

# Is incidental recovery of yeast from enteric pathogen stool cultures obtained from hospitalized patients clinically significant?

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## Abstract

A matched case-control study was conducted to investigate gastrointestinal colonization with yeast as a predictor of invasive candidiasis (IC) in patients who underwent an enteric pathogen test. No significant association was detected between gastrointestinal colonization and IC. However, gastrointestinal colonization with yeast was associated with increased antimicrobial exposure and median length of hospitalization.

## Introduction

Invasive candidiasis (IC) is a serious infection associated with a high mortality rate and limited definitive diagnostic signs.<sup>1-3</sup> Colonization is a key component of IC pathogenesis, yet the significance of gastrointestinal *Candida* colonization as a predictor of IC remains controversial.<sup>3-5</sup>

Although yeast are normal bowel flora and recovery of low numbers in stool cultures is common, some hospitalized patients exhibit large numbers of yeast in stools obtained from enteric pathogen screening. The clinical significance of this finding is not well defined. Hospitalized patients undergoing evaluation for a possible inflammatory etiology of diar-

rhea may heighten concern that heavy yeast colonization of the gastrointestinal tract could progress to IC. Clinicians question whether prophylaxis of IC is warranted in such cases, and clinical microbiologists question whether the reporting of heavy yeast carriage is necessary. The study objective was to determine if a relationship exists between IC and recovery of large numbers of yeast from stool cultured for enteric pathogens.

All inpatients at a 689-bed academic medical center from January 2004-July 2008 with an enteric pathogen stool culture revealing yeast were eligible for inclusion. Only stools with moderate to many yeast detected (growth in two or more quadrants of an isolation streak from the original stool on sheep blood agar) were evaluated. Routine surveillance cultures for gastrointestinal colonization were not performed. Sheep blood agar, incubated for 72 hours, was included as a primary medium to screen for *Aeromonas hydrophila* and recognize patients that lack stool flora. Each case patient, included only once, was matched by age, gender, and admission date in a 1:3 ratio to subjects with enteric pathogen stool cultures negative for yeast in a retrospective matched case-control study. Subjects with IC prior to the index stool and those who received systemic antifungals within 30 days after the index stool were excluded. The study received Institutional Review Board approval with a complete waiver of informed consent.

The primary outcome was development of IC, identified from an institutional database of patients diagnosed with IC and defined by a positive culture from blood, intra-abdominal abscess, peritoneal fluid, or cerebrospinal fluid indicative of IC. A subgroup analysis was planned for immunocompetent versus immunocompromised subjects.

A retrospective chart review was done to collect the following: demographics; admission/discharge dates; culture/susceptibility results; presence and date of IC; antimicrobial, immunosuppressant, and chemotherapy regimens; mechanical ventilation; catheterizations (intravascular and urinary); hemodialysis; and parenteral nutrition received during hospitalization, as well as internal prosthetic devices and surgical procedures performed within 30 days prior to index stool.

Wilcoxon rank sum and Chi-square or Fisher's exact tests were used for continuous and categorical variables, respectively. P-values less than 0.05 were considered significant.

In total, 115 unique subjects had a stool culture that revealed moderate to many yeast out of 2373 total unique stool cultures performed among hospitalized patients during the study period. Fifty-seven subjects were excluded [developed IC prior to index stool (n=1), received systemic antifungals after index stool (n=40), and outpatient status at time of cul-

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Conflict of interest: EDH is currently an employee of Cubist Pharmaceuticals, is a shareholder in Cubist Pharmaceuticals, has been a consultant for Ortho-McNeil Pharmaceuticals, Cubist Pharmaceuticals, and Forest Laboratories, and has received research funding from Pfizer and TheraDoc. MER has received research funding from Cubist Pharmaceuticals, Sanofi-Pasteur, Cardinal Health Foundation, 3M, and Molyndcke. All other authors report no conflicts of interest.

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ture (n=16)]. The remaining cases (n=58) were matched to 174 controls in a 1:3 ratio. Study subject characteristics are summarized in Table 1. No significant differences were detected between cases and controls for age, gender, and ethnicity, (*data not shown*) but antimicrobial use was significantly more common in cases versus controls (95% vs. 73%, P=0.0005). The length of hospitalization was significantly longer (median, 2.5 days longer) for cases (P=0.002).

