



## Review Article

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## The role of infections in the pathogenesis of bleeding among patients with haemophilia-A: A primer for haemophilia caregivers in the tropics

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### Abstract:

**Background:** Haemophiliacs are often transfusion-dependent, and are at risk of HIV and non-HIV immunosuppression, making them vulnerable to transfusion-transmissible infections (TTIs) and non-TTIs, many of which can cause infection-associated bleeding (IAB) even in non-haemophilic individuals. Haemophiliacs are particularly susceptible to IAB due to vicious interaction between pre-existing 'inherited' FVIII deficiency and infection-induced 'acquired' pro-haemorrhagic abnormalities. IAB in haemophiliacs manifests as undue musculoskeletal and/or mucocutaneous haemorrhages. It is thus important for haemophilia caregivers in general (and in the tropics in particular) to have thorough understanding of IAB. Clinico-pathological perspectives of IAB in haemophilia are fragmented, and not comprehensively appraised in previous literature. This review presents updated, comprehensive but concise overview of pathogenesis, trigger mechanisms, clinical implications, therapy and prevention of IAB in haemophiliacs as accrued from literature.

**Methodology:** Online databases such as PubMed, Medline, Google Scholar and others were interrogated using the search terms; 'haemophilia-A', 'viral, bacterial and parasitic, infections', 'bleeding', 'mucocutaneous', 'thrombocytopenia', 'ecchymosis', 'purpura', 'haematuria', 'melena', 'haematemesis', and 'haemoptysis' in various combinations.

**Results:** Pathogenesis of IAB in haemophilia include mucosal ulcerations, acquired coagulopathy, and/or portal hypertension. As long as the causative infections are untreated, IAB is often persistent or recurrent, predisposing patients to absenteeism from school/work, iron deficiency, excessive exposure to blood products, high risk of acquiring additional TTIs and increased risk of developing inhibitors to FVIII. Haemophilia caregivers should investigate stool, urine, sputum, blood and/or radiographs of all cases of persistent or recurrent bleeding, especially if bleeding is unabated by blood products transfusion alone, and more-so in patients presenting with constitutional and/or systemic indicators of infections such as pyrexia, asthenia, dysuria, cough, diarrhoea, jaundice, or history of passage of worms in the stool. Transfusion of blood products alone would not suffice for IAB, and transfusions of FVIII containing products without concurrent anti-infection chemotherapy may even promote the development of FVIII inhibitors since active infections and inflammations are important risk factors for inhibitor development in haemophiliacs.

**Conclusion:** It is therapeutically essential to combine transfusion therapy with anti-infective chemotherapy in order to achieve prompt and sustained stoppage of IAB. Haemophilia caregivers should also counsel patients on hygiene, barrier protection against vectors, and vaccination protocols.

**Keywords:** Haemophilic bleeding; bacteria, viral, parasitic, infections; pathogenesis

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## Le rôle des infections dans la pathogenèse des hémorragies chez les patients atteints d'hémophilie A: une introduction pour les soignants hémophiles sous les tropiques

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## Résumé:

**Contexte:** Les hémophiles sont souvent dépendants des transfusions et courent un risque d'immunosuppression liée au VIH et non liée au VIH, ce qui les rend vulnérables aux infections transmissibles par transfusion (ITT) et non-ITT, dont beaucoup peuvent causer des saignements associés à l'infection (IAB) même chez les personnes non hémophiles. Les hémophiles sont particulièrement sensibles à l'IAB en raison de l'interaction vicieuse entre le déficit préexistant en FVIII «héréditaire» et les anomalies pro-hémorragiques «acquises» induites par l'infection. L'IAB chez les hémophiles se manifeste par des hémorragies musculo-squelettiques et/ou cutanéomuqueuses excessives. Il est donc important pour les soignants hémophiles en général (et sous les tropiques en particulier) d'avoir une compréhension approfondie de l'IAB. Les perspectives clinico-pathologiques de l'IAB dans l'hémophilie sont fragmentées et ne sont pas évaluées de manière exhaustive dans la littérature précédente. Cette revue présente un aperçu actualisé, complet mais concis de la pathogenèse, des mécanismes déclencheurs, des implications cliniques, du traitement et de la prévention de l'IAB chez les hémophiles, tels qu'ils ressortent de la littérature.

**Méthodologie:** Des bases de données en ligne telles que PubMed, Medline, Google Scholar et d'autres ont été interrogées à l'aide des termes de recherche; «hémophilie A», «infections virales, bactériennes et parasitaires», «hémorragies», «mucocutanées», «thrombocytopénie», «ecchymoses», «purpura», «hématurie», «méléna», «hématémèse», et «hémoptysie» dans diverses combinaisons.

**Résultats:** La pathogenèse de l'IAB dans l'hémophilie comprend les ulcérations muqueuses, la coagulopathie acquise et/ou l'hypertension portale. Tant que les infections causales ne sont pas traitées, l'IAB est souvent persistante ou récurrente, prédisposant les patients à l'absentéisme scolaire/au travail, à une carence en fer, à une exposition excessive aux produits sanguins, à un risque élevé de contracter des ITT supplémentaires et à un risque accru de développer des inhibiteurs du FVIII. Les soignants hémophiles doivent examiner les selles, les urines, les expectorations, le sang et/ou les radiographies de tous les cas de saignement persistant ou récurrent, en particulier si le saignement n'est pas atténué par la transfusion de produits sanguins seuls, et plus encore chez les patients présentant des indicateurs constitutionnels et/ou systémiques de infections telles que pyrexie, asthénie, dysurie, toux, diarrhée, ictère ou antécédents de passage de vers dans les selles. La transfusion de produits sanguins seuls ne suffirait pas pour l'IAB, et les transfusions de produits contenant du FVIII sans chimiothérapie anti-infectieuse concomitante peuvent même favoriser le développement d'inhibiteurs du FVIII puisque les infections actives et les inflammations sont des facteurs de risque importants pour le développement d'inhibiteurs chez les hémophiles.

