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Source / Izvornik: **International Journal of Antimicrobial Agents, 2011, 37, 467 - 471**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.ijantimicag.2010.11.030

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:319572

Distributed lags time series analysis versus linear correlation analysis (Pearson r) in identifying the relationship between anti-pseudomonal antibiotics consumption and the susceptibility of Pseudomonas aeruginosa isolates in a single ICU of a tertiary hospital

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Abstract

The effect of antibiotic consumption on the selection of resistant strains has been studied mostly by employment of conventional statistical methods. A time delay in effect has to be anticipated, and this was rarely taken into account in previous studies. Therefore, we compared distributed lags time series analysis and simple linear correlation in their ability to evaluate this relationship. Data on monthly antibiotic consumption for ciprofloxacin, piperacillin/tazobactam, carbapenems and cefepime and *Psudomonas aeruginosa* susceptibility were retrospectively collected for the period April 2006-July 2007. Using distributed lags analysis we identified a significant temporal relationship between ciprofloxacin, meropenem and cefepime consumption and the resistance rates of *Pseudomonas aeruginosa* isolates to these antibiotics. This effect was lagged for ciprofloxacin and cefepime [1 month ($R=0.827$, $p=0.039$) and 2 months ($R=0.962$, $p=0.001$), respectively] and simultaneous for meropenem (lag 0, $R=0.876$, $p=0.002$). Furthermore, we identified a significant concomitant effect of meropenem consumption on the appearance of multidrug-resistant (resistance to ≥3 representatives of classes of antibiotics) *Pseudomonas aeruginosa* strains (lag 0, $R=0.992$, $p<0.001$). This effect was not delayed and therefore it was identified both by distributed lags analysis and the Pearson's correlation coefficient. Correlation coefficients analysis was not able to identify relationships between antibiotic consumption and bacterial resistance when the effect was delayed. These results indicate that the use of diverse statistical methods can yield in significantly different results, thus leading to introduction of possibly inappropriate infection control measures.

Key words: Antibiotic consumption; Bacterial resistance; Distributed lags time series analysis; Linear correlation analysis; *Pseudomonas aeruginosa*; Ecological study design

1. Introduction

The relationship between antibiotic consumption and the selection of resistant *Pseudomonas aeruginosa (P.aeruginosa)* strains has been studied extensively, mostly by the use of conventional statistical methods including simple and multiple linear regression or evaluation of correlation coefficients (Pearson r, Spearman), with a wide range of results [1,2,3,4]. One reason for these inconsistencies is the dynamics of the relationship which cannot always be discovered by the above mentioned methods. In the last decade time-series analysis, used particularly common in econometrics, is beginning to be used to evaluate this relationship [5]. The aim of our study was to compare 2 different commonly used statistical methods in their ability to investigate the relationship between anti-pseudomonal antimicrobials consumption and resistance rates of *P.aeruginosa* isolates in a single ICU of a tertiary hospital. The statistical methods compared in the analysis of the same data set were simple linear correlation (Pearson r) and distributed lags time series analysis. Our hypothesis was that the relationship is temporal in nature and delayed, and that these characteristics have to be taken into account in analysis of this relationship by choosing appropriate analysis methods. This is of crucial importance for implementation of measures targeted at the specific problem, i.e. traditional infection control measures or restriction of use of those antibiotics that facilitate the emergence of resistant strains of *P.aeruginosa*.

2. Materials and methods

2.1. Setting

University Hospital Zagreb is a 1.700-bed tertiary hospital. The Intensive Care Unit (ICU) of the Department of Medicine is an 11-bed ICU with a mean of 108 hospitalized patients per month (range 83-132) during the evaluation period. The evaluation was limited to a single ICU to limit the confounders associated with differences between various medical specialties.

2.2. Antibiotic consumption

Data on monthly antibiotic consumption for ciprofloxacin, piperacillin/tazobactam, imipenem, meropenem, and cefepime in the evaluated ICU were retrospectively obtained from the hospital pharmacy. The numerator used was DDD (defined daily dose); the denominator used was per-100 admissions. Data on admissions were collected from the administration office for the period April 2006- July 2007.

2.3. Bacterial strains and susceptibility testing

The microbiology data and the susceptibility testing results were obtained from the Department of Clinical Microbiology. Determination of MICs and interpretation was done according to CLSI criteria [6]. All clinical isolates of *P.aeruginosa* were included in the analysis.

