Perioperative laboratory monitoring in congenital haemophilia patients with inhibitors: a systematic literature review

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Although the use of clotting factor concentrates is the mainstay of haemophilia care, the development of inhibitors complicates disease management. Perioperative management of patients with inhibitors is therefore a challenge. A systematic literature review was performed to identify literature reporting on the perioperative monitoring and management of haemophilia. MEDLINE, Embase and Cochrane databases were searched from database inception to 26 March 2018. Recent congress proceedings were also searched. Titles and abstracts, then full texts, were screened for relevance by two reviewers. Quality of included studies was assessed using the Critical Appraisal Skills Programme checklist. Of the 2033 individual entries identified, 86 articles met the inclusion criteria. The identified studies were screened again to find articles reporting perioperative laboratory monitoring in patients with congenital haemophilia A or B, resulting in 24 articles undergoing data extraction. Routine perioperative assay monitoring practices were the most commonly reported (n = 20/24); thrombin generation assay was the least commonly reported (n = 2/24). Other monitoring practices described were factor VII and factor VIII coagulation activity (n = 8/24, n = 5/24, respectively), and thromboelastography or rotational thromboelastometry assessments (n = 3/24). The impact of monitoring on treatment decisions was, however, rarely reported. In conclusion, many methods of perioperative monitoring of haemophilia patients with inhibitors have been identified in this review, yet there is a lack of reporting in larger scale cohort studies. More detailed reporting on the impact of monitoring outcomes on treatment decisions is also needed to share best practice, particularly as new therapeutic agents emerge. Blood Coagul Fibrinolysis 30:309–323 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Haemophilia is a rare disease caused by a deficiency of coagulation factor VIII (FVIII) (haemophilia A) or factor IX (FIX) (haemophilia B) and leaves patients more prone to excessive bleeding [1]. The standard of care for severe haemophilia (factor activity <1 IU/dl), and some patients with moderate haemophilia (factor activity 1–5 IU/dl), is to prevent or minimize bleeding episodes using infusions of the missing factor concentrate (prophylaxis). Breakthrough bleeds may still occur requiring additional on-demand treatment. Treatment protocols, intensity of prophylaxis or choice to remain on-demand alone must be tailored to individual needs together with consideration of the local health economics [1].

In response to regular treatment, a subgroup of haemophilia patients of all severities can produce IgG antibodies, termed ‘inhibitors’, which work to neutralize clotting factors [2,3]. Inhibitors complicate prophylaxis and on-demand management by reducing or fully neutralizing the efficacy of infused factor concentrates, depending on the detected inhibitor titre [1,4].

Persistent inhibitors are a concern for haemophilia patients, particularly if undergoing surgical procedures [5]. Permanent tolerance induction in severe haemophilia (immune tolerance induction) is the preferable strategy to minimize future bleeding and/or management risks of surgery in the presence of an inhibitor [6,7]. Tolerising practices may also include the use of anti-CD20 mAb, immunoadsorption and plasmapheresis for additional short-term benefit [5]. Strategies for achieving tolerance in nonsevere haemophilia A are less well defined [8].

Knowledge of previous and/or current inhibitor status prior to surgery is crucial, either as repeat laboratory assessment ahead of surgery if time allows (severe haemophilia), reference to laboratory screening as the most...
recent FVIII concentrate exposure (nonsevere haemophilia A), or attention to in-vivo recovery and perioperative efficacy of infused concentrate (all severities) during the perisurgical and postsurgical course [6,9].

The monitoring and management of haemophilia patients with inhibitors undergoing surgical procedures is a particular challenge, and is the focus of this review.

Materials and methods

Search strategy for identification of studies

A systematic literature review was performed in accordance with a prespecified search protocol designed to identify literature reporting on the perioperative monitoring and management of haemophilia patients with inhibitors. The review process involved searching electronic databases, and hand-searching of key haemophilia/haematology conference proceedings from the last 2 years and reference lists of any relevant systematic reviews identified during the searches.

All electronic databases were searched on 26 March 2018. The databases searched to identify relevant published literature were: MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print (1946 to present); Embase (1974 to 23 March 2018); The Cochrane Database of Systematic Reviews: Issue 3 of 12, March 2018; The Database of Abstracts of Reviews of Effects (DARE): Issue 2 of 4, April 2015; The Cochrane Central Register of Controlled Trials (CENTRAL): Issue 2 of 12, February 2018.

In addition to the electronic database searches, hand-searches were performed to generate further evidence from a variety of sources. The bibliographies of published systematic reviews identified through the electronic database searches were hand-searched to identify any additional relevant studies for inclusion in the review. The proceedings of relevant haemophilia and haematology congresses that had taken place within approximately 2.5 years prior to December 2017 were also hand-searched, including: American Society of Hematology Annual Meeting (2015–2017); British Society for Haematology Annual Scientific Meeting (2016 and 2017); European Association for Haemophilia and Allied Disorders Annual Congress (2016 and 2017); Haemophilia and Thrombosis Research Society Scientific Symposium (2015 and 2017); European Hematology Association Congress (2016 and 2017); International Society for Thrombosis and Haemostasis Congress (2016, 2017); World Federation of Hemophilia World Congress (2016). The websites and abstract books of these congresses were searched, if available, using terms based on the complete list of electronic database search terms.

Full details of the search strategies for the electronic database searches and the congress searches are presented in Supplementary Tables 1–3, http://links.lww.com/BCF/A61.

Study selection

All articles retrieved through the electronic database searches and hand-searches were screened by two independent reviewers and included based on their alignment with the predefined eligibility criteria (Supplementary Table 4, http://links.lww.com/BCF/A61). The strategy was specifically designed to capture studies reporting on the monitoring and/or management of haemophilia patients with inhibitors undergoing surgery. All articles were initially screened based on their abstracts only. Following the abstract review stage, the full texts of remaining articles were then screened for relevance to produce the final list of included studies. For pragmatic reasons, additional study design eligibility criteria were applied during the screening of full texts to ensure that only interventional and observational studies were included in the final list. Study designs were determined by their description as reported by authors in the articles. In cases where the study design was not explicitly stated, the reviewers defined observational studies as those that examined and analysed the data of a patient cohort as a group, compared with an analysis of individual patient data only in case series. Studies that described patients being assigned to a specific treatment group were categorized as interventional. A full list of articles excluded, and the reasons for their exclusion, at the full text screening stages of the review is shown in Supplementary Table 5, http://links.lww.com/BCF/A61. In addition, a list of the case studies identified during the review and excluded based on study design prior to full text screening is available in Supplementary Table 6, http://links.lww.com/BCF/A61.

Data extraction and analysis

Following application of the eligibility criteria, there was still a large number of included studies. Therefore, the list was screened an additional time by one reviewer, and checked by a second reviewer, to identify the studies that reported perioperative laboratory monitoring in patients with congenital haemophilia A or haemophilia B. In cases of studies reporting on both congenital and acquired haemophilia patients, only information on congenital patients was extracted. Data were extracted from each article by a single individual, and reviewed by a second. As included studies are of different designs, their quality was assessed using the Critical Appraisal Skills Programme checklist most appropriate for the study design (e.g. case-control study, cohort study, randomized controlled trial).

Results

Search results

The literature search retrieved 1481 abstracts from electronic databases, 502 abstracts from conference proceedings and 50 articles from hand searches of existing review bibliographies. Following application of the eligibility
criteria to the identified abstracts and, subsequently, full text articles (Fig. 1), a final list of 86 relevant articles was identified (Table 1).

In the interest of focusing the review more specifically, the 86 full text articles were screened once more to identify the studies reporting perioperative laboratory monitoring in patients with congenital haemophilia A or haemophilia B and inhibitors. This resulted in a final list of 24 articles that underwent full data extraction (Table 2).

