Methodological considerations to be taken into account when setting up the next IGGI renal dosing table

BVIKM symposium 22 Nov 2018

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Background

Current IGGI table ‘Dosing in renal insufficiency’

Set up as a consensus document cfr talk Franky Buyle

POSOLOGIEEN BIJ ADOLESCENTEN EN VOLWASSENEN MET NIERINSUFFICIENTIE:
ANTIBIOTICA

VOORAFGAANDELIJKE OPMERKINGEN BETREFFENDE POSOLOGIEEN BIJ PATIENTEN MET NIERINSUFFICIENTIE

- ***Aminosiden***

ANTIBIOTICUM	EERSTE DOSIS/ OPLAADDOSIS	(GESCHATTE) GLOMERULAIRE FILTRATIESNELHEID			
		89 › 60 ML/MIN	59 › 30 ML/MIN	29 › 15 ML/MIN	< 15 ML/MIN (ESRD)
Amikacine iv of im (normale dosis).	25 tot 30 mg/kg	25 tot 30 mg/kg toegediend met de kortst mogelijke intervallen (minimum 24 uur) die toelaten dalserumconcentraties te bereiken van < 3 µg/ml.			
	15 tot 30 mg/kg	15 tot 30 mg/kg q24h	15 tot 30 mg/kg q48h	15 tot 30 mg/kg q72h	15 tot 30 mg/kg q96h
	25 mg/kg	15 mg/kg q24h	15 mg/kg q48h	Geen onderhoudstherapie (enkel éénmalig 15 mg/kg).	
	15 tot 25 mg/kg	15 tot 25mg/kg q24h	15 tot 25 mg/kg q24h		15 mg/kg q48h
	15 tot 25 mg/kg	15 mg/kg q24h	15 mg/kg q24h	15 mg/kg q48h	15 mg/kg q72h	15 mg/kg q96h

ANTIBIOTICUM	(GESCHATTE) GLOMERULAIRE FILTRATIESNELHEID				
	≥ 90 ML/MIN[1]	89 → 60 ML/MIN	59 → 30 ML/MIN	29 → 15 ML/MIN	< 15 ML/MIN (ESRD[2])
Amikacine iv (of im).	Doses van 25 tot 30 mg/kg toegediend met de kortst mogelijke intervallen (minimum 24 uur) die toelaten dalserumconcentraties te bereiken van < 3 µg/ml.				
	15 mg/kg q24h				
	25 mg/kg q24h				

Background

POSOLOGIEEN VAN ANTI-INFECTIEUZE GENEESMIDDELEN: ADOLESCENTEN EN VOLWASSENEN MET NIERINSUFFICIENTIE

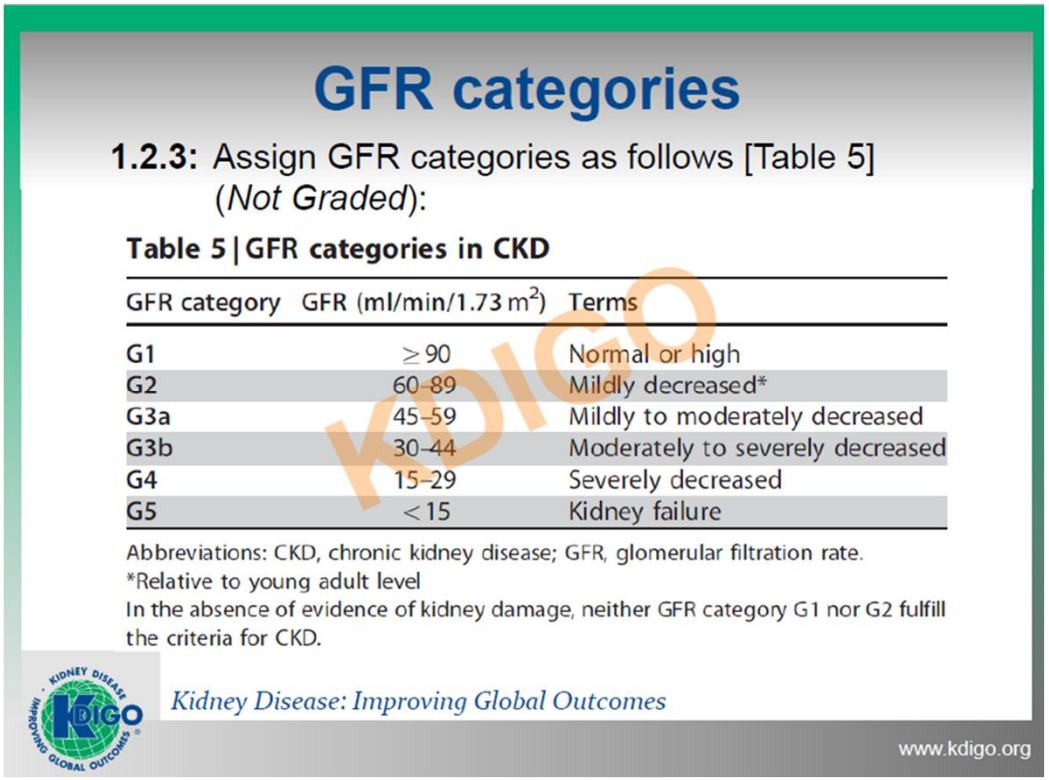
VOORAFGAANDELIJKE OPMERKINGEN BETREFFENDE DE POSOLOGIEEN VAN ANTI-INFECTIEUZE GENEES-MIDDELEN BIJ PATIENTEN MET NIERINSUFFICIENTIE

