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Phenotypic–Genotypic Concordance and Antibiotic Combination Synergy in Multidrug-Resistant Klebsiella pneumoniae: A Comparative Analysis of Clinical Isolates

(Research Paper based on the doctoral thesis)

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ABSTRACT

Background: Managing hospital infections caused by multidrug-resistant Klebsiella pneumoniae is challenging. Molecular resistance markers do not always predict phenotypic results. The aim of this study was to compare phenotypic and genotypic results of antimicrobial resistance and assess the preliminary in vitro activity of antimicrobial combinations. This single center laboratory study included 100 Enterobacteriaceae, 50 of which were K. pneumoniae. The isolates were tested for antimicrobial susceptibility to 13 antibiotics. Extended spectrum beta-lactamase (ESBL) and carbapenemase activity were tested. Five resistance genes were PCR amplified and 10 checkerboard assays were performed on neonatal isolates. Paired concordance was evaluated with Cohen's kappa and exact McNemar's test. Results: The 50 K. pneumoniae isolates were multidrug-resistant, and nine were extensively drug-resistant. ESBL activity was seen in 35 (70%) of the isolates, and 36 (72%) had CTX-M. Other genes identified were blaNDM-1 (24, 48%), blaKPC (11, 22%). ESBL and blaCTX-M concordance was 70% (kappa = 0.272). Blu Carba NP and blaNDM-1/blaKPC concordance was 62% (kappa = 0.317). MMV675968 combined with either colistin or meropenem yielded a FICI of 0.50. The solithromycin combination yielded a FICI of 0.75. Paired concordance was limited, and two of the combinations evaluated met the assay-specific synergy criteria. Molecular tests should not replace phenotypic tests. Results of checkerboard tests should be validated by other methods.

1. INTRODUCTION

Effective treatment of invasive bacterial infections is threatened by the development of antibiotic resistance. The World Health Organization (WHO) has identified antibiotic-resistant Enterobacterales (most notably Escherichia coli) and antibiotic-resistant *Klebsiella pneumoniae* as two of the most critical threats to public health. In the US and Europe, hospital-acquired infections and outbreaks due to multidrug-resistant (MDR) *Klebsiella pneumoniae* are of growing concern, and it has recently been classified as a critical threat to global public health. MDR-*K. pneumoniae*

lineages are capable of acquiring and distributing extensively mobile genetic elements (MGEs) that carry antimicrobial resistance [1,2,3,4,5].

It is important to note that the absence of a particular gene does not reflect resistance. Conversely, the presence of a given resistance gene does not necessarily confer resistance to that antibiotic. Resistance to an antibiotic is a multifactorial phenomenon, and an assortment of mechanisms may be operating in conjunction. The detection of a particular gene may reflect either the absence or presence of resistance to that particular antibiotic. For example, a positive PCR assay for a particular gene may reflect resistance to that antibiotic, or a negative assay may reflect the absence of resistance to that antibiotic [11].

A 2024 national surveillance report by India documented emerging multi-drug resistance of *K. pneumoniae*. This report reinforced the need for comprehensive research focused on characterizing the molecular and phenotypic basis of antibiotic resistance at individual hospitals and health care facilities [8]. The consequences of MDR-*K. pneumoniae* in neonatal populations are of particular concern. For example, in a multilateral study, *K. pneumoniae* was among the leading causes of culture-confirmed neonatal sepsis [9]. MDR-*K. pneumoniae* is a global public health threat and emerging evidence supports the need for more research focused on characterizing neonatal populations and neonatal outbreaks.

This study focuses on a static drug interaction test, which has limitations when used in the clinical setting. The study examines a defined collection of hospital isolates, and reanalyzes paired classifications. It also describes associations between selected resistance markers and antimicrobial susceptibility. It assesses fractional inhibitory concentration (FIC) indices between MMV675968 and colistin, meropenem, and solithromycin. This research provides reproducible agreement among three paired comparisons, and provides interpretable analysis of the same cohort's preliminary checkerboard studies.

