



Constitutional thrombocytopenia (CT): management of abnormal uterine bleeding (AUB)

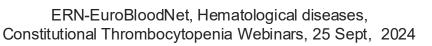
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Disclosures R d'Oiron



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Practical issues before starting



- √ 30-35min presentation (30 slides max) + 15 min Q&A session
- ✓ Microphones will be muted by host to avoid back noise
- ✓ Please, stop your video to improve internet conexion
- ✓ Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.







Learning objectives of the webinar



 Recognise abnormal uterine bleedings (AUB) and properly appreciate the impact of AUB on quality of life

 Be able to incorporate women-specific outcomes for girls and women with CT

 Understand potential areas of improvement for anticipation, prevention and treatment of AUB in CT, including the value of principles of care and joint clinics (OBGyn/hematology)







Agenda



- Not addressed during this webinar
 - Constitutional Thrombocytopathia (Glanzmann...)
 - No extensive description of the different CT
 - Pathogenesis
 - Diagnosis process and issues
 - Syndromic features, malignancies predisposition
 - Pregnancy, postpartum hemorrhages
 - Specific hemostatic treatments
 - teasing for other webinars







Agenda



- Disclaimer :
 - We refer to women and girls(WG) in this presentation, but the concept apply to all menstruating people
- Prevalence and Demographics of CT
- AUB in CT
 - Recognize and evaluate
 - Incorporate women-specific outcomes
- Medical management of AUB in CT
- Factors affecting severity







Demographics

WFH Annual Global Survey 2021: Demographics from 118 countries



386,966

People with bleeding disorders*

*Sex known

WFH: World Federation of Hemophilia

BD: bleeding disorders

H: Hemophilia

W: von Willebrand Disease

RED: Rare Factor Deficiencies

PD: Platelet Disorders

BDUC: BD of Unknown Cause



16.4%







WFH Annual Global Survey 2021: Demographics from 118 countries

386,966

People with bleeding disorders*

*Sex known

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RFD: Rare Factor Deficiencies

PP: Platelet Pathology

BDUC: BD of Unknown Cause









WFH Annual Global Survey 2020: identified patients by type of BD over time

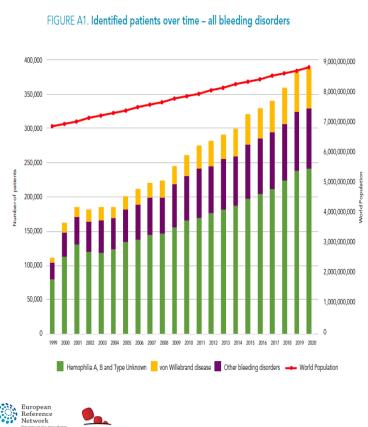
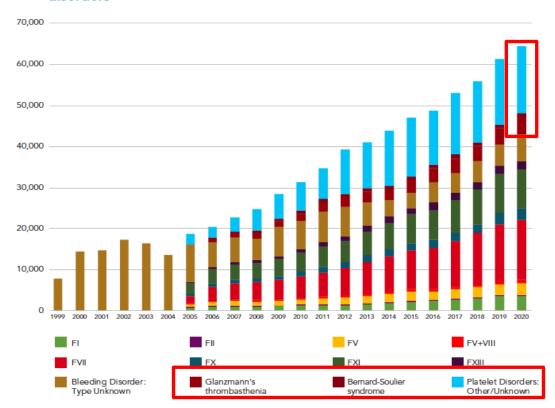


FIGURE A2. Identified patients over time - other rare bleeding disorders

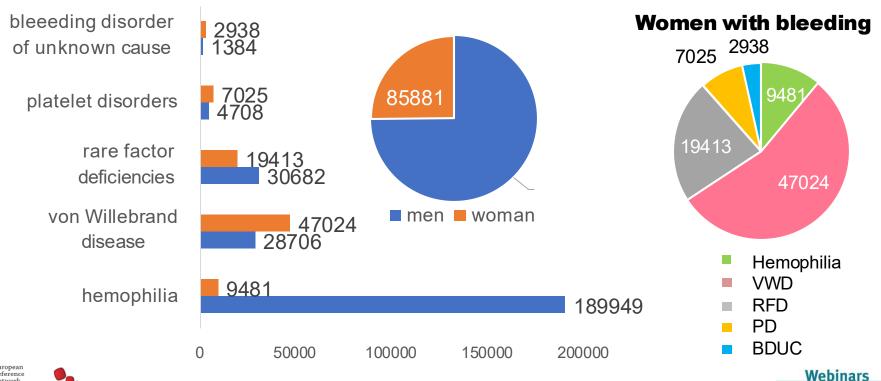






WFH Annual Global Survey 2020: Distribution by sex and type of bleeding disorder









EuroBleedNet :

WFH Annual Global Survey 2021: Women and Girls with platelet Disorders



Disorders	Countries reporting	Total Patients	Male	Percent male	Female	Percent female	Sex not known	Percent not known
Platelet disorder: Glanzmann's Thombasthenia	68	3,597	1,762	49%	1,685	47%	14	0%
Platelet disorder: Bernard- Soulier Syndrome	61	843	350	42%	429	51%	53	6%
Platelet Disorders: Other/ Unknown	61	17,951	5,927	33%	11,248	63%	213	1%







