Anemia Management of Pediatric Patients With Stages II-V Chronic Kidney Disease (CKD)

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Anemia affects over half of the 10 million Americans with CKD.

- Associated with increased mortality, hospitalizations, risk of progression of CKD, left ventricular hypertrophy, & adverse effects on quality of life in adults & children/adolescents.
- Treatment with erythropoiesis stimulating agents (ESAs) has ameliorated many of the adverse effects of anemia in CKD.
Recent RCT in CKD in adults showed increased risk of ESAs & cardiovascular events & mortality at higher hemoglobin (Hgb) targets >11 g/dL.

- Black Box warning issued by the FDA that called into question the safety of these agents in adults & children.
- Recommended starting ESA treatment for Hgb < 10g/dL in order to avoid the need for red blood cell transfusion; no target Hgb goal defined.
The safety concerns upon which the revised targets were based came from studies only in adults with CKD/ESKD with outcomes (severe cardiac events, mortality) that may not be applicable to pediatric patients with CKD/ESKD.

- Pediatric patients with CKD may need higher doses of ESAs & different target Hgb values in order to achieve optimal outcomes for growth, neurocognitive development & cardiovascular function.
Gaps in Knowledge

- No clinical trial assessing the optimal dosing and safety of ESAs in children with CKD have been performed.
  - Increased risk for hospitalizations & mortality associated with a Hgb<10 g/dL.
  - No data the impact of gender/age, weight, stage of CKD, use of concurrent medications, PK & PG measurements on ESA’s dosing & effect despite their use in 95% of children with CKD.
  - Determination of the appropriate target Hgb levels of these agents in children with CKD is unknown.
Short-term Outcomes of Anemia Treatment With ESA’s Needing Further Investigation in Children:

- Prospective studies of the safety/efficacy of dosing strategies for age/gender specific Hgb levels >95th% based on stage of CKD.

- Determination of target Hgb levels required to achieve maximal growth, neurocognitive development & avoidance of cardiovascular risks.

- PK & PG on ESA dosing & medication interactions.
Ancillary Studies

- Identification of new biomarkers to assess the efficacy and safety of ESA dosing in CKD/ESKD.

- Outcome & comparative effectiveness of therapies including determination of quality of life assessments in children with CKD/ESKD receiving ESAs.
Collaborators

- North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS)
- NIH Chronic Kidney Disease in Children Longitudinal Cohort Study (CKiD)
- Pediatric Trials Network
- Investigators from other disciplines (cardiology, endocrinology, neurology, epidemiology)
Pharmacokinetics of Life-Saving Medications in Critically Ill Children with Acute Kidney Injury Receiving Continuous Renal Replacement Therapy

Stuart L. Goldstein, MD
Director, Center for Acute Care Nephrology
Cincinnati Children’s Hospital Medical Center
Founder and Principal Investigator
The Prospective Pediatric CRRT Registry Group
Acute Kidney Injury in Children

- Epidemiology
  - More often a result of another system/organ illness or its treatment\(^1\)
  - Increasing incidence/prevalence in ICU population\(^2,3\)

- Treatment
  - Currently, mostly supportive
  - Continuous renal replacement therapy (CRRT) most common RRT modality provided to children\(^4\)

1. Hui-Stickle, Brewer, Goldstein AJKD 2005
3. Schneider et al Crit Care Med 2010
Outcomes: Gaps in Knowledge

- Mortality still very high for children with AKI who receive CRRT despite technological advancements
- No comprehensive, validated data to guide dosing of most medications in children who receive CRRT
- GAP in knowledge to treat critically ill children
  - *In vitro data*
  - *Extrapolated from patients with ESRD*
  - *Extrapolated from adult AKI studies*
The Patients Have OTHER Chronic Illness

- ppCRRT Registry Group
- 376 children from 13 US centers who received CRRT
- Chronic kidney diseases only 8% of population
- We don’t know how to dose life-saving medications for the entire pediatric critical care patient population with AKI on CRRT

Meropenem in CRRT

22.4 ml/min/1.73m² + 2 x CL_{(cr)} + UF

Population Pharmacokinetics

Model

- \( CL_{(Total)} = \beta_0 + \beta_1 \text{CL}_{(creatinine)} + \beta_2 \text{UF} \)
- \( Vd \text{ (L/kg)} = \beta_0 + (\% \text{ volume overload}) \beta_2 \)
- Other variables to consider: Age, albumin, modality, septic vs non septic
Short-term Goals

1. Devise highly predictive *in silico* drug disposition models with an area under the curve (AUC) within 20% of what will be tested in the subsequent aims of the study.

