Received: 6 April 2017 | Revised: 5 August 2017 | Accepted: 7 August 2017

DOI: 10.1111/myc.12680

ORIGINAL ARTICLE

WILEY mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Role of oral nystatin prophylaxis in cardiac surgery with prolongedextracorporeal circulation

Alessandro Russo[1] | Giovanni Carriero[2] | Alessio Farcomeni[1] | Giancarlo Ceccarelli[1] | Luigi Tritapepe[2] | Mario Venditti[1]

[1]Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Rome, Italy

[2]Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, "Sapienza" University of Rome, Rome, Italy

Correspondence
Prof. Mario Venditti, Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Rome, Italy.
Email: mario.venditti@uniroma1.it

Summary

Duration >120 minutes of extracorporeal circulation (ECC) during cardiopulmonary bypass procedure was associated to an increased risk of candidemia in the intensive care unit (ICU). To evaluate oral nystatin prophylaxis in cardiac surgery considering its exclusive effect on *Candida*, in the absence of systemic effects and selection of resistant strains to polyene. We conducted an observational study in the postcardiac surgery ICU of Policlinico "Umberto I" of Rome. From January 2014, all patients with a prolonged ECC >120 minutes were systematically treated with oral nystatin (Prophylaxis group). This group was compared with all patients hospitalised in the same ICU, who have not received oral nystatin after ECC >120 minutes (No prophylaxis group). Overall, 672 consecutive patients were analyzed: 318 (47.3%) patients belonged to the no prophylaxis group, and 354 (52.7%) patients to the prophylaxis group. Diagnosis of candidemia was confirmed in 7 (2.2%) patients, all belonged to the no prophylaxis group. At multivariate analysis, oral nystatin prophylaxis showed a protective effect for development of candidemia after cardiac surgery. Oral nystatin prophylaxis, in patients who underwent a ECC >120 minutes, seems to reduce development of candidemia; however, the real efficacy of such prophylaxis approach requires further investigation.

KEYWORDS

candidemia, extracorporeal circulation, heart surgery, nystatin, prophylaxis

1 | INTRODUCTION

The incidence of nosocomial candidemia in the intensive care unit (ICU) has dramatically increased in the last 10 years and now it is considered one of the most frequent infections in this setting.[1,2] In European cardiothoracic ICUs, *Candida* spp. was the fourth most common isolate with attributable mortality of 40%-50%, prolonged ICU stay, and increased costs for medical care.[3] Several risk factors have been evaluated but patients undergoing cardiac surgery were recognised as a specific population at risk of postsurgery infective complications[4]; moreover, >120 minutes of extracorporeal circulation (ECC) during cardiopulmonary bypass procedure was associated to an increased risk of candidemia and candidemia-related death.[3,5]

Colonisation by *Candida* spp. is the main risk factor for development of candidemia when risk factors, especially surgical procedures, can promote intestinal translocation and haematogenous dissemination.[6] Studies have focused on the degree of intestinal colonisation and oral nystatin in prophylaxis was previously proposed in the ICU setting[7,8]; the advantage of oral nystatin use is the exclusive effect on *Candida*, in the absence of systemic effects and selection of resistant strains to polyene.

This study represents a preliminary evaluation about the impact of oral nystatin prophylaxis on development of candidemia in ICU patients undergoing cardiac surgery with an ECC >120 minutes.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted an observational study in the postcardiac surgery ICU of Policlinico "Umberto I" in Rome, a 1200-bed teaching hospital in Italy, during the period from January 2012 to December 2015. In the period from January 2012 to December 2013 episodes of candidemia were observed exclusively in patients with a ECC >120 minutes. On this basis, from January 2014 all patients with a prolonged ECC >120 minutes were systematically treated with oral nystatin 500 000 U.I. × 4 times/day for 5 days (Prophylaxis group), according to an internal protocol. This group was compared with all patients hospitalised in the same ICU form January 2012 to December 2013 who had not received oral nystatin after ECC >120 minutes (No prophylaxis group). According to local ethical committee rules, an informed consent was not obtained from enrolled patients.

Data were extracted from medical charts and included: demographics (age and gender), comorbidities, the European system for cardiac operative risk evaluation (EuroSCORE) II, the additive EuroSCORE and the logistic EuroSCORE, laboratory and cardiac findings, duration of ECC (>120 or >180 minutes), incidence of early candidemia, simplified acute physiology score (SAPS II), length of ICU stay (in days), outcome.

All patients were followed up to death or to 1 month after heart surgery.

2.2 | Definitions

Candidemia was defined as the isolation of *Candida* spp. in one or more separate blood cultures with clinical evidence of infection. An early candidemia was defined as a postoperative isolation of *Candida* spp. from blood within 1 month after surgical procedure. Time to candidemia was considered the time between cardiac surgery and diagnosis of candidemia.

2.3 | Study endpoint and statistical analysis

The primary endpoint was analysis of factors independently associated with development of candidemia.

