ACUTE KIDNEY INJURY (AKI)

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Pathophysiology

- Kidney function undergoes developmental changes, including postnatal adaptation of **nephron recruitment until approximately 18 months** of age and **glomerular hypertrophy** thereafter.
- Accurate **assessment of kidney function** across post-conceptual age is important and needs to incorporate factors **associated with the person** (e.g., body habitus, growth, muscle mass, health status, illnesses, inflammation, and intra-personal variability), measurement technique (e.g., endogenous biomarkers, exogenous techniques, or imaging studies), and interpretation of measurements (e.g., equation used, correction factors, indexing to body surface area, or extracellular volume).

Pathophysiology

- While nephron endowment would be the most important factor for an accurate clearance calculation of more than 60%of drugs processed by the kidney, this cannot be assessed directly.
- Effective renal plasma flow (ERPF) may be better to assess nephron endowment as it does not undergo autoregulation or hyperfiltration, in contrast to glomerular filtration.
- However, glomerular filtration rate (GFR) is still the best surrogate tool for kidney function assessment.

Measuring kidney function

- The gold standard to measure kidney function is inulin clearance; however, this is impractical.
- Measurement of GFR using either radiolabeled (99Tc iohexol 99Tc DTPA, 51Cr EDTA, iothalamate.) or cold exogeneous substances such as iohexol, iothalamate, etc. now serve as replacement for more accurate GFR determinations. however, there are impractical.
- In the clinical routine, **endogenous markers** are used, especially serum creatinine and cystatin C.

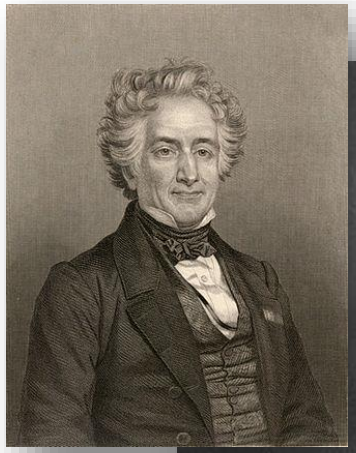
Measuring kidney function

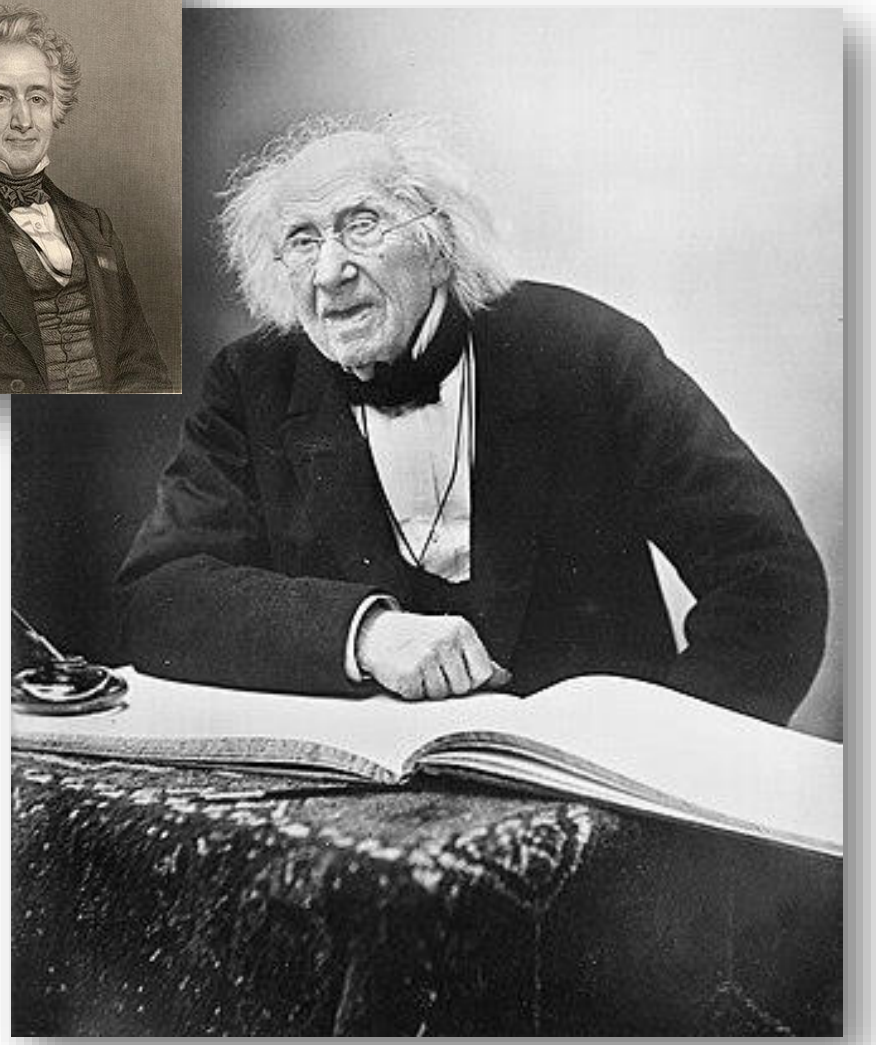
- Creatinine, albeit a marker afflicted with many technical problems, remains the most commonly used endogenous biomarker of kidney function measurement.
- Cystatin C (CysC) is a superior biomarker of kidney function that can be used even at 1 day of life, but its availability is limited.
- Beta trace protein and beta-2 macroglobulin may be future endogenous biomarkers used to assess kidney function

