

# Ertapenem

V. Adámková

Klinická mikrobiologie a ATB centrum 1. LF UK a VFN, Praha

# Konflikt zájmů

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# Spektrum účinku ertapenemu

- *Enterobacteriaceae* včetně producentů ESBL a AmpC beta-laktamáz
- Gramnegativní respirační patogeny /*Moraxella catarrhalis*, *Haemophilus influenzae*/
- Grampozitivní koky /penicilin citlivé i rezistentní pneumokoky a MSSA/
- Grampozitivní i gramnegativní anaeroby
- Neúčinný vůči *P. aeruginosa*

# Ertapenem

- Účinek závislý na čase – nevázaná frakce by měla být  $> 40\%$  dávkovacího intervalu nad MIC
- Standardní dávkovací interval 24 hod, vzhledem k poločasů eliminace (4 hod) u zdravých mladých jedinců
- Asi 80 % i.v. dávky je vylučováno močí

# Ertapenem

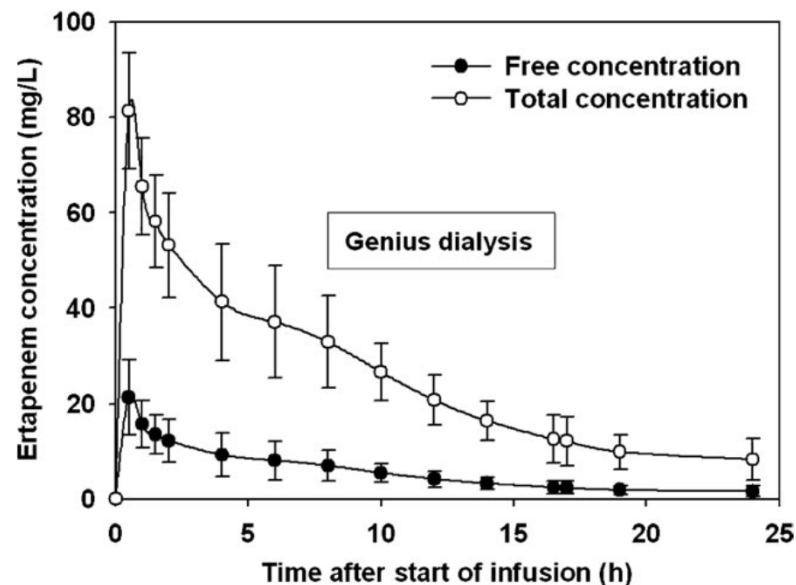
- U pacientů s renální insuficiencí (RI) se zvyšuje  $AUC_{0-\infty}$  ertapenemu o 7 % u mírné RI ( $CL_{CR}$  79 mL/min/ 1.73 m<sup>2</sup>), o 53 % u středně těžké RI ( $CL_{CR}$  40 mL/min/1.73 m<sup>2</sup>), o 158 % u těžké RI ( $CL_{CR}$  17 mL/min/1.73 m<sup>2</sup>) a o 192 % při konečném stádiu vyžadujícím HD
- Eliminační poločas ertapenemu je 4.4 h u mírné RI , 6.1 h u středně těžké RI , 10.6 h u těžké RI a 14.1 h při konečném stádiu vyžadujícím HD => redukce dávky na 0,5 g u těžké RI a konečného stadia

# Pharmacokinetics of ertapenem in critically ill patients with acute renal failure undergoing extended daily dialysis

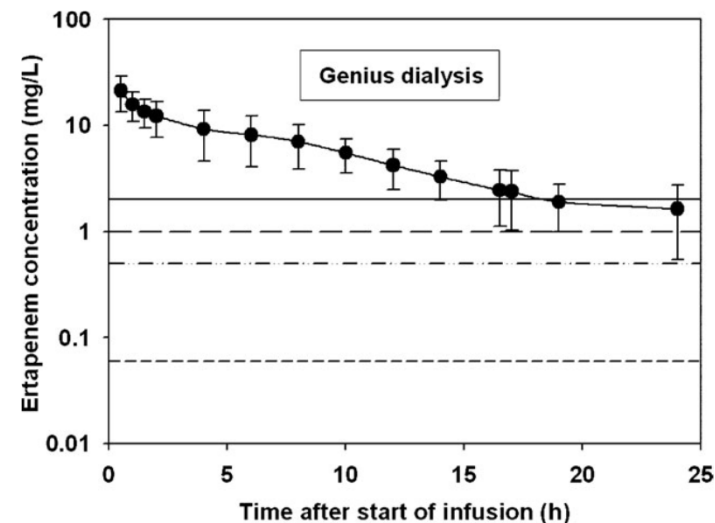
Olaf Burkhardt<sup>1,\*</sup>, Carsten Hafer<sup>2,\*</sup>, Anita Langhoff<sup>2</sup>, Volkhard Kaefer<sup>3</sup>, Vipul Kumar<sup>4</sup>, Tobias Welte<sup>1</sup>, Hermann Haller<sup>2</sup>, Danilo Fliser<sup>2</sup> and Jan T. Kielstein<sup>2</sup>

