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The impact of commonly administered ceftriaxone, piperacillin-tazobactam, and imipenem-cilastatin on human candida colonization

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ABSTRACT

Aim: Contrary to common belief, current literature lacks data comparing the individual effects of different antibiotic agents on candidal colonization across multiple body sites. We investigated the impact of ceftriaxone (CRO), piperacillin-tazobactam (TZP), and imipenem-cilastatin (IMP) on human candidal colonization.

Methods: Patients who received CRO, TZP, or IMP for 7–14 days between February 26 and October 26, 2011, were included. A control group was also enrolled. Cultures for *Candida* species were obtained from the mouth, rectum, urine, and skin. The candida colonization index (CCI) was recorded on days 0, 7, and 14 for each group. We examined whether there was a notable increase in the initial CCI values across the three drug groups, analyzed differences between these groups, and evaluated the impact of antibiotics on Candida colonization at the species level.

Results: CRO (n=23), TZP (n=14) and IMP (n=14) caused significant increases in CCI by day 7 primarily due to oral and rectal colonization (p=0.001, p<0.001 and p<0.001, respectively), with further increases observed by day 14 compared to the control group (n=48). The increase in CCI induced by IMP was significantly greater than that caused by CRO on both days 7 and 14, with no significant difference observed between IMP and TZP. The clinical CCI threshold value of 0.5 was reached around day 7 in the IMP group and by day 14 in the TZP group. Although not statistically significant, both CRO and IMP were associated with increased colonization by *C. albicans* and *C. glabrata* at the species level.

Conclusion: CRO, TZP and IMP increased CCI initially through oral and rectal colonization during the first week, followed by urinary colonization in the second week. IMP led to the most rapid and the strongest rise.

Key words: *Candida*, ceftriaxone, colonization, imipenem-cilastatin, piperacillin-tazobactam.

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1. Introduction

Candida infections are predominantly endogenous in origin [1,2]. Antibiotics influence colonization through direct and indirect effects, though mechanisms remain unclear [3-5]. Despite common belief, data on the individual effects of antibiotics on human *Candida* colonization are limited, relying mostly on animal models and retrospective studies in intensive care patients [5-9]. Notably, Samonis et al. provided important insights to the literature by examining gastrointestinal colonization in humans, and despite being

relatively old, their studies retain validity today [10-13]. In both animal and human studies, “broad-spectrum antibiotics” often serve as a catch-all term for diverse antibiotic agents [2,3,5]. Yet, literature offers few clear answers to specific questions, such as whether meropenem or imipenem leads to greater candidal colonization in humans [12,13]. Moreover, most animal studies restrict assessment to gastrointestinal fungal load while overlooking other sites such as the skin, oropharynx, and urinary tract, highlighting the need for more targeted and comprehensive human studies [9-11].

In this study, we prospectively examined candidal colonization across multiple anatomical sites in patients treated with ceftriaxone (CRO), piperacillin-tazobactam (TZP), or imipenem-cilastatin (IMP) for bacterial infections in hospital.

2. Materials and methods

2.1. Study design and Participants

Patients hospitalized at Istanbul Faculty of Medicine Hospital between February 26 and October 26, 2011, who received intravenous CRO, TZP, and IMP for 7 to 14 days to treat various infections, were prospectively included in the study. Antibiotic therapy was initiated based on recommendations from the infectious diseases consultation team or by the primary physicians. The researchers had no role in determining the indication, choice, modification, or discontinuation of antibiotic treatment.

A control group was established consisting of patients hospitalized for at least 14 days who did not receive antibiotics. Efforts were made to match the patient and control groups in terms of underlying conditions, age, gender, frequency of invasive procedures, and other relevant factors.

The exclusion criteria included being under 18 years old, having a hematological-oncological diagnosis within the past year, receiving cytotoxic chemotherapy or biological agents within the past three months, staying in an intensive care unit in the last month, undergoing abdominal surgery within the past month, being a transplant recipient, being neutropenic (neutrophil count <500/mm³), taking total parenteral nutrition, and using oral or inhaled corticosteroids.

