

# Intra-abdominal candidiasis in surgical intensive care unit – epidemiology characteristics and trends

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## ABSTRACT

**Objectives:** Intra-abdominal candidiasis (IAC) is an invasive fungal infection representing the most common type of invasive *Candida* infection in surgical intensive care units (ICUs). Recently, decreased antifungal susceptibility and progressive shift in the aetiology of invasive candidiasis has been observed worldwide. We explored IAC epidemiology in surgical ICU.

**Material and Methods:** We retrospectively reviewed the records of 64 patients with IAC admitted at our surgical ICU over a 4-year period (2013–2016). IAC incidence, microbiological results, antifungal therapy, and mortality were analysed.

**Results:** The cumulative IAC incidence was 18.4 cases per 1000 admissions (2013: 12.6; 2014: 17.7; 2015: 16.8; 2016: 24.5), including hospital-acquired IAC incidence (2013: 9.8; 2014: 13.3; 2015: 10.1; 2016: 13.3) and community-acquired IAC incidence (2013: 2.8; 2014: 4.4; 2015: 6.7; 2016: 11.2). *Candida albicans* represented the most common species (n = 35, 50.0%) followed by *Candida glabrata* (n = 15, 21.4%), *Candida tropicalis* (n = 6, 8.6%) and other yeasts (each < 5.0%). Incidence rate of *C. albicans* (2013: 7(78%); 2014: 10(59%); 2015: 6(35%); 2016: 12(44%)) and incidence rate of *C. non-albicans* (2013: 2(22%); 2014: 7(41%); 2015: 9(53%); 2016: 14(52%)) were different in trend. All fungal isolates were susceptible to echinocandins, amphotericin B and voriconazole. Regarding fluconazole susceptibility, *C. krusei* (n = 3) was resistant and *C. glabrata* (n = 9) was susceptible-dose dependent (SDD). The ratio of SDD *C. glabrata* isolates to all isolated *C. glabrata* strains was 9/15 (60%) (2013: 0/2; 2014: 0/2; 2015: 1/3; 2016: 8/8). Decreased fluconazole susceptibility for *C. glabrata* isolates was reported in both community-acquired IAC (n = 3) and hospital-acquired IAC (n = 6). Overall 30-day mortality rate was 25.0% (16/64).

**Conclusions:** We have revealed slowly raising of overall IAC incidence, more increasing trend in incidence of community-acquired IAC compared to rather steady incidence of hospital-acquired IAC. During period 2013–2016 we have observed a significant shift in the aetiology of IAC towards an increased proportion of non-*albicans* *Candida* species, particularly *C. glabrata*. Acquired decreased fluconazole susceptibility was related to *C. glabrata* isolates exclusively. Emergence of decreased antifungal susceptibility has been preceded by increase of non-*albicans* *Candida* isolates.

## KEYWORDS

intra-abdominal candidiasis – abdominal surgery – antifungal susceptibility – antifungal therapy – mortality

## SOUHRN

Ulrych J., Adámková V., Matek J., Komarc M., Frýba V., Schmidt D., Koželický P., Studená A., Břiza J., Krška Z.: Nitrobřišní kandidóza na chirurgické jednotce intenzivní péče – epidemiologické rysy a trendy

**Cíl:** Nitrobřišní kandidóza (NK) patří mezi nejčastější invazivní kandidové infekce na chirurgické jednotce intenzivní péče (JIP). V poslední době byla celosvětově pozorována změna v mikrobiální etiologii invazivních kandidových infekcí a postupný nárůst rezistence na antimykotické přípravky. Zaměřili jsme se proto na epidemiologii NK na chirurgické JIP.

**Materiál a metodika:** Retrospektivní analýza 64 pacientů s NK přijatých na chirurgickou JIP v průběhu 4 let (2013–2016) se zaměřením na vyhodnocení incidence NK, výsledků mikrobiologického vyšetření, antimykotické léčby a letality.

