Prevention and management of indwelling catheter-related-thrombosis in sickle cell disease and thalassaemia: A British Society for Haematology Good Practice Paper

Authors: Dr George Woodward[1], Dr Emma Drasar[1], Dr Shivan Pancham[2], Dr Nandini Sadasivam[3], Dr Thachil Jecko[3], Dr John Brewin[4].

Authors' affiliations:

[1]University College London Hospitals NHS Foundation Trust, London, UK

[2]Sandwell and West Birmingham NHS Foundation Trust, Birmingham, UK

[3]Manchester University NHS Foundation Trust, Manchester, UK

[4]King's College Hospital NHS Foundation Trust, London, UK

Correspondence:

BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK. E-mail: bshguidelines@b-s-h.org.uk

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Methodology

This guideline was compiled according to the British Society of Haematology (BSH) process at https://b-s-h.org.uk/media/19922/bsh-guidance-development-process-july-2021.pdf) The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org and the literature search is summarised in Appendix A.

Review of the manuscript

Review of the manuscript was performed by the BSH Haematology General Haematology Task Force, the BSH Guidelines Committee and the sounding board of BSH. It was also placed on the members section of the BSH website for comment.

Introduction

Sickle cell disease (sickle cell anaemia and related compound heterozygous states) manifests as a hypercoagulable state with high levels of chronic platelet activation, thrombin generation and inflammation. Venous thromboembolism (VTE) has been increasingly recognised as a common comorbidity in comprehensive reviews of sickle cell disease (SCD), with rates particularly increased when other risk factors for VTE are also present.

Regular red cell transfusion is an essential therapy for a subpopulation of patients with SCD or thalassaemia. The need for regular venous access can become challenging for a variety of reasons (e.g., poor peripheral veins or intense needle phobia,

especially in children), but attempts to persevere with this option should always be explored, including ultrasound guided cannulation or psychotherapy as indicated. Nonetheless, temporary or long term central venous access devices can become a necessity. Temporary line insertion on the day of procedure, especially insertion of femoral central venous catheters, is associated with increased rates of infective complications, bleeding risk and progressive tissue scarring making repeat insertion increasingly complex.(1) Furthermore, in some cases, venous access may be required at other times for patient care, e.g. ongoing chelation therapy. Indwelling central venous access devices (CVCs) require a surgical procedure for insertion, but have lower infection rates and present much simpler and quicker access on transfusion days and at other times. These are often therefore the preferred option for this patient cohort. However, catheter-associated VTE is a common and significant complication in these patients. Guidance for consideration of prophylactic anticoagulation to mitigate this risk has been developed based on published literature evidence.

Catheter-associated VTE was defined in most studies as a radiologically confirmed diagnosis of catheter-related thrombosis, right atrial or ventricular thrombus, upper or lower limb deep vein thrombosis (DVT), pulmonary embolism (PE) or VTE at other sites, confirmed by diagnostic imaging such as Doppler ultrasound, echocardiogram or computed tomography-pulmonary angiogram (CTPA).

Rates of venous thromboembolism in sickle cell disease

Based on retrospective studies, VTE has been shown to affect up to a quarter of adult SCD patients and is a risk factor for early mortality.(2) In a cross-sectional study of 404 sickle cell disease patients cared for at a quaternary centre in the US, Naik et al.

found that 25% of adult patients with sickle cell disease have a history of a VTE, a prevalence that is similar to that seen in patients with recognised thrombophilic states such as antithrombin, protein C or protein S deficiency (21%).(3) The largest study performed using the National Hospital Discharge Survey evaluated 1,804,000 SCD admissions from 1979 to 2003 and found that the prevalence of PE in hospitalized SCD patients <40 years of age was approximately 3.5 times higher than in African–American controls (4) whilst VTE incidence in patients with SCD is reported at 5.2 events/1000 person years with a cumulative occurrence of 11.3% by age 40 years.(5,6) Patients with SCD have a number of additional risk factors for VTE, including frequent hospitalization, high-risk surgery such as orthopaedic surgery for avascular necrosis (AVN), pregnancy, and use of indwelling CVCs (2,7). Brunsen et al.(5,6), demonstrated in their study that the VTE risk associated with sickle cell disease and multiple hospital admissions is greater than that conferred by multiple hospital admission alone as demonstrated versus matched controls.

Thus, SCD represents a pro-thrombotic state with a VTE risk 2.6 times greater than the general population (8) and fifty times greater than the quoted risk for under 40 year olds without SCD.(9)

Rates of venous thrombo-embolism in beta thalassaemia

Patients with thalassaemia are also recognised to have a hypercoagulable state. A paediatric study found 4% of 683 patients with transfusion-dependent beta-thalassaemia major (TDT) and 9.6% of 52 patients with non-transfusion-dependent thalassaemia (NTDT) had VTE events (10), while another study showed VTE affected up to 14% of the study population.(11) The main independent risk factors for

thrombotic events were splenectomy, iron overload (serum ferritin level >1000 ng/mL), age older than 35 years, and a haemoglobin concentration of less than 90 g/L.(11) In a separate study of splenectomised patients, the occurrence of VTE was 29% demonstrating how high risk this sub-cohort is.(12)

Central venous catheters and venous thromboembolism risk in sickle cell disease

CVCs are commonly used in SCD and can be a significant risk factor for VTE. A large cross-sectional study demonstrated that 30% of all episodes of VTE in a cohort of 404 patients with SCD were catheter associated, although the study did not provide information on the total number of different patients affected versus recurrent events in an individual.(3)

The literature includes a range of multicentre and single centre retrospective studies that look to quantify the incidence of thrombosis in sickle cell disease. These report that between 3–41% of CVCs are complicated by VTE with an incidence ranging from 0.14 to 0.99 VTE events per 1,000 catheter days.(7,13–18)

These studies typically include small patient numbers and lack consistency, making firm conclusions difficult to establish. They report on different types of CVC, from peripherally inserted central catheters (PICC) lines and temporary femoral CVC lines, to totally implantable venous access devices (TIVAD) such as single and dual lumen Port-a-caths.

When considering the adult population only, the catheter-related thrombus (CRT) occurrence per catheter is higher at 19–41%.(18–22) This even included asymptomatic line-associated right atrial thrombus, detected by echocardiogram or cardiac magnetic resonance imaging (MRI). Although the majority of these events are reported in patients with haemoglobin SS or Sβ thalassaemia^0, reflecting the high use of catheters in more severe genotypes, they were also reported in patients with other genotypes of sickle cell disease.(18)

Central venous catheter and venous thromboembolism risk in thalassaemia

Only two studies were identified reporting on the occurrence of CRT-associated VTE in patients with thalassaemia. Both these studies looked at patients in teenage and young adult age group. They identified a VTE occurrence that ranged from 32–57% in patients with an incidence of 0.41 to 0.48 per 1000 catheter days.(23,24)

Assessing the VTE risk factors and bleeding risk: risk stratification

Adults and the effect of age

Studies in adults report a higher rate of thrombosis than paediatric populations (Table 2). It is well recognised that thrombotic risk increases with age. There is an accumulation of associated comorbidities, vascular endothelial damage, and increased inflammation leading to a heightened procoagulant state. This increased VTE risk was also identified in the context of CRT in patients with SCD in studies by Shah et al., Woods et al. and Forté et al.(18,21,25)

Paediatric patients

In the general population, occurrence of VTE in children is exceedingly low (0.007 to 0.014 per 1,000) and 0.53 VTE/1,000 in paediatric hospital admissions.(26) There is a bimodal VTE risk profile in paediatrics, with a VTE rate of 14.5 per 10,000 per year in the neonatal period, and among adolescents (aged 15–17 years) the rate is quoted at 1.1 per 10,000 per year.(27) It is reported that more than 90% of VTE in children are associated with CVC.(28)

The rate of VTE in children with SCD with CVCs was harder to identify as several studies grouped the data or had a mixed age patient group of both children and young adults.(15–17,29) Woods et al. performed a single centre US retrospective study of VTE in children with SCD. They demonstrated that CVC use is an independent and primary predictor of VTE ($p<0.001$) (25) and reported a cumulative CRT rate of 22% per person with CVCs in-situ in their paediatric cohort.(25) However, they observed the patients with CVC-associated VTE were found to be significantly older when compared to the patients without VTE (15.9 years vs 11.8 years, $p=0.03$).(25)

Shah et al. reported a rate of 41% in their adult cohort, but only 10% in the paediatric patients. Jeng et al. reported 33% of patients had a catheter-related thrombotic event at a rate of 0.99 per 1,000 catheter days. The patients were aged 1.4–30 years; although the age of those with thrombotic events were not reported.(15) Bartram et al. found no thrombotic events in their 9 year single centre retrospective analysis of children aged 3–15 years of age.(30) Abdul-Rauf et al. reported 8% of their 25 patients with TIVADs had thrombotic complications, at a rate of 0.29 per 1000 catheter patient days.(17) They found an overall VTE occurrence of 2.8% in this cohort of 414 patients,

of which 75% were CVC-associated (Odds Ratio (OR) 33.8, 95% Confidence Interval (CI) 8.7–130.9; p<0.001) and the mean age at VTE-event was 15.9 years. Ordonez et al. report on a cohort of 54 paediatric patients with SCD or thalassaemia major (TM).(29) Most of these patients had single lumen TIVADs in situ. They reported a per-person thrombosis rate of 7.4%, and showed the thrombotic rate to be 0.038 per 1000 catheter days with single lumen TIVADs. Ilonze et al. found similarly low thrombotic rates in children with SCD with an incidence of catheter-related VTE of 0.03 per 1000 catheter days. In this cohort, single lumen infusion ports were used exclusively.

