Clinical Infectious Diseases

MAJOR ARTICLE

Predicting Antibiotic Resistance in Hospitalized Patients by Applying Machine Learning to Electronic Medical Records

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Background. Computerized decision support systems are becoming increasingly prevalent with advances in data collection and machine learning (ML) algorithms. However, they are scarcely used for empiric antibiotic therapy. Here, we predict the antibiotic resistance profiles of bacterial infections of hospitalized patients using ML algorithms applied to patients' electronic medical records (EMRs).

Methods. The data included antibiotic resistance results of bacterial cultures from hospitalized patients, alongside their EMRs. Five antibiotics were examined: ceftazidime (n = 2942), gentamicin (n = 4360), imipenem (n = 2235), ofloxacin (n = 3117), and sulfamethoxazole-trimethoprim (n = 3544). We applied lasso logistic regression, neural networks, gradient boosted trees, and an ensemble that combined all 3 algorithms, to predict antibiotic resistance. Variable influence was gauged by permutation tests and Shapely Additive Explanations analysis.

Results. The ensemble outperformed the separate models and produced accurate predictions on test set data. When no knowledge regarding the infecting bacterial species was assumed, the ensemble yielded area under the receiver-operating characteristic (auROC) scores of 0.73–0.79 for different antibiotics. Including information regarding the bacterial species improved the auROCs to 0.8–0.88. Variables' effects on predictions were assessed and found to be consistent with previously identified risk factors for antibiotic resistance.

Conclusions. We demonstrate the potential of ML to predict antibiotic resistance of bacterial infections of hospitalized patients. Moreover, we show that rapidly gained information regarding the infecting bacterial species can improve predictions substantially. Clinicians should consider the implementation of such systems to aid correct empiric therapy and to potentially reduce antibiotic misuse.

Keywords. antibiotic resistance; machine learning; database research; decision support systems; prediction.

Antibiotic resistance is a major threat to public health. Substantial increases in antibiotic resistance rates have raised concerns and bleak estimates as to the future of effective antibiotic treatment [1]. The emergence of antibiotic resistance is mainly shaped by the evolutionary forces of genetic variation (ie, mutations and horizontal gene transfer) and selection exerted by antibiotic usage. Correspondingly, antibiotic consumption has been repeatedly correlated with increases in antibiotic resistance rates [2]. However, decreases in antibiotic consumption can revert bacterial populations to antibiotic susceptibility, likely due to the fitness cost that antibiotic resistance incurs [3]. Hence, a straightforward intervention to reduce the burden of antibiotic resistance is to decrease antibiotic consumption, for example, by reducing inappropriate antibiotic use during empiric therapy [4].

Empiric antibiotic therapy is the commencement of antibiotic therapy before a patient's precise etiology, source of infection, or antibiotic resistance profile of the infecting pathogen are confirmed [5]. Empiric therapy is both crucial, as immediate action might be necessary, and, by definition, based on educated guesses, as it is mostly derived from partial data available to doctors. Two main types of errors occur during empiric therapy: the prescription of inefficient antibiotics (ie, the antibiotics prescribed do not clear the bacterial pathogen due to its resistance to them) and the prescription of antibiotics with coverage that is too broad (ie, antibiotics with lower coverage would suffice to treat the infection).

The first type of error has more immediate and obvious consequences. Treatment with inefficient antibiotics will allow resistant bacteria to keep infecting patients, putting them at risk [6–8], and to keep spreading, causing even greater harm in the future [9]. The second type of error is perhaps not as

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immediately pronounced but could be detrimental to public health in the long run. High-frequency usage of broad-spectrum antibiotics is likely to increase the frequency of resistance to such antibiotics in the population [10–13], rendering these antibiotics less efficient. In turn, this can increase the rate of incorrect empiric therapy of the first kind [14, 15] and lead to increased broad-spectrum antibiotic usage, forming a positive feedback loop of frequent broad-spectrum antibiotic prescription and increased resistance [16, 17]. Moreover, patients treated with broad-spectrum antibiotics can have a substantial part of their microbiome eliminated, enabling subsequent colonization by dangerous and persistent pathogens such as *Clostridioides difficile* [18, 19].