- ***Antibiotica***
  - Aminosiden.
  - Azaliden, ketoliden, lincosamiden, (neo)macroliden.
  - Carbapenems, monobactams.
  - Cefalosporines.
  - Fluoroquinolonen.
  - Glycopeptiden.
  - Penicillines.
  - Rifamycines.
  - Tetracyclines.
  - 5-nitro-imidazolen.
  - Diverse andere antibiotica.

- Review the current dosing table
- Comments sent to BVIKM board
- Opportunity to think and read about important issues in renal dosing

Background

- Several very important elements are already correctly addressed in the current dosing table
  - Division in **stages of renal insufficiency** (> 90, 89-60, 59-30, 29-15, < 15 mL/min)
    → corresponding to KDIGO stages for chronic kidney disease
  - **Standard dosing** is provided for patients with > 90 mL/min
  - **Several dosing regimens** are provided per antibiotic (e.g. for flucloxacillin: 4 x 1g; 4 x 2g and 6 x 2g/day)



KDIGO = Kidney Disease: Improving Global Outcomes

https://kdigo.org/guidelines/

Objectives

When thinking about an update of the IGGI renal dosing table,
3 questions should be discussed:

- **Q1. How can renal function best be assessed in the context of dose adjustments in patients with renal insufficiency?**
- **Q2. Should we always adjust doses?**
- **Q3. Can the same renal dosing table be applied in septic/critically ill patients?**

« Quick » wins

Q1. Assessment of renal function

Voor de berekening van de (geschatte) glomerulaire filtratie snelheid kunnen in de dagelijkse praktijk verschillende formules (MDRD, Cockroft-Gault, Salazar-Corcoran, …) gebruikt worden. In de onderstaande tabel worden vorken gehanteerd die breed genoeg zijn om eventuele verschillen die het gevolg zijn van het gebruik van deze verschillende formules te compenseren. Ieder laboratorium/ziekenhuis kan dus zijn eigen gewoontes aanhouden en toch gebruik blijven maken van de tabel.

Is this way of working really correct?

- Are estimators equal in accuracy when it comes to assessment of kidney function?
- Are estimators interchangeable when it comes to drug dosing?

http://www.bvikm.org/documenten

Q1. Assessment of renal function

- **HISTORY (1)**
  - Already in the late 50s , the relation between renal impairment (measured as 24h CrCl) and longer halflife of antibiotics was documented
  - **First renal dose adjustment** reported in patients with 'uremia' in the 1967
  - First systematic methodology for dose adjustments published by Dettli in 1970 - '**Dettli's rule** for dose adjustment' – basis for kidney dosing nomograms/tables
  - Not much uptake of Dettli's rule as a rapid and clinically practical method for assessing kidney function was lacking - only way to do this was measuring CrCl (surrogate for GFR) by **24h timed urinary collection**