Boechat et al. also reported a very low VTE occurrence in their paediatric retrospective study of 1063 children with SCD at 0.2%, and both these were CVC-associated (p<0.001).(31)

In these studies the occurrence of VTE in children and young adults (under 30) with CVCs in these studies was 0–33%. More recent studies that included only paediatric patients show a far lower rate of thrombosis of 0.03–0.29 per 1000 catheter days.(29,32) The rate of thrombosis in studies that included adolescent and young adults was higher. In addition, these older children and young adults often require dual lumen devices to facilitate automated red cell exchange transfusion, and such devices may also carry a greater thrombotic risk.

In conclusion, the presence of CVC is associated with a significant VTE risk in adults and adolescents with SCD. This mirrors the wider population of patients with SCD, where risk of VTE increases from teenage years and into adulthood.

Line-related risks

The site of line insertion, tip position, and the type of line used are all factors that influence VTE rates.

A number of the paediatric and adolescent studies demonstrated that dual lumen TIVADs were associated with higher thrombotic rates than single lumen TIVADs.(25,29,30,32) However, this may also be because dual lumen ports would be sited in preference to single lumen ports for older children undergoing red cell exchange, rather than simple top up transfusion. Shah et al., reported no difference between dual or single lumen devices in their adult retrospective study.(18)

Sharma et al. and Woods et al. found bilateral CVC placement to be an independent risk factor for VTE.(25,33)

It is difficult to compare types of port used across different studies, however, Forté et al. found the use of Port-a-cath CVCs to be associated with lower thrombotic risk than other types of CVAD including PICCs, Vortex and Xcela Power lines (Risk Ratio R=5.8 (1.3–25.9), p=0.02, and RR=58.2 (15.0–225.0), p<0.001, respectively). (20) This trend is also demonstrated in table 2 where studies that solely focus on Port-a-Cath generally have lower rates of VTE associated with CVC use.

In addition, both Forté et al. and Brewin et al., identified 8–10% occurrence of asymptomatic right atrial thrombus with the Vortex ports. Brewin et al., went on to examine tip positioning and suggested those lying deeper into the right atrium were

more strongly associated with atrial thrombus formation (3 of 7) than those positioned at the cavo-atrial junction or proximal right atrium (0 of 9).(20)

In Forté et al.'s study, hydroxycarbamide (hydroxyurea) usage was associated with significantly lower VTE rates in adult patients with SCD (RR = 20.5 (6.4–65.3), p<0.001). As a retrospective study, it is difficult to know how to appraise this finding. As the authors themselves note, other retrospective studies have found hydroxyurea to be positively associated with VTE rates.(20)

Recommendation

- **Port-a-Caths may confer a lower thrombotic risk than other devices.(Grade 2B)**
- **Bilateral CVC placement carries an increased risk of VTE and should only be considered if clinically necessary.(Grade 2D)**
- **CVC tip should be placed optimally in the cavo-atrial junction or proximal right atrium to reduce VTE risk.(Grade 2D)**
- **CVCs should be in situ for the minimum time necessary to facilitate treatment.(Grade 2D)**

Patient-related factors

Additional co-morbidities and events can increase the VTE risk in this cohort. Some of these are based on population-wide risk factors such as inherited thrombophilia, obesity and recent hospital admission (21). Others are more specific to SCD. It is difficult to derive strong evidence to support these conclusions from the published CRT

datasets as they are small and retrospective. Further support can be gained from analysis of VTE risk in the total SCD cohort.

Woods et al. found the haemoglobin SS genotype to be significantly associated with VTE (when compared with all other genotypes) (OR 10.7, 95% CI 1.4–83.5; p=0.006). They also reported central nervous system (CNS) vasculopathy (OR 19.4, 95% CI 5.6– 63.4; p<0.001), and chronic transfusion therapy (OR 30.6, 95% CI 8.9–122.2; p<0.001).(25) to significantly increase the risk, although these were not significant in multivariate analysis, likely because they over-represented the cohort with a CVC in situ. Only CVC in situ remained independently associated with VTE (OR 33.8, 95% CI 8.7-130.9).(25)

Naik et al. report that evidence of pulmonary hypertension as defined as a tricuspid regurgitant (TR) jet >2.5 m/s on transthoracic echocardiogram, was associated with increased thrombotic risk (RR 1.65; 95% CI, 1.12–2.45). A history of splenectomy (7,34) has also been found to increase VTE risk. This is a recognised complication with splenectomy outside of the context of SCD.(2,7)

In conclusion patients with CVCs are at higher risk of VTE if they have evidence of pulmonary hypertension, previous splenectomy or previous VTE. They are at short-term increased risk if they are experiencing concurrent illnesses such as sepsis, chest crisis, vaso-occlusive crisis or surgery or have additional markers of inflammation.

Assessing the risk of bleeding

Antithrombotic medications are well-known to be associated with an increased risk of bleeding. Several risk assessment tools have been developed to estimate this bleeding risk prior to the commencement of anticoagulation such as the HAS-BLED score, a very popular model which was developed based on the multivariate regression of the European Heart Survey database of atria.(35) The other risk scoring tools are the HEMORR2HAGES, ATRIA, ORBIT and ABC-bleeding scores which can assist in the decision process of the risk-benefit balance of anticoagulation treatment.(36) These risk scores were, however, created and validated in patients with atrial fibrillation, while patient with sickle cell disease or thalassaemia with CVCs in situ who suffered venous thromboembolism or are at risk for this complication are a clinically different cohort and also contain unique sickle bleeding characteristics.

Clinical guidelines for VTE management do recommend assessment of bleeding prior to initiating anticoagulant treatment, but validated tools are not yet common-place.(37) Experts suggest a detailed bleeding risk assessment to identify risk factors which can help in selecting the appropriate anticoagulant, can indicate what may be a safe dose for initial and extended treatment and the optimal treatment duration.(35) The HAS-BLED or RIETE score has been used to identify patients at high risk of major bleeding during the initial VTE treatment phase, while the VTE-BLEED score has been used to decide on extended/long-term anticoagulation in this clinical scenario.(38) General bleeding risk factors are detailed below as captured by the HAS-BLED, RIETE and VTE-BLEED.(39)

Table 1 Clinical scores to predict major bleeding with venous thromboembolism – taken from Nopp et al.(38)

	HAS BLED	RIETE	VTE-BLEED

	Derived in AF population	Derived in VTE population	Derived in VTE population
Risk factors			
Age ≥ 60 y			1.5 points
Age > 65 y	1 point		
Age > 75 y		1 point	
History of bleeding	1 point		
Recent bleeding		2 points	
Active cancer		1 point	2 points
Abnormal renal function	1 point	1.5 points	1.5 points
Abnormal liver function	1 point		
History of stroke	1 point		
Anaemia		1.5 points	1.5 points
Hypertension	1 point		1 point
Labile INR	1 point		
Antiplatelets/NSAIDs	1 point		
Alcohol abuse	1 point		
Clinically overt PE		1 point	
Risk stratification			
Low risk	0 points	0 points	0–1.5 points
Intermediate risk	1–2 points	1–4 points	
High risk	3–9 points	4.5–8 points	2–9 points

Abbreviations: AF = Atrial Fibrillation; INR = Internationalised Normalised Ratio; NSAID = non-steroidal anti-inflammatory; PE = Pulmonary Embolism; VTE = Venous thrombo-embolism.

