Dosing Optimization of Ampicillin-Sulbactam Based on Cystatin C in Elderly Patients with Pneumonia

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Ampicillin-sulbactam is a first-line therapy for pneumonia and is mainly excreted by the kidney. It is important to optimize the dose and dosing interval of ampicillin-sulbactam because in patients with decreased renal function and low skeletal muscle mass, such as the elderly, excess drug may burden renal function. In this study, we evaluated indices of renal function and optimized the dose and dosing interval of ampicillin-sulbactam based on pharmacokinetics (PK) and pharmacodynamics theory in elderly patients. The serum concentrations of ampicillin and sulbactam were measured by HPLC, and PK parameters were calculated. Correlations between the clearance of ampicillin or sulbactam and renal function were evaluated, and dosing optimization was calculated based on PK parameters. The PK parameters of ampicillin were $CL = 6.5 \pm 4.0 \text{L/h}$, $V_d = 19.3 \pm 0.2 \text{L}$, $K_e = 0.4 \pm 0.2$, and $t_{1/2} = 2.7 \pm 1.6 \text{h}$. The most correlated renal function index was estimated glomerular filtration rate (eGFRcys-c) calculated by serum cystatin-c ($r = 0.7374$, correlation formula; $CL$ of ampicillin $= 0.1937 \times eGFRcys-c - 0.6726$). Based on this formula, we calculated the clearance of ampicillin and developed dosing regimens for the elderly. Serum cystatin-c concentration is an ideal index to optimize ampicillin-sulbactam antimicrobial therapy in elderly patients with pneumonia.

Key words ampicillin-sulbactam; creatinine; cystatin-c; pharmacokinetics–pharmacodynamics

INTRODUCTION

Physiological changes in the elderly, such as an increase in body fat or decrease in body water, serum albumin, and renal function, may impact drug pharmacokinetics. Therefore, it is necessary to develop dosing regimens specifically for the elderly. Serum creatinine (Scr) concentrations are widely used markers for renal function, but Scr concentrations are affected by skeletal muscle volumes. Scr may not accurately reflect renal function in elderly patients because they have low skeletal muscle mass, which leads to the overestimation of renal function by indices such as glomerular filtration rate (GFR) and creatinine clearance (CLccreat).

Cystatin C (cys-c) is a low-molecular-weight protein and the product of a housekeeping gene expressed in all nucleated cells. Cys-c is stably produced even in the presence of inflammation and irrespective of muscle mass and gender. Serum cys-c (Scys-c) has been proposed as an alternative endogenous marker of renal function. Clearance of vancomycin, an antibiotic agent excreted from the kidney, is better correlated with Scys-c, especially in elderly patients, and its concentration is also better correlated with Scys-c than Scr concentration in elderly patients. Therefore, the dose of drugs excreted from the kidneys in elderly patients should be optimized based on Scys-c.

Ampicillin-sulbactam is a combination of beta-lactam and beta-lactamase inhibitors with broad spectrum antimicrobial activity against Gram-positive, Gram-negative, and anaerobic bacteria. Ampicillin and sulbactam have similar pharmacokinetics (PK), and both drugs are mainly excreted by the kidney via glomerular filtration and tubular excretion. A combination of antimicrobial agents should be administered less frequently in patients with renal failure depending on renal function. The antimicrobial activities of beta-lactam antibiotics, including ampicillin, correlate with the exposure time that the free drug concentration remains above the minimum inhibitory concentration (MIC) for the bacterium. It is important to optimize dose and dosing interval of the antimicrobial agent to maximize efficacy and minimize adverse events for antimicrobial agent chemotherapy. Although the PK profile for ampicillin-sulbactam in healthy and renal-impaired patients is well known, there is insufficient data for the administration of ampicillin-sulbactam based on the GFR estimated by Scys-c in elderly patients.

In this study, we analyzed the PK parameters of ampicillin-sulbactam and calculated the optimal dose and dosing interval based on GFR, which was estimated by Scys-c, in elderly patients.

