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

Abbreviated Title: PK of Ceftolozane/Tazobactam in Renal Impairment

Myra Wooley, Benjamin Miller, Gopal Krishna, Ellie Hershberger, and Gurudatt Chandorkar

Cubist Pharmaceuticals, Lexington, Massachusetts, USA

# Address correspondence to Myra Wooley, myra.wooley@cubist.com
Ceftolozane/tazobactam is a novel antipseudomonal cephalosporin/β-lactamase inhibitor. We investigated the pharmacokinetics (PK) and safety of ceftolozane/tazobactam in subjects with varying degrees of renal function. In two phase I, open-label studies, a single dose of ceftolozane/tazobactam was administered as a 1-h intravenous infusion to 24 subjects with normal, mild, or moderate renal impairment (1,000 mg/500 mg) and six subjects with severe renal impairment (500 mg/250 mg). Six subjects with end-stage renal disease (ESRD) received two doses of ceftolozane/tazobactam (500 mg/250 mg), pre- and post-hemodialysis (HD). PK parameters were determined by non-compartmental methods. Plasma exposure to ceftolozane/tazobactam increased as renal function declined with exposures only slightly increased in subjects with mild renal impairment; median area under the concentration-time curve (AUC$_{0-\infty}$) for ceftolozane and tazobactam increased 1.4- and 1.2-fold, respectively. In subjects with moderate renal impairment, AUC$_{0-\infty}$ increased 2.5- and 2.2-fold for ceftolozane and tazobactam, respectively. In subjects with severe renal impairment, the dose-normalized median AUC$_{0-\infty}$ for ceftolozane and tazobactam increased 4.4- and 3.8-fold, respectively. In ESRD subjects, ceftolozane and tazobactam concentrations declined rapidly following the start of HD with approximately 66% and 56% reductions in overall exposure based on the AUC$_{0-\infty}$ before and after dialysis. Slight increases in exposure with mild renal impairment do not warrant a dose adjustment; however, subjects with moderate and severe renal impairment and those on HD require a decrease in dose, change in frequency, or both, to achieve exposures...
within the established safety and efficacy margins of ceftolozane/tazobactam.  

Ceftolozane/tazobactam was well tolerated in all renal impairment groups.
INTRODUCTION

Ceftolozane/tazobactam is a novel antibacterial with activity against *Pseudomonas aeruginosa*, including drug-resistant strains, and other common Gram-negative pathogens including most extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (1,2). Ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins, resulting in inhibition of cell-wall synthesis and subsequent cell death (Cubist Pharmaceuticals. Data on file. 2009). Tazobactam, an inhibitor of most class A β-lactamases and some class C β-lactamases, protects ceftolozane from hydrolysis and broadens coverage to include most ESBL-producing Enterobacteriaceae (Cubist Pharmaceuticals. Data on file. 2006; 2013).

The pharmacokinetics (PK) of ceftolozane/tazobactam in patients with normal renal function are linear across a wide range of doses (up to 3,000 mg/1,500 mg as a single dose). Terminal elimination half-lives ($t_{1/2}$) are approximately 2.5 h for ceftolozane and 1 h for tazobactam. Both compounds exhibit low protein binding (approximately 20% for ceftolozane and 30% for tazobactam) and are primarily excreted in the urine; ceftolozane as unchanged parent drug suggesting minimal metabolism, and tazobactam with 80% as the unchanged parent drug and the remaining as inactive M1 metabolite (Cubist Pharmaceuticals. Data on file. 2004) (3,4). In the present studies, the PK and safety of ceftolozane/tazobactam were investigated in subjects with varying degrees of renal function, including subjects with end-stage renal disease (ESRD) on hemodialysis (HD).
MATERIALS AND METHODS

Study populations. Male and female subjects, aged 18 to 79 years, with varying degrees of renal function were enrolled in two, prospective, open-label, phase I studies of intravenous ceftolozane/tazobactam. A total of 36 subjects were enrolled into cohorts based on degree of renal function: normal ($n = 11$), mild impairment ($n = 6$), moderate impairment ($n = 7$), severe impairment ($n = 6$), and ESRD on HD ($n = 6$). To ensure subjects with ESRD were receiving effective HD, a target adequacy of HD calculated from the pre- and post-blood urea nitrogen ratios (Kt/V) of at least 1.2 for a minimum of 3 months prior to enrollment was required. Renal impairment groups were classified according to the 2010 U.S. Food and Drug Administration draft guidance using creatinine clearance (CrCl) estimated by the Cockcroft–Gault formula (normal impairment, >90 ml/min; mild impairment, 60 to 89 ml/min; moderate impairment, 30 to 59 ml/min; and severe impairment, 15 to 29 ml/min, ESRD <15 ml/min) (5).