**Conclusion:** Il est thérapeutiquement essentiel de combiner la thérapie transfusionnelle avec la chimiothérapie anti-infectieuse afin d'obtenir un arrêt rapide et durable de l'IAB. Les soignants hémophiles doivent également conseiller les patients sur l'hygiène, la barrière de protection contre les vecteurs et les protocoles de vaccination.

**Mots clés:** Saignement hémophilique; infections bactériennes, virales, parasitaires; pathogenèse

## Introduction:

Haemophilia-A is an X-linked recessive disorder of blood coagulation characterized by lifelong bleeding diathesis due to deficiency of FVIII in the intrinsic arm of secondary haemostasis (1,2). Deficiency of FVIII leads to inadequate formation of tenase, sub-optimal generation of thrombin, insufficient deposition of fibrin and defective clot formation (1,2). The clinical severity of haemophilia is principally determined by the residual levels of FVIII, and is thus categorized as severe (FVIII level <1%), moderate (FVIII level 1-5%) or mild (FVIII level 6-40%) (1,2). There is a clear correlation between clinical severity of haemophilia and the frequency and spontaneity of bleeding episodes. Severe haemophilia is typically associated with more frequent bleeding episodes, which often occur spontaneously (1,2). Non-severe haemophilia is generally associated with less frequent bleeding episodes,

which are usually triggered by obvious trauma (1,2). No organ or tissue is exempted from haemophilic bleeding (3). However, the pattern, frequency and spatial distribution of bleeding sites in haemophiliacs are significantly determined by the extent of extrinsic pathway inhibition and/or the level of tissue factor activity in any particular tissue as exemplified in four tissues (joint, skeletal muscle, brain and lungs) (3). The most classical example is the 'joint' within which the chondrocytes and synovial cells produce tissue factor pathway inhibitor, which attenuates intra-articular activity of extrinsic pathway and predisposes to recurrent haemarthrosis and chronic arthropathy (4). Another example is the 'skeletal muscle', which is only modestly endowed with procoagulant tissue factor activity (5) thus predisposing to recurrent intra-muscular bleeding and contractures (6). In contradistinction, the

'brain' has the highest concentration of tissue factor activity (5) and is thus associated with less frequent bleeding episodes (3). In similarity with the brain, the lungs have high concentration of tissue factor (5), thus spontaneous pulmonary haemorrhage and haemoptysis are rare manifestations of haemophilia (7). For these aforementioned reasons, musculoskeletal (joints and muscles) bleeding and complications are particularly common and virtually pathognomonic of haemophilia (3,6,8). Mucocutaneous bleedings also occur in haemophilia, but at much lower relative frequencies because primary haemostasis is well preserved in haemophilia (3,6,8). This natural pattern of bleeding clinically distinguishes haemophilia from von Willebrand disease, in which primary haemostasis is severely impaired and mucocutaneous bleeding (e. g., haematuria, melena, haematemesis, epistaxis, gum bleed, ecchymosis) occurs at relatively higher frequency than musculoskeletal bleeding (8).

We thus reckon that haemophilic bleeding can occur spontaneously or be triggered by a myriad of causes, which include accidental trauma, surgical procedures, peptic ulcers, gastrointestinal irritants such as iron pills or medications that have dual effects of gastrointestinal irritation and platelet function inhibition such as non-steroidal anti-inflammatory analgesics (3,9,10). Moreover, infections are important triggers of bleeding in haemophilia, and haemophiliacs are particularly susceptible to infections for two important reasons. First haemophiliacs are usually managed by chronic transfusion of blood products (fresh whole blood, fresh plasma, cryoprecipitate, FVIII concentrate) that are known to cause undesirable immune modulation (11), which culminates in transfusion-associated immune suppression (TAIS) even in the absence of HIV infections (12). Second, chronic transfusion of blood products predisposes haemophiliacs to acquisition of transfusion transmissible infections (TTIs) including HIV (13), which may progress to AIDS and aggravate any pre-existing TAIS (14). Consequently, haemophiliacs are at high risk of acquiring both TTIs and non-TTIs, many of which are potential triggers of infection-associated bleeding (IAB) even among haemostatically normal (non-haemophilic) persons. The risk of IAB would be especially high among haemophiliacs in Africa and other tropical regions, which carry the heaviest burden of infectious diseases (15). Moreover, haemophiliacs would be particularly susceptible to IAB due to a potentially vicious interplay between pre-existing 'inherited' FVIII deficiency and

infection-induced 'acquired' pro-haemorrhagic abnormalities. IAB in haemophiliacs manifests as undue musculoskeletal and/or mucocutaneous haemorrhages. There is therefore a need for thorough appraisal of IAB in haemophilia.

