Multivariate Regression Analysis to Determine Independent Predictors of Treatment Outcomes in the RESTORE-IMI 2 Trial

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Background

- Hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) account for up to 26% of hospital-acquired infections, with mortality rates of up to 50%[1-3]
- In the RESTORE-IMI 2 clinical trial, imipenem/cilastatin/relebactam (IMI/REL) was found to be noninferior to piperacillin/tazobactam (PIP/TAZ) for treating adults with HABP/VABP, in both the primary and key secondary end points[4]
  - The primary end point of this study was Day 28 all-cause mortality (ACM) and the key secondary end point was clinical response at early follow-up (EFU; 7–14 days after end of therapy)[4]
- IMI/REL was recently approved for HABP/VABP by the United States Food & Drug Administration[5]
- We conducted this post hoc analysis to determine independent predictors of efficacy outcomes in the RESTORE-IMI 2 study using a multivariate regression analysis

Methods

- RESTORE-IMI 2 was a multicenter, randomized, controlled, double-blind, phase 3 noninferiority study that compared IMI/REL (500 mg/500 mg/250 mg) vs PIP/TAZ (4 g/500 mg), administered as 30-minute intravenous infusions every 6 hours for 7–14 days, in adult participants with HABP/VABP[4]
- Using participant-level data from 531 participants in this study, a stepwise-selection logistic regression model was developed and used to conduct an exploratory analysis of independent predictors of Day 28 ACM and favorable clinical response at EFU in the modified intention-to-treat (MITT) population
  - The MITT population included all randomized participants who received ≥1 dose of study drug
  - Participants with only gram-positive cocci in their baseline respiratory specimen were excluded
- Baseline categorical variables (n=19) were preselected as candidates for inclusion based on clinical relevance (**Table 1**)

Table 1. Candidate Baseline Variables Preselected for Inclusion in Logistic Regression Model

Predictive variable	Measure
Baseline demographics	
Participant age	<65 vs ≥65 years of age
Participant sex	Female vs male
Participant race	White vs other vs missing
Region of enrollment	Americas vs Asia-Pacific vs Europe
Treatment arm	IMI/REL vs PIP/TAZ
Disease characteristics	
Type of pneumonia	Nonventilated HABP vs ventilated HABP/VABP
APACHE II score	<15 vs ≥15
CPIS	≤5 vs ≥6
Hospital service unit	Neurology vs other
ICU	Yes vs no
Concurrent bacteremia with any pathogen	Yes vs no
Number of LRT pathogens	Monomicrobial vs polymicrobial
Renal impairment	None[a] vs mild[b] vs moderate/severe[c]
Renal function	Augmented renal clearance[d] vs normal[e] vs impaired[f]
Treatment duration	≥7 vs <7 days
Pathogens	
Klebsiella pneumoniae	Present vs not detected
Pseudomonas aeruginosa	Present vs not detected
Escherichia coli	Present vs not detected
Acinetobacter calcoaceticus-baumannii complex	Present vs not detected

[a]CrCl ≥90 mL/min; [b]CrCl ≥60 to <90 mL/min; [c]CrCl ≥15 to <60 mL/min; [d]CrCl ≥150 mL/min; [e]CrCl ≥90 to <150 mL/min; [f]CrCl ≥15 to <90 mL/min.

APACHE, Acute Physiology and Chronic Health Evaluation; CPIS, clinical pulmonary infection score; CrCl, creatinine clearance; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; LRT, lower respiratory tract; PIP/TAZ, piperacillin/tazobactam; VABP, ventilator-associated bacterial pneumonia.

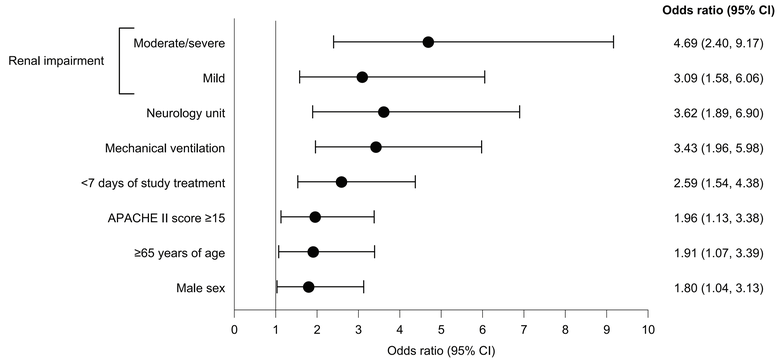
- All candidate variables had either 2 or 3 levels and had complete data except for the baseline pathogen variable; a baseline lower respiratory tract (LRT) specimen was available for 433 of the 531 participants
  - The variable for the number of baseline LRT pathogens included 2 levels: monomicrobial vs polymicrobial
  - The variable for specific pathogens also included 2 levels: present vs absent
- Variables were added to the model if significant ($P<.05$) and removed if their significance was reduced ($P>.1$) by the addition of other variables
- Two-factor interactions between treatment allocation and significant predictors were assessed for significance ($P<.05$)

