Statin Therapy and Decreased Incidence of Positive *Candida* Cultures Among Patients With Type 2 Diabetes Mellitus Undergoing Gastrointestinal Surgery

ELIAS K. SPANAKIS, MD; THEMISTOKLIS K. KOURKOUMPETIS, MD; GRIGORIOS LIVANIS, PhD;
ANTON Y. PELEG, MD, PhD, MPH; ELEFTERIOS MYLONAKIS, MD, PhD

OBJECTIVE: To assess whether statin therapy decreases the incidence of cultures positive for *Candida* species among high-risk hospitalized patients with type 2 diabetes mellitus (DM).

PATIENTS AND METHODS: We performed a retrospective cohort study analyzing the records of all patients with type 2 DM who were admitted to Massachusetts General Hospital for lower gastrointestinal tract surgery between January 1, 2001, and May 1, 2008. We defined statin exposure as the filling of at least 1 prescription of statins during the 6 months before hospitalization or during the current hospital stay. The primary outcome was a culture positive for *Candida* species during hospitalization. Clinical information on a wide range of covariates was collected. Logistic regression analysis was used to adjust for possible confounders.

RESULTS: Of the 1019 patients who were eligible for the study, 493 (48%) were receiving statins. A total of 139 patients (14%) had at least 1 culture positive for *Candida* species during hospitalization. An adjusted multivariate model based on a backward stepwise elimination procedure showed that statin therapy significantly decreased the incidence of cultures positive for *Candida* species (odds ratio, 0.60; 95% confidence interval [CI], 0.38-0.96; $P=.03$) with a statistically significant prolonged time to event compared with no statin therapy (adjusted hazard ratio, 0.62; 95% CI, 0.44-0.88; $P=.01$). The benefit of statins was more prominent in patients with type 2 DM who had greater comorbidities (Charlson Comorbidity Index ≥ 2) (adjusted odds ratio, 0.47; 95% CI, 0.27-0.79; $P=.01$).

CONCLUSION: Among patients with type 2 DM who underwent gastrointestinal surgery, use of statins correlated with a decreased incidence of cultures positive for *Candida* species.

Mayo Clin Proc. 2010;85(12):1073-1079

AOR = adjusted odds ratio; CCI = Charlson Comorbidity Index; CI = confidence interval; CVC = central venous catheter; DM = diabetes mellitus; HR = hazard ratio; ICU = intensive care unit; LOS = length of hospital stay; OR = odds ratio

From the Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston (E.K.S., T.K.K., E.M.); Department of Internal Medicine, Caritas St Elizabeth's Medical Center, Boston MA (E.K.S.); College of Business Administration, Northeastern University, Boston, MA (G.L.); and Department of Infectious Diseases, Alfred Hospital, and Department of Microbiology, Monash University, Melbourne, Australia, and Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA (A.Y.P.).

Dr Mylonakis has received research support from Astellas Pharma US and was a member of the speaker's bureau for Pfizer. Dr Peleg has acted as an advisor to Abbott Molecular and Ortho-McNeil-Janssen. None of the funders was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Individual reprints of this article are not available. Address correspondence to Eleftherios Mylonakis, MD, PhD, Harvard Medical School, Massachusetts General Hospital, Division of Infectious Diseases, 55 Fruit St, Gray Jackson 5, Room GRJ-504, Boston, MA 02114-2696 (emylonakis@partners.org or espanakis@gmail.com [Dr Elias K. Spanakis]).

© 2010 Mayo Foundation for Medical Education and Research

Candida is a genus of opportunistic microorganisms that commonly colonize cutaneous and mucosal surfaces. However, when these anatomic barriers are disrupted or host immunity is compromised, life-threatening invasive infection can ensue.¹ *Candida* species are the fourth most common cause of hospital-acquired bloodstream infections, and the annual number of cases of sepsis caused by fungal organisms in the United States has more than doubled during the past few decades.^{2,3} The crude mortality of nosocomial candidemia has been reported to be greater than 60%, with an attributable mortality of greater than 30%.⁴ Because of the high morbidity and mortality of *Candida* infection, the emerging antifungal resistance among *Candida* species, and the considerable toxicities associated with antifungal therapy, novel methods for preventing infection with *Candida* species are required.

