International Journal of Antimicrobial Agents 62 (2023) 106998

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Tolerability of pulsed high-dose L-AmB as pre-emptive therapy in patients at high risk for intra-abdominal candidiasis: A phase 2 study (LAMBDA study)

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ARTICLE INFO

Article history:
Received 4 June 2023
Accepted 4 October 2023

Editor: Prof S Wicha

Keywords:
Intra-abdominal candidiasis
BDG
L-AmB

ABSTRACT

Background: Intra-abdominal candidiasis (IAC) has a high mortality rate. However, the correct management of a critically ill patient with suspected IAC remains unclear. The aim of this study was to evaluate the safety of pulsed high-dose liposomal amphotericin B (L-AmB) in patients with suspected IAC managed with a beta-D-glucan (BDG)-guided strategy.

Methods: This phase 2 prospective study enrolled adult patients with intra-abdominal sepsis following surgery. Patients received a single dose of L-AmB 5 mg/kg on day 1. On day 3, L-AmB was discontinued in patients with a negative basal BDG result, and continued (3 mg/kg/daily) in patients with a positive basal BDG result or microbiologically confirmed IAC. The primary endpoint was the occurrence of adverse events, defined using the Common Toxicity Criteria classification.

Results: In total, 40 patients were enrolled from January 2019 to August 2022. Fifteen (37.5%) patients were male, and the median age was 65 [interquartile range (IQR) 49–76] years. Thirty-one (77.5%) patients underwent urgent surgery, and the principal indication was secondary/tertiary peritonitis (n=22, 55%); half of the patients had undergone a previous surgical operation within the preceding 30 days. Five (12.5%) patients met the criteria for septic shock at enrolment. The median APACHE II score on admission to the intensive care unit was 12 (IQR 10–15). IAC was excluded in 33 (85%) patients, but IAC was probable and proven in five (12.5%) and two (5%) patients, respectively. The single dose of L-AmB 5 mg/kg was well tolerated in all patients, and no early or late severe adverse events related to the drug were reported. L-AmB was discontinued in 65% of patients following a negative basal BDG result. The all-cause 30-day mortality rate was 15%, and no deaths were related to L-AmB administration or uncontrolled IAC. The mortality rates for patients with and without proven IAC were 0% and 15.8%, respectively (P=0.99).

Conclusions: The rate of proven IAC among critically ill high-risk patients was low (5%). A single dose of L-AmB 5 mg/kg, with prompt withdrawal in the case of a basal negative BDG result, seems to be a safe and effective approach in this population.

1. Background

Invasive candidiasis (IC), consisting of intra-abdominal candidiasis (IAC) with or without candidaemia, is historically burdened by high mortality and morbidity rates [1]. However, recent studies have demonstrated a relatively low rate of IC in critically ill patients with inherent risk factors [2], drawing into question the role of a risk-factor-driven antifungal pre-emptive approach, and highlighting the need for indirect markers of infection. Randomized clinical trials have failed to demonstrate a net benefit in preventing IC in high-risk patients managed with pre-emptive therapy based on echinocandins or fluconazole [3–5].

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https://doi.org/10.1016/j.ijantimicag.2023.106998

(1-3)Beta-D-glucan (BDG) is considered to be a useful tool to start antifungal pre-emptive therapy, although variable specificity has been reported and the need for two consecutive positive results has been advocated [6]. Some authors have suggested its potential role for early exclusion of IC/IAC, with early treatment withdrawal based on its high negative predictive value (NPV) [7].

Regarding the choice of an appropriate antifungal agent for IAC, fluconazole has been associated with a higher rate of treatment failure compared with fungicidal agents [8], and the penetration of echinocandins into the peritoneal fluid does not seem to be optimal [9]. Some studies have suggested favourable pharmacokinetic/pharmacodynamic (PK/PD) behaviour of L-AmB in abdominal tissues, implying a potential role in this setting [10]. L-AmB has concentration-dependent antifungal action, so its clinical action is mediated by achieving a high peak concentration and a favourable area under the concentration–time curve:minimum inhibitory concentration ratio [11].

Given this background, it was hypothesized that a higher initial dose of L-AmB may be sufficient to assure optimal tissue and plasma concentrations for 72 h in patients with suspected IC/IAC. Furthermore, the application of this strategy in combination with a BDG-driven approach for early antifungal withdrawal could result in lower rates of antifungal exposure and adverse events.

