



Risk Factors for Intra-Abdominal Candidiasis in Intensive Care Units: Results from EUCANDICU Study

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ABSTRACT

Introduction: Intra-abdominal infections represent the second most frequently acquired infection in the intensive care unit (ICU), with mortality rates ranging from 20% to 50%.

Matteo Bassetti and Antonio Vena equally contributed to this work.

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Candida spp. may be responsible for up to 10–30% of cases. This study assesses risk factors for development of intra-abdominal candidiasis (IAC) among patients admitted to ICU.

Methods: We performed a case–control study in 26 European ICUs during the period January 2015–December 2016. Patients at least 18 years old who developed an episode of microbiologically documented IAC during their stay in the ICU (at least 48 h after admission) served as the case cohort. The control group consisted of adult patients who did not develop episodes of

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IAC during ICU admission. Matching was performed at a ratio of 1:1 according to time at risk (i.e. controls had to have at least the same length of ICU stay as their matched cases prior to IAC onset), ICU ward and period of study.

Results: During the study period, 101 case patients with a diagnosis of IAC were included in the study. On univariate analysis, severe hepatic failure, prior receipt of antibiotics, prior receipt of parenteral nutrition, abdominal drain, prior bacterial infection, anastomotic leakage, recurrent gastrointestinal perforation, prior receipt of antifungal drugs and higher median number of abdominal surgical interventions were associated with IAC development. On multivariate analysis, recurrent gastrointestinal perforation (OR 13.90; 95% CI 2.65–72.82, $p = 0.002$), anastomotic leakage (OR 6.61; 95% CI 1.98–21.99, $p = 0.002$), abdominal drain (OR 6.58; 95% CI 1.73–25.06, $p = 0.006$), prior receipt of antifungal drugs (OR 4.26; 95% CI 1.04–17.46, $p = 0.04$) or antibiotics (OR 3.78; 95% CI 1.32–10.52, $p = 0.01$) were independently associated with IAC.

Conclusions: Gastrointestinal perforation, anastomotic leakage, abdominal drain and prior receipt of antifungals or antibiotics may help to identify critically ill patients with higher probability of developing IAC. Prospective studies

are needed to identify which patients will benefit from early antifungal treatment.

Keywords: *Candida*; Intra-abdominal infection; Invasive candidiasis; Risk factors

Key Summary Points

Intra-abdominal infections represent the second most frequently acquired infection in the intensive care unit, with mortality rates ranging from 20% to 50%.

Candida spp. may be responsible for up to 10–30% of cases.

Recurrent gastrointestinal perforation, anastomotic leakage and prior antibiotic therapy have been identified as risk factors for developing intra-abdominal candidiasis.

Prospective clinical studies are needed to identify which patients will benefit from early antifungal treatment.

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INTRODUCTION

Intra-abdominal infections represent the second most frequently acquired infection in the intensive care unit (ICU) [1, 2], with mortality rates ranging from 20% to 50% [1, 3–5]. They are more often caused by hospital isolates such as *Escherichia coli*, *Pseudomonas aeruginosa* or enterococci, but *Candida* spp. may be responsible for up to 10–30% of cases [1, 6, 7].

Although *Candida* spp. is increasingly recognized as a non-negligible cause of ICU-acquired intra-abdominal infection [4, 8–14], risk factors for developing an intra-abdominal candidiasis (IAC) in ICU patients are poorly understood [15, 16]. To the best of our knowledge, data on this disease are limited, fragmented, and usually consist of small collections of cases from single institutions [15–17]. Consequently, the characteristics of patients in whom there could be an increased risk of IAC and that may benefit the most from empiric

antifungal therapy had still to be clearly identified [18–21].

The aim of the present multicentre, multi-national, case–control study, conducted within the EUCANDICU project [22], was to assess independent risk factors for ICU-acquired IAC.

METHODS

This study was a retrospective, matched case–control study conducted to identify risk factors associated with IAC in ICU patients. Cases were identified via databases maintained by the microbiology laboratories of 26 ICUs from 25 large tertiary care European hospitals (12 in Italy, 5 in France, 2 in Greece, 1 in Belgium, 1 in Czech Republic, 1 in Germany, 1 in Ireland, 1 in Portugal, 1 in Spain, and 1 in the Netherlands). Twenty of the 26 centres (77%) were also included in a previous paper within the EUCANDICU project, detailing the incidence of invasive candidiasis in ICU (see

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supplementary material for more information) [22]. The primary study endpoint was development of ICU-acquired IAC.

