

## Coagulation disorders

Information on pre-travel preparation, tips to stay healthy abroad and links to useful resources for travellers with coagulation disorders

### Key messages

- **Travellers should be encouraged to research their destination, considering medical facilities and access to care, prior to booking.**
- **Anticoagulant therapy should ideally be well established prior to travel. For patients taking a vitamin K antagonist such as warfarin, the International Normalised Ratio (INR) should be as stable as possible and have been recently checked by the traveller's anticoagulation clinic prior to travelling.**
- **Travellers should know how to manage their INR whilst overseas and know how to manage episodes of bleeding.**
- **Measures to prevent travel-related venous thromboembolism are particularly important for those with an increased tendency for blood clots.**
- **Current guidance in the UK suggests that for those with bleeding disorders, most vaccines normally administered by the intramuscular route should be given by deep subcutaneous injection.**
- **Additional vaccines may be advised for those receiving regular blood products or plasma-derived clotting factors.**

### Overview

The coagulation (blood clotting) process involves a complex series of reactions involving platelets and clotting factors (currently, 13 are known), resulting in the formation of a clot and preventing loss of blood. This process is termed the 'clotting cascade' [1].

Coagulation disorders are conditions that affect the blood clotting process. This can lead to either

an increased risk of bleeding (bleeding disorders), or to an increased risk of clot formation (thrombophilia).

## Bleeding disorders

Bleeding disorders may result from faults at one of many different points within the clotting cascade, and can range in severity from life-threatening to mild conditions [1]. They can be classified as either inherited or acquired, and can also be a result of extrinsic factors such as anticoagulant medication.

### Inherited bleeding disorders

The most common inherited bleeding disorder is Von Willebrand's disease. This disorder is caused by reduced production or abnormality of Von Willebrand's factor, which promotes normal platelet function and stabilises factor VIII [1]. An estimated 1-2% of the general population may be affected by this disorder, although the majority of cases are not diagnosed due to the mild nature of the condition [2]. A minority have a more severe form of the disease.

Other, relatively rare inherited bleeding disorders include Haemophilia A, caused by a deficiency in factor VIII, and Haemophilia B (Christmas' disease), due to a deficiency in factor IX. Both these diseases can range in severity from mild to severe and require the individual to adapt their lifestyle to reduce the risk of trauma and bleeding. Medical management involves use of the appropriate missing clotting factor therapy, either as a prophylaxis, or for treatment in an acute setting [1, 2].

Conditions caused by deficiencies in other clotting factors are rare.

### Acquired bleeding disorders

Acquired disorders can result from underlying disease and include:

- Liver disease (leading to reduced production of clotting proteins and thrombocytopenia [abnormally low level of platelets]).
- vitamin K deficiency (vitamin K is needed for the production of certain clotting factors and may be deficient due to diet or gastrointestinal malabsorption).
- Shock, sepsis or malignancy (often through disseminated intravascular coagulopathy).
- Renal disease (due to platelet dysfunction and reduced aggregation).
- Autoimmune disorder (where there may be circulating autoantibodies to coagulation factors such as in systemic lupus erythematosus, or to platelets as in immune thrombocytopenic purpura).
- Vitamin C deficiency (which can lead to more fragile blood vessels as well as causing haemorrhage in surgical patients).
- Advanced age (which can be associated with fragile veins) [1].

## Anticoagulation therapy

Anticoagulation (blood thinning) treatment is given to patients to treat and prevent blood clots. The majority of patients on anticoagulation treatment take tablets, either Direct Oral Anticoagulants (DOACs) (e.g. apixaban, rivaroxaban, edoxaban or dabigatran) or vitamin K antagonists (VKAs) (typically warfarin) which require regular laboratory monitoring. Patients may also be on low molecular weight heparin injections. The type of anticoagulant may relate to the clinical indication, and while the majority of patients on anticoagulation to treat and prevent clots in the veins (and stroke in non-valvular Atrial Fibrillation) are on DOACs, many patients still take warfarin. Warfarin is used in patients anticoagulated with mechanical heart valves and other indications, including the antiphospholipid syndrome.

