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Invasive candidiasis: comparison of management choices by infectious disease and critical care specialists

Philippe Eggimann
Thierry Calandra
Ursula Fluckiger
Jacques Bille
Jorge Garbino
Michel-Pierre Glauser
Oscar Marchetti
Christian Ruef
Martin Täuber
Didier Pittet
for the Fungal Infection Network of Switzerland (FUNGINOS)

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P. Eggimann · D. Pittet (✉)
Infection Control Program,
University of Geneva Hospitals,
24 Rue Micheli-du-Crest, 1211 Geneva 14,
Switzerland
e-mail: didier.pittet@hcuge.ch
Tel.: +41-22-3729834
Fax: +41-22-3723987

T. Calandra · M.-P. Glauser · O. Marchetti
Infectious Diseases Service,
Department of Internal Medicine,
Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland

U. Fluckiger
Division of Infectious Diseases,
University Hospital,
Basel, Switzerland

J. Bille
Institute of Microbiology,
Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland

J. Garbino · D. Pittet
Division of Infectious Diseases,
Department of Internal Medicine,
University of Geneva Hospitals,
Geneva, Switzerland

C. Ruef
Division of Infection Control
and Prevention,
Universitätsspital,
Zurich, Switzerland

M. Täuber
Institute for Infectious Diseases,
University of Bern,
Bern, Switzerland

Present address:
P. EggimannSurgical ICU and Burn Unit,
Centre Hospitalier Universitaire Vaudois,
1011 Lausanne, Switzerland

Abstract *Objective:* To compare the management of invasive candidiasis between infectious disease and critical care specialists. *Design and setting:* Clinical case scenarios of invasive candidiasis were presented during interactive sessions at national specialty meetings. Participants responded to questions using an anonymous electronic voting system. *Patients and participants:* Sixty-five infectious disease and 51 critical care physicians in Switzerland. *Results:* Critical care specialists were more likely to ask advice from a colleague with expertise in the field of fungal infections to treat *Candida glabrata* (19.5% vs. 3.5%) and *C. krusei* (36.4% vs. 3.3%) candidemia. Most participants reported that they would change or remove a central venous catheter in the presence of candidemia, but 77.1% of critical care specialists would start concomitant antifungal treatment, compared to only 50% of infectious disease specialists. Similarly, more critical care specialists would start antifungal prophylaxis when *Candida* spp. are isolated from the peritonal fluid at time of surgery for peritonitis resulting from bowel perforation (22.2% vs. 7.2%). The two groups equally considered *Candida* spp. as pathogens in tertiary peritonitis, but critical care specialists would more frequently use amphotericin B than fluconazole, caspofungin, or voriconazole. In mechanically ventilated patients the isolation of 10^4 *Candida* spp. from a bronchoalveolar lavage was considered a colonizing organism by 94.9% of infectious disease, compared to 46.8% of critical care specialists, with a marked difference in the use of antifungal agents (5.1% vs. 51%). *Conclusions:* These data highlight differences between management approaches for candidiasis in two groups of specialists, particularly in the reported use of antifungals.

Keywords Antifungal treatment · Critical care specialists · Infectious disease · Invasive candidiasis · Switzerland · Treatment survey

Introduction

Invasive candidiasis is recognized as a leading cause of morbidity and mortality in critically ill non-immunocompromised patients, with crude and attributable mortality rates of more than 50% and 20%, respectively [1, 2, 3, 4, 5]. *Candida* spp. have been identified as a significant pathogen in the European Study on the Prevalence of Nosocomial Infections in Critically Ill Patients [6]. Candidemia represents 10-20% of candidiasis cases and is the fourth leading organism responsible for nosocomial bloodstream infection in the United States, preceded by coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci [7, 8]. In Europe *Candida* spp. range among the eighth to tenth leading nosocomial bloodstream pathogens in most countries [9, 10, 11, 12]. In critically ill patients, candidemia significantly prolongs the duration of mechanical ventilation and increases workload, length of stay, and treatment costs [1, 4, 5].