To the best of our knowledge based on literature search, the clinico-pathological perspectives of IAB in haemophilia are fragmented, and have neither been holistically nor comprehensively appraised in the literature. Nonetheless, IAB in haemophilia is of clinical significance for five reasons. First, IAB tends to be persistent or at best recurrent as long as the infection remains active and untreated, thereby increasing the frequency of hospital visits, which would lead to high rates of school absenteeism (in children) and work absenteeism (in adults); absenteeism is inimical to the educational and economic development of haemophiliacs (16,17). Second, the persistent and/or recurrent nature of IAB invariably increases patients' transfusion requirement, which is undesirable, particularly in the tropics where availability of blood products is low because donor inertia is high (18), female gender participation in blood donation is poor (19), voluntary donors are scarce (20), and potent anti-haemophilic blood products (such as cryoprecipitate and FVIII concentrates) are often out-of-stock or unaffordable (21,22,23). Third, persistent IAB would worsen the pre-existing high prevalence of iron deficiency, which is quite common among tropical haemophiliacs due to the combined effects of poverty, malnutrition and inadequate management of bleeding episodes (24). Fourth, IAB episodes cannot be effectively controlled by transfusion of blood products alone; optimal management of IAB requires detection of causative infection, followed by synchronized application of blood products and anti-infection chemotherapy. And fifth, infusions of FVIII containing blood products without concomitant anti-infection chemotherapy may promote the development of FVIII inhibitors since active infections and inflammations are important risk factors for inhibitor development in haemophilia (25). The aforementioned five reasons underscore the need for haemophilia caregivers in general (and in the tropics in particular) to have thorough understanding of the destabilizing effects of infections on the precarious thrombo-haemorrhagic balance of haemophilia patients.

It is thus pertinent to rekindle the awareness and clinical index of suspicion of haemophilia caregivers in order to ensure that pro-haemorrhagic infections in haemophiliacs are quickly diagnosed and promptly treated. Hence, the aim of this review is to present an

updated and comprehensive but concise overview of the pathogenesis, trigger mechanisms, clinical implications, therapy and prevention of IAB among haemophiliacs as accrued from the literature.

## Methodology and Results:

Literature search was conducted using relevant search terms; 'haemophilia-A', 'viral, bacterial, parasitic and infections', 'bleeding',

'mucocutaneous', 'thrombocytopenia', 'ecchymosis', 'purpura', 'haematuria', 'melena', 'haematemesis', and 'haemoptysis' in various combinations on online databases such as PubMed, Medline, Google Scholar, and others. A total of 114 publications were used for the review and this included 110 peer-reviewed journal articles, 3 technical reports of the World Health Organization (WHO), and 1 edited text book. The summary result of the literature search is outlined in Table 1

Table 1: Pathogenesis, mechanisms, clinical implications, therapy and prevention of infection associated bleeding in haemophiliacs

Categories of infection	Types of infection	Potential trigger mechanisms for bleeding	Clinical implications	Therapeutic strategy in addition to FVIII therapy	Preventive strategy
<b>Transfusion Transmissible Viruses</b>	HIV	HIV-associated ITP	Increased risk of MCC bleedings	Anti-viral therapy; immune modulation therapy for ITP	Improve local blood banking practices
	Hepatitis B virus	Hepatocytopathy; multi-factor deficiency; cirrhosis; portal hypertension	Increased risk of MSK and MCC bleedings	Anti-viral therapy; multi-factor concentrates; portal hypertension therapy	Improve local blood banking practices; vaccination
	Hepatitis C virus	Hepatocytopathy; multi-factor deficiency; cirrhosis; portal hypertension	Increased risk of MSK and MCC bleedings	Anti-viral therapy; multi-factor concentrates; portal hypertension therapy	Improve local blood banking practices
	Cytomegalovirus	GIT mucosal ulceration; CMV-associated ITP	Increased risk of MCC bleedings	Anti-viral therapy; immune modulation therapy for ITP	Improve local blood banking practices
<b>Haemorrhagic Fever Viruses</b>	Dengue Virus	Thrombocytopenia; hypofibrinogenemia	Increased risk of MCC bleedings	Platelet concentrate transfusion; fresh plasma transfusion	Nets and barrier protection; environmental vector control; vaccination
<b>Bacteria</b>	<i>Helicobacter pylori</i>	GIT mucosal ulceration; H pylori-associated ITP	Increased risk of gastric and other MCC bleedings	Antibiotics; anti-ulcer therapy; immune modulation therapy for ITP	Improve personal and environmental sanitation
	<i>Mycobacterium tuberculosis</i>	Respiratory mucosal ulceration; TB-associated ITP	Increased risk of haemoptysis and other MCC bleedings	Anti-tuberculosis chemotherapy; immune modulation therapy for ITP	Improve nutrition, personal and environmental sanitation; vaccination
<b>Parasites</b>	Intestinal helminths	GIT mucosal ulceration; secretion of anticoagulants by parasites	Increased risk of GIT bleedings	Anti-helminthic chemotherapy	Improve personal and environmental sanitation
	<i>Schistosoma haematobium</i>	Bladder mucosal ulceration; secretion of anticoagulants by parasites	Increased risk of haematuria	Anti-schistosomal chemotherapy	Improve personal and environmental sanitation
	<i>Plasmodium</i> species	Thrombocytopenia	Increased risk of MCC bleedings	Anti-malarial chemotherapy; platelet concentrate transfusion	Nets and barrier protection; environmental vector control; vaccination

ITP=Immune thrombocytopenic purpura; GIT=Gastrointestinal tract; MCC=Mucocutaneous; MSK=Musculoskeletal

## Discussion:

### Transfusion transmissible viral infections (TTVIs)

Viruses that are transmissible by blood transfusion possess a number of characteristics, which include having long incubation period and/or clinical latency with ability to cause sub-clinical disease and/or exist in a carrier state (26). Moreover, viruses must have significant blood phases as part of their cycles and they must remain stable and retain their infectivity during blood storage at temperatures of about 4°C for several days (26). Most transfusion transmissible viruses are either exclusively plasma-borne (extra-cellular) such as hepatitis B and C viruses that are readily transmitted by transfusion of infected plasma (and cellular products due to residual plasma) or are virtually cell associated (intra-cellular) such as cytomegalovirus (CMV) and readily transmitted by infected cellular blood products such as leucocytes and platelets concentrates but rarely transmitted by cell-free plasma (27-29). However, HIV is both plasma borne and cell-associated since it has special tropism for monocytes, T-helper lymphocytes and other CD4 receptor bearing cells (30). Therefore, HIV has significant cellular and plasma reservoirs throughout the course of infection, and is readily transmissible by both cellular concentrates and plasma derivatives (30)

Although haemophiliacs are at high risk of acquiring any transfusion transmissible viral infections (TTVIs), the aforementioned four TTVIs (HIV, hepatitis B and C, and CMV) constitute particular danger to the haemophiliacs because they are pro-haemorrhagic and have the capability to destabilize thrombo-haemorrhagic equilibrium and aggravate pre-existing haemophilic bleeding diathesis due to FVIII deficiency as described below.

