Acute Management of Hemarthrosis and Other Bleeding Complications

Annette von Drygalski, M.D., Pharm.D.
Associate Clinical Professor of Medicine
Director Hemophilia and Thrombosis Treatment Center
University of California San Diego
Outline

• Hemophilia and Basics of Treatment

• Hemophilic Arthropathy

• Diagnosis of Joint and Muscle Bleeding
ARS Question

1. A 25 yo patient with severe hemophilia presents to the ED with severe headaches. He has a history of migraines. His last clotting factor infusion was yesterday. You are paged to assist with management. What is your recommendation:

A. Obtain history, exam, labs and CT Head prior to deciding if additional clotting factor is indicated

B. Administer a dose of clotting factor prior to proceeding to history, labs, exam, and imaging studies

C. Administer iv pain medications and observe overnight
2. A 60 yo patient with severe Hemophilia A presents to the ED with melena. His Hgb has dropped from 12 gm/dL 3 months ago to 6 gm/dL. The patient cannot remember his last infusion of factor. You advise the ED physician to give FVIII immediately, at which dose?

A. 25 U/kg

B. 50 U/kg

C. 100 U/kg
ARS Question

3. Which modality appears to be most suitable to determine if joint pain is associated with hemarthrosis in hemophilia?

A. Patient examination and history
B. MRI without contrast
C. Musculoskeletal Ultrasound
D. MRI with contrast
Hemophilia

<table>
<thead>
<tr>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
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<tbody>
<tr>
<td>Factor VIII (FVIII)</td>
<td>Factor IX (FIX)</td>
</tr>
<tr>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>1/5,000 male births</td>
<td>1/25,000 male births</td>
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- Spontaneous joint and muscle bleeds
- Severe Hemophilia: Median ~ 45 bleeds per year without prophylaxis
- Hemophilic arthropathy is a debilitating comorbidity
- Cannot be avoided entirely despite factor replacement
- ~60%-80% patients with severe hemophilia have dysfunctional joints as young adults (age 18-40)
- High risk of intracranial hemorrhage
- Development of an inhibitor increases risk of death and arthropathy

“How to Treat”

Access to clotting factor and prophylaxis is key

<table>
<thead>
<tr>
<th>Bangladesh</th>
<th>France</th>
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<tbody>
<tr>
<td><strong>Clotting Factor</strong></td>
<td></td>
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<tr>
<td>✓ Replacement during surgeries and procedures</td>
<td></td>
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<tr>
<td>✓ Long-term replacement strategies</td>
<td></td>
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<tr>
<td>✓ Acute Bleeding</td>
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Evolution of Treatment for Patients with Hemophilia

1960s
- Cryo/FFP
- PD Factor Concentrates
- Viral Contamination

1992
- rFVIIIls

Late 1990s
- rFIX
- rFVIIa
- Improved Devices For Reconstitution

2000s
- Prolonged T½ FVIII, FIX
- Factor-Free Treatments
- Gene Therapies

2010s
“How to Treat”
Long-Term Factor Replacement “Old-New-Future”

1. **Old = 2000s:**
   Prophylactic vs On-Demand Treatments:
   Beneficial in Randomized Trials

2. **New = 2010s:**
   Prolonged $T^{1/2}$ Products:
   Lesser Infusions
   - $T^{1/2}$ extension FIX $\approx 3$- to 4-fold ($\sim 20$ h $\rightarrow \sim 80$ h)
   - $T^{1/2}$ extension FVIII $\approx 1.5$- to 2-fold ($\sim 10$ h $\rightarrow \sim 20$ h)

3. **Future = 2020s:**
   Non-Factor Treatments and Gene Therapy: Change Phenotype
General Factor Dosing Considerations

Dosing and Frequency of Infusions
T1/2, recovery, distribution volume

Factor Dosing – Non-Extended T1/2 products

FVIII \( (t_{1/2} \ 8-14h) \)

1 unit/kg of FVIII increases plasma FVIII activity by 2%
\rightarrow 50 \text{ u/kg result in 100% FVIII plasma activity}

FIX \( (t_{1/2} \ 18-24 \text{ h}) \)

1 unit/kg of FIX increases plasma FIX activity by 1%
\rightarrow 100 \text{ u/kg result in \sim 100% FIX plasma activity}

Choice of Factor Product

✓ Recombinant and plasma-derived factors are equivalent: Efficacy, safety, but PD less inhibitor formation (?)

