La Gestione Multidisciplinare delle Infezioni Complicate delle Vie Urinarie nel Terzo Millennio

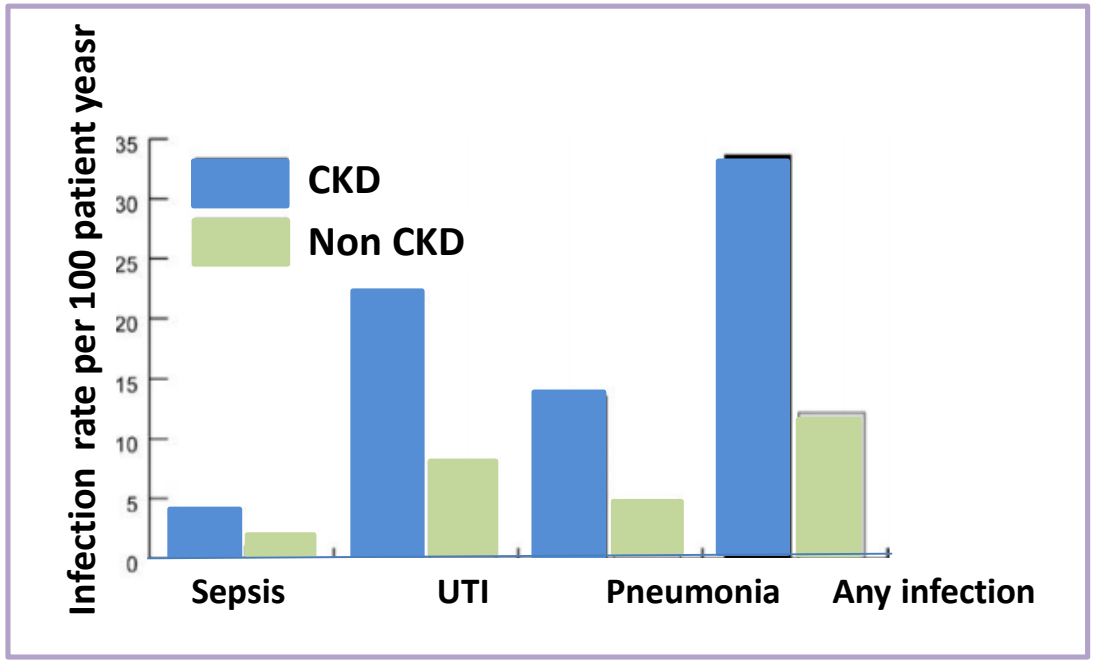
Ferrara, 5 Maggio 2017
Azienda Ospedaliera-Universitaria Ferrara
Nuovo "Arcispedale S. Anna"

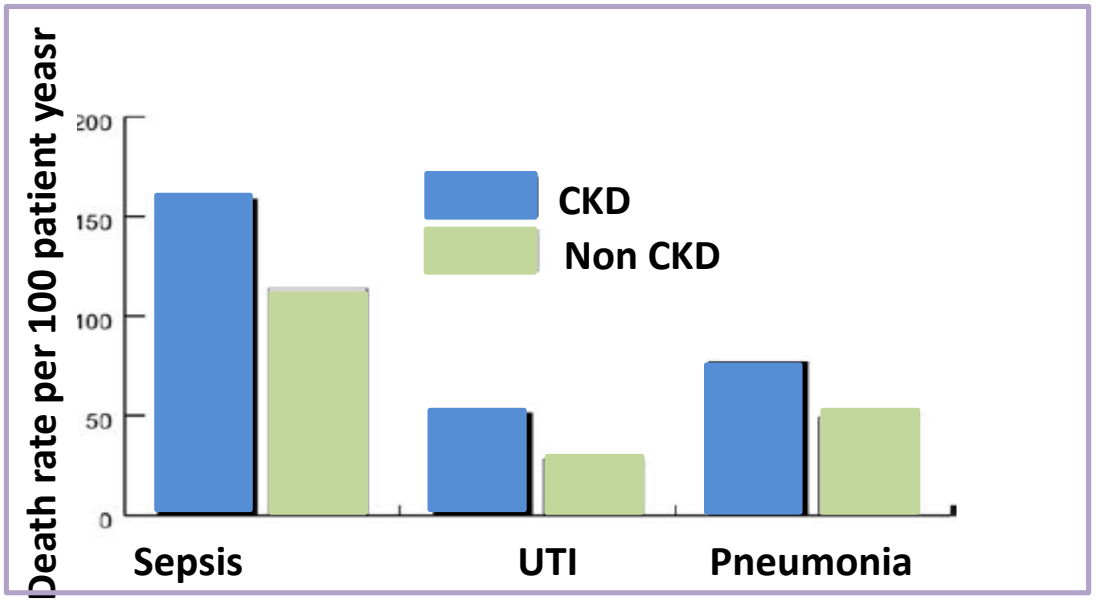
La terapia antibiotica nel paziente con insufficienza renale: farmacologo e nefrologo a confronto

Confronto con il farmacologo

M. Mandreoli (Imola)

.. Un po' di epidemiologia.....

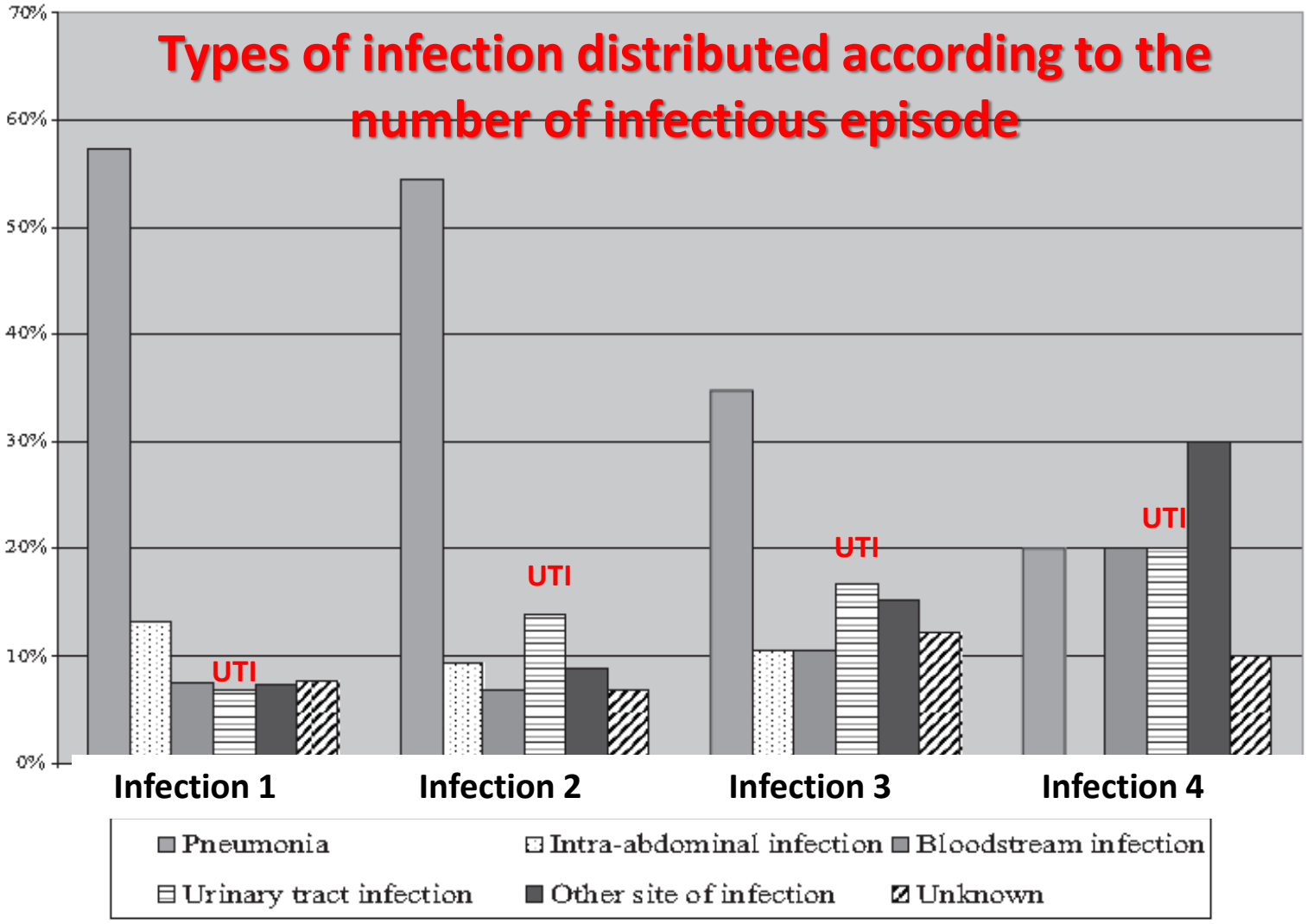




Le infezioni nei pazienti CKD sono circa 3 volte più frequenti che nella popolazione generale
Prevalgono le UTI

