13TH INTERNATIONAL HHT SCIENTIFIC CONFERENCE
SAN JUAN PUERTO RICO

Clinical Summary

Weiss: "Translational Science Happening Before our Eyes"

SESSION 1

- Liver Imaging – Ohlinger
  - 1. Detect and characterize vascular lesions
  - 2. Identify complications such as cholangitis and chronic liver injury
  - 3. Help distinguish between types of liver masses, such as focal nodular hyperplasia, nodular regenerative hyperplasia and other AVMs
  - 4. Phase contrast flow MRI and 4D flow are newer tools that may be useful in monitoring response to therapy.

  - Take home: Liver MR could be a new direction in the assessment of HAVM flow pre and post administration of antiangiogenics because it is reproducable. And, by looking at the size of the shunts, perhaps we can glean information about who will and won't respond to avastin.

SESSION 1: DIAGNOSIS OF HHT

- Hepatic Encephalopathy may occur
  - Check ammonia levels
- Subaortic Membranes may occur
  - Turbulent flow, high output failure, poor prognosis
- MR vs CT to detect pavm
  - MR missed only 16%....but only 2% of the “big” ones
- Echo technique” greyscale” may be better than counting bubbles

COUNTING BUBBLES IS PAINFUL

SESSION 3: SYSTEMIC TX OF HHT

- Systemic treatments for HHT epistaxis/anemia - Gossage
  - good nasal hygiene
  - iron
  - laser and/or sclerotherapy
  - doxycycline
  - tranexamic acid
  - Bevacizumab/pazopanib
  - …and thalidomide as a last resort

  - We seem to be on the same page but the order of use is all over the map!!

SYSTEMIC TX

- Iyer from Mayo and Dr. Vasquez from Dr. Serra's group in Buenos Aires: Avastin experience with HHTRB: One dose does not fit all. Significant variability between pts in need for maintenance and we need to personalize our approach to each pt.
- Kroon from St. Antonius noted the in itraconazole (anti VEGF is effective at reducing ESS, but it did not affect Hgb
- Keith McCrae: **Pomalidomide trial (PATH)**…the first ever NIH sponsored clinical trial in HHT patients!!

SESSION 5: LOCAL TREATMENT OF HHT (PAVMS)

- McWilliams tackled tough questions with near meta-analysis rigor.
  - Can we ignore small shunting on contrast echo….? Most likely, yes
  - Should we treat small avms…? Probably, but weak evidence
  - Should we treat PAVMs in pregnant women….? Most likely, yes.
  - Should we treat PAVMs in children…Depends on who you ask…wait for it…
- Cusumano discussed the challenges of re-treating re-canalized PAVMs. Distal occlusion is better for longer occlusion, but it is damn hard
- Schneider prospectively assessed cerebral complications of PAVM embolization in 94 pts with 259 PAVMs using pre and post MRI.
  - Only 1 patient had evidence of clinically silent emboli on MR (not even sure if it was periprocedural)…so procedure is safe.

SESSION 5: LOCAL TREATMENT OF HHT (EPISTAXIS)

- Topical:
  - Tacrolimus ointment study: Dr. Hermann from Lyon presented a prospective placebo trial bid x 6 weeks: Mild significant reduction in epistaxis duration
  - Etamsylate (Botella) spray: platelet aggregation and inhibits VEGF: reduces bleeding
- Surgical:
  - Laser (Ataya) is effective
  - Sclerotherapy (Marcos) 38 pts with epistaxis, it improves QOL and ESS scores…and it can be repeated without apparent long term sequelae

WORKSHOP 1: MECHANISM BASED THERAPEUTICS

- Ligand based therapies BMP9 and BMP10 are promising and on the horizon
  - PAH treatment
  - Calcification, cardiac and hepatotoxicity may be side effects

- Tranexamic acid was discussed, with no clear answers for how to navigate complex clinical scenarios in which bleeding and clotting are in direct conflict.

KEYNOTE

- Many thanks to Dr Andrei Kindzelski, MD, PhD, NIH
- Chernobyl (!)
- No magic bullet to get funding
- BIOLINCC An underutilized tissue repository
- Cover letter advice


Feb. 7, 1987

Dear Sir

My friend and I are very interested in space travel and have a great idea for a rocket ship. We were wondering if we could have a little sum of money ($10.00 maybe) to fulfill our project. We would most greatfull if you would send it to us.

