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GUIDELINE

BSH Guideline

A British Society for Haematology guideline on the assessment and management of bleeding risk prior to invasive procedures

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biopsy, bleeding risk, coagulation tests, invasive procedure, pre-operative

METHODOLOGY

This guideline was compiled according to the British Society for Haematology (BSH) process at https://b-s-h.org.uk/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate the levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in Appendix.

REVIEW OF MANUSCRIPT

Manuscript review was completed by the BSH Guidelines Haemostasis and Thrombosis Task Force, BSH Guidelines Executive Committee and the Haemostasis and Thrombosis sounding board of the BSH. Further review was performed by the British Society of Interventional Radiology; these organisations do not necessarily approve or endorse the contents.

INTRODUCTION

This guidance update from the BSH is focussed primarily on non-surgical invasive procedures, simply termed 'procedures' in this document, with the primary objective of giving pragmatic advice where evidence is limited. This guidance also aims to reduce unnecessary laboratory testing, inappropriate use of blood products and unnecessary delays in therapeutic procedures.[1] It should be read in conjunction with the Interventional Radiology (IR) procedure bleeding risk guidance produced by the British Society of Interventional Radiology (BSIR) and the BSH.[2] Recommendations are predominantly based on evidence from adult patients and therefore may not be applicable to neonates or very young children. Figure 1 gives a recommended pathway for the preprocedure assessment of bleeding risk.

RECOMMENDATIONS

- Routine coagulation screening is not recommended prior to a procedure, as it does not indicate the bleeding risk nor does a normal screen exclude a bleeding disorder (1C).
- We suggest against the routine use of global haemostatic or platelet function testing to assess bleeding risk prior to a procedure (2C).
- Prior to elective procedures associated with a risk of bleeding, consider performing a structured bleeding history including the personal and family history of spontaneous or procedure-related bleeding (e.g. HEMSTOP) (2D).
- If the bleeding history is positive, then consider referral to a haematologist for further advice (2D).
- In patients taking antiplatelet agents and/or anticoagulants who also require a procedure, it is recommended that during patient consent the balance of risks between bleeding and thromboembolism is discussed (1B).
- We suggest that a decision about continuation or cessation of dual antiplatelet therapy (DAPT), prasugrel or ticagrelor medications prior to invasive procedures should be discussed with the patient's relevant specialist for the indication prior to a procedure (2C).

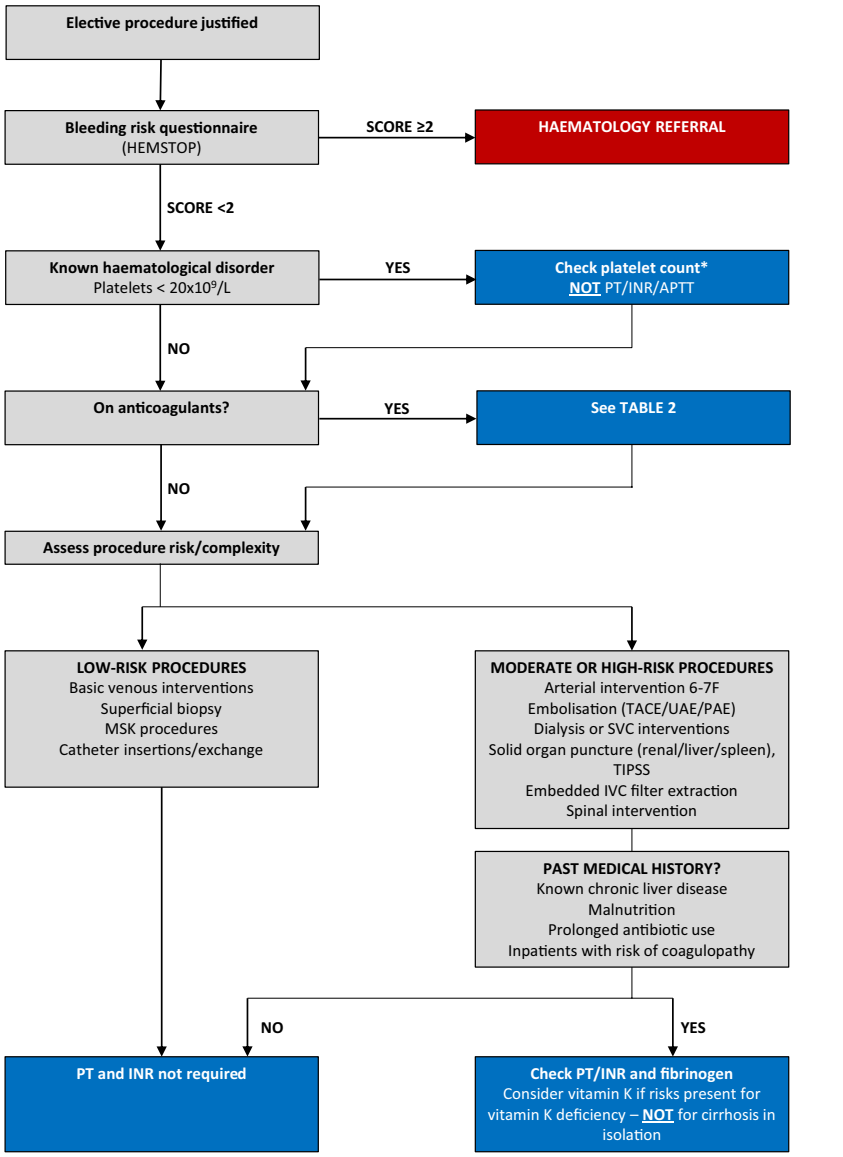

FIGURE 1 Bleeding risk assessment pathway for elective nonsurgical invasive procedures. APTT, activated partial thromboplastin time; CLD, chronic liver disease; IVC, inferior vena cava; INR, international normalised ratio; MSK, musculoskeletal; PAE, prostate artery embolisation; PCNL, percutaneous nephrolithotomy; PT, prothrombin time; PTC, percutaneous transhepatic cholangiogram; SVC, superior vena cava; TACE, transarterial chemoembolisation; TIPSS, transjugular intrahepatic portosystemic shunt; UAE, uterine artery embolisation.

