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Approval Sheet

A Population-Based Investigation of *Candida* Blood Stream Infections

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Abstract Cover Page

A Population-Based Investigation of *Candida* Blood Stream Infections

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An abstract of
A thesis submitted to the Faculty of
the Laney School of Graduate Studies of Emory University
In partial fulfillment of the requirement for the degree of
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ABSTRACT

A Population-Based Investigation of *Candida* Blood Stream Infections
By Sarah Kabbani (<300words)

Introduction: *Candida* Blood Stream Infection (BSI) is the fourth leading cause of BSI and is responsible for significant morbidity and mortality. Fluconazole resistant *Candida* BSI has been classified as a serious threat level in the report of "Antibiotic Resistant Threats, 2013" Center for Disease Control (CDC). However, the association of fluconazole resistance with mortality has not been well defined.

Methods: Population based surveillance for *Candida* BSI in Georgia and Maryland was performed as part of the Emerging Infections Program (EIP). Isolates were sent to CDC for species confirmation and antifungal susceptibility testing. *Candida* BSI cases in adults collected between 2008-2013 were analyzed to evaluate clinical and epidemiologic features, assess covariates associated with fluconazole resistance and mortality (deaths 2-30 days from index culture) using bivariate analysis, and to determine the association of mortality and fluconazole drug resistance using multivariate logistic regression, controlling for other important variables.

Results: At total of 3553 cases identified from 2008-2013 were analyzed; average incidence rate was 19.3 cases per 100,000, and the incidence decreased significantly over time. Fluconazole resistance was present in 7.2% of the cases. Crude mortality in the first 30 days was 922 (28.5%); 666 (20.6%) died between 2-30 days. On multivariate analysis, fluconazole resistance was not associated with increased mortality after adjusting for covariates. Increased age, HIV, liver disease, malignancy, hospital onset of infection, intensive care unit (ICU) stay, treatment with amphotericin B, and infection with *Candida albicans* and *Candida tropicalis* were associated with increased mortality. Central venous catheter (CVC) removal and treatment with fluconazole were associated with decreased mortality.

Conclusions: Incidence of *Candida* BSI has been decreasing over the last 5 years. Fluconazole resistance was not associated with increased mortality after adjusting for covariates. Future analyses should include a more comprehensive measurement of and adjustment for severity of illness.

Cover Page

A Population-Based Investigation of *Candida* Blood Stream Infections

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INTRODUCTION

Candida Blood Stream Infection (BSI) cause significant morbidity and mortality worldwide. [1-4] Fluconazole resistant *Candida* BSI has been classified as a serious threat level in the report of "Antibiotic Resistant Threats in the United States, 2013" recently published by CDC. [5]. However, the association of fluconazole resistance with all-cause mortality has not been well defined.

The overall purpose of this study was to evaluate the clinical, epidemiologic and microbiologic features of *Candida* BSI in metropolitan Atlanta, Georgia and in Baltimore, Maryland, and determine the impact of resistance to the antifungal agent fluconazole on clinical outcome. *Candida* BSI cases included in this study were identified through the *Candida* BSI surveillance project in the CDC-funded Emerging Infections program (EIP) from March 1, 2008 to Feb 28, 2013.

Multiple clinical risk factors have previously been associated with increased mortality. For the present analyses, known risk factors were divided into 4 categories designated patient-related, hospitalization-related, treatment-related, and organism-related. Many of those same clinical risk factors may be associated with increased fluconazole resistance thus there is a potential for confounding. For this reason, the association of fluconazole resistance on mortality was evaluated while controlling for the above listed covariates using multivariate logistic regression. The primary hypothesis was that fluconazole resistance increases the risk of all-cause mortality of *Candida* BSI in adults.

BACKGROUND

Significance and Risk Factors for *Candida* BSI

Candida BSI is the most common cause of invasive fungal diseases in humans. It is the fourth most common cause of BSI in the US and the developed world [1]. It is estimated that BSI due to *Candida* species occurs at a rate of 0.5-10 infections per 1000 hospital admissions, and has an annual incidence of 6-10 episodes per 100,000 population [2, 3, 6]. Because the sensitivity for detection of *Candida* BSI in standard blood cultures may be as low as 50-60%, the true incidence may be much higher than the reported rates [7]. A recent study by Zaoutis et al. found the attributable mortality of *Candida* BSI to be 10% for pediatric patients and 14.5% in adults. The cost analysis in this study showed that total hospital charges attributable to invasive candidiasis were $33,604-$45,602 per episode [8]. *Candida* BSI can lead to prolongation of hospital stay by as much as 34 days [9].

Several studies have described factors associated with increased risk of *Candida* BSI, which include race, age, extended ICU stay (>3 days), severity of illness, indwelling central venous catheter, total parenteral nutrition, previous administration of antimicrobial agents, hematologic or solid organ malignancies, hemodialysis, prior fungal colonization, gastrointestinal perforation or surgery, pancreatitis, diabetes, multiple blood transfusion, steroids and other immunosuppressant therapy [2, 10, 11].

Antifungal Drug Resistance

More than 90% of cases of invasive candidiasis have been attributed to five species; *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei*. Species differ in their pattern of fluconazole resistance, patient risk factors and outcomes. *C. albicans* remains the most common cause of *Candida* BSI, but BSI due to *Candida* non-*albicans* species, which are more likely to be resistant, have been increasing. [12] *C. glabrata* has emerged as an important pathogen particularly in the United States where it is second only to *C. albicans* as a cause of BSI [2]. Increasing incidence of *Candida* non-*albicans* BSI has been associated with multiple risk factors, particularly prior patient exposure to antifungal agents [2, 13]. Specifically *C. krusei* has been associated with fluconazole exposure and neutropenia; *C. glabrata* with increasing age and fluconazole use; *C. parapsilosis* with central venous catheters especially in infants and neonates; and *C. tropicalis* with neutropenia and leukemia [1, 12, 14]. A study by Chow attempted to determine factors predictive for the development of invasive infection with *C. albicans* compared with *Candida* non-*albicans* species in ICU patients to provide guidance for decisions about the use of prophylactic antifungal therapy. Multiple common risk factors were found in both infection categories, and they concluded that differentiation cannot be made based upon clinical characteristics alone [15].

C. glabrata has been associated with higher incidence of fluconazole resistance and recent emergence of echinocandin resistance, a cause for alarm among clinicians caring for critically ill patients. It is worth noting that *Candida* isolates with reduced echinocandin susceptibility have, to date, occurred following

prolonged exposure to the drug [16, 17]. However echinocandin resistance has been noted in *C. glabrata* mostly in the setting of concurrent fluconazole resistance, which emphasizes the importance of following the trends of fluconazole resistance, and the challenges of co-resistance, since alternative treatments are limited and significantly more toxic.

Role for antifungal prophylaxis

Antifungal prophylaxis has been shown to be effective in decreasing the incidence of *Candida* BSI and its associated mortality in immunocompromised/neutropenic patients, despite the risk of selecting for fluconazole resistant strains of *C. glabrata* and *C. krusei* [18]. In contrast, the risk benefit ratio and cost-effectiveness of antifungal prophylaxis in non-neutropenic, critically ill patients remains unclear [12]. A recent randomized controlled trial concluded that fluconazole prophylaxis did not decrease mortality in the ICU setting [19].

There have been multiple attempts at developing clinical prediction models and using data from fungal colonization for targeted antifungal prophylaxis in ICU patients [10]. Results of such studies have been variable with some identifying subpopulations at increased risk of invasive candidiasis [20]. However most were retrospective studies that will require further validation prospectively in a multicenter setting, and thus have not resolved this important clinical dilemma [12].

Experts agree that the key to an effective antifungal prophylaxis strategy is identifying patients at highest risk for the disease in order to maximize risk and cost

benefit ratio of the prophylaxis [21]. In addition, determining risk factors associated with mortality may help in determining the highest risk populations for targeted prophylaxis and improve outcomes.