<sup>1</sup>Department of Pulmonary Medicine, <sup>2</sup>Department of Nephrology, <sup>3</sup>Department of Pharmacology and Toxicology, Medical School Hannover, Hannover, Germany and <sup>4</sup>Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA

- Alterace PK parametrů ATB u pacientů v sepsi
- EDD u pacientů v intenzivní péči
- Prospektivní studie PK ertapenemu u pacientů v sept. šoku s akutním ren. selháním podstupujících EDD
- Parametry: maximální koncentrace v plazmě C<sub>max</sub>, čas T<sub>max</sub> potřebný k dosažení C<sub>max</sub>, plocha pod křivkou plazmatické koncentrace a času (AUC), clearance při dialýze, volná koncentrace ERT....



**Fig. 1.** Time courses of total and free, protein-unbound ertapenem plasma concentrations after administration of a single 1 g intravenous dose in ICU patients with acute renal failure undergoing extended daily dialysis. Infusion period 30 min. Values are geometric means  $\pm$  SD,  $n = 6$ .



**Fig. 2.** Time courses of mean free, protein-unbound ertapenem plasma concentrations after administration of a single 1 g intravenous dose in ICU patients with acute renal failure undergoing extended daily dialysis. Horizontal lines indicate  $MIC_{90}$  values for penicillin-resistant *Streptococcus pneumoniae* ( $MIC_{90} \leq 2.0$  mg/L; ---) most anaerobe bacteria ( $MIC_{90} \leq 1.0$  mg/L; ----), methicillin-susceptible *Staphylococcus aureus* and extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Klebsiella pneumoniae* ( $MIC_{90} \leq 0.5$  mg/L; -.-.-) and non-ESBL-producing Enterobacteriaceae ( $MIC_{90} \leq 0.06$  mg/L;).

**Table 2.** Comparison of ertapenem pharmacokinetic data obtained in critically ill patients with acute renal failure (ARF) undergoing extended daily dialysis with data of patients with end-stage renal disease (ESRD) requiring haemodialysis [4], data of critically ill patients with  $CrCl_r > 30$  mL/min [15] and data of healthy young volunteers [14] previously reported in the literature

| Parameter              | ICU patients with ARF and EDD ( $n = 6$ ) | Patients with ESRD requiring haemodialysis [4] ( $n = 7$ ) | ICU patients ( $CrCl_r > 30$ mL/min) [15] ( $n = 17$ ) | Healthy volunteers [14] ( $n = 6$ ) |
|------------------------|---|--|--|-------------------------------------|
| $C_{max}$ (mg/L)       | $81.3 \pm 12.1$                           | 138.9  | $90.5 \pm 26.1$  | $103.3 \pm 26.3$                    |
| $AUC_{0-inf}$ (mg h/L) | $687.4 \pm 212.0$                         | 1941.5   | $418.5 \pm 171.6$                                      | $359.7 \pm 66.5$                    |
| $T_{max}$ (h)          | 0.5 (0.5)                                 | 0.5  | 0.5 (0.5–1.0)  | 0.5 (0.5)                           |
| $T_{1/2off}$ (h)       | $18.9 \pm 5.4$                            | 14.1   | $4.1 \pm 1.3$  | $3.8 \pm 0.6$                       |
| $T_{1/2on}$ (h)        | $6.7 \pm 0.4$                             | NA   | NA   | NA                                  |
| MRT (h)                | $10.7 \pm 1.6$                            | NA   | $5.7 \pm 1.7$  | $4.6 \pm 0.9$                       |
| $V_z$ (L)              | $15.9 \pm 3.2$                            | NA   | $17.3 \pm 5.9$   | $15.5 \pm 3.4$                      |
| $CL_{off}$ (mL/min)    | $19.3 \pm 11.4$                           | NA   | $43.2 \pm 23.7$  | $48.0 \pm 8.5$                      |
| $CL_{dial}$ (mL/min)   | $49.5 \pm 10.9$                           | NA   | NA   | NA                                  |

$C_{max}$ : peak plasma concentration; AUC: area under the curve;  $T_{max}$ : time of maximal plasma concentration;  $T_{1/2off}$ : half-life off dialysis treatment;  $T_{1/2on}$ : half-life on dialysis treatment; MRT: mean residence time;  $V_z$ : volume of distribution;  $CL_{off}$ : drug clearance off extended dialysis;  $CL_{dial}$ : dialysis clearance; NA: not available; ICU: intensive care unit.

