Betalaktamy v intenzivní péči z pohledu farmakologa

K. Urbánek

Ústav farmakologie

Lékařská fakulta Univerzity Palackého a Fakultní nemocnice Olomouc

Přehled karbapenemů

Karbapenemová antibiotika

Skupina I **ertapenem,** panipenem, tebipenem

omezený účinek na G- nefermentující tyčky

Skupina II **imipenem, meropenem, *doripenem***

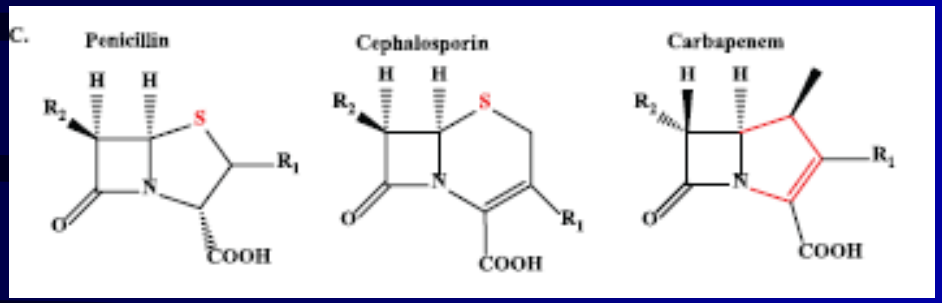
biapenem

dobrý účinek na G- nefermentující tyčky

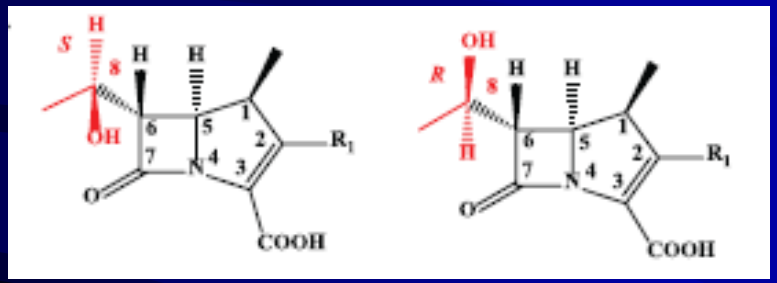
Skupina III není v praxi (tomopenem?)

účinek jako II rozšířený na MRSA

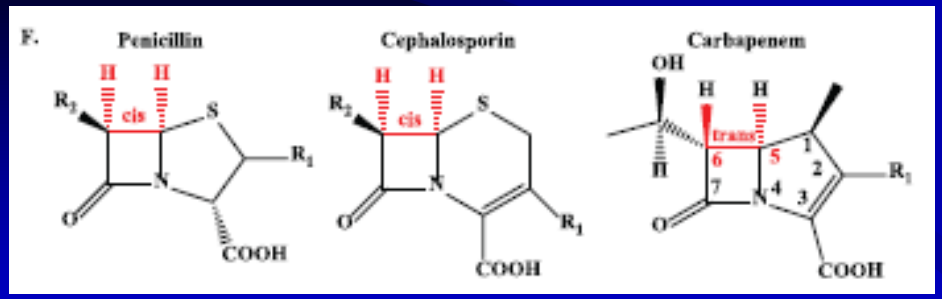
Chemická struktura



- C v pozici 1, dvojná vazba
  - Horší stabilita



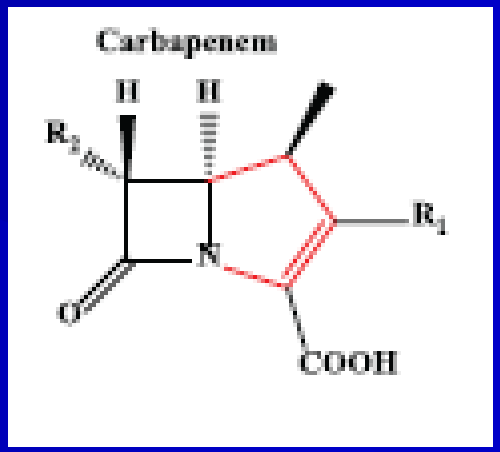
- R pozice hydroxyethylové skupiny
  - Zesílení účinku



- Trans konfigurace na C5 a C6
  - Zesílení účinku

Stabilita

- Ve formě prášku pro přípravu roztoků velmi vysoká
- V roztoku nízká
  - Závisí na teplotě, i na koncentraci (meropenem)
  - Ve fyziologickém roztoku při teplotě 15-25 °C
    - meropenem 6 hodin
    - imipenem 4 hodiny (cilastatin nedegraduje)
    - ertapenem 6 hodin
  - V 5% glukóze
    - meropenem 1 hodinu
    - Ostatní asi o 1/3 kratší než ve FR



Farmakokinetika

Látka	Imipenem	Meropenem		Ertapenem
Distribuční objem	0,31	0,35		0,11
Vazba na proteiny	20 %	2 %		95 %
Biologický poločas	1	1		3,8
Interval dávkování	6 h	8 h		24 h