2. MATERIALS AND METHODS

2.1 Study design and isolates. The laboratory analysis was performed at Aashirwad Multispeciality Hospital, Patiala, Punjab. Of 100 Enterobacteriaceae clinical isolates, 50 were identified as *Klebsiella pneumoniae*. The specimens included blood (n=15), sputum (13), urine (13), wound swab (8) and endotracheal aspirate (1). The ten isolates from the neonatal intensive care unit formed the pre-defined combination-testing subgroup. The study analyzes the data collected for the thesis; it does not assess newly collected specimens.

2.2 Phenotypic testing. Minimum inhibitory concentrations (MICs) and susceptibility/intermediate/resistance determinations for 13 antimicrobials reported in the thesis were abstracted. Also, phenotypic testing for ESBL, Blue Carba NP, and the MHT were abstracted. The reported assay methods and breakpoints were analyzed descriptively. CLSI M100 and EUCAST documents (11,12) were referenced for interpreting the standards applied. Particular caution was taken for colistin and tigecycline, as both the standards and the organism-drug breakpoints can vary.

2.3 Genotypic testing. Colony PCR was performed to detect blaCTX-M, blaNDM-1, blaKPC, mcr-1 and mcr-2. The combined carbapenemase gene comparator was positive if either blaNDM-1 or blaKPC was detected. The absence of blaOXA-48-like, blaVIM, blaIMP and chromosomal polymyxin resistance genes was considered an explicit analytical limit.

2.4 Checkerboard assay. Ten neonatal isolates were subjected to three paired-drug assays: MMV675968 along with colistin, meropenem and solithromycin. Each FIC was equal to the MIC of the drug in combination divided by the MIC of the drug alone; FICI was the sum of the two FICs. According to the source interpretation, FICI was ≤0.50, >0.50-4, and >4 indicated synergism, additive/indifference, and antagonism, respectively [17]. The recorded isolate-level FICI values were identical for each combination; therefore, no variation was expected between isolates or replicates and no significance test was performed.

2.5 Statistical analysis. Forty-nine isolates (denominator = 50, except subgroup analyses) were subjected to percentage agreement, Cohen's κ and McNemar's exact test. Wilson 95% confidence intervals of agreement proportions were reported. Association statistics of Blue Carba NP with meropenem resistance were reported by the source. All other statistics were reported by the source. A conventional $p < 0.05$ was used; however, due to multiple comparisons and small sample sizes, results were interpreted broadly.

3. RESULTS

3.1 Isolates and susceptibility. Fifty percent (50/100) of the initial Enterobacteriaceae collection was identified as *K. pneumoniae*. Blood was the most prevalent specimen at 30% (30/100). Sputum and urine each comprised 26% (26/100) of the collection. All (100%) of the 50 isolates were categorized as MDR, and 18% (9/50) were XDR. The mean number of resistant agents was 6.36 ± 1.48 of 13. Ampicillin had the highest level of resistance, 44/50 (88%). Thirty-eight of 50 (76%) isolates were resistant to tetracycline. Thirty-two of 50 (64%) of the isolates were resistant to levofloxacin. Twenty-eight of 50 (56%) of the isolates were resistant to trimethoprim. Resistance to cefoxitin, ceftazidime and ciprofloxacin each accounted for 27 (54%) of the 50 isolates. Meropenem had 16 (32%) of the 50 isolates resistant, and colistin had five (10%) of the 50 isolates resistant. The complete 13 agent profiles are presented in Table 1 and Figure 1.

3.2 Enzyme phenotypes and resistance genes. ESBL assays confirmed the presence of 35 (70%) of the 50 isolates. Of the remaining 15 (30%) of the isolates, Blue Carba NP and MHT detected 14 (28%) and 15 (30%) of the 50 isolates respectively. Of the 50 isolates, 47 (94%) contained at least one of the five target genes. blaCTX-M was the most prevalent target (36; 72%), followed by blaNDM-1 (24; 48%), blaKPC (11; 22%), mcr-1 (8; 16%) and mcr-2 (5; 10%). Figure 2 demonstrates molecular prevalence. Proportions of genes must not be summed, as expected overlap exists.