**Výsledky:** Kumulativní incidence NK činila 18,4 případů/1000 JIP pacientů (2013: 12,6; 2014: 17,7; 2015: 16,8; 2016: 24,5). Separovaně byla vyhodnocena incidence nozokomiální NK (2013: 9,8; 2014: 13,3; 2015: 10,1; 2016: 13,3) a incidence komunitní NK (2013: 2,8; 2014: 4,4; 2015: 6,7; 2016: 11,2). Nejčastěji izolovanou kvasinkou byla *Candida albicans* (35x; 50,0 %), *Candida glabrata* (15x; 21,4 %) a *Candida tropicalis* (6x; 8,6 %), ostatní druhy byly zachyceny ojediněle (< 5,0 %). Byly pozorovány rozdílné trendy v prevalenci kmenů *C. albicans* (2013: 7(78 %); 2014: 10(59 %); 2015: 6(35 %); 2016: 12(44 %)) a kmenů *C. non-albicans* (2013: 2(22 %); 2014: 7(41 %); 2015: 9(53 %); 2016: 14(52 %)). Všechny izoláty kvasinek byly citlivé na echinokandiny, amfotericin B a vorikonazol. V případě flukonazolu byly 3 izoláty *C. krusei* přirozeně rezistentní a 9 izolátů *C. glabrata* mělo na dávce závislou citlivost (DZC). Podíl izolátů *C. glabrata* s DZC na flukonazol ke všem kmenům *C. glabrata* byl 60% (9/15) (2013: 0/2; 2014: 0/2; 2015: 1/3; 2016: 8/8). Izoláty *C. glabrata* se sníženou citlivostí na flukonazol jsme zaznamenali nejen u nozokomiálních NK (6x), ale také u komunitních NK (3x). 30denní letalita v našem souboru byla 25 % (16/64).

**Závěry:** Celková incidence NK měla mírně vzestupný trend, přičemž přírůstek incidence byl patrný zejména u komunitní NK, zatímco incidence nozokomiální NK byla spíše setrvalá. V průběhu let 2013–2016 jsme zaznamenali změnu v mikrobiální etiologii NK ve smyslu postupného zvýšení výskytu non-*albicans* *Candida* kmenů, konkrétně pak nárůst počtu kmenů *C. glabrata*. Snížená

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citlivost na flukonazol byla pozorována právě v souvislosti s kmeny *C. glabrata*. Zvýšení výskytu kmenů *Candida non-albicans* tak časově předcházelo objevení se kvasinek se sníženou citlivostí na flukonazol.

### KLÍČOVÁ SLOVA

nitrobřišní kandidóza – abdominální chirurgie – citlivost na antimykotika – antimykotická léčba – letalita

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## INTRODUCTION

Invasive fungal infections in critically ill patients in the intensive care unit (ICU) are associated with considerable morbidity and mortality. The predominant type of invasive candidiasis is candidemia [1]. However, intra-abdominal candidiasis (IAC) is a frequent invasive *Candida* infection in surgical patients, representing the most common type of invasive candidiasis in surgical ICUs [2, 3]. *Candida* strains are obtained from an intra-operative intra-abdominal specimen in approximately 20–50% of patients with intra-abdominal perforation non-appendicular aetiology [4, 5, 6]. *C. albicans* is the most common causative agent of invasive candidiasis, but a shift towards non-*albicans Candida* species has been recently observed worldwide [7, 8, 9, 10, 11]. Moreover, global epidemiology trend is characterised by an increased prevalence of triazole-resistant *Candida* species, such as *C. glabrata* and *C. krusei*.

In 2016 emergence of decreased antifungal susceptibility for *Candida* species has been observed in culture isolates of *Candida* species in our surgical patients after abdominal surgery [12]. Therefore, this retrospective study was initiated to reveal the IAC epidemiology characteristics and trends in our surgical ICU patients over the period 2013–2016.

## MATERIAL AND METHODS

We performed a retrospective observational single-centre cohort study analysing patients which were hospitalized in the ICU of First Department of Surgery, First Faculty of Medicine, Charles University and General University Hospital in Prague within a period from January 1<sup>st</sup> 2013 till December 31<sup>st</sup> 2016. All patients admitted to ICU in the period mentioned above were identified via a search of the hospital medical database. Individuals with

