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PK/PD of β-lactams, aminoglycosides and other antimicrobial classes in the elderly:
translation into clinical practice

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AGING….

Pharmacokinetic parameters

- Absorption and Bioavailability: how much drug will be available (when given orally)
- Volume of distribution (Vd): where the drug distributes
- Protein binding: the unavailable fraction of a drug
- Half-life ($t_{1/2}$): how long the drug circulates
- Clearance: how the body clears the drug

Elimination parameters and elimination half-life

$$t_{1/2} = \frac{0.693 \ V_d}{CL_E}$$

$$k = \frac{0.693}{t_{1/2}}$$

$$CL_E = k \times V_d$$

$$t_{1/2} = \frac{0.693 \cdot V_{d(area)}}{CL_E}$$

Therefore, half-life is not a primary parameter

$t_{1/2}$ = elimination half-life
k = elimination rate constant
CL_E = elimination clearance

Pharmacokinetics of antimicrobials

- HYDROPHILIC
- β-lactams
- Glycopeptides
- Carbapenems
- Aminoglycosides
- Unable to cross cell membranes
- Limited Vd
- Inactive against intracellular pathogens
- Usually renal clearance

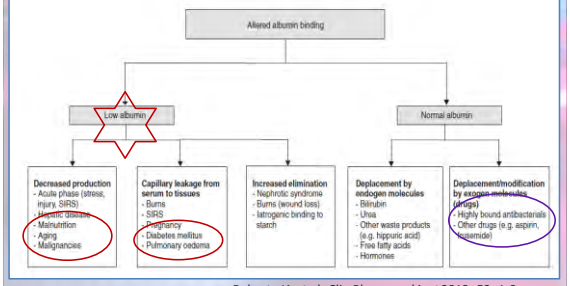
- LIPOPHILIC
- Oxazolidinones
- Rifampin
- Quinolones
- Azalides & Tetracyclins
- Free diffusion across cell membranes
- Wide Vd
- Active against intracellular pathogens
- Usually liver metabolism

Distribution in aging

- Body fat mass increases by 20-40%
- total body water and lean body mass decrease by 10-15%
  - Vd of lipophilic drugs increases with prolonged half-life
  - Hydrophilic drugs have a smaller Vd with a more rapid increase in plasma concentrations
  - The protein binding plays also a role..

Corsonello A, et al. Clin Microbiol Infect 2015; in press

Main factors potentially responsible for alterations in drug-albumin binding



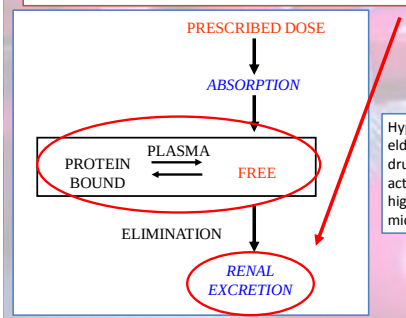
Roberts JA et al. *Clin Pharmacokinet* 2013; 52: 1-8

Are changes in protein binding likely to be therapeutically relevant?

- Highly protein-bound antimicrobials
  - ceftriaxone, teicoplanin, ertapenem (daptomycin)
  - theoretically, a change from 99 to 98% of protein binding will double the free active level (1 to 2%)
- Drugs with high clearance by glomerular filtration
- Drugs for which dosing is not titrated to effect
  - Typically antimicrobials

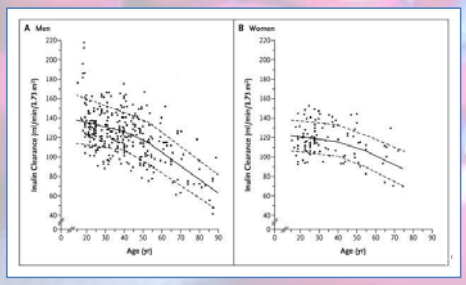
Loss of protein binding affects free active concentration of highly bound antimicrobials

ceftriaxone
ertapenem
teicoplanin



Hypoalbuminemia in elderly may greatly affect drug disposition and active concentration for highly bound anti-microbials (drug loss)