Although never verified as effective in a prospective, randomized, controlled trial in critically ill patients, early preemptive antifungal therapy may improve the prognosis of invasive candidiasis in the presence of risk factors for infection and/or significant *Candida* colonization [13, 14, 15]. In addition, it corresponds to current clinical practice among many experts, including Europeans [16, 17]. Colonization is the leading risk factor for infection in most series in which it has been adequately explored; *Candida* spp. carriage has been confirmed to be patient-specific and to precede bloodstream or invasive infections [18, 19]. While colonization may occur in a large proportion of critically ill patients, only a minority develop severe candidiasis [3, 20, 21, 22, 23]. In contrast to what is currently proposed for immunocompromised hosts [16, 24], systematic recourse to antifungal prophylaxis or preemptive therapy is not recommended for colonized critically ill patients. In the absence of large clinical series, patients susceptible to benefit from these approaches are difficult to identify, and current published recommendations are mostly derived from consensus conferences and expert opinion [25, 26, 27, 28, 29]. Accordingly, the clinical management of invasive candidiasis may differ among specialists.

The main objective of this study was to compare the management of invasive candidiasis between infectious disease and critical care specialists in Switzerland. We observed notable differences in the use of antifungals which may have important implications for the development of guidelines and postgraduate continuous education.

Material and methods

Setting

Clinical case scenarios of invasive candidiasis were presented during planned interactive sessions at the national meetings of the Swiss Society of Infectiology in March 2003 and the Swiss Society of Critical Care Medicine in May 2004. These cases included episodes of clinical sepsis related to candidemia, catheter-related candidemia, peritonitis, isolated and complicated candiduria, and clinical suspicion of ventilator-associated pneumonia. Each case is summarized in the corresponding paragraph of the results section.

Participants

Study participants included 65 infectious disease specialists and 51 critical care specialists who attended the interactive sessions. None attended both sessions. Critical care and infectious disease specialists directly involved in patient care worked in teaching hospitals (43.2% vs. 50%, respectively), university-affiliated hospitals (21.6% vs. 15.9%), community (12.7% vs. 2.3%), and private hospitals (1.6% vs. 15.9%). Among infectious disease specialists, 29.6% were also clinical microbiologists, and 13% were specialists in internal medicine. Among critical care physicians, 50% reported being board-certified in intensive care medicine, 15.9% in anesthesiology, 15.9% in internal medicine, 9.1% in pediatrics, and 2.3% in surgery. Participants worked in mixed (54.4%), medical (14.6%), surgical (12.3%), or pediatric (8.3%) intensive care units.

Methods

Participants gave their opinion by answering a series of questions using an anonymous electronic voting system. Response distribution was automatically recorded. In brief, participants were first asked to choose one of several therapeutic options for the management of patients with bloodstream infection due to *Candida albicans*, *C. glabrata*, and *C. krusei*. Various options for the management of the central venous access were then proposed. Participants' opinions regarding the possible pathogenicity of *Candida* spp. isolated from clinical specimens were similarly recorded. The additional cases presented concerned peritonitis from bowel perforation and tertiary peritonitis, simple and complicated candiduria, and a clinical condition with suspicion of ventilator-associated pneumonia.

Statistics

To avoid a multiple testing effect in small groups, Fisher's exact test was used to test responses with clinically relevant differences (more than 25%) between infectious disease and critical care specialists.

Results

Candidemia

– *Case presentation:* A 78-year-old diabetic man presented with abdominal pain. He underwent emergency surgery for sigmoid perforation due to obstructive colon cancer. On day 5 antimicrobial therapy was broadened from amoxicillin/clavulanate to a combi-

Table 1 Therapeutic options for the treatment of candidemia

	Infectious disease specialists		Critical care specialists		Total	
	n	%	*n*	%	*n*	%
C. albicans	63	–	47	–	110	–
Fluconazole	42	66.7	32	68.1	74	67.3
Amphotericin B	6	9.5	7	14.9	13	11.8
Other antifungals[a]	5	7.9	1	2.1	6	5.5
No treatment	4	6.4	1	2.1	5	4.5
I don't know, I would seek advice	6	9.5	6*	12.8	12	10.9
C. glabrata	58	–	41	–	99	–
Fluconazole	3	5.2	2	4.9	5	5.0
Amphotericin B	33	56.9	17	41.5	50	50.5
Other antifungals[b]	20	34.5	14	34.2	34	34.3
No treatment	0	–	0	–	0	–
I don't know, I would seek advice	2	3.5	8**	19.5	10	10.1
C. krusei	60	–	44	–	104	–
Fluconazole	0	–	1	2.3	1	0.9
Amphotericin B	34	56.6	16***	36.4	50	48.1
Other antifungals[c]	24	40.0	11	25.0	35	33.6
No treatment	0	–	0	–	0	–
I don't know, I would seek advice	2	3.3	16[4]*	36.4	18	17.3