✓ Extended vs Non-Extended T \( 1/2 \) product: lesser infusions
**Acute Bleeds**

<table>
<thead>
<tr>
<th>Desired Factor Level (%)</th>
<th>Dose FVIII</th>
<th>Dose FIX</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding ~ 50 %</td>
<td>25 (U/kg) Q12h</td>
<td>50 (U/kg) Q24h</td>
<td>1-3 days outpatient</td>
</tr>
<tr>
<td>Major bleeding ~ 100 %</td>
<td>50 (U/kg) q8-12h</td>
<td>100 (U/kg) q12-24 h</td>
<td>Until bleeding stops +10-14 d</td>
</tr>
</tbody>
</table>

**Bolus followed by continuous infusion**
Preferred for hospitalization and/or surgery
FVIII start at 2 U/kg/h and FIX at 5 U/kg/h with 1-2 x daily factor levels

- Reduced factor utilization
- Avoid peak and trough levels, with steady ~ 100% factor activity
- Facilitate lab monitoring

**Prior to elective surgery**

- Inhibitor status
- Possibly T½ study
FVIII: 50 unit/kg
FIX: 100 unit/kg

A/B 50/100 rule

Fellow emergency rules

No 1) Understand that hemophilia remains a life-long potentially rapidly fatal disease!

No 2) Your patient is always right!

No 3) Treat before you think!
Hemophilic Arthropathy – Sequelae of Bleeding

**Infancy:**
Joint and muscle bleeds at first onset of walking
Joints prone to bleeding: knees, elbows, ankles
Target joint: 2-4 bleeds over 3-6 months period

**Youth:**
Bleeds facilitated by growth spurts and physical activity

**Adulthood:**
Joint bleeds, fibrosis, scarring, deformities, arthropathy

Extent of Overlap with Other Arthritic Conditions is Unclear

- Rheumatoid Arthritis
  - Systemic inflammatory disease with predilection for joints

- Osteoarthritis
  - Degenerative disease of aging joints

- Hemophilic Arthropathy
  - Bleeding disorder causing hemarthrosis

**Common Denominator**
Cartilage and Bone Destruction
Joint Pains – Which Joint is Bleeding?

- Hemophilic Arthropathy
- Gouty Arthritis
- Rheumatoid Arthritis
- Reactive Arthritis
- Charcot Arthropathy
- Osteoarthritis
Many Structural Abnormalities Can Contribute to Pains

Tendons and Ligaments: Move the joint

Synovial Lining, Vascular Perfusion: Nutrition, Bleeding?

Cushion – Friction Protection – Shock Absorption

Joint Space, Recesses, Fluid

Cartilage and Menisci
Glycosamine-Glycans/Collagen

Fat Pads

Bursae
Pain in Arthropathic Joints Deserves Improved Diagnosis and Management

Is blood present?
Does bleeding contribute to pain?
Which imaging study?
Therapeutic option?

✓ Clinical Exam → unreliable and non-specific
✓ Patient Perception
✓ Imaging
  - X-ray → not sensitive to soft tissue changes, fluid or bleeding
  - CT → contrast and radiation
  - MRI → long exam, costly, difficult distinction bloody vs non-bloody

Musculoskeletal Ultrasound (MSKUS); power Doppler (PD)

Point-of-Care (POC) Ultrasound is Emerging Rapidly in Many Other Disciplines

- Medical students outperformed cardiologists’ and internists’ exams
- Currently introduced into medical education

The NEW ENGLAND JOURNAL of MEDICINE 2014

Point-of-Care Ultrasound in Medical Education — Stop Listening and Look
Scott D. Solomon, M.D., and Fidencio Saldana, M.D.

Technology is evolving fast

MRI (10 tons)

Laptop Ultrasound (10 kg)

Pocket Device
Use of POC Ultrasound – General Principles

- For a well defined purpose
- Question-Driven
- Quick
- Easily recognizable
- Easily learned
- Performed at bedside or in clinic

Example Emergency Medicine
eFAST Trauma Protocol

<table>
<thead>
<tr>
<th>Blood in the Abdomen</th>
<th>Yes/No?</th>
</tr>
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<tbody>
<tr>
<td>Pericardial Tamponade</td>
<td>Yes/No?</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Yes/No?</td>
</tr>
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</table>

Similar Presentation
Different Treatment
### How about MRI?

