34° CONGRESSO NAZIONALE

SOCIETÀ ITALIANA NEFROLOGIA PEDIATRICA

RAVENNA, 7-9 novembre 2018

Palazzo dei Congressi

Antibiotici e insufficienza renale

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Dipartimento di Pediatria e Specialità Pediatriche

IRCCS G. Gaslini, Genova

ISTITUTO
G. GASLINI

ai sensi dell'Accordo Stato-Regione in materia di formazione continua nel settore "Salute" (Formazione ECM) vigente,

Dichiarazione sul Conflitto di Interessi

Il sottoscritto Enrico Eugenio Verrina in qualità di:

□ responsabile scientifico □ moderatore □ docente X□ relatore □ tutor

dell'evento "_Minilettura «Raccomandazioni: Antibiotici e insufficienza renale»"

da tenersi per conto di **SIP n. 1172**

ai sensi dell'Accordo Stato-Regione in materia di formazione continua nel settore "Salute" (Formazione ECM) vigente,

Dichiara

X□ che negli ultimi due anni NON ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

□ che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario (indicare quali):

_____ _____
_____ _____
_____ _____
_____ _____

ID Week 2018, the 56th Annual Meeting of the Infectious Diseases Society of America (IDSA)

October 2-7, 2018

- The world is facing **an ever-increasing danger of infections that are resistant to most, if not all, available antibiotics**.
- Such infections account for **more than $20 billion in healthcare costs** and **>8 million additional and avoidable hospital days**.
- This problem is becoming more serious because of **reduced funding** for **development of new and more powerful antibiotics**.
- The **US Food and Drug Administration** approved 16 new antibiotics between 1983 and 1987 but has approved **only 2 since 2008**.
- The dearth of **drug development** has been made worse by:

  - the withdrawal of most pharmaceutical companies from antibiotic research because of lessening profit margins

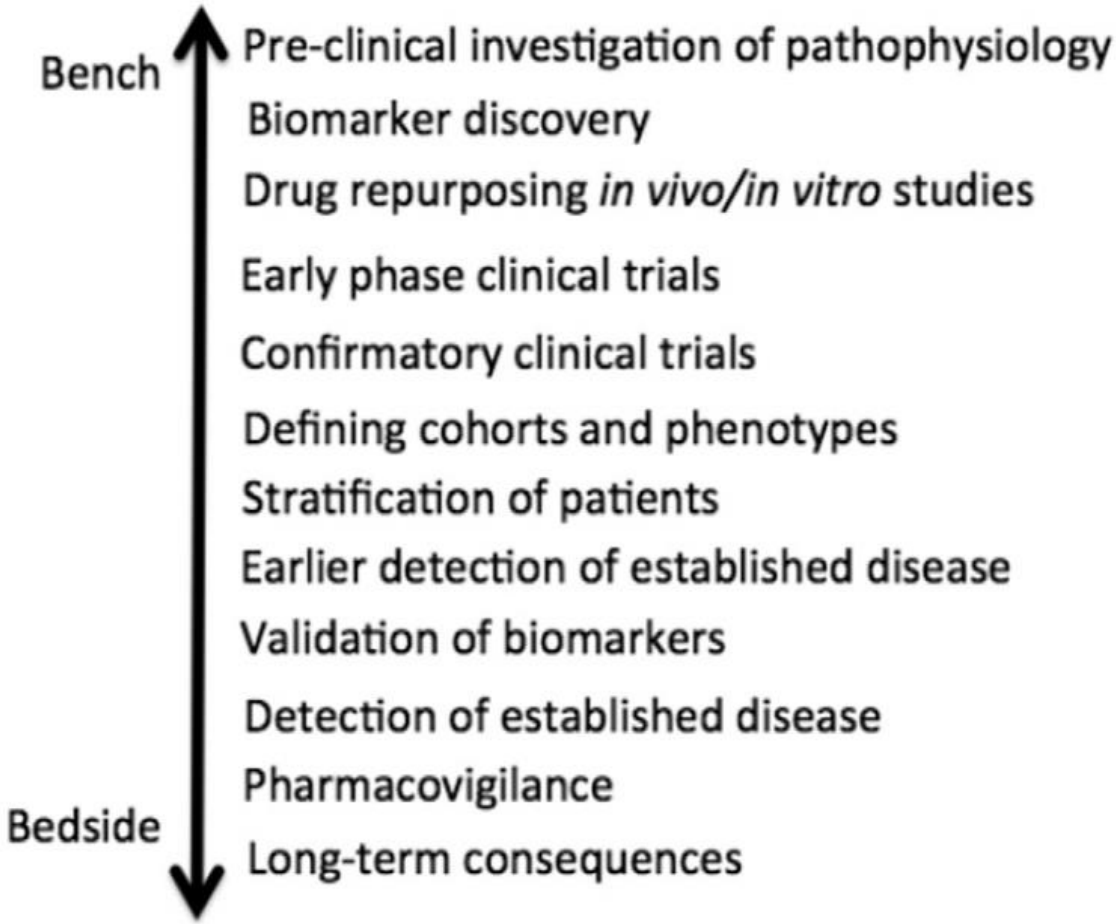
  - the increasing resistance to these drugs resulting from their inappropriate use.
- This has resulted in a **crisis** that has led the ***Infectious Disease Society of America*** to launch the **"10 by '20 Initiative"** which seeks a global commitment **to produce 10 new systemic antibiotics by the year 2020**.

A challenge!

Optimising the use of medicines to reduce acute kidney injury in children and babies

L Oni [a,b,*], DB Hawcutt [a,c], MA Turner [a,d], MW Beresford [a,e], S McWilliam [f], C Barton [f,g], BK Park [f], P Murray [f,h], B Wilm [f,h], I Copple [f], R Floyd [h], M Peak [i], A Sharma [j], DJ Antoine [f]

Pharmacology & Therapeutics 174 (2017) 55–62



The translational pathway - from'bench' to 'bedside' and back again - illustrating the clinical and research requirements in order to reduce drug-induced kidney injury

Obiettivi

- Valutare la necessità di **aggiustamento posologico** degli antibiotici in corso di insufficienza renale
- Identificare i principali **fattori di rischio** per **effetti collaterali avversi** in pazienti con insufficienza renale
- Verificare la metodologia utilizzata per calcolare il **GFR** dei pazienti
- Confrontare i diversi tipi di **terapia sostitutiva renale** per quanto riguarda la rimozione degli antibiotici
- Utilizzare i riferimenti della *clinical practice* e delle raccomandazioni per identificare l'aggiustamento posologico più adeguato alle caratteristiche del **singolo paziente** e del **trattamento** cui è sottoposto

Great Ormond Street Hospital for Children NHS Trust

NHS

Paediatric Drug Dosage Adjustments in Patients with Renal Impairment or on Renal Replacement Therapies for use on the Intensive Care and Renal Units

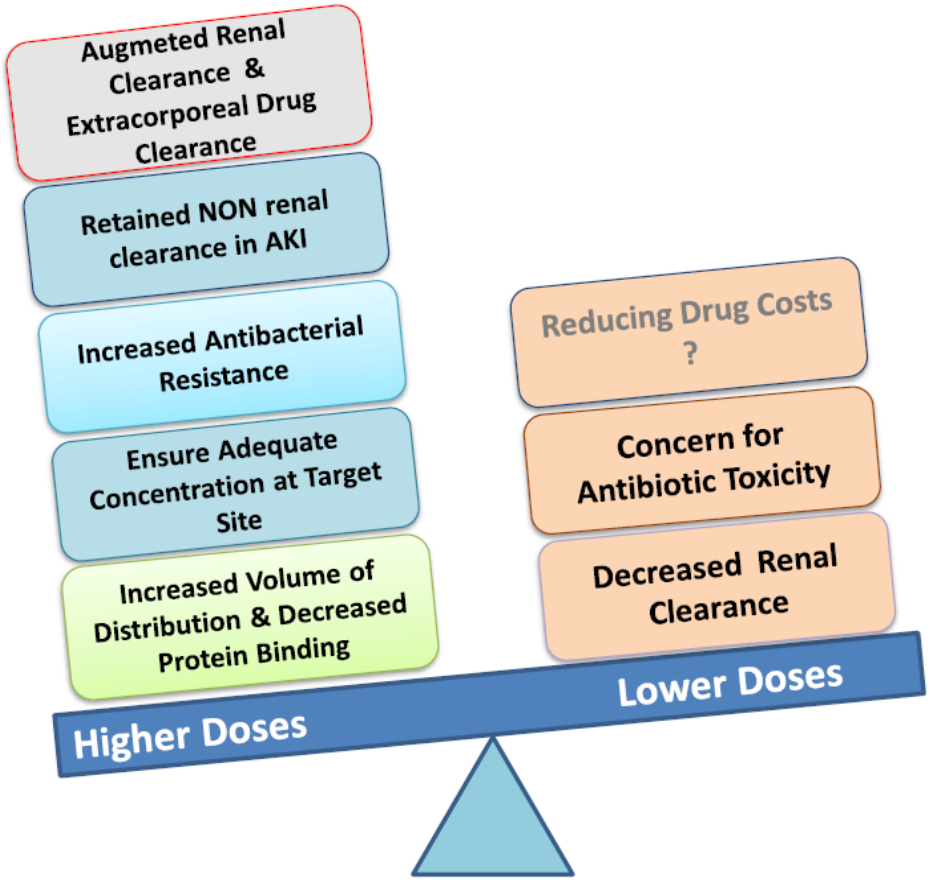
Introduction

When adjusting drug doses for patients with renal impairment or on renal replacement therapies, drug doses should be adjusted taking into account all of the following:

- the usual mechanism of clearance of the drug
- the degree of renal failure
- the potential nephrotoxicity of the drug (and general toxicity)
- the degree of removal of the drug by renal replacement therapies, and
- the severity of the condition being treated.

Inappropriate dosing
in patients with CKD
can cause
toxicity,
or ineffective therapy

Enough but not too much



Journal of Intensive Care Medicine

Susan J. Lewis, and Bruce A. Mueller J Intensive Care Med 2014;31:164-176

Optimising the use of medicines to reduce acute kidney injury in children and babies

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Pharmacology & Therapeutics 174 (2017) 55–62

- Children receiving antibiotics are **typically acutely unwell** and thus they will have confounding factors, such as **hypovolaemia, hypotension, and the additional use of concomitant drugs**, **that increase their propensity to develop (A)KI.**
- Around **20–30% of all children treated with an *aminoglycoside* for more than 5 days develop AKI** *(Zappitelli, Moffett, Hyder, & Goldstein, 2011)*.
- A study assessing 175 children with previously normal renal function, demonstrated that **after 48 h of *vancomycin*** treatment AKI occurred in **14%** of patients and was related to the **dose** used, the **length** of therapy, and the additional use of **concomitant drugs** *(Sinclair et al., 2014).*

Paziente con AKI

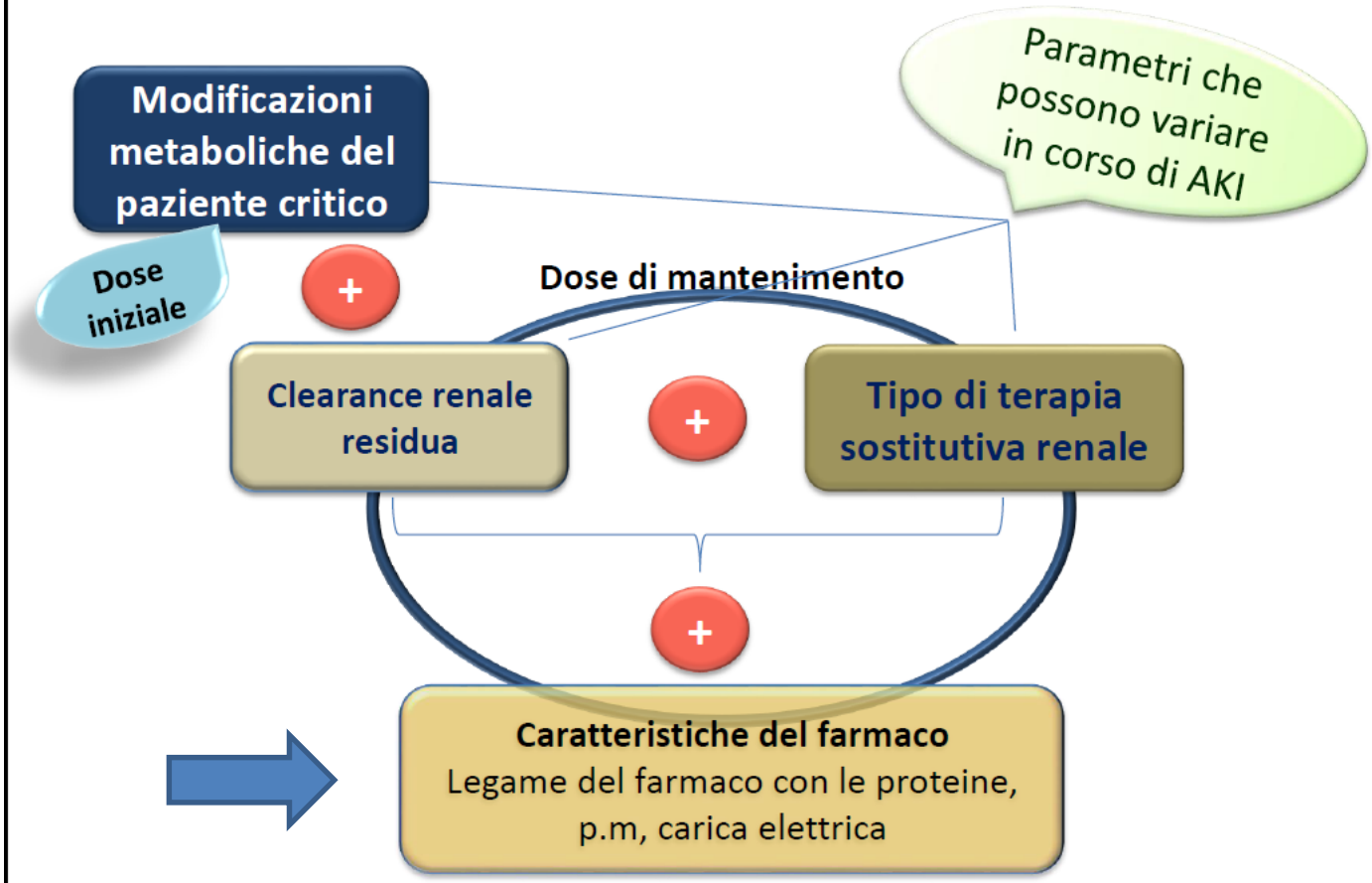
I pazienti con AKI ricoverati in Area Critica hanno un rischio 16 volte maggiore di sviluppare tossicità da farmaci e gli antibiotici rappresentano la principale causa di tossicità

Kane- Gill et al. Crit Care Med 2012; 40: 823

Gli studi sulla nefrotossicità da antibiotici, indicano un danno transitorio e reversibile dopo sospensione del farmaco. Tuttavia le valutazioni a breve termine non riflettono tutto lo spettro dell'antibiotico-tossicità, perché **a lungo termine** vi è un *effetto di trascinamento* con aumentato rischio di ulteriore progressione del danno renale e ridotta sopravvivenza di questi pazienti

Lewis SJ et al. Journ Intensive Care Medicine 2016; 31: 164

Nel raggiungimento del target terapeutico si deve tenere conto di:



PK/PD

- **PK (farmacocinetica):**

  descrive le **modificazioni "nel tempo" delle concentrazioni di farmaco nei tessuti e nei fluidi corporei** *

  →determina le dosi e la miglior strategia di somministrazione dei diversi antibiotici **in rapporto a:**

  → **MIC** del patogeno

- **PD (farmacodinamica): rapporto dose/effetto**

  nel caso degli antibiotici descrive:

  → **attività antimicrobica**

  → **effetti clinici**

  → **tossicità**

*** LADME:** liberation, absorption, distribution, metabolism and excretion

Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults

- Anatomical, physiological and biochemical changes that occur from birth affect PK and PD, and therefore the **bioavailability of drugs**
- Some **PK parameters** such as absorption, volume of distribution, plasma protein binding, metabolism and excretion are **age-related**
- In general, **absorption, plasma protein binding, metabolism** (enzyme expression) **and excretion** of children are **reduced,** while the **volume of distribution** is **increased**
- Furthermore, it is frequently assumed that the same plasma concentration of a drug and/or its metabolites in pediatric population and adults is responsible for the same pharmacological effect. This statement is far from correct due to the existence of **active metabolites**, diverse **receptor characteristics** (quantity and affinity) and **variable concentration reached at the site of action**, as well as **different membrane permeation**

→ Extrapolation from adults' data should not be done

- **Pediatrics studies** entail **difficulties and ethic limitations**. However, they are **necessary** to determine the **administration regimen** of drugs and estimate their fate once given

Pharmaceutics 2011; 3:53-72; Pharmacol Ther 2017; 174:55-62

Variazioni della cinetica dei farmaci nel **paziente critico**

Normale | Vd aumentato | Cl aumentata

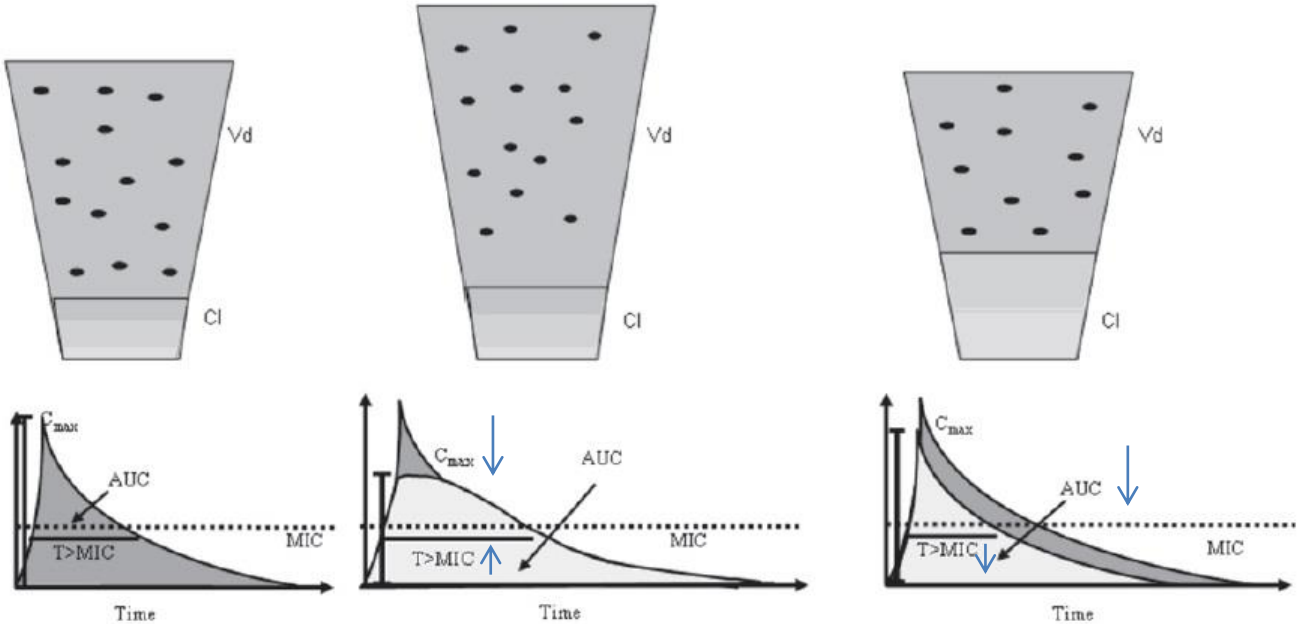
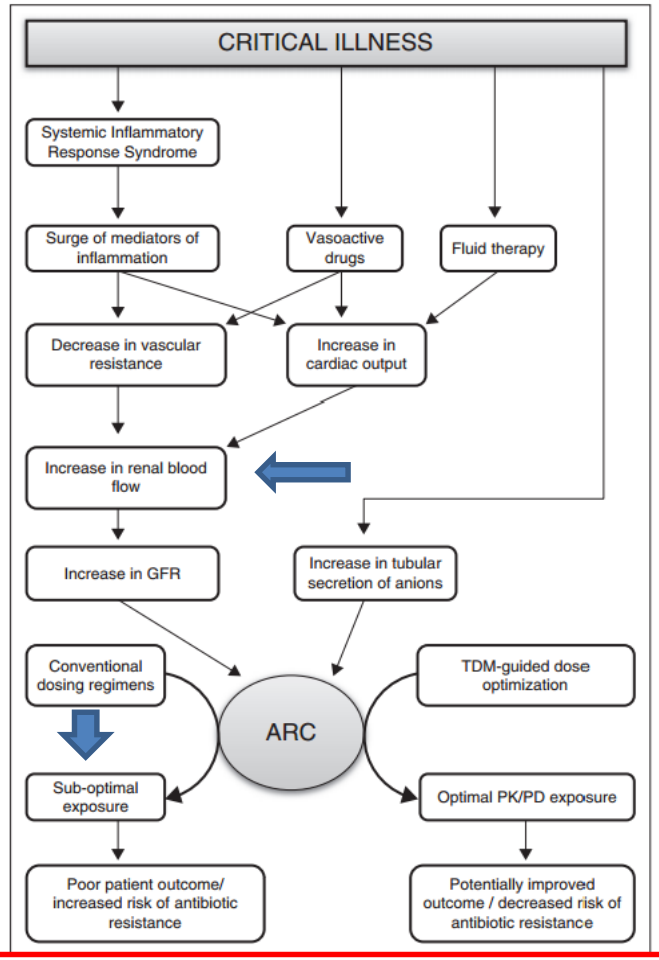


Figure 1 ICU patients present pharmacokinetic changes of antibiotics that may alter bacterial exposure. Concentration-time curve of antibiotics in healthy volunteers (left panel). A large volume of distribution (V_d) (middle panel) is often present in ICU patients, leading to decreased maximum concentration (C_{max}) but a longer half-life ($T_{1/2}$) and eventually higher time that the antibiotic concentration is above the bacteria minimum inhibitory concentration (T > MIC). The antibiotic area under the concentration time curve (AUC) remains virtually the same. An increase in drug clearance (Cl) (right) is associated with decreases in AUC, $T_{1/2}$ and T > MIC. Straight dotted lines-bacteria minimum inhibitory concentration.

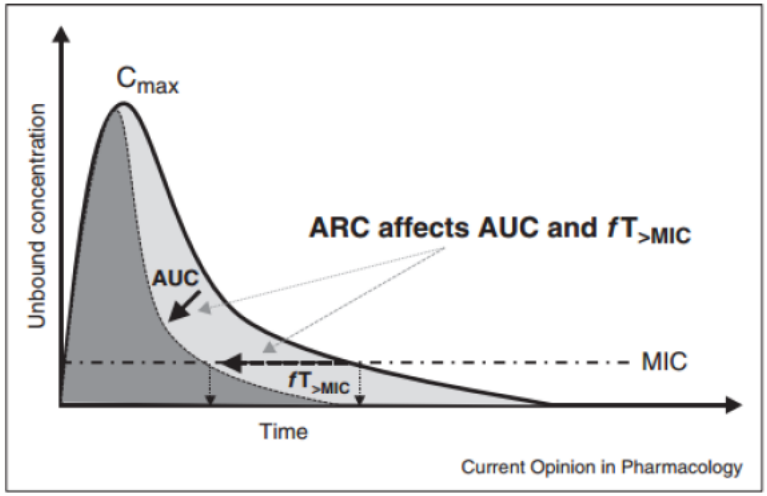
Augmented renal clearance

(defined as a creatinine clearance >130 mL/min/1.73 m^2)

Causes and consequences of augmented renal clearance in the critically ill



The influence of augmented renal clearance on pharmacokinetic/ pharmacodynamic parameters



Current Opinion in Pharmacology 2015, 24:1–6

Table 1 Changes in drug clearance for moderate to highly bound antibacterials in critically ill patients with hypoalbuminaemia compared with healthy volunteer data

Drug	% Protein binding in healthy volunteers	ICU/healthy subjects (*n*)	Change in clearance in ICU patients[a]	Change in V_d in ICU patients[a]
Aztreonam [26, 27]	60	48/7	15 % increase	Nil change
Ceftriaxone [10, 16]	85–95	6/11	99 % increase	32 % increase
Daptomycin [28, 29]	90–93	9/24	151 % increase	10 % increase
Ertapenem [30, 31]	85–95	17/10	113 % increase	200 % increase
Ertapenem [14]	85–95	8/16	462 % increase	624 % increase
Flucloxacillin [13, 32]	95	10/10	10 % increase	57 % increase
Fusidic acid [33, 34]	95–97	6/8	94 % increase	NA
Teicoplanin [8, 35]	90–95	12/6	36 % increase	NA

ICU intensive care unit (critically ill), *NA* not available, V_d apparent volume of distribution

[a] Calculated as (observed value − reference value/reference value) × 100

Ipoalbuminemia

→ aumento della concentrazione di farmaco libero

→ aumento della clearance e del volume di distribuzione

(per farmaci con legame proteico medio o alto)

Antibiotic dosing in critically ill patients with acute kidney injury

Rachel F. Eyler and Bruce A. Mueller

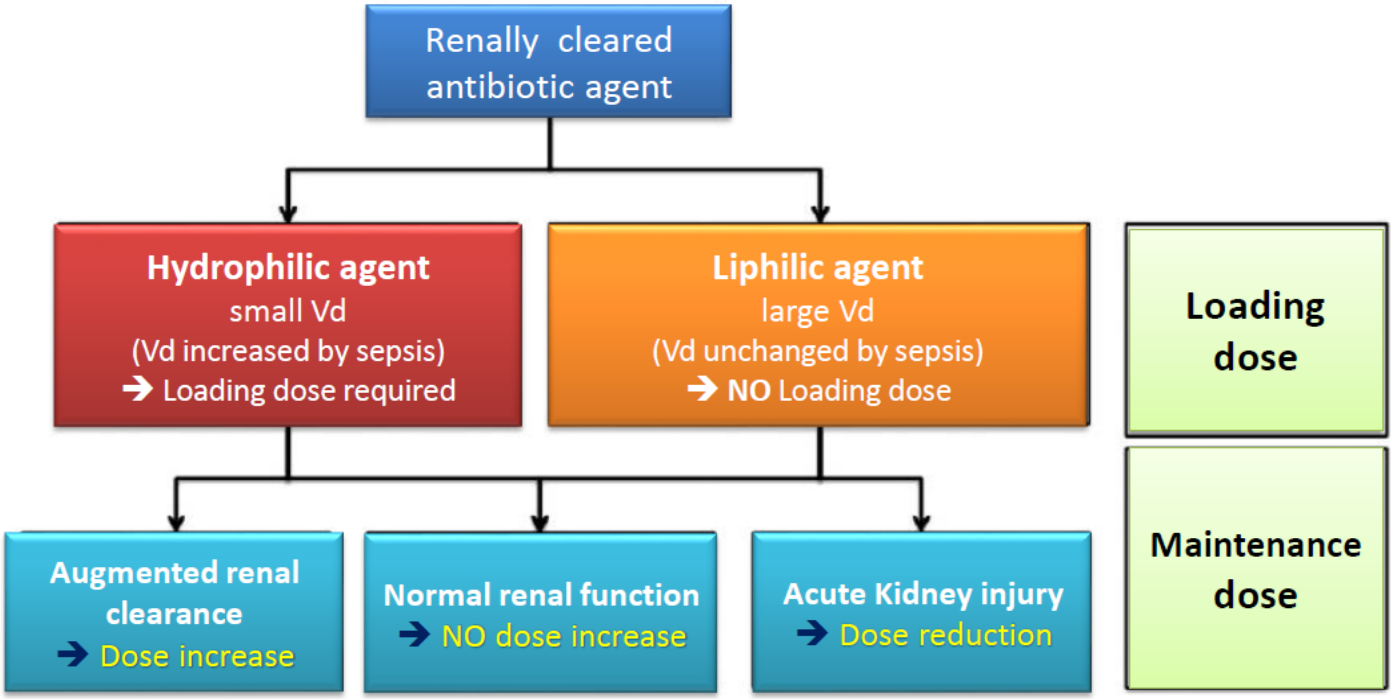
Nat. Rev. Nephrol. **7**, 226–235 (2011); published online 22 February 2011

Table 1 | Volume of distribution data from pharmacokinetic studies in adults

Antibiotic	Healthy volunteers (l/kg)	Patients with AKI receiving RRT (l/kg)
Lipophilic drugs		
Ciprofloxacin	1.98[76]	1.60,[77] 1.65[78]
Levofloxacin	0.96,[79] 1.13[80]	1.02,[81] 1.51[82]
Hydrophilic drugs		
Amikacin	0.18[83]	0.44[84]
Daptomycin	0.10[85]	0.23[26]
Meropenem	0.17,[86] 0.18,[87] 0.27[88]	0.26,[89] 0.35,[28] 0.37[29]
Piperacillin	0.15[90]	0.14,[91] 0.18[92]
Vancomycin	0.39,[93] 0.59,[94] 0.63[95]	0.57,[96] 0.65[97]

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

basic elements in antibiotic agent characteristics and renal pathophysiology impacting on loading dose and/or maintenance dosing



S. Blot et al. Diagnostic Microbiology and Infectious Disease 2014; 79: 77–84

Loading dose: initial higher dose of a drug given at the start of treatment

Maintenance dose: the rate of drug administration assumed to be equal to the rate of elimination when a steady state has been reached

Attività antibatterica in base a PK/PD

Profilo farmacodinamico	Parametro PK/PD che definisce l'efficacia	Classe di farmaci
Tempo-dipendente	**%t>MIC**	beta-lattamici
	%t>MIC AUC/MIC	linezolid
	AUC/MIC	macrolidi lincosamidi tetracicline (tigeciclina)
	AUC/MIC	glicopeptidi
Concentrazione - dipendente	AUC/MIC	polimixine (colistina)
	AUC/MIC e/o **Cmax/MIC**	chinoloni, **aminoglicosidi**, daptomicina, metronidazolo

