Infection prevention in patients with hereditary hemorrhagic telangiectasia

After reading the manuscript by Kritharis A *et al.*, with interest we agree that the prevention of future hereditary hemorrhagic telangiectasia (HHT) complications is as important as treating the immediate active issues.[1] For this reason, we would like to add an important part of the management of these patients that Kritharis A *et al.* did not mention in their manuscript, which is the prevention of severe infections through vaccination.[2]

Patients with HHT have an increased risk of infection potentially leading to serious infections requiring hospitalization, which according to the series is between 13.6% and 28.6% of the cases.[3,4] This increased risk is mainly due to the following:

a) Pulmonary arteriovenous malformations that can cause cerebral abscesses in up to 6.1% of cases (95% CI 3.9-8.5%) due to septic paradoxical emboli. This happens mainly through manipulation or dental infections and are most frequently caused by microaerophilic and anaerobic bacteria of the oral cavity. Streptococci are the main microorganisms responsible, growing in as many as 41% of positive isolates in the drainage of abscesses,[3,5-7] with *Haemophilus sp*. responsible in 9.4% to 21.4% of isolates.[3,7]

b) Mutations in the endoglin gene or in the related TGF-β receptor type I ACVRL1/ALK1 presented in HHT type 1. The endoglin is involved in the monocyte differentiation process and the expression of phagocytic enzymes of macrophages and neutrophils such as NAPH oxidase2 (Nox -2) and myeloperoxidase. In fact, an increased susceptibility to spontaneous infections has been observed in mice lacking this gene, possibly due to defects in phagocytic activity, alteration in the leukocyte recruitment, and reduction of proinflammatory cytokines TNF-α, IL-1β and Il-6, which affects the initiation of the innate immune response as well as a lack of splenic function that justifies vaccination against capsulated bacterias.[4,8-10]

c) The iron-deficiency anemia presented in these patients increases the infection risk.[11] In addition, the elevation of free iron from older intravenous iron components that are labile blood products can cause an elevation in the transferrin saturation that independently and significantly increases by 1.03 and 5.4 times, respectively, the risk of brain abscess due to transient iron overloads.[5] Not only that, but the immunomodulation secondary to transfusion,[12,13] and the possibility of post-transfusion iron overload that alters immune function through an oxidative mechanism of lymphocyte DNA.[4,11]

d) As the manufacturers highlight in the technical documentation, the drugs used to prevent bleeding[1] nearly double the frequency of moderate-severe infections, including pneumonia, that occurs in 10% of patients receiving Thalidomide, as well as the reactivation of hepatitis B or varicella zoster viruses that, in post-marketing studies, reported cases of acute liver failure and disseminated zoster. This fact justifies screening and vaccination against hepatitis B virus of patients with HHT without circulating surface antibodies against the virus[2,14] as well as zoster vaccination of patients aged 50 years or older with varicella zoster antibodies at least once a month before starting treatment.[10]

For these reasons, we consider that vaccination protocols should be implemented in the management of patients affected by HHT,[8] along with adequate oral hygiene and antibiotic prophylaxis prior to risky dental maneuvers. As previously mentioned,[2] we propose the vaccination protocol for patients with HHT shown in Table 1.

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Table 1. Vaccination protocol of the patient with hereditary hemorrhagic telangiectasia.

	Administer to diagnosis	Anti-angiogenic or Immunomodulatory drugs *Complete the recommended regimen for diagnosis by administering at least 15 days before the start of treatment*	Blood transfusión requirements
Adult	• Antipneumococcal conjugated 13-valent Vaccine. • Anti-*Haemophilus influenzae* b vaccine • Influenza vaccine at the beginning of each of the seasons	Add: • Antipneumococcal polysaccharide 23-valent vaccine • Antimeningococcal conjugated tetravalent A,C,Y,W135 vaccine • Antimeningococcal serogroup B vaccine (2/3 doses) • Zoster vaccine **	• Anti-Hepatitis B vaccine*
Children	Expand childhood calendar adding if not included: • Antipneumococcal conjugated 13-valent vaccine (3/4 doses from 2 months)	Add: • Antipneumococcalpolysaccharide 23-valent vaccine (from 23 months) • Antimeningococcal tetravalent A,C,Y,W135 vaccine (from 6th week) • Antimeningococcal B vaccine ***	• Anti-Hepatitis B vaccine* (from birth)

*Always check vaccination response after 6 weeks of last dose (HBsAc≥10 mUI/mL). **≥ 50 years old and IgG varicella zoster virus (+).ZOSTAVAX should not be administered to highly immunocompromised patients and at least 1 month before starting treatment. ***BEXSERO 3 doses from 2 months + booster between 12 years 23 months (for infants).