- $T_{>MIC}$  pro karbapenemy se udává 30 – 40 %, avšak u pacientů v sepsi/šoku by měl být  $T_{>MIC}$  60 – 80 %
- U pacientů v sepsi s ARF na EDD je bezpečné podávání 1 g ERT jednou denně, není nutná redukce dávky



# Ertapenem u chronicky dialyzovaných pacientů

- 10 pacientů – IHD (3x týdně)
- 1 g ertapenemu bezprostředně po dialýze
- MIC všech bakterií -> hladiny ERT nad MIC u všech během intervalu mezi HD
- Úspěšná klinická odpověď – 8 z 10
- Žádné NÚ

# Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis

A.J. Brink<sup>a,\*</sup>, G.A. Richards<sup>b</sup>, V. Schillack<sup>c</sup>, S. Kiem<sup>d</sup>, J. Schentag<sup>d</sup>

**Table 1**

Patient characteristics at enrolment (n=8; 5 female, 3 male).

| Patient         | Age (years)     | Weight (kg)     | APACHE II score | Creatinine ( $\mu\text{mol/L}$ ) | CL <sub>Cr</sub> (mL/min) | Protein (g/L) <sup>a</sup> | Albumin (g/L) <sup>b</sup> | ICU admission           | Pathogen/source                                   |
|-----------------|-----------------|-----------------|-----------------|----------------------------------|---------------------------|----------------------------|----------------------------|-------------------------|---|
| 1               | 43              | 55              | 8               | 89                               | 63                        | 90                         | 32                         | Severe CAP              | N/A   |
| 2               | 40              | 60              | 9               | 56                               | 132                       | 75                         | 25                         | Severe CAP              | <i>Morganella morganii</i> ,<br>tracheal aspirate |
| 3               | 43              | 43              | 15              | 64                               | 131                       | 42                         | 23                         | Post-surgical IA sepsis | N/A   |
| 4               | 56              | 80              | 4               | 51                               | 158                       | 41                         | 16                         | Post-surgical IA sepsis | N/A   |
| 5               | 21              | 60              | 4               | 67                               | 122                       | 79                         | 46                         | Guillain-Barré          | <i>Escherichia coli</i> ,<br>urine                |
| 6               | 42              | 75              | 7               | 134                              | 68                        | 46                         | 22                         | Post-surgical IA sepsis | N/A   |
| 7               | 24              | 60              | 18              | 147                              | 50                        | 85                         | 24                         | Malaria                 | <i>E. coli</i> , blood                            |
| 8               | 24              | 50              | 6               | 103                              | 50                        | 73                         | 27                         | Severe CAP              | N/A   |
| Mean $\pm$ S.D. | 36.6 $\pm$ 12.3 | 60.4 $\pm$ 12.2 | 8.9 $\pm$ 5.1   | 88.9 $\pm$ 36.3                  | 96.8 $\pm$ 43.3           | 66.4 $\pm$ 20.1            | 26.9 $\pm$ 9.0             |                         |   |
| Median          | 41              | 60              | 8               | 78                               | 95                        | 74                         | 25                         |                         |   |
| Range           | 21–56           | 43–80           | 4–18            | 51–147                           | 50–158                    | 41–90                      | 16–46                      |                         |   |

APACHE, Acute Physiology and Chronic Health Evaluation; CL<sub>Cr</sub>, creatinine clearance; ICU, intensive care unit; CAP, community-acquired pneumonia; N/A, not available; IA, intra-abdominal.

<sup>a</sup> Normal range 60–83 g/L.

<sup>b</sup> Normal range 35–52 g/L.

**Table 5**

Calculated time (h) of unbound plasma ertapenem above certain concentrations in critically ill patients with severe sepsis after 1 g 30-min infusions.

| Patient | Concentration (mg/L) |       |       |      |      |      |
|---------|----------------------|-------|-------|------|------|------|
|         | 0.06                 | 0.5   | 1     | 2    | 4    | 8    |
| 1       | 31.9                 | 21.5  | 18.2  | 14.8 | 11.4 | 8.0  |
| 2       | 14.2                 | 9.6   | 8.1   | 6.6  | 5.1  | 3.6  |
| 3       | 18.1                 | 9.8   | 7.1   | 4.4  | 1.7  | 0.0  |
| 4       | 22.8                 | 14.1  | 11.2  | 8.4  | 5.5  | 2.6  |
| 5       | 48.3                 | 31.9  | 26.5  | 21.2 | 15.8 | 10.4 |
| 6       | 27.6                 | 8.8   | 2.6   | 0.0  | 0.0  | 0.0  |
| 7       | 367.8                | 199.4 | 144.3 | 89.3 | 34.2 | 0.0  |
| 8       | 41.4                 | 29.3  | 25.3  | 21.3 | 17.4 | 13.4 |
| Median  | 29.8                 | 17.8  | 14.7  | 11.6 | 8.4  | 3.1  |
| Min.    | 14.2                 | 8.8   | 2.6   | 0.0  | 0.0  | 0.0  |
| Max.    | 367.8                | 199.4 | 144.3 | 89.3 | 34.2 | 13.4 |