<table>
<thead>
<tr>
<th>Comparison</th>
<th>MSKUS</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to assessment</strong></td>
<td>Hours</td>
<td>Days</td>
</tr>
<tr>
<td><strong>Speed of examination</strong></td>
<td>10–20 min</td>
<td>1–2 hours</td>
</tr>
<tr>
<td><strong>Contrast, sedation, claustrophobia</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pain with fixed positioning</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Cheap</td>
<td>Expensive</td>
</tr>
<tr>
<td><strong>Reliability of blood detection in the joint</strong></td>
<td><strong>High</strong></td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Operator Dependent</strong></td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td><strong>Deep Joint Structures</strong></td>
<td>No</td>
<td>Yes</td>
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**MSKUS**

**Ideal for joint bleed detection**
Conventional MRI Cannot Reliably Detect Diluted Blood

Experiment:
1) Joint Fluid was admixed with increasing concentrations of blood
2) MRI

Results:
1) T2 relaxation was unable to distinguish different percentages of blood
2) T1 may be able to distinguish between 0 and 100% blood
   Clinically not relevant

Courtesy of EY Chang, MD, Dept of Radiology, MSK Imaging, UCSD
54 year old male with moderate HA and persistent knee pain after fall

**MRI T2 sequences**

Findings:
- Signal Enhancement Suprapatellar Bursa

**Diagnosis: Effusion or Synovitis?**

If Effusion: Bloody vs Non-bloody?

**MSKUS**

Findings:
- Hypoechoic Compressible Fluid

**Diagnosis: Effusion**

 Likely Blood Products

**Chronic Changes**
- Synovial hypertrophy
- Menisceal/Cartilage destruction
- Marrow edema
POC MSKUS: Distinction of Bloody vs Non-bloody Effusion

Both: Compressible with transducer
Bloody: Hypoechoic with displaceable speckles or material
Non-Bloody: Anechoic

* Acute Complex Effusion: Hypoechoic with speckles

* Simple Effusion: Anechoic

* Subacute Complex Effusion: Hypoechoic with “material”

Lateral Recess
Bleeding is associated with vascular remodeling. Important new concept.

Odds of subclinical hemorrhage.

Power Doppler Signal

Power Doppler Live
Detection of vascular abnormalities
Extent of soft tissue inflammation
Case in Point

How does MSKUS assist in bleed detection?

Real world experience
John
Follow Bleed Resolution with MSKUS

**Baseline:**
- *Effusion, small*

**Acute Pain**
- *Large, complex*

**Day 5:** *Subsiding*

**2 Months:** *Small*

**Normal**

Olecranon Posterior

Martinoli C, et al. TH 2013
A case of chronic bloody effusions despite intensified prophylaxis

Visualization of abnormal vascularity with Power Doppler in proliferating tissues

Treatment Options?
A case of recurrent bleeding after liver transplantation

**Case Vignette**

55 yo; h/o severe Hemophilia A
8 years post liver transplant
Normal FVIII levels (80-120%)
Persistent vascular changes

**Synovial Ablation**

- Radio-Synovectomy
- Surgical Synovectomy
- Embolisation

i.a. steroid injections

Intractable elbow bleeds required embolisation

Vessel leakiness contributes to bleeding

*Kidder W, et al. Microcirculation 2016*
Anti-angiogenic effects may be associated with pain relief
3 Cases Illustrating POC MSKUS for Evaluation of Painful Hemophilic Joints
Case 1:
37 yo with severe Hemophilia A (+ inhibitor)
Acute knee pain, swelling, warmth, and perceived joint bleeding

Previously such episodes were treated with several days of bypassing therapy, rest, and ice with gradual pain relief

Bleeding or not?

“not” = Synovitis, Arthritis, +/- Effusion
Abnormal echogenic structure
Not compressible
PD - Hyperemia
PD - Thickened hypervascular synovium

Treatment
Bypassing agent infusion x 1 with simultaneous joint steroid injection provided prompt, long-lasting symptom relief

Case 2: 23 yo with severe Hemophilia B
History of nonadherence and denial
Believes that all his pains are “arthritic”

It’s not arthritis
It’s bleeding

Baseline
Compressible
Complex Effusion

Marked Volume Increase
A. Dors Ped

PD
Absence hyperemias

Treatment
FIX—infusion daily x 3 with reinstitution of prophylaxis
Improved patient adherence

Case 3: 23 year old with severe hemophilia A and autism
Presents with Mom, ankle swelling and suspected inversion injury
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Presents with Mom, ankle swelling and suspected inversion injury

Partial ATFL Sprain
Effusion
Inflammation

Treatment
FVIII infusions, X-rays
Ortho consult
Conservative management

UCSD Case Series
| Muscle and Soft Tissue Bleeding |
| Considerations for evaluation and treatment |

| Site | Are vital structures compromised? i.e. neck: airway compromise |
| Severity | Estimated size upon inspection Hemoglobin drop |
| Imaging Modality | POC MSKUS Discuss imaging with radiologist |
| Complications | Compartment syndrome Pseudotumor |
Quadriceps Bleed

Mild HA (12%), ran into object in garage; MSKUS 2 days later after 2 doses of FVIII

* R Thigh Bleed

L Control

Hematoma Dimensions; 2 planes

Femur
Quadriceps Bleed Cont’d – Time Course

- 7.6 x 3.8 cm, 2 days
- 6.1 x 2.8 cm, 2 weeks
- 3.6 x 1.3 cm, 2 months

- Bleed resolution takes a long time
- Uncertainty regarding frequency and length of factor administration
Iliopsoas Bleed