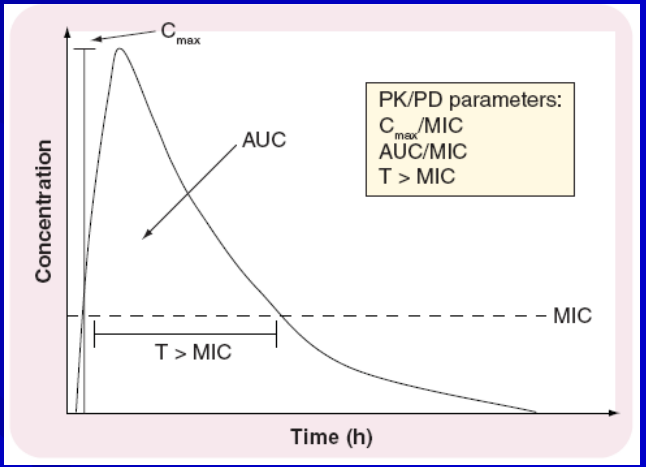
Farmakokinetika

Látka	Imipenem	Meropenem		Ertapenem
Dávka i.v. [g]	0,5	1		1
C_{max} [mg/l]	30-35	49-60		145-175
AUC [mg·h/l]	42	27-32		572
Exkrece močí (nezměněné) [%]	≈90 (60-70)	85-90 (70)		80 (40)

Farmakokinetika betalaktamů a způsoby parenterální aplikace

PK/PD charakteristika

- Účinek je závislý na čase
- C_{max} nemají zásadní význam
- Cílem dávkování je dosáhnout 40 - 100 % (?) dávkového intervalu koncentraci nad 4xMIC (?)
  - PAE karbapenemů může zajistit efekt i při suboptimálním dávkování
- Dosáhnout cíle lze
  - Zvýšením dávky
  - Prodloužením infúze
  - Kontinuálním podáním



Aktuální analýza

International Journal of Antimicrobial Agents 43 (2014) 105–113

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Prolonging β-lactam infusion: A review of the rationale and evidence, and guidance for implementation

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Prolonged infusion
Extended infusion
β-Lactams
Pharmacodynamics

ABSTRACT

Given the sparse antibiotic pipeline and the increasing prevalence of resistant organisms, efforts should be made to optimise the pharmacodynamic exposure of currently available agents. Prolonging the infusion duration is a strategy used to increase the percentage of the dosing interval that free drug concentrations remain above the minimum inhibitory concentration (*f*T > MIC), the pharmacodynamic efficacy driver for time-dependent antibiotics such as β-lactams. β-Lactams, the most commonly prescribed class of antibiotics owing to their efficacy and safety profile, have been the mainstay of therapy since the discovery of penicillin over 60 years ago. Mounting evidence, including the use of population pharmacokinetic modelling and Monte Carlo simulation, suggests that prolonging the infusion time of β-lactam antibiotics may have advantages over standard infusion techniques, including an enhanced probability of achieving requisite *f*T > MIC exposures, lower mortality and potentially reductions in infection/antibiotic-related costs. As a result of these favourable attributes, clinical practice guidelines support the use of prolonged-infusion β-lactams in the treatment of many severe infections. This article discusses the rationale and evidence for prolonging the infusion of β-lactam antibiotics and provides guidance for the implementation of a prolonged-infusion programme.

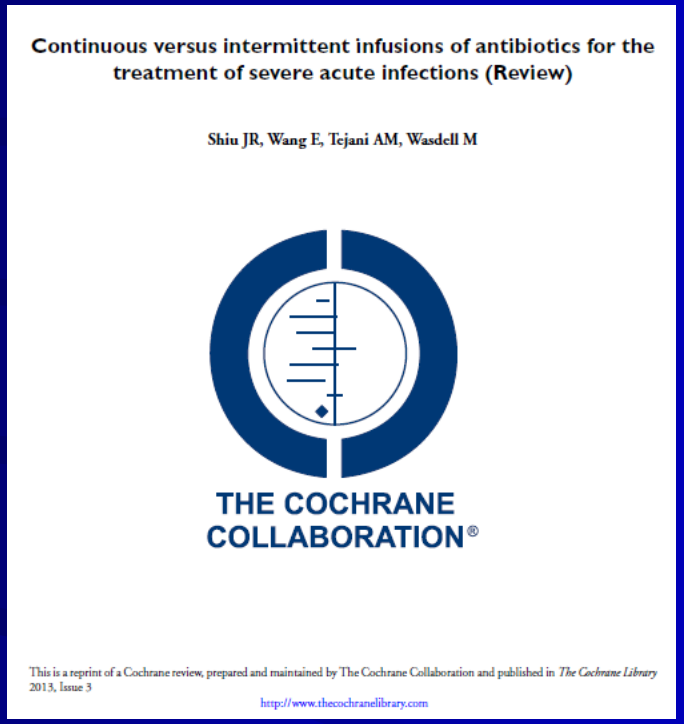
- Aplikace v prodloužených i.v. infúzich
  - Prokázán efekt na dosažení PKPD cíle
  - Není zcela jednoznačný přínos v klinických výstupech
  - U většiny ATB jde o off-label postup

Kontinuální aplikace

Teoretické předpoklady

- Kontinuální aplikace a bolus mají ekvivalentní farmakokinetiku vyjma údolních koncentrací
- Nestabilita roztoků se týká pouze karbapenemů
- Experimentální data a jediná studie s ceftazidimem naznačují lepší průnik do tkání u CI