2.4. Statistical analysis

Standard descriptive statistics were used to describe antimicrobial consumption and rates of *P. aeruginosa* resistance to evaluated antibiotics. Statistical significance was set at $p<0.05$. The normality of data was verified with the Kolmogorov- Smirnov test. We analyzed the same data set using 2 different statistical tests: analysis of correlation coefficients (Pearson r) and distributed lags analysis. Only the later method is able to identify a dynamic (delayed) relationship between variables.

2.4.1. Simple linear correlation (Pearson r)

Pearson correlation determines the extent to which values of the two variables are linearly related. The correlation is high if it can be "summarized" by a straight line called the regression line or least squares line. The correlation coefficient (r) represents the linear relationship between two variables. The test of significance is based on the assumption that the distribution of the residual values (i.e., the deviations from the regression line) for the dependent variable *y* follows the normal distribution, and that the variability of the residual values is the same for all values of the independent variable *x*.

We stress that the Pearson correlation coefficient is the same as the standardized coefficient for simple regression designes.

2.4.2. Distributed Lags Time Series Analysis

Distributed lags time series analysis is a specialized dynamic regression technique for examining the relationships between variables that involve some delay.

The simplest way to describe the relationship between a dependent variable *y* and an independent variable *x* would be in a simple linear relationship:

$$Y_t = \Sigma\ \beta_i * x_{t-i}$$

In this equation, the value of the dependent variable at time *t* is expressed as a linear function of *x* measured at times *t*, *t-1*, *t-2*, etc. Thus, the dependent variable is a linear function of *x*, and *x* is lagged by *1*, *2*, etc. time periods. The *Beta* weights (β_i) can be considered slope parameters in this equation. If the weights for the lagged time periods are statistically significant, we can conclude that the *y* variable is predicted with the respective lag.

As a measure of model adequacy, statistical significance of the estimated coefficients and the residual distribution analysis were used (analysis of histograms, normal and

half-normal probability plots). Furthermore, series were reviewed using the autocorrelation function and the partial autocorrelation function plots to exclude serial dependencies and to ensure appropriateness of the model.

2.5. Hygiene practices

There were no changes in infection control practices, disinfectants or the infection control team during the study period. Admission rates were stabile during the studied period.

2.6. Study design

The study is ecological in design. The previously mentioned data were collected retrospectively for each month of the studied period at the hospital level and analyzed using the appropriate statistical software: StatSoft, Inc. (2008), Statistica (data analysis software system) version 8.0. www.statsoft.com.

3. Results

A total of 89 non-duplicated *P.aeruginosa* isolates were collected from the ICU during the study period. The most common clinical specimens cultured were tracheal aspirates (51%), swabs (26%), urine (15%) and blood (6%). Thirty-seven percent of all *P.aeruginosa* isolates were multidrug resistant (resistant to representatives of three or more classes of antimicrobial agents). During the period of the study, the average observed monthly percentages of *P.aeruginosa* strains resistant/intermediately susceptible to evaluated anti-pseudomonals ranged from 19% to 61% (Table 1). Anti-pseudomonals included for analysis in this study comprised 32% of the overall volume of prescribed antibiotics during the study period.

Distributed lags analysis showed a significant temporal effect of the ICU use of ciprofloxacin, meropenem and cefepime on the susceptibility of *P.aeruginosa* isolates to ciprofloxacin, meropenem and cefepime that was delayed by 1 month, 0 months (simultaneous effect), and 2 months, respectively (Table 2). The changes in piperacillin/tazobactam and imipenem consumption did not yield in significant changes of *P.aeruginosa* susceptibility to these antibiotics. A significant relationship between the use of imipenem/cilastatin and the resistance to imipenem could not be established in this study probably due to marginal usage of imipenem/cilastatin during the first 7 months of the study and the preference for prescribing meropenem. Nevertheless, the resistance rates of *P.aeruginosa* strains to imipenem/cilastatin changed significantly in relation to meropenem consumption without a time delay (lag 0, R=851, p=0.002), indicating a significant cross-resistance of *P.aeruginosa* to imipenem/cilastatin and meropenem. Pearson's correlation coefficient analysis between meropenem consumption and resistance of *P.aeruginosa* isolates to

meropenem and imipenem nearly missed to identify this relationship as statistically significant (p=0.052 and 0.058, respectively) (Table 3). Since it doesn't take the possible dynamic relationship into account, Pearson's correlation coefficients analysis was not able to identify the relationship between ciprofloxacin and cefepime consumption and *P.aeruginosa* resistance to these antibiotics.

