Diagnosis and Treatment of Autoimmune Acquired Coagulation Factor Deficiencies: An Evidence-Based Review of Japanese Practice

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Abstract

Among the acquired coagulation factor deficiencies, autoimmune coagulation factor deficiencies (AiCFD) are rare and result from autoantibody production against coagulation factors. In Japan, a nationwide survey on AiCFD has been conducted since 2009. Autoimmune factor XIII, factor VIII, von Willebrand factor, factor V, and factor X deficiencies (AiF13D, AiF8D, AiVWFD, AiF5D, and AiF10D, respectively) have been enacted as "designated intractable disease-282." The incidence of AiF8D, AiF13D, and AiF5D was 1.83, 0.044, and 0.038 per million people/year, respectively, whereas that of AiVWFD and AiF10D was not calculable owing to the small number of patients. AiF13D and AiF8D were often idiopathic, whereas AiVWFD was often associated with plasma cell neoplasms. Epistaxis was a characteristic symptom of AiVWFD, intramuscular bleeding was frequent in AiF13D and AiF8D, and subcutaneous bleeding (purpura) was frequent in AiF13D and AiF10D, although none were specific to any one disease. Differential diagnosis cannot be made based on bleeding symptoms alone; therefore, rapid and accurate testing is mandatory. Definitive diagnosis of AiCFD necessitates identifying the presence of coagulation factor "inhibitors" and/or "autoantibodies." Therefore, these tests should be performed upon unexplained severe acquired coagulation factor deficiencies. The mainstay of treatment for AiCFD was hemostatic therapy and autoantibody eradication therapy, which included the replacement of coagulation factors or "bypass" agents and administration of immunosuppressants. The rate of hemorrhagic death was high in AiF13D (13%), followed by AiF5D (7%) and Ai10D (5%); therefore, early diagnosis and optimal treatment are essential for AiCFDs. Given the unknown long-term prognosis, "intractable disease platform registries" have begun to accumulate in Japan.

Keywords

- acquired hemorrhagic disorder
- autoimmune disease
- anticoagulation factor autoantibody
- coagulation factor inhibitor
- designated intractable disease

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The clotting cascade involves approximately 10 coagulation factors (►**Fig. 1**),[1,2] with von Willebrand factor (VWF) playing a crucial role in connecting subcutaneous tissue and platelets, or multiple platelets, while also binding and stabilizing factor VIII (FVIII).[3,4] Factor XIII (FXIII) serves to covalently connect fibrin molecules or fibrin and antifibrinolytic factor α_2-plasmin inhibitor (α_2-PI) through cross-linking to stabilize platelet/fibrin clots and enhances their mechanical strength and antifibrinolytic resistance.[5,6] VWF is present as a series of multimers to which various molecules are linked, whereas FXIII exists in blood as a heterotetramer comprising a dimer of the FXIII-A subunit and a dimer of the FXIII-B subunit.

Hereditary coagulation factor deficiency (CFD) arises from an inherited deficiency of any of these coagulation factors; these deficiencies block the formation of platelet/fibrin clots, resulting in impaired hemostasis and abnormal bleeding.[7–9] Acquired CFDs (acCFD) may also occur due to low production, increased consumption, or increased elimination of coagulation factors. Although rare, autoantibodies against coagulation factors may be generated (►**Fig. 2**), resulting in severe bleeding disorders,[10–13] known as autoimmune acCFDs (AiCFDs).[14,15]

We initiated a nationwide survey on autoimmune FXIII deficiency (AiF13D) in 2009 with support from the Japanese Ministry of Health, Labor and Welfare (MHLW). Subsequently, AiF13D was first established as a designated intractable disease (DID)-288. Following this, autoimmune VWF deficiency (AiVWFD) and autoimmune FVIII deficiency (AiF8D or acquired hemophilia) were added (►**Table 1**). Later, autoimmune factor V (FV) deficiency (AiF5D) and autoimmune factor X (FX) deficiency (AiF10D) were added, and patients with these five types of intractable bleeding diseases became eligible to receive medical and financial support through the Public Medical Expense Subsidy Program for MHLW-DIDs. While lupus anticoagulant-hypoprothrombinemia syndrome[16,17] is also a disease subject to investigation by the Japanese Collaborative Research Group (JCRG), it has not as yet been added to DID-288 by the Japanese MHLW.

Compared with "nonimmune" acCFDs, AiCFDs are very rare, posing diagnostic and therapeutic challenges even to hematologists. Given this rarity, disease-specific tests have not become generally available, making definitive diagnosis and initiation of optimal treatment difficult. Diagnosis of AiCFD is not possible based on bleeding symptoms alone; unless unique disease-specific tests are performed, patients will be diagnosed with a "bleeding disorder of unknown cause."

In this review, we aim to summarize the results of our surveys and studies conducted on five AiCFDs in Japan and compare their characteristic clinical features, laboratory findings, and treatment methods.[18–25] This evidence-based comprehensive review may contribute to facilitating earlier diagnosis and treatment of AiCFDs.

Clinical Features and Diagnosis

Number and Frequency of Autoimmune Coagulation Factor Deficiency Cases

AiF8D is the most common among all AiCFDs. Deriving an estimate from the number of patients diagnosed with AiF8D

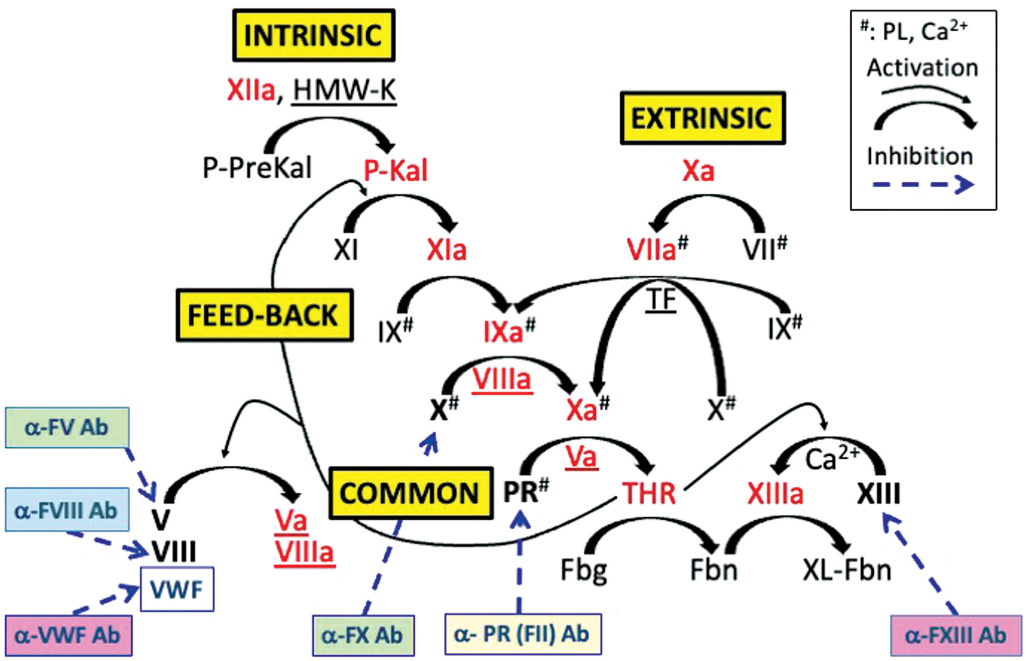

Fig. 1 Coagulation pathways and autoantibodies against coagulation factors. Anticoagulation factor autoantibodies against any coagulation factors can be produced. However, higher molecular weight coagulation proteins, such as FVIII, FXIII, FV, and VWF, have wider surfaces, and thus, they may have more epitopic sites, judging from the actual numbers of the patients with AiF8D, AiF13D, AiF5D, and AiVWFD. Activated coagulation factors are shown in red. α-F* Ab, anti-F* autoantibody; AiF5D, AiF8D, AiF13D, AiVWFD, and AiF10D, autoimmune factor V, factor VIII, factor XIII, von Willebrand factor, and factor X deficiencies, respectively; Fbg, fibrinogen; Fbn, fibrin; HWM-K, high molecular weight-kininogen; P-PreKal, plasma prekallikrein; PL, phospholipid; PR, prothrombin; TF, tissue factor; THR, thrombin; VWF, von Willebrand factor; XIII, factor XIII; XIIIa, activated factor XIII; XL-, crosslinked.

