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ADEPT 8
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Reliance on BSA Indexed GFR Values *vs* Individualized eGFR Values to Guide Drug Dosing in Adults and Implications to Pediatrics

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Contemporary Adult eGFR Equations Report BSA Indexed Results (mL/min/1.73 m^2)

Table 2. Current and New Equations to Estimate GFR.*

Model; Name of Equation†	Intercept μ (95% CI)	Coefficients for Creatinine (95% CI)‡		Coefficients for Cystatin C (95% CI)§		Coefficient c for Age (95% CI)	Coefficient d for Female Sex (95% CI)	Coefficient e for Black Race (95% CI)
		a_1	a_2	b_1	b_2			
2009 CKD-EPI creatinine[5]; eGFRcr(ASR), current	141 (139 to 144)	F: −0.329 (−0.428 to −0.230); M: −0.411 (−0.508 to −0.314)	−1.209 (−1.220 to −1.198)	—	—	0.9929 (0.9925 to 0.9933)	1.018 (1.007 to 1.029)	1.159 (1.144 to 1.170)
2009 CKD-EPI creatinine[5]; eGFRcr(ASR-NB), new	141 (139 to 144)	F: −0.329 (−0.428 to −0.230); M: −0.411 (−0.508 to −0.314)	−1.209 (−1.220 to −1.198)	—	—	0.9929 (0.9925 to 0.9933)	1.018 (1.007 to 1.029)	1
2021 CKD-EPI creatinine (2009 CKD-EPI creatinine fit without race); eGFRcr(AS), new	142 (139 to 144)	F: −0.241 (−0.344 to −0.138); M: −0.302 (−0.403 to −0.202)	−1.200 (−1.211 to −1.189)	—	—	0.9938 (0.9935 to 0.9942)	1.012 (1.000 to 1.023)	—
2012 CKD-EPI cystatin C[9]; eGFRcys(AS), current	133 (130 to 136)	—	—	−0.499 (−0.610 to −0.388)	−1.328 (−1.344 to −1.312)	0.9962 (0.9957 to 0.9966)	0.932 (0.921 to 0.944)	—
2012 CKD-EPI creatinine–cystatin C[9]; eGFRcr-cys(ASR), current	135 (132 to 137)	F: −0.248 (−0.364 to −0.132); M: −0.207 (−0.308 to −0.107)	−0.601 (−0.630 to −0.571)	−0.375 (−0.477 to −0.274)	−0.711 (−0.744 to −0.678)	0.9952 (0.9948 to 0.9957)	0.969 (0.958 to 0.980)	1.080 (1.067 to 1.093)
2012 CKD-EPI creatinine–cystatin C[9]; eGFRcr-cys(ASR-NB), new	135 (132 to 137)	F: −0.248 (−0.364 to −0.132); M: −0.207 (−0.308 to −0.107)	−0.601 (−0.630 to −0.571)	−0.375 (−0.477 to −0.274)	−0.711 (−0.744 to −0.678)	0.9952 (0.9948 to 0.9957)	0.969 (0.958 to 0.980)	1
2021 CKD-EPI creatinine–cystatin C (2012 CKD-EPI creatinine–cystatin C fit without race); eGFRcr-cys(AS), new	135 (132 to 137)	F: −0.219 (−0.336 to −0.101); M: −0.144 (−0.245 to −0.042)	−0.544 (−0.572 to −0.515)	−0.323 (−0.426 to −0.220)	−0.778 (−0.809 to −0.746)	0.9961 (0.9957 to 0.9965)	0.963 (0.952 to 0.974)	—

* The cells show coefficients to use in the following formula: $eGFR = \mu \times \min(Scr/\kappa, 1)^{a_1} \times \max(Scr/\kappa, 1)^{a_2} \times \min(Scys/0.8, 1)^{b_1} \times \max(Scys/0.8, 1)^{b_2} \times c^{Age} \times d[\text{if female}] \times e[\text{if Black}]$. Here, κ is 0.7 for female participants and 0.9 for male participants, min indicates the minimum of Scr/κ and 1, and max indicates the maximum of Scr/κ and 1. The 2009 and 2012 models were developed previously. Sex differences for eGFRcr and eGFRcr-cys equations are modeled as sex-specific creatinine coefficients as well as female sex coefficients. CKD-EPI denotes Chronic Kidney Disease Epidemiology Collaboration, F female, and M male.

