

COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT)

NICE guideline

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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 - How to use this guideline

Background

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is a syndrome that develops after a person has received a COVID-19 vaccination. VITT is also sometimes called vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or thrombotic thrombocytopenic syndrome (TTS).

Because VITT is a new condition, there is limited evidence available to inform clinical management. Identification and management of the condition is evolving quickly as the case definition becomes clearer.

This guideline was produced to support clinicians to diagnose and manage this newly-recognised syndrome. This guidance was adapted from the UK Expert Haematology Panel's guidance, which was hosted on the [British Society for Haematology's webpage](#).

We aim to update these recommendations frequently in line with new evidence or changes in practice and will produce new recommendations where gaps are identified. We search and screen the evidence weekly to produce living recommendations that reflect the latest best available evidence.

We have developed this guideline using our [methods and processes for guidelines developed during health and social care emergencies](#). For more details of the methods and processes used for this guideline, including details of the expert advisory panel members and declarations of interests, see the [methods and processes section](#).

Your responsibility

When using this guideline, follow the usual professional guidelines, standards and laws (including those on equalities, safeguarding, communication and mental capacity), as described in [making decisions using NICE guidelines](#).

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs,

preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian. All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

Using the guideline in MAGICapp

In MAGICapp, each recommendation is accompanied by layered supporting information. The supporting information presented differs depending on whether the recommendation was developed by consensus or evidence review.

At first publication, all the recommendations were developed by consensus because no evidence meeting the criteria in the evidence review protocols was identified. All recommendations are accompanied by a rationale and labelled as follows:

Consensus recommendation (Blue)

A consensus recommendation can be given for or against the intervention. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the panel still regards it as important to give a recommendation.

If sufficient evidence becomes available, additional supporting information will be added as follows:

Recommendation labels

Recommendation for (Green)

A strong recommendation is given when there is high-certainty evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

Recommendation against (Red)

A strong recommendation against the intervention is given when there is high-certainty evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional recommendation for (Yellow)

A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a substantial benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.

Conditional recommendation against (Orange)

A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but when this is not substantiated by strong evidence. This recommendation is also used when there is strong evidence of both beneficial and harmful effects, but when the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.

Supporting information

Research evidence

The overall effect estimates and references to the studies.

Certainty of the evidence

- **High:** We are very sure that the true effect is close to the estimated effect.
- **Moderate:** We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is statistically significantly different.

- **Low:** We have limited confidence in the estimated effect. The true effect may be statistically significantly different from the estimated effect.
- **Very low:** We have very little confidence in the estimated effect. The true effect is likely to be statistically significantly different from the estimated effect.

Evidence to decision

Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient preferences.

Rationale

Description of how the panel reached its decision.

Practical information

Practical information about the treatment and information on any special patient considerations.

References

Reference list for the recommendation.

2 - Introduction

VITT epidemiology

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is rare, with an incidence after first or unknown dose of COVID-19 vaccine of 14.2 per million doses. 419 cases of major thromboembolic events with concurrent thrombocytopenia were recorded in the [MHRA's weekly summary of Yellow Card reporting](#) (published 22 September 2021). Of these 419 cases, 150 had cerebral venous sinus thrombosis (CVST), making it the most common site of thrombosis. The remaining cases have affected a range of sites such as the splanchnic system, heart, lungs or limbs.

The natural history of VITT is still not well understood, with little published evidence available. Therefore, timescales for monitoring and stopping treatment for VITT are not definitive.

Scope and purpose

This guideline is for health and care practitioners, and those involved in planning and delivering services. It provides guidance on diagnosing and managing VITT. The guideline makes recommendations about care in all settings for adults with suspected or confirmed VITT.

Key questions

This section lists the key questions that the guideline addresses. These are a broad set of overarching review questions. Through our living approach, we will review the scope, and, where needed, develop more detailed and additional review questions to address gaps in content.

Case definition

What is the timeframe between receiving a COVID-19 vaccine and symptom onset?

What signs and symptoms are indicative of VITT, and need further clinical review and investigation?

Identifying and diagnosing VITT

What investigations or tests should be carried out, and when, to determine a probable or definite diagnosis of VITT?

Managing and treating VITT

What is the clinical effectiveness and safety of pharmacological and non-pharmacological treatments for VITT?

What monitoring should be used to assess deterioration or recovery in people with VITT?

Information and support needs of patients

What are the information and support needs of people with VITT?

Acknowledgement

This work was done by NICE. The views expressed in this publication are those of the authors.

3 - Identifying suspected VITT

Consensus recommendation

For people presenting to primary care or emergency care, or contacting NHS 111 with new or ongoing symptoms within 5 to 30 days of having had a COVID-19 vaccination, follow the advice from Public Health England on:

- recognising signs and symptoms of thrombocytopenia or thrombosis
- what to do if you suspect a case (this covers referral and reporting).

The signs and symptoms listed by Public Health England (accessed 06 July 2021) are as follows:

- new onset of severe headache, which is getting worse and does not respond to simple painkillers
- an unusual headache which seems worse when lying down or bending over, or may be accompanied by blurred vision, nausea and vomiting, difficulty with speech, weakness, drowsiness or seizures
- new unexplained pinprick bruising or bleeding
- shortness of breath, chest pain, leg swelling or persistent abdominal pain.

Rationale

The panel discussed the advice published by Public Health England on symptoms, referral and reporting was helpful, and agreed that it should be linked to from the guidance and the list of symptoms reproduced for ease of use.

In the panel's experience, symptoms are likely to develop slightly later than reported by Public Health England, so the period of time specified in the recommendation is based on consensus.

4 - Investigations and diagnosis

Consensus recommendation

When assessing people with suspected VITT, ask about their vaccination history, take into account their overall clinical condition, and:

- refer people who are acutely unwell to the emergency department immediately, or
- perform initial tests (full blood count) in primary care if:
 - the person is not acutely unwell, and
 - same day test results can be obtained, and if they show thrombocytopenia, the person can be referred to the emergency department immediately.

