Highlights from the Tenth Cooley's Anemia Symposium Chicago, Illinois October, 2015

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Neufeld Disclosures

- Consultancy
  - ApoPharma, BluebirdBio, Novartis
- Research Funding
  - Celgene, Novartis
- Data/Safety Monitoring Board
  - Acceleron

Areas of progress

- Basic Science
  - Regulation of globin genes
  - Regulation of iron metabolism (and hepcidins)
  - Targets and mechanisms for novel drugs
- Clinical science
  - MRI methods for iron
  - Gene Therapy – many new ideas and much progress
  - Trials of novel agents
- Clinical thalassemia
  - Transfusion Practice
  - Iron chelators and monitoring iron status
  - Complications and management
  - Non-Transfusion Dependent Thal

Progress since Ninth Cooley's/NYAS symposium, 2009

	2009	2016
Chelators	Exjade launch was 2006; Deferiprone only on compassionate basis. Combinations under study	Exjade firmly established Jadenu recently launched Deferiprone launch 2012 Combinations common
MRI	Most sites had started using; not much long-term data	Broad use has revolutionized care
Gene therapy and gene editing	Discussion of the first Bluebird patient; all else theoretical	Bluebird data much more advanced, BCL11a approaches discussed;gene editing advancing
Novel approaches (e.g. hepcidins, TMPRS6, luspatercept)	Theoretical or not even contemplated	Promising clinical trials or upcoming trials
Other key issues Pain, thrombosis, bone health, nutrition, adherence	All known to be extremely important	Incremental progress in all areas