Women and Girls with Bleeding Disorders (WGBD): The facts



- WGBD face additional and specific challenges
- Disparities in access to both diagnosis and treatment
- Lack of knowledge
 - both level of patients, families and non-specialist health care professionals



Neglected or late family inquiry, lack of open discussion with family members



Limited recognition of abnormal bleeding events and AUB



Unknown options, maternal and fetal risks



Underrated impact on QoL in daily life by 1st line actors, families, and even specialists: burden around frequency & intensity of bleeds, pain and fatigue

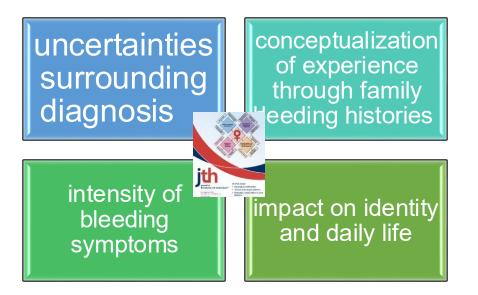






« Everything was blood when it comes to me »





- difficulty differentiating normal and abnormal bleeding symptoms
- lack of open discussion with family members & peers
- challenges with lack of diagnosis clarity
- unlikely to be referred to hematologists, remaining undiagnosed and undertreated



- Needs for improved tools
 - to differentiate normal and abnormal bleeding,
 - to use symptom-recognition based language,
 - early testing and accurate diagnoses





Abnormal Uterine Bleeding (AUB)

Challenges in measuring AUB



49% do not know that menstruations may induce medical issues*

For 37% (53% for 18-24y) pain is « normal » during periods*

No formal education on menstrual cycles in 56%*

Societal taboos surrounding menstruation (53%; 69% for 16-24 y)*

Difficulties
distinguishing between
normal and abnormal
menstrual cycles*

- 1/3 adolescents
- <u>1/5 adult women</u> in reproductive years*

Hesitancy among AUB women to seek medical support, leading to diagnosis delays (2/3 women with AUB)

1/4-1/5 women with AUB is concerned by gynecological disease

1/5 woman with AUB is concerned by a RBD

66-87% of BDUC are women, most of them with AUB

AUB : Abnormal Uterine Bleeding; RBD : Rare Bleeding Disorder; WGBD: women and girls with bleeding disorders BDUC: Bleeding Disorder of Unknown Cause Baker RI and O'Donnell JS, Blood, 2021;138:1795-1804

AUB in

^{*} OpinionWay online survey for « Règles Elémentaires », Sample of 1000 persons, 100 between 16-24y, April 2022

WGBD and AUB



Prevalence of BD in girls/women with AUB^{1,2}

Disorder	Women (%)	Adolescents (%)
VWD	5–20	5–36
Platelet dysfunction	<1–47	2–44
FXI deficiency	<1–4	<1–4
Haemophilia carrier	<1–4	8
Rare factor deficiencies	<1	13–20

Prevalence of AUB in WGBD^{1,2}

Disorder	Prevalence (%)
VWD	32–100
Platelet dysfunction	
Glanzmann's thrombasthenia	51
Bernard Soulier Syndrome	13–98
FXI deficiency	59
Haemophilia carrier	10–57
Rare factor deficiencies	35–70
FXIII deficiency	35–64

BD, bleeding disorder; AUB: acute uterine bleeding; VWD, von Willebrand Disease; WGBD: women and girls with bleeding disorders 1. James AH. *Haemophilia* 2010;16 (Suppl. 5):160–67; 2. Peyvandi et al. *J Thromb Haemost* 2011;9 Suppl 1:236–45

Inherited Platelet Disorders



- Mainly muco-cutaneous bleeding symptoms
- Highly variable severity
 - severe: Glanzmann's Thrombasthenia and Bernard Soulier Syndrome
 - milder ones much more common
- Some with associated with thrombocytopenia or non hematological syndromic features
- Exact prevalence unknown, higher when high consanguinity
- Diagnosis complex:
 - myriad of different CT
 - difficult in low income countries
 - labour intensive, difficult quality control (despite better standardization), need reproducible results and not single agonist for confirmation
 - many pre-analytical variables (dietary/drug/herbal factors)
 - ISTH algorithm for laboratory diagnosis from aggregometry to NGS







Inherited Platelet Disorders & AUB



- In severe PD:
 - 53% in BSS
 - Almost all GT
 - Acute major bleeding at menarche or after
 - Cyst rupture bleedings
 - Impact on fertility and pregnancy management
- Incidence of AUB in milder PD poorly described







Terms used to describe menstrual disorders that should no longer be used

- Anomalous uterine hemorrhage
- Anovulatory menorrhagia
- Dysfunctional uterine bleeding;
- Excessively heavy menstrual loss
- Epimenorrhea
- Epimenorrhagia
- Essential menorrhagia
- Functional uterine hemor/hage
- Functional menorrhagia
- Genuine menorrhagia
- Hypermenorrhea
- Idiopathic menorrhagia
- Idiopathic utering hemorrhage
- Menorrhagia
- Meno-metrorr/hagia
- Metropathia hemorrhagica
- Ovulatory menorrhagia
- Polymenorrhea
- Polymenorrhagia
- Primary menorrhagia
- Persistent menorrhagia
- Symptomatic menorrhagia
- Inexplained menorrhagia
 Uncomplicated menorrhagia