Mortality from Candida BSI

There are multiple factors that have been associated with increased risk of mortality from *Candida* BSI. Some are host factors usually related to the severity of the underlying illness. These include older age (>64yrs), ICU admission, higher severity of illness scores, hematological malignancies, and neutropenia [22-24] Other risk factors associated with increasing mortality are related to hospital interventions, including retention of central venous catheter, inadequate treatment dosing or duration, and delay in initiation of antifungal therapy [11, 14, 23, 25].

Fluconazole Resistance and Mortality

Fluconazole resistant *Candida* BSI has been classified as a serious threat level in the report of "Antibiotic Resistant Threats in the United States, 2013" recently published by CDC [5]. However fluconazole resistance has not been clearly defined as a risk factor for increased mortality in *Candida* BSI, and published data has been conflicting. A study done in non-neutropenic ICU patients in 2001-2005 in Athens, Greece, showed that mortality was higher in *Candida* non-*albicans* compared to *C. albicans* BSI (90% vs. 52.8%, P = 0.005) [26]. Although there was no difference between antifungal prophylaxis in both groups, it is possible the higher mortality rate was related to the delay in effective antifungal therapy in the non-*albicans*

group related to the higher rates of antifungal resistance. Another study done by Davis et al in non-neutropenic ICU patients failed to reproduce that result [14]. Two studies found a correlation of *Candida* MICs with therapeutic response [27, 28] . The study by Kovacicova in 2000 reported a significantly higher attributable mortality in patients with fluconazole resistant *Candida* (19% vs. 8.6%, $P < 0.01$) [29]. Thus the effect of fluconazole resistance on mortality in *Candida* BSI needs to be better defined.

A previous population-based surveillance study of candidemia done by the CDC from 1998-2000 emphasized the importance of monitoring trends in antifungal resistance, especially correlating resistance with outcome in future surveillance data [2]. Longitudinal programs of active, population-based surveillance allow for the description and detection of changes in trends, distribution, and emergence of resistance over a wide geographic location in diverse patient populations over time [12]. Preliminary data from population-based candidemia surveillance in Atlanta shows an increase in the proportion of BSI due to *Candida* non-*albicans* species over time (from 48% 1992-93 compared to 60% 2008-2010), in large part due to increases in *C. glabrata* and *C. parapsilosis*. A worrisome emergence of echinocandin-resistant *Candida glabrata* has been observed in Atlanta.

Given the emergence of non-*albicans* species and the growing problem of relative or absolute antifungal resistance, there is a need for further evaluation of the impact of these factors on clinical outcomes such as mortality. A better understanding of risk factors associated with the development of antifungal

resistance and with mortality, would provide valuable information to inform future recommendations for antifungal prophylaxis and empiric therapy.

METHODS

Research Goal

The main purpose of this study was to estimate the association of fluconazole resistance with all-cause mortality from *Candida* BSI in infected adults, while controlling for patient-related risk factors that are associated with either fluconazole resistance or all-cause mortality. A secondary goal was to assess the incidence of *Candida* BSI, and the association of patient-related and hospital-related risk factors for *Candida* BSI with fluconazole resistance.

Hypothesis

Relative or absolute antifungal drug resistance is associated with increased mortality in patients with *Candida* BSI.

Study Design

A prospective observational cohort study design was used for the analysis to assess factors associated with all-cause mortality occurring between 2-30 days after the index culture. The main exposure is fluconazole drug resistance. The main outcome is mortality from 2-30 days. Case-patients were those who died, and non-case patients were those who survived to 30 days or hospital discharge.

Patient Selection

Candida BSI cases included in this study have been identified through the active, Candidemia Surveillance Project within the Georgia (GA) and Maryland (MD) Emerging Infections Program (EIP) funded by the CDC. From 2008 onward GA EIP has performed prospective, population-based, laboratory surveillance for *Candida* BSI in residents of the 8-county metropolitan area of Atlanta that includes a population of 3.8 million. MD EIP performed the same surveillance in Baltimore city and county that includes a population of 1.4 million (for map of surveillance areas see Figure 1). Cases were collected between March 1, 2008 and Feb 28, 2013. Cases were defined as the first blood culture positive for *Candida* species collected from a resident in the surveillance area. For the purposes of this analysis, and due to published data on low sensitivity, autopsy cases were excluded. [30] Laboratory audits were done monthly to evaluate reporting accuracy and ensure capture of all cases.

Trained and experienced personnel used standardized case report forms to abstract basic demographics, clinical characteristics and outcomes. Sources of information used to complete the data forms were hospital notes (admission or discharge summary), face sheet and laboratory report. The outcomes are recorded at hospital discharge and at 30 days. The chart is reviewed again 2-3 months after the culture date to determine outcome.

A case was defined as a positive blood culture for a *Candida* species within a 30 day period; any additional cultures after 30 days were considered as a second episode. Cases were included between the period of March 1, 2008 to February 28,

2013. Cases in adults equal to or greater than 20 years of age were included. The case report form was modified after the first 2 years of surveillance to shorter the form. Only data points included on both forms were used for this analysis. All the variables were coded similarly, except for neutropenia, which will be discussed in more detail below.

Isolate Collection and Laboratory Testing

All available isolates were sent to CDC for species confirmation and antifungal susceptibility testing. A total of 2840/3553 (79.9%) of the case-isolates were available for analysis. Species identification was done using the Luminex assay or DNA sequencing of the D1-D2 subunit of the 28S rDNA [31]. When the species identification could not be done at CDC. the identification done at hospital or reference laboratories was used, which represented 707 (19.9%) of isolates. A concordance of >90% was previously noted between hospital/referral laboratory speciation and CDC results. Antifungal susceptibility testing was performed by broth microdilution for fluconazole, itraconazole, voriconazole, posaconazole, flucytosine, anidulafungin, caspofungin, and micafungin and interpreted per the Clinical and Laboratory Standard Institute (CLSI) M27-A3 guidelines [32]. Only the CDC antifungal susceptibility testing results were used in the bivariate and multivariate analyses. The hospital/reference laboratory species identification was only used in the descriptive analysis. Antifungal susceptibility among *Candida* species was categorized as "resistant" vs. "not-resistant", as shown in Table 1.

Measurements

The covariates included in the model were relevant variables found on the case report forms, including demographic data and known confounders and associated conditions in *Candida* BSI.

The main outcome was mortality from 2-30 days. Deaths in the initial 48 hours were excluded, as the results of blood cultures are generally not available in the initial 48 hours, and the patients are frequently not yet on antifungal therapy. Excluding the case-patients who died in the initial 48 hours is consistent with prior studies [23, 33].

The main exposure was fluconazole resistance, as defined in Table 1, using the new breakpoint definitions for classification of susceptibility testing results [32]. This is one of the first analyses looking at outcome using these new breakpoints. The reason for categorizing the "intermediate" category Susceptible Dose Dependent (SDD) with Sensitive (S) was the assumption that relative resistance can be overcome by appropriate antifungal drug dosing, and thus can be categorized with Sensitive. And since the effect of full fluconazole resistance was the exposure of interest, it was compared to the combined group of SDD and S isolates.

The other covariates analyzed were divided into the following groups: patient-related, hospital-related, treatment-related and species-related factors. These variables are shown in Appendix A. All the variables were dichotomized into categorical variables.

The group of patient-related variables included sex (male vs. female) and race (black vs. others). Age was initially categorized into three age groups, 20-44,

45-64, and ≥65 years. However in the final model the 2 categories above 45 years had similar trends and associations, thus were combined into one group. Patient-related variables also included chronic renal disease, chronic liver disease (excluding acute liver failure), diabetes, HIV, malignancy (divided into hematological and solid organ malignancy) and transplant (divided into solid organ and bone marrow transplant), surgery with a subcategory of abdominal surgery. Data on neutropenia was available only for the initial 2 years of surveillance, and was defined as an absolute neutrophil count <500. However, because those data were frequently incomplete, neutropenia was excluded from the analysis. Finally, included in this group, was recurrent disease, defined as a second episode of *Candida* BSI 30 days after the initial episode.