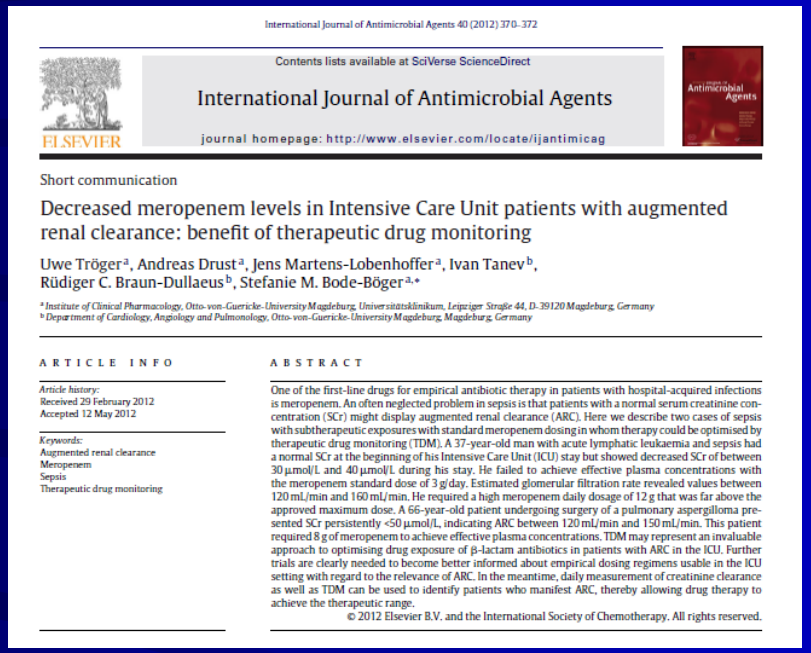
Aktuální Cochrane Review



- no differences in mortality, infection recurrence, clinical cure, superinfection post-therapy, and safety outcomes
- current evidence is insufficient to recommend the widespread adoption of continuous infusion antibiotics in the place of intermittent infusions of antibiotics

Dávkování betalaktamů při poruchách eliminace

Aktuální kazuistika



International Journal of Antimicrobial Agents 40 (2012) 370–372

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short communication

Decreased meropenem levels in Intensive Care Unit patients with augmented renal clearance: benefit of therapeutic drug monitoring

Uwe Tröger[a], Andreas Drust[a], Jens Martens-Lobenhoffer[a], Ivan Tanev[b], Rüdiger C. Braun-Dullaeus[b], Stefanie M. Bode-Böger[a,*]

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Keywords:
Augmented renal clearance
Meropenem
Sepsis
Therapeutic drug monitoring

ABSTRACT

One of the first-line drugs for empirical antibiotic therapy in patients with hospital-acquired infections is meropenem. An often neglected problem in sepsis is that patients with a normal serum creatinine concentration (SCr) might display augmented renal clearance (ARC). Here we describe two cases of sepsis with subtherapeutic exposures with standard meropenem dosing in whom therapy could be optimised by therapeutic drug monitoring (TDM). A 37-year-old man with acute lymphatic leukaemia and sepsis had a normal SCr at the beginning of his Intensive Care Unit (ICU) stay but showed decreased SCr of between 30 μmol/L and 40 μmol/L during his stay. He failed to achieve effective plasma concentrations with the meropenem standard dose of 3 g/day. Estimated glomerular filtration rate revealed values between 120 mL/min and 160 mL/min. He required a high meropenem daily dosage of 12 g that was far above the approved maximum dose. A 66-year-old patient undergoing surgery of a pulmonary aspergilloma presented SCr persistently <50 μmol/L, indicating ARC between 120 mL/min and 150 mL/min. This patient required 8 g of meropenem to achieve effective plasma concentrations. TDM may represent an invaluable approach to optimising drug exposure of β-lactam antibiotics in patients with ARC in the ICU. Further trials are clearly needed to become better informed about empirical dosing regimens usable in the ICU setting with regard to the relevance of ARC. In the meantime, daily measurement of creatinine clearance as well as TDM can be used to identify patients who manifest ARC, thereby allowing drug therapy to achieve the therapeutic range.

- Dvě kazuistiky ARC – Augmented Renal Clearance
  - 120- 160 ml/min
  - Meropenem v dávce 1 g co 8 h nedosahoval PKPD cíle
- U 37-letého pacienta s ALL cíl dosažen při 12 g / den
- U 66-letého pacienta v sepsi po výkonu při 8 g /den

Aktuální kazuistika

AAC
Journals.ASM.org

Optimal Meropenem Concentrations To Treat Multidrug-Resistant *Pseudomonas aeruginosa* Septic Shock

Fabio Silvio Taccone,[a] Frédéric Cotton,[b] Sandrine Roisin,[c] Jean-Louis Vincent,[a] and Frédérique Jacobs[d]