In addition, complications more unique to SCD and thalassaemia should be considered. Patients with SCD who have significant cerebrovascular disease, especially those with Moya Moya formation, are at significantly increased risk of intracerebral haemorrhage. Patients should also be assessed for evidence of active proliferative sickle retinopathy which predisposes to bleeding events.

Recommendations

- **All patients who may require anticoagulant treatment should have an assessment of their bleeding risks prior to their commencement. Currently, no specific SCD-related bleeding risk assessment tools are available.(Grade 2B)**
- **Risk factors for bleeding such as Moya Moya disease or cerebrovascular malformations and proliferative retinopathy should be considered before prescribing anticoagulation.(Grade 2B)**

Thromboprophylaxis in patients with sickle cell disease with central venous catheters

Despite the increased incidence of VTE in patients with SCD with CVCs in situ that has been recognised for many years, there is a lack of studies investigating the use of pharmacological thromboprophylaxis in this group.

No specific anticoagulation practices or guidelines were identified by systematic literature review specific to sickle cell disease. Limitations to the body of evidence identified includes their retrospective nature, the lack of randomised controlled trials to compare thromboprophylaxis in patients with SCD or thalassaemia with CVCs to those without. We identified only two retrospective cohort studies addressing this question: Forté et al. (n=49) and Brewin et al. (n=21).(20,21)

Forté et al., performed a retrospective case control study(21) that specifically examined the rates of VTE in patients with SCD with CVCs with thromboprophylaxis versus without thromboprophylaxis. This multicentre international retrospective cohort study (n=49 with CVC insertion) showed patients without thromboprophylaxis had higher VTE rates 40% (n=10/25) versus 16% (n=4/24) in the patients who did receive thromboprophylaxis.(21)

In this study, thromboprophylaxis type and intensity varied widely. Treatment dose anticoagulation was used in 58% and included either low molecular weight heparin (LMWH), direct oral anticoagulant (DOAC) at approved treatment dosing, or warfarin with a target international normalized ratio (INR) of 2.0–3.0. Thromboprophylaxis at

reduced dosing (42%) was defined as either LMWH, direct oral anticoagulant (DOAC) at approved prophylactic dosing, or warfarin with a target of INR 1.5–2.5, or <2.0, or aspirin at any dose.

On univariate analysis, the use of thromboprophylaxis was associated with a 4 fold (1.2–12.6) reduction in the rate of VTE (p=0.02) without adjustment for other confounding factors that are known VTE risk factors.(21)

On multivariable analysis, after adjustment for sex, age, additional VTE risk factors, hydroxyurea, thromboprophylaxis, body mass index (BMI), and CVC subtype, the relative rate reduction of VTE with thromboprophylaxis was 14.9 (2.0–108.7) (p=0.01).(21)

In a single centre UK retrospective cohort study data of SCD patients, Brewin et al gave a discrete breakdown of VTE events and thromboprophylaxis with CVCs data. They reported the VTE occurrence with venous catheter was 28% without thromboprophylaxis (n=5/18) and no VTEs in the group who utilised thromboprophylaxis (n=0/3) in their small study, although it should be noted that statistical significance was not calculated in this study due to the small sample size. In this very limited cohort on thromboprophylaxis, LMWH at prophylactic dosing was used for 6 weeks only after line insertion.(20)

These two studies offer some evidence of the protective effect of thromboprophylaxis in SCD patients with CVCs however we note the limitations of relying on two retrospective, non-randomised studies. There have been a number of larger studies

investigating the use of prophylaxis in the cancer population and although the recent Cochrane review suggested that there may be some benefit in thromboprophylaxis with a meta-analysis reporting RR 0.43, (95%CI 0.22-0.81) reduction in CRT for those given LMWH prophylaxis vs those not.(40) In addition, they reported no increase in major or minor bleeding.(40) In addition, use of pharmacological thromboprophylaxis was also reported to show a reduction in mortality by a separate meta-analysis of 8 studies of a metastatic cancer population (n = 2639, RR = 0.58, 95% CI:0.48–0.71).(41)

Except for a small number of patients with high bleeding risk complications, thromboprophylaxis prescription is likely to be a safe and beneficial intervention for these patients with CVCs. However, the duration and intensity of the thromboprophylaxis used is not clear cut.For primary prevention, prophylactic dosing is recommended, particularly in the setting of SCD where additional bleeding risks exist due to sickle retinopathy and cerebrovascular disease. For secondary prevention, Clark et al (42) showed that, in a non-SCD paediatric population, only full dose anticoagulation was effective. Selection of the optimal level of anticoagulation for individuals will require careful consideration of their bleeding and thrombosis risk.

There is limited evidence to support the use of any specific class of anticoagulant over another. DOACs, LMWH, and warfarin have all been reported to be effective. DOACs offer fixed dosing, no monitoring requirements, and fewer drug interactions whereas long-term use of LMWH can predispose to osteoporosis which is an important concern in patients with both SCD and thalassaemic conditions.

Recommendations

- **Consider primary thromboprophylaxis in all 16 years (or those post-pubertal) patients with SCD who require an indwelling CVC, balanced against a careful consideration of their bleeding risk.(Grade 2B)**
- **Patients with no additional pro-thrombotic risk factors may reasonably be managed with a short course (e.g. 6 weeks) of thromboprophylaxis to cover line insertion, and during acute episodes of increased risk (e.g., inpatient admission, significant VOC, acute illness, post-surgery).(Grade 2B)**
- **Patients with prothrombotic risk factors, including previous splenectomy, previous VTE, pulmonary hypertension and obesity should be considered for long-term full dose anticoagulation.(Grade 2B)**
-

Treatment of thrombosis and future plans for indwelling catheters

There is insufficient evidence to guide specific management of these CRTs, however, management should follow principles described in other patient groups.

Recommendations

- **If the CVC is functioning and remains important to the ongoing management of the patient it does not need to be removed. (Grade 2B)**
- **If the CVC remains in-situ following thrombosis, the patient should continue full dose anticoagulation for this period.(Grade 2B)**

- **If the CVC is removed, the patient should complete a minimum of 12 weeks of anti-coagulation, then consider ongoing therapy based on their relative thrombotic and bleeding risk factors.(Grade 2B)**

Thromboprophylaxis in patients with thalassaemia with central venous catheters

Our literature review identified only two studies in thalassaemia patients, Davis et al. and Miskin et al. (both presented in Table 2) who found 8 out of 25 catheters were linked to catheter associated VTE and 4 out of 7 patients with an incidence of 0.48 and 0.41 VTE events per 1000 catheter days respectively.(23,24) This is similar to the high VTE risk seen in SCD. Since 2000, the 3rd edition of the Thalassaemia International Federation guidelines has recommended use of prophylactic anticoagulation in thalassaemia major, as line thrombosis is relatively common.(23)

Risk factors identified in thalassaemia include advancing age, previous splenectomy, iron overload and long-term anaemia of <90 g/L are known risk factors for VTE in TDT and NTDT. Optimisation of both thalassaemic and non-thalassaemic risk factors are important to prevent and manage VTE. Those with previous splenectomy are reported to be at significantly increased risk for thrombosis.(43) As discussed in the SCD section, all methods of pharmaceutical anticoagulation are effective and choice can be based largely on local policy, with the caveat that long-term LMWH may increase the risk of osteoporosis in thalassaemic patients.

Recommendations

- **Consider pharmacological thromboprophylaxis for all thalassaemia patients over 16 years (or those post-pubertal) with**

CVCs balancing the patient's individual risk of VTE versus their risk of bleeding. This risk assessment should follow the National Institute for Health and Care Excellence (NICE) VTE guidelines, noting contraindications or unacceptable bleeding risks.

- **Full dose anticoagulation is recommended for secondary VTE prevention, or when the thrombotic risk of a patient is high. Disease specific pro-thrombotic risk factors to consider include previous splenectomy, current iron overload, long-term anaemia and age >35years (Grade 2B)**

- **An individual risk assessment should be performed in prepubescent thalassaemia patients. (Grade 2D)**

Table 2 VTE incidence in sickle cell disease or thalassaemia patients with a venous catheter identified from literature review.

