Deferasirox-Associated Renal Toxicity

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Outline

- Deferasirox-associated renal toxicity
- Challenges with monitoring renal function
  - Reliance on serum creatinine (S_{Cr})and creatinine clearance (CLCr) to guide drug dosing decisions
  - Utility and limitations of using prediction equations to estimate glomerular filtration rate (GFR)
- Updated renal dosing and monitoring labeling recommendations

Deferasirox-Associated Renal Toxicity

- Increase in S_{Cr} and proteinuria most common renal adverse events in clinical trials
- Proximal renal tubular dysfunction including Fanconi Syndrome
- Acute kidney injury (AKI)

Renal Proximal Tubular (PT) Toxicity

Amino aciduria
Organic aciduria
Low molecular weight proteinuria
Hypophosphataemia
Normoglycaemic glycosuria
Metabolic acidosis
Hypouricaemia
Hypokalaemia
Polyuria

Hall AM, et al. Drug-Induced Renal Fanconi Syndrome.
Quarterly Journal of Medicine 2014

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S_{CR}: Uses

Diagnosis and staging of AKI at bedside

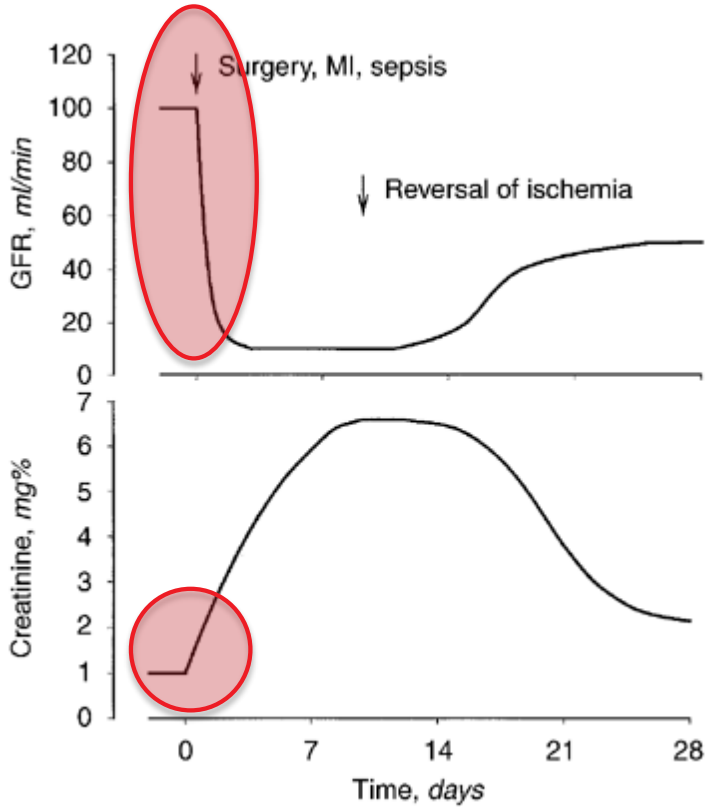
Stage	Change in serum creatinine[a]	Urine output
I	Increase 0.3 mg/dL[b] or increased 150–200 %[c]	<0.5 mL/kg/h for 6 h
II	Increase ≥200–300 %	<0.5 mL/kg/h for ≥12 h
III	Increase ≥300 %, serum creatinine ≥4 mg/dL or dialysis or estimated glomerular filtration rate <35 mL/min/1.73 m^2 for those <18yo	<0.3 mL/kg/h for 24 h or anuria for 12 h

[a]From baseline creatinine
[b]Change over 48 h
[c]Change over 7 days

KDIGO Clinical Practice Guideline for Acute Kidney Injury (AKI):
http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf

S_{CR} : Limitations

- Insensitive marker of early renal injury
- Less desirable to guide drug dosing decisions especially for drugs with low therapeutic index
  - Substantial intra- and interindividual variability



Star RA. Treatment of Acute Renal Failure. Perspectives in Renal Medicine, 1998.