Measuring kidney function

- Estimated GFR is more suitable and it should be based on serum creatinine and when available, CysC or para-aminohippuric (PAH).
- Creatinine, **2-imido-5-keto-3-methyl-tetrahydroimidazole** is the internal anhydride of creatine. Creatinine is derived from spontaneous nonenzymatic, nonreversible degradation of creatine and phosphocreatine in the muscle, and approximately 2% of **muscle** creatine is converted to creatinine daily. Many organs, including the **kidney**, **liver**, **pancreas**, and **testes**, contribute to creatine synthesis.

Michel Eugène Chevreul





Born	31 August 1786 Angers, France
Died	9 April 1889 (aged 102) Paris, France
Known for	Creatine (1832) Fatty acids Margarine Chevreul's salt Color analysis
Awards	Copley Medal (1857) Albert Medal (1873)
is one of 72 scientists whose name is inscribed on the first floor of the Eiffel Tower.	
Fields	Chemistry

Measuring kidney function

- Kidney clearance describes the volume of plasma that is completely cleared of a substance by the kidneys per unit of time. The kidney clearance of a substance x (Cx) is calculated as:

$C_x = U_x * V/P_x$

- where V is the urine flow rate (mL/min), Ux is the urine concentration of the substance x, and Px is the plasma concentration of substance x.
- Typically, Cx is expressed in mL/min, and normalized to 1.73 m2 body surface area (BSA).
- **If a substance is freely permeable across the glomerular capillary and is not synthesized, transported, or metabolized by the kidney, Cx is equal to the GFR**

The reasons which show creatinine is not an ideal marker for estimation of GFR

- Tubular secretion (Specifically in CKD)→ overestimation of GFR
- H2 blockers, trimethoprim and fenofibrate inhibit tubular secretion of creatinine resulting in higher serum creatinine without a change in GFR.
- Dependency on muscle mass
- Dependency on nutrition
- Non-renal clearance (Specifically in CKD) → overestimation of GFR

The reasons which show creatinine is not an ideal marker for estimation of GFR

- Issues with the **analytical method** (Despite **IDMS** traceability, the original **Jaffe** method is influenced by chromogens such as bilirubin, ketones, some proteins, and drugs like cephalosporines)
- Creatinine clearance with timed urine sampling (24 h urine sample collection can improve the accuracy of GFR estimation. However, timed urine collections are highly inaccurate in children, difficult to perform, time consuming, and impractical)
- Sex-Related Correction in Kidney Function

Serum creatinine values in pediatric patients vary with age and body mass.

- Newborn—0.3 to 1.0 mg/dL (27-88 µmol/L)
- Infant—0.2 to 0.4 mg/dL (18-35 µmol/L)
- Child—0.3 to 0.7 mg/dL (27-62 µmol/L)
- Adolescent—0.5 to 1.0 mg/dL (44-88 µmol/L)

Epidemiology of AKI

- To address the AKI, in 2014, the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study began as a prospective observational multinational study of AKI incidence, outcomes, and risk factors in critically ill children. This study, included patients 3 months to 25 years of age admitted to the ICUs in 32 hospitals in North America, Asia, Australia, and Europe.
- The overall incidence of AKI in the cohort (*N* = 4683) was **27%**. Over **11%** of patients developed **KDIGO** stage 2 or 3 (severe) AKI.
- **They found that solely using creatinine to define AKI would misclassify 67% of oliguric patients as not experiencing AKI.**

Epidemiology

- Multinational collaboration sought to develop a large retrospective cohort of critically ill **preterm and term neonates** (the Assessment of Worldwide Kidney Injury Epidemiology in Neonates [AWAKEN] study) to determine the incidence and risk factors for AKI.
- The KDIGO definition in this cohort was adapted such that baseline creatinine was instead the lowest recorded serum creatinine of each infant and stage 3 AKI was any serum creatinine more than 2.5 mg/dL (rather than 4.0 mg/dL).
- Overall, AKI incidence, similar to the AWARE cohort, was reported as **30%** and rates varied by gestational age group.