Hospital-related factors included hospital-onset infection which was defined as incident blood culture 48 hours after hospital admission, antibiotic use within the last 14 days, total parenteral nutrition (TPN) within the last 14 days, central venous catheter (CVC) within the last 48 hours, nursing home residence at the time of hospital admission and ICU admission.

Treatment-related factors included receiving antifungal therapy prior to the incident blood cultures, and central line removal within 7 days, which is recommended in the Infectious Diseases Society Guidelines [1] and antifungal treatment. Antifungal treatment was further sub-divided into separate variables: whether the patient received any therapy, the drug class they received (azoles, echinocandin or amphotericin b) and the predominant drug used (fluconazole, micafungin, amphotericin B). One of the limitations of this dataset is that it dose or

duration of therapy were not specified, and many cases received more than one drug during their course of therapy because of underlying conditions (patients who develop Candida BSI on fluconazole prophylaxis would be more likely to be started on an echinocandin), treatment guidelines, clinical response and final species identification.

Finally species were also included as categorical variables, and they were *C. albicans, C. dubliniensis, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. lusitaniae*, and a category of other species for the descriptive analysis. Based on the MIC data available, the 56 . *lusitaniae* isolates were not included in the final analysis because fluconazole breakpoints for *C. lucitaniae* were not published in the most recent CLSI update [32].

Sample Size and Power Calculations

Power calculations done before the analysis were based on the limited published literature. Attributable mortality in fluconazole resistant *Candida* was found to be 19% compared to 8.6% secondary to fluconazole sensitive *Candida* [29]. Initial calculations were done with crude all-cause mortality.

In the EIP candidemia dataset, crude 2-30 day mortality was 20.6% (666/3229). Fluconazole resistance was (205/2840) 7.2% overall. The expected sample size needed to achieve 80% power with 95% confidence intervals (CI) is summarized in Table 2. The sample size calculation was performed using a statistical calculator from the following website:

(http://www.sph.emory.edu/~cdckms/sample%20size%202%20grps%20cohort.html)

The sample size needed was 1,219, and mortality data was available for 3,229, thus this study was considered feasible.

Database management

Data was entered into a Microsoft Access 2007 database (Microsoft Corp., Redmond, WA) and statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

Analytic Plan

US census bureau census population estimates were used to calculate incidence rates by year. However, the numerator was the number of cases in each surveillance year (from March to February), whereas the denominator was based on calendar year. This was a minor limitation due to the time the surveillance system was established. Also because the population data for 2013 were not available at the time of this writing , the 2012 population data were used. Logistic regression, with year as the predictor variable and number of cases/total population as the dependent variable, was used to perform a trend analysis on incidence rates over the four year surveillance period. A p-value <0.05 was considered significant.

First the patient-related factors, hospitalization-related factors, treatment-related factors, organism-related factors were reported for all the *Candida* BSI cases in adults. Then a bivariate analysis was done to compare *Candida* BSI cases with and

without fluconazole resistance, and those who died and did not die to better define confounding. Differences in proportions of categorical variables were tested using $\chi 2$. All reported *p*-values were two sided, with α (the significance level<0.05). Odds ratios and 95% confidence interval were reported.

A Kaplan-Meier curve of overall mortality was used to show the proportion of cases in the initial 48 hours that were excluded. A Kaplan-Meier curve of those who died within 2-30 days was stratified by fluconazole resistance.

A univariate analysis compared *Candida* BSI case-patients who died between 2-30 days after incident blood culture with cases who survived more than 30 days. Differences in proportions of categorical variables were tested using $\chi 2$. All reported *p*-values were two sided, with α (the significance level<0.05). Odds ratios and 95% confidence interval were reported. This was followed by a multivariable logistic regression. The outcome was death from 2-30 days after incident blood culture, case-patients were those who died from 2-30 days, non-case patients were those or survived after 30 days. The exposure was fluconazole resistance as defined above. Covariates that were included in the model were those with a p value <0.1 on univariate analysis. However we included other covariates that were known from published literature to be biologically important (such as infection with *Candida albicans*). Interaction was assessed using the Breslow-Day method, and variables with a p value for interaction <0.05 were included as in interaction term in the model. Collinearity was assessed using the Collins Macro, using eigenvalues, condition indexes, and variance decomposition proportions [34]. A preliminary model was built using automated stepwise selection methods. The model was

adjusted based on treatment variables, where it was initially done with all drugs together, then drug classes, then specific drugs within every class. Also biologically important variables were forced into the model to evaluate for significance. We also ran the model with and without neutropenia due to issues with missing data and it did not affect the final model. They were kept in the final model if the p value was <0.05 or the change in parameter estimate was >10%. The approach to building the final model in shown in the schematic in appendix B.

$$\text{LogitP(Dead=1)}=\beta_0+\beta_1\text{FluconazoleResistance}+\beta_2X_2+\beta_3X_3+...$$

IRB Approval

This analysis is part of the population-based *Candida* surveillance study which has been approved by the Georgia and Maryland Departments of Public Health, Emory University and CDC Institutional Review Boards.

RESULTS

Incidence of *Candida* BSI

A total of 3553 of adult cases of *Candida* BSI were found in the surveillance period from March 1, 2008 to February 28, 2013. The average incidence rate was 19.3 per 100,000 population. Table 3 shows the incidence by surveillance year and there was a statistically significant decrease over the surveillance period.

Frequency of Exposure and Outcome

Antifungal susceptibility data were available for 2840/3553 (79.9%) of the cases, and 7.2% of the isolates were resistant to fluconazole. Figure 2 shows the proportion of isolates with resistance by species; with the highest rates among *C. krusei,* 100% resistant (by definition) followed by *C. glabrata* at 11.1%, the *C. tropicalis* at 6.2%, and the lowest being *C. albicans* at 1.3%. For comparison, fluconazole resistance using the older breakpoints (MIC≥64 for all species) was 3.6%.

Crude 30 day mortality was 922 (28.5%) and the 256 (7.9%) case-patients who died in the initial 48 hours were excluded from the mortality analysis, however were included in the descriptive analysis(Table 4). Thus 666 cases died between 2-30 days (20.6%) as shown in the Kaplan-Meier curve in Figure 3. Figure 4 shows a Kaplan-Meier curve stratified by fluconazole resistance, which shows a trend toward increased mortality with resistance, however it was not statistically significant.

Description of *Candida* BSI cases

Overall, 51.1% of the cases were male, and 59.7% were of black race. The most common co-morbid condition was diabetes at 37% followed by surgery at 33.9%. Sixty-five percent of cases were hospital onset and 93% had at least one of the following risk factors: antibiotic use, TPN use or presence of a central venous catheter. Most (88%) were treated with antifungal agents, and 70.8% had their central venous catheter removed in accordance with IDSA guidelines. If the cases who died in the initial 48 hours were excluded those numbers would be even higher (92.7% and 75.2% respectively). A small proportion of patients (4.2%) were treated with amphotericin B (Table 5).

Univariate Analysis of fluconazole resistance

Statistically significant increased risk of resistance was associated with the following covariates: previous fluconazole exposure, black race HIV, neutropenia, hematological malignancy, stem cell and solid organ transplant, second *Candida* BSI episode, hospital onset infection, presence of central venous catheter and infection with *C. glabrata*. Statistically significant decreased risk of resistance was associated with increasing age, liver disease, infection with *C. albicans* and *C. parapsilosis* (Table 6).

Univariate Analysis of mortality

Although fluconazole resistance was not associated with statistically significant increased mortality there was a trend toward increased mortality with an odds ratio of 1.34(0.95-1.89) [p value 0.0884]. Each of the following covariates was associated with a statistically significant increased risk of resistance: increasing age, renal and liver disease, HIV, neutropenia, hematological and solid organ malignancy, hospital onset infection, antibiotic use, presence of central venous catheter, ICU admission, previous fluconazole exposure, treatment with Amphotericin B, and infection with *C. krusei* and *C. tropicalis*. A second episode of *Candida* BSI, antifungal treatment (any treatment but specifically with fluconazole), and infection with *C. parapsilosis* were associated with a significantly decreased risk of resistance (Table 7).