S_{CR} : Limitations

		Chemistry									
		Female reference interval					Male reference interval				
Analyte	Age	Lower limit	Upper limit	No. of samples	Lower limit confidence interval	Upper limit confidence interval	Lower limit	Upper limit	No. of samples	Lower limit confidence interval	Upper limit confidence interval
Creatinine (Jaffe), mg/dL	0 to 14 days	0.42	1.05	158	0.33–0.48	0.97–1.06	0.42	1.05	158	0.33–0.48	0.97–1.06
	15 days to <1 year	0.32	0.53	130	0.31–0.33	0.51–0.54	0.32	0.53	130	0.31–0.33	0.51–0.54
	1 to <4 years	0.38	0.54	121	0.38–0.41	0.54–0.55	0.38	0.54	121	0.38–0.41	0.54–0.55
	4 to <7 years	0.44	0.64	146	0.43–0.45	0.62–0.67	0.44	0.64	146	0.43–0.45	0.62–0.67
	7 to <12 years	0.52	0.69	234	0.52–0.53	0.67–0.71	0.52	0.69	234	0.52–0.53	0.67–0.71
	12 to <15 years	0.57	0.80	184	0.55–0.58	0.80–0.86	0.57	0.80	184	0.55–0.58	0.80–0.86
	15 to <17 years	0.59	0.86	77	0.58–0.61	0.84–0.87	0.66	1.04	68	0.63–0.68	1.00–1.07
	17 to <19 years	0.60	0.88	88	0.59–0.61	0.86–0.90	0.69	1.10	86	0.67–0.71	1.07–1.13
Creatinine (enzymatic), mg/dL	0 to 14 days	0.33	0.93	147	0.27–0.40	0.89–0.97	0.33	0.93	147	0.27–0.40	0.89–0.97
	15 days to <2 years	0.10	0.36	168	0.10–0.12	0.35–0.37	0.10	0.36	168	0.10–0.12	0.35–0.37
	2 to <5 years	0.20	0.43	155	0.18–0.21	0.41–0.45	0.20	0.43	155	0.18–0.21	0.41–0.45
	5 to <12 years	0.31	0.61	321	0.29–0.32	0.60–0.62	0.31	0.61	321	0.29–0.32	0.60–0.62
	12 to <15 years	0.45	0.81	183	0.37–0.46	0.76–0.85	0.45	0.81	183	0.37–0.46	0.76–0.85
	15 to <19 years	0.49	0.84	161	0.48–0.51	0.80–0.88	0.62	1.09	151	0.53–0.66	1.06–1.12

Colantonio D, et al. Closing the Gaps in Pediatric Laboratory Reference Intervals Clinical Chemistry 2012

Creatinine Clearance (CLCr)

- Not synonymous with glomerular filtration rate (GFR)
- Reflects urinary creatinine filtered by glomeruli and secreted by proximal renal tubule
- Overestimates true GFR by fraction of urinary creatinine derived from tubular secretion

Cockcroft-Gault (CG) Equation

- Formula developed in 1973 to allow CLCr to be estimated from S_{CR} in patients with a stable S_{CR}
- FDA has historically used CLCr in pharmacokinetic studies to determine drug dosing in adults with renal disease
- Expressed in mL/minute and does not account for body surface area (BSA)
  - Not desirable in pediatric patients in whom kidney size is proportional to BSA
  - Uncorrected values would underestimate GFR for those with BSA less than mean (e.g. pediatric patients)

Creatinine-Based Prediction Equations

- Incorporate demographic and clinical variables (e.g. age, race, sex, weight) which are correlated with differences in average muscle mass to account for inter-individual variability
  - Modification of Diet in Renal Disease (MDRD)
  - Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
  - Schwartz equations (original and “Bedside”)

Schwartz Equations: Utility

$$eGFR^* = k \times height\ (cm)/S_{Cr}\ (mg/dL)$$

- Original equation developed in 1976
- Bedside equation developed in 2009 using new enzymatic S_{Cr} methodology (k=0.41)
- Accounts for BSA to eliminate variability in GFR caused by variations in body size

*eGFR = estimated GFR

Interpretation of eGFR

Age (yr)	GFR (ml/min/1.73 m^2) (mean ± SD)
3–4	111.2 ± 18.5
5–6	114.1 ± 18.6
7–8	111.3 ± 18.3
9–10	110.0 ± 21.6
11–12	116.4 ± 18.9
13–15	117.2 ± 16.1
2.7–11.6	127.1 ± 13.5
9–12	116.6 ± 18.1
16.2–34	112 ± 13

Schwartz GJ and Work DF CJASN 2009

Values > 90 mL/min/1.73m^2 normal in those with renal maturation

Schwartz Equations: Limitations

- Don't account for intra-individual variability in creatinine production
  - Volume status, activity, dietary protein consumption
- Assume S_{Cr} is at steady state
- Developed from data in 349 children age 1-16 years with chronic kidney disease (GFR 15-75 mL/min/1.73m^2)
  - Limited data in those with GFR > 75 mL/min/1.73m^2

