UTILITY OF A COMBINATION ANTIBIOGRAM FOR TREATING *PSEUDOMONAS AERUGINOSA*

[1]Lindsay Thurman, [1]Nathan Fewel, [1]Michael Rose and [2,3]Eileen Stock

[1]Central Texas Veterans Health Care System, Department of Veterans Affairs, Temple, TX, USA
[2]Center for Applied Health Research,
Central Texas Veterans Health Care System in Collaboration with Scott and White Healthcare, Temple, TX, USA
[3]Texas A and M Health Science Center, College of Medicine, Bryan, TX, USA

ABSTRACT

Empiric combination antibiotic therapy is often used to treat severe *P. aeruginosa* infections. Combination antibiograms have been employed to assist clinicians in selecting the most effective two-drug antibiotic regimens. The objectives of this study were to develop a combination antibiogram in order to compare beta-lactam monotherapy versus dual-therapy with a fluoroquinolone or aminoglycoside, identify optimal combination regimens, describe the differences between combination therapies with an aminoglycoside versus a fluoroquinolone and to evaluate susceptibility rates based on the source of infection and Intensive Care Unit (ICU) or non-ICU location. A retrospective observational study at a Veterans Affairs (VA) hospital in the Southwestern region of the U.S. was conducted. *P. aeruginosa* isolates were collected between January 2008 and February 2012 in hospitalized veterans. A total of 374 isolates were included, of which 61 (16%) were obtained from the ICU. Susceptibility rates for monotherapy with a beta-lactam ranged from 83.7 to 90.6%. Collectively, all *P. aeruginosa* isolates benefited in coverage with the addition of a fluoroquinolone or an aminoglycoside to one of the beta-lactams considered for monotherapy (p<0.01 for each comparison). Monotherapy with a beta-lactam could be considered for mild to moderate wound infections which had beta-lactam susceptibility rates greater than 90% and the addition of a fluoroquinolone did not significantly extend the spectrum. Combination susceptibility rates ranged from 89.0 to 99.2%. Dual therapy of a beta-lactam with amikacin or tobramycin resulted in significantly better coverage than with a fluoroquinolone (p<0.03 for all combinations). For severe infections dual therapy with tobramycin or amikacin may be preferred over fluoroquinolones, but the risks versus benefits of aminoglycoside therapy must be weighed for each patient. In conclusion, combination antibiograms are useful for evaluating the treatment of *P. aeruginosa*. Choosing the ideal antibiotic regimen ultimately deals with many factors and results of this combination antibiogram are only specific to this institution.

Keywords: Combination Antibiogram, *Pseudomonas aeruginosa*, Combination Therapy, Monotherapy

1. INTRODUCTION

Empiric combination antibiotic therapy is recommended for the treatment of *P. aeruginosa* infections particularly in the case of bacteremia, endocarditis, or pneumonia (Baddour *et al*., 2005; Baltch and Smith, 1985). The goal for using combination therapy to increase the likelihood of effective coverage, reduce the emergence of resistance and to provide additive or synergistic killing (Ibrahim *et al*., 2000; Iregui *et al*., 2002; Kollef *et al*., 1999; Garnacho-Montero *et al*., 2007; Lister and Wolter, 2005). Dual therapy usually consists of an antipseudomonal beta-lactam plus an aminoglycoside or fluoroquinolone, but increasing rates of fluoroquinolone resistance have decreased their efficacy in many areas. Lockhart *et al*. (2007) evaluated gram-negative bacilli resistance rates in ICUs from an average of 70 hospitals per year from 1993 to 2004. The percentage of *P. aeruginosa* isolates

Corresponding Author: Nathan Fewel, Central Texas Veterans Health Care System, Department of Veterans Affairs, Temple, TX, USA Tel: (254) 743-2944, Fax: (254) 743 - 2202

resistant to ciprofloxacin increased from an average of 11.2% at the beginning of the study period to 28.9% at the end of the study period.

