831. Traditional PK-PD Indices for Efficacy – Can We Do Better?

Elizabeth A. Lakota, Pharm.D., M.S.[1]; Justin C. Bader, Pharm.D., MBA[1]; Sujata M. Bhavnani, Pharm.D., M.S.[1]; David R. Andes, MD, FIDSA[2] and Paul G. Ambrose, Pharm.D., FIDSA[1]; [1]ICPD, Schenectady, New York, [2]University of Wisconsin School of Medicine and Public Health, Madison, WI

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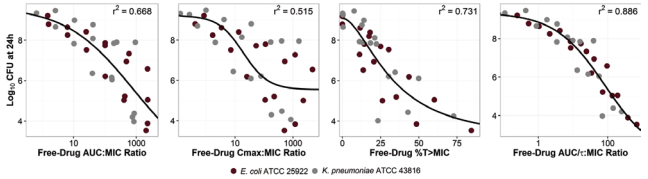
Background. The relationship between antimicrobial activity and exposure relative to MIC is typically evaluated using one of three PK-PD indices, AUC:MIC ratio, Cmax:MIC ratio, and %T>MIC. However, under certain circumstances, none of these PK-PD indices may be the most optimal. These include when the fitted Hill functions for each of the PK-PD indices do not allow for sufficient discrimination, the variability about the fitted functions is wide, and/or the pattern of dose fractionation data is non-informative. Relationships fit using the traditional PK-PD indices may be suboptimal for drugs which exhibit extreme PK characteristics such as abnormally short or long half-lives. As described herein, we explored the use of a fourth PK-PD index for such instances, AUC/τ:MIC ratio (τ = dosing interval).

Methods. Previously-described ceftolozane dose-fractionation data from a study using a neutropenic murine thigh-infection model were evaluated [AAC 2013; 57(4):1577–82]. In this prior study, mice were infected with *E. coli* ATCC 25922 (MIC = 0.5 mg/L) or *K. pneumoniae* ATCC 43816 (MIC = 1.4 mg/L). Ceftolozane doses ranged from 1.56 to 1600 mg/kg/24h given q3h, q6h, q12h, or q24h. Relationships between $\log_{10}$ colony forming units (CFU) at 24 hours and AUC:MIC ratio, Cmax:MIC ratio, %T>MIC, and AUC/τ:MIC ratio were evaluated by pathogen and pooled using Hill-type models and non-linear least squares regression.

Results. For evaluations of data by pathogen, AUC/τ:MIC ratio best described changes in $\log_{10}$ CFU at 24 hours. The coefficients of determination (r^2) for these pathogens were improved by 0.20 and 0.11, respectively, relative to the highest r^2 achieved using any of the traditional PK-PD indices. Similar results were observed when the data were evaluated using a pooled approach (Figure 1).

Conclusion. AUC/τ:MIC ratio may be useful to evaluate drugs demonstrating the extremes of PK. Accordingly, this PK-PD index best described ceftolozane PK-PD, an agent with a very short murine plasma half-life (<15 minutes). The use of the PK-PD index that allows for the best fit of the data to the Hill function and reduced variability about the fitted function will not only improve the characterization of PK-PD but will also improve the accuracy of future dose selection analyses.

Figure 1. Relationships between change in $\log_{10}$ CFU from baseline at 24 hours and ceftolozane free-drug plasma AUC:MIC ratio, Cmax:MIC ratio, %T>MIC, and AUC/τ:MIC ratio



Disclosures. **All authors:** No reported disclosures.

832. At the Crossroads of Stewardship and Technology: Impact of Pharmacokinetic-Pharmacodynamic (PK-PD) Integrated Electronic Decision Support Software (EDSS) on the Treatment of Patients Infected with Pneumonia

Justin C. Bader, Pharm.D., MBA; Catharine C. Bulik, Pharm.D.; Sujata M. Bhavnani, Pharm.D., M.S.; Christopher M. Rubino, Pharm.D.; Kim L. Sweeney, Pharm.D.; Paul G. Ambrose, Pharm.D., FIDSA and Robert C. Owens Jr., Pharm.D.; ICPD, Schenectady, New York

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Background. While many have advocated for the use of EDSS to enhance patient care, EDSS that incorporates PK-PD, the science behind antimicrobial stewardship, has thus far been an unattainable goal. Herein, we describe the use of such a technology and clinicians' therapy decisions when treating patients with pneumonia.

Methods. Data for patients with pneumonia entered into EDSS over a 20-month period that were evaluated included: 1) patient demographics, creatinine clearance, and pneumonia severity score; 2) pneumonia type; 3) pathogen; 4) clinician-selected antimicrobials; 5) EDSS-presented regimens; and 6) clinician-reported outcomes. Clinicians were provided probabilities of attaining PK-PD targets associated with efficacy for both clinician-selected and EDSS-presented regimens. A regimen with a probability of PK-PD target attainment ≥90% was considered PK-PD optimized.