#### HIV, HBV and HCV infections in haemophilia

These three TTVIs have comparable epidemiology in terms of their modes of spread including via sexual intercourse, blood-to-blood contacts such as unsterilized invasive procedures (e.g., injections, traditional skin incisions, unhygienic surgical practices) and transfusion of inadequately screened or unscreened blood and blood products. On the one hand, sexual contact and unsterilized blood-to-blood contact may be largely responsible for the relatively high prevalence of these infections among tropical populations and apparently healthy blood donors (15). On the other hand, transfusion of inadequately screened or

unscreened blood and blood products are largely responsible for high prevalence of these infections among transfusion dependent patients (including haemophiliacs) in the tropical and developing countries (13). The risks of acquiring these infections in developed countries have been greatly minimized as a result of modernization of blood safety protocols with efficient donor screening procedures, effective viral inactivation techniques and production of recombinant blood products (31). However, infection risks are particularly high in developing countries and the tropics where the prevalence of blood born infections is high among donor populations, donor screening procedures are inadequate, viral inactivation techniques are virtually absent, and recombinant blood products are unavailable (32,33). Consequently, the prevalence of TTVIs among multi-transfused haemophiliacs was reported to be as high as 24.7% in Nigeria in West Africa (34), 17.3-47.5% in Egypt, North Africa (35), while a staggering prevalence of more than 50% was previously reported from Pakistan in Asia (36). The acquisition of TTVIs has adverse clinical implications within the context of a pre-existing bleeding disorder such as haemophilia.

The hepatitis viruses (HBV and HCV) often cause chronic liver diseases (CLD) resulting in significant damage to hepatocytes, which are the main producers of all coagulation factors with the exception of FVIII and von Willebrand factor (vWF) (37). Therefore, acquisition of CLD essentially transforms haemophilia from a 'single-factor' to a 'multi-factor' deficiency disorder, which would not respond optimally to FVIII therapy alone. Hence, in addition to FVIII concentrate, haemophiliacs with liver disease may require supplementary use of blood products that contain multiple clotting factors such as fresh plasma and/or cryoprecipitate (38), anti-viral chemotherapy and immune modulators such as  $\alpha$ -interferon (39). Moreover, CLD can cause portal hypertension, which increases hydrostatic pressure and dilatation of the abdominal veins leading to increased risk of gastrointestinal bleeding (40). In addition, viral CLD may transform into hepatocellular carcinoma, which would further worsen the haemostatic profile of haemophilic patients (41).

Just like hepatitis, HIV is also inimical to the haemophilic patient, because in addition to causing AIDS with recurrent opportunistic infections, it can cause HIV-associated immune thrombocytopenia (42). Acquisition of any type of immune thrombocytopenia jeopardizes primary haemostasis and aggravates bleeding in haemophilia (43). Therefore, HIV-associated

thrombocytopenia should be treated adequately with anti-retroviral agents in conjunction with immuno-suppressants and/or immune modulators (42). Hence, the haemostatic defects acquired due to viral CLD and/or HIV infection can aggravate the pre-existing haemophilic bleeding tendency, increase bleeding rates and worsen the prognosis of infected haemophiliacs. TTVIs are particularly undesirable in haemophiliacs in tropical developing countries like Nigeria, as they would invariably worsen the prognosis of an already under-treated inherited bleeding disorder. The risk of acquiring TTVIs among haemophiliacs in Nigeria, and indeed other developing countries, can only be prevented by upgrading the National transfusion service and blood safety protocols. This must include efficient donor screening procedures, effective viral inactivation techniques, and local production or regular importation of recombinant blood products, including FVIII concentrates (33). Moreover, it is important that haemophiliacs are regularly and periodically screened for hepatitis and HIV infections so that anti-viral therapy can be started promptly in order to prevent the development of 'acquired-on-inherited' bleeding complications.

While effective vaccines have not yet been developed against HIV and hepatitis C infections, hepatitis B infection is preventable through the use of vaccines, and every haemophiliac should be vaccinated in order to thwart the risk of acquiring the virus. Nonetheless, every precaution must be observed in order to avoid the risk of bleeding (44). Thus, subcutaneous administration of vaccines is preferred over intramuscular injection, regardless of disease severity since vaccines delivered by the subcutaneous route are as effective as those injected intramuscularly among haemophiliacs (45). The routine application of ice to the injection site is recommended before and after vaccine administration (44). Compression of the injection site is recommended after vaccination, but rubbing the site of injection should be avoided (44). Needles with the smallest possible gauge should be used whenever haemophilia patients are vaccinated (44). There is insufficient scientific evidence supporting the association between vaccination in haemophiliacs and development of inhibitors against FVIII. Hence, there is no need to avoid vaccination in association with the administration of FVIII concentrate (on the same day) in patients with haemophilia (44), and pre-vaccination FVIII concentrates can be administered, if necessary, to minimize risk of bleeding (45).