In vitro studies have shown increased activity of either aminoglycosides or quinolones combined with a beta-lactam against *P. aeruginosa*, but there is limited clinical data to suggest that these combinations lead to improved patient outcomes (Giamarellou *et al.*, 1984; Hollander *et al.*, 1997; Karlowsky *et al.*, 2005; Lister *et al.*, 2006). Empiric combination therapy for *P. aeruginosa* bacteremia and ventilator-associated pneumonia has resulted in lower mortality compared to monotherapy (Hilf *et al.*, 1989; Fowler *et al.*, 2003). A meta-analysis by Paul *et al.* (2004) compared combination therapy with an aminoglycoside to monotherapy for severe infections and found that dual therapy did not provide a survival benefit and was associated with significantly greater rates of nephrotoxicity. Despite the inconclusive evidence for patient outcomes when using combination therapy, double coverage of *P. aeruginosa* remains a common practice.

To assist clinicians in selecting the most effective two-drug antibiotic regimen, combination antibiograms have been employed (Apisarnthanarak and Mundy, 2008; Christoff *et al.*, 2010; Fox *et al.*, 2008; Mizuta *et al.*, 2006; Pogue *et al.*, 2011). These antibiograms can be displayed in matrix form showing the percentage of isolates susceptible to various single agents and combinations of antibiotics. An advantage of a combination antibiogram is the ability to assess cross-resistance between specific antibiotics, whereas a standard antibiogram provides susceptibility rates for individual antibiotics. As susceptibility patterns are known to be institution-specific, it is important to develop antibiograms on a local basis. The aim of combination antibiograms is to permit clinicians to make a more informed decision in the section of empirical antimicrobial therapy, appropriately weighing the risks and benefit of combination antimicrobial treatment. With many areas having high rates of fluoroquinolone resistance it may be beneficial to evaluate combination susceptibility rates with fluoroquinolones and to compare it with aminoglycosides. Thus, the purpose of this study was to examine susceptibility rates for anti-pseudomonal beta-lactam agents, assessing the marginal effect of double-coverage with a fluoroquinolone or aminoglycoside. Differences in susceptibility rates between beta-lactam combinations and by isolate location and sources were also assessed.

2. MATERIALS AND METHODS

2.1. Study Design and Patient Population

A retrospective observational study was performed at a single Department of Veterans Affairs (VA) facility located in the Southwestern region of the U.S. The study was approved by the local institutional review board prior to study initiation. A report was generated that included all positive cultures for *P. aeruginosa* isolates collected from patients with an inpatient hospital stay at the facility between January 2008 and February 2012. Detailed patient information was obtained through Computerized Patient Record System (CPRS). Patients had to be age 18 to 89 years at the time of culture collection and be hospitalized within seven days of the date when the isolate was obtained. For patients with multiple qualifying hospitalizations, only their first culture collection was considered. A total of 374 *P. aeruginosa* isolates from patients meeting these criteria were identified.

2.2. Data Collection and Study Definitions

Isolates were collected from patients in the Intensive Care Unit (ICU) and non-ICU locations. The Central Texas VA's main medical center is a 189 bed teaching hospital with 18 ICU beds. Isolates were cultured from various sources including the urine, sputum, wound, blood and other sources (i.e., bone, testes and ulna). Antimicrobial susceptibility of *P. aeruginosa* to antimicrobial agents commonly used for empirical coverage of gram-negative pathogens at this facility was determined. Optimal beta-lactam monotherapy of piperacillin/tazobactam, cefepime and imipenem/cilastatin was assessed and compared to combination therapy involving one of these antibiotics with a fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin). Each isolate was recorded as susceptible or resistant to a specific antibiotic by accessing CPRS for culture results. Intermediate susceptibilities were classified as resistant. For dual therapy susceptibilities, if the isolate was susceptible to at least one of the two antibiotics, then the isolate was classified as susceptible. This approach was modeled after several earlier studies utilizing combination antibiograms. The antibiotic sensitivities of *P. aeruginosa* were tested using the VITEK 2 automated system (bioMérieux) with one exception, *P. aeruginosa* isolates were tested for susceptibility to piperacillin/tazobactam by disk diffusion. All tests were performed in compliance with the current standards of the Clinical and Laboratory Standards Institute (CLSI).