Sincerly
Terance Baylor

$10.00

SESSION 8: EMERGING ISSUES IN HHT

- Clancy: HHT Tracker App – patient and research tool
- Raj: HHT Specific QOL: tool ready to be deployed in studies
- Meir: Topical propranolol gel has a antiangiogenic effect in his prospective trial…it works…No bradycardia
- Hammill: SMAD4 → Loeys Dietz/JPS/HHT and **aortopathy**—screen q 2 years
- Schlacter (Yale): 176 pts pediatric pts: > 93% O2 sat→ no signif adverse events
- Juszczak: Nasal splints are well tolerated and pts think they work

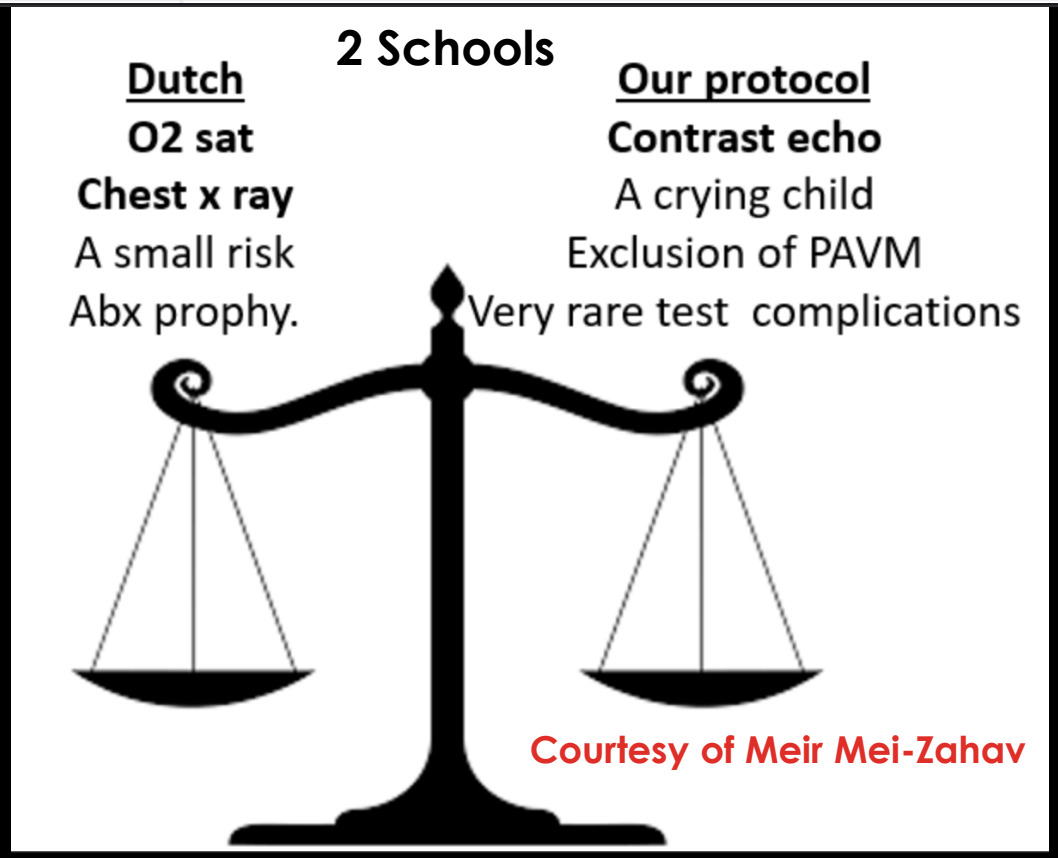
WORKSHOP ON PEDIATRIC PAVMS

Current Guidelines:

The expert panel recommends that clinicians screen all patients with possible or confirmed HHT for PAVMs. Although less evidence exists in children, the expert panel included children in the screening recommendation	•Level of evidence: III •Strength of recommendation: strong •Agreement: 96%

93% cutoff – Yale
SAE in kids are rare in kids with asymptomatic (small) PAVMs
Who gets abx?
What age to screen? 13-16?
PAVMs grow in kids 10%/yr
How *often* to screen?
Thrombotic risk is low in kids

Remaining questions:
What causes ped PAVMs to recur?
What is the effect of long term hypoxia on the brain?



WORKSHOP ON EPISTAXIS

- Lots of options with extensive variability in practice
- Local tx: Tacro, propranolol
- Systemic tx: Avastin/Paz
- Surgical management:
- Sclerotherapy: Seems to be safe, yes, the blindness case was brought up, but it seems to be effective, office based, reproducible.
- Coblation also discussed. Splints anyone?

- What is the role of allergic rhinitis on mucosal injury: steroids work!