The binary outcome has been analyzed by means of univariate and multivariate logistic regression models. Given the low number of events, Firth bias-correction was used to reduce bias of parameter estimates. The final multivariate model was chosen using a forward stepwise algorithm based on Takeuchi Information Criterion. The results obtained were analysed, using commercially available statistical software packages (SPSS, version 20.0; SPSS Inc., Chicago, IL, USA and R version 3.1.2; R Development Core Team, Vienna, Austria).

TABLE 1 Baseline characteristics of overall population and study groups

Variables	No prophylaxis group, N = 318 (%)	Prophylaxis group, N = 354 (%)	Overall population, N = 672 (%)
Age, mean (±SD)	65.7 ± 12.3	66.2 ± 11.7	66 ± 12
Male sex	180 (56.6)	218 (61.5)	398 (59.2)
COPD	37 (11.6)	32 (9)	69 (10.2)
Diabetes	83 (26.1)	77 (21.7)	160 (23.8)
Chronic renal disease	31 (9.7)	17 (4.8)	48 (7.1)
ECC >120 min	218 (68.6)	235 (66.4)	453 (67.5)
ECC >180 min	100 (31.4)	119 (33.6)	219 (32.5)
Additive EuroSCORE, mean (±SD)	6.1 ± 2.9	6.4 ± 3.4	6.3 ± 3.2
Logistic EuroSCORE, mean (±SD)	8.4 ± 8	27.2 ± 2.2	18.3 ± 16.5
EuroSCORE II, mean (±SD)	4.1 ± 0.5	6.4 ± 2.2	5.3 ± 1.7
PaO_2/FiO_2 ratio at admission in ICU, mean (±SD)	306.4 ± 142.4	287.1 ± 143.7	295.3 ± 144
LVEF <30%	71 (22.3)	96 (27.1)	167 (24.8)
Preoperative serum creatinine (mg/dL), mean (±SD)	1.7 ± 0.5	2.9 ± 1.5	2.5 ± 1.9
Preoperative HT level, mean (±SD)	37.6 ± 9.2	37.1 ± 3.3	37.2 ± 2.4
SAPS II score, mean (±SD)	35.9 ± 8.9	34.7 ± 13.9	35.3 ± 11.9
Length of ICU stay, mean (±SD)	5.3 ± 3.8	4.4 ± 3.3	4.9 ± 3.6
Candidemia	7 (2.2)	0	7 (1)
Time to candidemia, d	9.1 ± 7	—	9.1 ± 7
In-ICU mortality	11 (3.4)	12 (3.4)	23 (3.4)

SD, standard deviation; COPD, chronic obstructive pulmonary disease; ECC, extracorporeal circulation; EuroSCORE, European system for cardiac operative risk evaluation; ICU, intensive care unit; LVEF, left ventricular ejection fraction; HT, hematocrit level; SAPS, simplified acute physiology score.

TABLE 2 Characteristics of patients with extracorporeal circulation (ECC) >120 minutes and postsurgery candidemia

Aetiology	Type of surgery	ECC >180 min	Nystatin prophylaxis	Outcome
Candida albicans	Aortic valve replacement	No	No	Survived
Candida albicans	Coronary artery bypass grafting	No	No	Survived
Candida albicans	Coronary artery bypass grafting	No	No	Survived
Candida albicans	Coronary artery bypass grafting + mitral valve replacement	Yes	No	Dead
Candida parapsilosis	Aortic root replacement	Yes	No	Survived
Candida albicans	Prosthesis for abdominal aortic dissection	No	No	Survived
Candida sake Candida glabrata	Mitral valve replacement	Yes	No	Dead

TABLE 3 Univariate and multivariate analysis about predictors of postsurgery candidemia

	Univariate analysis			Multivariate analysis		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
Age (per y)	0.98	0.93-1.04	.49			
COPD	0.5	0.004-4.11	.6			
Diabetes	3.25	0.83-12.7	.09			
Chronic renal disease	5.12	0.92-20.68	.06			
Additive EuroSCORE	1.19	0.96-1.42	.1			
Logistic EuroSCORE	1.03	0.99-1.07	.13			
EuroSCORE II	1.05	0.99-1.10	.07			
PaO_2/FiO_2 ratio at admission in ICU	0.99	0.99-1.004	.65			
LVEF <30%	0.94	0.87-1.003	.06			
Preoperative serum creatinine (mg/dL)	1.15	0.004-1.34	.26			
Preoperative HT level	0.96	0.88-1.08	.47			
SAPS II score	1.1	1.04-1.17	.004	1.11	1.03-1.2	.03
Nystatin prophylaxis	0.24	0.02-0.81	.02	0.06	0.01-0.58	.01

COPD, chronic obstructive pulmonary disease; EuroSCORE, European system for cardiac operative risk evaluation; ICU, intensive care unit; LVEF, left ventricular ejection fraction; HT, hematocrit level, SAPS, simplified acute physiology score.