Abnormal Uterine Bleeding (AUB)

=

excessive menstrual loss which interferes with physical, social, emotional, and/or material quality of life

GT: proportion of Abnormal Uterine Bleeding (AUB) and pregnancies



	George 1990¹	Toogeh 2004 ²	Vijapurkar 2009 ³	Santoro 2010 ⁴	Siddiq 2011 ⁵	Fiore 2012 ⁶	GTR 2012 ⁸⁻¹⁰	Civaschi 2015 ⁷	Tarawah ¹¹ 2023
All patients	177	382	22	17	35	24	218	10	136
Females	102	178	22	9	35	14	127	10	67
Females >12 years	na	131	22	9	35	11	83	10	41?
Females with menorrhagia	98% (54/55)	13% (17/131)	77% (17/22)	55% (5/9)	68% (17/25)	na	48% (40/83)	na	86% (35/41?)
Females with pregnancies	29% 16*/55	7% 9/131	6% 1/17	44% 4**/9	35***	27% 3/11	4.8% 4/83	10***	? (<21%) ? / 28 °

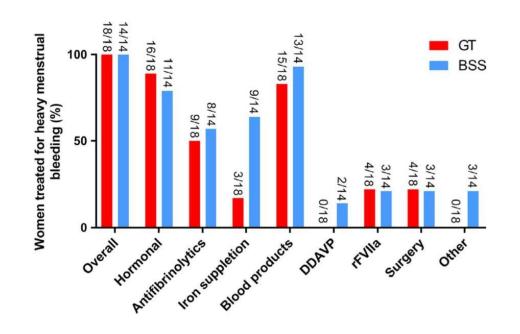
na, not available; *21 pregnancies; **7 pregnancies; *** only patients with pregnancies; o median parity 2

GT: Glanzmann thrombasthenia

Treatment of heavy menstrual bleeding according to the subtype of inherited platelet receptor defect.



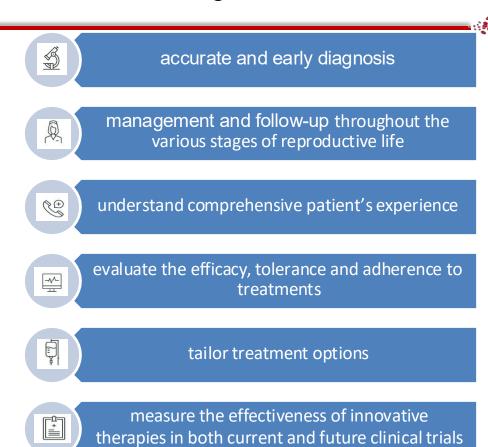
- 61 case reports/series and 8 cohort studies
- AUB defined by PBAC score > 100
 - 25% (13/52) of women with Bernard-Soulier syndrome
 - 22.1% (34/154) of women with Glanzmann thrombasthenia.



Expectations regarding outcomes in women and girls with WGBD

 Measuring abundance and impact of abnormal uterine bleeding (AUB) and postpartum hemorrhage (PPH) has a pivotal role in addressing the unique needs of WGBD

 Outcomes measures are essential at every stage

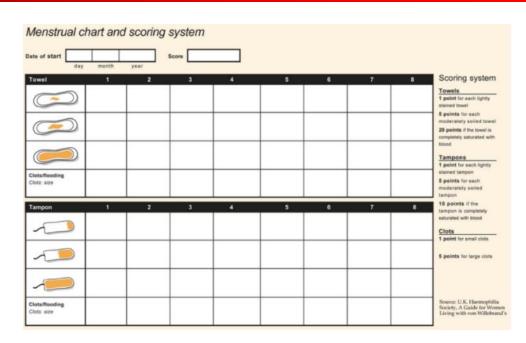


PBAC: Pictorial Bleeding Assessment Chart



Pr Jenny Higham

Higham score
Abnormal if > 100
(80 ml)



- infrequent use of the defined threshold of $\ll >80$ mL of blood loss per cycle », used mainly in clinical trials
- Some challenges in standardization and applicability in primary care

Higham J et al. Br J Obstet Gynaecol. 1990 Aug; 97(8):734-9.

Multiple examples of PBACs



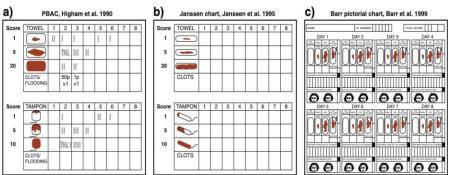
Lack of standardization

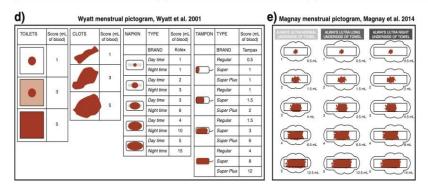
- Full tampon/towels
 - 20 points for both,
 - or 10 points for tampons and 20 points for full towels
 - 3-4-5 levels
- Clots
 - not included; or Small clot 1 point, Big clot 5 points
- Flooding rated/not rated
- Toilets, Day/night, Record of pain ...

