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Fractional Model of Susceptibility Characteristics of ESBL-Producing *K. Pneumoniae* Infections for Carbapenems and Piperacillin-Tazobactam

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Abstract: In this paper, we provide a fractional dynamical model of extended spectrum beta lactamase (ESBL)-producing *Klebsiella pneumoniae* to visualize future perspective of susceptibility characteristics of *K. pneumoniae* infections for antibiotics; carbapenems and piperacillin-tazobactam (PTZ). The model approach is based on the Caputo type fractional differential equation system. The existence and uniqueness of the system solution is demonstrated using Lipschitz conditions. Two equilibrium points were found, the absence of disease and the presence of disease, and stability analyzes were performed with the help of Hurwitz criterion. According to the SIS-type model, while non-ESBL *K. pneumoniae* infections seem to remain susceptible to both antibiotic groups, the opposite is true for ESBL-producing *K. pneumoniae* infections. For ESBL-producing *K. pneumoniae* infections, resistance to both carbapenems and PTZ will occur approximately 7.5 years later according to the mathematical modelling of our data. In addition, resistance to PTZ in ESBL-producing infections is observed to be less than to carbapenems. As a result, resistance against agents called last line antibiotics, which are preferred in the treatment of ESBL-producing infections, has been observed that will increase in the future, and necessary measures should be taken to delay this situation.

Keywords: Antibiotic resistance, Caputo type fractional derivative, extended spectrum beta lactamas, mathematical modeling.

1 Introduction

One of the most important problems encountered in the treatment of infectious diseases is antibiotic resistance. Excessive and inaccurate use of antibiotics has caused bacteria to develop resistance to these agents over time. One of the resistance mechanisms created is extended-spectrum beta-lactamase (ESBL) production. This resistance mechanism is frequently seen in members of the *Enterobacteriaceae* family, which are also the main cause of nosocomial infections [1]. Carbapenems are the antibiotics of choice for the treatment of ESBL-producing infections. Frequent use of carbapenems for empirical therapy has led to the development of carbapenem-resistant *Enterobacteriaceae*. Due to the limited treatment possibilities of carbapenem-resistant *Enterobacteriaceae*, particular attention needs to be given to the use of broad-spectrum antimicrobials [2]. Piperacillin-tazobactam (PTZ) has been considered as an alternative to treatment with carbapenem of certain infections, in order to reduce the formation of resistance to carbapenems [3].

As a result of a systematic review, it was evident that carbapenem treatment cannot be ignored as a treatment option in ESBL bloodstream infections, the evaluation of PTZ as an alternative agent depends on the source of the infection [4]. For the treatment of mild to moderate infections, the use of PTZ is preferred. In addition, given that urinary tract infections are also the most common infection, the use of alternative drugs is extremely important to reduce the use of carbapenems [5].

Although the contribution of mathematical modeling in the control of emerging infections is already well known, it is thought that it can be an effective tool in the regulation of the policies of health institutions in the control of antimicrobial resistance [6]. It has been observed that mathematical models make accurate predictions in studies on the emergence of

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resistance in malaria, MDR-TB and influenza, and mathematical models are used for the control of antimicrobial resistance in health facilities [7]. Especially recently, mathematical models have been widely used for coronavirus research [8,9].

Dynamic systems in mathematical models are widely used approaches in the study of biological phenomena. The use of fractional-order equations rather than integer-order equations for the interpretation of many biological phenomena, especially for modeling memory systems, provides more natural results [10,11,12].

Antimicrobial resistance and multidrug resistance depend on exposure times to drugs. Accordingly, the memory effect is important for both cases. Therefore, the fractional order formulation, which is related to memory systems, is convenient for the study of these phenomena [13,14].

Today, increasing antibiotic resistance, especially multi-drug resistant microorganisms, has turned the treatment of infectious diseases into a struggle. Difficulty in treatment reduces the patient's quality of life and increases medical costs. This study was conducted to predict the state of antibiotic resistance in the future for carbapenems which are defined as the last line antibiotics and PTZ that both are used in the treatment of *K. pneumoniae* infections.

This research was carried out as a continuation of a previous study [15] and an innovative approach was preferred. Carbapenem and PTZ susceptibility profiles of ESBL-producing *K. pneumoniae* infections were investigated by using fractional-order equations for better interpretation of antibiotic resistance. According to our study, after a certain period of time, carbapenems and PTZ will be insufficient in the treatment of ESBL-producing *K. pneumoniae* infections and other antimicrobials will be required. The creation of new antibiotics is difficult and time consuming. Thus, it was considered to determine a timeline for interventions to slow down the resistance formation process. Therefore, the aim of this study is to develop a mathematical model which will assist in the prediction of resistance probability against two important antibiotic groups effective in the treatment of a common nosocomial infectious agent such as *K. pneumoniae*. This data can then be used by physicians and other healthcare professionals in patient treatment approaches.