**Table 3**

Comparison of total ertapenem pharmacokinetic data after a single 1 g infusion obtained in critically ill patients with severe sepsis versus published data for critically ill patients with early-onset ventilator-associated pneumonia [7] and healthy volunteers [9,17].

| Parameter                 | This study (n=8) |                | Burkhardt et al. [7] (n=17) <sup>a</sup> | Majumdar et al. [9] (n=16) <sup>a</sup> | Pletz et al. [17] (n=10) <sup>b</sup> |
|---------------------------|------------------|----------------|--|---|---------------------------------------|
|                           | Mean ± S.D.      | Geometric mean |  |   |                                       |
| $t_{1/2}$ (h)             | 5.7 ± 4.9        | 4.5            | 4.15 ± 1.33                              | 3.8                                     | 4.5 (23)                              |
| $V_{ss}$ (L)              | 59.4 ± 85.7      | 26.8           | 14.8 ± 3.78                              | 8.2 ± 1.5                               | 5.7 (18)                              |
| $CL_T$ (mL/min)           | 200.5 ± 306.9    | 88.6           | 43.2 ± 23.7                              | 29.5 ± 3.4                              | 20.4 (18)                             |
| $CL_R$ (mL/min)           | 72.5 ± 98.3      | 33.2           | 31.8 ± 23.3                              | 12.9 ± 4.3                              | 9.38 (37)                             |
| $f_u$ (% of dose)         | 45.1 ± 30.3      | 36.7           | 54.8 ± 19.09                             | 44.4 ± 14.8                             | 45.1 (36)                             |
| $AUC_{0-\infty}$ (mg h/L) | 317.7 ± 274.6    | 188.0          | 418.5 ± 171.6                            | 572.1 ± 68.6                            | 817 (20)                              |
| $C_{max}$ (mg/L)          | 94.1 ± 79.0      | 52.3           | 90.5 ± 26.1                              | 154.9 ± 22.0                            | 253 (15)                              |

S.D., standard deviation;  $t_{1/2}$ , elimination half-life;  $V_{ss}$ , volume of distribution at steady state;  $CL_T$ , total body clearance;  $CL_R$ , renal clearance;  $f_u$ , urinary recovery;  $AUC_{0-\infty}$ , area under the concentration–time curve from 0 h to infinity;  $C_{max}$ , maximum plasma concentration.

<sup>a</sup> Data reported as mean ± S.D.

<sup>b</sup> Data reported as geometric mean [coefficient of variation (%)].

**Table 4**

Comparison of unbound ertapenem pharmacokinetic data after a single 1 g infusion obtained in critically ill patients with severe sepsis versus published data for young adults [9] and healthy elderly subjects [10].

| Parameter                 | This study (n=8) |                | Majumdar et al. [9] (n=16) <sup>a</sup> | Musson et al. [10] (n=8) <sup>a</sup> |
|---------------------------|------------------|----------------|---|---------------------------------------|
|                           | Mean ± S.D.      | Geometric mean |   |                                       |
| $t_{1/2}$ (h)             | 10.1 ± 18.2      | 4.8            | –                                       | 4.7                                   |
| $V_{ss}$ (L)              | 89.9 ± 92.3      | 54.3           | 123.1 ± 37.2                            | –                                     |
| $CL_T$ (mL/min)           | 316.2 ± 374.3    | 161.0          | 513.6 ± 80.8                            | –                                     |
| $CL_R$ (mL/min)           | 147.5 ± 219.2    | 63.4           | 223.3 ± 67.8                            | 122.4 ± 28.6                          |
| $AUC_{0-\infty}$ (mg h/L) | 180.6 ± 167.4    | 103.5          | 33.2 ± 5.5                              | 55.40 ± 7.6                           |
| $C_{max}$ (mg/L)          | 46.4 ± 40.5      | 29.5           | 12.9 ± 3.2                              | –                                     |

S.D., standard deviation;  $t_{1/2}$ , elimination half-life;  $V_{ss}$ , volume of distribution at steady state;  $CL_T$ , total body clearance;  $CL_R$ , renal clearance;  $AUC_{0-\infty}$ , area under the concentration–time curve from 0 h to infinity;  $C_{max}$ , maximum plasma concentration.

