Lack of Change in Susceptibility of *Pseudomonas aeruginosa* in a Pediatric Hospital Despite Marked Changes in Antibiotic Utilization

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ABSTRACT

Introduction: It is assumed that a direct relationship exists between the extent of use of any given antibiotic or antibiotic class and the degree of susceptibility or resistance on the part of various bacteria to that antibiotic or class.

Methods: *Pseudomonas aeruginosa* susceptibility rates and utilization of key antipseudomonal antibiotics in a pediatric hospital, reflected as grams/1,000 patient days, were studied over a 7-year period.

Results: While the volume of use of a number of antibiotics changed dramatically over this time period, susceptibility of *Pseudomonas* to these same agents remained relatively stable. The use of aminoglycosides decreased 14.5% while that of piperacillin/tazobactam increased

92% over the period of observation while susceptibility generally varied by <10%.

Conclusion: Contrary to popular belief, changes in antibiotic utilization patterns do not always result in changes in susceptibility thus emphasizing the importance of continual institutional monitoring of antibiotic use and susceptibility patterns.

Keywords: Antibiotic utilization; Infectious disease; Pediatrics; *Pseudomonas aeruginosa*; Susceptibility

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INTRODUCTION

It is assumed that there is a relationship between patterns of use of any given antibiotic or antibiotic class and extent of bacterial resistance to that antibiotic or class. More specifically, it is believed that as the use of an antibiotic increases over time, resistance to that antibiotic on the part of one or more bacteria will also increase as would rates of infections with antibiotic-resistant pathogens. Research in this area has indeed provided examples of such relationships although they are not predictably present [1, 2]. However, when such

relationships occur, they may well have implications for proactive stewardship initiatives and empiric prescribing decisions. Most, if not all investigations regarding these potential relationships have been performed in adult populations with few, if any, studies focusing in on pediatric drug use/resistance in pediatric hospitals. The purpose of the present study was to explore potential relationships between antipseudomonal antibiotic use and susceptibility of *Pseudomonas aeruginosa*, a common nosocomial pathogen, to these antibiotics in a pediatric hospital over a 7-year period.

METHODS

The Medical University of South Carolina Children's Hospital is a 186 bed facility including 50 neonatal specialty beds. Approximately, 4,700 children between the ages of 0 and 17 years are cared for annually. The study was approved by the institution's Institutional Review Board. The analysis in this article is based on existing data, and does not involve any new studies of human or animal subjects performed by any of the authors. Susceptibility data for inpatient-derived *P. aeruginosa* isolates collected between January 1, 2006 and December 31, 2012 were retrieved from hospital microbiology records and antibiotic use data were retrieved from the pharmacy database. The antibiotics of interest were amikacin, cefepime, ciprofloxacin, gentamicin, meropenem, piperacillin/tazobactam, and tobramycin and all drug use was expressed as grams/1,000 patient days. To have a statistically valid sample of tested isolates (≥ 30), periods of analysis were divided into six quarter increments (e.g., January 2006 through June 2007) and we thereby analyzed a

total of six periods within the 7-year time span. Analysis of potentially significant changes in either antibiotic use or susceptibility, over time (period 1 vs. period 4), was performed via paired *t* test and Chi-square test, respectively. A trend analysis (linear regression) of susceptibility over time was also completed. All statistical analyses were performed using SPSS v.21 (IBM, Armonk, NY, USA).

RESULTS

Little change was observed in susceptibility of *P. aeruginosa* over the time period of interest with the biggest change being a 12% difference from period 1 to period 4 for aztreonam (Table 1). Conversely, the utilization of most of the antibiotics increased over time with the greatest change observed for piperacillin/tazobactam (92% increase), although overall antibiotic utilization change was not statistically significant (Table 1). As a group, utilization of aminoglycosides decreased (14.5% decrease for the class). Use of both amikacin and gentamicin decreased while that of tobramycin increased. No changes in either susceptibility proportions or antibiotic utilization were statistically significant ($P > 0.05$). Trend analysis of susceptibility over time revealed poor data fits (as reflected by R^2) suggesting no or weak linearity. As susceptibility of *P. aeruginosa* was relatively stable over this time period, tests of correlation or cause-and-effect between antibiotic use over time and susceptibility over time were not pursued.

