Application of Simple Regression Models for the Prediction of Resistance Behavior of Klebsiella Pneumoniae Against Imipenem and Meropenem

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Abstract: The objective of the investigation was to determine the trend of bacterial resistance of Klebsiella pneumoniae by means of a simple regression model, starting from the hypothesis that there is a statistically significant relation between the tendency to increase bacterial resistance for each year Of study of the event; The published data on sensitivity and resistance of K. pneumoniae were taken as a source of information, compared to 13 antibiotics from 2001 to 2014 by the group GREBO (Group for the Control of Antimicrobial Resistance in Bogotá). A statistically significant correlation was found with six (6) antibiotics; (2) antibiotics, imepenem (MPI) and meropenem (MEM), with adjusted R2 values of 77.9% and (2) antibiotics were used to evaluate the efficiency of the model. 79.8% respectively. As conclusion, it was obtained that this specific model of K. pneumoniae against IPM and MEM, could predict that if the conditions are maintained the rate of increment of resistance to IPM and MEM will be of 0,84% 1,01% per year respectively, Projecting that by the year 2020 a resistance of 26.6% and 21.6% for Meropenem and Imipenem; Limiting the therapeutics in the management of infections produced by this bacterium.

Keyword: Multiple regression model, analysis of performance in soccer teams, behavior patterns, competition dynamics.

1. INTRODUCTION

Research into bacterial resistance has become increasingly important as multi-resistant bacteria appear on antibiotics; its dynamics has been studied in the hospital setting based on its epidemiological behavior, which includes: frequency of isolation by care service, type of infection, morbidity and mortality rates associated with the latter with increased care costs. In its molecular aspects, the appearance of intra- or extra-chromosomal genomic sequences that confer different degrees of resistance to different types of antibiotics, among other aspects; Complexity that requires a multidisciplinary approach [1], [2].

On the other hand the epidemiological behavior using mathematical tools describes quantitative data and differences between the percentages of resistances thrown year after year in addition to establishing the linearity and the sense of increase [3] - [10].

In this sense, it is considered the role that the exact sciences can play in the analysis of the evolution of bacterial resistance in such a way that antimicrobial therapy can be effectively controlled.

Given this scenario, regression models are an innovative tool that allows predicting the behavior and magnitude of the increase of resistance over the years, as Humberto Gutiérrez and Román de la Vara point out in their "The regression analysis aims to model in a mathematical way the behavior of a response variable as a function of one or more independent variables (factors)" [11], which opens the window to analyze the evolution Of bacterial resistance (response variable) through the passage of years (independent variable).

Taking as reference the resistance monitoring data published by the group GREBO (Group for the Control of Antimicrobial Resistance in Bogota), in its bulletins [12] - [16], a database that brings together 13 years of experience in the Surveillance of bacterial resistance, which guarantees the quality and homogeneity of the information used for the proposed methodology. It is proposed the research project whose objective is to formulate a mathematical regression model that allows to analyze the behavior of the resistance of Klebsiella pneumoniae to the antibiotics in the time and to establish yes the versatility of the phenomenon, is due to a substantial change of the resistance Or in its absence is a product of the variability inherent in the sampling processes, typical of studies that seek to calculate the percentage of resistance.

Therefore, the use of this specific model, which explains the statistical trend of resistance of K. pneumoniae to Imipenem and Meropenem, becomes a strategy with great impact in the plans for the monitoring and surveillance of bacterial resistance, to In order to control this increase and therefore to evaluate whether the actions that health institutions perform to control it are effective or not.