Rationale

The panel agreed that urgent referral was needed for people who are acutely unwell, because VITT is a potentially life-threatening condition and prompt treatment is important. However, VITT remains rare, meaning that initial assessments need to balance the risk of missing a case against the possibility of conducting unnecessary investigations.

The panel discussed the possibility of over-referral, which could potentially lead to exceeding the capacity of emergency departments. However, the panel broadly agreed that people with symptoms of suspected VITT often present to the most appropriate service anyway (that is, people presenting in primary care tend to be less acutely unwell, and people who are acutely unwell tend to present to emergency care), so the risk of over-referral may be minimal.

The panel noted that rapid turnaround testing for thrombocytopenia in primary care, if available, could help to avoid unnecessary referrals to emergency departments. However, if blood tests showed thrombocytopenia, the panel agreed that same-day referral to secondary care for further investigations was appropriate.

4.1 - Initial investigations

Consensus recommendation

If not already done in primary care, perform a full blood count to look for evidence of thrombocytopenia in people with suspected VITT.

Rationale

The panel noted that when a person presents with suspected VITT, they would first look for evidence of thrombocytopenia.

A full blood count was noted to be a standard part of clinical assessment in emergency care and widely available in primary care, although the time for results to return may vary across primary care services.

Consensus recommendation

If the full blood count confirms thrombocytopenia, or a strong clinical suspicion of VITT remains, do the following tests in secondary care:

- a coagulation screen, including Clauss fibrinogen assay and D-dimer measurement
- a blood film to confirm true thrombocytopenia and identify potential alternative diagnoses.

Possible causes of thrombocytopenia with thrombosis other than VITT include cancer, antiphospholipid syndrome, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura and paroxysmal nocturnal haemoglobinuria.

Rationale

The panel noted that once thrombocytopenia is confirmed, or a strong clinical suspicion of VITT remains, further tests become helpful. For example, as many conditions are associated with high D-dimer results, D-dimer was thought to not be specific enough as an initial test. However, high D-dimer accompanied by thrombocytopenia was thought to be suggestive of VITT.

Other factors such as normal prothrombin and activated partial thromboplastin levels and the fibrinogen level were thought to add to the overall clinical picture.

When making a diagnosis of VITT, take into account that:

VITT is probable in people with:

- thrombosis and thrombocytopenia with very high D-dimer and low or normal fibrinogen, or
- thrombosis and thrombocytopenia with high D-dimer and low or normal fibrinogen and strong clinical suspicion

VITT is unlikely in people with:

- no thrombocytopenia
- thrombocytopenia without thrombosis, and D-dimer at or near normal and normal fibrinogen, or
- thrombosis without thrombocytopenia, and D-dimer that is raised (but not the high and very high levels seen in VITT) and normal fibrinogen.

See the practical information tab for thresholds for platelets, D-dimer and fibrinogen.

Practical info

The thresholds listed below are based on expected values in a healthy adult. Factors such as pregnancy and illnesses other than VITT may change the expected values. There may also be differences in the reference ranges used by individual laboratories. FEU = fibrinogen-equivalent units, DDU = D-dimer units.

Thresholds for platelet count

Normal = 150×10^9 /litre or higher

Thrombocytopenia = less than 150×10^9 /litre

Thresholds for D-dimer

Very high = more than 4000 microgram/litre FEU or DDU [1]

High = more than 2000 microgram/litre up to 4000 microgram/litre FEU or DDU [1]

4000 microgram/litre is equivalent to 4 microgram/millilitre

Thresholds for fibrinogen

Normal = 2 to 4 g/litre

Low = less than 2 g/litre

4.2 - Further care when VITT is unlikely

Consensus recommendation

For people whose blood tests indicate it is unlikely they have VITT:

- think about alternative diagnoses and manage in line with the relevant NICE guideline, for example:
 - [diagnosis and management of venous thromboembolic diseases](#)
 - [diagnosis and management of headaches](#)
- tell them that it is unlikely they have VITT. Discuss the signs and symptoms of VITT, and when and where to seek further medical attention if their symptoms persist or worsen.

If a high clinical suspicion of VITT remains, consider:

- repeating the full blood count after 2 to 3 days or if symptoms worsen, or
- discuss the need for further investigations with a clinical haematologist.

The expert advisory panel noted that, in their experience, an estimated 5% of people with VITT did not have thrombocytopenia at presentation. Therefore, if thrombocytopenia is not seen but a strong clinical suspicion of VITT remains, a repeat platelet count may be justified.

Rationale

The panel agreed that if VITT was unlikely, it was important to investigate possible thrombosis (as indicated by the person's signs and symptoms at presentation), or think about alternative causes of the person's symptoms.

The panel acknowledged that most cases of acute thrombosis are unlikely to be associated with VITT, even in the context of a relevant vaccination history. However, the panel acknowledged that if a person's symptoms worsen they should seek further medical advice.

Further investigation for VITT may sometimes be prudent because some people with confirmed VITT do not have thrombocytopenia when they first seek medical attention, but it develops later. The panel agreed that it was important for clinicians to recognise that an initial normal platelet count would not fully exclude VITT. However, they appreciated the need to balance avoiding missing cases against the small number of people who may have VITT but no thrombocytopenia at initial testing.

4.3 - Further investigations for probable VITT

Consensus recommendation

For people with a high clinical suspicion of VITT, perform same-day imaging based on location of symptoms to confirm the site of thrombosis before starting treatment.

VITT is associated with both arterial and venous thrombosis in a variety of sites, and this should be taken into account when deciding on the imaging to detect thrombosis.