The present paper is structured as follows: In section 2, we provide a Caputo type fractional derivative order system for the susceptibility properties of ESBL-producing *K. pneumoniae* for carbapenems and PTZ. Equilibrium points, basic reproduction number and the stability analysis are also investigated in section 2. The results of our study are presented and discussed based on the research data in section 3. Finally, section 4 contains the conclusion of the study.

2 Materials and Methods

2.1 Collection, Identification and Antimicrobial Susceptibility Tests of Klebsiella Strains

Procedures were followed as mentioned in [15].

2.2 Adaptation of Susceptibility Properties for Carbapenems and Piperacillin-Tazobactam to the Mathematical Model

As the first stage of the study, a new model was created depending on the model included in the study by Bagkur et al. (see Figure 1) where the parameters are described in Table 1 [15].

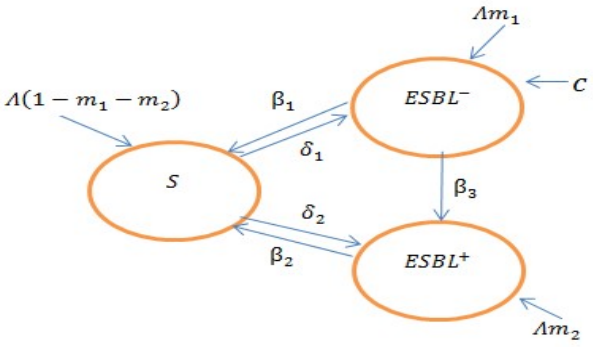

Fig. 1: A compartment model of ESBL- and ESBL + *K. pneumoniae* and susceptible individuals to *K. pneumoniae* infection [15].

Table 1: Descriptions of parameters of the compartment model.

Parameters	Descriptions
$\boldsymbol{S}$	Susceptible to *K. pneumoniae*.
$\boldsymbol{E^-}$	ESBL negative *K. pneumoniae.*
$\boldsymbol{E^+}$	ESBL positive *K. pneumoniae.*
$\boldsymbol{\Lambda}$	The number of hospital admission.
$\boldsymbol{m_1}$	The fraction of patients admitted with ESBL$^-$ *K. pneumoniae.*
$\boldsymbol{m_2}$	The fraction of patients admitted with ESBL$^+$ *K. pneumoniae.*
$\boldsymbol{C}$	Probability that person take drug one and be resistant to the drug.
$\boldsymbol{\delta_1}$	Transmission rate of susceptible patient infected with ESBL$^-$ *K. pneumoniae.*
$\boldsymbol{\delta_2}$	Transmission rate of susceptible patient infected with ESBL$^+$ *K. pneumoniae.*
$\boldsymbol{\beta_1}$	Transmission rate from ESBL$^-$ *K. pneumoniae* to susceptible class.
$\boldsymbol{\beta_2}$	Transmission rate from ESBL$^+$ *K. pneumoniae* to susceptible class.
$\boldsymbol{\beta_3}$	Transmission rate from ESBL$^-$ to ESBL$^+$ *K. pneumoniae.*

By adding carbapenem group antibiotics (K) and piperacillin-tazobactam (T) parameters, previous compartment model of ESBL$^-$ and ESBL$^+$ *K. pneumoniae* was improved and a new model was created. In this study, Caputo type fractional order model was obtained and the additional parameters of the new model are shown in Table 2. This model was created by applying the data of susceptibility properties of carbapenem group antibiotics (K) and piperacillin-tazobactam (T), used for the treatment of patients with ESBL$^+$ *K. pneumoniae* infections detected in a university hospital from 2016 to 2019. In the study, the carbapenem group antibiotics consisted of ertapenem, imipenem and meropenem, and resistance to at least one of them was evaluated as resistance to the group.

The Caputo fractional derivative of order α is denoted by D_*^{α} and it is defined by

$$D^{\alpha}{}_t f(t) = \begin{cases} \frac{1}{\Gamma(\mathrm{n}-\alpha)} \int_0^t (t-s)^{n-\alpha-1} \frac{d^n f(s)}{ds^n} ds, \text{if } \mathrm{n}-1 < \alpha < n, n \epsilon \mathbb{N} \\ \frac{d^n f(t)}{dt^n}, \quad if \alpha = n, \mathrm{n} \epsilon \mathbb{N} \end{cases}$$

where α is the order of the derivative and it is allowed to be a real or complex number.

Table 2: Descriptions of additional parameters of the Caputo type fractional order antibiotic model.

Parameters	Descriptions
$\boldsymbol{k}$	Rate of individuals with ESBL$^+$ *K. pneumoniae* infections that can be treated with carbapenems (K).
$\boldsymbol{p}$	Rate of individuals with ESBL$^+$ *K. pneumoniae* infections that can be treated with piperacillin-tazobactam (T).
$\boldsymbol{\alpha_1}$	Rate of individuals who recovered from taking carbapenems (K).
$\boldsymbol{\alpha_2}$	Rate of individuals who recovered from taking piperacillin-tazobactam (T).