Study	Study design	Year of study	VTE event with venous catheter of total VTEs / per person thrombotic rate	Incidence of catheter related thrombosis (per 1000 catheter days)	Rate of VTE without CVC	Rate of VTE in control patient with CVC	Risk ratio	Anticoagulation status
Forté et al.(21)	Multi-centre international retrospective cohort study in adults with SCD (n=949, 49 with CVC)	2022	40% (n=10/25) without thromboprophylaxis versus 16% (n=4/24) in with thromboprophylaxis	0.44 without thromboprophylaxis Versus 0.13 with thromboprophylaxis	NR	NR	4	25 patients not anticoagulated with CVC versus 24 who were anticoagulated with CVC
Brewin et al.(20)	Single centre UK retrospective cohort study in adults with SCD (n=21)	2020	23.8% (n=5/21) 28% (n=5/18) without thromboprophylaxis 0% (n=0/3) with thromboprophylaxis	NR	NR	NR	NR	18 patients not anticoagulated; 3 patient who were anticoagulated with CVC
Woods et al.(25)	Single centre US retrospective case-control study in children with SCD (n=414)	2018	22% (n=9/41)	0.14	0.75% (n = 3/402)	NR	33.8 (CI 8.7–130.9)	Not anticoagulated
Ordonez et al.(29)	Single centre Spanish retrospective cohort study in children with SCD and thal (n=54)	2020	7.4% (n=4/54)	0.32	NR	NR	NR	Unclear
Naik et al.(3)	Single centre US retrospective cross-	2012	30.7% (n=31/101)	NR	18.8% (n = 76/404)	NR	NR	Not anticoagulated

Study	Study design	Year of study	VTE event with venous catheter of total VTEs / per person thrombotic rate	Incidence of catheter related thrombosis (per 1000 catheter days)	Rate of VTE without CVC	Rate of VTE in control patient with CVC	Risk ratio	Anticoagulation status
	sectional study in adults with SCD (n=404)							
Shah et al.(18)	Single centre US retrospective cross-sectional study in adults with SCD (n=32)	2012	41% (n=10/32)	0.49	NR	NR	NR	Not anticoagulated
Jeng et al.(15)	Single centre US retrospective study in children and adults with SCD (n=15) patients aged 1.4–30 years)	2002	33%	0.99	NR	NR	NR	Not anticoagulated
Davis, BA and Porter J.(23)	Single centre UK retrospective cross-sectional study of adults with Thal (n=17)	2000	32% (n=8/25) / 47% (n=8/17)	0.48	NR	NR	NR	Not anticoagulated
Miskin et al.(24)	Single centre Israeli retrospective cohort study of adults with Thal (n=43)	2003	57% (n=4/7)	0.41	NR	NR	NR	Not anticoagulated
Alkindi et al.(19)	Single centre Omani retrospective case control study in adults with SCD (n=16)	2012	12.5% (n=3/24 CVADs) / 18.75% (n=3/16)	0.18	NR	NR	NR	Anticoagulated post year 2000 1mg warfarin daily
Raj et al.(16)	Single centre retrospective study in patients aged 7–20 with SCD (n=15)	2005	15% (n=3/15)	0.16	NR	NR	NR	Not anticoagulated

Study	Study design	Year of study	VTE event with venous catheter of total VTEs / per person thrombotic rate	Incidence of catheter related thrombosis (per 1000 catheter days)	Rate of VTE without CVC	Rate of VTE in control patient with CVC	Risk ratio	Anticoagulation status
Phillips et al.(14)	Single centre US retrospective cross sectional study in adults with SCD (n=8)	1988	20% (n=2/10) / 25% (n=3/8)	0.46	NR	3% (n=1/33)		NR
Abdul-Rauf et al.(17)	Single centre US retrospective cross sectional study in patients aged 8months–25years with SCD (n=25)	1995	8% (n=2/25)	0.29	NR	NR	NR	NR
Ilonze et al.(32)	Single centre US retrospective cohort (n=32) of paediatric patients with SCD	2021	9.4% (n=3/32)	0.03	NR	NR	NR	NR

Abbreviations: NR = Not recorded; SCD = sickle cell disease; Thal = thalassaemia.

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Declaration of Interests

The BSH paid the expenses incurred during the writing of this guidance.

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. All members of the writing group have no conflicts of interest to declare.

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 and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. 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 A

Literature review details

Searches were performed using the online search engine Medline (PubMed).
Search terms were: (Sickle cell anaemia OR sickle cell anemia OR sickle cell disease OR thalassemia OR thalassaemia) AND (Venous catheter OR intravenous catheter OR CVC OR CVAD OR central venous access device OR portacaths OR PICC OR peripherally inserted central catheter OR intravenous catheter) AND (Venous thromboembolism OR VTE OR pulmonary embolism OR thromboembolism OR deep vein thrombosis OR catheter associated thrombosis); (Sickle cell anaemia OR sickle cell anemia OR sickle cell disease OR thalassemia OR thalassaemia) AND (Venous thromboembolism OR VTE OR pulmonary embolism OR thromboembolism OR deep vein thrombosis OR catheter associated thrombosis); (Sickle cell anaemia OR sickle cell disease OR thalassemia) AND (central venous devices) AND (thrombosis OR thromboembolism); (Sickle cell anaemia OR sickle cell disease OR thalassemia) AND (thrombosis OR thromboembolism). Filters were applied to include only publications written in English, studies carried out in humans, meta-analyses, retrospective studies, randomised controlled trials, reviews, systematic reviews, and published between 01/01/2000 –01/04/2023.

Searches of individual journals were not implemented because it was felt that publications not captured during the database search process would have had limited availability and would have had little impact on the scientific community.

Criteria for Review and Data Collection

Titles and/or abstracts of publications obtained from the database searches described were manually reviewed and excluded if they do not adhere to the abstract review criteria.

Abstract review

An abstract screening was performed based on the following criteria.

Table 2 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Mentions sickle cell anaemia with intravenous catheters or thalassaemia patients with intravenous catheters	Does not mention sickle cell anaemia or thalassaemia
AND	OR
Venous thromboembolism	Does not mention venous catheters
	OR
	Case reports
	OR
	Literature reviews

Results

A literature search was initially undertaken to identify any association of venous thromboembolism with intravenous catheter devices in sickle cell anaemia and thalassaemia. 37 publications were identified and based on the abstract screening 16 articles were removed and 21 were retained.

All the papers can be sent on request. These are presented in Table A.

Table A Summary of Abstracts

	Citation	Abstract
1.	Venous Thromboembolism in Children with Sickle Cell Disease: A Retrospective Cohort Study. Woods GM, Sharma R, Creary S, O'Brien S, Stanek J, Hor K, Young J, Dunn AL, Kumar R.J Pediatr. 2018 Jun;197:186-190.e1. doi: 10.1016/j.jpeds.2018.01.073. Epub 2018 Mar 28.PMID: 29605397.(25)	Abstract Objectives: To describe the cumulative incidence of venous thromboembolism (VTE) in children with sickle cell disease (SCD) followed at a single institution and report on the risk factors associated with VTE development. Study design: Charts for all patients with SCD, aged 0–21 years, followed at Nationwide Children's Hospital over a 6-year period (January 1, 2009, to January 31, 2015) were reviewed. Data on VTE diagnosis, sex, body mass index/weight-for-length, SCD genotype, SCD clinical complications, central venous catheter (CVC) placement, and thrombophilia testing were collected. Results: Cumulative incidence of VTE in children with SCD followed at a single tertiary care institution was found to be 2.9% (12/414). Nine of the 12 VTE were CVC-associated. On univariate analysis, hemoglobin SS genotype (OR 10.7, 95% CI 1.4–83.5), CVC presence (OR 34.4, 95% CI 8.9–134.6), central nervous system vasculopathy (OR 19.4, 95% CI 5.6–63.4), chronic transfusion therapy (OR 30.6, 95% CI 8.9–122.2), and older age (P=.03) were associated with VTE. However, presence of CVC was the only independent risk factor identified on multivariable logistic regression analysis (OR 33.8, 95% CI 8.7–130.9). Conclusion: In our institution, nearly 3% of children with SCD had a history of VTE. CVC is an independent predictor of VTE in children with SCD. Keywords: sickle cell disease; venous thromboembolism.
2.	Alkindi S, Al-Ghadani AR, Al-Zeheimi SR, Alkindi SY, Fawaz N, Ballas SK, Pathare AV. Predicting risk factors for thromboembolic complications in patients with sickle cell anaemia - lessons learned for prophylaxis. J Int Med Res. 2021 Dec;49(12):3000605211055385.(7)	Objective: To assess the clinical and laboratory predictors of venous thromboembolism (VTE) in patients with sickle cell anaemia (SCA) and its relationship to morbidity and mortality. Methods: This retrospective case-control study analysed data from patients with SCA that experienced VTE compared with matched control patients with SCA but no VTE (2:1 ratio). Results: A total of 102 patients with SCA were enrolled (68 cases with VTE and 34 controls). Amongst the 68 cases (median age, 29.5 years), 26 (38.2%) presented with isolated pulmonary embolism (PE). A higher prevalence of splenectomy (73.5% versus 35.3%) was observed in the cases compared with the controls. A significantly higher prevalence of central venous catheter (CVC) insertion (42.6% versus 8.8%) was observed in the cases compared with the controls. High white blood cell counts, serum lactic dehydrogenase (LDH), bilirubin and C-reactive protein (CRP) and low haemoglobin (Hb) and HbF were significant risk factors for VTE. Forty-two cases (61.8%) developed acute chest syndrome, 10 (14.7%) had a stroke and seven (10.3%) died. Conclusions: VTE in patients with SCA has a high impact on morbidity and mortality. PE was the leading presentation of VTE, with CVC insertion, high LDH, bilirubin, CRP and white blood cell counts along with low Hb and HbF constituting other significant risk factors. Keywords: Venous thromboembolism; pulmonary embolism; sickle cell disease.

