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STATE OF THE ART REVIEW

Current Status and Future Directions of Chronic Cough in China

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Abstract
Chronic cough is one of the most common complaints for which patients in China seek medical attention. However, there are no nationwide data on the prevalence and socioeconomic burden of chronic cough. Although approximately 50% of Chinese men smoke, the vast majority of patients presenting for evaluation of chronic cough are never smokers. An equal sex distribution and a middle-aged predominance have been observed in the Chinese chronic cough population, despite demonstration of a higher cough reflex sensitivity in females and older patients. The role of air pollution in the distinct age and sex distribution requires further study. In terms of the etiologies of chronic cough in China, cough-variant asthma, upper airway cough syndrome, nonasthmatic eosinophilic bronchitis, and atopic cough are the most common causes, comprising 75.2% to 87.6% of cases across different regions. Chinese Guidelines for Diagnosis and Treatment of Cough were initially published in 2005, and updated in 2009 and 2016. In addition, the China Cough Coalition was established in 2016. Great progress has been made in both cough-related clinical practice and research in recent years, however, there are still challenges ahead. To facilitate optimal management of chronic cough in China, efforts promoting the dissemination and application of published guidelines will be essential, especially in community-based healthcare and in rural regions. As chronic refractory cough has been identified as a huge challenge to clinicians worldwide, continued international cooperation will be essential in optimizing evaluation and management of chronic cough.

Keywords Age distribution · Air pollution · Chronic cough · Cough reflex sensitivity · Sex distribution

Introduction

Chronic cough, defined in adults as a cough lasting for more than 8 weeks, is one of the most common complaints for patients seek medical attention in primary and secondary care. Chronic cough accounts for at least one-third of patients visiting respiratory specialists in China, thus causing a huge socioeconomic burden and considerable impairment in quality of life [1, 2]. In patients with a normal chest radiograph, the most common causes of chronic cough are upper airway cough syndrome (UACS), cough-variant asthma (CVA), nonasthmatic eosinophilic bronchitis (NAEB), and gastro-esophageal reflux related cough (GERC) [3]. In 12–42% of patients presenting to specialist cough clinics, the cough persists despite extensive investigations and therapeutic trials; this condition is referred to as unexplained cough or refractory cough [4], which poses a huge challenge to clinicians and researchers. At least nine respiratory societies worldwide have published guidelines on the diagnosis and management of chronic cough in recent years [3, 5–13]. Coincident with the publication of Chinese Guidelines for Diagnosis and Treatment of Cough, and the establishment of the China Cough Coalition, great progress has been made in both clinical practice and research. However, misdiagnosis and inappropriate treatment are still common in the community-based healthcare setting in China [2]. This review aims to elucidate the epidemiology and demographic features of chronic cough; to examine the relationship of chronic cough to smoking, air pollution and cough sensitivity; as well as to highlight the current situation and future directions in the field of chronic cough in China.

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Prevalence of Chronic Cough

A recent meta-analysis estimated that the global prevalence of chronic cough in the general adult population is as high as 10% [14]. Although chronic cough is a common medical problem in China, there is no nationwide epidemiological survey on its prevalence. A study conducted in Liaoning, China showed that the prevalence of chronic cough ranges from 2.0 to 2.7% among residents from different cities [15]. It has been found that chronic cough occurred in 3.3% of college students in Guangzhou, China [16]. Considering chronic cough is more common in middle-aged people [17], the prevalence might be higher in a community-based adult population. In regions where dust storms occur frequently, the prevalence of chronic cough was reported to be up to 28.3% [18]. The extent of the socioeconomic burden of chronic cough in China remains undefined. As reported by CHIS.SINOHEALTH, the market size of retail pharmacies in China for respiratory medications (calculated based on the terminal retail price) was 51.62 billion yuan in 2016, among which antitussive and cold medicines accounted for 76.2% (39.33 billion yuan). Clearly, based on these figures, chronic cough represents a huge socioeconomic burden. In addition, patients with chronic cough typically experience a significant delay in receiving proper diagnosis and treatment. A previous survey demonstrated that among 558 patients initially presenting to a specialist cough clinic, the mean duration of cough was 58.1 ± 83.7 months, the mean number of previous medical visits for cough was 20.8 ± 30.0, and furthermore, that 80.8% of the patients had been diagnosed with chronic bronchitis or pharyngitis, and 91.6% had been prescribed antibiotics [2].