2. MATERIALS AND METHODS

Starting from the bulletins published by the group GREBO (Group for the Control of Antimicrobial Resistance in Bogotá) monitoring the resistance of K. pneumoniae from year 2001-2014 [12] - [16], the data corresponding to Ceftazidime (CAZ), piperacillin / tazobactan (TZP), ampicillin / sulbactam (SAM), imipenem (IPM), meropenem (TC), ertapenem (ETP), gentamicin (GEN), amikacin (AK), ciprofloxacin (CIP), trimethoprim / sulfamethoxazole (SXT), tigecycline (TGC), to establish a specific model to explain and estimate Behavior of the resistance of this bacterium to a specific antibiotic in the short term; For this purpose, statisticians were applied whose objective was to select and study the suitability of the model in order to provide a tool to evaluate strategies for the monitoring and surveillance of the resistance of this bacterium.

3. GENERATION OF REGRESSION MODELS

For the selection of the model it was initially established if there were significant differences in the resistance of the 15 antibiotics during the published 13 years of study, for which the Chi-square statistic (p-value ≤ 0.05) was applied for difference of proportions in order to support the formulation of a mathematical model for the behavior of K. pneumoniae against resistance.

Once the antibiotics that showed significant differences were identified, Statgraphics XVI statistical software was used to formulate the simple regression models; among these mathematical models, the one that presented the highest R2 value was selected, since this statistic indicates the percentage of variability in K. pneumoniae resistance explained by the model.

To determine the predictive capacity of the model, a study was carried out to establish that the residuals (errors in the forecasts), do not depend on the values predicted by the model, years of study or the location of the row of information, through the analysis Of the generated scatter plots. In turn, the Kolmogorov-Smirnov test was applied to determine the probability that the residues follow a normal distribution, with a mean of zero (0) or very close to it.

4. RESULTS

Following are the results that allowed to formulate the model, which explains the tendency in the behavior of the resistance of the K. pneumoniae against all the antibiotics initially studied, also pointed out the p-Values of the Chi square test, the models Of regression generated, accompanied by the mathematical model and the adjusted R2 value. For the first phase in the model selection, the application of the Chi Square statistic (p-value ≤ 0.05), established that if there were significant differences in the resistance of the 15 antibiotics during the 13 years of study, formulating twenty-seven (27) models Of simple regression for each of the analyzed antibiotics.

The 95% significance test and a p-value of 0.05, for analysis of model suitability, showed a statistically significant correlation between bacterial resistance and the year of study, only against six (6) antibiotics: AK, CAZ , CIP, TZP, IPM and MEM.

However, when evaluating the efficiency of the model in the six antibiotics, it was established that the year variable alone was sufficiently explanatory of K. pneumoniae resistance behavior, compared to two (2) IPM and MEM antibiotics, with R2 values Adjusted by 77.9% and 79.8% respectively. See table N ° 1.