Naqki SV &Collins AJ. Advance in Chronic Kidney Disease 2006;13;199

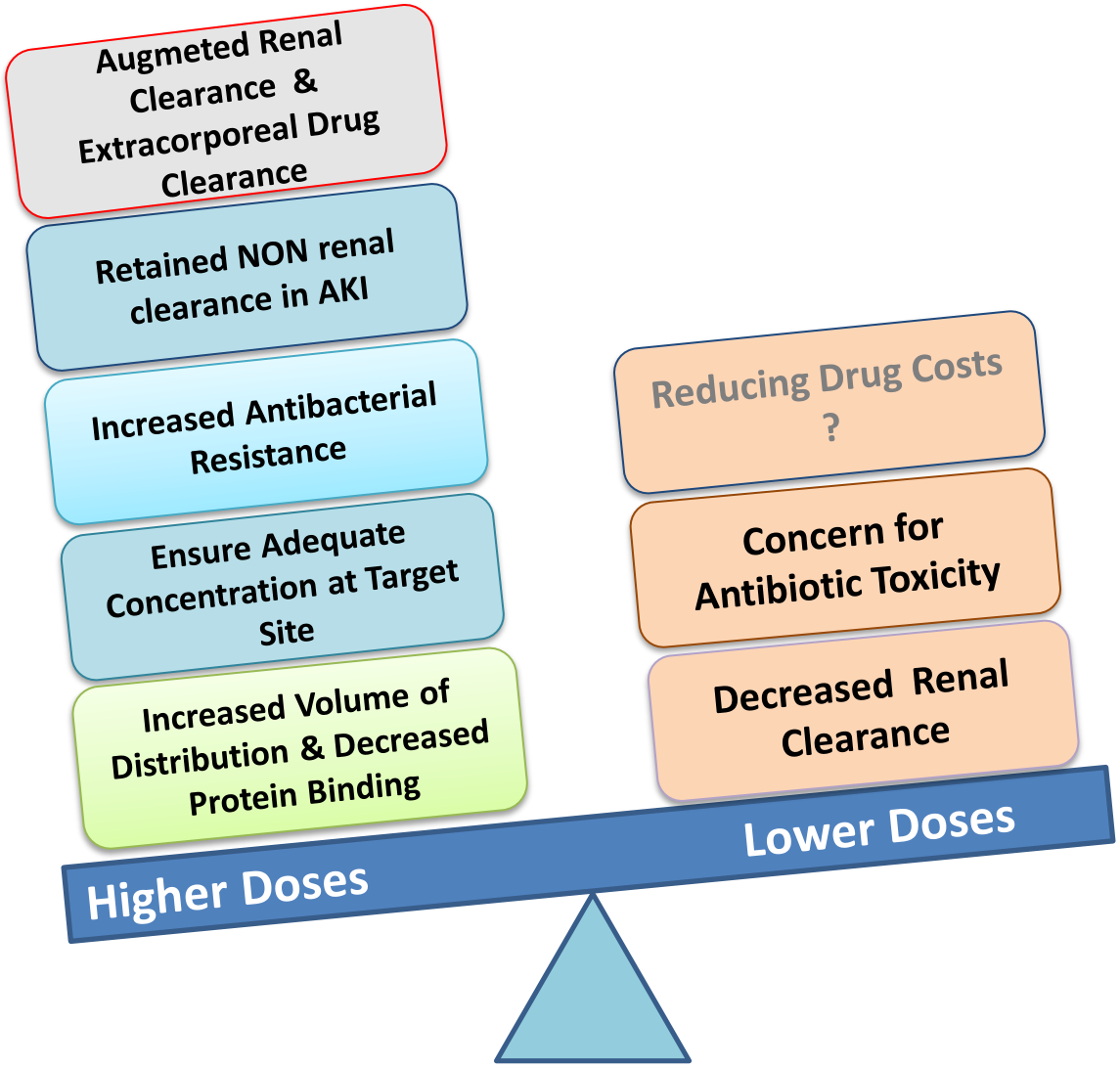
Epidemiology of infection in critically ill patients with acute renal failure



Reynvoet E et al. Crit Care Med 2009 ; 37: 2203

La terapia antibiotica nel paziente con insufficienza renale: ovvero il nefrologo tra Scilla e Cariddi

Enough but not too much

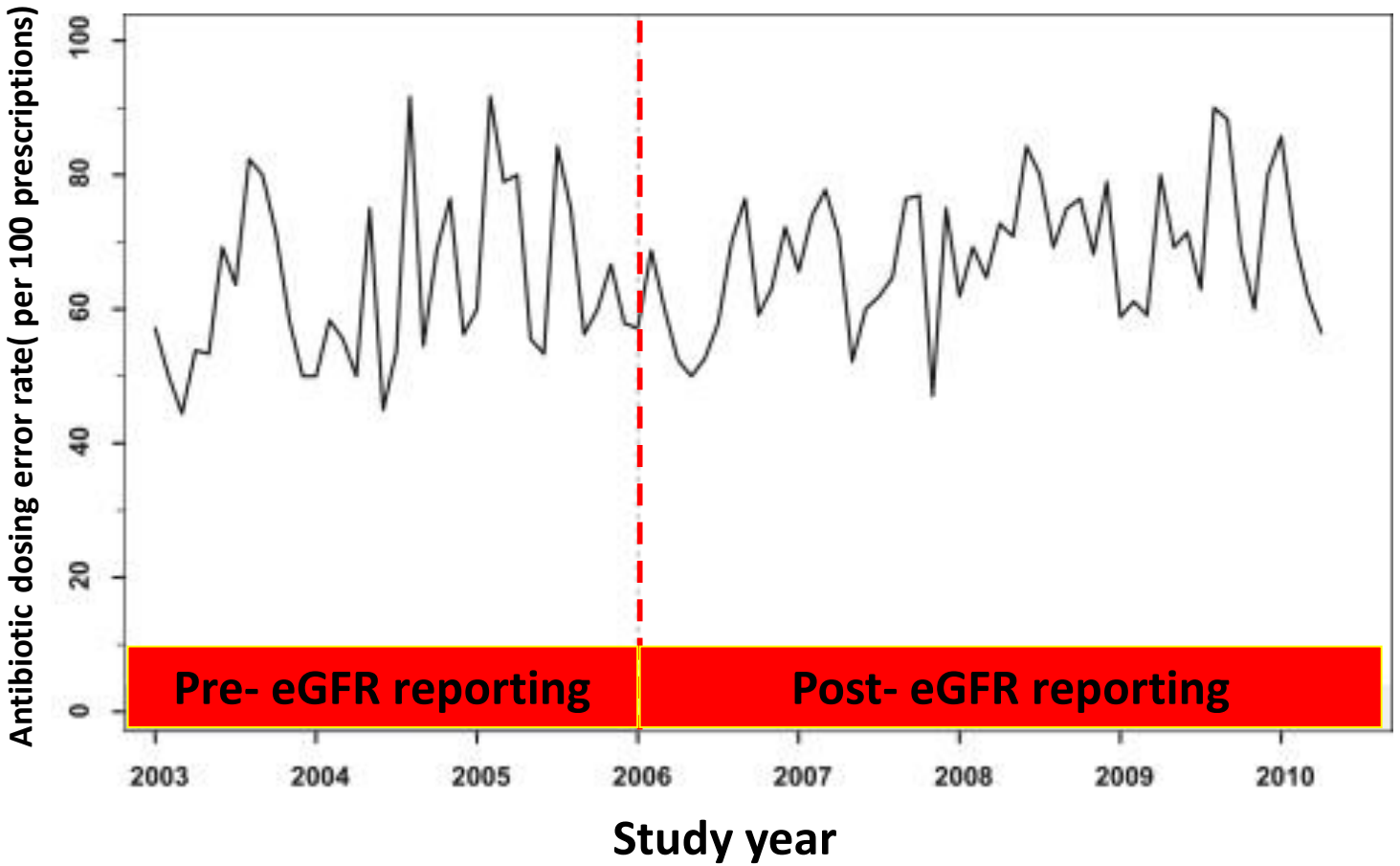


Journal of Intensive Care Medicine

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

Ambulatory antibiotic dosing errors in non–dialysis-dependent patients with stages 4-5 CKD

Ontario –CANADA: prescrizioni in **eccesso di dose** in pz anziani, ambulatoriali CKD 4-5 (antibiotici orali)

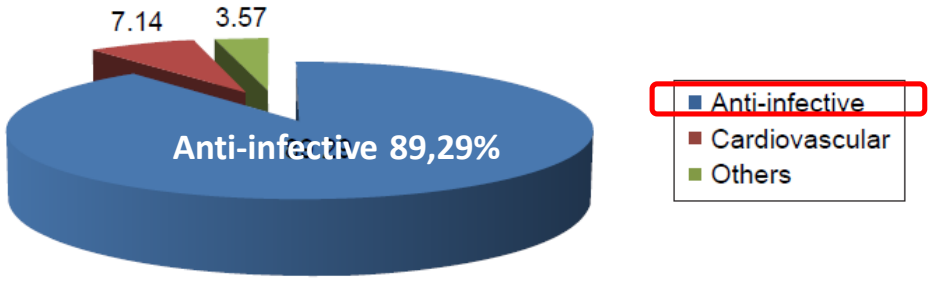


Farag A et al. American Journal of Kidney Diseases, 2014; 63: 422-428

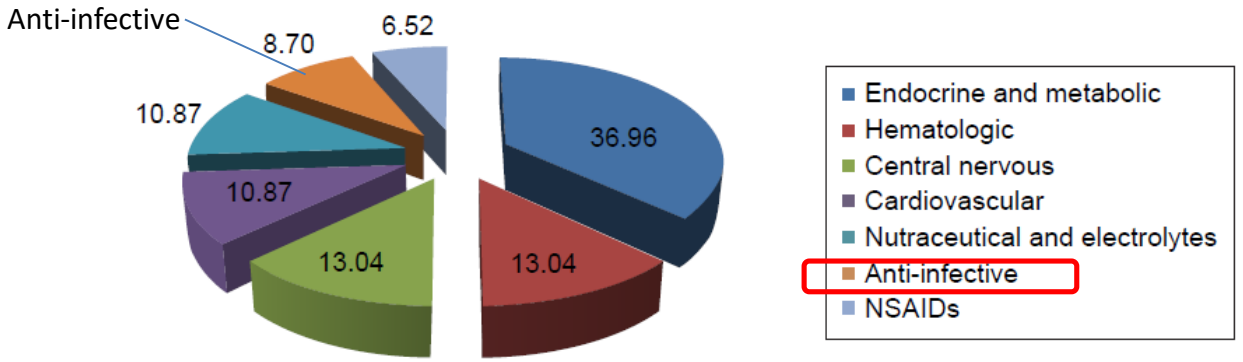
Inappropriateness of medication prescriptions about CKD patients