2. Validate models *in vivo* to optimize dosing to provide the clinically desired medication level and physiologic effect.

3. Refine models with *in vivo* PK/PD validation profiles
Preliminary Data: Short-term Goals Using the ppCRRT study

- Use parameters abstracted literature and the derived model to estimate meropenem clearance

- Apply model to population of interest: ppCRRT study
  - 372 patients
  - Database includes CRRT settings, residual renal function, age, weight

- Determine adequate dosing regimen by using clinical trial simulations
### Preliminary Data: the ppCRRT Study

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<th>Age (years)</th>
<th>Weight (kgs)</th>
<th>Height (cm)</th>
<th>Creatinine (mg/dL)</th>
<th>GFR (ml/min/1.73m²)</th>
<th>UF (ml/hr)</th>
<th>Time&gt;MIC (without CRRT)</th>
<th>Time&gt;MIC (without RRF)</th>
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This study will be a pilot to set up the paradigm for multicenter study

The network is in place (ppCRRT): 4 centers invested in current project (Thrasher Grant application)

The PK/PD expertise is in place (Sander Vinks, PhD)
Future Directions

- **For medications with unknown PK**
  - Any child, anywhere with AKI receiving CRRT (or not)
  - Clinician collaborator can access web-based sampling requirements
  - Collect samples and send to CCHMC for PK analysis

- **For medications with validated PK**
  - Any child, anywhere with AKI receiving CRRT (or not)
  - Clinician can access web-based dashboard and enter patient specific parameters to guide dosing
Anticoagulation in Children with Kidney Disease

Stuart L. Goldstein, MD
Frederick Kaskel, MD, PhD
Hypercoagulation Issues in Pediatric Kidney Diseases

- **Pediatric End-Stage Kidney Disease**
  - Catheter thrombosis
  - Fistula/Graft thrombosis
  - *Prevents delivery of maintenance dialysis*
  - Associated with increased morbidity

- **Pediatric Acute Kidney Injury**
  - Catheter/CRRT circuit thrombosis
  - *Prevents delivery of life-saving therapy*

- **Nephrotic Syndrome**
  - Hypercoaguable state
  - Venous and arterial thromboses
  - *Limb loss and stroke*
Gaps: Approved Therapeutic Options

- No medication is approved to prevent or treat vascular access thrombosis in children.
- No medication is approved for CRRT to anticoagulate CRRT circuits.
- Few data describe the best thrombosis prophylaxis or treatment regimens for nephrotic syndrome states.
Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

- Met November 2, 2011

- Identification of strategies to encourage and facilitate studies of anticoagulants in children that will result in
  - informative pediatric labeling
  - appropriate endpoints for studies of anticoagulants in pediatric patients
  - the role of PK/PD studies to support a pediatric indication for anticoagulants.
Medications of Interest for Each Patient Population

- ESKD receiving maintenance HD
  - Citrate
  - Heparin

- AKI CRRT
  - Citrate
  - Prostacyclin

- Nephrotic syndrome
  - LMWH
Studies Needed

- Epidemiology/surveillance of AKI, CKD/ESKD and nephrotic pediatric cohorts to identify the effects of age, gender, weight, stage of CKD, and use of other medications on the incidence/prevalence of thrombosis.

- Prospective clinical trials aimed at determining the ideal anti-coagulation in children with AKI, CKD/ESKD, and nephrotic syndrome as determined by safety and efficacy metrics.

- Performance of pharmacokinetic/pharmacogenomics measurements for determination of optimal dosing strategies of anti-coagulation therapies in AKI, CKD/ESKD and nephrotic children.
Ancillary Studies

- Identification of new biomarkers to assess the efficacy and safety of anti-coagulation therapies in AKI, CKD/ESKD, and nephrotic children.