Examples of suitable imaging include:

- head CT venogram or magnetic resonance angiography to look for cerebral venous sinus thrombosis (CVST), because plain head CT may not detect CVST
- abdominal ultrasound or CT, looking for portal or splanchnic vein thrombosis
- CT pulmonary angiography or ventilation/perfusion scanning
- duplex compression ultrasonography, looking for deep vein thrombosis in the lower or upper limbs.

CT imaging is superior to ultrasound, and should be used if there is a clinical suspicion of splanchnic vein thrombosis.

Rationale

The panel discussed the need for imaging, and agreed that it should be based on the location of symptoms because of the range of sites they have seen affected by VITT. This includes CVST, portal or splanchnic vein thrombosis, pulmonary embolism, deep vein thrombosis of limbs, and arterial thrombosis including myocardial infarction and stroke. People with VITT often have thrombosis at multiple sites, including asymptomatic thrombosis of the portal or splanchnic veins. This means a low threshold for considering abdominal imaging is justified, particularly for people with CVST.

The panel noted that the urgency of imaging would be based on clinical need, so people might have imaging before their blood test results had returned.

Consensus recommendation

For people whose blood tests suggest probable VITT, but no thrombosis is seen on initial imaging or there is clinical or laboratory suspicion of progression, discuss the need for repeat imaging in a multidisciplinary team.

The multidisciplinary team should include a consultant clinical haematologist with specialist knowledge of VITT, and clinicians with expertise relevant to the site of thrombosis.

Rationale

The panel noted that further imaging may be needed for people with a diagnosis of probable VITT who did not have thrombosis detected on initial imaging. The panel agreed that the need for further imaging is usually decided by a multidisciplinary team.

Consensus recommendation

For all people with probable VITT, use an enzyme-linked immunosorbent assay (ELISA) for platelet factor 4 antibodies to confirm the diagnosis.

Start treatment, in consultation with a clinical haematologist, without waiting for ELISA results.

Vaccine-induced thrombosis and thrombocytopenia has similarities to heparin-induced thrombocytopenia. In both conditions, people have antibodies to platelet factor 4, but people with VITT have not had heparin treatment in the past 3 to 6 months. These antibodies are reliably detected by ELISA. Other testing kits for heparin-induced thrombocytopenia have been noted to show false-negative results in VITT, so should not be used.

See [reporting cases](#) for further information on national testing services and reporting requirements in the UK.

Rationale

The panel discussed the use of ELISA for platelet factor 4 antibodies to confirm a diagnosis of VITT. Generally these tests need to be sent off-site for analysis, so results take 1 to 2 days to return. The

panel indicated that it was justifiable to begin treatment while awaiting the results of this test.

Consensus recommendation

If ELISA results are negative for a person with probable VITT:

take this information into account alongside all previous test results and the person's symptoms

think about other possible diagnoses, and whether to repeat the ELISA using a different type of assay

discuss whether continuing treatment for VITT is appropriate in a multidisciplinary team.

Rationale

The panel noted that although ELISA was generally thought to be accurate, false negative results remained a possibility. Therefore, a person meeting all the criteria for VITT whose ELISA result was negative may still be suspected to have VITT. A view of the full clinical picture was thought to be important in deciding whether other diagnoses should be looked into at this point.

5 - Management

5.1 - Person-centred care

Consensus recommendation

Explain to the person and their family members or carers, if appropriate, what a diagnosis of VITT means. Discuss treatments and possible outcomes, be prepared to answer any questions they might have about their care, and take into account their concerns.

Involve a clinical haematologist when making decisions about starting and adding treatments.

See the [NICE guideline on shared decision making](#) for information on communicating risks, benefits and consequences when making decisions about treatment and care.

The UK Expert Haematology Panel has produced a [patient information leaflet about vaccine-induced thrombosis and thrombocytopenia](#), which is available on the British Society for Haematology's website.

Thrombosis UK has produced [patient information and support for people with VITT](#).

Rationale

The panel noted the importance of good communication between healthcare professionals and people with VITT and their families and carers. This was thought to be particularly important for people who had experienced serious complications of vaccination.

5.2 - Managing thrombosis

5.2.1 - Anticoagulants

Consensus recommendation

Start anticoagulation treatment for people with VITT, including those who have only had arterial thrombosis, as soon as the benefit outweighs the risk of bleeding.

Review the person's response to anticoagulation if the person's clinical condition changes, and

adjust treatment if needed.

See the recommendation on [reviewing the need for ongoing treatments](#) for information on stopping anticoagulation.

Rationale

The panel agreed that drug treatment for thrombosis is a fundamental part of management for VITT. They were also aware that VITT has two opposing effects on haemostasis, namely that low platelets increases the risk of bleeding, but the platelet and coagulation activation caused by the VITT immune response is a risk factor for thrombosis. These risks need to be balanced when starting anticoagulant treatment. Arterial thrombosis is expected to be managed along standard pathways of care that could include surgery or stenting, but the nature of VITT as a systemic prothrombotic condition means that systemic anticoagulation will also be needed.

The panel also recognised the need to review anticoagulation needs if the person's clinical condition changes.

Consensus recommendation

Use non-heparin drugs for anticoagulation treatment for VITT, for example:

- direct oral anticoagulants
- fondaparinux
- danaparoid sodium
- argatroban.

When using argatroban as an anticoagulation treatment for people with VITT, switch to fondaparinux or a direct oral anticoagulant as soon as the bleeding risk has reduced.

Avoid using heparins, including heparin flushing solution in people with VITT. Avoid using warfarin in people with VITT until platelet count has returned to normal. Avoid using warfarin and direct oral anticoagulants in pregnant women.

In July 2021, the use of argatroban for VITT was an off-label use of this anticoagulant. See [NICE's information on prescribing medicines](#).

In July 2021, the marketing authorisation for the direct oral anticoagulants edoxaban or dabigatran specified the need for 5 days of parenteral anticoagulation before starting these treatments. Starting edoxaban or dabigatran without first completing 5 days of parenteral anticoagulation would therefore be an off-label use of these anticoagulants. See [NICE's information on prescribing medicines](#).

