Journal of Theoretical Biology 421 (2017) 112–126

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtbi

A unified inter-host and in-host model of antibiotic resistance and infection spread in a hospital ward

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ARTICLE INFO

Article history:
Received 27 October 2016
Revised 14 March 2017
Accepted 25 March 2017
Available online 30 March 2017

MSC:
92C60
92C50

Keywords:
Mathematical models
Antibiotic resistance
Nosocomial infection
Differential equations
Agent-based models

ABSTRACT

As the battle continues against hospital-acquired infections and the concurrent rise in antibiotic resistance among many of the major causative pathogens, there is a dire need to conduct controlled experiments, in order to compare proposed control strategies. However, cost, time, and ethical considerations make this evaluation strategy either impractical or impossible to implement with living patients. This paper presents a multi-scale model that offers promise as the basis for a tool to simulate these (and other) controlled experiments. This is a "unified" model in two important ways: (i) It combines inter-host and in-host dynamics into a single model, and (ii) it links two very different modeling approaches - agent-based modeling and differential equations - into a single model. The potential of this model as an instrument to combat antibiotic resistance in hospitals is demonstrated with numerical examples.

1. Introduction

Untested infection control protocols are of dubious value in clinical medicine, and yet, assessing the effectiveness of control measures remains difficult. This is particularly true of strategies to prevent or control hospital-acquired infections (HAI). HAIs, while not a new problem, have re-emerged as a major public health issue in recent years. Elimination of HAIs is an important healthcare priority, both at the national level and within individual hospitals (Office of Disease Prevention and Health Promotion, 2015). The U.S. Centers for Disease Control and Prevention (CDC) report that there were an estimated 722,000 HAIs in U.S. acute care hospitals in 2011, resulting in about 75,000 deaths (Magill et al., 2014). The problem is compounded by pathogen populations that have evolved increased tolerance for the antimicrobials normally used to control them. Antibiotic resistance (AR) makes HAIs more difficult to clear, by requiring higher (and possibly more-dangerous) doses of antibiotics. Additionally, AR can grant pathogens the ability to exist for longer periods of time in the local environment, thereby providing additional opportunities to cause infection. AR stands as a significant health challenge in its own right, responsible, according to CDC estimates, for at least two million infections and at least 23,000 deaths in the U.S. each year (Centers for Disease Control and Prevention, 2015).

A number of measures to control the appearance and rise of antibiotic resistance among the pathogens responsible for HAIs have been proposed. Many of these measures involve some form of management of antimicrobial use in the hospitals, both at the administrative level (e.g., by specifying which antimicrobials are available to a hospital's prescribing physicians) and in the management (e.g., drug and dosage selection, monitoring of progress) of individual patient infections. These control measures are predicated on the well-supported idea that the use of antimicrobial agents can potentially exert an important selective force that favors AR-mutations within a pathogen population. The connection between antibiotic use and AR pathogens has been suspected for almost as long as antibiotics have been in use. In fact, in his Nobel lecture in 1945, Alexander Fleming, a pioneer in antibiotic research, warned of exactly this: "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." (Fleming, 1999).

Ideally, one would evaluate these AR-HAI-control measures through a controlled experimental study comparing outcomes in two groups of patients randomized between the current protocol and the new one. However, cost, time, and ethical considerations make this evaluation strategy either impractical or impossible

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http://dx.doi.org/10.1016/j.jtbi.2017.03.025
0022-5193/

to implement with living patients. Realistic mathematical models, and their implementation as computer-based simulators, can provide valuable tools to conduct *in silico* versions of these controlled experiments, providing valuable insight to hospital epidemiology teams and other decision-making groups. These experiments can be simulated on a large number of virtual patients for many replications, all at minimal cost and in a short period of time, and without the ethical issues that accompany human experimentation. (As of this writing, virtual patients have presented fewer ethical issues, and have proven to be much less litigious than their flesh-and-blood counterparts.)

When considering any mathematical model of AR and HAI dynamics, there are two distinct levels of dynamics that are important to capture. The first, which we will call in-host dynamics, refers to bacterial-level processes that take place inside each individual human host, and includes factors like bacterial population dynamics, changes in resistance due to genetic mutations, pharmacokinetic and pharmacodynamic properties of antibiotics, antibiotic-bacteria interactions, bacterial interactions with the host's immune system, interactions between bacterial strains with different resistance profiles, and so forth. The second level of dynamics, which we will call inter-host dynamics, refers to interactions at the human-level, principally the transfer of bacteria between individuals.