Direct oral anticoagulants (DOACs) confer a number of advantages as they do not have interactions with food or alcohol, have a lower potential for drug-drug interactions and do not require regular laboratory tests [3].

## Thrombophilia

Thrombophilia refers to having an increased tendency to develop blood clots (thromboses).

Thromboses can form in an artery (arterial thrombosis) or vein (venous thrombosis). Clots forming in arteries of the heart can lead to myocardial infarction (heart attacks). Cerebrovascular accidents (strokes) result if there is a clot within the brain. Venous thrombosis often occurs in the deep veins in the legs (deep vein thrombosis - DVT). An embolism (part of a clot which becomes detached) may travel round the body and obstruct distant vessels or arteries e.g. pulmonary embolism (PE). Collectively, a DVT and PE are known as venous thromboembolism (VTE) [4].

There are many types of thrombophilia, which can be either inherited or acquired.

Inherited thrombophilia is caused by genetic conditions including Factor V Leiden, protein C deficiency, protein S deficiency, and antithrombin deficiency.

Antiphospholipid syndrome (APS) is an acquired thrombophilia [5]. Acquired thrombophilia may also be caused by lifestyle factors (such as immobility or smoking), or medical conditions (not exhaustive, but including heparin-induced thrombocytopenia, severe infection, tissue injury, inflammatory conditions such as Crohn's disease or rheumatoid arthritis, cancer; and venous stasis (caused by surgery or heart failure)) [5]. Additional risk factors include pregnancy and combined hormonal contraception, obesity, increased age and some medications. Environmental factors can also increase the risk of thrombosis, especially if a genetic abnormality is also present.

## Pre-travel preparation

Risk management advice for those with coagulation disorders should follow the usual advice given to all travellers, and tailored to the individual, considering underlying medical condition, severity of

disease, current treatment and medications.

Assessment of a travellers' risk and the suitability of their destination and plans should ideally be discussed with a healthcare professional (and / or specialist) prior to booking. Specific societies also offer information and support (see under Resources). Destination specific risks and risk management advice can be found on the [Country Information pages](#).

Medical facilities at the destination are important to consider, together with access to care. Travellers should consider how they would manage episodes of bleeding or a medical emergency when overseas. Specialist centres may be available worldwide, for example the World Federation of Haemophilia's [Global Treatment Centre Directory](#) lists haemophilia treatment centres around the world.

Carrying a letter from a haematologist/specialist with diagnosis and drug treatment is advised; this is particularly important if carrying medications or equipment such as needles and syringes, which need to be declared to the airline. Consulting the destination country to determine any restrictions on which medications can be carried is also necessary. Medications, including 'factor' preparations, should be carried in hand luggage as changes in temperature in an aircraft hold may affect potency, and luggage may be lost or containers broken from handling - see the [Medicines and travel](#) factsheet for further information.

Travellers should also be advised to carry their own necessary medication, as substandard or [falsified medication](#) can be a problem in some countries.

Written information relating to the individual's blood group should be carried in case of the need for emergency blood transfusion. However, travellers need to be aware that blood transfusions may not be reliable, nor available in many countries.

Anticoagulant therapy should ideally be well established prior to travel. The Vitamin K antagonists (VKA), (typically warfarin) require regular monitoring of the International Normalised Ratio (INR) via an anticoagulation clinic. This should be as stable as possible and checked before travelling; the anticoagulation clinic should be informed of the travel plans several weeks before leaving the country to help facilitate this. Management of INR whilst overseas is important, with knowledge of what to do if the INR either increases or decreases [6]. For longer trips, INR should be checked at intervals at the destination (as advised by the traveller's anticoagulation clinic), although travellers should be aware that laboratory testing methods to measure the INR may vary, making interpretation and comparison of results difficult. Self-monitoring of INR may be suitable under supervision of an anticoagulant clinic [7].

Vitamin K antagonists are prone to drug-drug interactions, resulting in either potentiation or inhibition of the anticoagulation effect [3]. This can lead to an increased risk of either bleeding or developing blood clots. Travellers should therefore be advised to inform his/her anticoagulation clinic (in advance where possible) of starting a new drug as the INR will need to be monitored more frequently. This has particular relevance for standby treatment of infection, and for malaria chemoprophylaxis (discussed under vector-borne disease).