Cases of IAC and controls were eligible for inclusion in the present study if they had an ICU stay of 48 h or longer and were admitted to the ICU from January 2015 to December 2016. Exclusion criteria were (i) age less than 18 years; (ii) receiving a diagnosis of invasive candidiasis prior to 48 h of the ICU stay or (iii) had concomitant intra-abdominal bacterial infections. During the study period surveillance swab screening was not a routine procedure in most of the ICU included in the study.

Patients who developed an episode of microbiologically documented IAC after at least 48 h of ICU stay were defined as cases. Each case patient was included only once, at the time of the first IAC episode, even if more than one episode was reported. The control group consisted of patients admitted to ICU for more than 48 h.

Matched controls (cases to control ratio 1:1) were selected by local investigators for each case. Matching criteria included ICU ward and time at risk for developing IAC (i.e. time from ICU admission to IAC development in each case was matched to a length of ICU stay at least equal to the corresponding control). Control patients were selected for case patients using the following mechanism: we determined the length of ICU stay prior to the development of IAC for a given case patient, restricted the roster of ICU patients to those who had lengths of stay at least as long as the case patient's time to infection, and then selected one control patient per case patient matching according to the same ICU and the same period. Most controls remained hospitalized in ICU after their inclusion in the study and they were followed up to ensure that (i) they did not develop subsequent episodes of invasive candidiasis based on negative cultures and (ii) did not receive any anti-fungal drugs during their remaining hospitalization.

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The study was approved by the ethics committee of the coordinating center (Regional Ethics Committee of Friuli-Venezia-Giulia Region, registry number CEUR-2017-Os-033-ASUIUD). Owing to its retrospective nature written informed consent was deemed unnecessary.

Data Collection

Investigators at each centre used a structured digital data collection instrument to retrieve clinical and laboratory data from the patients' medical records.

Risk factors were collected starting from 30 days prior to IAC diagnosis and included corticosteroids or other immunosuppressive drugs; acute kidney injury or need for renal replacement therapy; presence of a central venous catheter (CVC); invasive mechanical ventilation; receipt of antibiotics or antifungal drugs (being on antibiotic or antifungal treatment prior to IAC, for at least 7 days); parenteral nutrition; any bacterial infection; colonization of *Candida* at multiple non-sterile sites (i.e.

sputum, bronchoalveolar lavage, urine, feces and other non-sterile sites); major abdominal surgery; number of abdominal surgical interventions performed; recurrent gastrointestinal perforation; anastomotic leakage and abdominal drain. Other variables collected included demographics, comorbidities (also collectively expressed on the basis of the Charlson comorbidity index [23]), type of ICU ward (medical, surgical or mixed ICU); severity of illness at the time of ICU admission reflected by the SOFA score.

Definitions

ICU-acquired IAC was defined as an episode of IAC developing at least 48 h after ICU admission. IAC was defined according to previously published definitions [20, 24]. More specifically, IAC was defined as the presence of at least one of the following: (i) *Candida* detection by direct microscopy or growth in culture from necrotic or purulent intra-abdominal specimens obtained by percutaneous aspiration or during surgery; (ii) growth of *Candida* from bile or intra-biliary duct devices, or from abdominal

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organs biopsies; (iii) growth of *Candida* from blood cultures in the presence of secondary or tertiary peritonitis in the absence of other pathogens; (iv) growth of *Candida* from drainage tubes inserted less than 24 h before culture sampling [20]. Severe hepatic failure was defined as a prior history of Child B and C liver cirrhosis.

Microbiological Studies

Candida species identification and in vitro antifungal activity were assessed at participating hospitals using local routine methods and clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [www.eucast.org/clinical_breakpoints], respectively.

Statistical Analysis

The primary analysis was aimed at the identification of predictors of ICU-acquired IAC. To this aim, the possible difference of categorical and continuous variables with development of IAC was tested by means of the chi-squared (χ^2) and Wilcoxon rank-sum tests, respectively. Subsequently, variables associated with the development of intra-abdominal candidiasis in univariable comparisons ($p < 0.20$) were included in a multivariable, conditional logistic regression model for matched pairs (with the strata being composed of pairs of a case plus their control [25]) and further selected for the final multivariable model using a stepwise backward procedure. The analyses were performed with SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, 101 case patients with a diagnosis of IAC were included in the study. Of those, only seven patients (6.9%) had a concomitant blood cultures positive for *Candida* spp. The most commonly isolated species was *Candida albicans* (58.4% of the isolates), followed by *Candida glabrata* (15.8%) and *Candida*

tropicalis (4.0%). Other *Candida* species accounted for 5% of the isolates (*Candida krusei* 3.0%, *Candida dubliniensis* 1%, other 1%). The remaining 16.8% of cases had more than one *Candida* species isolated. Overall, resistance to fluconazole was detected in 17 out of 64 tested isolates (26.5%).