* p=0.076, ** p=0.015, *** p=0.049, [4]* p<0.0001 infectious disease vs. critical care specialists (Fisher's exact test)

[a] Caspofungin in 2 (3.2%) vs. 0, voriconazole in 1 (1.6%) vs. 1 (2.1%), and combined treatment in 2 (3.2%) vs. 0 among infectious disease and critical care specialists, respectively

[b] Caspofungin in 9 (15.5%) vs. 9 (22.0%), voriconazole in 8 (13.8%) vs. 5 (12.2%) and combined treatment in 3 (5.1%) vs. 0 among infectious disease and critical care specialists, respectively

[c] Caspofungin in 13 (21.7%) vs. 4 (9.1%), voriconazole in 7 (11.7%) vs. 7 (15.9%) and combined treatment in 4 (6.7%) vs. 0 among infectious disease specialists and critical care specialists, respectively

nation of cefepime and metronidazole because of persistent low-grade fever (37.5°C). On day 9 the patient was admitted to the ICU with acute heart failure and pulmonary edema requiring noninvasive ventilation. On day 13 meropenem was empirically started for a new episode of clinical sepsis with suspicion of nosocomial pneumonia; *Candida* spp. grew from blood cultures.

Therapeutic options for *C. albicans*, *C. glabrata*, and *C. krusei* candidemia among infectious disease and critical care specialists are shown in Table 1. Two-thirds of specialists in both groups proposed to treat *C. albicans* candidemia using fluconazole. In contrast, fluconazole was chosen by fewer than 5% in both groups for nonalbicans *Candida* strains. Critical care physicians were more likely than infectious disease specialists to seek the opinion of a colleague specialized in the management of patients with fungal infections, in particular for the treatment of *C. glabrata* and *C. krusei* candidemia. Infectious disease specialists reported choosing amphotericin B or newly licensed antifungal agents (voriconazole or caspofungin) more frequently for *C. krusei* infection.

Catheter-associated candidemia

– *Case presentation:* (The following information was added to the above-mentioned clinical scenario.) A central venous access in the left subclavian vein was used for parenteral nutrition since day 1.

The management options retained for such an episode of candidemia associated with a central venous line are shown in Table 2. Most participants reported that they would change or remove the line. As many as 77.1% of critical care specialists would start concomitant antifungals, compared to only 50% of infectious disease specialists (p<0.001).

Intra-abdominal infection

– *Case presentation:* A 75-year-old patient presented with abdominal pain. Emergency surgery with surgical drainage of the peritonitis and left colon resection was performed for perforated diverticulitis. On day 3 the patient was subfebrile (37.9°C) but remained stable. Peritoneal fluid cultures obtained during surgery grew *Escherichia coli* and *Proteus mirabilis* in moderate amount (++) and *C. albicans* in low amount (+).

Table 2 Management options for the treatment of catheter-associated candidemia

	Infectious disease specialists (*n*=52)		Critical care specialists (*n*=48)		Total (*n*=100)	
	n	%	*n*	%	*n*	%
Nothing	3	5.8	1	2.1	4	4.0
Change or remove without antifungals[a]	21	40.4	10	20.8	31	31.0
Change or remove with antifungals[b]	26	50.0	37*	77.1	63	63.0
I don't know, I would seek advice	2	3.9	0	–	2	2.0

* $p<0.0001$ infectious disease vs. critical care specialists (Fisher's exact test)
[a] Including change over a guidewire in 2 (3.8%) vs. 0 and removal with insertion of a new catheter at another site in 19 (36.5%) vs. 10 (20.8%) among infectious disease and critical care specialists, respectively
[b] Including change over a guidewire in 2 (3.8%) vs. 6 (12.5%) and removal with insertion of a new catheter at another site in 24 (46.1%) vs. 31 (64.6%) among infectious disease and critical care specialists, respectively ($p<0.0001$, by Fisher's exact test)

Table 3 Management options for *Candida* spp. peritonitis

	Infectious disease specialists		Critical care specialists		Total	
	n	%	*n*	%	*n*	%
Bowel perforation	55	–	45	–	100	–
Colonizing organism, no treatment	25	45.5	20	44.4	45	45.0
Colonizing organism, I start prophylaxis	4	7.2	10*	22.2	14	14.0
Pathogen, I start antifungals[a]	25	45.5	13	28.9	38	38.0
I don't know, I would seek advice	1	1.8	2	4.4	3	3.0
Tertiary peritonitis	58	–	37	–	95	–
Colonizing organism, no treatment	2	3.5	3	8.1	5	5.3
Colonizing organism, I start prophylaxis	1	1.7	0	–	1	1.0
Pathogen, I start antifungals[b]	53	91.4	34	91.9	87	91.6
I don't know, I would seek advice	2	3.5	0	–	2	2.1