3.3 Concordance. For ESBL-blaCTX-M, 28 double-positive pairs, 7 double-negative pairs, and 15 discordant pairs were found, yielding an observed agreement of 70.0% (95% CI 56.2-80.9%) and $\kappa = 0.272$. Exact McNemar test indicated no directional imbalance for the 7 discordant pairs ($p = 1.000$). Of the 22 Blue Carba NP-positive pairs, 14 were discordant, and 18 favored the gene. For the next test, wherein MHT was compared to the same gene, 28 pairs showed agreement (56.0%; 95% CI 42.3-68.8%), and $\kappa = 0.217$. Of the 56 discordant pairs, 20 were phenotype-negative/gene-positive, and the other 2 were reversed ($p < 0.001$). The remaining test wherein MHT was compared to Blue Carba NP yielded agreement of 62.0% (95% CI 48.2-74.1%), $\kappa = 0.317$. Of the 42 discordant pairs, 14 were positive for Blue Carba NP and MHT, 17 were negative for both, and 19 were discordant. The complete concordance data are summarized in Tables 2-4 and illustrated in Fig. 3.

3.4 Associations. Among the 16 meropenem-resistant isolates, 14 were Blue Carba NP-positive, and among the 34 meropenem-susceptible isolates, only 1 was Blue Carba NP-positive. Fisher's Exact Test yielded an odds ratio of 231.0 ($p = 1.82 \times 10^{-9}$), though sparse cells lead to imprecise measurement. The study noted an association between sample type and ESBL ($\chi^2 = 10.88$, four degrees of freedom, $p = 0.028$), however 6 of 10 expected cells contained less than 5 observations. The study also noted no strong association between ESBL and XDR (Fisher's $p = 0.705$) or between the number of resistance-conferring genes and the number of resistant antibiotics (Spearman $\rho = 0.107$, $p = 0.461$). The results discussed herein are not independent observations.

The ten neonatal isolates were multidrug resistant (MDR); four were extensively drug resistant (XDR). The MICs of MMV675968 in combination with colistin dropped from 4 μg/mL and 2 μg/mL to 1 μg/mL and 0.5 μg/mL, respectively, yielding a FIC Index (FICI) of 0.25 + 0.25 = 0.50. In the combination with meropenem, the MICs dropped to 2 μg/mL and 1 μg/mL yielding a FICI of 0.50. In combination with solithromycin the MICs dropped to 2 μg/mL and 4 μg/mL yielding a FICI of 0.25 + 0.50 = 0.75. The first two combinations (with colistin and meropenem) were synergistic according to the pre-defined synergy threshold of the study; solithromycin was additive/indifferent. No antagonism was observed. The measured pairwise interactions and the analysis workflow are summarized in Tables 4 and 5 respectively.

Table 1. Antimicrobial susceptibility results among clinical *K. pneumoniae* isolates (n = 50).

Antimicrobial agent	Susceptible, n (%)	Intermediate, n (%)	Resistant, n (%)
Ampicillin	1 (2%)	5 (10%)	44 (88%)
Tetracycline	8 (16%)	4 (8%)	38 (76%)
Levofloxacin	15 (30%)	3 (6%)	32 (64%)
Trimethoprim	22 (44%)	0 (0%)	28 (56%)
Cefoxitin	20 (40%)	3 (6%)	27 (54%)
Ceftazidime	16 (32%)	7 (14%)	27 (54%)
Ciprofloxacin	15 (30%)	8 (16%)	27 (54%)
Aztreonam	21 (42%)	8 (16%)	21 (42%)

Antimicrobial agent	Susceptible, n (%)	Intermediate, n (%)	Resistant, n (%)
Nitrofurantoin	23 (46%)	8 (16%)	19 (38%)
Tigecycline	32 (64%)	0 (0%)	18 (36%)
Meropenem	29 (58%)	5 (10%)	16 (32%)
Amikacin	32 (64%)	2 (4%)	16 (32%)
Colistin	45 (90%)	0 (0%)	5 (10%)

From thesis Table 4.5. Recorded categories are reproduced as reported; breakpoint-based categorization, particularly for colistin and tigecycline, may require reassessment against current standards. MDR: 50/50; XDR: 9/50.