In this study, the goal was to show the specific effect of antibiotic use on candida colonization by minimizing other predisposing factors. However, due to their high prevalence, factors such as diabetes and the use of foley catheter and nasogastric tubes could not be excluded. However, these factors in the control group did not result in any statistical disparities.

Patients were selected from the departments of infectious diseases, internal medicine, cardiology, neurology, physical therapy and rehabilitation, and hyperbaric medicine. Additionally, patients hospitalized in surgical units who had no history of surgery within the past three months were also included.

On the day antibiotic therapy was initiated, swabs from the patients' mouths, skin, and anus, and urine samples were taken. As long as antibiotic therapy continued, cultures were repeated at one-week intervals. The candida colonization index (CCI) was determined by the ratio of positive samples to the total number of samples. The CCI values for all patients on days 0, 7, and 14 were calculated. Since some patients received intravenous treatment for seven days, calculating the CCI on the 14th day was not feasible. Patients whose CCI values exceeded 0.25 on day 0 were excluded from the study. An increase of at least 0.25 in the CCI

was considered notable. We examined whether there was a notable increase in the initial CCI values across the three drug groups, analyzed differences between these groups, and evaluated the impact of antibiotics on *Candida* colonization at the species level. The patients' age, gender, admission and inclusion date, reason for admission, smoking and alcohol use, use of dentures, history of antibiotic use in the last 3 months, diabetes, kidney failure, hypertension, chronic obstructive pulmonary disease, as well as interventions such as foley catheter, central catheter, nasogastric tube, etc., have been recorded.

The oral culture was taken from the dorsum of the tongue and bilateral buccal mucosa using a cotton-tipped swab. Anal samples were taken with a cotton-tipped swab inserted 2-3 cm into the rectum or by directly dipping into fresh stool samples. Skin samples were taken from the inner part of both forearms, thighs, periumbilical, and bilateral inguinal areas using a 15 cm swab. All swabs were inoculated onto Sabouraud dextrose agar (Difco, Turkey) supplemented with vancomycin (0.01 mg/ml) and gentamicin (0.04 mg/ml). In the growing colonies, germ tube tests and differentiation of albicans with tween80 were performed first. The isolates were stored in storage tubes at -80°C and later revived in 2014. Species-level identification was performed using the fully automated VITEK 2 Compact® system with the YST ID card (bioMérieux, France).

2.2. Statistical analysis

Data were summarized as frequency, percentage, mean, and standard deviation. Patient characteristics were compared using χ^2, Fisher's exact, or Kruskal-Wallis tests. Changes in candidal colonization were analyzed with Fisher's exact test, and CCI increases with the Mann-Whitney U test. A *p*-value ≤ 0.05 was considered significant.

3. Results

3.1. Patient characteristics: Of 99 patients, 48 were in the control group and 51 in the antibiotic group (CRO 23, TZP 14, IMP 14). Overall, 55 patients (56%) were male, with a mean age of 58.3 ± 16.2 years (19–88). The control group had 25 males (52%), mean age 57.0 ± 14.2 (28–80). In the antibiotic subgroups: CRO had 14 males (60%), mean age 61.0 ± 18.5; TZP 8 males (57%), mean age 61.2 ± 18.2 (19–84); IMP 8 males (57%), mean age 55.1 ± 17.0 (31–88). No significant differences were observed in gender or age between groups. Time from admission to study inclusion was 4.1 ± 5.6 days in the control group, 5.0 ± 5.1 (CRO), 5.1 ± 4.7 (TZP), and 4.2 ± 7.6 (IMP), with no significant difference (p=0.42). Average HbA1c was 9.8% ± 2.4 (control), 8.5% ± 1.9 (CRO), 8.0% ± 0.3 (TZP), and 9.1% ± 2.3 (IMP), also without statistical difference (p=0.48). Frequencies of factors such as diabetes, recent antibiotic use, hospitalization, foley/nasogastric tubes, dental dentures, smoking, hemodialysis, central catheter use, and chronic obstructive pulmonary disease were compared between all antibiotic groups combined and the control group, due to the small number of cases and low occurrence of these conditions (Table 1).