- Testing of the platelet count is not recommended prior to low-risk procedures (e.g. paracentesis or central line insertion), unless there is a known haematological disorder where platelet count may be $<30\times10^9$/L (1C).
- We suggest against the routine testing of prothrombin time (PT)/international normalised ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and platelet count before low-risk procedures in patients with stable liver disease (e.g. therapeutic or diagnostic paracentesis) (2C).
- Consider performing a coagulation screen (PT/INR, APTT and fibrinogen) in patients undergoing a procedure with a high risk of bleeding and liver disease, malnutrition, prolonged antibiotic use and in patients with a risk of coagulopathy (e.g. *sepsis*/critical care patients) (2C).
- We recommend performing a preprocedure INR on patients on a vitamin K antagonist (VKA) (1C).
- Consider vitamin K replacement in patients with an increased INR, secondary to vitamin K deficiency, for example, cholestatic liver disease, malnutrition or prolonged antibiotic use (2D).
- Preprocedure vitamin K replacement is not recommended in individuals with cirrhosis without risk factors for vitamin K deficiency (1C).
- Routine use of fresh frozen plasma (FFP) or other replacement therapies to correct abnormal coagulation results is not recommended in patients undergoing a procedure (1C).
- We suggest against preprocedural testing of fibrinogen in non-critically ill patients (2C).
- We suggest aiming for a preprocedural fibrinogen level >1.0 g/L in critically ill patients undergoing a high-risk procedure (2C).
- The platelet count in isolation should not be used as a predictor of bleeding: The cause of thrombocytopenia, function of the platelets and patient and procedure-related risk of bleeding should be considered when deciding whether to give a prophylactic platelet transfusion (2C).
- A platelet transfusion can be considered in patients with a platelet count $<30\times10^9$/L requiring a tunnelled central venous catheter (1C).
- Thrombopoietin receptor agonists (TPO-RAs) can be considered for high-risk procedures in patients with liver disease, if the platelet count is $<50\times10^9$/L (2B).
- We suggest specialist input for patients with acute-on-chronic liver failure undergoing an essential procedure. Fibrinogen, platelet and other coagulation factor replacement can be considered on a case-by-case basis (2D).

PROCEDURAL RISK STRATIFICATION

Published guidance ranges from stratifying procedure risk into either three tiers—low, moderate and high risk—or a more simplified dichotomy between high and low risk. Due to differences in required haematological tests between low and moderate/high risk procedures, this guideline has used a two-tier approach for bleeding risk assessment prior to elective procedures (see Figure 1). However a three tier approach remains useful for quantifying procedural bleeding risk. Comprehensive lists of relevant procedures falling into different risk categories are provided elsewhere.[3,4] It has been proposed that high-risk procedures are those with a major bleeding risk of >1.5%.[5] Procedures could also be considered high risk by virtue of bleeding being more difficult to diagnose and treat (e.g. retroperitoneal bleeding versus superficial soft tissue bleeding) or with more significant consequences (e.g. bleeding secondary to spinal interventions).

Procedures involving percutaneous solid organ puncture, or deep intra-abdominal drainage or biopsy, should be considered high risk. Arteriography requiring less than a 6 French sheath for access should be considered moderate risk, whereas aortoiliac or other intra-abdominal interventions such as embolisation are high risk. While the majority of venous procedures (including fistula interventions) are moderate risk, transjugular intrahepatic portosystemic shunts and thoracic venous interventions are notable exceptions and should be considered high risk.

Procedural risk will also depend on the complexity of a particular procedure. On occasion, what are generally considered low-risk procedures might be more complex than usual, for example, tunnelled central venous catheter insertion in the presence of occlusive central venous disease or attempted inferior vena cava filter retrieval in the presence of filter tilt or long implantation duration. Such procedures should be considered high risk.

BLEEDING HISTORY

A key recommendation of the previous BSH and the more recent European Society of Anaesthesiology (ESA) guidance is the taking of a preprocedure bleeding history.[1,6] A 2015 survey of more than 700 members of the ESA revealed that less than half of the respondents utilised a standardised history to assess bleeding risk.[7] The majority of bleeding assessment tools have been developed specifically to identify subjects with an inherited bleeding disorder, most commonly von Willebrand disease (VWD).[8-11] Although bleeding assessment tools have also been recommended for use in the preprocedure setting, they have not been validated and their performance remains questionable. Vries et al. found that the International Society of Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool (BAT) questionnaire in the preoperative setting did not differentiate between patients with and without defined laboratory abnormalities.[12] Hence a consensus-based questionnaire, HEMSTOP (Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents), to assess preoperative bleeding risk was proposed.[13] This tool was developed to identify adults with bleeding symptoms for whom perioperative haemostatic

precautions should be considered. The HEMSTOP questionnaire contains five questions relevant to all patients and two gender-specific questions (Table 1). A HEMSTOP score of 2 or more had a specificity of 98.6% (95% confidence interval [CI], 92.3–100) and a sensitivity of 89.5% for patients requiring haemostatic precautions due to an elevated bleeding risk. With a HEMSTOP score of <2, the authors suggest that in a realistic prevalence scenario (bleeding disorder frequency of 1%), the negative predictive value would be >99%, essentially ruling out a patient-related bleeding risk requiring special precautions. The questionnaire is simple to apply and warrants further assessment and prospective validation. Although the study is too small to support a strong recommendation, it is felt that this score may have a role in the preassessment setting to indicate which patients need further haematological input. There are a number of additional caveats to consider. First, a positive score does not necessarily indicate a bleeding disorder with an estimated positive predictive value of 39%. Certain bleeding symptoms such as heavy menstrual bleeding and bruising are common in the normal population without haemostatic defects, whereas a lack of significant bleeding despite previous surgical or procedural interventions would suggest that a significant underlying bleeding disorder is unlikely. Second, there is a subjective element to the questions and so clinical judgement is required in interpretation, especially in patients already on antiplatelet agents or anticoagulants. Finally, although only 1.4% of healthy volunteers were found to have a score of 2 or more, this may not be reflective of the hospitalised population, and the capacity and resources to investigate patients identified through this tool remain unclear.[14]

MEDICATION HISTORY

Table 2 provides a list of antithrombotic and/or antiplatelet medications which should be highlighted in the assessment. The risk of bleeding associated with a procedure will determine the need to interrupt medication. The BSH has produced guidance for the perioperative management of anticoagulation and antiplatelet therapy.[15] There is no evidence to support routine laboratory testing in patients on anticoagulants or antiplatelet agents prior to procedures other than checking the INR in patients on vitamin K antagonists.