3.	Ordóñez J, Del Cañizo A, Beléndez C, García-Morín M, Pérez-Egido L, Fanjul M, García-Casillas MA, Cerdá J, Peláez D, Bardón E, de Agustín JC, Cela E. Complications of Central Venous Access Devices in Patients With Sickle Cell Disease and Thalassemia Major. J Pediatr Hematol Oncol. 2021 Jul 1;43(5):e655-e660.(29)	Pediatric patients with sickle cell disease and thalassemia major present clinical characteristics that could lead to a higher incidence of central venous access devices-associated complications (CVAD-C). With the objective of analyzing the safety of the use of CVAD in these patients, a retrospective review including all pediatric patients with these pathologies who required the implantation of a CVAD between 2004 and 2019 was performed. In all, 54 patients with 100 CVAD (65 totally implantable venous access port with subcutaneous reservoir, 35 single-lumen or double-lumen partially tunnelled catheter) were included. During 60,410 days at risk of suffering a CVAD-C, 55 complications (complication rate [CR]/1000 catheter-days at risk=0.91) were reported in 46 CVAD: 19 mechanicals (CR=0.32), 32 infectious (CR=0.53), and 4 thrombotic complications (CR=0.066). Incidence of mechanical and infectious complications was significantly higher in double-lumen partially tunnelled catheter than in totally implantable venous access port with subcutaneous reservoir (P<0.001). Lower age at insertion was related with a higher incidence of any complication (odds ratio=0.88/y, P=0.02). Patients who required a stem cell transplantation (31 patients and 65 CVAD) had no significant higher incidences of CVAD-C. In conclusion, our study supports the safety of using CVAD in these patients, with a low incidence of infectious, thrombotic, and mechanical complications.
4.	Boechat Tde O, do Nascimento EM, Lobo CL, Ballas SK. Deep venous thrombosis in children with sickle cell disease. Pediatr Blood Cancer. 2015 May;62(5):838-41. doi: 10.1002/pbc.25431. Epub 2015 Feb 12. PMID: 25683443.(31)	Deep venous thrombosis (DVT) is rare in children compared to adults. Its incidence and risk factors in children are not well known. This study determined these aspects of DVT in children with sickle cell disease (SCD). Procedure: A retrospective, observational and descriptive study was performed. Patients born between October 2000 and October 2012 with SCD and registered in HEMORIO, including those who died in HEMORIO, were included in this study. Patients whose medical records were inaccessible, who died in institutions other than HEMORIO, who died with implanted deep venous catheters, and those who were not monitored in HEMORIO for a period of 1 year or more were excluded from the study. Of a total of 1,519 patients, 456 were excluded and 1,063 patients were included in the study. Data were obtained from the computer system and the medical records at HEMORIO. Results: Of the 1,063 patients, 2 (0.2%) developed DVT with both cases being related to central venous catheters (CVCs) (P-value <0.001). Of the patients who required CVCs, the prevalence of DVT was 10%. No other variable was clinically or statistically significant with respect to DVT. Conclusion: The establishment of CVCs in children with SCD poses a high risk for DVT. If this procedure is necessary, the internal jugular vein should be utilized instead of the subclavian and femoral veins. The identification of associated risk factors may justify antithrombotic prophylaxis. Keywords: DVT; central venous catheter; deep venous thrombosis; sickle cell anemia; sickle cell disease; thrombosis.

5.	Jeng MR, Feusner J, Skibola C, Vichinsky E. Central venous catheter complications in sickle cell disease. Am J Hematol. 2002 Feb;69(2):103-8. doi: 10.1002/ajh.10047. PMID: 11835345.(15)	A review of patients with sickle cell disease (SCD) and central venous catheters (CVCs) was performed to evaluate the frequency of catheter complications (infections, thrombotic events, and premature CVC removal. Fifteen evaluable patients were identified during our review of a 7.5-year period. The median age was 18 years (range, 1.5–30 years); 14 were African American, and 1 was Latino; 5 were male, and 10 were female. Forty–one CVCs were placed (36 Mediport and 5 Broviac catheters) for a total of 12,120 CVC days. We observed a median of 2 CVCs per patient (range, 1–8 CVCs per patient) with 67 discrete episodes of CVC-associated infection (range, 0–18 per patient) involving 10 patients. The rate of CVC-associated infection for patients with SCD at our institution was 5.5 infections per 1,000 CVC days; this rate was significantly higher than the rate of CVC-associated infection in our patients with cancer (P<0.001). We also determined that the rate of CVC-associated thrombosis was 0.99 events per 1,000 CVC days and involved 33% of the patients with SCD; the rate of premature CVC removal was 3.15 per 1,000 CVC days, and 78% of CVCs were removed prematurely. We conclude that patients with SCD are at high risk for CVC-related complications, and improved care and close monitoring of CVCs should be encouraged to decrease morbidity in these chronically ill patients.
6.	Naik RP, Streiff MB, Haywood C Jr, Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. Am J Med. 2013 May;126(5):443-9. doi: 10.1016/j.amjmed.2012.12.016. PMID: 23582935; PMCID: PMC3627211.(3)	Background: Sickle cell disease is recognized as a hypercoagulable state; however, the frequency and characteristics of venous thromboembolism in sickle cell patients have not been well defined. The purpose of this study was to establish the prevalence and risk factors for venous thromboembolism in a large cohort of patients with sickle cell disease and determine the relationship between venous thromboembolism and mortality. Methods: We performed a cross-sectional study of 404 sickle cell disease patients cared for at the Sickle Cell Center for Adults at Johns Hopkins. Demographic, sickle cell disease-specific comorbidity, and venous thromboembolism data were collected on all patients. Results: One hundred one patients (25%) had a history of venous thromboembolism with a median age at diagnosis of 29.9 years. A history of non-catheter-related venous thromboembolism was found in 18.8% of patients. Sickle variant genotypes conferred a higher risk of non-catheter-related venous thromboembolism compared with sickle cell anemia genotypes (SS/Sβ(0)) (relative risk [RR] 1.77; 95% confidence interval [CI], 1.18-2.66). Tricuspid regurgitant jet velocity ≥2.5 m/s also was associated with non-catheter-related venous thromboembolism (RR 1.65; 95% CI, 1.12-2.45). Thirty patients (7.4%) died during the study period. Adjusting for all variables, non-catheter-related venous thromboembolism was independently correlated with death (RR 3.63; 95% CI, 1.66-7.92). Conclusion: Venous thromboembolism is common in adults with sickle cell disease. Sickle variant genotypes and tricuspid regurgitant jet velocity ≥2.5 m/s are associated with non-catheter-related venous thromboembolism. In addition, non-catheter-related venous thromboembolism appears to be an independent risk factor for death in our cohort. These results suggest that disease-specific prophylaxis and treatment strategies for venous thromboembolism should be investigated in sickle cell disease patients.