PATIENTS AND MATERIALS

Patients This study was approved by the Ethics Review Board of Ibusuki Kouzenkai Hospital (62). Thirty-eight adult patients who received ampicillin–sulbactam to treat aspiration pneumonia between December 2013 and May 2014 at Ibusuki Kouzenkai Hospital were included. On days 3–9 after the initial intravenous administration (under steady-state conditions), venous blood samples were drawn just before the next admin-

Note

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The concentration and 1 and 2 h after the end of the 0.8 ± 0.2 h infusion (maximum 3 points/patients). The blood biochemical test data were obtained from chart data for 1 week before and after the ampicillin-sulbactam sample collection.

**Estimation of Renal Function** The renal function indices for CLcreatin and estimated glomerular filtration rate (eGFR) were calculated using three formulas: CLcreatin was estimated by the Cockcroft–Gault formula (CG) (formula 1-1 for male, 1-2 for female). eGFRcreatin and eGFRcys-c were estimated using serum creatinine (Scr) (formula 2-1 for male, 2-2 for female) and Scr-c (formula 3-1 for male, 3-2 for female), respectively, based on the formulas from the Japanese Society of Nephrology. Body surface area (BSA) was calculated using the DuBois formula.

\[
CL_{\text{creatin}} = (\frac{(140 - \text{age}) \times \text{BW}}{72} \times \text{Scr})
\]  
(1-1)

\[
CL_{\text{creatin}} = (\frac{(140 - \text{age}) \times \text{BW}}{72} \times \text{Scr}) \times 0.85
\]  
(1-2)

\[
eGFR_{\text{creatin}} = (194 \times \text{Scr}^{-0.094} \times \text{age}^{-0.267} \times (\text{BSA}/1.73)
\]  
(2-1)

\[
eGFR_{\text{creatin}} = (194 \times \text{Scr}^{-0.094} \times \text{age}^{-0.267} \times 0.739 \times (\text{BSA}/1.73)
\]  
(2-2)

\[
eGFR_{\text{creatin}} = (104 \times \text{Scr}^{-1.019} \times 0.996^{0.094} - 8) \times (\text{BSA}/1.73)
\]  
(3-1)

\[
eGFR_{\text{creatin}} = (104 \times \text{Scr}^{-1.019} \times 0.996^{0.094} \times 0.929 - 8) \times (\text{BSA}/1.73)
\]  
(3-2)

**Materials** Ampicillin, acetonitrile (AcCN), and monobasic potassium phosphate (K₂HPO₄) were purchased from Nacalai Chemical Co., Inc. Dibasic potassium phosphate (KH₂PO₄) was purchased from Wako Pure Chemical Corporation (Osaka, Japan). Dichloromethane and imidazole were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan).

**Measurement of the Total Concentrations of Ampicillin and Sulbactam in Plasma** The total concentrations of ampicillin and sulbactam in plasma were immediately measured by HPLC with minor modifications of the method described by Martin et al. The analytical column was Mightysil RP-18, 4.6 mm. The UV wavelength for ampicillin was 219 nm, and the mobile phase consisted of 5% acetonitrile and 95% potassium phosphate buffer (0.1 mol/L, pH 4.7). The flow rate was 1.0 mL/min. The lowest detectable concentration of ampicillin was 0.1 µg/mL. For sulbactam, the UV wavelength was 322 nm, and the mobile phase consisted of 1% acetonitrile and 99% potassium phosphate buffer (0.1 mol/L, pH 6.4). The flow rate was 1.0 mL/min. The lowest detectable concentration of sulbactam was 0.1 µg/mL. For ampicillin and sulbactam, the intra- and inter-day accuracy (an absolute value for the relative error of the mean) and precision (the coefficient of variation) were within 10%.

**Pharmacokinetic Analysis** Pharmacokinetic analyses of ampicillin and sulbactam were performed using the MULTI software program. For each drug, total concentration-time data were fitted to a standard one-compartment model with a zero-order input and a first-order elimination. The differential equation was \(\frac{dX}{dt} = -X \times Ke\), where \(X\) was the drug amount in the compartment (mg) and \(Ke\) was the elimination rate constant (h⁻¹). The pharmacokinetic parameters were the volume of distribution (\(Vd\), L), the total clearance (CL, L/h), and the elimination half-life (\(t_{1/2}\)).

