Denver ASH Review

# Updates on Benign Hematology

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Division of Hematology

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## Disclosures

- Advisory board participation:
  - BioMarin
  - Novo Nordisk
  - Sanofi
- Research funding:
  - NIH (NHLBI)
  - American Thrombosis and Hemostasis Network / Genentech
- Discussion of off-label drug use:
  - Fitusiran, concizumab, mim8, pomalidomide, VAD044

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## Learning Objectives

1. Describe the recommended treatment approaches for heavy menstrual bleeding, iron deficiency, and post-partum hemorrhage in female individuals with bleeding disorders.

2. Summarize current and emerging treatment options for individuals with hemophilia A and B.

3. Understand emerging treatment options for hereditary hemorrhagic telangiectasia.

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## Goal for this talk… and apologies

- Tell you about <u>all</u> the exciting updates in non-cancer hematology
  **… if only that were possible!**
- Highlight several abstracts that I found interesting and describe how they might change my practice
- Limited time = many important topics are not included

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## Bleeding in Females

WGPPM

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## Case #1

16 year old female with heavy periods since menarche

- Missed school 4-5 times per year due to bleeding
- +flooding, +clots
- Diagnosed with VWD at age 15, started combined OCP (estrogen + progesterone)

Duration of periods decreased on OCP, but still heavy

- Does not desire LNG-IUD

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**556 Combatt HMB-Recon: Combination Therapy in Adolescents to Treat Heavy Menstrual Bleeding-Review of Charts to Observe Treatment Patterns**

*Lauren E. Amos, MD MS*[1], *Hung-Wen Yeh, Phd*[1*], *Ayesha Zia, MD, MSc*[2], *Meera Chitlur, MD*[3], *Lynn Malec, MD MSc*[4*] *and Allison P. Wheeler, MD*[5]

- Multi-center retrospective cohort study
- Inclusion criteria:
  - Female sex assigned at birth, inherited bleeding disorder diagnosis, <21 years old
- Demographic, diagnosis, clinical and treatment data, safety data
- Treatment modalities

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## Combatt HMB-Recon

- 221 patients, 1478 HMB-related healthcare encounters
- Six treatment categories:

| | n |
|---|---|
| Estrogen/progesterone | 164 |
| Progesterone | 85 |
| TXA | 64 |
| Estrogen/Progesterone + TXA | 26 |
| Progesterone + TXA | 23 |
| Other meds (factor, DDAVP, EACA) | 112 |

- Median 2 regimens per patient

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## Combatt HMB-Recon

- No thrombotic events occurred

HMB control:

OR 3.6 for hormonal tx + TXA vs. hormonal tx or TXA alone

| Treatment Regimen | # (%) reporting control of HMB |
|---|---|
| Estrogen/progesterone | 82 (71.3) |
| Progesterone | 48 (80.0) |
| TXA | 34 (69.4) |
| **Estrogen/progesterone + TXA** | **18 (90.0)** |
| **Progesterone + TXA** | **12 (92.3)** |

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## Case #1, continued

- You prescribe TXA 1300 mg three times daily during periods
  - Continue combined OCP
- Labs return the next day:
  - Hemoglobin "low-normal" at 13
  - Ferritin 23 mcg/L (lower limit of normal 15)

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## 277 Sex, Lies, and Iron Deficiency in 2024: Cost-Effectiveness of Screening Ferritin Thresholds for the Treatment of Iron Deficiency in Women of Reproductive Age

*Daniel Wang[1], Samira Glaeser-Khan, BS[1*], Daniel Y Wang[2*], Ranya Moshashaian Asl[3*], Karthik Chetlapalli, MS, BS[1], Satoko Ito, MD, PhD[4], Adam Cuker, MD MS[5] and George Goshua, MD, MSc, FACP[6]*

- Fe deficiency most common micronutrient deficiency in the world
- No universal screening recommendations in US
- Sensitivity of ferritin assay limited by inappropriately low "normal" values
- Markov model evaluating different ferritin thresholds for screening

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## 281 Cost-Effectiveness of Oral Versus Intravenous First-Line Treatment of Severe Iron Deficiency Anemia in Women with Heavy Menstrual Bleeding

