Ertapenem Pharmacokinetics and Pharmacodynamics during Continuous Ambulatory Peritoneal Dialysis

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Scant data exist for the pharmacokinetics (PK) of ertapenem in patients on continuous ambulatory peritoneal dialysis (CAPD). The goals of this study were to characterize the PK profile of ertapenem during CAPD, determine the extent of ertapenem penetration into the peritoneal cavity, and quantify the probability of the target attainment (PTA) profile in the serum and peritoneal cavity. A single-dose PK study was conducted in seven patients on CAPD. Population PK modeling and Monte Carlo simulation determined the probability that ertapenem at 500 mg intravenously (i.v.) every 24 h (q24h) would achieve concentrations in excess of the MIC for 40% of the dosing interval (40% T>MIC, where T is time) in the serum and peritoneal cavity. Monte Carlo simulation was also used to calculate the peritoneal cavity/serum mean and median penetration ratios by estimating the area under the concentration-time curve in the peritoneal cavity and serum (AUCPeritoneal/AUCSerum, respectively) from zero to infinity after a single simulated dose. The population mean (± standard deviation [SD]) values for the apparent volume in the central compartment, clearance, and apparent volume in the peritoneal cavity were 2.78 (0.62) liters, 0.24 (0.07) liters/hr, and 5.81 (2.05) liters, respectively. The mean (SD) AUCPeritoneal/AUCSerum ratio was 1.039 (0.861), and the median penetration ratio was 0.801 (interquartile range, 0.486 to 1.317). In both the serum and peritoneal cavity, ertapenem at 500 mg i.v. q24h was very likely (>90%) to achieve the pharmacodynamic target for MICs of ≤2 mg/liter. The simulations suggest that 500 mg of ertapenem i.v. q24h is very likely to achieve the exposure target associated with clinical efficacy in both the serum and peritoneal cavity against the range of MIC values deemed susceptible by the Clinical and Laboratory Standards Institute.

Despite advances in technology, systemic and peritoneal infections are still problematic for patients on peritoneal dialysis (PD) (25–27). Over the past 15 years, hospital admissions due to bloodstream infections among patients receiving PD have doubled (27). While there has been a decline in the incidence of infection due to Gram-positive organisms, infection rates due to bacteria in the Enterobacteriaceae family have remained steady or increased (3, 14, 15, 25). Currently, Enterobacteriaceae account for approximately one-quarter of all peritonitis cases, often leading to catheter removal, technique failure, hospitalization, and premature death (11, 25).

While aminoglycosides and broad-spectrum cephalosporins are considered the mainstays of therapy for infections secondary to Enterobacteriaceae among patients on PD, concerns exist regarding toxicity and resistance (15). Specifically, aminoglycosides are used cautiously due to the higher potential for both oto- and nephrotoxicity relative to the other drug classes. Empirical use of broad-spectrum cephalosporins has also been compromised by the emergence of enteric Gram-negative infections harboring extended-spectrum beta-lactamas (ESBLs) and hyperproducing AmpC beta-lactamas (1, 12, 21, 23, 24).

Due to its broad-spectrum activity, ertapenem, a 1-beta-methyl carbapenem, represents an attractive option for infections among patients receiving PD. In contrast to the broad-spectrum cephalosporins, it is active against ESBLs and enteric Gram-negative organisms that hyperproduce AmpC beta-lactamas (10). Several recent large-scale surveillance studies found ertapenem to be highly active against all species of Enterobacteriaceae, even organisms resistant to broad-spectrum cephalosporins (28). In addition to this favorable spectrum of activity, its once-daily dosing offers a convenient therapeutic option for PD patients receiving care in the ambulatory setting (19).

While ertapenem pharmacokinetic (PK) parameters are well described in the general population, there are scant data on the PK properties of ertapenem in patients receiving renal replacement therapies (4, 20). To date, there are no published studies evaluating the PK of ertapenem during PD, a dialysis modality used by 26,000 patients in the United States (27). The objectives of this study were the following: (i) to characterize the PK profile of ertapenem during continuous ambulatory peritoneal dialysis (CAPD), (ii) to determine the extent of ertapenem penetration in the peritoneal cavity following intravenous administration, and (iii) to quantify the probability of target attainment profile of an ertapenem dose of 500 mg administered intravenously (i.v.) daily in both serum and the peritoneal cavity.