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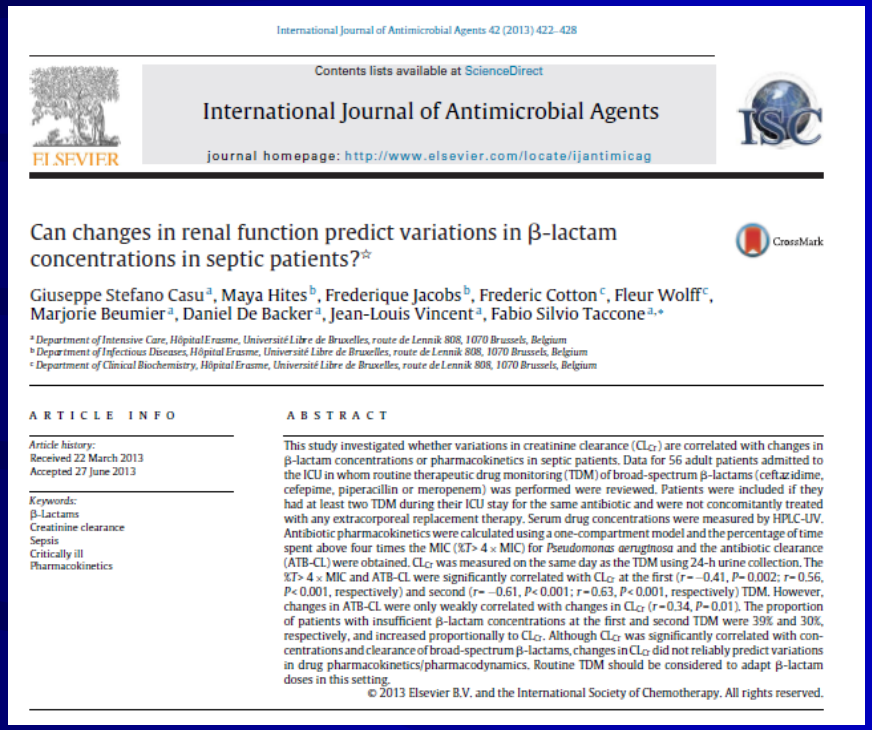
A patient with septic shock due to extensively drug resistant (XDR) *Pseudomonas aeruginosa* was cured by optimizing the meropenem (MEM) regimen to obtain at least 40% of the time between two administrations in which drug levels were four times higher than the MIC of the pathogen. As the standard drug dose did not achieve these optimal concentrations, the MEM regimen was progressively increased up to 12 g/day (3 g every 6 h in a 3-h extended infusion), which eventually resulted in sepsis resolution. High MEM dosage may represent a valuable therapeutic option for infection due to multidrug-resistant (MDR) strains, and drug monitoring would allow rapid regimen adjustment in clinical practice.

- Pacient v septickém šoku *P. aeruginosa*
- Podáván meropenem v 3-h infuzi
- PKPD cíl T nad 4xMIC ≥ 40 % dávkového intervalu
- Cíl dosažen až při dávce 3 g co 6 h v 3 h infuzi

Dávkování:
AKI a umělé eliminační metody

- Intermitentní hemodialýza
  - Doporučení dle SPC nebo publikovaných prací
  - Principem je doplnění plazmatické koncentrace po dialýze
  - U AKI spíše vyšší dávkování
- Kontinuální eliminační metody
  - Doporučení dle SPC nemusí být dostatečná
  - Obvykle potřeba téměř normálních dávek
  - Vysoká účinnost eliminace, zachovaná diuréza
    - Spíše normální dávkování
    - **Optimální by bylo TDM**

Aktuální studie



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Can changes in renal function predict variations in β-lactam concentrations in septic patients?☆

Giuseppe Stefano Casu[a], Maya Hites[b], Frederique Jacobs[b], Frederic Cotton[c], Fleur Wolff[c], Marjorie Beumier[a], Daniel De Backer[a], Jean-Louis Vincent[a], Fabio Silvio Taccone[a,*]

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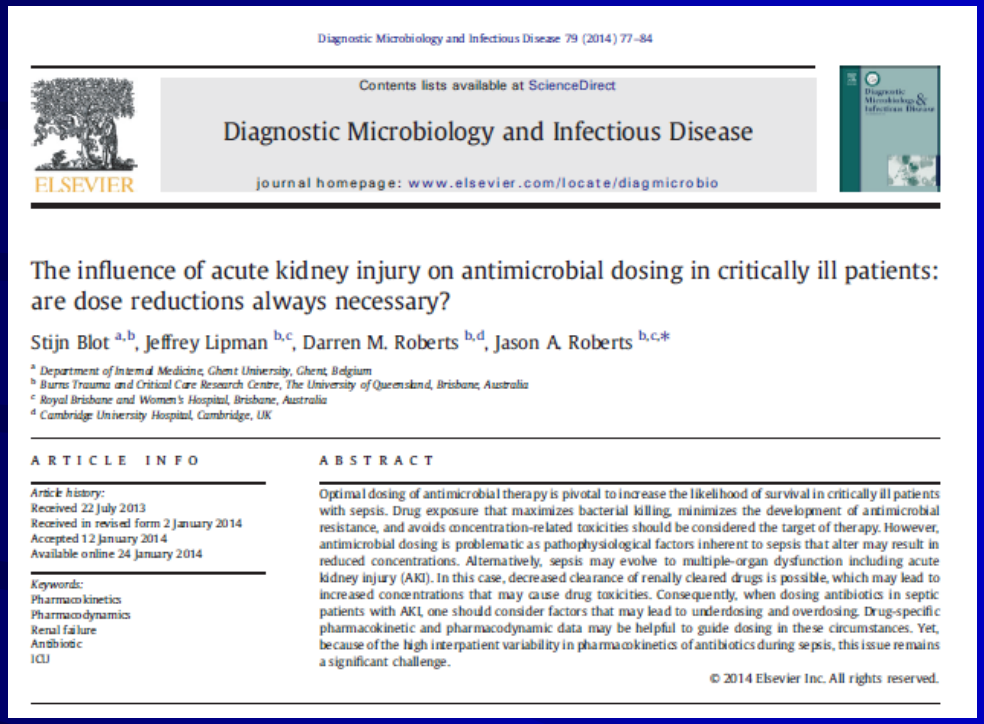
β-Lactams
Creatinine clearance
Sepsis
Critically ill
Pharmacokinetics

