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Brief Report

Antimicrobial stewardship impact on *Pseudomonas aeruginosa* susceptibility to meropenem at a tertiary pediatric institution

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Key Words:
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An antimicrobial stewardship program was implemented throughout 2012 at a tertiary pediatric institution with guideline development preceding prospective audit and feedback starting in 2013. Meropenem use decreased over 62% during the next 5 years. Non-cystic fibrosis *Pseudomonas aeruginosa* isolate susceptibility to meropenem increased from 89% in 2011 to 98% in 2017 ($P < .001$) and correlated with meropenem use the preceding year (R_s: −0.78, $P = .008$).

Potential methods for antimicrobial stewardship program (ASP) implementation include prospective audit and feedback (PAF) and guideline implementation, with most supporting studies occurring in adult populations.[1] Susceptibility patterns and antimicrobial use differ in the pediatric population and evidence is lacking regarding the impact of PAF and guideline implementation on antimicrobial susceptibility rates.[2-4] *Pseudomonas aeruginosa* is considered a health care–associated pathogen, and changes in *P aeruginosa* susceptibility rates could reflect changes in institutional antimicrobial susceptibility due to ASP implementations. We compared *P aeruginosa* susceptibility patterns to meropenem before guideline and PAF implementation (pre-PAF) and after guideline and PAF implementation (post-PAF). In addition, we assessed the correlation between meropenem use and susceptibility rates.

METHODS

The study was conducted at a 255-bed tertiary referral children's hospital in the United States. The pre-PAF study period was the calendar years 2008-2012 and post-PAF was 2013-2017. The combined pediatric and neonatal intensive care unit (ICU) beds increased from 55-90 in December 2010. The size of the intermediate care unit was increased, and a neurosurgical ICU was opened.

Throughout the 2012 calendar year, ICU antimicrobial guideline implementation and education occurred with full implementation at the end of August. In February 2013, PAF began by ASP pharmacists and infectious diseases physicians for broad-spectrum agents, especially meropenem, because of increased institutional use. The ASP also reviewed all positive sterile site cultures on a daily basis. Recommendations focused on appropriate antimicrobial selection and treatment duration based on indication and laboratory results. There were neither restrictions on prescribing of any antimicrobials, nor any use of decision support in the electronic medical record to guide antibiotic prescribing. A previous analysis of this program did not analyze susceptibility changes, but demonstrated reduced purchasing costs and broad-spectrum antimicrobial consumption, without a significant change in mortality.[4]

Antimicrobial use data, reported as days of therapy (DOT) per 1000 patient days (PD), were obtained from the Pediatric Health Information System database, derived from hospitals in the Children's Hospital Association. For the pre-PAF and post-PAF analysis, antimicrobial use from 2008-2017 was used. Susceptibility rates for 2008-2017 (excluding patients with cystic fibrosis) were determined using the yearly hospital-wide antibiogram. Meropenem use from 2007-2016 was used to assess for a correlation between use the preceding year and resulting susceptibilities the following year. Meropenem was the only carbapenem used throughout this period. The minimum inhibitory concentrations (MIC) for *P aeruginosa* isolates were determined using broth microdilution in the VITEK system (bioMerieux, Marcy l'Etoile, France). The same MIC breakpoints were used for susceptibility determination through the study period (an MIC of ≤4 mg/L was considered susceptible).

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Conflicts of interest: None to report.

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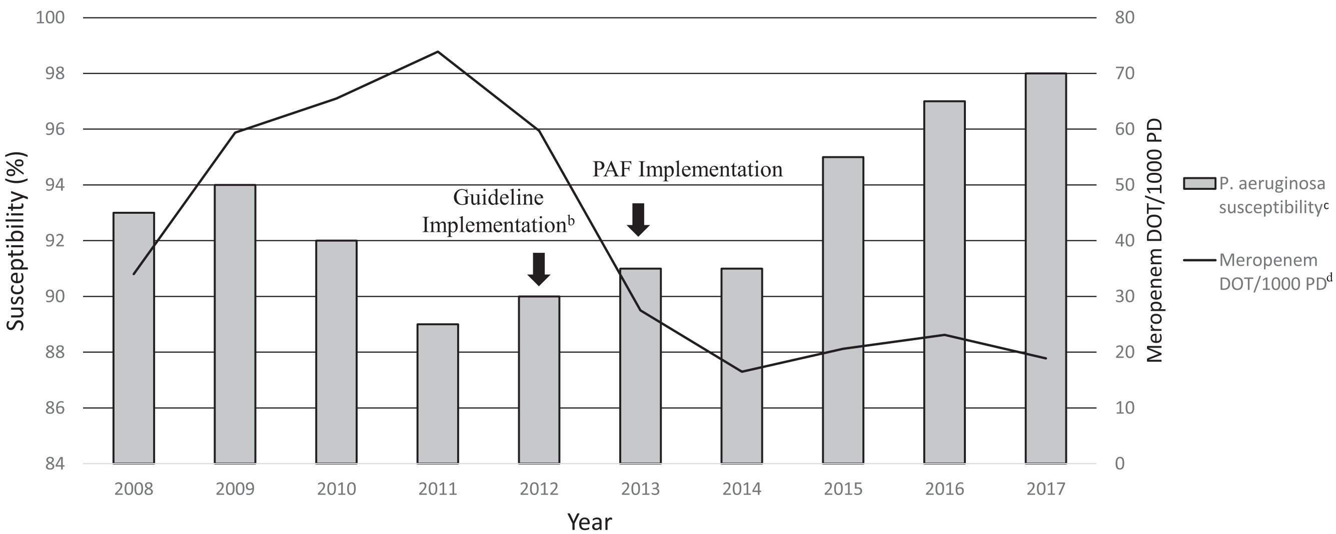

