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Interpretative reading of the antibiogram – a semi-naïve Bayesian approach

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ABSTRACT

Background: An antibiogram (ABG) gives the results of *in vitro* susceptibility tests performed on a pathogen isolated from a culture of a sample taken from blood or other tissues. The institutional cross-ABG consists of the conditional probability of susceptibility for pairs of antimicrobials. This paper explores how interpretative reading of the isolate ABG can be used to replace and improve the prior probabilities stored in the institutional ABG. Probabilities were calculated by both a naïve and semi-naïve Bayesian approaches, both using the ABG for the given isolate and institutional ABGs and cross-ABGs.
Methods and Material: We assessed an isolate database from an Israeli university hospital with ABGs from 3347 clinically significant blood isolates, where on average 19 antimicrobials were tested for susceptibility, out of 31 antimicrobials in regular use for patient treatment. For each of 14 pathogens or groups of pathogens in the database the average (prior) probability of susceptibility (also called the institutional ABG) and the institutional cross-ABG were calculated. For each isolate, the normalized Brier distance was used as a measure of the distance between susceptibility test results from the isolate ABG and respectively prior probabilities and posteriori probabilities of susceptibility. We used a 5-fold cross-validation to evaluate the performance of different approaches to predict posterior susceptibilities.
Results: The normalized Brier distance between the prior probabilities and the susceptibility test results for all isolates in the database was reduced from 37.7% to 28.2% by the naïve Bayes method. The smallest normalized Brier distance of 25.3% was obtained with the semi-naïve min2max2 method, which uses the two smallest significant odds ratios and the two largest significant odds ratios expressing respectively cross-resistance and cross-susceptibility, calculated from the cross-ABG.
Conclusion: A practical method for predicting probability for antimicrobial susceptibility could be developed based on a semi-naïve Bayesian approach using statistical data on cross-susceptibilities and cross-resistances. The reduction in Brier distance from 37.7% to 25.3%, indicates a significant advantage to the proposed min2max2 method ($p < 10^{99}$).

1. Introduction

When a patient presents at a hospital with a bacterial infection, antimicrobials will be administered to the patient. Before the antimicrobials are administered, samples will be taken from the patient, usually both a blood sample and a "local" sample from the site of infection, for example a urine sample if the patient is suspected of a urinary tract infection. Within a day or two bacteria are successfully isolated from these samples in approximately 30% of the patients [1]. Once isolated, the bacteria are tested for their *in vitro* susceptibility to a range of antimicrobials. The test results are called an antibiogram (ABG), which specifies the susceptibility of the pathogen to each tested antimicrobial. These ABGs often make it relevant to change the initial "empirical" treatment given to the patient into a "definitive" treatment, where it is known from the susceptibility results that the isolated bacteria are susceptible to the antimicrobial(s) given in the definitive treatment.

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At any given time a large number of antimicrobials are in use in a hospital. Out of these only a limited set of antimicrobials is tested due to practical and economic constraints. Therefore it occasionally happens that none of the tested antimicrobials are clinically acceptable. This may for example be due to allergies, to significant toxicity, to limited gastrointestinal absorption of the drug in severely septic patients, to preferences for bactericidal rather than bacteriostatic antimicrobials or due to preferences imposed by antimicrobial stewardship programs, where for example quinolones are considered a less desirable choice relative to cephalosporins (Danish Health and Medicines Authority, 2013) [2]. In such cases it is desirable to have additional information about the susceptibility of the isolated pathogens to antimicrobials for which no susceptibility results are available. Some information can be derived from the expert rules of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [3].

EUCAST expert rules come in three forms (edited in the interest of simplicity):

1. Intrinsic resistance: E.g. Rule 2.6: *Pseudomonas aeruginosa* is resistant to ampicillin.
2. Exceptional resistance phenotypes: E.g. Rule 6.1: *Staphylococcus aureus* is (almost always) susceptible to vancomycin, linezolid, quinupristin/dalfopristin, daptomycin and tigecycline.
3. Interpretive rules: E.g. Rule 8.6: If *Enterococcus spp.* is resistant to ampicillin, report as resistant to ureidopenicillins and carbapenems.

The first two forms extend the ABG with knowledge of respectively resistance and susceptibility for antimicrobials, which have not been tested. The third form extends the susceptibility results from the tested antimicrobials to some of those not tested.

These rules represent an improvement in the reporting of susceptibility results, but cover only a very limited number of pathogen/antimicrobial combinations.

