today. This topic has been the source of ongoing debate since the approval of Fab ovine antivenom (CroFab; BTG International Inc, Conshohocken, PA), and it has gained special importance in 2015 with the Food and Drug Administration's marketing approval of a competing F(ab')₂ equine antivenom (Anavip, Instituto Bioclon SA de CV, Mexico City, Mexico).

Late coagulopathy is a common event in patients treated for North American rattlesnake envenomation and may place the patient at risk for bleeding and death after they have left the health care setting. CroFab clinical trials showed a 53% rate of recurrent, late, or persistent coagulopathy 2 to 14 days after envenomation, including outpatient platelet counts as low as 12,000/mm³ and 1 case of clinically significant postsurgical bleeding associated with afibrinogenemia.²

After CroFab received market approval, an Arizona case series confirmed that recurrent or delayed hematotoxicity was common after routine use and recommended that all patients receive close outpatient monitoring of coagulation studies after completion of inpatient treatment.³ An in-depth case report, including prospectively collected serum, demonstrated the relationship of recurrent thrombocytopenia to the rapid clearance of Fab and secondary rise of venom in serum.⁴ Sporadic reports (including some mentioned by Kanaan and colleagues) have since explored the phenomenon and its possible treatment with alternative dosing regimens.^{5,6} Finally, a randomized Phase 2 trial specifically addressed the relationship of antivenom to venom levels and recurrent coagulopathy after treatment with Fab ovine antivenom in comparison with F(ab')₂ equine antivenom. In this trial, 2 of 6 recipients of Fab ovine antivenom required extended hospital treatment.⁷

In this context, the recent Food and Drug Administration approval of the first F(ab')₂ snake antivenom should be of great interest to clinicians, despite legal difficulties⁸ that have delayed its US use. Particularly in those parts of the United States and Canada where coagulopathy is common after snakebite, such as the *Crotalus atrox*-endemic southwest, vigilant management of very low platelet and fibrinogen levels remains essential after hospital discharge. It may be true that "medically significant late sequelae" are uncommon in US reports, but this is at least in part because of careful post discharge treatment reflected in published series. F(ab')₂ antivenoms for pit viper envenomation have been used in Canada and the United States for years through public health and zoo importation mechanisms as well as two clinical trials. These antivenoms are the standard of care in much of Latin America, and evidence-based guidelines should address their use regardless of legal settlements between manufacturers.

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In Reply to Drs Boyer and Ruha

To the Editor:

We appreciate the letter¹ contributed by Drs. Boyer and Ruha in reply to our practice guidelines² and welcome their comments. They focus on the serious complication of late coagulopathy, which has assumed greater clinical attention with the advent of Fab antivenom (AV) as the sole AV currently commercially available in the United States.

Our paper is intended as a broad guide for management of patients envenomed by pitvipers in the United States and Canada, and thus it includes necessarily

succinct coverage of numerous important topics with evidence-based recommendations for patient management. We agree that late coagulopathy is a common complication of rattlesnake envenomations that can even be fatal, and although mentioned in the guidelines, we welcome this opportunity to further discuss this concern, and increase the emphasis on the importance of diagnosing and treating late coagulopathy.

Our guidelines suggest repeat coagulation studies at 2 to 3 days and again 5 to 7 days after the final AV dose. The rationale for these recommendations was that detecting recurrence earlier would be more advantageous to the patient. These recommendations are similar to other consensus guidelines.³ Although it is difficult to directly compare studies, published data indicate a broad range of severely envenomed patients exhibiting late coagulopathy at 18% to 53%^{4–8} after treatment with Fab AV, with some evidence suggesting that mild envenomations have a lower incidence at 5%.⁵ Late coagulopathy can lead to the clinical sequelae of late bleeding, and although it is less common (0.9%; 95% CI, 0.4%–2.2% in a study of 1017 patients),⁹ the consequences can be fatal. Thus the clinician must be diligent in ensuring proper follow-up to envenomed patients and evaluating late coagulopathy.

It must be noted that our recommendations err on the conservative side as we suggest repeat laboratory evaluation for late coagulopathies beginning after the last dose of AV, rather than after the time of envenomation. In more severe envenomations that require repeat dosing of AV, this would extend the time period to pick up late coagulopathies. We concur that more extended follow-up and laboratory testing (eg, at 10 and 14 days after envenomation) would be reasonable, especially after severe envenomations. This recommendation was not included in our paper because we did not find sufficiently strong evidence for making such delineation, and thus recommended avoidance of activities that might predispose to or cause bleeding for 14 days.