Multivariate Analysis of mortality 2-30 days in cases *Candida* BSI

Interaction was found between age≥45 and fluconazole resistance, and the interaction term was included in the model but was not significant in the final model (Table 8). When assessing for collinearity, the presence of a central venous catheter was collinear with the intercept indicating that it did not vary with respect to the outcome, thus it was not included in the model (Figure 6). Fluconazole resistance was not significantly associated with crude mortality 2-30 days in the final model, after controlling for covariates (OR 1.32 95% CI 0.86-2.03). Increased age, HIV, liver disease, malignancy (solid organ and hematologic), hospital-onset infection, ICU stay, treatment with amphotericin B and infection with *C. albicans* and *C. tropicalis* were independently associated with increased mortality. Whereas treatment with

fluconazole and central line removal were associated with decreased mortality (Table 9). The final Model is shown in Appendix C.

DISCUSSION

The incidence of *Candida* blood stream infections has been declining. The decrease in trends has been well-documented in pediatric *Candida* BSI [35, 36], however it is unclear whether this is driven by increasing use of antifungal prophylaxis, empiric antifungal therapy, decreased use of broad spectrum antibiotics or infection control practices. The current study was not designed to address incidence trends, but instead focused on the impact of fluconazole resistance.

The percentage of isolates with fluconazole resistance was 7.2%, similar to other recently reported studies[37, 38], and published surveillance for the first 3 years of this EIP surveillance system [39]. However this is one of the first analyses looking at outcome using these new breakpoints. Using the older MIC breakpoints, overall fluconazole resistance was 3.6%, slightly increased over the 2.3% reported from 2004-2007 from sterile body sites collected from institutions across the US. [40]

Crude 30-day mortality in this dataset was 28.5%, within the range of crude mortality from *Candida* BSI that has previously been reported to range from 5-71%, with attributable mortality of 14.5% in adults in a recent systemic review [41].

The demographics characteristics and co-morbid conditions associated with *Candida* BSI in this surveillance system have been recently [42]. Factors found to be associated with fluconazole resistance were co-morbid conditions in which the

patients frequently either received fluconazole prophylaxis or treatment for other fungal infections (neutropenia, hematologic and solid organ malignancy and transplant, neutropenia). Prior fluconazole exposure is a well-established risk factor for fluconazole resistance. [1, 2] However it is unclear why increased age and chronic liver disease were associated with decreased resistance. Perhaps it is due to differences in species distribution and the likelihood of receiving prophylaxis with fluconazole.

Many of the risk factors associated with mortality in this study are well established in the literature. Increasing age, co-morbid conditions like HIV, malignancy, admission to the intensive care unit and infection with *C. albicans* were associated with increased mortality and have previously been reported. Likewise, antifungal treatment, specifically fluconazole, and removal of the central venous catheter have also been associated with decreased mortality in other studies [22, 23, 43-45].

Fluconazole resistance was not found to be associated with increased mortality on multivariate analysis. The published data so far has been conflicting, with some papers showing correlation between fluconazole MIC and therapeutic response [46] and increased mortality with fluconazole resistance [29]. However in other studies looking at differences in mortality between *C. albicans* and non-*albicans* infections, despite the fact that infections due to non-*albicans* are associated with a higher proportion of resistance, no significant differences in mortality were detected [47]. This may be explained by the fact that echinocandins, an alternative effective therapy for fluconazole resistant *Candida* BSI, that are

generally well tolerated with a low side-effect profile, have been used more commonly as alternative therapy in the past decade. Before that time, only amphotericin B and sometimes voriconzole (although not always effective) were used for fluconazole-resistant *Candida* infections. These drugs were generally more toxic and poorly tolerated. However, the question remains unresolved and deserves additional study. Also considering interaction with age, the effect of age needs to be evaluated further.

Curiously liver disease was found to have increased association with mortality. This has not been reported before. However many studies use the Charleson index or other severity of illness scores that incorporate liver disease to assess severity of illness, and they are usually associated with increasing mortality [48]. Considering that there no such scores were included in this analysis, this may have allowed liver disease to remain significant after adjusting for other covariates.

Candida species more commonly associated with increased mortality are thought to be *C. krusei, glabrata and albicans* [44, 49, 50]. *C. krusei* is generally rare in the US, and not commonly reported to be associated with increased mortality. This species is more common in South America, the Middle East and Southeast Asia [51]. It has been associated with malignancy, specifically hematologic malignancy [12]. It was found to have increased association with mortality although non-statistically significant [23]. Based on in-vitro studies and clinical observations it is thought to be more virulent than *C. albicans* in immunocompromised patients [52].

It is important to note, that amphotericin B was independently associated with increased mortality. This may be a reflection of the practice of using this drug

more commonly in immunocompromised patients, for other fungal infections, and the inherent toxicity of this drug.

The limitations in this analysis were driven by the nature of the data. This is observational data thus there is concern for unmeasured confounding. There is no marker of severity of illness other than ICU admission (ex: APACHE score or Charleson index), which may have effected some of the variables that remained in the final model. There were also limited variables describing immunocompromised status, which may be important in assessing *Candida* BSI and mortality. Dates, duration, and dosing of antifungal drugs given for treatment and prophylaxis were not available. Thus we cannot draw firm conclusions about the effect of the drugs administered on the clinical outcome.

However the study used data that was collected prospectively over an extended period of time, making it one of the largest datasets to date evaluating this problem. It is population-based, collected in multiple institutions over a large geographic area in 2 different states, and would less likely reflect the variability of individual institutional practices.

The findings of this analysis will need further validation. Future studies will also include analysis of data stratified by species, evaluation of the pediatric population, exploration the effect of age on fluconazole drug resistance and outcome, comparison of the outcomes between use of the new and old fluconazole MIC breakpoints defining resistance, and analysis of predictors of echinocandin resistance and mortality.

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Table 1: Definition and Breakpoints for "Resistant" *Candida*

Species	Old MIC			New MIC		
	"Not Resistant"		"Resistant"	"Not Resistant"		"Resistant"
	S	SDD	R	S	SDD	R
C. albicans	≤8	16-32	≥64	≤2	4	≥8
C. glabrata	≤8	16-32	≥64	-	≤32	≥64
C. krusei	-	-	-	-	-	-
C. parapsilosis	≤8	16-32	≥64	≤2	4	≥8
C. tropicalis	≤8	16-32	≥64	≤2	4	≥8

Abbreviations: MIC Minimum Inhibitory Concentration (μg/ml), S Susceptible, SDD Susceptible dose dependent, R resistant

Table 2: Sample Size Calculations

Proportion with mortality in sensitive *Candida* BSI	Proportion with mortality in resistant *Candida* BSI	Ratio of Sensitive: Resistant	Sample size of Resistant (exposed)	Sample size of Not Resistant (nonexposed)	Total Sample Size
0.086	0.19	12.8	205	2635	1219

Table 3: Incidence of *Candida* BSI in Adults in GA and MD

Surveillance Year	Total No. Of Cases/Year	Incidence*†
2008	824	24.33
2009	829	21.71
2010	788	21.35
2011	598	15.92
2012	514	13.68

* Incidence per 100,000 population

† p value <0.01, testing from trend in *Candida* BSI over the 5 year surveillance period

Table 4: Crude Mortality in cases with *Candida* BSI

Outcome	N	%
Mortality ≤ 30 days	922	26.5
Mortality ≤ 2 days	256	7.4
Mortality 2-7 days	666	20.6
Mortality 8-30 days	256	7.4
Median Time to death (IQR)	9 (3-23)	