2.3. Statistical Analysis

Monotherapy of the beta-lactam antibiotics versus double-coverage was compared collectively for all isolates, as well as by location and source. In order to examine improved susceptibility with combination therapy to beta-lactam monotherapy, McNemar's test

was employed to test the null hypothesis of marginal homogeneity. Evidence supporting the alternative hypothesis would suggest that combination therapy was superior to antibiogram monotherapy. Proportion tests were also employed to compare dual therapies of beta-lactam with an aminoglycoside to beta-lactam with a fluoroquinolone. A type I error of $\alpha = 0.05$ was assumed throughout. All analyses were performed using SAS, Version 9.2 (SAS Institute, Cary, NC).

3. RESULTS

Among the total of 374 isolates, 61 (16.3%) were obtained from the ICU. The most common sources of isolates were from urine sources (36.1%) and sputum (35.6%), followed by wounds (16.3%), blood (6.1%) and then other sources (5.9%). Patients from whom isolates were collected averaged 68 years of age (SD = 11), ranging from 34 to 89 years (median = 67).

For monotherapy of a beta-lactam, susceptibility rates of isolates were 83.7% (cefepime), 86.4% (piperacillin/tazobactam) and 90.6% (imipenem/cilastatin). Monotherapy of a fluoroquinolone or an aminoglycoside provided coverage of 75.9% (levofloxacin), 78.1% (ciprofloxacin), 84.8% (gentamicin), 94.1% (tobramycin) and 96.0% (amikacin). Collectively, all *P. aeruginosa* isolates benefited in coverage with the addition of a second antibiotic to one of the beta-lactams ($p<0.01$ for each comparison, **Table 1**). With dual therapy, coverage increased, ranging from 89.0% (cefepime + levofloxacin) to 99.2% (imipenem/cilastatin + amikacin).

Similar susceptibility rates for beta-lactam monotherapy were observed among isolates from non-ICU locations with the greatest coverage observed for imipenem/cilastatin (92.0%), then piperacillin/tazobactam (86.6%) and lastly cefepime (84.7%). In the ICU, susceptibility was greatest for piperacillin/tazobactam (85.3%). Comparing susceptibility rates across locations, the greatest difference in rates was observed for imipenem/cilastatin (83.6% ICU Vs. 92.0% non-ICU). Coverage for piperacillin/tazobactam varied the least (85.3% ICU Vs. 86.6% non-ICU).

Similar to the overall sample, patterns of increased coverage with dual therapy were observed among non-ICU isolates ($p<0.01$ for all comparisons). This was also true of most cases in the ICU, except for the addition of a fluoroquinolone to piperacillin/tazobactam, which did not significantly improve coverage.

Susceptibility of *P. aeruginosa* isolates from a urine source to monotherapy of a beta-lactam resembled that of the sample of all isolates (**Table 2**). For isolates from a wound source, susceptibility rates were larger and less variable than that of the overall sample for monotherapy with each of the beta-lactam agents (ranging 90.2 to 91.8%). The greatest variability in susceptibility between beta-lactam agents was observed for isolates with blood sources 82.6% (cefepime and piperacillin/tazobactam) to 100% (imipenem/cilastatin). Coverage with monotherapy of a fluoroquinolone was reduced among urine sources (68.2% ciprofloxacin; 64.4% levofloxacin). Among isolates from urine and sputum sources, greater coverage was achieved with dual therapy, except for the case of imipenem/cilastatin + levofloxacin for sputum sources (91% versus 93.2%; p = 0.08). In many of the remaining sources, dual therapy resulted in 100% coverage. For wound and blood sources, dual therapy with a fluoroquinolone did not improve coverage. *P. aeruginosa* susceptibility rates were the lowest for monotherapy with a fluoroquinolone for blood isolates (69.6%). Amikacin resulted in 100% coverage for isolates from wound and blood sources.