Strategie di terapia in situazioni critiche:

antibiotici con profilo farmacodinamico ***"time-dependent"*** *

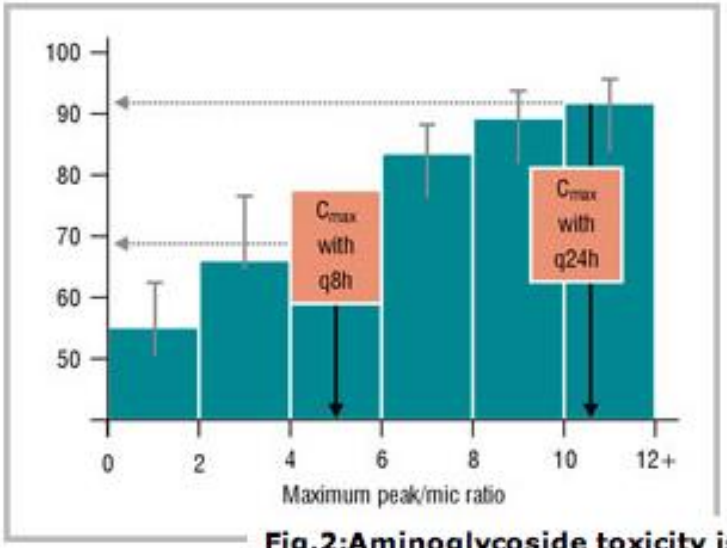
- aumento della dose (per alcuni neurotossicità per conc > 8xMIC)
- riduzione dell'intervallo tra le somministrazioni (aumento della frequenza: q8 → q6)
- **prolungamento del tempo di somministrazione**
  - **40-50% dell'intervallo fra le dosi**
  - **infusione continua**

    ↓ (nei pazienti in CRRT l'antibiotico viene somministrato con un rate simile a quello di rimozione)
- **in caso di ARC e/o ipoalbuminemia** l'infusione continua è probabilmente l'unica strategia possibile…

→ **comunque utile il monitoraggio dei livelli ematici (TDM)**

* beta-lattamici: penicilline, cefalosporine, carbapenemi; glicopeptidi; linezolid

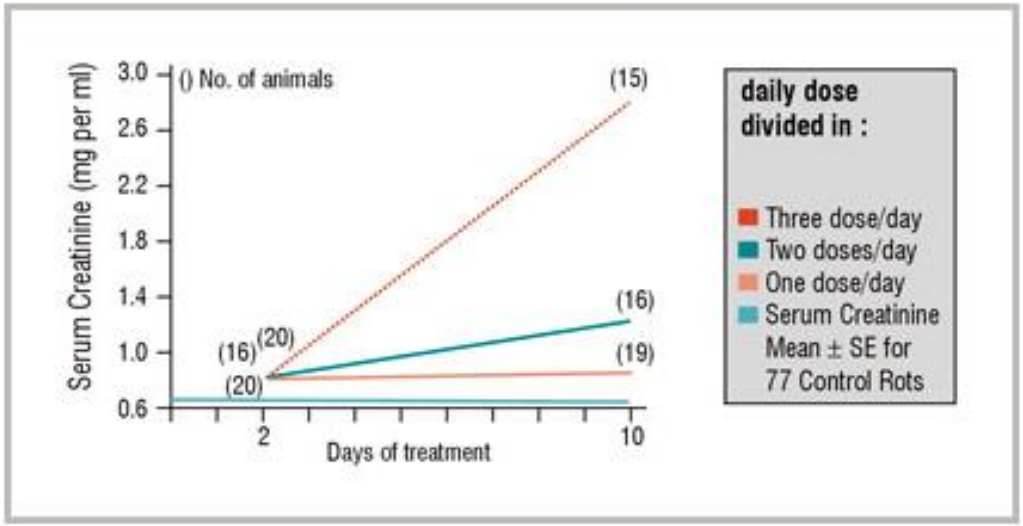
Fig.1: Amnioglycoside Peak/MIC ratio is predictive of efficacy



Profilo PD concentrazione-dipendente

Fig.2:Aminoglycoside toxicity is not linked to peak[2]

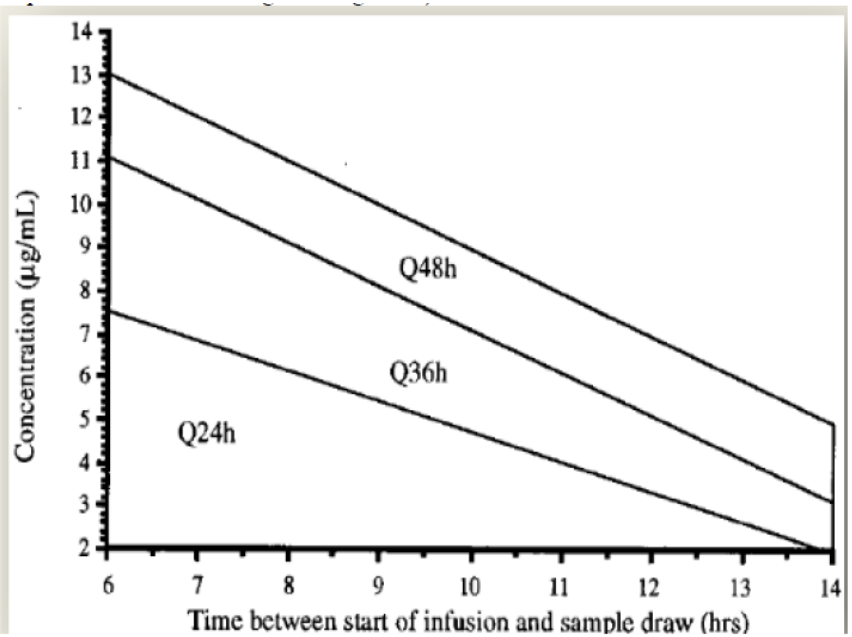
Aumento dell'intervallo fra le dosi
=
> Efficacia
< Tossicità



Therefore, data from 17 clinical studies6 lead to the conclusion that pulse dosing of aminoglycosides is safer than multiple dosing.

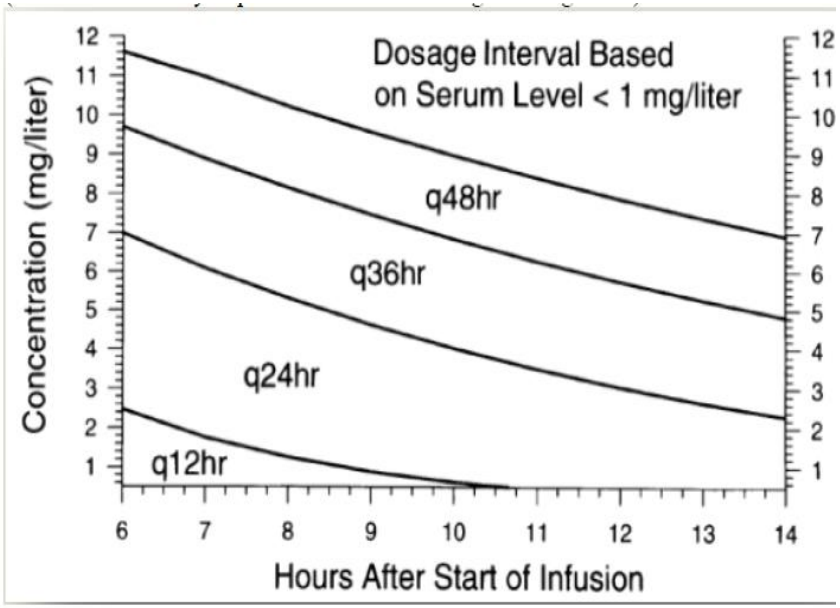
Diagrammi per il calcolo di frequenza e dose degli aminoglicosidi nel paziente in insufficienza renale

Calcolo della frequenza delle somministrazioni di amikacina – nomogramma di Hartford *



Effettuare il prelievo 8-12 ore dopo l'inizio dell'infusione. Dividere il valore di amikacina per 2 , quindi inserirlo nel grafico per valutare l'intervallo tra le dosi

Calcolo della frequenza delle somministrazioni di gentamicina e tobramicina – nomogramma di Urban & Craig *



Effettuare il prelievo 8-12 ore dopo l'inizio dell'infusione.

* Stanford University: *http://med.stanford.edu/bugsanddrugs.htm*

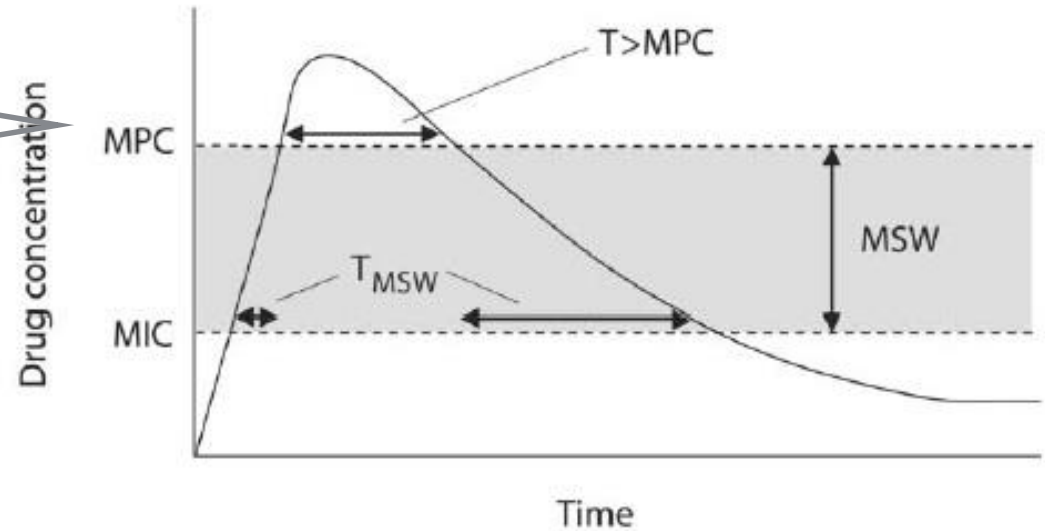
*"… **optimal antibiotic exposure** may not be achieved with **traditional dosing strategies** in a significant number of patients (e.g. **critically ill** or infected by **resistant organisms**),*
*which may lead to **microbiological and clinical failure**, and may promote the emergence of **antibiotic resistance**"*

Osthoff Swiss Med Wkly 2016

Parametri di PK/PD e selezione dei mutanti (resistenti)

La selezione delle resistenze è influenzata dalle dosi di antibiotico

MIC della popolazione meno suscettibile



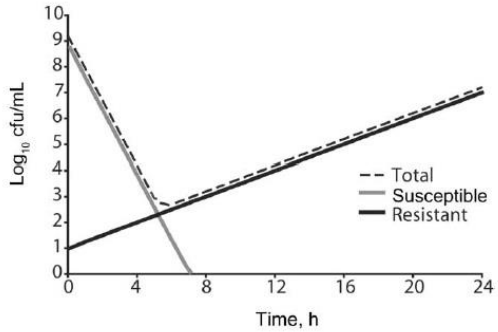


Figure 2. Emergence of resistance. The susceptible (wild-type) population is readily killed after drug exposure, whereas the resistant (mutant) population may be amplified. The total population is explained by the changes in the 2 different populations. Adapted from Drusano [32], with permission from the Nature Publishing Group.

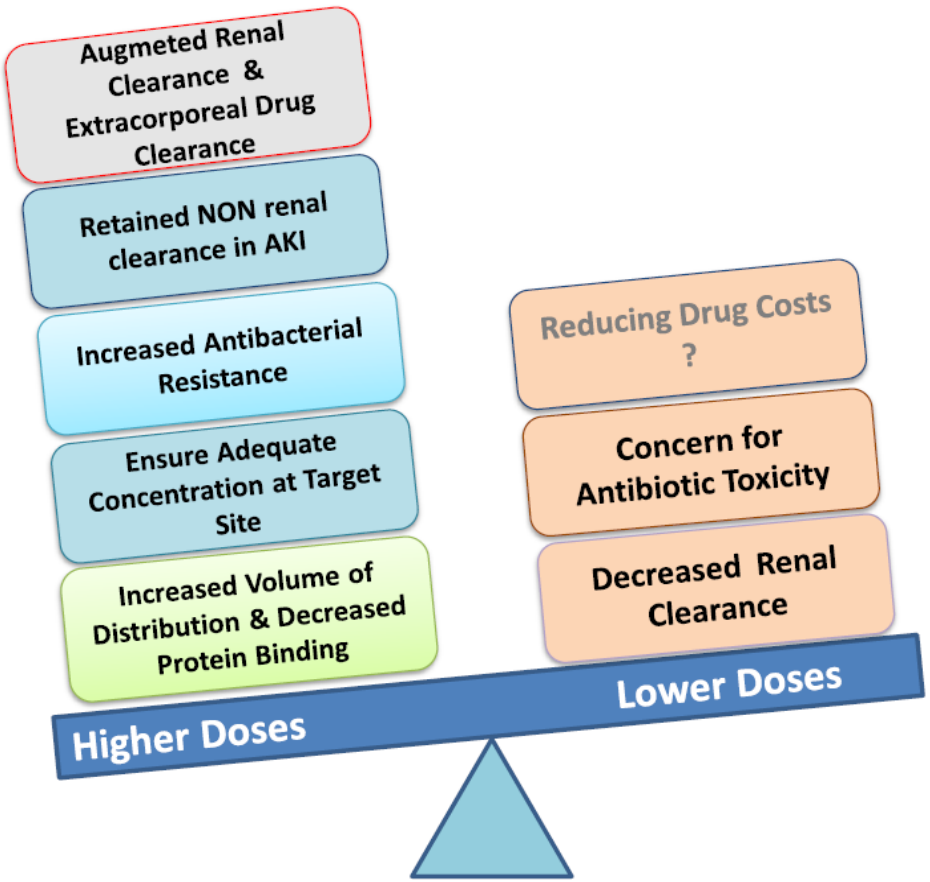
Figure 3. Illustration of the drug concentration over time and the concept of the mutant selection window (MSW). The hypothesis is that selection of resistant mutants occurs when drug concentrations are within the MSW *(shaded area)*—that is, between the MIC and the mutant prevention concentration (MPC). T > MPC, time above the MPC; T_{MSW}, time within the MSW.

Prevention of antibiotic-induced AKI

- **Avoid nephrotoxic antibiotics**
  → *cautious and/or judicious use of nephrotoxic antibiotics*
- Optimal dosing
  - adjust for patient's eGFR (on a daily basis)
  - extended dosing intervals and short-term therapy
  - adequate therapeutic drug monitoring (TDM)
- Improved, early detection of AKI
  - pRIFLE
  - biomarkers
  - electronic triggers
- Pharmacovigilance
  - Reporting and recording adverse drug events (ADEs)
- Drugs that induce biological systems
  - manipulation of biological pathways that directly contribute to kidney injury (drug repurposing)

Inappropriate dosing in patients with CKD can cause toxicity, or ineffective therapy

Enough but not too much



Journal of Intensive Care Medicine

Susan J. Lewis, and Bruce A. Mueller J Intensive Care Med 2014;31:164-176

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  - electronic triggers (→ *diapo ?)*
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- Drugs that induce biological systems
  - manipulation of biological pathways that directly contribute to kidney injury (drug repurposing) (→ diapo)

New Equations to Estimate GFR in Children with CKD

George J. Schwartz,* Alvaro Muñoz,† Michael F. Schneider,† Robert H. Mak,‡
Frederick Kaskel,§ Bradley A. Warady,‖ and Susan L. Furth†¶

J Am Soc Nephrol 20: 629–637, 2009

The updated ***Schwartz formula*** is

$$eGFR = 0.413 \times height\ (cm)/Scr\ (mg/dl)$$

showing a 25% reduction from the previous 0.55 *K* factor generated by the Jaffe-based Scr measurements, in keeping with the approximate reduction in apparent concentration by isotope dilution mass spectroscopy–referenced **enzymatic creatinine determinations**.