Travellers with a 'yellow' warfarin dosing record booklet or other similar record system, should take this (or a copy) when travelling.

A medical identification bracelet or pendant may be useful for all those with coagulation disorders, together with an alert card stating the condition and any additional important information.

Comprehensive travel insurance is essential for all travellers. A full declaration of medical conditions should be made to the insurers and all equipment and planned activities should also be covered. Individual societies may provide a list of insurance companies that provide cover for those with bleeding disorders (e.g. [Haemophilia Society](#)).

## **Journey risks**

Prolonged air travel is a risk for venous thromboembolism (VTE) and studies from the World Health Organization Research into Global Hazards of Travel (WRIGHT) project indicates that the risk of VTE approximately doubles after a long-haul flight (> 4 hours), and also with other forms of travel where travellers are seated and immobile [8].

Thrombophilia is one of a number of factors which increase the risk of VTE [4]. Travellers should be advised on measures to prevent travel related VTE, including remaining well hydrated (but avoiding alcohol) and maintaining mobility in-flight [9, 10]. Properly fitted compression stockings may be considered for some individuals. Additional information on reducing the risk of VTE can be found on the [Venous Thromboembolism](#) factsheet. Specialist advice may be needed on prevention for those with particular risk factors for VTE.

The use of direct oral anticoagulants (DOAC) for the prevention of travel related thrombosis for those at higher risk has not been established [3, 11, 12].

Travelling across different time zones can disrupt usual routines and managing medication safely needs to be considered before travel and should be discussed with the individual's specialist team.

## **Food and water-borne risks**

Many drugs and foods interact with vitamin K antagonists, and changes in diet and alcohol consumption can all affect anticoagulant control [3, 13].

Gastrointestinal illness may result in a reduced uptake of vitamin K (and some medication, including warfarin), potentially resulting in an unstable INR. Antibiotic treatment could further increase the problem by enhancing the anticoagulant effect of VKAs.

Travellers taking VKAs should therefore be aware of possible interactions and be prepared to liaise with their anticoagulant clinic or healthcare provider regarding the need for increased INR monitoring and the potential need to adjust the dose of VKA accordingly (only as advised by a healthcare professional).

An advantage of DOACs is that they do not interact with food and have lower potential for drug-drug interactions, although the BNF and individual SPCs should always be referred to when new medications are prescribed. Gastrointestinal illness and reduced food intake may affect the absorption of DOACs and the traveller should seek advice accordingly.

## Vector-borne risks

### Malaria

For those travelling to malaria endemic areas, the ABCD of malaria prevention should be discussed: **A**wareness of risk of malaria in the area they are travelling; practice good **B**ite prevention, as this is the first defence against malaria; use of appropriate **C**hemoprophylaxis; and recognise the importance of responding quickly to potential signs and symptoms of malaria to ensure prompt **D** iagnosis [7].

### Malaria chemoprophylaxis for those taking vitamin K antagonists (e.g. warfarin)

For those taking vitamin K antagonists, additional monitoring of INR may be needed when malaria chemoprophylaxis is recommended. INR should be stable and within the therapeutic range prior to travel. Practical guidance on monitoring INR when starting, during and completing malaria chemoprophylaxis is provided in the [ACMP Guidelines](#) [7].

Those taking VKAs may have underlying cardiovascular disease together with additional medication. Identifying any underlying medical history and drug therapy when deciding on appropriate malaria chemoprophylaxis is therefore essential.

The ACMP Guidelines, BNF and individual SPCs should be consulted for additional information on appropriate chemoprophylaxis and drug interactions. The local Medicines Information Service can also be consulted for advice regarding drug interactions.

### Malaria chemoprophylaxis for those taking direct oral anticoagulants (DOAC)

There is relatively limited experience of the use of antimalarial medication in those taking DOACs. However, this group have lower potential for drug interactions than the coumarins, and do not require laboratory monitoring [3]. Further information is available in the ACMP Guidelines, and the latest edition of the BNF should be consulted. Expert advice from a haematologist or the local Medicines Information Service should also be considered [7].