MATERIALS AND METHODS

This prospective, single-dose PK study of intravenous ertapenem in non-infected patients on CAPD was conducted at an outpatient dialysis clinic (Hortense and Louis Rubin Dialysis Center, Clifton Park, NY). The study was approved by the Institutional Review Board at the Albany College of Pharmacy and Health Sciences. All patients provided written informed consent.
The study was conducted in accordance with the Declaration of Helsinki.

**Study patients.** Adult (≥18 years), noninfected patients (afebrile, lack of constitutional symptoms, and no leukocytosis) on a stable PD regimen for at least 1 month, with or without residual kidney function, were eligible for participation. Patients with residual renal function prescribed medications with the potential to inhibit active tubular secretion (e.g., cimetidine, trimethoprim, or probenecid) were entered into the study only after a 2-week washout period. Patients were excluded if they had peritonitis within the previous 4 weeks, had clinical signs or symptoms of active infection, had an elevated white blood cell count, received treatment with any antibiotic during the previous 2 weeks, had hemoglobin concentrations of <11 g/dl, had stated or documented allergies to beta-lactam medications, were taking valproic acid, or were pregnant or breastfeeding.

**Dialysis prescription.** Eligible patients received a standardized CAPD prescription of four daily exchanges with 2 liters of 2.5% dextrose dialysate, having daily dwell periods of 6 h, 4 h, 6 h, and 8 h, beginning 3 to 7 days prior to the ertapenem administration day.

**Study procedure.** On the study day, patients arrived at the dialysis clinic, and for each patient the peritoneal cavity was drained and instilled with fresh dialysate via a PD catheter. Spent dialysate from the exchange was drained immediately prior to the i.v. infusion of ertapenem. Ertapenem at 500 mg i.v. was infused over 30 min after the initial dialysate exchange.

A total of 13 blood samples and 13 dialysate samples were obtained for ertapenem concentration determination. Blood samples were obtained via a peripheral venous catheter in the arm opposite that used for drug administration whenever possible. In the instance when the same site was used for drug administration and blood sampling, the line was flushed with saline before the first sample was drawn. Dialysate samples were collected between exchanges by draining 50 ml of peritoneal fluid through the Y-set into a small sterile bag.

Sample collection occurred over a 12-h period. Blood and dialysate samples were collected simultaneously during the study. A sample was collected prior to ertapenem administration. Seven blood and dialysate samples were collected during the first dwell, as follows: immediately following completion of ertapenem infusion and 5 min, 15 min, 1 h, 2 h, 4 h, and 6 h after infusion completion. The dialysate was then drained, and fresh dialysate was instilled. Five blood and dialysate samples were taken during the second dwell, as follows: at 10 min, 30 min, 2 h, 3 h, and 4 h after the end of dialysate instillation. Nonanuric patients were asked to void prior to drug administration. Subsequently, a timed urine collection was completed throughout the study day.

Blood samples were collected in standard blood collection tubes containing sodium heparin and stored on ice until serum was harvested. Serum was withdrawn following centrifugation at room temperature (at 3,000 to 4,000 rpm for 15 min). Serum and dialysate samples were stored at −80°C until assayed.

**Assay methodology.** Ertapenem concentrations in human dialysate fluid, human serum, and human urine were determined by high-pressure liquid chromatography (HPLC)-tandem mass spectrometry (LC-MS/MS). Into appropriately labeled autosampler vials containing 1.00 ml of water and 0.050 ml of meropenem as an internal standard (1.00 μg/ml), a 0.050-ml aliquot of each human dialysate fluid sample was added. Samples were vortexed and injected on the LC-MS/MS system. Human serum samples (0.050 ml) were deproteinized with methanol (0.150 ml), and 0.050 ml of the supernatant was transferred into an appropriately labeled autosampler vial containing 1.00 ml of HPLC water. These samples were also vortexed and injected onto the LC-MS/MS system. Into appropriately labeled autosampler vials containing 1.00 ml of water and meropenem as an internal standard (0.020 ml; 1.00 μg/ml), a 0.050-ml aliquot of each human urine sample (0.050 ml) was added. Samples were vortexed and injected onto the LC-MS/MS apparatus. Calibration standards and quality control samples for each matrix were similarly prepared and analyzed.