Of the 118 participants initially planned for the study, 19 were excluded due to baseline CCI >0.25, leaving 99 with complete CCI data for days 0 and 7. On day 14, data were available for 84 participants: all controls, but missing for 9 CRO, 2 TZP, and 4 IMP patients. The control group remained stable (0.08 → 0.12), while all antibiotics increased CCI. CRO increased moderately (0.13 → 0.26), TZP increased more (0.14 → 0.48), and IMP

showed the steepest rise (0.10 → 0.55) (Table 2).

Table 1. Statistical comparison of various factors that may affect candidal colonization between antibiotic groups and the control group.

Factors that may affect candidal colonization	**Control (n=48) n (%)**	**Ceftriaxone (n=23) n (%)**	**Piperacillin-Tazobactam (n=14) n (%)**	**Imipenem-cilastatin (n=14) n (%)**	**Antibiotics Total (n=51) n (%)**	***p***
Diabetes mellitus	17 (35.4)	8 (34.8)	4 (28.6)	4 (28.6)	16 (31.4)	*0.67*
Antibiotic use in the last 3 months	4 (8.3)	2 (8.7)	1 (7.1)	1 (7.1)	4 (7.8)	*1.00 #*
Hospitalization history in the last 3 months	9 (18.8)	4 (17.4)	3 (21.4)	3 (21.4)	10 (19.6)	*0.91*
Foley tube	12 (25.0)	9 (39.1)	5 (35.7)	4 (28.6)	18 (35.3)	*0.26*
Nasogastric tube	4 (8.3)	3 (13.0)	3 (21.4)	2 (14.3)	8 (15.7)	*0.26*
Use of removable dental dentures	17 (35.6)	10 (43.5)	2 (14.3)	2 (14.3)	14 (27.5)	*0.39*
Cigarette smoking	11 (22.9)	11 (47.8)	6 (42.9)	3 (21.3)	20 (39.2)	*0.08*
Use of central vein catheter	2 (4.2)	0 (0)	1 (7.1)	1 (7.1)	2 (3.9)	*1.00#*
Hemodialysis	2 (4.2)	0 (0)	1 (7.1)	1 (7.1)	2 (3.9)	*1.00#*
Chronic obstructive pulmonary disease	2 (4.2)	1 (4.3)	0 (0)	1 (7.1)	2 (3.9)	*1.00#*

 # It has been evaluated using Fisher's exact test. p ≤0.05, the difference between the two groups is statistically significant.

Table 2. Mean of candida colonization index values on days 0, 7, and 14 in the antibiotic groups and the control group.

Groups (n)	**CCI-0 * (n)**		**CCI-7 (n)**		**CCI-14 (n)**
Control (48)	0.08 (48)	→	0.10 (48)	→	0.12 (48)
Ceftriaxone (23)	0.13 (23)	→	0.28 (23)	→	0.26 (14)
Piperacillin-tazobactam (14)	0.14 (14)	→	0.37 (14)	→	0.48 (12)
Imipenem-cilastatin (14)	0.10 (14)	→	0.48 (14)	→	0.55 (10)

** :The candida colonization index (CCI) value calculated on day 0 is abbreviated as CCI-0; the CCI value on day 7 is abbreviated as CCI-7; and the CCI value on day 14 is abbreviated as CCI-*

During follow-up, one TZP group patient experienced a CCI increase from 0.25 to 1; TZP was stopped on day 14, and intravenous antifungal therapy began. In the CRO group, antibiotics were discontinued for two patients. One had a CCI rise from 0.25 to 0.75, leading to local antifungal treatment, while the other reached a CCI of 1, prompting intravenous antifungal therapy.

3.2. Day 0 Colonization

Day 0 oral colonization: On day 0, 30% (30/99) of patients had oral *Candida* spp. In controls, 9/10 had *C. albicans* and 1 had *C. parapsilosis*. Among 51 antibiotic-treated patients, 20 (39.2%) were colonized: *C. albicans* 14, *C. kefyr* 2, *C. lusitaniae* 1, *C. albicans*/*C. glabrata* 2, *C. krusei*/*C. kefyr* 1.