Dosing/design. All cohorts received ceftolozane/tazobactam as an intravenous infusion over 1 h. The normal, mild, and moderate renal impairment cohorts received a single dose of ceftolozane/tazobactam 1,000 mg/500 mg; the severe renal impairment cohort received a single dose of ceftolozane/tazobactam 500 mg/250 mg; the ESRD cohort received a dose of ceftolozane/tazobactam 500 mg/250 mg initiated at the end of HD on day 1 and another dose initiated 2 h before HD on day 4. Subjects with ESRD underwent HD for 3 to 4 h using a high-flux membrane as scheduled; average dialysis flow rate was 600 to 800 ml/min. Revaclear hemodialyzers (Gambro, Stockholm, Sweden) were used in 5 subjects (ultrafiltration coefficient 50 to 60 ml/h/mmHg, high flux membrane of 1.4 to 1.8 m²) and a CT 190G hemodialyzer (Baxter Healthcare,
McGaw Park, IL) was used in 1 subject (ultrafiltration coefficient 36 ml/h/mmHg, high flux membrane of 1.9 m²). The average blood flow rate was 400 to 600 ml/min with the exception of one subject with rates between 264 and 400 ml/min.

**Pharmacokinetic evaluations.** Plasma concentrations of ceftolozane and tazobactam were measured prior to, during, and following administration of ceftolozane/tazobactam. Blood samples were collected 30 min prior to administration, at the end of administration and at 5, 15, and 30 min and 1, 2, 3, 5, 7, 9, 11, 15, 25, and 35 h after completion of ceftolozane/tazobactam administration in the normal, mild, and moderate renal impairment cohorts. Severe renal impairment and ESRD cohorts off HD had samples taken 30 min prior to administration and at 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24, 36, and 48 h after the start of administration. On the day of and following HD, the subjects with ESRD had samples taken 30 min prior to administration and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 36, and 44 h after the start of the administration. The entire dialysate was collected at each of the following intervals: 0 to 1, 1 to 2, 2 to 3, and 3 h to the end of dialysis. Urine for PK analysis was obtained in the normal, mild, and moderate cohorts at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 36 h after the start of ceftolozane/tazobactam administration. In the ESRD and severe renal impairment cohorts, urine was collected during the confinement period pre-dose, 0 to 24 h, and 24 to 48 h after the start of the administration, unless the subject was anuric. A validated LC/MS/MS method was utilized to analyze all plasma, urine, and dialysate samples for ceftolozane and tazobactam (MicroConstants Inc, San Diego, CA) (4). The lower limit of quantification (LLOQ) in plasma was 0.25 μg/ml for ceftolozane and 0.1 μg/ml for tazobactam. The assay was linear between 0.25 and 150 μg/ml for ceftolozane and
between 0.1 and 50 μg/ml for tazobactam. The precision of the assay for ceftolozane and tazobactam ranged between 3.13 and 7.97% while the accuracy was ±1 and ±6.25%, respectively. The LLOQ in dialysate for both ceftolozane and tazobactam was 1 ng/ml and the assay was linear between 1 and 500 ng/ml. The precision of the assay in dialysate samples for ceftolozane and tazobactam ranged between 1.28 and 9.18% while the accuracy for ceftolozane and tazobactam was ±8.3 and ±9.67%, respectively. The LLOQ for ceftolozane and tazobactam in urine was 5 and 10 μg/ml, respectively, and the assay was linear between 5 and 5,000 μg/ml for ceftolozane and between 10 and 10,000 μg/ml for tazobactam. The precision of the assay for ceftolozane and tazobactam ranged between 3.71 and 9.06% while the accuracy was ±9.20 and 7.33%, respectively.

