Rationale for Fistula Maturation Study

- Dialysis Access Consortium AVF study
- 60% of new AVFs were unusable for dialysis at 4-5 months post surgery
- No predictors to identify which AVF is likely to succeed or fail

What is the Hemodialysis Fistula Maturation Study?

Prospective multi-center observational cohort study which aims to identify clinical and biological factors predictive of AVF maturation failure

Factors Contributing to AVF Maturation Failure

- Vascular Anatomy and Blood Flow (US)
- Vascular Biology (VFT/Histology/Blood)
- Clinical Patient-Level Attributes
- Processes of Care (Sx; procedures)

Study Objectives

- To improve prediction of AVF clinical maturation (usability)
  - Relationship of clinical usability and anatomy, biology, clinical attributes, and processes of care
- To explore mechanisms of AVF maturation failure
  - Relationship of fistula outcomes and anatomy, biology, clinical attributes, and processes of care

Study Strategy

- Observational study
- To observe while minimally interfering with routine clinical care

Watch rather than Intervene...
Study Design

- Multi-center prospective cohort study of approximately 600 patients undergoing AVF creation
- 7 HFMC clinical centers
  - Boston University
  - University of Cincinnati
  - University of Florida at Gainesville
  - University of Texas Southwestern
  - University of Utah
  - University of Washington
  - University of Alabama

HFMC Cores

- Ultrasound Core
  Michelle Robbin – U. Alabama
- Vascular Function Core
  Joseph Vita – Boston U. Medical Center
- Histology Core
  Charles Alpers – U. Washington

Study Population

- Adults with or nearing end-stage kidney disease
- Placement of a native arteriovenous fistula (i.e., no implanted synthetic graft material)
- 2 stage transpositions excluded

Major Categories of Clinical Outcomes

- Fistula Use
  - Unassisted Clinical Maturation (Primary)
  - Assisted Clinical Maturation
  - Time to Onset of Clinical Maturation
- Fistula Durability (primary & cumulative)
- Fistula Events
  - Thrombosis, Steal, & Pseudoaneurysm

Unassisted Clinical AVF Maturation Criteria

Use of the fistula with two needles for 75% of dialysis sessions within a 4-week period
And either:
A. Four consecutive sessions in which the dialysis machine blood pump speed is ≥300 ml/minute\(^1\).
OR
B. A measured spKt/V of ≥1.4\(^2\).

Vascular Biology

- Flow-mediated dilation (FMD)
  - tests endothelial function
- Pulse wave velocity
  - tests arterial compliance (e.g. medial calcification)
- Venous occlusion plethysmography
  - tests venous compliance (particularly important for AVF)
Can pre-surgery vascular function tests predict AVF maturation?

- Flow mediated dilation
- Marker of NO mediated endothelial function
- Vascular dilation
- Inhibits neointimal hyperplasia
- Blocks thrombosis

Flow mediated dilation in uremia

- FMD results in 450 patients
- Median = 3.95% (1.13-7.52); Normal = 6-8%
- Mean for diabetics = -2.0% (p<0.0001)
- Mean for patients on HD vs CKD = + 1.10% (p=0.03)

Are patients with decreased FMD at greater risk of AVF maturation failure?

Does pre-existing venous neointimal hyperplasia at surgery predict AVF maturation?

- Almost 60% of 400+ patients had > 20% stenosis as a result of pre-existing NH likely secondary to uremia, oxidative stress and inflammation

Blood Specimens

- WBC, plasma and serum samples pre-operative and 2-wk post-operative
- Stored at NIH repository
- Examples of assays
  - Cytokines
  - Oxidative stress markers
  - Genetic polymorphisms

Vascular Anatomy and Blood Flow (Slope of Flow and Diameter)

- Pre-op
- 2 day
- 2 weeks
- 6 weeks
- Around intervention or cannulation
What about Future Novel Therapies

- Identification of important biological pathways that could result in therapies that target the actual mechanisms involved in AVF maturation failure rather than the shot in the dark approach that we currently use.

Prediction and Stratification

- Get away from the “one size fits all” paradigm.

Individualize Vascular Access Care

- Stratify patients based on clinical and biological predictors identified in the HFM study.
- Offer them the dialysis access that is best suited for them.

Individualize Vascular Access Care based on HFM predictors

- 75 yr old with no negative HFM predictors needs an AVF + standard FU.
- 75 yr old with mildly negative HFM predictors needs an AVF + aggressive FU (endovascular/surgical intervention).
- 75 yr old with a TDC and moderately negative HFM predictors needs an AVG.
- 75 yr old with a TDC and moderately negative HFM predictors needs an AVF + novel therapy to promote maturation.
- 75 yr old severely negative HFM predictors needs a TDC.

Individualize Vascular Therapy

- Technology can Change Existing Clinical Paradigms!!

  - Catheter without infection, thrombosis or central stenosis.
  - *from* Fistula First to Catheter First and Last!!
Rationale for Fistula Maturation Study

- 877 AVFs randomized to Plavix or placebo x 6 wks (DAC AVF study)
- 6 week thrombosis rate decreased from 19% to 12%*
- No difference in suitability for dialysis between month 4-5 after surgery (only 40%!!!)

Intra-operative Venous Tissue Collection

- 5-mm + venous segment at anastomosis during AVF creation surgery
- Ship to Univ. of Washington Core Lab
- Tissue analyses
  - Histology
  - Morphometry (intima and media)
  - Immunohistochemistry and Gene expression
    - Proliferating cells + pro-inflammatory cells
    - Pathways of maturation failure and stenosis (e.g., MMP, oxidative stress + cytokines, growth factors)