The differential equation system of the model is given as follows;

$$D_*^{\alpha}S(t) = \Lambda(1-m_1-m_2) - \delta_1 E^- S - \delta_2 E^+ S + \alpha_1 K + \alpha_2 T + c\beta_1 E^- + \beta_2 E^+ - \mu S,$$

$$D_*^{\alpha}E^-(t) = \Lambda m_1 + \delta_1 E^- S - \beta_1 E^- - \mu E^-, \quad (1)$$

$$D_*^{\alpha}E^+(t) = \Lambda m_2 + \delta_2 E^+ S + (1-c)\beta_1 E^- - \beta_2 E^+ - (k+\ p)E^+ - \mu E^+,$$

$$D_*^{\alpha}K(t) = kE^+ - \alpha_1 K - \mu K,$$

$$D_*^{\alpha}T(t) = pE^+ - \alpha_2 T - \mu T.$$

With the initial no negative values;

$$\big(S(0), E^-(0), E^+(0), K(0), T(0)\big) = (S_0, E_0^-, E_0^+, K_0, T_0), \text{ where } \alpha \in (0,1] \text{ and } t \in (0,T].$$

System (1) can be written as a matrix form as follows;

$$D_*^{\alpha}(t) = A + BX(t) + E^- CX(t) + E^+ DX(t) = X^0,$$

where,

$$X(t) = \begin{bmatrix} S(t) \\ E^-(t) \\ E^+(t) \\ K(t) \\ T(t) \end{bmatrix}, X^0(t) = \begin{bmatrix} S(0) \\ E^-(0) \\ E^+(0) \\ K(0) \\ T(0) \end{bmatrix}, A = \begin{bmatrix} \Lambda(1-m_1-m_2) \\ \Lambda m_1 \\ \Lambda m_2 \\ K(0) \\ T(0) \end{bmatrix},$$

$$B = \begin{bmatrix} -\mu & c\beta_1 & \beta_2 & \alpha_1 & \alpha_2 \\ 0 & -\beta_1-\mu & 0 & 0 & 0 \\ 0 & (1-c)\beta_1 & -\beta_2-k-p-\mu & 0 & 0 \\ 0 & 0 & k & -\alpha_1-\mu & 0 \\ 0 & 0 & p & 0 & -\alpha_2-\mu \end{bmatrix},$$

$$C = \begin{bmatrix} -\delta_1 & 0 & 0 & 0 & 0 \\ \delta_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, D = \begin{bmatrix} -\delta_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \delta_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Let's consider $D_*^{\alpha}(t) = F(t, X(t))$, the solution $X* \in C_5$ of the system (1) bounded and the positive invariant region is,

$$\Omega = \left\{\big(S(t), E^-(t), E^+(t), K(t), T(t)\big) \in C_+^5 : N \leq \frac{\Lambda}{\mu}\right\}.$$

For $X^* = \begin{bmatrix} S^*(t) \\ E^{-*}(t) \\ E^{+*}(t) \\ K^*(t) \\ T^*(t) \end{bmatrix}$ and $X' = \begin{bmatrix} S'(t) \\ E^{-\prime}(t) \\ E^{+\prime}(t) \\ K'(t) \\ T'(t) \end{bmatrix}$, we have

$$\begin{aligned} \|F(X^*) - F(x')\| &= \left\|\left(A + BX^*(t) + E^- CX^*(t) + E^+ DX^*(t)\right)\right. \\ &\quad \left. - \left(A + BX'(t) + E^- CX'(t) + E^+ DX'(t)\right)\right\| \\ &\le \left\|B\left(X^*(t) - X'(t)\right)\right\| + \left\|C\left(E^{-*}X^*(t) - E^{-\prime}X'(t)\right)\right\| \\ &\quad + \left\|D\left(E^{+*}X^*(t) - E^{+\prime}X'(t)\right)\right\| \\ &\le \|B\|\|X^*(t) - X'(t)\| + \|C\|(\|E^{-*}\| + \|X'\|)\|X^*(t) - X'(t)\| \\ &\quad + \|D\|(\|E^{+*}\| + \|X'\|)\|X^*(t) - X'(t)\|. \end{aligned}$$

From the invariant set, $E^{-*} \le \frac{\Lambda}{\mu}$, $E^{+*} \le \frac{\Lambda}{\mu}$ and $\|X'\| \le \frac{\Lambda}{\mu}$, therefore, we have

$$\|F(X^*) - F(x')\| \le \left(\|B\| + \frac{\Lambda}{\mu}(\|C\| + \|D\|)\right)\|X^*(t) - X'(t)\|.$$

With choosing $L = \|B\| + \frac{\Lambda}{\mu}(\|C\| + \|D\|) > 0$, it is obtained

$$\|F(X^*) - F(x')\| \le L\|X^*(t) - X'(t)\|.$$

Therefore, the continuous function $F(X(t))$ satisfies the Lipschitz condition and so the system (1) has a unique solution.