Pre-dose values below the LLOQ values were set to zero and all missing values below the LLOQ obtained after the first quantifiable concentration were designated as missing and not included in the analysis. The maximum plasma concentration (C_{max}) and plasma concentration when the last quantifiable concentration was observed relative to the end of infusion (C_{last}) were taken directly from concentration-time data. Terminal elimination t_{1/2} was calculated as 0.693/λ_z where λ_z is the terminal elimination rate constant, estimated by regression of the terminal log-linear phase of the plasma concentration versus time curve. Area under the plasma concentration time curve (AUC) from time zero to the last measurable concentration (AUC_{0-t}) was calculated using the linear trapezoidal rule. The AUC extrapolated to infinity (AUC_{0-∞}) was estimated using the formula AUC_{0-last} + (C_{last}/λ_z) using the linear trapezoidal rule. Total body clearance from plasma (CL) was calculated as dose/AUC_{0-∞}. Volume of
distribution at steady-state \((V_{ss})\) was calculated as mean residence time\(*CL\). Renal clearance \((CL_r)\) in subjects that provided urine samples was calculated from the equation \(CL_r = A_e/AUC_{0-\infty}\) where \(A_e\) is the cumulative amount of drug recovered in the urine during the sampling period. Dialysis clearance was calculated as the amount of ceftolozane or tazobactam recovered in dialysate divided by AUC from the time of the second dose to the end of HD \((AUC_{(t_0-t_1)})\). The rate of decrease in plasma concentration \((RDHD)\) was calculated from the difference between the concentration at the end of dialysis \((C_2)\) and the concentration at the beginning of HD \((C_1)\). The percent reduction was calculated using the equation \(RDHD = 100\*\frac{(C_1-C_2)}{C_1}\). Extraction ratio was calculated as \(100\*\frac{(C_A - C_V)}{C_A}\) where \(C_A\) and \(C_V\) are pre- and post-dialyzer paired drug concentrations at the arterial and venous sites. Total effective removal was calculated with individual \(AUC_{0-\infty}\) values as \((AUC_{off-HD} - AUC_{on-HD})\) divided by \(AUC_{off-HD}\) (6). Dialysis clearance \((CL_D)\) was calculated as amount of drug in dialysate divided by \(AUC_{(t_0-t_1)}\).

The PK parameters were calculated by non-compartmental analysis using Phoenix WinNonlin version 6.1 (Pharsight Corporation, Mountain View, CA).

**Safety monitoring.** Safety was assessed by monitoring for adverse events \((AEs)\) from the first dose of drug through the last study evaluation, and by review of vital signs, physical examinations, 12-lead electrocardiograms, and clinical laboratory evaluations.

**RESULTS**

**Demographics and disposition.** A total of 36 subjects received ceftolozane/tazobactam. No subjects withdrew consent or discontinued due to an AE, and all subjects were included in the PK and safety analyses. The demographic
characteristics of the subjects are presented in Table 1. The majority were white, except in the ESRD cohort in whom five of the six subjects were black or African American. Subjects ranged in age from 40 to 79 years with a median age of 62 years.

Pharmacokinetic summary

Normal renal function and mild, moderate, and severe renal impairment. Compared with subjects with normal renal function, the concentration-time profiles of ceftolozane/tazobactam were increasingly altered in subjects with increasingly impaired renal function (Fig.1A and 1B). Pharmacokinetic parameters are summarized in Table 2 and Table 3 for ceftolozane and tazobactam, respectively. Ceftolozane and tazobactam plasma clearance by CrCl are provided in Fig. 2A and 2B, respectively. Exposure (AUC_{0-\infty} and C_{\text{max}}) was similar in subjects with normal renal function and mild renal impairment following a single ceftolozane/tazobactam 1,000 mg/500 mg dose as was \( t_{\frac{1}{2}} \). In subjects with moderate renal impairment, decreases in clearance led to increased ceftolozane and tazobactam exposure compared with subjects with normal renal function with median AUC_{0-\infty} and C_{\text{max}} increased for ceftolozane (2.5- and 1.2-fold, respectively) and tazobactam (2.2- and 1.6-fold, respectively). In subjects with severe renal impairment, the median AUC_{0-\infty} and C_{\text{max}} increased 4.4- and 1.3-fold for ceftolozane and 3.8- and 1.9-fold for tazobactam, respectively, compared with the dose-normalized exposure in the normal renal function group.