Table 1. Percentage of *P. aeruginosa* organisms susceptible to beta-lactam monotherapy versus combination antimicrobial therapy overall and by location (N = 374)

Location beta-lactams	Monotherapy N (%)	Aminoglycoside						Fluoroquinolones			
		Amikacin susceptible		Gentamicin susceptible		Tobramycin susceptible		Ciprofloxacin susceptible		Levofloxacin susceptible	
		%	p	%	p	%	p	%	p	%	p
All (n = 374)		359 (96.0)		317 (84.8)		352 (94.1)		292 (78.1)		284 (75.9)	
Piperacillin/tazobactam	323 (86.4)	370 (98.9)	<0.01	352 (94.1)	<0.01	359 (96.0)	<0.01	338 (90.4)	<0.01	338 (90.4)	<0.01
Cefepime	313 (83.7)	366 (97.9)	<0.01	342 (91.4)	<0.01	357 (95.5)	<0.01	335 (89.6)	<0.01	333 (89.0)	<0.01
Imipenem/cilastatin	339 (90.6)	371 (99.2)	<0.01	360 (96.3)	<0.01	366 (97.9)	<0.01	353 (94.4)	<0.01	354 (94.7)	<0.01
ICU (n = 61)		57 (93.4)		49 (80.3)		58 (95.1)		48 (78.7)		47 (77.1)	
Piperacillin/tazobactam	52 (85.3)	60 (98.4)	<0.01	57 (93.4)	0.03	59 (96.7)	<0.01	55 (90.2)	0.080	55 (90.2)	0.080
Cefepime	48 (78.7)	60 (98.4)	<0.01	53 (86.9)	0.03	58 (95.1)	<0.01	52 (85.3)	<0.05	52 (85.3)	<0.05
Imipenem/cilastatin	51 (83.6)	60 (98.4)	<0.01	56 (91.8)	0.03	59 (96.7)	<0.01	55 (90.2)	<0.05	55 (90.2)	<0.05
Non-ICU (n = 313)		302 (96.5)		268 (85.6)		294 (93.9)		244 (78.0)		237 (75.7)	
Piperacillin/tazobactam	271 (86.6)	310 (99.0)	<0.01	295 (94.3)	<0.01	300 (95.9)	<0.01	283 (90.4)	<0.01	283 (90.4)	<0.01
Cefepime	265 (84.7)	306 (97.8)	<0.01	289 (92.3)	<0.01	299 (95.5)	<0.01	283 (90.4)	<0.01	281 (89.8)	<0.01
Imipenem/cilastatin	288 (92.0)	311 (99.4)	<0.01	304 (97.1)	<0.01	307 (98.1)	<0.01	298 (95.2)	<0.01	299 (95.5)	<0.01

Table 2. Percentage of *P. aeruginosa* organisms susceptible to beta-lactam monotherapy versus combination antimicrobial therapy by isolate source (N = 374)