2.3 Equilibrium Points

With equalizing right hand side of each equation in system (1) to zero, we obtain two equilibrium points that are disease free equilibrium point $E_0 = \left(\frac{\Lambda}{\mu}, 0,0,0,0\right)$ (when both $m_1 = m_2 = 0$) and endemic equilibrium point $E_1 = \left(S^*, E^{-*}, E^{+*}, K^*, T^*\right)$,where

$E^{-*} = \frac{\Lambda m_1}{\mu + \beta_1 - \delta_1 S}$,

$E^{+*} = \frac{\Lambda m_2}{\beta_2 + k + p + \mu - \delta_2 S} + \frac{(1-c)\beta_1}{\beta_2 + k + p + \mu - \delta_2 S}\frac{\Lambda m_1}{\mu + \beta_1 - \delta_1 S}$,

$K = \frac{k}{\alpha_1}E^{+*}$,

$T = \frac{p}{\alpha_2}E^{+*}$,

and S^* is the solution of the following equation,

$$\begin{aligned} &\Lambda(1 - m_1 - m_2)(\mu + \beta_1 - \delta_1 S)(\beta_2 + k + p + \mu - \delta_2 S) + (c\beta_1 - \delta_1 S)(\beta_2 + k + p + \mu - \delta_2 S) \\ &\quad + (\beta_2 + k + p + \mu - \delta_2 S)[\Lambda m_2(\mu + \beta_1 - \delta_1 S) + (1 - c)\beta_1 \Lambda m_1] + \mu S = 0. \end{aligned}$$

2.4 Basic Reproduction Numbers

With using the Next Generation Matrix method, basic reproduction numbers are found as follows;

$$R_{0,1} = \frac{\delta_1 \Lambda}{\mu(\beta_1 + \mu)},$$

$$R_{0,2} = \frac{\delta_2 \Lambda}{\mu(\beta_2 + k + p + \mu)}.$$

2.5 Stability Analysis

Theorem 1: The disease free equilibrium point is locally stable when $R_{0,1} < 1$ and $R_{0,2} < 1$.

Proof:

The Jacobian matrix of the system (1) at the disease free point $E_0 = \left(\frac{\Lambda}{\mu}, 0,0,0,0\right)$ is

$$J(E_0) = \begin{pmatrix} -\mu & -\delta_1\frac{\Lambda}{\mu} + c\beta_1 & -\delta_2\frac{\Lambda}{\mu} + \beta_2 & \alpha_1 & \alpha_2 \\ 0 & \delta_1\frac{\Lambda}{\mu} - \beta_1 - \mu & 0 & 0 & 0 \\ 0 & (1-c)\beta_1 & \delta_2\frac{\Lambda}{\mu} - (\beta_2 + k + p + \mu) & 0 & o \\ 0 & 0 & k & -\alpha_1 & 0 \\ 0 & 0 & p & 0 & -\alpha_2 \end{pmatrix}.$$

The Eigenvalues of the Jacobian matrix are $\lambda_1 = -\mu, \lambda_2 = \delta_2\frac{\Lambda}{\mu} - (\beta_2 + k + p + \mu), \lambda_3 = \delta_1\frac{\Lambda}{\mu} - (\beta_1 + \mu), \lambda_4 = -\alpha_1, \lambda_5 = -\alpha_2$. Since λ_1, λ_4 and λ_5 are all negative, and λ_2 and λ_3 are negative whenever $\frac{\delta_2\Lambda}{\mu(\beta_2+k+p+\mu)} < 1$ and $\frac{\delta_1\Lambda}{\mu(\beta_1+\mu)} < 1$ that means, the disease free equilibrium E_0 is locally asymptotically stable whenever $R_{0,1} < 1$ and $R_{0,2} < 1$.

Theorem 2: The endemic equilibrium point $E_1 = \left(S^*, E^{-*}, E^{+^*}, K^*, T^*\right)$ is locally stable when $R_{0,1} > 1$ and $R_{0,2} > 1$.