The dialysate assay was linear over a concentration range from 0.050 to 25.0 μg/ml (r² > 0.992) for ertapenem. The interday precision (percent coefficient of variation [CV]) for the dialysate quality control samples analyzed in replicates of six at three concentrations on each analysis day (0.100, 1.00, and 10.0 μg/ml) was 6.48% or less, and the accuracy (percent recovery) ranged from 99.8% to 101%. The serum assay was linear over a concentration range from 0.100 to 250 μg/ml (r² > 0.993) for ertapenem. The interday precision (percent CV) for the serum quality control samples analyzed in replicates of six at three concentrations on each analysis day (0.500, 5.00, and 50.0 μg/ml) was 5.57% or less, and the accuracy (percent recovery) ranged from 99.8% to 106%. The urine assay was linear over a concentration range from 0.050 to 25.0 μg/ml (r² > 0.993) for ertapenem. The interday precision (percent CV) for the urine quality control samples analyzed in replicates of six at three concentrations on each analysis day (0.100, 1.00, and 10.0 μg/ml) was 4.05% or less, and the accuracy (percent recovery) ranged from 98.1% to 110%.

Chromatographic separation was performed using a ThermoScientific Hypersil Gold C18, column (5-μm particle size; 150- by 4.6-mm column) with an isocratic mobile phase consisting of 70% 0.1% formic acid in water and 30% methanol. The LC-MS/MS system was comprised of a Shimadzu Prominance HPLC system and an ABSciex API5000 LC-MS/MS instrument.

Ertapenem concentrations were obtained using LC-MS/MS monitoring the MS/MS transition m/z 476 → m/z 432 and, where employed, for meropenem monitoring the MS/MS transition m/z 238 → m/z 141. Analysis run time was 7.5 min.

**Data analysis.** (i) Population pharmacokinetic modeling. Pharmacokinetic data were analyzed in a population PK model using the Big Non-Parametric Adaptive Grid with adaptive γ (BigNPAG) software program (13). A description of our PK model has been previously published (5).

Briefly, the structural PK model was parameterized as a three-compartment model with zero-order infusion and first-order intercompartmental transfer and elimination. To properly model the PD exchanges, each was included as a separate differential equation in the structural model. Finally, a term was included in the model to account for residual drug from the previous exchange.

The following differential equations were used to characterize the PK profile of ertapenem:

$$
\frac{dX_1}{dt} = R_1 \left( k_{12} + \frac{CL}{V} + k_{13}R_2 + k_{13}R_3 \right) X_1 + k_{21}X_2 + k_{31}X_1R_2 + k_{31}X_1R_3
$$

$$
\frac{dX_2}{dt} = \frac{k_{21}X_2 - k_{31}X_2}{R_4R_C}\text{CONEX}_1
$$

$$
\frac{dX_3}{dt} = \frac{k_{31}X_1R_3 - k_{31}X_2R_3 + R_4R_C\text{CONEX}_1}{R_4R_C}
$$