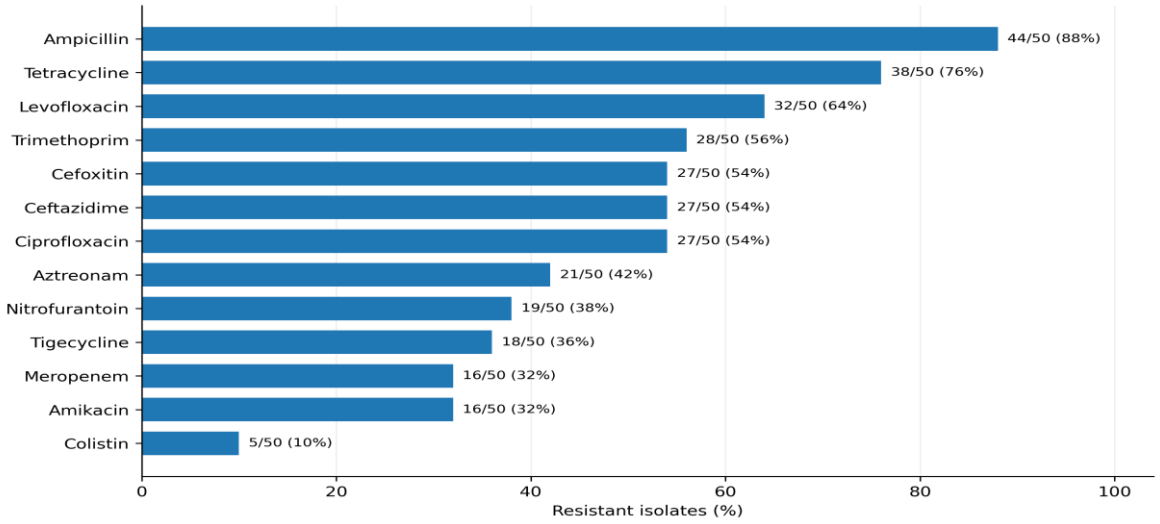


Figure 1. Proportion of isolates classified as resistant to 13 antimicrobial agents (n = 50).

Table 2. Paired phenotype–genotype findings (n = 50 per comparison).

Paired classification	Both +	Both –	Phenotype + / gene –	Phenotype – / gene +
ESBL versus blaCTX-M	28	7	7	8
Blue Carba NP versus blaNDM/KPC	14	17	1	18
MHT versus blaNDM/KPC	12	16	2	20

The carbapenemase genotype was defined as presence of blaNDM-1 and/or blaKPC. These panels are not independent clinical reference standards.

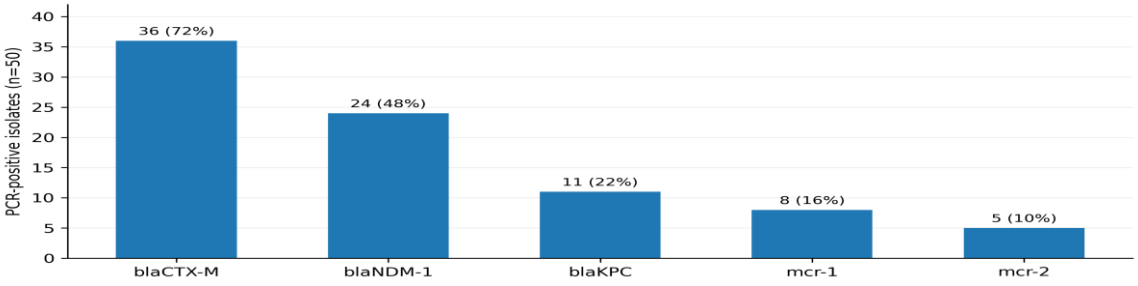


Figure 2. Prevalence of five PCR-detected resistance genes among 50 isolates.

Table 3. Chance-adjusted concordance and paired-test results calculated from thesis counts.

Comparison	Agreement (95% CI)	Cohen κ	Exact McNemar p
ESBL / blaCTX-M	70.0% (56.2–80.9%)	0.272	1.000
Blue Carba NP / blaNDM/KPC	62.0% (48.2–74.1%)	0.317	0.00008
MHT / blaNDM/KPC	56.0% (42.3–68.8%)	0.217	0.00012

Wilson confidence intervals for observed agreement. McNemar tests evaluate direction of discordance, not diagnostic accuracy. These estimates are calculated from documented 2×2 counts.