End-stage renal disease on hemodialysis. Median concentration-time profiles for ceftolozane and tazobactam in subjects with ESRD post-HD and on HD are shown in Fig. 3A and 3B, respectively. The PK parameters of ceftolozane and tazobactam...
differed substantially in subjects with ESRD compared with the other renal impairment
groups. Pharmacokinetic parameters are summarized in Table 2 and Table 3 for
ceftolozane and tazobactam, respectively. The median elimination \( t_{1/2} \) of ceftolozane
and tazobactam in subjects with ESRD during non-HD was prolonged and the median
\( C_{\text{max}} \) in plasma was 1.2- and 2.4-fold higher compared with subjects with normal renal
function when dose normalized. The \( t_{1/2} \) during the HD period for ceftolozane and
tazobactam were 1.13 and 0.91 h, respectively. The extraction ratios at 1 h and 2 h after
the start of HD and at end of HD for ceftolozane and tazobactam were 42, 48, and 47%
and 48, 54, and 55%, respectively. The average extraction ratio during HD was 46%
(±16) for ceftolozane and 53% (±22) for tazobactam. Ceftolozane and tazobactam
concentrations declined rapidly following the start of HD with approximately 66 and 56%
reductions in overall exposure to ceftolozane and tazobactam, respectively, based on
the \( \text{AUC}_{0-\infty} \) on and off HD. The median RDHD for ceftolozane and tazobactam was 92
and 95%, respectively, indicating significant removal by HD; however, in the period
following HD, plasma concentrations rebounded and peaked at approximately 17 and
6% of the original \( C_{\text{max}} \) of ceftolozane and tazobactam, respectively. The median \( CL_D \)
for ceftolozane and tazobactam was 5.75 and 4.39 liter/h, respectively.

**Safety.** Overall, seven of the 36 subjects experienced a total of 12 AEs. The most
common AE reported was headache in three subjects. All events reported were mild in
severity with the exception of one event of moderate headache in a subject with normal
renal function. Two subjects with normal renal function and one subject with mild renal
impairment reported the AE of headache. Diarrhea, infusion-site hemorrhage, and
injection-site hemorrhage were reported in one subject each in the mild impairment
group. Flatulence, glossodynia, myalgia, and vulvovaginal pain were reported in one subject each in the ESRD on HD group. No AEs were reported in the moderate or severe renal impairment groups. One serious AE of thrombosis of an arteriovenous fistula was reported in a subject with ESRD on HD 7 days after the last dose of the study drug. No subjects withdrew due to AEs. Review of clinical laboratory values, physical examination, and vital signs showed no meaningful changes from baseline.

**DISCUSSION**

Hospitalized patients with serious Gram-negative infections and impaired renal function are commonly encountered but represent a challenge for the treating clinician when prescribing antibacterials that primarily undergo renal elimination. It is important to ensure that renally impaired patients are not exposed to excessive drug concentrations, and that PK/pharmacodynamic (PD) targets predictive of favorable outcomes are achieved. This is further complicated when using a combination antibacterial such as ceftolozane/tazobactam. The therapeutic efficacy of cephalosporins has been shown to be correlated with the percentage of time during the dosing interval that the plasma drug concentration exceeds the MIC for the target organism (%T>MIC). A range of 20 to 75% T>MIC is most commonly reported for cephalosporin efficacy, depending on the cephalosporin evaluated, the disease under study, and the efficacy outcome measure (7-9). Similarly, the PD driver for tazobactam is thought to be the percentage of time above a threshold concentration (%T> threshold), which may be isolate or enzyme dependent (10). The median %T>MIC required for ceftolozane to achieve bacteriostasis and 1-log\(_{10}\) kill against Gram-negative bacilli is 24.8% and 32.2%, respectively (11). Renal impairment increases the %T>MIC for renally cleared antibiotics such as
ceftolozane/tazobactam. For this reason, appropriate dosing regimens in patients with renal impairment are imperative to minimize potential toxicity related to drug accumulation while maintaining the desired PK/PD index predictive of clinical efficacy (12).