One control subject developed IC. No association was identified between IC and risk factors collected. No difference between the development of IC among immunocompetent versus immunocompromised patients was detected.

Other studies investigating candidal colonization and systemic disease have neither focused on incidental demonstration of heavy gastrointestinal colonization from an enteric

pathogen culture nor firmly concluded a correlation between colonization and subsequent IC.

Magill *et al.* investigated whether colonization site impacted the likelihood of developing IC in 182 surgical intensive care unit (SICU) patients.<sup>5</sup> No sites (urine, oropharynx, trachea, gastric aspirate, or rectum/ostomy) were associated with a high positive predictive value for IC. Conversely, all patients with negative rectum/ostomy, urine, and tracheal aspirate cultures remained without IC. The high negative predictive values for these cultures suggest a limited strategy to identify patients who are unlikely to benefit from antifungal prophylaxis.<sup>5</sup>

Blumberg *et al.* assessed risk factors for candidemia in a multicenter, prospective cohort involving SICU patients (n=4276).<sup>4</sup> Recovery of *Candida* from rectum and urine samples was not associated with a significant risk of developing candidemia. The authors concluded urinary or rectal colonization alone did not predict patient populations for antifungal prophylaxis.<sup>4</sup>

While these findings, in addition to the present study, suggest that rectal/gastrointestinal colonization alone does not predict IC, another study suggested that gastrointestinal colonization was the source for *C. albicans* candidemia.<sup>6</sup> However, surveillance cultures were obtained after candidemia documentation, and thus, whether gastrointestinal tract colonization preceded candidemia was not elucidated.

Other investigators have incorporated colonization as one of many risk factors to be

included in rules to help predict whether a given patient is likely to develop IC.<sup>7-9</sup> These studies have focused on patients at high risk for IC and have included colonization sites other than the gastrointestinal tract. Additionally, the ability to include colonization with yeast in such a clinical prediction rule requires routine surveillance cultures, which are not performed at our institution. These studies demonstrate that the predictive value of colonization for invasive candidiasis is variable.

In our study, the only case of IC occurred in a control subject who did not have heavy gastrointestinal colonization with yeast. Thus, if a negative gastrointestinal culture had been used to decide upon prophylactic therapy, this patient would not have received prophylaxis.

This matched case-control study was intended to investigate the significance of incidental demonstration of substantial gastrointestinal yeast colonization as a predictor of IC. Although conducted in a general population not selected as high risk for IC, many risk factors were present in both cases and controls (Table 1). Since cultures collected for detection of enteric pathogens were used, these observations may not be applicable to other situations. Furthermore, only patients who had an enteric stool specimen submitted for analysis were included in the study, and thus, these results may not be generalizable to the majority of patients who do not have stool specimens collected. Other limitations include the retrospective, single-centered study design, small sample size, and lack of data regarding inten-

sive care unit days.

This study suggests an association between antimicrobial exposure and gastrointestinal colonization with yeast. Additionally, a significant difference was found in length of hospital stay between cases and controls, suggesting more time in the hospital may increase the probability of colonization. No significant correlation between IC and incidental yeast detection in stool cultures was observed.

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**Table 1. Patient characteristics comparing patients with gastrointestinal yeast colonization to those without colonization.**

Patient characteristic	Yeast in stool culture		P
	Positive (n=58) n (%)	Negative (n=174) n (%)	
Received antimicrobials <sup>a</sup>	55 (94.8)	127 (72.9)	0.0005
Received immunosuppressants <sup>a</sup>	24 (41.4)	63 (36.2)	0.481
Received chemotherapy <sup>a</sup>	0 (0)	2 (1.1)	0.99
Medical prosthetic devices <sup>b</sup>	12 (20.7)	20 (11.5)	0.08
Surgical procedures <sup>b</sup>	19 (32.8)	41 (23.6)	0.166
Mechanical ventilation <sup>a</sup>	11 (19)	20 (11.5)	0.148
Intravascular catheterization <sup>a</sup>	44 (75.9)	113 (65)	0.12
Hemodialysis <sup>a</sup>	4 (6.9)	12 (7.5)	0.99
Parenteral nutrition <sup>a</sup>	8 (13.8)	28 (16.1)	0.68
Total length of hospitalization [median (range)]	8.5 (1, 116)	6.0 (1, 231)	0, 002

<sup>a</sup>During hospitalization; <sup>b</sup>within 30 days of index stool culture.