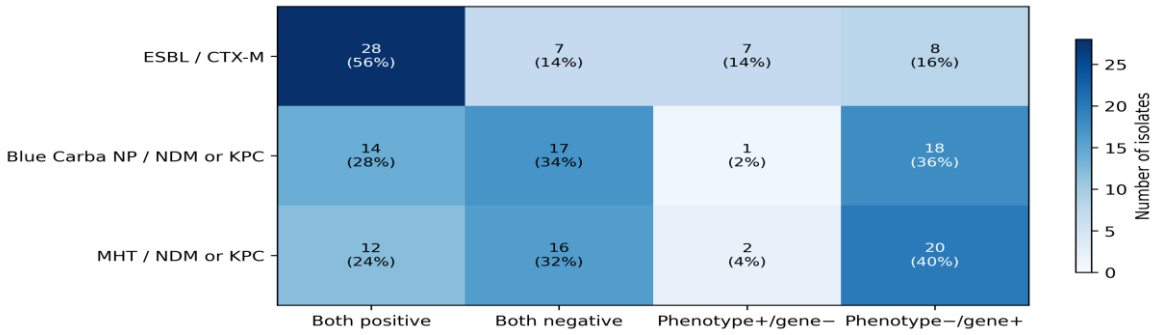


Figure 3. Paired classifications for the three phenotype–genotype comparisons (each n = 50).

Table 4. Thesis-reported neonatal checkerboard MICs (n = 10 isolates per drug pair).

MMV675968 plus	A MIC alone → paired	B MIC alone → paired	FICI	Classification
MMV675968 + colistin	4 → 1	2 → 0.5	0.50	Synergy
MMV675968 + meropenem	8 → 2	4 → 1	0.50	Synergy
MMV675968 + solithromycin	8 → 2	8 → 4	0.75	Additive/indifferent

MIC in μg/mL. A = MMV675968; B = named coagent. All 10 neonatal isolates had the same recorded MIC and FICI within each combination. FICI ≤0.50 was classified as synergy.

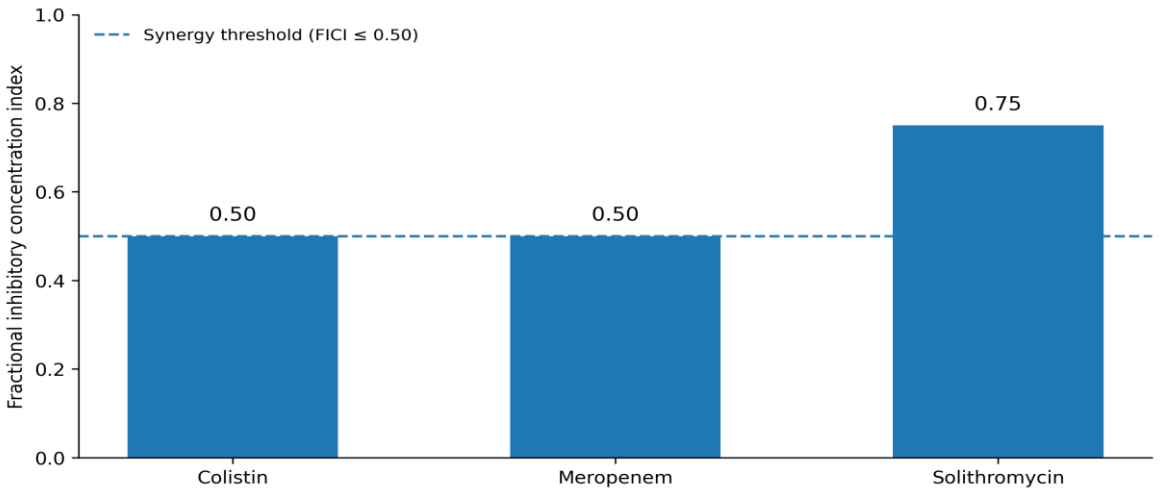


Figure 4. FICI values for the three combinations; dashed horizontal line denotes the threshold for synergy.