Colonization was higher in denture users (13/31, 42%) than non-users (17/68, 25%), but not statistically significant (p=0.08).

Day 0 rectal, urine, skin colonization: Rectal colonization was found in 10/99 patients (10%). In controls (n=6), *C. albicans* 3, *C. glabrata* 2, *C. krusei*/*C. glabrata* 1; in antibiotics (n=4), *C. krusei* 2, *C. albicans* 1, *C. glabrata* 1. Urine colonization occurred in 2 patients (2%), both with foley catheters (*C. krusei* 1, *C. glabrata* 1). No skin colonization was detected.

3.3. Day 7 Colonization

Day 7 oral colonization: On day 7, oral samples from 99 patients showed 48% colonization (48/99). In controls, 9/10 (90%) colonized patients had *C. albicans* and 1 had *C. parapsilosis*. Among 51 antibiotic-treated patients, 38 (74.5%) were colonized: *C. albicans* 26 (68.4%), *C. glabrata* 3 (7.8%), *C. lusitaniae* 2, *C. kefyr* 2, *C. parapsilosis* 1, dual *C. albicans*/*C. glabrata* 2, and dual *C. krusei*/*C. kefyr* 2.

Day 7 rectal, urine, skin colonization: On day 7,

Table 3. Statistical analysis of the increase in candida colonization index between groups from Day 0 to Day 7[#]

Groups	**0 (No increase in CCI)**	**0.25 increase in CCI**	**0.50 increase in CCI**	**0.75 increase in CCI**	**1.0 increase in CCI**	**Median (min- max)**	***Groups that were compared to one another (p)***
Control	44	4	0	0	0	0 (0 - 0.25)	*CRO vs. Control (0.001) * TZP vs. Control (<0.001) IMP vs. Control (<0.001)*
Ceftriaxone	14	5	3	1	0	0 (0 - 0.75)	*CRO vs. TZP (0.25) CRO vs. IMP (0.03) * TZP vs. IMP (0.06)*
Piperacillin-tazobactam	5	6	2	1	0	0.25 (0 - 0.75)	
Imipenem-cilastatin	1	5	8	0	0	0.50 (0 - 0.50)	

 # Statistical analysis was conducted using the Mann-Whitney U test between groups.

** p ≤0.05, the difference between the two groups is statistically significant.*

CRO: ceftriaxone, TZP:piperacillin-tazobactam, IMP: imipenem-cilastatin

rectal samples from 99 patients showed 36% colonization (36/99). In controls, 9/48 (18.7%) were colonized: *C. albicans* 6, and *C. glabrata*, *C. krusei*, *C. lusitaniae* 1 each. Among 51 antibiotic-treated patients, 27 (52.9%) were colonized: *C. glabrata* 10, *C. albicans* 9, *C. lusitaniae* 3, *C. krusei* 2, *C. parapsilosis* 1, dual *C. glabrata/C. albicans* 1, and dual *C. albicans/C. krusei* 1. Moreover, on day 7, urine samples from 99 patients showed 8% candidal colonization, absent in controls: *C. glabrata* 4, *C. albicans* 3, *C. krusei* 1. Skin swabs were positive in 2 patients: *C. albicans* 1, *C. glabrata* 1. No significant differences in urine colonization were observed between antibiotic groups and controls (IMP p=0.12, TZP p=0.40, CRO p=0.24).

3.4. Comparison of candida colonization index between day 0 and the 7th day

Most controls (44/48) had no CCI increase (median 0, 0–0.25), while antibiotics showed higher rises: CRO median 0 (0–0.75), TZP 0.25 (0–0.75), and IMP 0.50 (0–0.50). All antibiotics differed significantly from control ($p \leq 0.001$), with CRO vs. IMP also significant ($p = 0.03$). An increase of ≥0.25 in CCI was taken as clinically significant (Table 3).