Graph 1 shows the trend in the behavior of K. pneumoniae bacterial resistance against IPM and MEM during the 13 years of study.
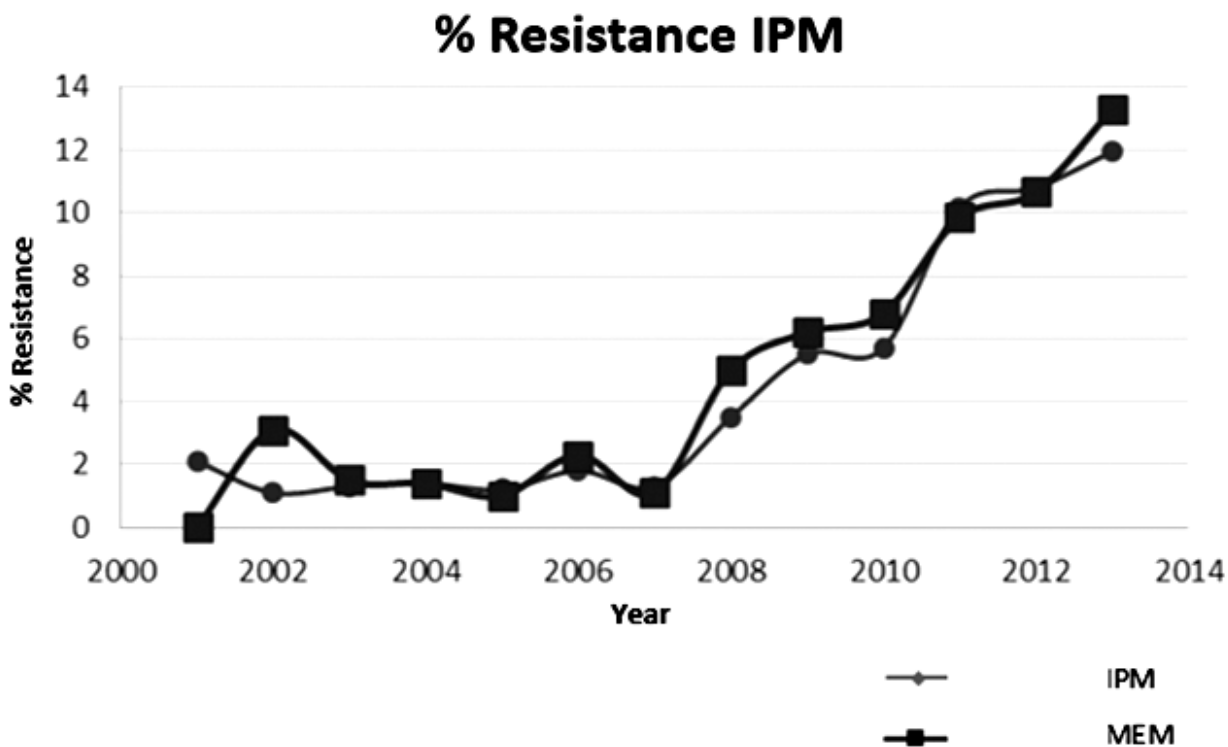

Figure 1: Evolution of bacterial resistance of Klebsiella pneumoniae for IPM and MEM

Table 1
Synthesis of results of the selection process and suitability
analysis of the mathematical model for Klebsiella pneumoniae. Source authors.

Antibiotics Betalactamicos	X^2	*P-value*	*Model*	*R^2 Tight*	*Analysis for each year*
Meropenem	0,0	0,00	$(-246{,}382 + 0{,}0000616462 \times Año^2)^2$	79,8%	For every year that passes, increase resistance to the antibiotic by 1.01%
Imipenem	0,0	0,00	$(-208{,}103 + 0{,}0000521394 \times Año^2)^2$	77,9%	For every year that passes, will increase resistance to the antibiotic by 0.84%
Amikacina	0,0	0,004	$e(-178{,}9 + 363269 / Año)$	73,17%	It is necessary to evaluate other factors besides the passage of the years since the value of Adjusted R2 is very low.
Piperacilina/ Tazobactan	0,0	0,015	$e(-23{,}2 + 0{,}000006)$	37,56%	
Ciprofloxacina	0,0	0,015	$(-22076{,}7 + 0{,}00552 \ast Año^2)^2$	37,55%	
Ceftazidima	0,0	0,042	$(-164381 + 3{,}3 \times 10^8 / Año)^2$	35,2%	
Ampicilina / Sulbactam	0,0	0,715	NA		Antibiotic resistance is not influenced by the passage of the years, to analyze other factors that can influence.
Aztreonam	0,0	0,066			
Ceftriazona	0,0	0,059			
Cefotaxima	0,0	0,367			
Cefepime	0,0	0,258			
Gentamicina	0,0	0,464			
Trimetoprim/ Sulfametoxazol	0,0	0,131			

In the validation stage, the dispersion graphs were generated, evidencing a random behavior of the residuals (errors in the forecasts) against the analyzed variables (year of study, predicted values and row location) for IPM and MEM antibiotics, Demonstrating that the mathematical model selected is a predictor of the behavior of resistance of K. pnuemoniae to these antibiotics.