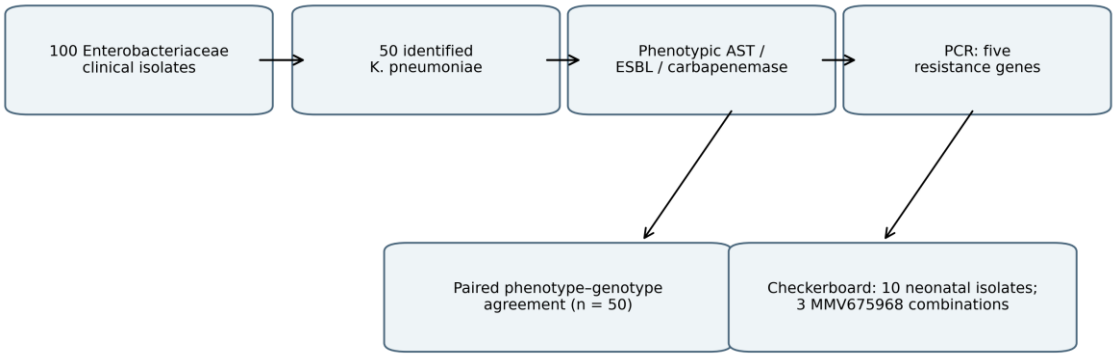


Figure 5. Overview of the thesis-derived isolate characterization and analysis workflow.

4. DISCUSSION

This analysis identified high resistant burden in a hospital cohort deliberately defined by a positive urine culture, and relatively low, chance-adjusted agreement between phenotypic and genotypic labels. In the context of neither test modality being a true comprehensive reference standard, the observed agreement of 70%, 62% and 56% was moderate. However, κ values of 0.217, 0.259 and 0.317, indicated that in all three cases, agreement was below expected chance, and reflected under-coverage.

The type of discordance is informative. Out of the eight blaCTX-M positive patients, all were ESBL negative. This could be due to expression differences, or methodological sensitivity/interference. Conversely, the seven ESBL positive patients were blaCTX-M negative, which does not preclude the presence of other determinants for ESBLs [6]. In both Blue Carba NP and MHT comparisons, the vast majority of positive cases were phenotype negative, and the reverse was observed. These types of disparities do not necessarily mean that the test or PCR is intrinsically incorrect; each provides evidence for a different biological construct, and the five-target panel excludes other relevant determinants. Published hospital-based studies have reported extended gene diversity and variable genotype-phenotype relationships [14-16].

The prevalence of blaCTX-M is consistent with CTX-M-type ESBLs' international dominance. The presence of blaNDM-1 reflects the South Asian penchant for metallo-β-lactamases. The high carriage of blaNDM-1 should not be interpreted to mean 50% of the isolates were resistant to meropenem. Only 32% of the isolates were found to be resistant to meropenem. Resistant isolates that tested negative for screened carbapenemases may reflect the presence of other mechanisms. Therefore, combination of phenotypic and genotypic approaches to screening is essential to overcome antimicrobial stewardship challenges.

The association of Meropenem-Blue Carba NP was striking. However, the odds ratio of the association is based on only 1 of 34 tested isolates. The extremely large odds ratio, based on sparse data, may not be reliable, and its interpretation should be done with caution. Likewise, the significant association of the specimens with ESBL should also be interpreted with caution because the assumption about expected counts was not satisfied. Broader

recruitment with sufficient sample size, appropriate contingency testing, and sufficient reporting of effect sizes and confidence intervals may provide better estimates and improve interpretability of small studies.

The cases of neonates deserve special consideration. Multinational neonatal sepsis surveillance and an Indian neonatal outbreak reported bloodstream infections of resistant *Klebsiella* [9, 13]. Four of the 10 neonatal isolates were XDR. However, this subgroup cannot reflect the hospital isolates. Reporting FICI values based on the MICs for all 10 isolates is not indicative of assay reproducibility. Without replicate level data, and given that different clinical isolates of the same organism may exhibit variability of antibiotic resistance, the values reported would be of limited utility to describe clinical synergism.