*Daniel Wang[1], Daniel Y Wang[2*], Samira Glaeser-Khan, BS[1*], Ranya Moshashaian Asl[3*], Karthik Chetlapalli, MS, BS[1], Satoko Ito, MD, PhD[4], Adam Cuker, MD MS[5] and George Goshua, MD, MSc, FACP[6]*

- Markov model evaluating cost effectiveness of three treatments for severe iron deficiency anemia (Hgb < 8) in females with HMB
  - Oral ferrous sulfate with 2nd line IV iron dextran if needed
  - IV iron dextran 1000 mg
  - IV iron sucrose 200 mg x 5 doses
- Outcome for both studies: ICER in cost per QALY

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## Fe deficiency screening: cost effectiveness

| Screening approach | Cost | QALY |
|---|---|---|
| No screening | $210,000 | 22.3 |
| Ferritin threshold < 15 mcg/L | $211,000 | 23.3 |
| Ferritin threshold < 25 mcg/L | $212,000 | 24.3 |

Using ferritin threshold < 25 mcg/L to screen for Fe deficiency is the most cost effective option, with ICER $940/QALY compared to no screening

*(US Willingness To Pay threshold is $50,000 - $150,000 per QALY)*

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## IV Iron vs. Oral Iron: cost effectiveness

Compared to oral ferrous sulfate:

Iron dextran 1000 mg x 1 dose: ICER $1300 / QALY

(Iron sucrose 200 mg x 5 doses was more expensive and less effective than iron dextran)

*(US WTP $50k - $150k / QALY)*

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## Case #1, resolution

- You prescribe TXA 1300 mg three times daily during periods
  - Continue combined OCP
- Labs return the next day:
  - Hemoglobin "low-normal" at 13
  - Ferritin 23 mcg/L (lower limit of normal 15)
- You prescribe IV iron dextran 1 g x 1 dose and schedule follow up in 3 months

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## Case #2

32 year old woman, heterozygous FIX deficiency ("carrier")

- Baseline FIX activity 47%, history of HMB
- First pregnancy, currently 32 weeks gestation, uncomplicated
- Third trimester FIX activity 60%

- Patient's brother has mild FIX deficiency
- Patient's mother had severe post partum hemorrhage with 1 of 2 deliveries, FIX activity never measured

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## 129 Postpartum Hemorrhage in Hemophilia a and B Carriers after Enhanced Prophylactic Clotting Factor Suppletion: The Pregnancy and Inherited Bleeding Disorders Study (PRIDES)*

*Anne de Vaan, MD[1], Marieke JHA Kruip, MD, PhD[2], Jeroen Eikenboom, MD, PhD[3], Marieke C Punt, MD, PhD[1], Michiel Coppens, MD, PhD[4,5], Laurens Nieuwenhuizen, MD PhD[6], Saskia EM Schols, MD, PhD[1], Anja BU Mäkelburg, MD, PhD[6], Floor CJI Moenen, MD, PhD[7], Hans JJ Duvekot, Md, PhD[1,8], Marjolein Peters, MD, PhD[1,11], Annemieke JM Middeldorp, MD, PhD[1,12], Kitty WM Bloemenkamp, MD, PhD[1,9], Roger EG Schutgens, MD, PhD, MSc[1,7], Titia AT Lely, MD, PhD[1,10] and Karin PM van Galen, MD, PhD[1]*

- PRIDES studies for HA / HB carriers
  - Old Dutch guidelines: >50% is ok Target 100% at delivery
  - New guidelines: >80% is ok Target 150% at delivery

| FVIII / FIX activity | Treated with factor | PPH (≥500 ml) | Severe PPH (≥1000 ml) |
|---|---|---|---|
| <80% (n=34) | 73.5% | 29.4% | 11.8% |
| ≥80% (n=136) | 2.2% | 34.6% | 12.5% |
| Dutch general pop. | -- | 19% | 4.5% |

- More to come looking at those with <50% in third trimester

*see also abstracts 2601, 1208, and 2595

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HEMATOLOGIC COMPLICATIONS IN PREGNANCY