A major possible improvement of empiric therapy can stem from use of large medical datasets in conjunction with machine learning (ML) algorithms. This approach has been gaining traction lately and is recognized as likely being a part of future treatment in many medical fields [20]. Various studies have identified risk factors for antibiotic-resistant infections based on patient comorbidities, demographics, previous treatments, and other patient characteristics [21]. However, identification of risk factors is not necessarily equivalent to highly accurate prediction. Indeed, substantially fewer works have produced models that try to predict antibiotic resistance of infecting bacteria based on patient data. Despite the high quality of many of these studies, they often lacked large datasets [22–24], were limited to specific types of infection [24–27], pertained to only a few bacterial species [23], or pertained to only outpatients [25].

Here, we used electronic medical records (EMRs) of patients hospitalized in Rabin Medical Center, Israel, to predict the antibiotic resistance of bacterial infections. The dataset contained more than 16 000 antibiotic-resistance tests of bacterial cultures of hospitalized patients with various types of infections, bacterial species, and examined antibiotics. We applied 3 ML models and an ensemble that combined their results to predict antibiotic resistance of the following 5 antibiotics commonly tested for resistance: ceftazidime, gentamicin, imipenem, ofloxacin, and sulfamethoxazole-trimethoprim (sul-trim). We show that accurate antibiotic-resistance prediction is possible by using EMRs and that a substantial increase in prediction accuracy occurs if information regarding the infecting bacterial species is available. Finally, we compare the different variables that have the greatest influence on antibiotic-resistance prediction and explore their effects on resistance probability using 2 forms of variable influence analysis of the ML models.

METHODS

Model Development and Evaluation

The earliest 85% of samples of each dataset were used to train the models while the remaining 15% were used to test them. We developed an ensemble composed of 3 submodels: L1 regularized logistic regression, gradient-boosted decision trees, and a neural network. Each submodel was trained separately and provided a number in the range of 0 to 1 as its prediction. The ensemble's prediction was based on the average predictions of the submodels. After performing hyperparameter tuning and variable selection on the training set (using cross-validation; see details in the Supplementary Materials), the chosen models were applied to the test set. The ensemble's predictions were compared to the actual resistance class of each data point to derive the area under the receiver-operating-characteristic curve (auROC) score.

To compute the balanced accuracy score, we first determined a prediction threshold $\rho \in (0, 1)$ under which each prediction was assigned to 1 (resistant) if above ρ and to 0 (susceptible) if below ρ. We applied the selected models to the training set and searched for ρ values that maximized the balanced accuracy scores on the training set. We then applied the models to the test set and dichotomized each prediction to 0 or 1 based on the obtained ρ values. Finally, we compared the ensemble's binary predictions to the actual class of each data point and derived the balanced accuracy score.

Variable Importance and Shapley Additive Explanations Influence Analysis

We performed permutation tests in order to measure variable importance. Each variable's values were randomly permuted in the test set, while other variables were kept as they were. After a permutation was performed, the auROC of the ensemble's prediction on the test set was recalculated. The difference of the resulting auROC from that obtained on the original test set was recorded. This was repeated 100 times (for each variable), and the average result was deemed as each variable's importance score (see Supplementary Materials).

To estimate variable influence, we performed Shapley Additive Explanations (SHAP) analysis. We applied the SHAP analysis to the training sets, conducting it separately for each submodel and then averaging the results to obtain the ensemble's scores (see Supplementary Materials).

Software Used

All analyses were performed using Python 3.6.

RESULTS

We retrieved EMRs of patients who had positive bacterial culture results from Rabin Medical Center, Israel, for the period May 2013 through December 2015. The dataset included the bacterial species isolated from the patients and their resistance profiles to the antibiotics tested, as well as the patients' demographics, comorbidities, hospitalization records, and previous antibiotic usage within the hospital (see Supplementary Materials). We focused on predicting resistance to the 5 antibiotics most commonly tested for resistance in our dataset: ceftazidime, gentamicin, imipenem, ofloxacin, and sul-trim.