**Table 1.** Basic characteristics, site of IAC origin, in hospital characteristics and mortality

	IAC (n = 64)	C-IAC (n = 23)	H-IAC (n = 41)	p*
<b>Basic characteristics</b>				
Gender (male/female)/n	30/34	12/11	18/23	0.525
Age (years) / mean (SD)	67.5 (± 12.8)	67.8 (± 16.0)	67.4 (± 10.8)	0.911
• 18–59 years	16 (25%)	7 (30%)	9 (22%)	0.452
• ≥ 60 years	48 (75%)	16 (70%)	32 (78%)	
BMI/mean (SD)	25.8 (± 6.2)	25.4 (± 3.9)	26.0 (± 7.2)	0.580
Malignancy/n	32 (50.0%)	6 (26.1%)	26 (63.4%)	0.004
Comorbidities/n	20 (31.2%)	6 (26.1%)	14 (34.1%)	0.504
<b>Site of IAC origin</b>				
• HPB origin/n	13 (20.3%)	0 (0.0%)	13 (31.7%)	0.002
• Gastroduodenal origin/n	14 (21.9%)	10 (43.5%)	4 (9.8%)	0.002
• Small intestine origin/n	10 (15.6%)	3 (13.0%)	7 (17.0%)	0.670
• Colorectal origin/n	23 (35.9%)	10 (43.5%)	13 (31.7%)	0.346
• Others/n	4 (6.3%)	0 (0.0%)	4 (9.8%)	0.122
<b>In hospital characteristics</b>				
SOFA score/mean (SD)	4.1 (± 3.9)	4.0 (± 4.2)	4.2 (± 3.7)	0.627
ICU stay (days) / mean (SD)	21.8 (± 20.1)	9.2 (± 11.7)	28.9 (± 20.4)	< 0.001
Hospital stay (days)/mean (SD)	38.0 (± 28.6)	16.8 (± 13.0)	50.2 (± 28.0)	< 0.001
<b>Mortality</b>				
30-day mortality/n	16 (25.0%)	6 (26.1%)	10 (24.4%)	0.880

Legends: n – number of patients; BMI – body mass index; HPB – hepatopancreatobiliary; IAC – intra-abdominal candidiasis (C – community-acquired, H – hospital-acquired); ICU – intensive care unit; p value – statistically significant < 0.05; SD – standard deviation; \* C-IAC vs. H-IAC.

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a positive culture for *Candida* species in the peritoneal fluid obtained during surgery or in the abdominal drain fluid during the post-operative period were included. A report form was completed for each study patient based on a review of the medical charts.

The following data were collected: demographic characteristics, underlying disease, antifungal therapy (antifungal agents, length of administration), length of stay in ICU, length of stay in hospital, 30-day mortality. The mycological and microbiological results of cultured peritoneal fluid and drain fluid were recorded. Microbiological techniques applied for culture and identification of bacteria and fungi, as well as antibiotic susceptibility testing, were those routinely used in the

microbiology laboratory. In the laboratory, culture for aerobic, anaerobic bacteria and fungi was performed. For bacterial isolation blood agar and chromogenic agar UriSelect4 (BioRad) was used. The plates were incubated at  $36 \pm 1$  °C for 24–48 hours. Cultures positive for bacterial growth were identified by MALDI-TOF mass spectrometer (Bruker). An antimicrobial susceptibility test of the identified bacteria was performed using the Kirby Bauer Disc Diffusion method following CLSI guidelines [13]. Sabouraud dextrose agar (SDA), as selective medium, was used for isolation of fungi and incubation was done at  $36 \pm 1$  °C for 48 hours. Positive cultures on SDA were identified by MALDI-TOF mass spectrometer (Bruker). Antifungal susceptibility tests were done by using an