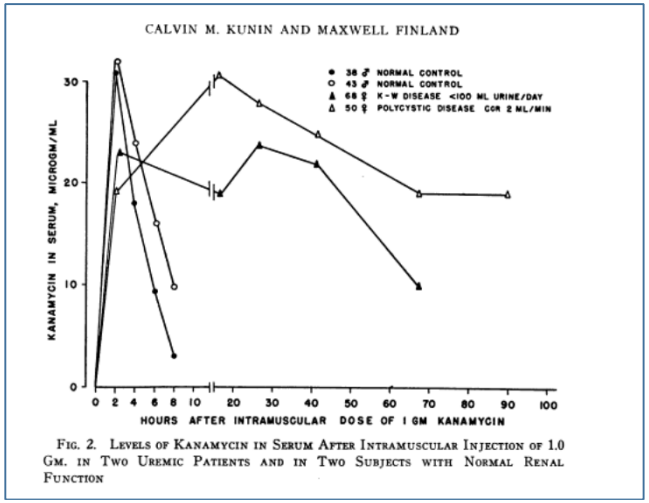


FIG. 2. LEVELS OF KANAMYCIN IN SERUM AFTER INTRAMUSCULAR INJECTION OF 1.0 GM. IN TWO UREMIC PATIENTS AND IN TWO SUBJECTS WITH NORMAL RENAL FUNCTION

individual elimination

$$Q = Q_0 + (1 - Q_0) \times \frac{GFR}{100\ [ml/min]}$$

Hudson & Nolin, Adv Chron Kidney Dis 2018; 25 (1): 14-20
Kunin CM et al. J Clin Invest 1959; 38: 1509-19
Dettli L JAMA 1970; 214: 1468-75.

Q1. Assessment of renal function

Cockcroft–Gault equation (eCCR in mL/min):

$$\frac{(140 - age) \times weight}{72 \times S_{cr}} \times (0.85 \text{ if female})$$

- **HISTORY (2)**

1976 - publication of **'Cockcroft-Gault formula' (CG)**

  - Estimates CrCl, validated vs. measured CrCl
  - Developed and validated only in caucasian men, small sample size
  - Knowledge of age, sex, weight, Scr
  - Correction factor for female patients was hypothetical

- Rapidly taken up because of **its simplicity and ease of use**
- Used instead of mCrCl in Dettli's rule
- Pushed development of other kidney dosing initiatives and real PK research

- **Taken up in 1998 FDA guidance (and afterwards also by EMA) in order to conduct phase I PK research to define dose adjustments in patients with renal insuffiency**

Hart L & Anderson G. Clinical Pharmacokinet 2018; 943-976.

Q1. Assessment of renal function

$$MDRD4-GFR = 186 \times SC^{-1.154} \times Age^{-0.203} \times [0.742 \ if \ patient \ is \ female] \times [1.210 \ if \ patient \ is \ black]$$

HISTORY (3)

1999 – publication of Modification of Diet in Renal Disease formula (MDRD)

- Estimates GFR, validated vs. Iothalamate
- Developed and validated in 1070 patients (caucasian, blacks, m/f, DM, Tx, ...)
- MDRD6, later adapted to MDRD4
- Knowledge of age, sex, race, Scr
- Results are indexed by a BSA of 1.73m2 – not accurate for very low or high BSA (de-indexing necessary)

- **Very accurate** in GFR < 60 mL/min.1.73m2
- Underestimates true GFR > 60 mL/min
- **Significantly improved precision and accuracy compared to CG**

Hart L & Anderson G. Clinical Pharmacokinet 2018; 943-976.