where $X_i$ is the amount of drug in the central compartment, $X_i$ is the amount of drug in the peripheral compartment, $X_i$ is the amount of drug in the first peritoneal exchange, $X_i$ is the amount of drug in the second peritoneal exchange, $CL$ is the nondialytic clearance from the central compartment (liters per hour), $V$ is the volume of the central compartment (liters), $k_{12}$ and $k_{23}$ are first-order intercompartmental transfer rate constants between the central and peripheral compartments (inverse hours), $k_{13}$ and $k_{31}$ are first-order intercompartmental transfer rate constants between the central and peritoneal compartments, CONEX is the amount of ertapenem remaining in the peritoneal compartment after drainage of first study exchange (mg), $R_i$ is the time-delimited zero-order drug input rate (piecewise input function) into the central compartment (mg per hour), $R_i$ is the rate constant for the first dwell constrained to 0 (first dwell turned off) or 1 (first dwell turned on), $R_i$ is the rate constant for the second dwell constrained to 0 (second dwell turned off) or 1 (sec-
TABLE 1 Study subject clinical characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for the parameter (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of male subjects</td>
<td>5</td>
</tr>
<tr>
<td>No. of female subjects</td>
<td>2</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>55.14 (17.28)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>92.03 (20.64)</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
<td>29.59 (5.63)</td>
</tr>
<tr>
<td>Cause of ESRD (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>1</td>
</tr>
<tr>
<td>Congenital disease</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>No. of anuric patients</td>
<td>3</td>
</tr>
<tr>
<td>No. of nonanuric patients</td>
<td>4</td>
</tr>
<tr>
<td>Mean dialysis vintage (m.o.)</td>
<td>63.6 (57.4)</td>
</tr>
</tbody>
</table>

a ESRD, end-stage renal disease.

b Residual renal function.

ond dwell turned on), \( R_d \) is the ertapenem dialysate concentration observed at the end of the first dwell, and \( R_i \) is the input rate for the residual amount of dialysate volume remaining after drainage of the first dwell.

The data of each patient were analyzed with this model in ADAPT II employing the maximum-likelihood estimation choice to obtain estimates of the weighting function for approximation to the homoscedastic assumption (8). Once convergence was attained, Bayesian estimates for each patient were determined within BigNPAG. After the Bayesian step, observed-versus-predicted plot regression, coefficients of determination, and log-likelihood values were used to determine a goodness-of-fit step using the mean, median, and population parameter estimates as the measure of a central tendency. Predictive performance was based on mean weighted error and precision bias-adjusted mean weighted squared error (measures of bias and precision, respectively).

(ii) Monte Carlo simulation. The mean parameter vector and major diagonal covariance matrix from the population PK model were embedded in subroutine PRIOR of the ADAPT II package of programs by D’Argenio and Schumitzky (8). The population simulation without the process noise option was employed. A 9,999-subject Monte Carlo simulation was performed for ertapenem at 500 mg intravenously every 24 h (\( 0.5 \) h infusion). Both normal and log-normal distributions were evaluated, and these were discriminated on their ability to recreate the original mean parameter values and corresponding standard deviations from the population analyses. The parameter values from the optimal distributions were employed to simulate steady-state concentrations (24 h after the start of dosing) and to generate serum concentration-time curves for each dosing regimen in both the serum and peritoneal cavity. Protein binding was assumed to be 90% in the serum (19). Ertapenem PK data in the peritoneal cavity were not adjusted for protein binding as no data are available. The fraction of simulated subjects whose concentrations were in excess of the MIC for 40% of the dosing interval (40% \( T > \text{MIC}, \text{where } T \text{ is time} \) in both the serum and peritoneal cavity for MIC values from 0.13 mg/liter to 8 mg/liter was calculated. The probabilities of achieving these pharmacodynamic endpoints were profiled because these indices were identified as critical pharmacodynamic targets for carbapenems both in vitro and in animal model studies (7, 9).

Monte Carlo simulation was used to calculate the peritoneal cavity/serum mean and median penetration ratios by estimating the area under the concentration-time curve in the peritoneal cavity and serum (AUC\(_{\text{peritoneal}} / \text{AUC}_{\text{serum}}\), respectively) from zero to infinity after a single simulated dose and computing the ratio. Monte Carlo simulation was also used to evaluate the predictive performance of the population pharmacokinetic model. The mean parameter vector values were used to simulate plasma and peritoneal cavity concentration-time profiles after a single intravenous dose of 500 mg of ertapenem infused over 30 min. The fidelity by which the concentration-time curves mirrored the raw data was assessed by visual inspection. Systat for Windows (version 10.2) was used for all data transformation.

RESULTS

Demographics. Clinical characteristics of study patients (\( n = 7 \)) can be found in Table 1.