<sup>a</sup> Data reported as mean ± S.D.

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Burkhardt O, Kumar V, Katterwe D, Majcher-Peszynska J, Drewelouw B, Derendorf H, et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. *J Antimicrob Chemother* 2007;59:277–84.

Majumdar AK, Musson DG, Birk KL, Kitchen CJ, Holland S, McCreagh J, et al. Pharmacokinetics of ertapenem in healthy young volunteers. *Antimicrob Agents Chemother* 2002;46:3506–11.

Pletz MWR, Rau M, Bulitta J, De Roux A, Burkhardt O, Kruse G, et al. Ertapenem pharmacokinetics and impact on intestinal microflora, in comparison to those of ceftriaxone, after multiple dosing in male and female volunteers. *Antimicrob Agents Chemother* 2004;48:3765–72.

- U pacientů v kritickém stavu nelze přejímat PK/PD údaje ze studií na zdravých dobrovolnících
- Nevázaná plazmatická koncentrace ertapenemu u kriticky nemocných pacientů s VAP dosahuje hodnot nad  $MIC_{90}$  pouze 6 hod po infuzi, tj. 25 % dávkovacího intervalu => zkrácení intervalu, nebo kontinuální infuze

Brink JA et al. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. *International Journal of Antimicrobial Agents* 33 (2009) 432–436

Burkhardt O, Kumar V, Katterwe D, Majcher-Peszynska J, Drewelouw B, Derendorf H, et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. *J Antimicrob Chemother* 2007;59:277–84.

# Pharmacokinetics of free ertapenem in critically ill septic patients: intermittent *versus* continuous infusion

D. BREILH <sup>1</sup>, C. FLEUREAU <sup>2</sup>, J.-B. GORDIEN <sup>1</sup>, O. JOANES-BOYAU <sup>2</sup>, J. TEXIER-MAUGEIN <sup>3</sup>, S. RAPAPORT <sup>2</sup>, E. BOSELLI <sup>4</sup>, G. JANVIER <sup>2</sup>, M.-C. SAUX <sup>1</sup>

TABLE II.—Steady-state serum free-ertapenem PK parameters following intravenous once-daily administration to critically ill septic patients: intermittent (ITI) versus continuous infusion (CI).

| Patient  | Pharmacokinetic parameters of free ertapenem in ICU patients |             |             |             |                     |               |              |           |           |
|--|--|-------------|-------------|-------------|---------------------|---------------|--------------|-----------|-----------|
|  | $fC_{\max}$  | $fC_{12h}$  | $fC_{\min}$ | $fC_{ss}$   | $T_{1/2\text{Kel}}$ | Kel           | $V_d$        | $CL_T$    | $fAUC$    |
| ITI (1 g of ertapenem once-daily)  |  |             |             |             |                     |               |              |           |           |
| 1  | 130.3  | 11.3        | 1.8         | –           | 4                   | 0.173         | 12.4         | 2.2       | 929       |
| 2  | 117.7  | 7.9         | 2.7         | –           | 10                  | 0.069         | 17.7         | 1.2       | 818       |
| 3  | 77.9   | 18.7        | 9.6         | –           | 12                  | 0.058         | 22.9         | 1.3       | 750       |
| 4  | 88.4   | 14.6        | 2.4         | –           | 6                   | 0.116         | 20.6         | 2.4       | 421       |
| 5  | 97.6   | 15.2        | 1.9         | –           | 4                   | 0.173         | 16.5         | 2.9       | 351       |
| 6  | 104.8  | 8.4         | 3.1         | –           | 8                   | 0.087         | 19.4         | 1.7       | 595       |
| 7  | 102.5  | 10.4        | 1.9         | –           | 3                   | 0.231         | 13.8         | 3.2       | 315       |
| 8  | 96.7   | 8.2         | 2.6         | –           | 4                   | 0.173         | 12.0         | 2.1       | 481       |
| 9  | 86.8   | 6.5         | 3.2         | –           | 4                   | 0.173         | 12.1         | 2.1       | 476       |
| 10   | 100.2  | 8.6         | 2.1         | –           | 3                   | 0.231         | 13.4         | 3.1       | 324       |
| Median   | 98.9   | 9.5         | 2.5         | –           | 4                   | 0.173         | 15.1         | 2.2       | 479       |
| IQR  | [90.5–104.2]   | [8.3–13.8]  | [2.0–3.0]   | –           | [4–8]               | [0.094–0.173] | [12.7–19.0]  | [1.8–2.7] | [369–711] |
| CI (1 g of ertapenem once-daily after a loading dose 1-g ertapenem on day 1) |  |             |             |             |                     |               |              |           |           |
| 11   | 76.2   | 15.0        | 11.4        | 15.0        | 6                   | 0.116         | 14.2         | 2.2       | –         |
| 12   | 51.4   | 15.3        | 10.9        | 10.9        | 4                   | 0.173         | 26.7         | 2.9       | –         |
| 13   | 64.5   | 20.8        | 16.5        | 16.5        | 6                   | 0.116         | 22.8         | 2.6       | –         |
| 14   | 77.8   | 17.2        | 19.1        | 17.2        | 6                   | 0.116         | 20.1         | 1.8       | –         |
| 15   | 69.7   | 15.8        | 16.5        | 15.8        | 6                   | 0.116         | 21.7         | 2.0       | –         |
| 16   | 58.3   | 14.4        | 25.8        | 24.3        | 4                   | 0.173         | 24.2         | 1.9       | –         |
| 17   | 68.8   | 15.6        | 14.9        | 15.9        | 6                   | 0.116         | 19.7         | 2.3       | –         |
| 18   | 66.5   | 14.3        | 14.2        | 15.6        | 4                   | 0.173         | 21.8         | 3.8       | –         |
| 19   | 64.9   | 16.2        | 15.8        | 15.6        | 4                   | 0.173         | 20.3         | 3.5       | –         |
| 20   | 72.6   | 19.8        | 17.6        | 17.8        | 4                   | 0.173         | 19.6         | 3.4       | –         |
| Median   | 67.7   | 15.7        | 16.2        | 15.9        | 5                   | 0.145         | 21.0         | 2.5       | –         |
| IQR  | [64.6–71.9]  | [15.1–17.0] | [14.4–17.3] | [15.6–17.0] | [4–6]               | [0.116–0.173] | [19.78–22.6] | [2.1–3.3] | –         |

