A nosocomial-pathogens-infections model with impulsive antibiotics treatment on multiple bacteria

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ABSTRACT

A nosocomial-pathogens-infections model with impulsive antibiotics treatment on multiple bacteria and time-dependent drug efficacy is proposed in this paper to describe the patients infected by the bacterial populations of both antibiotic-wild-type and antibiotic-resistant strains during the course of combination treatment. The purposes of this paper are to investigate the efficacies of periodic input of antibiotic dosage on bacterial populations with impulsive drug effects and to preserve or restore antibiotic effectiveness. Two antibiotics are used to induce instantaneous antibiotic efficacies at fixed times and antibiotic concentrations decay exponentially. Using the theories of asymptotic periodic systems, uniform persistence theory of discrete dynamical systems and monotone dynamics, sufficient conditions for treatment success as well as for treatment failure are established via the basic reproduction ratio of periodic compartment models. In particular, the results show that if any basic reproduction ratio for the patients infected by wild-type bacteria, resistant bacteria or those infected by both strains is larger than unity, then there will be persistent treatment failure for patients infected by resistant bacteria. This study indicates the significance of exploring a more effective therapeutic regimen for nosocomial infection. Numerical simulations have been performed to verify/extend our analytical results.

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1. Introduction

A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as Erythromycin-resistant and Vancomycin-resistant enterococci, are increasing rapidly throughout the world and pose a serious threat to public health. Many studies have indicated that the pharmacology of antibiotics (or other drug) of pharmacokinetics (PK) and pharmacodynamics (PD) had been regarded as separate disciplines. That is, PK describes the concentration-time courses of antibiotics in different body fluids where as PD describes the relationship between the concentration of antibiotics and their effects on target bacteria (such as growth, decay, etc.) in order to achieve the maximum elimination of bacteria from the infected patients [1–3].

Recently, the appearance and transmission of antibiotic-resistant bacteria in hospitals became more complex: patients, health-care workers and their interactions have been regarded as a serious public-health problem [4–8]. The emergence of antibiotic resistance during antibiotic therapy of an infected patient threatens the successful treatment of some bacterial

infections. The challenges are designing the suitable dosage, dosing frequency and number of antibiotics used in combination therapy to prevent the emergence of resistance. Hence, some mathematical models have been formulated in the context of the spread of the antibiotic-resistant bacteria to help design effective treatment programs over the last two decades (see [4,8–15]). Relevant to our study here are the works [4,8,10], where two antibiotics are considered to model the temporal fluctuations in the concentrations of antibiotics between regular doses or non-adherence to the prescribed treatment regimens.

In [4], Bonhoeffer et al. showed that, when more than one antibiotic is employed, different antibiotics are not as good as a combination of antibiotics. Sun et al. [8] modeled multiple antibiotic therapies, analyzed stabilities of various equilibria and showed that combining treatment is better than cycling treatment. In most existing mathematical models with the effects of drug treatment (see [4,8,10,15–20]), the effects of treatment are assumed to be constant. However, the effect of antibiotic treatment appears to change over time, probably due to pharmacokinetics variation, fluctuating adherence, the emergence of antibiotic-resistant and so on.

The primary goal of this study is to develop a mathematical description of patients infected by multi-bacteria to predict and design a dosing regimen during the course of considering combination (multiple-antibiotics) therapy. A system of ordinary differential equations is used to describe the patients with bacterial infections who may be treated with two antibiotics, while the successful treatment effects of antibiotics are characterized as saturating functions of antibiotic concentrations with maximum therapy effect E_{max} and half-maximum therapy achieved at concentration C_{50} [15]. We assume the antibiotic effects occur after the dosing time. Therefore, we have the impulsive differential equation to account for time-varying antibiotic concentrations in body fluids:

$$
\begin{aligned}
\dot{C}(t) &= -g_e C(t), \quad t \neq n\tau, \\
C(t^+) &= C(t) + C^0, \quad t = n\tau, \\
C(t_0^+) &\triangleq C^0 = \frac{D}{V_c},
\end{aligned}
\tag{1}
$$

and the successful treatment efficacy of antibiotics is given by

$$
f(t) = \frac{E_{max}C(t)}{C(t) + C_{50}},
\tag{2}
$$

where $C(t)$ denotes the plasma antibiotic concentration at time t and g_e is the elimination rate constant, and impulsive input of quantity C^0 at time t_0 (without loss of generality, we may assume $t_0 = 0$), the concentration for $t > t_0$ is described as (1), τ is a regular time interval, V_c is the "apparent volume of distribution" and the initial concentration is $C^0 = D/V_c$, where D is the drug dosage. By calculation, we derive the corresponding solution of model (1) on every interval $(n\tau, (n+1)\tau]$, $n = 1, 2, \ldots$, which is

$$
C(t) = \frac{D}{V_c} \cdot \frac{e^{-g_e(t-n\tau)}}{1 - e^{-g_e\tau}}.
\tag{3}
$$

Hence, $\lim\limits_{t\to\infty} C(t) = \frac{D}{V_c} \cdot \frac{1}{1-e^{-g_e\tau}}$, following Lou et al. [21] and Smith and Wahl [22], the antibiotic concentration is asymptotic to the following τ-periodic function:

$$
\widetilde{C}(t) = \frac{D}{V_c} \cdot \frac{e^{-g_e t(\mathrm{mod}\tau)}}{1 - e^{-g_e\tau}},
\tag{4}
$$

where $t(\mathrm{mod}\tau)$ denotes the modulus after division (t/τ).

From above analysis, by the time-varying antibiotic effects, we reduce the system to a non-autonomous system or asymptotically periodic if the dosage input occurs at a fixed interval. The introduction of the time-varying antibiotic effects in multiple bacterial infections system greatly increases the complexity of the model. Thus, the standard techniques here to address the computation formula of the basic reproduction ratio and the persistence theory of compartmental epidemic models in periodic environments are not applicable here. The calculations of basic reproduction numbers of autonomous epidemic models are derived by the next-generation infection matrix (see [24,25]). In addition, Bacaër and Guernaoui [26] and Wang and Zhao [27] have presented a general definition of the basic reproduction ratio in periodic environments.

According to the persistence theory of non-autonomous epidemic system, the disease becomes permanent when the basic reproduction ratio is more that unity (see [21,27–33]). Our work appears to be the first attempt to obtain explicit sufficient conditions for treatment success (that is the elimination of the bacteria) and for treatment failure (that is the persistence of the bacteria) by formulating impulsive antibiotic treatment system.

The rest of the paper is organized as follows. In the next section, we will formulate the mathematical model with impulsive antibiotic treatment of patients infected by bacterial populations and give some lemmas that will be essential to our proofs. The basic reproduction ratio as threshold parameters are derived in Section 3. In Section 4, the numerical simulations are carried out, which not only confirm the theoretical results, but are also complementary to those theoretical results with specific features. We finish this paper with a brief conclusion in Section 5.