## How I manage pregnancy in carriers of hemophilia and patients with von Willebrand disease

Frank W. G. Leebeek,[1] Johannes Duvekot,[2] and Marieke J. H. A. Kruip[1]

[1]Department of Hematology and [2]Department of Obstetrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

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# Hemophilia A and B

New Treatments

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## Case #3

62 year old man with mild hemophilia A (FVIII 12%), needs arthroscopic knee surgery

- Typical treatment plan calls for factor VIII concentrate doses:
  - Pre-op: 50 units/kg
  - POD 1 – 3: 50 units/kg
  - POD 4 – 7: 25 units/kg
- Does not self-infuse through PIV but knows how to infuse through PICC line
- Patient asks about longer-acting factor: Is it an option?

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**2582 Cost Comparison of Efanesoctocog Alfa with Existing Factor VIII Replacement Therapies for Major Surgeries in People with Severe Hemophilia A**

*Janice Staber, MD[1], Alix Arnaud, MSc[2], Ion Agirrezabal, MSc/PhD[3], Lane Anson, PharmD/MBA/RPH[4], Andrew Wilson, MS[4], Nana Kragh, MSc[5], Doris V. Quon, MD, PhD[6] and Allison P Wheeler, MD/MSCI[7]*

- Utilized published surgical data for four factor VIII products:
  - Octacog alfa (standard half life)
  - Rurioctacog alfa pegol (PEGylated – extended half life)
  - Efmoroctacog alfa (Fc fusion protein – extended half life)
  - Efanesoctacog alfa (Fc + XTEN + D'D3 – ultra long half life)
- (Total factor dose per surgery) * (Wholesale Acquisition Cost) = total **cost per surgery**

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| FVIII therapy | Clinical data source | Clinical data description | Reported perioperative period | Median FVIII consumption (IU/kg) | Cost ($/IU) |
|---|---|---|---|---|---|
| Octocog alfa | Registrational clinical study in FDA label[5] | 58 patients (aged ≥5 years) with severe HA who underwent 65 surgical procedures including 22 major surgeries[a] | During hospitalization | 228–1,825 | 1.90 |
| Turoctocog alfa pegol | Phase 3 clinical study in FDA label[7] (NCT01913405) | 21 previously treated male patients (aged ≥12–75 years) with severe HA who underwent 21 major surgeries[b] | 7 days | 464–1,457 | 2.49 |
| Efmoroctocog alfa | Phase 3 extension studies in FDA label[8] (NCT01181128, NCT01458106, and NCT01454739) | 21 patients (aged ≥12 years) with severe HA who underwent 23 major surgeries[c] | 14 days | 121–733 | 2.58 |
| Efanesoctocog alfa | Phase 3 clinical study in FDA label[9,10] (NCT04161495) | 12 patients (aged ≥12 years) with severe HA who underwent 13 major surgeries[d] | 14 days | 45–361 | 5.26 |

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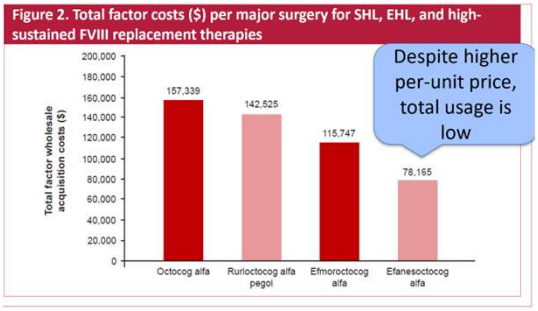
## Cost Comparison

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## HA / HB Drugs Approved and in Development

*(partial list)*

Rebalancing agents:

- Anti-TFPI

| Drug | FDA Approval | Disease(s) | Inhibitors? | Age | Admin. Freq. |
|---|---|---|---|---|---|
| Marstacimab | 10/11/2024 | HA, HB | No | ≥ 12 years | Weekly |
| Concizumab | 12/20/2024 | HA, HB | No | ≥ 12 years | Daily |

- Anti-thrombin lowering: fitusiran

Factor VIII mimetic:

- Mim8

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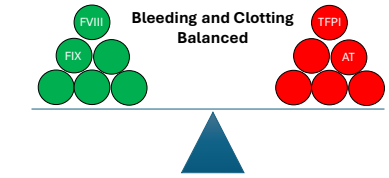
## Rebalancing Therapies




- CAUSES CLOT FORMATION (steps on the gas)
- INHIBITS CLOT FORMATION (puts the brakes on)

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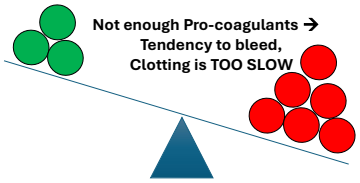
## Rebalancing Therapies




- **CAUSES CLOT FORMATION** (steps on the gas)
- **INHIBITS CLOT FORMATION** (puts the brakes on)

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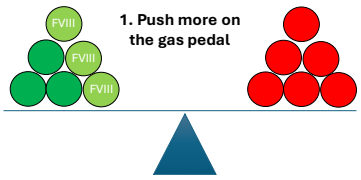
## Rebalancing Therapies




- **CAUSES CLOT FORMATION** (steps on the gas)
- **INHIBITS CLOT FORMATION** (puts the brakes on)
- REPLACEMENT FACTOR (more gas pedal)

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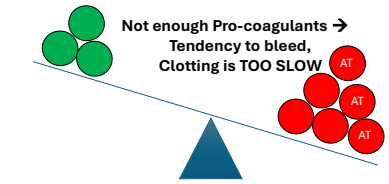
## Rebalancing Therapies




CAUSES CLOT FORMATION (steps on the gas)
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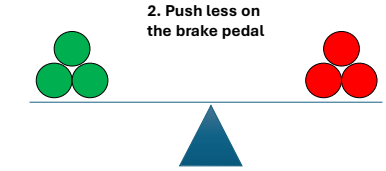
## Rebalancing Therapies




CAUSES CLOT FORMATION (steps on the gas)
INHIBITS CLOT FORMATION (puts the brakes on)

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## "Inhibit the inhibitor"

Two targets:

- Anti-thrombin (fitusiran) **siRNA**

INHIBITS CLOT FORMATION (medications "inhibit the inhibitor")

- Tissue factor pathway inhibitor (concizumab, marstacimab, BAY 1093884*, BAX 499†)

*terminated due to thrombosis
†terminated due to bleeding

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**What we don't know** (2020 version)

- How should we adjust dosing of factor / bypassing agent for bleeds or surgeries?
- How to respond if thrombosis occurs

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**What we don't know** (2020 version)

- How should we adjust dosing of factor / bypassing agent for bleeds or surgeries?
- How to respond if thrombosis occurs
- What impact do these medications have on treatment of bleeds? On ITI?

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**128 Reduced Doses of Factor Concentrates and Bypassing Agents to Treat Breakthrough Bleeds in Patients with Hemophilia A and B on Fitusiran Antithrombin-Based Dosing Regimen: ATLAS-OLE**

*Steven W. Pipe, MD[1], Kaan Kavakli[2*], Tadashi Matsushita, MD[3], Huyen Tran, MBBS (Hons), Master Clin Epi, FRACP, FRCPA[4], Bulent Zulfikar[5], Laurel Menapace[6*], Marja Puurunen, MD, PhD[7*], Wenruo Hu[8], Yuqian Shen[9*], Chanchala Kaddi[9*] and Vanessa Salinas[10*]*

- Thrombosis events in Phase 2 trial led to trial pause
- Target AT levels were increased (i.e., fitusiran doses were reduced) to 15-35%
- Factor doses used to treat bleeds were also reduced
  - ? Efficacy of lower doses for bleed treatment

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## Recommended Factor Dosing

| | Factor VIII | Factor IX SHL | Factor IX EHL | aPCC | rFVIIa |
|---|---|---|---|---|---|
| **Recommended single dose** | 10 IU/kg (maximum 20 IU/kg)[a] | 20 IU/kg (maximum 30 IU/kg)[a] | 20 IU/kg (maximum 30 IU/kg)[a] | 30 U/kg (maximum 50 U/kg)[a] | ≤45 µg/kg |
| **Repeat dosing** | Should not repeat in <24 hours[b] | | Should not repeat in <5–7 days[b] | Should not repeat in <24 hours[b] | Should not repeat in <2 hours[c] |