**Table 2.** Microbiological results in IAC, including C-IAC and H-IAC

Microbiological results / n (%)	IAC (n = 64)	C-IAC (n = 23)	H-IAC (n = 41)	p*
<b>Yeast species</b>	70	23	47	
• <i>Candida albicans</i>	35 (50.0%)	13 (56.5%)	22 (46.8%)	0.825
Non- <i>albicans</i> <i>Candida</i> spp.	32 (45.7%)	10 (43.5%)	22 (46.8%)	0.683
• <i>Candida glabrata</i>	15 (21.4%)	5 (21.7%)	10 (21.3%)	0.810
FLU-SDD <i>C. glabrata</i>	9	3	6	0.972
• <i>Candida tropicalis</i>	6 (8.6%)	1	5	0.406
• <i>Candida krusei</i>	3 (4.3%)	2	1	0.291
• <i>Candida dubliniensis</i>	3 (4.3%)	2	1	0.291
• <i>Candida kefyr</i>	2 (2.8%)	0	2	0.532
• <i>Candida lusitanae</i>	2 (2.8%)	0	2	0.532
• <i>Candida fabianii</i>	1 (1.4%)	0	1	1.000
Non- <i>Candida</i> species	3 (4.3%)	0 (0.0%)	3 (6.4%)	0.184
• <i>Saccharomyces</i>	3	0	3	0.252
<b>Candida isolation</b>				
Pure <i>Candida</i> abdominal infection	9	4	5	0.566
Bacterial co-infection	55	19	36	0.566
<b>Bacteria isolates</b>	142	48	94	0.860
<b>G-negative bacteria</b>	76 (53.5%)	26 (54.2%)	50 (53.2%)	0.514
<i>Enterobacteriaceae</i>	59	24	35	0.658
ESBL positive	14	1	13	0.011
• <i>Escherichia coli</i>	28	14	14	0.039
• <i>Klebsiella</i> spp.	14	2	12	0.056
• Others <i>Enterobacteriaceae</i>	17	8	9	0.153
Non-fermenting G-negative bacteria	17	2	15	0.024
• <i>Pseudomonas aeruginosa</i>	11	2	9	0.177
• Others non- <i>Pseudomonas</i> spp.	6	0	6	0.218
<b>G-positive bacteria</b>	48 (33.8%)	13 (27.1%)	35 (37.2%)	0.018
• <i>Enterococcus</i> spp.	29	2	27	0.001
• <i>Streptococcus</i> spp.	14	9	5	0.031
• Others	5	2	3	0.404
<b>Anaerobes</b>	18 (12.7%)	9 (18.7%)	9 (9.6%)	0.289

Legends: ESBL – extended spectrum beta-lactamase; FLU-SDD – fluconazole susceptible-dose dependent; IAC – intra-abdominal candidiasis (C – community-acquired, H – hospital-acquired); n – number of patients; p value – statistically significant below 0.05; \*C-IAC vs. H-IAC.

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E-test on RPMI 1640 medium supplemented with glucose to a final concentration of 2% following CLSI criteria [14]. In accordance with recently proposed criteria, *Candida* isolation was classified as intra-abdominal candidiasis in patients with clinical evidence of intra-abdominal infection and isolation of *Candida* species in a sample collected from an intra-abdominal site or from abdominal drains that were in place < 24 hours [15, 16]. Community-acquired IAC (C-IAC) was defined as intra-abdominal *Candida* infection characterised by onset of clinical abdominal manifestation before hospital admission or ≤ 48 hours after admission. Hospital-acquired IAC (H-IAC) was defined as *Candida* infection of abdominal cavity not present on admission that became evident > 48 hours after admission in hospitalised patients.

### Statistical analysis

Continuous normally distributed data are expressed as the mean and standard deviation (SD) and compared using independent group t test. Categorical data are expressed as the number and percentage and compared using  $\chi^2$  or the Fisher's exact tests. In all comparisons, p-values below 0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Demographics, basic characteristics of study group and microbiological results

In the period 2013–2016, we identified altogether 101 patients with a positive culture for fungi from the peritoneal fluid collected during abdominal surgery or from abdominal drain postoperatively. Criteria for IAC were met in 64 patients. Basic characteristics, site of IAC origin, in hospital characteristics and mortality are reported in Table 1.

In the 64 samples, 70 fungi isolates were identified. *Candida* species (n = 67) was the most frequent species followed by *Saccharomyces* (n = 3). Although *Candida albicans* (CAAL) was the most frequent *Candida* pathogen, the incidence rate of non-*albicans Candida* species (non-CAAL) was nearly the same (CAAL 50.0%; non-CAAL 45.7%). Yeast

species were the only organism cultured in 14% cases. Bacterial co-infection was present in 85.9% patients. In addition to fungi, 142 bacteria isolates were identified in the microbiological specimens of 55 patients with up to six different species per patient. The mean number of isolated bacteria was 2.2 isolates per sample. Detailed microbiological results, including the comparison of microbial aetiology in C-IAC and H-IAC, are reported in Table 2.