This formula is reliable in the range of **GFR from 15 to 75 ml/min per 1.73 m²**, but it has not been tested to estimate GFR in children with **higher kidney function**.

→ ***steady state serum creatinine levels***

Retooling the Creatinine Clearance Equation to Estimate Kinetic GFR when the Plasma Creatinine Is Changing Acutely

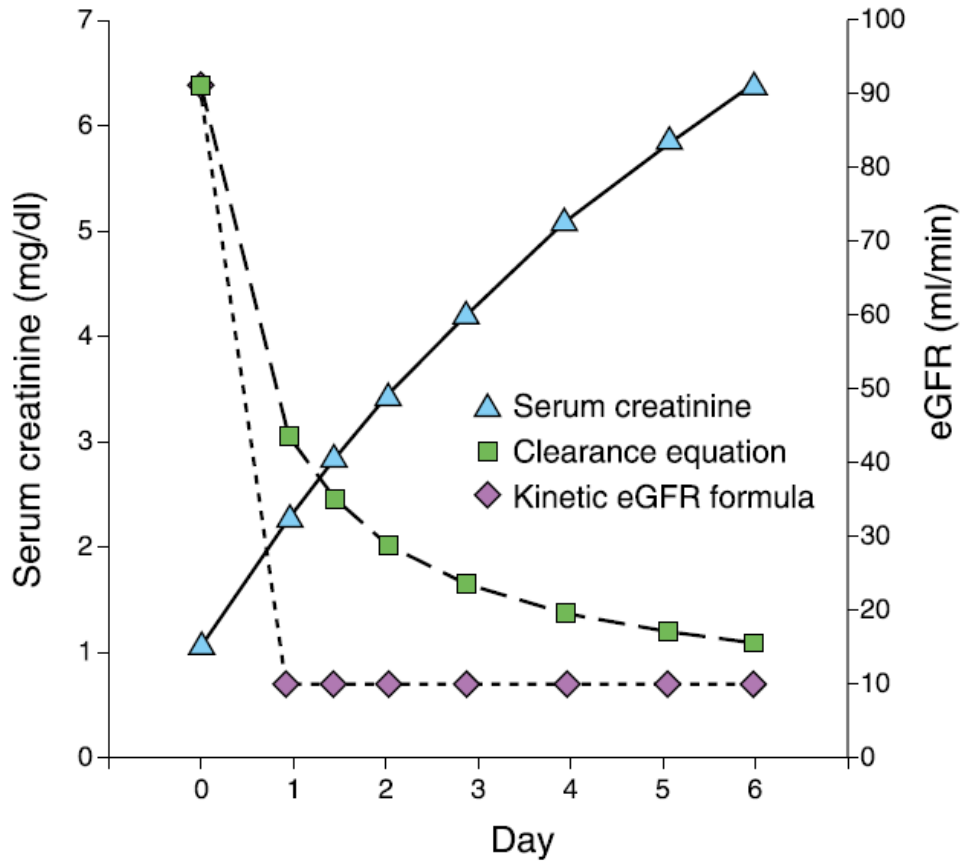
J Am Soc Nephrol 2013 May;24(6):877-88

Sheldon Chen

Division of Nephrology and Hypertension, Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, Illinois

$$KeGFR = \frac{SSP_{Cr} \times CrCl}{MeanP_{Cr}} \times \left(1 - \frac{24 \times \Delta P_{Cr}}{\Delta Time(h) \times Max\Delta P_{Cr}/Day}\right)$$

SSP_{Cr} = steady-state plasma creatinine (mg/dl)
Mean P_{Cr} = the arithmetic mean of the plasma Cr values at the beginning and end of the period of interest
*delta***P_{Cr}** = the change in plasma Cr between the 2 time points
*delta***Time** = time (hours) between the 2 Cr points
Max P_{Cr}/Day = the maximal change in plasma Cr that would occur if GFR were zero (estimated from the patient's rate of Cr production and the Cr *Vd*)



→ **not validated in pediatric patients**

Sunder et al. Journal of Intensive Care 2014, 2:31
http://www.jintensivecare.com/content/2/1/31

JOURNAL OF INTENSIVE CARE

REVIEW Open Access

Estimation of renal function in the intensive care unit: the covert concepts brought to light

Sham Sunder, Rajesh Jayaraman*, Himanshu Sekhar Mahapatra, Satyanand Sathi, Venkata Ramanan, Prabhu Kanchi, Anurag Gupta, Sunil Kumar Daksh and Pranit Ram

Two equations can be used to estimate GFR from cystatin C concentration:

(A) Grubb's equation [47]: GFR = 83.93 × Cystatin $C^{-1.676}$

(B) Larsson's equation [48]: GFR = 77.239 × Cystatin $C^{-1.2623}$; cystatin C is measured in mg/l.

47. Grubb A, Nyman U, Björk J, Lindström V, Rippe B, Sterner G, Christensson A: Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and the Counahan-Barratt prediction equations for children. *Clin Chem* 2005, **51**:1420–1431.
48. Larsson A, Malm J, Grubb A, Hansson LO: Calculation of glomerular filtration rate expressed in mL/min from plasma cystatin C values in mg/L. *Scand J Clin Lab Invest* 2004, **64**:25–30.

Cystatin C is a non-glycosylated protein **produced by all nucleated cells**. Its constant rate of production, low MW of 13 kDa, and positive charge at physiological pH makes it a suitable marker for glomerular filtration.

It is reabsorbed and almost completely catabolized in the proximal tubule.

It has many advantages including **its extreme sensitivity to small changes in GFR** and higher diagnostic accuracy than MDRD or CG formulae.

Moreover, its concentration is **least affected by infections, malignancies, steroid therapy, inflammatory disorders, and muscle mass.**

Prevention of antibiotic-induced AKI

- Avoid nephrotoxic antibiotics
  → *cautious and/or judicious use of nephrotoxic antibiotics*
- Optimal dosing
  - adjust for patient's eGFR (on a daily basis)
  - **reduced single doses and/or extended dosing intervals (PK/PD profile)**
  - **adequate therapeutic drug monitoring (TDM**)
- Improved, early detection of AKI
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- Pharmacovigilance
  - Reporting and recording adverse drug events (ADEs)
- Drugs that induce biological systems
  - manipulation of biological pathways that directly contribute to kidney injury (drug repurposing) (→ diapo)

Farmaci anti-infettivi di cui è possibile il dosaggio dei livelli ematici mediante HPLC-MS/MS al Gaslini

(Ottobre 2018)

ANTIBIOTICI:

- amikacina *
- amoxicillina
- ceftazidime
- ciprofloxacina
- colistina
- daptomicina
- gentamicina *
- linezolid
- meropenem
- piperacillina
- teicoplanina
- tigeciclina
- tobramicina
- vancomicina *

ANTIMICOTICI:

- Voriconazolo
- Posaconazolo
- Itraconazolo
- Isavuconazolo
- Micafungina
- Amfotericina B

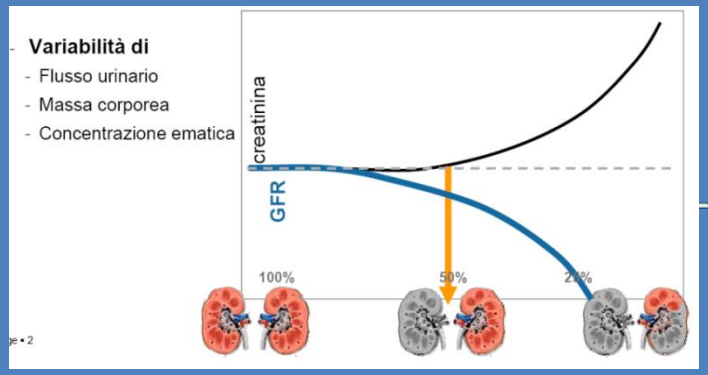
Giuliana Cangemi, ***Laboratorio Centrale di Analisi***
giulianacangemi@gaslini.org

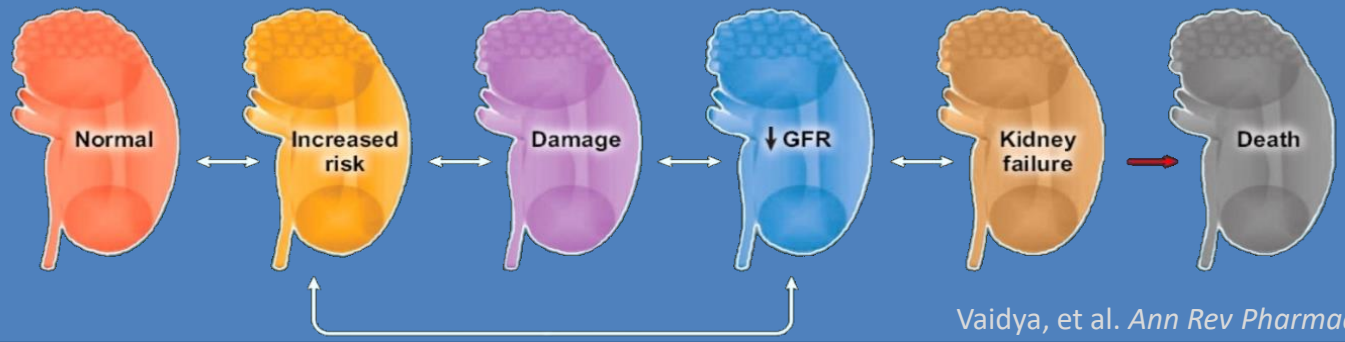
* *disponibili anche con immunoassay*

Prevention of antibiotic-induced AKI

- Avoid nephrotoxic antibiotics
  → *cautious and/or judicious use of nephrotoxic antibiotics*
- Optimal dosing
  - adjust for patient's eGFR (on a daily basis)
  - extended dosing intervals and short-term therapy
  - adequate therapeutic drug monitoring (TDM)
- **Improved, early detection of kidney injury**
  - **pRIFLE**
  - biomarkers
  - electronic triggers
- Pharmacovigilance
  - Reporting and recording adverse drug events (ADEs)
- Drugs that induce biological systems
  - manipulation of biological pathways that directly contribute to kidney injury (drug repurposing)

FASI DEL DANNO RENALE





Vaidya, et al. *Ann Rev Pharmacol Toxicol.* 2008;48:463-493.

RIFLE	Risk	Injury	Failure	Loss	ESRD
AKIN	I	II	III		
S Cr	**sCr 1.5-2 X o +0.3mg/dl eGFR -25%**	**SCr 2-3 X e-GFR -50%**	**sCr > 3X o > 4mg/dl**	**FAILURE > 4sett**	**FAILURE > 3mesi**
Output urine	**<0.5 ml/kg/h per 6 h**	**<0.5 ml/kg/h per 12 h**	**<0.3 ml/kg/h per 24 h o anuria x 12 h**		

Criteri RIFLE Pediatrici – pRIFLE

pRIFLE Class	*eGFR stimato con formula di Schwartz*	Output urinario
Risk	eGFR riduzione **del 25%**	**< 0.5** ml/kg/h per **8 h**
Injury	eGFR riduzione **del 50%**	**< 0.5** ml/kg/h per **16 h**
Failure	eGFR riduzione **del 75%** o eGFR **< 35 ml/min/1.73 m²**	**< 0.3** ml/kg/h per > **24 h** o **Anuria** per **12 h**
Loss	**Insufficienza renale > 4 sett**	
ESRD	**Insufficienza renale > 3 mesi**	

I livelli ematici di **creatinina** dipendono da diversi fattori, quali:
età, sesso, massa muscolare, dieta e nel neonato anche dalla Cr materna
→ **eGFR più attendibile**

Akcan-Arikan A et al, Kidney International 2007

Nakhjavan-Shahraki et al. BMC Nephrology (2017) 18:120
DOI 10.1186/s12882-017-0539-0

BMC Nephrology

RESEARCH ARTICLE Open Access

Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and meta-analysis

Babak Nakhjavan-Shahraki[1], Mahmoud Yousefifard[2], Neamatollah Ataei[1,3], Masoud Baikpour[4], Fatemeh Ataei[5], Behnaz Bazargani[1,3], Arash Abbasi[1,3], Parisa Ghelichkhani[6], Faezeh Javidilarijani[3,7] and Mostafa Hosseini[8*]

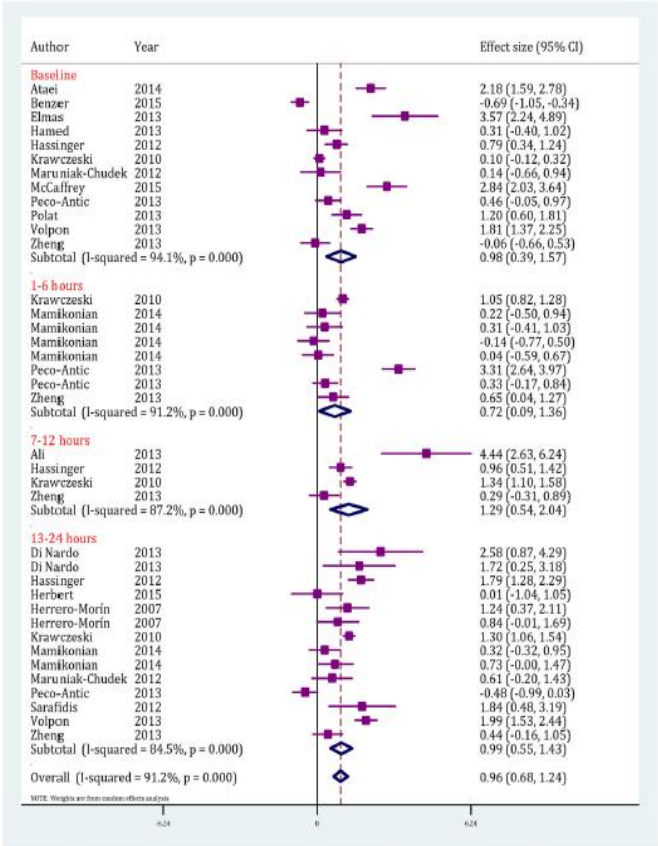


Fig. 2 Value of serum cystatin C in prediction of acute kidney injury by time assessment. CI, confidence interval. Effect size were assessed by calculating standardized mean difference

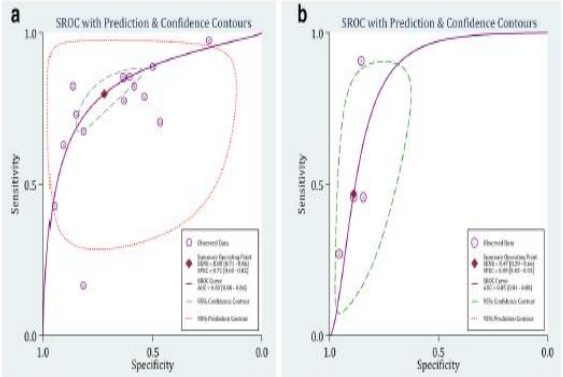


Fig. 4 Summary receiver operative curves (SROC) for cystatin C in detection of acute kidney injury. **a** Serum; **b** Urine. AUC: Area under the curve; SENS: Sensitivity; SPEC: Specificity

Conclusion

The present meta-analysis is the first to assess the prognostic value of cystatin C in detection of AKI in pediatric population. The findings of this study showed that **cystatin C has an acceptable prognostic value for prediction of AKI in children**, with its serum concentration diagnostic value being higher than that of its urine level. So, measuring cystatin C serum level in the first 24 h and considering a cut-off point of 0.4-1.0 mg/L provides the highest value in predicting AKI.

