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LETTER

Bastiaan H. Wittekamp
David S. Y. Ong
Olaf L. Cremer
Marc J. M. Bonten

Nystatin versus amphotericin B to prevent and eradicate *Candida* colonization during selective digestive tract decontamination in critically ill patients

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B. H. Wittekamp and D. S. Y. Ong contributed equally to this work as co-first authors.

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Dear Editor,

Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) aim to eliminate potential pathogenic microorganisms, such as Gram-negative bacteria and yeasts, from the oropharynx and digestive tract of intensive care unit (ICU) patients [1–3]. Amphotericin B is mostly used as the antifungal component in SOD and SDD, but is increasingly difficult to acquire due to scarcity of raw materials and is also becoming increasingly expensive. Nystatin is a potential substitute as it is also effective against a broad range of fungi and not absorbed from the digestive tract [4]. However, the effects of both agents on *Candida* colonization and eradication in SDD have never been compared.

We performed a before–after study evaluating two subsequent changes in SDD in a 32-bed medical-surgical ICU in the Netherlands. All patients admitted for 48 h or longer (i.e., eligible to receive SDD until discharge from the ICU) and who did not receive systemic antifungal therapy were included in the analysis. The local ethics committee waived the need for informed consent.

There were three study periods (Table S1): period 1 (16 months), SDD treatment included (q.d.s.) application of a mouth paste containing 2 % polymyxin E, 2 % tobramycin and 2 % amphotericin B, administration (q.d.s) of a suspension with the same components (100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B) through the nasogastric tube, and the systemic administration (q.d.s.) of cefotaxime during the first 4 days of ICU admission (Am/Am); period 2 (17 months), nystatin (2 × 10^6 units per dose) replaced amphotericin B in the enteral solution only (Am/Nys); period 3 (10 months), nystatin replaced amphotericin B in both the oropharyngeal paste and enteral solution (Nys/Nys).

From 1468 patients at least two rectum surveillance cultures were available, 1095 (75 %) were not colonized at the start of ICU admission and *Candida* acquisition in the rectum was analyzed. Patients' characteristics are on Table S2. Compared to the reference period (i.e., Am/Am) and after adjustment for baseline imbalances in a Cox regression analysis,

Table 1 Effectiveness of nystatin versus amphotericin B in preventing *Candida* acquisition and achieving decolonization

	Number of events/number of patients	Crude hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)
Candida acquisition in rectum			
Am/Am (reference group, period 1)	80/441	1	1
Am/Nys (period 2)	62/415	0.75 (0.54–1.05)	0.74 (0.53–1.03)[a]
Nys/Nys (period 3)	24/239	0.53 (0.33–0.83)	0.52 (0.33–0.83)[a]
Candida acquisition in sputum			
Am/Am (reference group, period 1)	61/295	1	1
Am/Nys (period 2)	79/215	1.23 (0.88–1.72)	1.21 (0.86–1.70)[b]
Nys/Nys (period 3)	31/156	0.87 (0.57–1.33)	0.85 (0.55–1.31)[b]
Candida decolonization in rectum			
Am/Am (reference group, period 1)	59/127	1	1
Am/Nys (period 2)	84/150	1.23 (0.88–1.72)	1.22 (0.87–1.70)[c]
Nys/Nys (period 3)	57/96	1.71 (1.19–2.48)	1.70 (1.18–2.45)[c]

[a] Covariables selected for multivariable analysis were APACHE IV score, diabetes mellitus, hypertension, immune deficiency and body mass index. Immune deficiency was defined as use of immunosuppressive medication (prednisone 0.1 mg/kg for at least 3 months, prednisone 75 mg/day during at least 1 week, or equivalent), chemotherapy/radiotherapy in the year preceding intensive care unit admission, and a known humoral or cellular immune deficiency

[b] Covariables selected for multivariable analysis were body mass index and COPD

[c] Covariables selected for multivariable analysis were gender, body mass index and corticosteroid use (a daily dose >100 mg hydrocortisone or equivalent)

the hazard ratios (HR) for acquisition of *Candida* colonization in the intestinal tract were 0.74 (95 % CI 0.53–1.03) during Am/Nys and 0.52 (95 % CI 0.33–0.83) during Nys/Nys (Table 1). After adjustment for baseline imbalances, the HR for decolonization of *Candida* in the rectum was 1.70 (95 % CI 1.18–2.45) during Nys/Nys (Table 1). In the 1378 patients with at least two sputum surveillance cultures available, acquisition rates of *Candida* in the respiratory tract were not significantly different in the three study periods (Table 1).

None of the included patients acquired candidemia, and the numbers of patients with at least one episode of bacteremia were 15.0, 14.2 and 17.7 per 1000 patient days for period 1, 2 and 3, respectively (Table S1).

In SDD, nystatin was more effective than amphotericin B in eradicating *Candida* from the rectum and preventing rectal *Candida* colonization, and is not inferior to amphotericin B in preventing *Candida* respiratory tract colonization. Nystatin use will improve the cost-effectiveness of SDD and SOD.

Compliance with ethical standards

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References

1. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS et al (2009) Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 360:20–31
2. de Jonge E, Schultz MJ, Spanjaard L, Bossuyt PM, Vroom MB, Dankert J et al (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 362:1011–1016
3. Ong DS, Klein Klouwenberg PM, Spitoni C, Bonten MJ, Cremer OL (2013) Nebulised amphotericin B to eradicate Candida colonisation from the respiratory tract in critically ill patients receiving selective digestive decontamination: a cohort study. Crit Care 17:R233
4. Eggimann P, Wolff M, Garbino J (2005) Oral nystatin as antifungal prophylaxis in critically ill patients: an old SDD tool to be renewed? Intensive Care Med 31:1466–1468

B. H. Wittekamp · D. S. Y. Ong · M. J. M. Bonten
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

D. S. Y. Ong · O. L. Cremer
Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

D. S. Y. Ong · M. J. M. Bonten
Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands

D. S. Y. Ong (✉)
G04.614 Postbus 85500, 3508 GA Utrecht, The Netherlands
e-mail: davidsyong@gmail.com
Tel.: 0031 (0)88 75 58108