**Prediction of the Free Concentration of Ampicillin in Plasma** Based on the means of the estimated \(Vd\) and CL values, the free concentration of ampicillin in plasma was predicted using the MULTI program, where the fraction of plasma protein binding was assumed to be 20% simulated using the pharmacokinetic parameters obtained after ampicillin (1 or 2 g)–sulbactam (0.5 or 1 g) administration via the initial intravenous infusion (1 h). The time that the free drug concentration remained above minimum inhibitory concentration (MIC) values (\(fT > MIC\)) was calculated. For assessing drug concentrations, a value of 1, 2, 4, or 8 µg/mL was employed as a threshold (pharmacodynamic target) for the free concentration of ampicillin in plasma because the MICS of ampicillin–sulbactam for 90% of clinical isolates (MIC90) of methicillin-sensitive Staphylococcus aureus (MSSA), Streptococcus pneumoniae, and Haemophilus influenzae are estimated to be 1, 2, and 4 µg/mL, respectively, in Japan. The \(fT > MIC\) target of ampicillin to achieve good bacterial outcomes is at least 50%.

**RESULTS**

**Patient Characteristics** Patient characteristics are shown in Table 1. All patients were older than 65 years, and the values of eGFRcys-c were 11.0–89.6 (mean 38.6 ± 17.8). A total of 102 points for ampicillin and 105 points for sulbactam plasma concentrations data were used in the pharmacokinetic analysis.

**Correlation between the CL of Ampicillin-Sulbactam and Renal Function** Table 2 gives the PK parameters of ampicillin and sulbactam using plasma samples from the patients. The correlation between the CL of ampicillin or sulbactam and CLcreatin, eGFRcreatin, or eGFRcys-c is shown in Fig. 1. The most strongly correlated renal function index was eGFRcys-c (ampicillin CL vs. eGFRcys-c; \(r = 0.7374\), sulbactam CL vs. eGFRcys-c; \(r = 0.7769\)) (Figs. 1E, F).

**Ampicillin fT > MIC Was Estimated Using Mean Pharmacokinetic Parameters and Different MICS for Dosing Regimens** There was a strong correlation between the ampicillin CL and eGFRcys-c (Fig. 1E). Ampicillin CL was calculated using the correlation formula \((CL = 0.1937 \times eGFRcys-c - 0.6726)\). When eGFRcys-c was 20, 40, or 60 mL/min and \(Vd\) was

\[\text{Table 1. Patient Characteristics}\]

| Sex (male/female) | 21/17 |
|-------------------|-------|
| Age (years)       | 85.7 ± 7.9 (69.0–98.0) |
| Body weight (kg)  | 44.1 ± 8.4 (29.9–68.2) |
| BUN (mg/dL)       | 23.2 ± 14.2 (5.2–69.4) |
| Scr (mg/dL)       | 1.0 ± 0.7 (0.2–4.0) |
| Seys-c (mg/L)     | 1.4 ± 0.5 (0.8–3.0) |
| CLcreatin (mL/min)| 45.1 ± 36.8 (5.9–234.9) |
| eGFRcreatin (mL/min)| 52.7 ± 53.8 (8.5–354.2) |
| eGFRcys-c (mL/min)| 38.6 ± 17.8 (11.0–89.6) |

Number of analyzed points (ampicillin/sulbactam) | 102/105 |

Data are expressed as mean ± standard deviation (S.D.) (range).
19.3 L (Table 2), the ampicillin CL was 3.2, 7.1, or 11.0 mL/min, respectively.

Ampicillin doses of 1 or 2 g every 6, 8, or 12 h administered to patients with 20, 40, or 60 mL/min for eGFRcys-c, mean values for $f_T > MIC$ were simulated (Table 3) using the estimated values of $V_d$ [L] = 19.3 (Table 2) and $CL$ [L/h] = $0.1937 \times eGFRcys-c$ [mL/min]−0.6726 (Fig. 1E). When the MIC was $1 \mu g/mL$, all dosing regimens achieved $\geq 50\%$ of $f_T > MIC$. When the MIC was $2 \mu g/mL$ and the eGFRcys-c was $60 \text{mL/min}$, the $f_T > MIC$ was $48.5\%$ at doses of 1 g every 12 h. When the MIC was $4 \mu g/mL$ and the eGFRcys-c was $60 \text{mL/min}$, the $f_T > MIC$ was $40.1\%$ at a dose of 1 g every 12 h. When the eGFRcys-c was $60 \text{mL/min}$, the $f_T > MIC$ was $\leq 50\%$ at doses of 1 or 2 g every 12 h and doses of 1 g every 8 h.