Results. Data for 126 cases were available. The median (min, max) age and creatinine clearance were 56.5 (18, >90) years and 72.5 (2.5, 193.3) mL/minute/1.73 m^2, respectively. Pneumonia types included community-acquired (39%), healthcare-associated (30%), ventilator-associated (18%), and hospital-acquired (13%). CURB-65 pneumonia scoring was used in 66% of cases with a median (min, max) score of 3 (0, 5). The most common pathogens were *P. Aeruginosa* (32%), MRSA (15%), and *S. pneumoniae* (14%). Multi-drug-resistant pathogens comprised 15% of all pathogens. PK-PD optimized regimens were selected in only 65% of cases despite such a regimen being presented in 91% of cases. For those cases in which outcome data were available (n = 36), 81% of patients were considered improved at 48 hours while only 64% were deemed clinically improved or a success at the final outcome assessment on Days 7–10. Among those cases for whom PK-PD optimized and non-optimized regimens were selected (64 and 36%, respectively), 78 and 62% of patients had successful clinical outcomes on Days 7–10, respectively.

Conclusion. Given that patients with pneumonia represent a vulnerable population and that options for therapy can be limited, selection of optimal early therapy is crucial. PK-PD integrated EDSS presents clinicians the opportunity to optimize therapy and improve outcomes for patients with pneumonia.

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833. Breaking New Ground: An Evaluation of Susceptibility Breakpoints for Echinocandins against *Candida* Species

Justin C. Bader, Pharm.D., MBA[1]; David R. Andes, MD, FIDSA[2]; Mariana Castanheira, PhD[3]; Paul G. Ambrose, Pharm.D., FIDSA[1] and Sujata Bhavnani, Pharm.D., M.S.[1]; [1]ICPD, Schenectady, New York, [2]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, [3]JMI Laboratories, Inc., North Liberty, Iowa

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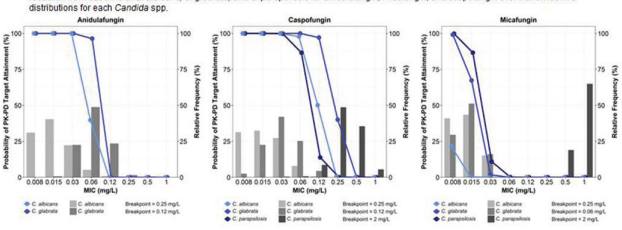
Background. The increasing prevalence of resistant *Candida* species has led to renewed interest in evaluating the utility of echinocandins. PK-PD target attainment analyses are increasingly used to inform decisions about susceptibility breakpoints. We carried out such analyses to evaluate anidulafungin, micafungin, and caspofungin Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints for *C. Albicans, C. glabrata,* and *C. parapsilosis*.

Methods. Monte Carlo simulations (n = 2000) were conducted using published population PK models [J Clin Pharmacol 2004; 44:590–598, ICAAC 2008; Abstr A-011, AAC 2013; 57:1664–1671]. The following labeled intravenous dosing regimens for the treatment of candidemia were evaluated: anidulafungin 200 mg followed by 100 mg daily, micafungin 100 mg daily, and caspofungin 70 mg followed by 50 mg daily. Day 1 free-drug plasma AUC values were calculated for simulated patients after administration of each agent. Free-drug plasma AUC:MIC ratio targets associated with 1-$\log_{10}$ CFU reductions from baseline of *C. Albicans* and *C. glabrata* for anidulafungin, micafungin, and caspofungin, derived from neutropenic murine disseminated candidiasis models, were used [AAC 2007; 52:539–550, AAC 2010; 54:2497–2506]. Similar such targets for *C. parapsilosis* were utilized to evaluate caspofungin and micafungin. Percent probabilities of PK-PD target attainment were computed by MIC. The results were evaluated in the context of MIC distributions for each pathogen from a collection of isolates obtained worldwide from 2014 to 2015 [ECCMID 2017; Abstr P1748].

Results. Among the CLSI susceptibility breakpoints evaluated, only one was supported by the analysis results shown in Figure 1 (caspofungin vs. *C. glabrata*), and only one other susceptibility breakpoint was within one dilution of the highest MIC at which the percent probability of PK-PD target attainment was ≥90% (anidulafungin vs. *C. glabrata*). All other susceptibility breakpoints were ≥2 dilutions above this MIC.

Conclusion. These results demonstrate the need to re-evaluate the echinocandin susceptibility breakpoints for *Candida* spp. Establishing appropriate susceptibility breakpoints will ensure appropriate prescribing and optimal patient outcomes.

Figure 1. Percent probabilities of PK-PD target attainment by MIC using free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline of *C. albicans, C. glabrata,* and *C. parapsilosis* for anidulafungin, micafungin, and caspofungin over worldwide MIC distributions for each *Candida* spp.



Disclosures. **All authors:** No reported disclosures.

834. *In Vitro* Antibacterial Activity of Ceftolozane/Tazobactam (C/T) Alone and in Combination with other Antimicrobial Agents against Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* (PSA)

Marguerite Monogue, PharmD[1] and David P. Nicolau, PharmD, FCCP, FIDSA[2]; [1]Center for Anti-Infective Research and Development at Hartford Hospital, McKinney, Texas, [2]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut

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Background. Broad-spectrum antimicrobial resistance in MDR PSA isolates significantly limits our therapeutic options. C/T has been shown to be highly active against MDR PSA isolates. To assist the clinical decision-making process regarding the selection of agents and dosages for this pathogen, we performed time-kill studies assessing various C/T concentrations alone and in combination with other anti-pseudomonal agents.

Methods. Four clinical MDR P. aeruginosa isolates were selected. MICs were determined via broth microdilution methods according to CLSI. Time-kill analyses