Demographics, Clinical Characteristics and Risk Factors for Intra-Abdominal Candidiasis

Table 1 shows the results of the univariate analysis of predictors of IAC. Variables associated with IAC included severe hepatic failure (7.9% vs. 1.0% in cases and controls, respectively, $p = 0.03$), prior receipt of antibiotics (69.3% vs. 41.6%, $p = 0.0001$), parenteral nutrition (64.4% vs. 48.5%, $p = 0.03$), abdominal drain (60.4% vs. 39.6%, $p = 0.005$), prior bacterial infection (53.5% vs. 20.8%, $p = 0.001$), anastomotic leakage (45.3% vs. 20.5%, $p = 0.007$), recurrent gastrointestinal perforation (31.4% vs. 6.8%, $p = 0.002$), prior receipt of antifungals (26.7% vs. 12.9%, $p = 0.02$) and higher median number of abdominal surgical interventions (median surgical interventions 3 vs. 1, $p = 0.04$). Controls had more frequently a prior history of heart disease (20.8% vs. 36.6%, $p = 0.02$) and neurological disease (5.9% vs. 16.8%, $p = 0.02$).

Multivariate Analysis

Table 2 shows the results from the multivariate analysis. The following factors remained independently associated with IAC: recurrent gastrointestinal perforation (OR 13.90; 95% CI 2.65–72.82, $p = 0.002$), anastomotic leakage (OR 6.61; 95% CI 1.98–21.99, $p = 0.002$), abdominal drain (OR 6.58; 95% CI 1.73–25.06, $p = 0.006$) and prior receipt of antifungal drugs (OR 4.26; 95% CI 1.04–17.46, $p = 0.04$) or antibiotics (OR 3.78; 95% CI 1.32–10.52, $p = 0.01$).

DISCUSSION

To our knowledge, the present study is the largest to evaluate independent risk factors for

Table 1 Univariate analysis of patient-related risk factors associated with intra-abdominal candidiasis in ICU

Variable	Case subjects <i>n</i> = 101 (%)	Control subjects <i>n</i> = 101 (%)	<i>P</i>
Age in years, mean (\pm SD)	63.3 \pm 13.3	64.1 \pm 13.0	0.65
Male gender	55 (54.5)	55 (54.5)	1
Type of ICU			
Medical	6 (5.9)	6 (5.9)	1
Mixed	33 (32.7)	33 (32.7)	1
Surgical	62 (61.4)	62 (61.4)	1
Underlying medical conditions			
Solid tumour	40 (39.6)	44 (43.4)	0.67
Heart disease	21 (20.8)	37 (36.6)	0.02
Diabetes mellitus	15 (14.9)	24 (23.8)	0.15
End-stage chronic renal disease	13 (12.9)	7 (6.9)	0.23
Chronic obstructive pulmonary disease	13 (12.9)	17 (16.8)	0.55
Severe hepatic failure*	8 (7.9)	1 (1.0)	0.03
Neurological disease	5.9%	16.8%	0.02
Solid organ transplant	6 (5.9)	2 (2.0)	0.27
Trauma	4 (4.0)	5 (5.0)	1
Hematological malignancy	3 (3.0)	3 (3.0)	1
HIV infection	3 (3.0)	0	0.24
Age-adjusted Charlson score, mean (\pm SD)	5.5 \pm 2.9	5.7 \pm 3.1	0.61
Immunosuppressive drugs*			
Corticosteroids	11 (10.9)	6 (5.9)	0.31
Others	11 (10.9)	5 (5.0)	0.19
SOFA score, median (IQR)**	6.4 \pm 4.4	5.5 \pm 4.6	0.14
Hospital management and clinical risk factors*			
Central venous catheter	92 (91.1)	92 (91.1)	1
Invasive mechanical ventilation	73 (72.3)	64 (63.4)	0.22
Receipt of antibiotics (7 or more days)	70 (69.3)	42 (41.6)	0.0001
Parenteral nutrition	65 (64.4)	49 (48.5)	0.03
Abdominal drain	61 (60.4)	40 (39.6)	0.005
Bacterial infection [#]	54 (53.5)	21 (20.8)	0.001
<i>Candida</i> colonization [#]	49 (48.5)	39 (32.6)	0.15
Acute kidney Injury	49 (48.5)	37 (36.6)	0.11