Additional considerations for argatroban use

Argatroban can be given as an infusion and has a relatively short half-life, which is useful for people with a higher risk of bleeding or who may need surgical interventions.

Argatroban monitoring results may not accurately represent anticoagulation levels.

Clauss fibrinogen assays may give falsely low results during argatroban use. Assays using high concentrations of thrombin (100 NIH units/ml) may be more accurate.

Rationale

The panel discussed that VITT has similarities to heparin-induced thrombocytopenia. It is not yet known whether heparin exacerbates the condition, but until further evidence is available they concluded that avoiding using heparins was a sensible approach. Similarly, because warfarin is avoided in people with heparin-induced thrombocytopenia, the panel agreed it should also be avoided in VITT - particularly while the person's platelet count remains low.

The panel recognised that, while there was currently no evidence for or against avoiding heparin and warfarin, it was reasonable to recommend the alternative drugs that are available instead to avoid any potential harm from them until more information is available.

Consensus recommendation

If surgery to treat the thrombosis is not planned, switch to oral anticoagulation with direct oral anticoagulants as soon as the person's clinical condition and platelet level allows. Continue the same anticoagulation treatment after discharge.

Rationale

The panel agreed that administering anticoagulation intravenously or subcutaneously may be necessary during acute treatment. However, once the person's clinical condition is stable, their

platelet counts have increased and they can take oral medicines, it was thought to be reasonable to switch.

Consensus recommendation

For people with VITT without confirmed thrombosis, but who have thrombocytopenia with very high D-dimer and a positive ELISA for platelet factor 4 antibodies, consider venous thromboembolism (VTE) thromboprophylaxis after taking into account the benefits and risks of treatment. Use non-heparin drugs such as direct oral anticoagulants, fondaparinux, or danaparoid sodium, and regularly reassess whether the benefits of thromboprophylaxis still outweigh the risks throughout treatment.

In July 2021, the use of direct oral anticoagulants or danaparoid for venous thromboembolism prophylaxis in VITT was an off-label use of these anticoagulants. See [NICE's information on prescribing medicines](#).

See further information on:

- [thresholds for blood test values](#)
- [additional considerations for argatroban use and](#)
- [reviewing the need for ongoing treatments](#).

Rationale

The panel agreed that considering VTE thromboprophylaxis is appropriate in people who have VITT but have not had a confirmed thrombosis, because people with a laboratory-confirmed VITT immune response have a high likelihood of developing thrombosis.

The panel noted that the dose and duration of anticoagulation treatment for VITT is not yet understood, so they recommended the risks and benefits of VTE thromboprophylaxis be taken into account before starting and throughout treatment. The panel noted that VTE thromboprophylaxis was expected to be needed until platelet factor 4 antibodies were no longer detected and blood test results had normalised, which may be at least 3 months.

5.2.2 - Additional considerations for treating thrombosis

Consensus recommendation

For people with VITT, consider fibrinogen replacement therapy with fibrinogen concentrate or cryoprecipitate to maintain a level of fibrinogen of at least 1.5 g/litre.

In July 2021, the use of fibrinogen replacement for VITT was an off-label use of this treatment. See [NICE's information on prescribing medicines](#).

Rationale

Low fibrinogen is a risk factor for bleeding, so the panel agreed that fibrinogen replacement therapy may be warranted in addition to anticoagulation to balance the overall risks of thrombosis and bleeding. This is because anticoagulation is a fundamental part of VITT treatment, but also increases the risk of bleeding.

Consensus recommendation

Discuss the need for transfer to specialist care, including for surgical interventions, with relevant specialists based on the location of the thrombosis. Take into account the person's clinical condition when determining the urgency of any transfer.

If the person has CVST:

- be aware that some people with CVST caused by VITT experience rapid deterioration after appearing clinically well
- consider pre-emptive transfer to a centre with neuroscience services, even if the person is still clinically well.

Rationale.

The panel agreed that specialist management of thrombosis (including surgery) would follow the standard care pathways, and that specialist management would differ depending on the location of the thrombosis and person's clinical condition.

However, the panel's experience suggested that people with CVST caused by VITT had much higher mortality than seen in CVST that is not related to VITT. Additionally, these patients could deteriorate quickly even if they appeared clinically well. Therefore, the panel thought that early transfer for people with CVST to a centre that had neuroscience services available is appropriate. This would enable urgent treatment if rapid deterioration occurred.

Consensus recommendation

For people with VITT who need surgery to treat the thrombosis and who are at higher risk of bleeding because of low platelets or low fibrinogen, give platelet transfusion or fibrinogen replacement.

Some people with VITT may have already had fibrinogen replacement treatment to reduce their risk of bleeding, as specified in the [recommendation to consider fibrinogen replacement](#) in people with low fibrinogen. However, because surgery creates a source of bleeding fibrinogen replacement is important in the period before surgery, and the need for this should be determined by the person's presurgical fibrinogen levels.

Rationale

The panel agreed that improving platelet and fibrinogen levels in people who needed surgery was a suitable approach to reducing the risk of bleeding associated with surgery. Surgery creates a source of bleeding, which fundamentally changes the bleeding risk compared with people with VITT who do not need surgery. Therefore, the panel made a stronger recommendation for people who have VITT and need surgery (give fibrinogen replacement) than for people with VITT who have low fibrinogen but may not need surgery (consider fibrinogen replacement).

The panel decided not to include specific targets for platelet and fibrinogen levels as they agreed any improvement in bleeding risk was beneficial, and that surgery should not be delayed solely because a target level had not been met.

Consensus recommendation

For people with VITT who have a very low platelet count (under 30×10^9 /litre), consider one of the following alternative anticoagulation strategies that may reduce the risk of bleeding:

- a critical illness dose of argatroban, or
- a therapeutic dose of argatroban, plus platelet transfusion.