Normal values for GFR in men and women

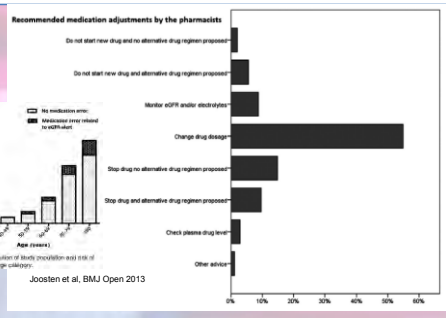


Limitations of creatinine based estimates

- SrCr is influenced by factors other than GFR
  - Muscle mass, diet, tubular secretion rate
- Equations use age, sex, race and weight, but probably not all factors involved
- Not accurate in individuals with extreme muscle mass or big size, dietary habits (important in frail, elderly, cancer patients and low muscle mass)
- Kidney function should be at steady state
  - Issues when kidney function rapidly changes
- Narrow therapeutic/toxic index drugs

Correct dosing in relation to kidney function

Primary care pharmacists supporting drug safety in renal impairment



Joosten et al, BMJ Open 2013

Pitfalls around the corner

- A low GFR implies a reduced reserve and vulnerability to drug overdosing (especially with water-soluble drugs that depend on GFR for excretion), and the insults which can precipitate AKI.
- The eGFR can be a guide to risk in the individual without the need to describe the individual as chronically diseased.
  - Risks and diseases are different
- The elderly and the very old deserve careful analysis before they are labelled as having a chronic disease based solely on a single laboratory measurement
  - especially one with inherent inaccuracies

Evaluation of the Chronic Kidney Disease Epidemiology Collaboration Equation for Dosing Antimicrobials

Kurt A Wargo and Thomas M English

Drug	Usual dosage	Dosage adjustment in relation to GFR values >50 ml/min/1.73 m^2	10-50 ml/min/1.73 m^2	<10 ml/min/1.73 m^2
Piperacillin/tazobactam	3.375-4.5 g every 6-8 hours	100%	2.25 g every 6 hours; every 8 hours if GFR < 20	2.25 g every 8 hours
Ciprofloxacin	400 mg IV or 500 to 750 mg orally every 12 hours	100%	50-75%	50%
Levofloxacin	250-750 mg every 24 hours	100%	500-750 mg initial dose, then 250-750 mg every 24 to 48 hours	500 mg initial dose, then 250-500 mg every 48 hours
Fluconazole	200-400 mg every 24 hours	100%	50%	50%

Dosing requirement according to refs [1-3].

adjustment depends upon the equation used to estimate renal function, one could consider a 85-year-old male patient having 1.3 mg/dl Scr and a body weight of 70 kg. Such patient will have a CG-BSA-estimated CCr of 39.0 ml/min/1.73 m^2, a MDRD-estimated GFR of 52 ml/min/1.73 m^2 and a CKD-EPI-estimated GFR of 50 ml/min/1.73 m^2. Such different estimates will lead to extremely different dosage adjustment for selected drugs frequently used in elderly and frail patients (see Appendix 1, Supplementary data available in *Age and Ageing* online, for examples).

Corsonello et al, Age Ageing 2011

A stricking balance between benefit and risk...

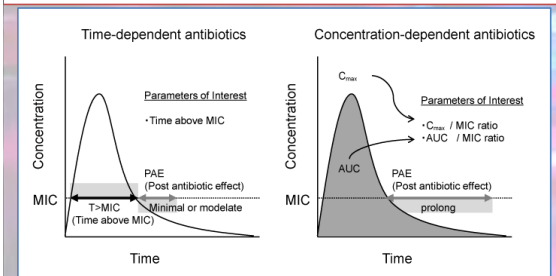
Clearance measurements may be necessary to estimate GFR