***IQR 25-75% interquartile range**

Table 5: Frequency of Covariates in Cases of *Candida* BSI

Variables	N	%
Patient Factors		
Male	1814	51.1
Black	2121	59.7
Age 20-44	720	20.3
Age 45-64	1447	40.7
Age ≥ 65	1386	39.0
Diabetes	1316	37.0
Renal Disease	630	17.7
Liver Disease	442	12.4
HIV	207	5.8
Hematologic Malignancy	117	3.3
Solid Organ Malignancy	550	15.5
Neutropenia*	32	1.7
Surgery	1204	33.9
Abdominal Surgery	628	9.3
Hospital Factors		
Hospital Onset	2301	65.0
Nursing Home	703	23.1
Intensive Care Unit	2196	63.0
At least one Risk Factor	3305	93.0
Antibiotics	2805	79.0
TPN	1134	31.9
Central Line	2953	84.3
Treatment Factors		
Prior Azole	330	9.3
Treatment	3039	88
Treatment (survived >48 hrs)	2942	92.7
Fluconazole	2223	68.6
Micafungin	1660	51.2
Amphotericin B	137	4.2
Central Line Removed	1994	70.8
Central Line removed (survived >48 hrs)	1948	75.2
Species		
C. albicans	1346	38.0
C. dubliniensis	58	1.6
C. glabrata	1072	30.2
C. krusei	54	1.6
C. lusitaniae	56	1.6
C. parapsilosis	558	15.8
C. tropicalis	347	9.8
Other	56	1.6

*Neutropenia cases only in years 2010-2013

Table 6: Frequency of Covariates in *Candida* BSI Cases with and without Fluconazole Resistance

Variable	Fluconazole Resistant N=205		Fluconazole Not Resistant N=2635		OR (95% CI)	*p*-value
Patient Factors	N	%	N	%		
Male	106	51.7	1350	106	1.37(1.02-1.83)	0.913
Black	141	70.5	1548	141	1.02(0.76-1.35)	0.0061*
Age≥45	150	73.2	2110	80.1	0.68(0.49-0.94)	0.0182*
Diabetes	73	35.6	985	37.4	0.93(0.69-1.25)	0.6133
Renal Disease	32	15.6	470	17.8	0.85(0.58-1.26)	0.4207
Liver Disease	15	7.3	347	13.2	0.52(0.3-0.89)	0.0155*
Neutropenia	7	8.2	21	1.7	5.25(2.16-12.72)	<0.0001*
HIV	28	13.7	149	5.6	2.64(1.71-4.06)	<0.0001*
Hematologic Malignancy	19	9.3	75	2.8	3.49(2.06-5.89)	<0.0001*
Solid Organ Malignancy	36	17.6	408	15.5	1.16(0.8-1.69)	0.4302
Stem Cell Transplant	4	2	7	0.3	7.47(2.17-25.74)	0.0002*
Solid Organ Transplant	11	5.4	55	2.1	2.66(1.37-5.16)	0.0027*
Surgery	58	28.3	898	34.1	0.76(0.58-1.04)	0.0912
Abdominal Surgery	35	17.1	464	17.6	0.96(0.66-1.4)	0.846
Hospital Factors						
Hospital Onset	143	69.8	1654	62.8	1.37(1-1.86)	0.0457*
Nursing Home	43	24.6	536	23.7	1.05(0.73-1.5)	0.803
Antibiotics	166	81	2077	78.8	1.14(0.8-1.64)	0.4664
TPN	75	36.6	823	31.2	1.27(0.94-1.71)	0.1124
CVC	184	90.6	2172	83.7	1.89(1.17-3.07)	0.0088*
ICU	121	59.9	1636	63.4	0.86(0.64-1.16)	0.3262
Second Episode	30	14.6	211	8.0	1.97(1.3-2.97)	0.001*
Prior Azole	53	25.6	200	7.6	4.24(3-5.99)	<0.0001*
Species						
C. albicans	14	6.8	1036	39.3	0.11(0.06-0.2)	<0.0001*
C. dubliniensis	2	1	54	2	0.47(0.11-1.95)	0.2868
C. glabrata	103	50.2	821	31.2	2.23(1.68-2.97)	<0.0001*
C. krusei	43	21	0	0		
C. parapsilosis	24	11.7	448	17	0.58(0.42-1)	0.0498*
C. tropicalis	17	8.3	257	9.8	0.84(0.5-1.4)	0.4951
Other	2	1	19	0.7	1.36(0.31-5.86)	0.682

† α=0.05, significant p-values marked with an asterisk

Table 7: Frequency of Covariates with *Candida* BSI Cases that died 2-30 days and survived >30 days

Variable	Died 2-30 days N=666		Survived >30 days N=2563		OR (95% CI)	*p*-value
Patient Factors	N	%	N	%		
Male	343	51.5	1305	51	1.02(0.86-1.21)	0.8163
Black	390	60.1	1572	63.1	0.88(0.74-1.05)	0.1648
Age≥45	578	87.2	1965	76.9	2.04(1.6-2.6)	<0.0001*
Diabetes	247	37.1	950	37.1	1(0.84-1.19)	0.992
Renal Disease	165	24.8	402	15.7	1.77(1.44-2.17)	<0.0001*
Liver Disease	109	16.4	282	11	1.58(1.24-2.01)	0.0002*
Neutropenia	12	3.7	20	1.7	2.25(1.09-4.66)	0.0243*
HIV	52	7.8	139	5.4	1.48(1.06-2.06)	0.0201*
Hematologic Malignancy	39	5.9	71	2.8	2.18(1.46-3.26)	<0.0001*
Solid Organ Malignancy	125	18.8	370	14.5	1.36(1.1-1.7)	0.0054*
Solid Organ Transplant	12	1.8	63	2.5	0.73(0.39-1.36)	0.3165
Surgery	230	34.5	887	34.6	1(0.83-1.19)	0.9717
Abdominal Surgery	106	15.9	471	18.4	0.84(0.67-1.06)	0.1397
Hospital Factors						
Hospital Onset	523	78.5	1600	62.4	2.2(1.8-2.69)	<0.0001*
Nursing Home	131	22.9	481	21.8	1.07(0.86-1.33)	0.5649
Antibiotics	575	86.3	2004	78.2	1.76(1.39-2.24)	<0.0001*
TPN	213	32	851	33.2	0.95(0.79-1.14)	0.5502
CVC	596	89.6	2114	83	1.76(1.35-2.32)	<0.0001*
ICU	345	60.6	1603	79.3	0.4(0.33-0.49)	<0.0001*
Second Episode	556	83.7	1425	56.4	3.97(3.19-4.95)	<0.0001*
Treatment Factors						
Prior Azole	53	25.6	200	7.6	4.24(3-5.99)	<0.0001*
CVC Removal	345	60.6	1603	79.3	0.4(0.33-0.49)	<0.0001*
Fluconazole	367	58.2	1801	74.7	0.47(0.39-0.57)	<0.0001*
Micafungin	354	56.2	1271	52.7	1.15(0.96-1.37)	0.12
Species						
C. albicans	14	6.8	1036	39.3	0.11(0.06-0.2)	<0.0001*
C. dubliniensis	2	1	54	2	0.47(0.11-1.95)	0.2868
C. glabrata	103	50.2	821	31.2	2.23(1.68-2.97)	<0.0001*
C. krusei	43	21	0	0		
C. parapsilosis	24	11.7	448	17	0.58(0.42-1)	0.0498*
C. tropicalis	17	8.3	257	9.8	0.84(0.5-1.4)	0.4951
Other	2	1	19	0.7	1.36(0.31-5.86)	0.682

† α=0.05, significant p-values marked with an asterisk (*)

Table 8: Association Between Fluconazole Resistance and Mortality Controlling for Covariates