Hepatitis A virus is transmitted mostly by faeco-oral route. Nevertheless, it is advocated that hepatitis B vaccine should be complemented with hepatitis A vaccine in haemophiliacs for two reasons (46). First, there had been reports of several outbreaks of hepatitis A among haemophiliac recipients of contaminated FVIII (47). Second, haemophiliacs with chronic hepatitis C may develop severe hepatic decompensation if they become co-infected with hepatitis A (48). Both hepatitis A and B vaccines are non-live vaccines, and can be safely administered to all haemophiliacs, including those with HIV infections (46). Ultimately, it is the responsibility of every country and haemophilia care centre to establish their own vaccination protocols and safety guidelines in accordance with local standards for best healthcare practices.

#### **Cytomegalovirus infection in haemophilia**

Unlike HIV, and hepatitis B & C viruses, CMV is usually not routinely screened in clinical blood transfusion practice in most countries despite the fact that CMV is transmissible in blood (29). In fact, CMV is highly contagious because in addition to blood, it is also spread via various other body fluids such as semen, saliva and excrements (29). The virus is known to infect both immune-competent and immune-compromised persons (49). However, while it often causes clinically severe disease in immuno-compromised persons, it usually causes mild disease in immuno-competent individuals (49). The virus has a worldwide distribution. The global blood donor seroprevalence of both CMV-IgG (indicating past exposure with less risk of transmission) and CMV-IgM (indicating recent or active infection with greater risk of transmission) was 83.16% as revealed in a recent meta-analytical study (50). Nonetheless, CMV donor seroprevalence varies from 40–100% in different parts of the world (50). Developed countries tend to have relatively lower prevalence, while developing countries tend to have higher prevalence because of factors such as poor personal and environmental sanitation (50). For example, the seroprevalence of CMV in Nigerian blood donors was reported to be 100% in a previous study (51).

Hence, transfusion-dependent haemophiliacs in developing countries are at high risk of acquiring CMV infection. In another example, a recent study from Iran revealed that more than 70% of multi-transfused haemophiliacs were sero-positive for CMV antibodies (52). While majority of haemophiliacs with normal

immune response may not develop clinically severe CMV disease, it is predictable that CMV would run severe clinical course in three categories of CMV-vulnerable haemophiliacs; first, haemophiliacs with HIV infection (49); second, haemophiliacs who have developed transfusion-associated immune-suppression in the absence of HIV infection (12); and third, haemophiliacs in the neonatal age, which is associated with immature immune system (53). In any case, severe CMV infection is undesirable in haemophiliacs for three reasons. First, CMV may cause mucosal injury, and severe upper and lower gastrointestinal bleeding have been reported even in non-haemophilic patients (54,55); second, CMV infection may cause severe and refractory immune thrombocytopenia, which would worsen any pre-existing gastrointestinal bleeding and trigger other mucocutaneous bleedings even in non-haemophilic patients (56); and third, CMV infection accelerates the progression of HIV infection to full blown AIDS in HIV-infected haemophiliacs (57). Consequently, CMV infection has been shown to increase the overall haemophilic bleeding risks (58) and aggravate immune status of HIV-infected haemophilia patients (57).

It is therefore imperative to conduct post-transfusion haemovigilance on multiply transfused haemophiliacs; any patient presenting with post-transfusion flu-like symptoms in association with undue bleeding should be investigated for CMV infection, which must be promptly treated with appropriate anti-viral medications (59). The prevention of transfusion transmitted CMV in haemophiliacs is more difficult because the staggering seroprevalence of CMV among blood donors, especially in the developing countries, makes it virtually impossible to offer CMV seronegative blood products to haemophiliacs, even for the 'three categories of CMV-vulnerable haemophiliacs'. Fortunately, CMV is a highly leuco-cytotropic virus and leuco-depleted blood is considered relatively CMV-safe irrespective of donor sero-status (60). Therefore, leuco-depletion should have been the best strategy for producing relatively CMV-free blood in the tropics where seropositivity for CMV antibodies is virtually 100% among donors (51). Regrettably, tropical transfusion services are under developed and cannot readily undertake leuco-depletion of donor blood. Hence, the only feasible method of producing CMV-safe blood in the tropics is by saline washing of red cells, which will wash-off most of the infected donor leucocytes and presumably reduce but not abolish the risk of CMV transmission (61). Unfortunately, 'red cell

washing' is not a rational procedure for haemophiliacs scheduled to receive transfusion of 'fresh whole blood' (an easy-to-make blood product that is commonly used to treat haemophilia in low resource tropical countries) because the haemostatically active anti-haemophilic factor (FVIII) is contained within the plasma, which is invariably washed off together with the leucocytes (21).

## Haemorrhagic fever viruses

Viral haemorrhagic fevers are caused by seven families of viruses; Ebola, Marburg, Lassa, Dengue, Yellow fever, Crimean-Congo, and Rift Valley fever virus (62). However, to the best of our knowledge based on literature search, only Dengue haemorrhagic fever has been documented in patients with haemophilia.

### Dengue haemorrhagic fever in haemophilia

Dengue haemorrhagic fever (DHF) is a mosquito vector-borne (*Aedes aegypti* and *Aedes albopictus*) viral disease caused by the Dengue virus, which belongs to the family filoviridae and genus flavivirus (63). Thrombocytopaenia and hypofibrinogenemia are consistent findings in DHF (64). Hypofibrinogenemia is due to plasma leakage into pleural and peritoneal cavities (i. e., effusions) (64). However, the dominant haemostatic abnormality in DHF is thrombocytopaenia, which is due to the dual effects of myelosuppression and immune mediated platelet destruction (64). Consequently, the haemorrhagic manifestation of DHF range from positive tourniquet test, to ecchymoses, epistaxis, gum bleeding and/or severe gastrointestinal haemorrhages even in non-haemophilic patients (64).