† The equations are referred to by the filtration marker or markers (creatinine [eGFRcr], cystatin C [eGFRcys], or creatinine–cystatin C [eGFRcr-cys]) and the demographic factors (age, sex, and race [ASR] or age and sex [AS]) that were used in their development. Non-Black (NB) refers to equations in which the Black race coefficient was omitted in computation of the eGFR value.

‡ The coefficient a_1 is used for levels of creatinine less than or equal to 0.9 mg per deciliter for male participants and 0.7 mg per deciliter for female participants. The coefficient a_2 is used for levels of creatinine greater than 0.9 mg per deciliter for male participants and 0.7 mg per deciliter for female participants.

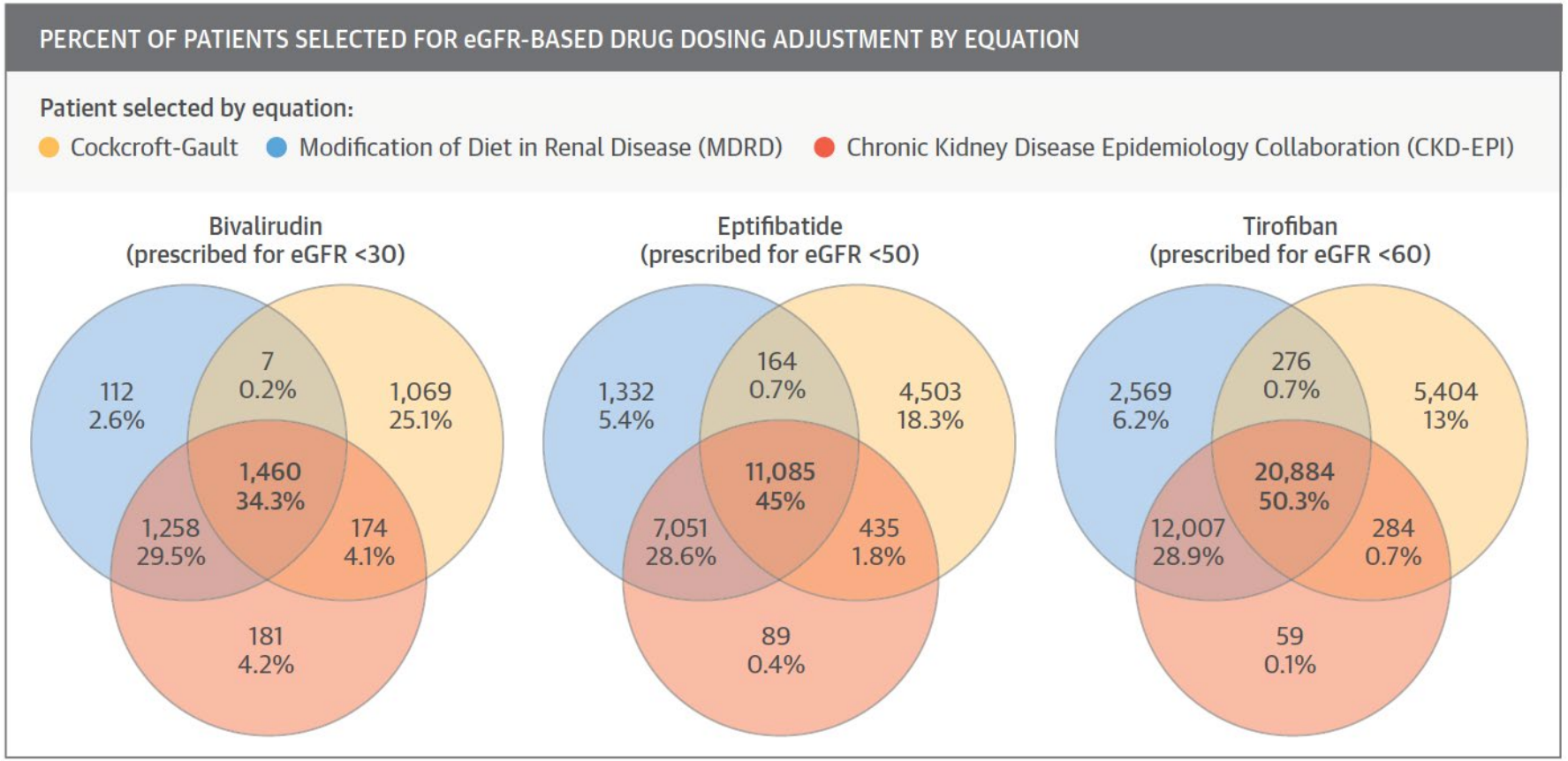
§ The coefficient b_1 is used for levels of cystatin C less than or equal to 0.8 mg per liter, and the coefficient b_2 is used for levels greater than 0.8 mg per liter.