Etiology of Chronic Cough

In terms of the etiologies of chronic cough in China, results similar to those reported in Western countries have been demonstrated. Cough-variant asthma (CVA), UACS, NAEB, and atopic cough (AC) were the most common causes, comprising 75.2% to 87.6% of cases across different regions of the country, whereas GERC was less common, with an average percentage of 4.6% [19]. Indeed, a lower prevalence of gastro-esophageal reflux disease has been reported in Asia [20]. However, in recent years, the prevalence of GERC has been shown to be increasing [21, 22], particularly in large cities such as Guangzhou [17] and Shanghai [23], which might be attributed to the rising prevalence of gastro-esophageal reflux disease in the ethnic Chinese [24] and the increasing awareness of the association between gastro-esophageal reflux disease and chronic cough. An increasing trend in the occurrence of GERC has also been observed in Japan [25, 26]. Notably, a higher proportion of corticosteroid-responsive cough (53.5–68.1%), namely CVA, NAEB, and AC, has been observed in cough clinics in China [19]. The underlying reasons remain unclear. National differences in the delivery of healthcare could be a possible explanation. Generally, to see a specialist in the United Kingdom (UK) under the National Health Service, patients require a referral from their general practitioner, suggesting that patients presenting to cough clinics in the UK are those who have cough refractory to first-line treatment by primary care physicians [27]. Since China does not have a strict referral system, patients are allowed to self-refer to specialist clinics. Thus, patients may directly visit cough clinics without first seeking medical attention in primary care (Fig. 1). In addition, growing evidence indicates that air pollution can induce airway eosinophilic inflammation [28–30], possibly explaining the high prevalence of eosinophilia-related chronic cough in China. This topic will be discussed in further detail in the "Air Pollution" section.

Demographics of Chronic Cough

A female predominance has been demonstrated in cough clinics in Western countries. As reported by a worldwide survey, the mean age of chronic cough patients was 55 years and two-thirds were female [27]. Similar results were shown by studies undertaken in other Asian countries. Referring to a multicenter study in Japan, the mean age of chronic cough patients was 51.8 ± 18.9 years and 59.7% of the patients were female [31]. A cross-sectional multicenter study in

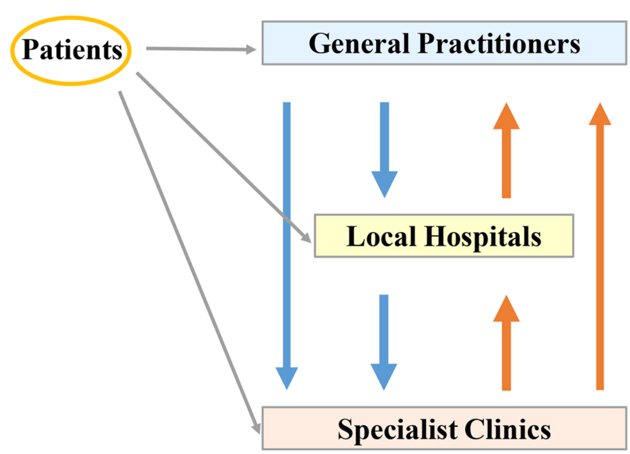

Fig. 1 Referral system in China. Patients are allowed to self-refer to specialist clinics without paying much more than if referred by their general practitioner