Out of all anti-pseudomonals included in the study, only the variability in meropenem consumption resulted in significant changes of the occurrence of MDR strains of *P.aeruginosa* (Table 2). This effect was not delayed and therefore could also be identified both by distributed lags analysis and the Pearson's correlation coefficient (Table 3). The temporal effect of ciprofloxacin, piperacillin/tazobactam and cefepime consumption on the occurrence of MDR *P.aeruginosa* strains could not be demonstrated in our study.

4. Discussion

Available studies investigating the rapidity of selection of antimicrobial resistance indicate that a certain time lag between the antibiotic consumption and the emergence of *P.aeruginosa* resistance in the clinical setting should be expected, endorsing the use of time series analysis in investigation of this relationship [5,7]. Resistance of *P.aeruginosa* to antibiotics can be both acquired by mutations in chromosomal genes or horizontal transfer of resistance genes and intrinsic [8]. Reinhardt et al. have suggested that resistant *P.aeruginosa* may be selected in less than 10 days independently of the antimicrobial class [9]. In contrast, study by Hocquet et al. identified various time delays (ranging 0-6 months) between meropenem, ciprofloxacine and cefepime use and the prevalence of clinical isolates of *P.aeruginosa* displaying an efflux based resistance to these antibiotics [10]. Carbapenemase production is a major acquired mechanism of *P.aeruginosa* resistance to beta-lactams whose occurrence is influenced by anti-pseudomonal antibiotics use and length of hospital stay [11].

In this study, we did not use all analytical possibilities of time series analysis in terms of modeling and forecasting (ARIMA), since this exceeded the aims of this study. We used distributed lags time series analysis, a dynamic regression model able to examine the relationships between variables that involve some delay.

The observed *P.aeruginosa* resistance rates to anti-pseudomonal antibiotics were notably higher than the average hospital resistance rates, as well as the average hospital resistance rates of *P.aeruginosa* in Croatia [12] (Table 1).

We stress that for the duration of this study, based on the hospital resistance rates of *P.aeruginosa*, anti-pseudomonals recommended for treatment of *P.aeruginosa* infections were piperacillin/tazobactam and cefepime. Although

piperacillin/tazobactam consumption plotted with the resistance of *P.aeruginosa* resulted in graphs that showed similar temporal movements, this relationship did not yield in statistical significance. Even though this result could be attributed to the relatively short study period, it corresponds with previous studies that also failed to demonstrate this relationship [13]. The consumption of piperacilline/tazobactam was lower as compared to ciprofloxacin, meropenem and cefepime, nevertheless the resistance of *P.aeruginosa* isolates to piperacillin/tazobactam remained high throughout the study period (Table 1) and could be attributable to high meropenem use since a positive relationship was identified between meropenem use and resistance to piperacilline/tazobactam (lag 0, R= 0.852, p=0.007) in our study as well as in previous studies [13,14]. If a possible dynamic relationship between variables was taken into account, resistance rates of *P.aeruginosa* to ciprofloxacin and cefepime could be ascribed to their consumption with a time delay of 1 month and 2 months, respectively, thus pointing to the need for their judicious use. Ciprofloxacin is not considered to be an antibiotic of choice in *P.aeruginosa* infection. Its high use registered during our study is attributable to its wide application in treatment of abdominal and urinary tract infections and no restrictions in place to limit its usage. Interestingly, although the pattern of cefepime use was significantly related to the pattern of *P.aeruginosa* susceptibility to cefepime, and its consumption was high, it remained the anti-pseudomonal agent with the best susceptibility profile to *P.aeruginosa* throughout the study period.

Meropenem was considered as the preferred carbapenem in treating serious infections in the evaluated ICU. Changes in *P.aeruginosa* resistance rates to both meropenem and imipenem were attributable to changes in meropenem consumption. In addition, without an identified delay in effect, meropenem showed the “fastest”

pressure for selection of *P.aeruginosa* strains resistant to meropenem (and imipenem) as well as for selection of MDR strains of *P.aeruginosa*. This simultaneous effect was identified by both statistical analysis methods, consequently pointing to a restriction of its use as a required measure of resistance control.

The results imply that more rigorous control of anti-pseudomonal antibiotics prescription is warranted, and that the preferred anti-pseudomonal antibiotic in the evaluated ICU should be cefepime.

4.1. Interpretation of results- Pearson's correlation coefficient

Using the Pearson's correlation coefficients analysis we identified only the use of meropenem as being significantly correlated to *P.aeruginosa* resistance. Subsequently, we could conclude that the anti-pseudomonal antimicrobials consumption was not the main problem in the evaluated ICU, with the possible exception of meropenem, but that the main problems is probably the insufficient implementation of basic infectious control measures and cross-transmission. Consequently, the focus would be set on more rigorous implementation of infection control measures, without a particular need to readjust the use of anti-pseudomonal antibiotics, except for required restrictions in meropenem use.