ABSTRACT

This study investigated whether variations in creatinine clearance (CL_{Cr}) are correlated with changes in β-lactam concentrations or pharmacokinetics in septic patients. Data for 56 adult patients admitted to the ICU in whom routine therapeutic drug monitoring (TDM) of broad-spectrum β-lactams (ceftazidime, cefepime, piperacillin or meropenem) was performed were reviewed. Patients were included if they had at least two TDM during their ICU stay for the same antibiotic and were not concomitantly treated with any extracorporeal replacement therapy. Serum drug concentrations were measured by HPLC-UV. Antibiotic pharmacokinetics were calculated using a one-compartment model and the percentage of time spent above four times the MIC (%$T > 4 \times$ MIC) for *Pseudomonas aeruginosa* and the antibiotic clearance (ATB-CL) were obtained. CL_{Cr} was measured on the same day as the TDM using 24-h urine collection. The %$T > 4 \times$ MIC and ATB-CL were significantly correlated with CL_{Cr} at the first ($r = -0.41$, $P = 0.002$; $r = 0.56$, $P < 0.001$, respectively) and second ($r = -0.61$, $P < 0.001$; $r = 0.63$, $P < 0.001$, respectively) TDM. However, changes in ATB-CL were only weakly correlated with changes in CL_{Cr} ($r = 0.34$, $P = 0.01$). The proportion of patients with insufficient β-lactam concentrations at the first and second TDM were 39% and 30%, respectively, and increased proportionally to CL_{Cr}. Although CL_{Cr} was significantly correlated with concentrations and clearance of broad-spectrum β-lactams, changes in CL_{Cr} did not reliably predict variations in drug pharmacokinetics/pharmacodynamics. Routine TDM should be considered to adapt β-lactam doses in this setting.

- 56 pacientů v sepsi na JIP, bez hemodialýzy
- Hodnocena korelace plazmatických koncentrací s ClCr
- 39 % pacientů nedostatečné koncentrace
- Změny v ClCr nepredikují změny plazmatických koncentrací

Aktuální analýza



Diagnostic Microbiology and Infectious Disease 79 (2014) 77–84

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Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

The influence of acute kidney injury on antimicrobial dosing in critically ill patients: are dose reductions always necessary?

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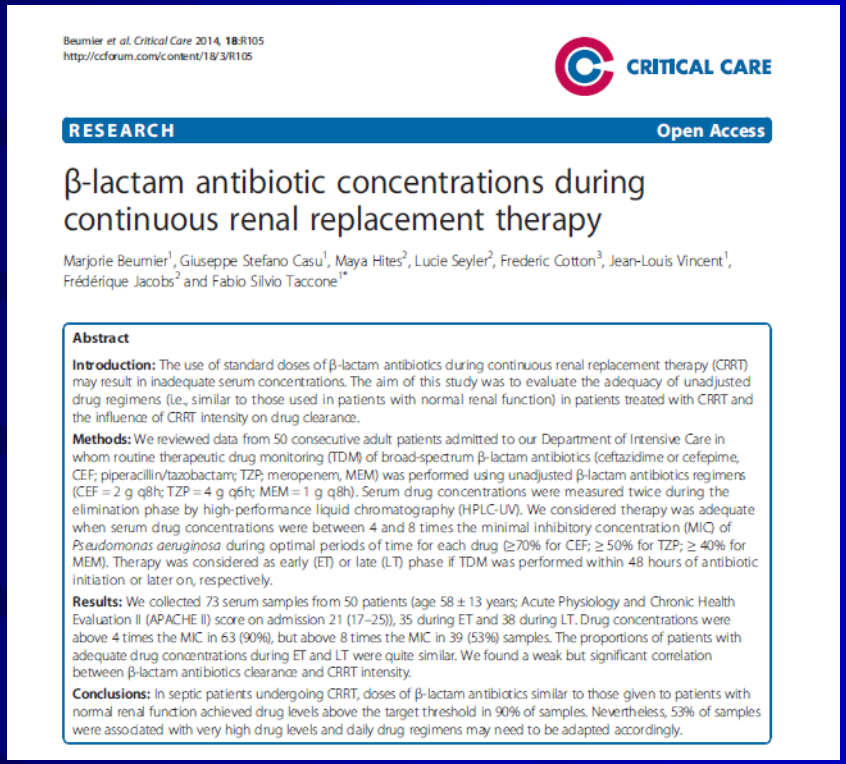
Pharmacokinetics
Pharmacodynamics
Renal failure
Antibiotic
ICU

ABSTRACT

Optimal dosing of antimicrobial therapy is pivotal to increase the likelihood of survival in critically ill patients with sepsis. Drug exposure that maximizes bacterial killing, minimizes the development of antimicrobial resistance, and avoids concentration-related toxicities should be considered the target of therapy. However, antimicrobial dosing is problematic as pathophysiological factors inherent to sepsis that alter may result in reduced concentrations. Alternatively, sepsis may evolve to multiple-organ dysfunction including acute kidney injury (AKI). In this case, decreased clearance of renally cleared drugs is possible, which may lead to increased concentrations that may cause drug toxicities. Consequently, when dosing antibiotics in septic patients with AKI, one should consider factors that may lead to underdosing and overdosing. Drug-specific pharmacokinetic and pharmacodynamic data may be helpful to guide dosing in these circumstances. Yet, because of the high interpatient variability in pharmacokinetics of antibiotics during sepsis, this issue remains a significant challenge.