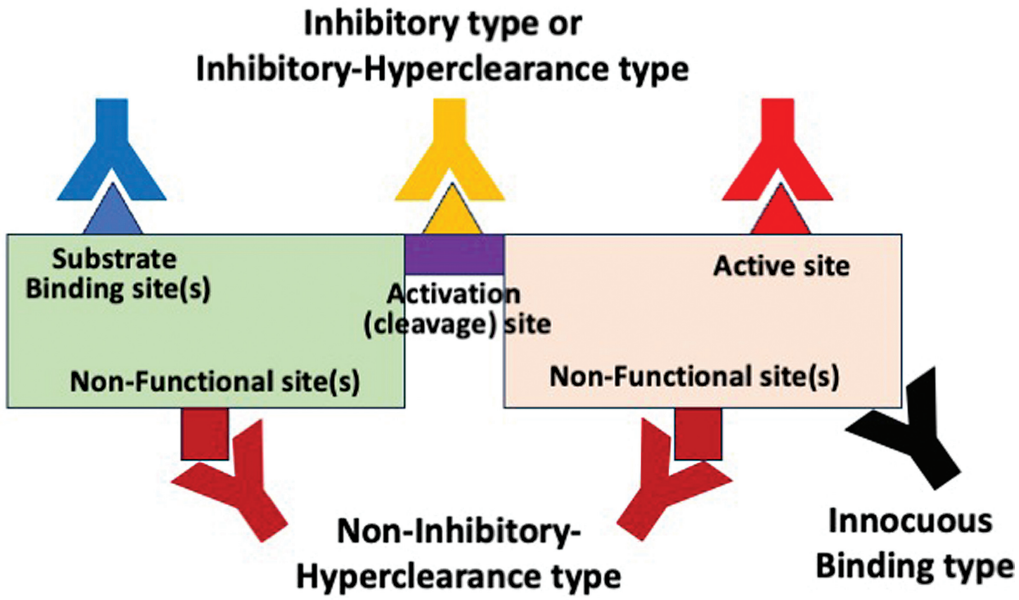

Fig. 2 Pathological mechanisms of anticoagulation factor antibodies (concept). Inhibitory type antibodies bind to the active site, activation (cleavage) site (s), and/or substrate binding site(s) of coagulation factors to inhibit these functions, whereas hyperclearance type antibodies bind nonfunctional site(s) of coagulation factors and exclusively enhance their elimination from the blood circulation. Some antibodies possess both inhibitory and hyperclearance natures. There may also be harmless autoantibodies that simply bind to coagulation factors (innocuous binding type).

Table 1 Summary of geographic characteristics of 5 Japanese Designated Intractable Diseases

Japanese DID code	288–1	288–2	288–3	288–4	288–5
Disease name	AiF13D	AiF8D	AiVWFD	AiF5D	AiF10D
Number of patients	125 (2021)	Not available	Not available	Not available	26 (2021)
Patients in Japan	87 (2021)	2,548 (estimated)	40 (2021)	201 (2021)	3 (2022)[26]
Incidence in Japan (mil/y[a])	0.044	1.83	Not calculable	0.038	Not calculable
Age (mean, SD)	71.8, 12.6 y	66.2, 18.3 y	55.0, 19.0 y	71.9, 11.9 y	56.5, 22.7 y
Age (median)	73 y	73 y	60 y	74 y	59 y
Sex ratio (male/female)	1.77	1.50	0.86	2.81	2.71
Underlying disease	None (idiopathic); 51%	None (idiopathic); 56%	Autoimmune; 29%	None (idiopathic); 29%	None (idiopathic); 35%
	Autoimmune; 17%	Autoimmune; 16%	MGUS; 26%	Cancer; 19%	Infection; 25%
	Cancer; 13%	Malignancies; 12%	Multiple myeloma; 18%	Infection; 19%	Severe burn; 8%
	Infection; 9%	Pregnancy; 4%	None (idiopathic); 3%	Autoimmune; 11%	Inf. bowel dis.; 8%
Bleeding sites/ symptoms (+; % of 71 events)	Intramuscular; 66%	Subcutaneous; 37%+	Epistaxis; 35%	Subcutaneous; 27%	Subcutaneous; 65%
	Subcutaneous; 59%	Intramuscular; 30%+	Gastrointestinal; 30%	Urinary; 24%	Gastrointestinal; 62%
	Postsurgical; 16%	Intracranial; 3%+	Oral; 28%	Gastrointestinal; 20%	Urinary; 52%
	Retro-, intraperitoneal; 15%	Epistaxis; 1%+	Subcutaneous; 28%	Postsurgical; 11%	Oral; 31%
	Intracranial; 8%	Intra-articular; 1%+	Intracranial; 0%	(Thrombosis; 5%)	–
Bleeding severity (grade)	Grade III (severe); 84%	Severe; 76%	Grade III (severe); 25%	Grade III (severe); 41%	Grade III (severe); 70%
	Grade 0 (none); 0%	Grade 0 (none); 0%	Grade 0 (none); 15%	Grade 0 (none); 30%	Grade 0 (none); 8%
Factor activity (C); mean, SD Median	FXIII:C; 7.2, 6.9%	FVIII:C; 2.5, 1.8%	VWF:RCo; 10.3, 9.7%	FV:C; 2.9, 2.9%	FX:C; 5.7, 6.5%
	FXIII:C; 5%	FVIII:C; 2%	VWF:RCo; 6%	FV:C; 3%	FX:C; 3.5%
Factor antigen (Ag); Mean, SD	FXIII:Ag; 56.4, 49.3; 45.5 (median)%	FVIII:Ag; 47, 29%[33]	VWF:Ag; 31.2, 58.3%	FV:Ag; 75.4, 14.4%[33]	FX:Ag; 31.9, 44.1%
Specific activity (C/Ag); mean, SD	0.46, 0.64; 0.18 (median)	0.04, 0.03; 0.03 (median)[33]	1.0, 1.7; 0.7 (median)	0.08, 0.12; 0.03 (median)[33]	0.26, 0.17; 0.21 (median)
Associated abnormal test; mean	FXIII:C of 1:1 mixing; 20.9%	Inhibitor titer; 47.0 BU/mL	Inhibitor titer; 3.5 BU/mL	Inhibitor titer: 46.3 BU/mL	Inhibitor titer: 1.6 BU/mL
	Inhibition potential; 37.9%[34]	Prolonged aPTT; 91.2 s	Reduced FVIII act; 18.6%	Prolonged PT; 56.3 s	Prolonged PT; 74.6 s

(*Continued*)

Table 1 (*Continued*)

Japanese DID code	288–1	288–2	288–3	288–4	288–5
	Reduced XL-α_2-PI; 7.6%	–	Prolonged aPTT; 62.6 s	Prolonged aPTT; 145.8 s	Prolonged aPTT; 86.4 s
	–	–	Prolonged BT; 13.3 min	–	–
Abnormal test; % of total (of tested)	–	–	–	Mixing test (+); 85%	Mixing test (+); 83%
	–	–	–	Normotest (−); 89%	–
	–	LA positive; 6%[33]	Reduced large multimer; 53% (91%)	Unmeasurable LA; 4% (54%)[33]	Unmeasurable LA; 4%
Autoantibody positive (of tested)	Anti-FXIIIA; 79% anti-FXIIIB; 13%[23]	Anti-FVIII; 100%[33]	Anti-VWF; 68% (93%)	Anti-FV; 18% (90%)	Anti-FX; 35% (82%)
Inhibitory type (of tested)	87%[40]	100%[33]	80% (94%)	85% (92%)	75% (56%)[25,26]
Non-neutralizing type[b] (of tested)	13% (7%, type B)[40]	0%[33]	5% (6%)	15% (8%)	25% (44%)[25,26]
Note	–	Unprolonged PT	Unestablished anti-VWF Ab detection assay	Cooccurrence of LA	–
	–	–	–	Inhibitor (−) and auto-Ab (+) cases	–
References	14,18–20,23,34,40–42	21,33	24,43	22,33	15,25,26

Abbreviations: Ab, antibody; AiF5D, AiF8D, AiF13D, AiVWFD, and AiF10D, autoimmune factor V, factor VIII, factor XIII, von Willebrand factor, and factor X deficiencies; aPTT, activated partial thromboplastin time; BT, bleeding time; Inf. bowel dis., inflammatory bowel disease; LA, lupus anticoagulant; MGUS, monoclonal gammaglobulinemia with undetermined significance; PI, plasmin inhibitor; PRT, prothrombin; PT; prothrombin time; SD, standard deviation; XL, cross-linked.
[a]Million people/year.
[b]Predominantly hyperclearance type.

in "G prefecture" (population: 1.93 million; as of October 1, 2021), we inferred that approximately 2,550 people were affected in Japan (population: ~126 million; as of October 1, 2021)[21] (►**Table 1**).