Q1. Assessment of renal function

Gender	Creatinine concentration	Formula
Woman	≤ 0.7	$GFR = 144 \times (Cr/0.7)^{-0.329} \times (0.993)^{age}$
	> 0.7	$GFR = 144 \times (Cr/0.7)^{-1.209} \times (0.993)^{age}$
Man	≤ 0.9	$GFR = 141 \times (Cr/0.9)^{-0.411} \times (0.993)^{age}$
	> 0.9	$GFR = 141 \times (Cr/0.9)^{-1.209} \times (0.993)^{age}$

HISTORY (4)

2009 – publication of Chronic Kidney Disease – Epidemiology Collaboration formula (CKD-EPI)

- Estimates GFR, validated vs. iothalamate and inulin
- Developed and validated in a very large dataset, including patients with high GFR
- As accurate as MDRD < 60 mL/min.1.73m2, **more accurate in patients 60-90 mL/min.1.73m2**
- **CKD-EPI is nowadays automatically reported by laboratories in patients' medical record**

2005-2010: Scr assay standardized to IDMS-traceable assay

- Scr concentrations 10-20% lower than before
- Improved accuracy of MDRD4 even more, when compared to CG
- CG equation can not be converted to IDMS-traceable Scr (samples used to validate CG are not available anymore)
- CrCl estimated by CG based on IDMS traceable are 5-10% higher than before

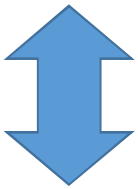
Hart L & Anderson G. Clinical Pharmacokinet 2018; 943-976.

Q1. Assessment of renal function

THE PROBLEM:

Until 2008, only the CG equation was mentioned in both FDA and EMA guidance for phase IPK research in patients with renal impairment

→ for the majority of currently marketed drugs, CG estimated CrCl is used to recommend dose adjustment in renal impairment



Clinical laboratories are now reporting CKD-EPI or MDRD4 in the medical record of the patient

CG is not well validated, estimates CrCl and overestimates since IDMS-Scr

→ **Can CKD-EPI instead of CG be used for dose adjustment in renal insufficiency?**

Consensusvergadering - 27 november 2014

Het rationeel gebruik van geneesmiddelen bij nierinsufficiëntie

De voorgestelde formule hangt af van de medische bijsluiter (Expert opinion, zwakke aanbeveling).

a. Ofwel wordt in de bijsluiter een dosisaanpassing voorgesteld volgens de creatinine klaring (in mL/minuut), dan kan de formule van Cockcroft-Gault aangewend worden.
b. Ofwel wordt in de bijsluiter een dosisaanpassing voorgesteld volgens de GFR (in mL/minuut/1,73 m^2) of volgens de CNI-classificatie (van 1 tot 5). Dan kan de geschatte GFR (eGFR) worden berekend via de MDRD-formule of de CKD-EPI-formule. Voor wat betreft de CNI-classificatie wordt de door KDIGO CKD voorgestelde classificatie gebruikt.

Package insert?

CEFTA-AVI

Table 2 Recommended intravenous doses for patients with estimated CrCL ≤ 50 mL/min

Estimated CrCL (mL/min)	Dose regimen[2]	Frequency	Infusion time
31-50	1 g/0.25 g	Every 8 hours	2 hours
16-30	0.75 g/0.1875 g	Every 12 hours	2 hours
6-15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD including on	0.75 g/0.1875 g	Every 48 hours	2 hours

Nierfunctiestoornissen

De intraveneuze dosering dient als volgt te worden a
van de nierfunctie (elke patiënt moet nauwgezet wor
stof; de dosering van het g
worden aangepast):

Creatinineklar (ml/min)
> 40
20-40
< 20

...avicefta on

VANCO

GFR (ml/min/1,73 m2) I.v. dosis Frequentie	I.v. dosis	Frequentie
50-30	15 mg/kg	12-uurs
29-10	15 mg/kg	24-uurs
< 10	10-15 mg/kg	Opnieuw doseren op basis van spiegels*
Intermitterende hemodialyse		
Peritoneale dialyse		
Continue niervervangende therapie	15 mg/kg	Opnieuw doseren op basis van spiegels*

AMOXI

Gestoorde nierfunctie

Bij volwassenen en ado
aangepast volgens onde
van deze dosisaanpassin

Creatinineklaring (ml/min)	mg of 1 g of
26-50	1 eenheidsdo
10-25	een halve eer
< 10	een halve eer

		< 40 kg#
		...g noodzakelijk
		...emaal daags
		(maximaal 500 mg tweemaal
minder dan 10	maximaal 500 mg/dag.	15 mg/kg toegediend als een enkelvoudige dagelijkse dosis (maximaal 500 mg)

Q1. Assessment of renal function

IS IT REALLY A PROBLEM?