| | | Aminoglycosides | | | | | | Fluoroquinolones | | | |
| | | Amikacin susceptible | | Gentamicin susceptible | | Tobramycin susceptible | | Ciprofloxacin susceptible | | Levofloxacin susceptible | |
Source *Beta-lactams*	Monotherapy N (%)	%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
Urine (*n* = 135)		132 (97.8)		113 (83.7)		125 (92.6)		92 (68.2)		87 (64.4)	
Piperacillin/tazobactam	115 (85.2)	133 (98.5)	<0.01	126 (93.3)	<0.01	128 (94.8)	<0.01	119 (88.2)	<0.05	119 (88.2)	<0.05
Cefepime	112 (83.0)	133 (98.5)	<0.01	123 (91.1)	<0.01	128 (94.8)	<0.01	118 (87.4)	0.010	116 (85.9)	<0.05
Imipenem/cilastatin	119 (88.2)	134 (99.3)	<0.01	130 (96.3)	<0.01	131 (97.0)	<0.01	125 (92.6)	0.010	126 (93.3)	<0.01
Sputum (*n* = 133)		121 (91.0)		107 (80.5)		123 (92.5)		113 (85.0)		111 (83.5)	
Piperacillin/tazobactam	114 (85.7)	131 (98.5)	<0.01	123 (92.5)	<0.01	127 (95.5)	<0.01	121 (91.0)	<0.01	121 (91.0)	<0.01
Cefepime	106 (79.7)	127 (95.5)	<0.01	117 (88.0)	<0.01	125 (94.0)	<0.01	120 (90.2)	<0.01	118 (88.7)	<0.01
Imipenem/cilastatin	121 (91.0)	131 (98.5)	<0.01	125 (94.0)	<0.05	129 (97.0)	<0.01	125 (94.0)	<0.05	124 (93.2)	0.08
Wound (*n* = 61)		61 (100)		58 (95.1)		61 (100)		51 (83.6)		51 (83.6)	
Piperacillin/tazobactam	56 (91.8)	61 (100)	---	61 (100)	---	61 (100)	---	57 (93.4)	0.32	57 (93.4)	0.32
Cefepime	55 (90.2)	61 (100)	---	60 (98.4)	0.030	61 (100)	---	56 (91.8)	0.32	58 (95.1)	0.08
Imipenem/cilastatin	56 (91.8)	61 (100)	---	60 (98.4)	<0.05	61 (100)	---	58 (95.1)	0.16	59 (96.7)	0.08
Blood (*n* = 23)		23 (100)		18 (78.3)		21 (91.3)		16 (69.6)		16 (69.6)	
Piperacillin/tazobactam	19 (82.6)	23 (100)	---	20 (87.0)	0.32	21 (91.3)	0.16	20 (87.0)	0.32	20 (87.0)	0.32
Cefepime	19 (82.6)	23 (100)	---	20 (87.0)	0.32	21 (91.3)	0.16	20 (87.0)	0.32	20 (87.0)	0.32
Imipenem/cilastatin	23 (100)	23 (100)	---	23 (100)	---	23 (100)	---	23 (100)	---	23 (100)	---
Other (*n* = 22)		22 (100)		21 (95.5)		22 (100)		20 (90.9)		19 (86.4)	
Piperacillin/tazobactam	19 (86.4)	22 (100)	---	22 (100)	---	22 (100)	---	21 (95.5)	0.16	21 (95.5)	0.16
Cefepime	21 (95.5)	22 (100)	---	22 (100)	---	22 (100)	---	21 (95.5)	---	21 (95.5)	---
Imipenem/cilastatin	20 (90.9)	22 (100)	---	22 (100)	---	22 (100)	---	22 (100)	---	22 (100)	---

Table 3. Proportion test results comparing the proportion of *P. aeruginosa* organisms susceptible to dual therapy of a beta-lactam with an aminoglycoside Vs. dual therapy of a beta-lactam with a fluoroquinolone, with p-values reported (N = 374)

| | Dual therapy with aminoglycosides Vs fluoroquinolones | | | | | |
| | Amikacin | | Gentamicin | | Tobramycin | |
Location *Beta-lactams*	Vs. ciprofloxacin	Vs. levofloxacin	Vs. ciprofloxacin	Vs. levofloxacin	Vs. ciprofloxacin	Vs. levofloxacin
All (*n* = 374)						
Piperacillin/tazobactam	< 0.01	< 0.01	0.06	0.06	< 0.01	< 0.01
Cefepime	< 0.01	< 0.01	0.38	0.27	< 0.01	< 0.01
Imipenem/cilastatin	< 0.01	< 0.01	0.23	0.29	0.010	0.020
ICU (*n* = 61)						
Piperacillin/tazobactam	0.05	0.05	0.51	0.51	0.14	0.14
Cefepime	0.01	0.01	0.79	0.79	0.07	0.07
Imipenem/cilastatin	0.05	0.05	0.75	0.75	0.14	0.14
Non-ICU (*n* = 313)						
Piperacillin/tazobactam	<0.01	< 0.01	0.07	0.07	0.01	0.01
Cefepime	<0.01	< 0.01	0.39	0.26	0.01	0.01
Imipenem/cilastatin	<0.01	< 0.01	0.21	0.29	<0.05	0.07

