Journal of Biomedical Informatics 84 (2018) 114–122

Contents lists available at ScienceDirect

Journal of Biomedical Informatics

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

A decision support system for antibiotic prescription based on local cumulative antibiograms

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ARTICLE INFO

Keywords:
Antibiotic efficacy
Cumulative antibiogram
Number needed to fail
Empiric therapy
Antimicrobial stewardship
Clinical decision support system

ABSTRACT

Background: Local cumulative antibiograms are useful tools with which to select appropriate empiric or directed therapies when treating infectious diseases at a hospital. However, data represented in traditional antibiograms are static, incomplete and not well adapted to decision-making.

Methods: We propose a decision support method for empiric antibiotic therapy based on the Number Needed to Fail (NNF) measure. NNF indicates the number of patients that would need to be treated with a specific antibiotic for one to be inadequately treated. We define two new measures, Accumulated Efficacy and Weighted Accumulated Efficacy in order to determine the efficacy of an antibiotic. We carried out two experiments: the first during which there was a suspicion of infection and the patient had empiric therapy, and the second by considering patients with confirmed infection and directed therapy. The study was performed with 15,799 cultures with 356,404 susceptibility tests carried out over a four-year period.

Results: The most efficient empiric antibiotics are Linezolid and Vancomycin for blood samples and Imipenem and Meropenem for urine samples. In both experiments, the efficacies of recommended antibiotics are all significantly greater than the efficacies of the antibiotics actually administered ($P < 0.001$). The highest efficacy is obtained when considering 2 years of antibiogram data and 80% of the cumulated prevalence of microorganisms.

Conclusion: This extensive study on real empiric therapies shows that the proposed method is a valuable alternative to traditional antibiograms as regards developing clinical decision support systems for antimicrobial stewardship.

1. Introduction

Antimicrobial resistance (AMR) is one of the most pressing problems in modern medicine. The European Center for the Prevention and Control of Diseases estimates that antimicrobial resistance leads to 25,000 deaths each year at a cost of 1.5 billion Euros in care and loss of productivity. In June 2017, the European Union, therefore, launched the European Single Health Action Plan, which specifies that the problem of resistance to antibiotics must be addressed from a global perspective, considering human health, animal health and the environment. The Antimicrobial Resistance and Health-care Associated Infections (ARHAI) program focuses on two fundamental aspects: antimicrobial resistance, the definition of the ability of microorganisms to become resistant to one or more antibiotic agents, thus becoming a multi-resistant microorganism (MMR), and healthcare associated infections (HAI) acquired in hospitals or healthcare centers. The sixty-eighth assembly of the World Health Organization, held in May 2015, adopted the Global Plan of Action on Antimicrobial Resistance [20].

The emergence of resistances is partially associated with the misuse of antimicrobial agents. The key principles of antimicrobial use include choosing the correct drug, at the correct dose for clinical conditions (site of infection, age, renal and hepatic function, interactions, etc.), for the appropriate duration [6]. An improved knowledge of pharmacokinetic and pharmacodynamic is also essential and makes a difference to the efficacy of drugs in different parts of the body, along with the potential to develop resistance. Other key issues not related to individual conditions are the global ecology, availability and cost that are related to local epidemiology.

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https://doi.org/10.1016/j.jbi.2018.07.003
Received 11 April 2018; Received in revised form 12 June 2018; Accepted 4 July 2018
Available online 05 July 2018
1532-0464/ © 2018 Published by Elsevier Inc.

From a clinical point of view, it is vital to start an appropriate therapy as early as possible in order to minimize morbidity, risks and complications, even in the absence of information regarding the microorganism that may be causing the infection, and it is for this reason that the selection of this treatment is based on heuristics and expert rules.

When a therapy is initiated without the aforementioned information, it is called empiric therapy. Empiric antimicrobials are typically broad-spectrum that act against a wide range of infectious microorganisms. When the information is available, the empiric treatment may be replaced with a narrow-spectrum treatment that is directed toward the already-known pathogen. Although broad-spectrum antimicrobials are recommended for empirical use, they have side effects such as the destruction of harmless bacterial flora.

In hospitals, there are two main sources of information that can be consulted in order to prescribe an appropriate empiric treatment, namely, Clinical Practice Guidelines (CPGs) and the cumulative local antibiogram. Although CPGs are international consensual guidelines that indicate, among other things, which antimicrobial can be administered for a specific infectious disease, they do not take into consideration the local flora or particular policies of the hospital. Several studies highlight the benefits of using local antibiograms in order to prescribe more suitable empiric treatments [7,9,14].

The *antibiogram* or *cumulative antibiogram* aggregates the *Antibiotic Susceptibility Testing* (AST) that reports the results of cultures performed on patients when there is a suspicion of bacterial infection. If the culture is positive and a bacterium is isolated, the AST reports the growth response or susceptibility of the organism identified to an individual drug or drugs. This response is interpreted and categorized into one of three terms: *sensitive* (or *susceptible*), *intermediate* and *resistant,* according to particular reference cut-off points, such as those defined by European Committee on Antimicrobial Susceptibility Testing (EUCAST) [11] and the Clinical and Laboratory Standards Institute (CLSI) [8].