Results

Predictors of Day 28 ACM

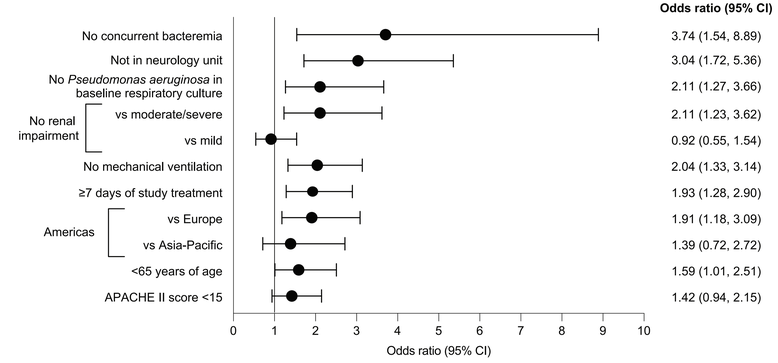
- Baseline variables that met the criteria for significant independent predictors of increased Day 28 ACM in the final selected regression model are shown in **Figure 1**
  - Renal impairment, treatment in a neurology hospital service unit, mechanical ventilation, <7 days on study treatment, Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥15, age ≥65 years, and male sex were significant independent predictors of higher Day 28 ACM
  - Participants treated in neurology units versus other units had greater disease severity (APACHE II scores ≥15 [55% (38/69) vs 46% (214/462)] and a higher incidence of bacteremia (13% [9/69] vs 5%; [22/462], respectively)

Figure 1. Independent Predictors of Greater Day 28 All-Cause Mortality (MITT population; N=531)



APACHE, Acute Physiology and Chronic Health Evaluation; MITT, modified intention-to-treat.

Figure 2. Independent Predictors of a Favorable Clinical Response at EFU (MITT population; N=531)



APACHE, Acute Physiology and Chronic Health Evaluation; EFU, early follow-up; MITT, modified intention-to-treat.
Note: Variables, as listed, are predictive of having a favorable clinical response at EFU, ie, participants without concurrent bacteremia were more likely to have a favorable clinical response at EFU than participants with bacteremia.

Predictors of Favorable Clinical Response at EFU

- Baseline variables that met the criteria for significant independent predictors of clinical response at EFU in the final selected regression model are shown in **Figure 2**
  - Predictive variables for favorable clinical response at EFU included absence of bacteremia, treatment outside of a neurology unit, lack of *Pseudomonas aeruginosa* in baseline respiratory cultures, no renal impairment (vs moderate/severe), no mechanical ventilation, enrollment in the Americas vs Europe, and age <65 years

Interactions Among Treatment Allocation and Predictors of Day 28 ACM and Favorable Clinical Response at EFU

- Treatment allocation, ie, randomization to IMI/REL or PIP/TAZ, was not a significant predictor of Day 28 ACM or clinical response at EFU
- There were no significant interactions between treatment allocation and independent predictors of Day 28 ACM or clinical response at EFU

Conclusions

- This analysis validated known independent predictors of clinical outcomes in HABP/VABP, including mechanical ventilation and high APACHE II score[3,6-8]
  - In critically ill (APACHE II score ≥15) participants with HABP/VABP enrolled in RESTORE-IMI 2, IMI/REL has demonstrated efficacy in reducing Day 28 ACM compared with PIP/TAZ[9]
- The presence of *P. aeruginosa* at baseline as a causative pathogen of HABP/VABP was associated with lower rates of clinical response regardless of assigned treatment arm, ie, IMI/REL or PIP/TAZ
- Randomized treatment allocation was not a significant predictor of Day 28 ACM or clinical response at EFU, which was not unexpected since RESTORE-IMI 2 demonstrated that IMI/REL was noninferior to PIP/TAZ for the treatment or HABP/VABP
- Since there were no interactions between predictors of primary and key secondary efficacy outcomes and treatment arm, this analysis supports the main noninferiority finding of RESTORE-IMI 2
- Participant- and disease-related factors (ie. age ≥65 years, mechanical ventilation, APACHE II score ≥15, and renal impairment) emerged as consistent independent predictors of poor outcome (ACM and clinical response at EFU)

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