TABLE 1 HEMSTOP questionnaire (each question scores 1 for yes).

1. Have you ever consulted a doctor or received treatment for prolonged or unusual bleeding (such as nosebleeds, minor wounds)?
2. Do you experience bruises/haematomas larger than 2 cm without trauma or severe bruising after minor trauma?
3. After a tooth extraction, have you ever experienced prolonged bleeding requiring medical/dental consultation?
4. Have you experienced excessive bleeding during or after surgery?
5. Is there anyone in your family who suffers from a coagulation disease (such as haemophilia and von Willebrand disease)?
Additional questions for females
6. Have you ever consulted a doctor or received treatment for heavy or prolonged menstrual periods (contraceptive pill, iron, etc.)?
7. Did you experience prolonged or excessive bleeding after delivery?

All patients on antiplatelet agents and anticoagulants should be counselled about the risks of bleeding from invasive procedures versus thrombosis associated with interruption of treatment within the consent process. One meta-analysis identified a threefold increase in major cardiac adverse events in patients who discontinued aspirin therapy given as secondary prophylaxis and a smaller study showed a similar odds ratio for ischaemic stroke.[16,17] Although these observational studies are not specific to percutaneous procedures and high-quality evidence is lacking, it is reasonable to assume some thrombotic risk to patients from pausing anticoagulants and antiplatelet agents, albeit likely <1% in most situations. Using the perioperative anticoagulant use for surgery evaluation (PAUSE) protocol in patients with atrial fibrillation requiring interruption of apixaban, dabigatran or rivaroxaban for surgery or procedures with a high bleeding risk, the overall 30-day risk of bleeding was ≤1.69% and the risk of arterial thromboembolism was ≤0.5%. Only a small minority were interventional radiology procedures and many patients will not have restarted the direct oral anticoagulant (DOAC) until 2–3 days post procedure.[18] When measured, the residual anticoagulant level was <50 ng/mL in 98.8% of cases. Routine measurement of DOAC levels before procedures is therefore not indicated when using the PAUSE protocol and there is currently an absence of evidence to support a clinical utility from testing.

Many low-risk procedures can be performed without pausing anticoagulants and aspirin. Procedures documented as not being associated with an increased bleeding risk if low-dose aspirin is continued include transbronchial lung biopsy, percutaneous biopsies and renal biopsy.[19-22] For newer antiplatelet agents, much of the data are derived from experience in cardiac surgery rather than non-surgical procedures. In vitro experiments indicate significant differences in the duration of action and reversibility of P2Y12 inhibitors in comparison with aspirin. The effects of aspirin wear off within 4 days in comparison with 7–10 days following clopidogrel cessation.[23] A greater percentage of normal platelets is required to normalise platelet aggregation in the presence of platelets inhibited by clopidogrel in comparison with aspirin. Until further clinical data become available, a conservative approach with the newer antiplatelet agents is reasonable because in many procedures, adequacy of haemostasis cannot be directly visualised and direct interventions to stop active bleeding are not feasible.

After a procedure associated with immediate and complete haemostasis, for example, soft tissue biopsy without significant vascular injury, recommendations are that DOACs can be restarted at 6–8 h postprocedure. Pragmatically, this could be the patient's next routine dose beyond this time period.[24] The PAUSE protocol recommends restarting the day after the procedure for low-risk procedures and a delayed

TABLE 2 List of antithrombotic and antiplatelet medication with recommendations for management before elective and urgent procedures associated with bleeding risk.

Drug	Elective	Urgent	Notes
Aspirin	Continue unless high bleeding risk	Continue	Expected to correct within 4 days of stopping
Clopidogrel Prasugrel Ticagrelor	Omit for 5–7 days Omit for 7 days Omit for 3–5 days	If cannot delay, consider stopping 24 h; tranexamic acid and platelet transfusion may be considered[15]	Patients on DAPT, prasugrel or ticagrelor should be discussed with a cardiologist
Dipyridamole	Omit on the day of procedure		Reversible weak platelet inhibitor
Low-molecular-weight heparin (all risk procedures)	Prophylactic last dose >12 h preprocedure Higher than prophylactic last dose >24 h preprocedure		
Unfractionated heparin	Omit for 4–6 h	Consider protamine only if very urgent	
Parenteral direct thrombin Inhibitors (argatroban or bivalirudin)	≥4 h	There is no reversal agent	
Fondaparinux	Omit 1–2 days after prophylactic dose and ≥3 days after therapeutic dose	There is no reversal agent	Half-life is approximately 17 h. Prolonged further if abnormal renal function
Warfarin	Omit for 5 days	Consider reversal with intravenous (IV) vitamin K if ≥6 h before procedure and with 4F-PCC if <6–12 h	IV vitamin K will approximately halve the INR after 6 h Bridging with LMWH should be considered if high risk for thromboembolism, for example, recent VTE <3 months, APS, high INR target (>2.5) and AF with CHADS2 ≥5
Direct oral anticoagulants	Omit for 2 days preprocedure unless low bleeding risk	Discuss with a haematologist	Omit for >2 days for patients on dabigatran with impaired renal function Idarucizumab can be used to reverse dabigatran prior to urgent procedures Routine preprocedure testing of DOAC levels is not recommended

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; AF, atrial fibrillation; APS, anti-phospholipid syndrome; DAPT, dual antiplatelet therapy; INR, international normalised ratio; IV, intravenous; VTE, venous thromboembolism.

restart after 2–3 days for high-risk procedures.[18] No high-quality data are available to guide the timing of restarting antiplatelet agents. However, the same timing could be applied as per DOACs unless there is a significant risk of delayed bleeding. Warfarin can be restarted on the evening of the procedure or the following day at the patient's usual dose.[15]