Fig 1. Meropenem use and *Pseudomonas aeruginosa*[a] susceptibility to meropenem: 2008-2017 (n = 2,877 isolates). [a]Isolates from cystic fibrosis patients were excluded. [b]Implementation occurred throughout 2012 with full guideline implementation at the end of August. [c]*P* <.001 comparing 2013-2017 by the χ^2 test and the Cochran-Armitage test, but all *P* >.05 comparing 2008-2012. [d]*P* = .001 comparing 2008-2012 and 2013-2017 by the Student t test. *DOT*, days of therapy; *PAF*, prospective audit and feedback; *PD*, patient days.

Descriptive statistics included percentages and means with 95% confidence intervals (CI). The Student t test was used to compare continuous data. The χ^2 test was used for proportional comparisons and the Cochran-Armitage test assessed trends in susceptibility over time. The Spearman's rank correlation was used to assess correlations between antimicrobial use and susceptibility within the same year and correlations between use the preceding year and susceptibility. All *P* values were 2-tailed.

RESULTS

In the pre-PAF period, meropenem susceptibility for *P aeruginosa* did not significantly change year over year, but, in the post-PAF period, susceptibility significantly differed year over year with a significant trend of increasing susceptibility over the 5-year period (Fig 1). There was an increase in susceptibility from 89%-98% between 2011 and 2017 ($P < .001$); for every 11 *P aeruginosa* isolates, 1 additional isolate was meropenem susceptible. The average yearly *P aeruginosa* susceptibility for all other antipseudomonal agents did not change (92.4% pre-PAF vs 92.6% post-PAF; $P = .9$).

Mean yearly meropenem use significantly decreased from pre-PAF implementation to post-PAF (58.5 DOT per 1000 PD, 95% CI: 40-77, vs 21.3 DOT per 1000 PD, 95% CI: 16.1-26.6, respectively; $P = .001$). Mean yearly overall antipseudomonal agent use excluding meropenem did not significantly change from pre-PAF to post-PAF (91.2 DOT per 1000 PD, 95% CI: 73.9-110.3, vs 97.4 DOT per 1000 PD, 95% CI: 87.6-107.1; $P = .4$). Meropenem use did not correlate with *P aeruginosa* susceptibility within the same year (R_s: −0.55; $P = .1$), but use from the preceding year correlated with susceptibility rates (Fig 2).