Picarillo and Geisthoff

GENOTYPE/PHENOTYPE CORRELATION: SESSION 11

- Denise Adams: Discussion of the scope of vascular anomalies. Goal is to reduce but seldom cure the anomaly and precision medicine targeted therapy will be the future.
- Jamie McDonald: HHT and overlap of phenotype with capillary malformation type 2 (CM-AVM2) mutation: epistaxis 79% in CM-AVM2. Look for innumerable telangiectasias and capillary malformations. Test for EPHB4!
- Al Samkari is leading INHIBIT Studies along with Vivek: Lots of variation among providers using Avastin for HOCF. Most get it authorized by insurance, induction is similar, but maintenance dose is variable

BRAIN AVMS: SESSION 12

- Majority of Sporadic AVMs are caused by KRAS mutation
  - Low risk features brain AVMs (unruptured) = 1%/yr (similar to HHT)
  - Flow is important to AVM growth and we 4D, iflow (angio) detect smaller lesions and measure flow

TAKE HOME POINTS

- Diagnosis: MRI liver, brain (noncon), cardiac echo, chest MRI
- Systemic Tx:
  - Avastin: 3 studies:
    - Meir 11 pts with HOCF
    - Serra: 7 pts with HOCF
    - Serra: 16 pts with bleeding
    - Iyer: 56 pts with HHT bleeding
  - Pomalidomide:
  - Propranol: 141 patients
  - Nintedanib: prospective study in France plannning
  - Octreotide
  - Doxycycline
  - Pazopanib
- Local Tx:
  - Propranolol:
  - Tacrolimus
  - Etamsylate spray
  - Avastin injections: 40 pts
  - Sclero therapy: STS foam
  - Timolol spray

<u>Avastin</u>

- 18 pts HOCF
- 72 pts with HHT related bleeding

<u>Doxycycline</u> trial results pending

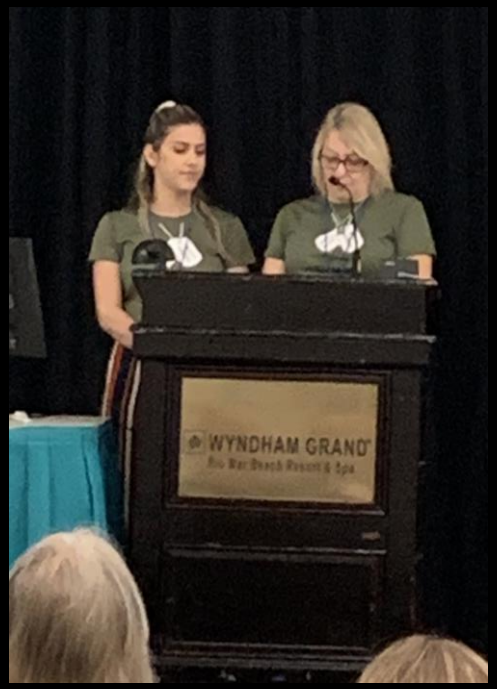
<u>PATH trial starting</u>

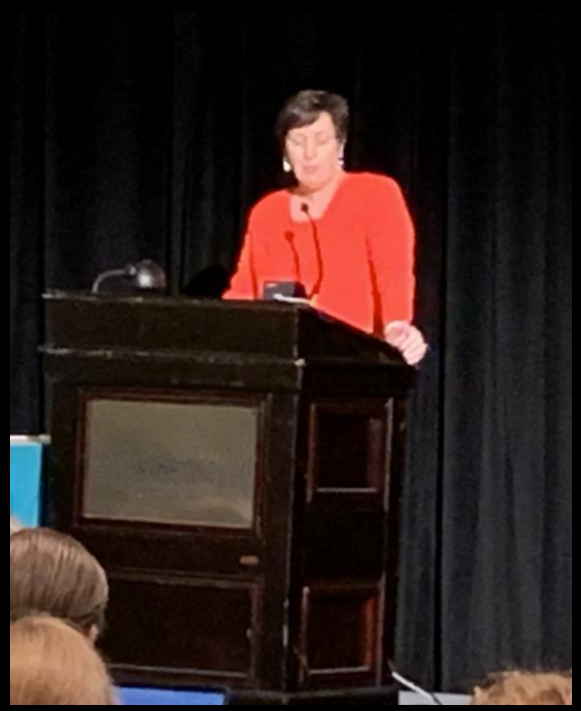
<u>Propranolol gel:</u> 10 pts

Data on sclero is good tool possibly not utilized enough

WE APPRECIATE THE FAMILIES

- Alicia and Christina Violante and the rest of Matty's Soldiers
- Chandra McMahon
- Anthony Anzell
- Nicholas Masters





GRACIAS A PUERTO RICO PARA TODO!!!

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