

Situation of laboratory diagnostics of bleeding disorders in Baltic countries

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Summary

Background. The study evaluates the current landscape of laboratory diagnostics for bleeding disorders across the Baltic countries, where outdated guidelines (2009–2010) hinder diagnostic accuracy and standardization.

Methods. An initiative Baltic working group for bleeding disorders developed a questionnaire to assess the operational status and diagnostic capabilities of laboratories in Lithuania, Latvia, and Estonia. This survey covered 48 laboratories, of which 36 responses were analyzed.

Results. Results indicate considerable variability in laboratory capabilities, accreditation status, and available diagnostic assays, with only half of the laboratories accredited under ISO 15189. Most laboratories employ basic screening tests like PT/INR, aPTT, and fibrinogen; however, advanced assays

and specialized diagnostics for conditions such as von Willebrand disease and haemophilia are limited. The findings reveal geographic and institutional disparities in methodologies (e. g., Quick vs. Owren method for PT), reflexive testing practices, and clinical algorithm implementation. Participation in EUHANET remains low, with few institutions recognized as comprehensive or treatment centers, signaling limited access to specialized networks.

Conclusions. To mitigate these gaps, updated guidelines tailored to the capabilities of laboratories across the Baltic region are recommended. These guidelines should align with international standards to enhance diagnostic quality and ensure equitable patient care.

Keywords: bleeding, questionnaire, laboratory, Baltic countries, von Willebrand disease, haemophilia.

BACKGROUND

Laboratory diagnostics for bleeding disorders is essential for the effective management of patients, especially those with conditions such as von Willebrand disease (VWD) and haemophilia [1]. In the Baltic countries, guidelines for bleeding disorders were last updated in 2009 and 2010. These guidelines are now outdated and require revision to ensure that laboratories have access to nationally adapted practical, up-to-date information for performing diagnostic haemostasis tests. A Baltic working group, comprising experts in haematology and laboratory medicine, developed a questionnaire to gather information on the capabilities of laboratories in the region. This questionnaire, as a

first step, aims to review and update the Baltic guidelines and improve their practicality for the laboratories performing haemostasis tests.

METHODS

An online questionnaire was distributed to laboratories in the Baltic countries to assess the current state of diagnostics for bleeding disorders. The survey covered various aspects, including laboratory capabilities, diagnostic assays, testing infrastructure, accreditation status, analytical platforms used, and prothrombin time (PT) measurement methods (Table 1). Questions were grouped into 4 in depth detail levels. The dataset collected for three months (June

to August 2024) contained 48 responses, out of which 12 responses were excluded from the analysis as these laboratories reported that they do not perform haemostasis testing.

Therefore, 36 responses were analyzed to evaluate the capabilities and current practices in diagnostics for bleeding disorders in the Baltic region.

