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Addressing Postinfectious Cough: Insights into Treatment Strategies from a Literature Review

Naveen Kizhakkayil Tency[1], Archa Roy[2]

Department of Internal Medicine, Government Medical College, Idukki, India
Email: *naveenktency21[at]gmail.com*

Department of Dermatology, Government Medical College, Idukki, India
Email: *archaelizabeth[at]gmail.com*

Abstract: ***Postinfectious cough is a common respiratory symptom that can persist following acute respiratory tractinfection. This review article provides an overview of the various treatment options for postinfectious cough based on the currently available evidence. A comprehensive search was performed, andrelevant studies were reviewed. The results revealed a variety of therapeutic possibilities including pharmaceutical agents, herbal remedies, and non - pharmacological interventions. However, the review identified a few shortcomings in the existing literature, including publication bias, inadequate number of significant human data, heterogeneity in the interventions, and small sample sizes. Despite these limitations, the review highlights the potential efficacy of certain interventions such as hyaluronic acid, honey, and coffee, inhaled salbutamol and ipratropium, inhaled beclomethasone dipropionate, and specific Chinese herbal preparations. The findings of this study emphasize the need for carefully planned clinical trials to determine the efficacy and safety of these treatments. These trials should include bigger sample sizes, standardized outcome measures, and longer follow - up times. Future research should also address these issues to broaden the understanding of postinfectious cough treatment, investigate potentially novel treatment targets, and address heterogeneity. By addressing these limitations and incorporating the recommended strategies, researchers can advance the understanding of postinfectious cough and guide the development of more effective and tailored treatment approaches.***

Keywords: postinfectious cough, postviral cough, chronic cough, treatment options, evidence - based, therapeutic possibilities, pharmaceutical agents, herbal remedies, non - pharmacological interventions, clinical trials, efficacy

1. Introduction and Background

One of the most frequent complaints among people seeking health services is coughing. Cough can be categorized as acute (less than three weeks), subacute (between three and eight weeks), or chronic (more than eight weeks) [1]. Respiratory viruses such as respiratory syncytial virus, adenoviruses, parainfluenza, and influenza have been identified as the cause of postinfectious cough (PIC), although an infectious origin is rarely established [1, 2]. Although the exact cause of PIC is unknown, epithelium disruption, airway inflammation, bronchial hyperresponsiveness, and cough hypersensitivity have all been implicated [1, 3 - 6]. Patients with postinfectious prolonged cough (PPC) frequently describe lingering, tickling, or irritating throat feeling that frequently result in coughing paroxysms [7].

A bothersome non - productive cough or the production of a small amount of white mucus sputum for three to eight weeks without obvious abnormalities on chest X - ray films are the hallmarks of PPC. Antibiotics, antitussive medications, antihistamines, antibiotics, and corticosteroids are some of the commonly given Western conventional medications (WCM) treatments. Central - acting antitussive agents are frequently used to treat persistent coughs; however, a sizeable minority of patients fail to benefit from them.

The central - acting antitussive medications codeine phosphate and dextromethorphan hydrobromide are not advised to be used according to the American College of Chest Physicians (ACCP) clinical practice recommendations [2]. Similarly, the small sample sizes and subpar reporting quality limit the information from randomized controlled trials (RCTs) that study Chinese herbal medicine (CHM) treatments for PIC [8]. Over - the - counter (OTC) drugs for persistent cough cost about 360 million dollars yearly, according to a survey conducted in the United States, whereas cough therapy costs more than 10 billion dollars worldwide [9]. However, successful outcomes are uncommon.

In 1995, Fujimori et al. in Japan were the first to put up the idea of postinfectious protracted cough [10]. PPC may not be linked to mortality and disability, but it can lead to morbidity and raise healthcare costs. PPC can be a bothersome issue for a significant portion of people, even though some people may choose to ignore it. These individuals are frequently sent to cough clinics where they are examined for further chronic coughing causes [2, 11].