- Personalized medicine relies on individual level data
- PK and renal drug clearance are proportional to an individual's GFR, not indexed GFR
- **Majority of existing renal dosing recs based on CL_{CR} in mL/min**

Inker et al. *N Engl J Med* 2021

How do we use new eGFR equations to dose drugs with dosing recommendations based on other kidney function assessments?

Implications in Dosing of Anticoagulants & Antiplatelet Medications



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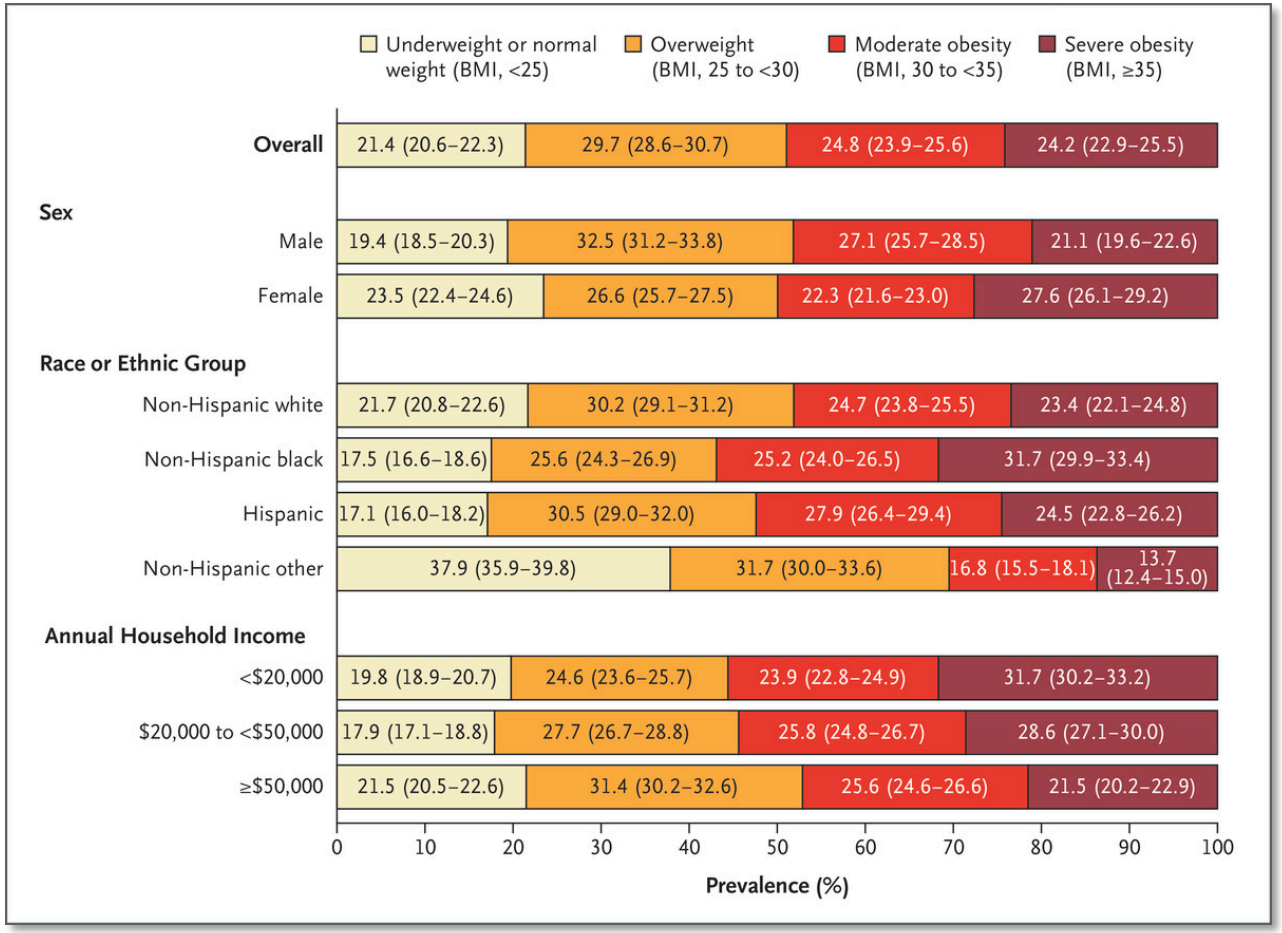
Parsh et al. *J Am Coll Cardiol* 2015