DISCUSSION

It is generally assumed that increased use of an antibiotic or antibiotic class within a healthcare environment will result in rising resistance to

Table 1 Changes in susceptibility (%) and antibiotic use (grams/1,000 PD) over time

	Isolates tested, <i>n</i>	Antibiotic							
		Amikacin	Aztreonam	Cefepime	Ciprofloxacin	Gentamicin	Meropenem	Piperacillin/Tazobactam	Tobramycin
Susceptibility, %									
Period									
1	34	100	85.3	91.2	97.1	94.1	91.2	91.2	100
2	44	97.7	81.8	100	100	97.7	100	100	97.7
3	44	100	87.8	100	97.6	100	100	100	100
4	61	91.1	73.8	88.5	90.2	93.4	91.8	88.5	91.3
<i>P</i> ^a		0.09	0.19	0.69	0.22	0.90	0.92	0.69	0.90
Absolute change ^b		−8.9	−11.5	−2.7	−6.9	−0.7	0.6	−2.7	−8.7
<i>R</i> ² ^c		0.560	0.364	0.031	0.501	<0.001	0.002	0.031	0.558
<i>P</i> ^d		0.252	0.397	0.825	0.292	0.992	0.953	0.825	0.253
Antibiotic use, grams/1,000 PD									
Period									
1		0.65	ND	75.47	6.11	5.12	34.67	172.36	6.83
2		1.26	ND	72.26	7.89	3.50	45.56	246.20	7.73
3		0.39	ND	84.81	6.68	3.27	64.92	351.79	6.48
4		0.31	ND	112.02	5.72	2.47	58.88	331.02	7.98
Percentage change, %		−52.01	ND	48.44	−6.51	−51.77	69.82	92.05	16.92

ND not done/calculated due to paucity of use, PD patient days

^a Period 1 vs. period 4; Chi-square test

^b Absolute change in % susceptible; period 1 to period 4

^c *R*² for trend of %S over time

^d *P* value for trend of %S over time

that drug or class. While not always the case, some studies have indeed demonstrated that relationship. By way of example, Plüss-Suard et al. [3] demonstrated a relationship between extent of carbapenem resistance in *P. aeruginosa* and carbapenem use in a study involving 20 acute care hospitals. Due to such experiences, it is not unusual to meet the challenge of rising resistance by decreasing the use of the apparent offending agent or class and encouraging the use of alternatives. Again, there is evidence that this maneuver can be effective. For example, Martin et al. [4] documented a reduction in the rate of ceftazidime-resistant *Klebsiella pneumoniae* after the removal of ceftazidime and cefotaxime from the hospital formulary. However, this strategy is not always successful, as the relationship between extent of use and extent of resistance does not always exist [5, 6]. Further, while this strategy may restore susceptibility to a given drug, it may result in rising resistance to other drugs that are used in its stead [7]. In the current analysis, no large changes in susceptibility were detected despite some rather large changes in utilization of individual antibiotics. As examples, susceptibility rates of *P. aeruginosa* to meropenem and piperacillin/tazobactam remained largely unchanged, despite increases in use of 70 and 92%, respectively, over the 7-year period of observation. Although no apparent cause-and-effect relationships seemed operative, these results might not pertain to other hospitals especially in light of the variation in antibiotic use from one pediatric hospital to the next [8]. The current study must be viewed in light of being a single-center experience with a limited number of tested isolates. All tested isolates were considered and no attempt was made to distinguish those causing infection from those that may have been colonizers. Further, this analysis did not

take into account possible effects from changing infection control practices during the period of interest. Lastly, it is also certainly possible that there could be a significant lag time between changes in antibiotic use and changes in resistance rates.

Regardless of these results, it is important that susceptibility rates be diligently monitored in the current age of rapidly rising antibiotic resistance, including in pediatric settings so that emergent resistant problems can be detected and addressed [9]. Results from a fairly recent survey of hospitals caring for pediatric patients were used to construct a national antibiogram for the years 2010 and 2011 [10]. With the exceptions of aztreonam and gentamicin, reported susceptibility rates for isolates of *P. aeruginosa* in that report were similar to those in our last period of observation. While such national averages may be helpful in settings where a local antibiogram cannot be prepared, local antibiograms are nonetheless the best resource in guiding empiric prescribing decisions.

CONCLUSION

In summary, the susceptibility of pediatric isolates of *P. aeruginosa* to a number of antibiotics remained relatively stable over a 7-year period despite major changes in utilization of several of these drugs. Thus, large increases in utilization of at least some antibiotics are not uniformly associated with subsequent changes in bacterial resistance.

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Conflict of interest. John Bosso declares that he has no conflicts of interest.

Compliance with ethics guidelines. The study was approved by the institution's Institutional Review Board. The analysis in this article is based on existing data and does not involve any new studies of human or animal subjects performed by any of the authors.

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