$fC_{\max}$ ,  $fC_{12h}$ ,  $fC_{\min}$  and  $fC_{ss}$  (mg/L);  $T_{1/2\text{Kel}}$ , elimination half-life (h);  $K_{el}$ , elimination rate constant ( $\text{h}^{-1}$ );  $V_d$ : volume of distribution (L);  $CL_T$ : total clearance (L/h);  $fAUC$ : area under the curve between 0 and 24 hours (mg.h/L); IQR: interquartile range [Q1–Q3] *i.e.*, 25<sup>th</sup> and 75<sup>th</sup> percentiles.

# ERT 1 g 5min vs 30min infuze

- Prospektivní, randomizovaná studie, 2 fáze
- 1 g ERT v 5min nebo 30min infuzi, 1x denně 3 dny; 4 dny pauza a opět stejný protokol
- ERT byl stejně snášen v obou skupinách se srovnatelnými NÚ
- ERT steady-state  $C_{\max}$   $193.3 \pm 43.3$  a  $165.7 \pm 20.4$  mg/l pro 5min a 30min infuze;  $AUC_{0-24}$   $561.2 \pm 77.0$  a  $531.3 \pm 56.9$   $\mu\text{g h/ml}$
- 5minutová infuze je bezpečná a se srovnatelnými parametry jako 30min infuze

# Assessment of extended-spectrum $\beta$ -lactamase, KPC carbapenemase and porin resistance mechanisms in clinical samples of *Klebsiella pneumoniae* and *Enterobacter* spp.



M.R. Jaskulski<sup>a,b</sup>, B.C. Medeiros<sup>a</sup>, J.V. Borges<sup>a</sup>, R. Zalewsky<sup>a</sup>, M.E.C. Fonseca<sup>a</sup>,  
D.R. Marinowicz<sup>a</sup>, M.P. Rocha<sup>c</sup>, P. Nodari<sup>b</sup>, D.C. Machado<sup>a,d,\*</sup>

<sup>a</sup> Laboratory of Cellular and Molecular Biology, Biomedical Research Institute of Pontifical Catholic University of Rio Grande do Sul (PUCRS), Av. Ipiranga 6690, CEP 90610-000, Porto Alegre, RS, Brazil

<sup>b</sup> Regional Integrated University, Av. Sete de Setembro 1621, CEP 99700-000, Erechim, RS, Brazil

<sup>c</sup> Enzilab Laboratory, Rua Marechal Deodoro 189, CEP 96810-110, Santa Cruz do Sul, RS, Brazil

<sup>d</sup> School of Medicine, Department of Internal Medicine, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Av. Ipiranga 6690, CEP 90610-000, Porto Alegre, RS, Brazil