How discordant are CKD-EPI (or MDRD4) and CG ?

- Park – dose adjustments for 26 approved drugs – comparison of MDRD (with de-indexed BSA) vs. CG
  - 12% discordance in recommended drug dosages
  - The majority of patients will receive the same dose
  - MDRD or CKD-EPI leads to **significantly higher eGFRs** in old patients (> 80 yrs), low weight (< 55 kg) or low SCr values

Table 3. Dosage Adjustments for Antimicrobials Based on Estimated GFRs in 207 Patients

Drug	Cockcroft-Gault Cl_{cr} Based on IBW and Adjusted S_{cr} (ml/min)				Discordance (%)
Cefepime	< 11	11–30	30–60	> 60	36.3
Unadjusted MDRD GFR (ml/min)					
< 11	1 (0.5)	1 (0.5)	0 (0)	0 (0)	
11–30	0 (0)	16 (7.7)	1 (0.5)	0 (0)	
30–60	0 (0)	17 (8.2)	42 (20.3)	0 (0)	
> 60	0 (0)	1 (0.5)	55 (26.6)	73 (35.7)	
Levofloxacin	10–20	20–50	> 50		31.0
Unadjusted MDRD GFR (ml/min)					
10–20	5 (2.4)	2 (1.0)	0 (0)		
20–50	7 (3.4)	34 (16.4)	0 (0)		
> 50	0 (0)	55 (26.6)	104 (50.2)		
Meropenem	< 10	10–25	25–50	> 50	32.4
Unadjusted MDRD GFR (ml/min)					
< 10	1 (0.5)	1 (0.5)	0 (0)	0 (0)	
10–25	0 (0)	10 (4.8)	0 (0)	0 (0)	
25–50	0 (0)	11 (5.3)	25 (12.1)	0 (0)	
> 50	0 (0)	1 (0.5)	54 (26.1)	104 (50.2)	
Piperacillin-tazobactam	< 20	20–40	> 40		22.8
Unadjusted MDRD GFR (ml/min)					
< 20	5 (2.4)	2 (1.0)	0 (0)		
20–40	7 (3.4)	18 (8.7)	0 (0)		
> 40	0 (0)	38 (18.4)	137 (66.2)		

Data are no. (%) of dosage adjustments.
GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; Cl_{cr} = creatinine clearance; IBW = ideal body weight; S_{cr} = serum creatinine concentration.

Golik et al. Pharmacotherapy, 2013

Hart L & Anderson G. Clinical Pharmacokinet 2018; 943-976.

Park EJ. Ann Pharmacother 2011; 1130-44.

Q1. Assessment of renal function

- **THE SOLUTION?**

- Sound clinical judgement
  - Both CKD-EPI and CG are estimates (and not measurements) of kidney function, influenced by many factors such as creatinine production, muscle mass, body weight (or BSA) etc
  - The need for dose adjustment also depends on the drug itself, and its therapeutic margin
  - When dose adjustment recommendations are not the same, the risk/benefit should drive the choice for a specific dose – a more aggressive dose might be preferred for e.g. betalactams

  (and then it is not a problem that CKDEPI and MDRD overestimate CG in some situations)

Q1: Assessment of renal function?

- Can be performed by CKD-EPI (can be adapted in next IGGI)

- CG is not accurate, not wel validated and not reliable anymore since IDMS-traceable Scr assay
- Using the same formula for diagnosis & management of kidney disease, drug development and dosing would be ideal
- CKD-EPI overestimates CG in some situations, but this is not a problem for AB
- In patients with overweight or obesity, CKD-EPI will underestimate CG – so a higher dosing might be preferred
- FDA has already taken up CKD-EPI in the 2010 draft guidelines for phase I PK in renal impairment

Q2: Should we always reduce the dose?