2. Materials and methods

2.1. Study design and setting

This prospective, interventional phase 2 study enrolled patients with sepsis following major intra-abdominal surgery, from January 2019 to September 2022, at IRCCS S. Orsola-Malpighi Hospital, a 1420-bed tertiary teaching hospital.

The study was approved by the Ethics Committee of Comitato Etico Indipendente di Area Vasta Emilia Centro (Ref. No. 645/2018/Farm/AOUBo). Informed signed consent was obtained from all enrolled patients.

2.2. Participants

All consecutive adult (age ≥18 years) patients with suspected intra-abdominal infection (IAI), based on the guidelines of the Infectious Diseases Society of America [12], and sepsis or septic shock with major risk factors for IC/IAC were enrolled in this study [13]. The exclusion criteria were: documented history of hypersensitivity or allergic reaction to L-AmB; pregnancy, lactation or patients at risk for pregnancy; neutropenia >grade 2, defined as absolute neutrophil count ≤1000/mm^3; and concomitant treatment with cyclosporine, aminoglycosides and pentamidine.

2.3. Study procedures

The following microbiological tests were carried out at baseline in all enrolled patients: two sets of blood cultures; Gram stain and culture of intra-abdominal operative samples; and serum BDG determination. Thereafter, a loading dose of 5 mg/kg L-AmB was administered on day 1, along with broad-spectrum antibiotic therapy. On day 3, the decision to start antifungal treatment dosage (standard dose 3 mg/kg/day) was based on the baseline BDG result (see Fig. 1 and definitions). Briefly, in the case of a negative baseline BDG result (<80 pg/mL), antifungal therapy was discontinued. If the baseline BDG result was significantly positive (>200 pg/mL) or IC/IAC was confirmed by culture result, the patient continued antifungal treatment for 7–14 days, as per the decision of the attending physician. In the case of a borderline positive BDG result (80–200 pg/mL), antifungal treatment was continued at the standard dose and was subsequently driven by BDG results on days 5, 7 and 14. In any case, if IC/IAC was confirmed by culture result, antifungal treatment was continued at the standard dose for 7–14 days, as per the decision of the attending physician. Patients were followed-up until 30 days after drug discontinuation.

2.4. Variables and definitions

Clinical charts and hospital electronic records were used as data sources. Pseudo-anonymous data were collected prospectively using a standard case report form.

The primary endpoint was the safety of this novel approach. Safety was assessed according to the incidence of grade 3/4 adverse events, based on the Common Toxicity Criteria classification, that were as definitely, possibly or probably related to the study drug. The monitoring of adverse events was conducted daily by performing physical examinations and blood tests. The incidence of adverse events was investigated from the first dose of L-AmB until 30 days after discontinuation. Secondary endpoints were length of intensive care unit (ICU) and/or hospital stay, and in-hospital all-cause mortality.

Complicated IAIs include postoperative peritonitis, recurrent gastrointestinal perforation, postoperative hepatobiliary and pancreatic disorders, intra-abdominal abscess and anastomotic leakage [12]. Sepsis and septic shock were defined according to standard criteria [14].

Candidaemia was defined as proven when microbiologically confirmed by isolation of *Candida* spp. from at least one blood culture. IAC was defined as proven when confirmed according to the results of intra-abdominal specimens yielding monomicrobial growth of *Candida* spp. IAC was defined as probable if intra-abdominal specimens yielded *Candida* spp. within a mixed flora (bacterial and fungal) isolation from intra-operative specimens and/or a BDG value >200 pg/mL.

2.5. Statistical analysis

Categorical variables are reported as count and percentage. Continuous variables are reported as mean ± standard deviation if normally distributed, or as median and interquartile range (IQR) if non-normally distributed. For the univariate analysis, categorical variables were compared using Chi-squared test or Fisher's exact test, as appropriate, and continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test depending on whether they were normally or non-normally distributed.