Take into account the risks and benefits of each option in relation to the person's clinical condition, and the person's preferences.

Information about the critical illness dose of argatroban can be found in the summary of product characteristics.

In July 2021, the use of argatroban for VITT was an off-label use of this anticoagulant. See [NICE's information on prescribing medicines](#).

See the information on [additional considerations for argatroban use](#).

Rationale

The panel discussed the need to adjust anticoagulation for people with VITT who have a very low platelet count because of a substantially increased risk of bleeding.

They acknowledged that there was no evidence to help clinicians to choose between the two possible options. The lower critical illness dose of argatroban may not sufficiently treat thrombosis, but not enough is currently known about the natural history of VITT to know whether platelet transfusion could lead to further immune thrombosis. Therefore, the risks and benefits need to be considered for every person with VITT before choosing a treatment option, if any.

5.3 - Managing the VITT immune response

5.3.1 - Initial treatment

Consensus recommendation

Give intravenous immunoglobulin immediately at a dose of 1 g/kg to people with a clinical diagnosis of probable VITT.

If there is inadequate response to treatment after 2 to 3 days (that is, no improvement in blood tests, or developing progressive thrombosis or thrombosis at a new site), consider a second dose of intravenous immunoglobulin or [adding further treatments](#).

The dose of intravenous immunoglobulin may be split over 2 days.

In July 2021, the use of intravenous immunoglobulin for VITT was an off-label use of this treatment. See [NICE's information on prescribing medicines](#).

Rationale

The panel acknowledged the absence of an evidence base for managing the VITT immune response. Intravenous immunoglobulin is understood to be the treatment most likely to influence the disease

process based on expert consensus, although there is no evidence on whether it is better or worse than plasma exchange. Therefore, intravenous immunoglobulin was agreed to be the first treatment for most people with VITT. Involving clinical haematologists in discussions about starting and adding treatments was agreed to be appropriate in these circumstances.

The panel discussed whether subcutaneous immunoglobulin was a possible treatment option, but they decided that it took too long to act compared with intravenous administration, so was unlikely to be suitable.

5.3.2 - Further treatments

Consensus recommendation

Consider adding corticosteroids if intravenous immunoglobulin treatment is insufficient (that is, if there is progression of thrombosis or the platelet count does not rise to an acceptable level).

See the [recommendation on intravenous immunoglobulin treatment](#) for information on assessing response to this treatment.

Short courses of high-dose steroids, such as methylprednisolone 1 g for 3 days or dexamethasone 20 to 40 mg for 4 days, have been used in more severe cases. Oral or intravenous administration may be appropriate depending on the person's clinical condition.

Rationale

The panel acknowledged that the effectiveness of corticosteroids for treating the VITT immune response is unknown. However, corticosteroids are commonly used to treat immune disorders. The autoimmune nature of the condition means it is appropriate to consider adding corticosteroids if the response to initial treatment is insufficient.

The panel provided examples of doses that they had seen used in practice when treating VITT.

Consensus recommendation

Consider plasma exchange with fresh frozen plasma (1 volume exchange a day) as an alternative to a second dose of intravenous immunoglobulin.

Plasma exchange may be needed daily for up to 5 days, or until platelets recover.

Rationale

The panel acknowledged the absence of evidence on the effectiveness of plasma exchange in treating the VITT immune response. Plasma exchange may be more effective at reducing the immune response than intravenous immunoglobulin, but as it is much more invasive and not as widely available it was not regarded as suitable as a first-line approach to treating the VITT immune response.

However, when a second dose of immunoglobulin is needed, considering plasma exchange as an alternative treatment becomes appropriate. This is because if the second dose of immunoglobulin is also insufficient, and plasma exchange is subsequently used, the second dose of immunoglobulin will be exchanged out of the person's plasma. This would result in a wasted dose of immunoglobulin, which the panel agreed would be prudent to avoid.

Consensus recommendation

Consider rituximab for people with VITT that has not responded to a second dose of intravenous immunoglobulin or plasma exchange.

Prescribe rituximab in line with its summary of product characteristics guidance and noting contraindications.

The dosage of rituximab used for people with VITT is 4 infusions of 375 mg/m² of body surface area (the licensed dose for cancer indications). Infusions of rituximab are given once a week for 4 weeks. In July 2021, the use of rituximab for VITT was an off-label use of this medicine. Rituximab is not recommended for pregnant women. See [NICE's information on prescribing medicines](#).

Rationale

Although there is no evidence on using rituximab to treat the VITT immune response, it has been used as an off-label treatment in other autoimmune conditions such as immune (idiopathic) thrombocytopenic purpura.

The panel therefore agreed that it would be appropriate to use rituximab when other treatments for VITT are ineffective. The panel's consensus was that when rituximab is used for treating VITT, the dosage used should be the same as the licensed dosage for cancer indications (4 infusions of 375 mg/m² of body surface area).

5.3.3 - Intensive treatment for people with signs of poor prognosis

Consensus recommendation

For people with VITT who have signs of poor prognosis, consider an intensive treatment strategy of plasma exchange and high-dose steroids.

Signs of poor prognosis in people with VITT include any of the following:

- having CVST
- having thrombosis at multiple sites
- developing secondary bleeding
- having very low platelet levels (less than 30×10^9 /litre).

Rationale

The panel identified some characteristics of VITT that were associated with poor prognosis, and noted that they justified an early intensive approach to treatment rather than waiting to see if the response to immunoglobulin was sufficient.

6 - Ongoing management

6.1 - Patient-centred care

Consensus recommendation

Before discharge from hospital, discuss follow-up and what to do if symptoms get worse after discharge with people with VITT and their families and carers, as appropriate. Also provide them with information on these topics to take away.

Give people with VITT details of support resources such as [Thrombosis UK](#).

See the [NICE guideline on shared decision making](#) for information on communicating risks, benefits and consequences when making decisions about treatment and care.