3.5. Day 14 Colonization

Day 14 oral colonization: Day 14 data from 84 patients (after excluding missing data of 9 CRO, 2 TZP, 4 IMP) showed 45% oral colonization (38/84). In controls, 25% (12/48) were colonized: *C. albicans* 11, *C. parapsilosis* 1. Among antibiotic-treated patients, 72.2% (26/36) were colonized: *C. albicans* 18 (69.2%), *C. lusitaniae* 2, *C. krusei* 2, *C. kefyr* 1, *C. glabrata* 1, *C. parapsilosis* 1, dual *C. kefyr/krusei* 1, and *C. albicans/glabrata* 1.

Day 14 rectal, urine, skin colonization: On day 14, rectal colonization was found in 42% (35/84) of patients; *C. albicans* was isolated in 40%. In controls, 10/48 were colonized: *C. albicans* 5, *C. glabrata* 1, *C. krusei* 1, *C. guilliermondii* 1, and dual *C. glabrata/kefyr* 2. In antibiotic groups, 69.4% (25/36) were colonized: *C. glabrata* 8, *C. albicans* 7, *C. lusitaniae* 3, *C. krusei* 2, *C. parapsilosis* 2, and one case each of *C. kefyr/krusei*, *C. albicans/dubliniensis*, and *C. albicans/krusei*. Out of 84 patients with complete day 14 data, candidal colonization occured in the urine of 9 patients. One individual in the control group had *Candida albicans* (2%, 1/48). Among the 8 patients in the antibiotic groups (22.2%, 8/36), 5 had *C. glabrata* (62.5%, 5/8), 2 had *C. albicans*, and 1 had *C. lusitaniae*. Skin colonization was limited to one TZP patient with *C. albicans*.

3.6. Comparison of candida colonization index between day 0 and the 14th day

CCI changes are shown in 0.25 increments. Increases were higher in the IMP, CRO, and TZP groups compared with controls ($p < 0.001$, 0.03, < 0.001). Compared with CRO, IMP ($p = 0.001$) and TZP ($p = 0.046$) showed greater increases. Although TZP did not differ significantly from CRO by day 7, a notable rise was observed by day 14, primarily associated with urinary and rectal colonization (Table 4).

3.7. Comparison of candida colonization index between day 7 and the 14th day

CCI increased more in IMP and TZP groups than controls (p=0.026, p=0.001), while CRO showed no difference (p=0.33). Between days 7–14, IMP increases were mainly due to urinary colonization, whereas TZP rises were driven by both urinary and rectal colonization (Table 5).

Table 4. Statistical analysis of the increase in candida colonization index between groups from Day 0 to Day 14[#]

Groups	0 (No increase in CCI)	0.25 increase in CCI	0.50 increase in CCI	0.75 increase in CCI	1.0 increase in CCI	Total (n)	Median (min- max)	*Groups that were compared to one another (p)*
Control	42	5	1	0	0	48	0 (0 - 0.50)	*CRO vs. Control (0.03)** *TZP vs. Control (<0.001)* *IMP vs. Control (<0.001)*
Ceftriaxone	7	6	1	0	0	14	0,125 (0 – 0.50)	*CRO vs. TZP (0.046)** *CRO vs. IMP (0.001)* *TZP vs. IMP (0.41)*
Piperacillin-tazobactam	3	3	4	2	0	12	0,375 (0 - 0.75)	
Imipenem-cilastatin	1	1	7	1	0	10	0,50 (0 - 0.75)	

 # The Mann Whitney U test was used to compare the increases in candida colonization index values among the groups.
** p ≤0.05, the difference between the two groups is statistically significant.*
CRO: ceftriaxone, TZP:piperacillin-tazobactam, IMP: imipenem-cilastatin.