Korea found that the mean age was 54.5 ± 15.9 years and the proportion of females was 65.7% for newly referred chronic cough patients [32]. However, the majority of studies conducted in China suggest an equal sex distribution and a much younger age [17, 22, 33, 34]. Recently, we analyzed consecutive chronic cough patients presenting to our cough clinic in Guangzhou, China from 2003 to 2017 [17]. Mean age of patients was 43.0 ± 13.7 years, and patients aged ˂ 50 years accounted for over two-thirds of the cough population. In addition, the proportion of women (51.5%) was almost equal to males (Fig. 2). These results were consistent with a previous multicenter study evaluating chronic cough patients from South, North, East, Northeast and West China [19], in which the mean age of the patients was largely uniform across the five regions (mean: 40.4 years, range: 35.5–42.5 years), and a roughly equal sex distribution was shown in most of the regions except for East China (Shanghai). It is not clear why there is a greater percentage of male patients and young patients presenting with chronic cough in China. Men constitute the main labor force of pollution-intensive industries, which could contribute to the near-equal gender distribution of chronic cough in China. According to previous studies, males account for 79.6% of industrial workers [35], 85.6% of traffic police [36], 97.5% of professional taxi drivers [37], and 94.8% of bus drivers [38]; their mean age ranges from 37.6 years to 38.5 years. In our cough clinic, more males (19.0%) reported a history of occupational or home environment exposure than females (15.2%) [17]. In addition to a higher proportion of occupational and environmental exposures, males were found to have a 45% larger minute ventilation compared with females, thus lead to a 30% greater deposition rate, namely, particles depositing per unit of time [39].

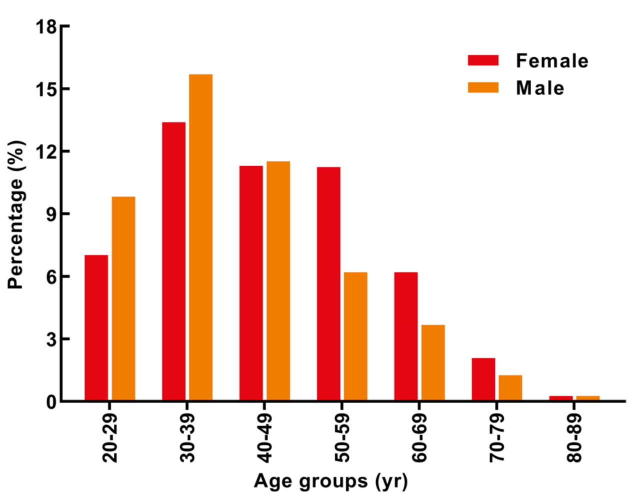

Fig. 2 Age and sex distribution of Chinese chronic cough patients. Percentage (%): ratios of the number of females or males to the total number of cough patients ($n = 1822$) [17]

Smoking Status of Patients with Chronic Cough

It is well known that smoking is a major risk factor for chronic cough. A cohort study of the general adult population in Denmark reported that the prevalence of chronic cough was 3% in never smokers, 4% in former smokers, and 8% in current smokers [40]. A dose-dependent relationship between cumulative cigarette consumption and the prevalence of chronic cough was also found in rural regions of Beijing [41]. Approximately 50% of men smoke in China, compared with a smoking rate of only 2% in women [42, 43]. The much higher smoking rate in men could be a contributor to the male predominance in chronic cough patients observed in community-based studies [15, 44]. However, similar to the findings of other countries [32, 45], only 4.5% of chronic cough patients presenting to cough clinics in China were current smokers and 8.6% were former smokers [17]. Potential reasons for the discrepant results between epidemiological studies and the experience in cough clinics are as follow. First, growing evidence suggests that smoking leads to diminished peripheral cough reflex sensitivity [46, 47] and heightened neural activity in brain cough suppression networks in otherwise healthy smokers [48]. Second, smokers with isolated cough tend to ascribe their cough to tobacco use, or consider the cough mild and not troublesome, and therefore rarely seek medical attention before the development of other symptoms, such as breathlessness and wheezing [49]. In addition, although smokers who developed chronic obstructive pulmonary disease (COPD) and lung cancer were more sensitive to cough triggers and had higher daily cough frequency compared with healthy nonsmokers [50–52], they were usually referred to COPD clinics or lung cancer clinics rather than cough clinics due to their abnormal radiographic findings. The severity of existing airway inflammation and dysfunction of the individual smokers were considered to be responsible for the conflicting findings in cough reflex sensitivity between otherwise healthy smokers and those who had developed COPD and lung cancer [53].