- Extremes of age (children, old and very old)
- Extremes of body size (obesity, low body mass index < 18.5 kg/m^2
- Severe malnutrition (cirrhosis, ESRD)
- Grossly abnormal muscle mass (amputation, paralysis)
- High or low intake of creatine (vegetarian diet, dietary supplements)
- Prior to dosing (high toxicity drugs, excreted by the kidney)

Risk factors for Acute Kidney Injury in the elderly

- Age-related changes in the kidney, systemic vasculature or immune system
- Co-existing illnesses
  - chronic kidney disease, cardiovascular, hypertension, diabetes, obstructive uropathy or infection
- Hypovolemia
- Sepsis
- Medication-related toxicity
  - NSAIDs, diuretics, ACE inhibitors or nephrotoxic antibiotics
- Contrast-induced nephropathy
- Perioperative factors

Age-related changes in PD: PK/PD modeling



Bowie MW & Slattum PW. Am J Geriatr Pharmacother 2007.
Mouton JW et al, J Antimicrob Chemother 2005.
Noreddin AM et al, Recent Pat Antiinfect Drug Discov 2008.
Noreddin AM et al, Drugs Aging 2007

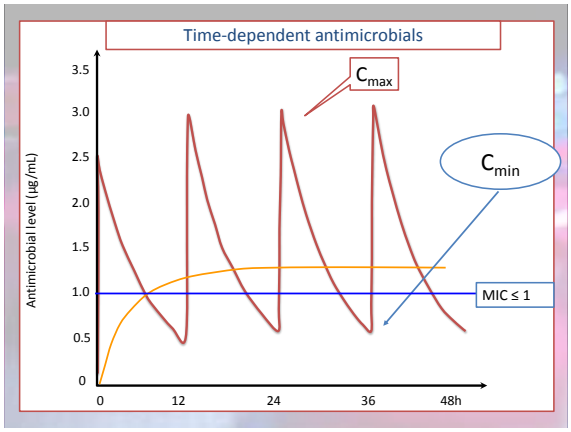
Antimicrobial pharmacodynamics

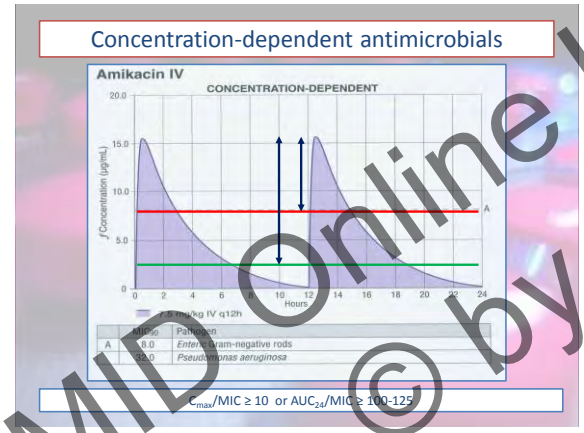
Time-dependent	Concentration-dependent
• β-lactams • Glycopeptides • Oxazolidinones • Carbapenems	• Aminoglycosides • Rifampin • Quinolones • Azalides & Glycilcyclins
• Usually weak PAE • Steady concentrations over 24 hrs.	• Strong PAE • Peak over the MIC, regardless of timing

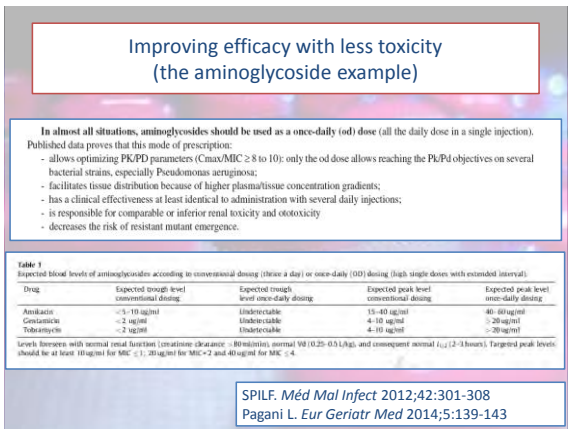
Cefepime dosing

- 1 gram q8h gives same t > MIC exposure as 2 g q12h
  - Target attainment (70% t > MIC) 78% vs 77%, respectively
- Use empirically targeted at higher MIC pathogens
- Saves approximately $ 10 per patient per day due to use of ¼ less drug
- Lessen potential toxic effects (CNS)