It would therefore be desirable to have a computationally feasible method that retains the advantages of the EUCAST expert rules, but which may also provide some help when none of these apply. This will be achieved by compiling institutional ABGs from the isolate databases maintained by most clinical microbiology laboratories. For example, in the institutional ABG compiled from the isolate database used in this study, we can read that the prior probability of Escherichia coli (*E. coli*) isolates being susceptible to cefuroxime is 83%. This information indicates that prescription of cefuroxime against an *E. coli* infection may well be useful, even if the *E. coli* isolate's susceptibility to cefuroxime has not been tested. Institutional cross-ABGs, containing statistics on the conditional probabilities of susceptibility for pairs of antimicrobials can likewise be compiled. For example, in the cases where *E. coli* was susceptible to ofloxacin, we can read from the institutional cross-ABG that the conditional probability of susceptibility to cefuroxime given susceptibility to ofloxacin is 96%. This can be used to prescribe cefuroxime with good certainty (96%) that it will cover the *E. coli* infection. This particular case, where the quinolone, ofloxacin, may be replaced by the cephalosporin, cefuroxime, would be an example of antibiotic stewardship, in line with for example the Danish guidelines on prescribing of antibiotics [2], where the use of quinolones is more restricted than the use of cephalosporins. We will refer to the conditional probabilities as institutional cross-susceptibilities, or institutional cross-resistances, if conditional on resistance. Jointly, the institutional cross-susceptibilities and the cross-resistances will be referred to as the institutional cross-ABGs.

The purpose of this paper is to develop a method of interpretative reading of susceptibility test results where posterior probabilities of susceptibilities of an isolate to untested antimicrobials are calculated from the institutional ABG (the priors) and the institutional cross-ABG, given the tested isolate's ABG.

2. Methods and Material

2.1. The isolate database

An isolate database of bacterial pathogens isolated from blood cultures taken from patients suspected of bacterial infections will be used to illustrate the methods for estimation of posterior probabilities of susceptibility. The database was compiled between 2002 and 2004 at Rabin Medical Center in Israel and includes 3347 clinically significant pathogens.

The isolate database contains the pathogen identity and an ABG for each isolate. The susceptibility results are reported in the so-called S-I-R system. If S (sensitive) is reported as the result of the susceptibility test, then the antimicrobial can eradicate the pathogen *in vitro* and with some exceptions this will also lead to clinical success, i.e. *in vivo* eradication of the pathogen. R (resistant) is expected to result in clinical failure and I (intermediate) may lead to either. For the purposes of this paper intermediate test results (I) will be considered as resistant (R).

2.2. Compilation of institutional ABGs and institutional cross-ABGs

For each of the 14 pathogen groups in the isolate database an institutional ABG was compiled, containing the (prior) probability of an isolate from a given group being susceptible to a given antimicrobial. From the isolate database the cross-susceptibility and cross-resistance tables can also be compiled, as previously described by Zalounina et al. (2007) [4]. These tables contain conditional probabilities of susceptibility for pairs of antimicrobials and they are called cross-susceptibilities when conditional on susceptibility and cross-resistances, when conditional on resistance. Table IV gives an example of the compilation of cross-susceptibilities and cross-resistances. The cross-susceptibilities and cross-resistances are joined into the institutional cross-ABG tables where they are expressed as odds ratios for increased or decreased susceptibility (Appendix Eq. (8)). Fisher's exact test is used to determine the significance of the odds ratios. When most isolates are tested with the same antimicrobials the observations are dependent, with missing values. Therefore Fisher's exact test may underestimate the significance of some odds ratios.

2.3. Calculation and validation of posterior probabilities of susceptibility

The posterior probabilities will be calculated by several versions of naïve and semi-naïve Bayesian methods. In the naïve Bayes method all significant odds ratios in the cross-ABG will be used. In the semi-naïve Bayesian methods only some of the significant odds ratios will be used.

Each method for calculation of posterior probabilities is validated by 5-fold cross-validation, where the isolate database is divided in a learning set and a validation set. The institutional ABGs and institutional cross-ABGs compiled from the learning set are used to calculate posterior probabilities in the validation set. The quality of the calculated probabilities will be assessed by deleting one susceptibility test result at a time for a given isolate in the validation set and then using the method to calculate the posterior probability of susceptibility given the remaining susceptibility test results for that particular isolate. This will be repeated for each of the test results for the given isolate and subsequently for all isolates in the 5-fold validation set. The accuracy of the posterior probabilities will be assessed by calculating the distance (Appendix Eq. (11)) between each test result in the ABG and its calculated posterior probability. The normalized Brier distances are then calculated by adding all distances and normalizing (Appendix Eq. (12)).