Air Pollution

It has been noted that air pollution is able to cause or exacerbate both upper and lower respiratory tract diseases, which may in turn induce chronic cough. Compared to residents with a home-road distance > 300 m, those with a home-road distance within 100 m and 200 m had odds ratios of 2.54 (95% CI 1.57–4.10) and 1.97 (95%

CI 1.16–3.37) of suffering from chronic cough [54]. Pollutants including ozone, cinnamaldehyde, isothiocyanate, and acrolein are capable of activating transient receptor potential ankyrin 1 (TRPA1), which is a well-known cough receptor [55, 56]. Exposure to traffic-related air pollution can result in enhanced cough reflex sensitivity in both guinea pigs [30] and healthy volunteers [57]. Even short-term exposure to pollutants encountered by walking down a busy street increased cough frequency in patients with COPD [58]. Furthermore, growing evidence suggests a crucial role for air pollution in the mechanisms of eosinophilia-related chronic cough, which provides a possible explanation for the relatively high prevalence of EB and CVA in China. It has been found that urban particulate matter < 2.5 µm (PM2.5) and Asian sand dust (ASD) can exacerbate allergic eosinophilic airway inflammation in mice [28, 29]. In addition, our recent work has demonstrated that exposure to real-world traffic-related pollutants induces non-allergic eosinophilic airway inflammation in guinea pigs [30]. A consistent finding was also reported in humans. An increment in ozone levels has been shown to be associated with a significantly higher blood eosinophil count in non-smoking healthy individuals [59]. Type 2-promoting cytokines released by impaired epithelial cells, for instance, IL-33 and TSLP, were thought to play an important role in the pathogenesis of pollution-related eosinophilia, since it has been shown that type 2 promoting cytokines are able to activate type-2 innate lymphoid cells, and to initiate and perpetuate airway eosinophilia [60].

Cough Reflex Sensitivity

It is now well accepted that cough hypersensitivity, in which peripheral and central neural pathways capable of eliciting cough display heightened activity and/or sensitivity, is a unifying feature of patients with chronic cough [61]. Cough challenge tests employing inhalation of tussive agents can provide insights into the cough reflex. Studies conducted in China have shown similar results as those in Western countries regarding cough reflex sensitivity. Namely, significantly heightened cough reflex sensitivity was found in patients with chronic cough compared with healthy volunteers; in females compared with males; and, in older chronic cough patients (aged ≥ 50 years) compared with younger patients (aged < 50 years) [17, 62]. In recent years, our understanding of cough hypersensitivity has dramatically increased. Belvisi et al. demonstrated the heterogeneity of cough hypersensitivity between refractory chronic cough patients and those with other airway conditions. In their study, patients with refractory chronic cough showed an enhanced cough response to both capsaicin and citric acid, while patients with COPD displayed a heightened cough response to capsaicin and a diminished cough response to PGE_2. Patients with asthma demonstrated an increased cough reflex sensitivity to citric acid [63]. By assessing cough reflex sensitivity mediated by TRPA1, and transient receptor potential vanilloid 1 (TRPV1), we found heterogeneity of cough hypersensitivity within a population of patients with chronic cough [62]. In addition to TRPV1 and TRPA1 channels, the adenosine triphosphate (ATP)-gated P_2X_3 receptor has gained attention as an important neural pathway involved in the pathogenesis of cough [64]. Cough response to ATP was heightened in patients with chronic cough compared with healthy volunteers [65], and an antagonist of the P_2X_3 receptor significantly reduced cough frequency in clinical trials [66, 67]. In recent studies TRPV4 was found to have a role in ATP release, implying that the TRPV4/ATP pathway may be partially responsible for cough hypersensitivity [67, 68]. Neurokinin-1 (NK-1) receptor and its ligand substance P are also implicated in cough hypersensitivity, given that orvepitant, a selective antagonist of the NK-1 receptor, caused a significant improvement in objective daytime cough frequency as well as in subjective measures [69]. Many patients with chronic cough report an upper airway infection as the trigger of their persistent cough. Mechanisms underlying this condition remain unknown. Deng et al. showed that IFNγ causes a direct influx of Ca^{2+} into vagal sensory neurons, supporting the possibility that IFNγ can induce and perpetuate cough hypersensitivity [70]. Moreover, enhanced midbrain activity and an impaired cough suppression network were demonstrated in patients with chronic cough [71, 72]. Cough challenge tests using a specific protussive compound reveal only one element of the complexity of clinical cough, thus, it is not surprising that cough reflex sensitivity only weakly correlated with objective cough frequency as well as patient-rated cough severity and cough-specific quality of life [52, 73, 74]. For clinicians and researchers, there is a need for more comprehensive approaches that can reveal different facets of cough, hence allowing better phenotyping of chronic cough, particularly for cough refractory to treatment and cough with an unexplained cause.