(not on dialysis) in a Chinese Tertiary Teaching Hospital

A Percentage of prescriptions with unreasonable dosage medicines

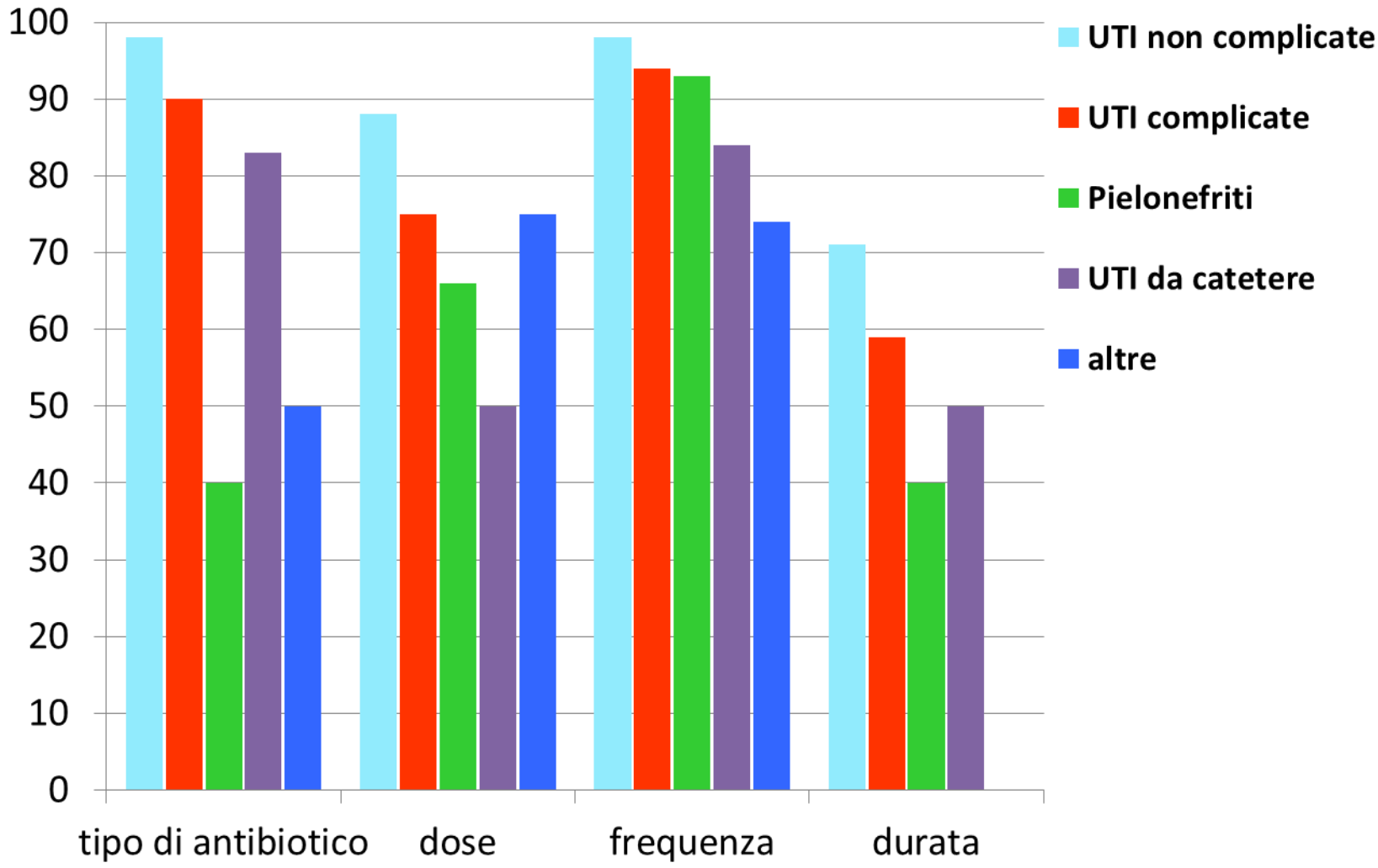


B Percentage of prescriptions with contraindicated used medicines



Yang P et al. Therapeutics and Clinical Risk Management 2016:12 1517–1524

Appropriatezza nel tipo di antibiotico, dose, frequenza, e durata di terapia



Sigler M et al. Southern Medical Journal 2015 ; 108:300

Acute kidney Injury induced by antimicrobial agents in the elderly: Awareness and mitigation strategies

Reazioni da farmaci:

- **Adverse drug reaction**
- **Drug-drug interaction**
- **Drug induced AKI:**

  - Tubular necrosis: Aminoglycosides. Amphotericin B, vancomicyn, cephaloridine, quinolones
  - Interstitial nephritis: Penicillin, methicillin, ampicillin, ciprofloxacin, rifampicin, cephalosporins, clarithromycin, trimethoprim, vancomycin
  - Tubular obstruction: Acyclovir, indinavir, foscarnet, ganciclovir

Mizokami F & Muzuno T. Drugs Aging 2015; 32;1-12

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

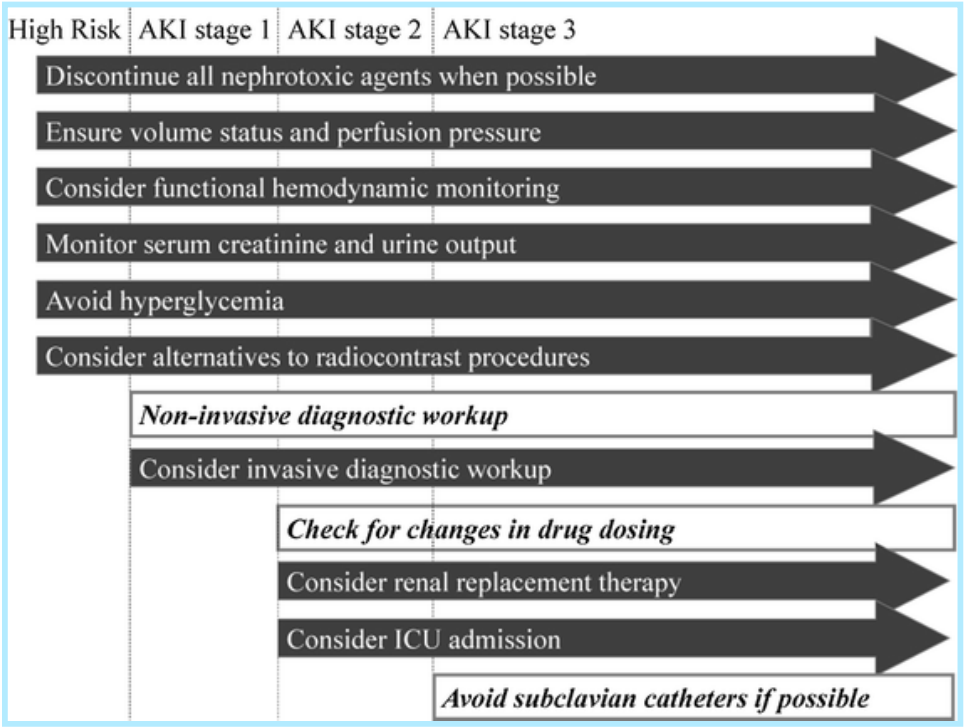
Gli studi sulla nefrotossicità da antibiotici, indicano un danno transitorio e reversibile dopo sospensione del farmaco. Tuttavia le valutazioni a breve termine non riflettono tutto lo spettro dell'antibiotico-tossicità, perché **a lungo termine** vi è un *effetto di trascinamento* con aumentato rischio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

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

Acute kidney Injury induced by antimicrobial agents in the elderly: Awareness and mitigation strategies