Commonly used GFR equations

Equation name	Equation
Equations with serum CysC and without serum creatinine or urea	
1. **Bökenkamp** [117].	GFR (mL/min/1.73 m^2) = 137/serum CysC – 20.4
2. **Filler** [115].	GFR (mL/min/1.73 m^2) = 10^(1.962+ (1.123 * LOG (1/serum CysC))
3. **Grubb** [185].	GFR (mL/min/1.73 m^2) = 84.69 * serum CysC $^{-1.68}$ x 1.384 for age < 14 y
4. **Zappitelli (CysC)** [186].	GFR (mL/min/1.73 m^2) = 75.94/[serum CysC 1.17] if renal transplant, x 1.2
5. **Schwartz improved 2012 (CysC only)** [128].	GFR (mL/min/1.73m^2) = (40.9 ± 0.3)*[1.8/CysC (mg/L)]$^{(0.931 \pm 0.020)}$
6. **Grubb standardized material 2014** [187].	GFR (mL/min/1.73 m^2) = 130*CysC$^{-1.069}$*age[years]$^{0.117}$–7

Commonly used GFR equations

Equation name	Equation
Equations with serum creatinine and without serum CysC or urea	
7. **Schwartz improved 2012 (Cr only)** [128].	GFR (mL/min/1.73m^2) = (42.3 ± 0.3)*((height (m)/SCr (mg/dL)))$^{(0.780 \pm 0.016)}$
8. **Pottel full age Spectrum formula** [188].	GFR (mL/min/1.73m^2) = 107.3/(SCr/Q) for ages 2–40 years GFR (mL/min/1.73m^2) = 107.3/(SCr/Q)*0.988$^{(Age-40)}$ for ages >40 years; where Q-values are the mean or median SCr value for age-sex-specific healthy populations.

Commonly used GFR equations

Equation name	Equation
Equations with serum urea and without serum CysC or creatinine	
9. **Schwartz improved 2012 (urea only)** [128].	GFR (mL/min/1.73m^2) = (41.0 ± 0.5)*[30/BUN (mg/dL)]$^{(0.613 \pm 0.024)}$
Equations with serum CysC and serum creatinine	
10. **Bouvet** [189]	[(SCr (μM)/96) $^{(-0.35\ (+/-0.20))}$]*[(CysC (mg/L)/1.2$^{(-0.56\ (\pm 0.19))}$]*[(body weight (kg)/45)$^{(0.30\ (\pm 0.17))}$]*[age (years)/14)$^{(0.40\ (\pm 0.16))}$]
11. **Schwartz improved 2012** [128] **(CysC + Cr).**	GFR (mL/min/1.73m^2) = (41.6 ± 0.3)*((height (m)/Scr (mg/dL)))$^{(0.443 \pm 0.026)}$ *[1.8/CysC (mg/L)]$^{(0.479 \pm 0.031)}$
12. **Zappittelli (CysC + Cr)** [186].	GFR (mL/min/1.73 m^2) = (507.76*$e^{0.003*\text{height}}$)/ (CysC$^{0.635}$*SCr$^{0.547}$ [μmol/L]) If renal transplant, x1.165 If spina bifida, x(SCr$^{0.925}$ [μmol/L])/40.45

Commonly used GFR equations

Equation name	Equation
Equations with serum creatinine and serum urea	
13. **Schwartz improved 2012 (Cr + urea)** [128].	$GFR\ (mL/min/1.73m^2) = (41.9 \pm 0.3)^* [(height\ (m)/Scr\ (mg/dL))]^{(0.662 \pm 0.021)*} [30/BUN\ (mg/dL)]^{(0.171 \pm 0.021)}$
Equations with serum CysC and serum urea	
14. **Schwartz improved 2012 (CysC + urea)** [128].	$GFR\ (mL/min/1.73m^2) = (40.8 \pm 0.3)^*[1.8/CysC\ (mg/L)]^{(0.796 \pm 0.027)\ *} [30/BUN\ (mg/dL)]^{(0.157 \pm 0.022)}$
Equations with serum CysC, serum creatinine, and serum urea	
15. **Schwartz improved 2012 (Cr + CysC + urea)** [128] .	$GFR\ (mL/min/1.73m^2) = (41.5 \pm 0.3)^*((height\ (m)/Scr\ (mg/dL)))^{(0.417 \pm 0.026)} *[1.8/CysC\ (mg/L)]^{(0.431 \pm 0.032)} *[30/BUN\ (mg/dL)]^{(0.088 \pm 0.019)}$