May be restrictive and unsuitable for modern menstrual products (cups, pants)

Missing other symptoms than quantity (pain, mood, tiredness)

Impact may be high even if PBAC< 100





Clinical ISTH Bleeding Assessment Tools (ISTH-BAT)

Online ISTH-BAT

https://practical-haemostasis.com

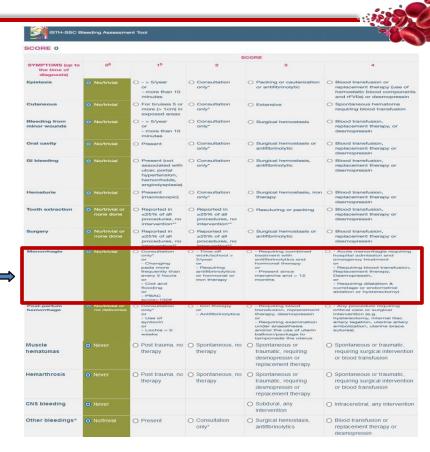
/ Risk-Assessment-algorithms / Bleeding Assessment / ISTH Bleeding Assessment Template (BAT)

Normal range

- 0-3 adult men
- 0-5 adult women
- 0-2 children

Abnormal Score

- ≥ 4 adult men
- ≥ 6 adult women
- ≥ 3 children



ISTH-BAT Bleeding Assessment Tools (BATs)



Item on AUB as example:

SCORE 0	0	1	2	3	4
SYMPTOMS (up to the time of diagnosis)	0 [§]	1 [§]	2	3	4
Menorrhagia	No/trivial	Consultation only* or - Changing pads more frequently than every 2 hours or - Clot and flooding or - PBAC score>100#	- Time off work/school > 2/year or - Requiring antifibrinolytics or hormonal or iron therapy	Requiring combined treatment with antifibrinolytics and hormonal therapy or Present since menarche and > 12 months	- Acute menorrhagia requiring hospital admission and emergency treatment or - Requiring blood transfusion, Replacement therapy, Desmopressin, or - Requiring dilatation & curretage or endometrial ablation or hysterectomy)

BATs and possible limitations

Limitations

- lack of sensitivity in those without hemostatic challenges (such as children and men)
- recall bias
- score saturation with recurrent symptoms
- inability of positive BATs to distinguish between different types of mild to moderate bleeding disorders

- Normal aging leads to increased variability of ISTH-BAT scores in healthy adult females
 - Further refinement with age-adjusted reference ranges may improve the sensitivity and specificity of the tool among females?

Population	Normal Range	Cut-off/Abnormal BS
Women, 18 – 30 years	0 – 4	≥5
Women, 31 – 51 years	0 – 5	≥6
Women, 52 – 88 years	0 – 6	≥7
Men, 18 years and older	0 – 3	≥4
Children, < 18 years	0 – 2	≥3

Recognise AUB

- Improve differentiation of normal/abnormal
 - Use symptom-recognition based language
- Not that simple in practice



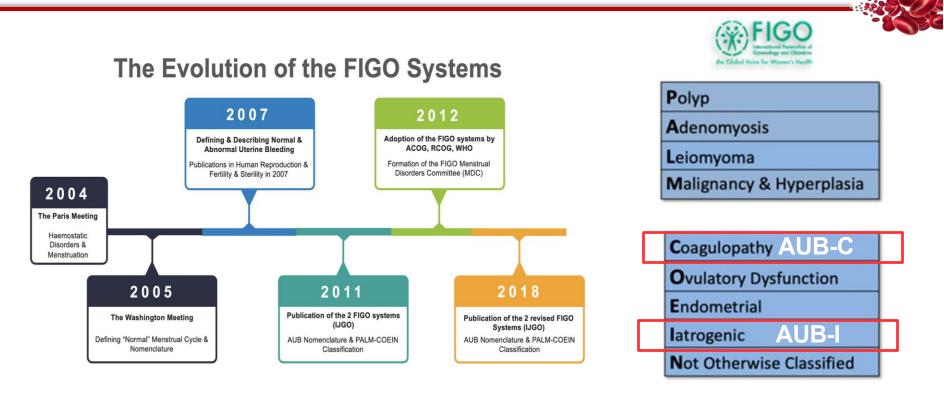
Any of the following in term of blood loss:

- Lasting ≥ 8 days
- Consistently soaks through 1 or more sanitary protections every 2 hours on multiple days
- Requires use of > 1 sanitary protection item at a time
- Requires changing sanitary protection during night
- Associated with repeat passing of blood clots