Proof:

The Jacobian matrix of the system (1) at the endemic equilibrium $E_1 = \left(S^*, E^{-*}, E^{+^*}, K^*, T^*\right)$ is

$$J(E_1) = \begin{pmatrix} -\delta_1E^{-*} - \delta_2E^{+^*} - \mu & -\delta_1S^* + c\beta_1 & -\delta_2S^* + \beta_2 & \alpha_1 & \alpha_2 \\ \delta_1E^{-*} & \delta_1S^* - \beta_1 - \mu & 0 & 0 & 0 \\ \delta_2E^{+^*} & (1-c)\beta_1 & \delta_2S^* - (\beta_2 + k + p + \mu) & 0 & o \\ 0 & 0 & k & -\alpha_1 & 0 \\ 0 & 0 & p & 0 & -\alpha_2 \end{pmatrix},$$

with the Eigenfunction,

$$\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5.$$

Where,

$$\begin{gathered} a_1 = \alpha_1 + \alpha_2 - a - r_1 - r_2, \\ a_2 = \alpha_1\alpha_2 - a(r_1 + r_2) - b\delta_1E^- - d\delta_2E^+, \\ a_3 = \alpha_1\alpha_2(r_1 + r_2 - a) - (\alpha_1 + \alpha_2)\,(a(r_1 + r_2) + r_1r_2 + b\delta_1E^- + d\delta_2E^+) - ar_1r_2 - b\delta_1r_2E^- - d\delta_2r_1E^+ - d\delta_1E^- \\ + \delta_2E^+(k\alpha_1 + p\alpha_2), \\ a_4 = -(ar_1r_2 + b\delta_1r_2E^- + d\delta_2r_1E^+ + de\delta_1E^-)(\alpha_1 + \alpha_2) - (\alpha_1\alpha_2)\,(a(r_1 + r_2) - r_1r_2 + b\delta_1E^- + d\delta_2E^+) \\ + (k + p)\alpha_1\alpha_2\delta_2E^+ + \delta_1eE^- + \delta_2r_1E^+, \\ a_5 = -ar_1r_2 - b\delta_1r_2E^- - d\delta_2r_1E^+ - de\delta_1E^- + (k + p)(\delta_1E^-e + \delta_2E^+r_1)(\alpha_1\alpha_2), \end{gathered}$$

and

$$\begin{gathered} a = -(\delta_1E^- + \delta_2E^+ + \mu), \\ b = -\delta_1S^* + c\beta_1, \\ d = -\delta_2S^* + \beta_2, \\ e = (1-c)\beta_1, \\ r_1 = \delta_1S^* - \beta_1 - \mu, \\ r_2 = \delta_2S^* - \beta_2 - k - p - \mu. \end{gathered}$$

Since all parameters are positive and when the basic reproduction numbers $R_{0,1}$ and $R_{0,2}$ are greater than one, a, b, and d are negative and e, r_1 and r_2 are positive, therefore the all coefficients a_1, a_2, a_3, a_4 and a_5 of the Eigenfuncitons are positive. Hence, from the Hurwitz stability criteria the endemic equilibrium point $E_1$is locally stable.

3 Results and Discussion

Susceptibility Model for Carbapenems and Piperacillin-Tazobactam

Using the SIS-type model of non-ESBL (E^-) *K. pneumoniae* and ESBL-producing (E^+) *K. pneumoniae*, a mathematically adapted model was created with carbapenem (K) and piperacillin-tazobactam (T) antibiotic groups used in the treatment of ESBL-producing *K. pneumoniae* infections.

The following graph was created by applying the data obtained from the hospital to the differential equation system created for the model. Figure 2 shows the efficacy of carbapenem (K) and piperacillin-tazobactam (T) antibiotic groups against non-ESBL (E^-) and ESBL-producing (E^+) *K. pneumoniae* infections for the coming years.

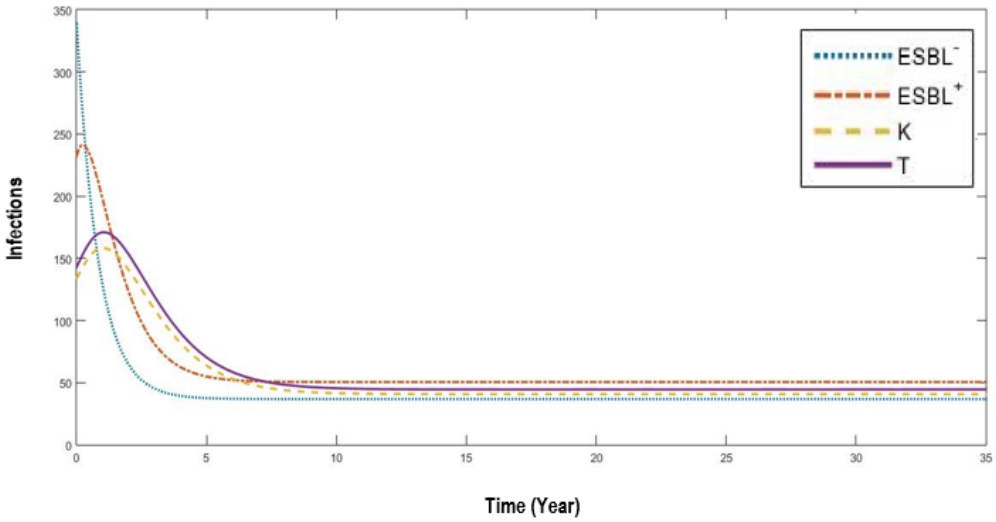

Fig. 2: Graph of susceptibility in *K. pneumoniae* infections with the use of carbapenem (K) and piperacillin-tazobactam (T) antibiotics for the coming years.

