that C-fibre terminating in the upper and lower airways is responsible for transducing cough and causing the sensation of dyspnoea, respectively. Overall, the heightened cough reflex associated with SARS-CoV-2 induces neurotropism, neuroinflammation and neuroimmunomodulation via the vagal sensory nerves.[39]

DIAGNOSTIC APPROACH

The cough lasting for more than three weeks (subacute to chronic) from diagnosis of COVID-19 needs to be evaluated. A persistent cough (defined here as cough persisting for >3 weeks) in COVID-19 can be due to enhanced cough reflex due to SARS-CoV-2, COVID-19 pulmonary sequelae, aggravation of pre-existing lung disease or secondary infection, like bacterial, fungal or tuberculosis. Other common causes of chronic cough like a history of ACE inhibitors, cough variant asthma, GERD, etc., should also be considered as non-COVID conditions. Post-COVID-19 fungal complications shall also be considered as one of the differentials of cough in a subset of patients. A case series of seven post-COVID-19 patients showed pulmonary cavitation attributed to COVID-19-associated pulmonary aspergillosis (CAPA) in 5, mucormycosis in 1 and mycobacterium tuberculosis infection in another.[40] The history and clinical examination are always vital in the evaluation of any symptoms. Patients with a persistent cough should be evaluated with a chest X-ray PA view and a comparison with previous imaging must be done. In suspected cases, CT chest may be performed for further characterisation of opacity seen on chest X-ray. If chest X-ray is normal or consists of post-COVID-19 residual changes without any new opacity then consider the possibility of a post-viral enhanced cough reflex, which would subside during follow-up. SARS-CoV-2 infection may be a cause for the worsening of pre-existing lung diseases that need to be optimised with treatment. COVID-19 patients may develop tuberculosis, fungal (COVID-associated pulmonary mycosis) and bacterial infection in patients with new opacity on chest X-rays. The diagnostic approach is summarised in Figure 1.

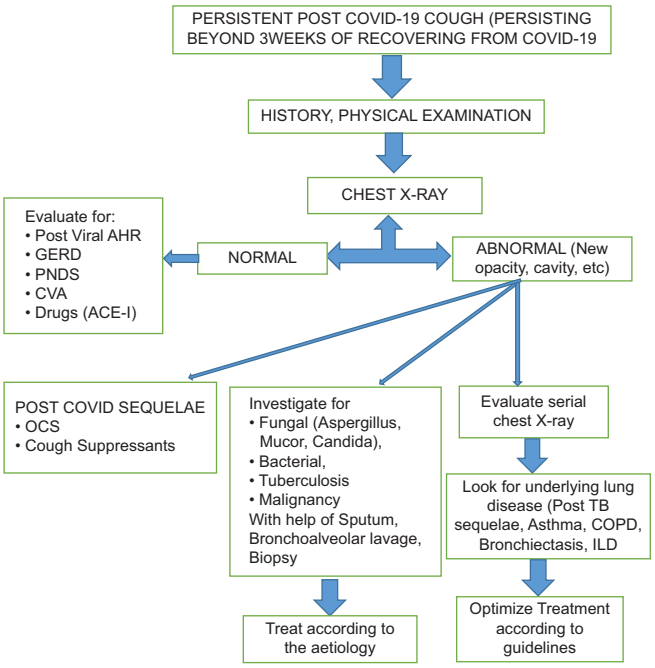

Figure 1: Overview of the evaluation of Persistent post-COVID-19 cough. ACE-I: angiotensin converting enzyme inhibitor; AHR: Airway Hyperreactivity; CVA: Cough Variant Asthma; PNDS: post-nasal drip syndrome; GERD: gastro-oesophageal reflux disease; COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial lung disease