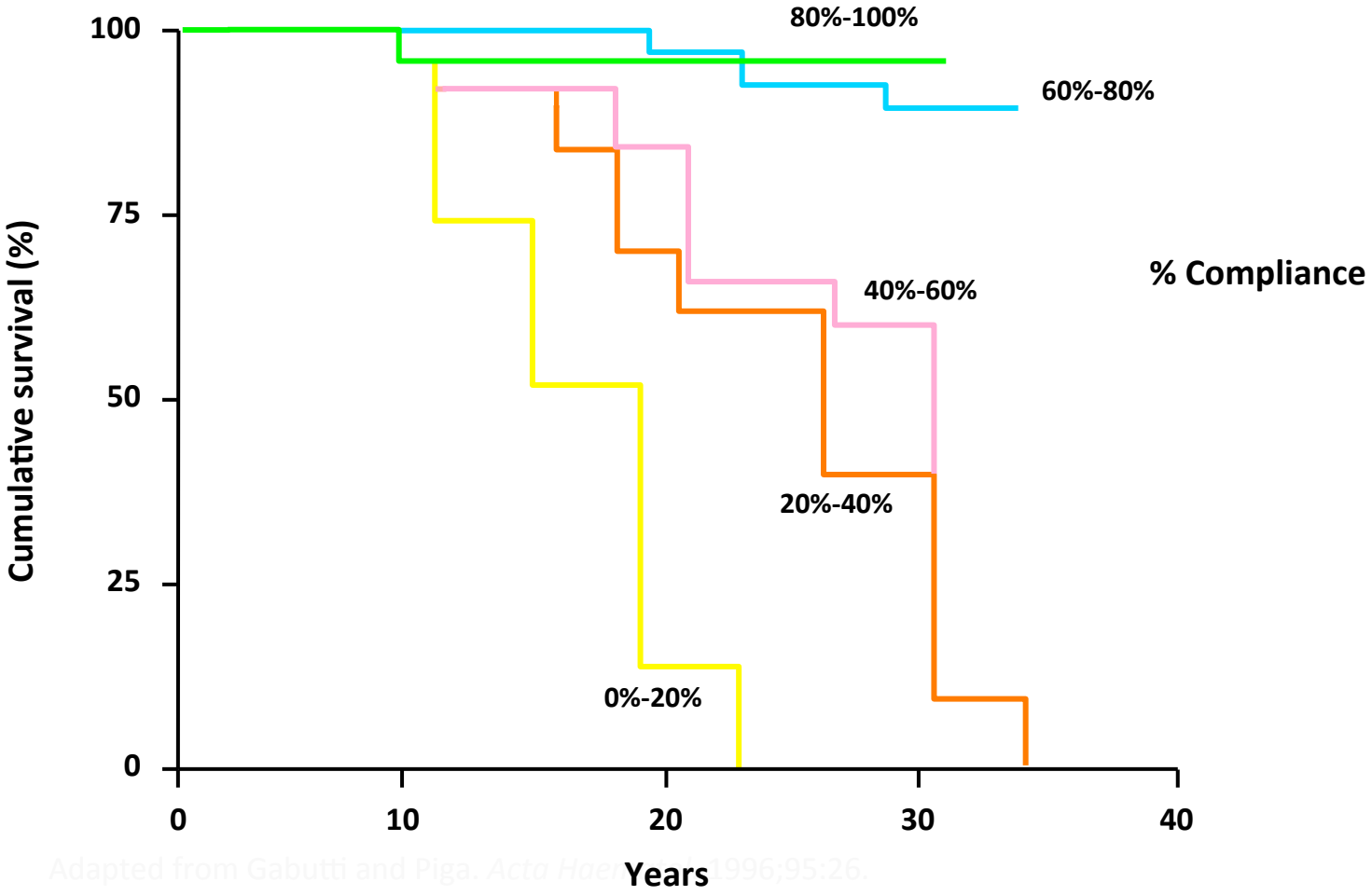
Basic Science

- *Ineffective erythropoiesis*
  - Red cell precursors die in the marrow before they fully develop into circulating blood cells.
  - Marrow works overtime, leading to bone disease.
- Clinical success of the Acceleron/Cellgene agents has changed how we think about the mechanism
  - The mouse equivalent of luspatercept rescues mouse erythroblasts in thalassemia.
  - A variety of proteins and genes not previously considered in thalassemia seem to be major players
  - Possible focus for new agents ,especially in thalassemia intermedia

Clinical Focus on Adherence

- There are many barriers to taking treatments as prescribed
- For Deferasirox (Exjade, Jadenu), missing around 10% of doses (3 a month!) makes treatment less effective
- For Deferoxamine, especially before the oral drugs were available, this was a particularly awful problem

Survival Benefit of Deferoxamine Is Highly Dependent on Compliance



Adapted from Gabutti and Piga. *Acta Haematol* 1996;95:26.

From Torino 1965-1997

Barriers, Facilitators and Interventions: Creating a Supportive Environment for Adherence to Treatment

- Goals of presentation: Present qualitative data from CAF research that has informs interventions with patients

- Describe evidenced based interventions to increase Adherence/QOL
  - Cognitive Behavior Therapy
  - Dialectical Behavior Therapy
  - Motivational Interviewing

- Discuss the use of mindfulness, problem solving, distress tolerance and patient responsibility for care

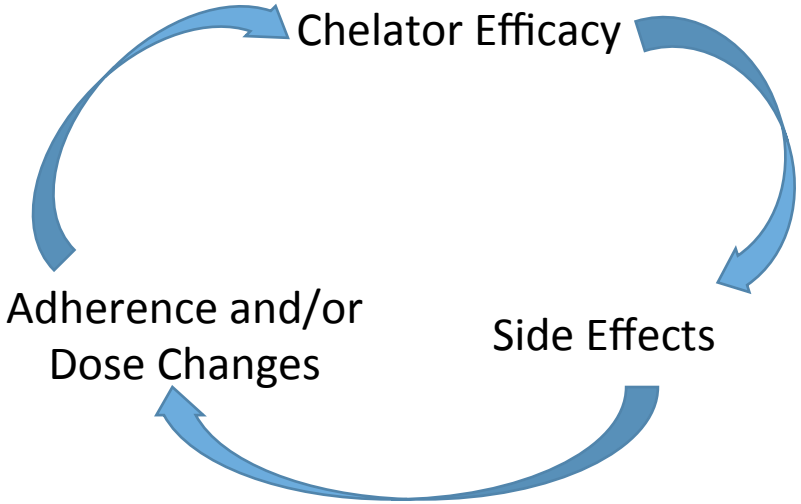
- Discuss how this can generate future research ideas in adherence

Clinical focus on targets for iron levels – benefits of aiming low

- Dr. Coates reviewed the rationale for aiming for more normal ferritin and tissue iron (liver, heart, pancreas, etc) than has been traditional
- As we get better at monitoring by MRI and chelator choices expand, aiming lower may get more practical.
- A healthy debate ensued, but there is ample ground for agreement.