Rationale

The panel recognised that people with VITT, and their families or carers, would need additional information to help them understand what happens after discharge from hospital, in particular because the nature of VITT means that ongoing care and monitoring is necessary.

Consensus recommendation

Consider referral for psychological support for people who have, or have had, VITT. Take into account that family members and carers of people with VITT may also benefit from psychological support, particularly if the person has been seriously ill, and give them information on available support services.

Thrombosis UK has produced [patient information and support for people with VITT](#).

Rationale

The panel highlighted that people with VITT may have need of psychological support, even if they did not have clinically-diagnosed anxiety or post-traumatic stress disorder. VITT is a disorder that only occurs in the context of vaccination, which people have to protect their health and that of the population. In the panel's experience, VITT mainly affects people who are previously fit and healthy,

but now have an ongoing potentially life-threatening medical condition. People with VITT may therefore have lost confidence in vaccination, which is a notable psychological challenge to be addressed.

The panel noted that people with VITT may have differing levels of support needs and that this may be related to the severity of their condition. Post-intensive care syndrome is a recognised condition, meaning that people with VITT who need treatment in intensive care may have higher psychological support needs than other people with VITT. However, some people with VITT may have their psychological needs met by good communication and information provision, particularly when interacting with primary care services.

The panel's experience indicated that psychological support services were not always made available to people with VITT. The panel agreed that making a recommendation about psychological support was important to improve practice in this area. The psychological needs of family members and carers of people with VITT were also recognised as important by the panel.

6.2 - Monitoring response and treating relapse

Consensus recommendation

After discharge from hospital, keep the person under the care of the haematology department, and assess symptoms and monitor as follows:

- measure D-dimer, fibrinogen and platelet counts every 2 to 3 days for the first 2 weeks
- repeat ELISA for platelet factor 4 antibodies weekly for the first 4 weeks
- after the initial periods noted above, repeat monitoring tests monthly for the first 6 months and, if no relapses occur, reduce the frequency of testing to every 3 months.

When platelet 4 antibodies are no longer detected, review the need for ongoing treatment and monitoring.

Monitoring of platelet factor 4 antibodies is done by secondary care services.

Monitoring of D-dimer, fibrinogen and platelets is generally done in secondary care, but blood tests could be done in primary care. If the person with VITT prefers monitoring in primary care, ensure that both the person's GP and their local haematology service are aware that the person's haematology department are responsible for interpreting blood test results and making treatment

decisions.

Rationale

The panel discussed that the natural history of VITT is still not well understood, with little published evidence available, so based the recommendations on monitoring on their experience of treating people with VITT.

They noted that relapses after initial response to treatment can happen quickly, meaning that intensive monitoring is advisable in the first weeks after diagnosis.

Most people with VITT continue to have platelet factor 4 antibodies after discharge from hospital, and the panel expected that monitoring would need to continue until these antibodies were no longer detected. If no relapses were detected after 6 months, the panel agreed that reducing the frequency of monitoring to every 3 months would be justified.

The panel discussed the need for monitoring to be managed by clinical haematologists. It was acknowledged that some people with VITT might not be able to attend hospital for all monitoring. In these circumstances, blood samples could be taken in primary care but the responsibility for interpreting those results and making treatment decisions would remain with the haematology department.

Consensus recommendation

When reviewing the need for ongoing treatments based on the results of monitoring tests:

- if the person is taking corticosteroids and a decision is made to stop this treatment, ensure that the dose is tapered down
- continue anticoagulation for at least 3 months, or until platelet factor 4 antibodies are no longer detected. If anticoagulation needs to be stopped sooner, discuss the risks and benefits of stopping treatment with a clinical haematologist and the person with VITT

See the [NICE guideline on shared decision making](#) for information on communicating risks, benefits and consequences when making decisions about treatment and care.

Rationale

The panel acknowledged the difficulties in making recommendations about stopping treatment

because evidence was extremely limited.

The panel agreed that tapering down corticosteroid dosing to reduce withdrawal effects was thought to represent good practice.

The panel considered that theoretically, it may be safe to stop anticoagulation when the person does not have thrombocytopenia and platelet factor 4 antibodies are no longer detectable. However, in practice, as of July 2021 most patients have not reached the point at which stopping anticoagulation may be appropriate. Therefore, decisions about stopping anticoagulation need to take account of the risks and benefits, with advice from a clinical haematologist.

Consensus recommendation

For people who had coronary artery thrombosis or arterial thrombosis in vessels without atherosclerosis, and no evidence of venous thrombosis:

- continue anticoagulation for at least 1 month, and consider adding antiplatelet agents
- if normal fibrinogen, D-dimer and platelet levels are maintained after 1 month, consider stopping anticoagulation and switching to antiplatelet agents only, and discuss the risks and benefits of this approach with a clinical haematologist and the person with VITT.

See the [NICE guideline on shared decision making](#) for information on communicating risks, benefits and consequences when making decisions about treatment and care.

Rationale

The panel highlighted that the lack of evidence was a problem for understanding ongoing management in people with VITT who had arterial thromboses only.

Arterial thrombosis would not normally be treated with anticoagulation, although the systemic nature of VITT means that an initial period of anticoagulation is justified. Therefore, decisions to switch to antiplatelet agents need to take account of risks and benefits, with advice from a clinical haematologist.

Consensus recommendation

Consider a further course of oral corticosteroids, rituximab, or intravenous immunoglobulin if relapse is detected. That is, if:

- platelet levels drop substantially from the previous measurement, or
- new thrombosis occurs despite therapeutic anticoagulation.

Rationale

The panel discussed that a drop in platelet levels was a key sign of possible relapse. The panel decided not to give absolute values for a reduction in platelet levels that might raise concern, as they agreed that any clear drop in platelets from their previous value was a reason for concern. Similarly, they concluded that the platelet level after the drop does not need to meet the definition of thrombocytopenia before considering further treatment.