In view of DHF-associated haemostatic derangement, DHF has been reported to aggravate bleeding diathesis among haemophiliacs who are already battling with a pre-existing inherited FVIII deficiency (65). Thus, in addition to FVIII replacement, the management of co-morbid DHF in haemophilia requires the administration of platelet concentrates in cases compounded by severe thrombocytopenia (65, 66). Of special concern is when haemophilic patients with comorbid DHF develop respiratory distress due to pleural plasma effusion (67). In such cases, the effusion should be drained only after good primary and secondary haemostasis are achieved by optimal infusion of platelet and FVIII concentrates (65,66,67), otherwise the pleural effusion may be compounded by haemothorax. Suffices to say that significant pleural effusion, ascites, shock and haemoconcentration signify active plasma leakage

(64,67), which may require supplementation with fresh plasma. In this setting, fresh plasma is of triple clinical value as it would mitigate coagulopathy by replacing any fibrinogen that is lost in leaked plasma, alleviate haemo-concentration by acting as a haemo-dilutor and ameliorate shock by acting as a blood-volume expander (64,67).

Because of the complexities of managing DHF in haemophilia, it is important that haemophiliacs presenting with fever, thrombocytopenia and undue bleeding in DHF endemic area should be promptly screened for the infection by both serological and antigen detection methods in order to start early blood products transfusion and other relevant supportive therapies as there is no specific anti-viral therapy at the moment (63). It is paramount for DHF endemic countries to control the spread of the disease through environmental hygiene and vector control programs (63). Moreover, haemophilia care givers should also counsel and encourage haemophiliacs to use insecticides, bed nets and other barrier protection methods, and be vaccinated with the dengue fever vaccine (Dengvaxia) (63). Dengvaxia is a live-attenuated dengue vaccine (63), hence it cannot be given to HIV-infected persons, including haemophiliacs (46). The vaccine has been shown in clinical trials to be efficacious and safe in persons who have had a previous dengue virus infection (63). However, it carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination. Hence, the W.H.O. recommends that only persons aged 9-45 years with evidence of a past dengue infection should receive the vaccine (63). Therefore, only non-HIV-infected haemophiliacs aged 9-45 years, and are living in Dengue endemic areas with a past history of dengue infection are eligible to receive Dengvaxia (63).

### Bacterial infections:

Haemophiliacs, especially if immuno-suppressed, may be vulnerable to a myriad of bacterial infections. However, based on literature search, *Helicobacter pylori* and *Mycobacterium tuberculosis* are the only bacteria that have been specifically associated with IAB in patients with haemophilia.

#### ***Helicobacter pylori* infection in haemophilia**

*Helicobacter pylori* is a highly ubiquitous Gram-negative bacterial pathogen with global distribution and at least half of the world population has been estimated to be infected (68). The bacterium is most likely spread by

contaminated food and water via faeco-oral route (69) hence the risk of infection is higher in tropical and developing countries [68]. When *H. pylori* is ingested, it survives the acidity of gastric fluid via urease-mediated production of ammonia, and it subsequently attaches to the gastric epithelium upon which it releases bacterial toxins (70). These toxins cause epithelial damage and peptic ulceration, which increases the risk of gastrointestinal bleeding even in haemostatically normal persons (70). *H. pylori* infection is therefore undesirable in haemophiliacs for three important reasons. First, *H. pylori* infection significantly raises the risk of upper gastrointestinal bleeding due to peptic ulceration (71). Second, *H. pylori* infection may induce immune thrombocytopenic purpura (ITP), which will aggravate any pre-existing bleeding from peptic ulcers and trigger other mucocutaneous bleeding; hence, *H. pylori*-associated ITP must be treated with immuno-suppressants, but bacterial eradication is the ultimate therapy (72). Third, *H. pylori* infection increases the risk of iron deficiency due to chronic blood loss, especially among haemophiliacs (73).

It is therefore pertinent that haemophiliacs who present with recurrent symptoms of gastritis and upper gastrointestinal bleeding should be screened for *H. pylori* infection by non-invasive but accurate technique such as the urea breath test (74); and positive cases should be promptly treated with appropriate antibiotics (in combination with anti-ulcer drugs), which is usually in the form of triple or sequential therapy using a proton pump inhibitor in combination with antibiotics (metronidazole, amoxicillin, clarithromycin) (75). It must be appreciated that infusion of FVIII-containing blood products alone, without appropriate antibiotics, would not be therapeutically sufficient in achieving sustainable stoppage of gastrointestinal bleeding in patients with haemophilia, unless the causative micro-organism is eradicated and the ulcer healed with the use of appropriate chemotherapy (75). Moreover, haemophiliacs should be counseled on how to improve environmental, food, water, and personal hygiene in order to prevent faeco-oral acquisition of *H. pylori* in the future. Although there are no vaccines for *H. pylori* infection at the moment, a number of candidate vaccines are currently in the pipeline of investigations (76).

#### ***Mycobacterium tuberculosis* infection in haemophilia**

In similarity with the brain, the lungs have high concentration of tissue factor (5),



thus pulmonary haemorrhage and spontaneous haemoptysis are relatively rare manifestations of haemophilia (7,77). Previous studies had shown that whenever haemoptysis is seen in haemophilia, it is usually associated with pulmonary comorbidities such as malignancies and/or infections, including TB (7,78). Tuberculosis is a febrile chronic granulomatous inflammatory disease that mainly affects the respiratory tract wherein it causes epithelial damage and tissue cavitations resulting in haemoptysis (79), which can be severe and sometimes life threatening even among non-haemophilic patients (80). As expected, the background inherited FVIII deficiency makes even mild haemophiliacs to be unduly vulnerable to recurrent haemoptysis if and when they acquire pulmonary TB (78).