**DISCUSSION**

Pneumonia is a serious and growing health problem and a common cause of morbidity, mortality, and hospital admission in elderly patients. The Health, Labour and Welfare Ministry found that death from pneumonia and aspiration pneumonitis...
in Japan was almost 6.9 and 2.9%, respectively in 2019. The majority of deaths from pneumonia occur in elderly people, and the rate of patient death from pneumonia will increase because the population in Japan is aging. In guidelines published by the Japanese Society of Chemotherapy, ampicillin-sulbactam is recommended as a first-line therapeutic drug for bacterial pneumonia.\(^{20}\) Therefore, proper use of ampicillin-sulbactam is important, but there are little data about ampicillin-sulbactam dosing regimens in elderly patients who have low renal function.

Creatinine clearance estimated by the Cockcroft–Gault equation\(^ {13}\) is a standard index of renal function in the clinical practice. However, renal clearance estimated by this method may not be accurate in elderly patients. Scys-c concentration is an ideal endogenous marker of renal function and a more sensitive marker of early renal dysfunction in patients with various glomerular diseases.\(^ {1,21,22}\) Therefore, proper use of ampicillin-sulbactam in elderly patients is important, but there are little data about ampicillin-sulbactam dosing regimens in elderly patients who have low renal function.

Table 3. Ampicillin \(\frac{T}{MIC}\) Estimated Using Mean Pharmacokinetic Parameters and Different MICs for Dosing Regimens (1-h Infusions)

| Dose (g) | Dosing interval (h) | eGFRcys-c (mL/min) | \(\frac{T}{MIC}\) > MIC (% of 24h) |
|----------|---------------------|-------------------|---------------------------------|
|          |                     | 1 \(\mu g/mL\)   | 2 \(\mu g/mL\) | 4 \(\mu g/mL\) | 8 \(\mu g/mL\) |
| 1        | 6                   | 99.8              | 99.6               | 99.4             | 99.0          |
| 1        | 8                   | 99.8              | 99.6               | 99.4             | 99.0          |
| 1        | 12                  | 99.8              | 99.6               | 99.4             | 99.0          |
| 2        | 6                   | 99.8              | 99.8               | 99.6             | 99.4          |
| 2        | 8                   | 99.8              | 99.8               | 99.6             | 99.4          |
| 2        | 12                  | 99.8              | 99.8               | 99.6             | 99.4          |

|          |                     | 60                 | 99.8              | 99.6               | 99.4             |
| 1        | 6                   | 88.4              | 72.7               | 56.7             |
| 1        | 8                   | 88.4              | 72.7               | 56.7             |
| 1        | 12                  | 88.4              | 72.7               | 56.7             |
| 2        | 6                   | 99.8              | 99.8               | 99.6             |
| 2        | 8                   | 99.8              | 99.8               | 99.6             |
| 2        | 12                  | 99.8              | 99.8               | 99.6             |

The incidence of side effects due to overdose in elderly patients. The \(\frac{T}{MIC}\) is also recommended as a PK/PD index of ampicillin. It is important to calculate the renal clearance accurately. These data suggest that renal function, estimated by eGFRcys-c, needs to be considered in geriatric patients.

Vancomycin is mainly excreted via the kidney, and therefore optimization of its dose can be estimated by renal function. Vancomycin clearance correlates with Scys-c, especially in elderly patients.\(^ {3,4,27}\) In our study, ampicillin CL was the most correlated with eGFR estimated by Scys-c (ampicillin CL vs. CLcreat \((r = 0.4913)\), eGFRcreat \((r = 0.3333)\), eGFRcys-c \((r = 0.7374)\)) compared with CLcreat or eGFRcreat (Fig. 1). Using the correlation equation calculated by Fig. 1E, we estimated ampicillin CL by eGFRcys-c. An MIC of 1, 2, 4, or 8 \(\mu g/mL\) was employed as a threshold for the free concentration of ampicillin in plasma.\(^ {10}\) According to a previous report on the pharmacokinetic analysis of ampicillin, an MIC >50% in patients with CLcreat 15–30 mL/min and an MIC of 8 \(\mu g/mL\) occurred when 3 g ampicillin/sulbactam was administered 2 times a day.\(^ {12}\) In patients with a CLcreat 30–60 mL/min and an MIC of 8 \(\mu g/mL\) 3 g ampicillin/sulbactam needed to be administered 3 times a day for a MIC >50%.\(^ {12}\) These results were similar to ours, and we also considered two doses of ampicillin (1 and 2 g) to evaluate not only efficacy but also safety for avoiding adverse events.