- Betalaktamová antibiotika
  - Standardní dávkování během prvních 24 hodin AKI
  - Potom vhodná redukce dávky dle SPC nebo doporučení

Aktuální studie



Beumier *et al. Critical Care* 2014, **18**:R105
http://ccforum.com/content/18/3/R105

CRITICAL CARE

RESEARCH Open Access

β-lactam antibiotic concentrations during continuous renal replacement therapy

Marjorie Beumier[1], Giuseppe Stefano Casu[1], Maya Hites[2], Lucie Seyler[2], Frederic Cotton[3], Jean-Louis Vincent[1], Frédérique Jacobs[2] and Fabio Silvio Taccone[1*]

Abstract

Introduction: The use of standard doses of β-lactam antibiotics during continuous renal replacement therapy (CRRT) may result in inadequate serum concentrations. The aim of this study was to evaluate the adequacy of unadjusted drug regimens (i.e., similar to those used in patients with normal renal function) in patients treated with CRRT and the influence of CRRT intensity on drug clearance.

Methods: We reviewed data from 50 consecutive adult patients admitted to our Department of Intensive Care in whom routine therapeutic drug monitoring (TDM) of broad-spectrum β-lactam antibiotics (ceftazidime or cefepime, CEF; piperacillin/tazobactam; TZP; meropenem, MEM) was performed using unadjusted β-lactam antibiotics regimens (CEF = 2 g q8h; TZP = 4 g q6h; MEM = 1 g q8h). Serum drug concentrations were measured twice during the elimination phase by high-performance liquid chromatography (HPLC-UV). We considered therapy was adequate when serum drug concentrations were between 4 and 8 times the minimal inhibitory concentration (MIC) of *Pseudomonas aeruginosa* during optimal periods of time for each drug (≥70% for CEF; ≥ 50% for TZP; ≥ 40% for MEM). Therapy was considered as early (ET) or late (LT) phase if TDM was performed within 48 hours of antibiotic initiation or later on, respectively.

Results: We collected 73 serum samples from 50 patients (age 58 ± 13 years; Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission 21 (17–25)), 35 during ET and 38 during LT. Drug concentrations were above 4 times the MIC in 63 (90%), but above 8 times the MIC in 39 (53%) samples. The proportions of patients with adequate drug concentrations during ET and LT were quite similar. We found a weak but significant correlation between β-lactam antibiotics clearance and CRRT intensity.

Conclusions: In septic patients undergoing CRRT, doses of β-lactam antibiotics similar to those given to patients with normal renal function achieved drug levels above the target threshold in 90% of samples. Nevertheless, 53% of samples were associated with very high drug levels and daily drug regimens may need to be adapted accordingly.

- 50 nemocných s CRRT na JIP léčených MER, PIP/TAZ, CEF
- Standardní dávkovací režimy
- Měření plazmatických koncentrací, PKPD cíl 4x MIC
- Cíl dosažen u 90 %, ale 53 % mělo koncentrace nad 8 x MIC