Quality assessment
Quality assessments were carried out for the interventional and observational studies that underwent data extraction (Supplementary Tables 7 and 8, http://links.lww.com/BCF/A61). Overall, the issues addressed by the interventional studies were clearly focused and all patients were properly accounted for. The most substantial limitation of the interventional studies was a lack of blinding (eight of nine studies), which may have led to bias in the ascertainment and reporting of outcomes. For the observational studies, follow-up was almost always...
Table 1  Studies included following full text screening

| Reference | Study type | Country | Monitoring reported |
|-----------|------------|---------|---------------------|
| Perez-Alenda et al. [10] | Observational | Spain | Not reported |
| Antmen et al. [11] | Observational | Turkey | Not reported |
| Antmen et al. [12] | Observational | Turkey | Not reported |
| Balkan et al. [13] | Observational | Turkey | Laboratory monitoring |
| Bensaïd et al. [14] | Observational | Algeria | Not reported |
| Carulli et al. [15] | Observational | Italy | Not reported |
| Caviglia et al. [16] | Observational | Argentina | Not reported |
| Caviglia et al. [17] | Observational | Argentina | Not reported |
| Chaplin et al. [18] | Observational | The United States | Not reported |
| Cavarella et al. [19] | Interventional | Italy | Not reported |
| Danielson et al. [20] | Observational | Finland | Laboratory monitoring |
| Dimichele and Negrier [21] | Observational | The United States and Europe | Not reported |
| Freiberghaus et al. [22] | Observational | Sweden | Not reported |
| He et al. [23] | Observational | China | Not reported |
| Holstrom et al. [24] | Interventional | Norway and Sweden | Laboratory monitoring |
| Ingerslev et al. [25] | Observational | Multiple | Laboratory monitoring |
| Ingerslev [26] | Observational | Denmark | Not reported |
| Jenkins et al. [27] | Observational | The United Kingdom | Not reported |
| Sasmaz et al. [28] | Observational | Turkey | Not reported |
| Kitchens [29] | Observational | The United States | Not reported |
| Kižkočić et al. [30] | Observational | Turkey | Not reported |
| Kruse-Jarres et al. [31] | Interventional | Multiple | Not reported |
| Lauroua et al. [32] | Observational | France | Both (clinical and laboratory monitoring) |
| Lim et al. [33] | Observational | The United States | Not reported |
| Loxer et al. [34] | Observational | Multiple | Not reported |
| Ludmila et al. [35] | Interventional | The United Kingdom and Italy | Laboratory monitoring |
| Mahasandana et al. [36] | Observational | Thailand | Not reported |
| Manuso et al. [37] | Observational | Italy | Not reported |
| Morado et al. [38] | Observational | Spain | Not reported |
| Negrier et al. [39] | Interventional | Multiple | Not reported |
| Nguyen et al. [40] | Observational | Vietnam | Not reported |
| Novack et al. [41] | Observational | Sweden | Laboratory monitoring |
| O’Connell et al. [42] | Observational | Ireland and The United Kingdom | Clinical monitoring |
| Oldenburg et al. [43] | Observational | Multiple | Not reported |
| Özdemir et al. [44] | Observational | Turkey | Not reported |
| Pruthi et al. [45] | Interventional | The United States | Laboratory monitoring |
| Quintana-Molina et al. [46] | Observational | Spain | Laboratory monitoring |
| Rodriguez-Merchan [47] | Observational | Spain | Not reported |
| Rodriguez-Merchan et al. [48] | Observational | Spain | Not reported |
| Sasmaz et al. [49] | Observational | Turkey | Not reported |
| Sasmaz et al. [50] | Observational | Turkey | Not reported |
| Sasmaz et al. [51] | Observational | Turkey | Not reported |
| Szczepanik et al. [52] | Observational | Poland | Not reported |
| Serban et al. [53] | Observational | Romania | Not reported |
| Shapiro et al. [54] | Interventional | The United States | Laboratory monitoring |
| Shapiro and Cooper [55] | Observational | The United States | Not reported |
| Smith [56] | Observational | Ireland and The United Kingdom | Both (clinical and laboratory monitoring) |
| Solimeno et al. [57] | Observational | Italy | Not reported |
| Takedani et al. [58] | Observational | Japan | Not reported |
| Acquired haemophilia | | | |
| Gringeri et al. [59] | Observational | Europe | Laboratory monitoring |
| Lak et al. [60] | Observational | Iran | Laboratory monitoring |
| Lizon et al. [61] | Observational | France | Laboratory monitoring |
| Ma et al. [62] | Interventional | The United States | Not reported |
| Novak et al. [63] | Observational | Multiple | Not reported |
| Both congenital and acquired haemophilia | | | |
| Atalar et al. [64] | Observational | Turkey | Not reported |
| Boadas et al. [65] | Observational | Venezuela | Both (clinical and laboratory monitoring) |
| Carulli et al. [66] | Observational | Italy | Not reported |
| Castama et al. [67] | Observational | Italy | Not reported |
| Croteau et al. [68] | Interventional | The United States | Not reported |
| Furukawa et al. [69] | Interventional | Japan | Laboratory monitoring |
| Gatti and Manucci [70] | Interventional | Italy | Laboratory monitoring |
| Habermann et al. [71] | Observational | Germany | Laboratory monitoring |
| Hilgartner and Knatterud [72] | Observational | The United States | Not reported |
| Ju et al. [73] | Observational | South Korea | Clinical monitoring |
| Zülkiker et al. [74] | Observational | Turkey | Not reported |
| Kraut et al. [75] | Observational | The United States | Laboratory monitoring |
| Linari et al. [76] | Observational | Italy | Not reported |
| Manussu et al. [77] | Observational | Italy | Laboratory monitoring |
| Mauser-Bunschoten et al. [78] | Observational | The Netherlands and Belgium | Both (clinical and laboratory monitoring) |
| Mauser-Bunschoten et al. [79] | Observational | The Netherlands | Both (clinical and laboratory monitoring) |
| Negrier et al. [80] | Observational | France | Not reported |
Table 1 (continued)

| Reference            | Study type     | Country                                  | Monitoring reported                                      |
|----------------------|----------------|------------------------------------------|----------------------------------------------------------|
| Negrier et al. [81]  | Observational  | Worldwide: Colombia, France, Germany, Italy, South Korea, Sweden and The United Kingdom | Both (clinical and laboratory monitoring)                 |
| Polyanska et al. [82]| Observational  | Russia                                    | Clinical monitoring                                       |
| Rangarajan et al. [83]| Observational  | The United Kingdom                        | Clinical monitoring                                       |
| Rodriguez-Merchan [84]| Observational  | WorldWide                                | Not reported                                              |
| Rodriguez-Merchan [87]| Observational  | Spain                                     | Not reported                                              |
| Santagostino et al. [85]| Observational | Italy                                     | Laboratory monitoring                                     |
| Sasmaz et al. [86]   | Observational  | Turkey                                    | Not reported                                              |
| Scharf et al. [87]   | Observational  | Poland                                    | Not reported                                              |
| Scherrer [88]        | Interventional | Germany                                   | Both (clinical and laboratory monitoring)                 |
| Serban et al. [89]   | Observational  | Romania                                   | Both (clinical and laboratory monitoring)                 |
| Smith et al. [90]    | Interventional | Unclear                                   | Both (clinical and laboratory monitoring)                 |
| Szczepanik et al. [82]| Observational  | Poland                                    | Not reported                                              |
| Takeda et al. [58]   | Observational  | Japan                                     | Clinical monitoring                                       |
| Tjonnfjord [91,92]   | Observational  | Norway                                    | Laboratory monitoring                                     |

*Outcomes not reported separately for inhibitor patients so data not extracted.*

Perioperative monitoring

Overall, 40% (34/86) of articles identified through the review mentioned how patients were monitored; of these, nearly three quarters (24) of the articles mentioned the use of laboratory monitoring in patients with inhibitors complicating congenital haemophilia A or haemophilia B, either in the methods section or when describing the outcomes of the study (Table 1). However, even in studies which mentioned laboratory monitoring, the use and impact of specific monitoring protocols on treatment decisions was often not well described. Instead, it was common for the details of perioperative monitoring to be provided for information only, or to report the haemostatic efficacy of the treatment.