Finding effective treatments for postinfectious cough (PIC) requires a comprehensive study since doing so can enhance patient outcomes and lessen the financial and medical burden the condition places on society. It can pinpoint the most effective pharmaceutical and non - pharmacological treatments, highlight knowledge gaps, and direct future research initiatives. This study offers a thorough and objective evaluation of the data that are readily available and required for therapeutic decision - making. Understanding the body of data can aid in identifying PIC treatments that have a high likelihood of being effective and safe. These interventions may be further investigated in rigorous experimental studies.

2. Review

Methodology

Search Strategy and Search Terminologies

To identify the studies that answer our question of available treatment strategies for postinfectious cough in adults we conducted a comprehensive literature search in PubMed and Google Scholar. In PubMed, we used the term: ((postinfectious cough) OR (post viral cough)) AND (treatment) without any time limit and obtained 477 articles. In Google Scholar, we used the terms: (postinfectious cough OR postviral cough) AND (treatment OR management OR intervention) AND (pharmacological OR non - pharmacological) AND (adults OR adult patients) AND (clinical trial OR RCT OR case report). We limited the timeline to between 2015 - 2023 to include only the most relevant papers. This resulted in finding 488 articles.

Inclusion and Exclusion Criteria

All papers reporting the management of postinfectious cough in human adult subjects were included. Any interventions that are pharmacological or natural methods have been considered for review. The outcome for each was to identify a decrease in cough frequency, duration, or quality of life after the intervention. Articles that reported on outcomes in animals and children, as well as research that did not provide any outcome, articles without any interventions, etc., were omitted. Articles written in languages other than English were not considered.

Data Collection and Extraction

Articles found (965) using the terms mentioned were exported into EndNote X9. We followed the Preferred Reporting Items for Systematic Reviews and Meta - Analysis (PRISMA) [12] approach to identify the studies for review. Figure 1 shows the flow diagram of our approach. After the removal of duplicates, we filtered out irrelevant studies by removing all the studies that did not have “cough” in the title.21 studies were sought out for retrieval of which 2 were not available 11 did not meet our criteria. Thus, eight studies have been selected for further review. In all stages of the literature search, two authors (NKT and AR) independently conducted the steps, and any disagreements were resolved through discussion.

