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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

Table 1. Microbiological isolates in studies describing infections in HHT patients.

Study	Type of Infection (Number)	Microbiological Isolate (Number)[a]
Press 1984[2] 31 patients, 31 infections[bc]	Cerebral abscess (31)	Actinomyces (2) Actinomyces bovis (1) Anaerobic Gram-negative rods (1) Bacteroides (1) Enterococcus (1) Gram-positive cocci (3) Gram-positive rods (2) Haemophilus (1) Haemophilus aphrophilus (1) Klebsiella (1) Nocardia (1) Peptostreptococcus (1) Streptococcus (2) Streptococcus (alpha-hemolytic) (2) Streptococcus (anaerobic) (2) Streptococcus (microaerophilic) (1) Streptococcus (nonhemolytic) (1) Streptococcus (viridans group) (1)
Cottin 2007[3] 34 patients, 47 infections	Cerebral abscess (25) Pneumonia (6) Soft tissue abscess (4) Tuberculosis (4) Meningitis (2) Hepatic abscess (1) Pleural empyema (1) Endocarditis (1) Brucellosis (1) Peritonitis (1) Pyelonephritis (1)	Actinomyces (1) Actinomyces meyeri (2) Capnocytophagia (1) Clostridium sordellii (1) Fusobacterium nucleatum (1) Haemophilus (1) Haemophilus aphrophilus (1) Pasteurella multocida (1) Peptostreptococcus (1) Streptococcus intermedius (1)
Dupuis-Girod 2007[4] 48 patients, 67 infections	Cerebral abscess (22) Septicemia (9) Arthritis or osteomyelitis (6) Skin abscess/erysipelas (6) Intramuscular abscess (5) Hepatic abscess (5) Spondylodiskitis (4) Other (10)	Actinomyces meyeri (2) Eikenella corrodens (1) Enterococcus faecalis (1) Fusobacterium (2) Gram-positive cocci (1) Haemophilus aphrophilus (3) Micromonas micros (1) Peptostreptococcus micros (1) Pseudomonas aeruginosa (2) Staphylococcus aureus (14) Streptococcus (1) Streptococcus (anaerobic) (3) Streptococcus (viridans group) (1)
Sell 2008[9] 53 patients, 53 infections[bc]	Cerebral abscess (53)	Actinomyces (4) Actinomyces meyeri (1) Actinomyces odontolyticus (1) Bacteroides (3) Capnocytophagia (1) Coryneform rods (1) Enterobacter (1) Enterococcus (1) Fusobacterium (1) Fusobacterium nucleatum (2) Gram-negative bacilli (2) Gram-positive bacilli (1) Gram-positive branching rods (1) Gram-positive cocci (1) Haemophilus aphrophilus (1) Klebsiella (1) Peptostreptococcus (3) Peptostreptococcus micros (1) Staphylococcus epidermidis (1) Streptococcus (3) Streptococcus (alpha-hemolytic) (4)

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Study	Type of Infection (Number)	Microbiological Isolate (Number)[a]
		Streptococcus (anaerobic) (2) Streptococcus anginosus (2) Streptococcus (atypical) (1) Streptococcus (group F) (1) Streptococcus intermedius (1) Streptococcus (microaerophilic) (1) Streptococcus milleri (4) Streptococcus mitis (1) Streptococcus mutans (1) Streptococcus (nonhemolytic) (4) Streptococcus salivarius (2) Streptococcus (viridans group) (1)
Mathis 2012[7] 26 patients, 26 infections	Cerebral abscess (26)	Actinomyces (2) Eikenella (1) Fusobacterium (3) Gemella (1) Haemophilus (3) Peptostreptococcus (2) Streptococcus (anaerobic or facultatively anaerobic) (8)
Musso 2014[10] 9 patients, 9 infections[bd]	Septic arthritis (2) Endocarditis (2) Bacteremia (1) Spondylodiskitis (1) Empyema (1) Liver abscess (1) Perivalvular abscess (1)	Peptostreptococcus (1) Prevotella (1) Staphylococcus aureus (5) Streptococcus anginosus (1) Streptococcus mutans (1)
Boother 2017[8] 37 patients[e], 37 infections	Cerebral abscess (37)	Actinomyces (4) Bacteroides (2) Gemella (1) Gram-positive cocci (1) Gram-positive rods (2) Peptostreptococcus (1) Porphyromonas (1) Propionibacterium (1) Staphylococcus aureus (1) Staphylococcus intermedius (1) Streptococcus (alpha hemolytic) (1) Streptococcus anginosus (2) Streptococcus milleri (7) Streptococcus (nonhemolytic) (1) Unspecified anaerobe (1)