These studies indicate that renal impairment substantially affected the clearance, AUC$_{0-\infty}$, and $t_{1/2}$ of both ceftolozane and tazobactam. The dose normalized C$_{max}$ of tazobactam was influenced across renal impairment groups and the V$_{ss}$ was affected in ESRD subjects while on HD. Minimal impact of renal impairment on the ceftolozane V$_{ss}$ and dose-normalized C$_{max}$ was observed (1.1- to 1.3-fold changes compared with normal renal function), with the exception of a 3.7-fold change in V$_{ss}$ in the ESRD subjects while on HD. Due to the limitations of the 48-h sampling period, ceftolozane $t_{1/2}$ in the ESRD cohort was calculated based on data from only one half-life period and thus may not represent the true terminal phase $t_{1/2}$ for ceftolozane in the ESRD cohort. Although the presence of renal impairment affected both ceftolozane and tazobactam, the data indicate that the effect was marginally less for tazobactam than for ceftolozane.

Renal clearance of ceftolozane indicates that between 70 and 90% of the administered dose was recovered in the urine in subjects with normal renal function and in subjects with varying degrees of renal impairment. However, the data in subjects with severe renal impairment should be interpreted with caution as urine sampling was conducted for approximately one half-life and was not adequate to have full recovery of the drug in the urine due to the prolonged ceftolozane $t_{1/2}$ of 40.5 h. Similarly, for tazobactam, the renal clearance of between 70 and 80% in subjects with normal renal function and subjects with mild, moderate, and severe renal impairment is consistent with...
with previous observations (3). A lower observed renal clearance in subjects with severe renal impairment is likely due to a greater conversion of tazobactam to the inactive M1-metabolite.

The PK parameters of ceftolozane/tazobactam were influenced substantially in subjects with ESRD on HD with almost 90% of the initial plasma concentration being removed during the 3- to 4-h HD session. Although a large proportion of ceftolozane/tazobactam was initially removed during HD, the AUC₀₋∞ suggests that a slow redistribution of ceftolozane/tazobactam into the plasma occurred following HD. The AUC₀₋∞ values show that the total effective removal of ceftolozane and tazobactam was 66 and 56%, respectively. The calculated CL₀ should be considered an approximation. In three subjects, the cumulative amounts of ceftolozane recovered in the dialysate were greater than the administered dose. This can be due to carryover from the previously administered dose on day 1 and incomplete collection of the dialysate.

Overall, our findings are similar to prior published data in a study of piperacillin/tazobactam PK in subjects with varying degrees of renal impairment. The changes in tazobactam t₁/₂ and plasma clearance are consistent with those previously described (13). In ESRD subjects, the 2.3-fold change in tazobactam Cₘₐₓ with ceftolozane/tazobactam in our study differed from the 1.6-fold change observed with piperacillin/tazobactam. Additionally, with ceftolozane/tazobactam, the Vₕₜ of tazobactam observed in ESRD subjects while on HD was more pronounced (1.9-versus 1.1-fold change). The removal of tazobactam by HD when administered as ceftolozane/tazobactam in the present study (56%) is consistent with the 52% removal
reported when administered as piperacillin/tazobactam (13). Additionally, our findings are similar to the piperacillin/tazobactam prescribing information with 45% removal by HD (40% as tazobactam and 5% additionally removed as the tazobactam metabolite) (3).

Ceftolozane/tazobactam was generally well tolerated in patients with renal impairment. Adverse events were mild to moderate in severity. In this single-dose study, there was no apparent difference in the incidence or severity of AEs between subjects with renal impairment and subjects with normal renal function. Despite the increase in overall exposure to ceftolozane/tazobactam observed in subjects with mild, moderate, or severe renal impairment and in subjects with ESRD during non-HD days, no major safety concerns were identified following a single dose.