Table 1. Summary Statistics of the Dataset

	Ceftazidime	Gentamicin	Imipenem	Ofloxacin	Sulfamethoxazole-Trimethoprim
Samples, n	2942	4360	2235	3117	3544
Resistance, %	42	32	16	47	50
Age, mean (SD), y	72 (16)	72 (16)	72 (16)	72 (17)	72 (16)
Female, %	42	41	40	43	42
Most common bacterial species	*Escherichia coli* (29%)	*Escherichia coli* (20%)	*Escherichia coli* (22%)	*Escherichia coli* (22%)	*Escherichia coli* (24%)
Second-most common bacterial species	*Klebsiella pneumoniae* (18%)	*Klebsiella pneumoniae* (12%)	*Pseudomonas aeruginosa* (18%)	*Staphylococcus* coagulase negative group (16%)	*Klebsiella pneumoniae* (15%)
Third-most common bacteria species	*Pseudomonas aeruginosa* (14%)	*Staphylococcus* coagulase negative group (12%)	*Klebsiella pneumoniae* (16%)	*Klebsiella pneumoniae* (13%)	*Staphylococcus* coagulase negative group (14%)
Latest hospitalization duration, mean (SD), days	6.1 (10.4)	6.1 (10.2)	7.1 (11.4)	6.1 (10.4)	5.9 (10.1)

Abbreviation: SD, standard deviation.

Table 1 presents essential summary statistics of the data aggregated across unique samples.

We found varying frequencies of antibiotic resistance between antibiotics and different bacterial species. The frequencies of antibiotic resistance also fluctuated through time, yet average resistance frequencies remained similar in the training and test sets (Figure 1).

We used a supervised ML approach to classify each isolated bacterial culture as either susceptible or resistant to each antibiotic (see the Methods section and Supplementary Materials). The final model chosen for predicting antibiotic resistance was an ensemble composed of 3 submodels: L1 regularized logistic regression, gradient-boosted decision trees, and a neural network. The models were trained on early samples (training set) and evaluated on later, distinct samples (test set; Figure 1B). We examined the success of the ensemble in predicting antibiotic resistance in 2 data conformations: one where the ensemble was trained and evaluated separately on each antibiotic and another where the ensemble was trained and evaluated on data containing all 5 antibiotics combined. In addition, training and testing of the ensemble were performed once on a dataset that included the identity of the isolated bacterial species and once on the same data, barring the identity of the isolated bacterial species.

The ensemble achieved high classification success both in terms of auROC and balanced accuracy (ie, the unweighted average of the sensitivity and specificity rates; Figures 2 and 3; additional metrics in Supplementary Materials, Supplementary Figures 1–4). In addition, the ensemble was found to slightly outperform the submodels in most scenarios, especially when the identity of the isolated bacterial species was included in the data (Figure 3).