Routine laboratory monitoring

Among the studies reporting perioperative laboratory monitoring practices, routine laboratory monitoring practices, such as platelet count, prothrombin time, activated partial thromboplastin time (APTT), fibrinogen levels, D-dimer levels and antithrombin (ATIII) were the most commonly reported. This monitoring information was frequently provided to demonstrate efficacy, or lack thereof, and determine safety, of the haemostatic agent, particularly in the context of interventional studies [35,93]. In the majority of studies it was unclear whether the outcomes of laboratory tests were available to the care team within the timeframe necessary to influence treatment decisions (Table 3) [13,70].

When the influence of monitoring on clinical decisions was discussed, this was mainly in the context of individual patient cases, such as reduction in activated prothrombin complex concentrate (aPCC) treatment following elevation in D-dimer levels [75], as opposed to providing insight into how laboratory monitoring influenced treatment decisions and outcomes on a cohort-wide level. In other cases, laboratory tests were only utilized in patients who experienced an adverse event [88]. Overall, very limited information was found in the identified studies to indicate the influence of perioperative monitoring results on clinical decisions.

Factor VII

A total of eight of the 17 extracted studies describing treatment with recombinant factor VIIa (rFVIIa), administered continually or using bolus doses, described the monitoring of FVII coagulation activity (FVII:C) (Table 4). Two studies published by the same centre described monitoring FVIIa levels using a one-stage coagulation assay suggesting that coagulation activity as opposed to protein levels was assessed. The studies from this centre also report that the specific FVIIa assay (Staclot; Diagnostica Stago, Parsippany, New Jersey, USA) was not found to be practical or reliable [78,79].

Even where FVII:C monitoring is mentioned, FVII:C was rarely used to make dosing decisions. In one study investigating continuous infusion of rFVIIa, observed bleeding was used to deduce that the target FVII:C of 10 IU/dl was insufficient [90]. Two other studies noted that in patients with ineffective haemostatic efficacy, FVII:C often exceeded the target 30 IU/ml [35,45].

When comparing continually to bolus administration, one study found that FVII:C levels were consistently higher in patients undergoing continually; however, the difference was not statistically significant, and there was no difference in haemostatic efficacy between groups (75 vs. 73%, respectively) [45].

Thromboelastography/Rotational thromboelastography analysis

Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) coagulation assessments were used in three of the more recent studies assessing a variety of
Table 2  Overview of studies reporting perioperative laboratory monitoring

| Reference          | Study design                              | Patients                      | Procedures | Haemostatic treatment | Haemostatic outcome |
|--------------------|-------------------------------------------|-------------------------------|------------|-----------------------|---------------------|
| Balkan et al. [13] | Single-centre, retrospective observational study | 30 HA patients with high responding inhibitors | 11 Major, 42 Minor | aPCC, or fVIIa, or Sequential use of aPCC and fVIIa | aPCC: 22/22 (100%) bleeding controlled |
| Danielson et al. [20] | Single-centre, retrospective observational study | 6 HA patients with inhibitors (n = 2 low-responding, n = 4 high-responding) | 15 Orthopaedic | Cryoprecipitate, or Coagulation FVIII (pdFVIII or FVIII), or aPCC, or fVIIa (posttreatment switch in some individual cases) | 8/15 (53%) Bleeding controlled (listed as 'good', indicating no difference in bleeding compared with normal arthroplasty) |
| Furukawa et al [69] | Single-centre, prospective interventional study | 8 HA patients with inhibitors | 8 Elective | aVIII, or aPCC | 8/8 (100%) Bleeding controlled |
| Gatti and Mannucci [70] | Single-centre, prospective, uncontrolled interventional study | 5 HA patients with inhibitors | 3 Minor, 2 Major | Bolus porcine FVIII (Hyate:C) (minor dental), or Continuous porcine FVIII (Hyate:C) (major) | 2/2 (100%) Bleeding controlled (only reported for major surgery) |
| Habermann et al. [71] | Single-centre, retrospective observational study | 4 HA patients with inhibitors | 6 Orthopaedic | Anivafiof (Actavis Laboratories FL, Inc., Fort Lauderdale, Florida, USA) (containing TXA) in combination with Bolus FVIII (low inhibitor titre) Immunoabsorbant therapy (Therasorb; Miltenyi Biotech, Bergisch Gladbach, Germany) followed by bolus FVIII (high inhibitor titre) Continuous rFVIIa infusion when inhibitor titres rose could not be eliminated or FVIII response decreased | 5/6 (83%) Bleeding controlled |
| Holmström et al. [24] | Two-centre, prospective interventional study | 6 HA patients with high responding inhibitors | 2 Minor, 5 Major | Bolus aPCC in combination with TXA | 6/7 (86%) Bleeding controlled |
| Ingerslev et al. [25] | Multicentre, retrospective observational study | 11 HA patients and 1 HB patient with inhibitors | 13 Major | Bolus rFVIIa | 12/12 (100%) Bleeding controlled (outcome not reported in n = 1 case) |
| Kraut et al. [75] | Multicentre, retrospective chart review | 6 HA patients with inhibitors | 21 Various | Bolus aPCC monotherapy, or Bolus rFVIIa monotherapy, or Bolus continuous combination therapy | 14/21 (67%) Bleeding controlled |
| Laurou et al. [31] | Single-centre, retrospective observational study | 7 HA patients with inhibitors | 8 Major elective, 2 Major emergency, 2 Minor elective | Bolus aPCC as first-line treatment | Haemostatic outcomes were consistent with noncoagulopathic patients undergoing similar procedures |
| Ludlam et al. [35] | Prospective, interventional study | 9 HA patients with inhibitors | 9 Major orthopaedic | Continuous rFVIIa | 8/9 (88.9%) Bleeding controlled at end of surgery |
| Mancuso et al. [77] | Single-centre, prospective, observational study | 10 HA patients with inhibitors | 11 Major orthopaedic | Bolus doses of rFVIIa aPCC Sequential therapy with rFVIIa and aPCC | 10/11 (91%) Bleeding controlled |
| Mauser-Bunschoten et al. [78] | Multicentre, retrospective observational study | 3 HA patients with inhibitors | 2 Dental extraction, 2 Hip arthroplasty | Continuous rFVIIa | 3/4 (75%) Bleeding controlled |
| Mauser-Bunschoten et al. [79] | Multicentre, prospective observational study | 4 HA patients and 1 HB patient with inhibitors | 4 Dental extraction, 1 Orthopaedic surgery | Continuous rFVIIa | NR except 2 dental extractions rated 'ineffective' and 2 rated 'partially effective' |
| Reference                          | Study design                        | Patients                                      | Procedures                                             | Haemostatic treatment                                      | Haemostatic outcome                                      |
|-----------------------------------|-------------------------------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|
| Négrier et al. [81]                | Multicentre, prospective, observational study | 18 HA patients and 2 HB patients with inhibitors | 35 Various (including procedures performed on n = 4 acquired haemophilia patients) | Bolus aPCC                                                   | 31/34 (91%) Bleeding controlled (rated as ‘excellent’ or ‘good’; full population including acquired haemophilia patients; concomitant medication documented in n = 34/35 surgical procedures) |
| Pruthi et al. [45]                | Multicentre, prospective interventional study | 24 HA/HB patients with inhibitors (A/B subgroups not specified) | 24 Elective surgery                                      | Bolus and continuous infusion of rFVIIa                     | 17/23 (75%) Bleeding controlled overall (n = 1 patient excluded from efficacy analysis) |
| Quintana-Molina et al. [46]       | Single-centre, retrospective observational study | 45 HA patients 3 HB patients with inhibitors | 10 Major elective and emergency 54 Minor elective and emergency | Bolus doses of rFVIIa, or aPCC, or FVIII concentrate       | rFVIIa: 14/18 (78%) bleeding controlled aPCC: 31/32 (97%) bleeding controlled FVIII concentrate: 15/15 (100%) bleeding controlled (based on outcomes reported in article tables) |
| Santagostino et al. [85]          | Multicentre, prospective, observational study | 25 HA patients with inhibitors (unclear how many had surgery) | 11 Major 14 Minor                                      | Continuous rFVIIa                                           | Surgical patients’ results not reported separately (based on outcomes reported in article tables) |
| Scharrer [88]                     | Multicentre, prospective interventional study | 19 HA/HB patients with inhibitors (A/B subgroups not specified) | 5 Major 17 Minor full population including patients with acquired inhibitors/FVII deficiency | Bolus rFVIIa                                               | 100% Minor/60% Major surgical procedures bleeding controlled (during surgery) |
| Serban et al. [89]                | Single-centre, retrospective observational study | 13 HA/HB patients with inhibitors (not clear whether A or B) | Invasive orthopaedic (n NR)                             | Bolus doses and continuous infusion of FVIII/FIX concentrates | Reported but not for population of interest               |
| Shapiro et al. [54]               | Multicentre, prospective interventional study | 25 HA patients and 3 HB patients with inhibitors | 29 (including 1 procedure for a patient with acquired haemophilia) 11 Major 18 Minor | Bolus rFVIIa                                               | 23/29 (79%) Bleeding controlled (may include 1 acquired haemophilia patient’s procedure) |
| Smith et al. [56]                 | Multicentre, prospective interventional study | 6 HA patients with inhibitors                   | 6 Major                                                | Bolus dose followed by continuous infusion of rFVIIa        | 2/6 Bleeding controlled                                   |
| Smith [56]                        | Two-centre, retrospective chart review | 12 HA patients with inhibitors                 | 19 CVAD insertion/removal 1 Multiple dental extraction  | Bolus rFVIIa                                               | 20/20 (100%) Bleeding controlled (n = 2 cases of minor bleeding after treatment had ended were resolved with retreatment of rFVIIa) |
| Tjonnfjord [91,92]                | Single-centre, retrospective observational study | 8 HA patients with inhibitors                   | 12 Minor 6 Major                                       | Bolus aPCC                                                  | 18/18 (100%) Bleeding controlled                          |