### COVID-19

Some individuals with coagulation disorders may be considered clinically vulnerable to COVID-19, depending on the underlying cause of their bleeding disorder or thrombophilia. An individual risk assessment will be needed.

Groups considered clinically vulnerable to COVID-19 and who continue to be offered COVID-19 vaccination in the UK can be found in Tables 2 and 3 in [Chapter 14a](#), COVID-19 in the Green Book (Immunisation against Infectious Disease).

Travellers with coagulation disorders should assess their individual circumstances, including medical facilities at their destination, and consider whether postponing travel would be appropriate.

All individuals should follow [current UK recommendations](#) to reduce their risk of catching COVID-19 and passing it on to others.

General guidance regarding [risk assessment for travel](#) during the COVID-19 pandemic and information about the [COVID-19 vaccination programme](#) is available.

## Vaccination

Those with coagulation disorders should be up to date with routine immunisations and boosters as [recommended in the UK](#). Those receiving regular medical interventions / blood products should be vaccinated against hepatitis B [14]. Those with haemophilia who are receiving plasma-derived clotting factors should also be immunised against hepatitis A [15].

Coagulation disorders alone are not considered a contraindication for most vaccines. However, as in all travel consultations it is important to consider any underlying medical condition, treatment or drug therapy which may be considered a precaution, or contraindicate the use, of any vaccine.

Data continues to emerge on specific adverse events associated with the relatively new COVID-19 vaccines (see below). The Green Book and specific SPCs should be consulted for updated information relating to these and other vaccines to be administered. Specialist advice may be needed.

## Blood clotting events associated with COVID-19 vaccines

(Information correct at the time of writing; Green Book; COVID-19 chapter 14a: 4 September 2023)

### **Thrombosis and Thrombocytopaenia syndrome (TTS) occurring after COVID-19 vaccination**

Serious thromboembolic events accompanied by thrombocytopaenia have been recognised following the AstraZeneca COVID-19 vaccine. However, there is no evidence of any underlying risk factors in individuals affected by this condition, which is believed to be an idiosyncratic reaction

related to an immune response to the AstraZeneca vaccine. Because this is a likely immune mechanism, there is currently no reason to believe that individuals with a past history of clots or certain thrombophilic conditions would be more at risk of this very rare condition [16].

Although pregnancy increases the risk of clotting conditions, there is no evidence that pregnant women, those in the post-partum or women on the contraceptive pill are at higher risk of the specific condition of thrombosis in combination with thrombocytopenia after the AstraZeneca vaccine [16]. There have been no confirmed cases reported in pregnant women to date (September 2022) [16].

Caution is necessary however, when vaccinating individuals with a history or a previous episode of heparin induced thrombocytopenia and thrombosis [16].

Extremely rare reports of capillary leak syndrome have been reported after AstraZeneca and Moderna vaccines in individuals with a prior history of this condition. These individuals should be carefully counselled about the risks and benefits of vaccination and advice from a specialist should be sought [16].

### **Thrombocytopenia following COVID-19 vaccination**

Cases of thrombocytopenia (without accompanying thrombosis) have been reported to occur rarely in the first four weeks after receiving Covid-19 vaccination [17, 18]. Some of these cases occurred in individuals with a history of immune thrombocytopenia (ITP). In three case series the reported risk of relapse following Covid-19 vaccination in those with existing ITP was 3-12% [19-21]. Most relapses were identified between 2 and 7 days after vaccination.

Previous ITP is not a contra-indication for vaccination, but individuals should be aware of the potential risk of relapse. Guidance from the UK ITP Forum Working Party advises discussing the potential for a fall in platelet count in patients with a history of ITP who receive any Covid-19 vaccine, and recommend a platelet count 2-5 days after vaccination [16].

Data is limited on whether a subsequent dose of COVID-19 vaccine would precipitate a further exacerbation. Evidence to date suggests patients with ITP / ITP-relapse after COVID-19 vaccine experienced a further significant fall in platelets with a subsequent dose /rechallenge (27%). Individual risk assessment by a haematologist, patient discussion and platelet monitoring is therefore recommended prior to further doses [22].