In summary, the exposure to ceftolozane/tazobactam in subjects with mild renal impairment was increased relative to that in normal controls, but the increase was small and not clinically meaningful, suggesting that no dose adjustment is necessary in this population. However, data from these phase I studies suggest that a decrease in dose or frequency of administration, or both, is necessary in those with moderate or severe renal impairment, or with ESRD. Data from these studies along with population PK data from patients will be utilized in PK/PD modeling and simulations. The models will take into account the probability of target attainment for different dosing regimens in patients with varying degrees of renal impairment. Final dosing recommendations for patients with moderate and severe renal impairment and for patients with ESRD on HD will be derived following evaluation of exposure–efficacy and exposure–safety relationships.
ACKNOWLEDGMENTS

Parts of these analyses were presented at the Joint Meeting of the European Congress of Clinical Microbiology and Infectious Diseases and International Congress of Chemotherapy (ECCMID-ICC 2011); May 7–12, 2011; Milan, Italy; Poster 1519 and at IDWeek, October 2–6, 2013; San Francisco, USA; Poster 723. We thank MicroConstants for the bioanalytical analyses and Pharsight for the PK analyses. Editorial support was provided by PAREXEL and funded by Cubist Pharmaceuticals. The studies were funded by Cubist Pharmaceuticals, Lexington, Massachusetts. M.W., B.M., G.K., E.H., and G.C. are employees of Cubist Pharmaceuticals.
REFERENCES


Figure Legends

**FIG 1** Median (range) plasma concentration-time profiles of [A] ceftolozane and [B] tazobactam following single-dose administration of intravenous ceftolozane/tazobactam (semi-log plot). \(^{a}\)C/T, ceftolozane/tazobactam. \(^{b}\)RI, renal impairment.

**FIG 2** Regression plot of [A] ceftolozane and [B] tazobactam plasma clearance versus CrCl following single-dose administration of intravenous ceftolozane/tazobactam. \(^{a}\)C/T, ceftolozane/tazobactam. \(^{b}\)RI, renal impairment.

**FIG 3** Median (range) plasma concentration-time profiles of ceftolozane and tazobactam following administration of intravenous ceftolozane/tazobactam (500 mg/250 mg) in subjects with ESRD on [A] day 1 (post-HD) and [B] day 4 (on HD) (semi-log plot).
## TABLE 1 Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal (n = 11)</th>
<th>Mild RI&lt;sup&gt;a&lt;/sup&gt; (CrCl&lt;sup&gt;b&lt;/sup&gt; ≥ 60 to &lt;90 ml/min) (n = 6)</th>
<th>Moderate RI (CrCl ≥ 30 to &lt;60 ml/min) (n = 7)</th>
<th>Severe RI (CrCl &lt;30 ml/min) (n = 6)</th>
<th>ESRD (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females, n (%)</td>
<td>5 (45.5)/6 (54.5)</td>
<td>2 (33.3)/4 (66.7)</td>
<td>3 (42.9)/4 (57.1)</td>
<td>1 (16.7)/5 (83.3)</td>
<td>4 (66.7)/2 (33.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (90.9)</td>
<td>4 (66.7)</td>
<td>5 (71.4)</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (9.1)</td>
<td>0</td>
<td>2 (28.7)</td>
<td>1 (16.7)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>2 (33.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>61.5 (7.1)</td>
<td>72.3 (7.8)</td>
<td>65.6 (18.7)</td>
<td>66.2 (6.7)</td>
<td>50.0 (11.1)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>84.1 (10.2)</td>
<td>65.4 (15.4)</td>
<td>83.9 (22.6)</td>
<td>65.3 (13.9)</td>
<td>83.4 (31.9)</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;, mean (SD)</td>
<td>28.6 (2.7)</td>
<td>24.9 (12.7)</td>
<td>29.8 (18.9)</td>
<td>25.5 (5.8)</td>
<td>28.9 (7.7)</td>
</tr>
<tr>
<td>Estimated CrCl, ml/min, mean (SD)</td>
<td>118.0 (19.7)</td>
<td>70.6 (15.1)</td>
<td>43.6 (14.9)</td>
<td>21.5 (2.3)</td>
<td>NA&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> RI, renal impairment.

<sup>b</sup> CrCl estimated by the Cockcroft–Gault formula.

<sup>c</sup> BMI, body mass index.