- Impact of unique PK/PGen characteristics on the efficacy and safety of anti-coagulation therapies to prevent and lower the risk for thrombosis.
Reduction of Future CV Risk and Management of Dyslipidemia / Hyperlipidemia in Children with CKD

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Children with moderate CKD reaching ESRD:
- 50% in 5 years
- 70% in 10 years

#1 cause of death in young adult survivors of ESRD:
- CV events (frequently CVA)

CKiD Study Fact:
- 45% persistent dyslipidemia

SHARP
Study of Heart and Renal Protection

- Recent double blind placebo-controlled RCT, Age ≥ 40
- Simvastatin 20mg / Ezetimibe 10 mg (Vytorin®)
- N ~ 9000 (~3000 on dialysis)
- NO entry criteria for dyslipidemia
- Results: Lower LDL, fewer “major atherosclerotic events”
  - Effect ~ 30-40 events per 1000 patients treated for 5 years
  - “Yes and no” conclusions in dialysis patients
  - Fewer events result mainly from less revascularization procedures
  - No change in mortality
- Vytorin® new labeling 11/2/11 for CKD
  - Except for dialysis patients

Baigent, C, Landry M., KI 2003
**Short Term Safety/Dosing:**

**Key Needs:**

- Not just quantify known safety issues—need to systematically identify potentially unknown issues

- **No PK or safety data directly from children with CKD**
  - decreased GFR (“classic CKD”) and/or
  - significant proteinuria / hypoalbuminemia (nephrotic syndrome)

- **Differences from children with FH / adults with CKD**
  - Currently labeled indications for statins or simva / ezetimibe

- **Unknown safe lower limits of lipid levels by age**

- **Little or no data derived directly about how therapeutic agents interact with other agents commonly used in children with CKD**
Short Term Study Recommendations:

- PK, pharmacogenomic, and safety studies in children with CKD or ESRD; broadly inclusive
  - Begin with: simva+ezetimibe, other statins, omega-3’s, sevelamer.

- Define efficacy target
  - 1 mmol/L (39 mg/dl) drop in LDL-C (correlates to ~25% lower event risk)
  - Or less than 50th percentile for age

- Entry NOT based on lipid levels
  - Except exclude those with low non-HDL-C (say < 50th percentile)

- Study mechanisms of dyslipidemia in pediatric CKD
  - Different than FH (only pediatric labeling currently)
  - Can be built into PK studies
  - Increase prospects of best directed therapy
Responsible Planning: Gaps in Long-Term Safety

Long term safety concerns:
- Potentially unknown: need to systematically identify
- Cancer? (no sign of it in SHARP but only 5 years)
- Development (e.g. neurocognitive or pubertal effects)
- Coexisting issues (e.g. HTN, acidosis, bone disease)
Responsible Planning: Impediments for Study of Long-Term Effects

Need surrogate / intermediate markers of clinical efficacy

- Lipid levels are a starting point but not sufficient
- The atherosclerotic event “risk horizon” is distant
  - CV Risk at age 10-30 is a log-scale lower than age > 40
- Unknown time course of treatment benefit
  - Between birth and age 40, when to start treatment?
  - If continuous and cumulative risk reduction:
    » Start as early as possible to realize most benefit
  - If limited or finite maximal risk reduction?
    » Avoid early treatment for no benefit
    » Match the time to maximum benefit with the risk horizon
Responsible Planning: Goals of Long-Term Study

- Validate surrogate markers of future CV disease
- Define the risk horizon of atherosclerotic and non-atherosclerotic events

- Profile subjects at regular intervals over 10-20-30 years
- Track CV and non-CV outcomes
- Focus NOT on any particular stage of CKD, but rather the individual who over time might pass through multiple stages of CKD or ESRD.
Responsible Planning: Extend CKiD Study to Meet Goals

- CKiD does NOT follow children after ESRD
- Lost opportunity to study CV event outcomes and to quantify atherosclerotic burden in a group where pediatric status is extremely well recorded.
- CKiD could begin yielding data within a few years.
  - Existing cohort so most cost effective
  - Need to extend the duration of the study
  - Need to extend eligibility to keep subjects with ESRD