aPCC, activated prothrombin complex concentrate; CVAD, central venous access device; FX, factor IX; FVII, factor VII; FIX, factor VIII; HA, haemophilia A; HB, haemophilia B; NR, not reported; pdFVIII, plasma-derived factor VIII; rFVIIa, recombinant factor VIIa; rFVIII, recombinant factor VIII; TXA, tranexamic acid.
### Table 3  Routine laboratory testing

| Reference                  | Monitoring methods                                                                 | Monitoring results                                                                 |
|----------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Balkan et al. [13]         | Laboratory assessment (postoperative) of                                          | APTT did not return to normal by using the haemostatic agents                      |
|                            | Platelet count                                                                     | Significant shortening of PT                                                        |
|                            | PT                                                                                 |                                                                                     |
|                            | APTT                                                                               |                                                                                     |
|                            | Fibrinogen                                                                         |                                                                                     |
|                            | D-Dimer                                                                            |                                                                                     |
| Gatti and Mannucci [70]    | Laboratory assessment of                                                          | NR                                                                                  |
|                            | Clinical effectiveness                                                             |                                                                                     |
|                            | The prevalence of anamnestic antibody responses and                                |                                                                                     |
|                            | of severe or milder side effects                                                  |                                                                                     |
|                            | Platelet counts                                                                    |                                                                                     |
|                            | Haematuric                                                                          |                                                                                     |
| Habermann et al. [71]      | Laboratory assessment of                                                          | Only on the day of surgery was a slight increase of the c-dimer level seen. On     |
|                            | D-Dimer                                                                            | the postoperative days, the c-dimer levels were within the normal range             |
| Ingerslev et al. [25]      | Laboratory assessment of                                                          | Small reductions in platelet numbers                                                |
|                            | Platelet count                                                                     |                                                                                     |
|                            | PT                                                                                 |                                                                                     |
|                            | APTT                                                                               |                                                                                     |
|                            | Fibrinogen                                                                         |                                                                                     |
|                            | D-Dimer                                                                            |                                                                                     |
|                            | ATIII                                                                              |                                                                                     |
| Kraut et al. [75]          | Laboratory assessment, including platelet function                                 | aPCC treatment was reduced after monitoring indicated an                           |
|                            | analysis, of:                                                                       | elevation in c-dimer levels                                                         |
|                            | c-Dimer levels                                                                     |                                                                                     |
|                            | Haemoglobin level                                                                  |                                                                                     |
| Lauroua et al. [32]        | Consumption coagulopathy and thrombogenicity                                       | Monitoring of c-dimer, fibrinogen and fibrin degradation products                  |
|                            | evaluated with laboratory assessment of                                           | showed no consistent activation of coagulation or increase in                        |
|                            | Platelets                                                                          | fibrinolysis                                                                        |
|                            | Fibrinogen                                                                         |                                                                                     |
|                            | c-Dimer or fibrinogen and fibrin degradation products                              |                                                                                     |
|                            | Haemoglobin level                                                                  |                                                                                     |
| Ludlam et al. [35]         | Laboratory assessment of                                                          | Neither platelet consumption nor fibrinogen depletion observed                      |
|                            | Complete blood counts                                                              | postoperatively                                                                      |
|                            | Fibrinogen                                                                         |                                                                                     |
|                            | D-Dimer                                                                            |                                                                                     |
|                            | ATIII (assessed by chromogenic determination)                                       |                                                                                     |
| Mancuso et al. [77]        | Laboratory assessment of                                                          | All but one c-dimer sample showed results below the limits of                      |
|                            | Fibrinogen (functional clauss method)                                              | specified abnormality                                                                |
|                            | c-Dimer (latex enhanced turbidimetric immunoassay)                                 |                                                                                     |
|                            | PT (PT-based one-stage assay)                                                     | ATIII showed no tendency to decrease                                               |
|                            |                                                                                     |                                                                                     |
| Mauser-Bunschoten et al. [78]| Laboratory assessment of                                                           | aPCC treatment was reduced after monitoring indicated an                           |
|                            | PT                                                                                 | elevation in c-dimer levels                                                         |
| Mauser-Bunschoten et al. [79]| Laboratory assessment of                                                           |                                                                                     |
|                            | PT                                                                                 |                                                                                     |
| Négrier et al. [81]        | Laboratory assessment of                                                          | Abnormal, significant haemoglobin levels were observed in 5                         |
|                            | Haemoglobin                                                                        | patients with inhibitors                                                             |
|                            | Red blood cell count                                                               |                                                                                     |
|                            | Haematuric                                                                          |                                                                                     |
|                            | Liver enzyme levels                                                                |                                                                                     |
| Pruthi et al. [45]         | Laboratory assessment of                                                          | No statistically significant differences between pre and                            |
|                            | Fibrinogen                                                                         | postoperative platelet counts, fibrinogen, c-dimer and F 1.2                        |
|                            | D-Dimer                                                                            | concentrations between bolus infusion, continuous infusion or                       |
|                            | PT                                                                                 | control patients                                                                     |
| Quintana-Molina et al. [46]| Laboratory assessment (postoperative and control tests at least every 48h) of   |                                                                                     |
|                            | Platelet count (obtained by impedance and optically)                               |                                                                                     |
|                            | PT and cephaline time (monitored by two apparatuses based on different              |                                                                                     |
|                            | techniques, either optical density or                                              |                                                                                     |
|                            | magnetic force                                                                      |                                                                                     |
|                            | Fibrinogen (Clauss method)                                                         |                                                                                     |
|                            | c-Dimer (turbidimetry)                                                             |                                                                                     |
| Santagostino et al. [85]   | Laboratory assessment of                                                          | Platelet count decreased during 2 courses of treatment given for                    |
|                            | PT                                                                                 | knee replacement                                                                      |
|                            | APTT                                                                               |                                                                                     |
|                            | D-Dimer                                                                            |                                                                                     |
|                            | Platelet count                                                                     |                                                                                     |
agents (including rFVIIa, aPCC and FVIII) (Table 5). In one study, ROTEM analysis on in-vitro samples was used to identify the minimum necessary dose of activated coagulation products and most suitable treatment (rFVIIa vs. aPCC) for perioperative haemostatic control in patients with inhibitors [69]. This study found that pre-operative in-vitro ROTEM analysis more accurately predicted the impact of treatment with rFVIIa than with aPCC [69]. The other studies used ROTEM intraoperatively to demonstrate haemostatic efficacy, but did not report how the outcomes impacted clinical treatment decisions [24,89].