* $p=0.04$ infectious disease vs. critical care specialists (Fisher's exact test)
[a] Fluconazole in 23 (41.8%) vs. 13 (28.9%), amphotericin B in 2 (3.6%) vs. 0, caspofungin in 0 vs. 0, and voriconazole 0 vs. 0 among infectious disease and critical care specialists, respectively
[b] Fluconazole in 50 (86.2%) vs. 29 (78.4%), amphotericin B in 1 (1.8%) vs. 4 (10.8%) ($p=0.007$), caspofungin in 2 (3.4%) vs. 0, and voriconazole 0 vs. 1 (2.7%) among disease and critical care specialists, respectively

As shown in Table 3, *C. albicans* isolated during initial surgery for peritonitis was considered as a colonizing organism by a majority of physicians in both groups (66.6% vs. 52.7%). However, a higher proportion of critical care specialists would start antifungal prophylaxis (22.2% vs. 7.2%; $p=0.04$). Overall, antifungal treatment (whether considered prophylaxis or therapy) would be prescribed by more than 50% of specialists in both groups.

– *Case presentation:* Ovarectomy was performed in a 65-year-old woman with adenocarcinoma. On day 4 she required revision laparatomy with resection of a perforated ileal section and end-to-end anastomosis. She received meropenem and mixed bacterial flora grew from the intraperitoneal swabs. After initial improvement, fever and clinical signs of peritonitis relapsed on day 7. Because of the lack of clinical improvement and onset of organ dysfunction, abdominal computed tomography was performed and showed diffuse peritonitis without abscess. Microbiological sampling performed at time of computed tomography recovered low amounts (+) of coagulase-negative staphylococci and *Enterococcus faecium*, both resistant to meropenem, and *C. albicans* in large amounts (+++) grew from ascitis.

The great majority of infectious disease and critical care specialists considered *C. albicans* as a pathogen during the course of tertiary peritonitis (Table 3). Most physicians from both groups recommended using fluconazole as a therapeutic option for *C. albicans* infection. However, 10.8% of critical care specialists would select amphotericin B, compared to 1.8% of infectious disease physicians only ($p=0.007$).

Urinary tract infection

– *Case presentation:* A 75-year-old woman underwent total hip prosthesis. Intravenous line and urinary catheter were removed on day 2. She developed fever (38.5°C) on day 7 without clinical focus of infection. Routine microscopic urine examination showed 10–20 leukocytes per low power field and culture grew *C. albicans* (10^4 cfu/ml).

Table 4 Management options for *Candida* spp. candiduria

	Infectious disease specialists		Critical care specialists		Total	
	n	%	*n*	%	*n*	%
Isolated candiduria	60	–	51	–	111	–
Colonizing organism, no treatment	33	55.0	31	60.8	64	57.6
Colonizing organism, I start prophylaxis	0	–	3*	5.9	3	2.7
Pathogen, I start antifungals[a]	23	38.3	17	33.3	40	36.0
I don't know, I would seek advice	4	6.7	0	–	4	3.6
Complicated candiduria	61	–	45	–	106	–
Colonizing organism, no treatment	32	52.5	27	60.0	59	55.7
Colonizing organism, I start prophylaxis	4	6.6	3	6.7	7	6.6
Pathogen, I start antifungals[b]	23	37.7	14	31.1	37	34.9
I don't know, I would seek advice	2	3.3	1	2.2	3	2.8

* p=0.09 infectious disease vs critical care specialists (Fisher's exact test)
[a] Fluconazole in 17 (28.3%) vs. 16 (31.4%), amphotericin B in 4 (6.7%) vs.1 (1.9%), caspofungin in 1 (1.7%) vs. 0, and voriconazole 1 (1.7%) vs. 0 among infectious disease critical care specialists, respectively
[b] Including fluconazole in 21 (34.4%) vs. 13 (28.9%), amphotericin B in 0 vs. 1 (2.2%), caspofungin in 0 vs. 0, and voriconazole 2 (3.4%) vs. 0 among infectious disease and critical care specialists, respectively

Table 5 Management options for clinical suspicion of ventilator-associated pneumonia