Statins are the most commonly prescribed lipid-lowering agents. More than 24 million Americans are estimated to be currently receiving statins, a significant increase from 1999-2000.⁵ Interestingly, statins may also have antifungal effects. Similarities exist between the cholesterol synthesis pathway in humans and the ergosterol pathway in fungi, with laboratory evidence indicating a direct effect of statins on *Candida* species.^{6,7} However, the clinical relevance of this finding is limited. The gastrointestinal tract represents the ultimate human reservoir for most *Candida* species,⁸ with prevalence rates of more than 21% in the human jejunum and colon.^{9,10} To study a population with a high prevalence of statin use and increased incidence of cultures positive for *Candida* species, we focused on patients with type 2 diabetes mellitus (DM), especially those who underwent abdominal operations involving the lower gastrointestinal tract.

PATIENTS AND METHODS

We conducted a retrospective cohort study to evaluate whether the use of statins was associated with a decreased incidence of cultures positive for *Candida* species among patients who were adult at the day of admission, had a diagnosis of type 2 DM (coded as 250 by *International Classification of Diseases, Ninth Revision*), and underwent lower gastrointestinal tract surgery (for coding details, see eDocument in Supporting Online Material, a link to which

TABLE 1. **Baseline Characteristics of Diabetic Patients Exposed or Not Exposed to Statin Therapy^{a,b}**

Characteristic	Statin group (n=493)	No-statin group (n=526)	P value
Charlson Comorbidity Index, median (IQR)	5 (3-8)	5 (2-7)	.07
Age (y), mean $\pm$ SD	67.83 $\pm$ 10.98	64.91 $\pm$ 13.67	<.001
Length of stay (d), median (IQR)	7 (4-13)	7 (4-13)	.52
Male sex	261 (52.9)	282 (53.6)	.83
White race	437 (88.6)	437 (83.1)	.01
HIV ⁺	1 (0.2)	1 (0.2)	.99
Intensive care unit stay	123 (24.9)	140 (26.6)	.54
Gastrointestinal perforation or anastomotic leak	105 (21.3)	118 (22.4)	.66
CRF	61 (12.4)	48 (9.1)	.09
CRF requiring hemodialysis	21 (4.3)	19 (3.6)	.63
Solid malignancy	279 (56.6)	299 (56.8)	.94
Hematologic malignancy	14 (2.8)	15 (2.9)	.99
Neutropenia	6 (1.2)	11 (2.1)	.33
Central venous catheter	142 (28.8)	166 (31.6)	.34
Foley catheter	461 (93.5)	483 (91.8)	.30
Tube feeding	104 (21.1)	128 (24.3)	.22
Total parenteral nutrition	60 (12.2)	76 (14.4)	.28
Medications			
Gastric suppressants	411 (83.4)	425 (80.8)	.28
Chemotherapeutic agents	36 (7.3)	67 (12.7)	.004
Corticosteroids	31 (6.3)	34 (6.5)	.91
Other immunosuppressants	21 (4.3)	22 (4.2)	.95
Antibiotics	277 (56.2)	294 (55.9)	.92
Diabetes management			
Diet	103 (20.9)	168 (31.9)	<.001
Oral antidiabetic agents	252 (51.1)	221 (42.0)	.004
Insulin	138 (28.0)	137 (26.0)	.49

^a CRF = chronic renal failure; HIV = human immunodeficiency virus; IQR = interquartile range.

^b Data are provided as number (percentage) of patients, unless otherwise indicated. Statistically significant P values appear in boldface.

is provided at the end of this article). All patients were admitted to Massachusetts General Hospital between January 1, 2001, and May 1, 2008. All patients who had received any antifungal treatment before the culture was obtained were excluded from the study.

We collected the data from each patient's electronic medical record, which included laboratory test results, radiographic imaging, medication records, and hospital notes. All patients also had a nonelectronic medical record file. The study protocol was approved by the Massachusetts General Hospital Institutional Review Board and was aligned with the principles of the Declaration of Helsinki. A waiver of informed consent was obtained.