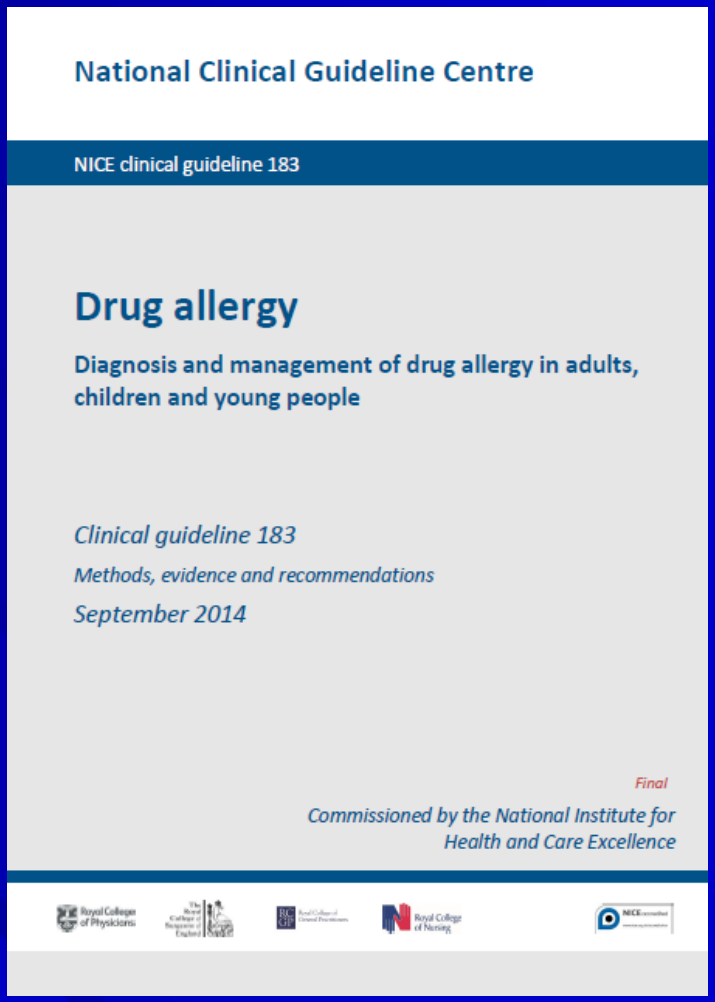
Nežádoucí účinky betalaktamů

Nežádoucí účinky betalaktamů

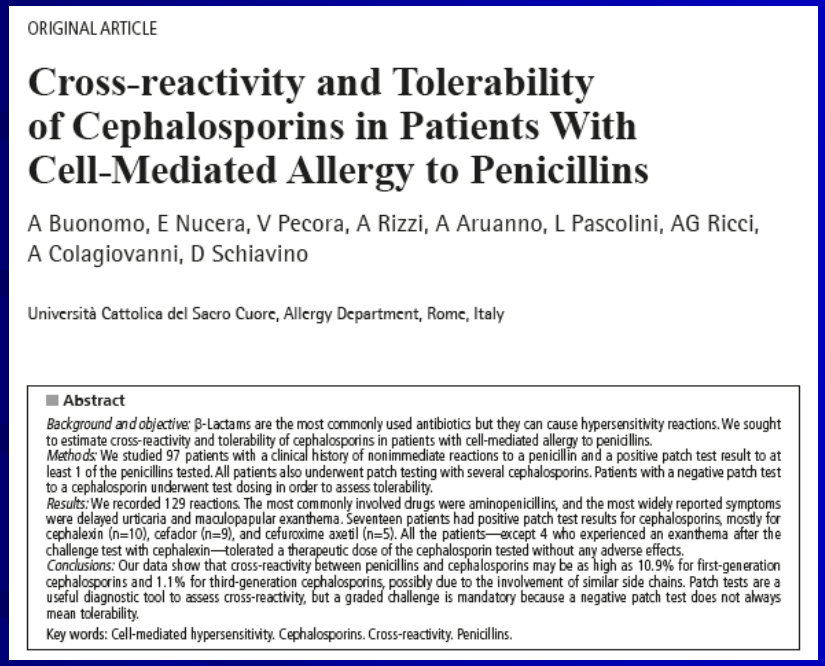
- Časté
  - Superinfekce
    - Postantibiotický průjem
      - Vzácně kolitis pseudomembranosa
    - Vaginální dysmikrobie
  - Reakce z přecitlivělosti
    - Kožní reakce I. typu
    - Vzácně opožděné reakce
  - Karbapenemy - křeče

Aktuální doporučení

- About 10% of the general population claim to have a penicillin allergy
- this has often been because of a skin rash that occurred during a course of penicillin in childhood
- Fewer than 10% of people who think they are allergic to penicillin are truly allergic
- those with a label of penicillin allergy are more likely to be treated with broad-spectrum antibiotics, such as quinolones, vancomycin, and third-generation cephalosporins



Aktuální studie



ORIGINAL ARTICLE

Cross-reactivity and Tolerability of Cephalosporins in Patients With Cell-Mediated Allergy to Penicillins

A Buonomo, E Nucera, V Pecora, A Rizzi, A Aruanno, L Pascolini, AG Ricci, A Colagiovanni, D Schiavino

Università Cattolica del Sacro Cuore, Allergy Department, Rome, Italy

Abstract

Background and objective: β-Lactams are the most commonly used antibiotics but they can cause hypersensitivity reactions. We sought to estimate cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins.
Methods: We studied 97 patients with a clinical history of nonimmediate reactions to a penicillin and a positive patch test result to at least 1 of the penicillins tested. All patients also underwent patch testing with several cephalosporins. Patients with a negative patch test to a cephalosporin underwent test dosing in order to assess tolerability.
Results: We recorded 129 reactions. The most commonly involved drugs were aminopenicillins, and the most widely reported symptoms were delayed urticaria and maculopapular exanthema. Seventeen patients had positive patch test results for cephalosporins, mostly for cephalexin (n=10), cefaclor (n=9), and cefuroxime axetil (n=5). All the patients—except 4 who experienced an exanthema after the challenge test with cephalexin—tolerated a therapeutic dose of the cephalosporin tested without any adverse effects.
Conclusions: Our data show that cross-reactivity between penicillins and cephalosporins may be as high as 10.9% for first-generation cephalosporins and 1.1% for third-generation cephalosporins, possibly due to the involvement of similar side chains. Patch tests are a useful diagnostic tool to assess cross-reactivity, but a graded challenge is mandatory because a negative patch test does not always mean tolerability.

Key words: Cell-mediated hypersensitivity. Cephalosporins. Cross-reactivity. Penicillins.

- 97 nemocných s anamnézou opožděných alergických reakcí
- Kožní testy, in vitro testy a expoziční testy
- Zkřížená reaktivita mezi peniciliny a cefalosporiny 10.9% pro cefalosporiny 1. generace a 1.1% pro 3. generaci

Nežádoucí účinky: křeče

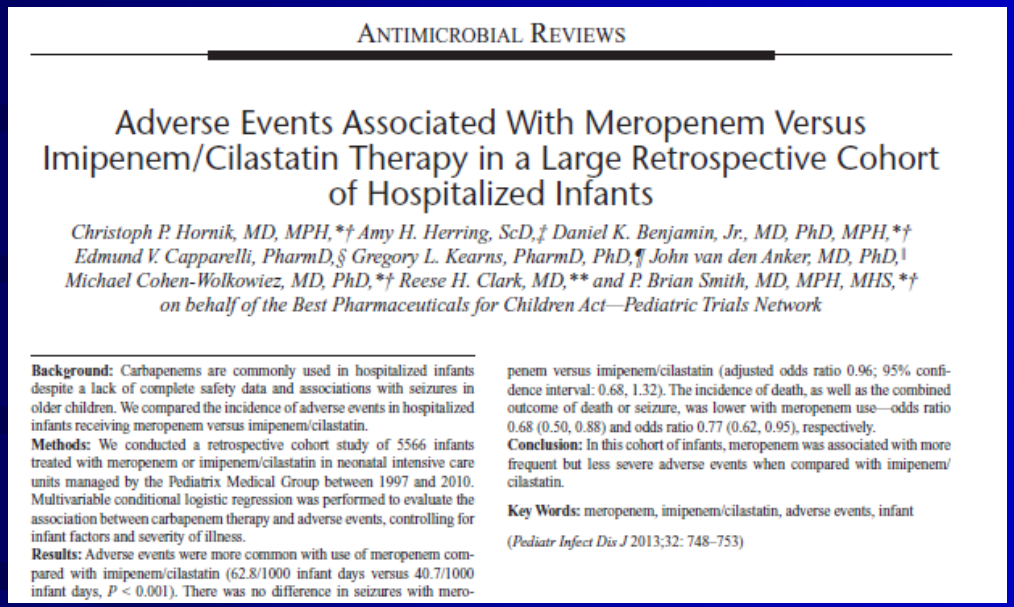
- Incidence
  - Imipenem/cilastatin 3-33 %
  - Ostatní do 1 %
- Mechanismus vzniku
  - GABA antagonismus
  - NMDA agonismus
- Terapie
  - benzodiazepiny