The risk of acquiring tuberculosis (TB) among haemophiliacs is three-fold. First, the risk of acquiring infectious diseases in general, and TB in particular, is high in Africa and other tropical regions, which carry the heaviest global burden of infectious diseases (15), thus it is not surprising that haemophiliacs in low resource countries are at higher risk of getting TB (81). Second, chronically transfused haemophiliacs often suffer from transfusion-associated immune-suppression (TAIS) (12). TAIS had been shown to increase the susceptibility of haemophiliacs to TB with a significant correlation between the amount of transfused blood products and the development of TB among multi-transfused haemophiliacs (82). Third, chronic transfusion predisposes haemophiliacs to the acquisition of HIV (13), which may progress to AIDS (14), and subsequently predispose to TB (83). It is therefore recommended that HIV infected haemophiliacs should be promptly screened for TB (by using sensitive techniques such as PCR) at the appearance of the earliest indices of suspicion such as fever and cough (84). This will allow prompt case-detection and the commencement of anti-TB chemotherapy in order to avert disease advancement, significant lung damage and life-threatening haemoptysis (84).

Apart from lung injury, another pro-haemorrhagic complication of TB is ITP (85). Tuberculosis-associated ITP can cause severe thrombocytopenia, which would worsen haemoptysis and increase the risk of other mucocutaneous bleeding episodes. It is therefore important that any haemophiliac with a pre-existing TB who presents with aggravated haemoptysis and/or onset of other mucocutaneous bleedings in association with thrombocytopenia should be promptly screened for

ITP in order to commence appropriate immunosuppressive therapy (85).

Acquisition of TB can be effectively prevented by the use of BCG vaccine, which has stood the test of time in terms of efficacy and safety (86). Accordingly, haemophiliacs living in TB endemic countries should be counseled to receive BCG vaccine. However, BCG is a live-attenuated vaccine (87), hence it can only be given to non-HIV-infected haemophiliacs and not to HIV-infected haemophiliacs (46). Nonetheless, unvaccinated HIV-infected haemophiliacs can decrease their risks of contracting TB by maintaining good personal hygiene and optimal nutritional status (88).

### **Parasitic infections:**

Most of the literature on haemophilia originated from non-tropical developed countries, hence only little is known about parasite-induced bleeding and its effect in haemophiliacs. Nevertheless, our literature search revealed that intestinal helminthiasis, urinary schistosomiasis and malaria, and their haemorrhagic effects have been 'scantly' reported among haemophiliacs.

#### **Intestinal helminthiasis in haemophiliacs**

Intestinal helminths cause iron deficiency by inducing malabsorption and gastrointestinal haemorrhage (GIH) even in haemostatically normal persons (89). Intestinal helminths, especially the soil-transmitted helminths, cause GIH by inducing mucosal injuries leading to a wide spectrum of chronic or intermittent blood losses that range from occult bleeding to melena, haematemesis, and haematochezia (90-94). In addition to mucosal injuries, some intestinal helminths such as hook worms have the capacity to manipulate the host haemostatic system by actively secreting anti-coagulants (anti-FXa and anti-FIXa), which can aggravate bleeding from mucosal ulcers (95). Because intestinal helminthiasis is an important risk factor for GIH even in haemostatically normal individuals, it is easy to infer that haemophiliac would be particularly vulnerable to the haemorrhagic effects of intestinal helminths.

The haemorrhagic impact of intestinal helminths on haemophilia has not been adequately studied because the vast majority of publications on haemophilia arose from developed nations where parasitic diseases are not prevalent. Nevertheless, our literature search revealed only two pertinent studies regarding helminthiasis in haemophilia. The first study was conducted in Nigeria and revealed that up

to 35.7% of haemophiliacs were infected by single or multiple intestinal helminths (*Ancylostoma duodenale*, *Ascaris lumbricoides* and/or *Trichuris trichiura*) (96), and as expected, infected haemophiliacs had significantly higher frequency of GIH and iron deficiency than their counterparts without helminthiasis (96). The second study was conducted in India and found out that up to 20.4% of haemophiliacs were infected by *Strongyloides stercoralis* (97), which in addition to GIH (98), can potentially cause life-threatening disseminated hyper-infection among HIV-infected haemophiliacs when they develop AIDS (99).

These two studies (96,97) have shown that haemophiliacs living in the tropics are at risk of helminthiasis, and because of the pre-existing FVIII deficiency, haemophiliacs would be particularly susceptible to parasite-induced haemorrhage and iron deficiency. The findings of these studies have triple clinical implications on haemophilia care in parasite-endemic tropical countries. First, all haemophiliacs presenting with GIH, especially those with past history of passage of worms in stool, should have their stool screened for intestinal helminths, and positive cases should receive specific anti-helminthic chemotherapy (if only one parasite found) or broad spectrum anti-helminthic chemotherapy (if multiple parasites are found) (100). Second, all haemophiliacs should undergo periodic screening and de-worming program in consonance with WHO recommendations for endemic countries (100), and third, haemophiliacs should be counseled to constantly observe personal and environment sanitary measures to prevent re-infections (100).

#### Urinary schistosomiasis in haemophiliacs

Urinary schistosomiasis, caused by *Schistosoma haematobium*, is a tropical haemorrhagic parasitic disease (15). The adult parasites preferentially settle in the vesical plexus where they reproduce and deposit eggs leading to extensive inflammation, epithelial damage, haematuria and anaemia even in haemostatically normal patients (101). In addition to epithelial injuries, *S. haematobium* parasite is known to secrete serine protease inhibitors with anti-thrombin properties that manipulate the host haemostatic system and escalate the severity of the haematuria (102). It can therefore be easily deduced that haemophiliacs would be particularly vulnerable to the haemorrhagic effects of urinary schistosomiasis.

In similarity with intestinal helminthiasis, there is extreme paucity of studies on urinary schistosomiasis in haemophiliacs even within the literature from tropical countries.

