New Imaging Modalities
- Point-of-care Musculoskeletal Ultrasound for Joint Bleed Detection and Evaluation of Hemophilic Arthropathy

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Abbreviations

• POC = Point-of-Care
• MSKUS = Musculoskeletal Ultrasound
POC MSKUS: Ideal to Answer Specific Questions Related to Arthritic Symptoms and Findings

Non-specific Clinical Presentations

- 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 Glycosaminoglycans/Collagen
Fat Pads
Bursae
POC Ultrasound Is Emerging Rapidly in Many Other Disciplines

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

Technology Is Evolving Fast

MRI (10 Tons)  
Laptop Ultrasound (10 kg)
Use of POC Ultrasound – General Principles

• For a well-defined purpose
• Question-driven
• Quick
• Findings are easy to recognize
• 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>
</thead>
<tbody>
<tr>
<td>Pericardial Tamponade</td>
<td>Yes/No?</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Yes/No?</td>
</tr>
</tbody>
</table>

Similar Presentation
Different Treatment
POC MSKUS – Hemophilia

• Etiology of acute and chronic joint pains
  Effusion: Yes-No
  Hemarthrosis: Yes-No
  Hypervascularity: Yes-No
  Tendon Sprain: Yes-No
  … etc.

• Precision to guide intraarticular needle placement
  – Aspiration
  – Injections (such as corticosteroids)

• Long-term follow-up of joint findings

Images provided by Annette von Drygalski.
POC MSKUS—Hemophilia

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Images provided by Annette von Drygalski.
Inaccurate Diagnosis of Joint Bleeds Results in Suboptimal Treatment

- Patient and physician perceived pain etiology correct in only ~1/3rd of painful episodes
- Symptoms and findings were similar whether there was bleeding or not and did not permit the distinction
- Factor activity levels at the time of MSKUS demonstrated substantial over- or under-treatment
- Many other conditions present
  - Synovitis
  - Fat pad fat inflammation
  - Tendinosis/Tendinitis
  - Bursitis
  - Sprains
- Probably contributed to pain
- Were treatable

Pain in Arthropathic Joints Deserves Improved Diagnosis and Management

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

**Clinical Exam**
Patient Perception

Unreliable and Non-specific


**Imaging**

- **X-ray** → Not sensitive to soft tissue changes, fluid or bleeding
- **CT** → Contrast and radiation
- **MRI** → Long exam, inconvenient, costly


**Difficult distinction bloody vs. non-bloody effusions**

**MSKUS AND POWER DOPPLER**
# Focus in Hemophilia: POC Imaging

Presence of Effusions, Bleeding and Inflammation

54-year-old male with hemophilic arthropathy and knee pain after fall

<table>
<thead>
<tr>
<th>MRI T2 Sequences</th>
<th>MSKUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Findings:</strong> Signal Enhancement Suprapatellar Bursa</td>
<td><strong>Findings:</strong> Hypoechoic Compressible Fluid</td>
</tr>
<tr>
<td><strong>Diagnosis:</strong> Effusion or Synovitis?</td>
<td><strong>Diagnosis:</strong> Effusion</td>
</tr>
<tr>
<td><strong>If Effusion:</strong> Bloody vs Non-bloody?</td>
<td>Likely Blood Products</td>
</tr>
</tbody>
</table>

**Chronic Changes**
- Synovial hypertrophy
- Meniscal/Cartilage destruction
- Marrow edema
Conventional MRI Cannot Reliably Detect Diluted Blood

Experiment:
- Joint Fluid was admixed with increasing concentrations of blood
- MRI

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

Images: courtesy of Eric Y Chang, MD, Dept of Radiology, MSK Imaging, UCSD. Nguyen S et al., ISTH 2017
MSKUS: Time Course of Blood Appearance in Syringe

Anticoagulated (heparin)

Post draw 30 Min

Red blood cells swirling

3 Days

Without anticoagulant

Clots Different Echogenicities

Plasma expressed from the clot

1 Week

Images provided by Annette von Drygalski.
Nguyen S et al. ISTH 2017
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
Power Doppler: Extent of Abnormal Intra-articular Vascularity Indicating Inflammation and Vascular Remodeling

Severe Hemophilia B, 36 ys, s/p TKR 2 Years Earlier

Severe Hemophilia A, 53 ys, 2 Weeks Post Ankle Bleed

Severe Hemophilia A, 25 ys, Target Joint, Subclinical Bleeding

Lateral Recess
KNEE
Subtalar Joint
ANKLE
Olecranon Fossa
ELBOW
POC Musculoskeletal Ultrasound (MSKUS) – Hemophilia

