However, one small study found family history of lung cancer to be associated with an increased risk of MM in elderly patients,[12] a finding not observed in our previous Swedish MM study.[6] In contrast to two prior studies focusing on solid cancers in MM families,[7,8] we did not find a significantly increased risk of prostate cancer among MGUS relatives. Based on small numbers, we found excess risk of spinal cancer among MGUS relatives. Because we evaluated a large number of malignancies, it cannot be ruled out that this finding is due to chance. Finally, we did not find an increased risk of myeloid malignancies among first-degree relatives suggesting that myeloid and lymphoid hematologic malignancies have different mechanisms with regard to etiology. Our study has several strengths, including its large size as well as the application of high-quality data. The use of the nationwide register-based case-control design ruled out recall-bias, ensured a population-based setting, and generalizability of our findings. The nature of this study is hypothesis-generating and one has to interpret our findings with caution due to the large number of tested malignancies.

Our findings support a role for a shared susceptibility (genetic, environmental, or both) that predisposes to MGUS and certain solid tumors, supporting the application of gene mapping and candidate gene approaches in high-risk families and case-control studies.

Sigurdur Y. Kristinsson,[1] Lynn R. Goldin,[2] Magnus Björkholm,[1] Ingemar Turesson,[3] and Ola Landgren[1,2]

[1]Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; [2]National Cancer Institute, National Institutes of Health, Bethesda, Md, USA; [3]Department of Medicine, Section of Hematology, Malmö University Hospital, Malmö, Sweden.

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Correspondence: Sigurdur Yngvi Kristinsson, M.D., Department of Medicine Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden. Phone: international +46.8.51770000; Fax: international +46.8.318264. E-mail: sigurdur.kristinsson@karolinska.se

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Cautions and caveats to the treatment of acquired hemophilia A

We thank Pier Mannnucci and Flora Peyvandi for their recent editorial[1] in which they drew attention to and largely concurred with our international recommendations for the diagnosis and treatment of patients with acquired hemophilia A,[2] both published in the April issue of Haematologica. We would, however, like to re-emphasize three important issues relevant to treating patients with autoantibodies to FVIII.

Congenital hemophilia complicated by alloantibodies presents a serious therapeutic challenge in the treatment of bleeding episodes, and several recent studies indeed support the use of rFVIIa in a single large dose (270 mcg/kg) rather than repeated smaller doses in treating hemarthroses in these patients.[3,4] Due to safety concerns, we strongly caution against the use of single high-dose rFVIIa in the typically much older and multi-morbid patient population with considerable thromboembolic risk factors who present with bleeding related to acquired hemophilia.[5,6] Younger acquired hemophilia patients who bleed post-partum may represent a different patient profile. However, we emphasize that so far there has been no experience with single-dose rFVIIa in acquired hemophilia. It is also important to recognize that joint bleeding in acquired hemophilia is unusual, and because most bleeds are soft, they may not respond well to higher single doses of rFVIIa.

The high risk of life-threatening bleeding in acquired hemophilia patients justifies an aggressive therapeutic approach to inhibitor eradication, with the aim of minimizing the time during which the patient may experience

fatal bleeding. While we concur that complications related to immunosuppressive therapy are common,[7-9] we emphasize that a rapid eradication of autoantibodies and a short duration of treatment are of primary importance. The literature does not support any preference for treatment with corticosteroids alone compared to combination therapy with cyclophosphamide,[8-11] therefore we do not recommend one regimen over the other unless contraindications are present, the patient has been pre-treated with corticosteroids for other conditions or is of childbearing age.

Due to the variable phenotypic presentation associated with this disorder, patients with acquired hemophilia typically present with either spontaneous or traumatic bleeding or an isolated prolonged pre-operative aPTT without bleeding symptoms. Initial presentation is frequently to a physician unfamiliar and/or inexperienced with the disorder. We agree with Drs Mannucci and Peyvandi that the single most important recommendation to the non-specialist physician confronted with a possible case of acquired hemophilia is to suspect this disorder and seek professional advice from a hemophilia center with expertise in managing inhibitors as soon as possible. Furthermore, guidance for initial emergency treatment if the patient is unstable and cannot be transferred immediately may be beneficial. In order to achieve this goal, a general awareness and understanding of this rare but often fatal disorder within the general medical community is necessary to ensure rapid diagnosis, appropriate treatment and avoid mistreatment such as even minor invasive procedures.

Finally, in the absence of high-level clinical evidence or the means with which to generate data in this rare and diverse patient population, we encourage all physicians who treat patients with acquired hemophilia to actively contribute to existing registries that document and monitor patient management and outcomes.

*Angela Huth-Kühne on behalf of the International Expert Panel on Acquired Hemophilia (IPAcHe)**

**International Expert Panel on Acquired Hemophilia (IPAcHe): Angela Huth-Kühne, Francesco Baudo, Peter Collins, Jørgen Ingerslev, Craig M. Kessler, Hervé Lévesque, Maria Eva Mingot Castellano, Midori Shima and Jean St-Louis*

Key words: treatment, acquired hemophilia A.

Correspondence: Angela Huth-Kühne, SRH Kurpfalzkrankenhaus and Haemophilia Centre Heidelberg gGmbH, Bonhoefferstrasse 5, 69123 Heidelberg, Germany.
E-mail: angela.huth-kuehne@kkh.srh.de

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