Reported FICI values for colistin and meropenem are at the synergy boundary. Reproducibility for classifying antimicrobial combinations as synergistic requires that orthogonal time-kill and checkerboard assays be performed [17]. The outcome of a combination of antibiotics in a given synergistic assessment may be largely attributable to the components of the combination. Colistin or fosfomycin combinations may have shown synergism in laboratory assessments against *K. pneumoniae* [18, 19], and combinations of newer β-lactam antibiotics may have shown synergism against carbapenem-resistant *K. pneumoniae* [20]. Like all antibiotic combinations, clinical applications of MMV675968 must be assessed in the context of different *Klebsiella* clinical isolates.

Favorable checkerboard interactions only suggest potential synergy in a regimen. Results from a randomized trial of colistin-based therapy did not establish meropenem added to colistin-based therapy as having general superiority for serious infections due to carbapenem-resistant organisms. Elsewhere, guidance recommends a more rational selection of antimicrobials based on the resistance mechanisms in the organism, with caution against indiscriminate use of older broad spectrum antibiotics. The clinical development of MMV675968 would require further evaluation for safety, mechanism of action, exposure/dose, and the anticipated effect of the regimen. As the challenge of antimicrobial drug discovery remains (including the lack of new classes of antibiotics), an acceptable level of exploration of MMV675968 appears justified.

When considering results from gene-panel testing, kappa adds value by accounting for marginal distribution and prevalence. These should be interpreted in the context of the testing platforms, the specimen and the cohort.

Additional consideration should be given to interpret colistin results. Chromosomal mechanisms, including efflux, may play a role in colistin resistance. Positive results from molecular markers of resistance should be validated through standardized broth microdilution and other cell-based assays.

Generally, the use of a molecular method to determine synergy should be complemented by phenotypic MIC testing. These should be integrated with available epidemiology, the infection site and stewardship to guide appropriate management.

Also, the three combination arms were tested in the same ten isolates, rather than three unrelated groups. Percentages, based on thirty determinations, capture the essence of an assay; however, they do not necessarily represent thirty independent patient observations. This distinction is critical when making formal comparative inference. In addition, the quoted variances should be interpreted along the lines of the sample-size calculations for future studies.

Though the dataset is helpful at the local level, a sample comprised solely of MDR isolates also gives a biased, yet elevated, estimate of the frequency of resistance determinants. Therefore, estimates reported here are specific to the sample and should not be attributed to the general population.

Future, larger, multicentre studies should document the order of participant recruitment, prior exposure to antibiotics, and the source of the sample, as well as whether the sample is an infection or a colonization. MIC dilution series, PCR and DNA controls, assay replicates, and identifiers of the analyzed isolates should also be reported. This would enable investigators to resolve inconsistencies across studies. The combination assessment should be done using independent repeated checkerboard and time-kill assays. Reporting the actual data, rather than classified categories, would be helpful for both interpretation and definition of the following research.

5. STUDY LIMITATIONS

Restricted to a single hospital, 50 *K. pneumoniae* isolates, and 10 neonatal isolates undergoing combination testing, limited the scope of this study. The five-gene PCR panel does not offer a complete characterization of the resistome, and therefore, this study was limited in predicting mechanisms of antibiotic resistance. The study was further restricted by the lack of inclusion of whole-genome sequencing, time-kill studies, pharmacokinetic studies, and the evaluation of clinical outcomes. MHT is less reliable compared to newer carbapenemase tests, and it may be the case that different methods or breakpoints may not be directly equivalent to the latest standards. The 50 *K. pneumoniae* isolates in this study were all classified as MDR, thus limiting comparisons to susceptible controls. Small and sparse contingency cells restrict the ability to enhance precision, and identical recorded checkerboard values do not allow for variation between isolates. No raw technical replicate data were available for comparison to assess the quality of assays and validate isolate discrepancies.

6. CONCLUSION

K. pneumoniae isolates exhibited extensive phenotypic antibiotic resistance and carriage of target β-lactamase genes. Phenotype-genotype correlation was 56% to 70% with overall low-to-moderate adjusted concordance and high directional discordance in comparisons of carbapenemases. From the data collected, integrated approaches of phenotypic susceptibility testing and molecular surveillance were more preferable over substitution of one approach over the other. Based on the results of checkerboard assays, MMV675968 met the criteria for synergy with meropenem and colistin, however, FICI values were exact at the cutoff and were from the small, neonatal, subset.

Furthermore, independent experiments and broader molecular characterization are warranted prior to considering clinical utility.

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