Predictors of Negative Clinical Outcomes Among Patients Treated with Meropenem-Vaborbactam for Serious Gram-Negative Bacterial Infections: Impact of Delayed Appropriate Antibiotic Selection

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Background

- A growing number of studies have observed a relationship between delayed appropriate antibiotic therapy and negative clinical outcomes (NCO), including mortality in various infections including Gram-negative bacterial infections (GNBI)[1]
- The combination of meropenem with vaborbactam (MVB) received Food and Drug Administration (FDA) approval for the treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP) caused by susceptible organisms in August 2017 and was associated with positive clinical outcomes when used to treat GNBI in the real-world setting[2-3]
- We aim to quantify the delay before appropriate therapy with MVB that is associated with an increased risk of NCO among patients with GNBI

Methods

- Multi-center, retrospective cohort study from October 2017 to March 2020. We included adult patients with GNBI treated with MVB for ≥72 hours
- We excluded 1) pregnant women 2) prisoners 3) patients who received alternative appropriate antibiotics for GNBI and 4) patients with unknown index culture dates
- The primary outcome was NCO defined as 30-day mortality and/or microbiological recurrence measured from index culture collection date/time
- Classification and Regression Tree (CART) analysis was performed to determine the time breakpoint (BP) that delineates risk of NCO
- Independent predictors of NCO were determined by multivariable logistic regression analyses where variables associated with NCO at a P-value < 0.2 in bivariate analyses were entered into model simultaneously and removed in a backward stepwise fashion. Variables were retained in the final model if the adjusted P value was <0.1. Model fit was assessed with Hosmer-Lemeshow goodness-of-fit with P values < 0.05 considered adequate
- The independent association between time BP, dichotomized at the CART derived cut-point, was then examined through multivariable logistic regression. Analysis using SPSS Statistics, IBM SPSS software, version 26.0 (IBM Corp., Armonk, NY)

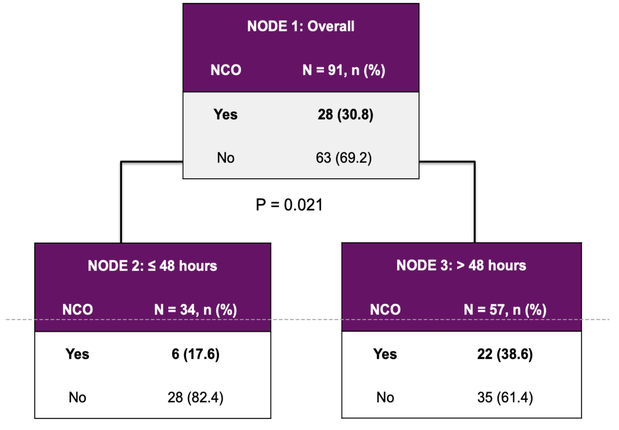
Results

Table 1. Bivariate analysis of baseline demographics, comorbid diseases and clinical criteria

Characteristics	Negative clinical outcomes (n=28)	Positive clinical outcomes (n=63)	P-value
Age, years	60 (46 – 67)	48.5 (33 – 68)	0.222
Sex, male	18 (66.7)	41 (64.1)	0.812
Admission from nursing home	3 (10.7)	15 (23.8)	0.148
Chronic kidney disease	12 (42.9)	18 (28.6)	0.181
Chronic dialysis	6 (21.4)	7 (11.1)	0.194
Antimicrobials > 24 hours in 90 days before index culture	21 (75.0)	39 (61.9)	0.244
APACHE II Score	21 (17 – 31)	15.5 (9.2 – 22.8)	0.001
CCI	6 (3-8)	3 (2-6)	0.022
Combination therapy	16 (57.1)	38 (60.3)	0.776
ICU admission	19 (70.4)	20 (31.3)	0.001
ID consult	28 (100)	62 (98.4)	0.503
Nosocomial infection	22 (78.6)	34 (54.0)	0.026
Positive blood culture	5 (17.9)	18 (28.6)	0.278
Intraabdominal source	2 (7.1)	16 (25.4)	0.044
Respiratory source	15 (53.6)	17 (27.0)	0.014