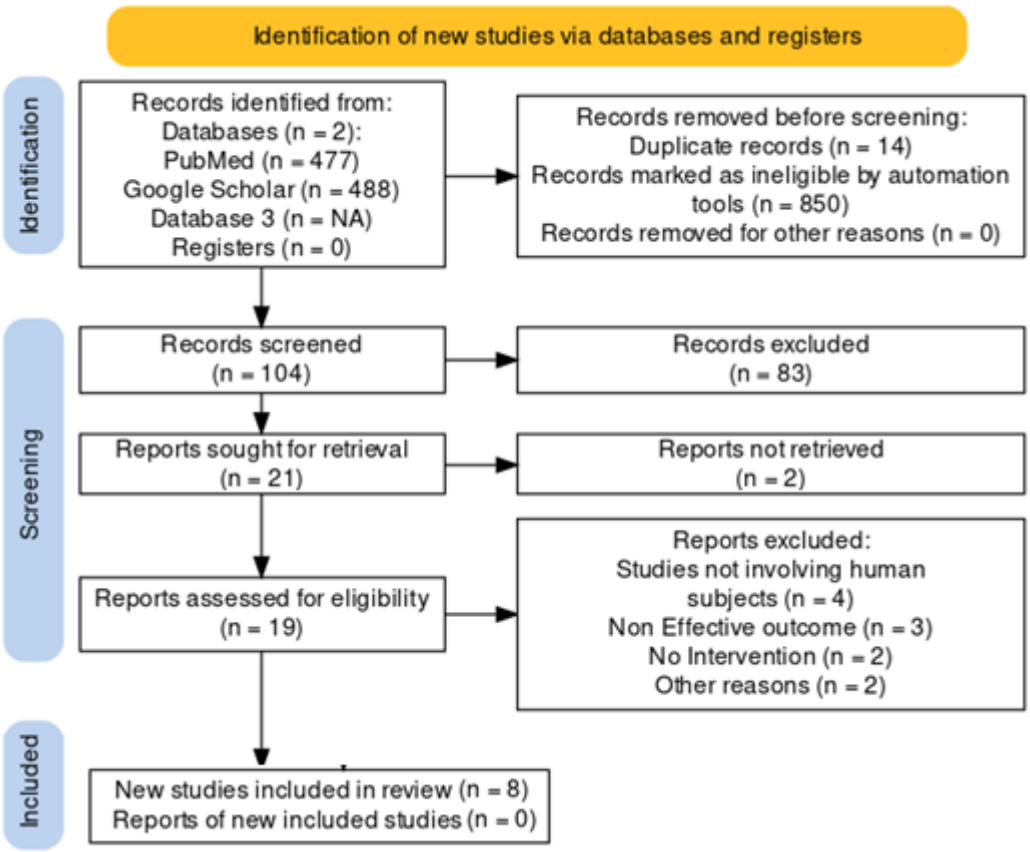

Figure 1: PRISMA approach implemented for literature screening

3. Results

After conducting a comprehensive literature search following the PRISMA guidelines, eight articles were selected for review, which provides insights into the effective treatment modalities available for postinfectious cough (PIC). The details of each included study and their respective results are summarized in Table 1. The selected studies encompass various study designs including randomized controlled trials, meta - analyses, review articles, and clinical trials, providing a diverse range of evidence to address the research question regarding the treatment of PIC.

Article	The type of Study	Intervention	Control	Remark/Result
Baranova, IV et al. [13]	Randomized controlled trial	0.1% solution of hyaluronic acid twice a day with a cycle of treatment consisting of 12–16 sessions	Dextromethorphan 30 mg three times a day, daily dosage 90 mg	Full remission of postinfectious cough hypersensitivity syndrome was achieved in all patients of the main group ($p < 0.001$) because of the conducted treatment
Ciprandi, G. Tosca, M. A. [14]	Review article	Non - Pharmacological interventions	Not Applicable	Evidence for honey, glycerol, Althea officinalis, Drosera rotundifolia, Grindelia, Hedera helix, Pelargonium sidoides, Sambucus nigra, Thymus vulgaris, hyaluronic acid, and saline solutions
Ding, P. et al. [15]	Meta - Analysis of Randomized Trials	SuhuangZhike Capsule (SZC)	Western conventional medicine (WCM) and other Chinese medicine	Compared to others, SZC could effectively improve the efficacy rate (OR 2.68, 95% CI, 1.48 - 4.84, P = 0.001; OR 4.86, 95% CI, 1.50 - 15.73, P = 0.008, separately). However, more evidence is needed to prove the earlier antitussive effect (MD - 1.31, 95% CI, - 3.06~0.45, P = 0.14)
Gillissen, A. Richter, A. Oster, H. [16]	Randomized controlled trial	Extrafine HFA - beclomethasone diproprionate (400 micrograms twice daily for 7 days followed by 200 micrograms twice daily for 4 days)	Placebo	The frequency of cough epochs/h at the end of treatment (Day 11) was significantly reduced compared to the placebo ($P < 0.05$)
Irifune, K. et al. [17]	A controlled clinical pilot study	Bakumondoto (TJ - 29) + procaterols hydrochloride	Only procaterol hydrochloride	Group B showed a significant improvement in cough score compared to Group A, demonstrating an early antitussive effect
Jiang, Hongli, et al. [18]	The multicenter, randomized, double - blind, placebo - controlled clinical trial	Group A: QingfengGanke granule (QFGKG) 6 g plus QFGKG - matched placebo6 g; Group B: QFGKG 12 g	Group C: QFGKG - matched placebo 12 g	Groups A and B showed significantly greater improvements in cough severity scores, visual analog scale (VAS), cough - specific quality of life questionnaire (CQLQ), and traditional Chinese medicine (TCM) syndrome compared to placebo. Group B had a faster time to cough resolution compared to Group A
Raeessi, M. A. et al. [19]	A double - blind randomized controlled trial	Honey plus coffee ('HC')	Prednisolone ('S')	A significant difference in mean cough frequency before and after treatment was observed in the HC group versus the S group ($p < 0.001$)
Zanasi, A. et al. [20]	A randomized, placebo - controlled, double - blind trial	The combination of salbutamol 1.875 mg/0.5 mL and ipratropium bromide 0.375 mg/0.5	Placebo	Daytime and night - time cough severity was significantly reduced in both groups, more prominent in the active treatment group vs. placebo after 10 days of treatment (P = 0.003 for day cough; P = 0.061 for night cough), whereas at the end of the follow - up period cough severity was comparable between the two groups.