For the IPM and MEM antibiotics the following dispersion graphs were generated (see graph 2 and figure 3), showing that there is no behavior pattern of the residues, indicating that there were no situations that affected the behavior of the Residues, against the variables year of study, predicted values and location in the row; Proving in this way that the model is adequate to be able to estimate the future behavior of the resistance against IPM and MEM. View charts

The Kolmogorov-Smirnov test determined that residues for the model formulated for imipenem follow a normal distribution with a mean of 0.15 and a p-value = 0.92, for the case of meropenem the mean was 0.19 And
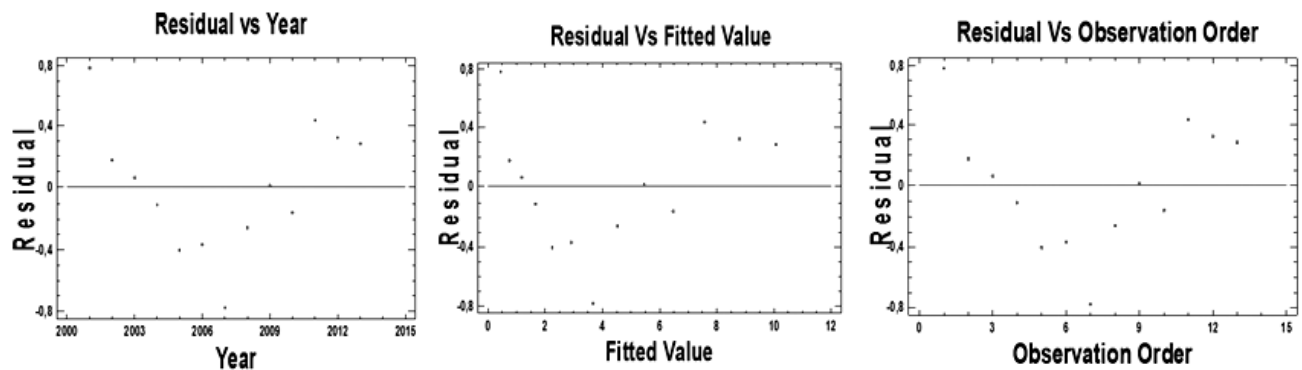
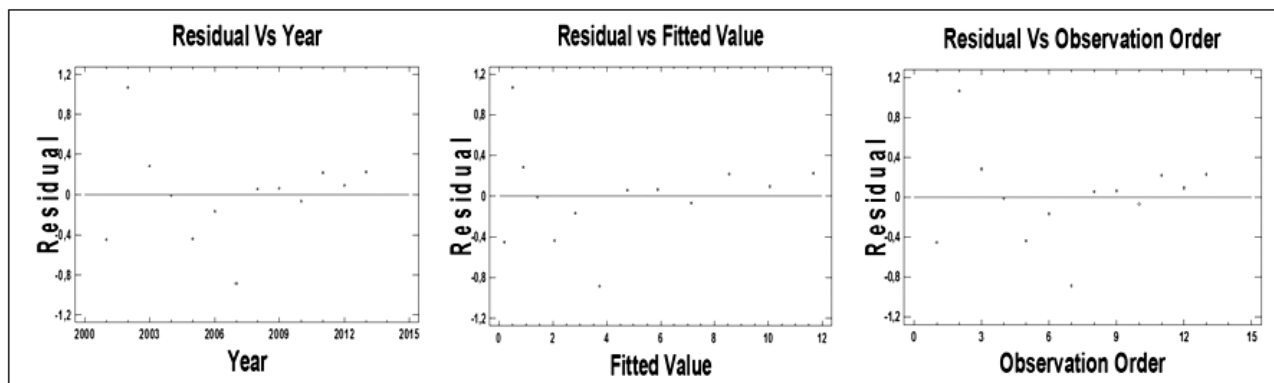**Figure 2: IMIPENEM. Residuals / vs year / predicted vs. vs row number**

