POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

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BOARD SCIENTIFICO
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Malattie emorragiche
Difetti acquisiti della coagulazione

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DICHIARAZIONE

VALERIO DE STEFANO

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NOVARTIS)**
- Partecipazione ad Advisory Board **(AOP-HEALTH, BRISTOL MYERS SQUIBB, GRIFOLS, GSK, NOVARTIS, SOBI, TAKEDA)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Outlines

- Vitamin C deficiency
- Acquired Hemophilia
- Acquired von Willebrand Disease
- Acquired Factor XIII deficiency

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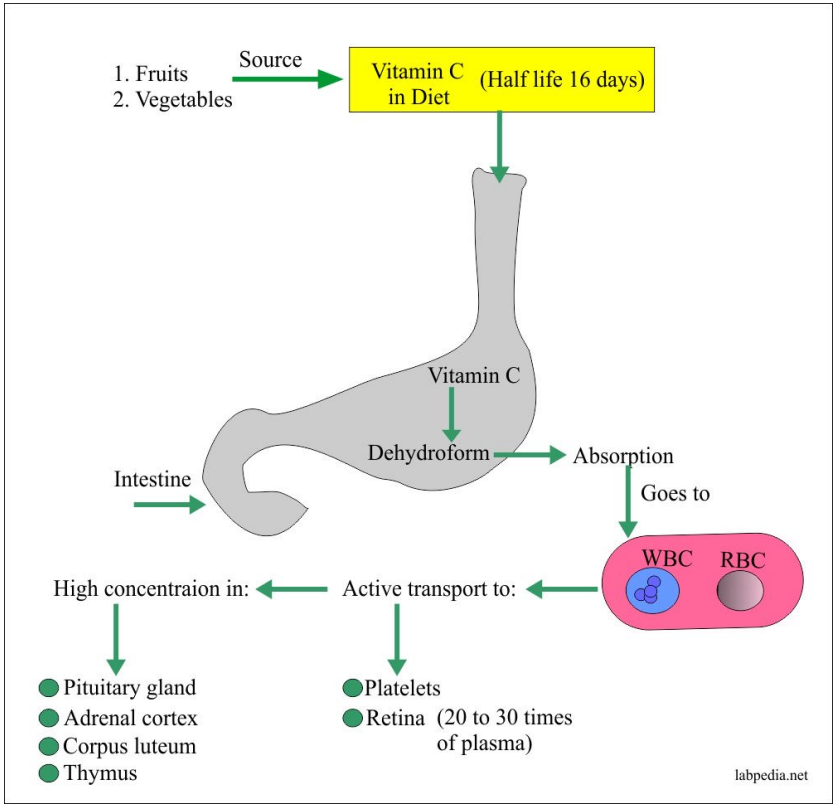
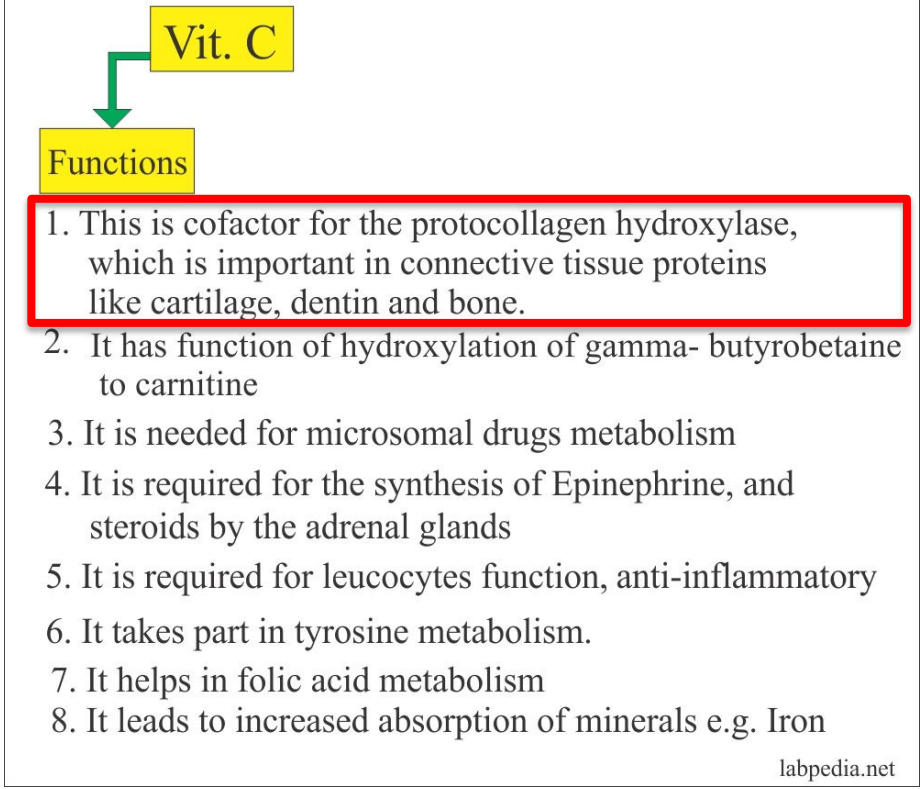
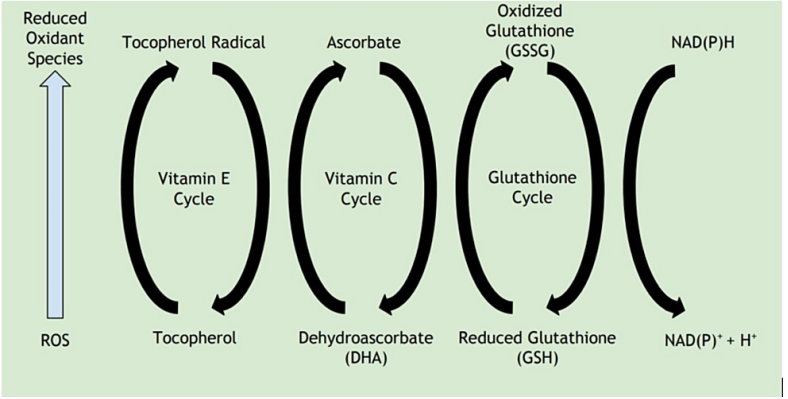