<sup>d</sup> NA, not applicable.
### TABLE 2

Median pharmacokinetic values for ceftolozane following single-dose administration of intravenous ceftolozane/tazobactam

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Normal (n = 11)</th>
<th>Mild RI (n = 6)</th>
<th>Moderate RI (n = 7)</th>
<th>Severe RI (n = 6)</th>
<th>ESRD (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, µg/ml</td>
<td>3.1 (2.4–3.6)</td>
<td>3.3 (2.9–3.8)</td>
<td>5.6 (2.9–10.8)</td>
<td>11.1 (7.7–14.9)</td>
<td>40.5 (20.8–58.1)</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>4.3 (3.2–6.2)</td>
<td>3.2 (2.9–3.9)</td>
<td>1.7 (1.1–3.3)</td>
<td>1.0 (0.7–1.2)</td>
<td>0.7 (0.5–1.0)</td>
</tr>
<tr>
<td>CL, liter/h</td>
<td>14.6 (8.9–24.7)</td>
<td>12.3 (9.2–13)</td>
<td>13.9 (10.6–18.6)</td>
<td>12.5 (11.3–20.4)</td>
<td>17.9 (11.9–31.7)</td>
</tr>
<tr>
<td>Vss, liter</td>
<td>40.5 (20.8–58.1)</td>
<td>43.2 (32.8–56.9)</td>
<td>44.2 (30.2–60.6)</td>
<td>41.1 (17.5–56.4)</td>
<td>1629 (466–2750)</td>
</tr>
</tbody>
</table>

- C/T, ceftolozane/tazobactam.
- The $t_{1/2}$ on HD was calculated from the terminal elimination phase post HD.
- Incomplete urine recovery over 48 h.
- ND, not determined. As a majority of the subjects with ESRD were anuric CL, could not be determined.
<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Normal ( (n = 11) )</th>
<th>Mild RI ( (n = 6) )</th>
<th>Moderate RI ( (n = 7) )</th>
<th>Severe RI ( (n = 6) )</th>
<th>ESRD ( (n = 6) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2}, \text{ h} )</td>
<td>1.1 (0.8–1.6)</td>
<td>1.1 (0.9–1.6)</td>
<td>1.8 (1.4–2.2)</td>
<td>2.5 (1.9–3.3)</td>
<td>4.2 (3.4–9.1)</td>
</tr>
<tr>
<td>( C_{\text{max}}, \mu g/ml )</td>
<td>17.0 (14.7–31.4)</td>
<td>21.9 (18.9–28.3)</td>
<td>27.1 (23.3–28.7)</td>
<td>16.3 (10.2–18.3)</td>
<td>20.2 (15.9–30.3)</td>
</tr>
<tr>
<td>( AUC_{0-i}, \mu g*h/ml )</td>
<td>29.8 (21.6–40.1)</td>
<td>34.4 (28.9–43.1)</td>
<td>65.3 (48.9–91.2)</td>
<td>53.7 (34.2–68.1)</td>
<td>107 (45.3–169)</td>
</tr>
<tr>
<td>( AUC_{0-\infty}, \mu g*h/ml )</td>
<td>30.1 (21.7–40.4)</td>
<td>34.7 (29.1–43.4)</td>
<td>65.9 (49.1–91.9)</td>
<td>56.5 (35.8–70.9)</td>
<td>109 (46.0–170)</td>
</tr>
<tr>
<td>( CL, \text{ liter/h} )</td>
<td>16.6 (12.4–23.0)</td>
<td>14.4 (11.5–17.2)</td>
<td>7.6 (5.4–10.2)</td>
<td>4.4 (3.5–7.0)</td>
<td>2.4 (1.5–5.4)</td>
</tr>
<tr>
<td>( CL_{r}, \text{ liter/h} )</td>
<td>12.0 (9.2–14.9)</td>
<td>10.2 (9.4–15.9)</td>
<td>5.3 (3.2–7.6)</td>
<td>1.6 (1.2–2.9)</td>
<td>ND</td>
</tr>
<tr>
<td>( V_{ss}, \text{ liter} )</td>
<td>19.9 (13.8–26.1)</td>
<td>16.0 (12.7–22.0)</td>
<td>16.8 (13.9–21.1)</td>
<td>15.7 (12.2–23.5)</td>
<td>15.2 (11.5–27.1)</td>
</tr>
</tbody>
</table>

\( a \) The \( t_{1/2} \) on HD was calculated from the terminal elimination phase post HD.