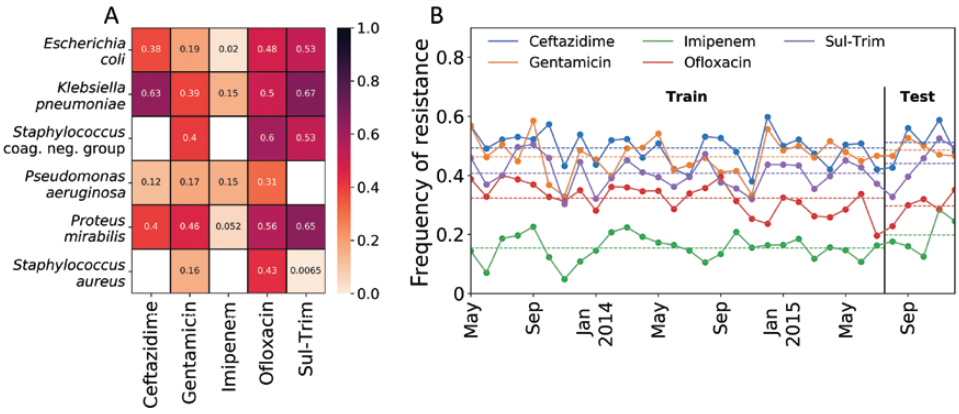

Figure 1. Frequency of antibiotic resistance. *A,* A heat map showing the frequencies of antibiotic resistance for each antibiotic and bacterial species combination. Empty cells represent combinations for which there were fewer than 100 data points. *B,* A time series plot of the frequency of antibiotic resistance observed in each month, for each antibiotic, across all bacterial species. Horizontal dashed lines represent the average resistance frequencies of each antibiotic, separately for the training set and the test set. Abbreviations: coag. neg., coagulase negative; Jan, January; Sep, September; Sul-Trim, sulfamethoxazole-trimethoprim.

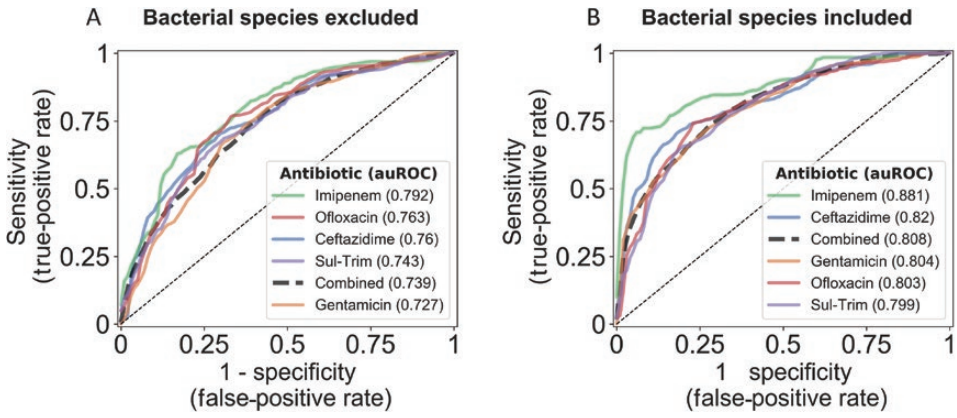

Figure 2. ROC curves of the ensemble are presented separately for each antibiotic and for all antibiotics combined for the datasets excluding (*A*) and including (*B*) the bacterial species' identities. The legends show the auROC for each antibiotic, ordered from highest to lowest. The curves represent the ensemble performance on the test set, averaged over 10 training–testing sessions (as the training itself contains stochastic elements). Abbreviations: auROC, area under the receiver-operating-characteristic; Sul-Trim, sulfamethoxazole-trimethoprim.

In contrast to classic statistical methods such as regression analysis, the influence of variables on model output is often difficult to gauge in ML models such as boosted trees and neural networks. Thus, we performed 2 types of analysis to determine the influence of variables on our ensemble model predictions. First, we performed a permutation-based variable importance analysis (see Methods section). Briefly, each variable was randomly permuted to break its association with the outcome. Then, predictions were made using the new dataset with the permuted variable, and the change in the ensemble's auROC

