Poster 1450

Frequency of Carbapenem-resistant *Pseudomonas aeruginosa* Among Respiratory Pathogens Impacts First-Line Beta-Lactam Susceptibility: Potential Role for Ceftolozane/Tazobactam and/or Imipenem/Relebactam

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Background

- Respiratory infections are a leading cause of mortality in the United States.[1]
- In hospital settings, gram-negative bacteria are implicated as primary pathogens in patients with hospital-acquired (HABP) or ventilator-associated bacterial pneumonia (VABP). In particular, *P. aeruginosa* is observed in approximately 25% of cases.[1,2]
- The challenge with *P. aeruginosa* is an increasing frequency of resistance to 1st line treatment options recommended by clinical guidelines.[3] In particular, carbapenem-resistant (CR) isolates create clinical challenges due to:
  1) Co-resistance among 1st line agents (*e.g.*, meropenem, piperacillin/tazobactam, and cefepime) used in the management of HABP/VABP.
  2) Delays to timely effective therapy resulting in poor outcomes.[1,4,5]
- Due to co-resistance among common empiric 1st line beta-lactams, a simple strategy for assessing risk for ineffective empiric therapy is evaluating institutional, unit-specific, or syndromic frequency of carbapenem-resistant *P. aeruginosa* (CRPA).
- The aim of this analysis is to identify beta-lactam susceptibility patterns based on CRPA frequency amongst lower respiratory tract specimens collected from intensive care unit (ICU) patients and determine whether CRPA can be used as a marker for early susceptibility testing of newer beta-lactams.

Methods

- In 2016-2019, ~20 US institutions per year submitted up to 250 consecutive, aerobic or facultatively anaerobic, gram-negative pathogens from blood, intra-abdominal, urinary, and lower respiratory tract infections as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART).
- A total of 871 *P. aeruginosa* isolates were collected from lower respiratory tract specimens obtained from ICU patients.
- MICs were determined using CLSI broth microdilution and interpreted with CLSI 2020 or FDA breakpoints.
- Institutions were then stratified into one of three categories based on CRPA frequency: CRPA rates ≤20% (CR Group 1), 21 – 40% (CR Group 2), and ≥41% (CR Group 3).
- Beta-lactam susceptibility was then evaluated relative to CRPA frequency.

Results

Table 1. Susceptibility data for *P. aeruginosa* lower respiratory tract isolates collected from ICU patients

	n	C/T	I/R	FEP	TZP	IMI	MEM	LVX	AMK
All isolates	871	93.9	90.8	74.3	67.6	64.9	71.6	61.1	96.6
FEP-NS	224	77.7	72.8	-	5.8	36.1	38.4	29.0	91.1
TZP-NS	282	82.3	77.0	25.2	-	41.1	43.3	32.6	92.9
MEM-NS	247	82.6	67.6	44.3	35.2	4.5	-	24.7	91.9
FEP, TZP, MEM-NS	117	67.5	59.0	-	-	-	-	12.0	88.0
MDR	306	83.0	76.1	28.4	12.8	36.3	38.6	26.1	91.2
DTR	95	65.3	56.8	-	-	-	-	-	85.3

C/T: Ceftolozane/tazobactam; I/R: Imipenem/relebactam; FEP: Cefepime; TZP: Piperacillin/tazobactam; IMI: Imipenem; LVX: Levofloxacin; AMK: Amikacin; NS: Non-susceptible; MDR: Multi-drug resistant; DTR: Difficult-to-treat resistance
MDR[6]: Defined as non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories
DTR[7]: Defined as intermediate/resistant to all ß-lactam categories, including carbapenems and fluoroquinolones

- In ICU patients with lower respiratory tract infections, resistance to piperacillin/tazobactam, cefepime, and meropenem was common and reported in 32.4%, 25.7%, and 28.4% of isolates, respectively.
- In meropenem non-susceptible isolates, resistance to piperacillin/tazobactam and cefepime increased by ~30% with 64.8% and 55.7% of isolates reported as NS, respectively. Thus, highlighting a high frequency of co-resistance among 1st line agents.
- Beyond a high incidence of CRPA, the frequency of MDR *P. aeruginosa* in ICU lower respiratory tract infections was elevated at 35.1% (306/871).

Table 2. Carbapenem Resistance Stratification

	CR Group 1	CR Group 2	CR Group 3
CR Frequency (% of isolates)	≤ 20	21 – 40	≥ 41
Number of institutions (N)	37	25	18
Number of isolates (n)	264	363	244

- During the analysis period, 80 US institutions submitted *P. aeruginosa* isolates. Frequency of carbapenem resistance varied between institutions. Therefore, institutions were categorized by frequency of CRPA to determine impact on beta-lactam susceptibility.

Table 3. *P. aeruginosa* susceptibility among ICU lower respiratory tract isolates stratified by frequency of carbapenem resistance

Antimicrobial	CR Group 1 (N = 37) (n = 264, %)	CR Group 2 (N = 25) (n = 363, %)	CR Group 3 (N = 18) (n = 244, %)
Cefepime	83.7	74.9	63.1
Piperacillin-tazobactam	79.6	68.9	52.9
Meropenem	91.3	73.6	47.5
Levofloxacin	68.6	66.1	48
Ceftolozane/tazobactam	96.6	94.2	90.6
Imipenem/relebactam	98.1	91.7	81.6

- Stratifying by CR classification highlights the frequency of co-resistance existing between beta-lactams.
  - In organizations with a low frequency of CRPA (*i.e.*, CR Group 1), empiric 1st line beta-lactams maintain susceptibility with ≤ 20% of isolates resistant.
  - As CR frequency increases (transitioning from Group 1 to Group 3), institutions observe significant declines in cefepime and piperacillin/tazobactam susceptibility
- In contrast, ceftolozane/tazobactam and imipenem/relebactam susceptibilities are preserved in the setting of increasing carbapenem resistance.
  - Despite a 44% decline in meropenem susceptibilities, ceftolozane/tazobactam and imipenem/relebactam maintained robust activity with minor reductions in susceptibility of 6% and 16.5%, respectively. These data highlight the potency of these agents against *P. aeruginosa*.

Conclusions

- CRPA identified in ICU patients with respiratory infections is common.
  - Co-resistance among 1st line beta-lactams (piperacillin/tazobactam, cefepime, and meropenem) is frequently observed and limits empiric choices for the management of HABP/VABP.
- Assessing CRPA frequency may be useful for identifying inflection points in which newer agents could be considered.
  - Based on these data, in settings where CRPA frequency ≥ 20%, susceptibility testing of newer antipseudomonal agents (ceftolozane/tazobactam; imipenem/relebactam) or consideration for antibiotic modification may be warranted.
- Despite the frequency of CRPA, ceftolozane/tazobactam and imipenem/relebactam may provide robust activity against isolates obtained from lower respiratory tract specimens.

Citations

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