Clinical focus on safety, efficacy and side effects of chelators

- Chelators suffer from narrow gap between doses high enough to work and not so high to be toxic
- "Therapeutic Window" or "therapeutic index"



This loop can be
Bad (viscous cycle) *or*
*Good (*positive feedback)

Maximum Tolerated Dose
(per patient or population)

vs.

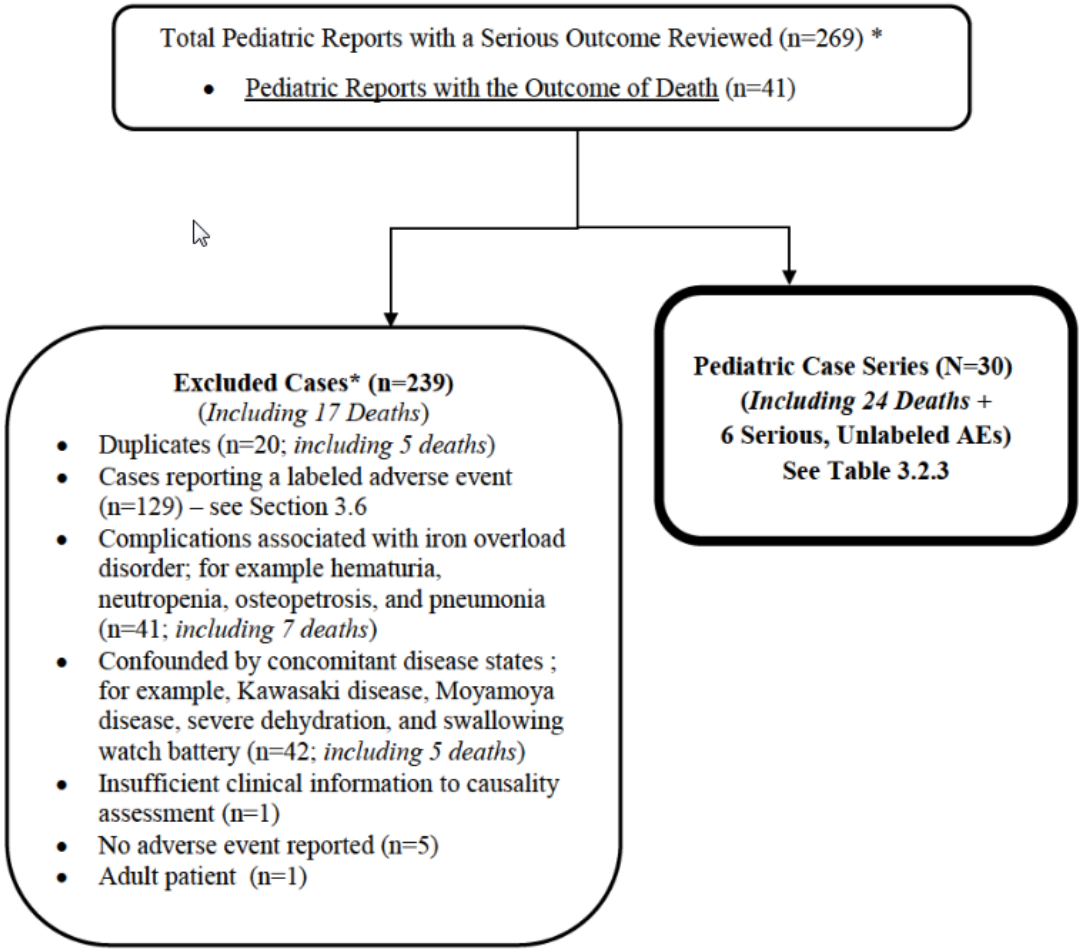
Dose Limiting Toxicity
(per population or patient)

vs.