BSA of ‘average’ US adult likely not 1.73 m^2

Projected Prevalence of BMI Categories by 2030



- 50% of US population projected to be obese by 2030
- BSA of ‘average’ US adult likely not 1.73 m^2
- Impacts assessment of kidney function for medication related decisions

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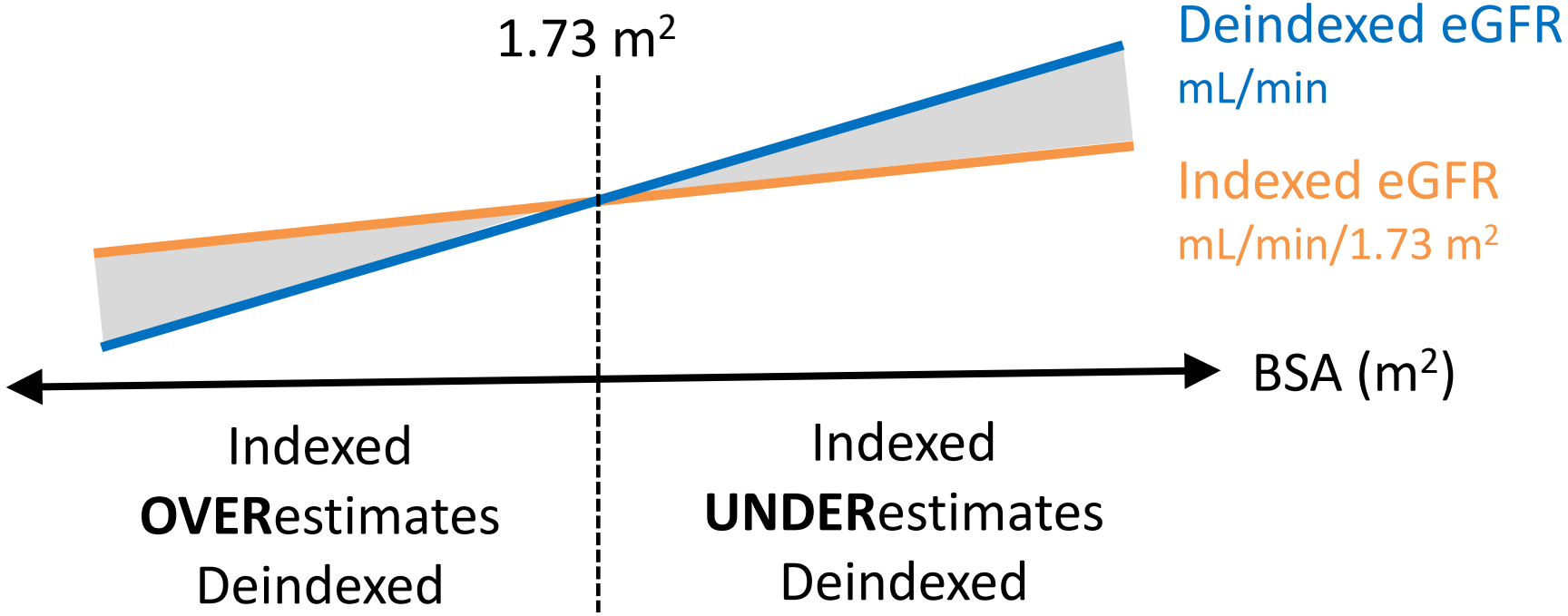
Ward Z et al. *N Engl J Med* 2019

