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

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Background: Adult & Pediatric

- **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.

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Background: Adult & Pediatric

- **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.

Gaps in Knowledge

- **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.

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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.**

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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)**

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Pharmacokinetics of Life-Saving Medications in Critically Ill Children with Acute Kidney Injury Receiving Continuous Renal Replacement Therapy

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Cincinnati Children's Hospital Medical Center

Founder and Principal Investigator

The Prospective Pediatric CRRT Registry Group

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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
2. Akcan-Arikan et al Kid Int 2007
3. Schneider et al Crit Care Med 2010
4. Warady, Bunchman Ped Neph 2000

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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*

Demographic Characteristics of Pediatric Continuous Renal Replacement Therapy: A Report of the Prospective Pediatric Continuous Renal Replacement Therapy Registry

Jordan M. Symons,* Annabelle N. Chua,† Michael J.G. Somers,‡ Michelle A. Baum,‡ Timothy E. Bunchman,§ Mark R. Benfield,‖ Patrick D. Brophy,¶ Douglas Blowey,** James D. Fortenberry,†† Deepa Chand,‡‡ Francisco X. Flores,§§ Richard Hackbarth,§ Steven R. Alexander,‖‖ John Mahan,¶¶ Kevin D. McBryde,*** and Stuart L. Goldstein†

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**

Table 5. Principal diagnoses and survival[a]

Parameter	*n*	Survivors	% Survival
Sepsis	81	48	59
Bone marrow transplant	55	25	45
Cardiac disease/ transplant	41	21	51
Renal disease	32	27	84
Liver disease/ transplant	29	9	31
Malignancy (no tumor lysis syndrome)	29	14	48
Ischemia/shock	19	13	68
Inborn error of metabolism	15	11	73
Drug intoxication	13	13	100
Tumor lysis syndrome	12	10	83
Pulmonary disease/ transplant	11	5	45
Other	7	5	71

[a] $P\ (\chi^2) < 0.001$.

Symons J.M., et al. (2007). Demographic characteristics of pediatric continuous renal replacement therapy: A report of the prospective pediatric continuous renal replacement therapy registry. *Clinical Journal of the American Society of Nephrology,* 2(4):732–8.

Meropenem in CRRT

$22.4\ ml/min/1.73m^2 + 2 \times CL_{(cr)} + UF$

- **Population Pharmacokinetics**
- **Model**
  - $CL_{(Total)} = \beta_0 + \beta_1 CL_{(creatinine)} + \beta_2 UF$
  - $Vd\ (L/kg) = \beta_0 + (\%\ volume\ overload)\ \beta_2$
  - Other variables to consider: Age, albumin, modality, septic vs non septic

Short-term Goals

- **1. <u>Devise highly predictive *in silico* drug disposition models</u> with an area under the curve (AUC) within 20% of what will be tested in the subsequent aims of the study.**
- **2. <u>Validate models *in vivo*</u> to optimize dosing to provide the clinically desired medication level and physiologic effect.**
- **3. Refine models with *in vivo* PK/PD validation profiles**

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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

Age (years)	Weight (kgs)	Height (cm)	Creatinine (mg/dL)	GFR (ml/min/ 1.73m^2)	UF (ml/hr)	Time>MIC	Time>MIC (without CRRT)	Time>MIC (without RRF)
3	17	103	2.0	21	711	50%	72%	74%
3	13.2	91	1.1	34	835	34%	48%	58%
15	66.4	175	3.1	23	2381	78%	100%	100%
14	61	169	0.8	87	2791	36%	44%	98%
1	11	71	0.6	49	748	26%	36%	50%

Current Structure

- **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*

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Gaps: Approved Therapeutic Options

- **No medication is approved to prevent or treat vascular access thrombosis in children.**
- **No medication is approved for CRRT to anti-coagulate CRRT circuits.**
- **Few data describe to the best thrombosis prophylaxis or treatment regimens for nephrotic syndrome states.**

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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**

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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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The Problem: CV Outcomes After Childhood CKD

Children with moderate CKD reaching ESRD:

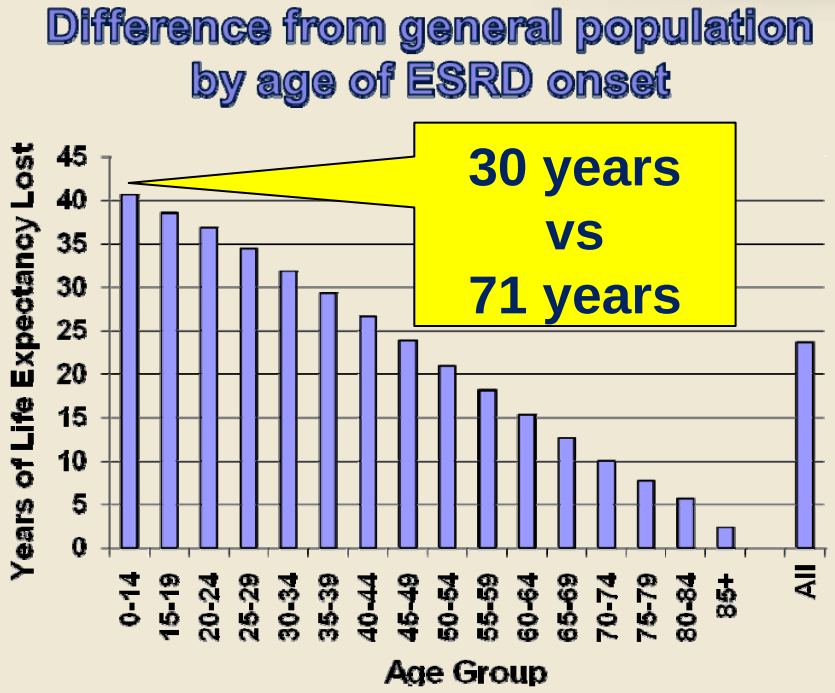
- **50% in 5 years**
- **70% in 10 years**

#1 cause of death in young adult survivors of ESRD:

- **CV events (frequently CVA)**

CKiD Study Fact:

- **45% persistent dyslipidemia**



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Saland J.M., et al. (2010). Dyslipidemia in children with chronic kidney disease. *Kidney International,* 78(11):1154–63.

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**

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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**

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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

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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

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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.**

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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**

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