No significant differences in susceptibilities were found when comparing dual therapies involving ciprofloxacin versus dual therapies involving levofloxacin. Dual therapy of a beta-lactam with amikacin or tobramycin resulted in significantly greater coverage than with a fluoroquinolone (p<0.03 for all combinations; **Table 3**). Comparing locations, amikacin resulted in greater susceptibility in non-ICU settings when combined with any beta-lactam and ICU settings if combined with cefepime compared to a fluoroquinolone with a beta-lactam. Combination therapy with tobramycin was observed to have greater susceptibility than with a fluoroquinolone in the non-ICU settings, except for in the case of imipenem/cilastatin + levofloxacin (p = 0.07). Improved coverage with tobramycin versus other fluoroquinolones among isolates from the ICU was not detected. A difference in coverage between gentamicin and a fluoroquinolone with a beta-lactam was also not observed in the sample.

4. DISCUSSION

Several conclusions can be made based on the results of the combination antibiogram. Dual antibiotic therapy

with a fluoroquinolone or an aminoglycoside was superior to monotherapy with a beta-lactam. Monotherapy with a beta-lactam could be considered for mild to moderate wound infections which had beta-lactam susceptibility rates greater than 90% and the addition of a fluoroquinolone did not significantly extend the spectrum. Ciprofloxacin and levofloxacin had very similar susceptibility profiles and were only 64 to 68% effective against urine cultures and did not provide significant benefit when combined with a beta-lactam for blood isolates. Imipenem/cilastatin outperformed other beta-lactams for blood and sputum isolates. Infections from the urine, sputum and blood had the most resistant isolates. For severe infections dual therapy with tobramycin or amikacin may be preferred over fluoroquinolones, but the risks versus benefits of aminoglycoside therapy must be weighed for each patient. Critically ill patients such as those with septic shock may be at greater risk for drug toxicity due to unstable pharmacokinetics and drug interactions. For approximately every 15 to 20 patients treated with dual therapy, 1 patient would benefit from tobramycin or amikacin versus a fluoroquinolone combination. If a *P. aeruginosa* isolate was resistant to a beta-lactam, amikacin would be active 87 to 92% of the time, tobramycin would be active 71 to 78% of the time and a fluoroquinolone would be active 29 to 43% of the time. Combination antibiotic therapy should be deescalated to a single active agent once microbiology and susceptibility results are confirmed. An interdisciplinary approach to managing aminoglycoside therapy including a pharmacy pharmacokinetic consult service may help to improve safety and optimize dosing and monitoring.

There are several limitations to interpreting the results of this study. It was observational and retrospective using isolates over several years and resistance rates fluctuate over time. We encountered a small sample size for patients in the ICU and for bacteremia. Therefore, this limits some of the conclusions we can make for these patients and increases our chances of making a Type II error. The results of this combination antibiogram are only specific to our institution. Resistance rates and frequencies can vary widely between institutions and even wards within the same institution. Another limitation to this study is that it did not examine clinical outcomes and future studies are needed to determine if susceptibility results are related to improved clinical outcomes. Although aztreonam typically has activity against *P. aeruginosa*, we did not include aztreonam in our susceptibility analysis because it is not routinely listed on our microbiology reports. Collecting susceptibility results for aztreonam would not have been feasible for this study. Similarly, colistimethate and polymyxin B were not included in this analysis.

