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Evaluation by Data Mining Techniques of Fluconazole Breakpoints Established by the Clinical and Laboratory Standards Institute (CLSI) and Comparison with Those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)▽

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The EUCAST and the CLSI have established different breakpoints for fluconazole and *Candida* spp. However, the reference methodologies employed to obtain the MICs provide similar results. The aim of this work was to apply supervised classification algorithms to analyze the clinical data used by the CLSI to establish fluconazole breakpoints for *Candida* infections and to compare these data with the results obtained with the data set used to set up EUCAST fluconazole breakpoints, where the MIC for detecting failures was >4 mg/liter, with a sensitivity of 87%, a false-positive rate of 8%, and an area under the receiver operating characteristic (ROC) curve of 0.89. Five supervised classifiers (J48 and CART decision trees, the OneR decision rule, the naïve Bayes classifier, and simple logistic regression) were used to analyze the original cohort of patients (Rex's data set), which was used to establish CLSI breakpoints, and a later cohort of candidemia (Clancy's data set), with which CLSI breakpoints were validated. The target variable was the outcome of the infections, and the predictor variable was the MIC or dose/MIC ratio. For Rex's data set, the MIC detecting failures was >8 mg/liter, and for Clancy's data set, the MIC detecting failures was >4 mg/liter, in close agreement with the EUCAST breakpoint (MIC > 4 mg/liter). The sensitivities, false-positive rates, and areas under the ROC curve obtained by means of CART, the algorithm with the best statistical results, were 52%, 18%, and 0.7, respectively, for Rex's data set and 65%, 6%, and 0.72, respectively, for Clancy's data set. In addition, the correlation between outcome and dose/MIC ratio was analyzed for Clancy's data set, where a dose/MIC ratio of >75 was associated with successes, with a sensitivity of 93%, a false-positive rate of 29%, and an area under the ROC curve of 0.83. This dose/MIC ratio of >75 was identical to that found for the cohorts used by EUCAST to establish their breakpoints (a dose/MIC ratio of >75, with a sensitivity of 91%, a false-positive rate of 10%, and an area under the ROC curve of 0.90).

The antifungal susceptibility testing subcommittees of the European Committee on Antimicrobial Susceptibility Testing (AFST-EUCAST) and of the Clinical and Laboratory Standards Institute (AFST-CLSI) have established breakpoints for fluconazole and *Candida* spp. (7, 20, 23). Those breakpoints are shown in Table 1. Despite the fact that the reference methodologies developed by both antifungal susceptibility testing subcommittees, described in the CLSI M27-A3 and EUCAST EDef 7.1 documents (14, 15, 22), provide very similar results (8, 24), the breakpoints for fluconazole are somewhat different (Table 1). The breakpoints established by the CLSI are largely based upon experience in treating human immunodeficiency virus (HIV)-infected patients with oropharyngeal candidosis and candidemia (20). In addition, some other articles have validated the CLSI fluconazole breakpoints by studying candidemia (5, 11, 18). On the other hand, the fluconazole breakpoints established by AFST-EUCAST are based on two cohorts of patients with oropharyngeal candidosis and candidemia (7, 23). The correlation of patient outcome with MIC has usually been analyzed with the "90-60 rule." This rule observes that infections due to susceptible isolates respond to appropriate therapy ~90% of the time but that infections due to resistant isolates respond ~60% of the time (19). Another approach, using machine learning methods to analyze the correlation of MIC with patient outcome, has recently been employed (7). In that work, the fluconazole breakpoints established by AFST-EUCAST were validated using five different data mining algorithms. This complex analysis provides an opportunity to use statistical theory for building a model using a clinical data set in an independent way.

The aim of the current work is to use supervised classification algorithms to analyze the clinical data used by CLSI to establish fluconazole breakpoints for *Candida* infections and to compare the results with those obtained with the data set used to set up EUCAST fluconazole breakpoints.