Prevention of antibiotic-induced AKI

- Avoid nephrotoxic antibiotics
  → *cautious and/or judicious use of nephrotoxic antibiotics*
- Optimal dosing
  - adjust for patient's eGFR (on a daily basis)
  - extended dosing intervals and short-term therapy
  - adequate therapeutic drug monitoring (TDM)
- **Improved, early detection of AKI**
  - pRIFLE
  - **biomarkers**
  - electronic triggers
- Pharmacovigilance
  - Reporting and recording adverse drug events (ADEs)
- Drugs that induce biological systems
  - manipulation of biological pathways that directly contribute to kidney injury (drug repurposing)

Renal biomarker qualification submission: a dialog between the FDA-EMEA and Predictive Safety Testing Consortium

NATURE BIOTECHNOLOGY VOLUME 28 NUMBER 5 MAY 2010

The first formal qualification of safety biomarkers for regulatory decision making marks a milestone in the application of biomarkers to drug development.
Following submission of **drug toxicity studies** and **analyses of biomarker performance** to the Food and Drug Administration (FDA) and European Medicines Agency (EMEA) by the Predictive Safety Testing Consortium's (PSTC) Nephrotoxicity Working Group, **7 renal safety biomarkers** have been **qualified for limited use in nonclinical and clinical drug development** to help guide **safety assessment**:

kidney injury molecule-1 (KIM-1),
albumin,
total protein,
β2-microglobulin,
cystatin C,
clusterin and
trefoil factor-3.

This was a pilot process, and the experience gained will both facilitate better understanding of how the qualification process will probably evolve and clarify the minimal requirements necessary to evaluate the performance of biomarkers of organ injury within specific contexts.

Electronic health record identification of nephrotoxin exposure and associated acute kidney injury

Goldstein SL[1], Kirkendall E, Nguyen H, et al. **Pediatrics.** **2013** Sep;132(3):e756-67.

In the **NINJA study** (Nephrotoxic Injury Negated by Just-intime Action) **systematic screening of electronic health records** was instituted to identify **children receiving IV aminoglycosides** for ≥3 days or ≥3 simultaneous nephrotoxins. In the patients enrolled in this study, **daily monitoring of serum creatinine** was recommended.
The mean weekly AKI rate was 25.5 % for nephrotoxin-exposed patients using the pRIFLE criteria.
A 42 % reduction in AKI intensity (from 33.6 to 19.5 days/100 exposure days) was reported during 1 year of implementation of the screening program.

A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

Goldstein SL[1], Mottes T[2], Simpson K[2],et al. **Kidney Int.** **2016** Jul;90(1):212-21

The results of a **follow-up analysis of this project after 3 years of implementation** revealed that there had been a

- **38 % reduction in exposure to nephrotoxic medications** (11.63 to 7.24 exposures/1000 patient days), and a
- **64 % reduction in the AKI rate** (2.96 to 1.06 episodes/1000 patient days)

Pediatr Nephrol (2017) 32:2015–2025
DOI 10.1007/s00467-016-3533-z

CrossMark

REVIEW

Aminoglycoside-induced nephrotoxicity in children

Stephen J McWilliam[1] · Daniel J Antoine[2] · Rosalind L Smyth[3] · Munir Pirmohamed[2]

Table 3 Comparative description of three novel urinary biomarkers and their utility in aminoglycoside-induced nephrotoxicity

Biomarker	Description	Utility in aminoglycoside-induced nephrotoxicity	Comments
Kidney Injury Molecule-1 (KIM-1)	Cell membrane glycoprotein upregulated by proximal tubule epithelial cells in response to toxicity [73] Confers a phagocytic phenotype [74]	Outperforms, with respect to sensitivity and specificity, traditional and novel biomarkers of AKI (serum creatinine, blood urea nitrogen, and NAG), as confirmed by histopathology in animal models [46] Early diagnostic marker for AKI and predictor of mortality risk [75] Elevated during aminoglycoside exposure in preterm neonates [47] and children with CF [49, 50]	Specific to proximal tubule Outperforms other biomarkers in pre-clinical models of aminoglycoside--induced nephrotoxicity
Neutrophil Gelatinase-associated Lipocalin (NGAL)	25-kDa protein expressed by kidney epithelial cells (and other tissues, as well as neutrophils) [76]	Upregulated in response to nephrotoxins in mouse models [77] Sensitive early predictor for AKI [75] Elevated during aminoglycoside exposure in preterm neonates [47]	Levels elevated in sepsis/inflammation [78] which may limit specificity
N-acetyl-β-D-glucosaminidase (NAG)	130- to 140-kDa lysosomal enzyme specific to proximal tubule epithelial cells [79]	Widely used in pre-clinical and clinical studies of aminoglycoside-induced nephrotoxicity [80] Elevated during aminoglycoside exposure in preterm neonates [47]	Outperformed by KIM-1 in pre-clinical models of aminoglycoside--induced nephrotoxicity

AKI, Acute kidney injury; CF, cystic fibrosis

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Development and Performance of Electronic Acute Kidney Injury Triggers to Identify Pediatric Patients at Risk for Nephrotoxic Medication-associated Harm

E.S. Kirkendall[1,2,3,4]; W.L. Spires[2]; T.A. Mottes[5]; J.K. Schaffzin[3]; C. Barclay[6]; S.L. Goldstein[5]

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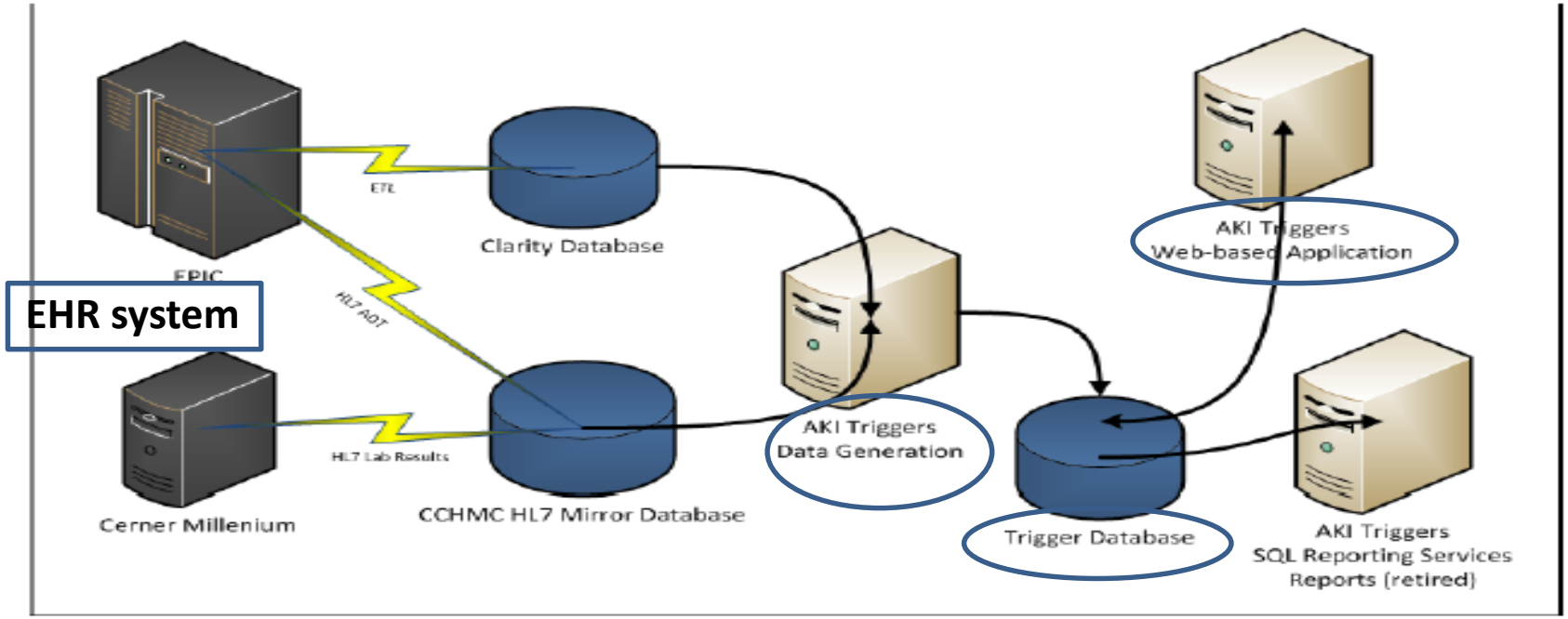

Fig. 1 AKI Trigger Report Generation Process & Data Flow: Data flow diagram, starting with the EHR system (Epic™) and lab system (Cerner™) sources. This clinical data is then extracted, transformed, and loaded (ETL) or messaged via HL7 protocols to our research databases. The automated AKI triggers are then executed on the aggregated data, with query results stored in a standalone trigger database. The query results can then be accessed via SQL reporting services or through the AKI triggers web-based application described in this paper (ADT = Admit, Discharge, Transfer; AKI = Acute Kidney Injury; ETL = Extract, Transform, Load; HL7 = Health Level 7; CCHMC = Cincinnati Children's Hospital Medical Center).

Development and Performance of Electronic Acute Kidney Injury Triggers to Identify Pediatric Patients at Risk for Nephrotoxic Medication-associated Harm

E.S. Kirkendall[1,2,3,4]; W.L. Spires[2]; T.A. Mottes[5]; J.K. Schaffzin[3]; C. Barclay[6]; S.L. Goldstein[5]

Table 2 **List of Nephrotoxic Medications (NTMx) screened.** Forty-five medications were used in the exposure queries.

Acyclovir	Enalaprilat	Mesalamine
Ambisome	Foscarnet	Methotrexate
Amikacin	*Gadopentetate dimeglumine	Nafcillin
Amphotericin B	*Gadoxetate disodium	Piperacillin/tazobactam
Captopril	Ganciclovir	Piperacillin
Carboplatin	Gentamicin	Sirolimus
Cefotaxime	Ibuprofen	Sulfasalazine
Ceftazidime	Ifosfamide	Tacrolimus
Cefuroxime	*Iodixanol	Ticarcillin/clavulanic acid
Cidofovir	*Iohexol	Tobramycin
Cisplatin	*Iopamidol	Topiramate
Colistimethate	*Ioversol	Valacyclovir
Cyclosporine	Ketorolac	Valganciclovir
Dapsone	Lisinopril	Vancomycin
Enalapril	Lithium	Zonisamide

*radiologic contrast agents

Development and Performance of Electronic Acute Kidney Injury Triggers to Identify Pediatric Patients at Risk for Nephrotoxic Medication-associated Harm

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E.S. Kirkendall[1,2,3,4]; W.L. Spires[2]; T.A. Mottes[5]; J.K. Schaffzin[3]; C. Barclay[6]; S.L. Goldstein[5]

Table 3 **Acute Kidney Injury Exposed Trigger Performance Measures:** Performance characteristics of the exposure triggers over the first two years of the study (PPV = positive predictive value, NPV = negative predictive value).

Month	Non-ICU Census Days	True Positives (TPs)	False Positives (FPs)	False Negatives (FNs)	True Negatives (TNs)	Sensitivity	Specificity	PPV	NPV
Sep-11*	3806	172	40	28	3566	0.86	0.989	0.81	0.992
Oct-11	6814	373	38	31	6372	0.92	0.994	0.91	0.995
Nov-11	6646	345	92	48	6161	0.88	0.985	0.79	0.992
Dec-11	6888	344	260	50	6234	0.87	0.960	0.57	0.992
Jan-12	6564	350	58	97	6059	0.78	0.991	0.86	0.984
Feb-12	6509	396	75	74	5964	0.84	0.988	0.84	0.988
Mar-12	6733	437	64	45	6187	0.91	0.990	0.87	0.993
Apr-12	7046	373	15	51	6607	0.88	0.998	0.96	0.992
May-12	6538	313	17	69	6139	0.82	0.997	0.95	0.989
Jun-12	7187	276	22	32	6857	0.90	0.997	0.93	0.995
Jul-12	8362	411	37	22	7892	0.95	0.995	0.92	0.997
Aug-12	7334	395	23	9	6907	0.98	0.997	0.94	0.999
Sep-12	7454	327	23	15	7089	0.96	0.997	0.93	0.998
Oct-12	8434	367	36	10	8021	0.97	0.996	0.91	0.999
Nov-12	6975	256	13	32	6674	0.89	0.998	0.95	0.995
Dec-12	7637	209	17	35	7376	0.86	0.998	0.92	0.995
Jan-13	8057	211	5	20	7821	0.91	0.999	0.98	0.997
Feb-13	6878	242	22	28	6586	0.90	0.997	0.92	0.996
Mar-13	7249	237	26	10	6976	0.96	0.996	0.90	0.999
Apr-13	7316	308	27	21	6960	0.94	0.996	0.92	0.997
May-13	7540	321	18	15	7186	0.96	0.998	0.95	0.998
Jun-13	7346	355	10	2	6979	0.99	0.999	0.97	1.000
Jul-13	7606	398	8	1	7199	1.00	0.999	0.98	1.000
Aug-13	7354	371	12	8	6963	0.98	0.998	0.97	0.999
Sep-13	7795	356	14	4	7421	0.99	0.998	0.96	0.999
Totals	**178,068**	**8143**	**972**	**757**	**168,196**				

[a] Electronic triggers started September 17th, 2011 – not a full month of data

Prevention of antibiotic-induced AKI

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- **Pharmacovigilance**
  - **Reporting and recording adverse drug events (ADEs)**
- **Drugs that induce biological systems**
  - manipulation of biological pathways that directly contribute to kidney injury ***(drug repurposing)***

COMMENTARY

Repurposing Statins for Renal Protection: Is It a Class Effect?