TABLE 10–5 Risk Factors for Drug-Induced Seizures

- Cancer
- Compromised blood–brain barrier
- Concomitant use of central nervous system stimulant drugs
- History of epilepsy or seizures
- Impaired metabolism of hepatically metabolized potentially seizure-inducing drugs in patients with liver disease
- Impaired elimination of renally eliminated potentially seizure-inducing drugs in patients with kidney disease

Miller AD et al. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. Pharmacotherapy. 2011 Apr;31(4):408-23.

Aktuální studie



ANTIMICROBIAL REVIEWS

Adverse Events Associated With Meropenem Versus Imipenem/Cilastatin Therapy in a Large Retrospective Cohort of Hospitalized Infants

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Background: Carbapenems are commonly used in hospitalized infants despite a lack of complete safety data and associations with seizures in older children. We compared the incidence of adverse events in hospitalized infants receiving meropenem versus imipenem/cilastatin.

Methods: We conducted a retrospective cohort study of 5566 infants treated with meropenem or imipenem/cilastatin in neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2010. Multivariable conditional logistic regression was performed to evaluate the association between carbapenem therapy and adverse events, controlling for infant factors and severity of illness.

Results: Adverse events were more common with use of meropenem compared with imipenem/cilastatin (62.8/1000 infant days versus 40.7/1000 infant days, $P < 0.001$). There was no difference in seizures with meropenem versus imipenem/cilastatin (adjusted odds ratio 0.96; 95% confidence interval: 0.68, 1.32). The incidence of death, as well as the combined outcome of death or seizure, was lower with meropenem use—odds ratio 0.68 (0.50, 0.88) and odds ratio 0.77 (0.62, 0.95), respectively.

Conclusion: In this cohort of infants, meropenem was associated with more frequent but less severe adverse events when compared with imipenem/cilastatin.

Key Words: meropenem, imipenem/cilastatin, adverse events, infant

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- Retrospektivní, kohorta 5556 dětí s IMI a MER
- Signifikantně vyšší výskyt NÚ pro meropenem
- Žádný rozdíl pro výskyt křečí (OR 96 %)
- Nižší mortalita u meropenemu

Aktuální studie

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Elevated Beta-lactam concentrations are associated with neurological deterioration in ICU septic patients.

Beumier M[1], Casu GS, Hites M, Wolff F, Cotton F, Vincent JL, Jacobs F, Taccone FS.

Author information

Abstract

INRODUCTION: Although β--lactams are considered to have a safe therapeutic profile, neurotoxicity has been reported. The aim of this study was to assess the association between --lactam concentrations and neurological alterations in septic ICU patients.

METHODS: Retrospective study on all ICU patients who were treated with meropenem (MEM), piperacillin--tazobactam (TZP) or ceftazidime/cefepime (CEF) and in whom at least one β--lactam trough concentration (Cmin) was determined. Drug levels were measured using high--performance liquid chromatography; Cmin was normalized to the clinical breakpoint of Pseudomonas aeruginosa (as determined by EUCAST) for each drug (Cmin/MIC). Changes in neurological status were evaluated using changes in the neurological sequential organ failure assessment score (ΔnSOFA) using the formula: ΔnSOFA = nSOFA(day of TDM) -- nSOFA(ICU admission). Worsening neurological status (NWS) was defined as a ΔnSOFA ≥1 for an nSOFA on admission of 0--2.

RESULTS: We collected 262 Cmin in 199 patients (130 MEM, 85 TZP, 47 CEF). Median APACHE II score and GCS on admission were 17 and 15, respectively. Overall ICU mortality was 27 %. There were no differences in the occurrence of NWS between antibiotics (39% for MEM, 32% for TZP and 35% for CEF). The occurrence of NWS increased with increasing Cmin/MIC ranges (p=0.008);; this correlation was found for TZP (p=0.05) and MEM (p=0.01), but not for CEF. Cmin/MIC was an independent predictive factor for NWS (OR 1.12 [1.04--1.20]).

CONCLUSIONS: We found a correlation between high β--lactam trough concentrations and increased occurrence of neurological deterioration in septic ICU patients. Although our data cannot determine causality, monitoring of --lactam levels should be considered when deterioration of neurological status occurs during critical illness.

- 199 nemocných na JIP s MER, PIP/TAZ, CEF
- Měření minimálních plazmatických koncentrací
- Změny v neurologickém státu SOFA skóre
- Korelace mezi vysokým C_{trough} a neurologickou deteriorací

Závěry

- Betalaktamy zůstávají nejvýznamnějšími antibiotiky v intenzivní péči
- Všeobecně přijímané je použití prodloužených způsobů aplikace
- Stále přibývá informací o TDM betalaktamů
- Problém je epidemie alergií na peniciliny
- Otázkou je toxicita vyšších plazmatických koncentrací

Děkuji za pozornost!