

A Combination Antibigram to Guide Empiric Therapy for *Pseudomonas aeruginosa* Infections. Year-to-Year Variation and Influence of Day of Hospitalization Isolation

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Abstract

Background: Infections with multidrug resistant *Pseudomonas aeruginosa* are often encountered in some practice settings/patient populations and may require empiric treatment with combination therapy. Institution and/or organism-specific antibiograms should help to inform empiric combination therapy in such cases.

Objectives: To create annual combination antibiograms spanning several years to inform empiric therapy for suspected or known *Pseudomonas aeruginosa* infections. Secondary objectives were to assess year-to-year variation in results and compare isolates cultured before and after day three of hospitalization.

Methods: Using available susceptibility data for the years 2009 through 2012, annual combination antibiograms, using an antipseudomonal β -lactam as the primary antibiotic, were constructed and results compared. In addition, results for organisms isolated on day three or later of hospitalization were contrasted against those collected prior to day three.

Results: Combination antibiograms developed to determine best combinations for the years 2009 through 2012 suggested a β -lactam plus an aminoglycoside provided optimal coverage in our setting regardless of length of hospitalization.

Conclusion: Annual combination antibiograms for *Pseudomonas aeruginosa* isolates provide guidance for empiric therapy and varied little from year-to-year over this 4-year period of observation within our institution.

Keywords: Antibigram; *Pseudomonas aeruginosa*

Introduction

Pseudomonas aeruginosa is responsible for a variety of serious nosocomial infections including ventilator-associated pneumonia and catheter-associated urinary tract infections [1]. As this pathogen is capable of expressing numerous resistance mechanisms including beta-lactamase production, decreased permeability of the outer bacterial membrane and active efflux, [2] selection of appropriate treatment is challenging and related infections are associated with significant morbidity and mortality [3]. A number of rationales have been described for the empirical institution of combination therapy in treating *Pseudomonas aeruginosa* or other gram-negative infections including expansion of the spectrum of activity, potential synergy, avoidance of adverse drug reactions (presuming smaller doses of each antibiotic), and prevention of resistance [4]. While there is a paucity of data to support most of these rationales, there is no question that a properly selected combination of agents, based upon local susceptibility data, will indeed broaden the spectrum of activity and increase the odds that one of the agents will possess *in vitro* activity against the pathogen. This practice has, in fact, been incorporated into the current national guidelines for the treatment of hospital-acquired pneumonia [5]. Thus, selection of the two antimicrobials is critical and an institution-specific combination antibiogram should inform these decisions in cases of suspected or proven *Pseudomonas aeruginosa* infections. Combination antibiograms, which consider the activity of two antibiotic combinations

against a collection of bacterial isolates, can be used to guide such therapy. The objectives of this study were to prepare a combination antibiogram for *Pseudomonas aeruginosa* at our institution and secondarily to assess year-to-year variation and the influence of hospital day of isolation on the results.

Methods

Pseudomonas aeruginosa susceptibility data for the antibiotics of interest for the years 2009 through 2012 represented results from tests performed by our institution's Clinical Microbiology Laboratory. These data were de-identified prior to any analysis. Our academic medical center is a 709 bed, tertiary care facility providing care for both adult and pediatric patients although only isolates from adult patients were considered in this analysis. Each year's data were assessed separately and duplicate isolates (same organism from same patient, regardless of body site, from same year) were not included. Isolates from patients with cystic fibrosis were not included in this analysis as these often exhibit higher levels of resistance and have been shown to skew the average numbers generated for antibiograms [6]. Susceptibility was determined using disk diffusion as per CLSI guidance [7] and interpretive criteria were not changed by our laboratory during the study period. For purposes of our analysis, organisms were considered either susceptible or non-susceptible. The antibiotics of interest were the formulary anti-pseudomonal beta-lactams,

aminoglycosides and fluoroquinolones. These specific medications included cefepime, meropenem, aztreonam, piperacillin/tazobactam, amikacin, tobramycin, gentamicin and ciprofloxacin. To determine the combined *in vitro* activity or coverage for a given combination in a given year, the number of total isolates susceptible to a given β -lactam was first determined. Subsequently, the number of non-susceptible isolates to each β -lactam that were susceptible to each of the other antibiotics was enumerated. In this way the total number/percent of isolates in a given year susceptible to any given combination was determined and the most active or best combinations identified. Once this exercise was complete the rank order of possible combinations, based upon combined activity, was determined. Additionally, variability between years was assessed. In addition to performing this analysis for all isolates in the database, we repeated the exercise for those isolates cultured from patients within the first two days of hospitalization and those from day three onward for comparison for the years 2011 and 2012, as those in the latter group might be more reflective of hospital-acquired strains. As not all isolates were tested to both drugs in a given combination, calculations for percent susceptible to a combination were based on the number tested to both drugs.

Results

The total number of isolates (n=249, 244, 304 and 297 for years 2009, 2010, 2011 and 2012, respectively) considered and the three most active combinations for each year are presented in table 1 while the same results for isolates cultured within the first two days of hospitalization versus those collected on day three and onward are presented in table 2. The combinations with the greatest combined activity each year, in most cases, included an anti-pseudomonal β -lactam and an aminoglycoside. In only one instance each did a second or third ranked combination include ciprofloxacin or two β -lactams. Most combinations provided combined coverage in excess of 90% except those with aztreonam (data not shown). The comparison for best combinations for isolates collected within the first two days of hospitalization vs those collected on day three or beyond

yielded similar results. As little variation in the most active combinations was seen from year-to-year, it was determined that inferential statistical testing was not necessary to interpret the data.