- The goal of renal dose adjustments is off course to achieve equal exposures in patients with normal vs. impaired renal function, in order to avoid toxicity without compromising efficacy
- However, in many of the recently approved new antibiotics, a lower efficacy has been shown in patients with moderate renal impairment
- Precautionary statements in SmPCs of e.g. ceftazidim-avibactam, ceftolozane-tazobactam and telavancin – **all stating that clinical response is reduced in patients with CrCl 30-50 mL/min**

----------WARNINGS AND PRECAUTIONS----------

- Decreased efficacy in cIAI patients with baseline CrCl of 30 to less than or equal to 50 mL/ min. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of AVYCAZ accordingly. (*5.1*)

---------- WARNINGS AND PRECAUTIONS ----------

- Decreased efficacy in patients with baseline CrCl of 30 to ≤50 mL/min. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly. (5.1)

Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program

John E. Mazuski,[1] Leanne B. Gasink,[2] Jon Armstrong,[5] Helen Broadhurst,[5] Greg G. Stone,[3] Douglas Rank,[4] Lily Llorens,[4] Paul Newell,[5] and Jan Pachl[6]

[1]Washington University School of Medicine, St Louis, Missouri; [2]AstraZeneca, Wilmington, Delaware; [3]AstraZeneca, Waltham, Massachusetts; [4]Actavis, Oakland, California; [5]AstraZeneca, Alderley Park, United Kingdom; and [6]The Charles University, Prague, Czech Republic

No clinically meaningful trends in outcomes were observed between patient or disease baseline characteristic subgroups, except in patients with moderate renal impairment at baseline. Within this population, there was a response trend in favor of meropenem in the mMITT (between-group difference, −29.1%; 95% CI, −50.05 to −5.36) and MITT (−25.6%;−44.53 to −4.78) populations (Figure 2). Numerically, this trend was also seen in the clinically evaluable population (between-group difference −16.0; 95% CI, −38.23 to 6.87). Within the first 48–72 hours of dosing, 67.9% of patients with an estimated CrCl <50 mL/min at baseline across both study drug groups showed rapid improvement to an estimated CrCl >50 mL/min (ceftazidime-avibactam plus metronidazole, 67.5%; meropenem, 69.8%).

underdosed early in the study. Because the protocol-specified reduction in total daily dose in renal impairment for ceftazidime-avibactam (−66%) was greater than for meropenem (−33%), this increased the risk of underdosing in patients receiving ceftazidime-avibactam. These results should be interpreted with caution because patients with renal impairment at baseline represented only a small subgroup (8% of the MITT population); however, similar results have also been noted with ceftolozane-tazobactam, another β-lactamase/β-lactam combination [22].

Mazuski JE et al. CID 2016; 62:1380-9.

Q2: Should we always reduce the dose?

- Renal dose adjustments are based on AUC measurements in phase I studies including a small number of healthy patients **with CKD**
- In many acutely infected patients, renal impairment will be acute and transient, rather than chronic, especially in hospitalized patients
- Renal dosing protocols , based on data gathered in not acutely ill patients with CKD
  - Are usefull for adjusting chronic medication (NOAC, metformin, ...) in patients with CKD
  - ! But might lead to inappropriate antibiotic dose reduction in acutely infected patients potentially explaining the lower efficacy in moderate renal impairment