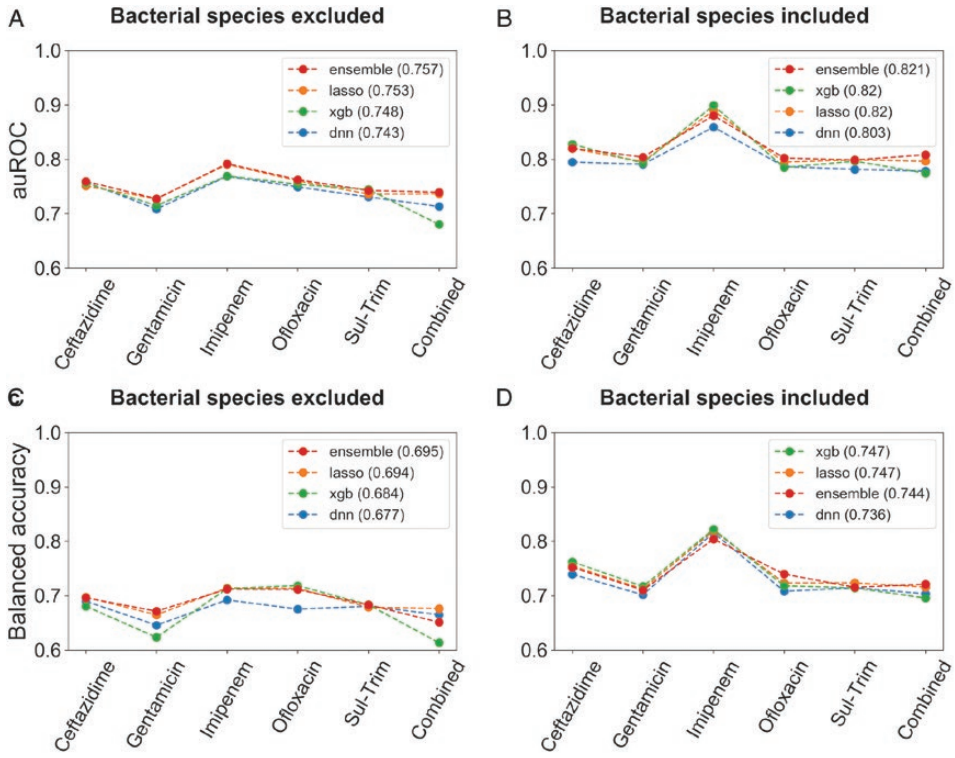

Figure 3. The auROC and balanced accuracy scores of the ensemble and its submodels. The auROC (*A*, *B*) and the balanced accuracy (*C*, *D*) of the ensemble and its 3 submodels, based on data that exclude the identity of the bacterial species (*A*, *C*) and on data that include the identity of the bacterial species (*B*, *D*). The legends show the score of each model, averaged over the 5 antibiotics and ordered from highest to lowest. The results represent the ensemble performance on the test set, averaged over 10 training–testing sessions (as the training itself contains stochastic elements). Abbreviations: auROC, area under the receiver-operating-characteristic; dnn, dense neural networks; Sul-Trim, sulfamethoxazole-trimethoprim; xgb, extreme gradient boosting.

was recorded. Variables for which permutations resulted in substantial decreases in auROC were deemed important. This analysis revealed that the two variables with the highest average effect (across all five antibiotics) were (1) the proportion of past antibiotic-resistance infections, that is, previous same-bacterial species resistance to the same antibiotic (previous resistance–specific) and to any antibiotic (previous resistance–general) when including information of the bacterial species and (2) the previous any-bacterial species resistance to the same antibiotic (previous any-bacteria resistance–specific) and to any antibiotic (previous any-bacteria resistancegeneral) when excluding information about the infecting bacterial species (Supplementary Materials, Supplementary Tables 1 and 2).

Furthermore, we performed a SHAP analysis [28] (see Methods section). The SHAP analysis allowed us to estimate the marginal contribution of each variable to the final prediction of the ensemble. We performed the SHAP analysis separately for each of the 5 antibiotics tested, both with and without information regarding the infecting bacterial species. We present the variables that had a substantial contribution to prediction of antibiotic resistance (as defined in the Methods section) for all 5 antibiotics in Figure 4. When information regarding the bacterial species was excluded, the 2 top contributing variables were consistent with the permutation-based importance analysis: previous any-bacteria resistance–specific and general. These were followed by variables that indicated whether the infection was nosocomial or community-acquired and whether the patient was previously treated in the hospital with antibiotics of the same family (antibiotics were categorized into beta-lactams, fluoroquinolones, aminoglycosides, and sulfonamides). Other important variables were the patients' functioning and independence levels and previous hospitalization duration. Similarly, when data regarding the bacterial species were included, the average previous resistance of the same bacteria to the same/any antibiotic (previous resistance–specific/general, respectively) remained among the top most affecting variables, alongside indicator variables of the infecting bacterial species.