1. Fruits
2. Vegetables
Source
Vitamin C in Diet
(Half life 16 days)
Vitamin C
Dehydroform
Absorption
Intestine
Goes to
WBC
RBC
High concentraion in:
Active transport to:
Pituitary gland
Adrenal cortex
Corpus luteum
Thymus
Platelets
Retina (20 to 30 times of plasma)
labpedia.net


Vit. C
Functions
1. This is cofactor for the protocollagen hydroxylase, which is important in connective tissue proteins like cartilage, dentin and bone.
2. It has function of hydroxylation of gamma- butyrobetaine to carnitine
3. It is needed for microsomal drugs metabolism
4. It is required for the synthesis of Epinephrine, and steroids by the adrenal glands
5. It is required for leucocytes function, anti-inflammatory
6. It takes part in tyrosine metabolism.
7. It helps in folic acid metabolism
8. It leads to increased absorption of minerals e.g. Iron
labpedia.net

There is evidence that vitamin C is depleted during severe physiological stress, indicated by decreases in vitamin C levels, and parallel increases in the oxidized forms of the vitamin, i.e., dehydroascorbate and ascorbate free radical.

In a healthy person, an intake of 0.1 g/day of vitamin C is enough to maintain a normal plasma level, but much higher doses (1–4 g/ day) are needed for critically ill patients to increase vitamin C levels to within the normal range.

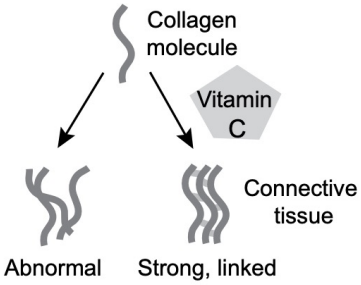
The increased level of vitamin C utilization in critically ill patients does not disappear with a few doses, and may persist for the period of the critical illness.

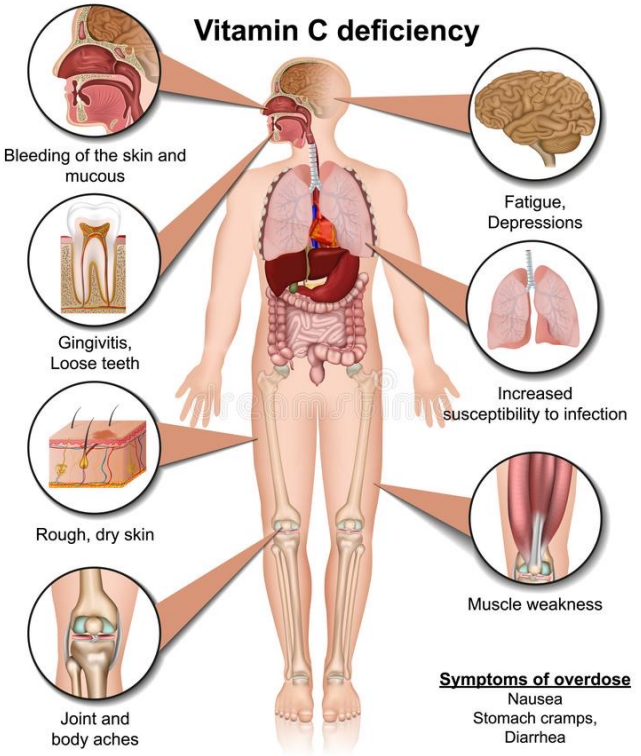


Levine M, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci USA. 1996;93:3704–9
Long CL, et al. Ascorbic acid dynamics in the seriously ill and injured. J Surg Res. 2003;109:144–8.
de Grooth HJ, et al. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four iv regimens. Chest. 2018;153:1368–77.

SCURVY

- Vitamin C deficiency
  - gingival bleeding(ANY mucous membrane)
  - bleeding into muscles
  - bleeding into subcutaneous tissues
  - bleeding around hair follicles; corkscrew-like hair
- Normal collagen synthesis depends upon the hydroxylation of proline and lysine
- enzymes that catalyze the hydroxylation require ascorbic acid





593 Prevalence of Vitamin C Deficiency and Bleeding at a Tertiary Care Center: Mayo Clinic Florida (MCF) Experience

Program: Oral and Poster Abstracts; Type: Oral

ErinMarie O. Kimbrough, MD[1], et al.

- Retrospective review of MCF patients from January 1, 2018 through December 31, 2019 who underwent AA testing. Deficiency was defined as an AA level ≤0.3 mg/dL.
- 1,124 patients who underwent AA testing over 24 months; n=245 (21.8%, 95% CI: 19.5% - 24.3%) were deficient.
- Of those, n=23 (9.4 %) reported symptoms of mucocutaneous bleeding (predominantly ecchymosis, easy bruising or epistaxis) and n=19 (7.8%) had GI or genitourinary (GU) bleeding.
- There were 42 bleeding events among 39 patients (15.9%), 3 of whom had combined mucocutaneous and GU bleeding.

3.5% of the cohort (39 / 1,124) showed bleeding symptoms due to AA deficiency

Table 1: Comparison of characteristics according to vitamin C level in patients with a vitamin C deficiency