Table 1 continued

Variable	Case subjects <i>n</i> = 101 (%)	Control subjects <i>n</i> = 101 (%)	<i>P</i>
Abdominal surgery	45 (52.3)	30 (68.2)	0.09
Anastomotic leakage	39 (45.3)	9 (20.5)	0.007
Recurrent gastrointestinal perforation	27 (31.4)	3 (6.8)	0.002
Receipt of antifungal drugs (7 or more days)	27 (26.7)	13 (12.9)	0.02
Renal replacement therapy	23 (22.8)	13 (12.9)	0.09
Number of abdominal surgical interventions, median (IQR)	3.1 ± 2.3	1.8 ± 2.4	0.04

*Unless otherwise indicated risk factors were collected within 30 days before intra-abdominal candidiasis (cases) or matched time period (controls)

**SOFA score calculated at the time of ICU admission

#Within previous 3 months

developing intra-abdominal candidiasis in a large population of patients admitted to ICU. We found that recurrent gastrointestinal perforation, anastomotic leakage, abdominal drain and receipt of antifungal drugs or antibiotics for more than 7 days were independently associated with the development of IAC.

An important increase in *Candida* spp. among the pathogens involved in intra-abdominal infections has been reported in the last decade [8–11]. *Candida* is currently one of the most important causative agent of intra-abdominal infection, because of its reported association with increased morbidity and mortality [4, 8–12, 20, 24]. In some reports, *Candida* accounts for more than 50% of all isolated pathogens occurring in intra-abdominal infection in ICU [4, 8–12], and ranks as the second to fourth most common microorganism in several intra-abdominal infection series [8–11].

Unfortunately, our understanding of risk factors associated with IAC had been mostly extrapolated from studies including patients with candidemia or from patients with non-postoperative intra-abdominal infections [15–17], a population mainly coming from the community, with unique characteristics that may not be relevant to critically ill patients with prolonged ICU stay, who are those in whom IAC mostly develops. These studies showed that length of stay before surgery, peroperative

cardiovascular failure, generalized peritonitis, upper gastrointestinal tract perforation, *Candida* colonization or number of organ dysfunctions were associated with *Candida* isolation in the abdomen [15–17].

The present study is a better reflection of daily clinical practice because we included only patients admitted to ICU, which corresponds to the largest proportion of patients affected by IAC [26–28]. In our report, variables independently associated with IAC were recurrent gastrointestinal perforation, anastomotic leakage, abdominal drain and prior antifungal drugs or antibiotics more than 7 days. The association with recurrent gastrointestinal perforation or anastomotic leakage was not unexpected. Indeed, both factors cause gastrointestinal barrier destruction and create a permissive environment that allows the seeding of *Candida* cells into the peritoneal cavity [20, 29]. Therefore, our findings support previous recommendation to consider an antifungal treatment for patients with recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage [13, 20].

The presence of abdominal drain was also associated with a higher probability of developing IAC in patients admitted to the ICU. In this study, the management of abdominal devices was left to the operating surgeon's discretion and no protocol was available indicating

Table 2 Independent predictors of intra-abdominal candidiasis among patients admitted to ICU on the basis of multivariate logistic regression analysis

Risk factors ^a	OR (95% CI)	<i>p</i>
Recurrent gastrointestinal perforation	13.90 (2.65–72.82)	0.002
Anastomotic leakage	6.61 (1.98–21.99)	0.002
Abdominal drain	6.58 (1.73–25.06)	0.006
Receipt of antifungal drugs (7 or more days)	4.26 (1.04–17.46)	0.04
Receipt of antibiotics (7 or more days)	3.78 (1.32–10.52)	0.01

Only variables retained in the final multivariate models are presented. Risk factors were collected within 30 days before intra-abdominal candidiasis (cases) or matched time period (controls)

^aVariables with $p < 0.20$ in the univariate analysis (heart disease; diabetes mellitus; severe hepatic failure; immunosuppressive drugs other than corticosteroids; SOFA score; prior receipt of antibiotics (7 or more days); parenteral nutrition; abdominal drain; bacterial infection; *Candida* colonization; acute kidney injury; abdominal surgery; anastomotic leakage, recurrent gastrointestinal perforation; prior receipt of antifungal drugs > 7 days; renal replacement therapy; number of abdominal surgical intervention) were considered for the multivariate model of cases vs. controls group. The Hosmer–Lemeshow goodness of fit test results indicate a p value of 0.34

the conditions for using them. Ours is the first study to show this association. We could speculate that a foreign material in a contaminate field might be a “culture medium” for *Candida*, supporting the onset of postoperative IAC. In addition, yeasts are typically associated with the ability to form biofilms on implanted devices [30, 31], suggesting that *Candida* spp. may be associated with IAC development caused by formation of biofilm on prosthetic devices. However, in order to give a definitive conclusion, future studies are recommended.