Factor VIII coagulation activity
Four studies were found to have analysed human FVIII:C, while one analysed porcine FVIII:C (Table 6) [20,24,70,71,89]. The use of FVIII:C to identify cases of ‘resistance’ to porcine FVIII concentrate was discussed in an early study [70], however, only one recent study mentioned how FVIII:C monitoring influenced treatment decisions [20]. This retrospective observational study involved routine monitoring of FVIII:C and when one patient’s FVIII:C levels declined after a total knee replacement, their treatment was switched from cryoprecipitate to plasma-derived FVIII (pdFVIII), leading to a good haemostatic outcome [20].

Thrombin generation
Only two articles described monitoring using a thrombin generation assay (TGA) (Table 7) [24,77]. In one of these studies, TGA parameters were used to assess haemostatic efficacy, with no indication of how the results impacted care decisions [24]. The other, a 2016 study involving 10 inhibitor patients undergoing orthopaedic surgery, investigated the association between TGA and clinical bleeding events, finding that there was no difference in the TGA values between patients who did and did not experience bleeding complications [77].

Discussion
While this review uncovered evidence on the methods of monitoring and management used in haemophilia patients undergoing surgery, there was very little information to indicate how the outcomes of laboratory monitoring practices were used to influence treatment decisions. In articles where the impact of monitoring was mentioned, this tended to be described on an individual patient basis. Therefore, it is difficult to use the available evidence to understand to what extent laboratory monitoring is used in clinical practice and how it could be utilized to improve patient care.

Another barrier to understanding the impact of perioperative monitoring in haemophilia patients is the lack of a generalizable assay for aPCC and rFVIIa. Monitoring of patients undergoing treatment with these agents is currently conducted according to local protocols, instead of a global standard, with centres forced to evaluate treatment efficacy through clinical, rather than laboratory, assessments.
In addition, while some evidence related to monitoring and management with traditional treatments, such as rFVIIa, aPCC and FVIII was found, the review did not identify published literature reporting on such practices in patients treated with emerging therapeutics, such as emicizumab, concizumab and fitusiran. There are currently only anecdotal data about surgical haemostasis planning in patients on these agents on board [31,94]. In such scenarios, monitoring for all these agents will be complex, both in terms of consideration of appropriate laboratory assays, together with interpreting results in the context of global haemostatic potential.

Emicizumab, a recombinant, humanized, bispecific mAb recently approved for treatment of haemophilia A with inhibitors by the Food and Drug Administration, works by acting similarly to activated FVIII in bridging activated FIX and factor X to trigger the coagulation cascade [95]. As emicizumab affects intrinsic pathway clotting-based laboratory tests, including activated clotting time and all assays based on APTT, intrinsic pathway clotting-based laboratory test results should not be used to monitor emicizumab activity, determine dosing for factor replacement or anticoagulation, or measure FVIII inhibitor titres in patients receiving this treatment [96]. A recent case study describing the use of rescue aPCC

| Table 4  | Factor VII monitoring |
|----------|----------------------|
| Reference | Haemostatic treatment | Reported factors monitored | Method of monitoring | Monitoring results |
| Ingerslev et al. [25] | Bolus rFVIIa | Levels of postinfusion FVII:C FVII:C FVIIa:C levels | Laboratory assessment Plasma FVII:C was assessed by an automated one-stage FVIII clot method on an automated laboratory analyser FVII:C was assessed using a specific automated assay | NR | Mean (range) FVII:C levels Effective haemostasis, end of surgery: 37 IU/ml, (29–51 IU/ml), n = 8 Ineffective haemostasis, end of surgery: 27 IU/ml, n = 1 Effective haemostasis, 8 h after wound closure: 38 IU/ml (24–79 IU/ml), n = 5 Partially effective haemostasis, 8 h after wound closure: 42 IU/ml, (37–57 IU/ml), n = 4 |
| Ludlam et al. [35] | Continuous rFVIIa | | | |
| Mauser-Bunschoten et al. [78] | Continuous rFVIIa | Plasma FVIIa levels | FVIIa: one-stage coagulation assay FVIIa levels maintained above 10 U/ml through flow rate adjustment | NR |
| Mauser-Bunschoten et al. [79] | Continuous rFVIIa | Plasma FVIIa levels | FVIIa: one-stage coagulation assay | |
| Pruthi et al. [45] | Bolus and continuous infusion of rFVIIa | FVII:C | Samples for FVIIa were collected within 30 min prior to and at 10 min after the initial 90 μg/kg rFVIIa bolus infusion, at 0, 8, 24, 48 and 72 h after wound closure and daily from postoperative day 4–10 or until discharge (and prior to any supplemental bolus infusion of rFVIIa). FVII:C was measured in a central laboratory | At wound closure, FVII:C levels were higher in continuous vs. bolus infusion patients, which as sustained through 72 h but not statistically significant In patients for whom therapy was ineffective, FVII:C levels were in excess of 30 IU/ml at the time therapy was declared ineffective |
| Santagostino et al. [85] | Continuous rFVIIa | FVII:C | One-stage coagulation assay FVII:C levels were significantly higher during continuous infusion courses given for major surgery than minor surgery rFVIIa clearance was significantly lower in courses given for major surgery than for minor surgery | |
| Shapiro et al. [64] | Bolus rFVIIa | FVII:C | Laboratory analysis of blood sample FVII:C could not be analysed in terms of haemostatic outcome due to timings of blood sampling | |
| Smith et al. [90] | Bolus dose followed by continuous infusion of rFVIIa | FVII:C | Laboratory assessment Target FVII:C of 10 IU/dl was found to be insufficient to prevent bleeding | |

FVII:C, factor VII coagulation activity; FVIIa, factor VIIa; FVIIa:C, factor VIIa coagulation activity; NR, not reported; rFVIIa, recombinant factor VIIa.
treatment to provide additional haemostatic control during a spontaneous bleeding event in a patient receiving prophylactic emicizumab used TGA to determine the optimal aPCC dosage to maintain haemostatic efficacy while limiting the risk of thrombotic complications [97]. While this review identified an interventional study reporting the use of emicizumab in haemophilia patients with inhibitors undergoing surgery, no information on perioperative laboratory monitoring was provided [31].