4.2. Interpretation of results- distributed lags analysis

By the use of distributed lags analysis we identified changes in ciprofloxacin, cefepime and meropenem consumption as being significantly temporally related to changes in *P.aeruginosa* resistance. According to the results of this analysis, we would conclude that the main problem in the evaluated ICU is most probably the imprudent use of anti-pseudomonal antibiotics. Consequently, the focus needs to be set on more restricted and controlled use of all anti-pseudomonal antibiotics in addition to the continuous implementation of basic infection control measures.

This study is ecological in design and it cannot be used to determine whether individual patients with resistant isolates of *P.aeruginosa* were actually exposed to the relevant antibiotic, other antibiotics or other risk factors associated with resistance, which is an important limitation.

Although the problem of antimicrobial resistance was reported to be primarily ecological, using only ecological data may underestimate the impact of antibiotic misuse [15]. The correlation between antibiotic usage and bacterial resistance is complex, thus complete understanding and evaluation of these mechanisms is not possible without the inclusion of both ecological and patient level data to allow adjustments for confounding. Since patient level data were not included in the study, we were not able to extract and include only ICU-acquired isolates of *P.aeruginosa* in the analysis. Therefore, the possible impact of confounding factors outside the evaluated ICU could not be assessed (e.g. antibiotic use outside the ICU).

Another limitation of this study is the lack of differentiation between colonization and infection. However, the primary endpoint in our study was not the change in the incidence of *P.aeruginosa* infection, but the change in the overall susceptibility of *P.aeruginosa* isolates to prescribed anti-pseudomonal antibiotics.

This study is limited to *P.aeruginosa*, therefore similar conclusions for other pathogens cannot be made.

Despite aforementioned biases, we believe that the presented approach was able to demonstrate the necessity to statistically account for time delays when analyzing the relationship between antibiotics consumption and the emergence of bacterial resistance.

5. Conclusion

We showed that the use of diverse statistical methods can yield in significantly different results, thus leading to commencement of different and possibly inappropriate infection control measures. Due to mentioned limitation of this study, the evaluation of this approach should be followed by more detailed analyses, with inclusion of more data points and, if possible, patient level data.

References

[1] Rogues AM, Dumartin C, Amadeo B, Venier AG, Marty N, Parneix P, Gachie JP. Relationship Between Rates of Antimicrobial Consumption and the Incidence of Antimicrobial Resistance in Staphylococcus aureus and Pseudomonas aeruginosa Isolates From 47 French Hospitals. Infect Control Hosp Epidemiol 2007;28:1389-1395.

[2] MacDougall C, Harpe SE, Powell JP, Johnson CK, Edmond MB, Polk RE. Pseudomonas aeruginosa, Staphylococcus aureus, and Fluoroquinolone Use. Emerg Infect Dis 2005;11:1197-1204.

[3] Carmeli Y, Troillet N, Elipoulos GM, Samore MH. Emergence of antibiotic-resistant Pseudomonas aeruginosa: comparison of risks associated with different antipseudomonal agents. Antimicrob Agents Chemother 1999;43:1379-1382.

[4] Shigemi A, Matsumoto K, Yaji K, Shimodozono Y, Takeda Y, Myyonahara H et al. Correlation between meropenem and doripenem use density and the incidence of carbapenem-resistant Pseudomonas aeruginosa. Int J Antimicrob Agents 2009;34(&):589-591.

[5] Lopez-Lozano JM, Monnet DL, Yague A, Burgos A, Gonzalo N, Campillos P et al. Modeling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. Int J Antimicrob Agents 2000;14:21-31.

[6] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Fifteenth Informational Supplement. M100-S15. Wayne, PA: CLSI; 2005.

[7] Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections

from 1991-2003 at a university hospital in Taiwan. Int J Antimicrob Agents 2005;26:463-471.

[8] Strateva T and Yordanov D. Pseudomonas aeruginosa- a phenomenon of bacterial resistance. J Med Microbiol 2009;58;1133-1148.

[9] Reinhardt A, Kohler T, Wood P, Rohner P, Dumas JL, Ricou B, van Delden C. Development and Persistence of Antimicrobial Resistance in Pseudomonas aeruginosa: a Longitudinal Observation in Mechanically Ventilated Patients: Antimicrob Agents Chemoth 2007;51(4):1341-1350.