References

1. Kritharis A, Al-Samkari H, Kuter DJ. Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. Haematologica. 2018;103(9):1433-1443.
2. Rodríguez-García J, Fernández-Santos R, Zarrabeitia-Puente R, García-Erce JA. Vaccination of patients with hereditary hemorrhagic telangiectasia. Med Clin (Barc). 2015;144(12):572-573.
3. Dupuis-Girod S, Giraud S, Decullier E, et al. Hemorrhagic hereditary telangiectasia (Rendu-Osler disease) and infectious diseases: an underestimated association. Clin Infect Dis.2007;15;44(6):841-845.
4. Guilhem A, Malcus C, Clarivet B, Plauchu H, Dupuis-Girod S. Immunological abnormalities associated with hereditary haemorrhagic telangiectasia. J Intern Med. 2013;274(4):351-362.
5. Boother EJ, Brownlow S, Tighe HC, Bamford KB, Jackson JE, Shovlin CL. Cerebral abscess associated with odontogenic bacteremias, hypoxemia, and iron loading in immunocompetent patients with right-to-left shunting through pulmonary arteriovenous malformations. Clin Infect Dis. 2017;65(4):595-603.
6. Sell B1, Evans J, Horn D. Brain abscess and hereditary hemorrhagic telangiectasia. South Med J. 2008;101(6):618-625.
7. Mathis S, Dupuis-Girod S, Plauchu H, et al. Cerebral abscesses in hereditary haemorrhagic telangiectasia: a clinical and microbiological evaluation. Clin Neurol Neurosurg. 2012;114(3):235-240.
8. Ojeda-Fernández L, Recio-Poveda L, Aristorena M, et al. Mice lacking endoglin in macrophages show an impaired immune response. PLoS Genet. 2016;12(3):e1005935.
9 Cirulli A, Loria MP, Dambra P, et al. Patients with hereditary hemorrhagic telangiectasia (HHT) exhibit a deficit of polymorphonuclear cell and monocyte oxidative burst and phagocytosis: a possible correlation with altered adaptive immune responsiveness in HHT. Curr Pharm Des. 2006;12(10):1209-1215.
10. Rubin LG, Levin MJ, Ljungman P, et al. Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309-318.
11. Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis.Science.2012;338(6108):768-772.
12. Weingarten TN, Hanson JW, Anusionwu KO, et al. Management of patients with hereditary hemorrhagic telangiectasia undergoing general anesthesia: a cohort from a single academic center's experience. J Anesth. 2013;27(5):705-711.
13. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta analysis. JAMA. 2014;311(13):1317-1326.
14. Noval Menéndez J, Nuño Mateo F, Anitúa Roldán MJ, López Muñiz A, Fuente Martín E, Gallo Alvaro C. Familial study of patients with hereditary hemorrhagic telangiectasia. An Med Interna. 1998;15(10):534-537.

Reply to the comment "Infection prevention in patients with hereditary hemorrhagic telangiectasia"

Infections and vaccination in hereditary hemorrhagic telangiectasia: microbiological evidence-based considerations

We would like to thank Rodríguez-García and colleagues for their correspondence regarding our review article.[1] In their comment, Rodríguez-García and colleagues discuss infection prevention through vaccination and propose a vaccination schedule for patients with hereditary hemorrhagic telangiectasia (HHT), noting that this was not mentioned in our comprehensive HHT review. We thank the Editors for the opportunity to reply to Rodríguez-García and colleagues in consideration of this important issue.

We agree that certain infectious complications are more common in HHT patients, as we stated in our review article and as is discussed by Rodríguez-García and colleagues in their comment. As was described in our review, there is clear evidence that HHT patients may develop cerebral abscesses in the setting of pulmonary arteriovenous malformations (AVMs) which can be quite morbid.[2-4] In their comment, Rodríguez-García and colleagues also postulate a possible immunodeficiency in HHT patients with endoglin or ALK1 mutations based on a study in endoglin-deficient mice describing impaired immune responses[5] and a study in 22 HHT patients describing reduced phagocytic and oxidative burst function by polymorphonuclear leukocytes and monocytes in a majority of patients.[6] Finally, Rodríguez-García and colleagues discuss the possible contribution of iron deficiency, iron infusion, and red cell transfusion to increased infectious risk.

While we agree that these studies are intriguing, and that prevention of infections is an important aspect of HHT management, we question the utility of the specific vaccines recommended by Rodríguez-García and colleagues for the general HHT patient population. In the vaccination protocol given in Table 1 of their comment, they propose vaccination against three encapsulated organisms (*Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis*), yearly influenza vaccination, and vaccination against varicella-zoster virus (VZV) and hepatitis B virus (HBV), with certain vaccines recommended in all patients and others recommended when administering anti-angiogenic therapies. As yearly influenza vaccination is recommended for all members of the general population without contraindications, we of course follow and have no objection to this non-HHT-specific recommendation. However, while we considered the topic of special vaccination against encapsulated organisms in HHT patients while preparing our review article, we concluded that the accumulated evidence is not in support of this intervention. In addition to our center's clinical experience (we do not see these infections in our large HHT population), there is no evidence to suggest that an immunological defect in HHT, if present, leads to a particular susceptibility to these three encapsulated bacteria. As an example, HHT patients do not have an increased propensity for septicemia from these encapsulated organisms as do asplenic patients.

A review of the accumulated microbiological data published in the HHT population supports our position. On reviewing the literature, we found 6 retrospective studies[2-4, 7-9] and a case series[10] describing infectious complications in HHT patients published from 1984 to 2017 that included detailed microbiological isolate data, which is summarized in Table 1. These studies described cerebral abscesses as well as various other infections. Review of all microbiological isolates from all of these studies reveals not even a single case of infection with *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Neisseria meningitidis* documented in any patient. As the vaccines used to immunize against these organisms do not impart cross-protection against other organisms in the same genus and in fact impart protection only against certain serotype(s) of the species and not others, the available evidence does not support the vaccination recommendations described by Rodríguez-García and colleagues in their comment. There are dozens of species in