Variable	N	Median (minimum, maximum) or No. (%) of patients Vitamin C level 0.1 (N=58)	Vitamin C level 0.2 (N=92)	Vitamin C level 0.3 (N=95)	P-value
Age (years)	245	52.5 (19.0, 78.0)	50.5 (20.0, 77.0)	50 (20, 84)	0.78
Sex (Male)	245	14 (24.1%)	26 (28.3%)	25 (26.3%)	0.87
Ethnicity (Hispanic or Latino)	235	1 (1.8%)	2 (2.2%)	9 (10.0%)	0.036
Race (White)	240	46 (80.7%)	73 (80.2%)	72 (78.3%)	0.94
Symptoms					
Cutaneous bleeding	245	6 (10.3%)	6 (6.5%)	11 (11.6%)	0.52
Gingival/ocular symptoms	245	1 (1.7%)	1 (1.1%)	4 (4.2%)	0.45
Arthralgia/MSK pain	245	23 (39.7%)	41 (44.6%)	34 (35.8%)	0.47
Impaired wound healing	245	1 (1.7%)	2 (2.2%)	1 (1.1%)	0.84
Anemia	245	16 (27.6%)	27 (29.3%)	26 (27.4%)	0.95
Other bleeding (GI/GU)	245	4 (6.9%)	9 (9.8%)	6 (6.3%)	0.72
Alopecia	245	5 (8.6%)	2 (2.2%)	4 (4.2%)	0.18
Drug use	243	3 (5.2%)	10 (10.9%)	2 (2.2%)	0.049
Alcohol use	244				1.00
Current		30 (51.7%)	49 (53.3%)	50 (53.2%)	
Prior heavy use		1 (1.7%)	1 (1.1%)	1 (1.1%)	
Never		27 (46.6%)	42 (45.7%)	43 (45.7%)	
Smoking	244				0.53
Current		5 (8.6%)	7 (7.6%)	6 (6.4%)	
Former		21 (36.2%)	24 (26.1%)	34 (36.2%)	
Never		32 (55.2%)	61 (66.3%)	54 (57.4%)	
History of hematologic disorder	245				0.039
None		46 (79.3%)	69 (75.0%)	81 (85.3%)	
Sickle cell		0 (0.0%)	0 (0.0%)	0 (0.0%)	
Thalassemia		0 (0.0%)	0 (0.0%)	0 (0.0%)	
Hematologic malignancy or BMT		1 (1.7%)	1 (1.1%)	5 (5.3%)	
Iron overload due to other reasons		11 (19.0%)	22 (23.9%)	9 (9.5%)	
History of eating disorder or restrictive diet	245	44 (75.9%)	74 (80.4%)	71 (74.7%)	0.65
Gastric bypass	245	42 (72.4%)	59 (64.1%)	70 (73.7%)	0.33
Type 1 diabetes	245	1 (1.7%)	2 (2.2%)	0 (0.0%)	0.35
IBD or small bowel resection	245	4 (6.9%)	4 (4.3%)	2 (2.1%)	0.29
PPI use	245	20 (34.5%)	41 (44.6%)	41 (43.2%)	0.42
Multivitamin use	245	19 (32.8%)	37 (40.2%)	44 (46.3%)	0.26
BMI	245	37.2 (18.0, 57.4)	38.9 (14.0, 69.0)	39.3 (13.8, 68.3)	0.70
Lab values					
Hemoglobin	244	13.1 (9.0, 16.8)	12.7 (6.4, 17.7)	12.9 (9.4, 17.7)	0.54
Platelets	244	231 (115, 451)	248.5 (107, 565)	242.5 (5, 1302)	0.58
WBC	243	6.8 (3.5, 12.9)	6.5 (3.0, 28.5)	6.7 (2.3, 27.5)	0.89
ESR	23	12.5 (2.0, 102.0)	10 (1, 46)	8.0 (1.0, 47.0)	0.58
C-reactive protein	13	3.3 (3.0, 109.5)	4.9 (3.0, 287.0)	3.0 (3.0, 109.3)	0.59
High sensitivity C-reactive protein	195	5.4 (0.2, 55.1)	6.0 (0.2, 79.0)	4.8 (0.2, 161.2)	0.48
Ferritin	229	70.5 (6, 906)	61 (5, 2596)	60 (3, 1118)	0.22
Folate	177	10.2 (2.4, 20.0)	9.3 (3.6, 20.0)	10.8 (4.1, 20.0)	0.42
B12	239	335 (118, 1400)	348 (112, 1400)	374 (125, 1400)	0.41
Copper	225	1.2 (0.7, 2.9)	1.2 (0.1, 3.1)	1.3 (0.6, 2.3)	0.45
Albumin	236	4.2 (3.1, 5.7)	4.2 (2.2, 4.9)	4.2 (2.6, 5.2)	0.65

P-values result from a Kruskal-Wallis rank sum test (continuous variables) or Fisher's exact test (categorical variables).

We describe a case of a 33 year old Caucasian female seen in our clinic for easy bruising of 10 years duration. She would wake up in the morning with bruised arms and legs without any inciting trauma. She denied prolonged bleeding after dental extractions, frequent nose bleeds, menorrhagia any genitounrinary or gastrointestinal blood loss. Her exam revealed ecchymoses on her arms and legs with no evidence of perifollicular hemorrhage or gingival hyperplasia.

Workup including CBC, Coagulation profile and Von Willebrand factor levels were all within normal limits. She had a vitamin C level of 0.1mg/dl.

She was subsequently advised to increase vitamin C intake through fruits and vegetable and was started on vitamin C supplementation with 500mg twice a day for four weeks. Her repeat vitamin C level on her one month follow up was noted to be 1.9mg/dl. She noticed complete resolution of her symptoms.

This case illustrates the fact that vitamin C deficiency should be excluded in adults presenting with bruising

Zaidi & Moffett, ASH 2013

Outlines

- Vitamin C deficiency
- Acquired Hemophilia
- Acquired von Willebrand Disease
- Acquired Factor XIII deficiency