For AiCFDs other than AiF8D, the actual numbers of affected patients are known, as confirmed by our research group (JCRG), and are all smaller than the number of patients with AiF8D. By the end of December 2021, a total of 201 and 87 cases of AiF5D[22] and AiF13D,[14,18–20,23] respectively, and 40 cases of AiVWFD were identified.[24] As only three cases of AiF10D in Japan were reported,[26] we conducted a comprehensive literature search on AiF10D patients worldwide and discussed all 26 cases reported.[15,25] In Japan, the estimated annual incidence of AiF8D, AiF13D, and AiF5D was 1.83 (G prefecture only),[21] 0.044, and 0.038 cases per million people/year,[23] respectively.

The target antigens of the autoantibodies directly responsible for AiF13D, AiVWFD, AiF8D, and AiF5D are FXIII, VWF, FVIII, and FV, respectively. The molecular weights of these proteins are much higher than that of other proteins such as FX, which are typically in the range of tens of kilodaltons, suggesting that these proteins have a larger surface area and therefore potentially more target sites (epitopes) for antibodies to bind to.

Age and Sex

The number of diagnosed AiCFD cases is gradually increasing, parallel with the increased aging of the population.[18–25] The median age at diagnosis of AiF13D, AiF8D, and AiF5D was in the 70s.[21–23] Approximately 50% of AiF13D and AiF8D were idiopathic, suggesting aging itself as a contributing factor to onset. For AiVWFD and AiF10D, the median age at diagnosis was in the 60s,[15,24] approximately 13 years younger than that of the other three AiCFDs. The reason for this age difference is unknown. AiVWFD often occurs in myelo- and lymphoproliferative diseases and multiple myeloma,[24] whereas AiF10D includes young patients with infections and severe burns,[15] which may be contributing factors. Additionally, AiF8D includes pregnancy-related cases,[21] and thus, one of the characteristics is a small peak in the age of onset of this disease in young women of childbearing age.[27] AiF5D and AiF10D are three times more common in men than in women[15,22]; however, the underlying cause for this sex-related disparity is unknown.

Etiology

More than half of AiF13D[23] and AiF8D[21] cases and approximately 30% of AiF5D[22] and AiF10D[15] cases are idiopathic, whereas idiopathic AiVWFD cases are extremely rare.[24] Other autoimmune diseases (e.g., 13 cases with systemic lupus erythematosus among a total 379 AiCFD cases) similar to AiCFD are observed in 10 to 30% of individuals with all AiCFDs except AiF10D.[15] Malignant tumors/cancers are observed in 10 to 20% of individuals with AiF13D, AiF8D, and AiF5D but not in those with AiVWFD[24] and AiF10D[15,25]; plasma cell neoplasms (monoclonal gammopathy of undetermined significance, multiple myeloma) occur in 43% of individuals with AiVWFD.[24] Regarding AiF10D, 25% of individuals have infections.[15,25] A single pregnant young woman was found to have AiF8D,[21] as previously mentioned.

Autoimmune diseases, neoplastic diseases, infectious diseases, and pregnancy cause chronic, acute, and recurrent disturbances in immune and inflammatory responses, which may lead to the breakdown of immune tolerance. In AiF13D

and AiF8D, involvement of human leucocyte antigen (or histocompatibility)-related genes has been reported,[28,29] indicating the importance of genetic factors. Immune- and tumor-related inflammatory markers are correlated to AiF13D and AiF8D, which has been demonstrated by proteomic analysis of patient plasma specimens,[30] suggesting that both environmental and genetic factors contribute to the onset of AiF13D and AiF8D. Consequently, AiF13D and AiF8D are considered to be a multifactorial disease.

Bleeding Symptoms, Sites, and Severity

Bleeding is the main symptom of all AiCFDs; although there are no distinct bleeding symptoms or bleeding sites specific to a particular disease, each has some specific characteristics that can help with diagnosis.[14–25] For example, the proportion of intramuscular hemorrhage was higher in AiF13D and AiF8D (66 and 30%, respectively) than in other AiCFDs. In contrast, subcutaneous hemorrhage was observed in a high proportion of AiF10D and AiF13D (65 and 59%, respectively); however, this symptom is nonspecific, because it occurs in approximately 30% of other AiCFDs.

Epistaxis was observed in 35% of AiVWFD cases,[24] but not in AiF8D (1%)[21] or other AiCFDs and is a relatively specific symptom for AiVWFD. In AiVWFD and AiF10D, gastrointestinal and oral hemorrhages are common (mucocutaneous hemorrhages are predominant).[15,24] Gross hematuria including kidney hemorrhage was observed in 52 and 24% of AiF10D and AiF5D cases,[15,22] respectively. Conversely, intraarticular hemorrhage was rarely observed, even in AiF8D,[21,27] aiding in distinguishing it from (hereditary) hemophilia A. Fatal central nervous system hemorrhage and peritoneal/retroperitoneal hemorrhage were associated with AiF13D and AiF8D, requiring caution.[14,21]

The following proportions of severe bleeding (Grade III: defined as "spontaneous major bleeding: hematomas [hospitalization required], hemarthrosis, central nervous system, gastrointestinal and umbilical cord bleeding) were observed as per the bleeding severity classification of the International Society on Thrombosis and Haemostasis-Scientific and Standardization Committee[31]: AiF13D (84%), AiF8D (76%), AiF10D (70%), AiF5D (41%), and AiVWFD (25%). AiF5D and AiVWFD are therefore considered moderate to mild bleeding disorders. Notably, AiF10D had a higher bleeding severity than "hereditary" F10D.[15] In contrast, the proportion of bleeding-free (grade 0) cases was 0% for AiF13D and AiF8D,[14,21] whereas 8, 15, and 30% of AiF10D, AiVWFD, and AiF5D, respectively, were diagnosed without bleeding symptoms (cases were "captured" due to abnormal laboratory findings identified by attending physicians).

In AiF5D, thrombosis was observed to occur in 5% of cases,[22] but other AiCFDs such as AiF13D also had such complications[32]; therefore, attention toward possible thrombosis risk should be paid to AiF5D in addition to other AiCFDs. Presumably, administration of activated coagulation factor preparations (such as recombinant activated factor VII [rFVIIa] and activated prothrombin complex concentrates [APCC]) and/or inhibition of anticoagulant properties by anticoagulation factor autoantibodies (e.g., activated protein C cofactor function of FV inhibited by anti-FV autoantibodies) and/or a coexisting vascular disorders were involved in the cause of thrombosis.

Abnormal Laboratory Findings Important for Diagnosis

A critical item in the diagnosis of AiCFD was the result of the clotting/coagulation test. A drastic decrease in any coagulation factor results in bleeding and a definitive diagnosis can be reached by searching for abnormalities in the coagulation cascade according to the algorithm described later (►**Fig. 3**).

The coagulation factor activity (F*:C), the "core test" that represents the direct cause of bleeding in each AiCFD, was markedly decreased without exception (►**Table 1**).[14–25] Additionally, the amount of coagulation factor antigen (F*:Ag) was often reduced by varying degrees. As a result, specific activity, defined as the ratio of coagulation factor activity to the amount of coagulation factor antigen (F*:C/F*:Ag), was also reduced by varying degrees in most cases because F*:C often decreases more severely than F*:Ag due to inhibitory type antibodies (►**Fig. 2**).[14–25] For example, in AiF8D[21] and AiF5D,[22] coagulation factor activity (F*:C) were markedly decreased compared with the slight decrease in antigen amount (F*:Ag),[33] resulting in remarkably low specific activity (►**Fig. 2**; Inhibitory type antibody).

However, depending on the characteristics of autoantibodies against the coagulation factor, elimination (clearance) of the coagulation factor itself may be predominantly or selectively promoted (►**Fig. 2**; Non-Inhibitory-Hyperclearance type antibody and Inhibitory-Hyperclearance type antibody). Consequently, the coagulation factor antigen level and activity may decrease in parallel at the same time. As a result, specific activity often remains normal, i.e., approximately 1.0 (such as in AiVWFD,[24] ►**Table 1**).

As FVIII is an intrinsic coagulation factor and FV and FX act in the common clotting pathway, their decreased activity was confirmed by isolated prolongation of activated partial thromboplastin time (aPTT) for AiF8D and concomitant prolongation of aPTT and prothrombin time (PT) for AiF5D and AiF10D.