	Infectious disease specialists (n=39)		Critical care specialists (n=47)		Total (n=86)	
	n	%	*n*	%	*n*	%
Colonizing organism, no treatment	37	94.9	22*	46.8	59	68.6
Colonizing organism, I start prophylaxis	0	–	1	2.1	1	1.2
Pathogen, I start antifungals[a]	2	5.1	23**	48.9	25	29.1
I don't know, I would seek advice	0	–	1	2.1	1	1.2

* p<0.0001, ** p<0.001 infectious disease vs. critical care specialists (Fisher's exact test)
[a] Fluconazole in 1 (2.6%) vs. 23 (48.9%), amphotericin B in 1 (2.6%) vs. 0, caspofungin in 0 vs. 0, and voriconazole 0 vs. 0 among infectious disease and critical care specialists, respectively (p=0.001)

– *Case presentation:* A 30-year-old man was admitted to the ICU for multiple trauma requiring mechanical ventilation. Initial amoxicillin/clavulanate given empirically on admission for fever of unknown origin was stopped after 3 days. On day 10, low-grade fever (38.0–38.5°C) persisted without clinical focus of infection. Blood cultures were sterile and urine culture obtained through the urinary catheter used from day 1 grew *C. albicans* (10^5 cfu/ml). *Candida* spp. were not isolated from any other body site.

As shown in Table 4, approx. one-third of infectious disease and critical care specialists considered *Candida* spp. candiduria as a true fungal infection in both simple and complicated conditions.

Respiratory tract infection

– *Case presentation:* A 30-year-old man was admitted to the ICU for multiple trauma requiring mechanical ventilation. Initial amoxicillin/clavulanate given empirically for fever of unknown origin was stopped after 3 days. Fever (39.0°C) developed on day 14 with bilateral pulmonary infiltrates. Bronchoalveolar lavage was performed and grew *Pseudomonas aeruginosa* (10^2 cfu/ml), *Acinetobacter baumani* (10^2 cfu/ml), and *C. albicans* (10^4 cfu/ml). *Candida* spp. were not isolated from any other body site. Blood cultures remained negative.
Candida spp. counts of 10^4 cfu/ml recovered from a bronchoalveolar lavage performed in this patient with clinical suspicion of ventilator-associated pneumonia were considered as a colonizing organism by 94.9% of infectious disease specialists, compared to 46.8% of critical care specialists (p<0.0001; Table 5). Antifungals would have been prescribed by 5.1% of infectious disease specialists, compared to 51% of critical care specialists (p<0.001).

Discussion

Delay or absence of antifungal therapy is associated with poor outcome from invasive candidiasis [1, 2, 3, 4, 5]. Both intensive care and infectious disease specialists are confronted with such critical conditions. To our knowledge, this is the first report comparing the clinical management and therapeutic options for invasive candidiasis

in critically ill, non-immunosuppressed patients in these two specialty groups.

Experts and consensus conferences recommend treating all episodes of candidemia with antifungals [25, 26, 27, 28, 29]. In this study, a large majority of participants from both groups of physicians reported to start antifungal therapy in patients with single blood culture-positive episodes of candidemia. Of note, a higher proportion of critical care specialists would ask colleagues for advice in cases of *C. albicans*, *C. glabrata* and *C. krusei* candidemia; infectious disease specialists appear to have a better knowledge of microbiological aspects. We were surprised by the low proportion of specialists choosing new antifungals for the treatment of non-albicans *Candida* spp. candidemia [30]. Importantly, at least 10 of 63 (15.9%) infectious disease specialists either would not treat or would seek advice from a colleague experienced in fungal infections. This may suggest that recommendations for the management of fungal infections should be promoted. In a recent prospective multicenter study in 24 adult intensive care units in Paris, France, the majority (78%) of patients with documented candidemia were treated with fluconazole, while a significant proportion (52%) received amphotericin B [31]. In our study we did not survey what would have been the nature of the initial antifungal therapy given to candidemic patients by physicians at time of awareness of blood cultures positive for *Candida* spp., but before knowledge of the species' identification.

Intravenous catheters are the leading source of candidemia. To date, no randomized, controlled study has been specifically designed to assess the benefit of systematic line removal; thus management remains controversial [25, 26, 27, 28, 29, 32, 33]. Data from 15 series in which the outcome of candidemia was studied in relation to vascular access management have been reviewed elsewhere [34, 35]. They support the current recommendation to remove all vascular accesses at time of candidemia, in particular for unstable, critically ill patients [15, 25, 26, 27, 28, 29, 32]. A large majority of participants indicated that they would remove the central venous line in a candidemic patient, but three-quarters of critical care specialists would concomitantly start antifungals, compared to only one-half of infectious disease specialists.