The present work aims to provide a highly realistic model of patient, health-care worker (HCW), bacterial, and antibiotic dynamics as they relate to the rise and spread of antibiotic-resistant HAIs, offering the potential to carefully and systematically test proposed prevention and control strategies and, possibly, to generate new strategies. Our model:

- *combines in-host and inter-host dynamics into a single, unified, realistic model.* The differences in time-scale and dynamics between person-to-person interactions and bacterial growth require different approaches to modeling the two sets of dynamics, with the further challenge of linking the two in a practical and realistic way.
- *accurately represents the relationship between AR and HAI.* HAIs will occur even in the absence of AR, but AR will often make an HAI more serious, by making it more difficult, or even impossible, to clear.
- *allows for testing of many different control strategies, including those involving antibiotic-management protocols.* This is accomplished by incorporating many of the treatment parameters, including antibiotic selection, dosage size, mode and frequency of administration, treatment duration, and possible adjustments to existing protocols, as more information (e.g., culture results and resistance profiles) becomes available.
- *naturally includes a heterogeneous population of patients and HCWs in the hospital ward.* The risk of developing an AR-HAI is not uniform across patients, and depends on individual factors such as age, antibiotic-usage history, immunocompetence, colonization state, and co-morbidities. Our model permits heterogeneity in such factors across the patient and HCW population.
- *allows for multiple levels of antibiotic-susceptibility for multiple pathogen species across a wide range of antibiotic classes.* It is a commonly-held misconception that antibiotic resistance is binary, i.e., an individual pathogen is either totally susceptible to or totally unkillable by the antibiotic in question. In reality, a pathogen population will include individuals across a range of different tolerance levels. This is key to the theory that AR-strains arise through natural selection (Levy, 1998).
- *simulates the appearance of antibiotic-resistant members of pathogen populations via random genetic mutation, with their fates determined by natural selection.* It is unfortunate that popular media continues to characterize the development of antibiotic-resistance in human pathogens as an intentional retaliatory decision on the part of the bacteria, when, in fact, these microbes are simply going about their lives and trying to survive. It is now widely accepted in the biomedical community that the rise of AR strains within these pathogen populations is primarily due to changes (e.g., use of antibiotics in insufficient concentrations) in the local environment, thereby selecting for these very strains.
- *allows for multiple colonization and infection statuses within each human.* We designed our model to reflect the fact that infections and their spread as HAIs depend not only on the pathogens involved, but also the infection's physical location - a skin or upper respiratory infection will spread to another person more readily than, say, a heart valve infection.
- *incorporates the effects of the immune system response*: The immune response to bacterial infection has a great impact on the course of the infection. In fact, it has been postulated that immunocompromised patients (e.g., the elderly, and patients in oncology wards or transplant wards) may play an important role in the ability of antibiotic-resistant pathogens to survive long-term in hospitals (Moellering and Blumgart, 2002).

The balance of this paper is organized as follows: Section 2 discusses related work. The in-host and inter-host models are described in Section 3. Section 4 presents preliminary experiments and results using our model, and Section 5 provides conclusions and future directions.

2. Related work

Some efforts have been made to model antibiotic resistance at the in-host level, typically involving standard population dynamics models (D'Agata et al., 2008; Felton et al., 2013; Garber, 1987; Geli et al., 2012; Lipsitch and Levin, 1997; 1998; Ternent et al., 2015). Modeling at the inter-host level has received much more attention in the mathematical modeling literature. (See, for example, Armeanu and Bonten (2005); Bergstrom et al. (2004); Cooper et al. (2004); D'Agata et al. (2005); Doan et al. (2016); Haber et al. (2010); Sypsa et al. (2012).) By far, the most common approach is to base inter-host infection dynamics models on the well-established ecologically-based SIR-type models of infectious disease. This approach, made popular by the work of Anderson and May (1991), begins by dividing the patient population (and, when included in the model, the HCW population) into a small number of distinct and disjoint categories. The individuals within each category are assumed to be identical to each other in all relevant ways. The model then consists of a system of differential equations (or, less-frequently, a Markov process (Chamchod and Ruan, 2012b; Pelupessy et al., 2002; Schultsz et al., 2013)) designed to describe the rates at which individuals move from one category to another, thereby simulating infection-spread within the patient population. Those researchers who have used models to investigate resistance-control strategies have used infection dynamics models to do so. Most commonly, reports utilizing SIR-type models have assessed hand hygiene (Armeanu and Bonten, 2005; Cooper et al., 2004; Sebille et al., 1997), patient isolation (Cooper et al., 2004), and various forms of antibiotic restriction/management (Bergstrom et al., 2004; D'Agata et al., 2012; Sebille et al., 1997; Sypsa et al., 2012).

The appeal of deterministic SIR-type models stems largely from the potential for theoretical analysis of these models (e.g., the basic reproductive number R_0). In this regard, such infection-spread models have been widely successful. However, in the context of infection dynamics within a hospital ward, this approach is limited by the inherent assumption that the patient (and HCW) population consists of a small number of perfectly homogeneous subgroups,