FXIII acts on the fibrin cross-linking reaction after clotting occurs, whereas VWF acts on the platelet aggregation reaction; specific measurements, such as transglutaminase activity in AiF13D and Ristocetin cofactor activity (VWF:RCo) in AiVWFD, are decreased respectively, in almost all cases.[24,34] In AiF13D, a test that mixes plasma specimens of patients and healthy controls in a ratio of 1:1 (mixing test, MXT), demonstrated that inhibition (inhibitor) is detected based on decrease in residual FXIII:C in the mixed samples. In addition, the strength of the inhibitor was confirmed by the degree of inhibition, and reduction in FXIII:C was also indirectly confirmed by a reduction in the amount of cross-linked α_2-PI.[34,35]

In AiF8D, aPTT was significantly prolonged owing to the decrease in FVIII:C, and residual FVIII:C was markedly decreased when patient samples diluted in various ratios were mixed with control plasma samples (Bethesda inhibitor assay), indicating a high inhibitory potency.[33] In AiVWFD,

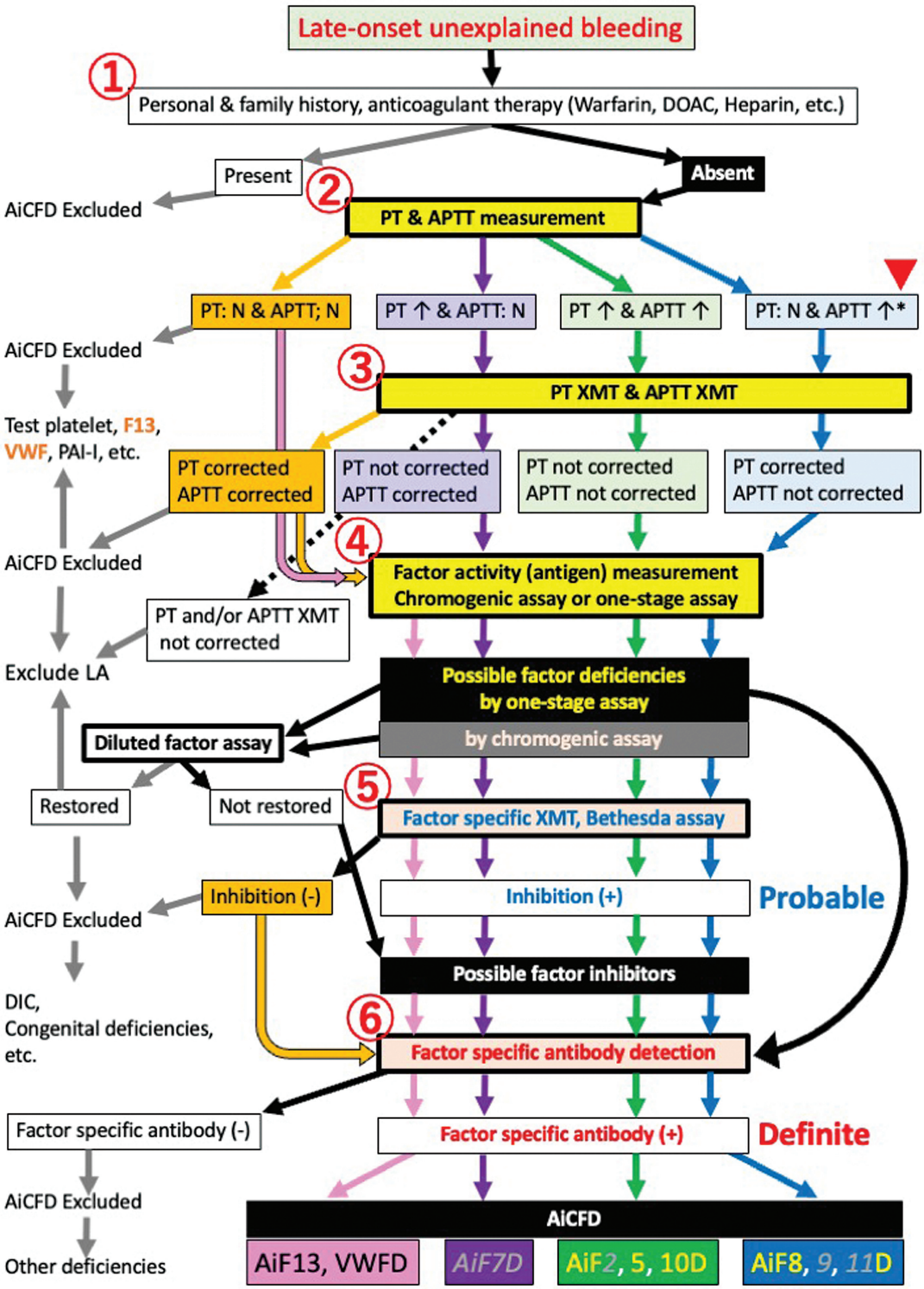

Fig. 3 Algorithm for laboratory tests and diagnosis of AiCFDs. When physicians meet new patients with bleeding who have no family and past histories of hemorrhagic tendency, or excessive anticoagulation, the activities (as well as antigen levels, if possible) of coagulation factors should be measured. When patients' coagulation factor activities are unexplainably low, detailed functional and immunological examinations are highly recommended to definitively diagnose AiCFDs. Orange lines indicate options for the detection of patients with non-neutralizing coagulation factor antibodies. It is important to understand that autoantibodies to coagulation factors and autoantibodies to phospholipids (e.g., LA) can simultaneously coexist in one patient and may interfere with each other. If the attending physician of a patient with unexplained bleeding follows the pink, green, and blue lines, he or she may arrive at a diagnosis of AiF13D and AiVWFD, AiF5D and AiF10D, and AiF8D, respectively. * (with a large red triangle), aPTT is often prolonged in patients with AiVWFD. AiCFD, autoimmune coagulation factor deficiencies; F2, 5, 7, 8, 9, 10, 11, and 13, factor II, V, VII, VIII, IX, X, XI, and XIII; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulopathy; DOAC, direct oral anticoagulants; LA, lupus anticoagulant; N, normal; PAI-I, plasminogen activator inhibitor type I; PT, prothrombin time; VWF, von Willebrand factor; XMT, cross-mixing test.

a secondary FVIII:C decrease, consequent prolongation of aPTT, and absence/decrease in high-molecular-weight VWF multimers were observed.[24] In particular, AiVWFD is characterized by prolonged bleeding time, a decrease in VWF:RCo, and low VWF:Ag.

In AiF5D and AiF10D, simultaneous prolongation of aPTT and PT, positive MXT, and high[22] and low[15,26] titers, respectively, in the Bethesda assay are common abnormal findings. However, AiF5D is characterized by a normal Normotest (Hepaplastintest; Complex factor H"Kokusai", Sysmex Corp., Kobe, Japan).[22,36,37] Approximately 4% of patients with AiF5D reported unmeasurable for lupus anticoagulant (LA) [22] because of extremely prolonged clotting times,[33] thereby requiring diagnostic caution.[38] For example, 8 out of 13 (54%) of AiF5D patients had a diluted Russell viper venom time (dRVVT) of more than 200 and 130 seconds (T1 without excess phospholipid and T2 with excess phospholipid, respectively) measured by a commercial laboratory service (SRL Ltd., Hachioji, Japan) using the LA Test Gradipoa (MBL, Ina, Japan; reference range of T1/T2, <1.3). In contrast, all 18 AiF8D patients showed a T1 of dRVVT between 35.8 and 82.7 seconds and a T2 of dRVVT between 35.3 and 75.4 seconds (mean and standard deviation of T1/T2; 1.15 and 0.11).[33]

Laboratory Findings Essential for Definitive Diagnosis

Anti-coagulation factor autoantibody positivity is a requirement for a "definite" diagnosis, and coagulation factor inhibitor positivity is a requirement for a "probable" diagnosis of AiCFDs[14,22,24,39] (►**Table 1**).

Autoantibodies were positive in most cases tested for detection. Specifically, in AiF13D, autoantibodies for FXIII-A subunit (FXIII-A), autoantibodies for FXIII-B subunit (FXIII-B), and autoantibodies for native FXIII-A (Aa type) and autoantibodies against activated FXIII-A (Ab type) were positive, all of which were detected using published methods.[40–42] An autoantibody detection test performed at our laboratory using a commercial kit (Zymutest Anti-FVIII IgG MonoStrip, Hyphen BioMed, Neuville sur Oise, France) was positive in all AiF8D.[33] Autoantibodies detection methods for AiF5D and AiVWFD, although not standardized,[43] were positive in most cases.[24,33] The autoantibodies detection method for AiF10D, immunological laboratory tests that are not commercially available (e.g., enzyme-linked immunosorbent assay [ELISA], radioimmunoassay, western blotting, and/or crossed immune electrophoresis),[26,44,45] showed a positive rate of 82% (9 of 11 patients).

For coagulation factor inhibitors, indirect cross-MXTs using aPTT or PT (aPTT- or PT-based cross-MXT) and factor-specific cross-MXTs using individual coagulation factor activity assays or Bethesda assay-like titration have been performed.