Future Directions

Approximately 20 years ago, systematic cough research began in China. Since then, induced sputum differential cell counts, 24-hour esophageal pH monitoring, as well as FeNO testing were established and employed by increasing numbers of medical institutions. Meanwhile, great progress has been achieved in basic research and clinical management of cough [34, 70, 75]. The Chinese Guidelines for Diagnosis and Treatment of Cough were released in 2005 [76], and subsequently updated in 2009 [77] and 2015 [78]. The China

Cough Coalition was established in 2016. Started in 2017, an ongoing lecture tour organized to disseminate the published cough guidelines has been held in 81 cities, and has attracted 11,868 attendees from 3,818 hospitals. Moreover, in order to help clinicians and researchers to better understand the latest advances in the field of cough, the China Cough Forum has been held annually since 2007, and the International Cough Conference has been held once every three years since 2013. However, there are still challenges ahead. First, nationwide epidemiological surveys focusing on the prevalence and socioeconomic burden of chronic cough are needed. Second, the large number of patients suffering from chronic cough necessitates more cough clinics and clinical laboratories. More widespread availability of the induced sputum technique among the nation's medical institutions is needed, given the important role of eosinophil measurement in the diagnosis and management of cough. It is important to find a simple biomarker for guiding the treatment of corticosteroid-responsive cough and chronic refractory cough. The cut off value of FeNO in diagnosing eosinophilia-related cough seems different from asthmatic patients. Our previous study indicated that a higher FeNO level (> 31.5 ppb) suggested a high likelihood of corticosteroid-responsive cough [34], but further study is needed. Third, it has been reported that although NAEB recurred in up to 59.6% of patients after successful treatment, NAEB is not an early stage of asthma or COPD [75]. Understanding why NAEB exhibits similar airway eosinophilic inflammation as CVA and responds to corticosteroid therapy, but does not show airflow obstruction is a vital step in formulating better clinical management strategies for classic asthma. Fourth, traditional Chinese medicine has a long history and rich experience in treating chronic cough, yet the therapy is based on empirical knowledge of individual clinicians. Evidence-based studies that allow traditional Chinese medicine to be applied widely are required. Fifth, for clinicians, satisfaction arising from therapeutic success continues to be balanced by the shared frustration resulting from cases with cough refractory to currently available antitussive therapies. Growing evidence suggests that there are heterogeneous processes governing cough hypersensitivity among different diseases and individuals. To achieve therapeutic success in individual patients, studies focusing on the heterogeneity of cough hypersensitivity are needed. Sixth, clarifying how environmental irritants cause cough will bring insights to the prevention and management of pollution-related cough. Last but not least, since chronic cough poses challenges to clinicians and researchers around the world, international cooperation in areas that hinder successful management of chronic cough should be promoted. For example, there is an urgent need to develop validated tools that allow objective assessment of clinical response. Practical biomarkers that help target treatable traits are also required, so that unnecessary therapeutic trials can be avoided. In addition, clinical trials testing the safety and efficacy of new antitussives will bring hope to patients suffering from refractory chronic cough.

Conclusion

In summary, chronic cough is one of the most common complaints for which patients seek medical attention in China. Chinese chronic cough patients demonstrate an equal sex distribution and a middle-aged predominance, despite a higher cough reflex sensitivity in females and older patients. Further research is needed to examine the role of air pollution in the pathophysiology of chronic cough. Although great progress has been achieved in both basic research and clinical management of cough in recent years, there are still a lot of challenges ahead. To improve the management of chronic cough, international cooperation between China and other countries should be strengthened.

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Compliance with ethical standards

Conflict of interest None declared.

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