Pediatric Thalassemia Population: eGFR Interpretation

- Overestimate true GFR
  - Low baseline S_{Cr} (reduced muscle mass, malnutrition, vegetarian diet)
  - Use original Schwartz equation with enzymatic S_{Cr} values
- Underestimate true GFR
  - High baseline S_{Cr}
    - Drug-related reduced proximal tubular secretion of Cr
    - Transient decreased renal perfusion due to volume depletion
  - Use Bedside Schwartz equation with non-enzymatic S_{Cr} values
- Chronic anemia associated with glomerular hyperfiltration

Safety Analyses

- Goal was to inform deferasirox labeling
- Relied on eGFR derived from Schwartz equations rather than on S_{Cr}
  - Exposure-response analyses
  - Evaluating 5 year registry data
  - Define AKI in nested case control study

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Prior Approved Labeling
Boxed Warning

WARNING: RENAL, HEPATIC FAILURE AND/OR GASTROINTESTINAL HEMORRHAGE

Exjade may cause:

- **renal impairment, including failure**
- **hepatic impairment, including failure**
- **gastrointestinal hemorrhage**

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes (MDS), underlying renal or hepatic impairment or low platelet counts ($<50 \times 10^9$/L) [*see Contraindications (4), Warnings and Precautions (5.1- 5.7)*].
Exjade therapy requires close patient monitoring, including measurement of:

- **serum creatinine and/or creatinine clearance prior to initiation of therapy and monthly thereafter; in patients with underlying renal impairment or risk factors for renal impairment, monitor creatinine and/or creatinine clearance weekly for the first month, then monthly thereafter;**
- **serum transaminases and bilirubin prior to initiation of therapy, every two weeks during the first month and monthly thereafter.**

Current Approved Labeling
2018 Boxed Warning

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

Renal Failure

- **Exjade can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.**
- **Evaluate baseline renal function prior to starting or increasing Exjade dosing in all patients. Exjade is contraindicated in adult and pediatric patients with eGFR less than 40 mL/min/1.73 m^2. Measure serum creatinine in duplicate prior to initiation of therapy. Monitor renal function at least monthly. For patients with baseline renal impairment or increased risk of acute renal failure, monitor renal function weekly for the first month, then at least monthly. Reduce the starting dose in patients with pre-existing renal disease. During therapy, increase the frequency of monitoring and modify the dose for patients with an increased risk of renal impairment, including use of concomitant nephrotoxic drugs, and pediatric patients with volume depletion or overchelation *[see Dosage and Administration (2.1, 2.4, 2.5), Warnings and Precautions (5.1) Adverse Reactions (6.1, 6.2)]*.**

Approved Labeling

Section 4 Contraindications

Prior: Serum creatinine (S_{Cr}) > 2 times age-appropriate upper limit of normal (ULN) or creatinine clearance (CLCr) < 40 mL/minute

2018: Estimated GFR less than 40 mL/min/1.73m^2

Prior Approved Labeling

Section 2 Dosage and Administration

- Prior to starting therapy, obtain baseline S_{Cr} in duplicate and determine CLCr (Cockroft-Gault method)
- For patients with baseline renal impairment (CLCr 40-60 mL/minute), reduce starting dose by 50%

Current Approved Labeling

Section 2 Dosage and Administration

- Prior to starting therapy, obtain baseline SCr in duplicate ~~and determine CLCr (Cockroft-Gault method) (subsection 2.1 and 2.2]~~
- Calculate eGFR. Use a prediction equation appropriate for adult patients (e.g. CKD-EPI, MDRD method) and in pediatric patients (e.g. Schwartz equations)
- Obtain urinalyses and serum electrolytes to evaluate renal tubular function
- For patients with baseline renal impairment (eGFR ~~CLCr~~ 40-60 mL/min/1.73m^2), reduce starting dose by 50%

Current Approved Labeling

Section 2 Dosage and Administration

- Monitor renal function monthly
- Interrupt dosing for pediatric patients who have acute illnesses which can cause volume depletion such as vomiting. Diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal.

Current Approved Labeling

Subsection 2.5 Dose Modifications for Increases in SCr

Age 2-17 years

- Reduce the dose by 10 mg/kg/day if eGFR decreases by greater than 33% below the average baseline measurement and repeat the eGFR within 1 week
- …evaluate the risk benefit profile of continued Exjade use. Use the minimum effective Exjade dose and monitor renal function more frequently, by evaluating tubular and glomerular function. Titrate dosing based on renal injury. Consider dose reduction or interruption and less nephrotoxic therapies until improvement in renal function. If signs of renal tubular or glomerular injury occur in the presence of other risk factors such as volume depletion, reduce or interrupt Exjade to prevent severe and irreversible renal injury.

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