The SHAP analysis also allowed us to determine whether the different variables in our model act to decrease or increase the probability of antibiotic resistance (Figure 4B, 4D). Reassuringly, the probability of resistance in our model increased in accordance with known risk factors of antibiotic resistance: previous antibiotic resistant infections, previous hospitalizations, nosocomial infections, previous antibiotic usage, location of sample derivation, and contraindications of patient independence (eg, nursing home residence and dependence in feeding) [23, 25, 27, 29, 30]. When information on the infecting bacterial species was included, additional patterns emerged. For example, while the presence of *Acinetobacter baumannii* in cultures increases the probability of resistance, *Staphylococcus aureus* decreases it. The patients' sex was found to have only a minor effect on the resistance probability, with increased probability of resistance for males. The sample date, which was coded as a numeric variable from the date of the earliest culture in the dataset, was also found to have some effect, probably due to the fluctuating resistance frequencies through time captured by our model.

DISCUSSION

ML is widely applied in various fields of medicine and is likely to become an invaluable part of medical decision-making and treatment [20]. However, ML is rarely used in aiding the decision of empiric antibiotic therapy. Only a handful of studies have previously used the prediction abilities of ML models for the rapid detection of antibiotic resistance from patient EMRs.

Our work demonstrates the ability to predict antibiotic resistance from patient EMRs, even with relatively incomplete patient data, with accuracy and extends previous research in the field in several ways. Rather than relying on a single algorithm, we used an ensemble that combines several algorithms that differ substantially in their underlying prediction methods (logistic regression, boosted decision trees, and neural networks) to produce robust results, avoiding pitfalls of each single algorithm. Importantly, we performed a controlled procedure of hyper parameter selection on a training subset of the data and then continued to test our predictions on a disjoint, previously unexplored subset of the data. Furthermore, we predicted antibiotic resistance on a large and heterogeneous dataset that comprised more than 16 000 antibiotic-resistance tests of bacterial cultures of hospitalized patients, tested for various antibiotics, and containing multiple bacterial species and infection sites.

Despite the heterogeneity of our data, we were able to train models that achieved highly competitive results. If information regarding the infected bacterial species was excluded, we obtained auROC scores in the range of 0.73–0.79, while inclusion of the bacterial species yielded even higher auROC scores in the range of 0.8 to 0.88. Previous studies that included information regarding the infecting bacterial species obtained auROC scores in the range of 0.6 to 0.83 for antibiotics comparable to those examined in our dataset [27, 31]. Other studies, restricted to 1 bacterial species or to only 1 type of infection, had auROC scores in the range of 0.7 to 0.83 [23–25]. Even when previous auROC results were comparable to those achieved in our study, previous studies did not have such a heterogenic dataset that included patients with different infections, bacterial species, and antibiotics. This added a substantial challenge, which was successfully tackled by our models and is likely to decrease the predictive power of methods used in other studies.

The methods we applied should be generalizable to other healthcare facilities. The dataset we used included patient variables commonly recorded in EMRs, yet other researchers may have additional information available (eg, blood panel results). Such information can conceivably improve predictions even further and should be examined as additional predictors to the