ESTIMATION OF GLOMERULAR FILTRATION RATE

- **The *Schwartz equation*** is the traditional formula used to calculate estimated GFR (eGFR) in children. The Schwartz equation is based on serum creatinine determined by the Jaffe method.

eGFR (mL/min/m2) = *k* × height (cm)/serum creatinine (mg/dL)

k = Muscle factor:

Premature infant younger than 1 year of age = **0.3**325

Term infant younger than 1 year of age = **0.4**526

Child or adolescent girl = **0.5**5

Adolescent boy = **0.7**

ESTIMATION OF GLOMERULAR FILTRATION RATE

- **Bedside Schwartz formula:**

eGFR (mL/min/m2) = 0.413 × height (cm)/serum creatinine (mg/dL)

- It should be noted that the above formulas assume **the patient to be in a steady state and serum creatinine to be stable**. In patients with AKI and rising creatinine, these formulas are not accurate.

Normal Glomerular Filtration Rate (GFR)

Values for Children

Children reach adult levels of GFR by the age of 2.

Age	GFR (mL/min/1.73 m^2)	Range (mL/min/1.73 m^2)
Preterm (<34 wk)		
2–8 days	11	11–15
4–28 days	20	15–28
30–90 days	50	40–65
Term (>34 wk)		
2–8 days	39	17–60
4–28 days	47	26–68
30–90 days	58	30–86
1–6 mo	77	39–114
6–12 mo	103	49–157
12–19 mo	127	62–191
2–12 y	127	89–165

Modified from Heilbron DC, Holliday MA, al-Dahwi A, et al. Expressing glomerular filtration rate in children. *Pediatr Nephrol.* 1991;5:5–11.

Etiology (AWARE study)

- **At-risk children**; including
  - Stem cell and solid organ transplant recipients
  - Post-cardiac surgery patients
  - Premature infants
  - Patients treated with immune-modulating treatments
  - Chronic mechanical ventilation
  - Extracorporeal membranous oxygenation (ECMO).

Etiology (AWAKEN study)

- **At-risk infant**; including
  - 21% to 44% (KDIGO stages 2 and 3) for patients with **severe sepsis**.
  - 62% for those requiring **ECMO** support
  - 45% for **burn** patients
  - 38% to 61% for children undergoing **corrective surgery of congenital heart disease** (incidence is inversely proportionate to age at time of surgery)
  - 55% for patients with **hematopoietic stem cell transplant** (HSCT)

Acute Kidney Injury Risk Stratification Scores

Renal angina index (RAI) scoring system (in PICU)		
Variable		Score
Acute kidney injury risk strata		
Intensive care unit (ICU) admission (moderate risk)		1
Solid organ or stem cell transplant (severe risk)		3
Mechanical ventilation or vasoactive support, or both (very high risk)		5
Clinical injury signs		
Decrease in Estimated creatinine clearance (eCrCl%)	Fluid overload (FO%)	
No change	≤ 5	1
0–<25	5–<10	2
25–<50	10–<15	4
≥ 50	≥15	8

Total RAI score = injury risk × injury signs

Assessment of Glomerular Function and Injury

KDIGO Acute Kidney Injury Criteria		
Stage	Change in Serum Creatinine (SCr)	Urine Output
1	↑≥0.3 mg/dL over 48 h or ↑ 150%–200% over 7 days	<0.5 mL/kg/h for 8 h
2	↑≥200%–300%	<0.5 mL/kg/h for 16 h
3	↑≥300%, SCr ≥4 mg/dL, or dialysis or eGFR<35 mL/min/1.73 m2 for patients<18 y	<0.3 mL/kg/h for 24 h or anuria for ≥12 h

eGFR, Estimated glomerular filtration rate.

Kidney Disease: Improving Global Outcomes (KDIGO)

Assessment of Glomerular Function and Injury

The AKIN classification/staging system of acute kidney injury		
Stage	Serum Creatinine (SCr)	Urine Output
1	↑ SCr ≥26.5 µmol/L (≥0.3 mg/dL) or ↑SCr ≥150 a 200% (1.5 - 2×)	<0.5 mL/kg/h (>6 h)
2	↑ SCr >200 - 300% (>2 - 3×)	<0.5 mL/kg/h (>12 h)
3[b]	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 µmol/L (≥4 mg/dL) ↑SCr ≥44.2 µmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

[a]SCr, serum creatinine; UO, urine output.