The fact that the line representing non-ESBL infections is below the lines representing the antibiotic groups indicates that both antibiotic groups will continue to be effective in the treatment of non-ESBL infections.

Data obtained as a result of the administration of carbapenem and piperacillin-tazobactam antibiotics to ESBL+ *K. pneumoniae* patients detected from 2016 to 2019 were applied to the differential equation system of the model, and the graph in Figure 3 was obtained.

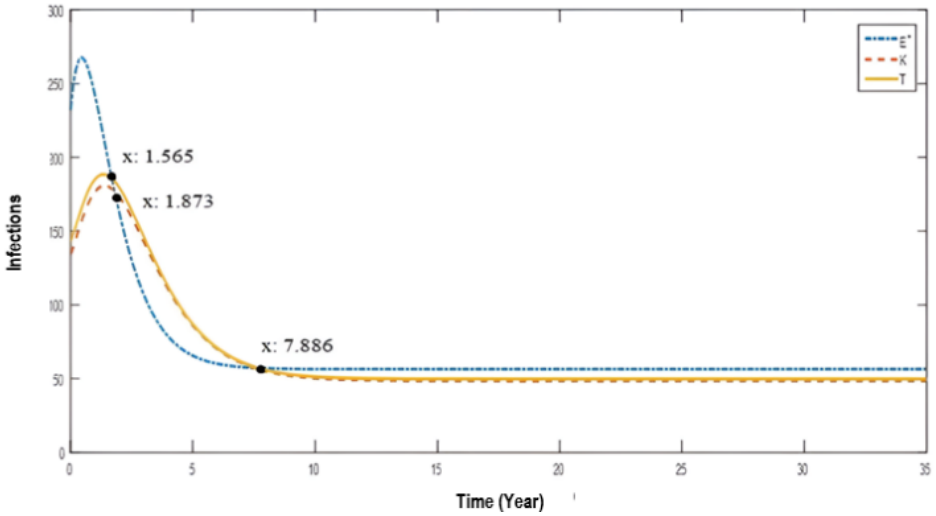

Fig.3: Efficacy of carbapenem (K) and piperacillin-tazobactam (T) antibiotics on ESBL-producing (E^+) *K. pneumoniae* infections for the coming years.

Based on the graph in Figure 3, it appears that carbapenems and piperacillin-tazobactam will continue to be effective for the treatment of ESBL$^+$ *K. pneumoniae* infections for another 7.5 years. After approximately 7.5 years, it is estimated that these two groups of antibiotics will be insufficient in the treatment of ESBL$^+$ *K. pneumoniae* infections (resistance will increase). Therefore, it can be interpreted that other groups of antibiotics will be needed as the treatment of ESBL$^+$ infections are not improving in time by the use of carbapenems and PTZ as can be seen in Figure 3.

PTZ is one of the important alternatives to carbapenems in the treatment of ESBL-producing infections. A growing number of studies show that PTZ can be as effective as carbapenems [2,16,17]. Resistance to third- and fourth-generation cephalosporins by ESBL-producing bacteria poses challenges for the usability of existing antibiotics. Treatment of these increasingly common infections with carbapenems leads to the formation of carbapenem-resistant Gram-negative bacteria. Therefore, beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations that encourage sparing use of carbapenem group antibiotics such as piperacillin-tazobactam are considered for such infections. Members of the *Enterobacteriaceae* harboring ESBL are generally susceptible to PTZ in vitro [18].

On the other hand, the available evidence for piperacillin-tazobactam (PTZ) as an effective treatment alternative is controversial. In the study conducted by Tullos et al., PTZ had a similar clinical response rate to carbapenems. There was no significant difference in results compared to carbapenems when PTZ was used for the treatment in patients with urinary tract infections caused by ESBL-producing *Enterobacteriaceae*. Although further studies are needed and carbapenems are the treatment of choice in patients with more severe clinical manifestations such as bloodstream infection, the study demonstrates that PTZ may be an effective alternative in patients with ESBL-associated infections from a urinary source only [2].

In the study conducted by Sharara et al., it was concluded that PTZ may be a suitable alternative to the use of carbapenems for the treatment of pyelonephritis caused by ESBL-producing organisms, except for bacteremia [17]. Tamma et al. also stated that PTZ is less effective than carbapenem in the treatment of ESBL bacteremia, and early carbapenem treatment should be considered in patients with a high risk of invasive ESBL infection [19].