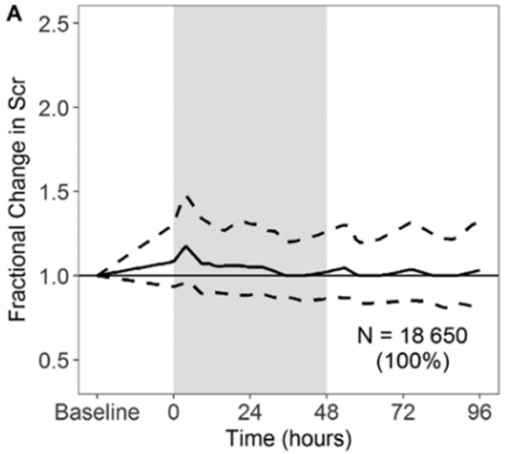
Crass RL. CID 2018

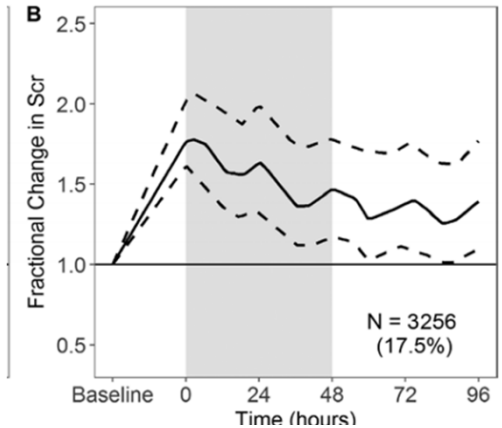
Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor; [2]Departments of Pharmacy Practice and Medicine, Colleges of Pharmacy and Medicine, University of Illinois at Chicago

- Illustration of the dynamic nature of renal impairment in acutely infected patients
  - Retrospective study
  - 18500 patients included with cUTI (41%) or acute bacterial pneumonia (11%) or SSI (32%) or cIAI (16%)
  - Total population:
    - Rate of AKI on admission: 17.5%
    - Kidney injury resolved in 57% of patients after 48h
  - Subgroup with moderate RI (16.4%)
    - Rate of AKI on admission: 38%
    - Kidney injury resolved in 46% of patients after 48h





Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor; [2]Departments of Pharmacy Practice and Medicine, Colleges of Pharmacy and Medicine, University of Illinois at Chicago

- Conclusion
  - Adequate antibiotic exposure is very important in the first 48h - the authors call this 'THE CRITICAL PERIOD'
  - For antibiotics with a wide safety margin (e.g. betalactams) dose adjustments should be deferred until 48h after initiation when the trajectory of the patient's renal function is better known
  - If renal impairment persists: dose adjustment should be carried out on day 3 to minimize toxicity

Q2: Should we always reduce the dose?

- Dose adjustments in RI go back to small regulatory studies carried out in patients with CKD
- AKI might be transient during infection

→ Renal dosing tables might overestimate dose reductions in AKI

The following recommendations should be added in the IGGI table:

- For betalactams: dose reductions should be postponed to 48h
- For vancomycin, aminoglycosides, colistin: dose reductions should not be deferred as this carries a risk for toxicity

Q3: Can the same renal dosing table be applied in septic patients/ICU?

YES…

BUT… a specific text should be added in IGGI on '**considerations to be taken into account for renal dosing in critically ill patients'**

1) Assessment of renal function
   - None of the estimators (CG, MDRD4, CKD-EPI) have been validated in critically ill patients
   - Creatinine clearance should be measured via 24h timed urinary collection - CrCl (mL/min) =[Ucreat] x Vdiuresis/ [Screat] x 1440
2) Importance of high loading doses
3) Maintenance doses
   - Standard dosing can be maintained during 'the critical period' (first 48h)
   - Higher maintenance dosing might be necessary in septic patients
4) Renal replacement therapy: additional category for drug dosing during IHD and CVVH
5) Recommendation to perform TDM if possible

www.antibioticagids.be

Q3: Can the same renal dosing table be translated to septic patients/ICU?

- In the future, we might also think about adding an extra category on dosing in patients with ‘augmented renal clearance’ (ARC)
  - ARC has been shown to strongly correlate with lower exposure of hydrophilic antibiotics
  - Literature on the link between ARC and worse clinical outcome is more conflicting
  - Ongoing studies (popPK modeling) are seeking optimal maintenance dosing regimens for hydrophilic antibiotics in patients with ARC
  - Potential impact of ARC on loading doses should be evaluated

Q3: Can the same renal dosing table be translated to septic patients/ICU?

As critically ill infected patients

- have a high mortality risk,
- show a significantly altered and unpredictable PK and
- are often treated with hydrophilic AB for which underdosing is far more common than overdosing

→A specific guidance is needed in IGGI on how to use the renal dosing table in this setting

→When taking these recommendations into account, maintenance doses can be reduced accordingly to what is mentioned in the table

DOSERING BIJ GESTOORDE NIERFUNCTIE: AANPASSINGEN

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21/11/2018 21:41:47

OP INTENSIEVE ZORGEN

Antibioticadosering bij acute nierinsufficientie en extracorporele epuratie (dialyse, hemofiltratie, hemodiafiltratie)

Algemene principes

1. Bij kritiek zieke patiënten en vooral bij ernstige sepsis en septische shock is het risico van onderdosering van antibiotica (inefficiëntie met potentieel verhoogde mortaliteit) groter dan het risico van overdosering (toxiciteit).