MATERIALS AND METHODS

Literature search. A MEDLINE (National Library of Medicine, Bethesda, MD) search (PubMed service from NCBI) was undertaken, using the key words "fluconazole," "breakpoints," and "*Candida*" as well as text word searching. In

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TABLE 1. CLSI and EUCAST fluconazole breakpoints for *Candida* spp.

Organization	MIC (mg/liter)			
	Susceptible	S-DD[c]	Intermediate[d]	Resistant
CLSI[a]	≤8	16–32		>64
EUCAST[b]	≤2		4	>4

[a] The CLSI breakpoints do not apply to *Candida krusei*, as it is considered inherently resistant to fluconazole.

[b] The EUCAST breakpoints do not apply to *Candida glabrata* or *C. krusei*.

[c] S-DD (susceptible, dependent upon dose) indicates that maximizations of dosage and bioavailability are critical to successful therapy.

[d] The intermediate category denotes strains that are considered neither susceptible nor resistant.

addition, the reference sections of the articles obtained by the MEDLINE search were reviewed.

Criteria for inclusion of cases. All references found using the above-mentioned key words were reviewed (5, 11, 16, 17, 20, 21, 25), but there were only two articles with enough information for construction of a database indicating the individual MIC or dose/MIC ratio for each of the isolates and the respective outcome of the infection (5, 20). There was an article (1) providing enough information, but the correlation of the MICs was done with respect to mortality instead of treatment success. Therefore, as the endpoints used were different, this article was not included in the database.

Brief summary of previously published articles. (i) Rex's data set. Rex et al. (20) analyzed the data for 519 *Candida* isolates from 460 episodes of infection in 316 patients enrolled in six trials, including a trial of fluconazole as therapy for oropharyngeal candidiasis in patients with AIDS and three trials of fluconazole as therapy for nonneutropenic patients with bloodstream or visceral *Candida* infection. The MICs of fluconazole for the isolates were obtained according to the CLSI M27-T broth macrodilution methodology (12). The clinical outcomes of the patients were assessed by generally accepted clinical criteria. Successful therapy for oropharyngeal candidiasis required resolution of all clinical symptoms as well as complete resolution of visible lesions, while a successful outcome of therapy for systemic infection required resolution of fever and clearance of the infected site or organ(s).

(ii) Clancy's data set. Clancy et al. (5) analyzed the clinical data for 32 patients who had been treated with fluconazole in a prospective multicenter study of candidemia. Therapeutic failure was defined as either persistence of *Candida* in the bloodstream despite 3 days of therapy with fluconazole or development of breakthrough candidemia during treatment with fluconazole for ≥3 days as empirical therapy. In all other cases, the response to therapy was considered a success. Antifungal susceptibility testing was performed in accordance with CLSI M27-A (13).

Once both data sets were analyzed by data mining techniques, the results were compared with those obtained by Cuesta et al. (7) (Cuesta's data set) for 126 candidemia patients and 132 episodes of oropharyngeal candidosis in 110 HIV-positive patients. For candidemia patients, cure was defined as eradication of candidemia and resolution of the associated signs and symptoms. Failure was defined as persistent candidemia despite 4 days of fluconazole treatment. For oropharyngeal candidosis, clinical resolution was defined as the absence of lesions compatible with oral thrush after 10 days of therapy.

Antifungal susceptibility testing was performed by following the guidelines established by the antifungal susceptibility testing subcommittee of EUCAST for fermentative yeasts (22).

Computational methods. The following information for each patient was entered in an Excel sheet (Microsoft Iberica, Spain): the MIC of the isolate, the dose/MIC ratios, and the treatment outcome for the patient. When required, MIC data were transformed to $\log_2$ values to approximate a normal distribution. In the models, the target variable was the outcome of the infections, and the predictor variable was the MIC or dose/MIC ratio.

The models were built using WEKA software (version 3.6.0) (26) and Correlation and Regression Trees (CART) software (version 6.0; Salford Systems, San Diego, CA).

Five classifiers were used to analyze the database: J48 and CART decision trees, the OneR decision rule, the naïve Bayes classifier, and simple logistic regression. These classifiers cover a wide spectrum of methodologies (trees, rules, and probabilistic classifiers) and were chosen because of their sound theoretical basis and their suitability for intuitive interpretation. The main characteristics of the classifiers are described in reference 7.