Non-dose-related or
idiosyncratic side effects

FDA Adverse Events Reporting System (FAERS) Exjade® pediatric SAE review

- Of 239 reports over two year period, 54% (n=129) were excluded because they covered label adverse events (including 17 deaths)
- "complications associated with Iron overload" excluded (n=41) [neutropenia + pneumonia?)
- Of the 30 cases studied, there were 24 deaths and only 6 serious *non-label* AE.
- Review of the 30 cases yielded few conclusions
  - Few if any autopsies.
  - Cases short on details.
  - Causal links difficult to assess
- (Adult events, and especially adult deaths markedly outnumber pediatric events, but the details weren't reviewed). 13-fold more deaths in undefined total population.



http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM461193.pdf

Summary of Lessons from FDA Exjade Review

- Process exposes reporting problems not unique to Exjade or chelators
  - Physicians under-report
  - Serious examples of known toxicities are not reported
  - Even if serious known toxicities ARE reported, regulator might set aside
  - Details of cases are usually lacking
    - No autopsies in fatal cases
    - Rare details to support regulatory conclusions
  - FDA can't go back and ask for more information; they welcome but rarely get supplemental reports (manufacturers can ask for more details)
- Thalassemia is the third most common US indication for deferasirox
- Label is silent on what to do with deferasirox in febrile illness

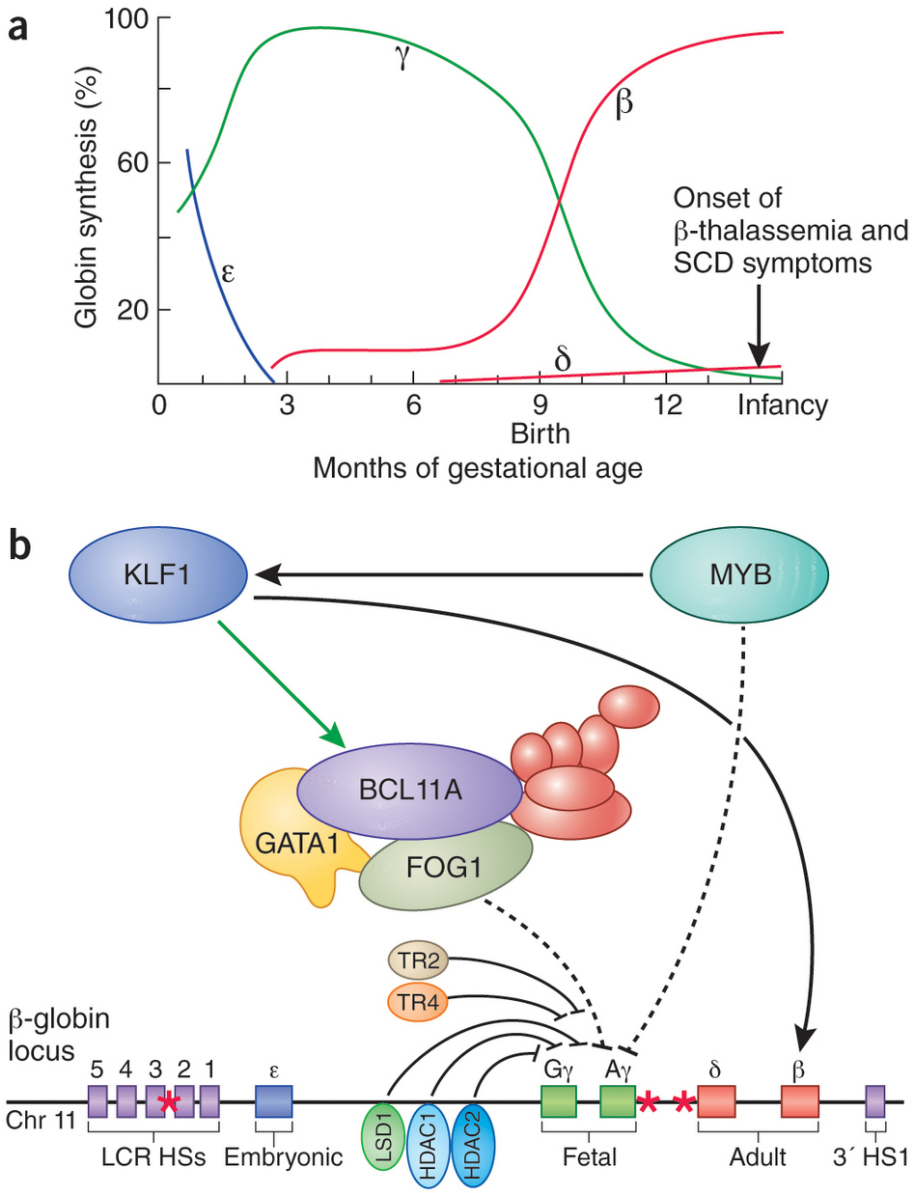
How do basic science discoveries spill over to clinical care?