DEFINITIONS OF STATIN EXPOSURE AND OUTCOME VARIABLES

We defined statin exposure as the filling of at least 1 prescription of statins during the 6 months before hospitalization or during the current hospital stay (including statins newly prescribed during the hospital stay). We also recorded the time (in days) to a culture positive for *Candida*

species and the type and dose of statins prescribed. All end points were monitored from the day of admission until discharge. Our primary outcome was at least 1 culture positive for *Candida* species as determined by reviewing all microbiological culture data obtained from each patient (from blood, urine, sputum, or peritoneal fluid) during hospitalization (eTable; Supporting Online Material, a link to which is provided at the end of this article). In our study, we made no distinction between colonization and infection. Thus, all patients who had a culture positive for *Candida* species, whether that represented an infection or colonization, were included in our study. Only patients with cultures positive for *Candida* species after the initiation of statin therapy were included in the statin-exposed group. The occurrence of a culture positive for *Candida* species, even if it represented simple colonization, has been repeatedly shown to be an independent risk factor for candidiasis, with reported odds ratios (ORs) as high as 10.37.^{11,12} Furthermore, it is associated with increased length of hospital stay (LOS) and increased health care costs among critically ill patients.¹³ Secondary outcomes were (1) incidence of cultures positive for *Candida* species in patients with a higher Charlson score,¹⁴ (2) differences in the incidence of a culture positive for *Candida* species between patients who were receiving statins on admission but discontinued them during hospitalization and patients who continued receiving statins during their hospital stay, and (3) differences in the incidence of a culture positive for *Candida* species between patients receiving different types of statins or different doses.

COVARIATES

Detailed clinical information was obtained for baseline characteristics (Table 1), including Charlson Comorbidity Index (CCI), a widely accepted and validated method for quantifying the comorbidities of every patient¹⁵; patient demographics (age, sex, and race); LOS; history of human immunodeficiency virus infection; admission to an intensive care unit (ICU); gastrointestinal perforation or anastomotic leak (as a reason for hospital admission or as a complication); chronic renal failure requiring or not requiring dialysis; underlying solid or hematologic malignancy; neutropenia (defined as neutrophil count <500/ μ L for at least 72 hours); presence of a central venous catheter (CVC) or Foley catheter; administration of enteral tube feeding or total parenteral nutrition; use of gastric acid-suppressing drugs at the date of admission; chemotherapeutic drugs in the past 6 months; corticosteroid use (defined as use of 10 mg of prednisone or equivalent a day for at least 14 days before admission); receipt of immunosuppressants other than corticosteroids in the preceding 6 months (≥ 1 dose of chemotherapy qualified);

and systemic antibiotic use for at least 72 hours. Regarding diabetes management, patients were further categorized according to treatment with diet, oral antidiabetic agents, or insulin.

STATISTICAL ANALYSES

Continuous variables are presented as mean $\pm$ SD and were compared between groups using a *t* test for normally distributed variables (assessed through the use of the Kolmogorov-Smirnov test). Nonnormally distributed continuous variables are presented as medians with interquartile ranges and were compared between groups using the nonparametric Mann-Whitney test. Dichotomous variables were compared between groups using χ^2 analysis or the Fisher exact test (when appropriate). Differences were assessed with 2-sided tests and an α level of 0.05.

This was an observational study, so the investigators had no control over which patients received statins and which did not. As a result, significant differences on important demographic and comorbidity variables were likely to occur, which could have led to a biased estimate of the effect of statin exposure on our primary and secondary end points. Therefore, we conducted an adjusted multivariate logistic regression analysis on the basis of a backward stepwise elimination procedure. We first conducted univariate analysis to examine the association between the occurrence of the end point of interest (dependent variable was any culture positive for *Candida* species) and independent variables, such as demographic and comorbidity characteristics of the patients (Table 1).

All variables with a *P* value less than or equal to .20 in the univariate analysis (Table 2) were entered into the backward stepwise multivariate logistic regression model, except for the oral and insulin diabetes management variables to prevent overfitting of the model. However, results are robust to different specifications (eg, incorporating the 2 diabetes management variables). In the multivariate model, variables were selected by a backward stepwise elimination procedure using a *P* value of .05 as a removal criterion) that also addresses potential issues with multicollinearity. For robustness, we also used a *P* value of .10 as the removal criterion, but the results did not change. Adjusted ORs (AORs) and 95% confidence intervals (CIs) were calculated for all independent predictors. All *P* values were 2-sided, and *P* < .05 was considered statistically significant.