Table 1. Questions according to the detail levels

Question type	Question	Level
Main questions	In which country is your laboratory situated?	1
	What is the name of your institution? (not mandatory)	
	What is the type of your laboratory?	
	Does your laboratory work 24/7?	
	Is your institution part of EUHANET (European Haemophilia Network) as HTC (Haemophilia Treatment Center) or CCC (Comprehensive Care Center)?	
	Does your laboratory perform haemostasis testing?	
Haemostasis screening tests	Are your haemostasis tests accredited according to ISO 15189 standard?	2
	What analytical platform do you use for haemostasis testing? Provide the model name of analyzer and the manufacturer.	
	Which screening assays of haemostasis do you perform?	
	Which method of prothrombin time do you use?	
	Which clotting activator is used in your aPTT assay?	
	What is your method for fibrinogen?	
	Please provide method information for other screening assays performed in your lab, except for PT, aPTT and fibrinogen.	
Reflexive testing	Are reflexive testing principles implemented in your laboratory for haemostasis testing?	2
Definition of reflexive testing principles	Please provide short description of reflexive testing principles implemented for haemostasis	3
	How reflexive testing works in your laboratory?	
Algorithms	Have you implemented any algorithms in haemostasis testing? (i.e. for bleeding disorders, for evaluation of clotting test prolongation, <i>lupus</i> anticoagulant analysis etc.)	2
Definition of algorithms	Please provide short description of algorithms implemented in your laboratory.	3
Haemophilia testing	Do you perform haemophilia testing?	2
Definition of haemophilia testing	If your laboratory is a network, do you perform haemophilia testing on-site or in centralized laboratory?	3
	Which assays for haemophilia are available in your laboratory?	
	Please provide method data for factor VIII assays: 1. assay, 2. reagent manufacturer, 3. LOD (limit of detection), 4. EQA provider.	
	Please provide method data for factor IX assays: 1. assay, 2. reagent manufacturer, 3. LOD (limit of detection), 4. EQA provider.	
	Please provide method data for other (except FVIII and FIX) assays: 1. assay, 2. reagent manufacturer, 3. LOD (limit of detection), 4. EQA provider.	
	Which assay do you perform for coagulation factor inhibitors?	
	Which type of factor analysis methods are used in factor inhibitor analysis?	
	Is emicizumab level measurement available in your lab?	
Emicizumab details	Which assays do you apply for emicizumab treated patients?	4
	Please provide additional information for chromogenic factor VIII and/or IX assays performed for emicizumab treated haemophilia patients (1. assay, 2. origin of the substrate (bovine, human etc.), 3. controls, 4. calibrator 5. and their manufacturer).	
VWD testing	Do you perform VWD (von Willebrand disease) testing?	2
Definition of VWD testing	If your laboratory is a network, do you perform VWD testing on-site or in centralized laboratory?	3
	Which assays for VWD are available in your laboratory?	
	Please provide method data for VWF:Ag and VWF:Ac assays: 1. assay, 2. reagent manufacturer, 3. LOD (limit of detection), 4. EQA provider.	
	Please provide method data for VWF:RCO, VWF:CBA and VWF:FVIIIIB assays: 1. assay, 2. reagent manufacturer, 3. LOD (limit of detection), 4. EQA provider.	
	Please provide method data for VWF:MM assay: 1. reagent manufacturer 2. EQA provider. EXAMPLE: Sebia, ECAT.	
FXIII testing	Do you perform factor XIII testing?	2
Definition of FXIII testing	List FXIII assays your lab performs (please provide data of each assay: 1. assay 2. reagent manufacturer, 3. LOD (limit of detection), 4. EQA provider).	3
Platelet function testing	Do you perform platelet function testing?	2

Definition of platelet function testing	Which platform do you use for PLT function testing? (provide the model's name and the manufacturer, working principle (i.e. LTA, WBA, other))	3
	Which vacuum tubes do you use for PLT function testing?	
	What is the most common purpose of PLT function testing in your lab?	
	Which tests are performed for bleeding risk assessment? If none, just write "NOT PERFORMED".	
	If anti-platelet drug monitoring is performed, which drugs are monitored?	
	Which reference values or cut-offs do you use for PLT function testing?	
DOAC testing	Are DOAC's (direct oral anticoagulants) monitored in your lab?	2
Definition of DOAC testing	Which DOAC's are monitored in your lab?	3
	Which assay do you use for dabigatran?	
	Which assay do you use for FXa inhibitors (rivaroxaban, apixaban, edoxaban etc.)?	
Global haemostasis assays	Which global haemostasis assays are performed in your lab or in other departments of your institution as POCT?	2

RESULTS

Out of the 36 laboratories that responded, 10 were in Lithuania, 12 – in Latvia, and 14 – in Estonia. A significant proportion of these laboratories (n=32, 89%) were standalone public laboratories or part of public hospitals/polyclinics (with or without academic status), with a few being private standalone labs or private hospital departments. Approximately 28% of laboratories reported not working on a 24/7 basis, being both from public and private sector, reflecting limitations in emergency diagnostic coverage for bleeding disorders.

Regarding EUHANET participation, 2 of the responding laboratories (both from Estonia) reported affiliation with EUHANET as Haemophilia Treatment Centers (HTCs). Between remaining laboratories there were 5 (4 Latvian and 1 Lithuanian) who were unsure of their status.