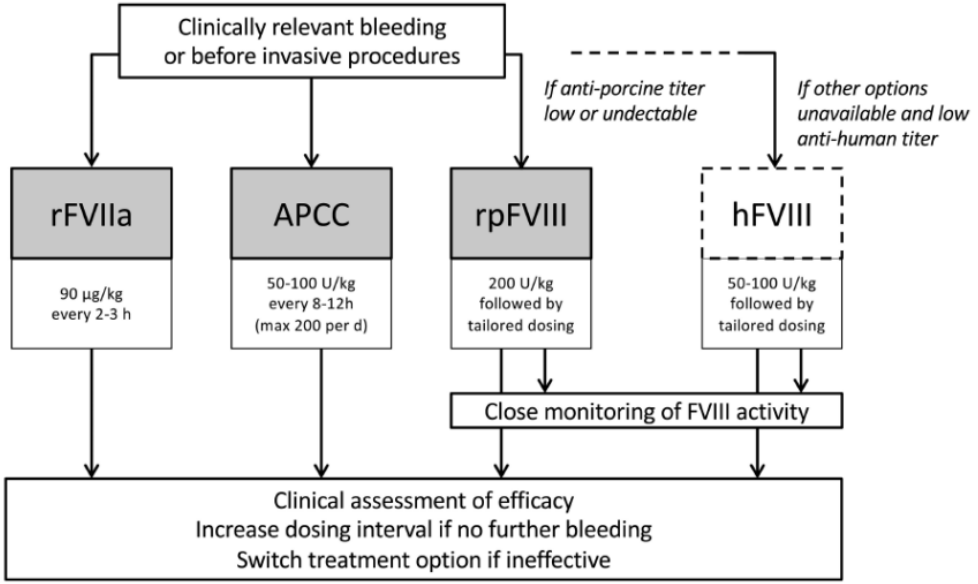
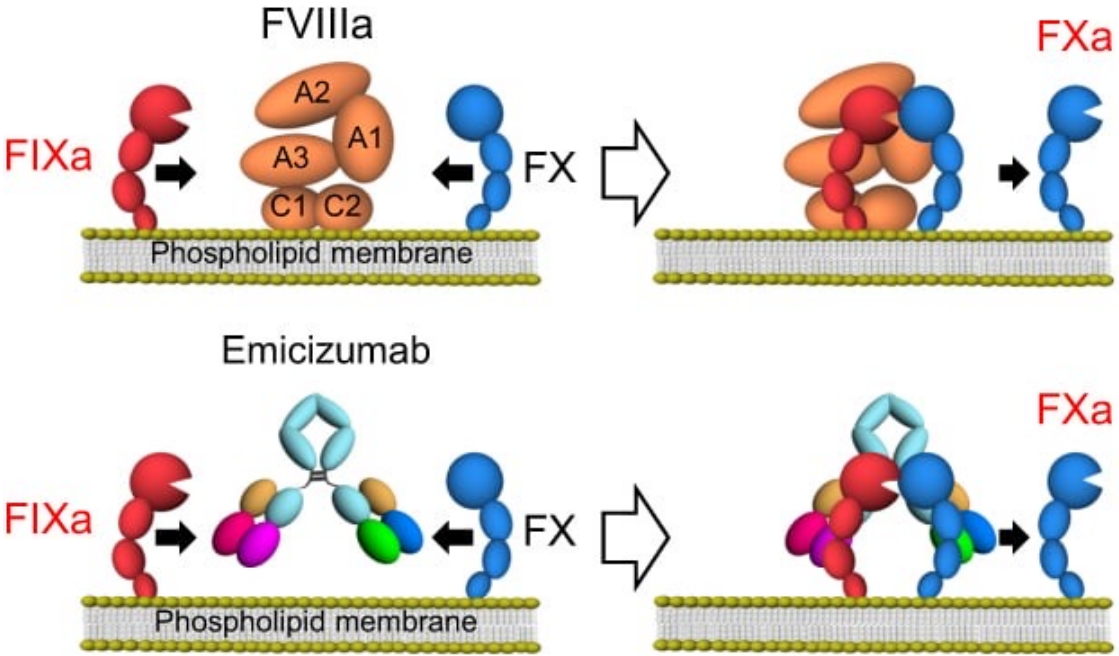


Figure 2. Choice and monitoring of hemostatic therapy in acquired hemophilia A. rFVIIa, recombinant activated factor VII (eptacog alfa); APCC, activated prothrombin complex concentrate; rpFVIII: recombinant porcine factor VIII (susoctocog alfa), hFVIII, human (plasma-derived or recombinant) factor VIII; h: hour; d: day.

Tiede et al, Haematologica 2020

Emicizumab in Hemophilia A



1153 Efficacy and Safety of Emicizumab Prophylaxis in Patients with Acquired Hemophilia a Who Were Deemed Ineligible for Immunosuppressive Therapy: Additional Data from the Ageha Study

Program: Oral and Poster Abstracts, Poster I

Hidekazu Nishikii et al.

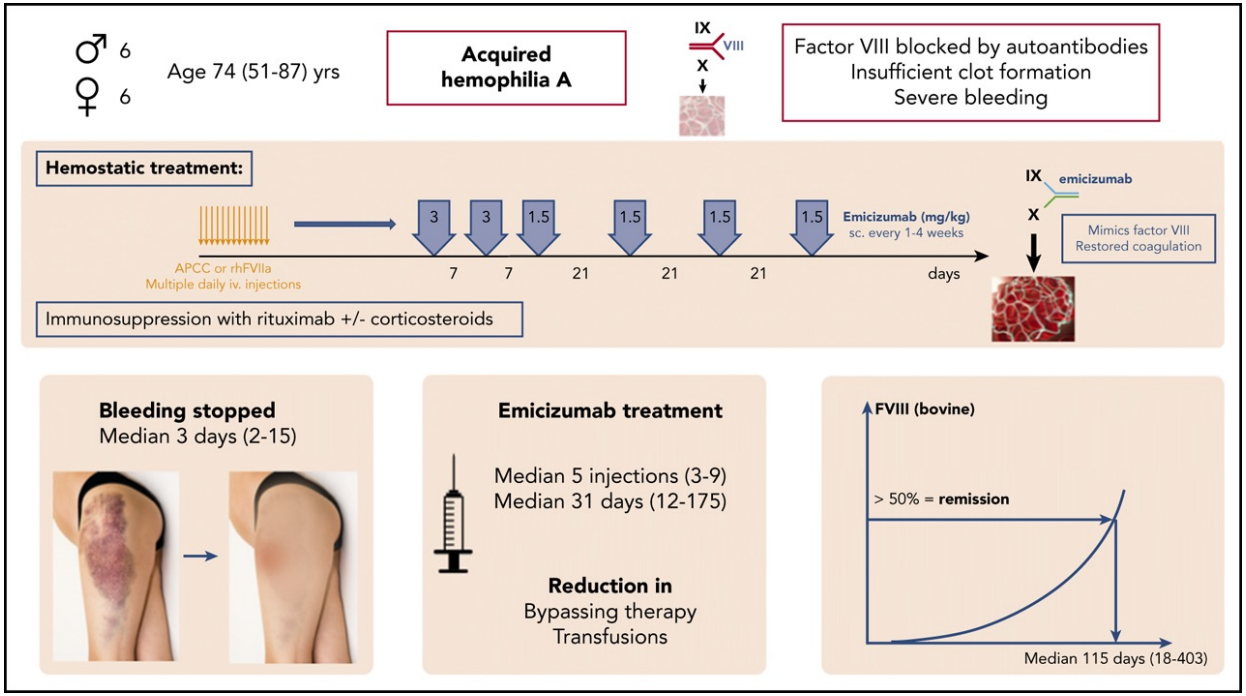
AGEHA consisted of 2 cohorts: patients already undergoing or scheduled to immediately undergo IST at enrollment (Cohort 1), and patients deemed ineligible for IST at enrollment (Cohort 2). Emicizumab was administered subcutaneously at 6 mg/kg on Day 1 and 3 mg/kg on Day 2 followed by 1.5 mg/kg once weekly from Day 8.