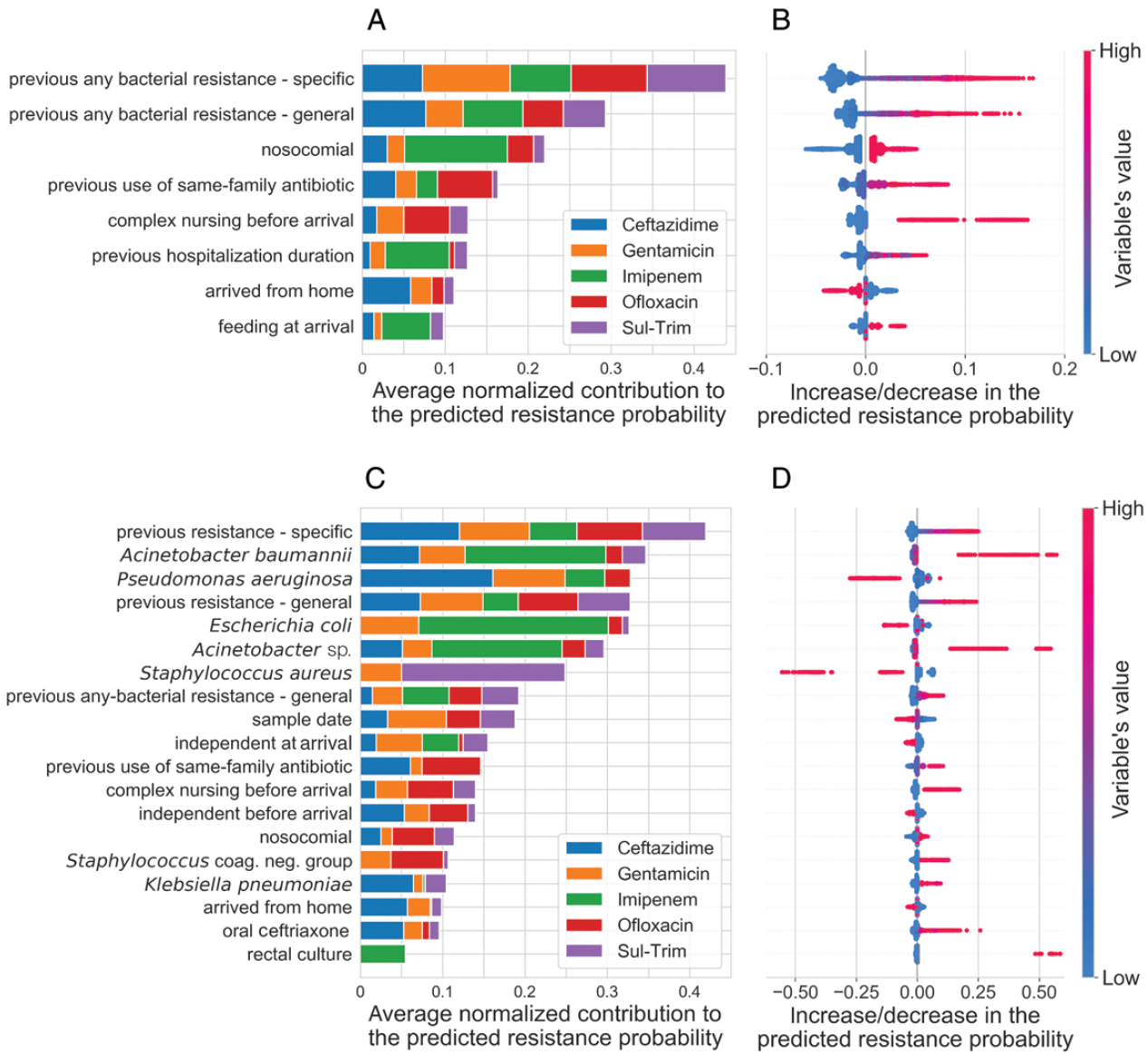

Figure 4. Variable importance analysis using Shapley Additive Explanations (SHAP). *A* and *C*, The absolute marginal contribution to predicted probabilities, normalized by the predicted population resistance prevalence (*x*-axis), is plotted for each antibiotic (color-coded), both for data that exclude information on the bacterial species (*A*) and data that include information on the bacterial species (*C*). The presented variables are those with an effect of at least 0.05 in any of the 5 antibiotics. *B* and *D*, The marginal changes in predicted resistance probability derived from the same variables shown in panels *A* and *C*, respectively, are plotted for all antibiotics combined, both for data that exclude information on the infected bacterial species (*B*) and data that include information on the infected bacterial species (*D*). Each row in panels *B* and *D* shows the distribution of the data in 2 dimensions, and each dot represents 1 sample. The color represents the value of the variable in a schematic scale from low value to high value (binary variables are represented by the 2 colors on the edges of the color bar); the position on the *x*-axis represents the marginal change in probability of antibiotic resistance due to the variables' values. The results represent the ensemble performance on the training set, averaged over 25 training sessions (as the training and SHAP analysis contain stochastic elements). Abbreviations: coag. neg., coagulase negative; Sul-Trim, sulfamethoxazole-trimethoprim.