7.	Brewin JN, Crowley MP, Kesse-Adu R, Stuart-Smith S, Awogbade M, Howard J. Catheter associated thromboses in patients with sickle cell anaemia and dual lumen Vortex apheresis ports are common and can be clinically asymptomatic. Br J Haematol. 2020 Jun;189(5):e198-e200. doi: 10.1111/bjh.16619. Epub 2020 Mar 24. PMID: 32207154.(20)	Correspondence
8.	Stone RH, Bress AP, Nutescu EA, Shapiro NL. Upper-Extremity Deep-Vein Thrombosis: A Retrospective Cohort Evaluation of Thrombotic Risk Factors at a University Teaching Hospital Antithrombosis Clinic. Ann Pharmacother. 2016 Aug;50(8):637-44. doi: 10.1177/1060028016649601. Epub 2016 May 17. PMID: 27189014.(43)	Background: Upper-extremity deep-vein thrombosis (UEDVT) causes significant morbidity and mortality and is not well characterized in the existing literature, particularly in underrepresented minorities such as African Americans. Objective: To describe the characteristics of a cohort of patients with UEDVT seen at an urban academic medical center. Methods: This was a retrospective cohort study among patients with a confirmed UEDVT at the University of Illinois Hospital and Health Sciences System between 1996 and 2011. Patients were identified by ICD-9 code for UEDVT. Variables collected include thrombotic risk factors and outcomes, including recurrent thrombosis and bleeding. Results: We identified 229 patients with UEDVT; 71% were African American, and 11% were diagnosed with sickle cell disease. The average number of UEDVT risk factors was 4.40 ± 1.5, the most common being central venous catheter (CVC) use (178, 78%). In the year following UEDVT, 13% experienced recurrent thrombosis, and 6% experienced major bleeding. Of 181 patients receiving warfarin after an UEDVT, 36% of international normalized ratio (INR) values were therapeutic. Patients with sickle cell disease had a lower proportion of INRs within the target range (25% vs 38%, P<0.01), and were more likely to be lost to follow-up (67% vs 46%, P=0.05) and experience a recurrent thrombotic event (29% vs 11%, P=0.02). Conclusion: A CVC is the most common risk factor for UEDVT; however, patients with sickle cell disease demonstrate additional unique demographics and risk factors. Patients included in this underrepresented demographic cohort had a low quality of anticoagulation control, particularly those with sickle cell disease.

9.	Alkindi S, Matwani S, Al-Maawali A, Al-Maskari B, Pathare A. Complications of PORT-A-CATH® in patients with sickle cell disease. J Infect Public Health. 2012 Mar;5(1):57-62. doi: 10.1016/j.jiph.2011.10.004. Epub 2011 Dec 6. PMID: 22341844.(19)	Background: Red cell exchange/transfusion is frequently used in the management of patients with medical complications related to acute severe sickle cell disease (SCD). However, peripheral venous access is often difficult without central venous catheters (CVCs) in adult patients with moderate or severe SCD. Aims: To review our experience with the use of the PORT-A-CATH(®) device in sixteen patients with SCD undergoing exchange or simple transfusions. Methods: Among a cohort of 550 patients who frequently visited the inpatient service, sixteen SCD patients required the insertion of a PORT-A-CATH(®) device. These patients included 3 males and 13 females, aged 25–44 years [31.1 ± 2.3; mean ± SD]. A total of 24 PORT-A-CATH(®) devices were implanted in these 16 patients during the study period. Eleven patients had 1 device implanted, three patients had 2 devices, one patient had 3 devices, and one patient had 4 devices implanted. Results: Out of the 24 devices implanted, 17 required removal, due to either infection associated with sepsis and/or thrombosis. The organisms involved were Candida spp.(3), C. Parapsilosis (2), C. albicans (1), C. famata (1), C. lusitanice (1), Staphylococcus spp.(6), and S. aureus (3), as well as the coagulase-negative Staphylococcus (2), alpha hemolytic Streptococcus (1), Diphtheroid bacilli (2), Pseudomonas aeruginosa (2), Ps. Spp.(3), Escherichia coli (3), Klebsiella oxytoca (1), Klebsiella pneumoniae (1), Klebsiella spp.(1), Serratia liquefaciens (1), Serratia fanticola (1), Achromobacter spp.(2) Chromobacterium violaceum (1), Delftia acidovirans (1), Stenotrophomonas maltophile (1), Alcaligenes faecalis (1), and Enterobacter cloacae (1). Two episodes of documented thrombosis were observed. One case presented with right atrial thrombosis/SVC syndrome and the other case presented with left upper arm thrombosis. Two patients died with ports in situ, while five patients had ports in place at the time of this study. The median working life of the ports was 688.5 days (range: 39–3925). The rate of infective complications was 2.63 infections per 1000 catheter days, and the number of infections was significantly correlated with the number of ports [Pearson's r=0.66; p<0.01]. Discussion: Our results suggest that patients with SCD suffer infective complications associated with the PORT-A-CATH(®), which often necessitate its removal. Although these devices are extremely useful, their optimal beneficial potential is only realized if the patients receive proper care at special centers well-versed in the maintenance of such devices by experienced staff.
10.	Impact of erythrocytapheresis on natural anticoagulant levels in children with sickle cell disease: A pilot study. Sharma R, Woods GM, Creary S, O'Brien S, Stanek J, Hor K, Gallagher C, Dunn AL, Kumar R.Pediatr Blood Cancer. 2019 Apr;66(4):e27588. doi: 10.1002/pbc.27588. Epub 2018 Dec 13.PMID: 30548773.(33)	Venous thromboembolism (VTE) is being increasingly recognized in children with sickle cell disease (SCD). In a retrospective cohort study, we identified bilateral central venous catheter (CVC) placement as an independent risk factor for VTE. At our institution, the only indication for bilateral CVC placement in children with SCD is erythrocytapheresis. To investigate the impact of erythrocytapheresis on coagulation, we measured levels of natural anticoagulants in 11 patients with SCD on chronic erythrocytapheresis, immediately before and after apheresis. We demonstrated a statistically significant reduction in most parameters. Additional studies are needed to further investigate the exact etiology and clinical impact of this acute decrease.

11.	Forté S, De Luna G, Abdulrehman J, Fadiga N, Pestrin O, Pham Hung d'Alexandry d'Orengiani AL, Aneke JC, Guillet H, Budhram D, Habibi A, Ward R, Bartolucci P, Kuo KHM. Thromboprophylaxis Reduced Venous Thromboembolism in Sickle Cell Patients with Central Venous Access Devices: A Retrospective Cohort Study. J Clin Med. 2022 Feb 23;11(5):1193. doi: 10.3390/jcm11051193. PMID: 35268283; PMCID: PMC8910838.(21)	Sickle cell disease (SCD) induces a chronic prothrombotic state. Central venous access devices (CVADs) are commonly used for chronic transfusions and iron chelation in this population. CVADs are an additional venous thromboembolism (VTE) risk factor. The role of thromboprophylaxis in this setting is uncertain. The objectives are: (1) to determine whether thromboprophylaxis reduces VTE risk in SCD patients with CVAD and (2) to explore characteristics associated with VTE risk. We identified adults with SCD and CVAD intended for chronic use (≥3 months) at two comprehensive SCD centers. Thromboprophylaxis presence; type; intensity; and patient-, catheter-, and treatment-related VTE risk factors were recorded. Among 949 patients, 49 had a CVAD (25 without and 24 with VTE prophylaxis). Thromboprophylaxis type and intensity varied widely. Patients without thromboprophylaxis had higher VTE rates (rate ratio (RR) = 4.0 (95% confidence interval: 1.2–12.6), p=0.02). Hydroxyurea was associated with lower VTE rates (RR = 20.5 (6.4–65.3), p < 0.001). PICC lines and Vortex and Xcela Power implantable devices were associated with higher rates compared with Port-a-Cath (RR = 5.8 (1.3–25.9), p=0.02, and RR = 58.2 (15.0–225.0), p < 0.001, respectively). Thromboprophylaxis, hydroxyurea, and CVAD subtype were independently associated with VTE. The potentially protective role of thromboprophylaxis and hydroxyurea for VTE prevention in patients with SCD and CVAD merits further exploration.
12.	Yu TT, Nelson J, Streiff MB, Lanzkron S, Naik RP. Risk factors for venous thromboembolism in adults with hemoglobin SC or Sβ(+) thalassemia genotypes. Thromb Res. 2016 May;141:35-8. doi: 10.1016/j.thromres.2016.03.003. Epub 2016 Mar 2. PMID: 26962984; PMCID: PMC4856579.(34)	Introduction: Venous thromboembolism (VTE) is common in sickle cell disease (SCD); however, the risk factors associated with VTE in patients with sickle variant syndromes are not known. The primary aim of this study was to determine hematologic and clinical risk factors for VTE in adults with hemoglobin SC or Sβ(+) thalassemia genotypes. Materials and methods: We conducted a retrospective cross-sectional analysis of patients with hemoglobin SC and Sβ(+) thalassemia genotypes followed at the Sickle Cell Center for Adults from 2008 to 2012. Data on baseline hematologic parameters and SCD-specific comorbidities were collected from review of electronic records. Results: A total of 116 patients, 85 (73%) with hemoglobin SC disease and 31 (27%) with Sβ(+)-thalassemia, were included for analysis. Thirty-two (28%) patients had a verified history of non-catheter related VTE. Mean baseline hemoglobin levels were higher among individuals with a history of VTE compared to those without (11.7g/dL vs. 11.0g/dL, p=0.003). In addition, the prevalence of surgical splenectomy was higher among patients with VTE compared to those without (25.0% vs. 4.8%, p=0.001). On multivariate analysis, elevated baseline hemoglobin (odds ratio [OR] 2.45 (95% confidence interval [CI] 1.42–4.23)) and history of surgical splenectomy (OR 5.76 [CI 1.43–23.22]) were independently associated with VTE risk. Conclusions: Higher baseline hemoglobin is a risk factor for non-catheter-related VTE in patients with hemoglobin SC or Sβ(+) thalassemia genotypes. Surgical splenectomy, which is a known risk factor for VTE in other hemoglobinopathies such as β-thalassemia intermedia, is also associated with VTE in sickle variant syndromes. Future studies are needed to validate these findings and to investigate the mechanisms of hypercoagulability observed in patients with hemoglobin SC and Sβ(+) thalassemia.