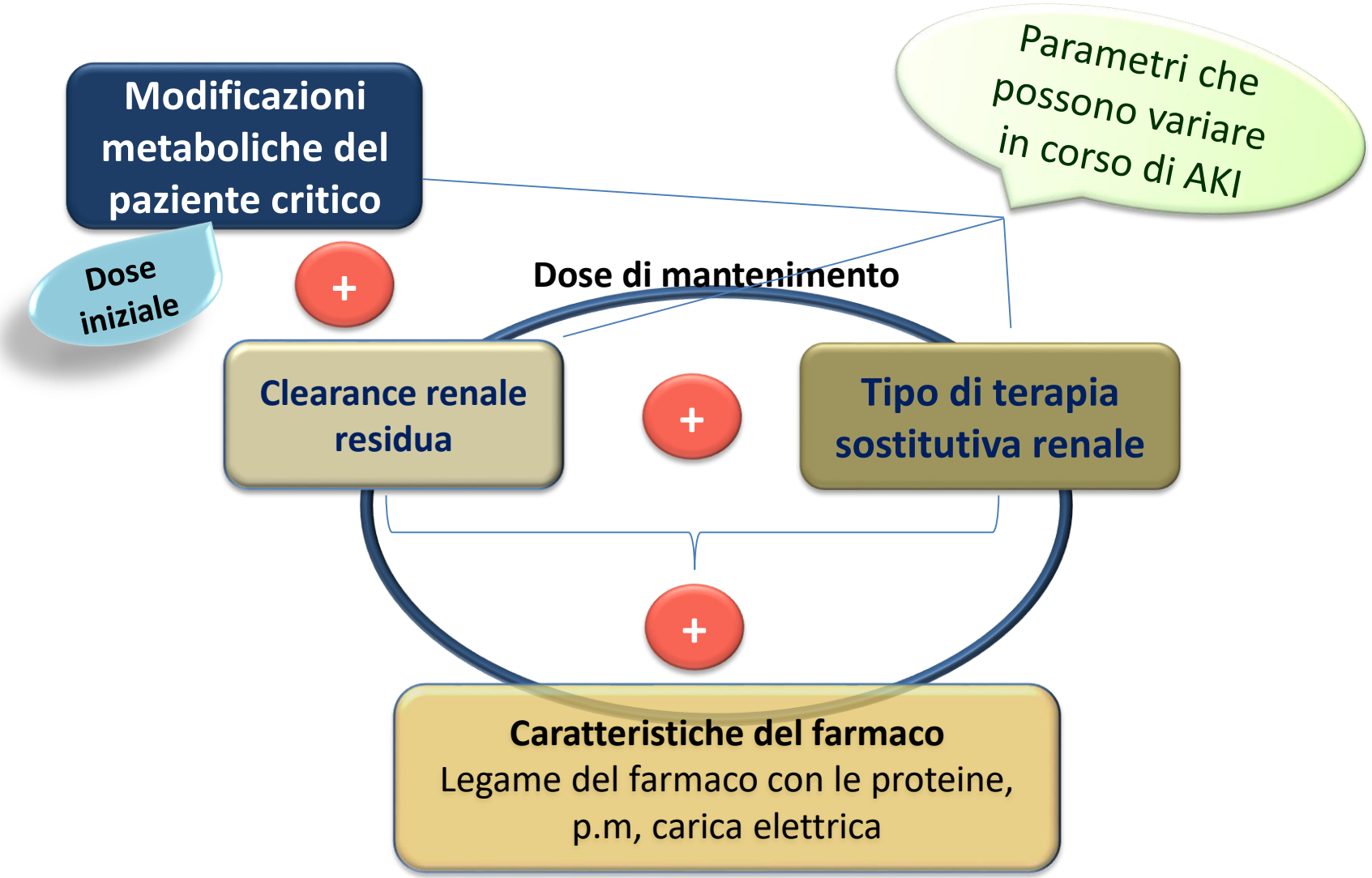
Prescribing Antimicrobials in the Elderly

La strategia migliore per evitare l'insorgenza di AKI nel paziente anziano è cercare di rimuovere le potenziali cause: poli-farmaco terapia, interazioni negative tra farmaci, adeguare la dose, dopo aver valutato la funzione renale *"reale"*



Mizokami F & Muzuno T. Drugs Aging 2015; 32:1-12

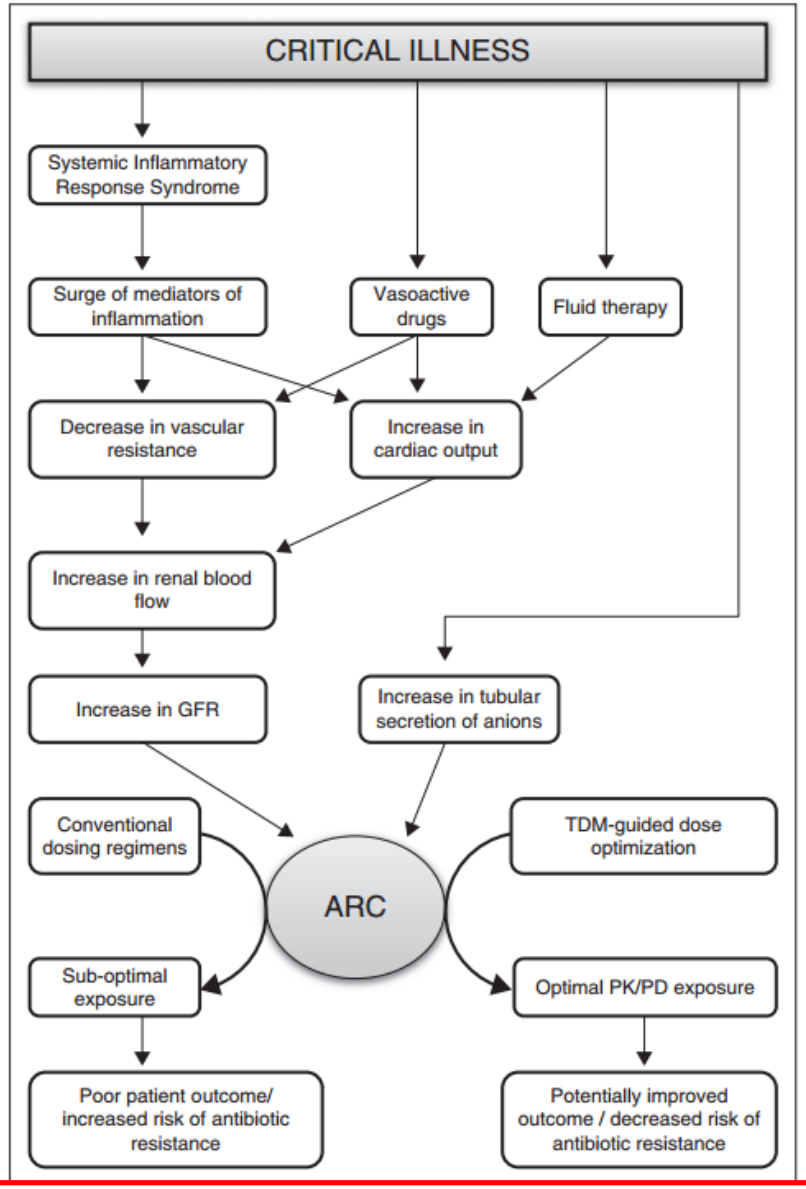
Nel raggiungimento del target terapeutico si deve tenere conto di:



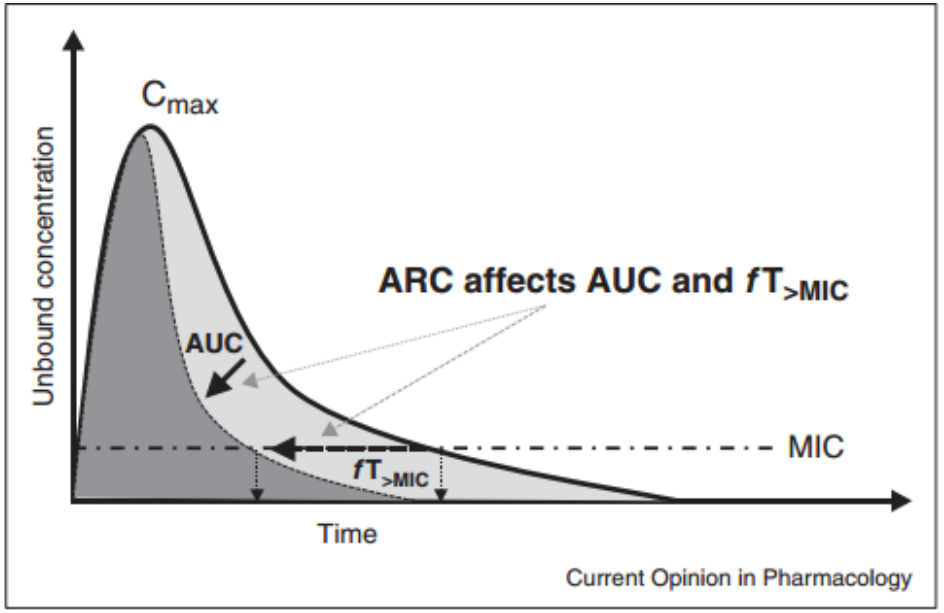
I° spunto di discussione

- Quanto e in che modo l'iperfiltrazione deve essere considerata nell'aggiustamento posologico di una terapia antibiotica?