Legends: HFA - Hydrofluroalkane, QingfengGanke granule (QFGKG), SuhuangZhike Capsule (SZC), visual analog scale (VAS), cough - specific quality of life questionnaire (CQLQ), and Traditional Chinese Medicine (TCM) syndrome, Western conventional medicine (WCM)

4. Discussion

Cough has been one of the most common complaints in patients presenting to primary care physicians worldwide. It has been recognized that the common cause of acute cough (<3 weeks) [11] is upper respiratory tract infection. Most of the time it resolves on its own [21]. Curley et al. described that 46 % of the cough associated with the common cold can be explained by throat clearing and 47 % as throat clearing due to postnasal drip. These symptoms can be effectively treated with antihistamine - decongestant treatment [21]. A postinfectious cough or postviral cough lasts for more than 3 weeks after a URTI [11]. Even though it has been a major cause of concern for many and one of the common causes of primary clinic visits, satisfactory therapeutic options are not available. However, it is common to use various narcotic antitussives, despite their potential side effects, and the wide range of over - the - counter (OTC) medications available around the world. However, recent review articles have identified that there are no adequate clinical trials providing evidence for or against the effectiveness of OTC medicines in acute cough. M. Smith et al. warn us to take this into consideration when prescribing antihistamines and centrally active antitussive agents in children, drugs that are known to have the potential to cause serious harm. [22]

The pathogenesis of postinfectious cough can be due to many causes, such as persistent inflammation, post - nasal drip, irritation of cough receptors, bronchial hyperresponsiveness due to local inflammatory cytokine release [6], etc. However, the most widely accepted theory is the involvement of the nervous system, as Undem BJ. et al. described, virus infection can impact both peripheral sensory nerves and central processing involved in cough, leading to alterations in the cough reflex and the persistent urge to cough experienced by affected individuals. Understanding these mechanisms is important for developing targeted treatments for cough associated with viral infections. [23]

In our review, we tried to find an effective treatment modality for these conditions. We have found a few

randomized clinical trials and review articles that specifically studied post infectiousetiology. The findings from different studies provide insights into the effectiveness of different interventions in alleviating postinfectious cough symptoms. Baranova et al. conducted a randomized controlled trial where a 0.1% solution of hyaluronic acid was administered twice a day for a cycle of 12 - 16 sessions [13]. The study reported full remission of post infectious cough hypersensitivity syndrome in all patients receiving the treatment, demonstrating the effectiveness of hyaluronic acid in relieving post infectious cough.

In a review article by Ciprandi and Tosca, non - pharmacological interventions were discussed as potential treatment options for postinfectious cough [14]. The article highlighted several interventions, including honey, glycerol, Althea officinalis, Drosera rotundifolia, Grindelia, Hedera helix, Pelargonium sidoides, Sambucus nigra, Thymus vulgaris, hyaluronic acid, and saline solutions. Although the review provided evidence for the potential efficacy of these interventions, further research is needed to establish their effectiveness in treating postinfectious cough.