### Incidence

In the period 2013–2016, altogether 3487 patients were admitted to surgical ICU and there were a total 64 episodes of IAC. The cumulative IAC incidence in ICU was 18.4 cases per 1000 admissions. The trend in incidence of IAC in abdominal surgery patients, including C-IAC and H-IAC, is shown in Figure 1.

### Antifungal susceptibility testing

All fungal isolates were susceptible to echinocandins, amphotericin B and voriconazole, however antifungal susceptibility testing revealed decreased fluconazole susceptibility in 12 (17.1%) *Candida* isolates. All *Candida albicans* isolates were susceptible to fluconazole. The three *C. krusei* isolates were resistant to fluconazole (intrinsic resistance) and the nine *C. glabrata* isolates had fluconazole MIC 32 mg/l, thus, reported as susceptible-dose dependent (SDD). Other non-*albicans Candida* species were susceptible to fluconazole. Of all tested *Candida glabrata* isolates, 60% (9/15) were fluconazole SDD.

### Microbiological results and trends

Detailed analysis of *Candida* species incidence during the observed period is reported in Table 3. The ratio of fluconazole SDD *C. glabrata* isolates to all isolated *C. glabrata* strains was reported in 4-year period (2013: 0/2, 0.0%; 2014: 0/2, 0.0%; 2015: 1/3, 33.3%; 2016: 8/8, 100.0%). Statistically significant increased incidence of *C. glabrata* isolates with decreased susceptibility to fluconazole was reported in the period 2015–2016 (9/11, 81.8%) compared to the period 2013–2014 (0/4, 0.0%) (p = 0.006). Moreover, in 2016 all isolates of *C. glabrata* (8/8) were SDD to fluconazole and decreased fluconazole susceptibility for *C. glabrata* isolates was reported in both C-IAC (3/3) and H-IAC (5/5).

### Antifungal therapy and mortality

Only 39.1% (25/64) of patients with IAC received antifungal therapy. However, antifungal therapy was more frequently administered in cases of H-IAC (21/42, 51.2%) compared to cases of C-IAC (4/23, 17.4%) (p = 0.008). In 25 patients, empiric monotherapy was administered using fluconazole (n = 19), voriconazole (n = 1), anidulafungin (n = 4) and micafungin (n = 1). In four cases de-escalation therapy was performed, echinocandin was replaced by fluconazole. Per the *Candida* species identification and susceptibility results, empiric an-

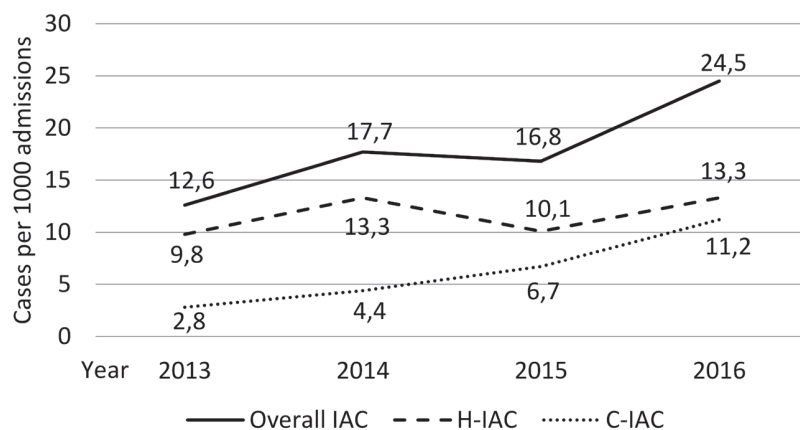


Figure 1. Trend in Incidence of IAC



**Table 3.** Incidence of yeast species in the period 2013–2016

	Period 2013–2016			
	2013	2014	2015	2016
<b>Yeast species</b>	9	17	17	27
<b><i>Candida albicans</i></b>	7 (78%)	10 (59%)	6 (35%)	12 (44%)
<b><i>Candida non-albicans</i> spp.</b>	2 (22%)	7 (41%)	9 (53%)	14 (52%)
<b><i>Saccharomyces</i> spp.</b>	0 (0%)	0 (0%)	2 (12%)	1 (4%)

tifungal treatment appeared as inadequate in 20.0% (5/25) of patients. Inadequate antifungal therapy was administered more frequently in the period 2015–2016 (5/14; 35.7%) compared to the period 2013–2014 (0/11; 0.0%).