Finally, we performed time-to-event analyses to explore whether patients with diabetes who were exposed to statins exhibited shorter time to an in-hospital culture positive for *Candida* species than patients without statin exposure. Survival time was measured from hospital admission and censored at hospital discharge. A Cox proportional hazards model was used to determine crude hazard ratios (HRs)

TABLE 2. Patient Characteristics and Univariate Analysis for Factors Associated With a Culture Positive for *Candida* Species^{a,b}

Characteristic	Positive (<i>Candida</i>) culture (n=139)	Negative (<i>Candida</i>) culture (n=880)	<i>P</i> value
Age (y), mean $\pm$ SD	67.60 $\pm$ 13.35	66.12 $\pm$ 12.38	.22
Length of stay (d), median (IQR)	22 (11-47)	6 (4-10.75)	<.001
Statin exposure	56 (40.3)	437 (49.7)	.04
HIV ⁺	0 (0.0)	2 (0.2)	.99
Intensive care unit stay	98 (70.5)	165 (18.8)	<.001
Male sex	70 (50.4)	473 (53.8)	.47
Corticosteroids	20 (14.4)	45 (5.1)	<.001
Other immunosuppressants	4 (2.9)	39 (4.4)	.50
Chemotherapeutic agents	7 (5.0)	96 (10.9)	.03
Gastrointestinal perforation	38 (27.3)	185 (21.0)	.09
CRF	29 (20.9)	80 (9.1)	<.001
CRF requiring hemodialysis	18 (12.9)	22 (2.5)	<.001
Neutropenia	4 (2.9)	13 (1.5)	.27
Central venous catheter	112 (80.6)	196 (22.3)	<.001
Foley catheter	132 (95.0)	812 (92.3)	.29
Tube feeding	79 (56.8)	153 (17.4)	<.001
Gastric suppressants	133 (95.7)	703 (79.9)	<.001
Total parenteral nutrition	66 (47.5)	70 (8.0)	<.001
Antibiotics	130 (93.5)	441 (50.1)	<.001
Solid malignancy	40 (28.8)	538 (61.1)	<.001
Hematologic malignancy	2 (1.4)	27 (3.1)	.41
White race	116 (83.5)	758 (86.1)	.40
Diabetes management			
Diet	39 (28.1)	232 (26.4)	.68
Oral antidiabetic agents	45 (32.4)	428 (48.6)	<.001
Insulin (any combination)	55 (39.6)	220 (25.0)	.001
Charlson Comorbidity Index, median (IQR)	6 (3-8)	5 (3-7)	.29

^a CRF = chronic renal failure; HIV = human immunodeficiency virus; IQR = interquartile range.

^b Data are provided as number (percentage) of patients, unless otherwise indicated. Statistically significant *P* values appear in boldface.

and 95% CIs. Furthermore, a multivariate Cox proportional hazards model was evaluated to assess the effect of baseline characteristics on the association of statin exposure and a culture positive for *Candida* species. Specifically, all variables in Table 2 with a *P* value less than .20 were entered into the model (except for LOS, which was used as the dependent variable for the patients who did not have a culture positive for *Candida* species, and the oral and insulin diabetes management variables), and then a backward stepwise Cox proportional hazards procedure with .05 removal criterion based on a likelihood ratio test was used to select the variables (results are robust to using a *P* value of .10 as the removal criterion and to incorporating the 2 diabetes management variables). The proportional hazards assumption was confirmed by the Schoenfeld residual test,¹⁶ and survival curves for patients with a culture positive for *Candida* species were generated from unadjusted and adjusted Cox models. All statistical analyses were performed with SPSS, version 17.0 (SPSS, Chicago, IL).

RESULTS

FIGURE 1. Flow chart of patients included in and excluded from the study. DM = diabetes mellitus; GI = gastrointestinal.

During the 8-year study period, 1138 patients were identified as being eligible for study entry. Of these, 119 were excluded for insufficient data ($n=26$) or for coding errors because they had a diagnosis of diabetes other than type 2 ($n=32$), did not have a lower gastrointestinal tract operation ($n=24$), were younger than 18 years ($n=3$), or had received systemic antifungal exposure before the positive culture ($n=34$) (Figure 1). The characteristics of the 1019 patients included in the study are shown in Table 1.

A total of 493 patients (48.4%) were included in the statin-exposed group. Characteristics were similar between patient groups, with a few exceptions. Statin-exposed patients were more likely to be older and white and to manage their diabetes with oral hypoglycemic agents. In contrast, patients not exposed to statins were more likely to have a history of chemotherapy and to manage their diabetes by diet alone. No significant differences in the level of comorbidities were observed between groups. Of the 493 statin-exposed patients, 333 (67.5%) received atorvastatin, followed by simvastatin (20.1%), pravastatin (6.1%), lovastatin (2.6%), fluvastatin (2.4%), and rosuvastatin (1.2%). For patients receiving atorvastatin, the median dose was 20 mg (interquartile range, 5-40 mg).