Concizumab, a humanized mAb against tissue factor pathway inhibitor, is under investigation for the

### Table 5  Thromboelastography/rotational thromboelastometry analysis

| Reference         | Haemostatic treatment                          | Reported factors monitored                           | Method of monitoring | Monitoring results                                      |
|-------------------|-----------------------------------------------|-----------------------------------------------------|----------------------|--------------------------------------------------------|
| Furukawa et al. [69] | rFVIIa or aPCC                               | Coagulation process                                 | ROTEM                | Clotting time and clot formation time ROTEM parameters shortened significantly after infusion of bypassing products |
| Holmström et al. [24] | Bolus aPCC in combination with TXA          | Whole blood coagulation profiles                     | ROTEM                | Clot formation time was shorter than normal in most cases after treatment with rFVIIa |
| Serban et al. [89]   | Bolus doses and continuous infusion of FVIII/FIX concentrates rFVIIa | FVIII/FIX activity                                   | TEG                  | During surgery, TEG showed significant improvement in CT, MaxVel and tMaxVel after aPCC and TXA and MCF increased towards normal |

### Table 6  Factor VIII coagulation activity

| Reference         | Haemostatic treatment                          | Reported factors monitored                           | Method of monitoring | Monitoring results                                      |
|-------------------|-----------------------------------------------|-----------------------------------------------------|----------------------|--------------------------------------------------------|
| Gatti and Mannucci [70] | Bolus porcine FVIII (Hyate:C) (minor dental), or Continuous porcine FVIII (Hyate:C) (major) | The antibody cross-reactivity with porcine FVIII The relationship between preinfusion antibody titre, FVIII dosage given and its postinfusion plasma levels The problems of ‘resistance’ | Platelet counts and haemotocrits were measured with standard methods FVIII coagulant activity measured by a one-stage method Anti-human FVIII antibody measured in fresh plasma by the Bethesda assay method Anti-porcine FVIII antibody measured using method based on same principles as Bethesda assay | Haemostatic efficacy was dependent on achieving and maintaining target levels of FVIII:C (40–50 U/dl for dental surgery) FVIII:C was used to identify cases of ‘resistance’ to bypassing therapy, with treatment adjusted as appropriate |
| Danielson et al. [20] | Cryoprecipitate, or Coagulation FVIII (pdFVIII or rFVIII), or aPCC, or rFVIIa (posttreatment switch in some individual cases) | FVIII:C Development of disseminated intravascular coagulation, anaemia, or thrombocytopenia | Routine blood coagulation test | One patient experienced a decline in FVIII:C which led to a treatment switch |
| Habermann et al. [71] | Anti-TXA (containing TXA) and bolus FVIII or continuous rFVIIa infusion | FVIII:C levels and inhibitors | Laboratory assessment | A decrease of FVIII levels down to zero was measured on days 4–6 in all patients substituted with FXII. Simultaneously an increase of the inhibitors against FVIII was noticed |
| Holmström et al. [24] | Bolus aPCC in combination with TXA          | FVIII:C                                              | One-stage clotting assay (FVIII activity) | NR |
| Serban et al. [89]   | Bolus doses and continuous infusion of FVIII/FIX concentrates rFVIIa | FVIII/FIX activity                                   | Laboratory assessment | NR |

aPCC, activated prothrombin complex concentrate; CT, clotting time; FIX, factor IX; FVIII, factor VIII; MaxVel, maximum velocity of clot formation; MCF, maximum clot formation; NR, not reported; rFVIIa, recombinant factor VIIa; ROTEM, rotational thromboelastometry; TEG, thromboelastography; tMaxVel, time until maximum velocity; TXA, tranexamic acid.
prophylactic treatment of haemophilia A and haemophilia B patients with inhibitors in a phase II trial due to complete in 2019 (NCT03196284) [98]. Previous studies have used TGA to demonstrate concizumab activity, suggesting that this may be a potential method of evaluating efficacy in clinical practice [99]. Lastly, fitusiran, an investigational RNA interference therapy, works by targeting ATIII mRNA to suppress ATIII production [100]. One interventional study examining fitusiran treatment in haemophilia patients undergoing surgery was identified in this review, but no details on perioperative laboratory monitoring were reported [39]. As these emerging therapies enter the market it will be important to establish an understanding of the standard of care used to monitor patients receiving these treatments.

While data on these emerging therapies are currently limited it is difficult to predict response to treatment during surgery, as well as expectations from monitoring. Efforts have been made to standardize TGA, but these developments are rarely shared outside of research settings. More information is therefore needed to understand their use in patients with inhibitors undergoing surgery in clinical practice. As the availability of data on suitable assays remains limited, the United Kingdom Haemophilia Centres Doctors’ Organisation has recommended that nonurgent major surgery in haemophilia patients with inhibitors receiving novel prophylaxis agents is delayed, until more specific methods of monitoring these patients can be found or treatment algorithms and risks are better understood [101].

For pragmatic reasons, the scope of the review was limited to include only interventional and observational studies. The results of this review indicate that the currently available higher quality evidence base provides little insight into the standard of care for the use of laboratory monitoring in the management of haemophilia patients with inhibitors undergoing surgery. This topic has also been addressed in case studies and series, including a case series reported by Dargaud et al. [102]. This article investigated the use of TGA in monitoring efficacy of agents in surgical procedures for six patients and showed that TGA results correlated with clinical bleeding risk and endogenous thrombin potential can be used to monitor agent efficacy in their hands [102]. These results were not supported by a later, larger scale study involving 10 inhibitor patients undergoing surgery identified by our review however, as no significant differences in TGA parameters between haemophilia patients with inhibitors who did and did not experience bleeding complications following surgery were found [77]. While case studies and series can provide valuable insight, they are considered to be a source of lower quality evidence due to their risk of bias and potential lack of generalizability to a wider patient population. The results of this review, therefore, highlight the need to report higher quality evidence on monitoring and managing surgical haemophilia patients with inhibitors to establish a standard of care in this area.

Conclusion

In conclusion, this systematic literature review demonstrated that there are multiple methods of laboratory monitoring used in haemophilia patients with inhibitors undergoing surgery, although these are largely reported in the context of clinical trials looking to evaluate unforeseen complications of candidate haemostatic agents. Currently no generalizable assays exist for examining treatment efficacy against high titre inhibitors, and instead clinicians are forced to rely on empirical dosing and consensus guidance. With the introduction of novel agents, this landscape may be complicated further. Where data on monitoring of inhibitor treatment exist, there is little information from higher quality evidence sources to indicate how the outcomes of such practices are used to inform treatment decisions. There is a need to develop more robust evidence in this area to establish a standard of care for perioperatively monitoring haemophilia patients with inhibitors who are treated with current and emerging haemostatic therapies.

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Table 7  Thrombin generation

| Reference          | Haemostatic treatment                                                                 | Factors monitored | Method of monitoring | Monitoring results                                                                 |
|--------------------|---------------------------------------------------------------------------------------|-------------------|----------------------|-----------------------------------------------------------------------------------|
| Holmström et al. [24] | Bolus aPCC in combination with TXA                                                    | LT, ETP, peak and ttPeak | TGA (on platelet-poor plasma)           | TGA showed shortened LT, ttPeak and a higher ETP and peak after aPCC+TXA administration compared with baseline, but not exceeding the values of healthy controls |
| Mancuso et al. [77]   | Bolus doses of rFVIIa and aPCC                                                          | Platelet count      | TGA                  | No significant difference was found in TGA values (PRP and PPP) measured during the postoperative period by comparing procedures with (n=7) and without (n=4) bleeding complications (data not shown) |

aPCC, activated prothrombin complex concentrate; ETP, endogenous thrombin potential; LT, lagtime; PPP, platelet-poor plasma; PRP, platelet-rich plasma; rFVIIa, recombinant factor VIIa; TGA, thrombin generation assay; ttPeak, time to peak; TXA, tranexamic acid.
Conflicts of interest

D.P. has received research support from Octapharma, Bayer and Shire, speaker and/or consultancy honoraria from Pfizer, Shire, Sobi, Biominar, Unicoire, Roche, Octapharma, Novo Nordisk and Biotest; C.R.M.H. has attended advisory boards organized by Roche, received research support from Novo Nordisk, Pfizer, Shire, Bayer and Sobi, and acted as speaker in sponsored symposia for Pfizer, Shire, Bayer, Sobi and Biotest; R.L. has received speaker fees from Octapharma, BPL and Bayer, consultancy fees from Bayer, Octapharma, Novo Nordisk, Shire and Grifols, has attended an advisory board organized by Roche, and was an investigator for the HAVEN 2 study; G.T. is an employee of Roche Products Ltd; B.D.M. is an employee of Costello Medical; M.M. has provided consultancy to CSL Behring and Novo Nordisk and attended advisory boards organized by Shire and Bioverativ.