[a]All isolates from HHT patients described in each study are listed. Isolates were not obtained for every reported infection (secondary to negative cultures, etc.), and some isolates were polymicrobial. [b]These studies describe new cases as well as a collection of cases from the literature. [c]A portion of the cases reviewed from the literature appear in both of these two studies. [d]Literature review included non-cerebral abscess cases from Cottin *et al.* 2007, omitted in this entry as the entire Cottin *et al.* 2007 study is described in a separate entry in this table. [e]34 of 37 had confirmed HHT; the remaining 3 patients had pulmonary AVMs but HHT was not confirmed

the genera *Streptococcus* and *Haemophilus*,[11,12] each of which may have many immunologically-distinct serotypes that colonize and/or cause disease in humans. Many of these species are important members of the salivary microbiome, and so a high incidence of other species of *Streptococcus* or *Haemophilus* aside from *S. pneumoniae* and *H. influenzae* in the microbiological isolates from these studies does not support the use of the vaccinations specific to these organisms.

Review of Table 1 reveals that the great majority of infections in HHT patients occur secondary to oral anaerobes, such as *Actinomyces*, *Fusobacterium*, *Peptostreptococcus* and anaerobic species of *Streptococcus*. The accumulated evidence strongly suggests that in the setting of pulmonary AVMs, transient bacteremia (secondary to surgical procedures, intravenous line placement, or dental disease) may result in abscesses of the brain and other organs. Additionally, *Staphylococcus aureus* is a frequently identified agent in HHT patients; given that *S. aureus* colonizes the nares of humans, HHT patients with prolonged epistaxis episodes may have an increased susceptibility to *S. aureus* bacteremia and seeding of various sites (such as vertebrae or joints).[4] No available vaccine protects against the multitude of mouth anaerobes or *S. aureus*, the bacteria that cause the great majority of serious infections in HHT patients (Table 1). Recognition of this formed the basis for our non-microbe-specific infectious prevention recommendations, which include antibiotic prophylaxis prior to surgical procedures (including dental procedures) and use of intravenous lines with filters in patients with evidence for pulmonary AVMs (mentioned in Table 2 of our review). While the risks

associated with vaccination are low, they are not zero, and these vaccines may present a burdensome out-of-pocket cost in certain countries, where they may not be covered by insurance or national health services without a clear evidence-based indication. Given this and the microbiological evidence suggesting that they are unlikely to be helpful, we did not recommend special vaccination against these three encapsulated organisms in our review. For those situations that these vaccinations and the suggested viral vaccines are recommended for the general population (in pediatric patients and the elderly, for example), or in the case of a disease-specific evidence-based indication (such as asplenia), we of course administer them to HHT patients as we would any other patient according to published evidence-based guidelines.[13]

Lastly, Rodríguez-García and colleagues additionally recommend antiviral vaccination against HBV and VZV in HHT patients receiving "anti-angiogenic and immunomodulatory drugs" in their vaccination protocol table. This is a heterogenous group of medications, including the anti-VEGF monoclonal antibody bevacizumab and the immunomodulatory drug (IMiD) thalidomide, among others. Screening and vaccination for HBV and vaccination for VZV prior to administration of immunosuppressive or immunomodulatory drugs is a non-HHT-specific consideration in a broad range of patients receiving these agents given the risks of viral reactivation.[14,15] As such, we administer VZV and/or HBV vaccination to our HHT patients as we would for non-HHT patients when indicated, with impending immunosuppressive or immunomodulatory therapy known to precipitate viral reactivation as just one potential indication. For example, in a given HHT patient, this indication could be an IMiD as anti-angiogenic therapy or rituximab to treat another illness unrelated to the patient's HHT. Bevacizumab, on the other hand, is not immunosuppressive, and no evidence suggests that special vaccination is warranted in patients receiving it. This is true in HHT patients as well as oncology patients who have considerable immunosuppression secondary to receipt of concurrent cytotoxic chemotherapy.

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