A decision tree (e.g., J48 and CART) basically defines at its nodes a series of tests of predictor variables organized in a tree-like structure. Each terminal node (called a "leaf") gives a classification that applies to all instances that reach the leaf after being routed down the tree according to the values of the predictors tested in successive nodes. The tree is constructed by recursively splitting the data into smaller and smaller subsets so that after each split the new data subset is purer (i.e., represents less entropy) than the old data subset. The CART system was proposed by Breiman et al. (2).

OneR (9) is a simple classification rule. It is a one-level decision tree expressed as a set of rules testing only one particular predictor variable.

The naïve Bayes classifier (4) is a simple probabilistic classifier based on application of Bayes's theorem with strong (naïve) independence assumptions.

The simple logistic method builds logistic regression models, i.e., a linear model based on a transformed target variable determined using the logit transformation (10).

Every classifier develops a model when it searches for the MIC or the dose/MIC ratio that best splits the populations of successes and failures. Tenfold cross validation was the method used to estimate the performance of each classifier. This was assessed by determining values for (i) sensitivity, (ii) specificity, (iii) false-positive rate (1 − specificity), (iv) area under the receiving operating characteristic (ROC) curve, and (v) Matthews correlation coefficient (MCC). The MCC is a measure of the quality of two-class classifications. It takes into account true and false positives and negatives and is generally regarded as a balanced measure which can be used even when classes are of very different sizes. Analysis using the MCC returns a value between −1 and +1. A coefficient of +1 represents a perfect prediction, 0 an average random prediction, and −1 an inverse prediction.

RESULTS

Figure 1 shows distributions of therapeutic response related to the MIC of fluconazole for each study mentioned above and for all data sets analyzed together. Rex's data set contained 450 successes (87%) and 69 failures (13%). Clancy's data set contained 15 successes (47%) and 17 failures (53%). Cuesta's data set contained 156 successes (60%) and 102 failures (40%). For the whole data set, 77% of the cases were successes and 23% were failures.

Table 2 shows the MICs predicting failure for each classifier as well as the sensitivities, false-positive rates, areas under the ROC curve, and MCC indexes for the cohorts of patients studied by Rex et al. (20), Clancy et al. (5), and Cuesta et al. (7). As the MICs splitting failures and successes were similar among all three groups, and in order to increase the sample size, a database containing all cases was built and analyzed (5, 7, 20). The results of this analysis are also shown in Table 2.

The CART classifier exhibited the greatest ability to split clinical successes and failures for the three cohorts of patients. For Rex's data set, the MIC for detecting failures was >8 mg/liter, with a false-positive rate of 18% (Table 2). For Clancy's and Cuesta's data sets, the failures were detected with a MIC of >4 mg/liter, with false-positive rates of 6% and 8%, respectively (Table 2). As the results of the analysis of the three data sets (5, 7, 20) were similar, we put together all data. The CART classifier provided the best statistical results, with a sensitivity of 75%, a false-positive rate of 18%, an area under ROC curve of 0.78, and a failure-detecting MIC of >4 mg/liter. Figure 2 shows the tree generated by CART for the combination of the three cohorts of the patients (5, 7, 20).

The article by Clancy et al. (5) provided enough information to analyze dose/MIC ratio versus patient outcome. Table 3 shows the dose/MIC ratios predicting treatment success for each classifier and the values for sensitivity, false-positive rate,