We also found that prior exposure to antibiotics was an independent risk factors for IAC in ICU patients [15]. Our results are consistent with several earlier studies in which exposure to antibiotic agents was strongly associated with invasive candidiasis [32–34]. The prolonged use of antibiotics could create a selective pressure for the overgrowth and endurance of *Candida* in the gut, which could increase the likelihood of subsequent IAC development [35–37]. Further studies should clarify the relationships between the spectrum of antimicrobial activity and the duration of previous antibiotic use with IAC development. Moreover, the independent association between previous antifungal drugs and subsequent

development of IAC may reflect the severity of patients’ underlying diseases.

In the absence of clinical evidence supporting the systematic benefit of antifungal prophylaxis [38–40], other strategies to decrease rates of IAC should be considered. On the basis of our findings, attempts aimed at implementing adequate surgical procedures and supportive therapies may have a higher impact on reducing episodes of IAC in ICU [41]. Moreover, previous studies have shown a decrease of invasive candidiasis by improving antimicrobial stewardship strategies and/or infection control measures [42, 43]. Therefore, audits of the use of antimicrobial agents should be considered for understanding the real need for antibiotics and guide their judicious use, especially in the presence of other risk factors for IAC.

In contrast to previous studies, we could not demonstrate that *Candida* colonization was a risk factor for IAC [2, 17]. However, this could be explained by the policy of some centres included in the EUCANDICU study to not actively and systematically screen for *Candida* carriers in all patients admitted to ICU. This represents a clear limitation of the present observational study.

As for etiology of IAC in terms of the relative prevalence of the different *Candida* species,

information remains partially elusive [20, 44]. In our study, which mainly includes centres from southern European regions, we observed the typical distribution of *Candida* species of this geographical area, where *C. albicans* is predominant, followed by *Candida parapsilosis* and *C. glabrata* [45, 46]. Of interest, fluconazole-non-susceptible strains occurred in about a quarter of tested strains. This finding may have important implications for the selection of empirical antifungal therapy among patients with IAC hospitalized in European ICUs.

There are several potential limitations to our study that should be addressed. First, selection bias is normally of concern in a case-control study; however, cases and controls were selected from the same distinct source cohort (ICU admission), thus minimizing the likelihood of selection bias. Second, we were not able to recruit more than one control patient per case, thus limiting the statistical power of the present study; however, this limitation reflects the “real life” difficulty to identify patients admitted to ICU who surely develop no invasive candidiasis. Third, although the EUCANDICU study is a multicentre study including a large number of patients, the generalizability of the observations may be limited by differences in *Candida* epidemiology between geographical areas or by differences in medical practice or health system organization. Nevertheless, these data are important, because they reflect the most robust series of patients with ICU-acquired IAC in a large group of centres coming from several European countries. Fourth, the study population gathers together different clinical situations such as secondary or tertiary peritonitis, abdominal abscess, cholangitis, cholecystitis and infected pancreatic necrosis [47] that were not differentiated in our study. Accordingly, future studies should aim for a homogenous cohort of patients to more closely address the risk factor issue of this complex population. Fifth, other unmeasured factors such as previous antibiotic exact duration or reasons for previous antibiotic treatment (complicated intra-abdominal infections versus other reasons) might have significantly contributed to development of intra-abdominal candidiasis. In addition, we could not control for the type of

abdominal surgery performed or the precise location of perforation or leakage, factors that have been previously shown to be associated with the frequency of *Candida* isolation in abdominal fluid samples (gastroduodenal, small intestine, biliary tract). Lastly, another limitation of our study is the lack of data regarding fungal biomarkers or comprehensive information regarding prior *Candida* colonization and the inherent possibility of having missed some cases of IAC. Therefore, our results cannot be considered as definitive but rather as a starting point to justify costlier and time-consuming longitudinal studies in the near future.

CONCLUSIONS

On the basis of these findings, recurrent gastrointestinal perforation or anastomotic leakage in addition to prior antibiotic therapy may help clinicians to identify a subgroup of critically ill patients with higher probability of developing intra-abdominal candidiasis. A large multicentre study is needed to prospectively and externally validate our findings, and to potentially create a dedicated prediction score to better identify patients at risk of ICU-acquired IAC.

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Data Availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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