### **Route of administration**

There is an increased risk of inducing bleeding following vaccination in many individuals with bleeding disorders [23]. When considering route of administration, it is important to balance efficacy of vaccination against risk of trauma associated with the procedure. The subcutaneous route can itself be associated with an increase in localised reactions and it has been suggested that this route may not offer the same degree of protection as intramuscular vaccination [24, 25].



Few studies have been published on administration of vaccines by the intramuscular route in those with bleeding disorders. One study on administration of intramuscular hepatitis B vaccine in those with haemophilia resulted in a low bruising rate [26]. Published data on influenza vaccine administered intramuscularly to those taking oral anticoagulation reported no local complications [27, 28]. However, it is unknown whether results from these studies can be generalised to other vaccines within these patient groups [6, 29].

Current guidance in the UK suggests that for those with bleeding disorders, most vaccines normally administered by the intramuscular route should be given by deep subcutaneous injection [30]. However, influenza and COVID-19 vaccines may be administered intramuscularly to those with bleeding disorders if, in the opinion of a doctor familiar with the individual's bleeding risk, the vaccine can be administered with reasonable safety by this route [24]. A fine needle (23 or 25 gauge) is recommended, followed by firm pressure applied to the site (without rubbing) for at least two minutes [24].

For those on stable anticoagulant medication, intramuscular influenza and COVID-19 vaccines may also be considered so long as INR testing is up to date, and INR is below the upper level of the patient's therapeutic range. However, the clinician responsible for prescribing or monitoring the individual's anticoagulant therapy should be consulted [24].

DOACs have a relatively short half-life, which is an advantage with regard immunisations given via the intramuscular route. There are no specific recommendations when administering intramuscular vaccines to those taking DOACs.

Those administering vaccines to patients with bleeding disorders should consult the UK Green Book together with the SPC for the individual vaccine for further information. Specialist advice may be needed.

## **Other health risks**

### **Climate**

An increase in temperature can increase bleeding tendency due to vasodilation [6]. Seasonal variations in INR have also been documented, with lower INR values found in spring and summer compared to autumn and winter. Possible explanations include a higher consumption of vegetables rich in vitamin K in the summer, and a higher incidence of febrile infectious diseases in autumn and winter [31, 32].

### **Altitude**

The effect of altitude on clotting remains under debate. One study suggested that staying at altitudes above 2,400m increased the risk of INR values falling below the target range, although the cause remains unclear [33]. However, the likely remoteness from medical help at altitudes would suggest caution should be advised for those on anti-coagulation therapy or with bleeding disorder

wishing to travel to these areas [34].

## Daily activities

Lifestyle changes such as increased or decreased activity can influence hormone balance and impact on oral anticoagulation with vitamin K antagonists. Changes in diet and alcohol consumption may also affect INR control.

Travellers with bleeding disorders and those on anticoagulation therapy are advised not to try out new activities which might result in injury, and therefore an increased risk of bleeding [6].

## Skin

Avoidance of injury is important and care with skin to prevent breakdown and bruising / bleeding in those with clotting disorders.

## Illness abroad

Travellers should know when and how to seek prompt medical advice. An important consideration is how a traveller might manage an episode of bleeding overseas, and where appropriate medical advice can be sought.

Travellers should keep any receipts for treatment and the travel insurance company should be informed as soon as possible. In European Union (EU) countries, travellers should carry a [European Health Insurance Card \(EHIC\)](#) or a [Global Health Insurance Card \(GHIC\)](#), as this will allow access to state-provided healthcare in some countries at a reduced cost, or for free. The [GOV.UK](#) website should be checked for updates and advice. The EHIC or GHIC however, is not an alternative to travel insurance.

## Resources

- [British Society for Haematology](#)
- [World Federation of Hemophilia](#)
- [Global Treatment Centre Directory for Haemophilia](#)
- [The Haemophilia Society](#)
- [Irish Haemophilia Society](#)
- [The ITP Support Association](#)
- [Lymphoma Action](#)
- [Thrombosis UK](#)

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