3. Results

Overall, 40 patients were enrolled in this study. The median age was 65 (IQR 49–76) years, and 15 (37.5%) patients were male (see Table 1). According to the McCabe score, 26 (65%) patients had life expectancy >5 years, and the median Charlson Comorbidity Index was 3 (IQR 0–4). The main indications for surgery were: secondary or tertiary peritonitis (*n*=22, 55%), Crohn's disease (*n*=9, 22.5%) and colorectal cancer (*n*=4, 10%). Half of the patients had undergone previous abdominal surgery within 30 days preceding enrolment. Seven (17.5%) patients underwent elective surgery, 31 (77.5%) patients underwent urgent surgery and 2 (5%) patients needed immediate surgery. Intra-abdominal samples, baseline BDG and blood cultures were collected in all patients, and all patients received a single dose of 5 mg/kg L-AmB on the first postoperative day, in accordance with the study protocol. The median APACHE II score on ICU admission was 12 (IQR 10–15). Mechanical ventilation and continuous renal replacement therapy (CRRT) were needed in 33 (82.5%) and five (12.5%) patients, respectively. Five (12.5%) patients had septic shock at enrolment. In four (10%) patients, blood cultures yielded bacterial growth in accordance with intra-abdominal

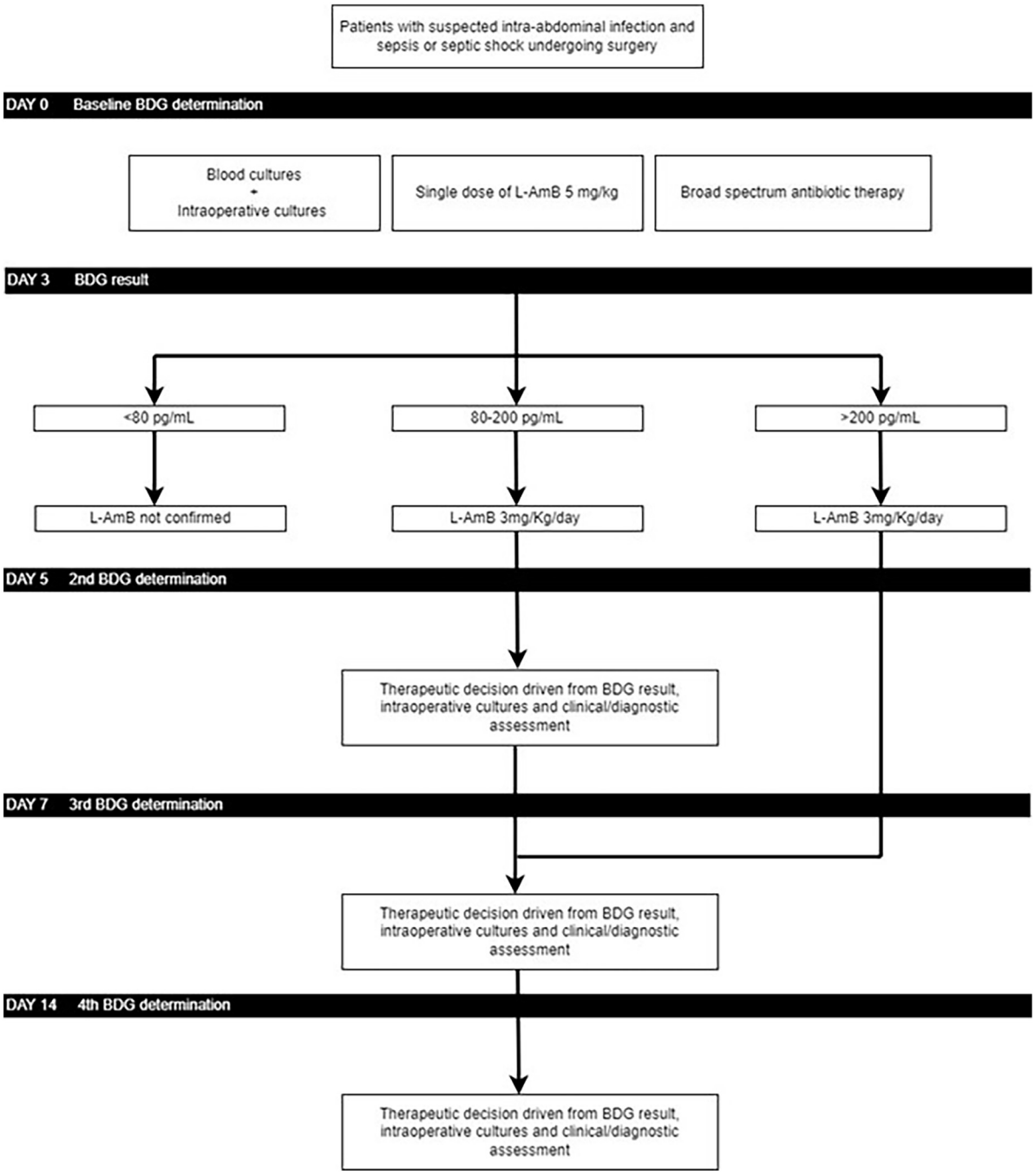

Figure 1. Study flowchart. BDG, beta-D-glucan; L-AmB, liposomal amphotericin B.