Of the 1019 patients, 139 (13.6%) developed at least 1 culture positive for *Candida* species during their hospital stay (Table 3). Fifty-six (40.3%) of the 139 patients were receiving statin therapy and 83 (59.7%) were not. On univariate analysis, statin exposure was significantly protective against the development of a culture positive for *Candida* species in this high-risk population (OR, 0.68; 95% CI, 0.47-0.98; $P=.04$) (Table 3). Other covariates, including established risk factors for a culture positive for *Candida* species, were also investigated (Table 2). Included in the univariate analysis were LOS ($P<.001$), ICU stay ($P<.001$), corticosteroid use ($P<.001$), chronic renal fail-

TABLE 3. Impact of Statins on Primary and Secondary End Points^{a,b,c}

Outcomes	Statin (n=493)	No statin (n=526)	Unadjusted analysis		Adjusted analysis	
			P value	OR (95% CI)	P value	AOR (95% CI)
Primary outcome						
Culture positive for <i>Candida</i> species (n=139)	56 (40.3)	83 (59.7)	.04	0.68 (0.47-0.98)	.03	0.60 (0.38-0.96)
Secondary outcomes						
Patients with Charlson score ≥ 2	n=401	n=392				
Culture positive for <i>Candida</i> species (n=105)	43 (41.0)	62 (59.0)	.04	0.64 (0.42-0.97)	.01	0.47 (0.27-0.79)
Patients with Charlson score <2	n=92	n=134				
Culture positive for <i>Candida</i> species (n=34)	13 (38.2)	21 (61.8)	.75	0.88 (0.42-1.87)	.22	2.07 (0.64-6.72)

^a AOR = adjusted odds ratio; CI = confidence interval; OR = (unadjusted) odds ratio.

^b Data are provided as number (percentage) of patients, unless otherwise indicated. Statistically significant P values appear in boldface.

^c The Hosmer-Lemeshow goodness-of-fit test (χ^2 -test statistic, 7.68; degrees of freedom, 8; $P=.47$).

ure requiring or not requiring dialysis (in both subgroups, $P<.001$), CVC placement ($P<.001$), tube feeding ($P<.001$), use of gastric suppressant agents ($P<.001$), total parenteral nutrition ($P<.001$), prior antibiotic use ($P<.001$), and insulin therapy ($P=.001$). It is interesting to note that patients with a medical history of chemotherapy, solid malignancy, or use of oral antidiabetic agents were less likely to develop a culture positive for *Candida* species. However, in the backward stepwise multivariate model subsequently described, in addition to statins, only a history of underlying solid malignancy was significantly associated with decreased incidence of cultures positive for *Candida* species, a result which should be further explored in future studies.

To determine whether statin therapy was protective against the development of a culture positive for *Candida* species, we used a backward stepwise multivariate logistic regression model, showing that statin therapy decreased the incidence of a culture positive for *Candida* species (AOR, 0.60; 95% CI, 0.38-0.96; $P=.03$), with a 40% reduction in the incidence of a culture positive for *Candida* species (Table 3). Increased LOS (AOR, 1.05; 95% CI, 1.03-1.07; $P<.001$), ICU stay (AOR, 2.13; 95% CI, 1.24-3.66; $P=.01$), presence of a CVC (AOR, 3.24; 95% CI, 1.82-5.78; $P<.001$), and use of systemic antibiotics (AOR, 2.98; 95% CI, 1.39-6.42; $P=.01$) were also independent predictors of a culture positive for *Candida* species (Table 4). Of note, a history of solid malignancy was associated with a statistically significant 62% reduction in the development of a culture positive for *Candida* species (AOR, 0.38; 95% CI, 0.24-0.61; $P<.001$).

We also performed a backward stepwise Cox proportional hazards regression model, showing that patients exposed to statins were less likely to have a shorter time to a culture positive for *Candida* species when compared with patients not exposed to statins (crude HR, 0.68; 95% CI, 0.48-0.96; $P=.03$). In the backward stepwise adjusted multivariate model, patients exposed to statins had a decreased incidence of a culture positive for *Candida* species compared with patients not exposed to statins (adjusted HR, 0.62; 95% CI, 0.44-0.88; $P=.01$). A time-to-event curve, representative of adjusted Cox models, is shown in Figure 2.