[b]Stage 3 also includes patients requiring RRT independent of the stage (defined by SCr and/or UO) they are in at the moment they initiate RRT.

Assessment of Glomerular Function and Injury

Modified RIFLE classification in critically ill children (pRIFLE)		
Stage	GFR criteria*	Urine output criteria
Risk	eCCr decreased > 25%	<0.5 mL/kg/h for 8 h
Injury	eCCr decreased > 50%	<0.5 mL/kg/h for 16 h
Failure	eCCr decreased > 75% or eCCr <35 mL/min/1.73 m^2	<0.3 mL/kg/h for 24 h or anuria for 12 h
Loss of function	persistent acute renal failure >4 weeks	
End-stage renal disease	complete loss of kidney function >3 month	

***GFR was calculated based on Updated Schwartz formula:**

eGFR = 0.413 x (height/Serum creatinine)

eCCr = estimated creatinine clearance; GFR = glomerular filtration rate.

Ciccia E, Devarajan P. Pediatric acute kidney injury: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis. 2017;10:77-84.

Research Paper

Clinical and Laboratory Characteristics of Acute Kidney Injury in Critically Ill Children: A Single Center Study

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Citation Baryar Langroudi F, Mohammadjafari H, Rostami Rad H, Momeni M, Guran M, Naveeifar MR. Clinical and Laboratory Characteristics of Acute Kidney Injury in Critically Ill Children: A Single Center Study. Journal of Pediatrics Review. 2023; 11(4):363-372.
http://dx.doi.org/10.32598/jpr.11.4.23.12

http://dx.doi.org/10.32598/jpr.11.4.23.12

Demographic and clinical variables in 255 children with (24.7%) and without acute kidney injury

Variable		Without AKI (n=192) (%)*	With AKI (n=63) (%)*	Unadjusted P-value	Unadjusted OR (95%CI)	Adjusted*** P-value	Adjusted OR (95%CI)
Age, month (Median, IQR)		17 (5-53)	24 (7-72)	0.070	NA	0.015	1.01 (1.00-1.02)
Sex -male		94 (49)	38 (60.3)	0.153	1.6 (0.91-2.85)	NE	NE
PRISM (Median, IQR)		4 (0-7)	6 (4-11)	0.002	NA	NA	NA
Organ dysfunction state	No organ dysfunction	108 (56.3)	31 (49.2)	0.382	1.33 (0.75-2.35)	Reference	NA
	Respiratory	27 (14.4)	19 (30.6)	0.004	2.6 (1.31-5.22)	0.882	0.93 (0.37-2.36)
	Neurologic	41 (21.7)	12 (19.4)	0.695	0.9 (0.45-1.81)	0.865	0.93 (0.37-2.36)
	Cardiovascular	7 (3.7)	5 (8.1)	0.177	2.3 (0.74-7.52)	0.285	2.05 (0.55-7.66)
	Hematologic	17 (8.9)	9 (14.3)	0.216	1.7 (0.71-4.13)	0.937	0.95 (0.28-3.29)
	Hepatic	5 (2.6)	6 (9.5)	0.025	3.9 (1.28-13.44)	0.673	0.95 (0.28-3.29)
Multiple organ dysfunction**		31 (16.1)	31 (49.2)	0.000	5.03 (2.69-9.41)	0.000	4.36 (2.25-8.46)
Nephrotoxic agents		147 (76.6)	49 (77.8)	0.843	1.1 (0.52-2.14)	0.697	0.87 (0.42-1.78)
Cause of admission	Infectious	99 (51.6)	29 (46)	0.471	0.80 (0.45-1.42)	0.941	0.97 (0.45-2.08)
	Respiratory	15 (7.8)	4 (6.3)	1.000	0.80 (0.26-2.51)	0.796	1.19 (0.33-4.32)
	Endocrine	8 (4.2)	5 (7.9)	0.238	1.98 (0.62-6.30)	0.257	2.12 (0.58-7.77)
	Gastrointestinal	7 (3.6)	0	0.199	NA	0.999	0.00 (0.00)
	Surgery-Trauma	11 (5.7)	11 (17.5)	0.004	3.48 (1.43-8.48)	0.107	2.48 (0.82-7.45)
	Neurologic	52 (27.1)	14 (22.2)	0.445	0.77 (0.39-1.51)	Reference	NA

* percent is within group, ** organ failure except renal failure, *** adjusted for PRISM score using multivariable regression,

THANK YOU