Although the addition of tazobactam reduces the hydrolyzing effect of beta-lactamase enzymes on the beta-lactam ring of piperacillin, reduced activity of tazobactam has been observed when high concentrations of bacteria are present (inoculum effect) [20]. This may explain why carbapenems are more effective than PTZ in the treatment of bloodstream infections.

Figure 3 demonstrates that although PTZ is considered as an alternative in place of carbapenem treatment, resistance to both carbapenems and PTZ will develop simultaneously after approximately 7.5 years. Although it can be observed from the graph that other antibiotic groups will be required for ESBL$^+$ *K. pneumoniae* infections, the fact that PTZ (T) is observed above carbapenem (K) in the graph can be interpreted as PTZ is expected to be more effective compared to carbapenems in treatments.

The presence of other mechanisms of beta-lactam resistance, such as AmpC beta-lactamase production or additional ESBLs, in a given bacterium further complicates the bacterial environment, reducing the efficacy of PTZ [19]. The effectiveness of PTZ antibiotics on ESBL-producing *Enterobacteriaceae* depends on the type and amount of enzyme produced. The efficacy of PTZ may be reduced when organisms produce more than one ESBL, particularly if AmpC beta-lactamase presents. In addition, the effect differs between beta-lactamase classes [21].

On the other hand, there are three main mechanisms by which *Enterobacteriaceae* are resistant to carbapenems: enzymatic hydrolysis of carbapenems by carbapenemases (such as NDM, KPC, VIM, OXA and IMP), expression of efflux pumps that actively extrude carbapenems from bacterial cell and reduction of outer membrane permeability through the production of beta-lactamases (AmpC) with changes in the bacterial cell membrane (porin mutations in OmpK35 and OmpK36) [22].

Based on the above information, it can be suggested that PTZ has a more advantageous position against resistance mechanisms such as carbapenemase, efflux pumps and porin mutations that affect carbapenems, due to its beta-lactamase inhibitor (tazobactam). This can be used to understand why PTZ is more effective against ESBL$^+$ *K. pneumoniae* infections as demonstrated in Figure 3, through its advantage over carbapenem resistance mechanisms.

Considering the preference of carbapenem treatment in patients with high risk invasive ESBL infection and the low treatment rate of PTZ in the treatment of ESBL bacteremia, it is seen that the susceptibility of these two groups of antibiotics against ESBL$^+$ infections in the coming years is of concern. Treatment practices need to be developed to prevent this situation and it should be emphasized that it is very important for clinicians to administer antibiotics to patients according to their resistance profiles during the treatment.

4 Conclusion

Gram-negative bacteria resistant to carbapenems are a major clinical concern as they cause virtually incurable infections, as carbapenems are among the antimicrobial agents of last resort. Therefore, alternative treatment options should be evaluated in order to prevent resistance to carbapenem. Although piperacillin-tazobactam is an antibiotic chosen as an alternative to carbapenem, it is not as effective as carbapenems in the treatment of certain infections. According to the data of the current study, resistance to both types of antibiotics will lead to a dead end in treatment if precautions are not taken.

Our study, which is an example of fractional calculus and its applications, makes a difference in many antibiotic resistance studies using mathematical modeling by including the antibiotic groups preferred as a last resort in treatment and predicting the future resistance to these antibiotic groups. We think that the results of our study will be enlightening for clinicians in the treatment of *K. pneumoniae* infections, other nosocomial infectious agents and resistant microorganisms.

For future studies, optimal control methods can be applied to determine which parameters are more effective in delaying the development of antibiotic resistance.