However, a solitary study from Nigeria reported that urinary schistosomiasis was responsible for about 20% of cases of haematuria seen among haemophiliacs (103). Moreover, the study revealed that schistosomal haematuria was severe and associated with significant anaemia in contradistinction to spontaneous haematuria, which was mild and not associated with significant anaemia (103). Therefore, healthcare givers in the tropics should ensure that all haemophiliacs presenting with haematuria in schistosomiasis endemic countries should be properly investigated by urinalysis and blood cell count for early detection and treatment (103). In particular, haemophiliacs who present with apparently spontaneous haematuria in association with dysuria and eosinophilia should evoke the strongest clinical suspicion for urinary schistosomiasis (103). While infected haemophiliacs with active haematuria should be treated with anti-schistosomal chemotherapy, all haemophiliacs in endemic countries should be periodically screening by urinalysis and counseled on personal and environmental sanitary measures to prevent infections (100).

#### Malaria in haemophiliacs

Malaria is endemic in many tropical countries (15). Five *Plasmodium* species; *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*, have been documented to infect humans, with the first two being the most important (15). Haemophiliacs in tropical countries are doubly exposed to the risk of acquiring malaria via mosquito bites and via blood transfusions, because a significant proportion of tropical blood donors have asymptomatic malaria (104). Isolated thrombocytopenia (malarial thrombocytopenia) is a well-known complication of acute malaria (105). The pathophysiologic mechanisms of malarial thrombocytopenia include reduced bone marrow production and/or accelerated peripheral destruction of platelets (106,107,108). Malarial thrombocytopenia, especially in severe cases, can compromise primary haemostasis, and has been reported to cause significant mucocutaneous bleeding (malarial thrombocytopenic bleeding) even in non-haemophilic children and adults (109,110). Hence, malarial thrombocytopenia (MT) and malarial thrombocytopenic bleeding (MTB) are highly undesirable in the haemophiliacs who are already battling with a lifelong congenital bleeding diathesis due to FVIII deficiency.

In similarity with intestinal helminthiasis and schistosomiasis, there is paucity of studies on MTB in haemophiliacs in the lite-

ture, nonetheless, our literature search revealed two pertinent studies. The first study is a case report that was published more than five decades ago (in 1967) by Vartan (111) who described the adverse thrombocytopenic effect of transfusion transmitted malaria due to *P. malariae* in a British patient with haemophilia-B, which is pathophysiologically and clinically very similar to haemophilia-A. The patient was inadvertently transfused with malaria infected red cells from a donor who returned from a malaria endemic country. The second study is a recent retrospective cohort analysis of *P. falciparum* infected haemophiliacs in Nigeria (112). The reported incidence of MTB among haemophiliacs in the study with MT was up to 16.8%. The study further revealed that the risk of MTB was not affected by severity of haemophilia, but the risk was increased in young age (<5 years), and by the severity of parasitemia and thrombocytopenia as well as inheritance of non-O blood groups and HbAA phenotypes (112). It is thus recommended that haemophiliacs presenting with a triad of fever, thrombocytopenia and mucocutaneous bleeding in the tropics should be investigated for MTB, and positive cases should be promptly treated with parenteral anti-malarial chemotherapy and platelet concentrates in addition to FVIII containing blood components (112).

Vaccine-based malaria-prevention strategy remains a high priority for sustained, substantial, and cost-effective malaria control in tropical countries. However, the RTS,S/AS01 vaccine has shown only low to moderate efficacy in preventing clinical *P. falciparum* malaria (113). Although RTS,S/AS01 vaccination alone might not be sufficient for global malaria eradication, it should be considered as another addition to the malaria-control program and not as an eradication tool because of its relatively low to modest efficacy (113). Eventually, in October 2021, the RTS,S/AS01 vaccine was endorsed by the WHO for use in children in conjunction with other malaria-control programs such as insecticide treated nets for barrier protection, and environmental vector control (114). Therefore, haemophiliacs living in *P. falciparum* endemic countries should be counseled to receive RTS,S/AS01 vaccine. The vaccine is a non-live recombinant protein-based vaccine (114) hence it can be given to all haemophiliacs including those with HIV infection (46).

## Conclusion and Recommendations:

Haemophiliacs are often transfusion-dependent, and are therefore at risk of HIV and

non-HIV immunosuppression, which makes them vulnerable to both transfusion-transmissible infections (TTIs) and non-TTIs, many of which can cause infection-associated bleeding (IAB) even in non-haemophilic individuals. Haemophiliacs are particularly susceptible to IAB due to interplay between pre-existing 'inherited' FVIII deficiency and infection-induced 'acquired' pro-haemorrhagic abnormalities such as mucosal ulcerations, perturbation of synthesis and/or functions of clotting factors, portal hypertension, and /or thrombocytopenia. Hence, IAB in haemophiliacs manifests as undue persistent or recurrent musculoskeletal and/or mucocutaneous haemorrhages. It is thus important for haemophilia caregivers in general (and in the tropics in particular) to have high clinical index of suspicion for IAB in patients whose bleeding is unabated by blood products transfusion alone and/or is accompanied by constitutional or systemic symptoms suggestive of active infection.

The management of IAB requires early identification of the infective agent, followed by dual combination of 'transfusion therapy' with 'anti-infection chemotherapy' in order to achieve prompt and sustained stoppage of IAB. It should be realized that transfusions of FVIII containing blood products without concurrent anti-infection chemotherapy may even promote the development of FVIII inhibitors since active infections and inflammations are important risk factors for inhibitor development in haemophilia. It is also recommended that hemophilia caregivers should offer appropriate counseling on personal and environmental hygiene, barrier protection against disease-spreading vectors, and the role of vaccines in preventing certain types of infections.

## Conflict of interest:

Authors declare no conflict of interest

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