3 | RESULTS

Overall, 672 clinical charts of consecutive patients (hospitalised in post-cardiac surgery ICU) were analyzed in the study period: out of these, 318 (47.3%) patients belonged to the no prophylaxis group, and 354 (52.7%) patients to the prophylaxis group. Baseline characteristics of overall population and study groups are reported in Table 1: the mean age was 66 ± 12 years with a predominance of male sex (59.2%); out of cardiovascular diseases, diabetes (23.8%), chronic obstructive pulmonary disease (10.2%), and chronic renal disease (7.1%) were the comorbidities most frequently observed. The mean SAPS II score was 35.3 ± 11.9 points, while the mean logistic EuroSCORE was 18.3 ± 16.5%; moreover, the mean length of ICU stay was 4.9 ± 3.6. Finally, the overall in-ICU mortality was 3.4% with the same rates of death observed in the 2 study groups.

Diagnosis of candidemia was confirmed in 7 (2.2%) patients, all belonged to the no prophylaxis group. Time to candidemia was 9.1 ± 7 days, and characteristics of these patients are reported in Table 2. Finally, in-ICU mortality was observed in 2 (28.6%) out of 7 candidemic patients.

Univariate and multivariate analysis about predictors of postsurgery candidemia (see Table 3) showed that an increased SAPS II score was associated with increased risk of early postsurgery candidemia (OR 1.11, 95% CI 1.03-1.2, *P* = .03), while oral nystatin prophylaxis showed a protective effect for development of candidemia after cardiac surgery (OR 0.06, 95% CI 0.01-0.58, *P* = .01).

4 | DISCUSSION

There are few reports in the literature regarding the effective use of oral non-absorbable antifungal prophylaxis to prevent fungal infections. Many concerns remain about the use of azoles for prophylaxis, including the emergence of resistance among previously susceptible strains or isolation of non-albicans species (*C. glabrata* or *C. krusei*) with high incidence of resistance to azoles.[9] Moreover, no adverse effects of nystatin are reported and its low-cost makes the use highly cost-effective.[7] A meta-analysis of Ho et al[10] on critically ill patients demonstrated a significant reduction in urinary tract fungal infections,

and 2 other works considered the risk of *Candida* infection, with and without nystatin prophylaxis, in very low birth weight infants and patients with burn injury.[11,12] Giglio and coworkers showed that nystatin prophylaxis significantly reduces fungal colonisation in surgical/trauma ICU patients, even if already colonised, since colonisation can be observed on admission in up to 50% of ICU patients.[7]

Postsurgery candidemia is a relatively frequent complication during heart surgery, especially in patients who require more than 48 hours of mechanical ventilation.[5] Michalopoulos et al[3] reported that duration >120 minutes of cardiopulmonary bypass procedure was associated to an increased risk of candidemia and candidemia-related death. Pasero et al[5] confirmed a higher mortality (47%) in patients with postoperative candidemia 2 months after cardiac surgery, compared to patients who did not develop candidemia. In our analysis of a shorter follow-up period, we observed a mortality rate of 28.6% (2 out of 7 cases) in patients who developed an early postsurgery candidemia.

Candida spp. can coexist with the bacterial microbiome and grow during antibiotic perturbations of the microbiome, colonising the inflamed mucosa and disseminate into bloodstream. Most individuals are asymptomatically colonised with *Candida* spp. and, when environmental conditions permit the overgrowth of *Candida* spp., colonisation can lead to infection and invasion of host tissues.[13] Many studies have shown that prolonged damage of the intestinal mucosa might be directly correlated with *Candida* translocation.[3,14] Of interest, patients undergoing cardiac surgery were at higher risk for candidemia because prolonged duration of the surgical procedure is frequently associated with postoperative splanchnic hypoperfusion, leading to intestinal intramucosal acidosis and increased intestinal mucosal permeability.[14] Moreover, the ability of *Candida* spp. to adhere on surfaces with production of biofilm is another crucial virulence factor that might have severe clinical implications in our specific setting of patients with implanted medical devices, like central venous catheters, pacemakers, and mechanical or biological heart valves.[15]

This study has some important limitations: first, this is a single-centre experience and data may not be generalisable; second, data about *Candida* colonisation at time of ICU admission were not evaluated; third, a prolonged follow-up of these patients would provide more accurate information; finally, the observational design of the study cannot allow definitive conclusions and randomised trials should be necessary to validate these observations.

In conclusion, this study shows that oral nystatin prophylaxis in cardiosurgery patients who underwent an ECC >120 minutes significantly reduced development of early postsurgery candidemia, possibly due to a direct action on intestinal *Candida* colonisation. However, the assessment of the real efficacy of this prophylaxis approach requires further study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ORCID

A. Russo http://orcid.org/0000-0003-3846-4620
A. Farcomeni http://orcid.org/0000-0002-7104-5826
G. Ceccarelli http://orcid.org/0000-0001-5921-3180
L. Tritapepe http://orcid.org/0000-0003-0480-1705
Mario Venditti http://orcid.org/0000-0003-2639-0281

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How to cite this article: Russo A, Carriero G, Farcomeni A, Ceccarelli G, Tritapepe L, Venditti M. Role of oral nystatin prophylaxis in cardiac surgery with prolongedextracorporeal circulation. *Mycoses*. 2017;00:1-4. https://doi.org/10.1111/myc.12680