Reduced doses and frequency of BPA/CFC were **effective in controlling breakthrough bleeds**

Fewer infusions and substantially lower doses of CFC/BPA required to treat breakthrough bleeds compared with clotting factor prophylaxis

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## Other Hemophilia Treatment Abstracts

- Mim8 718 1212
- Concizumab 715 **3977**
- Marstacimab 716 1210 1215

- Bemiltenase alfa **1213**

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## 3977 Concizumab As a Possible Treatment for Bleeding Disorders of Unknown Cause

***Paula Acuña***[1*], *Elena Monzón Manzano, PhD*[1*], *María Teresa Alvarez-Román, PhD, MD*[1,2*], *Elena G Arias-Salgado, PhD*[1*], *Eduardo Garcia Perez*[1*], *Monica Martin Salces, PhD, MD*[1*], *Maria Isabel Rivas Pollmar, PhD, MD*[1*], *Rick Kapur, MD, PhD*[3,4], *Victor Jimenez Yuste, MD, PhD*[1,2*] *and Nora Butta, PhD*[1*]

- *In vitro* study of thrombin generation using patient samples with and without concizumab

- 47 patients with bleeding of unknown cause and reduced thrombin generation
  - 44 / 47 had increased thrombin generation when concizumab was added to samples
  - Improvement appeared to be dose-dependent
  - Suggests potential role for rebalancing agents in BDUC

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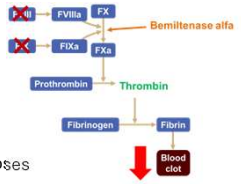
## 1213 A Specific Coagulation Factor X Activator for on-Demand Treatment in Hemophilia with Inhibitors

*Wei Liu, MD[1*], Hu Zhou[2], Ruibin Huang, MD[3], Xin Du[4], ZePing Zhou, MD, PhD[5], Changcheng Zheng, MD[6], Shifeng Lou, MD[7*], Xinyue Dai, MD[1*], Renchi Yang, MD[1] and Lei Zhang[1]*

- Bemiltenase alfa: first-in-class bypassing agent
  - Activates factor X (FX) to FXa
  - Developed for treating bleeds in people with hemophilia A and B with inhibitors
- Phase Ib/II clinical trial (NCT05027230)
- 63 patients with HAwI and 4 HBwI
- No VTE, no serious AE, no drug antibodies
- Most bleeds successfully treated with 1-2 doses

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# Hereditary Hemorrhagic Telangiectasia

New therapies in development

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## 553 A Randomized, Placebo-Controlled, Multicenter Proof-of-Concept (POC) Study to Assess the Safety and Efficacy of the Novel Allosteric AKT Inhibitor, VAD044, in Adults with Hereditary Hemorrhagic Telangiectasia (HHT)

*Hanny Al-Samkari, MD[1,2], Josefien Hessels, MD[3], Antoni Riera-Mestre, MD[4], Sophie Dupuis-Girod, MD[5], Thibaut Van Zele, MD[6], Vincente Gómez del Olmo, MD[7], Pierre Saint-Mezard, PhD[8], Hedvika Lazar, MSc, MPH[8], Damien Picard, MD[8], Debra Barker, MD[8], Elizabetta Buscarini, MD[9] and Hans-Jurgen Mager, MD[8]*

- 75 adults with HHT, severe epistaxis and iron deficiency
- Randomized to 40 mg, 30 mg, or placebo
- 6 / 75 discontinued due to adverse events; all serious AEs deemed unrelated to study drug; expected drug class effects were mild and reversible (diarrhea, hyperglycemia, rash)
- Decreased severity and frequency of epistaxis in treatment groups
- Global rating of change: **60% of 40 mg group rated epistaxis as "much better" compared to 17% of placebo group**

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**558 Long-Term Safety and Effectiveness of Pomalidomide for Bleeding in Hereditary Hemorrhagic Telangiectasia**

*Ellen Zhang, MD[1], Pamela G Hodges, PhD, ANP[2,*], Josanna Rodriguez-Lopez, MD[3,4*] and Hanny Al-Samkari, MD[2,4]*