Urine collection and analysis. A timed urine collection averaging 10 h 45 min was conducted while patients were at the clinic on the study day. Four out of seven patients made at least 100 ml of urine over this time period. For these nonanuric patients, the median volume was 325 ml. Ertapenem concentrations in the urine ranged from 23.5 to 190 mg/ml. Based on this, the median amount of ertapenem cleared in the urine during the study period was 19.5 mg. Because of the minimal contribution to total clearance, urinary clearance was not included in the population PK analysis.

Population PK modeling. The CAPD population PK model parameter estimates for ertapenem as identified by BigNPAG are provided in Table 2. The predictive performance and goodness of model fit can be found in Table 3. Using the population median parameter values as the measure of central tendency, the overall fit of the model to the data was good, and the observed-predicted plots for both serum and dialysate (exchanges 1 and 2) after the Bayesian step showed slopes and intercepts very close to the ideal values of 1.0 and 0.0, respectively. The coefficients of determination (\( r^2 \)) were \( >0.96 \) for all outputs, and the measures of bias and precision were highly acceptable.

Monte Carlo simulation. A 9,999-subject Monte Carlo simulation was performed to estimate the probability of target attainment profiles in both the serum and peritoneal cavity. Log-normal distributions were selected for the population simulation based on their ability to recapitulate the original mean parameter values and corresponding standard deviations. As shown in Fig. 1, the probability of achieving 40% \( T > \text{MIC} \) exceeded 90% in both the serum and peritoneal cavity for MIC values of \( <4 \) mg/liter. The mean (± standard deviation [SD]) AUC\(_{\text{peritoneal}} / \text{AUC}_{\text{serum}} \) ratio was 1.039 (0.861), and the median penetration ratio was 0.801 (interquartile range, 0.486 to 1.317).

The simulated plasma and peritoneal cavity concentration-time profiles of a single intravenous dose of 500 mg of ertapenem (infused over 30 min) are displayed in Fig. 2. The simulated plasma and peritoneal cavity concentration-time curves mirrored the patient’s clinical characteristics, demographic information, and simulation results.
the central tendency of the raw data reasonably well; the vast majority of the data points were evenly distributed around the plasma and peritoneal cavity concentration-time curves.

**DISCUSSION**

Adequate antibiotic concentrations at the site of infection are critical to ensure the highest probability of favorable clinical and microbiological responses (16, 17). Significant advances have been made in identifying the exposure target associated with the maximal response for many classes of antibiotics (2, 7, 9, 16, 17). For carbapenem antibiotics such as ertapenem, studies have demonstrated that the microbiological response is optimized when concentrations exceed the MIC for 30 to 40% of the dosing interval (7, 9, 22, 29). To translate this knowledge into clinical practice, mathematical modeling techniques (i.e., population PK modeling and Monte Carlo simulation) can be used to predict whether the dosing regimen will actually achieve the exposure target associated with success in both the serum and at the site of infection (16, 17). Because of their versatility, these techniques have become the standard methodology for assessing the clinical viability of both experimental and approved antimicrobials (16, 17).

While population PK modeling and Monte Carlo simulation have become standard methodology for assessing the appropriateness of an antibiotic dosing regimen, it is of the utmost importance to consider the population PK model used in the simulator program. Often the model is derived from hospitalized patients or healthy volunteers. While these simulations offer valuable insights into the pharmacodynamic profiles of regimens used in practice, they may not be applicable to specialized populations. Patients on peritoneal dialysis represent one such specialized population with altered drug clearance due to reduced kidney function, changes in drug distribution, and dialysis removal of drug. When possible, the PK model should be derived in the population of interest.

Cognizant of this issue, we derived a population PK model applicable to patients receiving CAPD. In addition, rather than using a noncompartmental modeling approach, we fit a structural PK model to the data to mimic the physiologic conditions that occur during CAPD.