Discussion

Infections with multidrug resistant Gram-negative pathogens, including *Pseudomonas aeruginosa*, are not only associated with considerable morbidity and mortality but present an economic burden as well, as they are associated with greater hospital/treatment costs and longer lengths of stay when compared to those associated with their drug-susceptible counterparts [8]. As rapid institution of an effective combination appears related to improved patient outcomes and shortened hospital stays, it is critical that information is readily available to the clinician making these therapeutic decisions [4]. Empiric or definitive antibiotic selection for an infection with a suspected or known pathogen is based upon such considerations as *in vitro* activity and favorable pharmacokinetics/pharmacodynamics, given the nature of the infection and patient characteristics. As *in vitro* activity is a prime consideration, construction of a combination antibiogram, based upon institution-specific susceptibility data as done here, can provide that guidance. Further, such information would serve to ensure that choices recommended on an institution's clinical pathways or order forms for *Pseudomonas aeruginosa*-associated infections are appropriate based on local data.

The creation and use of combination antibiograms to inform empiric combination antibiotic therapy decisions for suspected or proven *Pseudomonas aeruginosa* infections has been described and advocated by others. Similar to our findings, Mizuta et al. [9] reported an anti-pseudomonal combination antibiogram in which the most active combinations included a β -lactam and an aminoglycoside. Combinations with the widest coverage over a four year span included ceftazidime, piperacillin/tazobactam or cefepime with either tobramycin or amikacin. As with our study, little year-to-year variation was noted. Others have constructed and used intensive care unit-specific antibiograms for

Year	No. Isolates ^a	Most Active Combinations	% Susceptible to the β -lactam	% Susceptible to the Combination
2009	249	Meropenem+Gentamicin	83.1	98.0
	249	Piperacillin/tazobactam+Amikacin	88.8	97.6
	249	Cefepime+Amikacin	88.8	96.0
2010	244	Piperacillin/tazobactam+Amikacin	89.3	95.9
	244	Meropenem+Ciprofloxacin	86.9	95.1
	244	Cefepime+Amikacin	87.2	94.6
2011	246	Cefepime+Tobramycin	88.8	96.1
	305	Piperacillin/tazobactam+Gentamicin	87.8	95.4
	305	Meropenem+Cefepime	89.8	94.7
2012	298	Cefepime+Tobramycin	85.5	97.0
	259	Piperacillin/tazobactam+Tobramycin	85.9	96.3
	251	Meropenem+Amikacin	87.2	96.9

Table 1: Best Coverage Combinations by Year (all isolates) ^aNumber of isolates tested to both drugs in the combination

Year	Isolates Collected <3 Days of Hospitalization				Isolates Collected \geq 3 Days of Hospitalization			
	No. Isolates ^a	Best Coverage Combinations	% Susceptible to the β -lactam	% Susceptible to the Combination	No. Isolates ^a	Best Coverage Combinations	% Susceptible to the β -lactam	% Susceptible to the Combination
2011	126	CEF+TOB	89.6	99.2	126	CEF+TOB	89.2	96.3
	126	MER+TOB	91.1	97.7	167	CEF+GEN	89.2	95.8
	126	P/T+TOB	90.4	97.0	125	P/T+AMK	86.2	95.8
2012	120	CEF+TOB	86.9	98.1	114	MER+AMK	86.2	100
	120	MER+TOB	88.1	97.5	114	P/T+AMK	83.3	99.3
	120	P/T+TOB	88.1	96.9	114	CEF+AMK	84.1	99.2

Table 2: Best Coverage Combinations for Isolates Collected <3 vs \geq 3 Days of Hospitalization ^aNumber of isolates tested to both drugs in the combination AMK: Amikacin; CEF: Cefepime; GEN: Gentamicin; MER: Meropenem; P/T: Piperacillin/tazobactam; TBO: Tobramycin

gram-negative pathogens [10,11]. Again, β -lactam/aminoglycoside combinations provided the best coverage.

While our creation of a combination antibiogram for *Pseudomonas aeruginosa* is not unique, its replication on a year-by-year basis over a four-year time span is important as it illustrates, at least for our institution that the best combinations may not vary appreciably over time. Whether this would hold true over longer time periods or at other institutions remains to be determined. However, our results suggest that a combination antibiogram based on susceptibility results from a given year would provide suitable guidance for the ensuing year. Further, the observation that results for isolates collected on day three or later of hospitalization, more likely representing nosocomial pathogens, did not vary dramatically from those in isolates collected earlier is also of interest and potential importance even though it only compares two years. It should be noted, however, that this definition of “hospital-acquired” is a loose one. Although frequently used as a discriminator, one would in fact need sequential cultures starting on hospital admission and then continued daily until a pathogen is first detected to confidently label it as “hospital-acquired”. Our observation in this regard should be viewed in that light.

These results should be viewed with some caution. It must be appreciated that this was a single center study considering only *Pseudomonas aeruginosa* and that our results may not apply elsewhere or for other gram-negative, multidrug resistant pathogens. A combination antibiogram considering multiple pathogens might have yielded different results and conclusions. It is also reasonable to speculate that custom combination antibiograms for individual patient care units might well yield different results from those generated with the institution’s combined susceptibility database [12,13]. However, a sufficient number of isolates must be available to make such a sub-analysis reliable. As in our case, these numbers are often lacking at the individual unit level for any specific organism. As already mentioned above, whether our 4-year time frame for analysis adequately reflects or predicts more long-term changes is unknown. Also, our exclusion of isolates from cystic fibrosis patients might have affected results and subsequent conclusions.

The process of creating a combination antibiogram is neither complex nor unreasonably time consuming. Despite the theoretical limitations of our study, we are comfortable recommending that production of combination antibiograms should be considered by other institutions dealing with infections associated with multidrug-resistant pathogens and requiring combination therapy as a means to inform empiric prescribing decisions.

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Conflicts of Interest

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