13.	Yeral M, Boga C, Oguzkurt L, Asma S, Kasar M, Kozanoglu I. Short-term central venous catheter complications in patients with sickle cell disease who undergo apheresis. J Thromb Thrombolysis. 2014;37(2):97-101. doi: 10.1007/s11239-013-0914-z. PMID: 23504572.(13)	Patients with sickle cell disease (SCD) are prone to develop thrombosis and infection due to their inflammatory and immune deficiency state. These patients require red cell exchange therapy for treatment or prevention of hemoglobin S associated complications. Owing to vascular access problems, adult patients need central venous catheterization (CVC) for exchange procedures. Procedure related complications have been reported for long-term CVCs in pediatric patients. However, short-term CVC complications in adult patients are not clear. This report represents the results of documented complications of short-term CVCs in patients with SCD who undergo apheresis. A total of 142 non-tunneled catheters with average median diameter of 9 F (range 8–16 F) were implanted for apheresis. The catheters were mainly inserted through the right internal jugular vein (66.2 %). Total days of catheter were 412. Results were reported as a complication rate and event according to 1,000 catheter days and compared to a control group including 37 healthy stem cell donors. In the patient group, 1 (1 %) hematoma and 1 (1 %) infection were observed for internal jugular vein catheterization (3.7 hemorrhages and 3.7 infections according to 1,000 catheter days), whereas four (8.9 %) cases of thrombosis and 1 (2.2 %) infection (27 and 6.9 according to 1,000 catheter days) developed in femoral vein. There was a significant difference in terms of thrombosis (P=0.009). In the control group, only individual developed thrombosis in internal jugular vein. Short-term CVC inserted through to the internal jugular vein seems to be safer than femoral vein in patients with SCD.
14.	Shah N, Landi D, Shah R, Rothman J, De Castro LM, Thornburg CD. Complications of implantable venous access devices in patients with sickle cell disease. Am J Hematol. 2012 Feb;87(2):224-6. doi: 10.1002/ajh.22230. Epub 2011 Nov 12. PMID: 22081438.(18)	Implantable venous access devices (VADs) are used in sickle cell disease (SCD) for patients with poor venous access to facilitate chronic blood transfusions and manage acute complications. We attempted to define the frequency of bloodstream infections (BSI) and thrombosis in adults and children with SCD and VADs. We performed a single-institution, retrospective review of VAD-associated infection and thrombosis in patients with SCD. Thirty-two patients (median age 20 years, range, 1–59) had 86 VADs placed (median, 2.7 VADs per patient, range, 1–7) with a total of 41,292 catheter days (median, 1,376 days; range, 323–3,999). Mean catheter lifespan in adults (691 days ± 123) was not significantly higher than children (614 days ± 154). A total of 66 VAD-associated BSI (1.59 infections per 1,000 catheter days) occurred in 17 of 32 (53%) patients. Children with VADs had fewer BSI (3 of 10; 30%) than adults (14 of 22; 64%, P=0.08). 24 catheter-associated thromboses (0.49 thromboses per 1,000 catheter days) occurred in 10 of 32 (41%) of patients. Children also had fewer VAD-associated-thrombosis (1 of 10; 10%) than adults (9 of 22; 40%, P=0.08). In conclusion, the use of VADs in SCD was linked to a significant rate of infection and thrombosis.
15.	Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia. Blood. 2000 Feb 15;95(4):1229-36. PMID: 10666195.(23)	The optimal regimen of intravenous deferoxamine for iron overload in high-risk homozygous beta-thalassemia is unknown because only short-term follow-up has been described in small patient groups. We report the outcome over a 16-year period of a continuous 24-hour deferoxamine regimen, with dose adjustment for serum ferritin, delivered via 25 indwelling intravenous lines for 17 patients. Treatment indications were cardiac arrhythmias, left ventricular dysfunction, gross iron overload, and intolerability of subcutaneous deferoxamine. Cardiac arrhythmias were reversed in 6 of 6 patients, and the left ventricular ejection fraction improved in 7 of 9 patients from a mean (+/- SEM) of 36 +/- 2% to 49 +/- 3% (P=.002, n = 9). The serum ferritin fell in a biphasic manner from a pretherapy mean of 6281 +/- 562 microg/L to 3736 +/- 466 microg/L (p=0.001), falling rapidly and proportionally to the pretreatment ferritin (r(2) = 0.99) for values >3000 microg/L but falling less rapidly below this value (at 133 +/- 22 microg/L/mo). The principal catheter-related complications were infection and thromboembolism (1. 15 and 0.48

		per 1000 catheter days, respectively), rates similar to other patient groups. Only one case of reversible deferoxamine toxicity was observed (retinal) when the therapeutic index was briefly exceeded. An actuarial survival of 61% at 13 years with no treatment-related mortality provides evidence of the value of this protocol.(Blood. 2000;95:1229-1236)
16.	Ilonze C, Anderson M, Stubblefield A, Journeycake J, Sinha AA. Use of infusion ports in patients with sickle cell disease: Indications and complications. Pediatr Blood Cancer. 2022 Feb;69(2):e29445. doi: 10.1002/pbc.29445. Epub 2021 Nov 16. PMID: 34786823.(32)	Background: Peripheral venous access in patients with sickle cell disease (SCD) can become difficult over time due to frequent access and scarring. Infusion ports provide reliable central venous access. Deep venous thrombosis (DVT) and infections are complications associated with SCD and infusion ports. Methods: We performed a 17.5-year single-institution retrospective chart review (January 2000 to July 2018) with literature review regarding use of infusion ports in patients with SCD. Results: We identified 32 patients with infusion ports placed for a total of 63 devices (48 for chronic transfusion [CT] and 15 for poor venous access [PVA], not on CT) for a total of 99,272 catheter days. The mean age at first insertion was 8 years (range 1–20 years). Complications included malfunction, infection, thrombosis, difficult access, and pain over infusion port site. The rate of infection was 0.2 per 1000 catheter days. Thrombosis was identified in three devices (5%) in three patients (9%), with a rate of 0.03 per 1000 catheter days. There was no difference in complications by site in either the left or right subclavian vein (p=1). The rate of premature removal was 0.36 per 1000 catheter days, which was higher among patients with infusion ports solely for PVA (0.87 per 1000 catheter days) compared with those placed for CT (0.29 per 1000 catheter days). Conclusion: Infusion ports in patients with SCD was associated with low rates of thrombosis, infection, and malfunction, and may be considered as an alternative to frequent intravenous access, especially in patients requiring CT.