- Open label extension of PATH-HHT, a 6 month study of safety and efficacy of oral pomalidomide for treatment of epistaxis in HHT
- 48 patients enrolled; 15 discontinued study drug (8 due to TEAE, 7 due to lack of effect); AEs were mostly mild
  - One thrombosis occurred (rate 1.66 per 100 patient-years)
- Primary outcome: maintain clinically important improvement in epistaxis for ≥ 6 months
  - 84% had durable epistaxis response
- Less impact on GI bleeding: those with GIB still required transfusion or iron infusion support

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# Omissions

Sickle cell disease, thrombosis, gene therapies, many others

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## Summary: My ASH takeaways

- For pts with HMB, using TXA while on OCP is safe and effective
- Consider increasing cutoff of "abnormal" ferritin and treat more iron deficiency with IV iron as first line therapy
- Treat carriers and VWD patients if their 3rd trimester levels are <80%, target 150% peak
- Efanesoctacog may be cost-viable option for perioperative management of hemophilia A (with reduced # infusions)
- Treating bleeds in patients on rebalancing agents for HA/HB may require lower factor doses than those on factor prophylaxis
- More options to come for those with HHT

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# Educational Sessions

Spotlight on three outstanding sessions

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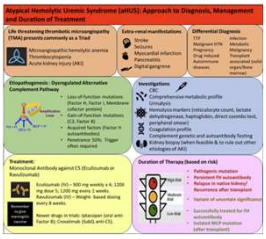
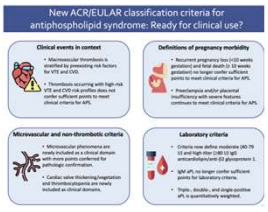
## Beyond TTP: “Atypical” TMAs for the Hematologist




Java. Atypical hemolytic uremic syndrome: diagnosis, management, and discontinuation of therapy. *Hematology Am Soc Hematol Educ Program* 2024; 2024 (1): 200–205.




Andrew B. Song, Rebecca K. Leaf; New definitions for antiphospholipid syndrome: ready for clinical use?. *Hematology Am Soc Hematol Educ Program* 2024; 2024 (1): 222–226.

https://ashpublications.org/hematology/issue/2024/1

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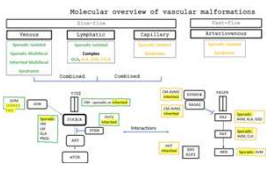
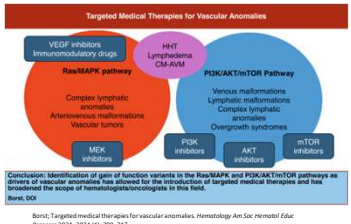
## Vascular Anomalies, Vascular Malformations, and the Role of the Hematologist




Seront et al. Molecular landscape and classification of vascular anomalies. *Hematology Am Soc Hematol Educ Program* 2024; 2024 (1): 700–708.




Borst; Targeted medical therapies for vascular anomalies. *Hematology Am Soc Hematol Educ Program* 2024; 2024 (1): 709–717.

https://ashpublications.org/hematology/issue/2024/1

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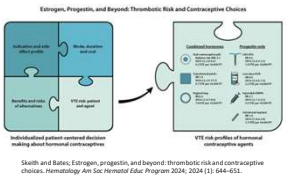
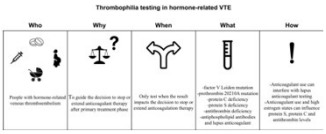
## Sex Hormones, Contraceptives, and Thrombotic Risk: Where are We Now?




Skeith and Bates; Estrogen, progestin, and beyond: thrombotic risk and contraceptive choices. *Hematology Am Soc Hematol Educ Program* 2024; 2024 (1): 644–651.




Scheres and Middeldorp; Hormone-related thrombosis: duration of anticoagulation, risk of recurrence, and the role of hypercoagulability testing. *Hematology Am Soc Hematol Educ Program* 2024; 2024 (1): 664–671.

https://ashpublications.org/hematology/issue/2024/1

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## Thank you

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