TREATMENT

Therapies for post-COVID-19 cough aim at the suppression of cough reflex. In such patients, several potential causes of chronic cough must be excluded before chronic cough may be considered directly linked to COVID-19. So aiming at suppression of the cough reflex, we have drugs that suppress the central cough reflex (dextromethorphan, gabapentin, amitriptyline and opioids),[8,41] drugs that suppress sensory neurons (lidocaine, benzonatate)[42] and those that are believed to act on airways to reduce inflammation, smooth muscle contraction and mucus secretion (beta-agonists, leukotriene antagonists, macrolide antibiotics).[43] Patients with chronic cough also often seek antitussive therapies, but it is unknown to a larger extent whether such approaches are effective in post-COVID-19 cough patients. Inhaled tiotropium also elucidates antitussive action in studies by inhibiting cough reflex sensitivity to capsaicin apart from bronchodilation.[44]

For a dry cough, we have cough syrups with the main ingredient being dextromethorphan, butamirate, dropropizine and levodropropizine. For cough with expectoration, we have medications that help to modify the character of mucus and reduce its viscosity, thereby easing expectoration (ambroxol, bromhexine, acetylcysteine, carbocysteine) that can be used in post-COVID-19 patients. Antihistaminics[45] and CystLT1 receptor antagonists (Montelukast)[46] have shown promising results in post-COVID-19 cough as evidenced by various clinical trials.

Several agents have been evaluated for long COVID cough that can be considered in daily practice [Table 2]. A role for inhaled steroids is not established but is possible.[47,48] According to Swiss recommendations, it is recommended to give empiric inhaled topical steroids in patients with long COVID cough.[49] Drugs like pregabalin[50] and gabapentin[51] have been shown to improve cough severity, cough

Table 2: Pharmacological treatment for post-COVID cough

Drug Class	Examples	Citing studies	Sample size	Dose and Duration	Remarks
Antihistaminics	Levocetirizine Dextromethorphan	Sepiashvili R *et al*. (2021)[45]	56	80% of patients had sooth in cough as a symptom.	
Centrally acting antitussive drugs/ Neuro-modulating drugs	Gabapentin	Ryan *et al*. (2012)[41]	32	1800 mg od	Improved cough specific QoL
		Soltani Rasool *et al*. (2022)[51]	76	300 mg tds ×5 days	Improved cough frequency and severity
	Pregabalin	Vertigan AE *et al*. (2016)[50]	40	300 mg od ×4 weeks along with SPT$	Reduces cough symptoms and improves QOL
Leukotriene receptor antagonist (LTRA)	Monteleukast	Mohamed Hussein A.A.R. *et al*. (2022)[46]	32	10 mg/day ×14 days	Decrease number of cough paroxysm/day, cough severity index, cough QoL, cough duration
P2X3 Antagonist	Gefapixant (AF-219/ MK-7264)	McGarvey L P *et al* (2022)[52]	244	45 mg bid ×12 wks (COUGH 1)	Reduction in 24 hour cough frequency and Improvement in cough questionnaire score
			440	45 mg bid ×24 wks (COUGH 2)	
Charged sodium channel blocker	NTX-1175 (Nebulised)	Ongoing trial (EuraCT 2020-004715-27)[56]			
NK#-1 Receptor antagonist	Aprepitant Orvepitant	Smith J *et al*.[54]	13	30 mg od ×4 weeks (VOLCANO 1)	Improvement in objective daytime cough frequency, cough VAS and QoL.
Muscarinic antagonist	Inhaled Tiotropium	Dicpinigaitis PV *et al*. (2008)[44]	11	18 mcg od ×7 days	Inhibits cough reflex sensitivity to capsaicin
Inhaled steroids	Glycopyrronium/ Formoterol/Budesonide	Yamaya M *et al*. (2020)[48]	Inhibit CoV replication partly and modulate infection-induced inflammation in the airway.		
TRPV 1 antagonist*	SB-705498	Khalid S *et al*. (2014)[55]	21	600 mg single dose	Improvement in cough reflex sensitivity to capsaicin
Immunomodulatory drugs	Thalidomide	ClinicalTrials.gov Identifier: NCT04273529[57]		100 mg od× 14 days (results not posted yet)	
Mast cell stabilizer	Inhaled Sodium Cromoglycate	ClinicalTrials.gov Identifier: NCT05077917[58]		2 ml of 1% cromolyn sodium solution delivered via nebulizer 4 times a day for 4 days followed by 4% cromolyn solution administered intranasally 4 times per day for 14 days	