COMMENTARY TO THE EDITOR: von Willebrand disease: propung definitions for future research blood advances Nathan T. Connell ^{1,4} Paula D. James, ^{2,4} Romina Brignardello-Petersen, ³ Rezan Abdul-Kadir, ⁴ Barbara Ameer, ^{5,6} Alice Arapshian, ⁷ Sandra Haborichter, ¹³ Sandra Haborichter, ¹³ Vicki Jacobs-Pratri Nathan T. Connell, ^{1,4} Paula D. James, ^{2,4} Romina Brignardello-Petersen, ³ Rezan Abdul-Kadir, ⁴ Barbara Ameer, ^{8,6} Alice Arapshian, ⁷ Barbara A. Konkle, ^{15,1} e Peter Kouicles, ¹⁷ Michael Laffan, ¹⁸ Michelle Lavin, ¹⁹ Frank W. G. Leebeek, ²⁰ Claire McLintock, ²¹ Simen McRae Susic Couper, ⁸ Jorge Di Paola, ⁹ Jeroen Eikenboom, ¹⁹ Nicolas Giraud, ¹¹ Jean M. Grow, ¹² Sandra Haberichter, ¹³ Vicki Jacobs-Pratt, ¹⁴ Gobert Montgomery, ²⁸ Sarah H. O'Bnicn, ²⁴ James S. O'Donnell, ¹⁹ Marcareth C. Ozelo, ²⁸ Nikole Scappe, ²⁸ Robert Sidonlo Jr. ²⁷ Simon McRae, ²² Barbara A, Konkle, ^{15, 16} Peter Kouides, ¹⁷ Michael Laffan, ¹⁶ Michael Lavin, ¹⁹ Frank W, G, Leebeek, ²⁰ Claire McLintock, ²¹ Sarah H, O'Brion, ²³ James S, O'Donnell, ¹⁹ Margareth C, Ozelo, ²⁵ Nikole Scappo, ²⁶ Robort Sidonio Jr., ²⁹ Nedaa Husainat, ²⁰ Reem A, Mustafa, ²⁰ and Veronica H, Flood²³ Robert Montgomery, 23 Sarah H. O'Brien, 24 James S. O'Donnell, 19 Margareth C. Ozelo, 25 Nikole Scappe, 26 Robert Sidenio Jr. 27 Angela C. Weyand, 29 Mohamad A. Kalot, 20 Nedaa Husainat, 30 Reem A. Mustafa, 20 and Veronica H. Flood 23 and Veronica H. Flood 23

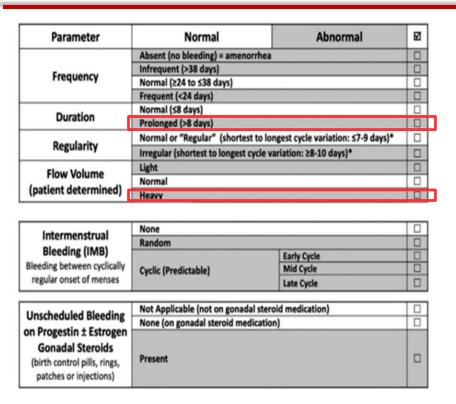
ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

FIGO AUB System 2. PALM-COEIN system for classification of causes of AUB in the reproductive years



FIGO, International Federation of Gynecology and Obstetrics; IJGO, International Journal of Gynecology & Obstetrics; ACOG, American College of Obstetricians & Gynecologists; RCOG, Royal College of Obstetricians & Gynecologists; WHO, World Health Organization; AUB, Abnormal Uterine Bleeding; MDC, Menstrual Disorders Committee
FIGO AUB system. adapted from Munro et al. Int J Gynecol Obstet 2018: 143: 393–408

Nomenclature and definitions of AUB symptoms according FIGO AUB System2: some differences compared to the haemostasis field



FIGO AUB System

- >8 days
- Volume « patient determined»
 - · Light / Normal / Heavy
- Frequency of cycles :
- Absent / Long (>38d) / Normal (≥24 to ≤38d) / Short (<24d)
- Regularity of cycles (shortest to longest)
 - Regular ≤7-9d / Irregular ≥8-10d
- Intermenstrual bleeding:
- None / Random / Cyclic (early, mid, late)
- Unscheduled bleeding on progestin alone or + estrogen

ISTH/ASH/WFH of other

- ≥ 8 days, >12 months or since menarche
- x2 protections, nb changes
- Overflow
- Frequency of changes (≤2h)
- Night changes/overflow
- Higham (PBAC) score >100
- ISTH-)BAT
 - Blood clots
 - Anemia, iron deficiency
 - Missing school/work>2/y
 - Emergency clinics
 - Treatments
 - Iron / TXA / progestin alone or + estrogen
 - transfusion / DDAVP or factor / uterine procedure

(Normal values in white, abnormal values in grey)

Evolution of instruments for measuring AUB



Quantify bleeding:

- Alkaline haematin technique
- Pictorial Blood Loss Assessment Charts (PBACs)
- Menstrual pictograms (estimated menstrual blood loss)



Assess symptoms associated to bleeding:

- Menstrual Evaluation Questionnaire (MEQ)
- Menstrual Symptom Questionnaire (MSQ)
- Evaluation Period ImPact and Pain Assessment (PIPPA)



Multidimensional questionnaire (menstrual symptoms and QoL):

- Abersdeen Menorrhagia Severity Scale (AMSS)
- Menorrhagia Multiattribute Scale (MMAS)
- Menstrual Impact Questionnaire (MIQ)
- Menstrual Bleeding Questionnaire (MBQ)
- Adolescent Menstrual Bleeding Questionnaire (aMBQ)