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Resistance

## ABSTRACT

The emergence and spread of resistance mechanisms in Gram-negative bacilli has complicated the treatment of serious nosocomial infections. Current automated systems for detection of *Klebsiella pneumoniae* carbapenemase (KPC)-producing isolates are unreliable. One possible straightforward alternative method is evaluation of ertapenem resistance. However, the accuracy of this method is affected by other resistance mechanisms such as AmpC gene expression or extended-spectrum  $\beta$ -lactamase production associated with porin loss. This study included 128 samples of *K. pneumoniae* and *Enterobacter* spp. that were non-susceptible to ertapenem. The disk diffusion and Etest method were applied to determine susceptibility to imipenem, meropenem and ertapenem. Isolates exhibiting intermediate or complete resistance to ertapenem were evaluated for resistance mechanisms. *bla*<sub>TEM</sub>, *bla*<sub>SHV</sub>, *bla*<sub>CTX-M</sub>, *bla*<sub>CTX-M-2</sub> and *bla*<sub>KPC</sub> genes were tested for by PCR, and the presence of outer membrane protein was investigated by dot-blot assay. *bla*<sub>TEM</sub> was detected in 52.9% and 10.3%, *bla*<sub>SHV</sub> in 29.4% and 0.94%, *bla*<sub>CTX-M</sub> in 41.4% and 1.9% and *bla*<sub>CTX-M-2</sub> in 23.5% and 1.9% of *K. pneumoniae* and *Enterobacter cloacae* isolates, respectively. The *bla*<sub>KPC</sub> gene was present in 12.6% of *Enterobacter* spp. isolates. OmpC and OmpF were present in 6.6% of *E. cloacae* isolates. These results indicate that several resistance mechanisms contribute to potential therapeutic failure of carbapenem therapy and point to the need for better detection methods and surveillance strategies.

## Assessment of extended-spectrum $\beta$ -lactamase, KPC carbapenemase and porin resistance mechanisms in clinical samples of *Klebsiella pneumoniae* and *Enterobacter* spp.

M.R. Jaskulski<sup>a,b</sup>, B.C. Medeiros<sup>a</sup>, J.V. Borges<sup>a</sup>, R. Zalewsky<sup>a</sup>, M.E.C. Fonseca<sup>a</sup>, D.R. Marinowic<sup>a</sup>, M.P. Rocha<sup>c</sup>, P. Nodari<sup>b</sup>, D.C. Machado<sup>a,d,\*</sup>

**Table 2**

Carbapenem susceptibility of *Klebsiella pneumoniae* and *Enterobacter* spp. isolates (N= 128) by Etest and disk diffusion.

| Result       | Etest [n (%)] |            |            | Disk diffusion [n (%)] |           |            |
|--------------|---------------|------------|------------|------------------------|-----------|------------|
|              | IPM           | MER        | ERT        | IPM                    | MER       | ERT        |
| Susceptible  | 74 (57.8)     | 100 (78.1) | 0 (0.0)    | 104 (81.3)             | 97 (75.8) | 0 (0.0)    |
| Intermediate | 32 (25.0)     | 15 (11.7)  | 18 (14.1)  | 12 (9.4)               | 18 (14.1) | 12 (9.4)   |
| Resistant    | 22 (17.2)     | 13 (10.2)  | 110 (85.9) | 12 (9.4)               | 13 (10.2) | 116 (90.6) |

IPM, imipenem; MER, meropenem; ERT, ertapenem.



**Table 3**

Resistance mechanisms and minimum inhibitory concentrations (MICs) detected in ertapenem-non-susceptible isolates of *Klebsiella pneumoniae* and *Enterobacter* spp.