Several studies have been published previously on the benefits of a combination antibiogram. A study by Mizuta *et al*. (2006) compared the susceptibility results of 3,134 *P. aeruginosa* isolates to determine optimal combinations for *P. aeruginosa* infections in hospitalized patients. They concluded the optimal combination therapy consisted of an aminoglycoside and a beta-lactam. Fluoroquinolones were not a component of the optimal combination for any year of the study. Another study by Fox *et al*. (2008) attempted to determine the in vitro efficacy of various dual antimicrobial combinations based on susceptibility results from 700 blood and respiratory isolates of Enterobacteriaceae and *P. aeruginosa* from hospitalized patients. They determined combination regimens with imipenem/cilastatin were the most effective. The addition of ciprofloxacin did not significantly improve the in vitro efficacy of piperacillin/tazobactam (87% versus 91%) or cefepime (89% versus 93%). A retrospective study by Christoff *et al*. (2010) looked at over 5000 isolates of gram-negative organisms, including *P. aeruginosa*, in the ICU. They reported combination antimicrobial therapy significantly increased the likelihood that the gram-negative organism was adequately covered in the ICU using piperacillin-tazobactam, ceftazidime, or imipenem/cilastatin plus an additional agent. They concluded that reporting antibiotic susceptibility data in the form of a combination antibiogram may be useful to clinicians who are considering empirical antimicrobial therapy in the intensive care unit. A study by Pogue *et al*. (2011) examined the susceptibility and resistance patterns of 467 gram negative ICU respiratory isolates. They found that the addition of a fluoroquinolone to an antipseudomonal beta-lactam did not substantially improve coverage, since nearly all beta-lactam resistant isolates were subsequently cross-resistant to fluoroquinolones. They concluded that optimal empiric therapy selection based on combination antibiogram data can identify the optimal combination regimen against all gram-negative ICU respiratory pathogens.

5. CONCLUSION

Combination antibiograms improve the ability to compare susceptibility rates with monotherapy versus

dual-therapy, identify optimal combination regimens and quantify the difference between dual-therapy with a fluoroquinolone versus an aminoglycoside. Choosing the ideal antibiotic regimen ultimately deals with factors such as suspected pathogens, likely site of infection, patient allergies, drug penetration into different tissue sites and drug toxicity. Utilizing antibiograms to assist with the selection of empiric therapy is only one component of the decision-making process which may not apply to every hospitalized patient.

6. ACKNOWLEDGEMENT

7. REFERENCES

Apisarnthanarak, A. and L.M. Mundy, 2008. Role of combination antibiogram in empirical treatment of infection due to multidrug-resistant Acinetobacter baumannii. Infect. Control Hosp. Epidemiol., 29: 678-679. DOI: 10.1086/588681

Baddour, L.M., W.R. Wilson, A.S. Bayer, V.G. Fowler Jr and A.F. Bolger *et al.*, 2005. Infective endocarditis: Diagnosis, antimicrobial therapy and management of complications: A statement for healthcare professionals from the committee on rheumatic fever, endocarditis and kawasaki disease, council on cardiovascular disease in the young and the councils on clinical cardiology, stroke and cardiovascular surgery and anesthesia, American heart association: Endorsed by the infectious diseases society of America. Circulation, 111: e394-e434. DOI: 10.1161/CIRCULATIONAHA.105.165564

Baltch, A.L. and R.P. Smith, 1985. Combinations of antibiotics against *Pseudomonas aeruginosa*. Am. J. Med., 79: 8-16. DOI: 10.1016/0002-9343(85)90185-8

Christoff, J., J. Tolentino, E. Mawdsley, S. Matushek and D. Pitrak *et al.*, 2010. Optimizing empirical antimicrobial therapy for infection due to gram-negative pathogens in the intensive care unit: Utility of a combination antibiogram. Infect. Control Hosp. Epidemiol., 31: 256-261. DOI: 10.1086/650446

Fox, B.C., G. Shenk, D. Peterson, C.A. Spiegel and D.G. Maki, 2008. Choosing more effective antimicrobial combinations for empiric antimicrobial therapy of serious gram-negative rod infections using a dual cross-table antibiogram. Am. J. Infect. Control, 36: S57-61. DOI: 10.1016/j.ajic.2007.08.003

Fowler, R.A., K.E. Flavin, J. Barr, A.B. Weinacker and J. Parsonnet *et al.*, 2003. Variability in antibiotic prescribing patterns and outcomes in patients with clinically suspected ventilator-associated pneumonia. Chest, 123: 835-844. DOI: 10.1378/chest.123