Variables	Stratum Specific OR		Adjusted OR (95% CI)	*p*-value
	OR_1	OR_0		
Age≥45	1.1048	3.193	1.42(1.00-2.00)	0.0061*
Renal Disease	1.572	1.3355	1.38(0.98-1.94)	0.7208
Liver Disease	1.0714	1.4178	1.38(0.98-1.95)	0.657
HIV	1.4429	1.2796	1.30(0.92-1.84)	0.8071
Hematologic Malignancy	1.3037	1.2489	1.26(0.89-1.78)	0.9395
Solid Organ Malignancy	0.9713	1.437	1.33(0.94-1.87)	0.3798
Second Episode	1.6461	1.3488	1.38(0.98-1.95)	0.7106
Hospital Onset	1.3745	0.9957	1.29(0.91-1.83)	0.4832
Antibiotics	1.4687	0.6274	1.34(0.95-1.90)	0.1779
ICU	1.4185	1.4272	1.42(1.00-2.03)	0.9885
CVC removal	1.4919	1.0241	1.33(0.92-1.92)	0.3583
Prior Antifungal	1.4837	1.0118	1.19(0.83-1.70)	0.3036
Fluconazole	1.6995	0.953	1.30(0.91-1.85)	0.1073
Micafungin	1.1423	2.0274	1.40(0.99-1.99)	0.1169
Amphotericin B	1.5961	1.2351	1.29(0.90-1.84)	0.6064
C. albicans	1.1242	1.4067	1.38(0.98-1.96)	0.7443
C. parapsilosis	1.5653	1.2932	1.32(0.94-1.86)	0.7308
C. tropicalis	2.2931	1.2703	1.35(0.96-1.91)	0.2862

Crude OR (95% C.I.): 1.34(0.95-1.89)
OR1 is stratum specific odds ratio for presence of covariate, OR0 for absence of covariate
Adjusted OR by Matel-Haenszel method
Breslow-Day $\chi 2$, α=0.05, Significant p-values marked with an asterisk (*)

Table 9: Multivariate Analysis for predictors of Mortality in Cases with *Candida* BSI

Variable	Estimated Coefficient	Estimated Standard Error	Estimated Odds Ratio (95% CI)	*p*-value*
Fluconazole Resistance	0.276	0.2209	1.32(0.86-2.03)	0.2114
Age≥45	0.7556	0.1696	2.13(1.53-2.97)	<.0001*
Liver Disease	0.3851	0.1766	1.47(1.04-2.08)	0.0292*
HIV	0.5024	0.2392	1.65(1.03-2.64)	0.0357*
Hematologic Malignancy	1.0765	0.2622	2.94(1.76-4.91)	<.0001*
Solid Organ Malignancy	0.392	0.1565	1.48(1.09-2.01)	0.0123*
Hospital Onset	0.6414	0.147	1.9(1.42-2.53)	<.0001*
ICU	1.2232	0.1543	3.4(2.51-4.6)	<.0001*
CVC removal	-0.861	0.1309	0.42(0.33-0.55)	<.0001*
Fluconazole	-0.7501	0.128	0.47(0.37-0.61)	<.0001*
Amphotericin B	0.928	0.2539	2.53(1.54-4.62)	0.0003*
C. albicans	0.2983	0.135	1.35(1.03-1.76)	0.0271*
C. tropicalis	0.6512	0.1966	1.92(1.3-2.82)	0.0009*

Intercept±standard error: -2.5923 ± 0.2571
-2 Log-likelihood: 1768.577
*α=0.05, Significant p-values marked with an asterisk (*)

Figure 1. Map of Surveillance area

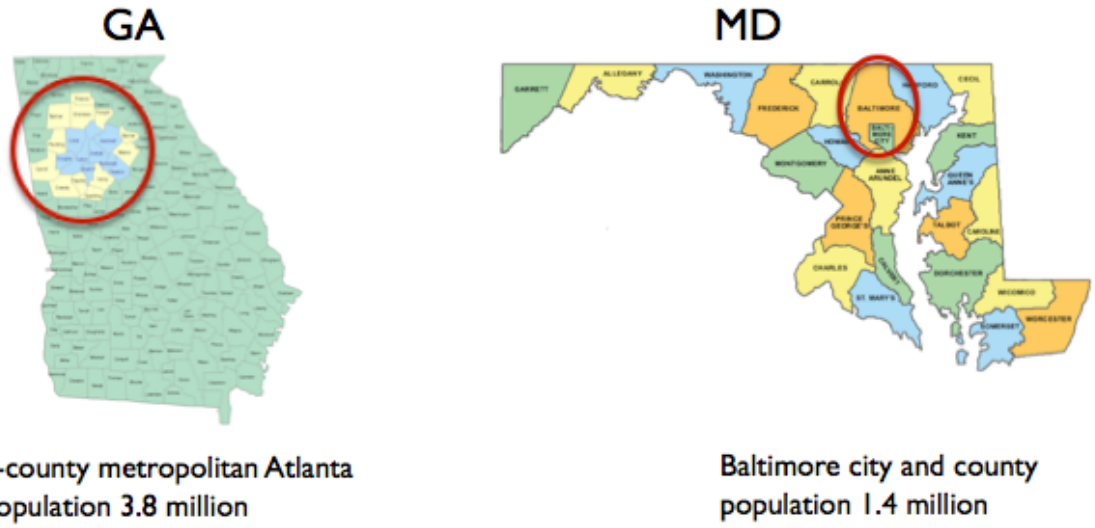


Figure 2. Fluconazole Susceptibility by *Candida* species (% resistant)