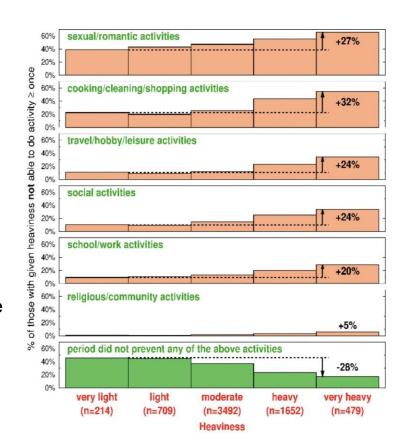
Multidimensional questionnaire (menstrual symptoms and QoL)

- Menstrual Bleeding Questionnaire (MBQ):
 - 20 items HRQoL related to AUB
 - perceived heaviness, bleeding pattern, pain, social impact, family activities (fear, embarrassment, behavioral changes), satisfaction
 - 0 (least) 100 (worst impact)
- Adolescent Menstrual Bleeding Questionnaire (aMBQ):
 - validated instrument
 - to measure the impact of AUB among adolescents

- Evaluation Period ImPact and Pain Assessment (PIPPA):
 - validated instrument
 - menstrual disturbance and its impact on daily activities
- Report on tolerance and adhesion to treatment rarely assessed

Period-associated disruption of daily activities collected by app

- Compare online survey and apptracked data in app users
- Real-time app-tracking facilitates quick daily recording of several aspects of bleeding-associated experiences
- May limit recall bias
- Collect bleeding and beyond (activities, pain, fatigue, digestive symptoms, mood changes, headaches)
- High satisfaction levels and compliance



percent of persons

- with a reported heaviness (listed on the x-axis, increasing from left to right)
- who were not able to do the activity at least once

AUB management

The 5 pillars of symptomatic treatment for abnormal uterine bleeding for improved quality of life



Hormonal therapy

TXA tranexamic acid

Pain killers

Psychological support and education

Iron

Can be started before specific diagnosis, alone or in combination +++

± specific treatments (some outside of approval): platelets, ddavp, rFVIIa, eltrombopag,...

Role of 1st line actors in early diagnosis of women and girls with bleeding disorders: education+++

- Paediatrician
- ER specialist
- General practitioner
- OB-GYN
- Dentist
- Anaesthesiologist
- Surgeon
- School nurses
- Social workers
- Any person close to young girls
- . . .



- Recognise abnormal bleeding symptoms
- BATs?



- Family history of bleeding
- 1st prescription (blood count, iron, PT, aPTT, fibrinogen, ±VWF)



- Refer to haemostasis specialist (have an organised network)
- Start symptomatic treatment without delay



Antifibrinolytics: Tranexamic acid (TXA)



- Orally 5–25 mg/kg x 3 /day (1 to 3 g/day in adult)
- IV 10 mg/kg x 3 /day
- More effective than DDAVP in 116 women with bleeding disorders
- Rare adverse events
- Dose to be adapted if renal deficiency
- Contra-indications
 - Active thrombosis
 - Haematuria (±)
 - Epilepsy (±)

AUB: Hormonal therapy



- Reduces endometrial proliferation and menstrual blood flow
- Prevent haemorrhagic ovarian cyst, dysmenorrhea and irregular cycles
- Raise FVIII and VWF
- Different according countries: progestins, combined oral contraceptives
- Others, less frequently required
 - Levonorgestrel intrauterine system
 - GnRH therapy + add back therapy (be careful to flare up 5–14 days after)
 - Medroxyprogesterone acetate
 - Balloon tamponade, minimally invasive endometrium surface resection, endometrial ablation, thermocoagulation, embolisation, hysterectomy (if no desire for future fertility or as life-saving measure)

Safety of long-term hormonal treatment



Hepatic adenomas

CASE REPORT

Norethisterone-induced hepatic adenomas can cause life-threatening bleeding in girls with inherited platelet disorders

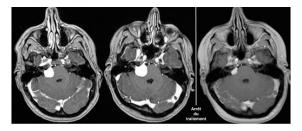
Hélène Crosnier, M.D., a,b,c Elisabeth Thibaud, M.D., a,b Catherine Duflos, M.D., a,b and Michel Polak, M.D., Ph.D. a,b

Centre de Référence des Maladies Gynécologiques Rares, Necker-Enfants Malades University Hospital, AP-HP, Université Paris-Descartes, Paris; Department of Pediatric Endocrinology, Gynecology and Diabetes, Necker-Enfants Malades University Hospital, APHP, Paris, and Department of Pediatrics, General Hospital, Poirb, Prance

Case	Chronologic age at norethisterone initiation (y)	Norethisterone dosage (mg/d)	Time on norethisterone (y)	Liver function	Number of adenomas (size of the largest, cm)	Outcome
1	11.0	20	13.0	Not done	1 (4)	Hepatic adenoma completely resolved
2	12.4	10–20	1.5	Normal	6 (5.8–6.3)	Shrinkage of the adenomas 1 y later; complete resolution 2 y later
3	15.5	20	2.5	Cytolysis ^a cholestasis	20 (4.7–7.2)	Only two adenomas left 24 mo later
4	11.0	10	10.0	Cytolysis ^b cholestasis	Multiple (largest 20)	50% decrease in adenoma size 6 mo later

Meningiomas

- With cyproterone acetate, chlormadinone acetate, nomegestrol acetate
- Likely age, dose and duration related
- Warning and limited prescription : <u>Follow label</u> (caution with dose and duration)



Crédit : Service de neurochirurgle de l'hôpital Lariboisière

0015-0282/\$36.00 Fertility and Sterility® Vol. 94, No. 6, November 2010 doi:10.1016/i.fertnstert.2010.03.045 Copyright @2010 American Society for Reproductive Medicine. Published by Elsevier Inc.