- "Translation" of science into practice
  - Two way street
  - PATIENT discoveries and samples to the LABORATORY
  - LABORATORY discoveries to new drugs to clinical trials.

- Clinical trial phase 1,2,3 (and later phase 4)
- "Breakthrough" drugs or drugs for rare diseases may get by without a full phase 3 study.
  - Not enough patients to randomize
  - Phase 2 trial may be very clear.

BCL11A as a critical target

- In normal development, BCL11A binds to, and shuts off gamma globin (fetal Hb) after birth.
- Strategies to get rid of BCL11A expression can turn on fetal hemoglobin
- Efficient means of “undoing” beta thalassemias



Luspatercept (ACE536)

- Very promising results from phase 2 trials
- Reduction in transfusion burden and improvements in iron status
- Dr. Coates will discuss

Gene therapy trials

- Bluebird Lentiglobin

- Upcoming
  - Sangamo trial of BCL 11a inhibition
  - Other groups with fetal or beta globin gene therapy
    - San Raffaelle, Milan, Italy
    - Memorial Sloan Kettering, NY

- Patient Interview
  - College student who chose gene therapy at age 18
  - Insights about decision making
  - Requirement for stem cell transplant
    - Patient's own stem cells, no risk of graft vs host disease
    - Requirement for ablative marrow therapy

High expectations about gene therapy aren't just for patients anymore.

Clinical status in thalassemia intermedia

- Management of anemia
- Splenectomy and risk of thrombosis
- Bone disease
- Pulmonary hypertension
- New classification system for severity
- Better understanding of chelation and transfusion
- Likely future role of any of several novel strategies

Bone

- Prevention of bone problems deserves high attention by patients and their treaters.
- Fortunately there are many prevention and treatment strategies available.
  - Optimize vitamin D, calcium, zinc
  - Lots of experience with IV bisphosphonates (e.g. Zoledronic acid); less with other new drugs (RANKL inhibitors)
- See an expert!
- The expert bone advice needs to be filtered back by your hematologist and obstetrician if applicable (multidisciplinary team approach required)

Best Chelation Strategies

- Experts may disagree about some details, but generally agree about the big picture.
- Some Centers are now aiming for low target iron burden.
- We understand chelation complications and tolerability better than we used to.
- Jadenu (tablet Deferasirox) was too new to be addressed in detail at the conference, but all signs suggest that it is widely preferred to Exjade.

Combination chelation

- More clinical data available than at 2009 conference
  - Deferoxamine/Deferiprone
  - Deferoxamine/Deferasirox
  - Deferaprox/Deferiprone (least well studied)

- Ideally we would have good data on the combination of the two oral agents
  - Safety
  - Dosage ranges
  - Efficacy
  - tolerability

Conclusions

- Slowly but surely, advances in basic science are working their way into improved thalassemia care

- Clinical advances have occurred in nearly every realm
  - Transfusion
  - Chelation
  - Avoiding toxicity
  - Avoiding end-organ damage and bone disease

- Curative therapies (transplant and gene therapy) have arrived on the scene but aren't for everyone yet (stay tuned)