Causes and consequences of augmented renal clearance in the critically ill

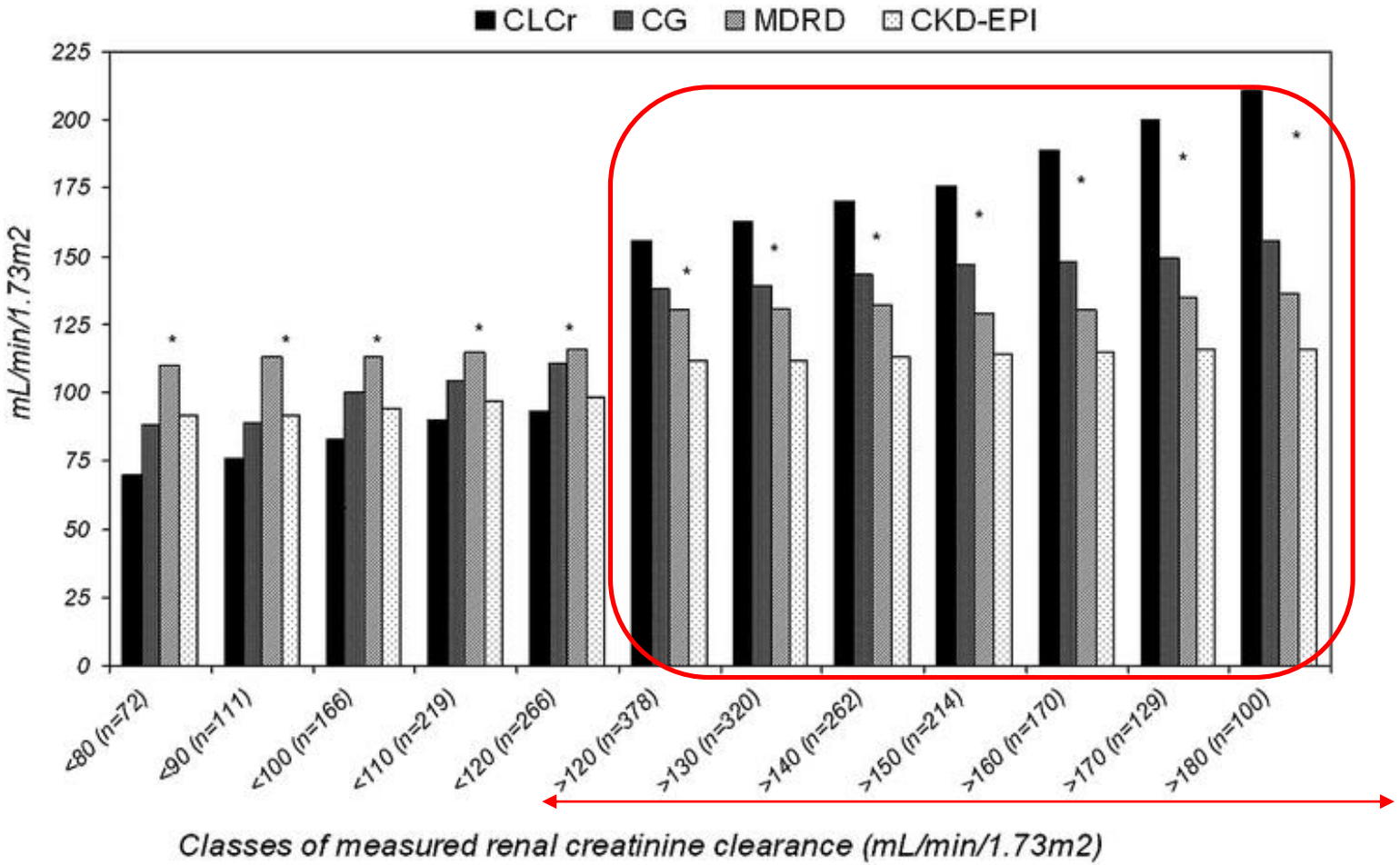


The influence of augmented renal clearance on pharmacokinetic/ pharmacodynamic parameters



Current Opinion in Pharmacology 2015, 24:1–6

Comparison of measured and estimated median values of glomerular filtration



Baptista JP et al. Journal of Nephrology 2014; 27: pp 403–410

II° spunto di discussione

- Pensando ai pazienti con patologie proteinuriche, che livelli di ipoalbuminemia si possono considerare patologici? Che valore aggiunto può avere la supplementazione con albumina?

Indicazioni *occasionalmente* appropriate all'uso di albumina umana

Ove siano soddisfatti ulteriori criteri

SINDROME NEFROSICA

Un aspetto particolare della sindrome nefrosica è l'aumento della proteinuria post-infusione di albumina, che ne vanifica in tempi brevi ogni effetto sull'albuminemia e sulla volemia. **Considerazioni di ordine fisiopatologico possono suggerire l'impiego di albumina in pazienti con albuminemia < 20 g/L che presentino manifestazioni cliniche di grave ipovolemia** e/o edema polmonare. L'uso di albumina può essere indicato nella sindrome nefrosica acuta, all'inizio della terapia steroidea

Albumin in critically ill patients: the ideal colloid?

KEY POINTS

1) Albumin is one of the main determinants of the integrity of the endothelial glycocalyx, thus cooperating in the maintenance of the intravascular compartment volume.

2) In decompensated cirrhosis, albumin may reverse immune-paralysis associated with prostaglandin E2 release, and preserve myocardial contractility by blocking inducible nitric oxide synthase.

3) Although its administration in critically ill patients may have heterogeneous effects, human albumin administration may be advantageous in burn patients, whereas it may increase the risk of acute kidney injury in patients after cardiac surgery.

4) **In severe sepsis, the ALBIOS trial did not show any survival benefit associated with albumin administration**, while reporting **a reduction in 90-day mortality in the subgroup of patients with septic shock, at post-hoc and not predefined analysis**.

5) All the eight meta-analyses performed on the use of albumin in sepsis have shown no improvement in survival as associated with its administration in patients with sepsis or severe sepsis, while suggesting a beneficial effect in patients with shock, yet to be confirmed.

Caironi P et al. Curr Opin Crit Care 2015, 21:302–3

III° spunto di discussione

- Quali equazioni per la predizione del GFR sono più affidabili? Quali utilizzare nel paziente con IRC?

o meglio:

- per la valutazione della funzione renale meglio la misurazione o la stima del GFR? e in questo caso quale formula ?

Cosa dicono le Autorità Regolatorie ?

Update and trends on pharmacokinetic studies in patients with impaired renal function: practical insight into application of the FDA and EMA guidelines

The current draft FDA and full EMA guidelines describe how pharmaceutical companies should develop posology instructions for renal impaired subjects. While the guidelines are quite similar, agency-specific requirements such as methodology for GFR assessment differ. Furthermore, the FDA has modified their definition of ESRD to meet the growing challenges of 'worst case scenario' patient identification and recruitment. **It is anticipated that the FDA full guidelines will include this new position and will address the use of updated GFR estimates (e.g. CKD-EPI)**, currently recommended by numerous kidney research organizations and initiatives

Key issues

- **Renal impaired pharmacokinetic studies are necessary** to determine if a therapeutic compound will require dose adjustment in patients with renal dysfunction or are contraindicated for patients with certain stages of chronic kidney disease.
- Both the FDA and EMA have issued detailed guidelines for renal impaired pharmacokinetic studies, while many of the requirements are similar between the two agency instructions, GFR methodology and reporting differ.
- An updated position on the FDA draft guidelines redefines end-stage renal disease as <30 mL/min, and states this patient population is suitable for a 'worst case scenario' reduced study.
- Under certain circumstances, population pharmacokinetic and PBPK modeling analysis may provide sufficient information to instruct renal impairment labeling

Paglialunga S et al. Expert Review of Clinical Pharmacology 2017; 10 (3): 273-

IV° spunto di discussione

- Quale dose di linezolid suggerire nel paziente con IRC?

RESEARCH Open Access

Effects of continuous renal replacement therapy on linezolid pharmacokinetic/ pharmacodynamics: a systematic review

Wide variability in linezolid PK/PD parameters has been observed across critically ill patients with sepsis, especially those with AKI treated with CRRT. The effects of the extracorporeal treatment on antibiotic PK/PD target achievement should be carefully considered and adapted to the individual patient's physio-pathological characteristics. Similar to other serious conditions, **a TDM could be an effective method to ensure adequate antibiotic exposure**, especially in critically ill patients with sepsis and AKI, who are on CRRT. If TDM is not routinely available, **increased posology of linezolid might be alternatively considered for these patients during treatments performed with high diffusive/convective and/or adsorption clearance.** Furthermore, different modalities of administration might be considered, such as continuous infusion.

Villa G et al. Critical Care 2016 20:374

V° spunto di discussione

- Cosa devo rispondere a chi mi chiede come aggiustare la posologia dei (nuovi) antibiotici in pazienti che fanno CRRT?

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)

Clearance (Cl) dei farmaci

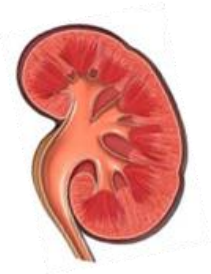
Cl totale corporea

=

Cl epatica + Cl renale + altre vie metaboliche

+ Cl RRT

la clearance renale e la clearance extra corporea per essere significativa deve essere > 25-30% della Cl totale corporea

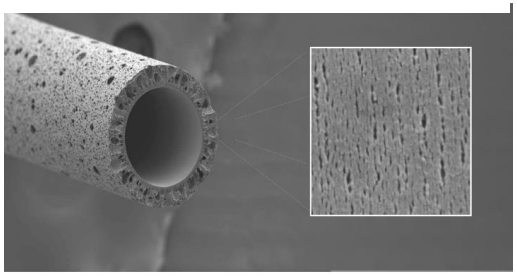


+ clearance dispostivi dialitici

- Farmaci di piccole dimensioni, con basso legame proteico e con volume di distribuzione < 1L/Kg sono facilmente eliminati con la dialisi.
- In corso di AKI, se si riduce patrimonio albuminico, aumenta il volume di distribuzione e aumenta la clearance dialitica del farmaco
- Variabilità legate alla metodica (continua/intermittente; diffusiva/convettiva; superficie e permeabilità dei filtri)
- Prediluizione/Post-diluizione: in RRT con alti volumi di effluente (es > 2 L/hr) è necessario usare dosi maggiori di farmaco