Individually, AST reports can be used to optimize a particular patient's therapy because they provide information regarding the resistance of the microorganism to certain antibiotics, while in the aggregate, they provide a powerful tool with which to support the prescription of antibiotics in the absence of information.

Fig. 1 provides a partial example of a conventional antibiogram for the group of gram-positive bacteria. The antibiogram is represented as a table in which each cell indicates the percentage of sensitive susceptibilities for a microorganism (row) and an antibiotic (column). However, despite its usefulness, a tabular representation of antibiograms has some disadvantages [13]: first, too many tables are required to present all the data (from 3 to 30 tables); second, the content is static and incomplete; for instance, since data usually cover a fixed period of time (six months or one year), only the most representative microorganisms and antibiotics are represented; and finally, this tabular representation is not well adapted to decision-making. Nevertheless, thanks to the increasing adoption of computer-based information systems in hospitals, such as electronic health records or databases, it is not difficult to integrate data from laboratory, pharmacy and hospital information systems in order to build more comprehensive, efficient and dynamic real-time antibiograms [19]. Moreover, the digitalized antibiogram has the potential to be managed and displayed more quickly and easily [1,4,17].

In this paper, we describe the development and evaluation of a method with which to recommend empiric and directed therapy based on the *Number Needed to Fail* which is calculated from the cumulative antibiogram of the hospital. The remainder of this paper is structured as follows. The Methods section provides the definitions and dataset description used. We then describe the experiments carried out and their results, after which we discuss the validity and applicability of those results. Finally, we provide the conclusion of this work.

2. Materials and methods

2.1. Concepts and definitions

The CLSI approved the M39-A document [8], entitled "Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data", which provides guidance to clinical laboratories as regards reporting a cumulative antibiogram. This document recommends that results be presented as the percentages of isolates that are sensitive. Clinicians are accustomed to working with the sensitivity percentage because it focuses on the likelihood of a successful therapeutic response. Isolates that have intermediate susceptibility should not be included in the calculation of the sensitivity percentage because physicians avoid prescribing antibiotics if a test result indicates intermediate susceptibility.

For the sake of clarity, we formally introduce the following definitions.

Definition 1 (*Sensitivity and resistance*). Let M be the set of m microorganisms and A a set of n antibiotics. The sensitivity and the resistance of the i-th microorganism $M_i \in M$ for the j-the antibiotic $A_j \in A$ is defined as:

$$Sensitivity(M_i, A_j) = \frac{S_{i,j}}{S_{i,j} + R_{i,j}} \cdot 100,$$

$$Resistance(M_i, A_j) = \frac{R_{i,j}}{S_{i,j} + R_{i,j}} \cdot 100$$

where $S_{i,j}$ is the number of isolates in M_i that are sensitive to A_j, and $R_{i,j}$ is the number of isolates in M_i whose susceptibility is resistant or intermediate to A_j, in which $1 \leqslant i \leqslant m$, $1 \leqslant j \leqslant n$.

Note that $S_{i,j} + R_{i,j}$ is the total number of isolates of microorganism M_i with AST information concerning an antibiotic.

In epidemiology, in order to effectively communicate the result of a procedure or a treatment, a measure that is expressed in a number of patients is normally used rather than a percentage [10]. The advantage of this measure is that it is easier to understand and quantify. We define efficacy in terms of *Number Needed to Fail* (NNF), as shown in the following definition.

Definition 2 (*Efficacy, NNF*). The efficacy or NNF of a microorganism M_i and an antibiotic A_j is defined as

$$\mathrm{NNF}(M_i, A_j) = \begin{cases} \left\lceil \frac{100}{Resistance(M_i, A_j)} \right\rceil, & \text{if } Resistance(M_i, A_j) \geqslant 1 \\ 100, & \text{otherwise.} \end{cases}$$

NNF is, therefore, an integer number with ranges from 1 to 100. NNF expresses the number of patients infected by a specific microorganism that would need to be treated with a specific antibiotic before finding a resistance to that antibiotic. For example, if the resistance of *Escherichia Coli* to Fosfomycin is 3.4%, then NNF would be 30 (⌈100/3.4⌉). This means that 30 patients infected with *Escherichia Coli* and treated with Fosfomycin will be susceptible before finding a resistance. High values of NNF, therefore, indicate more effective antibiotics.

We define the *accumulated efficacy* (ANNF) and *weighted accumulated efficacy* (WANNF) of a particular antibiotic with respect to a set of microorganisms as the arithmetic mean and the weighted arithmetic mean of their efficacy. To this end, we firstly introduce the concept of the *prevalence* of a microorganism.

Definition 3 (*Prevalence*). Let M be the set of m microorganisms isolated in a period of time, and let c_i be the number of isolates of microorganism $M_i \in M$. The prevalence of a microorganism M_i is defined as:

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