Patient 13 was an 82-year-old female. She was judged ineligible for IST because of her poor performance status and diabetes. After starting emicizumab, the bleeding symptoms immediately disappeared and her general condition dramatically improved.

Patient 14 was a 59-year-old female with AHA of long disease duration (1009 days) who had been receiving a prophylactic regimen of activated prothrombin complex concentrate before enrollment. She was judged ineligible for IST because IST had not been effective for a long time in the past, and because IST was nearly contraindicated due to a complication of infections associated with osteonecrosis of the jaw.

During the pre-treatment period, the 2 patients experienced a total of 3 treated bleeds, 1 of which was a treated major bleed in Patient 13. During the on-treatment period, no treated bleeds and no major bleeds occurred in either patient.
Durations of emicizumab treatment were 7.1 weeks in Patient 13 and 16.3 weeks in Patient 14.

Emicizumab for the treatment of acquired hemophilia A



Paul Knoebl,Johannes Thaler,Petra Jilma,Peter Quehenberger,Karoline Gleixner,Wolfgang R. Sperr, Emicizumab for the treatment of acquired hemophilia A, Blood, ASH 2021.

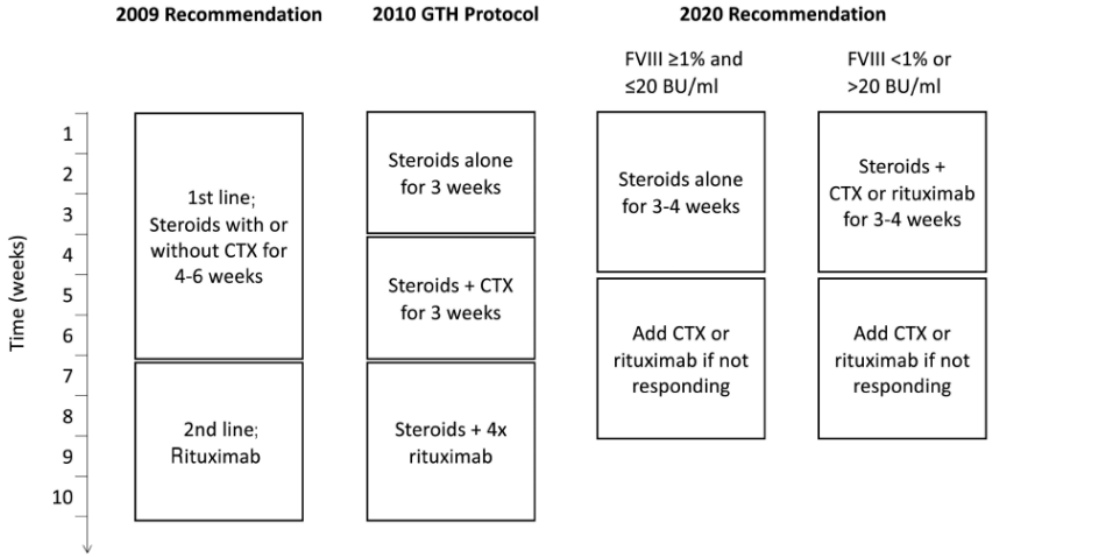


Figure 3. Recommendations regarding immunosuppressive therapy in patients with acquired hemophilia A. Comparison of immunosuppressive therapy regimens recommended in the 2009 international recommendations by Huth-Kühne *et al.*[1] the GTH study[10] and the current paper. FVIII; factor VIII activity; BU: Bethseda unit; CTX, cyclophosphamide.

We suggest rituximab at a dose of 375 mg/m2 weekly for a maximum of four cycles (GRADE 2B). Tiede et al, Haematologica 2020

Efficacy of Rituximab for the Treatment of Acquired Hemophilia A: A Systematic Review

A total of 105 studies involving 186 patients with acquired hemophilia A were included in the analysis. Males were 56.6%. The median age was 71 years (interquartile range; IQR, 56-78). Median factor VIII clotting activity (FVIII: C) was 0.02% (IQR 0-2), and the median FVIII inhibitor was 31 Bethesda unit/mL (IQR 10-128). Rituximab was used as a single agent in 23 patients (12.4%). The rest of the patients received rituximab in combination with either corticosteroid, cytotoxic agents, mycophenolate mofetil, or others.

Overall response rate was 85.0% (complete remission 72.6%, partial remission 12.4%). Rituximab treated as first-line therapy was associated with a higher rate of complete remission as comparing to second-line therapy, 82.1% and 64.7%, respectively.

Moonla et al, ISTH Congress 2021

1148 Rituximab and Bortezomib for Patients with Newly Diagnosed Acquired Haemophilia: Single Arm, Single Center, Prospective Phase 2 Study

Program: Oral and Poster Abstracts, Poster I

Huacong Cai et al.