The panel also wished to highlight that any new thrombosis is also thought to be a sign of relapse.

The panel noted that there was no evidence to provide guidance on the preferred treatment or order of treatments for relapse when making this recommendation.

7 - Reporting cases

Consensus recommendation

Clearly record the eventual diagnosis in the person's medical notes and in their hospital discharge summary. Code the diagnosis appropriately, using clinical coding for the types of thrombosis identified, and record any immunoglobulin use on the [national immunoglobulin database](#).

Follow reporting procedures for all probable, confirmed, and relapsed cases, including:

- the [MHRA's COVID-19 Yellow Card scheme](#)
- the UK Expert Haematology Panel and [Public Health England's clinical reporting scheme](#).

See practical info for information on coding VITT.

Rationale

The panel recognised the need to follow national procedures for reporting cases of VITT. The Yellow Card scheme is important for monitoring safety issues, and data captured could lead to regulatory changes for relevant vaccines or treatments for VITT. Such changes could then drive future updates to the recommendations on diagnosis and management of VITT.

They also agreed that because VITT is a rare and emerging condition, it might prove difficult to conduct randomised controlled trials to inform future recommendations on treatment. Therefore, it was recognised as important to ensure that VITT was recorded clearly in medical records to ensure any future research based on analysis of real world data sources would be as accurate as possible.

Practical info

When coding, use the primary code for the condition followed by 'U07.7 COVID-19 vaccines causing adverse effects in therapeutic use'.

8 - Further vaccination

Consensus recommendation

For people who have had suspected or confirmed VITT, follow advice on further COVID-19 vaccination in the [Green book \(chapter 14a\)](#).

Rationale

The panel recognised the need to follow national guidance on subsequent vaccination for people with VITT.

9 - Equality considerations

9.1 - Equalities impact assessment during scoping

Is the proposed primary focus of the guideline a population with a specific communication or engagement need, related to disability, age or other equality consideration?

No

Have any potential equality issues been identified during the check for an update or during development of the draft scope and, if so, what are they?

Exacerbating inequalities

There is potential for recommendations to exacerbate inequalities, if individual circumstances are not acknowledged. Protected characteristics and assumptions about individual circumstances need to be considered:

Sex

None identified.

Age

The risk of VITT appears to be higher in younger age groups. However, national advice on choice of vaccination should reduce this risk.

Ethnicity

None identified.

Disability

Some people with disabilities may have communication needs that need to be considered for example:

- face masks worn by staff may impair communication with people who have hearing loss, autism, or dementia.
- when providing information about VITT at diagnosis and after discharge.

Socioeconomic factors

None identified.

Gender reassignment

None identified.

Pregnancy and maternity

Pregnant women may be at higher risk of VITT; however national advice on choice of vaccination should have reduced the number of pregnant women having vaccinations associated with the highest risk of VITT.

Religion or belief

None identified.

Sexual orientation

None identified.

Other definable characteristics

Examples are:

- refugees
- asylum seekers
- migrant workers
- people who are homeless.

People with these characteristics may have reduced access to vaccination services, which would

reduce their risk of VITT. However, after vaccination they may be less likely to engage with health care services which could increase the risk of poor outcomes from VITT. People who are homeless may be disadvantaged because the condition needs ongoing treatment and follow-up, which may be more difficult for a person who does not have a permanent address.

What is the preliminary view on the extent to which these potential equality issues need addressing by the panel?

Children and young people have been excluded from the scope.

Available vaccines are not licensed for use in children and the national COVID-19 vaccination strategy has not reached this age group. Since this guideline is being developed using a living approach, we can broaden the scope to include children when this becomes appropriate.

Although younger age in adults has been identified as a possible risk factor for VITT, we have not identified any areas to be addressed in the guideline that are likely to result in recommendations that would increase inequalities associated with age.

Pregnant women may be unable to have the same treatments as other adults or evidence for the safety of treatments may be absent, which may lead to poor outcomes from VITT.

The potential difficulties in communicating with people with disabilities when wearing face masks is a broad issue for care in a pandemic situation. Recognising and adapting to the differing communication needs of people with disabilities is also a broad issue that applies across all health and care services. We have not identified any issues in these areas that are unique to VITT.

The possibility that refugees, asylum seekers, migrant workers and people who are homeless may be less likely to engage with services is similarly a broad issue and we have not identified any issues unique to VITT.

9.2 - Equalities impact assessment during guideline development

Have the potential equality issues identified during the scoping process been addressed by the panel, and, if so, how?

In the scoping process, a range of potential equality issues were identified. These have been addressed as follows:

Age

At scoping it was highlighted that the risk of VITT may be higher in younger age groups, but national advice on choice of vaccination should have reduced the number of younger people having vaccinations associated with the highest risk of VITT.

None of the recommendations were considered to contribute to inequalities related to age.

Disability

Regarding communication and shared decision making, specific consideration may need to be given to people with a learning disability, people with physical impairments, people with cognitive impairment, and people with mental health issues. The recommendations cross refer to the [NICE guideline on shared decision making](#), which comprehensively addresses adapting communication and the approach to shared decision making to the person's needs. This guideline therefore did not replicate content on shared decision making. The guideline also recommends involving families and carers where appropriate to support discussions relating to care and shared decision making.

We state that this guideline should be used alongside usual professional guidelines, standards and laws (including equalities, safeguarding, communication and mental capacity).

Pregnancy and maternity

At scoping it was highlighted that pregnant women may be at higher risk of VITT; however national advice on choice of vaccination should have reduced the number of pregnant women having vaccinations associated with the highest risk of VITT.

The panel did not raise any further concerns about VITT in pregnant women or new mothers, which may reflect a successful vaccination strategy that avoids using vaccines with the highest risk of VITT in women of childbearing age.