It is interesting to note that the benefit of statins on reducing the incidence of a culture positive for *Candida* species was more pronounced among patients with a higher CCI (Table 3). Of the 793 patients (78%) with a CCI greater than 2 (moderate to severe risk), statin exposure was associated with a 53% reduction in the incidence of in-hospital cultures positive for *Candida* species (AOR, 0.47; 95% CI, 0.27-0.79; $P=.01$). The 226 patients (22%) with CCI less than or equal to 2 demonstrated no difference in the development of a culture positive for *Candida* species, regardless of whether they were receiving statins (AOR, 2.07; 95% CI, 0.64-6.72; $P=.22$).

TABLE 4. Independent Predictors of Positive *Candida* Culture From Multivariate Logistic Regression Analysis^{a,b}

Independent variable	P value ^c	AOR (95% CI)
Statins	.03	0.60 (0.38-0.96)
Length of hospital stay	<.001	1.05 (1.03-1.07)
Intensive care unit stay	.01	2.13 (1.24-3.66)
Central venous catheter	<.001	3.24 (1.82-5.78)
Antibiotics	.01	2.98 (1.39-6.42)
Solid malignancy	<.001	0.38 (0.24-0.61)

^a AOR = adjusted odds ratio; CI = confidence interval.

^b The Hosmer-Lemeshow goodness-of-fit test (χ^2 -test statistic, 7.68; degrees of freedom, 8; $P=.47$).

^c Statistically significant P values appear in boldface.

We also examined whether the discontinuation of statin therapy had any impact on the protective antifungal effect of statins, comparing patients whose statins were discontinued with patients who continued to receive statins after hospital admission. Multivariate logistic regression analysis showed no differences when we restricted the sample to statin users who were taking statins before hospitalization and to users who were taking statins before and during hospitalization ($n=469$). This finding suggests that patients who were taking statins and had their prescription discontinued on admission had no difference in the incidence of a culture positive for *Candida* species, compared with patients who were taking statins before and continued their prescription during hospitalization (AOR, 1.54; 95% CI, 0.64-3.72; $P=.34$).

We also investigated whether the beneficial effect of statins was dose-related. We focused our analysis on atorvas-

FIGURE 2. Time-to-event curve comparing the risk of a culture positive for *Candida* species between patients with vs without statin exposure (adjusted Cox proportional analysis).

tatin-exposed patients because this was the most commonly prescribed statin (67.5%). No relationship between atorvastatin dose and development of a culture positive for *Candida* species was observed (OR, 0.93; 95% CI, 0.52-1.67; $P=.80$). When we repeated our analysis independently of statin dosage and assumed equal potency between statin types, we still found no dose-response relationship (OR, 1.00; 95% CI, 0.99-1.02; $P=.49$). We also assessed for any differences in the effect of statins on cultures positive for *Candida* species between statin types, regardless of dose, and again we found no significant differences (data not shown). Notably, this analysis was limited by small patient numbers in statin groups other than the atorvastatin group and was thus likely underpowered.

DISCUSSION

In this evaluation of a large cohort of 1019 patients with type 2 DM who had undergone a lower gastrointestinal tract operation, patients who were exposed to statins had a significantly lower chance of developing a culture positive for *Candida* species compared with patients who did not receive statins (AOR, 0.60; 95% CI, 0.38-0.96; $P=.03$), demonstrating a 40% relative reduction in the development of a culture positive for *Candida* species (Table 3). The benefit of statins was more pronounced among patients with greater comorbidities, defined by a Charlson score of 2 or greater,¹⁴ with a 53% reduction in the incidence of in-hospital cultures positive for *Candida* species ($P=.01$). It is important to note that the antifungal benefit persisted even after discontinuation of statin therapy on hospital admission. This finding indicates that statins probably require long-term use to achieve their anticandidal effect, which may persist for a considerable period of time after the discontinuation of statin therapy. Taken in their totality, these findings suggest that the antifungal benefit of statin therapy persists, allowing patients to attain this antifungal advantage even if they discontinue statins on hospital admission (for example, surgical patients who are unable to receive medications by mouth). Interestingly, no dose-response effect or differences among types of statins were observed, indicating that the antifungal benefit of statin therapy can be achieved with any type of statin, regardless of dose.