[10] Hocquet D, Muller A, Blanc K, Plesiat P, Talon D, Monnet DL et al. Relationship between Antibiotic Use and Incidence of MexXY-OprM Overproducers among Clinical Isolates of Pseudomonas aeruginosa. Antimicrob Agents Chemother 2008;52(3):1173-1175.

[11] Zhang JF, Chen BL, Xin XY, Zhao HB, Wang HY, Song H et al. Carbapenem resistance mechanism and risk factors of P.aeruginosa clinical isolates from a University Hospital in Xi'an, China. Microb Drug Resist.2009;15(1):41-45.

[12] In: Bacterial susceptibility and resistance to antibiotics in Republic of Croatia in 2007. Published by The Croatian Academy of Medical Sciences, 2007.

[13] Carmeli Y, Troillet N, Eliopoulos GM, Samore MH. Emergence of antibiotic-resistant Pseudomonas aeruginosa: comparison of risks associated with different antipseudomonal agents. Antimicrob. Agents Chemother 1999;43:1379-1382.

[14] Troillet N, Samore MH, Carmeli Y. Imipenem-resistant Pseudomonas aeruginosa: risk factors and antibiotic susceptibility patterns. Clin Infect Dis 1997;25:1094-1098.

[15] Wilcox MH. The tide of antimicrobial resistance and selection. Int J Antimicrob Agents 2009;34:6-10.

Table 1. Average percentage of ICU anti-pseudomonal antibiotic consumption and *P.aeruginosa* resistance rates during the study period.

Antibiotic	**Antibiotic consumption**	***P.aeruginosa* resistance rates**		
	ICU (%)[a]	**ICU (%)**[b]	**UH Zagreb (%)**[c]	**Croatia (%)**[d]
ciprofloxacin	8.6	61	36	22
piperacillin/tazobactam	5.2	48	22	20
imipenem	2.2	57	32	11
meropenem	8.9	55	30	11
cefepime	7.2	19	17	8

[a] % of overall ICU antibiotic consumption (April 2006- July 2007)
[b] monthly average ICU *P.aeruginosa* resistance rates (April 2006- July 2007)
[c] average hospital *P.aeruginosa* resistance rates in 2007
[d] average resistance of hospital strains of *P.aeruginosa* in Croatia in 2007

Table 2. Distributed lags analysis between the dependent variable (monthly percentage of *P.aeruginosa* isolates resistant to the target antibiotic/monthly percentage of MDR isolates of *P.aeruginosa*) and the independent variable (antimicrobial consumption expressed as DDD/100-admissions).

Antibiotic consumption (DDDs/100-admissions)	**P.aeruginosa isolates resistant to the target antibiotic**				
	Regression coefficient	**Standard Error**	**t**	**Lag[a]**	**P value**
Ciprofloxacin	0.827	0.349	2.371	1	0.039
Piperacillin/tazobactam	-	-	-	None identified	-
Imipenem	-	-	-	None identified	-
Meropenem Meropenem[b]	0.876 0.879	0.277 0.275	3.937 3.922	0 0	0.002 0.002
Cefepime	0.962	0.041	5.035	2	0.001
	MDR isolates of P.aeruginosa resistant to the target antibiotic				
Ciprofloxacin	-	-	-	None identified	-
Piperacillin/tazobactam	-	-	-	None identified	-
Imipenem	-	-	-	None identified	-
Meropenem	0.992	0.221	4.492	0	0.0006
Cefepime	-	-		None identified	-

[a]only the most significant lags are mentioned
[b]meropenem consumption vrs *P.aeruginosa* resistance to imipenem

Table 3. Pearson's correlation coefficients (r) between the dependent variable (monthly percentage of *P.aeruginosa* isolates resistant to the index antibiotic/MDR *P.aeruginosa* isolates) and the independent variable (antimicrobial consumption expressed as DDD/100-admissions).

Antibiotic consumption (DDDs/100-admissions)	**P.aeruginosa isolates resistant to the target antibiotic**		**MDR P.aeruginosa isolates**	
	r	**p-value**	**r**	**P value**
Ciprofloxacin	- 0.266	0.319	- 0.353	0.181
Piperacillin/tazobactam	- 0.313	0.238	- 0.139	0.702
Imipenem	- 0.181	0.504	- 0.181	0.504
Meropenem Meropenem[a]	0.495 0.483	0.052 0.058	0.659	0.005
Cefepime	0.287	0.281	0.400	0.125

[a]correlation between the meropenem consumption and resistance rates of *P.aeruginosa* to imipenem