In AiF13D, 87% of autoantibody positives were inhibitory, whereas 13% were noninhibitory when tested using 1:1 MXT or five-step dilution cross-MXT[23,34,40]; Anti-FXIII autoantibodies that cause this disease are classified into three types: type Aa inhibits the heterotetramer assembly and activation of FXIII; type Ab inhibits the enzymatic activity of activated FXIII; and type B enhances the elimination of FXIII from the blood.[40] Type B autoantibodies were 4%, and the remaining 9% were considered to be of the noninhibitory hyperclearance type (►**Fig. 2**).

AiVWFD was also tested with factor-specific MXT, and 6% of autoantibody-positive results were of the "non" inhibitory type.[24]

AiF8D and AiF5D had high antibody titers (mean: 47 and 46.3 BU/mL, respectively) in functional assays,[21,22] whereas AiVWFD and AiF10D had low titers (mean: 3.5 and 1.6 BU/mL, respectively) in functional assays.[15,24]

In AiCFDs other than AiF8D, noninhibitory autoantibodies were also detected (44% in AiF10D[25,26]); therefore, autoantibodies for each coagulation factor should be measured whenever possible to prevent oversight.

Laboratory Testing and Diagnostic Algorithm

The following steps are performed when diagnosing patients with unexplained bleeding symptoms (especially older individuals) (►**Fig. 3**; ►**Table 2**):

1. Confirm no prior history of abnormal bleeding, no family history, and no history of administration (especially overdose) of anticoagulants/antiplatelets.
2. Check for any prolongation of PT and aPTT, and if there is no abnormality, examine platelet count, FXIII:C, α_2-PI, plasminogen activator inhibitor type-1, and VWF:RCo. If any of these items are abnormal, proceed to their specific evaluation in the next steps.
3. In case of prolongation of PT and aPTT, plasma samples of the patient and healthy controls are mixed in several ratios to measure PT and aPTT (aPTT- and PT-based cross-MXTs) and to determine whether the prolongation of PT and aPTT is corrected (normalized).
4. Simultaneously, prolonged clotting times should be classified into three types: PT (extrinsic pathway) only, aPTT (intrinsic pathway) only, and both (common pathway). The amounts of antigens of coagulation factors should be measured, because it is useful for diagnosis.
5. If prolonged PT and aPTT was not corrected by MXT, the residual activity of the coagulation factor whose activity was specifically decreased should be measured by mixing the plasma samples of patients and healthy controls in a ratio of 1:1 or other ratios (factor-specific MXT or cross-MXT) to determine the presence/absence of inhibition. Inhibitor titer is measured by Bethesda (-like) assay, and if it is $\geq$ 0.5 (or 1.0 for AiF8D) BU/mL, the patient is determined to have a "probable" diagnosis of AiCFD.
6. Regardless of the presence or absence of inhibitors, anticoagulation factor autoantibodies are tested, and if positive, a "definite" diagnosis of AiCFD is made.

Even if PT and aPTT are normal in the search in Step 2, follow the orange (and pink) arrows (►**Fig. 3**), and if a decrease in FXIII:C or VWF:RCo is observed in Step 4, check for them in Step 5 (and hopefully in Step 6).

Table 2 Comparison of 5 Japanese Designated Intractable Diseases among autoimmune coagulation factor deficiencies

Japanese DID code	288–1	288–2	288–3	288–4	288–5
Disease name	AiF13D	AiF8D	AiVWFD	AiF5D	AiF10D
Occurrence	Rarely	Not rarely	Very rarely	Rarely	Extremely rarely
Peak age	Early 70's	Later 60's	Mid 50's	Early 70's	Mid 50's
Sex difference	Male-dominant tendency	No sex difference	No sex difference	Male-dominant	Male-dominant
Underlying disease	Often idiopathic	Often idiopathic	Often plasma cell neoplasms	Not uncommon idiopathic	Not uncommon idiopathic
	Not rarely autoimmune, Not rarely cancer	Not rarely autoimmune, Not rarely malignancies	Not uncommon autoimmune	Not rarely cancer, Not rarely infection,	Not uncommon infection
	–	Rarely pregnancy-related	Very rarely idiopathic	Not rarely autoimmune	Rarely severe burn
Bleeding sites/ symptoms	Often intramuscular, Often subcutaneous	Not uncommon subcutaneous, not uncommon intramuscular	Not uncommon epistaxis, Not uncommon gastrointestinal	Not uncommon subcutaneous, Not uncommon urinary	Often subcutaneous, Often gastrointestinal
	Not rarely retroperitoneal, Not rarely intraperitoneal	Very rarely epistaxis, Very rarely intra-articular	Not uncommon oral, Not uncommon subcutaneous	Not rarely gastrointestinal	Often urinary
	Rarely intracranial	–	Very rarely intracranial	Rarely thrombosis	Not uncommon oral
Bleeding symptoms	Mostly severe	Mostly severe	Not uncommon severe	Not uncommon severe	Often severe
	No none-bleeding	No none-bleeding	–	Not uncommon none-bleeding	Rarely none-bleeding
Factor activity (C)	Always severely reduced	Always severely reduced	Always variably reduced	Always severely reduced	Always severely reduced
Factor antigen (Ag)	Mildly ∼ severely reduced	Mildly ∼ severely reduced	Mildly ∼ severely reduced	Mildly ∼ modestly reduced	Mildly ∼ modestly reduced
Specific activity (C/Ag)	Mostly reduced	Always severely reduced	Often variably reduced	Always reduced	Often variably reduced
Associated abnormal test (*; defined in ref. 34)	Mostly factor XIII 1:1 mixing test (+)	Always Severely Prolonged aPTT	Often low inhibitor titer	Always prolonged PT, Always prolonged aPTT	Always prolonged PT, Always prolonged aPTT
	Mostly increased inhibitory potential*	Always mixing test (+) Mostly high inhibitor titer	Often reduced large multimer	Mostly mixing test (+), Mostly high inhibitor titer	Mostly mixing test (+), Mostly low inhibitor titer
	Often reduced XL-α_2-PI	(Often type II inhibitor)	Often reduced FVIII:C, often prolonged aPTT	Mostly hepaplastin test (−)	–
	–	Rarely LA (+)	Mostly prolonged BT	Often unmeasurable LA	–
Autoantibody detection	Mostly anti-F13A (+), not rarely anti-F13B (+)	Always (+)	Often ∼ mostly (+)	Not rarely (+)	Not uncommon (+)
Inhibitor detection	Mostly (+)	Always (+)	Mostly (+)	Mostly (+)	Mostly (+)
Diagnostic criterion	JMHLW and ISTH/SSC	JMHLW	JMHLW	JMHLW	JMHLW
Definite diagnosis	Always antibody (+)	Always antibody (+)	Always antibody (+)	Always antibody (+)	Always antibody (+)
Probable diagnosis	Mostly inhibitor (+)	Mostly inhibitor (+)	Mostly inhibitor (+)	Mostly inhibitor (+)	Mostly inhibitor (+)
Differential diagnosis	Hereditary FXIII deficiency	Hereditary FVIII deficiency	von Willebrand disease	Hereditary FV deficiency (FVD)	Hereditary FX deficiency (FXD)
	DIC (AAA, cancer, etc.)	AiVWFD	Other acquired VW syndrome	Nonimmune acquired FVD	AL-amyloidosis
	Leukemia	–	–	Hereditary FX, PRT deficiency	Secondary FXD including DIC
	–	Other AiCFDs	Other AiCFDs	Antiphospholipid syndrome	Other AiCFDs

Abbreviations: AAA, abdominal aortic aneurysm; AiCFD, autoimmune coagulation factor deficiencies; AiF5D, AiF8D, AiF13D, AiVWFD, and AiF10D, autoimmune factor V, factor VIII, factor XIII, von Willebrand factor, and factor X deficiencies; aPTT, activated partial thromboplastin time; BT, bleeding time; DIC, disseminated intravascular coagulation; ISTH/SSC, International Society on Thrombosis and Hemostasis; JMHLW, Japanese Ministry of Health, Labor, Welfare; LA, lupus anticoagulant; PI, plasmin inhibitor; PRT, prothrombin; PT; prothrombin time; XL, cross-linked.
Note: Order of frequency: always > mostly > often > not uncommon > not rarely > rarely > very rarely > extremely rarely > no. (+), positive; (−), negative.

Differential Diagnosis

►**Table 2** summarizes the characteristics of each aforementioned AiCFD. If the attending physician proceeds with the "coagulological" examination according to the algorithm, the five types of hemorrhagic DIDs can be delineated.