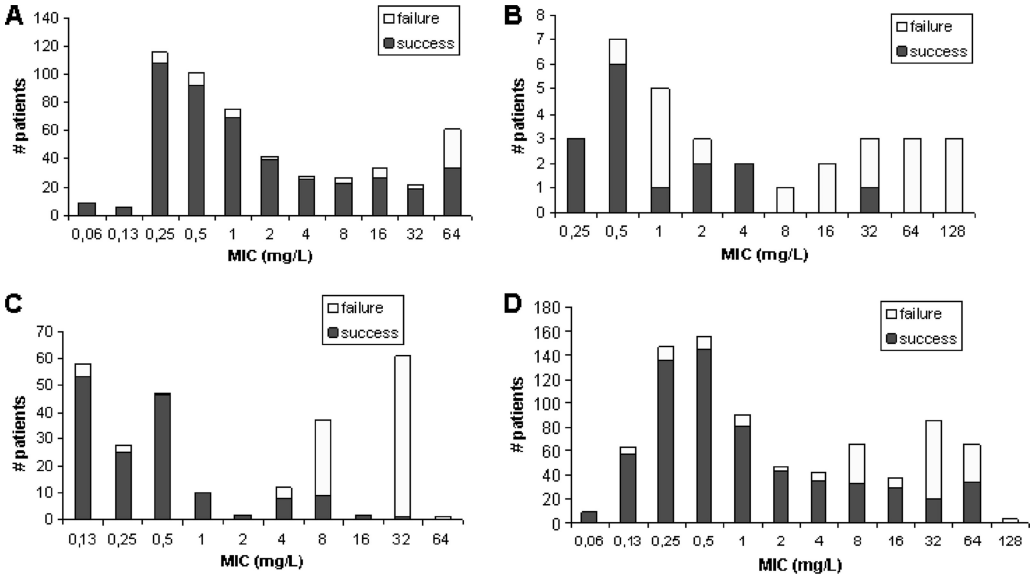

FIG. 1. Therapeutic response stratified by MIC. Results are shown for Rex's data set (A), Clancy's data set (B), Cuesta's data set (C), and all above-mentioned data sets joined (D).

area under the ROC curve, and MCC index for the cohort of patients with candidemia described by Clancy et al. (5). CART was again the strongest algorithm, showing a dose/MIC ratio of >75 as the value best splitting successes and failures for both cohorts of patients (5, 7). The combination of false-positive rate, area under ROC curve, and MCC was in general higher for CART than for the rest of the algorithms. An exception was found in Clancy's data set, where the false-positive rate was worse for CART (29%) than for OneR or the naïve Bayes classifier (12%). However, the rest of the measures were better for CART, especially sensitivity (93%), which is a relevant index in this analysis. As the results of the analysis of the two data sets (5, 7) were similar, we joined all data and analyzed them together. The CART classifier provided the highest statistical results, with a sensitivity of 90%, a false-positive rate of 12%, an area under ROC curve of 0.89, and a success-detect-

TABLE 2. Sensitivity, false-positive rate, area under the ROC curve, and MCC for MIC as a predictor of therapeutic failures

Reference or source	Classifier	MIC predicting failure (mg/liter)[a]	Sensitivity (%)	False-positive rate (%)	Area under the ROC curve	MCC
20	J48	NC				
	CART	>8	52	18	0.70	0.24
	OneR	NC				
	Naïve Bayes	>8	0	0	0.70	
	Simple logistic	NC				
5	J48	>4	76	27	0.78	0.50
	CART	>4	65	6	0.72	0.60
	OneR	>0.5	82	40	0.71	0.44
	Naïve Bayes	>2	65	20	0.80	0.45
	Simple logistic	>2	65	20	0.83	0.45
7	J48	>4	87	8	0.86	0.80
	CART	>4	87	8	0.89	0.80
	OneR	>4	87	8	0.89	0.80
	Naïve Bayes	>2	91	13	0.91	0.77
	Simple logistic	>2	91	13	0.91	0.77
All data[b]	J48	>4	52	10	0.77	0.45
	CART	>4	75	18	0.78	0.51
	OneR	>4[c]	50	9	0.71	0.45
	Naïve Bayes	>4	56	10	0.80	0.48
	Simple logistic	>16	53	9	0.80	0.48

[a] NC, not calculated (the classifier did not find a value splitting the populations of successes and failures).
[b] "All data" refers to the data provided by Rex et al. (20), Clancy et al. (5), and Cuesta et al. (7) combined and analyzed by means of the classifiers shown in the table.
[c] The high value of the complex rule.