Overall 30-day mortality rate was 25.0% (16/64), including mortality of 32.0% (8/25) in the period 2013–2014 and mortality of 20.5% (8/39) in the period 2015–2016 ( $p = 0.300$ ). The mortality in the subgroups of patients with C-IAC and H-IAC was 26.1% (6/23) and 24.4% (10/41), respectively ( $p = 0.880$ ).

## DISCUSSION

Invasive fungal infection in ICUs ranges from 4.7 to 28.0 episodes per 1000 admissions; however, most studies have reported the incidence of candidemia while the incidence of intra-abdominal candidiasis has remained unknown [2, 3, 17, 18, 19]. In the Czech Republic multicentre study assessing epidemiology of invasive candidiasis in 2012–2015 authors analysed only episodes of candidemia [20]. We have revealed cumulative incidence of IAC of 18.4 cases per 1000 admissions in our surgical ICU. It means that IAC incidence in surgical ICUs is comparable to the incidence of candidemia in medical ICUs (6.7–34.3 episodes per 1000 ICU admissions) [17, 18, 21, 22]. In addition, we observed a trend towards slow increase in IAC incidence during period. It should be mentioned that significant difference in incidence trend was observed in C-IAC compared to H-IAC. Incidence rate of H-IAC was steady within the whole period while C-IAC demonstrated increasing incidence during this 4-year period. In 2016 C-IAC incidence reached nearly same level as H-IAC incidence. Based on this data, *Candida* species should be considered in aetiology of hospital-acquired intra-abdominal infections as well as in aetiology of community acquired intra-abdominal infections. There is no doubt that healthcare exposure is the most important risk factor for IAC, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis. However, there is a lack of data regarding risk factors for C-IAC. Increasing incidence of C-IAC supports the theory that the abdomen may be an important reservoir of *Candida* species in community. Unfortunately, the fungal colonization of otherwise healthy hosts and characteristic of human gut mycobiome have not been yet completely explored. We need to better identify and define the significant risk factors for C-IAC particularly.

Many different *Candida* species are known to be aetiological agents of invasive fungal infection, however, 90% of invasive infections are caused by *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* [19, 23,

24]. Our epidemiology study is consistent with the literature, *C. albicans* followed by *C. glabrata* and *C. tropicalis* were the most frequently isolated species from the peritoneal specimens. It is well recognized that just *C. glabrata* predominates as the second most frequent pathogen of invasive candidiasis in the North and Centre of Europe [25, 26, 27]. Moreover, non-CAAL species, including *C. glabrata*, *C. tropicalis* and *C. krusei*, were repeatedly reported in older patients in association with recent major abdominal surgery [25, 28, 29]. Regarding epidemiology trends, shift in the aetiology of IAC was observed in our surgical ICU. The first half of the period (2013–2014) was characterized by a predominance of *C. albicans* species. In the second half of the period (2015–2016) *C. albicans* decreased proportionally and non-CAAL species accounted for more than 50% of isolates.

Antifungal susceptibility/resistance is really important epidemiology characteristic. Generally, azole resistance for *Candida* species is more frequent than echinocandin resistance. In Europe the reported rate of *Candida* species with reduced susceptibility to fluconazole is 11–28% in patients with IAC [2, 16, 30]. Echinocandins demonstrate excellent activity for *Candida* species, accounting < 4% *Candida* isolates resistant to echinocandins worldwide [31, 32]. Bassetti et al. observed in 481 patients included in a multicentre study of abdominal candidiasis a total of 98% of *Candida* strains susceptible to echinocandins [16]. *Candida* species exhibit varying rates of susceptibility to the azole agents. *C. albicans* and some non-CAAL species, such as *C. tropicalis*, *C. parapsilosis*, *C. lusitanae*, *C. kefyr* and *C. dubliniensis*, remain highly susceptible to fluconazole (susceptibility rate > 98.0% and > 90.0%, respectively) [33, 34]. By contrast, decreased fluconazole susceptibility for *C. glabrata* (susceptibility rate 92–68.7%) has been reported and *C. krusei* is associated with intrinsic fluconazole resistance [33, 34]. Concerning antifungal resistance pattern in our surgical ICU, decreased antifungal susceptibility to azole drugs and excellent activity of echinocandins have been demonstrated. Prior fluconazole exposure and echinocandin sparing strategy may explain this shift towards to decreased fluconazole susceptibility. Acquired decreased fluconazole susceptibility was reported for *C. glabrata* exclusively. We have observed reduced susceptibility to fluconazole in association with increased prevalence of non-CAAL species. Moreover, aetiology shift towards to increase of non-CAAL isolates preceded sudden emergence of decreased fluconazole susceptibility in 2016. Therefore, we propound that changing antifungal susceptibility was predictable based on the shift in aetiology. Interestingly, increased prevalence of fluconazole SDD *C. glabrata* has been observed in H-IAC as well as in C-IAC. Prior fluconazole exposure explains