COAGULATION TESTING

NICE NG45 has recommended against routine coagulation testing prior to elective surgical procedures.[25] In the previous BSH guidance, Chee et al. reviewed nine observational studies (three prospective) indicating a positive predictive value (0.03–0.22) and a likelihood ratio (0.94–5.1) for coagulation tests, concluding that the PT and APTT are poor predictors of bleeding.[1] A subsequent meta-analysis consisting predominantly of observational studies (in the absence of a large randomised controlled trial [RCT]) has come to the same conclusion that unselected testing is not supported by evidence.[26] The clinical utility of the PT and APTT as a screening tool is therefore extremely limited.[27] This is not altogether unexpected as the PT and APTT are in vitro tests which can identify clinically irrelevant reductions in clotting factors such as in vitro inhibitors not associated with bleeding such as the lupus anticoagulant, and do not measure the complex haemostatic rebalancing seen in patients with acute illness and liver disease. In addition, many of the commonest bleeding disorders are not associated with an abnormal coagulation profile, including platelet function defects, mild VWD and even moderate factor deficiencies of clinical relevance.

Evidence has shown that extensive laboratory testing in patients with a bleeding history has significant limitations. Vries et al. found that patients with and without a bleeding history prior to procedures had a similar frequency of abnormal laboratory findings, reflecting the poor correlation of

many laboratory results with clinical phenotype.[12] To complicate matters further, patients with a clinically suspected mild bleeding disorder often remain uncharacterisable in terms of a defined laboratory abnormality, and the procedure-related bleeding risk is high even with prophylactic treatment.[28-30]

GLOBAL HAEMOSTATIC AND PLATELET FUNCTION TESTING FOR PREDICTING BLEEDING PRIOR TO INVASIVE PROCEDURES

Devices such as platelet function analyser, multiple electrode platelet aggregometry (multiplate analyser), viscoelastic haemostatic assays (TEG/ROTEM) have all been used to assess bleeding risk prior to surgery or invasive procedures. This guideline does not cover the use of viscoelastic testing during surgery or the use of other established point-of-care (POC) tests such as the activated clotting time (CT) during cardiac bypass.

Platelet function analyser (PFA-100/200)

There are no large prospective RCTs to date, but several small studies demonstrate that non-selective screening with the PFA has no predictive value for bleeding or transfusion requirement in patients undergoing invasive procedures, including those with renal failure.[31-35] Only Sucker et al. suggested a possible role for PFA in preoperative risk stratification based on 50 patients with aortic valve disease.[36]

Multiple electrode platelet aggregometry

The multiple electrode platelet aggregometry (multiplate) detects the effects of aspirin (ASPItest), ADP receptor (P2Y12) inhibitors (clopidogrel, prasugrel and ticlopidine) (ADPtest) and GpIIb/IIIa antagonists (TRAPtest). The recovery of platelet reactivity following the discontinuation of P2Y12 receptor blockers is highly variable. Several studies have indicated that the assessment of platelet function using multiplate analysis can predict bleeding risk, thereby reducing blood product requirements.[37-40] This was confirmed by a systematic review (30 observational studies [3044 patients] and 9 RCTs [1057 patients]) and a meta-analysis of POC platelet function tests for predicting blood loss and transfusion requirements in cardiac surgical patients.[41] However, there are no comparable studies for other types of surgery.

Viscoelastic testing: Thromboelastography (TEG) and thromboelastometry (ROTEM)

The value of TEG and ROTEM in the diagnosis of coagulopathy and the use of haemostatic support are discussed in a separate BSH document.[42] Data on TEG/ROTEM in predicting bleeding or the use of blood products in patients without liver disease undergoing invasive procedures, and use within the critical care setting are limited. The level of evidence is low due to the heterogeneity in the design of the studies, use of different control groups, a lack of reference standards and variability in chosen end-points.[43] In a prospective pilot study of 119 patients in an intensive care unit (ICU), tracheostomy was performed without bleeding complications in cases with normal ROTEM results (EXTEM CT) despite increased PT-INR and without the administration of FFP.[44] In a retrospective study of 1879 ICU patients, there was a significant reduction in blood product use without any bleeding complications after the implementation of ROTEM prior to intervention.[45] In this study, if the prothrombin ratio was >1.5, the platelet count was $>50 \times 10^9$/L and the APTT ratio was <1.5, then ROTEM was performed. If the EXTEM CT was normal (40–80 s), then the procedure was performed without prophylactic FFP administration. As a consequence, FFP and platelet transfusion reduced by 35% and 3%, respectively in the first year and 52% and 20% in the second year after the introduction of ROTEM use.[45]

Evidence has shown that TEG and ROTEM parameters predict blood loss during liver transplantation.[46-48] De Pietri et al. randomised patients (60 patients with significant coagulopathy [INR >1.8/Platelets $<50 \times 10^9$/L]) to standard of care (FFP/platelet transfusion) or TEG-guided transfusion prior to intervention.[49] Postprocedural bleeding occurred in only one patient post abdominal paracentesis. TEG-guided transfusion led to a significant reduction in blood product use without an increase in bleeding complications. This finding has been replicated with both TEG and ROTEM-guided transfusions prior to endoscopic procedures.[50,51] Emerging evidence suggests a potential role for TEG/ROTEM in reducing transfusion support in the periprocedural management of liver disease patients, with TEG maximum amplitude being a potential predictor of bleeding.[52,53] However, the lack of validated thresholds to guide haemostatic management necessitates further research to validate the efficacy of global haemostasis assays in this setting.

PROPHYLACTIC USE OF PLASMA PRODUCTS PRIOR TO INVASIVE PROCEDURES

Fresh frozen plasma

Numerous studies have demonstrated no significant benefit from using prophylactic FFP or cryoprecipitate prior to procedures in non-bleeding patients with abnormal clotting tests[54-57] with evidence that FFP transfusion in practice usually fails to correct abnormal PT ratio/INR values.[58] In a separate BSH guideline,[59] it is noted that the impact of commonly used doses of FFP to correct clotting results, or

TABLE 3 Recommended platelet threshold for patients undergoing invasive procedures.