Scys-c is not frequently measured in Japan because of the health insurance system. However, in an increasing elderly society, accurate estimation of renal function is important. Optimization of the dose and dosing interval for drugs by estimating renal function with Scys-c provides fundamental information for clinical care, and Scys-c can be measured by routine clinical biochemical examination of the blood.

In conclusion, we found that eGFRcys-c was useful to estimate renal function in elderly patients. Furthermore, we developed dosing regimens of ampicillin-sulbactam in elderly patients with various degrees of renal function.

**Author Contributions** Study concept and design: Ms. Kayoko Matsubara, Dr. Kazuaki Matsumoto, Dr. Yuta Yokoyama, Ms. Erika Watanabe, Ms. Akari Shigemi, Dr. Kazuro Ikawa, Dr. Tamao Ohshige, Dr. Yasuo Takeda. Acquisition of data: Ms. Kayoko Matsubara, Dr. Kazuaki Matsumoto, Dr. Yuta Yokoyama, Dr. Kazuaki Ikawa, Dr. Norifumi Morikawa. Preparation of manuscript: Ms. Kayoko Matsubara, Dr. Kazuaki Ikawa, Ms. Erika Watanabe, Dr. Yuki Enoki, Ms. Akari Shigemi, Dr. Kazuho Ikawa, Dr. Hideyuki Terazono, Dr. Norifumi Morikawa, Dr. Tamao Ohshige, Dr. Yasuo Takeda.

**Conflict of Interest** The authors declare no conflict of interest.

**REFERENCES**

1. Dhamnidharka VR, Kwon C, Stevens G. Serum creatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am. J. Kidney Dis.*, 40, 221–226 (2002).

2. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, Grubb A. Cystatin C as a marker of GFR—history, indications, and...
future research. Clin. Biochem., 38, 1–8 (2005).
3) Hermida J, Tutor JC. Serum cystatin C for the prediction of glomerular filtration rate with regard to the dose adjustment of amikacin, gentamicin, tobramycin, and vancomycin. Ther. Drug Monit., 28, 526–331 (2006).
4) Okamoto G, Sakamoto T, Kimura M, Ukishima Y, Sonoda A, Mori N, Kato Y, Maeda T, Kagawa Y. Serum cystatin C as a better marker of vancomycin clearance than serum creatinine in elderly patients. Clin. Biochem., 40, 485–490 (2007).
5) Rafailidis PI, Ioannidou EN, Falagas ME. Ampicillin/sulbactam: current status in severe bacterial infections. Drugs, 67, 1829–1849 (2007).
6) Lode HM. Rational antibiotic therapy and the position of ampicillin/sulbactam. Int. J. Antimicrob. Agents, 32, 10–28 (2008).
7) Ripa S, Ferrante L, Prenna M. Pharmacokinetics of sulbactam/ampicillin in humans after intravenous and intramuscular injection. J. Antimi. Chemother., 36, 185–192 (1990).
8) Foulds G. Pharmacokinetics of sulbactam/ampicillin in humans: a review. Rev. Infect. Dis., 8 (Suppl. 5), S503–S511 (1986).
9) Noguchi JK, Gill MA. Sulbactam: a beta-lactamase inhibitor. Clin. Pharm., 7, 37–51 (1988).
10) USP: UNASYN (ampicillin sodium/sulbactam sodium). U.S. Pharmacopeial Convention, MD, U.S.A. (2012).
11) Benson JM, Nahata MC. Sulbactam/ampicillin, a new beta-lactamase inhibitor/beta-lactam antibiotic combination. Drug Intell. Clin. Pharm., 22, 534–541 (1988).
12) Soto E, Shoji S, Muto C, Tomono Y, Marshall S. Population pharmacokinetics of ampicillin and sulbactam in patients with community-acquired pneumonia: evaluation of the impact of renal impairment. Br. J. Clin. Pharmacol., 77, 509–521 (2014).
13) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron, 16, 31–41 (1976).
14) Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition, 5, 303–311, discussion, 312–303 (1989).
15) Martin C, Cotin A, Giraud A, Beccani-Argeme M, Alliot P, Mallet MN, Argeme M. Comparison of concentrations of sulbactam-ampicillin administered by bolus injections or bolus plus continuous infusion in tissues of patients undergoing colorectal surgery. Antimicrob. Agents Chemother., 42, 1093–1097 (1998).
16) Yamaoka K, Tanigawara Y, Nakagawa T, Uno T. A pharmacokinetic analysis program (multi) for microcomputer. J. Pharmacobiodyn., 4, 879–885 (1981).
17) Shimizu T. Studies on protein binding of cefazolin and other antibiotics. Jpn. J. Antibi., 27, 296–301 (1974).
18) Yanagihara K, Watanabe A, Aoki N, et al. Nationwide surveillance of bacterial respiratory pathogens conducted by the surveillance committee of Japanese Society of Chemotherapy, the Japanese Association for Infectious Diseases, and the Japanese Society for Clinical Microbiology in 2012: general view of the pathogens’ antibacterial susceptibility. J. Infect. Chemother., 23, 587–597 (2017).
19) Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. Clin. Infect. Dis., 36 (Suppl. 1), S42–S50 (2003).
20) Mikasa K, Aoki N, Aoki Y, Abe S, Iwata S, Ouchi K, Kasahara K, Kadota J, Kishida N, Kobayashi O, Sakata H, Seki M, Tsukada H, Tokue Y, Nakamura-Uchiyama F, Higa F, Maeda K, Yanagihara K, Yoshida K. JAID/JSC guidelines for the treatment of respiratory infectious diseases: the Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy-The JAID/JSC guide to clinical management of infectious disease/guideline-preparing committee respiratory infectious disease WG. J. Infect. Chemother., 22 (Suppl.), S1–S65 (2016).
21) Finney H, Bates CJ, Price CP. Plasma cystatin C determinations in a healthy elderly population. Arch. Gerontol. Geriatr., 29, 75–94 (1999).
22) Wasen E, Isoaho R, Mattila K, Vahlberg T, Kivela SL, Irijala K. Estimation of glomerular filtration rate in the elderly: a comparison of creatinine-based formulae with serum cystatin C. J. Intern. Med., 256, 70–78 (2004).
23) Meyers BR, Wilkinson P, Mendelson MH, Walsh S, Bourouzas C, Hirschman SZ. Pharmacokinetics of ampicillin-sulbactam in healthy elderly and young volunteers. Antimicrob. Agents Chemother., 35, 2098–2101 (1991).
24) Rho JP, Jones A, Woo M, Castle S, Smith K, Bawdon RE, Norman DC. Single-dose pharmacokinetics of intravenous ampicillin plus sulbactam in healthy elderly and young adult subjects. J. Antimicrob. Chemother., 24, 573–580 (1989).
25) Majcher-Peszynska J, Loebermann M, Klammt S, Frimmel S, Mundkowski RG, Welte T, Reisinger EC, Drewelow B. Ampicillin/sulbactam in elderly patients with community-acquired pneumonia. Infection, 42, 79–87 (2014).
26) Imanishi K, Nakakura I, Miyabe T, Sako R, Yamauchi K. Comparison of safety between high and low doses of sulbactam/ampicillin: a retrospective observational study in Japanese patients with pneumonia. J. Infect. Chemother., 26, 1152–1157 (2020).
27) Suzuki A, Imanishi Y, Nakano S, Niwa T, Ohmori T, Shirai K, Yoshida S, Furuta N, Takemura M, Ito H, Ieiri I, Seishima M, Ogura S, Itoh Y. Usefulness of serum cystatin C to determine the dose of vancomycin in critically ill patients. J. Pharm. Pharmacol., 62, 901–907 (2010).