Ding et al. conducted a meta - analysis of randomized trials to evaluate the effectiveness of the SuhuangZhike Capsule (SZC) compared to Western conventional medicine and other Chinese medicine [15]. The analysis showed that SZC was more effective in improving the efficacy rate, showing its potential as a treatment option for postinfectious cough. However, more evidence is required to confirm its antitussive effect

Gillissen et al. performed a randomized controlled trial using extra fine HFA - beclomethasone diproprionate (BDP) in the treatment of postinfectious cough [16]. The study demonstrated a significant reduction in cough frequency compared with the placebo, indicating the effectiveness of extra - fine HFA - BDP in managing postinfectious cough. Irifune et al. conducted a controlled clinical pilot study comparing Bakumondoto (TJ - 29) plus procaterol hydrochloride to procaterol hydrochloride alone [17]. The results showed that the group receiving Bakumondoto and procaterol hydrochloride exhibited a significant improvement in cough scores, showing an early antitussive effect of the combined treatment.

A multicenter, randomized, double - blind, placebo - controlled clinical trial by Jiang et al. investigated the efficacy of QingfengGanke granule (QFGKG) in treating postinfectious cough [18]. The study revealed that groups receiving QFGKG (Group A) had significantly greater improvements in cough severity scores, visual analog scale (VAS), cough - specific quality of life questionnaire (CQLQ), and Traditional Chinese Medicine (TCM) syndrome compared to the placebo group. Additionally, Group B, which received a higher dosage of QFGKG, experienced a faster time to cough resolution compared to Group A. In a double - blind randomized controlled trial, Raeessi et al. compared the effectiveness of honey plus coffee (HC) to prednisolone (S) for treating postinfectious cough [19]. The study found a significant difference in mean cough frequency before and after treatment in the HC group compared with the S group, suggesting the potential of honey plus coffee as an alternative treatment option.

Finally, Zanasi et al. conducted a randomized, placebo - controlled, double - blind trial to evaluate the efficacy of a combination of salbutamol and ipratropium bromide in managing postinfectious cough [20]. The study reported a significant reduction in daytime and night - time cough severity in both.

All these treatment modalities have the potential for the treatment of postviral cough. But further clinical trials are needed to establish conclusive evidence for the use of various treatment modalities in the management of postviral cough in daily practice. One promising prospective study conducting by Merlo C et al. focuses on the effectiveness of oral corticosteroids in treating postinfectious cough [24]. The already widespread use of oral corticosteroids by general practitioners highlights the importance of conducting a randomized clinical trial to validate its efficacy. Considering the involvement of cough receptors and nerves in the pathogenesis of chronic cough and postviral cough, exploring the therapeutic potential of other options such as opioids, neurokinin receptor antagonists, GABA receptor antagonists, cannabinoid CB2 receptor agonists, local anesthetics, and potassium channel openers [25 - 32] is crucial.

Opioids, such as a peripherally acting polar enkephalin analog and nociceptin, have shown promising results in animal studies but lack human data. [25] Neurokinin receptor antagonists, particularly NK2 receptor antagonist SR 48968, have demonstrated inhibition of cough in guinea pigs, while the antitussive effect of NK1 receptor antagonists remains debated. [26] Gamma - aminobutyric acid (GABAB) receptor agonists, including baclofen, have shown inhibitory effects on capsaicin - induced cough in animal models and exhibited some benefits in patients with chronic cough. [27, 28] Cannabinoid CB2 receptor agonists have shown potential as antitussive treatments in guinea pigs but lack clinical data in humans. [29] Local anesthetics such as lignocaine have demonstrated transient attenuation of capsaicin - induced cough but come with the risk of oropharyngeal anesthesia. [30] Transient receptor potential (TRP) channels, such as (cold and menthol - sensitive receptors) CMR1 and TRPV1 have shown associations with cough, and compounds targeting these channels are currently in clinical development. [31] Potassium channel openers, specifically NS1619, have shown inhibition of sensory nerve function and cough in animal models. [32] Overall, these findings highlight various potential targets and treatment options for chronic cough, although further research is needed to evaluate their efficacy in human populations.