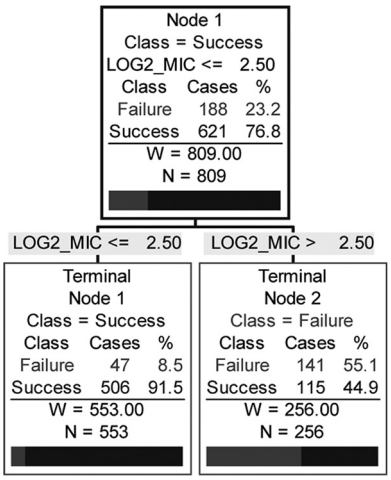

FIG. 2. CART tree showing values for the combination of Rex's, Clancy's, and Cuesta's data sets for MIC versus outcome (data were taken from references 5, 7, and 20). A LOG2_MIC of 2.5 is equivalent to a MIC of 4 mg/liter.

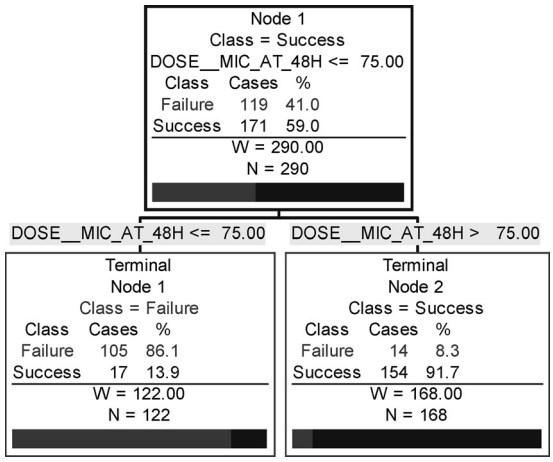

FIG. 3. CART tree showing values for the combination of Clancy's and Cuesta's data sets for dose/MIC ratio versus outcome (data were taken from references 5 and 7).

ing dose/MIC ratio of >75. Figure 3 shows the tree generated by CART for the combination of the two cohorts of patients (5, 7).

DISCUSSION

The antifungal susceptibility testing subcommittees of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and of the Clinical and Laboratory Standards Institute (CLSI) have developed two different reference methodologies (described in the EUCAST EDEF 7.1 and M27-A3 documents, respectively) for antifungal susceptibility testing of *Candida* spp. (15, 22). Different studies have demonstrated a high level of agreement between the results obtained with the two methods, and thus, the MICs obtained using the EUCAST broth microdilution method are in close agreement with those obtained using the CLSI reference procedure (6, 8). In addition, a specific analysis of the correlation between the results obtained using the CLSI and EUCAST methodologies for fluconazole showed that both standards produced identical MICs up to 2 mg/liter, with 2-fold-higher dilutions obtained using the CLSI method for values above this MIC; e.g., a MIC of 4 mg/liter obtained using the CLSI method is equivalent to a MIC of 2 mg/liter obtained using the EUCAST method (24). Despite this fact, both subcommittees produced different breakpoints for fluconazole (Table 1), which is, to some extent, peculiar. There have been several studies dealing with correlation of CLSI fluconazole MIC with patient outcome (1, 3, 11, 16, 18, 25). Rex et al. (20) performed the first correlation study, and on the basis of this study, the CLSI published fluconazole breakpoints (Table 1). Subsequent studies (1, 11, 16, 17, 18, 25) were aimed to validate CLSI breakpoints. Among them, that by Pfaller et al. (17) was a review of all studies dealing with

TABLE 3. Sensitivity, false-positive rate, area under the ROC curve, and MCC for dose/MIC ratio as a predictor of treatment success