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the emergence of decreased fluconazole susceptibility in H-IAC. However, reason of emergence of fluconazole SDD *C. glabrata* in C-IAC is obscure.

Characteristics of patients and IAC risk factors were statistically analysed just for the purpose of comparisons of C-IAC and H-IAC. Both subgroups of patients were comparable in most characteristics (gender, age, BMI, comorbidity, etc.) (see Table 1). Targeted analysis of risk factor correlations was out of the interest. Concerning antifungal therapy and mortality, there is limited evidence of study outcomes due to the retrospective design of the study and missing considerable variables. Except many variables, mismatched aetiology is major limitation of analysis of therapy, mortality and prognosis in IAC. The clinical significance of *Candida* species recovered from intra-abdominal peritoneal fluid is the most controversial factor. The role of *Candida* species in the pathophysiology of polymicrobial peritonitis has not been conclusively defined. The differentiation between contamination, colonization and infection remains the main diagnostic challenge. Colonisation index and *Candida* score are used for identifying high risk patients for IAC and non-culture-based methods including (1→3)-β-d-glucan, mannan antigen, anti-mannan antibodies are recommended for detection of *Candida* species [35]. However, more studies are needed to assess the optimal criteria in high-risk patients and the efficiency of fungal biomarkers in the differentiation of colonisation and infection. This is a keystone of the unconvincing outcomes of most IAC studies. Empirical antifungal therapy has been demonstrated to decrease mortality significantly in a specific patient population. Bassetti et al. reported association between the absence of an adequate initial antifungal therapy and increased mortality in patients with adequate source control of IAC and septic shock [16]. Similarly, in a retrospective multi-centric analysis of 258 patients with intra-abdominal candidiasis in Spain, ICU patients that did not receive antifungal therapy for an IAC episode had a ~6-fold increase in mortality; however, the benefit of antifungal therapy was not observed in non-ICU patients [36]. Conversely, the current evidence does not demonstrate efficacy of antifungal therapy in improving outcomes in patients with IAC caused by perforated peptic ulcer [37]. Antifungal therapy in these patients may be considered overtreatment altering the outcomes. Prospective multicentre study and multivariable analysis are required for identification of IAC risk factors and determination of causative relationships of antifungal therapy and mortality.

Considering this study, the main limitation is the low number of included patients with IAC, which has resulted in a lower power of statistical significance of statistical analysis. However, our study outcomes underscore the importance of knowledge of the local epidemiology and resistance patterns for *Candida* species. Local epidemiology is crucial for guiding therapeutic decision making.

## CONCLUSIONS

We have revealed slowly raising of overall IAC incidence. Interestingly, more increasing trend in incidence of C-IAC compared to rather steady incidence of H-IAC has been discovered. During period 2013–2016 we have

observed a significant shift in the aetiology of IAC towards to an increased proportion of non-CAAL species, particularly *C. glabrata*. Acquired decreased susceptibility to fluconazole was related to *C. glabrata* isolates exclusively. Emergence of decreased antifungal susceptibility has been preceded by increase of incidence of non-CAAL isolates. Therefore, we assume that emergence of antifungal resistance may be predictable based on the shift in aetiology. In terms of antifungal susceptibility, significant risk of antifungal resistance may be related to H-IAC as well as C-IAC. Knowledge of local epidemiology is crucial for guiding therapeutic decision making.

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#### Declaration

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