Stephen J. McWilliam[1,*], Daniel J. Antoine[2] and Munir Pirmohamed[2]

Clin Transl Sci 2018; 11: 100-102

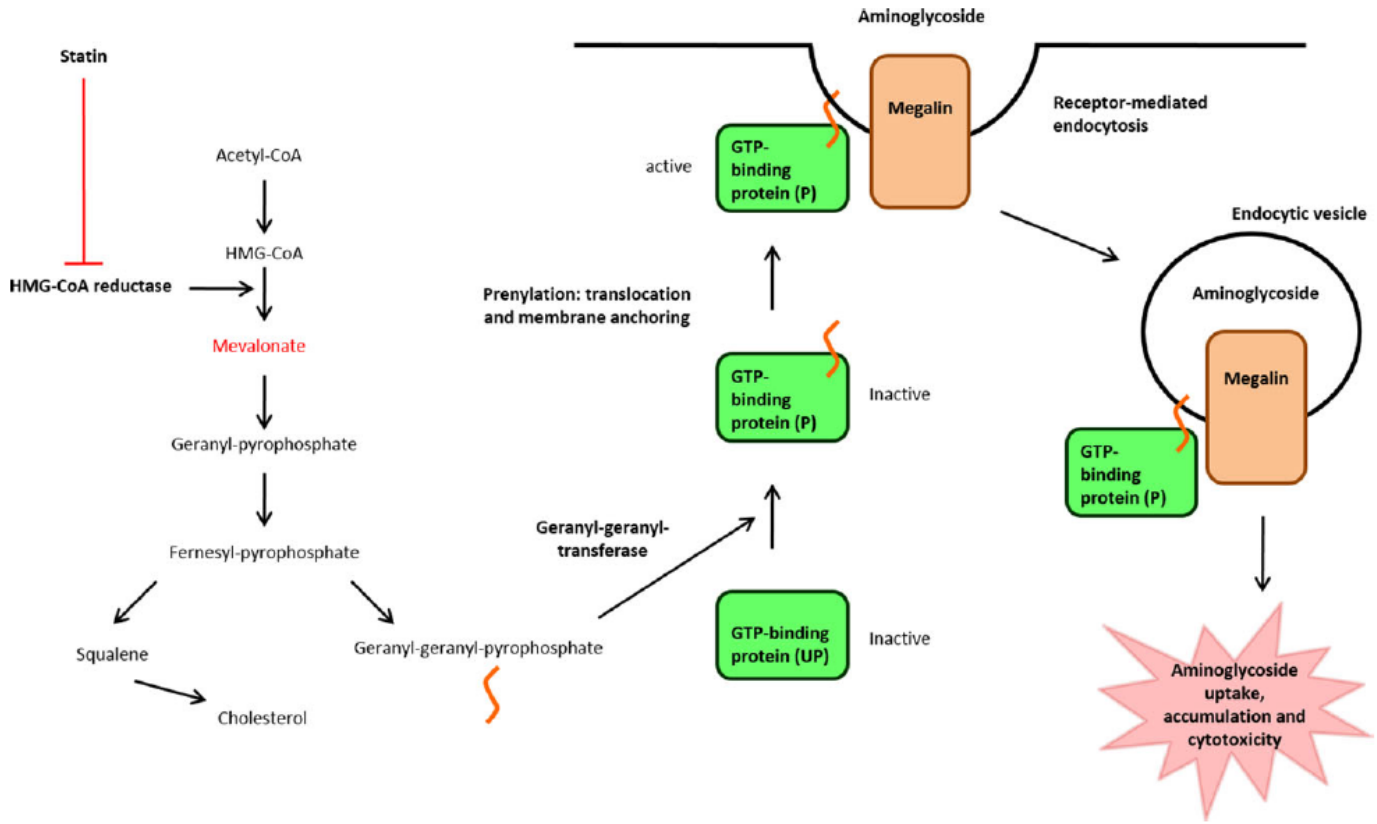

Figure 1 Mechanism of aminoglycoside-induced cytotoxicity in proximal tubule epithelial cells, and proposed mechanism for inhibition by statins. Adapted from Biochemical Pharmacology, Antoine, D.J. *et al.* Statins inhibit aminoglycoside accumulation and cytotoxicity to renal proximal tubule cells, **79**, 647–654, ©2010, with permission from Elsevier.

Statins inhibit aminoglycoside accumulation and cytotoxicity to renal proximal tubule cells

Daniel J. Antoine*, Abhishek Srivastava, Munir Pirmohamed, B. Kevin Park

MRC Centre for Drug Safety Science, Department of Pharmacology & Therapeutics, University of Liverpool, Merseyside, L69 3GE, UK

Biochemical Pharmacology 79 (2010) 647–654

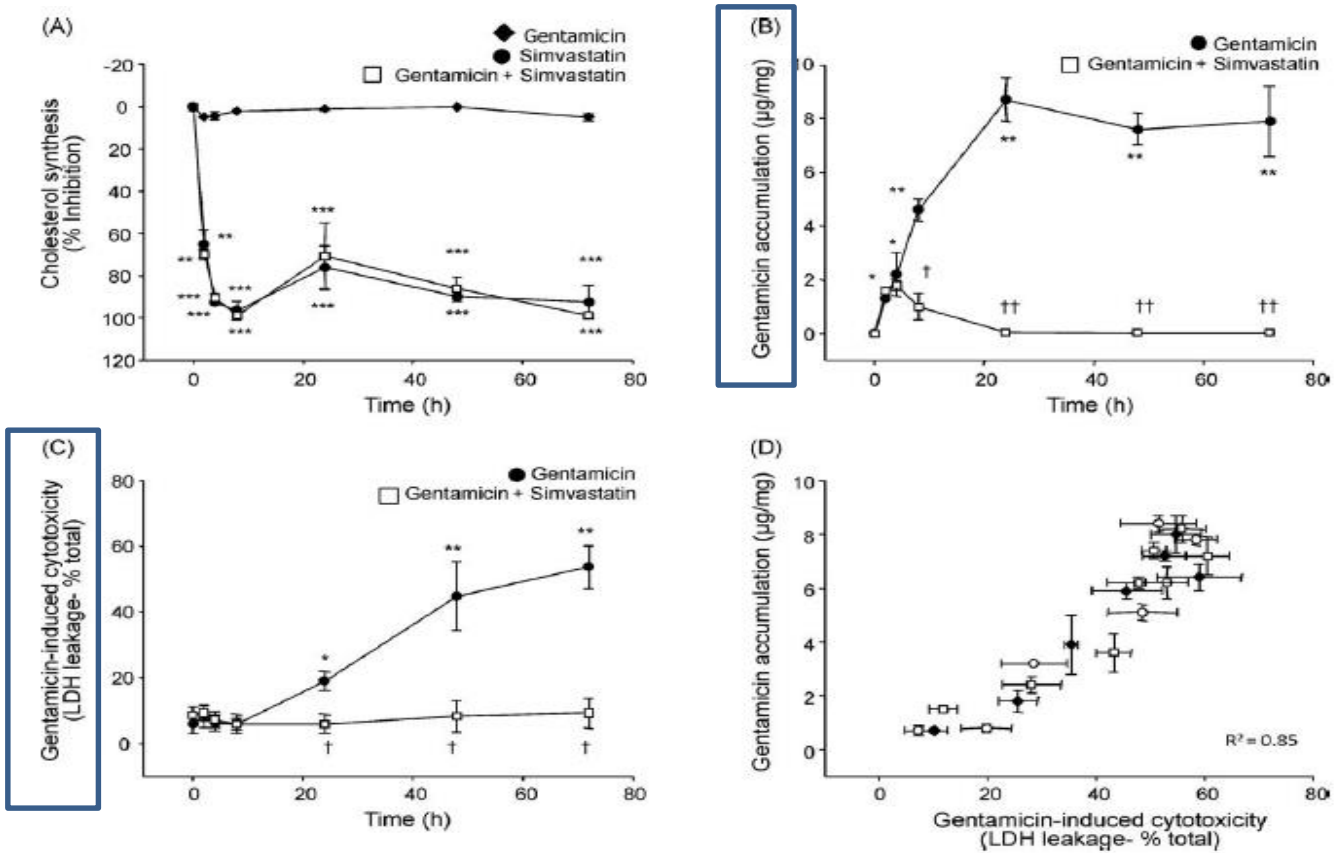

Fig. 3. Gentamicin is accumulated and causes toxicity to OK cells which can by inhibited by simvastatin. (A) The effect of gentamicin (0.25 mg/ml), simvastatin (10 µM) and simvastatin (10 µM) + gentamicin (0.25 mg/ml) on cholesterol synthesis (inhibition of HMG-CoA reductase) in OK cells over time. The effect on cholesterol synthesis was determined by the addition of [2-C^{14}] acetate for the final 5 h and the inhibitory effect of statins on the incorporation into cholesterol was determined as % inhibition 24 h after the statin dose. (B) The effect of simvastatin (10 µM) on the time dependent intracellular accumulation of gentamicin (0.25 mg/ml) in OK cells. (C) The effect of simvastatin (10 µM) on the time (0–72 h, 0.25 mg/ml) dependent cytotoxicity induced by gentamicin in OK cells. Gentamicin accumulation was determined by LC–MS/MRM (µg gentamicin/mg cellular protein) and cytotoxicity was determined by LDH leakage into cell culture media (U/l). (D) The linear relationship between gentamicin accumulation and cytotoxicity in OK cells. Correlation coefficient is given where required (□; OK cells incubated with 30 µM pravastatin and 0.25 mg/ml gentamicin over 0–72 h) (●; OK cells incubated with 10 µM simvastatin and 0.25 mg/ml gentamicin over 0–72 h). Data is given as mean ±S.D of three independent experiments. Statistical significance was assigned relative to time matched vehicle dosed controls $^{*}p < 0.05$, $^{**}p < 0.01$ or simvastatin + gentamicin compared to gentamicin alone $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$.

COMMENTARY

Repurposing Statins for Renal Protection: Is It a Class Effect?

Stephen J. McWilliam[1,*], Daniel J. Antoine[2] and Munir Pirmohamed[2]

Clin Transl Sci 2018; 11: 100-102

- These findings informed the design of a **phase IIa randomized controlled clinical trial** of **rosuvastatin** for the **prevention of aminoglycoside-induced nephrotoxicity** in **children with CF.**

  The PROteKT study (EudraCT 2014-002387-32, UKCRN ID 16993, ISRCTN26104255)
- In this multicenter trial, **50 children with CF** receiving clinically indicated treatment with aminoglycosides were randomized equally to cotreatment with rosuvastatin or to current standard of care.
- A dose of **10 mg rosuvastatin** was used in the trial based on allometric scaling from the guinea pig experiments.
- **Recruitment** to this trial is now **complete**, and **results will be published in the near future.**
- This phase IIa study, **if positive**, will be used **to design a multicenter, phase III trial** to evaluate the effect of **rosuvastatin in preventing aminoglycoside-induced kidney injury.**

1Department of Women's and Children's Health, University of Liverpool, Merseyside, UK; 2Department of Molecular and Clinical Pharmacology, and MRC Centre for Drug Safety Science, University of Liverpool, Liverpool, Merseyside, UK

Pharmacogenetics & Pharmacogenomics

- The terms '**pharmacogenomics'** and **'pharmacogenetics' are often used interchangeably to describe how genetic determinants affect an individual's response to a medication**.
- **Pharmacogenetics**, the narrower term, is defined as 'the study of **interindividual variations in DNA sequence** related to **drug response**'.
- However, it has become clear that the sequence of individual genes is not the only factor involved, but **many genes interact** with each other and, thereby, affect the functioning of the cell, organ and individual.
- **Pharmacogenomics** is a broader term, covering these additional factors, defined as 'the study of the variability of the expression of individual genes relevant to the disease susceptibility as well as drug response at cellular, individual or population level'.
- **It is estimated that 10–20% of ADRs are genetically determined**

Pharmacol Ther 2017; 174:55-62

Drug-induced Ototoxicity: Mechanisms, Pharmacogenetics, and Protective Strategies

C Lanvers-Kaminsky[1], AG am Zehnhoff-Dinnesen[2], R Parfitt[2] and G Ciarimboli[3]

The **A1555G mutation** in the mitochondrial genome **has been associated with an increased risk for aminoglycoside ototoxicity.**

This mutation is **located in the gene which codes for the mitochondrial 12S rRNA**.

- By replacement of the adenine by guanine in position 1555, the guanine can form an additional base pair with the cytosine in position 1494 in the ternary structure of the
- 12S rRNA. This renders the mutated 12S rRNA more similar to the bacterial 16S rRNA, the key target of aminoglycosides.44

Aminoglycosides bind with higher affinity to the mutated 12S rRNA than to the wild type 12S rRNA. This is supposed to be the reason for the increased risk of aminoglycoside-induced ototoxicity in patients carrying the **A1555G mitochondrial DNA mutation.**

Additional mutations in the mitochondrial genome have been identified, which also predispose for aminoglycoside-induced hearing impairment. Many of these polymorphisms are located in the **gene coding for the 12S rRNA**, suggesting that this is a ***hot spot*** for non-syndromic aminoglycoside-induced **hearing loss**.

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Printed in U.S.A.
© 2002 by The American Society for Biochemistry and Molecular Biology, Inc.

Megalin Deficiency Offers Protection from Renal Aminoglycoside Accumulation*

Received for publication, October 15, 2001
Published, JBC Papers in Press, November 7, 2001, DOI 10.1074/jbc.M109959200

Christian Schmitz‡, Jan Hilpert‡, Christian Jacobsen§, Christian Boensch‡, Erik Ilsø Christensen¶, Friedrich C. Luft‖, and Thomas E. Willnow‡**‡‡

*"We demonstrate that the **uptake of aminoglycosides into the kidney** directly correlates with **renal megalin activity** and is **completely eliminated in mice lacking the receptor**.*
*Thus, our studies provide unequivocal evidence that megalin is the only major pathway responsible for renal aminoglycoside accumulation and that the receptor represents **a unique drug target to prevent aminoglycoside-induced nephrotoxicity in patients."***

Decreased renal accumulation of aminoglycoside reflects defective receptor-mediated endocytosis in cystic fibrosis and Dent's disease

Pflugers Arch - Eur J Physiol (2011) 462:851–860

Claudia Raggi · Kunio Fujiwara · Teresinha Leal · François Jouret · Olivier Devuyst · Sara Terryn

*"… we investigated gentamicin uptake and renal accumulation in mice **lacking functional CFTR** (CftrΔF/ΔF) or **knock-out** for the **Cl– /H+ exchanger ClC-5** (Clcn5Y/−).*
*As compared with controls, CftrΔF/ΔF and Clcn5Y/− mice showed **a 15% to 85% decrease in gentamicin accumulation in the kidney**, respectively, in **absence of renal failure**.*
*These results show that the **functional loss of these 2 chloride transporters** is associated with **impaired uptake of AG in PT cells**, reflected by a **decreased renal accumulation of the drug."***

Management of drug-induced AKI

- Reducing further nephrotoxic insults
- Assessing and supporting adequate hydration
- Monitoring fluid overload & electrolytes to initiate renal replacement therapy, if required
- Ensuring resolution of renal function
- Screening for **risk factors for CKD** (hypertension and proteinuria)

Renal follow-up

Long-term risk of CKD from use of nephrotoxic antibiotics

- As many patients with drug-induced AKI have additional co-morbidities, it is difficult to determine the precise long-term risk of CKD from use of each drug

- In a large study by Goldstein's group[1], 70 out of 100 of children who were exposed to either > 3 days of aminoglycoside or > 3 nephrotoxic agents for at least 1 day, and who developed AKI, demonstrated features of **residual kidney damage at 6 months post AKI** *(reduced eGFR, hyperfiltration, proteinuria, or hypertension)*

- Longer-term studies are required to confirm these findings, however, this is in keeping with studies on the cumulative effect of aminoglycosides **in patients with CF:**

  reduced GFR *in* ***31-42%*** *of patients* ***with multiple exposure to*** **aminoglycosides** [2]

→Reducing the long-term consequence of kidney injury and inflammation associated with drugs administered during childhood is therefore an important healthcare priority

[1] J Pediatrics 2014; 165 (3): 522-527 [2]Pediatric Pulmonol 2005; 39: 15-20.

Management of drug-induced AKI

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- Assessing and supporting adequate hydration
- Monitoring fluid overload & electrolytes to initiate **renal replacement therapy**, if required
- Ensuring resolution of renal function
- Screening for risk factors for CKD (hypertension and proteinuria)

Renal follow-up

Fattori che possono influenzare la clearance di un farmaco in corso di terapia sostituiva renale (RRT)

Caratteristiche del pz

- Peso/h
- Overload di volume
- Livelli di albuminemia
- Clearance renale residua
- MOF ?
- Altri potenziali farmaci nefrotossici
- Amine ?