*TRPV 1 - Transient receptor potential vanilloid 1. #NK-1 - Neurokinin-1

frequency and QoL of patients with chronic cough. These neuromodulators can be considered for the post-COVID-19 syndrome for other symptoms accompanying cough, such as pain, but beware of their potential to worsen any cognitive dysfunction.[41] Newer investigational drug AF-219 (Gefapixant),[52] a P2X3 receptor antagonist, showed very promising phase two results in chronic cough, and its use in COVID-19-associated cough can be supported by the evidence that ACE2 is frequently co-expressed with P2X3 in dorsal root ganglion sensory neurons.[53] The endogenous receptor for substance P is neurokinin 1 receptor (NK1R) might also be a potential target for intervention, hence NK1R antagonists (aprepitant/orvepitant) can be tested in COVID-19 cough because TRPV1 in sensory neurons is upregulated by various viral infections (human rhinovirus).[7,54] TRPV-1 antagonist (SB-705498) showed a significant improvement in cough reflex sensitivity to capsaicin at 2 hours and a borderline significant improvement at 24 hours.[55]

Thalidomide has also shown promising results in controlling the disabling cough in ILD patients at a dose of 50–100 mg per day dosing. Thalidomide has been shown to reduce persistent cough and lung damage, improving patient life quality. It appears to be able to do this by blocking the inflammatory response.[59] Thus, thalidomide can also be further studied in research among the potential drugs for treating respiratory complications associated with COVID-19 based on its potent anti-inflammatory properties and its activity in attenuating exaggerated inflammation and cytokine storms. It is also known to be an upregulator for NK and T cells and thus can reverse the down-regulatory effect of COVID-19.[57]

Inhaled PA101 (Sodium Cromoglycate) 40 mg TDS could be a treatment option, and it has been studied for chronic cough in patients with IPF. Studies showed that it reduced daytime cough frequency by 31·1%, from a mean of 55 coughs per hour at baseline to 39 coughs per hour at day 14.[60] Mast cell activation in response to viral infection (COVID-19) may lead to protective function by directly fighting infection or helping the immune system. However, extensive mast cell activation leads to increased levels of inflammatory cytokine and chemokine release that further worsen inflammation and increase disease severity.[58] Few drugs like NTX-1175, a permanently charged sodium channel blocker, are yet under phase II clinical trials.[56]

Along with pharmacological treatment, other measures can be incorporated in patients recovering from a post-COVID-19 syndrome, including speech and language therapy along with physiotherapy, including slow, deep breath and gentle, relaxed breathing and huffing.[61]

Clinicians and researchers have focused on the acute phase of COVID-19, but continued monitoring after discharge for long-lasting effects is needed. In this review, we tried to focus on the epidemiology, pathophysiology and possible management of post-COVID-19 cough, which could help

clinicians in their daily practice. More randomized control trials (RCTs) of novel cough therapies in patients with post-COVID-19 cough using various outcome measures need to be studied in future research.

CONCLUSION

The majority of patients with persistent cough following SARS-CoV-2 infection are due to residual airway inflammation leading to hyperreactivity airway. The symptomatic treatment in the form of a cough suppressant, cysteine leukotriene, may be an attempt for relief. It is important to remember that SARS–CoV-2 infection may be a cause for the overt manifestation of pre-existing subclinical allergic bronchitis. Chest X-ray, markers of allergic inflammation [blood eosinophil, Fractional exhalation of Nitric oxide (FeNO), Serum total IgE] and spirometry may help in identifying the underlying cause and accordingly treatment. For a patient who does not respond to early symptomatic treatment, Inhaled corticosteroids can be given a trial to suppress airway inflammation. There are many investigational drugs that are yet under evaluation for persistent cough due to non-COVID aetiology or idiopathic cause and can be attempted in refractory cases. However, there is a dire need at present to establish recommendations or guidelines from a major association.

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Conflicts of interest
There are no conflicts of interest.

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