Abstract #168

Creation and Internal Validation of a Clinical Predictive Model for Fluconazole Resistance in Patients with *Candida* Bloodstream Infection

Adriana M. Rauseo, MD[1]: Margaret A. Olsen, PhD, MPH[1]; Lindsey Larson, MPH[1]; Dustin Stwalley, MA[1]; Kevin Hsueh, MD[1]; William G. Powderly, MD[1]; Andrej Spec, MD, MSCI[1]

[1]Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, MO

BACKGROUND

- *Candida* is a common cause of hospital-acquired bloodstream infections associated with high morbidity and mortality.
- Fluconazole is recommended as first-line therapy in patients with candidemia considered low risk for fluconazole resistance.
- Prolonged echinocandin use is due to lack of a clinical mechanism to determine risk of resistance and poor access to rapid sensitivity.
- We aimed to develop a clinical predictive model (CPM) to identify patients at low risk for fluconazole resistance where first-line use of fluconazole therapy would be acceptable without requiring resistance testing.

METHODS

Study Design and Setting: Retrospective cohort analysis at Barnes-Jewish Hospital from January 2013 to January 2018.

Inclusion criteria: All hospitalized patients ≥18 years with *Candida* spp. isolated from at least one blood culture (index blood culture).

Data collected:

- Demographics, comorbidities, procedures, medications, vital signs, laboratory parameters and microbiology data.
  - ICD-9/10 CM and Elixhauser comorbidity index were determined during index admission and within 365 days prior.
  - Prior medications were documented within 90 days of index blood culture.
  - Microbiology data was collected within 365 days prior to index admission.
- Fluconazole resistant (Fluc-R) *Candida* was determined using Sensititre™ YeastOne™ YO9 AST Plate, with cutoffs for each *Candida* species based on CLSI performance standards for antifungal testing (M60).

Model development and Statistical analysis:

- Bivariate analyses were performed to evaluate the potential risk factors. Multivariable logistic regression model was developed using backwards stepwise regression including only variables with clinical plausibility and p <0.1 in bivariate analyses.
- Bootstrap validation and backward stepwise elimination on bootstrapped samples was performed to test individual variable stability and estimate CI.
- Graph of observed vs expected values was used to assess model performance and c-statistic was used to assess discrimination.
- Performed with SAS v9.4 Software (SAS Institute Inc. Cary, NC, USA). For descriptive statistics, used $\chi 2$ or Fisher exact tests for categorical variables and Mann- Whitney U test for continuous variables, as appropriate for non-normally distributed variables.
- All statistical tests were 2-tailed and significance was set at $p \leq 0.05$.

RESULTS

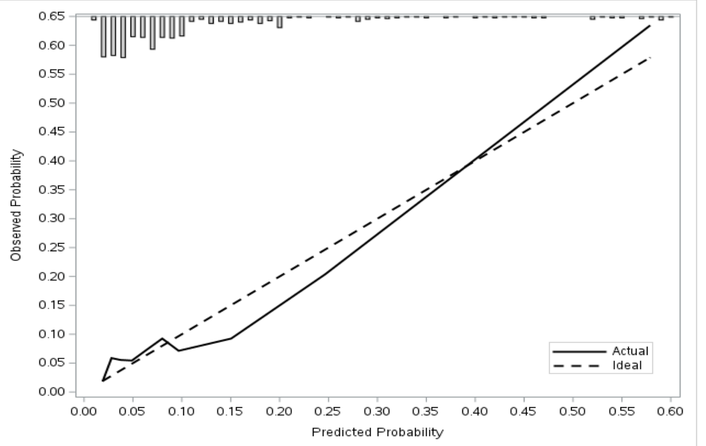
- Total of 539 patients with *Candida* bloodstream infection identified during the study period and 72 (13.4%) had Fluc-R.
- Patients with Fluc-R candidemia were significantly more likely to have:
  - Hematological malignancy, BMT, MDS, neutropenia, immunodeficiency, bacterial septicemia, CDI and enterocolitis 1 year prior.
  - Chemotherapy and certain medications (antifungals and other anti-infectives) 90 days before positive blood culture (Table 1).
- Increased risk of Fluc-R in the multivariable logistic regression model was associated with age, receipt of azoles 90 days prior to candidemia, bacterial septicemia, BMT, and MDS within 1 year prior to index admission (Table 2).
- The model predicted fluconazole resistance well (c-statistic 0.788).
- The variables in the final selected model were tested for stability by determining their inclusion using backward selection in 500 bootstrapped samples. All variables were retained in at least 65% the bootstrapped samples, except BMT which was retained in 44%.
- The plot shows good calibration of the model with very small differences between observed and expected probability of developing Fluc-R candidemia (Figure 1).