Other definable characteristics

For people whose first language is not English, there may be communication difficulties, especially relating to shared decision making and minimising risk of infection. The recommendations cross refer to the [NICE guideline on shared decision making](#), which comprehensively addresses adapting communication and the approach to shared decision making to the person's needs. This guideline therefore did not replicate content on shared decision making.

People who are homeless, refugees, asylum seekers and migrant workers may be both less likely to receive vaccinations and may also experience difficulties in accessing services if they have an adverse reaction to the vaccine. No recommendations were made specifically for people who are homeless, refugees, asylum seekers and migrant workers.

Have any other potential equality issues (in addition to those identified during the scoping process) been identified, and, if so, how has the panel addressed them?

No new issues were identified.

Do the preliminary recommendations make it more difficult in practice for a specific group to access services compared with other groups? If so, what are the barriers to, or difficulties with, access for the specific group

No. None identified.

Is there potential for the preliminary recommendations to have an adverse impact on people with disabilities because of something that is a consequence of the disability?

No

Are there any recommendations or explanations that the panel could make to remove or alleviate barriers to, or difficulties with, access to services identified, or otherwise fulfil NICE's obligation to advance equality?

None identified.

10 - Methods and processes

Development

This guideline was developed using the methods and process in our [interim process and methods for guidelines developed in response to health and social care emergencies](#). This included convening an independent advisory expert panel, scoping, identifying and reviewing evidence, panel discussion of recommendations, targeted peer review with stakeholders and conducting an equalities impact assessment. A further detailed description of the specific methods used for this guideline is given below.

Advisory panel

NICE convened an expert advisory panel including representatives from relevant medical specialties with direct experience in treating VITT and people with lived experience of VITT. The panel included the following medical specialties – haematology, general practice and emergency medicine.

Expert advisory panel members and declarations of interest

Declarations of interest (DOI) were recorded according to the [2019 NICE conflicts of interest policy](#). For a list of panel members and corresponding DOI registry for this guideline see the [NICE guideline page on managing VITT](#).

Scope development

Nationally-recognised UK guidance (version 1.7) from the VITT Expert Haematology Panel (EHP) was used to develop the scope. This guidance included consensus recommendations covering diagnosis, management and reporting of VITT and was used to inform the key themes to be covered in the scope of the NICE guideline. Review questions were developed to address the themes outlined in the scope. The scope did not undergo external stakeholder consultation, due to the need to produce guidance promptly, but was reviewed and approved by the expert advisory panel. This guideline is developed using a living approach, which means that the scope will be reviewed as part of ongoing surveillance and updating, once published.

See the [introduction](#) for details about the scope of this guideline.

Equality impact assessment

The impact on equality was assessed during guidance development according to the principles of the NICE equality policy. Potential equality issues identified were discussed with the expert advisory panel to ensure they were addressed, if appropriate.

See [equalities considerations](#) for details about the equality impact assessment.

Structure of the guideline

The guideline structure follows the main themes and overarching questions set out in the scope. The EHP guidance on COVID-19 VITT was used to inform the initial structure of the content and subsections. The structure was designed to allow flexibility to refine, remove or add sections in future iterations in a living approach.

Reviewing the evidence

VITT is an emerging area – the syndrome was first recognised in March 2021. A search for evidence was undertaken on 28 May 2021, which identified 117 reports. Of these, 74 were considered to be potentially relevant to the guideline and were selected for further evaluation. For the search strategy see the [NICE guideline page on managing VITT](#). No relevant evidence was identified to address the review questions outlined in the scope, therefore an initial consensus-based approach informed by the panel's expert knowledge and experience was deemed to be suitable for developing recommendations. Although no studies were identified that could directly inform recommendations, 9 reports (8 case series and one review) were thought to support the panel's experiences and so were included as supporting references in the version of the guideline published on 29 July 2021.

Mapping of existing content

The EHP guidance on COVID-19 VITT was used as the starting point for developing recommendations. NICE extracted content from the EHP guidance on COVID-19 VITT relevant to the scope of this guideline. The content was added to the appropriate section in the draft structure of the new NICE guideline and adapted. The mapping of content was subject to NICE technical and clinical quality assurance and editorial input.

After the initial mapping, NICE presented the draft recommendations to the panel for discussion. The NICE expert advisory panel identified gaps in the guidance and any recommendations that should be revised. The panel were also asked whether any of the recommendations could be removed, if no longer relevant, due to recommendations being context specific or no longer relevant to current practice. Any changes to recommendation content were based on the consensus view of the expert advisory panel. The panel ratified the final recommendations.

The guideline thus represents the consensus view of the expert advisory panel informed by their experience of managing VITT and the theoretical risks and benefits of interventions.

Consideration of barriers to implementing the recommendations

The panel discussed potential barriers to implementing the recommendations. For example:

capacity issues associated with unnecessary referrals to the emergency department

capacity issues and practical considerations around decisions to transfer people with VITT to facilities for specialist care depending on the site of thrombosis and severity of the patients clinical condition.

No evidence was available to conduct formal analysis of the costs associated with any of the recommendations.

Some drug treatments recommended in the guideline were considered to be high cost. However, the overall costs associated with treating VITT may include hospital stay, imaging, and surgery on the thrombosis. Additionally, because the condition is rare, the costs were viewed as unlikely to have a substantial impact on the health care system.

Quality assurance and sign-off

Pragmatic checks and review were undertaken iteratively throughout guideline development by NICE staff with responsibility for quality assurance.

Final recommendations were ratified by the expert advisory panel and external stakeholders through a targeted peer review process. For the thematic summary of peer review comments and the actions taken see the [NICE guideline page on managing VITT](#).

NICE's Guidance Executive signed off the guideline before publication.

Future updates

We have also taken a living approach to identifying relevant published evidence or changes in practice that could impact on the recommendations to allow timely incorporation of new evidence in this area. This includes weekly searches for new published evidence on this topic and a search for ongoing studies. We will check for publication of these ongoing studies regularly. We will update the guideline when substantial new evidence becomes available.

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