For all AiCFDs, hereditary CFD should be excluded based on conditions such as age of onset, past history, family

Table 3 Summary of managements and outcomes of 5 Japanese Designated Intractable Diseases (DIDs)

Japanese DID code	288–1	288–2	288–3	288–4	288–5
Disease name	AiF13D	AiF8D	AiVWFD	AiF5D	AiF10D
Diagnostic criterion	JMHLW and ISTH/SSC	JMHLW	JMHLW	JMHLW	JMHLW
Hemostatic therapy	None; 10%	None; 32%	None; 28%	None; 14%	None; 9%
	Plasma-derived FXIII conc.; 80%	rFVIIa; 64%	FVIII/VWF conc.; 40%	Fresh frozen plasma; 42%	Fresh frozen plasma; 83%
	Fresh frozen plasma; 19%	APCC; 12%	DDAVP; 32%	Platelet conc.; 15%	Vitamin K; 48%
	–	(FVIII; 0%)	Cryoprecipitate; 8%	Vitamin K; 14%	PCC; 30%
	(Antifibrinolytic; 27%)	–	(Antifibrinolytic; 12%)	PCC; 4%	rFVIIa; 13%
Antibody eradication Therapy (not approved)	Prednisolone; 81%	Prednisolone; 96%	Prednisolone; 53%	Prednisolone; 73%	Prednisolone; 48%
	(Cyclophosphamide; 27%)	(Rituximab; 16%)	(Cyclophosphamide; 3%)	(Steroid pulse; 14%)	(Steroid pulse; 22%)
	(Rituximab; 18%)	Cyclophosphamide; 12%	(Rituximab; 3%)	(Cyclophosphamide; 5%)	(Rituximab; 13%)
	(Steroid pulse; 14%)	–	(Chemotherapy; 13%)	–	(Cyclophosphamide; 9%)
	None; 10%	None; 4%	None; 13%	None; 17%	None; 13%
Autoantibody reduction Therapy	Plasma exchange; 4%	Plasma exchange; 0%	Plasma exchange; 3%	Plasma exchange; 17%	Plasma exchange; 35%
	Immunoadsorption; 0%	–	–	–	–
Miscellaneous therapy	High-dose IVIG; 4%	High-dose IVIG; 0%	High-dose IVIG; 9%	High-dose IVIG; 0%	High-dose IVIG; 43%
Outcomes/ prognosis	Recovery; 36%	Remission; 88%	Remission; 74%	Recovery; 74%	Recovery; 90%
	Under treatment; 41%	Relapse; 12%	Relapse; 18%	(Spontaneous rec.; 11%)	(Spontaneous rec.; 0%)
	–	–	–	Relapse; 11%	–
	Death; 19%	Death; 28%	Death; 6%	Death; 15%	Death; 10%
Cause of death (% of death)	Hemorrhage; 14% (57%)	Hemorrhage; 0%	Hemorrhage; 0%	Hemorrhage; 7%	Hemorrhage; 5%
	Infection; 9% (30%)	Infection; 28%	Aspiration pneumonia; 3%	Infection; 4%	Infection; 5%
	Underlying disease; 1% (4%)	–	Underlying disease; 3%	Respiratory failure; 2%	–
Day to recovery	Not available	57.5 d	51.7 d	40.8 d	26.5 d
Note (not approved)	(rec. FXIII product)	Bispecific antibody preparation; Emicizumab	(Two rec.VWF products)	(rec. FV product)	(rec. FX product)
	Therapy-resistant cases	–	–	–	(Plasma-der FX product)
References	14,18–20,23,34,40–42	21,33	24,43	22,33	15,25,26

Abbreviations: APCC, activated prothrombin complex concentrates; conc., concentrates; DDAVP, 1-desamino-8-D-arginine vasopressin; IVIG, intravenous immunoglobulin; PCC, prothrombin complex concentrates; rFVIIa, recombinant activated factor VII.

history, and lack of recovery of coagulation factor after treatment.

Attention should be paid to AiF13D[14] because chronic disseminated intravascular coagulation is associated with aortic aneurysms and malignant tumors,[46,47] which increase with age and result in decreased activity based on sustained consumption of FXIII. However, even if an exclusion diagnosis can be made, it is often difficult to cure the primary disease and control bleeding, especially in older individuals. Decreased FXIII activity is also observed in leukemia but often not severe.

In AiF8D, characteristic intra-articular hemorrhage observed in hereditary hemophilia A is absent,[21] and differentiation from AiVWFD is based on a severe decrease in FVIII:C with no epistaxis and no decrease in VWF activity. It is important to distinguish AiVWFD from "nonimmune" acquired von Willebrand syndrome—secondary to various causes and pathologies. Testing to detect VWF autoantibodies is essential for a definitive diagnosis.[24] Since there is no standardized assay for detecting anti-VWF autoantibodies, we deemed it positive if the results of two or more immunological test methods for detection of anti-VWF autoantibodies (e.g., an ELISA using plasma-derived purified VWF and that using recombinant VWF) matched.[43]

In AiF5D, the clotting time is markedly prolonged, and LA is often unmeasurable,[33] making differential diagnosis difficult. Irrespective of the presence of LA, a positive diagnosis of AiF5D is confirmed if the anti-FV autoantibody is positive. Measurement of antiphospholipid antibodies is also useful in differentiation.[22]

A low FX level may be secondary to AL-amyloidosis and should be considered as a differential to AiF10D, as FX:C reduction is common in both.[15,48,49] In AiF10D, abnormal fibrinolytic parameters based on bleeding symptoms,

especially increased fibrin/fibrinogen degradation products (FDP) and D-dimer released from hematoma clots, are also observed; the presence or absence of FX inhibitors and anti-FX autoantibodies is decisive.[26] Absence of amyloid deposition on biopsy also contributes to the exclusion of AL-amyloidosis.

Treatment and Prognosis

All AiCFD treatments are centered on immediate cessation of bleeding by hemostatic therapy and eradication therapy for autoantibodies that cause bleeding (►**Table 3**). Radical therapy is essential when the underlying disease is clear; however, it is often difficult to implement this therapy in older individuals.

Hemostatic Therapy

In the case of severe bleeding or bleeding in vital organs, a preparation containing a large amount of the deficient coagulation factor is immediately administered to reduce pain caused by bleeding, symptoms of organ ischemia, anxiety, and other conditions. Given the high possibility of exacerbation of symptoms by stimulating the production of antibodies against the relevant coagulation factors, it is desirable to administer preparations that bypass the deficient coagulation factors (bypass agents); however, some products are not commercially available and/or cannot be obtained. In principle, an immunosuppressive drug should be administered in tandem with the relevant coagulation factor-containing drug.

Frozen fresh plasma (FFP) is used in emergencies when coagulation factor preparations are not readily available; however, the amount of each coagulation factor contained is 1 unit/mL or less, and a large amount of such blood products cannot be administered as to avoid excessive circulating blood volume. It is not uncommon for patients with mild bleeding to be followed up without hemostatic treatment (9–32%).

In AiF13D, purified FXIII concentrates derived from human plasma were used in 80% of cases, and when they were not readily available, FFP was administered in 19% of emergencies. Overall, 27% of AiF13D were treated with antifibrinolytics, as in AiF13D, "FXIII with antifibrinolytic activity" is markedly reduced.[34]

rFVIIa and APCC are "bypass agents" often used to treat AiF8D. As bypass agents are available, FVIII products are rarely administered.[21] It is also because the administered FVIII preparations are easily overwhelmed by high-titer anti-FVIII autoantibodies, and hemostatic effects are rarely observed. Recently, plasma-derived FX/FVIIa[50,51] and a so-called bispecific antibody preparation (Emicizumab; Hemlibra, Chugai Pharmaceutical Co., Tokyo, Japan)[52] have been marketed and covered by health insurance for AiF8D.

In AiVWFD, FVIII/VWF concentrates derived from human plasma and desmopressin acetate (DDAVP [1-desamino-8-D-arginine vasopressin]), which stimulate the release of VWF from endothelial cells, were administered in 40 and 32% of cases,[24] respectively, probably because no clear bypass agents exist. In the past, cryoprecipitates rich in macromolecular proteins such as VWF were sometimes used; however, these are now limited to emergency cases where FVIII/VWF concentrates are unavailable.

In AiF5D, FFP was administered in 42% of cases[22]; FV is unstable, its concentrate is not commercially available, and a concentrated platelet solution was used in 15% of cases. We recommend administration of the concentrated platelet solution, because the granules of platelets contain a large amount of FV.[53] Vitamin K and prothrombin complex concentrates (PCC) are administered for emergency treatment for serious bleeding; this is unavoidable, because it is often "before" a definitive diagnosis.