Paterson DL. ICAAC 2002



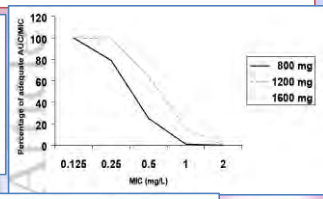




SPILF. *Méd Mal Infect* 2012;42:301-308
Pagani L. *Eur Geriatr Med* 2014;5:139-143

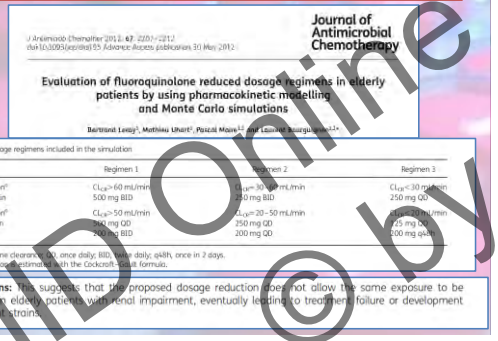
The Ciprofloxacin Target AUC/MIC Ratio Is Not Reached in Hospitalized Patients with the Recommended Dosing Regimens

Haeseker M et al. *Br J Clin Pharmacol* 2013; 75:180-185



The majority of hospitalized patients did not reach the target AUC/MIC ratio with the current iv doses. Taken into account the increasing resistance for ciprofloxacin worldwide, TDM and subsequent dose adjustment may decrease development of ciprofloxacin resistance. A large randomized clinical trial of ciprofloxacin treatment is needed to confirm the AUC/MIC>125 or higher AUC/MIC ratios (>250) are needed for good clinical and microbiological outcome.

Beware of underdosing ! Here we are with fluoroquinolones



Journal of Antimicrobial Chemotherapy

Evaluation of fluoroquinolone reduced dosage regimens in elderly patients by using pharmacokinetic modelling and Monte Carlo simulations

Table 2. Dosage regimens included in the simulation

	Regimen 1	Regimen 2	Regimen 3
Renal function[a] ciprofloxacin	Cl_{cr} > 60 mL/min 500 mg BID	Cl_{cr} = 30 – 60 mL/min 250 mg BID	Cl_{cr} < 30 mL/min 250 mg QD
Renal function[a] levofloxacin ofloxacin	Cl_{cr} > 50 mL/min 500 mg QD 200 mg BID	Cl_{cr} = 20 – 50 mL/min 250 mg QD 200 mg QD	Cl_{cr} < 20 mL/min 250 mg QD 200 mg q48h

Cl_{cr}, creatinine clearance; QD, once daily; BID, twice daily; q48h, once in 2 days.
[a]Renal function estimated with the Cockcroft–Gault formula.

Conclusions: This suggests that the proposed dosage reduction does not allow the same exposure to be achieved in elderly patients with renal impairment, eventually leading to treatment failure or development of resistant strains.

Linezolid

- PK of linezolid is not significantly altered in elderly patients (65 years or older)
- Dose adjustment for geriatric patients is overall unnecessary either
- PK of linezolid is not altered in patients with mild to severe renal impairment, nor in patients with mild-to-moderate hepatic impairment (Child-Pugh class A or B)

Linezolid

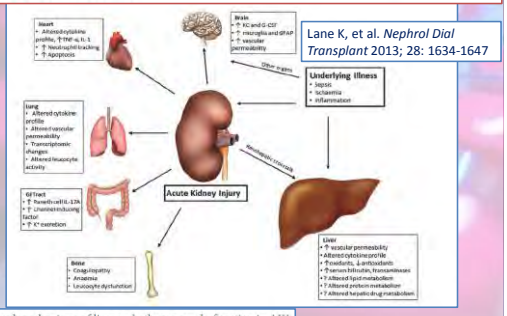
- the two primary metabolites of linezolid accumulate in patients with severe renal impairment, with the amount of accumulation increasing with the severity of renal dysfunction
- also associated to hypoglycemia episodes through its MAO inhibitory properties
- Be careful with concomitant paroxetine and in diabetic patients!