Table 5. Statistical analysis of the increase in candida colonization index between groups from Day 7 to Day 14[#]

Groups	0 (No increase in CCI)	0.25 increase in CCI	0.50 increase in CCI	0.75 increase in CCI	1.0 increase in CCI	Total (n)	Median (min- max)	*Groups that were compared to one another (p)*
Control	45	3	0	0	0	48	0 (0 - 0.25)	*CRO vs. Control (0.33)** *TZP vs. Control (0.001)* *IMP vs. Control (0.026)*
Ceftriaxone	12	2	0	0	0	12	0 (0 - 0.25)	*TZP vs. IMP (0.58)*
Piperacillin-tazobactam	7	4	1	0	0	12	0 (0 - 0.50)	
Imipenem-cilastatin	7	3	0	0	0	10	0 (0 - 0.25)	

The Mann Whitney U test was used to compare the increases in candida coloniation index values among the groups.
* p ≤0.05, the difference between the two groups is statistically significant.
CRO: ceftriaxone, TZP:piperacillin-tazobactam, IMP: imipenem-cilastatin

3.8. Distribution of Candida species across groups: In the CRO group, *Candida* spp. spread to new sites in 5 cases and appeared in 7 previously uncolonized patients (4 *C. glabrata*, 3 *C. albicans*). In the TZP group, spread occurred in 7 cases, while 8 new colonizations developed (2 each *C. glabrata*, *C. albicans*, *C. lusitaniae*; and 1 each *C. krusei*, *C. kefyr*, *C. parapsilosis*). In the IMP group, spread occurred in 3 cases, with 8 new colonizations (7 *C. albicans*, 4 *C. glabrata*, 1 *C. lusitaniae*, 2 *C. krusei*, 2 *C. parapsilosis*, 1 *C. kefyr*). In

controls, spread was seen in 3 cases, with 3 new sites (*C. glabrata*, *C. albicans*, *C. guilliermondii*). Overall, patients receiving CRO and IMP exhibited an increased colonization of *C.albicans* and *C.glabrata* compared to the control group. However, this difference was not statistically significant.

4. Discussion

In our study, patients on CRO showed a rise in oral and rectal colonization during the first week, but this did not progress further; their mean CCI was 0.28 on day 7 and slightly declined to 0.26 by day 14. Both TZP and IMP groups, however, experienced ongoing increases. For TZP, colonization began in the mouth and rectum during the first week and shifted to the urinary tract in the second, raising the CCI from 0.37 to 0.48. IMP patients showed stronger early oral and rectal colonization together with steady urinary involvement, with CCI rising from 0.48 to 0.55. Notably, the critical CCI threshold of 0.5—associated with invasive candidiasis risk—was crossed as early as day 7 in IMP and by day 14 in TZP, suggesting that antibiotic use was the main driver of these changes. Although the CCI was designed to identify high-risk surgical ICU patients and guide pre-emptive antifungal therapy, its routine use has remained limited because of the labor-intensive process and associated costs, which may explain the small number of studies evaluating it [7,14]. At this point, we would also like to emphasize that the particularly small subgroup sizes in our cohort and the reliance on qualitative rather than density-adjusted assessment of colonization may limit the ability to draw robust clinical conclusions. Nonetheless, given that in real-world practice colony counts for *Candida* are not reported—apart from urine and BAL samples—we believe that even qualitative reporting can still provide meaningful guidance to clinicians.

In our study, CRO and IMP patients showed increased *C. glabrata* alongside *C. albicans* versus controls, though not statistically significant. Pultz et al. found that subcutaneous ceftriaxone, piperacillin-tazobactam, clindamycin, and metronidazole increased fecal *C. glabrata* in mice, whereas cefepime, levofloxacin, and aztreonam did not, suggesting antibiotics targeting anaerobic gut flora promote *C. glabrata* colonization [15]. In this study, colonies underwent germ tube testing and albicans differentiation with Tween 80, were stored at –80 °C, and later revived in 2014 for further identification using the automated VITEK 2 Compact® system. While the potential impact of long-term storage on isolates can be considered, we believe that storage at –80 °C is methodologically sound, as it enabled reliable species-level analysis.