- From March 2018 to May 2022, 30 patients were eligible for the study.
- Overall, 19 patients were male (63.3%). The median age was 53.5 years (range 22 - 90 years).
- The underlying disorders that could be associated with AHA included rheumatoid arthritis, systemic lupus erythematosus and pemphigus. One patient was diagnosed at her postpartum. One patient was diagnosed soon after surgery. Traditional Chinese medicine was suspected as the inducement in one patient. No patient in our cohort was reported to have coexisting malignancy. 24 patients (80.0%) were regarded as idiopathic AHA.
- The median time from disease onset to the diagnosis was 36.5 days (range 10–249 days).
- The median FVIII activity at baseline was 1.5 IU/ml (range 0 to 10.4 IU/ml), and the median inhibitor concentration was 25.6 BU/ ml (range 2.7 to 600 BU/ ml).

1148 Rituximab and Bortezomib for Patients with Newly Diagnosed Acquired Haemophilia: Single Arm, Single Center, Prospective Phase 2 Study

Program: Oral and Poster Abstracts, Poster I

Huacong Cai et al.

Rituximab 375mg/m² intravenous infusion on day 0 and bortezomib 1.3 mg/m² subcutaneous on day 1,4,8,11.

- Overall, 23 patients (76.7%) achieved CR, 6 patients (20.0%) achieved PR and 1 patients died of cardiac events 3 month after last dose of bortezomib. The ORR was 96.7%. Median time to CR was 74 days (range 12-179 days). After a median follow-up of 39 months (range 3–50 months), one patient had relapse of the disease, 2 months after achieved CR.
- One patient (3.8%) had grade 3 neutropenia; One patient (3.8%) had grade 4 thrombocytopenia and grade 3 thrombocytopenia each. Eight patients experienced infectious fever, including 2 grade 3 and 2 (7.7%) grade 4. Five patients (19.2%) developed grade 1-2 peripheral neuropathy.No treatment-related deaths occurred.

Outlines

- Vitamin C deficiency
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- Acquired von Willebrand Disease
- Acquired Factor XIII deficiency

Acquired von Willebrand Syndrome

- Acquired vWS is much less common than inherited vWD, and also is less recognized.
- Mechanisms and etiologies of acquired vWS:

Mechanism	Potential Etiologies
Autoantibodies to vWF	• Lymphoproliferative disorders (e.g. lymphoma, multiple myeloma, Waldenstrom macroglobulinemia) • Myeloproliferative disorders (e.g. polycythemia vera, essential thrombocythemia) • Autoimmune disease
vWF adsorption onto cancer cells (and subsequent enhanced clearance)	• Lymphoproliferative disorders • Myeloproliferative disorders
Shear stress-induced proteolysis	• Severe aortic stenosis • Hypertrophic obstructive cardiomyopathy • Left ventricular assist device (LVAD) • Extracorporeal membrane oxygenation (ECMO)

- A diagnosis of AvWS should be suspected when new onset mucosal bleeding occurs in a patient with a known predisposing condition, and in whom the platelet count and prothrombin time (PT) are both normal.
- aPTT may be normal or high.
- Diagnosis can be confirmed by measuring vWF activity, vWF antibodies, and VIII activity.
- Treatment options for acute bleeding in AvWS include:
  - vWF concentrate
  - Desmopressin (a.k.a. DDAVP)
  - IVIG (in the presence of anti-vWF antibodies)
- The best long-term treatment of AvWS is treatment of the underlying disorder

International Registry aVWS

(266 literaure cases and 186 registry cases)

(Thromb Haemostas 2000,84,245-9)

- Lymphoproliferative diseases / MGUS 48%
- Myeloproliferative neoplasms 15%
- Cancer 5%
- Autoimmune diseases 2%
- Cardiovascular disease 21%
- Others 9% (drug-related, hypotiroidism, diabetes, uremia, sarcoidosis, IBD)

4216 Waldenstrom Macroglobulinemia and the Clinical Implications of Acquired Von Willebrand Syndrome

Program: Oral and Poster Abstracts, Poster III

Karan Chohan et al.

- Consecutive pts with a diagnosis of WM evaluated at Mayo Clinic, MN, FL and AZ who underwent von Willebrand factor (VWF) testing from 01/2002 to 01/2022 were included.
- Of 2210 pts with a diagnosis of WM, 73 (3%) received testing for VWF, and 11 (15% of those tested and 0.5% of all pts) were diagnosed with AVWS.
- The most common underlying reason for testing was bleeding symptoms, observed in 9 (82%) pts. Other reasons for testing included pre-surgical (n=1) and routine screening (n=1). Recurrent epistaxis was the most observed bleeding symptom and was seen in 6 (55%) pts. Other observed symptoms included spontaneous hematoma (n=2), gastrointestinal (GI) bleeding (n=2), retinal hemorrhage (n=2), and subarachnoid hemorrhage (n=1)

Table 1: Summary of Individual Outcomes in Patients with Acquired von Willebrand Syndrome (AVWS) and Waldenstrom Macroglobulinemia (WM)

ID	Presenting Symptoms of AVWS	Reason for AVWS Testing	AVWS-Directed Therapy	Response to AVWS-Directed Therapy	Diagnosis of WM and AVWS	WM-Directed Therapy After AVWS Diagnosis	Response of AVWS to WM-Therapy	Best WM Response
1	Spontaneous intraabdominal hematoma	Bleeding	Desmopressin, Prednisone	Improvement	Prior to WM diagnosis	Zanbrutinib	Resolution	MR
2	Recurrent GI bleeding	Bleeding	IVIG, desmopressin, Factor VIII/VWF	Improvement	Prior to WM-directed frontline therapy	BR	Resolution	VGPR
3	Spontaneous wrist hematoma	Bleeding	IVIG, Factor VIII/VWF	Improvement	Prior to WM diagnosis	BDR	Resolution	MR
4	Subarachnoid hemorrhage, retinal hemorrhage, epistaxis	Bleeding	None		Progressive WM, after frontline therapy	2nd line: DRC	Resolution	PR
5	Retinal hemorrhage, epistaxis	Bleeding	Desmopressin, Factor VIII/VWF	Improvement	Prior to WM diagnosis	Plasma exchange followed by BR	Resolution	PR
6	Epistaxis	Bleeding	None		Prior to WM diagnosis	BDR	Resolution	MR
7	Epistaxis	Bleeding	Desmopressin	Improvement <3 months	Prior to WM-directed frontline therapy	Rituximab	Continued bleeding symptoms	PD
8	Epistaxis	Bleeding	None		Prior to WM diagnosis	Ibrutinib	Worsening epistaxis after 2 weeks of therapy	PD
9	GI Bleeding, Epistaxis	Bleeding	None		During WM-directed frontline therapy	BR	Worsening cutaneous bleeding after cycle 1	SD
10	None	Pre-surgical screening	IVIG, Factor VIII/VWF	Improvement	Prior to WM-directed frontline therapy	DRC	None	PR
11	None	Routine Screening	None		Progressive WM, after frontline therapy	2nd line: Rituximab	None	PR