Viswanathan P et al; CID 2014;59:e93-e95

"Organ crosstalk"..?

- AKI may exert effects on other organs, including the lung, liver, heart and brain, in a process called 'organ crosstalk'
- Organ crosstalk has not been defined precisely
- The term derives from electronics, denoting any signal or circuit that unintentionally affects another
- In molecular biology, crosstalk is used to describe instances when one or more components of a signal transduction pathway affect a different pathway, either at the transmembrane or at the intracellular level

Renohepatic crosstalk: does acute kidney injury cause liver dysfunction?



Lane K, et al. *Nephrol Dial Transplant* 2013; 28: 1634-1647

Proposed mechanisms of liver and other organ dysfunction in AKI.

Table 2. Drugs incidentally recognized to exhibit altered hepatic excretion in AKI

Drug	Normal renal function clearance (mL/min)	AKI (failure category) clearance (mL/min)
Imipenem	90–95 [92]	130 [91]
Vancomycin	45–60 [93]	40–60 [94]
Meropenem	40 [95]	15 [96]

Adapted from [90]: Tegeder *et al.* postulate the enhanced imipenem clearance in AKI to be due to elevated non-renal clearance [91].

Vilay AM et al. *Crit Care* 2008; 12:235-243
Tegeder I et al. *Antimicrob Agents Chemother* 1997; 2540-2545
Rogers JD et al. *Rev Infect Dis* 1985; 7: S435-S446
Leroy A et al. *Eur J Clin Pharmacol* 1992; 42: 535-538
Giles KJ et al. *Crit Care Med* 2000; 28: 632-637
Golper TA et al. *Clin Pharmacol Ther* 1988; 43: 565-570
Macias WL et al. *Clin Pharmacol Ther* 1991; 50: 688-694

Then…

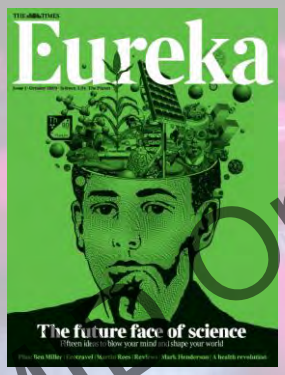
- Alterations in drug handling in patient with AKI may significantly contribute to morbidity and mortality.
- When altered drug disposition is due to organ(s) dysfunction, mainly aged patients may be inadvertently under-dosed and over-dosed with medication.

Take home messages

- For short half-life, hydrophilic antimicrobials (β-lactams and carbapenems) prefer split doses and extended infusions (no PAE)
  - Minor daily exposure (about 1/4 to 1/3 less each day) with greater results on outcome and resistance
- Concentration-dependent usually with prolonged PAE: amikacin, gentamicin, ciprofloxacin and levofloxacin require higher single shot delaying next administration (Cmax/MIC > 10)
  - CIP 1 x 750 mg rather than 2 x 500 mg (1/4 less/day)
  - C_{max} TDM for therapeutic levels
  - C_{min} TDM for toxicity

To summarise...

- Pharmacokinetics of antimicrobials in aged people still misunderstood
- Many PK factors may affect drug disposition
  - renal function, adsorption, fluid replacement, protein binding and hypoalbuminemia, …
- Age as a misleading factor in severe infections
  - cave of underdosing hydrophilic drugs!
  - consider dosage increase in critically ill aged people
  - TDM whenever possible (even beyond ICU)



Young scientists for older patients….

It's in your hands !!