Our study focused on patients with type 2 DM because this group represents almost 8% of the population and, according to the Adult Treatment Panel III, patients with diabetes have a target low-density lipoprotein level of less than 100 mg/dL (to convert to mmol/L, multiply by 0.0259).¹⁷ This target is often difficult to achieve without the aid of a lipid-lowering drug, thus increasing the possibility of our patients' receiving statins. Because patients with type 2 DM have low-density lipoprotein targets that are difficult

to achieve with diet alone, statins represent a "standard of care" for most of these patients, and this was one of the reasons why we performed a retrospective study (approval for a prospective placebo-controlled trial is not feasible). In our study, we also found that increased LOS ($P<.001$), ICU stay ($P=.01$), CVC placement ($P<.001$), and use of antibiotics ($P=.01$) were independently associated with in-hospital development of a culture positive for *Candida* species (Table 4). These findings are confirmed by several previous studies assessing risk factors for nosocomial infection with *Candida* species.¹¹ Of note, a history of solid malignancy was associated with a statistically significant 62% reduction in the development of a culture positive for *Candida* species (AOR, 0.38; 95% CI, 0.24-0.61; $P<.001$), an effect that we could not justify and that should be further examined in future studies.

As previously discussed, statins have been shown to have a direct antifungal effect.⁶ Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by statins leads to a reduction of mevalonate and other intermediates, leading eventually to decreased levels of cholesterol in humans and possibly ergosterol in fungi. Ergosterol is an essential lipid component of fungal cell membranes and is the primary target for antifungal agents such as the polyenes and the azoles. In vitro studies have suggested that statins can inhibit the growth of several *Candida* species.¹⁸ Supplementation with ergosterol or cholesterol can rescue *Candida* growth in the presence of statins,¹⁹ and combination of statins with antifungal drugs has a synergistic effect against several *Candida* species.²⁰ Interestingly, statins also appear to have pleiotropic effects, and several clinical studies have suggested that statins may improve outcomes in patients with bacterial infections, which may be partially explained by their anti-inflammatory properties.²¹ Statins reduced the risk of subsequent sepsis among patients hospitalized for acute coronary syndrome or ischemic stroke²²; in patients with sepsis²³ or bacteremia,²⁴ statins reduced the severity of sepsis or decreased overall mortality. A recently published review summarizes these findings and concludes that statins are effective in patients with sepsis or at risk of sepsis, community-acquired pneumonia, or bacteremia and can also serve as a preventive measure for infections in the postoperative period.²⁵

More specifically, in addition to the inhibition of the ergosterol synthesis pathway, statins may elicit immunomodulatory effects in the host, affecting multiple components of adaptive immune response.²⁶ Statins have been repeatedly shown to reduce high-sensitivity C-reactive protein levels in large cohorts of patients,²⁷ and our results may be at least partially explained by their effect on the adaptation of the immune and inflammatory pathways.

Although our study expands our knowledge of the pleiotropic effects of statins, it has certain limitations. Because

of the retrospective design, the single-center setting, and the particular population of patients with type 2 DM undergoing gastrointestinal surgery, our findings cannot be safely generalized to the general population. However, prospective interventional studies could be difficult to accomplish and, given the proven benefit of statins, an assignment to a control group receiving placebo could raise important ethical issues. A study involving a more generalized segment of the population would most likely validate our findings.

A recently published retrospective matched cohort study examined the effect of statins on mortality rate in 45 patients with documented candidemia.²⁸ Patients who were receiving statins had lower mortality rate in the bivariate model (OR, 0.09; 95% CI, 0.11-0.75; $P=.03$) but not in the multivariate model (OR, 0.22; 95% CI, 0.02-2.4; $P=.21$). Limitations of this study include its small size and retrospective nature. Although the group of patients who were receiving statins in this study had increased incidence of coronary artery disease ($P<.01$) and peripheral vascular disease ($P=.03$), they appeared to be healthier, as evidenced by lower Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ($P=.03$). Finally, the purpose of the study by Forrest et al²⁸ was quite different from ours. Forrest et al focused on the general effect of statins on mortality rates in patients with already documented candidemia, whereas we focused on the effect of statins in the development of a culture positive for *Candida* species.

CONCLUSION

Among patients with type 2 DM who underwent gastrointestinal surgery, use of statins reduced the incidence of a culture positive for *Candida* species, and that effect was more pronounced in patients with a CCI of 2 or greater. These clinical results corroborate in vitro data and expand our knowledge of the potent beneficial effects of statins. Our findings could potentially be applied to other patient groups. Clinicians should review the need for statin therapy either as a preventive measure for *Candida* colonization or infection or perhaps as a combination therapy with antifungal agents, especially among patients at high risk for candidiasis. However, randomized controlled trials are needed to support this notion.