BSA-Indexed eGFR vs Deindexed eGFR



PK and renal drug clearance are proportional to an individual's GFR, not indexed GFR

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Titan S et al. *Am J Kidney Dis* 2020

BSA-Indexed eGFR vs Deindexed eGFR

Implications in Dosing of Medications

- 65 yo M, COVID +
- Scr = 1.6 mg/dL

Height	5’10”
Actual BW	250 lb
BSA (m^2)	2.37
Indexed eGFR (mL/min/1.73 m^2)	**48**
Deindexed eGFR (mL/min)	**63**

PAXLOVID™ (nirmatrelvir + ritonavir)

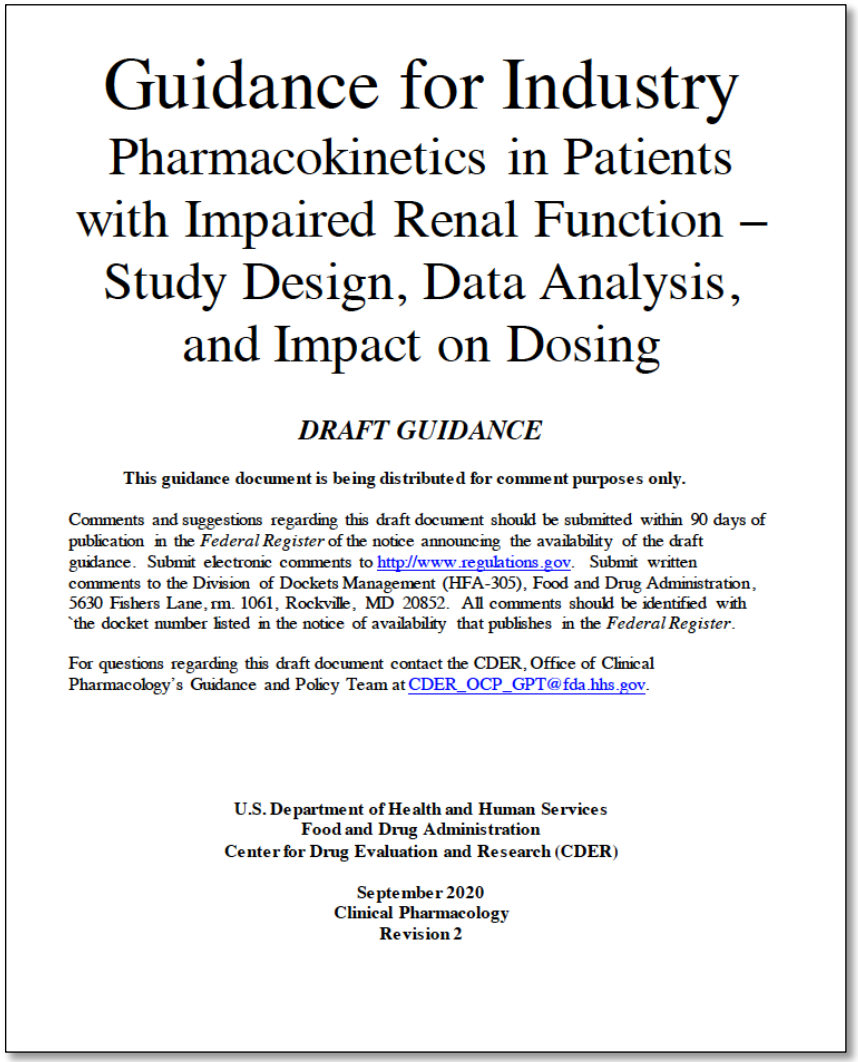
- Approved label 2023
- Dose reduction for eGFR <60 mL/min
- Not recommended in eGFR less than 30 mL/min

Mosteller R. *N Engl J Med* 1987

https://www.kidney.org/professionals/kdoqi/gfr_calculator

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf

2020 Revision to PK Guidance



Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the CDER, Office of Clinical Pharmacology's Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2020
Clinical Pharmacology
Revision 2