In geval van twijfel is overdosering steeds te verkiezen boven onderdosering, zeker voor de beta-lactam antibiotica die een relatief brede therapeutische marge hebben.

2. De farmacokinetiek van kritiek zieke patiënten is ernstig verstoord en in belangrijke mate onvoorspelbaar. Het beste wat we kunnen bereiken is dus een "goede benadering" van de correcte dosis.

Mogelijke veranderingen in farmacokinetiek zijn

- een toename van het distributievolume (Vd) van hydrofiele geneesmiddelen (met nood aan een hogere oplaadingsdosis) (aminoglycosiden, glycopeptiden en beta-lactamantibiotica). Concreet wordt bijvoorbeeld aanbevolen voor amikacine om op te laden met 25 mg/kg bij ICU patiënten met severe sepsis en septische shock.
- een toename van de renale klaring (ClR) bij hyperdynamische circulatie (met nood aan een hogere onderhoudsdosis)
- een daling van de klaring als gevolg van orgaandysfunctie (met nood aan een lagere onderhoudsdosis)
- het gebruik van extracorporele epuratie (dialyse, hemofiltratie en hemodiafiltratie)

Praktijk

1. Bij patiënten met nierinsufficiëntie is de oplaaddosis van een antibioticum in principe dezelfde als voor patiënten met een normale nierfunctie. Gebruik de oplaaddosis die past bij de ernst van de infectie. Bij kritiek zieke patiënten kan het Vd van hydrofiele geneesmiddelen (zoals de aminoglycosiden, de beta-lactams en de glycopeptiden) erg gestegen zijn (vochtresuscitatie, oedemen) en moet dus een hogere oplaadddosis gegeven worden. Concreet wordt bijvoorbeeld aanbevolen voor amikacine om op te laden met 25 mg/kg bij ICU patiënten met severe sepsis en septische shock.

Oplaaddosis = Vd x target concentratie

2. De aanwezigheid van een (acute) nierinsufficiëntie zal een reductie van de onderhoudsdosis vereisen bij geneesmiddelen met belangrijke renale klaring (= renale klaring meer dan 20% van totale klaring). Voor aanpassing zie "tabel voor volwassen zaalpatiënten". Het is belangrijk te weten dat de formules voor estimatie van de glomerulaire filtratie (CKD-EPI, Cockroft-Gault, MDRD) niet gevalideerd zijn bij kritiek zieke patienten. Indien mogelijk is een gemeten creatinine klaring (op basis van 24-uurscollectie) te verkiezen (Ucreat x Uvol/Screat x1440). Indien twijfel, moet voor de hoogste dosis gekozen te worden.

3. De manier waarop de dosisaanpassing wordt uitgevoerd wordt bepaald door de farmacodynamische eigenschappen van het antibioticum: bij dosisreductie van concentratie-afhankelijke antibiotica (aminoglycosiden, fluoroquinolones) is een verlenging van het doseringsinterval te verkiezen, voor tijdsafhankelijke antibiotica (beta-lactams, glycopeptiden) een reductie van de onderhoudsdosis.

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« Quick » wins

- Loading/first doses are not mentioned in the current table
  - Potential risk that reduced maintenance dose is given instead of loading dose
  - Important to add that loading doses never should be adjusted to the patient's renal function
- Addition of antifungals (candins, L-AmB, azoles), tuberculostatics (pyrazinamide, rifabutin, isoniazide), other antimicrobials (dapto, cefta-avi)
- Addition of dose adjustments for patients on IHD & CVVH
- Calculator to estimate CKD-EPI & Schwartz (for children) can be added

Conclusion → Discussion

- Do you agree that
  - CKD-EPI can be used as estimator for patient's renal function?
  - Maintenance doses of betalactams should not be adjusted during the first 48h in acutely ill patients ?
  - A specific guidance is needed when the table is used in the ICU?
  - The quick wins can be realized in the next version?