BDR, Bortezomib-rituximab-dexamethasone; BR, bendamustine-rituximab; DDAVP, desmopressin; DRC, Dexamethasone-rituximab-cyclophosphamide; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

366 Screening for Acquired Von Willebrand Syndrome in Myelofibrosis – Poor Correlation with Bleeding Risk

Program: Oral and Poster Abstracts, Poster III

Raphael Costa Bandeira de Melo, MD[1*],

- Samples from forty-six patients (52% male) were collected for this study. MF was primary in 33 cases (72%) and post-ET/PV in 13 cases (28%). Median age was 70 years (IQR 63-80), and the median time from diagnosis to sample collection was 5.3 years (2.8-9.2)..
- Median level of von Willebrand factor antigen (vWF:Ag) and activity of vW (vWF) were 148% (IQR 125-169) and 71% (IQR 46-100), respectively. Median vWF:RCO/vWF:Ag was 0.48 (IQR 0.32-0.62), being <0.7 in 35/46 (76%) samples.
- After collecting the samples, patients were followed for 30 months (range 1-44). Seventeen patients died after the study, mostly related to disease complications. In addition, one major bleeding event was reported, and one patient had a stroke.
- **Conclusion**: A high prevalence of aVWS defined by the vWF:RCO/vWF:Ag ratio was found, even in the absence of thrombocytosis. Mechanisms of this qualitative change in the homeostasis of the Von Willebrand Factor remain elusive. One possible explanation is consumption by an increased platelet activation. The presence of laboratory aVWS criteria did not associate with clinically significant bleeding.

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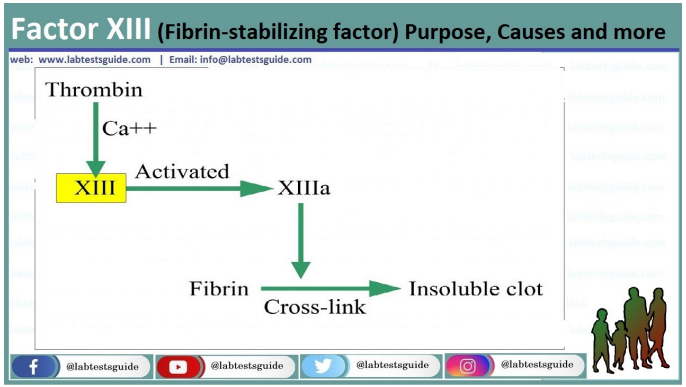
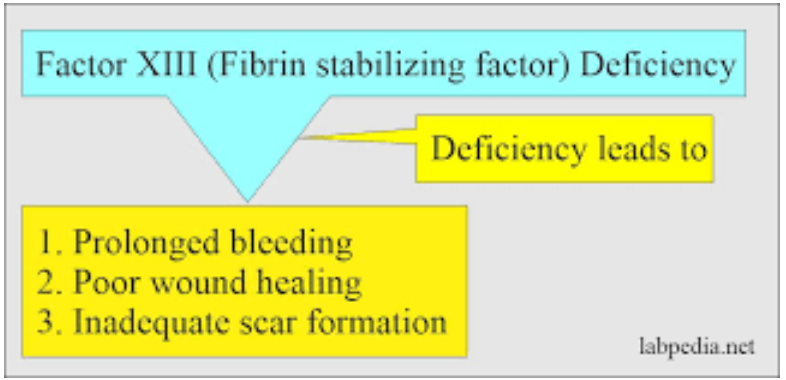




Factor XIII

Subunits A of human factor XIII (potentially catalytic) are made primarily by platelets and other cells of bone marrow origin. Subunits B are secreted into blood by hepatocytes. Units A and B combine within blood to form heterotetramers of two A units and two B units.

594 Acquired Factor XIII Deficiency Is Associated with High Morbidity and Mortality in Critically Ill Patients

Program: Oral and Poster Abstracts, Type: Oral

Miguel López Esteban et al.

Methods: In this retrospective, non-interventional study, we screened all patients with acquired FXIII deficiency admitted to Gregorio Marañon Hospital in Madrid, Spain, between January 2020 and March 2022. FXIII activity at our hospital is routinely measured in patients who experience bleeding despite a normal conventional coagulation test. A level of <70% is considered to indicate FXIII deficiency. All patients with FXIII levels lower than 70% were included in the study. Clinical, analytical and transfusion data were retrospectively collected.

Results: Seventy-one patients were diagnosed with acquired FXIII deficiency, of which 5 outpatient diagnosis were excluded from the analysis. Characteristics at baseline and at the time of FXIII deficiency diagnosis are shown in Table 1. Of note, this group of patients had a remarkable comorbidity burden (80.3%) and a high admission rate to Intensive Care Unit (ICU) (86.3%).

A significantly lower level of FXIII activity was found in patients with vasopressor requirements at the time of diagnosis (46% vs 38%, $p<0.05$) and those who presented multiorgan disfunction syndrome (MODS) at any time during hospitalization (51% vs 42%, $p<0.05$).No statistically significant difference was found in transfusion requirements when a cut-off of 36.5% in FXIII activity was used, except for fresh frozen plasma requirements (85% vs 58%, $p<0.05$). Nevertheless, a tendency towards significance was noticed in need for bleeding control, development of MODS and global mortality. Indeed, patients with FXIII activity less than 36.5% experienced less survival time during the first 2 years after hospital admission ($p=0.004$) (Fig.1).