We excluded discussion of F(ab')₂ AV pharmacotherapy in our recommendations, but will take the opportunity now to expand on the topic. Crotalidae Immune F(ab')₂ is an equine-derived AV (immunized with venom of *Bothrops asper* and *Crotalus durissus*) indicated for the management of adult and pediatric patients with North American rattlesnake envenomation. Venom-specific F(ab')₂ fragments of immunoglobulin G bind and neutralize venom toxins, which allows redistribution away from target tissues and elimination from the body. Each vial contains 120 mg of protein that will neutralize 780 to 790 times the mouse median lethal dose of *B asper* and *C durissus* venom, respectively. Package insert dosing instructions of F(ab')₂ begin with a 10-vial initial

dose, 10-vial additional dose(s) as needed to achieve initial control, and 4-vial observation and late dosing,¹⁰ and thus differ from Fab AV recommended 4 to 6 vials.

Our objective was to provide actionable guidelines for current practice. Although F(ab')₂ AV received US Food and Drug Administration (FDA) approval in May 2015 and current evidence supports its use for the treatment of rattlesnake envenomation, it is not expected to be available for general use until 2018 owing to legal action and subsequent settlement. We echo the sentiments of Drs. Boyer and Ruha¹ and lament the fact that F(ab')₂ AV was not made commercially available immediately after FDA approval, as patients may have benefited from its use, as well as the potential price reductions that could result from having an AV competitor in the market. However, we refrained from suggesting the use of F(ab')₂ AV in the current practice guidelines for the Wilderness Medical Society until it is generally available. Making such recommendations could cause confusion and unintentionally contribute to inconsistent management of patients through the recommendation of a preferred therapy that is not yet generally available. When F(ab')₂ AV becomes commercially available, we look forward to updating our recommendations to reflect its availability.

It is important to emphasize that the incidence of late coagulopathy requires further careful study, specifically regarding F(ab')₂ AV pharmacotherapy. Although a single comparative study of Fab and F(ab')₂ AVs¹¹ provided good quality evidence that F(ab')₂ has a more favorable pharmacokinetic profile resulting in improved clinical outcomes (ie, lowered risk of late coagulopathy),¹² analysis of clinical experience is still quite limited. Additional investigations of the risks and benefits of F(ab')₂ AV pharmacotherapy and the aggregation of clinical use data would be beneficial.

We appreciate the comments and opinions of Boyer and Ruha,¹ and are pleased to reinforce the importance of careful follow-up of all patients who have been envenomed by pitvipers and further discuss F(ab')₂ AV.

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In Response to Epidemiology of Search and Rescue in Baxter State Park: Dangers of Descent and Fatigue

To the Editor:

We appreciate the attention to wilderness search and rescue (SAR) in New England as provided in the recent Baxter State Park article.¹

In 2010 we published a review of 18 years of SAR activity on Denali.² We note that there were similarities between the SAR activity on Denali and the SAR activity on and around the rugged terrain of Mount Katahdin that deserve mention. Specifically, we noticed similarities regarding some of the central themes of the Baxter State Park article, including fatigue, age, and direction of travel. The risks of descent and older age are also comparable to published Mount Everest data.

Regarding fatigue, Welter et al¹ state that “the wilderness SAR literature has not described fatigue as it relates to the need for SAR response.” From 1990 to 2008 on Denali we reported that the leading general medical reason for SAR was “fatigue.” We commented that fatigue “is not usually ascribed as a top medical problem in the wilderness” but that it “commonly prompts SAR.” Thus we note similarities in fatigue as a common cause for SAR response on both Denali and in Baxter State Park. Although on Denali listing fatigue as the primary cause for SAR was less prevalent than in the study in Baxter State Park, medical reasons on Denali were attributed to more than half of all SAR events. One could speculate also that in many of the Denali altitude and hypothermia cases, fatigue could still play an important and adverse role.

Regarding age, Welter et al¹ indicate that “little is known about the influence of older age on wilderness SAR events.” Of Denali SAR activity we analyzed age and found that “the risk of a rescue increased by 3% per year as age increases (odds ratio, 1.03; 95% confidence interval, 1.01–1.04; $P < .0001$).” Although we did not compare age and fatigue directly in our study, our data would support