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- Long-term follow-up of joint findings

Images provided by Annette von Drygalski.
POC MSKUS Is Helpful to Guide Treatment Decisions

Directed therapy improved symptoms in many patients
- Clotting Factor Adjustment
- Physical Therapy
- Anti-Inflammatory Agents
- **Intraarticular Injections**


MSKUS-guided Intraarticular Needle Placement

1. Safe, atraumatic, tissue visualization
2. Permits access to tight joint spaces underneath the capsule
3. PD for vessel localization

Images provided by Annette von Drygalski
Painful hemophilic joints: Efficacy of intra-articular MSKUS-guided corticosteroid injections

**Extent of pain relief**

![Graph showing joint pain relief before and after injections.]

**Duration of pain relief**

![Bar chart showing duration of pain relief for 12 weeks after injection.]

**Reduction of vascularity**

- Infrapatellar Knee
- Olecranon Elbow

![Images of ultrasound-guided injections at infrapatellar and olecranon sites.]

4 Cases Illustrating POC MSKUS for Evaluation of Painful Hemophilic Joints
CASE 1
37-Year-Old with Severe Hemophilia A (+ Inhibitor)

Presents with acute pain, swelling and perceived knee bleeding

Bleeding or not?
“not”= Synovitis, Arthritis, +/- Effusion

Prior to POC MSKUS use in clinic
Several days of FVIIa-based bypassing
Rest/Ice
Hope for pain relief
CASE 1 (cont.)
37 Year Old with Severe Hemophilia A (+ Inhibitor)

It’s not bleeding, It’s synovitis

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-Year-Old with Severe Hemophilia B: Poor Adherence to Prophylaxis

Presents with acute pain, NO swelling. Perceived arthritic pain

Baseline

Marked Volume Increase

Compressible Complex Effusion

Dorsalis Pedis Artery

Absence of hyperemia

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

CASE 3
55-Year-Old with H/O Severe Hemophilia A, Intractable Bleeding

Presents with acute pain and unstoppable bleeding despite normal FVIII levels 8 years post liver transplantation

Persistent vascular changes and leaky vessels

Treatment: Synovial Embolisation

Before Embolisation

Immediately After

Power Doppler
F/U 2 years later

CASE 4
23-Year-Old with Severe Hemophilia A and Autism

Presents with Mom, ankle swelling and suspected inversion injury

Effusion

Fibula Malleolous

Talus

ATFL Partially Torn

Inversion

Tear
CASE 4
23-Year-Old with Severe Hemophilia A and Autism

Presents with Mom, ankle swelling and suspected inversion injury

Fibula Malleolous
ATFL Partially Torn

Effusion
Talus

Positive PD Signal

Partial ATFL Sprain
Effusion
Inflammation

Treatment
FVIII infusions, X-rays
Ortho consult
Conservative management
Fly Into the Future: Pocket Tele-Ultrasound

One Simple Question: Bleeding or Not?

Patient-Performed ➔ Home, Office, School
Allied Health Professional-Performed ➔ Centers or Remote Clinics
Comparison with Conventional Ultrasound Demonstrates that Pocket Device Can Detect Effusions

Zhou J, et al. ASH 2016 and ISTH 2017
POC Musculoskeletal Ultrasound (MSKUS) – Hemophilia

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• Long-term follow-up of joint findings

Images provided by Annette von Drygalski.
Long-Term Evaluation of Joint Status

Clinical Hemophilia Joint Health Score (0-20)

X-ray (Pettersson Score 0-13)

MRI (IPSG Score 0-17)

Musculoskeletal Ultrasound – Scoring Algorithms
Martinoli C, et al. *TH* 2013

Semi-Quantitative
Cartilage Integrity
Soft Tissue Expansion

J A D E = Joint Activity and Damage Exam

**Objective**

- Quantitative approach
- Capture dynamic tissue changes
- Recognized to contribute to hemophilic arthropathy
OMERACT
• International initiative in Rheumatology
• Standardizes imaging
• Provides clear guidelines for validation

Devise Concept for an Imaging Algorithm and Protocol
• 30 Patients → 180 Joints → 2 Year Follow Up → 600 MSKUS Examinations ≈ 6000 Image Views

Corner Stones of Validation
• Reliability of pathology recognition and discrimination
  → comparative analyses between imaging modalities
• Development of tissue quantification methods
  → inter-reader and intra-reader reliability
  → validate applicability in a clinical cohort