REFERENCES

1. Cole GT, Halawa AA, Anaissie EJ. The role of the gastrointestinal tract in hematogenous candidiasis: from the laboratory to the bedside. *Clin Infect Dis*. 1996;22(suppl 2):S73-S88.
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.
3. Hospital Infections Program; National Center for Infectious Diseases; Centers for Disease Control and Prevention (CDC); Public Health Service; US Dept of Health and Human Services (DHS). National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990-May 1999, issued June 1999. *Am J Infect Control*. 1999;27(6):520-532.
4. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis*. 2003;37(9):1172-1177.

5. Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines. *Ann Pharmacother*. 2008;42(9):1208-1215.
6. Sun HY, Singh N. Antimicrobial and immunomodulatory attributes of statins: relevance in solid-organ transplant recipients. *Clin Infect Dis*. 2009;48(6):745-755.
7. Parks LW, Casey WM. Physiological implications of sterol biosynthesis in yeast. *Annu Rev Microbiol*. 1995;49:95-116.
8. Krause W, Matheis H, Wulf K. Fungaemia and funguria after oral administration of *Candida albicans*. *Lancet*. 1969;1(7595):598-599.
9. Cohen R, Roth FJ, Delgado E, Ahearn DG, Kalser MH. Fungal flora of the normal human small and large intestine. *N Engl J Med*. 1969;280(12):638-641.
10. Stone HH, Geheber CE, Kolb LD, Kitchens WR. Alimentary tract colonization by *Candida albicans*. *J Surg Res*. 1973;14(4):273-276.
11. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia: a matched case-control study. *Arch Intern Med*. 1989;149(10):2349-2353.
12. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. *Ann Surg*. 1994;220(6):751-758.
13. Olachea PM, Palomar M, Leon-Gil C, et al. Economic impact of *Candida* colonization and *Candida* infection in the critically ill patient. *Eur J Clin Microbiol Infect Dis*. 2004;23(4):323-330.
14. Santos Arrontes D, Fernandez Acenero MJ, Garcia Gonzalez JJ, Martin Munoz M, Paniagua Andres P. Survival analysis of clear cell renal carcinoma according to the Charlson comorbidity index. *J Urol*. 2008;179(3):857-861.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
16. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):293-241.
17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.
18. Wikke K, Westermeyer C, Macreadie IG. Biological consequences of statins in *Candida* species and possible implications for human health. *Biochem Soc Trans*. 2007;35(pt 6):1529-1532.
19. Macreadie IG, Johnson G, Schlosser T, Macreadie PI. Growth inhibition of *Candida* species and *Aspergillus fumigatus* by statins. *FEMS Microbiol Lett*. 2006;262(1):9-13.
20. Chin NX, Weitzman I, Della-Latta P. In vitro activity of fluvastatin, a cholesterol-lowering agent, and synergy with fluconazole and itraconazole against *Candida* species and *Cryptococcus neoformans*. *Antimicrob Agents Chemother*. 1997;41(4):850-852.
21. McFarlane SI, Muniyappa R, Francisco R, Sowers JR. Clinical review 145: pleiotropic effects of statins: lipid reduction and beyond. *J Clin Endocrinol Metab*. 2002;87(4):1451-1458.
22. Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. *Lancet*. 2006;367(9508):413-418.
23. Martin CP, Talbert RL, Burgess DS, Peters JI. Effectiveness of statins in reducing the rate of severe sepsis: a retrospective evaluation. *Pharmacotherapy*. 2007;27(1):20-26.
24. Kruger P, Fitzsimmons K, Cook D, Jones M, Nimmo G. Statin therapy is associated with fewer deaths in patients with bacteraemia. *Intensive Care Med*. 2006;32(1):75-79.
25. Kopterides P, Falagas ME. Statins for sepsis: a critical and updated review. *Clin Microbiol Infect*. 2009;15(4):325-334.
26. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol*. 2006;6(5):358-370.
27. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286(1):64-70.
28. Forrest GN, Kopack AM, Perencevich EN. Statins in candidemia: clinical outcomes from a matched cohort study. *BMC Infect Dis*. 2010;10:152.

Supporting Online Material

www.mayoclinicproceedings.com/content/85/12/1073/suppl/DC1
eDocument
eTable