TABLE 1. Comparison of characteristics between patients with Fluc-NR and Fluc-R candidemia

Variable	Fluc-NR N=467 N (%)	Fluc-R N=72 N (%)	Total N=539 N (%)	p	OR (95% CI)
Age (median [IQR])	58 (44-67)	55 (47-61)	--	0.1452	--
Female	199 (42.61)	32 (44.44)	231 (43.52)	0.7700	1.07 (0.65-1.77)
Non-white	141 (30.19)	19 (26.39)	160 (28.29)	0.5108	0.82 (0.47-1.45)
Comorbidities					
Diabetes mellitus	208 (44.54)	32 (44.44)	240 (44.49)	0.9879	0.99 (0.60-1.64)
Valvular heart disease	119 (25.48)	20 (27.78)	139 (26.63)	0.6785	1.12 (0.64-1.96)
Renal failure	182 (38.97)	23 (31.94)	205 (35.45)	0.2529	0.73 (0.43-1.24)
Liver disease	123 (26.34)	16 (22.22)	139 (24.48)	0.4574	0.79 (0.44-1.44)
Metastatic cancer	69 (14.78)	11 (15.28)	80 (15.03)	0.9111	1.04 (0.52-2.07)
Drug abuse	81 (17.34)	6 (8.33)	87 (12.83)	0.0530	0.43 (0.18-1.03)
Hematological malignancy[a]	84 (17.99)	41 (56.94)	125 (37.46)	<.0001	6.03 (3.5-10.1)
Solid organ malignancy	158 (33.83)	32 (44.44)	190 (39.13)	0.0794	1.56 (0.94-2.58)
Other potential predisposing factors					
Bone marrow transplant	49 (10.49)	31 (43.06)	80 (26.77)	<.0001	6.45 (3.71-11.2)
Solid organ transplant	26 (5.57)	3 (4.17)	29 (4.87)	0.6239	0.73 (0.21-2.50)
Myelodysplastic syndrome	14 (3)	13 (18.06)	27 (10.53)	<.0001	7.12 (3.19-15.90)
Neutropenia (ANC <1500 cells/mm^3)	78 (16.70)	33 (45.83)	111 (31.26)	<.0001	4.21 (2.50-7.12)
Chemotherapy	81 (17.34)	37 (51.39)	118 (34.36)	<.0001	5.03 (2.99-8.47)
Immunodeficiency	246 (52.68)	55 (76.39)	301 (64.53)	0.0002	2.90 (1.63-5.15)
Bacterial septicemia	150 (32.12)	40 (55.56)	190 (43.84)	0.0001	2.64 (1.59-4.37)
C. difficile infection	13 (2.78)	8 (11.11)	21 (6.94)	0.0007	4.36 (1.73-10.9)
Bacterial enterocolitis	45 (9.64)	22 (30.56)	67 (20.1)	<.0001	4.12 (2.29-7.42)
Bacterial peritonitis	14 (3)	5 (6.94)	19 (4.97)	0.0910	2.41 (0.84-6.92)
Total parenteral nutrition	264 (56.53)	43 (59.72)	307 (58.12)	0.6107	1.14 (0.68-1.88)
Central venous catheter	191 (40.90)	34 (47.22)	225 (44.06)	0.3112	1.29 (0.78-2.12)
Urinary catheter	145 (31.05)	26 (36.11)	171 (33.58)	0.3903	1.25 (0.74-2.10)
Dialysis	57 (12.21)	5 (6.94)	62 (9.57)	0.1928	0.53 (0.20-1.38)
Medications					
Azoles	59 (12.63)	39 (54.17)	98 (33.4)	<.0001	8.17 (4.77-13.9)
Other antifungals	155 (33.19)	44 (61.11)	199 (47.15)	<.0001	3.16 (1.89-5.27)
Dapsone	4 (0.86)	11 (15.28)	15 (8.07)	<.0001	29.87 (6.44-67.59)
Antibiotics	409 (87.58)	69 (95.83)	478 (91.70)	0.0396	3.26 (0.99-10.7)
Sulfonamide	32 (6.85)	13 (18.06)	45 (12.45)	0.0014	2.99 (1.48-6.02)
Antiviral	111 (23.77)	40 (55.56)	151 (39.66)	<.0001	4.00 (2.40-6.68)
Antiherpes antivirals	101 (21.63)	37 (51.39)	138 (36.51)	<.0001	3.83 (2.29-6.39)
Other antivirals	15 (3.21)	6 (8.33)	21 (5.77)	0.0366	2.73 (1.02-7.30)

Note: Fluc-NR, fluconazole non-resistant; Flu-R, fluconazole resistant. [a]Includes leukemia, multiple myeloma, non-Hodgkin's lymphoma

FIGURE 1. Graph comparing observed vs expected probability of Fluc-R



Bars included on the top parameter of the graph indicate the number of individuals, illustrating the distribution of the sample.

TABLE 2. Multivariable logistic regression of independent risk factors for Fluc-R

Variable	OR (95% CI)
Bacterial septicemia	2.14 (1.20-3.79)
Prior azole use	5.47 (2.92-10.26)
Bone marrow transplant	2.63 (1.31-5.29)
Myelodysplastic syndrome	3.13 (1.14-8.60)

Note: Fluc-R, fluconazole resistant
Adjustment for age was performed using a cubic spline.

CONCLUSION

- We identified five risk factors (age, receipt of prior azole, bacterial septicemia, BMT and MDS) that were significantly associated with risk fluconazole resistance.
- Our CPM provides a potential tool for identifying patients at low risk for fluconazole resistant candidemia to receive empiric therapy with azoles and reduce use of echinocandins.
- Further studies are needed to evaluate utility in other populations and perform external validation.

Funding by:
Washington University Institute of Clinical and Translational Sciences grant UL1TR002345 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH).

Contact Information:
Adriana M. Rauseo, MD
660 S. Euclid Ave. Box 8051, St. Louis, MO 63110
a.rauseoacevedo@wustl.edu