CORRESPONDENCE

Hereditary Angioedema

TO THE EDITOR: In their review of hereditary angioedema, Busse and Christiansen (March 19 issue)[1] suggest that plasma-derived C1 inhibitor is the preferred short-term prophylactic agent to be used before any medical or surgical procedures are performed and that recombinant human C1 inhibitor, icatibant, and ecallantide are not preferred owing to the shorter half-lives of these drugs. In a case series of 51 patients who underwent a total of 70 dental or surgical procedures, the attack rate after 48 hours was 2.9% among those who received recombinant human C1 inhibitor prophylaxis as compared with 76.9% among those who did not.[2] This result is similar to that reported in a study of plasma-derived C1 inhibitor, in which breakthrough attack rates were 6% among those who received treatment and 68.9% among those who did not.[3] These findings are also consistent with an integrated analysis of 62 patients who together had had a total of 280 acute attacks. No relapse occurred within 24 hours after treatment with recombinant human C1 inhibitor and the recurrence rate among these patients 72 hours after treatment was 7%.[4] Thus, its clinical efficacy is based more on the relationship between dose and efficacy than on its half-life.[5] We agree with Busse and Christiansen that regardless of the agent selected for short-term prophylaxis, an effective on-demand treatment should be made readily available to patients before surgical or dental procedures owing to the risk of a serious attack of hereditary angioedema.

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TO THE EDITOR: Busse and Christiansen describe cutaneous angioedema as an asymmetric, disfiguring, and nonpitting condition, as it has frequently been described in the literature.[1] However, it should be pointed out that in some episodes, particularly those involving the hands and feet, pitting may occur (Fig. 1). The edema is usually nonpitting until the terminal phase of the attack, as described by Frank et. al.[2] In short, the term "nonpitting" should not be used to describe the cutaneous involvement in an attack of hereditary angioedema.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Busse and Christiansen describe four products currently available to abort an attack of hereditary angioedema: plasma-derived C1 inhibitor, recombinant human C1 inhibitor, icatibant, and ecallantide. These agents are very expensive (ranging from $3,000 to $15,000 per dose), and three of these products (plasma-

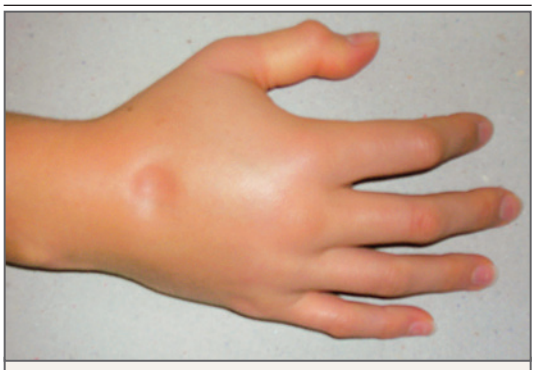

Figure 1. Pitting on the Back of the Right Hand during the Terminal Phase of a Cutaneous Attack in a Patient with Type I Hereditary Angioedema.

derived C1 inhibitor, recombinant human C1 inhibitor, and ecallantide) are associated with a risk — albeit rare — of anaphylaxis.

Since such agents are often not available in low-income countries or in smaller hospitals and pharmacies, and since they are so expensive, it is important for clinicians to be aware that the heparins, especially low-molecular-weight heparin, have been reported as promising prophylactic treatments and have terminated attacks of acute hereditary angioedema.[1-4] In one study,[3] among 34 patients with hereditary angioedema who had a combined history of 256 attacks, the administration of nadroparin after the onset of prodromes resulted in a complete response in 90% (with complete response defined as total cessation of an attack within 2 hours), a partial response in 8%, and failure in 2%. Thus, studies that compare the effectiveness of the much less costly and widely available low-molecular-weight heparin with that of the aforementioned agents must be conducted.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Valerieva and colleagues report on their recently published retrospective international case series regarding the successful use of recombinant human C1 inhibitor for short-term prophylaxis in patients with hereditary angioedema.[1] Although there have been previous case reports of its successful use,[2] its brief half-life (3 hours) as compared with that of plasma-derived C1 inhibitor (30 to 39 hours) has been cause for concern. We are pleased to have the opportunity to bring this new information to the attention of the readership of the *Journal*.

Fernández Romero raises the interesting question of whether the description of angioedema should be revised to include a specific reference to pitting during the terminal phase of the attack. In his seminal 1888 report, Osler defined the hereditary nature of "angioneurotic edema," now classified as hereditary angioedema C1 inhibitor deficiency, with the following observation: "when fully out it does not pit but does so when going down."[3] We disagree with Fernández Romero that the term "nonpitting" should not be used in reference to cutaneous involvement during an attack. During the development of angioedema, the characterization "nonpitting" distinguishes angioedema from edematous swelling, which involves pitting from the outset. We thank Fernández Romero for reminding clinicians of the trajectory of an attack of hereditary angioedema.

We share the hope expressed by Chan and Majluf-Cruz that therapy for patients with hereditary angioedema will become widely accessible, but their recommendation for the use of heparin, given its affordability, is premature. In the wake of the initial enthusiasm for this treatment in case reports, a double-blind, double-dummy study of heparin failed to show efficacy.[4] The report cited by Chan and Majluf-Cruz in which nadroparin was administered after the onset of prodromes is of interest, but its use is not consistent with current consensus guidelines for treatment after the onset of an attack. Ery-

thema marginatum, the prodrome for an attack in patients with hereditary angioedema C1 inhibitor deficiency, appears to be the most predictive symptom of attack and was recently reported to correlate with activation of the plasma contact system on threshold-stimulated kallikrein activity assay.[5] However, larger studies are needed to evaluate a priori whether a given prodromal event truly heralds an impending hereditary angioedema attack and should therefore guide treatment decisions.

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Since publication of their article, the authors report no further potential conflict of interest.

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