**Method:** Compare MRI and MSKUS findings

**MRI Sequences:** Conventional, UTE, Subtraction Images

**Soft Tissue Structures:** Determine to what extent MSKUS can discriminate between pathological soft tissues

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**Intra-capsular Fat**
- Extra-synovial fat pads
  - Prefemoral
  - Suprapatellar
  - Infrapatellar

**Synovial Tissue**
- With or without proliferation
- With or without fatty metaplasia
Result Example: Suprapatellar Bursa
High Spatial Resolution, Poor Tissue Discrimination

Coagulated Blood

Synovial Proliferation, No Hemosiderin

Hemosiderin-laden Synovium

Hemosiderin-laden Fat and Trace Fluid

JADE: Synovial Evaluation and Measurements: MSKUS – MRI

Conventional MRI
- Hemosiderin artefacts concealing synovium
- “Zero signal” and “black out”

UTE MRI
- 3-dimensional volume

MSKUS
- High spatial resolution
- 2-dimensional measurements
**JADE: Osteochondral Evaluation and Measurement: MSKUS – MRI**


<table>
<thead>
<tr>
<th>MSKUS</th>
<th>MRI: Conventional</th>
<th>UTE</th>
</tr>
</thead>
</table>

Recognition of a wide spectrum of osteochondral abnormalities: Cartilage wear, erosions and osteophytes

**MSKUS**

**MRI**

**UTE**
Validation Cont’d
Inter- and Intra-Reader Reliability

8 MSKUS experienced hemophilia providers (repeat readings after 1 month)
23 inexperienced hemophilia providers
Reading 45 knee images → tissue recognition and measurements
Adjudicator MSK radiologist

Results:
1. Landmark recognition nearly 100% for all providers
2. Intra-Class Correlation Coefficient and Fleiss’Kappa: Excellent
3. Measurements of structures feasible to as little a 1/10th mm (at 12 mHz axial res ~0.06 mm)

<table>
<thead>
<tr>
<th>Measurement (Knee)</th>
<th>EXPERIENCED PROVIDERS</th>
<th>Inexperienced PROVIDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inter-Rater Reliability First Assessment</td>
<td>Inter-Rater Reliability Second Assessment</td>
</tr>
<tr>
<td>Cartilage Thickness Point 1</td>
<td>0.79</td>
<td>0.84</td>
</tr>
<tr>
<td>Cartilage Thickness Point 2</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>Osteochondral Interface</td>
<td>0.70</td>
<td>0.83</td>
</tr>
<tr>
<td>Soft Tissue Expansion</td>
<td>0.89</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fleiss’ Kappa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power Doppler</td>
<td>0.91</td>
<td>0.94</td>
</tr>
<tr>
<td>Anechoic vs. Mixed Echogenicity</td>
<td>0.88</td>
<td>0.90</td>
</tr>
<tr>
<td>Simple vs. Complex Effusion</td>
<td>0.88</td>
<td>0.90</td>
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Volland L, et al. ISTH 2017
Summary

MSKUS

- Is valuable for POC assessment of joint bleeding and other musculoskeletal abnormalities
- Improves diagnostic accuracy of musculoskeletal conditions
- Enables convenient POC imaging in clinic
- Empowers patients to participate in their care
- Enables personalized management of hemophilic joints
- Deserves continued development and validation
COLLABORATORS

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Eric Y Chang, MD
VA San Diego Healthcare System Radiology Service, San Diego

Randy E Moore, DC RDMS RMSK
General Musculoskeletal Imaging Inc. Cincinnati, OH

Lena Volland, DPT – San Diego
Accredited Training Opportunities

General MSKUS Courses
such as Gulfcoast Ultrasound Institute, FL
https://www gcus com

Online MSKUS Modules
such as by the European League against Rheumatism
http://www eular org/edu_ online_course_msus cfm

Hemophilia-Specific MSKUS Courses at UCSD
“MSKUS in Hemophilia” or Joint Injection/Aspiration Class
https://cme ucsd edu/muh/

Hemophilia-Specific Online MSKUS Modules
https://cme ucsd edu/muh/
Musculoskeletal Ultrasound in Hemophilia

UCSD
CME-Accredited Course
Visit San Diego

Interactive Curriculum
- Lectures
- Hands-on
- Case studies

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

and/or contact:
Marlene Zepeda
mxzepeda@ucsd.edu

2015/16/17
≈ 150 Trainees (15 International)
Weekly MSKUS Rounds! Join Us!

For Everyone
Each Tuesday 7.30 am PST

Staged by
UCSD – BloodWorks Northwest - Indiana HTC

Web Based – Share your Desktop and Case