Procedure	Platelet threshold $\times 10^9$/L	Level of evidence
Venous central lines (both tunnelled and untunnelled), inserted by experienced staff using ultrasound guidance techniques	≥20[a]	1B
Lumbar puncture	≥40	2C
Major surgery	≥50	1C
Minor surgery	≥30	1C
Insertion/removal of epidural catheter	≥80[b]	2C
Neurosurgery or ophthalmic surgery involving the posterior segment of the eye	≥100	1C
Percutaneous liver biopsy	≥50	2B
Percutaneous renal biopsy	≥50[c]	2D

Note: Adapted from the recommendation of the BSH guidelines on the use of platelet transfusions[75] and evidence review: the periprocedural use of blood products.[76]

[a]In patients requiring a tunnelled central venous catheter, a platelet count >30 × 10^9/L may be a preferable target.[77]

[b]A platelet count of ≥70 has been recommended for epidural in otherwise stable patients with no bleeding concerns and ≥50 × 10^9/L for spinal anaesthetic where there are risk factors for general anaesthetic.[78,79]

[c]MacGinley et al.[80] A survey of Australasian renal physicians found that 52% preferred a threshold of 100 × 10^9/L.[81]

to reduce the bleeding risk, is very limited particularly when the PT ratio/INR is between 1.5 and 1.9.

Fibrinogen replacement

Fibrinogen has a critical role in clot formation, providing a matrix and mesh network essential for clot strength.[60] Maintaining a haemostatic level of fibrinogen is an important therapeutic target in bleeding patients, particularly in the perioperative setting.[61] However, the level of fibrinogen required prior to an invasive procedure is yet to be determined. Transfusion guidelines have published conflicting optimal fibrinogen levels in patients with bleeding, or prior to intervention.[59,62] 'Normal' reported fibrinogen levels vary but are generally considered to range from 1.5 to 4.5 g/L.[63,64] POC coagulation testing using viscoelastic measurements of clot strength (maximal amplitude/maximum clot firmness) is also dependent on fibrinogen concentration.[65] The critical level of fibrinogen in maintaining haemostasis depends on multiple factors and clinical situations.[66] Consensus recommendations suggest fibrinogen levels of at least 1.5–2.0 g/L to achieve haemostasis in a patient with major bleeding or undergoing an invasive procedure.[62,65,67]

Furthermore, there can be both quantitative and acquired qualitative changes in fibrin formation. In the ISTH guidelines on the periprocedural management of abnormal coagulation parameters and thrombocytopenia in patients with cirrhosis, it is noted that in vitro tests suggest an enhanced thrombogenicity of the fibrin clot in patients with cirrhosis and that fibrinogen is rarely <1 g/L in non-critically ill patients. They also suggest that fibrinogen should not be routinely measured in the non-critically ill prior to elective procedures.[68]

Fibrinogen replacement can be with cryoprecipitate or fibrinogen concentrates, and clinical practice varies according to their availability and licensing status.[59,69] There is no evidence to support a specific fibrinogen level at which replacement should be given prior to an invasive procedure. However, this guideline recommends that in unwell hospitalised patients, replacement should be considered if the fibrinogen level in a critically unwell patient is <1.0 g/L.[70]

Platelet transfusion

The relationship between platelet count and bleeding risk is not linear and depends on platelet function and other patient-specific variables. Large studies suggest that the risk of spontaneous bleeding is difficult to predict until platelet count is reduced to approximately 10 × 10^9/L.[71] There are no high-quality data quantifying the bleeding risk according to platelet count in invasive procedures.

In one single-centre retrospective study of 18 204 patients undergoing interventional radiological procedures, prophylactic platelet transfusions did not reduce bleeding or improve clinical outcomes.[72] In patients with platelet counts <50 × 10^9/L, prophylactic platelet transfusions did not reduce the use of red cell transfusion. In addition to platelet count, risk of bleeding is affected by factors such as the platelet function, presence of inflammation and cause of thrombocytopenia, for example, patients with immune thrombocytopenia were less likely to bleed.[71]

The most common indication for preprocedure platelet transfusion has been found to be central venous catheter insertion.[73] There is no strong evidence to indicate that preoperative testing of platelet levels is necessary prior to low bleeding risk procedures. Patients with haematological disorders that cause thrombocytopenia are one notable exception. Where known, platelet count should be >20 × 10^9/L. However, platelet transfusion is almost always contraindicated in patients with thrombotic thrombocytopenic purpura. A systematic review of central venous catheter

placement in patients with platelet levels of $<50 \times 10^9$ demonstrated no major bleeding complications.[74]

For high bleeding risk procedures, it is reasonable to check an up-to-date platelet count of any patient at risk of thrombocytopenia. Table 3 summarises suggested thresholds for platelet transfusion for different invasive procedures. Figures are based on low-quality evidence, expert opinion or practice review, with only a small number of RCTs of small sample size.[75,82,83] The value of platelet transfusion to achieve target levels remains uncertain, especially in patients with liver disease and portal hypertension.

SPECIAL POPULATIONS

Patients with liver disease

Both acute and chronic liver disease is associated with distinct changes in haemostatic and haemodynamic pathways. The liver is the major site for the synthesis of many pro-coagulant and anticoagulant factors. Therefore, the PT, APTT and fibrinogen are markers of synthetic function, but nevertheless conventional in vitro tests of coagulation are of limited value in assessing overall haemostatic competency in liver disease.