References

[1] Z. Breijyeh, B. Jubeh and R. Karaman, Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it, *Molecules*. **25(6)**, 1340 (2020).
[2] J. B. Tullos, L. L. Stoudenmire and J. D. Pouliot, Piperacillin-tazobactam versus carbapenems for the treatment of nonbacteremic urinary tract infections due to extended-spectrum beta-lactamase-producing enterobacteriaceae, *Hosp. Pharm*. **55(1)**, 44-49 (2020).
[3] M. W. Petersen, A. Perner, F. Sjövall, A. B. Jonsson, M. Steensen, J. S. Andersen and M. H. Møller, Piperacillin/tazobactam vs carbapenems for patients with bacterial infection: Protocol for a systematic review, *Acta Anaesthesiol. Scand.* **63(7)**, 973-978 (2019).
[4] D. B. Chastain, B. P. White, D. A. Cretella and C. M. Bland, Is It Time to rethink the notion of carbapenem-sparing therapy against extended-spectrum β-lactamase–producing enterobacteriaceae bloodstream infections? A critical review, *Ann. Pharmacother*. **52(5)**, 484-492 (2018).
[5] T. Asakura, M. Ikeda, A. Nakamura and S. Kodera, Efficacy of empirical therapy with non-carbapenems for urinary tract infections with extended-spectrum beta-lactamase-producing enterobacteriaceae, *J. Glob. Infect. Dis.* **29**, 91-95 (2014).
[6] H. Heesterbeek, R. M. Anderson, V. Andreasen, S. Bansal, D. De Angelis, C. Dye, ... and Isaac Newton institute IDD collaboration, Modeling infectious disease dynamics in the complex landscape of global health, *Science*. **347(6227)**, aaa4339 (2015).
[7] A. M. Niewiadomska, B. Jayabalasingham, J. C. Seidman, L. Willem, B. Grenfell, D. Spiro and C. Viboud, Population-level mathematical modeling of antimicrobial resistance: a systematic review, *BMC Med*. **17(1)**, 1-20 (2019).
[8] I. Ahmed, G. U. Modu, A. Yusuf, P. Kumam and I. Yusuf, A mathematical model of coronavirus disease (COVID-19) containing asymptomatic and symptomatic classes, *Resul. Phys*. **21**, 103776 (2021).
[9] P. Riyapan, S. E. Shuaib, and A. Intarasit, A mathematical model of COVID-19 pandemic: a case study of Bangkok, Thailand, *Comput. Math. Meth. Med*. **2021**, (2021).
[10] M. F. Elettreby, A. S. Alqahtani and E. Ahmed, Fractional-order model for multi-drug antimicrobial resistance, *CMES - Comput. Model. Eng. Sci.* **124(2)**, 665-682 (2020).
[11] M. F. Elettreby, A. S. Alqahtani and T. Nabil, Complex dynamical behavior of a discretize fractional-order multi-drug antimicrobial resistance model, *Alex. Eng. J*. **59(5)**, 3119-3131 (2020).
[12] D. Baleanu, F. A. Ghassabzade, J. J. Nieto and A. Jajarmi, On a new and generalized fractional model for a real cholera outbreak, *Alex. Eng. J.* **61(11)**, 9175-9186 (2022).
[13] R. Capponetto, G. Dongola, L. Fortuna and I. Petras *Fractional order systems: modelling and control applications*, In World Scientific Series in Nonlinear Science (Vol. 72), Singapore: Series A, 2010.
[14] E. Ahmed, A. S. Elgazzar and A. A. Elsadany, Simple mathematical models of antimicrobial resistance, *J. Fractional Calc. & Appl*. **11(1)**, 22-25 (2020).
[15] C. Bagkur, E. Guler, B. Kaymakamzade, E. Hincal and K. Suer, Near future perspective of ESBL-producing klebsiella pneumoniae strains using mathematical modeling, *Comput Mod. Eng Sci*. **130(1)**, 111-132 (2022).
[16] M. Ayhan, B. Kayaaslan, I. Hasanoglu, A. K. Kalem, D. Asilturk, M. A. Tasyaran and H. R. Guner, Comparison of the effectiveness of piperacillin-tazobactam and carbapenems in nosocomial infections with extended-spectrum beta-lactamase-producing escherichia coli and klebsiella pneumoniae, *Mediter. J. Infect. Micr. Antimicrob.* **9**, NA-NA (2020).
[17] S. L. Sharara, J. Amoah, Z. D. Pana, P. J. Simner, S. E. Cosgrove and P. D. Tamma, Is piperacillin-tazobactam effective for the treatment of pyelonephritis caused by extended-spectrum β-lactamase–producing organisms?, *Clin. Infect. Dis*. **71(8),** e331-e337 (2020).
[18] P. N. Harris, P. A. Tambyah, D. C. Lye, Y. Mo, T. H. Lee, M. Yilmaz, ... and D. L. Paterson, Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial, *Jama*. **320(10)**, 984-994 (2018).
[19] P. D. Tamma, J. H. Han, C. Rock, A. D. Harris, E. Lautenbach, A. J. Hsu... and S. E. Cosgrove, Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia, *Clin. Infect. Dis*. **60(9)**, 1319-132 (2015).
[20] L. López-Cerero, E. Picón, C. Morillo, J. R. Hernández, F. Docobo, J. Pachón, ... and A. Pascual, Comparative assessment of inoculum effects on the antimicrobial activity of amoxycillin-clavulanate and piperacillin-tazobactam with extended-spectrum β-lactamase-

producing and extended-spectrum β-lactamase-non-producing Escherichia coli isolates, *Clin. Microbiol. Infect*. **16(2)**, 132-136 (2010).

[21] B. Pilmis, V. Jullien, A. Tabah, J. R. Zahar and C. Brun-Buisson, Piperacillin–tazobactam as alternative to carbapenems for ICU patients, *Ann. Intensive Care*. **7(1)**, 1-17 (2017).

[22] N. Alizadeh, M. A. Rezaee, H. S. Kafil, A. Hasani, M. H. S. Barhaghi, M. Milani, ... and R. Ghotaslou, Evaluation of resistance mechanisms in carbapenem-resistant Enterobacteriaceae, *Infect. Drug Resist.*.**13**, 1377 (2020).