Candida infections following abdominal surgery are characterized by mortality rates higher than 50% [13, 23, 36]. However, there is no consensus nor are there criteria for the diagnosis of fungal peritonitis. Some investigators consider the presence of *Candida* spp. in any abdominal specimen as pathogenic and recommend systematic empirical antifungal treatment, while others consider it as contamination in most situations, particularly in the case of peritonitis resulting from bowel perforation [37, 38]. There is currently no consensus about the usefulness of empirical or prophylactic antifungal therapy except in patients with pancreatitis or *Candida* spp. recovery from tertiary peritonitis [21, 23, 36, 37, 39]. According to our observations, although a higher proportion of critical care specialists would initiate antifungal prophylaxis when *Candida* spp. are isolated in the case of peritonitis from bowel perforation, more than one-half of the physicians in both groups would use antifungal treatment in such a condition. Such a difference in strategy might be explained by the different types of patient population both groups of specialists have been exposed to during their respective clinical practice.

The clinical significance of candiduria is generally unknown. It can be detected in 20–30% of critically ill patients equipped with a urinary catheter, can remain asymptomatic and disappear spontaneously, lead to pyelonephritis, or manifest occasionally as a marker of candidemia [40]. Systematic antifungal treatment of asymptomatic candiduria may not be beneficial, and experts recommend considering risk factors and underlying conditions before deciding upon eventual treatment [25, 26, 27, 28, 29, 41]. In the case of *C. albicans* candiduria, whether complicated or not, only one-third of participants in both groups of specialists would start antifungal therapy. More than 90% of participants in both groups indicated that they would use fluconazole for the treatment of *Candida* spp. candiduria. The low use of other antifungals may reflect the very low incidence of infections due to non-albicans strains of *Candida* in Switzerland [12]. A recent prospective multicenter study in 24 French intensive care units reported that 25% of patients treated for documented candiduria effectively received antifungal therapy, mostly fluconazole [42].

Candida spp. are often isolated from the upper respiratory tract of mechanically ventilated patients and they figure regularly among the frequent pathogens responsible for nosocomial pneumonia [43]. However, *Candida* spp. have a very low affinity for pneumocytes, and histologically confirmed candidal pneumonia is rare; thus the clinical significance of *Candida* spp. even when recovered from bronchoalveolar lavage or protected brush specimen remains difficult to determine [44, 45]. The existence of true candidal pneumonia is doubted by most investigators, who require histological demonstration of invasive disease [44, 46]. In addition, thresholds for positive quantitative cultures of bronchoalveolar lavage fluid for *Candida* spp. have never been evaluated and validated. Experts repeatedly recommend considering the recovery of *Candida* spp. from the respiratory tract as colonization that does not require antifungal therapy [25, 26, 27, 29]. Surprisingly, in our survey, in contrast to the majority of infectious disease physicians, one-half of all critical care specialists would consider the growth of high amounts of *Candida* spp. in a bronchoalveolar lavage as pathogenic and treat accordingly. Almost all participants of both groups indicated that they would use fluconazole

for the treatment of *Candida* spp. ventilator-associated pneumonia.

The major limitation of our study, as in similar reports, is that it consisted of a descriptive survey of management options without validation of practices at the bedside [25, 26, 28]. Direct monitoring of physician practices would, however, be beyond the capacity of investigation. Whether reported management options correspond to practice in reality remains to be studied. The participants were nevertheless a large sample of board-certified intensive care (38%) and infectious disease (65%) specialists in Switzerland. Whether participants in the current evaluation were truly representative of all critical care and infectious disease physicians in the country, or whether participation bias could explain for the differences observed between the groups remains unknown. Furthermore, whether differences observed between Swiss specialists could be generalized to other countries deserves further investigation. Finally, this study also suggests the lack of a consistent pattern of management strategies for invasive candidiasis among specialists within the same specialty that would require further investigation. A possible future approach would be to organize a consensus conference with the two groups of specialists in an attempt to produce co-authored sets of clinical guidelines to help homogenize infection definitions and management options.

These data highlight key differences between management approaches for candidiasis among infectious disease specialists and critical care physicians. The lack of overall consensus between and among the different groups of physicians suggests that continuous educational efforts should be provided to both types of specialists.

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