In AiF10D, FFP was administered in 83% of cases, followed by vitamin K (48%) and PCC (30%).[15] rFVIIa was administered in 13% of cases. FX, which is downstream to FVII in the coagulation cascade, is drastically reduced; therefore, the use of recently marketed plasma-derived FX/FVIIa concentrates is reasonable,[50,51,54] although not covered by insurance.

Autoantibody Eradication Therapy

As AiCFD is an autoimmune disease, it is rarely completely cured; to ameliorate the deficiency of the coagulation factor, treatments aimed at stopping the production of autoantibodies and eradicating them are essential. AiCFDs are mainly caused by the breakdown of the maintenance mechanism of autoimmune tolerance; therefore, immunosuppressive drugs are administered to suppress excessive immune reactions to self-coagulation factors. In total, 96 and 81% of patients with AiF8D and AiF13D,[21,23] respectively, received regular doses of prednisolone, followed by 73, 53, and 48% of patients with AiF5D, AiF10D, and AiVWFD, respectively.[15,22,24]

Steroid pulse therapy, a short-term high-dose prednisolone administration, was also administered in 22 to 14% of AiF10D, AiF5D, and AiF13D cases.[15,22,23] However, prednisolone is not covered by insurance if the dosage is high. Cyclophosphamide or rituximab was administered when normal doses of prednisolone did not achieve remission. Cyclophosphamide was administered to 27% of patients with AiF13D, who often became resistant to treatment,[14,39] and only 5 and 3% of patients with AiF5D and AiVWFD, respectively. Underlying plasma cell neoplasms are common in AiVWFD,[24] and chemotherapy was performed in 13% of cases, and they reported improvement in AiVWFD, confirming that the treatment of underlying disorders is the principle for all AiCFDs.

Corticosteroids may not be administered in conditions such as infection, comorbid diabetes, possible adverse events such as thrombosis, or asymptomatic cases; patients in these cases may be followed up without treatment (10–17%). For AiF8D, 4% of the patients were untreated.[21]

Autoantibody Reduction Therapy

Plasma exchange was performed in 35 and 17% of AiF10D and AiF5D cases,[15,22] respectively, to quickly reduce the autoantibody levels (antibody reduction therapy). For these diseases, no concentrates of the relevant coagulation factors are available; instead of factor replacement therapy, plasmapheresis can be used as it reduces antibodies and makes it

possible to replenish the relevant coagulation factors (as a large volume of normal plasma is administered). In AiF13D, AiF8D, and AiVWFD, where coagulation factor concentrates are available, plasma exchange is performed only in 0 to 4% of cases.[14,21,24]

Antibody adsorption therapy—in which immunoglobulin (Ig), including autoantibodies, is adsorbed to column beads to reduce levels quickly—has been practiced in some parts of Europe and the United States, but not in Japan.

Antibody reduction therapy does not suppress autoantibody production but provides a temporary reduction in autoantibody levels; however, it has the advantage of completing the hemostatic process in the meantime.

Intravenous immunoglobulin (IVIG) therapy (intravenous administration of large doses of Ig) has been performed in 43 and 9% of patients with AiF10D and AiVWFD,[15,24] respectively; however, no reports are available on its implementation in other AiCFDs. It is assumed to block the Ig receptors on the cell surfaces of the reticuloendothelial system and inhibit the removal of immune complexes.[55] IVIG has been reported to increase the plasma level of administered VWF for weeks.[56]

Treatment Results and Prognosis

Remission/recovery of AiCFD was good at 74 to 90%. However, with AiF13D, recovery was noted in only 36% of patients, and 41% of patients have been under treatment for more than a year.[14,39] Although the cause of this treatment resistance is unknown, FXIII-A is originally an intracellular protein, and its antigenicity and antibody-inducing ability may differ from those of other plasma proteins (FVIII, VWF, FV, and FX).

The time to remission/recovery was the longest for AiF8D (57.5 days),[21] shortest for AiF10D (26.5 days),[15] and intermediate for AiVWFD and AiF5D. In AiF13D, more patients remained under treatment than who recovered, and the time to remission/recovery was not calculated.

In AiVWFD, AiF8D, and AiF5D, relapse/recurrence occurred in 18, 12, and 11% of cases,[21,22,24] respectively, necessitating long-term close follow-up. As most autoantibodies are IgG, and the amount and ratio of subtypes IgG1 to IgG4 vary depending on the case, the autoantibody IgG subtype may be related to inhibitor titer,[57] underlying diseases,[57,58] clinical course/symptoms,[57,59] and outcomes.[57]

The mortality rates of AiF8D, AiF13D, and AiF5D were 28, 19, and 15%, respectively,[21–23] a condition with a mortality rate of >10% qualifies as a "fatal disease." AiF10D and AiVWFD have mortality rates of 9.5 and 6%,[15,24] respectively. Every AiCFD requires a strict treatment protocol.

The mortality rate due to the primary disease was not high, at 3 and 1% for AiVWFD and AiF13D, respectively. AiCFD reportedly undergoes remission after removal of the underlying malignant tumor, confirming that treatment of the primary disease is crucial.

Cause of Death

Regarding the cause of death in AiCFDs, hemorrhagic death was the most common in AiF13D at 14% (57% of all deaths),[14] followed by AiF5D and AiF10D at 7 and 4% in Japan, respectively. Conversely, AiF8D and AiVWFD had no hemorrhagic deaths.[21,24] The hemorrhagic death rate for AiF8D substantially differs from that (50%) 10 years ago,[60] suggesting progress in clinical practice.

Since nearly 40% of deaths in closely followed AiF13D cases occur early after onset (within 3 months) owing to bleeding, bleeding control in the acute stage is critical (►**Fig. 4**). Regarding recent deaths due to bleeding, because there were no cases marked "patient dead on arrival of plasma sample[14,20]" and the recent hemorrhagic death rate was 42%[23] in 2022, lower than the previously reported rate of 71%[20] in 2015, early diagnosis and early treatment have seemingly become widely implemented at least for AiF13D.

All deaths in AiF8D (28% of patients) were due to infection,[21] compared with the 9 to 4% in other AiCFDs. This may be attributed to the adverse effects of the immunosuppressive drugs used in almost all cases (96%) for autoantibody eradication therapy, necessitating optimization of autoantibody eradication therapy.

Discussion, Limitations, and Residual Issues

Concept of Anticoagulation Factor Autoantibodies

The following are the causes of decreased coagulation factor activity (►**Fig. 2**): (1) autoantibodies bind to coagulation factor proteins and complexes of the coagulation factor proteins and autoantibodies (immune complexes) are rapidly removed from the blood (hyperclearance type); (2) autoantibodies bind to the site involved in the activity of the coagulation factors and inhibit their activity (inhibitor type); and (3) combination of both of these (hyperclearance and inhibitor type).

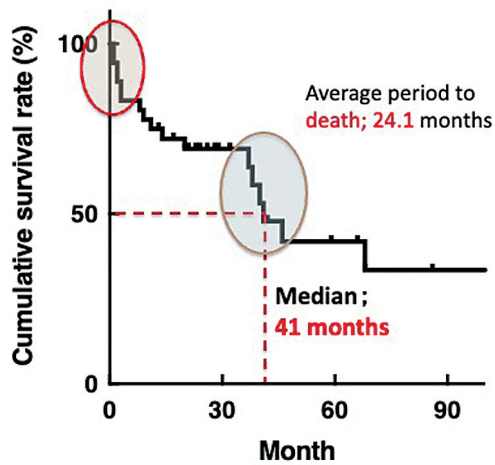

Fig. 4 Survival rate and cause of death in AiF13D cases. In total, 37 cases were followed up closely, and the average period from onset to death was 24.1 (median = 41) months for the 19 patients (51%) who died: 7 of 19 patients (37%) had died by 3 months, primarily from bleeding (5/7, 71%). Three patients died 20, 41, and 112 months after onset owing to gastrointestinal bleeding, intracranial + splenic bleeding, and intracranial bleeding, respectively, after relapse. The causes of death in the remaining nine patients were sepsis (5 patients), cancer (2 patients), intestinal rupture of unknown cause (1 patient), and acute myocardial infarction (1 patient). Red oval, early death; brown oval, later death.

Since autoantibodies are generally polyclones,[61,62] these three types are present in varying proportions in a single patient plasma; some may be predominant, or the proportion may change over time, requiring physicians' attention. In blood, coagulation factor-bound (complexed) and -unbound (free) autoantibodies exist. The bound autoantibodies do not inhibit further coagulation factor activity, but the unbound autoantibodies usually do.

