Therefore, the decision not to treat because cough might resolve over time is not an optimal approach. We recommend that a first-generation antihistamine-decongestant (our choice is sustained release brompheniramine, 12 mg, and pseudoephedrine, 120 mg every 12 h) be administered as the initial therapy whatever the duration of cough, unless there is a contraindication to one of these drugs. This empiric approach makes sense because postnasal drip syndromes appear to be the most common causes of cough; this approach has been shown to work in patients with acute cough, subacute cough, and chronic cough. If 2 weeks of therapy is ineffective, we would proceed with a BPC. Many of these patients will have either cough-variant asthma or virus-induced transient airway hyperresponsiveness. As the results of the study by Kwon et al show, these patients will have either cough-variant asthma or virus-induced transient airway hyperresponsiveness. As the results of the study by Kwon et al show, these patients will have either cough-variant asthma or virus-induced transient airway hyperresponsiveness.

We agree that when a patient seeks medical attention because of a troublesome cough, the goal of making a specific etiologic diagnosis is desirable. It is important for the physician to remember, however, that usually the primary objective for the patient is eliminating this highly disruptive symptom as quickly as possible. The up-front use of first-generation antihistamine-decongestant therapy helps to facilitate both goals. Indeed, in the just released new guidelines on cough from the American College of Chest Physicians, the initial use of antihistamine-decongestant therapy as both a diagnostic and therapeutic trial for cough is recommended in most cases.

Based on the new cough guidelines, there are two other points that we would like to emphasize. Because it is not known whether upper airway disease causes cough through the final common pathway of postnasal drip or whether, in fact, in some circumstances they cause irritation or inflammation of upper airway structures that directly stimulate cough receptors and produce cough independently or in addition to any associated postnasal drip, the guidelines recommend that the term upper airway cough syndrome replace the term postnasal drip syndrome. Moreover, unless the upper airway cough syndrome is histamine-mediated (ie, allergic), the guidelines recommend that first-generation antihistamines with anticholinergic activity be the antihistamines of choice. With respect to cough due to the common cold, the first-generation antihistamines have been effective, while the new, relatively non-sedating antihistamines have not been effective.

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Anticoagulation Control With Vitamin K Antagonists

How Well Are We Doing?

Over half a century since their initial inception, vitamin K antagonists (VKAs), in particular warfarin, still represent the cornerstone of oral anticoagulation (OAC) therapy worldwide. Despite their proven antithrombotic efficacy across a broad spectrum of patient groups, VKAs are beset by numerous inherent problems. The complex pharmacokinetic profile of VKAs means that they have a narrow therapeutic range requiring regular monitoring, a slow onset/offset of action, and are subject to multiple interactions with food, alcohol, and medications. Further, they also exhibit potential ethnic, genetic, and age-related variations in their dose response.
It is well established that anticoagulant control with the care of maintenance of the international normalized ratio (INR) within the therapeutic range results in reductions in all-cause mortality, stroke, and thromboembolic events. While numerous analyses of the efficacy of VKAs in relation to outcomes have been reported, a clear overview of the various studies investigating the proportion of time spent in the therapeutic INR range and the factors that may influence INR control is needed.

In this issue of CHEST (see page 1155), van Walraven et al provide a systematic review and metaregression analysis of INR control in >50,000 patients from 67 studies who were receiving OAC for various indications (mainly atrial fibrillation [AF], venous thromboembolism, and valvular heart disease) during the last 20 years, and demonstrates that the study setting, type of OAC, and method of INR monitoring significantly affected the mean percentage of time patients spent in the therapeutic INR range. Significantly better INR control was achieved in randomized controlled trials and anticoagulation clinics (absolute percentage of time in therapeutic range, 12.2% and 8.3% higher, respectively) when compared to community practices and among patients who self-monitored their INR (7.0%; 95% confidence interval [CI], 0.7 to 13.3%). Although patients receiving warfarin achieved significantly poorer INR control (60.6%) than patients receiving acenocoumarol (68.1%), this difference was not significant in the metaregression model. This analysis also revealed that INR control was worst in patients who received warfarin and were managed in the community, without self-monitoring; these patients achieved only one half of their time within the therapeutic INR range.

Unfortunately, the majority of patients receiving long-term OAC therapy are characterized by those factors associated with the poorest INR control. Equally concerning is the finding that among all patients receiving OAC, more than one third of the time is spent outside the therapeutic range, especially since a 10% increase in the time out of the therapeutic range has been associated with an increased risk of death, ischemic stroke, or other thromboembolic events. It is also particularly disappointing to discover that anticoagulation control has only improved marginally over the last 20 years (from 1987 to 1997, 62.2%; vs from 1998 to 2005, 65.0%; p = 0.08).