Overall, the model fit the data extremely well, and the results of the simulation suggest that 500 mg of ertapenem i.v. q24h provides adequate drug exposure to treat infections seen in clinical practice. In the serum, the tested regimen had a high likelihood of achieving 40% free ertapenem (\(T>MIC\)) for MIC values of \(\leq 2\) mg/liter. The median peritoneal cavity penetration ratio

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**TABLE 3 Goodness of fit and predictive performance of the population PK model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum</th>
<th>Peritoneal cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression line</td>
<td>Obs = 1.04 × Pred − 1.56</td>
<td>Obs = 1.00 × Pred − 0.40</td>
</tr>
<tr>
<td>(r^2)</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Bias (mg/liter)(^{a})</td>
<td>1.14</td>
<td>0.12</td>
</tr>
<tr>
<td>Precision (mg/liter)(^{b})</td>
<td>1.14</td>
<td>0.83</td>
</tr>
</tbody>
</table>

\(^{a}\) Mean weighted error.

\(^{b}\) Bias-adjusted mean weighted squared error.

\(^{c}\) Obs, observed drug concentration; Pred, predicted drug concentration.
(AUC_{peritoneal}/AUC_{serum}) approached 1, and this was reflected in the favorable probability of the target attainment (PTA) profile in the peritoneal cavity. Similar to the result in serum, the probability of achieving 40% $T_{>}$MIC in the peritoneal cavity was in excess of 90% for MIC of $\leq$2 mg/liter. If one considers that for Enterobacteriaceae the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint is $\leq$0.25 mg/liter, the tested regimen would clearly provide adequate drug exposure in both the central and peritoneal compartments (6, 19). This suggests that 500 mg of ertapenem i.v. q24h is an appropriate therapeutic option for susceptible infections in a patient on CAPD.

Several things should be considered in interpreting the results. First, the study used noninfected patients on CAPD to derive the PK model. However, we demonstrated that even in the absence of inflammation, ertapenem penetration into the peritoneal cavity was adequate to achieve the pharmacodynamic target at MICs of $\leq$1 mg/liter. If inflammation were present, as it would be in an infected state, we speculate that penetration into the peritoneal cavity would increase (18). Therefore, it is expected that inflammation would only improve the PTA profile at higher MICs. However, significant inflammation may also reduce serum ertapenem concentrations if peritoneal penetration substantially increases. Further study in infected patients is needed. Second, although standardizing the dialysis regimen for study patients provided methodological advantages, the dose of delivered dialysis during the study period may have been altered from patients’ normal dialysis regimens. If dialysis adequacy was reduced during the study, the estimation of ertapenem clearance from this study...
could be an underestimation for other patients on CAPD. However, upon hospitalization for infection, patients on peritoneal dialysis may be switched from their regular modality to CAPD and may use a different dialysate. These changes may affect dialysis adequacy in the short term, not unlike what occurred during this study. An additional consideration is the fact that PK data in the peritoneal cavity were not adjusted for protein binding as no data are available. If significant binding occurs in the peritoneal compartment, reducing the free fraction, more drug may be required to achieve the pharmacodynamic target. Lastly, the influence of residual renal function on ertapenem clearance must be considered. Half of the study patients had some remaining kidney function; however, the relative contribution to drug clearance was minimal. Based on our results, less than 10% removal can be expected in the urine over 24 h.

The PK model derived from this study cannot be used to simulate intraperitoneal administration of ertapenem. Intraperitoneal administration is preferred in peritonitis to provide the highest local concentration in the peritoneal cavity. However, additional PK and stability data are needed before this route can be recommended. The manufacturer labeling for ertapenem states that the drug should not be reconstituted with dextrose due to stability concerns (15). Furthermore, the favorable PTA profile observed in our study of the peritoneal cavity penetration ratio (AUCPeritoneal/AUCSerum) suggests that i.v. dosing is a reasonable option, especially in the absence of intraperitoneal data.

In summary, a population-based modeling approach was used to assess the FDA-approved dosing regimen of i.v. ertapenem in reduced kidney function (i.e., 500 mg every 24 h) for patients on CAPD. The regimen provided a high PTA profile in both serum and the peritoneal cavity for MIC values deemed susceptible by the CLSI. Although these findings require validation in the clinical arena, results suggest that i.v. ertapenem may be appropriate to treat susceptible bloodstream infections or peritonitis in CAPD.

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REFERENCES