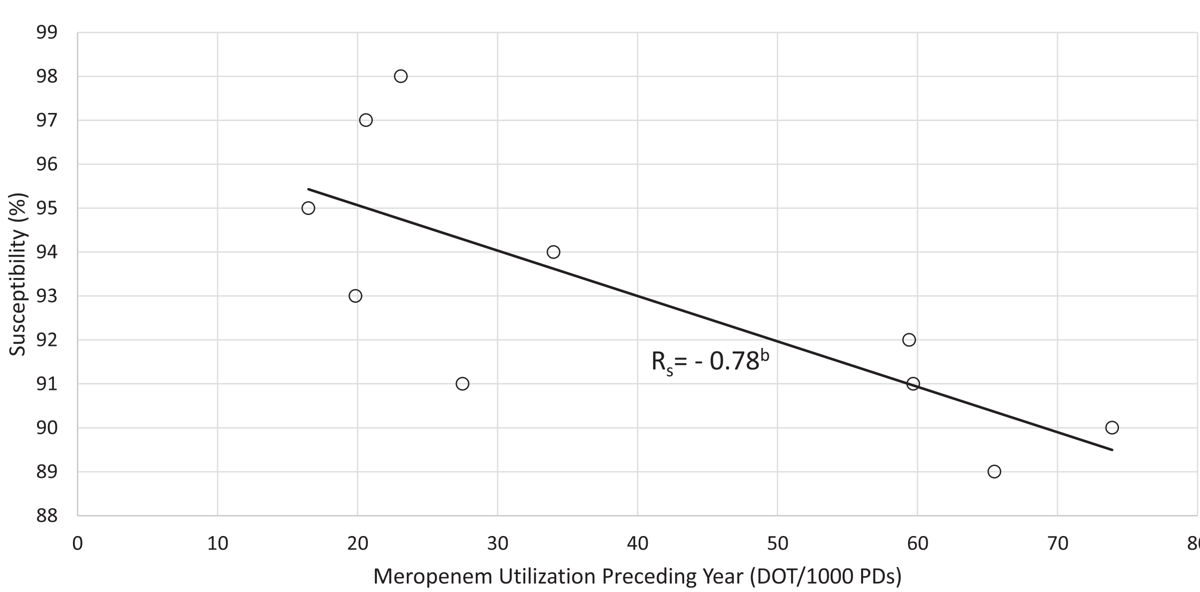

Fig 2. Meropenem use in preceding year and *Pseudomonas aeruginosa*[a] susceptibility to meropenem from 2008-2017. [a]Isolates from cystic fibrosis patients were excluded. [b]*P* = .008 by the Spearman's correlation. *DOT*, days of therapy; *PD*, patient days.

DISCUSSION

These data suggest that changes in meropenem use following guideline implementation and 5 years of PAF were associated with a significant increase in *P aeruginosa* isolate susceptibility to meropenem at our institution. The susceptibility changes occurred despite an increase in the number of ICU beds; ICU admission has been consistently described as a risk factor for *P aeruginosa* resistance to meropenem.[5] The change in meropenem use was not the result of substitution with another antipseudomonal agent suggesting there was unnecessary use of agents covering *P aeruginosa* before ASP implementation. *P aeruginosa* isolate susceptibility to other β-lactams did not change; thus, it is unlikely that hospital-wide *P aeruginosa* isolates were more susceptible to all β-lactams. Fluoroquinolone use, which has been associated with meropenem susceptibility patterns, also did not change between the 2 periods.[6]

An analysis from Japan illustrated changes in *P aeruginosa* susceptibilities to meropenem in the pediatric population after implementation and sustainment of an ASP based mainly on restriction and preauthorization. Susceptibility rates were 86.3% in year 1 and 96.2% in year 6, with *P aeruginosa* susceptibility changes not occurring for the initial 2-3 years.[7,8] We achieved similar results using guideline creation followed by PAF. Our study also found that the changes in *P aeruginosa* susceptibilities to meropenem did not occur in the first year and only correlated with use from the preceding year. This is a unique finding and this delay in susceptibility changes should be considered in future analyses of hospital-wide antimicrobial use and changes in susceptibilities.

Our study had limitations. Our institution cares for many immunocompromised patients, but we do not have an inpatient hematology-oncology population, and therefore, these data may not apply to that patient population. As has been recommended in prior studies,[9] *P aeruginosa* isolates from cystic fibrosis patients were not included. Therefore, our results are also not applicable to that population. Finally, although this analysis attempted to elucidate other possible causes for the increased susceptibility rates noted, it is still possible the results were owing to other factors unknown to us.

CONCLUSIONS

These data suggest guideline implementation followed by PAF in a tertiary pediatric institution was associated with reduced meropenem use for over 5 years and increased *P aeruginosa*, a common health care–associated pathogen, susceptibility to meropenem.

References

1. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51-77.
2. Newland JG, Stach LM, De Lurgio SA, Hedican E, Yu D, Herigon JC, et al. Impact of a prospective-audit-with-feedback antimicrobial stewardship program at a children's hospital. J Pediatric Infect Dis Soc 2012;1:179-86.
3. Di Pentima MC, Chan S, Hossain J. Benefits of a pediatric antimicrobial stewardship program at a children's hospital. Pediatrics 2011;128:1062-70.
4. Lee KR, Bagga B, Arnold SR. Reduction of broad-spectrum antimicrobial use in a tertiary children's hospital post antimicrobial stewardship program guideline implementation. Pediatr Crit Care Med 2016;17:187-93.
5. Raman G, Avendano EE, Chan J, Merchant S, Puzniak L. Risk factors for hospitalized patients with resistant or multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis. Antimicrob Resist Infect Control 2018;7:79.
6. Cook PP, Gooch M, Rizzo S. Reduction in fluoroquinolone use following introduction of ertapenem into a hospital formulary is associated with improvement in susceptibility of *Pseudomonas aeruginosa* to group 2 carbapenems: a 10-year study. Antimicrob Agents Chemother 2011;55:5597-601.
7. Horikoshi Y, Suwa J, Higuchi H, Kaneko T, Furuichi M, Aizawa Y, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. Int J Infect Dis 2017;64:69-73.
8. Horikoshi Y, Higuchi H, Suwa J, Isogai M, Shoji T, Ito K. Impact of computerized preauthorization of broad spectrum antibiotics in *Pseudomonas aeruginosa* at a children's hospital in Japan. J Infect Chemother 2016;22:532-5.
9. Heintz BH, Halilovic J. Lessons learned from surveillance of antimicrobial susceptibilities of *Pseudomonas aeruginosa* at a large academic medical center. Pharmaceuticals (Basel) 2010;3:1070-83.