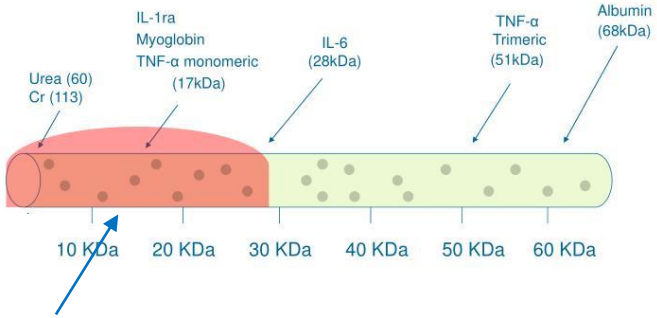
Caratteristiche Filtro

Pore Size



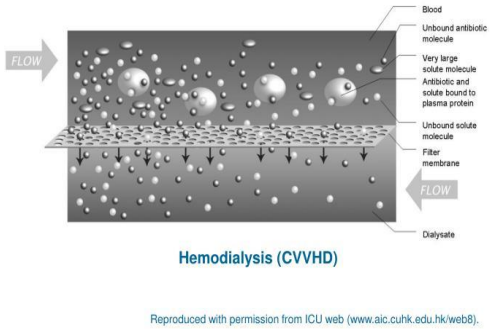
Membrane high flux 60Da

Size is important – but……



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

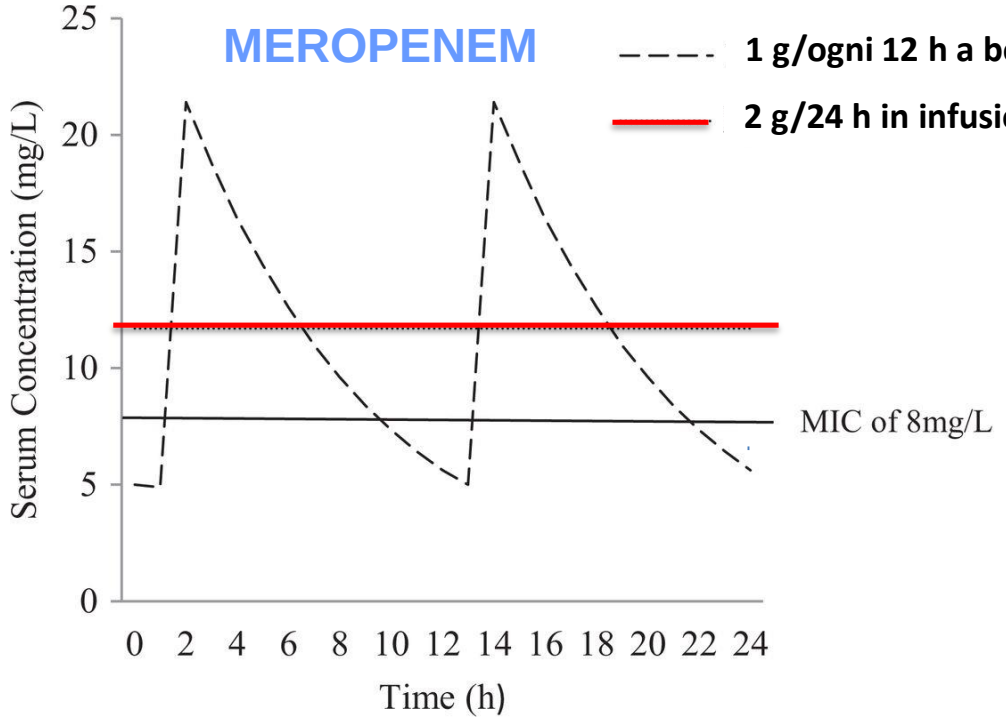
Importance of protein binding



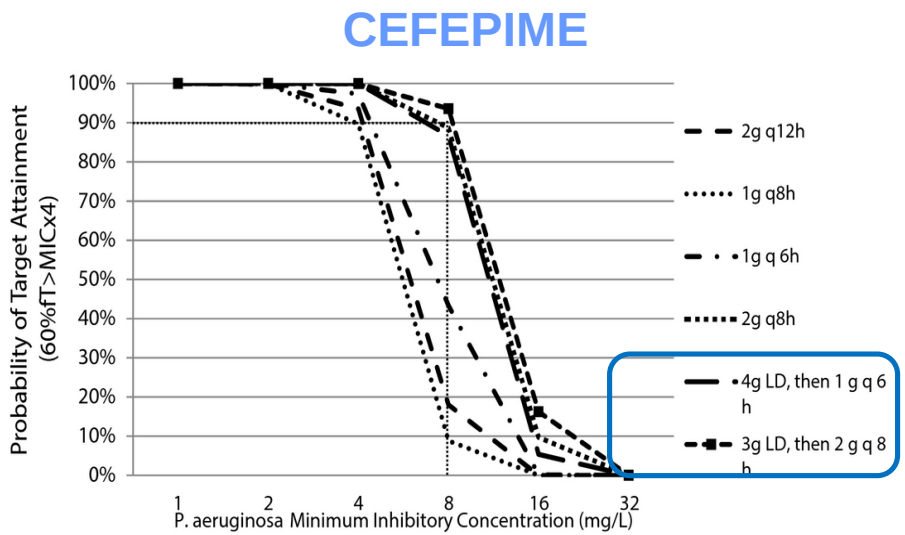
Hemodialysis (CVVHD)

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

Modeled meropenem steady state concentrations with continuous infusion versus intermittent infusion in a patient on continuous renal replacement therapy (CRRT



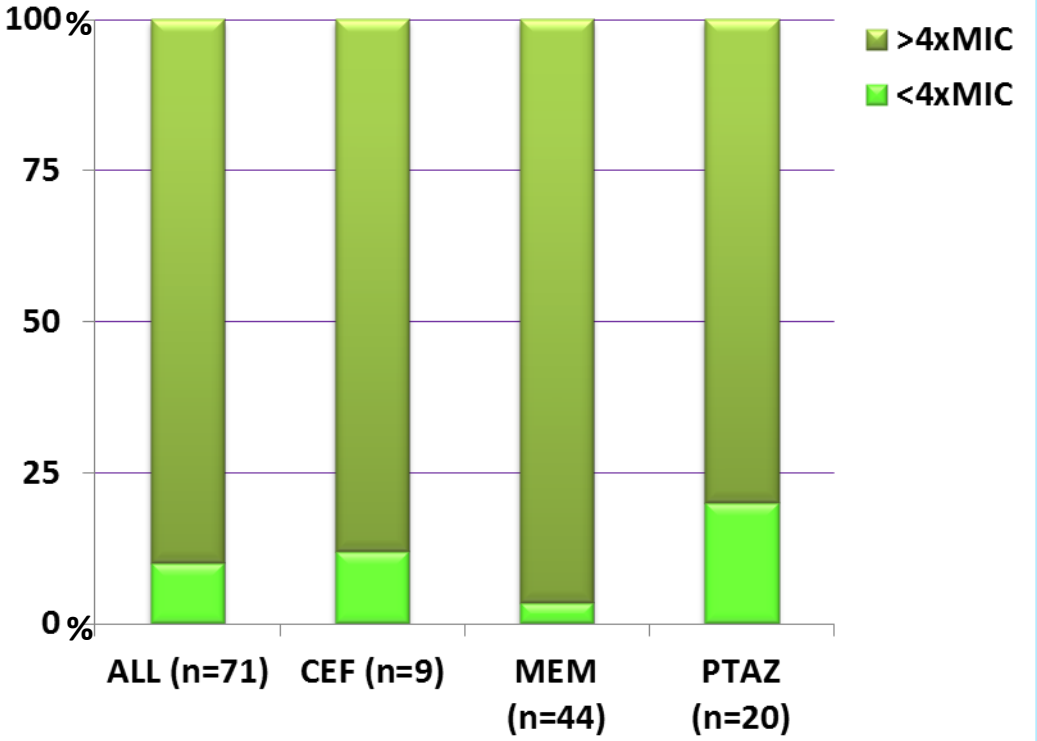
Lewis SJ and Mueller BA. J Intensive Care Med 2016;31:164-176



Shaw AR et al. Semin in Dialysis 2016

Journal of Intensive Care Medicine

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

CEFTOLOZANE/TAZOBACTAM (ZERBAXA®)

Class: Novel Cephalosporin + Beta Lactamase Inhibitor

FDA Approval Date: December 19, 2014

FDA Approved Indications:

- **Complicated Intra-Abdominal Infections** (cIAI)
  - Used in combination with metronidazole
- **Complicated Urinary Tract Infections** (cUTI)
  - Including pyelonephritis

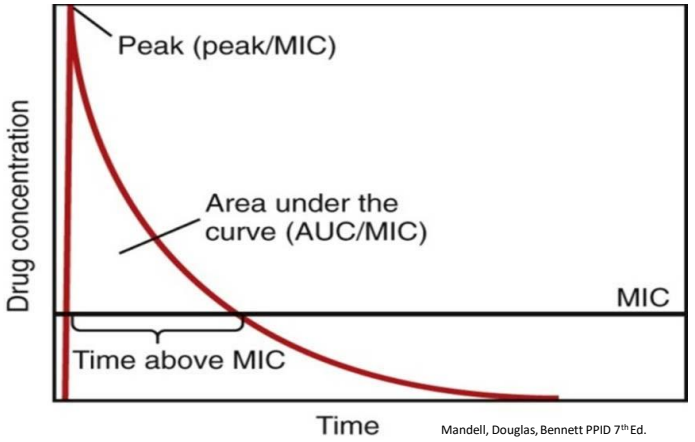
CEFTOLOZANE/TAZOBACTAM (ZERBAXA®)

Pharmacokinetics

- Absorption
  - IV only
- Distribution
  - Ceftolozane 16-21% protein bound
  - Tazobactam 30% protein bound
- Metabolism
  - Ceftolozane eliminated unchanged
  - Tazobactam is hydrolyzed to inactive metabolite (M1)
- Elimination
  - Renal

Pharmacodynamics

- Time dependent killing
  - Time > MIC
- No effect on cardiac electrophysiology



Mandell, Douglas, Bennett PPID 7th Ed.