| Isolate                     | Resistance mechanism      |                           |                             |                               |                           |      |      | MIC (µg/mL) |       |     |
|-----------------------------|---------------------------|---------------------------|-----------------------------|-------------------------------|---------------------------|------|------|-------------|-------|-----|
|                             | ESBLs                     |                           |                             |                               | Carbapenemase             | OMPs |      | IPM         | MER   | ERT |
|                             | <i>bla</i> <sub>TEM</sub> | <i>bla</i> <sub>SHV</sub> | <i>bla</i> <sub>CTX-M</sub> | <i>bla</i> <sub>CTX-M-2</sub> | <i>bla</i> <sub>KPC</sub> | OmpC | OmpF |             |       |     |
| <i>K. pneumoniae</i>        |                           |                           |                             |                               |                           |      |      |             |       |     |
| 1002                        | x                         | x                         |                             |                               |                           |      |      | 2           | 3     | >32 |
| 1006                        | x                         | x                         | x                           |                               |                           |      |      | 0.5         | 1     | >32 |
| 1011                        | x                         |                           | x                           | x                             |                           |      |      | 1           | 1.5   | 12  |
| 1034                        | x                         |                           | x                           | x                             |                           |      |      | 0.25        | 0.125 | 1   |
| 1035                        |                           |                           | x                           | x                             |                           |      |      | 2           | 3     | >32 |
| 1052                        |                           | x                         |                             |                               |                           |      |      | 2           | 2     | >32 |
| 1099                        | x                         |                           | x                           | x                             |                           |      |      | 0.5         | 0.25  | 1   |
| 1158                        | x                         | x                         | x                           |                               |                           |      |      | 0.5         | 0.5   | 2   |
| 2008                        | x                         |                           |                             |                               |                           |      |      | 2           | 0.25  | 4   |
| 2011                        |                           |                           | x                           |                               |                           |      |      | 2           | 0.19  | 6   |
| 2010                        | x                         |                           |                             |                               |                           |      |      | 0.5         | 0.19  | 1.5 |
| 2006                        | x                         | x                         |                             |                               |                           |      |      | 0.25        | 0.094 | 1   |
| <i>Enterobacter cloacae</i> |                           |                           |                             |                               |                           |      |      |             |       |     |
| 1004                        | x                         |                           |                             |                               |                           |      |      | 1           | 0.5   | 8   |
| 1005                        |                           |                           |                             |                               | x                         |      |      | 0.38        | >32   | >32 |
| 1008                        | x                         |                           | x                           | x                             |                           |      | x    | 0.38        | 0.5   | 4   |
| 1010                        |                           |                           |                             |                               |                           |      |      | >32         | >32   | >32 |
| 1014                        | x                         | x                         | x                           | x                             |                           |      |      | 0.75        | 0.75  | 6   |
| 1018                        |                           |                           |                             |                               |                           |      | x    | 0.38        | 0.25  | 6   |
| 1019                        | x                         |                           |                             |                               |                           |      |      | 1           | 0.25  | 4   |
| 1022                        |                           |                           |                             |                               | x                         |      |      | 2           | 0.5   | 3   |
| 1041                        | x                         |                           |                             |                               |                           |      | x    | 0.75        | 0.38  | >32 |
| 1042                        |                           |                           |                             |                               | x                         |      | x    | 1.5         | 0.25  | 2   |
| 1044                        |                           |                           |                             |                               | x                         |      |      | 3           | 3     | >32 |
| 1053                        | x                         |                           |                             |                               |                           |      |      | 0.5         | 1.5   | >32 |
| 1068                        | x                         |                           |                             |                               |                           |      |      | 0.75        | 0.5   | 1.5 |
| 1079                        |                           |                           |                             |                               |                           |      | x    | 1           | 2     | 3   |
| 1082                        |                           |                           |                             |                               |                           |      | x    | 0.5         | 0.38  | >32 |
| 1090                        | x                         |                           |                             |                               |                           |      |      | 1           | 1     | 1   |
| 1097                        | x                         |                           |                             |                               |                           |      |      | 1           | 0.38  | 4   |
| 1102                        | x                         |                           |                             |                               | x                         |      | x    | 1           | 1     | 4   |
| 1113                        | x                         |                           |                             |                               |                           |      |      | 1           | 0.5   | 3   |
| 1128                        |                           |                           |                             |                               |                           |      |      | >32         | >32   | >32 |
| 1129                        |                           |                           |                             |                               |                           |      |      | 4           | 0.75  | 6   |
| 1132                        |                           |                           |                             |                               |                           |      |      | 4           | 0.75  | 8   |
| 1136                        |                           |                           |                             |                               |                           |      |      | 2           | 0.75  | 4   |
| 1138                        |                           |                           |                             |                               |                           |      |      | 1           | 0.75  | 6   |
| 1159                        |                           |                           |                             |                               |                           |      |      | 1           | 1     | >32 |

ESBL, extended-spectrum β-lactamase; OMP, outer membrane protein; IPM, imipenem; MER, meropenem; ERT, ertapenem.

# KPC pozitivní kmeny enterobakterií

- ATB s účinkem vůči KPC-pozitivním izolátům - polymyxiny, tigecyklin a aminoglykosidy
- Ačkoliv je MIC meropenemu nízká, tak použití v terapii je spojeno s vysokým rizikem selhání při monoterapii systémové infekce
- **Ertapenem** – laboratorní markr

# Závěr

- Ertapenem:
  - je bezpečný a účinný u pacientů na JIP/kriticky nemocných
  - má prokázanou aktivitu vůči ESBL+ kmenům
  - u pacientů s renální insuficiencí na EDD není nutná redukce dávky
  - 5minutová infuze je bezpečná
  - laboratorní markr snížené citlivosti ke KAR
- CI 1 g ertapenemu =>  $T_{>MIC}$  100 %

Děkuji za pozornost.