Caratteristiche dell'Antibiotico

- Idrosolubile/liposolubile
- p.m./ carica elettrica
- legame con le proteine
- via di eliminazione
- Tempo dipendente/Concentrazione dipendente
- PK/PD at target site

Caratteristiche della metodica depurativa

- Intermittente/continua
- Diffusiva/convettiva/mista
- Prediluizione/post diluizione
- $Q_b/Q_d/Q_{uf}$
- High flux/Low flux//Superficie filtro
- Adsorbimento dell'AB (es. Amikacina e Colistina) sulla membrana dialitica (es. PMMA e teicoplanina)

Consigli pratici di carattere generale

Dose carico iniziale per raggiungere il target ematico (> MIC) ,
senza aggiustamenti (150% dose normale per gli antibiotici idrosolubili)

Antibiotici idrosolubili (basso Vd): sono suscettibili di rimozione significativa con RRT e necessitano di aggiustamenti posologici
Per le dialisi intermittenti tenere conto del rebound di farmaco post-dialitico

Antibiotici liposolubili : sono per la maggior parte ad eliminazione epatica, attraversano le membrane cellulari e hanno Vd elevato.
La rimozione extracorporea è modesta e l'aggiustamento posologico è meno frequentemente necessario

Quando possibile dosare i livelli ematici (aminoglicosidi, vancomicina, teicoplanina) e guidare la terapia in base alle concentrazioni plasmatiche (paziente critico)

Di quanti antibiotici riusciamo ad avere un ***Therapeutic Drug Monitoring*** in tempi utili e alla portata dei nostri Laboratori ?

Peritoneal Dialysis International, Vol. 32, pp. 532–586
doi: 10.3747/pdi.2011.00091

0896-8608/12 $3.00 + .00
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ISPD GUIDELINES/RECOMMENDATIONS

CONSENSUS GUIDELINES FOR THE PREVENTION AND TREATMENT OF CATHETER-RELATED INFECTIONS AND PERITONITIS IN PEDIATRIC PATIENTS RECEIVING PERITONEAL DIALYSIS: 2012 UPDATE

GUIDELINE 9 – ADMINISTRATION OF ANTIBIOTICS

9.1 We recommend that antibiotics for the treatment of bacterial peritonitis be administered by the intraperitoneal route (1B).

9.2 In non-anuric patients receiving intermittent intraperitoneal doses of glycopeptide antibiotics (vancomycin or teicoplanin), we recommend monitoring blood levels of the antibiotics (2A).

9.3 We recommend that beta-lactam antibiotics be administered continuously (1B).

"Furthermore, we recommend monitoring the blood levels of antibiotics (within 2 – 4 days of first administration) in patients receiving glycopeptides intermittently—at least in patients with significant residual renal function. Although not established in routine clinical practice, monitoring of dialysate concentrations may provide even more relevant information."

LIMITATIONS

The pharmacokinetic and pharmacodynamic basis for intermittent drug dosing, particularly in patients undergoing APD with frequent short cycles, is limited to a few adult and even fewer pediatric studies.

RESEARCH RECOMMENDATIONS

- The **kinetics of drug disposition** after intermittent intraperitoneal administration should be studied in all pediatric age groups for all antibiotics listed in the present guideline.
- The effects of PD prescription modifications (fill volume, number and duration of cycles) on peritoneal drug resorption and clearance should be assessed by computer simulation, using experimentally established PK characteristics.
- Predictive value of plasma and dialysate antibiotic levels for bacterial eradication and clinical outcomes should be studied.

Fattori che possono influenzare la clearance di un farmaco in corso di CRRT

I) Fattori farmaco-specifici

- peso molecolare
- volume e conformazione della molecola
- idrosolubilità e carica elettrica
- legame proteico
- volume di distribuzione *(Vd < 1 L/kg: rimozione significativa in CRRT)*
- metabolismo

II) Fattori CRRT-specifici

- permeabilità della membrana del filtro *(alta permeabilità)*
- modalità di CRRT: diffusiva, convettiva, mista
- pre- *versus* post-diluizione
- dose dialitica (*dose effluente totale*)
- durata del trattamento (*downtime*, tempo di utilizzo del filtro)

III) Fattori paziente-specifici

- funzione renale residua
- modificazioni della quota di eliminazione extra-renale (disfunzione epatica, MOF)
- variazione del volume di distribuzione (*> nei pazienti con AKI per alcuni antibiotici)*
- stato infiammatorio
- ipoalbuminemia
- interferenza con altri farmaci (amine, farmaci nefrotossici)

Drug properties to consider in order to determine likelihood of drug removal by haemofiltration

The following drug properties are required in order for a drug to be removed by haemofiltration:

- Low molecular weight (< 10000 daltons)
- Low volume of distribution (< 1L/kg)
- High degree of water solubility
- Low degree of protein binding

Small, water soluble molecules with low volume of distribution and low protein binding are more likely to be removed by the filter; however it is important to remember that there are other factors such as stearic hindrance at the membrane site which may affect drug clearance and which may be difficult to predict.

G Ital Nefrol 2012; 29 (4): 425-444 RASSEGNA

FARMACOCINETICA DEGLI ANTIBIOTICI NELLE TERAPIE SOSTITUTIVE RENALI CONTINUE (CRRT)

Santo Morabito[1], Valentina Pistolesi[1], Umberto Maggiore[2], Enrico Fiaccadori[2], Alessandro Pierucci[1]

[1]Dipartimento Nefrologia e Urologia, Umberto I, Policlinico di Roma, "Sapienza", Università di Roma, Roma
[2]Dipartimento di Clinica Medica e Nefrologia, Università di Parma, Parma

Pertanto, con l'impiego di membrane *"high-flux" (AN69HF, PAN, polisulfone,* poliamide, ecc.) la *clearance diffusiva* di farmaci a PM elevato, come la vancomicina (PM 1448 Da), è tutt'altro che trascurabile e può ridurre i livelli ematici del farmaco al di sotto della soglia terapeutica.

Tuttavia, rispetto alle metodiche convettive, il coefficiente di saturazione tende a ridursi progressivamente con l'aumentare del PM (Cl diffusiva < Cl convettiva) anche con l'impiego di membrane *"high-flux"*.

Ai fini del passaggio del farmaco attraverso la membrana, assumono importanza anche le proporzioni geometriche e il volume effettivo della molecola, che sono determinate, oltre che dal PM, anche dalla forma e dalla carica elettrica.

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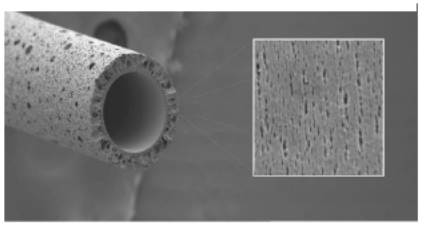
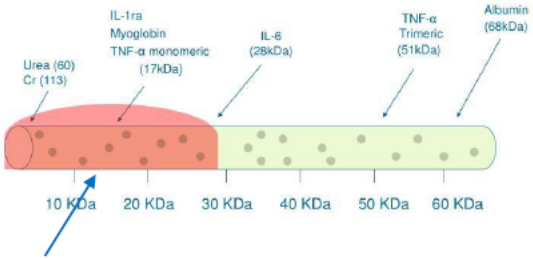
Caratteristiche Filtro

Pore Size



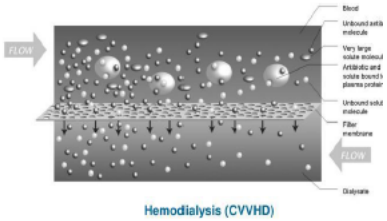
Membrane high flux 60Da

Size is important – but……



Vancomicina pm 1448 Da
Teicoplanina pm 1885 Da
Daptomicina 1620Da
Colistina 1155Da

Importance of protein binding



Le membrane high-flux (cut-off 20.000-30.000 Da) di impiego diffuso nelle CRRT sono ad elevata porosità e non costituiscono una barriera al trasporto di farmaci con PM >1000-1500 Da

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vancomicina PM 1448 D – teicoplanina PM 1885 D

G Ital Nefrol 2012; 29 (4): 425-444 RASSEGNA

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- permeabilità della membrana del filtro *(alta permeabilità)*
- **modalità di CRRT: diffusiva, convettiva, mista**
- pre- *versus* post-diluizione
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- durata del trattamento (*downtime*, tempo di utilizzo del filtro)

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- <u>funzione renale residua</u>
- modificazioni della quota di eliminazione extra-renale (disfunzione epatica, MOF)
- variazione del volume di distribuzione (> *nei pazienti con AKI per alcuni antibiotici)*
- stato infiammatorio
- ipoalbuminemia
- interferenza con altri farmaci (amine, farmaci nefrotossici)

Medication	Usual Dosage	Dialysate Rates	CVVHD Dose Recommendation
Acyclovir	5-10 mg/kg[a] IDEAL BODY WEIGHT IV q8h	CVVHD ≥ 2 to < 6 L/hr	5-10 mg/kg IV q12h
		CVVHD < 2 L/hr	5-10 mg/kg IV q24h
Ampicillin[b]	2g IV q4h	CVVHD ≥ 2 to < 6 L/hr	2g IV q4h
		CVVHD < 2 L/hr	2g IV q6h
Ampicillin-Sulbactam[b]	1.5-3 g IV q6h	CVVHD ≥ 2 to < 6 L/hr	1.5-3 g IV q6h
		CVVHD < 2 L/hr	1.5-3 g IV q8h
Aztreonam[b]	2g IV q8h	CVVHD ≥ 2 to < 6 L/hr	2g IV q8h
		CVVHD < 2 L/hr	2g IV x1 then 1g IV q8h
Cefazolin[b]	0.5 g IV q8h *(Surgical Prophylaxis)*	CVVHD ≥ 2 to < 6 L/hr	0.5 g IV q8h
		CVVHD < 2 L/hr	0.5 g IV q12h
	1 g IV q8h	CVVHD ≥ 2 to < 6 L/hr	1 g IV q8h
		CVVHD < 2 L/hr	1 g IV q12h
	2 g IV q8h	CVVHD ≥ 2 to < 6 L/hr	2 g IV q8h
		CVVHD < 2 L/hr	2 g IV q12h
Cefepime	1-2[c] g IV q8h	CVVHD ≥ 2 to < 6 L/hr	1-2g IV q8h
		CVVHD < 2 L/hr	1-2g IV q12h
Ceftazidime	2 g IV q8h	CVVHD ≥ 2 to < 6 L/hr	2 g IV q8h
		CVVHD < 2 L/hr	2 g IV q12h
Colistin	5 mg/kg/day IDEAL BODY WEIGHT IV divided q8-12h	CVVHD ≥ 2 to < 6 L/hr	5 mg/kg/day IV divided q8-12h
		CVVHD < 2 L/hr	3 mg/kg/day IV divided q12h
Daptomycin	4-6 mg/kg[d] ACTUAL BODY WEIGHT IV q24h	CVVHD ≥ 2 to < 6 L/hr	8 mg/kg IV q48h
		CVVHD < 2 L/hr	4-6 mg/kg IV q48h
Fluconazole	100-200 mg IV/PO q24h *(Prophylaxis Dosing)*	CVVHD ≥ 2 to < 6 L/hr	100-200 mg IV/PO q24h
		CVVHD < 2 L/hr	100 mg IV/PO q24h
	400-800 mg IV/PO q24h *(Treatment Dosing)*	CVVHD ≥ 2 to < 6 L/hr	400-800 mg IV/PO q24h
		CVVHD < 2 L/hr	200-400 mg IV/PO q24h
Ganciclovir	5 mg/kg ACTUAL BODY WEIGHT IV q12h *(Induction Dosing)*	CVVHD ≥ 2 to < 6 L/hr	5 mg/kg IV q24h
		CVVHD < 2 L/hr	2.5 mg/kg IV q24h
	5 mg/kg ACTUAL BODY WEIGHT IV q24h *(Maintenance/Prophylaxis)*	CVVHD ≥ 2 to < 6 L/hr	2.5 mg/kg IV q24h
		CVVHD < 2 L/hr	1.25 mg/kg IV q24h
	6 mg/kg ACTUAL BODY WEIGHT IV q24h (liver transplant)	CVVHD ≥ 2 to < 6 L/hr	2.5 mg/kg IV q24h
		CVVHD < 2 L/hr	1.25 mg/kg IV 24h
Levofloxacin	250 mg IV/PO q24h	CVVHD ≥ 1 L/hr	250 mg IV/PO q24h
	500 mg IV/PO q24h	CVVHD ≥ 1 L/hr	500 mg IV/PO x 1 then 250 mg q24h
	750 mg IV/PO q24h	CVVHD ≥ 2 to < 6 L/hr	750 mg IV/PO x 1 then 500 mg q24h
		CVVHD < 2 L/hr	750 mg IV/PO x1 then 500 mg q48h
Meropenem	1 to 2[c] g IV q8h	CVVHD ≥ 2 to < 6 L/hr	1-2 g IV q8h
		CVVHD < 2 L/hr	1-2 g IV q12h
Penicillin G[b]	3-4 million units IV q4h	CVVHD ≥ 2 to < 6 L/hr	2 million units IV q4h
		CVVHD < 2 L/hr	2 million units IV q6h
Piperacillin-Tazobactam	Mild to moderate infections: 4.5 g IV q8h	CVVHD ≥ 2 to < 6 L/hr	4.5 g IV q8h
		CVVHD < 2 L/hr	2.25 g IV q6h
	Severe/Life threatening infections: 4.5 g IV q6h	CVVHD ≥ 2 – 6 L/hr	4.5 g IV q6h
		CVVHD < 2 L/hr	4.5 g IV q8h
Trimethoprim-sulfamethoxazole[e]	15-20 mg/kg/day ACTUAL BODY WEIGHT of trimethoprim component IV/PO divided q6h *(Treatment dosing)*	CVVHD ≥ 2 to < 6 L/hr	15-20 mg/kg/day divided q6-8h for first 48 hours, then reassess
		CVVHD < 2 L/hr	10-15 mg/kg/day divided q8h for first 48 hours, then reassess
Vancomcyin	15 – 20 mg/kg ACTUAL BODY WEIGHT IV q8-12h	CVVHD ≥ 2 to < 6 L/hr	20-25 mg/kg x1 (loading dose) then 15 mg/kg IV q24h
		CVVHD < 2 L/hr	20-25 mg/kg x1 (loading dose) then dose by level

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Created: 1/2015

Dialysate rate (Qd)
= flusso soluzione di dialisi
= quota "diffusiva"
= HD, emodialisi

+

Reinfusion solution rate (Qr)
= flusso di reinfusione
= quota "convettiva"
=HDF, emodiafiltrazione