Zerbaxa Prescribing Information. Cubust Pharmaceuticals, 2014. Accessed March 2015.

Impact of Renal Function on the Pharmacokinetics and Safety of Ceftolozane-Tazobactam

Antimicrobial Agents and Chemotherapy
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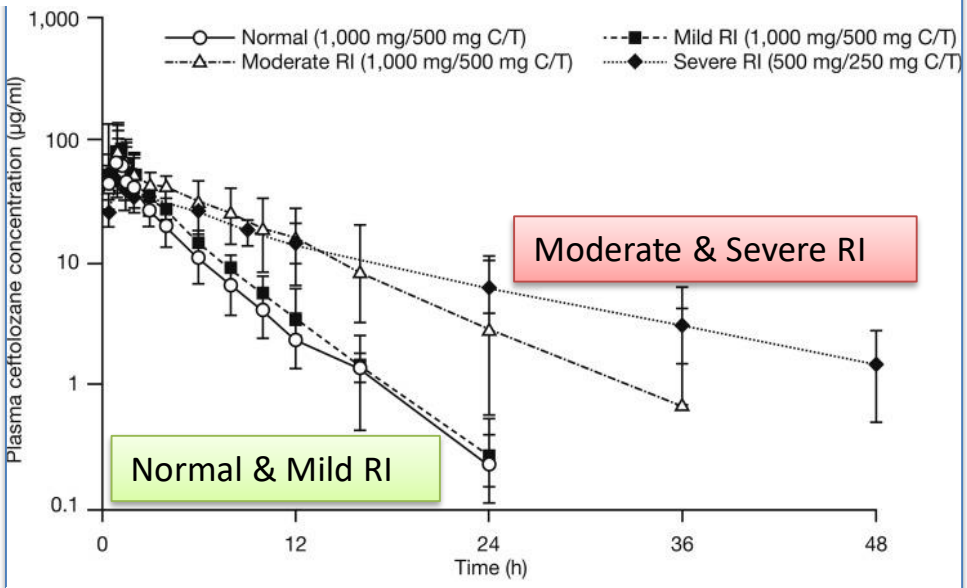
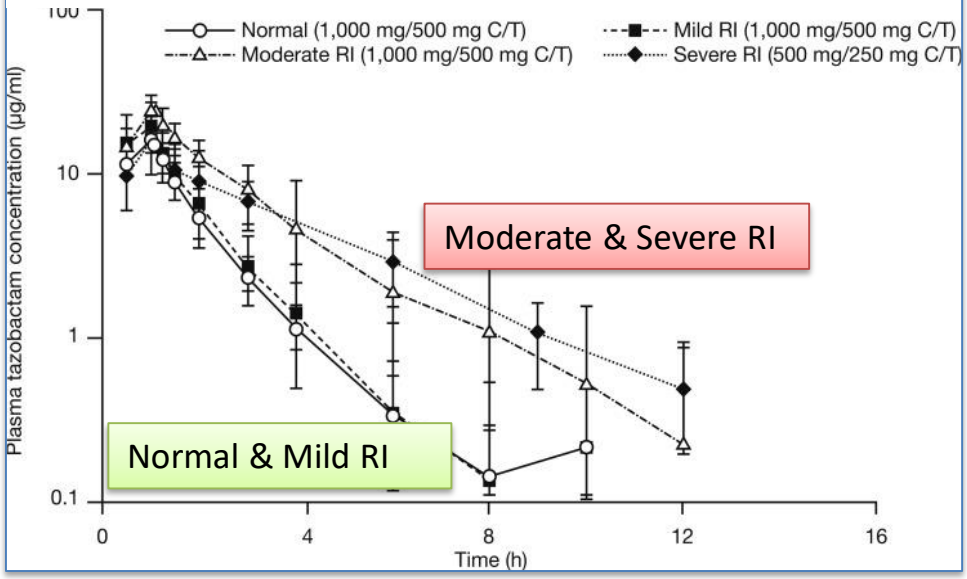
A) Ceftolozane



B) Tazobactam



Plasma exposure to ceftolozane-tazobactam increased as renal function declined with only slightly increased exposures in subjects with mild renal impairment; the median **area under the concentration-time curve** from time zero to infinity ($AUC_{0-\infty}$) for ceftolozane and tazobactam **increased 1.4- and 1.2-fold**, respectively. In subjects with moderate renal impairment, **the $AUC_{0-\infty}$ increased 2.5- and 2.2-fold** for ceftolozane and tazobactam, respectively. **Slight increases in exposure with mild renal impairment do not warrant a dose adjustment**; however, **subjects with moderate or severe renal impairment and those on HD require a decrease in the dose**, a change in the frequency of administration, or both to achieve exposures within the established safety and efficacy margins of ceftolozane-tazobactam. Ceftolozane-tazobactam was well tolerated by all renal impairment groups

Wooley M et al Antimicrob Agents Chemoter. 2014; 58: 2249

CEFTOLOZANE/TAZOBACTAM: DOSING & ADMINISTRATION

1.5 g (1 g ceftolozane + 0.5 g tazobactam) IV every 8 hours

Duration of Treatment: cIAI 4-14 days, cUTI 7 days

Renal Dose Adjustment Required

Estimated CrCl	Dose
30-50 mL/min	750 mg IV q8h
15-29 mL/min	375 mg IV q8h
ESRD or Hemodialysis	750 mg IV x 1, then 150mg IV q8h

Zerbaxa Prescribing Information. Cubust Pharmaceuticals, 2014. Accessed March 2015.

Administration

- Preparation
  - Compatible with NS or D5W
  - Dilute in 100 mL
  - Stable 24 hours
- Give over 1 hour
- Compatibility with other drugs not established

For both ceftolozane and tazobactam, which are primarily renally eliminated, clearance was influenced by renal function

Chandorkar G et al. J Clin Pharmacol. 2015; 55: 230–239

Ex vivo Ceftolozane/Tazobactam Clearance during Continuous Renal Replacement Therapy

BACKGROUND/AIMS: To determine ceftolozane/tazobactam transmembrane clearances (CLTM) in continuous hemofiltration (CHF) and continuous hemodialysis (CHD) and to determine optimal ceftolozane/tazobactam dosing regimens for patients receiving continuous renal replacement therapy (CRRT).

METHOD: Validated, ex vivo CHF and CHD bovine blood models using polysulfone (HF1400) and AN69 (Multiflow 150-M) hemofilters were used to evaluate adsorption and CLTM at different effluent flow rates. Monte Carlo simulations (MCS) using pharmacokinetic parameters from published studies and CLTM from this study were used to generate ceftolozane/tazobactam dosing for patients receiving CRRT.

RESULTS: CHF and CHD CLTM did not differ at equivalent effluent rates. CLTM approximated effluent flow rates. No adsorption of ceftolozane/tazobactam occurred for either hemofilter. Effluent flow was the most important determinant of MCS-derived doses.

CONCLUSION: CRRT clearances of ceftolozane/tazobactam **depended on effluent flow rates but not hemofilter types**. MCS-derived ceftolozane/tazobactam doses of 750 (500/250)-1,500 (1,000/500) mg every 8 h met pharmacodynamic targets for virtual patients receiving CRRT at contemporary effluent rates

Chaijamorn W. et al Blood Purif 2017;44(1):16-23

CEFTAZIDIME/AVIBACTAM (AVYCAZ®)

- Class: 3rd Generation Cephalosporin
- + Novel Beta Lactamase Inhibitor
- FDA Approval Date: February 25, 2015
- **FDA Approved Indications**:
  - **Complicated Intra-Abdominal Infections (cIAI)**
    - Used in combination with metronidazole
  - Complicated Urinary Tract Infections (cUTI)
    - Including pyelonephritis

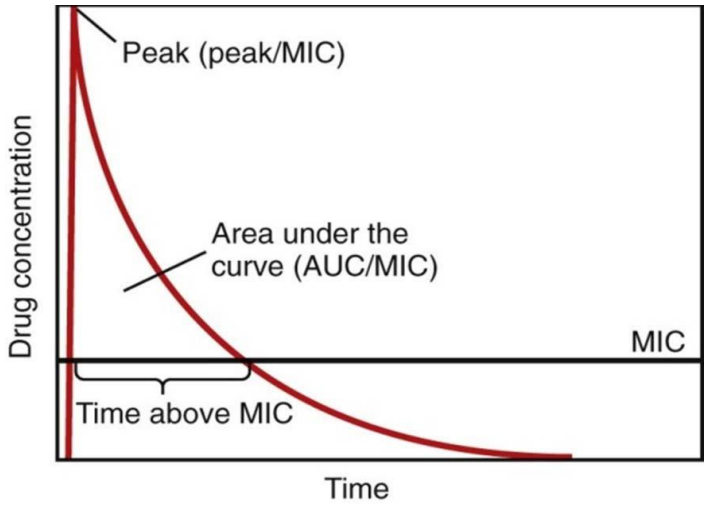
Avycaz Prescribing Information. Actavis, 2015. Accessed March 2015.