In our study, IMP, TZP, and CRO increased oral and rectal candidal colonization (in addition to CCI) by day 7, with minimal urine or skin involvement. Ceftriaxone and similar antibiotics have been shown to raise intestinal yeast populations when given ≥7 days [9,12]. Imipenem has also been reported to increase intestinal candidal colonization in rats and humans, especially with prolonged use [11,13]. In a prospective case–control study, ceftriaxone was not linked to candidemia, while piperacillin–tazobactam and imipenem were [16]. Samonis et al. observed gastrointestinal *Candida albicans* colonization in surgical patients receiving cefepime and meropenem [12]. Consistently, our study found that imipenem–cilastatin significantly increased oral and rectal colonization by day 7 versus controls ($p < 0.001$). During follow-up, one patient in the TZP group developed a CCI increase requiring discontinuation of antibiotics

and initiation of intravenous antifungal therapy, while antibiotics were discontinued in two CRO patients. Given the small numbers, no firm conclusions can be drawn, and the absence of an observed association with clinical outcomes such as invasive candidiasis warrants further investigation.

We found that at least two weeks of antibiotic treatment were needed to increase urine and skin candidal colonization; one week was insufficient. In patients receiving TZP or IMP who develop candiduria, concurrent oral and rectal colonization is already likely, which may assist clinicians in patient management. A prior study linked candiduria to ceftriaxone, TZP, and IMP, especially meropenem and ceftazidime [17]. In our study, ceftriaxone had no effect, while IMP significantly increased urinary colonization by day 14 ($p = 0.01$).

Our study aimed to reduce factors influencing candidal colonization, yet smoking prevalence was higher in the ceftriaxone (48%) and TZP (42.9%) groups compared to the controls (22.9%) and IMP group (21.3%). Although these differences were not statistically significant, the findings indicate that smoking deserves consideration regarding oral colonization [18]. On day 0, oral colonization was observed in 45% of smokers versus 23% of non-smokers ($p=0.05$), consistent with prior research [18-21]. No significant associations were observed for denture use ($p=0.08$) or diabetes ($p=0.16$). Nonetheless, individuals using dentures showed higher colonization rates (42% compared to 25%), a finding consistent with existing research [22-25]. It's important to note that excluding cases of multi-site colonization may have restricted our ability to detect an association with diabetes [26-28].

Additionally, the choice of sampling method could have influenced the results. We employed an oral swab technique, whereas mouth rinse cultures, which are considered superior in the literature [29,30], might have provided higher detection rates of oral candidal colonization. This methodological decision could partially explain the lower colonization rates observed in our study relative to potential actual prevalence. Our study has several limitations. A larger sample size in the antibiotic groups would have increased statistical power. We assessed colonization qualitatively (‘present’ or ‘absent’) rather than using adjusted CCI values, which consider colonization density—an important factor that should be included in future studies. Genotyping strains from previously negative sites could also clarify colonization pathogenesis. Although the study was conducted in 2011 and expanded in 2014, prospective data on antibiotic effects on candidal colonization—especially from Turkiye—remain limited, and we firmly believe that our study continues to fulfill an important and largely unaddressed need in examining the individual impact of antibiotics on candidal colonization.

4.1. Conclusions

Our study demonstrates that ceftriaxone, piperacillin-tazobactam, and imipenem-cilastatin significantly increase candidal colonization, with imipenem-cilastatin inducing the most rapid and pronounced effect. The early colonization observed in oral and rectal sites, followed by urinary involvement, highlights the sequential pattern of *Candida* expansion under antibiotic pressure. Clinically, this underscores the importance of careful risk stratification for invasive candidiasis in patients receiving broad-spectrum antibiotics, using the colonization index as a guiding tool. Recognizing patterns of early colonization may inform antifungal stewardship, including timely prophylactic or preemptive interventions,

ultimately improving patient outcomes. Although the study is limited by its sample size and qualitative assessment of colonization, it provides valuable insight into the individual impact of broad-spectrum antibiotics on fungal colonization dynamics. Given the ongoing scarcity of such prospective studies, particularly in Türkiye, our findings underscore the importance of continued research in this field.

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