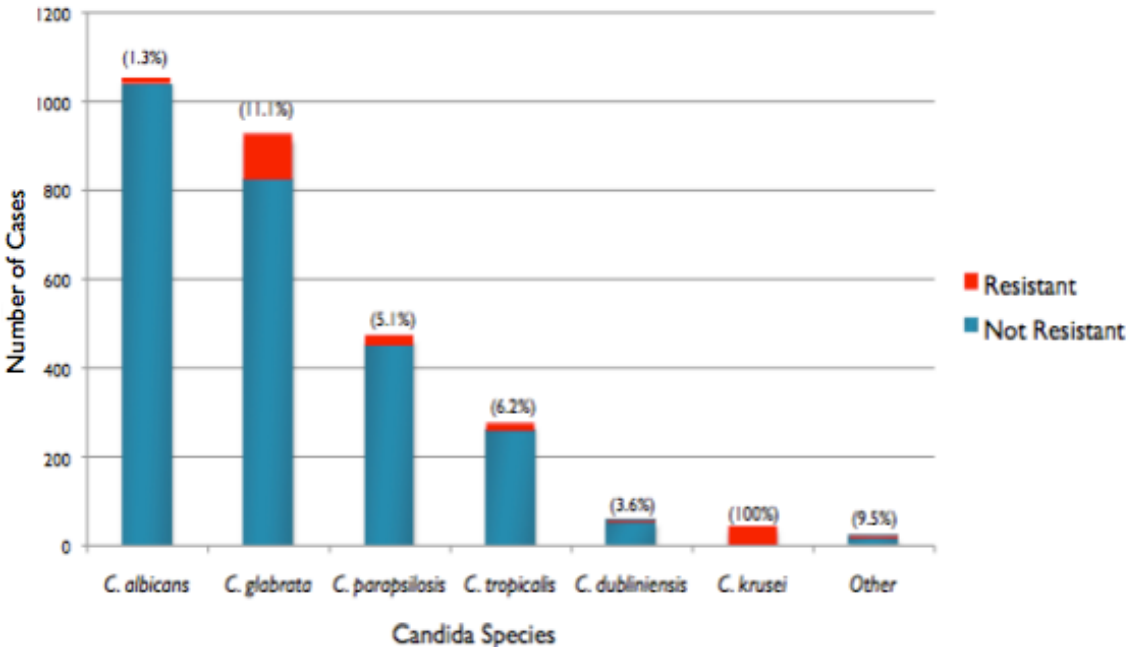


Figure 3. Kaplan-Meier Curve for Survival

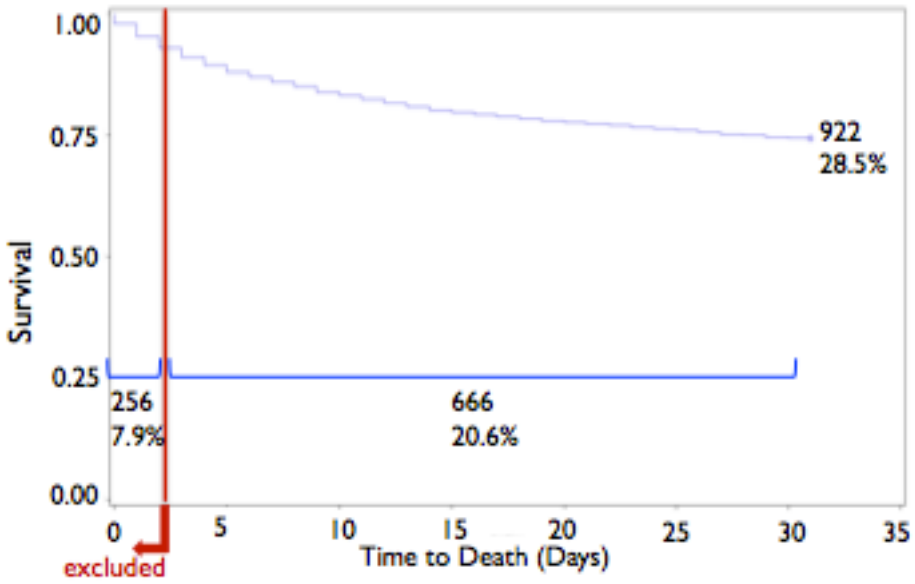


Figure 4. Kaplan-Meier Curve for Survival Stratified by Fluconaozle Resistance

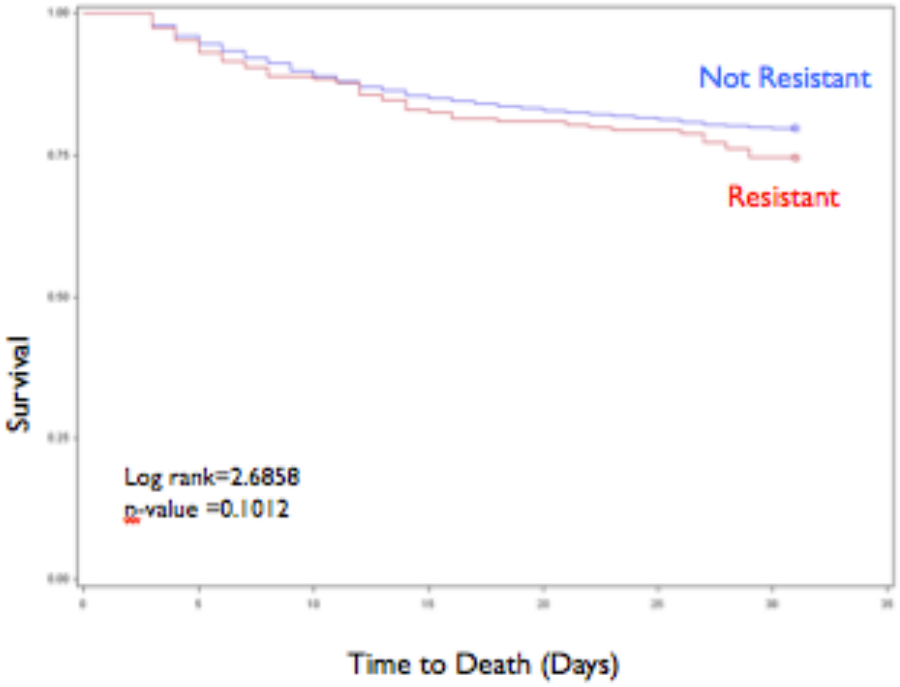


Figure 5. Log-Log Curve for Fluconazole Resistance

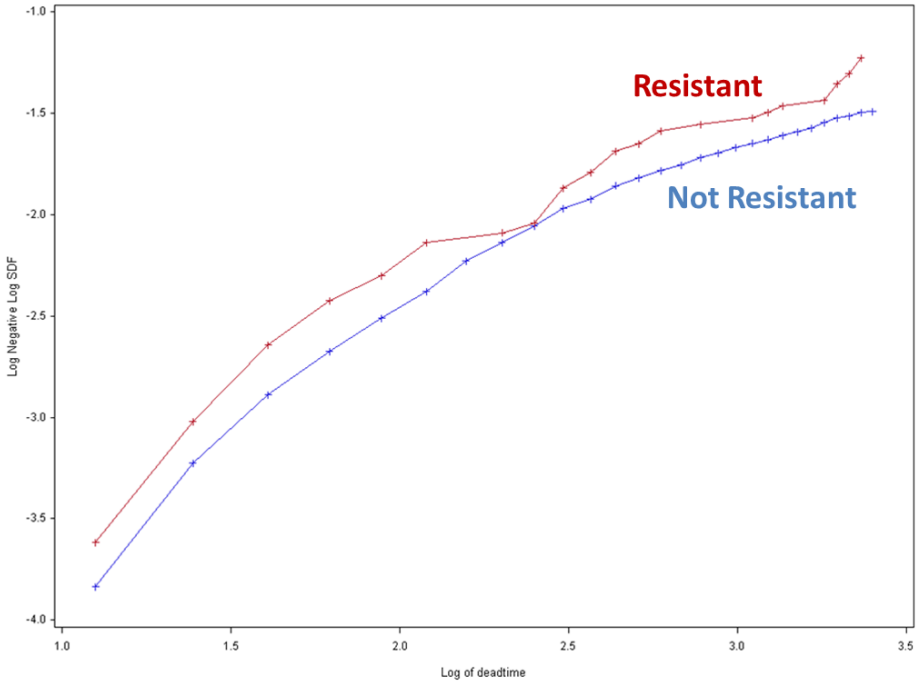
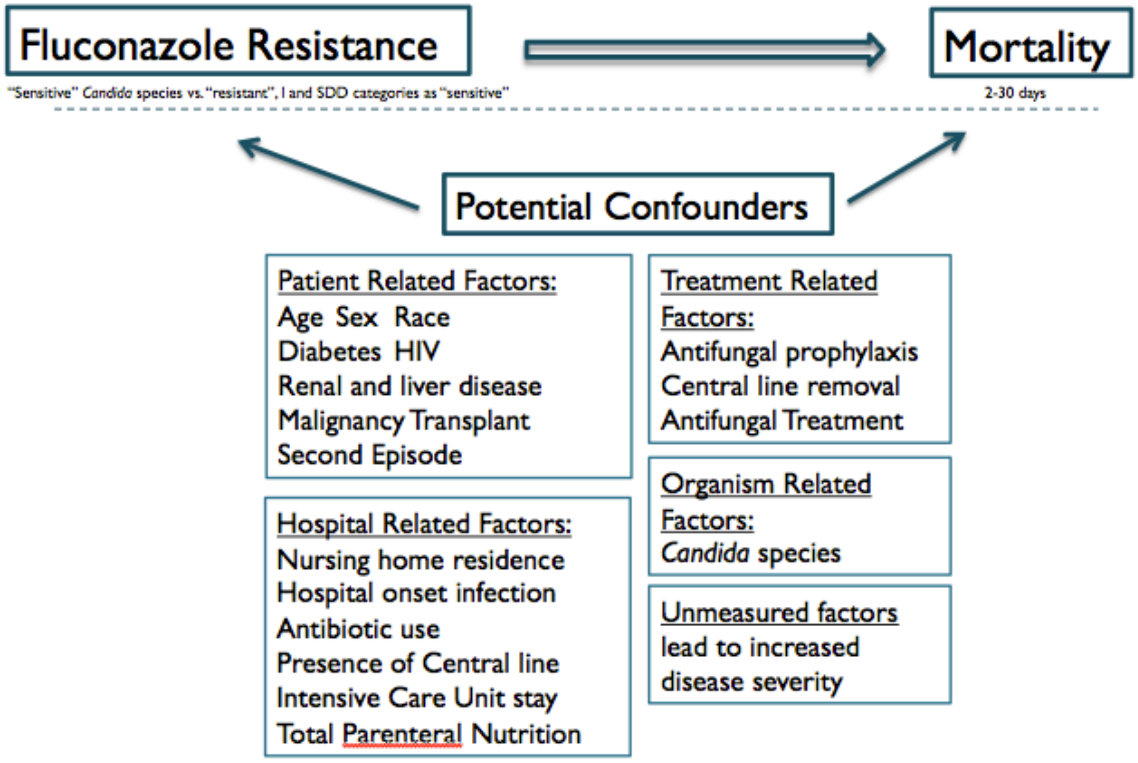