model, where accessible. Moreover, larger sample sizes, which may be available in other healthcare facilities due to larger capacity or better data accessibility and digitization options, are also likely to improve model predictions. As patient variables included in EMRs may vary between different healthcare facilities and due to the dynamic and local nature of bacterial infections, any such model should be retrained in new settings [32]. It should also be periodically retrained, as resistance patterns can change over time, reflecting larger-scale antibiotic consumption levels [2].

Our dataset did not enable a direct comparison of our results to doctors' predictions of resistance. Moreover, it is not straightforward to perform such a comparison as the observable result of antibiotic prescription is affected by various factors (eg, hospital policy, patient allergies) and hence does not directly reflect the doctors' predictions. Interestingly, in a recent

study, it was found that an ML approach based on prediction of resistance superseded doctors in reducing superfluous antibiotic prescription [33]. Although we lacked data to perform such a comparison, our models achieved higher performance scores than the aforementioned model and therefore have the potential to further improve reduction of superfluous usage if similarly applied. Moreover, even if our models underperform doctors' average predictive ability, they can still aid in situations where doctors have low confidence in their ability to predict the resistance, as is commonly used in other medical fields [34].

Despite the complex nature of the models used, further complicated by their combination into an ensemble model, we were able to provide interpretation of the influence of different variables on the ensemble's predictions. Reassuringly, most of the variables that were found to be influential in our analysis have been previously identified as increasing the risk of infections by antimicrobial-resistant pathogens. In addition to further validating our model against prior knowledge, understating which variables are influential can help indicate important drivers of antibiotic resistance. For example, the variables that were consistently highly ranked as important in our models were those that pertained to previously resistant bacterial cultures. The importance of those variables might imply the persistence of resistant bacteria in patients and may warrant further investigations into treatments that restore the normal microbiota after antibiotic treatments, especially in patients at risk for rehospitalization [35]. However, we are extremely wary in any causal interpretation of our results. The models we deployed are suited for optimizing prediction rather than estimating causal effects. Further research on causality in antibiotic resistance dynamics is of paramount importance. Although our group has made initial steps in pursuing this [36], application of ML algorithms that estimate such causal effects (eg, using [37]) is still rather rare.

An especially important variable in our models was the identity of the bacterial species causing the infection. It is plausible that biological differences and different exposures to antibiotics produce the observed differences between resistance frequencies of different bacterial species (Figure 1). Hence, this information is predictive in our models. Although not routinely performed in most hospitals, rapid identification of the infecting bacterial species is possible, for example, through polymerase chain reaction–based methods [38]. If our model is to be implemented in real-time clinical settings, adding such rapid bacterial species identification tools might be cost beneficial, given the improvement in our prediction results and the major cost incurred by antibiotic-resistant infections [39].

Additional potentially important predictors for resistance are various community-derived risk factors, such as antibiotic use outside the hospital [25, 40, 41], residency location [12], microbiome composition, diet, and exercise [42–45]. Unfortunately, these were not available to us, but future work should consider their inclusion when available.

To conclude, our results present an ensemble-based ML approach to predict antibiotic resistance of bacterial infections of hospitalized patients using the patients' EMRs. Our method autonomously identified known risk factors of antibiotic resistance and provided robust predictions based on the complex interactions between them and other patient information. Importantly, our approach can serve as a template for other healthcare facilities. It should encourage efficient collection and accessibility to EMRs and can be a stepping-stone for achieving highly informed, personalized empiric antibiotic therapy. Such therapy should result in less antibiotic misuse and hopefully aid in the fight against antibiotic resistance.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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