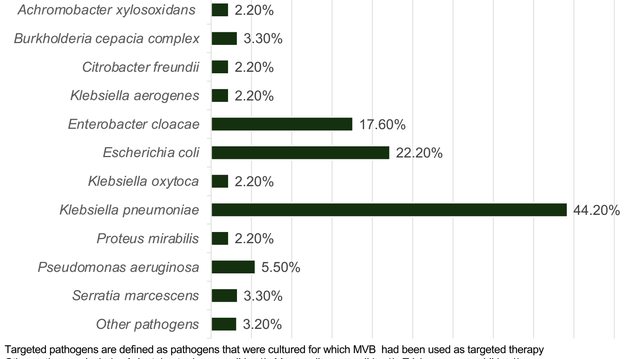
APACHE II: acute physiology and chronic health evaluation, CCI: Charlson Comorbidity Score, ICU: intensive care unit, ID: infectious diseases. All data presented as median (Inter Quartile Range) or n (proportions)

Figure 2. CART-derived meropenem-vaborbactam initiation time breakpoint for negative clinical outcomes



*The time breakpoint illustrated was the only time breakpoint identified by Classification and Regression Tree analysis
NCO: negative clinical outcome defined as mortality or recurrence

Figure 1. Meropenem-vaborbactam targeted pathogens



Targeted pathogens are defined as pathogens that were cultured for which MVB had been used as targeted therapy
Other pathogens include: *Acinetobacter baumannii* (n=1), *Morganella morganii* (n=1), *Trichosporon asahii* (n=1)

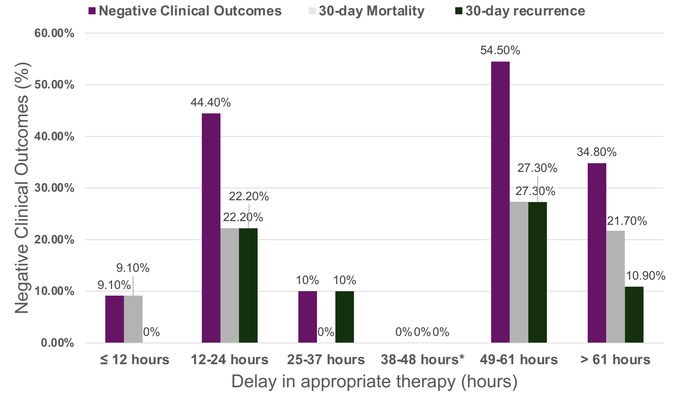
Table 2. Independent predictors of negative clinical outcomes

Variable	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Timely MVB[1]	0.387 [0.098-1.522]	0.174	0.277 [0.081 – 0.941]	0.040
APACHE II score	1.083 [1.012 – 1.159]	0.021	1.095 [1.029 – 1.166]	0.004
Nosocomial Infection[2]	2.298 [0.583-9.055]	0.234	4.041 [1.132 – 14.426]	0.031
Heart Failure	5.313 [1.188 – 23.763]	0.029	4.216 [1.129-15.733]	0.032
Intraabdominal infection	0.162 [0.022 – 1.206]	0.076	0.151 [0.027 – 0.835]	0.030

[1]: Timely MVB is defined as MVB within 48 hours (i.e. at CART break point)
[2]: Defined as infection within 48 hours of inpatient admission date /time
APACHE II: acute physiology and chronic health evaluation, MVB: meropenem vaborbactam
Hosmer-Lemeshow goodness-of-fit: 0.302. Variance inflation factor for all factors in the model: 1-5
Variables in the model: Age, APACHE, admission from nursing home, CCI, chronic kidney disease, chronic dialysis, dementia, heart failure, timely MVB, tumor without metastasis, source is an intraabdominal infection, source is a respiratory tract infection, liver disease, nosocomial infection, surgery within the past 30 days of index culture,

Results

Figure 3. Negative clinical outcomes, 30-day mortality and 30-day recurrence stratified by delay in receiving appropriate therapy



* Indicates 0% negative clinical outcomes, 0% 30-day mortality and 0%30-day recurrence

Discussion and Conclusions

- Classification results can create biased trees when certain variables dominate (i.e. when therapy is not started until cultures come back positive within 24-48 hours) possibly causing type II error as suggested from the lack of NCO in the 38-48 hours period
- Timely MVB start (i.e. within 48 hours from index culture) was independently associated with reduced risk of NCO
- Our findings underscore the importance of early MVB initiation to achieve 30-day survival and/or lack of 30-day recurrence

References

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Disclosures

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