Key Updates

- New section on determination of kidney function
  - Softer language related to assessment of kidney function and use of specific eGFR equations ("contemporary equation")
  - Clarification of language related to use of eGFR vs creatinine CL in dosing recs
  - **Use of consistent units when comparing them** (i.e., deindexing eGFR to express it in mL/min)

https://www.fda.gov/media/78573/download

Key Considerations in Adults

Units of Measurement

- C-G CL_{CR} reported in mL/min
- eGFR indexed for BSA (in mL/min/1.73 m^2)
- Should convert eGFR to 'individualized' or deindexed value for comparison to CL_{CR} and use of standard dosing tables
  - eGFR (mL/min) = eGFR (mL/min/1.73 m^2) x BSA/1.73 m^2

Size Descriptors

- Use descriptor specified in product labeling, if available
  - Actual body weight (e.g., daptomycin, dofetilide)
  - Ideal body weight (e.g., adefovir, tenofovir)
  - 'Adjusted' body weight in obese

Implications to Pediatrics?

Units of Measurement

- Pediatric eGFR equations also BSA indexed (mL/min/1.73 m^2)
  - May facilitate translation of adult dosing recs based on indexed eGFR
  - How should kidney function ranges that are based on CLcr (in mL/min) and corresponding dosing recs be translated to pediatrics?
    - Assume mL/min ≅ mL/min/1.73 m^2 ?

Adult Patients

Table 3. Dosage of AVYCAZ in Adult Patients with Renal Impairment

Estimated Creatinine Clearance (mL/minute)[a]	Dose for AVYCAZ (ceftazidime and avibactam)[b]	Frequency
31 to 50	AVYCAZ 1.25 grams (ceftazidime 1 gram and avibactam 0.25 grams) intravenously	Every 8 hours
16 to 30	AVYCAZ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) intravenously	Every 12 hours
6 to 15[c]	AVYCAZ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) intravenously	Every 24 hours
Less than or equal to 5[c]	AVYCAZ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) intravenously	Every 48 hours

[a] As calculated using the Cockcroft-Gault formula
[b] All doses of AVYCAZ are administered over 2 hours
[c] Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days

Pediatric Patients

Table 4. Dosage of AVYCAZ for cUTI and cIAI in Pediatric Patients 2 years and older with Renal Impairment[a]

Estimated eGFR[b] (mL/min/1.73m^2)	Dose for AVYCAZ (ceftazidime and avibactam)[c]	Frequency
31 to 50	AVYCAZ 31.25 mg/kg to a maximum of 1.25 grams (Ceftazidime 25 mg/kg and avibactam 6.25 mg/kg to a maximum dose of ceftazidime 1 gram and avibactam 0.25 grams)	Every 8 hours
16 to 30	AVYCAZ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 12 hours
6 to 15	AVYCAZ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 24 hours
Less than or equal to 5[d]	AVYCAZ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 48 hours

[a] Dosing was derived based on the population PK modeling, which assumed similar proportional effects of renal impairment in adults and pediatric patients 2 years and older *[see Clinical Pharmacology (12.3)]*
[b] As calculated using the Schwartz bedside formula
[c] All doses of AVYCAZ are administered over 2 hours
[d] Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206494s005,s006lbl.pdf

Implications to Pediatrics?

Size Descriptors and Dosing

- Pediatric dosing recommendations typically weight based
- Given evolving nature of body habitus and GFR, relationships between weight, BSA, and PK or renal drug CL progressively more complex → *one size does not fit all*
  - In older children with ‘mature’ kidney function and as pediatric dosing values reach adult doses, use of adult dosing recs and deindexing of GFR (if recs in mL/min) suggested

Summary

- Use of a single kidney function estimate for management of kidney disease and medication decisions, and harmonization across disciplines and populations is essential
- eGFR playing increasing role in drug dosing
- Updated recommendations in 2020 FDA Renal PK Guidance will facilitate development of eGFR based dosing recommendations
- Must consider units of measurement when using dosing tables and translating adult dosing data to pediatrics
- Clarity on translation of kidney function ranges that are based on CLcr (in mL/min) and corresponding dosing recs to pediatrics may be needed