In terms of accreditation, half of laboratories reported having accreditation according to ISO 15189 standard indicating a focus on quality assurance and standardized practices in diagnostics. Most of those laboratories reported having accredited specialized haemostasis tests, and 4 of them – the

screening tests only. There was no clear country wise or private/public wise tendency between accredited laboratories. Many laboratories used automated coagulometers from manufacturers such as Siemens (Germany), Diagnostica Stago (France), and Werfen (USA), with some variability between countries.

As expected, the most frequent (80%) combination of screening assays was prothrombin time / international normalization ratio (PT/INR), activated partial thromboplastin time (aPTT) and fibrinogen. Only one fifth of laboratories included d-dimer, an even less (14%) – thrombin time as haemostasis screening assay. There were 6 laboratories performing only PT/INR, mostly with point-of-care testing (POCT) devices. For prothrombin time (PT) measurements, there was a 50/50 split between laboratories using the Quick method and those using the Owren method. In Estonia and Latvia, the Quick method is slightly more popular in contrast to Lithuania, where the Owren method is more prominent, highlighting differences in standard practices across the Baltic region. Variations in basic coagulation assays are summarized in Table 2.

Table 2. Variations of haemostasis screening assays between Baltic countries. EE – Estonia, LV – Latvia, LT – Lithuania, PT – prothrombin time, aPTT – activated partial thromboplastin time

	Country	PT	aPTT	Fibrinogen
Dominating coagulation screening assays	Baltics	16 Quick / 36 (44.4%) 16 Owren / 36 (44.4%)	25 silica / 32 (78.1%)	24 Clauss / 28 (85.7%)
	EE	8 Quick / 14 (57.1%)	10 silica / 10 (100%)	9 Clauss / 10 (90%)
	LV	7 Quick / 12 (58.3%)	6 silica / 12 (50%)	7 Clauss / 9 (77.8%)
	LT	7 Owren / 10 (70%)	9 silica / 10 (90%)	8 Clauss / 9 (88.9%)
	Baltics	4 both PTs / 36 (11.1%)	7 other / 32 (21.9%)	4 other / 28 (14.3%)
Variations in responses	EE	4 Owren / 14 (28.6%) 2 both PTs / 14 (14.3%)	0 / 10 (0 %)	1 PT derived / 10 (10%)
	LV	5 Owren / 12 (41.7%)	4 ellagic acid / 12 (33.3%) 2 unspecified / 12 (16.7%)	1 PT derived / 9 (11.1%) 1 antigen assay / 9 (11.1%)
	LT	1 Quick / 10 (10%) 2 both PTs / 10 (20%)	1 kaolin / 10 (10%)	1 PT derived / 9 (11.1%)

Only 8/36 (22%) respondents answered that laboratory applies reflexive testing principles. In those laboratories automatic or manual action would be taken due to doubtful or critical results, PT and/or aPTT prolongation, for lupus anticoagulant screening purposes, and would result in performing mixing studies. One laboratory noted that reflexive

testing is done on a case-by-case basis in cooperation with the attending physician and the laboratory physician. 8 laboratories replied they are using algorithms in haemostasis testing (4 the same who apply and 4 who do not apply reflexive testing). Clinical algorithms such as diagnosis of bleeding disorders, evaluation of clotting test prolongation,

lupus anticoagulant analysis and antiphospholipid syndrome diagnosis, thrombophilia screening, evaluation of the effectiveness of direct oral anticoagulant (DOAC) and/or antiplatelet treatment, control of massive bleedings, and evaluation of the necessity of blood transfusions is in place of those institutions (interestingly, dominated mainly by Estonian labs).

It was observed that while most laboratories perform basic coagulation assays, the availability of more specialized assays was limited (Table 3). Regarding haemophilia diagnostic capabilities, mainly one stage aPTT based factor VIII and/or IX assays for screening/diagnosis/treatment monitoring purposes, with different assay availability, highly variable limits of detection (LODs), variable availability of external quality assessment (EQA) schemes are available. Classical Bethesda methods with several exceptions of modified Nijmegen assay are performed by both one stage clotting and chromogenic methods. There are still laboratories applying one stage clotting assays for emicizumab treated patients. Only one Estonian lab is performing emicizumab level analysis.