References

1. Sinhastava A, Breuer K, Maisser-Bunschoten EP, Key NS, Kitchen S, Linas A, et al. Guidelines for the management of hemophilia. Haemophilia 2013; 19:e1–e47.
2. Eckhardtl CL, van Velzen AS, Peters M, Astemark J, Brons PP, Castaman G, et al. Factor VIII gene (F8) mutation and risk of inhibitor development in nonsevere hemophilia A. Blood 2013; 122:1954–1962.
3. Pehrsund F, Mannucci PM, Garaglia I, El-Beshawy A, Elalfy M, Neme D, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Engl J Med 2016; 374:2054–2064.
4. Ingerslev J, Hemophilia. Strategies for the treatment of inhibitor patients. Haemostatologica 2000; 95 (Suppl 1):15–20.
5. Teitel JM, Carcao M, Lillcrap D, Mulder K, Rivard GE, St-Louis J, et al. Orthopaedic surgery in haemophilia patients with inhibitors: a practical guide to haemostatic, surgical and rehabilitative care. Haemophilia 2009; 15:227–239.
6. Collins PW, Chalmers E, Hart DP, Lissner R, Ranganjar S, Talks K, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: a fourth edition. Br J Haematol 2013; 160:153–170.
7. Hay CRM, Demichels DM. The principal results of the International Immune Tolerance Study: a randomized dose comparison. Blood 2012; 119:1335–1344.
8. van Velzen AS, Eckhardt CL, Hart DP, Peters M, Ranganjar S, Mancuso ME, et al. Inhibitors in nonsevere haemophilia A: outcome and eradication strategies. Thromb Haemost 2015; 114:46–55.
9. Batty P, Austin SK, Khar K, Millar CM, Palmer B, Ranganjar S, et al. Treatment burden, haemostatic strategies and real world inhibitor screening practice in nonsevere haemophilia A. Br J Haematol 2017; 176:796–804.
10. Querol-Giner M, Perez-Alenda S, Irdi A, Carrasco J, Calatayud J, Casaña J, et al. Synoviotherapy in the treatment of recurrent haemorrhagic in haemophilia patients with inhibitors. Haemophilia 2016; 22:24.
11. Antmen BA, Sasmaz I, Karagun BS, Leblebisatan G, Kiico Y, Arioglan A, et al. The usage of recombinant activated factor VII (FFVIIA) during major and minor surgeries in severe hemophilia patients with inhibitor. XVIII Congress of the International Society on Thrombosis and Haemostasis, 2015:1–997.
12. Antmen B, Sasmaz I, Karagun BS, Leblebisatan G, Kiico Y, Arioglan A, et al. Circumcision in patients with hemophilia and the other bleeding disorders in southern part of Turkey. Haemophilia 2018; 24 (Suppl 1):01.
13. Balkan C, Karapinar D, Aydoğdu S, Ozcan C, Ay Y, Akın M, Kavaklı K. Surgery in patients with haemophilia and high responding inhibitors: İzmir experience. Haemophilia 2010; 16:902–909.
14. Bensadok M, Chennoukh WK, Aboura C, Ariou M, Zidani N, Boutiba S, et al. Haemophilia with inhibitors, update from Algiers experience, about one center. XVII Congress of the International Society on Thrombosis and Haemostasis, 2015:1–997.
15. Caniulli C, Rizzo AF, Linari S, Zago M, Pieri L, Castaman G, Innocenti M. Joint replacements for severe haemophiliac arthropathy in patients with inhibitors: a long-term experience at a single institution. Blood Transfus 2017; 15 (Suppl 4):s546.
16. Cauglia H, Candela M, Galatro G, Neme D, Moretti N, Bianco RP. Elective orthopaedic surgery for haemophilia patients with inhibitors: single centre experience of 40 procedures and review of the literature. Haemophilia 2017; 17:910–919.
17. Cauglia H, Galatro G, Gavagni G, Landro ME, Candela M, Neme D. Treatment of subchondral cysts in patients with haemophilia. Haemophilia 2016; 22:292–297.
18. Chapin J, Batterie J, Daha R, Chasles D, Desancho M. Outcomes in patients with hemophilia and von Willebrand disease undergoing invasive or surgical procedures. Clin Appl Thromb Hemost 1997; 23:148–154.
19. Ciavrarella N, Antoncicchi S, Ranieri P. Efficacy of porcine factor VIII in the management of haemophiliacs with inhibitors. Br J Haematol 1984; 58:841–848.
20. Danielson H, Lasilla R, Ylenin P, Yrjonen T. Total joint replacement in inhibitor-positive haemophilia: long-term outcome analysis in fifteen patients. World J Orthop 2017; 8:777–784.
21. Demichele D, Negrier C. A retrospective postlicensure survey of FEIBA efficacy and safety. Haemophilia 2006; 12:352–362.
22. Fidrighaus H, Berrope L, Elsman M, Gunnarssson M, Kliberg BM, Nilsson LM. Immunoadsorption for removal of inhibitors: update on treatments in Malmo–Lund between 1980 and 1995. Haemophilia 1999; 4:16–20.
23. Hs T, Zhou X, Cui H, Gao W, Zhou B, Liu Y. Surgical management of haemophilic pseudepitheliomatous: experience in a developing country. J Invest Surg 2017; 32:127–136.
24. Holmström M, Tran HT, Holme PA. Combined treatment with APCI (FEIBA(R)) and tranexamic acid in patients with haemophilia A with inhibitors and in patients with acquired haemophilia A – a two-centre experience. Haemophilia 2018; 18:544–549.
25. Ingerslev J, Freidman D, Gastineau D, Gilchrist G, Johnsson H, Lucas G, et al. Major surgery in haemophilia patients with inhibitors using recombinant factor VIIa. Haemostasis 1996; 26 (Suppl 1):118–123.
26. Ingerslev J. Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilia patients with factor VIII and factor IX inhibitors. Semin Thromb Hemost 2000; 26:425–432.
27. Jenkins PJ, Ekrol I, Lawson GM. Total knee replacement in patients with haemophilia: the Scottish experience. Scott Med J 2013; 58:229–237.
28. Sasmaz I, Antmen B, Karagun B, et al. Experience with Use of Port-a-cath in Children with Hemophilia: Single Center Study. Haemophilia 2016; 22:77–78.
29. Kitchens CS. Surgery in hemophilia and related disorders. A prospective study of 100 consecutive procedures. Medicine (Baltimore) 1986; 65:34–45.
30. Kalliacos H, Ozdemir N, Ozcan R, Celkan T. Circumcision in children with haemophilia. J Thromb Haemost 2016; 14 (Suppl 1):1–168.
31. Kruse-Jarres R, Callaghan MU, Croteau SE, Jimenez-Yuste V, Khoo L, Lissner R, et al. Surgical experience in two multicenter, open-label phase 3 studies of emicizumab in persons with hemophilia a with inhibitors (HAVEN 1 and HAVEN 2). Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH. 2017; 130(Supplement 1).
32. Laurou P, Fother AM, Guinrin V. Successful major and minor surgery using factor VIII inhibitor bypassing activity in patients with haemophilia A and inhibitors. Haemophilia 2006; 15:1300–1307.
33. Lim MY, Nielsen B, Lee K, Kristhus RS, Key NS, Ma AD. Rituximab as first-line treatment for the management of adult patients with nonsevere hemophilia A and inhibitors. J Thromb Haemost 2014; 12:897–901.
34. Lozier JN, Santagostino E, Kasper CK, Teitel JM, Hay CR. Use of porcine factor VIII for surgical procedures in hemophilia A patients with inhibitors. Semin Hematol 1993; 30 (2 Suppl 1):10–21.