Liver disease promotes complex haemostatic abnormalities with increases in factor VIII and von Willebrand factor and deficiency of other pro-coagulant and anticoagulant factors, endothelial dysfunction, reduced platelet count/function, low-level activation of the coagulation system and hypo- and hyperfibrinolysis. These fluctuations have led to the concept of rebalanced coagulopathy in acute and chronic liver disease—a clinical state that is supported by clinical and laboratory data, often to a marginally pro-thrombotic state.[84-89] However, acute-on-chronic decompensated liver failure (ACLF) and other factors such as acute kidney injury or infection may impact on this rebalancing and increase the risk of bleeding.[52,89,90,91,92] ACLF that is associated with an acute inflammatory response may also result in hyperfibrinolysis and coagulopathy with platelet dysfunction that increases bleeding risk.[93] In one study, a platelet count $<30 \times 10^9$/L, fibrinogen level <0.6 g/L and APTT values >100 s were the strongest independent predictors of the new onset of major bleeding although portal hypertension was a key factor. All but the most essential invasive procedures should be avoided under these circumstances.[91,94]

The use of INR to guide bleeding risk following invasive procedures in liver patients is not supported by clinical evidence. No clinical trials have established precise thresholds for PT and APTT at which invasive procedures can be considered safe. A number of studies have investigated the safety of liver biopsy in patients with coagulopathy, with data indicating that bleeding does not correlate with indices of peripheral coagulation.[95-100] Conversely, there is also evidence suggesting a weak association between bleeding and INR, acknowledging a substantial overlap of INR and platelet count between bleeders and non-bleeders.[101-103] Portal hypertension, the presence of venous collaterals and other anatomical changes related to liver cirrhosis may modify bleeding risk following liver biopsy, for which the INR is just a surrogate marker.[94] An observational study of 302 patients undergoing liver biopsy and comprehensive haemostatic profiling (thrombin generation, ROTEM, clot lysis assays and PFA-100) found no association between haemostatic profiles and procedural bleeding.[104] Indeed, the only identified predictor of bleeding was pain 2 h post procedure.

A broad overview of the literature demonstrates low rates of bleeding complications in hepatology patients undergoing invasive procedures. Townsend et al. reported no major bleeding complications in 240 end-stage liver patients (INR 0.93–2.35) undergoing cardiac catheterisation.[105] Puchalski et al. reported that thoracentesis can be performed safely in patients with prolonged INR (>1.5), secondary to either warfarin or liver disease, without correction of coagulopathy.[57] Somani et al. found that only 1/150 patients experienced significant bleeding after a range of invasive procedures, including liver biopsy, pleural tap, intercostal drain insertion and central venous catheterisation, although severe coagulation abnormalities (INR >1.8) were present in only 25% of patients.[106] Shah et al. undertook a prospective study of 380 patients with cirrhosis undergoing invasive procedures.[107] Patients were divided into two groups according to the presence or absence of coagulopathy (defined as INR >1.5 and/or platelet count $<50 \times 10^9$/L). No bleeding events were seen in either group following low-risk procedures such as paracentesis. However, there was an increased risk of bleeding in the coagulopathic group following high-risk procedures or liver biopsy, although this was not statistically significant.[107] Napolitano et al. reported a prospective study of 852 invasive procedures in 363 cirrhotic patients. Postprocedure bleeding was rare (1.2%) and not predicted by low platelets or prolonged INR.[108] The analysis of 1076 ultrasound-guided thoracentesis cases found no haemorrhagic complications even in the 139 cases where INR was >2.0; another study of thoracenteses showed no evidence of haemothorax in any of the 312 patients undergoing the procedure (including 44 patients with INR >1.5).[56,57] A larger study of 9320 thoracentesis procedures (2306 with an INR ≥1.5) showed only 17 bleeding complications with no association between INR and bleeding.[109] A study of 3117 ultrasound-guided paracentesis cases found major haemorrhage to be extremely rare, with only six cases identified, despite INR being >2.0 in 437 cases.[110] A large prospective multicentre observational study of procedural bleeding in 1187 hospitalised patients with decompensated cirrhosis or ACLF undergoing 3006 procedures reported an overall low incidence of major bleeding (0.9% of procedures).[111] No relationship was identified between INR, platelet count and procedural bleeding. Independent predictors of bleeding were high bleeding risk procedures (OR 4.6, 95% CI: 2.4–8.4), liver disease severity (evaluated with model for end-stage liver disease OR 2.37, 95% CI: 1.5–3.9) and body mass index (OR 1.4, 95% CI: 1.1–1.8).

Table 4 shows a list of low bleeding risk procedures and guidelines have recommended against routinely correcting thrombocytopenia and coagulopathy in this setting.

Conventional haemostasis assays have been used prior to invasive tests both to risk stratify patients and to guide therapeutic correction of coagulation abnormalities. However, there is no evidence that prophylactic transfusion of blood products such as FFP or platelets reduces haemostatic complications following invasive procedures.[113] Transfusion of FFP appears to be at best ineffective and may cause harm.[114-117] Thrombin generation in cirrhotic patients does not appreciably change after supplementation with pooled normal plasma despite reductions in PT and may enhance an existing prothrombotic state.[118-120] An increasing number of international guidelines now advise against the prophylactic use of FFP before invasive procedures.[68,112,121,122,123]

There is no evidence to support the use of vitamin K replacement in patients with cirrhosis. In a retrospective study of 85 patients, the majority with Child–Pugh class C cirrhosis, the absolute change in INR was −0.07 ± 0.35 following vitamin K administration. There was no difference in absolute INR change between single versus multiple dose administration or between PO versus IV administration.[124]

In a study of 497 patients receiving 10 mg IV vitamin K for 3 days, two-thirds of patients with cirrhosis had no improvement in the INR and those that did show a partial response were more likely to have alcoholic cirrhosis.[125] It continues to be acceptable to consider high-dose IV vitamin K replacement in patients with an increased INR secondary to vitamin K deficiency, for example, cholestatic liver disease, malnutrition or prolonged antibiotic use.[93,94,112,126] However, procedures should not be delayed awaiting INR confirmation if an adequate dose has been given (e.g. 10 mg IV) and a suitable time interval has elapsed (>6 h).