Figure 6: Collinearity assessment of covariates

Input DATASET info, Submitted 02FEB2014
COLLINEARITY DIAGNOSTICS FOR NONLINEAR MODELS USING THE INFORMATION MATRIX: EIGENVALUES, CONDITION INDEXES, AND VARIANCE DECOMPOSITION PROPORTIONS (VDP'S)

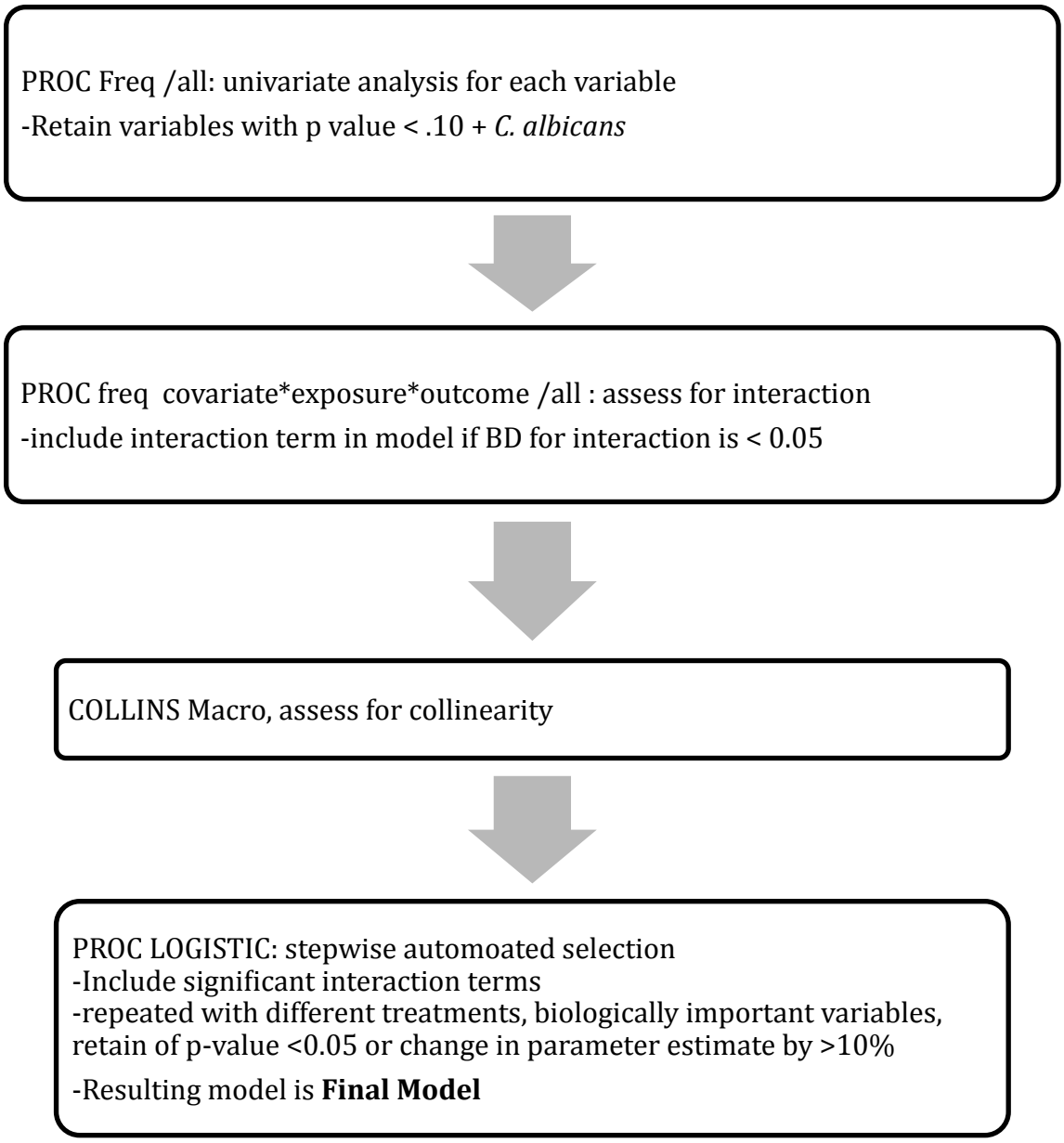
VARIABLE	VDP1	VDP2	VDP3	VDP4	VDP5	VDP6	VDP7	VDP8	VDP9	VDP10	VDP11	VDP12	VDP13	VDI
EIGENVAL	0.00	0.0563	0.10491	0.16487	0.19525	0.26214	0.30267	0.38187	0.43038	0.55135	0.63089	0.69522	0.72781	0.75
CONDINDX	30329.38	12.5233	9.17575	7.31950	6.72603	5.80477	5.40216	4.80939	4.53027	4.00256	3.74174	3.56442	3.48371	3.41
	.	.	.	.	.	.	.	.	.	.	.	.	.	
Intercept	1.00	0.0000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00
chi_FlucResistant	0.00	0.0023	0.00148	0.00278	0.00021	0.00679	0.00390	0.00059	0.00400	0.63173	0.00119	0.00215	0.06961	0.00
highriskage	0.00	0.2699	0.30841	0.38626	0.01752	0.00202	0.00617	0.00058	0.00284	0.00009	0.00025	0.00003	0.00012	0.00
chi_HO	0.00	0.0016	0.35010	0.18413	0.36023	0.02477	0.06333	0.00018	0.00119	0.00091	0.00266	0.00068	0.00060	0.00
chi_ABX	0.00	0.4184	0.51623	0.00611	0.02297	0.00825	0.02163	0.00000	0.00100	0.00002	0.00264	0.00018	0.00000	0.00
chi_CVC	1.00	0.0000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00

Appendix A: Covariates included in Multivariate Analysis



Patient Related Factors	Hospital Related Factors	Treatment Related Factors	Organism Related Factors
Age ≥45	Hospital Onset	Prior Antifungal	Fluconazole Resistant
Renal Disease	Antibiotic Use	Central Line Removal	*C. albicans*
Liver Disease	TPN	Azole Treatment	*C. krusei*
HIV	Central line	Fluconazole Treatment	*C. parapsilosis*
Neutropenia	ICU Admission	Echinocandin treatment	*C. tropicalis*
Hematologic Malignancy	Nursing home resident	Micafungin Treatment	*C. lusitaniae*
Solid organ Malignancy		Amphotericin B Treatment	*C. glabrata*
Second Episode			Other species

Appendix B: Strategy of Covariate Selection



Appendix C: Final Model

$$\text{logit}P(\text{Dead}=1) = \beta_0 + \beta_1\text{FluconaozleResistance} + \beta_2\text{Age}\geq 45 + \beta_3\text{HIV} + \beta_4\text{LiverDisease} + \beta_5\text{HematologicMalignancy} + \beta_6\text{SolidOrganMalignancy} + \beta_7\text{HospitalOnset} + \beta_8\text{IntensiveCareUnitStay} + \beta_9\text{CentralLineRemoval} + \beta_{10}\text{TreatmentwithFluconazole} + \beta_{11}\text{TreatmentwithAmphotericinB} + \beta_{12}C.albicans + \beta_{13}C.tropicalis$$