Long Axis

Moderate Hemophilia A (6%)
Age 25, after vigorous exercise

PD Signal: Neovascularization

* R Iliopsoas Bleed
Skeletal complication: Pseudotumors

Etiology
✓ Non-resolving, organizing hematomas
✓ Intraosseus, cortex, muscle

Symptoms
✓ Persistent pain, palpable tumor, function deficits

Diagnosis
✓ Imaging

Intervention
✓ Surgical

Hematoma with fibrosing tissues

MRI with intraosseous manifestation

Summary

✓ Hemophilia care as a career: A most rewarding decision

✓ Developing MSKUS as an enabling point-of-care tool to diagnose and manage musculoskeletal bleeds: A most rewarding experience

✓ Having spent all day teaching you: A most rewarding use of my time

✓ Most important take home point:
  Bleeding emergencies in hemophilia:
  Don’t think – Apply the 50/100 A/B rule

✓ Career decisions:
  Be passionate
  Monday morning happiness matters
Musculoskeletal Ultrasound in Hemophilia

UCSD CME-Accredited Course
Visit San Diego for 3 Days

Interactive Curriculum
- Lectures
- Hands-on
- Case studies

Registration Link
https://cme.ucsd.edu/muh/

2015/16
≈ 100 Trainees
(10 International)

and/or contact
Marlene Zepeda
mxzepeda@ucsd.edu

"I thought the design of the course was extremely thoughtful, and the coursework was paced perfectly. I was skeptical that I would be able to acquire images, and begin to identify normal anatomy as well as pathologic variants, but the course allowed me to do just...

At the conclusion of this activity, the participants should be able to:
Special Fellowship
Thrombosis/Hemostasis
1-2 year Fellowship
Ask for the curriculum
Contact me
avondrygalski@ucsd.edu

HEMOPHILIA & THROMBOSIS TREATMENT CENTER
AT UC SAN DIEGO HEALTH

FELLOWSHIP RECRUITMENT

The Fellowship at the Hemophilia & Thrombosis Treatment Center at UC San Diego Health (HTTC) is designed to provide a year of specialized training in hemophilia and other bleeding and thrombotic disorders. Eligible candidates have successfully completed Internal Medicine Residency, and are ideally, but not necessarily, enrolled in or have completed a hematology/oncology fellowship program. The objectives of the fellowship are to provide advanced training in the diagnosis and treatment of bleeding and thrombotic disorders including hemophilia, von Willebrand disease, platelet function disorders, rare factor deficiencies, as well as venous and arterial thrombosis. The fellowship provides the opportunity to participate in and develop innovative research ideas in the area of hemostasis and thrombosis.

The HTTC conducts numerous research projects including NIH and Industry-sponsored basic research, Industry-sponsored clinical trials, and HTTC based projects focusing on cardiovascular health, joint health and musculoskeletal ultrasound in hemophilia. HTTC based endeavors of note include a cutting edge CME accredited training course in Musculoskeletal Ultrasound and a therapeutic rock climbing program in conjunction with the HTC in Munich, Germany. The HTTC is part of the American Thrombosis and Hemostasis Network (ATHN) and receives funding from the Centers for Disease Control and Prevention (CDC) to participate in its network of HTCs.

THERE WILL BE AMPLE OPPORTUNITIES TO PARTICIPATE IN AND DEVELOP COMMUNITY OUTREACH AND EDUCATIONAL PROGRAMS TOGETHER WITH THE LOCAL HEMOPHILIA CHAPTER AND PATIENT ADVOCACY GROUPS.

THE FELLOWSHIP IS DIRECTLY MENTORED BY DR. ANNETTE VON DRYGALSKI, THE HTTC MEDICAL DIRECTOR, AND IS SUPPORTED BY AN EXCEPTIONAL MULTI-DISCIPLINARY TEAM DEDICATED TO THE CARE OF PATIENTS WITH

Applicants should send a CV, personal statement, and three letters of recommendation to Dr. Annette von Drygalski at avondrygalski@ucsd.edu of the Hemophilia & Thrombosis Treatment Center at UC San Diego Health or by mail to 9500 Gilman Drive MC0878 San Diego, CA. 92093-0878

For more details about UCSD and the HTC, please visit our website at:
http://health.ucsd.edu/hemophilia
SAN DIEGO IS A SPECIAL PLACE

Work: Bleed or not?

Acknowledgements
Eric Y Chang, M.D
VA San Diego Healthcare System, Radiology Service, San Diego, USA

Entire HTTC Team

Get a tan

Basic Science Research Institute
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