There are no prospective studies evaluating the periprocedural role of cryoprecipitate/fibrinogen concentrates in cirrhotic patients and no evidence to support the use of prothrombin complex concentrate (PCC) or recombinant factor VIIa or tranexamic acid periprocedure. Concern exists about the potential harm with PCC in ACLF.[68,127]

Anti-fibrinolytic therapy has been recommended as an option in patients with postprocedure bleeding when there is evidence of hyperfibrinolysis, but guidelines have not recommended routine tranexamic acid prophylaxis prior to procedures. The HALT-IT study indicates that exposure to continuous tranexamic acid for 24 h may increase the risk of venous thrombosis in patients with liver disease.[112,121]

Evidence for a platelet threshold above which invasive procedures can be safely performed is limited. In vitro studies using plasma from cirrhotic patients show that a platelet count >56×10^9/L allows thrombin generation above the 10th percentile of the healthy population.[118] In a study of liver biopsies in patients with hepatitis C infection, bleeding rate was the highest in patients with a platelet count <60×10^9/L. However, the majority of bleeds occurred in patients with platelet count >100×10^9/L.[128] As with the INR, the platelet count may also be a surrogate marker for risk factors such as fibrosis and portal hypertension. In one large retrospective study of patients undergoing percutaneous liver biopsy, the implementation of less stringent guidelines for preprocedure blood product (FFP/platelet) use (INR ≥2 and platelets <25×10^9/L) was associated with fewer haemorrhagic complications than historical cut-offs (INR ≥1.5 and platelets ≤50×10^9/L).[129]

In cirrhotic patients, transfusion of a single pool of platelets results in only a small increase in platelet count without normalising either thrombin generation or TEG tests and may be associated with harmful transfusion reactions.[130]

TPO-RAs are now available for use prior to elective procedures in thrombocytopenic patients with liver disease, as an alternative to platelet transfusion. TPO-RAs may be preferable to platelet transfusion.[112] The treatment period required prior to intervention is 9–14 days. Although not seen in all studies, TPO-RAs have been associated with an increased risk of thrombosis, including portal vein thrombosis so should be used with caution in patients considered to be prothrombotic, especially as these patients were excluded from investigative trials.[94,131] Although TPO-RAs appear more effective in increasing platelet counts compared to platelet transfusion, there remains uncertainty regarding impact on bleeding risk.[132,133]

To optimise clot formation in advanced liver disease, the American Gastroenterology Association guidelines recommend transfusion thresholds during active bleeding or prior to high-risk procedures of haematocrit ≥25%, platelet count >50×10^9/L and fibrinogen >1.2 g/L.[112]

TABLE 4 Low bleeding risk procedures performed in patients with chronic liver disease.

Diagnostic endoscopic procedures and variceal ligation
Transoesophageal echocardiogram
Paracentesis
Thoracentesis
Peripheral venous line insertion/central venous catheter exchange or removal
Dental procedures including extractions
Skin biopsy

Note: Adapted from Refs [68,112].

The critical care patient

In critical care patients, acquired coagulation (PT, APTT and INR) abnormalities are common. In a UK prospective study (ISOC-1), 30% of patients had an INR >1.5 at some point during their admission.[134] Most derangements are short term and mild (INR <2.5) but are independently associated with a significantly increased risk of death even adjusting for illness severity.[135-137] Sepsis is associated with both a quantitative and qualitative impact on platelets.[138,139] Thrombocytopenia is also common in this patient group with up to 60% being thrombocytopenic at critical care

admission and 13%–44% developing thrombocytopenia while in the ICU.[140] A multicentre observational study in the United Kingdom reported 13% of patients had a platelet count $<50\times10^9$/L.[137]

Taking a clinical history on the ICU may be impractical, and the conventional tests of coagulation neither reflect in vivo haemostasis nor predict procedure-related bleeding.[44,141,142,143,144,145,146] Invasive procedures including the insertion of vascular access catheters, percutaneous tracheostomy and thoracentesis are common in critical care, and observational data suggest these can be carried out with a low risk of bleeding.[137,139,142,146,147,148]

Plasma products are frequently administered to patients in ICU without any evidence to support this practice. In a 2011 UK multicentre observational study of 1923 ICU admissions, 31% of the 404 FFP treatment episodes were to patients without PT prolongation, and 41% were to patients without recorded bleeding and only mildly deranged INR (<2.5). Procedural prophylaxis was the documented transfusion reason in 15%.[136,137] Evidence that FFP prevents periprocedural bleeding complications in the non-bleeding critical care patients is lacking.[74,134,144,149]

The TOPIC trial assigned 81 ICU patients with an INR of 1.5–3 to receive either no FFP or 12 mL/kg FFP prior to central venous catheter insertion, tracheostomy, chest drain insertion or abscess drainage.[55] There was no significant difference between the two groups in terms of postprocedural bleeding, although the study was limited by its small size. The dose of FFP was sufficient to correct the INR to <1.5 in only 54% of patients. Coagulation factor assays at baseline suggested a similar rebalancing to that seen in liver disease, with reduction in natural anticoagulants as well as procoagulant factors, along with normal viscoelastic testing and normal thrombin generation in the great majority.[150] FFP can be associated with transfusion-associated circulatory overload which is the leading cause of transfusion-related death, multiorgan failure and increased susceptibility to infection.[59,151,152]

Platelet transfusions are also commonly administered without evidence to support this practice. The aforementioned, multicentre UK study of 1923 critically ill patients found 9% received platelet transfusion during their admission. Of the 534 treatment episodes, 40% of patients had a platelet count $>50\times10^9$/L at the time of transfusion and 55% of patients were not bleeding at the time of administration.[149] The median increment in platelet count was 15×10^9/L (interquartile range 2–35.5×10^9/L). Similar findings were reported in a multicentre observational audit in Australasia, with 33% of platelet transfusions given to simply prevent procedural bleeding.[153] There is a lack of evidence to support prophylactic platelet transfusion in the periprocedural setting.[75,154]

A recent non-inferiority RCT of platelet transfusion versus no intervention prior to central venous catheter insertion in haematology patients with a platelet count of $10–50\times10^9$/L (including 161 ICU patients) reported a reduction in major bleeding in the platelet transfusion cohort (defined as WHO grade ≥2).[77] Sensitivity analyses suggest platelet transfusion reduced bleeding specifically in patients either undergoing subclavian line insertion or in those with platelet count $<30\times10^9$/L. Major bleeding rates were higher in patients undergoing tunnelled line insertion. A small RCT in critically ill patients with severe thrombocytopenia undergoing tracheostomy ($n=57$) reported no difference in blood loss between those receiving platelet transfusion and those without.[155] Platelet transfusion in non-critical care settings has been associated with adverse patient outcomes, particularly increased mortality.[156]

OPERATOR AND PROCEDURAL RISK FACTORS FOR BLEEDING

The risk of periprocedural bleeding may also be increased or mitigated by operator and technical factors as well as patient anatomy and physiology independent of haemostatic disorders and medication.