Dose effluente totale
= Qd + Qr + UF netta
L/ora → ml/kg/ora

es. 2 L/ora = 28 ml/kg/ora
6 L/ora = 86 ml/kg/ora

Terapie sostitutive

- **CRRT**: i farmaci maggiormente rimossi sono quelli a **più basso peso molecolare**,

  con **basso legame proteico** e

  idrofili

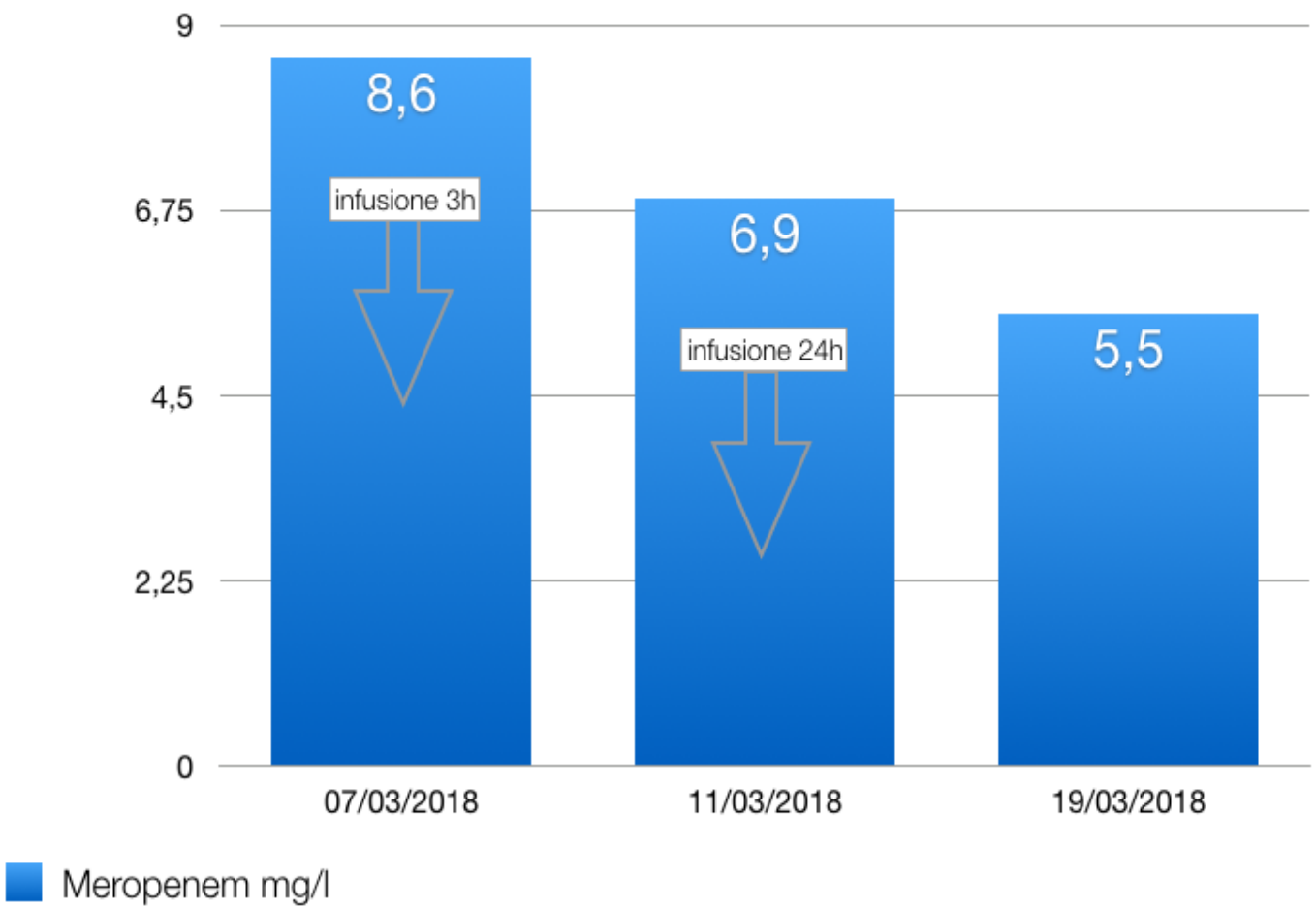
- **ECMO:**

  introduce un'ulteriore difficoltà nell'aggiustamento posologico degli antibiotici perché determina:
  - **aumento del volume di distribuzione**
  - **alterazioni del legame proteico**
  - **potenziale sequestro di farmaci nei circuiti**

ECMO + CRRT

K.pneumoniae OXA 48 (carbapenemasi):
MIC MEM: 16 mg/l
Meropenem 120 mg/kg

MIC = 16 mg/l



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- **durata del trattamento** (*downtime*, **tempo di utilizzo del filtro**)

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→ alta variabilità da paziente a paziente, e in corso di trattamento nello stesso paziente

Istituto GIANNINA GASLINI Genova	**Form** **Specifica Operativa/**	Joint Commission International Ospedale accreditato Joint Commission International Certificato ISO 9001 : 2000
U.O.C. Malattie Infettive **U.O.C. Nefrologia e Trapianto Rene, Centro di Dialisi**	**Somministrazione di farmaci anti-infettivi e.v. (e di oseltamivir per os) nel paziente in insufficienza renale**	**Standard di riferimento soddisfatti:** MOI.9.1 QPS.3

Titolo del Documento	Specifica operativa/procedura per la somministrazione di farmaci anti-infettivi e.v. (e di oseltamivir per os) nel paziente in insufficienza renale
Data Emissione	Giugno 2018
Scadenza periodicità della revisione	
Responsabile Redazione	E.Castagnola, Responsabile U.O.C. Malattie Infettive E.Verrina, Responsabile Centro Dialisi, U.O.C. Nefrologia e Trapianto Rene
Responsabile Approvazione	Si intende il Responsabile dell'Unità Operativa di riferimento che ne dispone l'archiviazione come documentazione a valenza interna; deve comunque essere sottoposto all' approvazione del Comitato di Dipartimento (parere favorevole)
N.ro revisione	1.1
Motivazione della revisione	Contiene il razionale della modifica apportata (indicazione non obbligatoria, solo quando ritenuta opportuna)

farmaco	**AMIKACINA**	
Parametri farmacologici	Legame proteico: Peso molecolare:	<20% 585.60 daltons
	Può essere diluita con	Soluzione fisiologica
	Concentrazione massima da infondere consigliata	2,5 mg/ml
Dose normale:	Neonato pretermine PMA (s) ≤ 29 - PNA (g) 0-7 PMA (s) ≤ 29 - PNA (g) 8-28 PMA (s) ≤ 29 - PNA (g) ≥ 29 PMA 30-34 (s) - PNA (g) 0-7 PMA 30-34 (s) – PNA (g) ≥ 8	 18 mg/kg q24h, monitorando I livelli ematici 15 mg/kh q36h, monitorando I livelli emati 15 mg/kg q24h, monitorando I livelli emati 18 mg/kg q36h, monitorando I livelli emati 15 mg/kg q24h, monitorando I livelli emati
	Neonato a termine (PMA (s) ≥ 35) e altre età	15-20 mg/kg (max 1.5g) q24h, monitorando i livelli ematici
	fibrosi cistica:	20-30 mg/kg (max 1.5g) q24h, monitorando i livelli ematici
Aggiustamento della dose in insufficienza renale:	Dose normale iniziale, poi secondo i livelli ematici	
Aggiustamento della dose in emodialisi:	Dose normale iniziale, poi secondo i livelli ematici	
Aggiustamento della dose in dialisi peritoneale	Dose normale iniziale, poi secondo i livelli ematici	
Dose intraperitoneale	Dose iniziale 25 mg/L, dose di mantenimento 12 mg/L	
Aggiustamento della dose in CRRT:	Dose normale iniziale, poi secondo i livelli ematici	
Note	Nel paziente obeso calcolare la dose sul peso corretto. Eseguire monitoraggio dei livelli ematici per tossicità ed efficacia. Parametro PK/PD: C_{max}/MIC >10 Livello per tossicità: deve essere < 10 mg/l a 10 ore dal termine dell'infusione. Per le modifiche dei tempi e/o della dose vedere diagramma di Hartford o di Urban & Craig (Stanford University)	

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Istituto Giannina Gaslini. Raccomandazioni per la terapia antibiotica delle infezioni da patogeni resistenti. Vers. 2.0-2018

Istituto Giannina Gaslini. Raccomandazioni per la gestione delle complicanze infettive nel paziente sottoposto a chemioterapia antineoplastica o trapianto di cellule staminali emopoietiche, oppure affetto da aplasia midollare o neutropenia congenita Vers 1.1-2016

In conclusione...

- La tossicità renale e generale associata all'uso degli antibiotici rappresenta un problema rilevante nei pazienti pediatrici, soprattutto in area critica

- L'aggiustamento posologico deve basarsi sulla valutazione delle caratteristiche di PK/PD del farmaco

- La conoscenza dei meccanismi attraverso i quali si determina la nefrotossicità è importante al fine di:

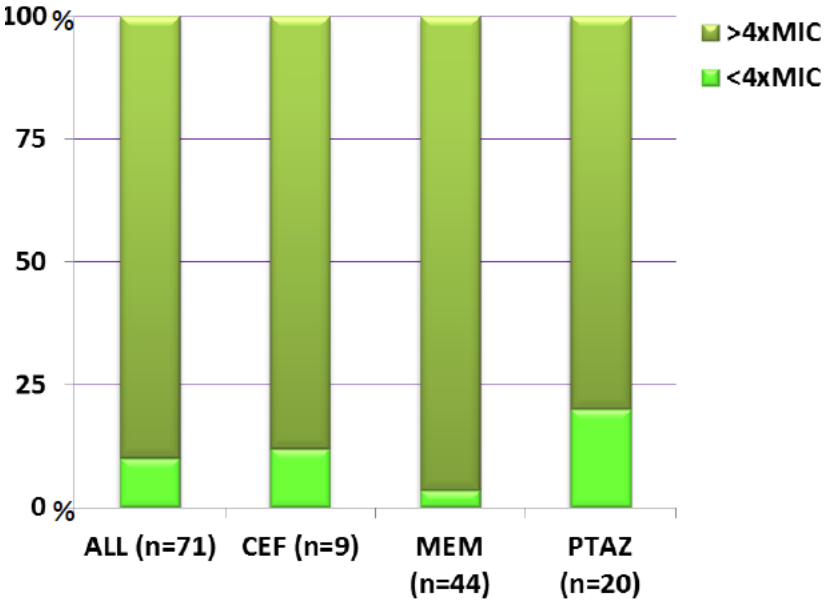
→ *valutare i possibili fattori di rischio*

→ *individuare biomarkers precoci ed affidabili*

→ *sviluppare strumenti per limitare le conseguenze della tossicità*

- I protocolli di terapia adottati devono essere confrontati con le raccomandazioni disponibili e continuamente adattati alla situazione clinica del singolo paziente

β-lactam antibiotic concentrations during Continuous Renal Replacement Therapy



Conclusions

During CRRT, β-lactam antibiotics regimens similar to those recommended for patients with normal renal function should be given to avoid under-dosing as empirical therapy. However, drug accumulation occurs rapidly and daily doses should be rapidly reduced, especially in case of very susceptible bacteria. Given the wide variability in drug PK parameters in this population of patients, **TDM could be considered to adjust drug regimens**. Drug prescription should also take into account the intensity of CRRT

Beumier M et al. Crit Care 2014; 18(3): R105

Una possibile strategia per il paziente critico

1. Fare diagnosi di infezione e scegliere un antibiotico sulla base di:
    1. quadro clinico
    2. patogeno più probabile o identificato
    3. pattern di sensibilità in ospedale o nel caso dato
2. Identificare le **caratteristiche fisio-patologiche** del paziente:
    1. età
    2. peso
    3. clearance della creatinina (anche calcolata)
    4. albuminemia
    5. carico/sovraccarico di liquidi
    6. presenza di eventuali circuiti extracorporei
3. Sulla base di questi dati stabilire la **1a dose** da somministrare
4. Iniziare la terapia rapidamente e con **tempi di somministrazione** adatti al tipo di farmaco scelto (*monodose, infusione continua/prolungata*)
5. Eseguire prelievi per la **determinazione dei livelli ematici (TDM)** in tempi stabiliti e rivalutare in base ai risultati

Great Ormond Street Hospital for Children NHS Trust

Paediatric Drug Dosage Adjustments in Patients with Renal Impairment or on Renal Replacement Therapies for use on the Intensive Care and Renal Units

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Approved by: Drugs & Therapeutics Committee
Date document created: November 2011
Date of interim review: May 2014 **Reviewed by:** Venetia Horn (PICU Senior Pharmacist) **Checked by:** Vani Suri (NICU Pharmacist)
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Version: 3

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Timing di somministrazione:

Aminoglicosidi → dose carico pre-dialisi alto picco di concentrazione per massimizzare efficacia antibatterica; la rimozione dialitica consente di ridurre la tossicità di una esposizione prolungata

beta-lattami → nelle dialisi intermittenti somministrare post-dialisi; nelle CRRT infusioni prolungate o piccole dosi a intervallli ravvicinati

Linezolid → somministrare post dialisi

Glicopeptidi → nell'ultima ora di dialisi (nelle dialisi intermittenti)

AMINOGLICOSIDI

- Bersaglio della tossicità: tubulo prossimale
  endocitosi tramite il recettore megalina → soggetto a «saturazione» → dose singola: «extended interval dosing» («concentration dependent PD profile»)
- Meccanismo tossicità:
  fosfolipidosi lisosomiale → danno mitocondriale → apoptosi
- Variabilità nella sensibilità individuale
- TDM: *a 10 h ~~(< 10 mg/L~~)*
- IR non-oligurica con disfunzione tubulare, da 5 a 10 gg dall'inizio della terapia
- Reversibile nella maggior parte dei casi,
  ma esposizione ripetuta → danno cronico
- *a*

Pediatr Nephrol (2017) 32:2015–2025
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REVIEW

Aminoglycoside-induced nephrotoxicity in children

Stephen J McWilliam[1] · Daniel J Antoine[2] · Rosalind L Smyth[3] · Munir Pirmohamed[2]

Primary criteria	Secondary criteria
• Rise in serum creatinine that presents as or progresses to stage 2 (KDIGO) 2–2.9× reference serum creatinine or higher • If child has a baseline serum creatinine of <0.5 mg/dl (44 μmol/L), must double serum creatinine to get to at least 0.5 mg/dl (44 μmol/L) or above OR • Decline by at least 50 % from peak serum creatinine over 7 days in relationship to change in drug-dosing adjustment or discontinuation within 2 weeks	• Oliguric <0.5 ml/kg per hour for 12 h (KDIGO stage 2) • Non-oliguric >1 ml/kg per hour for 24 h (paediatrics) • Urinalysis findings: granular and muddy casts consistent with acute tubular necrosis, urinary eosinophils, proteinuria • Fractional excretion of sodium of >1 % • Negative ultrasound findings • Positive gallium scan for acute interstitial nephritis • Clinical symptoms for acute interstitial nephritis: fever, rash and joint pains

The phenotypic criteria for drug-induced acute kidney injury presented in this table are adapted from Mehta et al.

→ **Baseline and serial measurements of novel renal biomarkers to asses the predictive value of these markers for AKI**

→ **DNA samples should be collected for pharmacogenomic analyses**

Key points

■■Altered drug pharmacokinetics in critically ill patients with acute kidney injury (AKI) and heterogeneous renal replacement therapy (RRT) techniques in intensive care units preclude standardized antibiotic dosing

■■Most critically ill patients with AKI exhibit altered antibiotic pharmacokinetics that necessitate increased doses in spite of decreased renal clearance, particularly when serious infections are implicated

■■Drug dosing decisions must take into account pharmacodynamic as well as pharmacokinetic considerations

■■Clinicians should compare their RRT protocols to those in published guidelines and ensure that their recommendations are applicable to the individual patient's clinical situation

■■Hybrid RRTs require the same antibiotic dosing alterations as do continuous RRTs, but for hybrid therapies the dose timing must also be considered ?????