Table 3. Number of laboratories performing specialized haemostasis testing in Baltic countries. VWD – von Willebrand disease, DOAC – direct oral anticoagulant, EE – Estonia, LV – Latvia, LT – Lithuania

Specific area	Baltics total	EE	LV	LT
Haemophilia	8 / 36 (22.2%)	2	3	3
VWD	8 / 36 (22.2%)	2	3	3
FXIII deficiency	1 / 36 (2.8%)	0	0	1
Platelet dysfunction	8 / 36 (22.2%)	3	3	2
DOAC treatment	6 / 36 (16.7%)	2	2	2
Global haemostasis	7 / 36 (19.4%)	3	2	2

Dominating assays for von Willebrand disease diagnostics in Baltic countries are von Willebrand factor antigen (VWF:Ag; all 8 labs) and activity (VWF:Ac; 6 labs). Only one lab in Estonia and one in Lithuania are available for von Willebrand multimers (VWF:MM) analysis. One Estonian laboratory is performing whole blood aggregometry (WBA), otherwise named as multiple electrode aggregometry (MEA), with low and high ristocetin concentrations. LODs and availability of EQA schemes are highly variable. Von Willebrand factor ristocetin cofactor (VWF:RCO), collagen binding (VWF:CBA), and factor VIII binding (VWF:FVIIIIB) assays are not available at all.

Half of the respondents, who perform platelet function testing, are the same labs performing haemophilia and/or VWD diagnostic tests with variable availability of light transmittance aggregometry (LTA), WBA (MEA), platelet function analyzer (PFA) methods with manufacturer defined reference ranges. The type of anticoagulant for platelet function analysis depends on which method is used, but there is discrepancy in laboratories who use WBA (MEA) method (hirudin versus lithium heparin tubes). Almost every laboratory uses their methods for both bleeding risk and drug monitoring purposes. Tests for aspirin, clopidogrel, prasugrel, ticagrelor, tirofiban, and abciximab are variably available, most with manufacturer defined cut-offs. All tests are performed in the laboratories, and none as POCT.

Tests for DOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, are variably available in Baltic countries. Labs performing dabigatran use only ECA assay, and all labs are using anti-Xa calibrated for individual drug for rivaroxaban, apixaban, and edoxaban. Reference assay LC/MS for DOACs is not available in Baltic countries. DOAC testing in urine is available in 4 Estonian labs.

Global haemostasis testing situation is also very limited. Dominant assay is ROTEM. One Estonian lab uses SEER method by Quantra. Thrombin generation assays are not available in Baltic countries.

DISCUSSION

The analysis of the survey responses highlights the significant variability in laboratory capabilities across the Baltic countries. Similar situations were shown in laboratories in different countries [2–4].

It is well-established that the International Normalized Ratio (INR) was introduced to standardize prothrombin time (PT) results for patients undergoing anticoagulant therapy with warfarin [5]. In recent years, the use of warfarin has declined across the Baltic countries [unpublished data], yet INR remains a commonly reported parameter in laboratory results. This trend underscores the need for interdisciplinary collaboration. Our survey also revealed that some Baltic laboratories utilize Owren-type prothrombin time as a screening test. Notably, the Owren-type PT was designed specifically for monitoring vitamin K antagonist therapy and is not sensitive to deficiencies in factor V or fibrinogen [6].

The aPTT assay is available in all Baltic laboratories, with 22% additionally performing reflexive coagulation tests through various methods. Implementing further evaluations in haemostasis laboratories is unwarranted without clinical information, which should be mandatory on laboratory requests [7]. Although the question about availability of clinical information, such as bleeding or thrombosis symptoms, risk, antithrombotic treatment etc., was not provided in our questionnaire, we speculate that very few or even none of the labs receive such clinical information routinely.

Although the International Council for Standardization in Haematology (ICSH) recommends the Clauss fibrinogen assay as the first-line method in hospital laboratories [8], only 85.7% of responding laboratories reported using the functional activity test known as the Clauss assay. In comparison, a survey of haemostasis testing in Croatian laboratories [3] found that all laboratories employed the Clauss method, indicating room for improvement within the Baltic region.