Measures to reduce the risk of procedural bleeding should always be considered (Table 5). A meta-analysis evaluating femoral artery access with and without the use of ultrasound guidance showed a significant reduction in vascular complications when ultrasound guidance was used, with fewer needle passes required.[169] Reduced number of passes and fewer complications have also been observed in central venous catheter insertion when using ultrasound compared with the traditional landmark technique.[74] Although some operators favour micropuncture needles in arterial or venous access, there are no clear data to suggest a benefit in terms of bleeding risk reduction.[170,171] This is also illustrated by Strobel et al. examining percutaneous intra-abdominal interventions and Atwell et al. examining percutaneous biopsy. Both trials showed no significant increase in major bleeding when larger needles were used.[20,172] It has been suggested that procedures requiring an arterial access sheath size of more than 7 French should be considered high risk. Furthermore, there are mixed data regarding whether vascular closure devices are protective against access site haemorrhage.[3,173]

Operator experience and familiarity with particular techniques are also important. Data have shown a higher incidence of femoral artery access bleeding complications when this approach is used by experienced cardiologists, who primarily use radial artery access for intervention. Lower rates of major bleeding are also documented at high-volume centres.[174,175]

Sznadjer et al. considered 50 procedures to be the threshold for competency of central venous catheter insertion, with significantly higher complication rates reported among inexperienced operators.[157,158] Despite this, a meta-analysis of bleeding complications post liver biopsy highlighted conflicting data on its relationship with operator experience. Conversely, another study showed a significantly higher bleeding complication rate from operators adjudged to be experienced compared to their less experienced

TABLE 5 Operator, procedural and patient factors associated with the risk of procedural bleeding.

Operator factors	Evidence	Recommendation
Operator experience	More experienced operators have fewer complications for vascular/body cavity access, drainages/ catheterisation[101,157,158,159]	High-risk procedures should be undertaken or assisted by a suitably experienced operator

Procedural factors	Evidence	Recommendations
Use of ultrasound	Non-RCT evidence indicates the use of image guidance is associated with a lower bleeding risk for vascular access, organ biopsy and body cavity drainage[157-162] Reduction of puncture frequency decreases overall complication rate for femoral venous access but not for bleeding risk[158,161] Decreased risk for paracentesis and thoracentesis[163]	Ultrasound image guidance should be used when available
Choice of equipment	Evidence is lacking; however, small-bore vascular access and chest drain catheters may reduce incidence of bleeding[158]	Use the smallest appropriate size of catheter/drain for any procedure
Choice of technique	Ultrasound-guided venous access reduces bleeding[158,164] Midline approach to paracentesis reduces risk *Transjugular approach can be considered for liver biopsy in patients with increased risk of bleeding*[94]	Consider anatomical factors
Unfavourable anatomy, prior surgery or radiotherapy	Lumbar puncture; ankylosing spondylitis, spinal stenosis[165]	Recommend use of ultrasound, optimal patient positioning, detailed anatomical knowledge and experienced operator

Patient factors	Evidence	Recommendations
Age	Risk factor for cardiac surgery and renal biopsy[161,166]	High-risk procedures should be undertaken or assisted by an experienced operator, if patient of an advanced age
Hypertension Systolic >160 mmHg Diastolic >100 mmHg MAP >120 mmHg	Increased risk of postrenal biopsy bleeding[111,162] Evidence suggests surgical procedures should not be delayed but hypertension treated >180/110 with antihypertensive medications[167]	Seek history of hypertension Experienced operator Enhanced postoperative monitoring Consider oral antihypertensive agent
High serum creatinine	Marker of a higher risk procedure—with increased risk of bleeding postrenal biopsy >177 μmol/L,[168] and thoracentesis >520 μmol/L[96] Correlation between renal disease and paracentesis haemorrhagic risk[158]	Experienced operator Enhanced postoperative monitoring
Obesity	Increased risk of failure of landmark-based intervention; lumbar puncture[158,165]	Image guidance; fluoroscopy/ultrasound
Red cell volume/haematocrit	Preoperative anaemia or small body size is a risk factor for blood transfusion in cardiac surgery[166]	Experienced operator Enhanced postoperative monitoring
Infection	Increases the risk of bleeding in patients with acute-on-chronic liver failure[90]	Treat infection

Abbreviations: MAP, mean arterial pressure; RCT, randomised controlled trial.

counterparts.[160] However, this finding is thought to be explained by a more complex/higher risk cohort of cases undertaken.[176]

AUTHOR CONTRIBUTIONS

Will Lester chaired the writing group. All authors contributed to writing, editing and reviewing the manuscript, including the final submission.

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CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a full declaration of interests to the BSH and Task Force Chairs, which may be viewed on request. The authors have no relevant conflicts of interest to declare relating to this guideline.

REVIEW PROCESS

Members of the writing group will inform the writing group chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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APPENDIX

METHODOLOGY

MEDLINE (OVID) 1946 to 3 May 2023

EMBASE (OVID) 1974 to 2019 week 18

CENTRAL (Cochrane Central Register of Controlled Trials)

Main keywords used (alternative spellings/related terms also searched) and search structure:

surgical procedures; operative; surgery; surgical; invasive procedure; interventional radiology; biopsy; percutaneous AND

blood coagulation disorders; blood coagulation tests; hematologic tests; bleeding time; prothrombin time; partial thromboplastin time; international normalised ratio; APTT; PT; PTT; INR; bleeding risk assessment; coagulopathy; PFA-100; thromboelastogram; ROTEM; bleeding history; bleeding questionnaire AND

surgical blood loss; blood transfusion; postoperative haemorrhage/bleed; post-intervention haemorrhage/bleed; post-biopsy haemorrhage/bleed; post-procedure haemorrhage/bleed incidence AND

vitamin K; prevalence AND

vitamin K; vitamin K deficiency; hypovitaminosis K; PIVKA