Garnacho-Montero, J., M. Sa-Borges, J. Sole-Violan, F. Barcenilla and A. Escoresca-Ortega *et al.*, 2007. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy. Crit. Care Med., 35: 1888-1895. DOI: 10.1097/01.CCM.0000275389.31974.22

Giamarellou, H., N.P. Zissis, G. Tagari and J. Bouzos, 1984. In vitro synergistic activities of aminoglycosides and new beta-lactams against multiresistant *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother., 25: 534-536. DOI: 10.1128/AAC.25.4.534

Hilf, M., Y. VL, J. Sharp, J.J. Zuravleff and J.A. Korvick *et al.*, 1989. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: Outcome correlations in a prospective study of 200 patients. Am. J. Med., 87: 540-546. PMID: 2816969

Hollander, J.G., A.M. Horrevorts, M.L. Van Goor, H.A. Verbrugh and J.W. Mouton, 1997. Synergism between tobramycin and ceftazidime against a resistant *Pseudomonas aeruginosa* strain, tested in an in vitro pharmacokinetic model. Antimicrob. Agents Chemother., 41: 95-100. PMID: 8980762

Ibrahim, E.H., G. Sherman and S. Ward, 2000. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest, 118: 146-155. DOI: 10.1378/chest.118.1.146

Iregui, M., S. Ward and G. Sherman, 2002. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest, 122: 262-268. DOI: 10.1378/chest.122.1.262

Karlowsky, J.A., M.E. Jones, C. Thornsberry, A.T. Evangelista and Y.C. Yee *et al*., 2005. Stable antimicrobial susceptibility rates for clinical isolates of *Pseudomonas aeruginosa* from the 2001-2003 tracking resistance in the United States today surveillance studies. Clin. Infect. Dis., 40: S89-98. DOI: 10.1086/426188

Kollef, M.H., G. Sherman and S. Ward, 1999. Inadequate Antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. Chest, 115: 462-474. DOI: 10.1378/chest.115.2.462

Lister, P.D. and D.J. Wolter, 2005. Levofloxacin-Imipenem combination prevents the emergence of resistance among clinical isolates of *Pseudomonas aeruginosa*. Clin. Infect. Dis., 40: S105-S114. DOI: 10.1086/426190

Lister, P.D., D.J. Wolter, P.A. Wickman and R.D. Reisbig, 2006. Levofloxacin/imipenem prevents the emergence of high-level resistance among *Pseudomonas aeruginosa* strains already lacking susceptibility to one or both drugs. J. Antimicrob. Chemother., 57: 999-1003. DOI: 10.1093/jac/dkl063

Lockhart, S.R., M.A. Abramson, S.E. Beekmann, G. Gallagher and S. Riedal *et al*., 2007. Antimicrobial resistance among gram-negative bacilli causing infections in intensive care unit patients in the United States between 1993 and 2004. J. Clin. Microbiol., 45: 3352-3359. DOI: 10.1128/JCM.01284-07

Mizuta, M., D.R. Linkin, I. Nachamkin, N.O. Fishman and M.G. Weiner *et al*., 2006. Identification of optimal combinations for empirical dual antimicrobial therapy of *Pseudomonas aeruginosa* infection: Potential role of a combination antibiogram. Infec. Control Hosp. Epidemiol., 27: 413-415. DOI: 10.1086/503175

Paul, M., I. Benuri-Silbiger, K. Soares-Weiser and L. Leibovici, 2004. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: Systematic review and meta-analysis of randomized trials. BMJ, 328: 668. DOI: 10.1136/bmj.38028.520995.63

Pogue, J.M., C. Alaniz, P.L. Carver, M. Pleva and D. Newton *et al*., 2011. Role of unit-specific combination antibiograms for improving the selection of appropriate empiric therapy for gram-negative pneumonia.Infec. Control Hosp. Epidemiol., 32: 289-292. DOI: 10.1086/658665