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Patients with inhibitors.

A, Baudo F, Scaraggi FA, Gringeri A, Lienhart A, Numerof R, Stephens D, Wong WY, Baghai F, Yee TT. SURFical interventions with FEIBA (SURF): international registry of surgery in haemophilia patients with inhibitory antibodies. *Haemophilia* 2013; 19:143–150.

Negrier C, Lienhart A, Numerof R, Stephens D, Wong WY, Yee TT. Experience of recombinant activated factor VII usage during surgery in patients with haemophilia with inhibitors. *Haemophilia* 2012; 18:997–1002.

Rangarajan S, Yee TT, Wilde J. Experience of four UK comprehensive care centres using FEIBA(R) for surgeries in patients with inhibitors. *Haemophilia* 2011; 17:28–34.

Rodríguez-Merchan EC. Surgery in haemophilic patients with inhibitors. *Haemophilia* 2004; 10 (Suppl 2):1–2.

Santagostino E, Morfini M, Rocino A, Baudo F, Escorihuela JMA, Mier M, Gringeri A. Relationship between factor VIII activity and clinical efficacy of recombinant factor VIIIa given by continuous infusion to patients with factor VIII inhibitors. *Thromb Haemost* 2001; 86:954–958.

Sasmaz I, Antmen B, Guvenc B, Karagun B, Kilinc Y, Aridogan A. Circumcision and complications in adolescent and adult patients with hemophilia in southern part of Turkey. 20th Congress of The European Hematology Association. Vienna, Austria, 2015:1–804.

Scharf R, Kucharski W, Nowak T. Surgery in hemophilia A patients with factor VIII inhibitor: 10-year experience. *World J Surg* 1996; 20:1171–1181.

Scharrer I. Recombinant factor VIII for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Haemophilia* 1999; 5:253–259.

Serban M, Poenaru D, Decourchelle L, Savaescu D, Ionita H, et al. Risks and challenges of orthopaedic invasive interventions in haemophilia in a low-resource country. *Hamostaseologie* 2014; 34 (Suppl 1):S30–S39.

Smith MP, Ludlam CA, Collins PW, Hay CR, Wilde JT, Gringeri A, et al. Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU/ml is associated with an increased incidence of bleeding. *Thromb Haemost* 2001; 86:949–953.

Negrier C, Goudemand J, Bertrand M, Rothschild C, Lauroa P. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA Study Group. Factor Eight Bypassing Activity. *Thromb Haemost* 1997; 77:1113–1119.

Negrier C, Lienhart A, Numerof R, Stephens D, Wong WY, Baghai F, Yee TT. SURFical interventions with FEIBA (SURF): international registry of surgery in haemophilia patients with inhibitory antibodies. *Haemophilia* 2013; 19:143–150.

Negrier C, Lienhart A, Numerof R, Stephens D, Wong WY, Baghai F, Yee TT. SURFical interventions with FEIBA (SURF): international registry of surgery in haemophilia patients with inhibitory antibodies. *Haemophilia* 2013; 19:143–150.

Polyanskaya T, Zorenko V, Karpov E, Sampiev M, Mishin G, Vasilev D. Targeting of antithrombin in hemophilia A or B with RNAi therapy. *Haemophilia* 2012; 18:997–1002.

Rangarajan S, Yee TT, Wilde J. Experience of four UK comprehensive care centres using FEIBA(R) for surgeries in patients with inhibitors. *Haemophilia* 2011; 17:28–34.

Rodriguez-Merchan EC. Surgery in haemophilic patients with inhibitors. *Haemophilia* 2004; 10 (Suppl 2):1–2.

Santagostino E, Morfini M, Rocino A, Baudo F, Escorihuela JMA, Mier M, Gringeri A. Relationship between factor VIII activity and clinical efficacy of recombinant factor VIIIa given by continuous infusion to patients with factor VIII inhibitors. *Thromb Haemost* 2001; 86:954–958.

Sasmaz I, Antmen B, Guvenc B, Karagun B, Kilinc Y, Aridogan A. Circumcision and complications in adolescent and adult patients with hemophilia in southern part of Turkey. 20th Congress of The European Hematology Association. Vienna, Austria, 2015:1–804.

Scharf R, Kucharski W, Nowak T. Surgery in hemophilia A patients with factor VIII inhibitor: 10-year experience. *World J Surg* 1996; 20:1171–1181.

Scharrer I. Recombinant factor VIII for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Haemophilia* 1999; 5:253–259.

Serban M, Poenaru D, Patracscu J, Ursu E, Savescu D, Ionita H, et al. Risks and challenges of orthopaedic invasive interventions in haemophilia in a low-resource country. A single-center experience. *Hamostaseologie* 2014; 34 (Suppl 1):S30–S39.

Smith MP, Ludlam CA, Collins PW, Hay CR, Wilde JT, Gringeri A, et al. Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU/ml is associated with an increased incidence of bleeding. *Thromb Haemost* 2001; 86:949–953.

Tjonnfjord GE. Activated prothrombin complex concentrate (FEIBA) treatment during surgery in patients with inhibitors to FVIII/IX: the updated Norwegian experience. *Haemophilia* 2004; 10 (Suppl 2):41–45.

Tjonnfjord GE. Surgery in patients with hemophilia and inhibitors: a review of the Norwegian experience with FEIBA. *Semin Hematol* 2006; 43 (2 Suppl 4):S18–S21.

Pruthi R, Mathew P, Valentino L, Seremetis S. An open-label, randomized, parallel, multicenter trial comparing the safety and efficacy of rFVIIa when administered as IV bolus or IV continuous infusion to hemophilia patients with inhibitors during and after surgery. *Blood* 2004; 104:3975.

Santagostino E, Marcuzzo ME, Novembrino C, Boscolo MA, Clerici M, Pasta G. Management of joint replacement in hemophilia a with inhibitors during emicizumab prophylaxis. *Blood* 2017; 130 (Suppl 1):2360.

Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MJ, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med* 2017; 377:809–818.

Genetech, HEMLIBRA™ (emicizumab-kohw) injection, for subcutaneous use. FDA; 2017; Available from: https://www.gene.com/download/pdf/hemlibra_prescribing.pdf. [Accessed 16 April 2019].

Dargaud Y, Lienhart A, Janbain M, Le Queuic S, Enjolras N, Negrier C, et al. Use of thrombin generation assay to personalize treatment of breakthrough bleeds in a patient with hemophilia and inhibitors receiving prophylaxis with emicizumab. *Haematologica* 2018; 103:e181–e183.

Novo Nordisk A/S. A trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia A and B patients with inhibitors (explorome™ 4). 2017; Available from: https://clinicaltrials.gov/ct2/show/NCT03196284. [Accessed 16 April 2019].

Waters EK, Singh J, Friedrich U, Hilden I, Sorensen BB. Concizumab, an antithrombin factor pathway inhibitor antibody, induces increased thrombin generation in plasma from haemophilia patients and healthy subjects measured by the thrombin generation assay. *Haemophilia* 2017; 23:769–776.

Pasi KJ, Rangarajan S, Georgiev P, Mant T, Creagh MD, Lissitchkov T, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. *N Engl J Med* 2017; 377:819–828.

Collins P, Liesner R, Makris M, Tants K, Chowdry P, Chalmers E, et al. Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab. Guidance from UKHCDO Inhibitor Working Party and Executive Committee. 2018; Available from: http://www.ukhcdo.org/wp-content/uploads/2018/01/UKHCDO-guideline-for-treatment-of-bleeds-whilst-on-Emicizumab-10.1.18-fl_.pdf. [Cited 03/05/2018].

Dargaud Y, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. *Blood* 2010; 116:5794–5797.