Number of patients, n	66	
Baseline characteristics		
Male sex, n (%)	57 (86.3%)	
Age (years)	61.5 (41,5-72)	
ASA classification, I:II:III:IV, n (%)	3:14:32:17 (4.2%/21.2%/48.4%/23.6%)	
Comorbidities, n (%)	53 (80.3%)	
Oncological patient, n (%)	23 (34.8%)	
Medical/scheduled surgery/emergent surgery, n (%)	29 (43.9%)/ 15 (22.7%)/ 22 (33.3%)	
Clinical and analytical characteristics	**Admission data**	**Diagnosis data**
ICU admission, n (%)	57 (86.3%)	-
APACHE II score	12 (7.75-16)	-
SOFA score	4.96 + 3	4.74 + 3.5
Hemoglobin (g/dL)	11.0 ± 2.5	8.7 ± 1.5
Platelets (10^3/µl)	176 (118-221)	151 (89-258)
PT (sec)	13.8 (12.5-15.4)	13.2 (12.1-14.3)
APTT (sec)	30.9 (27.9-33.2)	28.5 (26.6-32.4)
Fibrinogen (mg/dl)	431 (332-676)	459 (336-673)
Leucocytes (10^3/µl)	10.55 (6.57-17.45)	9.75 (6.7-14.4)
Neutrophil to lymphocyte ratio	10.25 (4.29-20)	11.72 (4.97-21.06)
FXIII activity (%)	-	44.4 ± 13.5
Transfusion requirements		
Red blood cell concentrates, units	14 (2.75-32.75)	
Pooled platelets, units	1 (0-3.25)	
Fresh frozen plasma, units	3.5 (0-12.25)	

Table 1. Clinical, analytical and transfusion characteristics of FXIII deficient patients. Variables following a normal distribution are expressed as mean ± standard deviation. Variables not following a normal distribution are expressed as median (interquartile range). Abbreviations: *APACHE II score* Acute Physiology and Chronic Health disease Classification System II; *APTT* Activated Partial Thromboplastin Time; *ASA classification* American Society of Anesthesiologists Physical Status Classification System; *FXIII* Factor XIII; *ICU* Intensive Care Unit; *n* number; *PT* Prothrombin time; *SOFA score* Sepsis related Organ Failure Assessment.

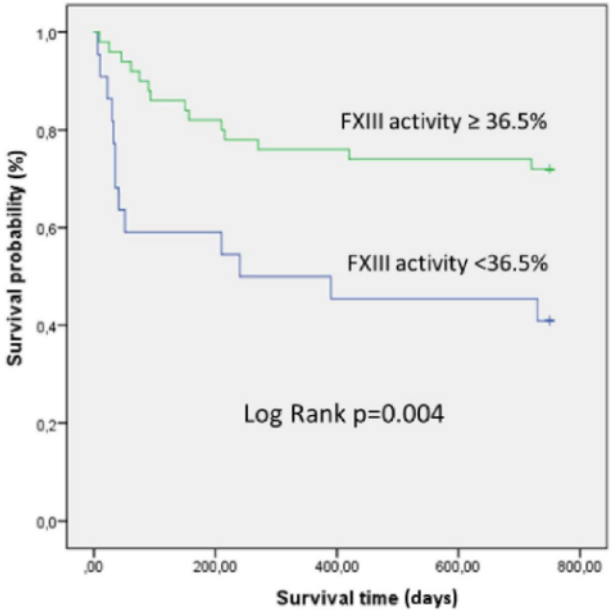
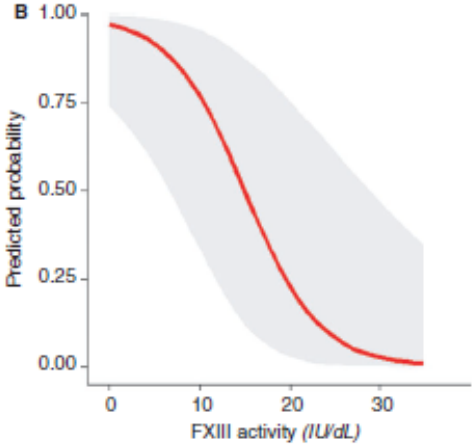


Figure 1. Kaplan-Meier analysis of survival of FXIII deficient patients. Two different groups are shown. Green line represents survival of patients with FXIII activity ≥36.5%. Blue line represents survival of patients with FXIII activity

Evidence from the literature suggests that FXIII levels of 3%–10% of the normal population mean (0.03–0.1 IU/mL) are sufficient to prevent spontaneous bleeds.

15% FXIII activity was the level under which the probability of spontaneous major bleeding sharply increases (from 50% for levels of 15% to more than 90% for levels of 5%or lower)

Menegatti M et al, J Thromb Haemost 2017



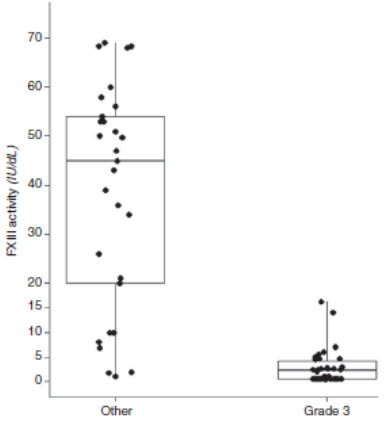


Fig. 3. Distribution of factor (F) XIII activity levels according to presence or absence of grade III bleeding. The box plots represent the interquartile ranges, the solid horizontal line inside each box plot is the median value and the vertical bars delimit the minimum and maximum values of the distribution. The black circles identify single observations.

Comment

In this setting (moderate) deficiency of factor XIII seems a biomarker of severity of illness (MODS, liver failure) rather than a risk factor for bleeding.