What can we do to improve compliance with VKAs? The inconvenience of regular INR checks for VKA treatment at a hospital outpatient clinic or general practice is an inherent problem that significantly affects compliance. The benefits of anticoagulation clinics and self-management of INR over traditional community- or clinic-based testing, as illustrated by van Walraven et al, are further supported by a recent systematic review and meta-analysis of self-monitoring of OAC. Significant reductions in thromboembolic events (odds ratio, 0.45; 95% CI, 0.30 to 0.68), all-cause mortality (odds ratio, 0.61; 95% CI, 0.38 to 0.98), and major hemorrhage (odds ratio, 0.65; 95% CI, 0.42 to 0.99) were demonstrated. Further, trials combining self-monitoring and self-adjusted therapy also demonstrated significant reductions in thromboembolic events (odds ratio, 0.27; 95% CI, 0.12 to 0.59) and death (odds ratio, 0.37; 95% CI, 0.16 to 0.85), but not major hemorrhage (odds ratio, 0.93; 95% CI, 0.42 to 2.05). Improvements in the mean proportion of INRs in range were reported in 11 of the 14 trials, which were significant in 6 trials. Thus, the option of self-monitoring of the INR and dose adjustment for selected patients may be a viable alternative to outpatient or general practice checks. Improving education and knowledge about the risks and benefits of OAC therapy have also been shown to improve the safety and efficacy of such treatment.

Maintaining therapeutic anticoagulation is not the only hurdle to achieving effective anticoagulation. Given that less than one half the patients with nonvalvular AF requiring long-term OAC for stroke thromboprophylaxis are actually prescribed it, due to a combination of institutional-, patient-, and physician-related factors, one obvious potential solution lies in the increased the availability of newer, safer, and more effective anticoagulants.

Unfortunately, while an appetizing concept, the potential “front runners” in the race to replace warfarin, such as the as oral direct thrombin inhibitors (DTIs), still have some way to go in their clinical development before they can be fully advocated. Indeed, the DTI ximelagatran has so far failed in its bid for approval by the US Federal Cardiovascular and Renal Drugs Advisory Committee for use in any of its intended anticoagulation indications, and has just been fully withdrawn from further development owing to liver safety concerns. The recent results of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for the Prevention of Vascular Events (warfarin arm) study suggest the superiority of warfarin over aspirin-clopidogrel antiplatelet combination, for the prevention of stroke among patients with nonvalvular AF. Other new oral agents—such as new DTIs and oral Factor Xa inhibitors—are in development, but we still have to wait patiently, pending clinical trial data.

Thus, the VKAs will continue to have an extensive...
role to play in OAC therapy for the foreseeable future. Any efforts at maximizing their potential use, both safely and efficaciously, remains a great priority.

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Reducing Oral Steroids With Inhaled Steroids

Is That All That Can Be Achieved?

When inhaled corticosteroids were first investigated, some of the earliest clinical trials that showed compelling evidence of their efficacy were performed in patients who were dependent on oral corticosteroids. Although the design of these studies was far from ideal, the efficacy of even low-dose inhaled steroids in reducing or frequently eliminating the need for oral corticosteroids was striking.1 This was confirmed when they became available in clinical practice; the first target groups of patients were those dependent on oral steroids or requiring frequent rescue courses of steroids. The next major development of inhaled corticosteroids was the introduction of high-dose inhaled beclomethasone dipropionate (BDP).2 Again, clinical experience with this preparation preceded well-performed clinical trials, but the efficacy of high-dose inhaled BDP in reducing the requirement of oral steroids was quite striking.3 Since then, a feature of the development of each new inhaled corticosteroid has been a trial demonstrating the ability to reduce or eliminate oral steroid requirement in severe asthma.4–7 Typically, in comparison with placebo, more than three fourths of patients are able to eliminate regular oral steroids, and consequently the mean dose of inhaled corticosteroids is markedly reduced. A superficially surprising result of these trials6,7 is that despite the elimination of oral steroids, lung function improves. The explanation for this phenomenon is probably that clinicians, when prescribing oral steroids, perform a balancing act; rather than administer a higher dose of oral steroids, with the aim of producing better lung function, they prefer to administer a lower dose of oral steroids, leaving lung function impaired and patients symptomatic but with fewer side effects. When more effective treatment is administered, there is still room for lung function to improve. Although most inhaled steroids have been investigated for their oral steroid-sparing ability, the number of well-designed and controlled trials is still limited and some important questions remain. No controlled trial of inhaled steroids > 2,000 µg/d has been reported; although inhaled steroids are used by clinicians above these doses, the value is unclear. No head-to-head comparisons of different inhaled steroids have been performed to compare oral steroid sparing. Although there is clearly a difference between low-dose and high-dose inhaled steroids in terms of efficacy and oral steroid sparing, the evidence that there is a dose-response relationship...