There appears to be a lack of uniformity in the availability of advanced diagnostic assays, which may limit the effective diagnosis and management of patients with complex bleeding disorders. For example, a quarter of survey participants perform testing for haemophilia diagnosis. The study revealed highly variable limits of detection (LODs), ranging from 0.3 to 8.0 IU/dL for both FVIII and FIX measurements, raising significant concerns due to the potential risk of severe haemophilia misdiagnosis. It is crucial that FVIII reagents, in particular, demonstrate sufficient sensitivity (LOD < 1 IU/dL) to accurately

detect all types of haemophilia, from mild to severe haemophilia A [9]. Only one-third of these laboratories offer FVIII measurement using the chromogenic method, which is essential for diagnosing haemophilia A carriers [10] and for patients undergoing treatment with emicizumab [11]. Notably, some laboratories continue to apply one-stage clotting assays for patients treated with emicizumab, leading to erroneous FVIII interpretations (incorrectly normal or elevated results), which is not recommended [12]. Currently, all laboratories requiring emicizumab evaluation send samples to a laboratory in Estonia, where emicizumab concentration can be assessed using a drug-specific calibrator [13].

The full panel of first-line laboratory tests for von Willebrand disease (VWD) or acquired von Willebrand syndrome (AVWS) – including VWF:Ag, VWF:Ac (without distinguishing between VWF:GIBR and VWF:GPIbM), FVIII, and platelet function assays – is available in only half of the laboratories reporting the capability to diagnose VWD. Only two laboratories offer the VWF antigen assay, which is inadequate without a concurrent VWF activity assay for accurate VWD diagnosis [14]. One laboratory each in Estonia and Lithuania provides VWF multimer analysis, which is considered sufficient, as samples can be collected and transported from other facilities. However, the absence of VWF:RCO, VWF:CBA, and VWF:FVIII assays across the Baltic region highlights further limitations in the diagnostic capabilities for VWD.

Nearly all laboratories who perform platelet function testing with light transmittance aggregometry (LTA), whole blood aggregometry (WBA) by multiple electrode aggregometry (MEA) instruments, or platelet function analyzer (PFA) methods rely on manufacturer-defined reference ranges, with only one laboratory utilizing clinically verified cut-offs. Experts recommend the verification of clinical cut-off values and reference ranges [15]. Most laboratories employ these methods for both bleeding risk assessment and drug monitoring purposes. A survey of clinical centers in Northern Europe showed that all participating laboratories utilize aggregometry to evaluate platelet function disorders, with half using multiple electrode aggregometry (MEA) in whole blood and the other half using light transmittance aggregometry (LTA) in platelet-rich plasma (PRP) [4]. Recently, Roche (Germany) discontinued the production of the ristocetin reagent (RISTOtest) for WBA (MEA). However, an alternative ristocetin reagent has been demonstrated to be a viable substitute [16].

The discrepancy in anticoagulant types used for platelet function analysis among laboratories utilizing the whole blood aggregometry (WBA) or multiple electrode aggregometry (MEA) method is concerning and highlights a lack of harmonization. Previous studies have shown that hirudin remains preferable to lithium heparin as an anticoagulant in WBA (MEA) assays [17]. The successful adoption of hirudin tubes in laboratories across Northern Europe serves as a strong example of effective harmonization [4].

Routine laboratory monitoring of direct oral anticoagulants (DOACs) is generally not recommended; however, it may be necessary in certain clinical emergencies [18]. Currently, only 16.7% of Baltic laboratories offer testing for dabigatran, rivaroxaban, apixaban, and edoxaban, though availability remains inconsistent.

The limited number of laboratories associated with EUHANET indicates a potential gap in access to specialized care and international networks, which could be addressed in future guidelines. As of the 16th of August of 2024, officially, there is one EHCCC (European Haemophilia Comprehensive Care Centre) and one EHTC (European Haemophilia Treatment Centre) in Lithuania. Estonia has three EHTC centers (two of them located in Tallinn), and there is none in Latvia [19]. Given this fact, one may draw the conclusion that laboratories are not fully aware of their institution's affiliation with EUHANET.