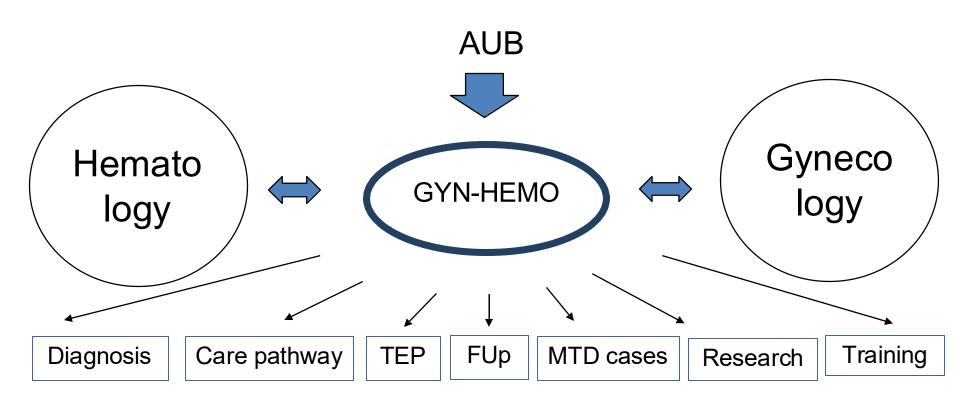
AUB prevention: role of multidisciplinary (MDT) clinic

- Only half of centres have joint clinics (EHC survey, 709 WGBD, 32 countries)¹
- Anticipate menarche
 - Assess pubertal change & predict time of menarche
 - Prepared prescription at home in advance
 - tranexamic acid
 - hormonal treatment
 - haemoglobin controls
 - haemostatic treatment
 - Break taboos in treatment (TXA, hormons, sport, menses)
 - Education +++

- Follow-up by MDT
 - Proven beneficial experience of combined gynaecologist / haematologist / nurse / psychologist clinics²
 - Assess efficacy / tolerance and adapt treatment regularly based on clinical/biological criteria
 - Pay attention to long cycles (risk of functional ovarian cyst and bleeding rupture)
 - Prevent additional causes of bleeding (omission of pills, infections)
 - Education +++ (double pill if omission or abnormal bleeding)

Joint clinics gynecology-hematology







EUROPEAN PRINCIPLES OF CARE FOR WOMEN AND GIRLS WITH INHERITED BLEEDING DISORDERS







Equitable access and quality of care for all individuals with bleeding disorders, irrespective of gender



Timely and accurate diagnosis of bleeding disorders in women and girls



Awareness of the additional challenges faced by WGBD throughout life



Comprehensive care of bleeding disorders requires a family centred approach which includes WGBD



Inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team



Education of WGBD and their families regarding the menstrual cycle and management



Early recognition and optimal management of heavy menstrual bleeding



Provision of preconception counselling and access to prenatal diagnostics



Provision of a patient centred comprehensive management plan throughout pregnancy and the post partum period



Involvement of WGBD in registries, clinical research and innovation

EAHAD Principles of care: educational needs according life stage



	S -5	•••					20		Action 1
Life stage	Infancy/ childhood	Adolescence	Young adulthood	(Pre) Conception	Pregnancy	Delivery	Breast feeding	Mid/late adulthood	Menopause
Education needs	Testing for clotting factor levels	Normal menstrual cycle	PBAC HMB	Genetic counselling	PND	PPH Primary Secondary	Safe use of TXA	PBAC HMB	Hormonal suppression
	Bleeding symptoms Introduce MDT	Sexual education ID(A) symptoms	Ovulation bleeding Hormonal suppression	Choices including PGD	MD delivery plan	ID(A) symptoms	Contraception / hormonal suppression	Treatment options depending on fertility choices	Gynae input
		Genetic testing	Inheritance	Current treatment perspectives					

van Galen K and EAHAD women with bleeding disorders working group et al. *Haemophilia* 2021;27(5):837–47

FIGURE 3 Educational needs on additional challenges of WGBD. Abbreviations: WGBD, woman and girls with inherited bleeding disorders; HMB, heavy menstrual bleeding; PBAC, pictorial bleeding assessment chart; PND, prenatal diagnostics; PGD, pre-implantation genetic diagnosis; MD(T), multidisciplinary (team); ID(A), iron deficiency (anaemia); PPH, post-partum haemorrhage; TXA, tranexamic acid; Gynae, gynaecologist

National Guidelines:

"Protocole National de Soins" for AUB

Joined initiative Gynecologist/hematologist











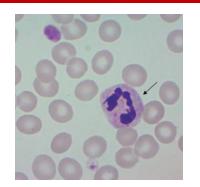
WGBD: not only AUB

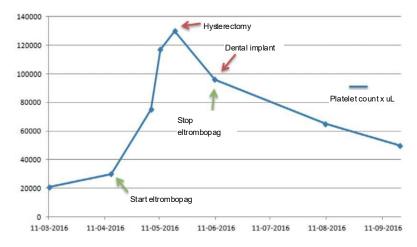
- More likely associated with
 - Anemia, severe anemia, iron deficiency and tiredness
 - Pain, dysmenorrhoea
 - Hemorrhagic ovarian cyst
 - Endometrial hyperplasia
 - Hypo/Infertility
 - Hysterectomy: more and earlier
 - Pregnancy-related concerns (mother & neonate)
 - (Endometriosis?)
- Reduced quality of life +++:
 - Limitations of social, sexual and occupational lives, lifestyle disruptions, anxiety and depression
 - Time lost from work/school (repeatedly)
 - 1. Kadir R et al. Haemophilia 2010;16(5):832-9; Rubin G et al. Haemophilia 2004;10:477-482; 2. Ragni MV. Haemophilia 1999;5:313-317;
 - 3. Zia A et al. Haemophilia 2016;22:199–207; 4. Hacioglu S et al. J Obstet Gynaecol 2016;36:1041–1045; 5. Ragni MV. Haemophilia 2016;22:397–402;
 - 6. Kirtava A et al. Haemophilia 2003;9:292-297

Clinical case of pregnancy and surgery in a patient with MYH9, treated with eltrombopag



- 35,000 /uL during 1st pregnancy at 21y
 - Vaginal delivery, no bleeding
 - Wrong diagnosis "ITP", no response to IVIg
- 51y, uterine bleeding
 - 3,000–65,000 /uL, giant platelets,
 Dohle leukocyte inclusions
 - MYH9 gene, encoding the non–muscle myosin heavy chain II-A:
 - variant ex31 c.4270G>A, p(Asp1424Asn), heterozygous
 - 50 mg/d orally eltrombopag → 130,000 /uL
 → hysterectomy without bleeding
- Several affected family members (autosomal dominant)



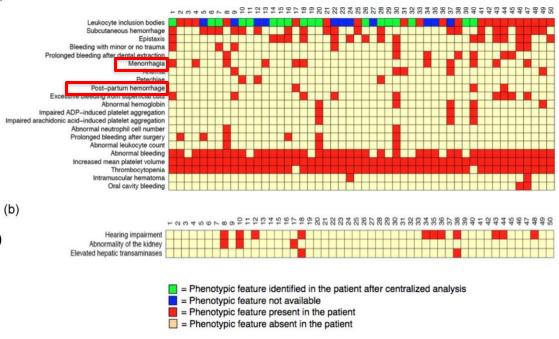


Haematological (a) and (b) non-haematological symptoms in MYH9-RD

(b)



- UK, 50 patients with MYH9- ^(a)
 RD variants
- All except 2 had thrombocytopenia
- Some degree of bleeding in 41/50 patients
- Non-haematological signs
 - 11 patients with hearing impairment
 - 3 renal failure
 - 2 elevated liver enzymes



Slide No. 48

AUB and CT: Factors affecting severity

CT non syndromic: Factors affecting severity



- CT forms with reduced platelet count as the only clinical phenotype throughout the life
 - No significant platelet dysfunction
 - thrombocytopenia remains stable throughout life (except for gray platelet syndrome, in which thrombocytopenia progressively may worsen with age)
 - presence and severity of bleeding correlate with the degree of thrombocytopenia
 - ACTN1, GP1BB, GP1BA, CYCS, TUBB1, TRPM7, TPM4, THPO, or IKZF5: modest or non clinical relevance (variability in the platelet count among healthy individuals rather than a real disease)
 - platelet-type von Willebrand disease (PTvWD) decreased platelet count (stress, infection, pregnancy,..)
- CTs with platelet dysfunction,
 - bleeding tendency is usually more severe than expected based on the platelet count
 - BSS is most severe CT + platelet functional defect, (severity of bleeding tendency is independent of platelet count, suggesting that the impaired adhesion of platelets to the subendothelium due to the GPI/IX/V deficiency is the major determinant of bleeding)
 - variable severity, even among patients with same disorder







Syndromic CT: Factors affecting severity



Evolutive nature of these complex disorders

- Some characterized by clinically significant platelet functional defects resulting in a bleeding tendency disproportionate to the platelet count
- MYH9: degree of thrombocytopenia is variable and remains stable over time. The majority of patients have no or mild spontaneous bleeding







CT with or without platelet function defect: Factors affecting severity



- Definite diagnosis of the few CTs with clinically relevant defects of platelet function is important to
 - identify subjects who, in spite of a mild or moderate thrombocytopenia,
 are at high risk of bleeding on the occasion of hemostatic challenges
 - Identify subjects in whom the degree of thrombocytopenia is expected to increase or decrease over time has obvious practical consequences







Take Home messages

Take Home messages



- Awareness increasing with imprved number of patients diagnosed with CT, including women and girls
- New outcomes measures for women and girls need to be extended and implemented
- Fields of improvement
 - Pathway of care
 - Joined clinics and multidisciplinary team
 - Diagnosis
 - Education
 - Research, data collection, registries







Thank you for your attention and many thanks to:

Centres de Référence Hémophilie, Willebrand, Pathologies **Plaquettaires**







Filière de Santé Maladies Rares MHEMO





European Haemophilia Consortium

Association Française des Hémophiles Women's Committee

World Federation of Hemophilia



















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