Pharmacokinetics

- Absorption
  - IV only
- Distribution
  - <10% protein bound
- Metabolism
  - Minimal
    - 80-90% ceftazidime eliminated unchanged
  - No avibactam metabolism
- Elimination
  - Renal

Pharmacodynamics

- Time dependent killing
  - Time > MIC
- No effect on QTc interval



CEFTAZIDIME/AVIBACTAM:
DOSING & ADMINISTRATION

2.5 g (2 g ceftazidime + 0.5 g avibactam) IV every 8 hours

Duration of Treatment: cIAI 5-14 days, cUTI 7-14 days

Renal Dose Adjustment Required

Estimated CrCl	Dose
31-50 mL/min	1.25g (1g/0.25g) IV q8h
16-30 mL/min	0.94g (0.75g/0.19g) IV q12h
6-15 mL/min	0.94g (0.75g/0.19g) IV q24h
≤ 5 mL/min	0.94g (0.75g/0.19g) IV q48h

Administration

- Preparation
  - Compatible with NS, D5W, LR
  - Dilute in 50-250 mL
  - Stable 12-24 hours
- Give over 2 hours
- Compatibility with other drugs not established

Pharmacokinetics and Dialytic Clearance of Ceftazidime-Avibactam in a Critically Ill Patient on Continuous Venovenous Hemofiltration

Abstract

Ceftazidime-avibactam 1.25 g every 8 hours was used to treat multi-drug resistant *Pseudomonas aeruginosa* bacteremia in a critically ill patient on continuous venovenous hemofiltration (CVVH). Pre-filter plasma drug concentrations of ceftazidime and avibactam were measured at 0, 1, 2, 4, 6, and 8 hours along with post-filter and ultrafiltrate concentrations at hours 2 and 6. Plasma pharmacokinetic parameters of ceftazidime and avibactam, respectively, were C_{max} 61.10 and 14.54 mg/L, C_{min} 31.96 and 8.45 mg/L, $t_{1/2}$ 6.07 and 6.78 hours, V_{ss} 27.23 and 30.81 liters, CL_{ss} 2.87 and 2.95 L/h, and AUC_{0-8} 347.87 and 85.69 mg · h/L. Concentrations of ceftazidime in plasma exceeded the ceftazidime-avibactam MIC (6 mg/L) throughout the 8 hour dosing interval. Mean CVVH extraction ratio % for ceftazidime and avibactam, respectively, were 14.44% and 11.53% and mean sieving coefficients were 0.96 and 0.93, respectively. **The calculated mean clearance of ceftazidime by CVVH was 1.64 L/h and for avibactam it was 1.59 L/h, representing 57.1% of the total clearance of ceftazidime and 54.3% of the total clearance of avibactam**. Further data including multiple patients and dialysis modes are needed to verify the optimal dosing strategy of ceftazidime-avibactam during critical illness and CVVH.

Wenzler E. et al. AntimicrobAgents Chemoter. 2017 Apr 17

Consigli pratici:

- Dose carico iniziale per raggiungere il target sierico desiderato → senza aggiustamenti (150% usual dose per gli AB idrofilici
- Quando possibile dosare i livelli ematici (aminoglicosidi, vancomicina, teicoplanina) e guidare la terapia in base alle concentrazioni plasmatiche
- Per le dialisi intermittenti tenere conto del rebaund di farmaco post-dialitico

- **Gli antibiotici idrosolubili** (basso Vd) sono suscettibili di rimozione significativa con RRT con necessità di aggiustamenti posologici
- **Gli antibiotici liposolubili** (macrolidi, tetracicline, linezolid) sono per la maggior parte ad eliminazione epatica, attraversano le membrane cellulari, hanno Vd elevato. La rimozione extracorporea è abbastanza trascurabile e l'aggiustamento posologico raramente è necessario

Timing di somministrazione:

aminoglicosidi ➔ dose carico pre-dialisi alto picco di concentrazione per mmassimizzare 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)

VI° spunto di discussione

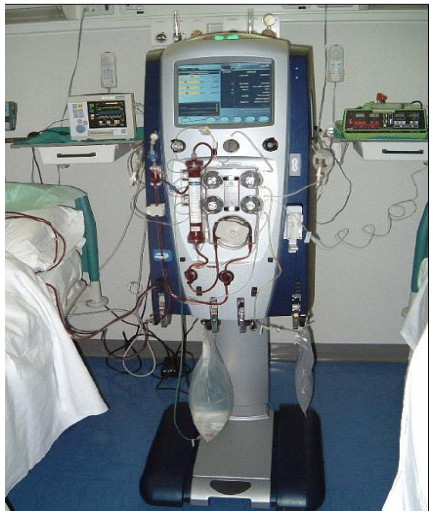
- Quanto viene realmente utilizzato/considerato il TDM per aggiustare la posologia nel paziente con IRC?

Impact of β-lactam antibiotic therapeutic drug monitoring on dose adjustments in critically ill patients undergoing continuous renal replacement therapy

The objective of this study was to describe the effect of therapeutic drug monitoring (TDM) and dose adjustments of β-lactam antibiotics administered to critically ill patients undergoing continuous renal replacement therapy (CRRT) in a ICU.

A total of 111 TDM samples from 76 patients.

The duration of antibiotic therapy was between 2 days and 42 days



Highlights

- Antibiotic dosing in continuous renal replacement therapy in ICU patients is highly challenging.
- **Over one-third** of patients had concentrations outside the therapeutic range.
- **24% of TDM results manifested un-necessarily high antibiotic concentrations**.
- TDM is useful for ensuring optimised dosing.
- Hospital-acquired pneumonia patients had the highest rates of excessive antibiotic concentrations

Economou CJP et al. Int J antimicrob Agents 2017 May;49(5):589-594

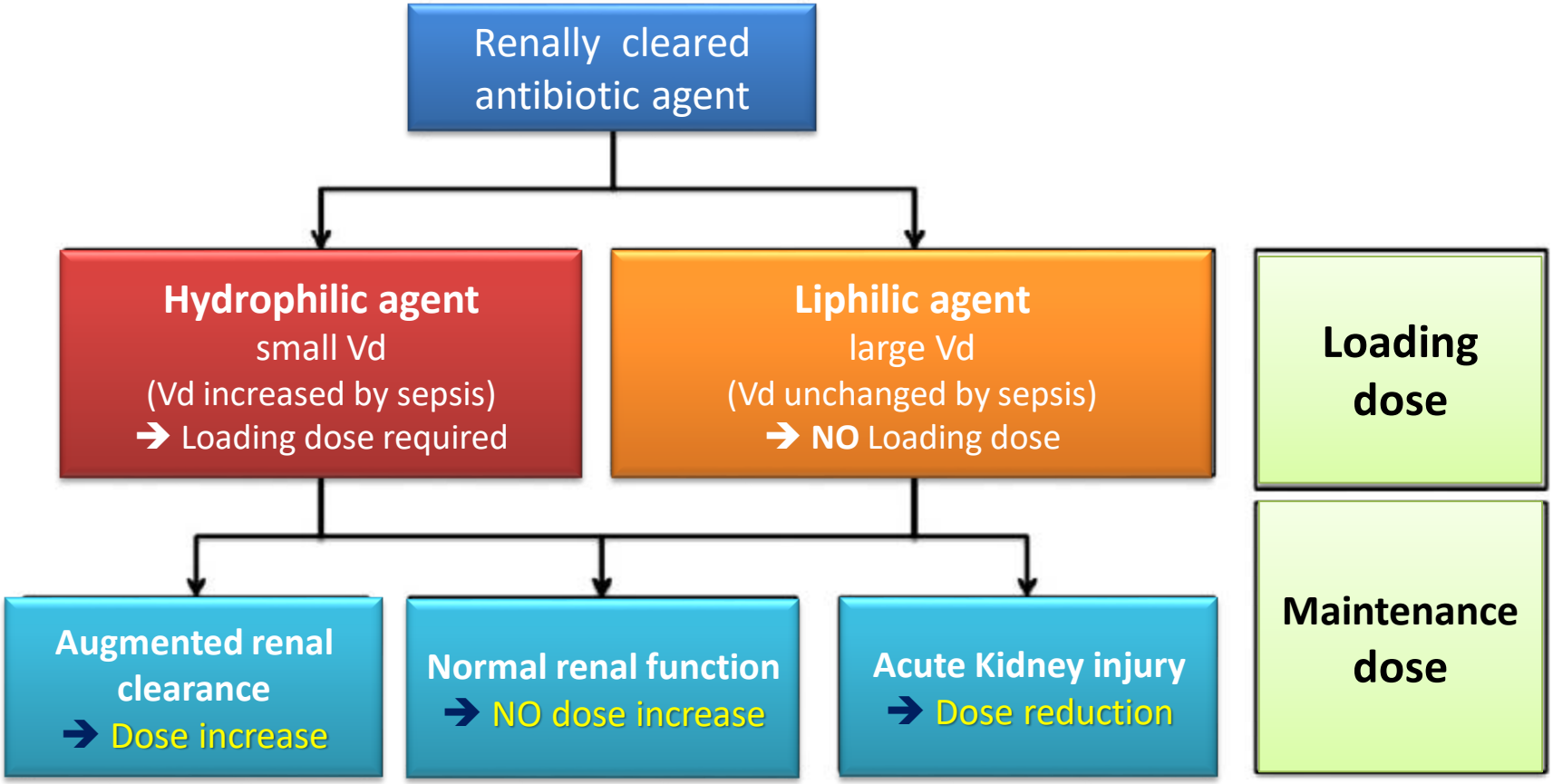
VI° spunto di discussione

- Quanto viene realmente utilizzato/considerato il TDM per aggiustare la posologia nel paziente con IRC?

➔**Vorrei rovesciare la domanda:**

Di quanti antibiotici riusciamo ad avere un TDM in tempi utili e alla portata dei nostri Laboratori ?

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