5. Limitations

The review article on the treatment modalities for postinfectious cough based on the provided articles faces several limitations. Firstly, there is a notable lack of extensive human data, with several studies relying primarily on animal models or having limited human data. This highlights the need for more comprehensive clinical trials to assess the effectiveness of these treatments in human

populations. Secondly, the heterogeneity of interventions poses a challenge in drawing definitive conclusions. The studies encompass a wide range of interventions, including different medications, herbal remedies, and non - pharmacological approaches. Such variation makes it difficult to determine the effectiveness of specific treatment modalities.

Additionally, several studies in the review have small sample sizes, limiting the generalizability and statistical power of the findings. Larger - scale studies are needed to validate the results and provide more robust evidence. Moreover, the lack of standardized outcome measures across the studies complicates the comparison and combination of results. The inclusion of standardized measures would enhance the comparability of results and facilitate meta - analyses.

Furthermore, many of the studies may have focused on short - term outcomes or had relatively short follow - up periods, neglecting the long - term effects of the treatments. Given that chronic cough can persist, it is crucial to assess the long - term effectiveness and safety of the treatments. Longer follow - up periods would provide a better understanding of the durability of treatment effects and potential adverse events. Addressing these limitations and considering the heterogeneity and quality of the studies would enable a more comprehensive and accurate evaluation of the available treatment modalities for postinfectious cough.

6. Conclusion

Our review article provides an overview of the treatment modalities for postinfectious cough based on the available data. The findings suggest a range of potential options, including pharmaceutical agents, herbal remedies, and non - pharmacological interventions. However, several limitations need to be acknowledged. Limitations include the lack of extensive human data, the heterogeneity of interventions, small sample sizes, the lack of standardized outcome measures, and short - term follow - up periods. Despite these limitations, the review highlights the potential efficacy of certain interventions such as hyaluronic acid, honey and coffee, inhaled salbutamol and ipratropium, inhaled beclomethasone dipropionate, and specific Chinese herbal preparations, etc.

7. Future Scope

To overcome the limitations of the current review, future researchers should consider conducting large - scale randomized controlled trials to further investigate the efficacy and safety of the identified treatment modalities for post infectious cough. Additionally, exploring novel therapeutic targets and interventions may provide valuable insights into potential breakthrough treatments for this condition. Furthermore, incorporating standardized outcome measures and using well - defined patient cohorts would enhance the comparability and generalizability of findings across studies, ultimately leading to improved clinical management strategies for post infectious cough.

In conclusion, while the review article provides a comprehensive overview of the available treatment modalities for post infectious cough, the limitations highlight the need for further research. Overcoming these limitations and addressing the advice outlined above will contribute to a deeper understanding of post infectious cough and pave the way for more effective and tailored treatment strategies in the future.

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Author Profile

Dr. Naveen Kizhakkayil Tency is a beginner researcher with a passion for Internal Medicine. Having recently completed MBBSfrom India, he is eager to make meaningful contributions to the field. With a solid educational background and a commitment to continuous learning, Dr. Tency is enthusiastic about exploring innovative ideas and engaging in scholarly pursuits. He is excited to collaborate with experienced mentors and researchers to gain valuable insights and contribute to the advancement of Internal Medicine.

Dr. Archa Roy is a budding researcher who has recently embarked on a journey in the field of Medicine after completing her MBBS in India. With a strong academic foundation and a keen interest in Internal Medicine, she is enthusiastic about gaining hands - on research experience. Despite being new to the research community, Dr. Roy is eager to delve into the intricacies of Internal Medicine and contribute to its growth. She embraces challenges with a curious and open mindset and looks forward to collaborating with experienced researchers to expand her knowledge and make meaningful contributions to the field.