Figure 3: MEROPENEM. Residuals / vs year / predicted vs. vs row number
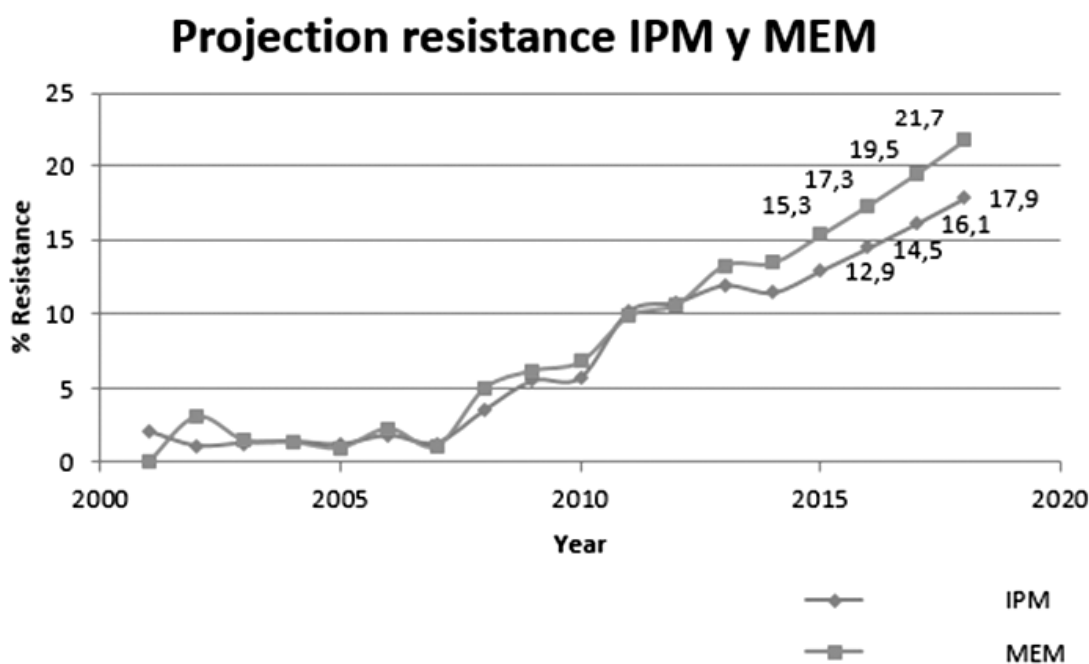

Figure 4: Projection of bacterial resistance to IPM and MEM

the p-value of 0.95 and thus fulfilling the last criterion validation of the formulated models. With the application of the generated regression model it was possible to predict until the year 2020 a trend of increase in resistance for each year that passes, from 0.84% for imipenem and 1.01% against meropenem.

5. DISCUSSION

The global report on antibiotic resistance monitoring [17] focuses on the resistance of seven bacteria responsible for serious common infections, including the behavior of K. pneumoniae over carbapenem antibiotics, an alarming situation since they are considered the last therapeutic resource, resulting in an epidemiological alert for public health in the world. Hence the importance of generating proposals aimed at controlling the high resistance rates of K. pneumoniae. Mathematical modeling becomes a novel alternative, which has been used to study the phenomenon of resistance, some research aimed at understanding how the acquisition occurs in the face of variables such as monotherapy or multiple therapy, the rate of supply of the Antibiotic, describe the dynamics of susceptible bacterial interactions and resistant against antibiotic concentration or to describe the percentages of

resistance over time [18] - [23]. On the contrary, the mathematical model proposed here predicts the future behavior of K. pneumoniae resistance and the percentage increase of resistance over the years, identifying that the versatility of the phenomenon is due to a substantial change in the behavior of bacteria.

6.   CONCLUSIONS

This type of transdisciplinary proposal becomes an innovative alternative of great impact to study the behavior of the bacterial resistance being able to replicate this methodology to evaluate the behavior against other antibiotics and other bacteria

This specific model of K. pneumoniae against IPM and MEM was able to predict that if the current conditions are maintained, by 2020 the trend of resistance increase to IPM and MEM will be 0.84% 1.01% respectively; Projection with "devastating" implications since it would limit the therapeutics in the management of infections produced by this bacterium.

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