Autoantibody Detection Methods

Presently, anti-FVIII and anti-FV antibody detection kits (Zymutest Anti-FVIII IgG Mono Strip and Anti-FV IgG detection kit; both from Hyphen BioMed, Neuville sur Oise, France) are commercially available[33,63] in Japan (and in Europe); however, commercial anti-FXIII, anti-VWF, and anti-FX antibody detection kits are not. We have developed and implemented homemade detection tests for these diseases.[26,40–42] Consequently, autoantibodies against each coagulation factor have been able to be measured in most specimens. When AiCFD-suspected cases are referred to the JCRG by attending physicians inside Japan, immunological workups are performed, and a diagnosis can then be definitively made.[14–20,22–25]

The presence of non-neutralizing (noninhibitory) autoantibodies may often be overlooked, as these autoantibodies are not measured unless their presence is suspected. This underscores the importance of generalizing anticoagulation factor autoantibody detection tests; sensitive autoantibody tests should be conducted promptly whenever AiCFD is suspected. However, the positive detection rates of the various ELISA methods used to detect anti-VWF autoantibodies vary from 0 to 80%.[24] Thus, no detection methods have yet been proven to be reliably sufficient. Confirmation of the presence of anti-VWF autoantibodies is a requirement for a definite diagnosis of AiVWFD,[24] and urgent standardization is needed.

We have developed a homemade anti-FXIII autoantibody detection method employing immunochromatography as rapid point-of-care clinical testing[41,42]; however, it is not generally available, and its wider adoption is desired to address missed AiF13D cases. Because "nonimmune" acquired F13D is extremely common,[64] anti-FXIII autoantibody detection is required to differentiate it from AiF13D.

Coagulation Factor Inhibitor Detection Methods

Globally, regular coagulation factor activity and its inhibitors are widely measured using the one-stage clotting assay; however, the possibility of misdiagnosis due to the detection of false LA in the functional coagulation test (false positive) cannot be denied. Therefore, the presence of LA should be confirmed by immunologically testing for antiphospholipid antibodies (other than LA) or by measuring coagulation factor activity after diluting the sample.[33] When measuring coagulation factor activity, even after dilution, potent LA can still interfere with the one-stage clotting assay. Therefore, we recommend the use of a "synthetic substrate" method,[33] which is less susceptible to LA interference.[65,66] In Japan, activity measurement using the synthetic substrate method is covered by health insurance only for FVIII and FIX (and FXIII in a sense), while those for other coagulation factors such as FV and FX are undeveloped, unmarketed, and/or not covered.

If both the detection of anticoagulation factor autoantibodies and coagulation factor inhibitors get insurance coverage, out-of-pocket costs for patients and medical institutions will be reduced. By doing so, it is hoped that the current Public Medical Expense Subsidy Program for MHLW-DIDs enacted by the Japanese MHLW will become even more useful.

Coagulation Factor Preparations in Hemostatic Therapy

Coagulation factor preparations, essential for AiCFD hemostatic therapy, are developed, marketed, and covered by insurance for the treatment of hereditary CFDs. Currently, human plasma-derived FXIII concentrate for AiF13D therapy, and rFVIIa, APCC, and the "bispecific antibody preparation (Emicizumab)" for AiF8D therapy are covered by insurance. Recombinant human coagulation factor preparations (rFXIII-A,[67] rVWF,[68] rFVIII, rFIX, etc.) are commercially available, however; they are not covered by health insurance for AiCFD therapy in Japan (►**Fig. 5A**).

Although factor-specific replacement therapy is not presently available for AiVWFD, and the only method is to administer nonfactor-specific blood preparations (i.e., FVIII/VWF concentrates), rVWF cannot be administered (despite being developed and marketed) because it is not covered by public health insurance. Similarly, rFXIII-A cannot be used for AiF13D, because it is not covered by public health insurance. Expanding the indication of these clotting factor concentrates to the respective AiCFDs is desirable.

Immunosuppressants in Antibody Eradication Therapy (Including Cytotoxic Agents)

Regarding antibody eradication therapy for all AiCFDs, only corticosteroids such as prednisolone are covered by insurance. Most recently, cyclophosphamide was approved for use in public health insurance for the treatment of AiF8D, i.e., acquired hemophilia A (since Feb. 27, 2023). In many cases of AiCFD, remission cannot be obtained with prednisolone alone, whereas remission has been obtained in many cases with steroid pulse therapy or additional drugs such as cyclophosphamide, rituximab, azathioprine, and tacrolimus.[14–25]

We recommend expanding the indications to enable "step-up therapy,[14]" where prednisolone is the first-line drug and other drugs are gradually added or switched (►**Fig. 5B**). Conversely, we also recommend implementing "top–down therapy," in which steroid pulses or rituximab are first administered to achieve rapid remission.

Administration of targeted coagulation factors to stimulate the proliferation of autoantibody-producing B cells and increase their sensitivity to cytotoxic drugs may lead to success in subsequent antibody eradication therapy against AiCFD, although further clinical trials are needed.

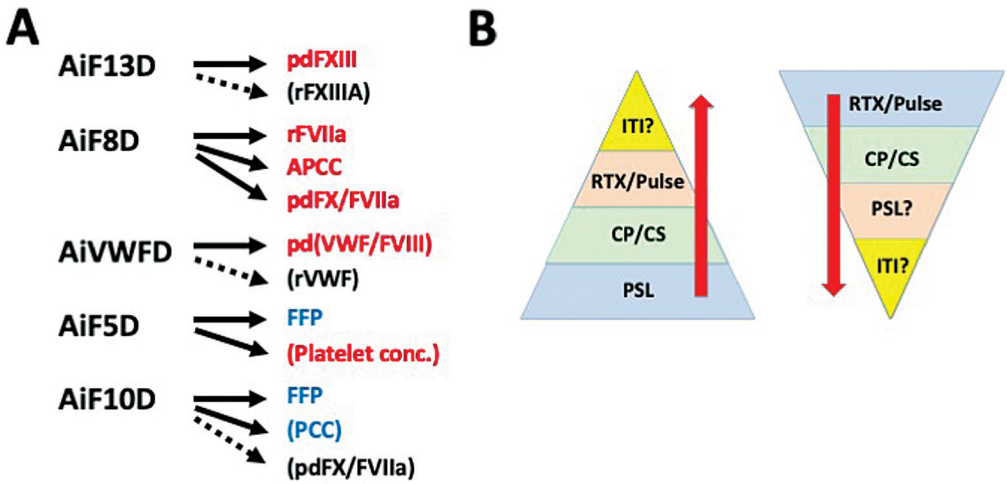

Fig. 5 Treatment strategies for hemostasis (**A**) and autoantibody eradication (**B**). (**A**) Coagulation factor preparations used in hemostatic therapy. Solid lines indicate a selection of formulations currently approved by public insurance, and dashed lines indicate unapproved formulations. The formulations that the authors consider optimal for hemostatic treatment of the respective AiCFD are shown in red. (**B**) "Bottom-up" therapy starts with a regular-dose oral corticosteroid, whereas "top-down" therapy starts with a steroid pulse or rituximab. Upward and downward red arrows indicate the selection order. AiCFD, autoimmune coagulation factor deficiencies; APCC, activated prothrombin complex concentrates; conc., concentrates; CP, cyclophosphamide; CS, cyclosporine; FFP, fresh frozen plasma; FVIIa, activated FVII; ITI, immune tolerance induction; PCC, prothrombin complex concentrates; pd, plasma-derived; PSL; prednisolone; Pulse; steroid pulse, r, recombinant; RTX; rituximab.

Long-Term Prognosis Survey

AiF13D is resistant to treatment, and as many patients are under long-term treatment, accurate calculation of remission rate is not possible.[14] Some AiCFD cases were not in remission, recovery, or death during the observation period, and accurate remission rates could not be determined. Several cases have not been included in the follow-up investigations, owing to changes in residences or hospitals or transfers of patients with AiCFD and/or their attending physicians.

Consequently, in February 2021, we launched a case registration system called the "Designated Intractable Disease Database Platform.[69]" By increasing the number of diagnosed cases and accumulating a long-term database, we hope to contribute to improvement in AiCFD medical care through research on the effects of first- and second-line drugs and long-term prognosis.

Conclusion

The number of diagnosed cases of AiCFDs is gradually increasing, likely because of the relatively high frequency of AiF8D and the nationwide research work of the authors over 13 years. However, more research is still needed. We hope that this review article will benefit physicians other than coagulation specialists, leading to early diagnosis and initiation of appropriate treatment of more patients.

Authors' Contributions

M.S. and T.O. conducted experimental examinations, statistical analyses, and proofread the manuscript. A.I. initiated and designed the study, extracted data, wrote, edited, and proofread the manuscript.

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Conflict of Interest

None declared.

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