17.	Abdul-Rauf A, Gauderer M, Chiarucci K, Berman B. Long-term central venous access in patients with sickle cell disease. Incidence of thrombotic and infectious complications. J Pediatr Hematol Oncol. 1995 Nov;17(4):342-5. doi: 10.1097/00043426-199511000-00011. PMID: 7583391.(17)	Abstract Purpose: Central venous access devices (CVAD) have been used with increasing frequency in recent years among pediatric patients. We retrospectively reviewed our experience in 25 children and young adults with sickle cell disease (SCD) over a 4 1/2 year period in an attempt to define occurrence rates of perioperative complications, thrombosis requiring catheter removal, and infectious episodes. Patients and methods: The setting was a university-associated tertiary children's hospital. Patients were 25 children and young adults (ages 8 months to 23 years) with SCD who required CVAD placement between February 1987 and April 1992. A total of 31 catheters (totally implantable ports and partially implanted catheters) were placed for 17,444 patient catheter days. Results: Rates of significant perioperative complications, thrombotic events requiring catheter removal, and infectious episodes were recorded. No perioperative complications were noted. Five episodes of catheter occlusion requiring replacement occurred in two patients (0.29 per 1,000 catheter patient days, involving 8% of patients and 16% of catheters). Fifteen episodes of catheter-associated bacteremia occurred in eight patients (0.86 per 1,000 catheter patient days involving 32% of patients and 26% of catheters). Three catheters required removal because of infection unresponsive to antibiotic therapy. Conclusion: The occurrence of thrombosis requiring catheter removal and infection in our population of patients with SCD was comparable to that reported in patients with malignant disease, cystic fibrosis and acquired immune deficiency syndrome. CVAD represents an effective, reliable, and reasonably safe means of establishing and maintaining venous access for a selective group of children and young adults with SCD who have limited peripheral venous access and require intravenous therapies.
18.	Phillips G, Slingluff C, Hartman J, Thomas P, Akwari O. Totally implantable intravenous catheters in the management of sickle cell anemia. Am J Hematol. 1988 Nov;29(3):134-8. doi: 10.1002/ajh.2830290303. PMID: 3189307.(14)	Totally implantable catheters (TICs) have recently been employed for long-term central venous access in patients with sickle cell disease (SCD). We have reviewed our experience with 10 TICs inserted in patients with SCD. These were compared to 33 TICs inserted in patients without SCD (controls). The primary diagnosis was malignancy in most of the controls. The SCD patients experienced a marked increase in total complications (70 vs. 24%), as well as in complications requiring catheter removal (50 vs. 3%). No variable explained these differences except the presence of SCD. The complications requiring catheter removal from SCD patients were infections, catheter thrombosis, and venous thrombosis. The increased risk of these complications must be considered before a catheter is inserted; however, the average useful life of these catheters exceeded 12 months. They remained useful in the care of patients with poor venous access and multiple complications of SCD.

19.	Miskin H, Yaniv I, Berant M, Hershko C, Tamary H. Reversal of cardiac complications in thalassemia major by long-term intermittent daily intensive iron chelation. Eur J Haematol. 2003 Jun;70(6):398-403. doi: 10.1034/j.1600-0609.2003.00075.x. PMID: 12756023.(24)	Abstract Objectives: In patients with thalassemia major (TM) who are non-compliant with long-term deferoxamine (DFO) chelation, survival is limited mainly because of cardiac complications of transfusional siderosis. It was recently shown in a small group of TM patients with established cardiac damage that continuous 24-h DFO infusion via an indwelling intravenous (i.v.) catheter is effective in reversing cardiac toxicity. The aim of the present study was to evaluate the results with intermittent daily (8–10 h) i.v. DFO. Patients: Eight TM patients with cardiac complications treated with intensive intermittent DFO were retrospectively evaluated by the mean annual serum ferritin, radionucleated ventriculography and 24-h electrocardiography recordings. Results: The median age at diagnosis of cardiac disease was 17.5 yr (range 14–21), and the median follow-up time was 84 months (range, 36–120). In the majority of patients (seven of eight) high-dose DFO (mean 95 +/- 18.3 mg/kg/d) was administered via a central venous line. During follow-up, there was a significant decrease in the mean ferritin levels (5828 +/- 2016 ng/mL to 1585 +/- 1849 ng/mL, P<0.001). Both cardiac failure (mean ejection fraction 32 +/- 5) and cardiac arrhythmias were resolved in four of five patients. One non-compliant patient died during the follow-up. Following discontinuation of the i.v. therapy, compliance with conventional DFO therapy improved. The complications of this regimen, mainly catheter-related infections and catheter-related thrombosis, were similar to those described earlier. Conclusions: These results with the longest follow-up period in the literature suggest that i.v. high-dose DFO for 8–10 h daily may be as effective as continuous 24-h infusion for the reversal of established cardiac disease in TM.
20.	Bartram JL, O'Driscoll S, Kulasekararaj AG, Height SE, Dick M, Patel S, Rees DC. Portacaths are safe for long-term regular blood transfusion in children with sickle cell anaemia. Arch Dis Child. 2011 Nov;96(11):1082-4. doi: 10.1136/adc.2009.173856. Epub 2010 Jul 6. PMID: 20605863.(30)	BACKGROUND: Deep venous thrombosis (DVT) is rare in children compared to adults. Its incidence and risk factors in children are not well known. This study determined these aspects of DVT in children with sickle cell disease (SCD). PROCEDURE: A retrospective, observational and descriptive study was performed. Patients born between October 2000 and October 2012 with SCD and registered in HEMORIO, including those who died in HEMORIO, were included in this study. Patients whose medical records were inaccessible, who died in institutions other than HEMORIO, who died with implanted deep venous catheters, and those who were not monitored in HEMORIO for a period of 1 year or more were excluded from the study. Of a total of 1,519 patients, 456 were excluded and 1,063 patients were included in the study. Data were obtained from the computer system and the medical records at HEMORIO. RESULTS: Of the 1,063 patients, 2 (0.2%) developed DVT with both cases being related to central venous catheters (CVCs) (p-value<0.001). Of the patients who required CVCs, the prevalence of DVT was 10%. No other variable was clinically or statistically significant with respect to DVT. CONCLUSION: The establishment of CVCs in children with SCD poses a high risk for DVT. If this procedure is necessary, the internal jugular vein should be utilized instead of the subclavian and femoral veins. The identification of associated risk factors may justify antithrombotic prophylaxis.

21.	Yacobovich J, Barzilai-Birenboim S, Steinberg-Shemer O, Stark P, Pazgal I, Tamary H. Splenectomy in childhood for non-malignant haematologic disorders - long-term follow-up shows minimal adverse effects. Br J Haematol. 2020 Sep;190(6):909-915. doi: 10.1111/bjh.16657. Epub 2020 Apr 28. PMID: 32342506.(42)	Splenectomy is considered therapeutic in various non-malignant haematologic diseases. Adverse events - specifically infections and thromboembolism - are not extensively documented in the paediatric population, maintaining the concern over risks-versus-benefits of the procedure. We studied a cohort of paediatric haematology patients undergoing splenectomy between 1977 and 2015 to determine short- and long-term complications. We summarised all the patients of the haematology clinic in our major Israeli tertiary centre undergoing splenectomy for therapeutic reasons, capturing infectious and thromboembolic events. The data of 103 patients, comprising 1657 follow-up years, were analysed. The cohort included 33 patients with transfusion-dependent thalassaemia, seven with non-transfusion-dependent thalassaemia, four with sickle-thalassaemia, 41 with hereditary spherocytosis, and 18 with immune thrombocytopenia. Standard presplenectomy vaccinations were noted in most. No typical cases of overwhelming postsplenectomy infection (OPSI) were identified, nor were typical OPSI bacteria isolated. Thalassaemics with central lines were most prone to infection and thrombosis. Beyond this subgroup, thrombotic events were anecdotal. This is the largest study to date to comprehensively analyse infectious and thrombotic complications of childhood splenectomy for the treatment of haematologic diseases. The use of splenectomy appears to be a relatively safe therapeutic option in paediatric patients with proper preoperative vaccination and follow-up care; use of central venous lines or catheters increase the risk in thalassaemic patients and should be avoided if possible.
Abbreviations: AIS = Arterial ischaemic stroke; CI = Confidence Interval; CT = Computed topography; CRP = C-reactive protein; CVC = Central venous catheter; CVAD = Central venous access device; DFO = deferoxamine; DVT = deep venous thrombosis; Hb = Haemoglobin; LDH = lactic dehydrogenase; PE = pulmonary embolism; OPSI = overwhelming postsplenectomy infection; OR = Odds Ratio; RR = Relative Risk; SCA = sickle cell anaemia; SCD = sickle cell disease; TM = Thalassaemia Major; TIC = Totally implantable catheters; TIVAD = Total implantable access devices, UEDVT = Upper extremity deep vein thrombosis; VTE = Venous thromboembolism.		

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