Reference or source	Classifier	Dose/MIC predicting success[a]	Sensitivity (%)	False-positive rate (%)	Area under the ROC curve	MCC
5	J48	>50.0	93	35	0.71	0.60
	CART	>75.0	93	29	0.83	0.65
	OneR	>150	60	12	0.74	0.51
	Naïve Bayes	>180	60	12	0.82	0.51
	Simple logistic	NC				
7	J48	>50.0	87	10	0.87	0.77
	CART	>75.0	91	10	0.90	0.80
	OneR	>37.5	86	7	0.90	0.80
	Naïve Bayes	>674.0	91	41	0.86	0.50
	Simple logistic	NC				
All data[b]	J48	>50.0	90	15	0.86	0.75
	CART	>75.0	90	12	0.89	0.78
	One R	>75.0	92	17	0.87	0.76
	Naïve Bayes	>607	46	7	0.84	0.42
	Simple logistic	NC				

[a] NC, not calculated (the classifier did not find a value splitting the populations of successes and failures).
[b] "All data" refers to the data provided by Clancy et al. (5) and Cuesta et al. (7) combined and analyzed by means of the classifiers shown in the table.

correlation of fluconazole MIC with *in vivo* outcome. The strategy of this review was to classify percentages of responses according the CLSI breakpoints for susceptibility, susceptibility with dependence on dose, and resistance, checking whether the 90-60 rule was fulfilled. As a whole, the response rate for susceptible strains was 85%, and that for resistant strains was 42%. In other words, what we know for this approach are just percentages of response at certain MICs. In a previous work, Cuesta et al. (7) analyzed by means of data mining the outcomes for patients with oropharyngeal candidosis and candidemia in relation to the MICs of the isolates. The strategy of this analysis is completely different because the algorithms look for the MIC that best splits the populations of successes and failures, giving performance measures of sensitivity, specificity, false-positive rate, area under ROC curve, and MCC. Unlike with the 90-60 rule, these splitting values are objectively and automatically obtained from models induced by means of algorithms taking into account statistical characteristics of data. Cuesta et al. (7) validated the breakpoints set by EUCAST, applying five classifiers (J48, CART, OneR, the naïve Bayes classifier, and simple logistic regression). CART was the classifier which obtained the best statistical results, with a MIC of >4 mg/liter for detecting failures. Therefore, it seemed reasonable to analyze CLSI data with the same methodology in order to see what results are produced with this kind of analysis. Most CLSI studies showed aggregated data that prevented the use of data mining (3, 11, 18, 25). Therefore, only two articles, showing individual data (5, 20), have been used in this work, one of them being the original study (20) used to set the CLSI breakpoints.

CLSI data sets were analyzed, and the results found were similar. Thus, the MICs splitting populations of successes and failures were >8 mg/liter and >4 mg/liter for Rex's and Clancy's data sets, respectively (Table 2). The statistical results of both analyses were acceptable (Table 2). Therefore, we decided to put together all data and analyze them. The CART classifier provided the best model for the whole data set, with a sensitivity of 75%, a false-positive rate of 18%, an area under ROC curve of 0.78, and a failure-detecting MIC of >4 mg/liter.

Regarding dose/MIC ratio targets, CART revealed >75 as the value predicting treatment success for Clancy's data set, in agreement with the result obtained for Cuesta's data set (Table 3). The CART classifier provided the best model for the combined data set, with a sensitivity of 90%, a false-positive rate of 12%, an area under ROC curve of 0.89, and a treatment success-predicting dose/MIC ratio of >75. A dose/MIC ratio of >75 means that a fluconazole dose of 400 mg/day would cover all strains with a fluconazole MIC of 4 mg/liter or less.

In summary, separate analyses of the sets used to establish the CLSI and EUCAST fluconazole breakpoints by means of data mining showed similar results. Rex's data set showed a MIC of >8 mg/liter for detecting failures, whereas for Cuesta's data set, the MIC was >4 mg/liter. Analysis of fluconazole MIC correlation between the CLSI and EUCAST methodologies showed 2-fold-higher dilutions for the CLSI methodology when the MICs were above 2 mg/liter (24). In addition, Clancy's data set, used to validate the CLSI breakpoints, produced results for MIC and dose/MIC ratio identical to those obtained by Cuesta et al. (7).

These results provide an opportunity to reach an agreement regarding the CLSI and EUCAST fluconazole breakpoints.

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