The differences in accreditation status, analytical platforms, haemostasis screening and advanced testing methods underscore the need for updated, practical guidelines that cater to the varied capabilities of laboratories in the Baltic region. By addressing gaps in diagnostics and providing standardized recommendations, the revised guidelines could enhance the quality of bleeding disorder diagnostics and ensure that patients receive timely and accurate diagnoses, irrespective of where they are in the region.

This survey faced several limitations that should be considered when interpreting the findings. Firstly, not all laboratories in the Baltic countries participated, which may introduce selection bias and limit the generalizability of the results. The exclusion of certain laboratories that do not perform haemostasis testing might have also led to an incomplete understanding of diagnostic capabilities across the region. Furthermore, critical information, such as the clinical context provided in test request forms (e.g., patient bleeding history, antithrombotic treatment status), was not included in the questionnaire. This lack of clinical data limits the ability to comprehensively assess laboratory practices in context with patient-specific needs. Additionally, the survey did not explore certain aspects of laboratory infrastructure, such as staff competency and workload, which could influence diagnostic quality. Lastly, the reliance on self-reported data may introduce reporting bias, as laboratories might overstate or understate their capabilities.

CONCLUSIONS

This study provides an overview of the current state of laboratory diagnostics for bleeding disorders in the Baltic countries. The findings reveal considerable heterogeneity in the availability of diagnostic assays, testing infrastructure, accreditation, analytical platforms, and methods. To address these disparities, updated Baltic guidelines for bleeding disorders should focus on practical implementation for laboratories of varying capacities and ensure alignment with international standards. Improving access to advanced diagnostic assays and participation in networks such as EUHANET could significantly enhance the management of bleeding disorders in the Baltic region.

Conflicts of Interests

The authors declare no conflict of interests.

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Santrauka

KRAUJAVIM AIS PASIREIŠKIANČIŲ LIGŲ LABORATORINĖS DIAGNOSTIKOS SITUACIJA BALTIJOS ŠALYSE

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Baltijos šalių kraujavimais pasireiškiančių ligų darbo grupės vardu

Įvadas. Atlikta apklausa leido įvertinti dabartinę kraujavimais pasireiškiančių ligų laboratorinės diagnostikos situaciją Baltijos šalyse, kur, manoma, dėl pasenusių gairių (2009–2010 m.) taikymo nėra užtikrinamas diagnostinis tikslumas ir standartizacija.

Metodai. Baltijos šalių kraujavimais pasireiškiančių ligų darbo grupė parengė klausimyną, siekdama įvertinti laboratorijų veiklos būklę ir diagnostines galimybes Lietuvoje, Latvijoje ir Estijoje. Apklausa apėmė 48 laboratorijas, ir buvo išanalizuoti iš jų gauti 36 respondentų atsakymai.

Rezultatai. Rezultatai parodė reikšmingą laboratorijų galimybių, akreditacijos būklės ir turimų tyrimo metodų įvairovę – tik pusė laboratorijų yra akredituotos standarto ISO 15189 atitikčiai. Dauguma laboratorijų taiko pagrindinius atrankinius PL/TNS, ADTL ir fibrinogeno tyrimus, tačiau specifiniai tyrimai ir specializuota tokių būklių kaip Vilebrando ligos ar hemofilijų diagnostika yra ribota. Rezultatai atskleidžia geografinius ir tarpinstitucinius metodikų (pvz. *Quick* ir *Owren* protrombino laiko metodų) skirtumus, refleksinių tyrimų taikymo praktiką ir klinikinių algoritmų įgyvendinimą. Dalyvavimas EUHANET tinkle yra ribotas, tik keletas institucijų yra pripažintos visapusišką priežiūrą ir gydymą teikiančiais centrais, o tai parodo ribotą prieigą prie specializuotų paslaugų.

Išvados. Siekiant pašalinti šiuos trūkumus, rekomenduojama parengti atnaujintas gaires, pritaikytas laboratorijų galimybėms Baltijos regione. Šios gairės turėtų atitikti tarptautinius standartus, užtikrinti lygiavertę pacientų priežiūrą, kad pagerėtų diagnostikos kokybė.

Reikšminiai žodžiai: kraujavimas, klausimynas, laboratorija, Baltijos šalys, Vilebrando liga, hemofilija.

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