cultures, while 28 (70%) patients had a bacterial positive culture from intra-operative specimens; no cases of mixed (bacterial and fungal) flora were reported. IAC, defined as monomicrobial *Candida* spp. growth, was diagnosed in two (5%) patients.

Baseline BDG results were <80, 81–200 and >200 pg/mL in 31 (77.5%), three (7.5%) and six (15%) patients, respectively. In patients with intermediate baseline BDG (81–200 pg/mL), the second determination on day 5 was negative in all cases. Proven and probable IAC was diagnosed based on baseline BDG results and intra-operative cultures in two (5%) and five (12.5%) cases, respectively (see Table 2). Overall, L-AmB administration was confirmed at the standard dose (3 mg/kg/day) on day 3 in 35% of cases.

No grade 3/4 serious adverse events related to L-AmB were recorded (see Table 3). During the follow-up period, six (15%) patients died within a median of 6 (IQR 2–16) days of drug discontinuation, and deaths were recorded as severe adverse events in accordance with the study protocol. None of these deaths were related to L-AmB administration. The median creatinine baseline plasma value was 0.9 mg/dL, and a significant increase was not observed during the study period. Reversible moderate hypokalaemia was reported in three (8.6%) patients. Finally, three (8.6%) and two (5.7%) patients with stage 1 and 2 acute kidney injury, respectively, according to RIFLE criteria were observed, but these events were considered to be related to underlying conditions.

A comparison between survivors and non-survivors was performed (Table 1). The non-survivors had higher APACHE II scores (16.5 vs. 12; P=0.08), a longer median period of mechanical ventilation (7.5 vs. 1 days; P=0.007) and greater need for CRRT (50%

Table 1
Characteristics of study population and comparison between survivors and non-survivors.

	Overall *n*=40	Survivors *n*=34 (85%)	Non-survivors *n*=6 (15%)	*P*-value
Demographic data				
Age (years) [median (IQR)]	65 (49–76)	62.5 (46–75)	69 (56–82)	0.36
Sex, male	15 (37.5)	12 (35.3)	3 (50)	0.65
Comorbidities				
McCabe score				1
Non-fatal	26 (65)	3 (8.8)	0 (0)	
Rapidly fatal	11 (27.5)	9 (26.5)	2 (33.3)	
Ultimately fatal	3 (7.5)	22 (64.7)	4 (66.7)	
Charlson Comorbidity Index [median (IQR)]	3 (0–4)	2 (0–4)	4 (1–8)	0.32
Underlying disease				0.64
Secondary/tertiary peritonitis	22 (55)	19 (55.9)	3 (50)	
Crohn's disease	9 (22.5)	8 (23.5)	1 (16.7)	
Colorectal cancer	4 (10)	3 (8.8)	1 (16.7)	
Previous surgery (within 30 days)	20 (50)	17 (50)	3 (50)	1
Classification of intervention				0.4
Elective	7 (17.5)	7 (20.6)	0 (0)	
Urgent	31 (77.5)	25 (73.5)	6 (100)	
Immediate	2 (5)	2 (5.9)	0 (0)	
Postoperative variables				
Any complication	11 (27.5)	9 (27.3)	2 (33.3)	1
Apache II score at ICU admission [median (IQR)]	12 (10–15)	12 (10–14)	16.5 (11–19)	0.08
Mechanical ventilation	33 (82.5)	27 (79.4)	6 (100)	0.56
Length of mechanical ventilation (days) [median (IQR)]	1 (1–7)	1 (1–2)	7.5 (3–20)	0.007
CRRT	5 (12.5)	2 (5.9)	3 (50)	0.02
Septic shock	5 (12.5)	3 (8.8)	2 (33.3)	0.15
Microbiological data				
Positive blood cultures	4 (10)	3 (8.8)	1 (16.7)	0.49
Positive intra-operative/drainage cultures	28 (70)	23 (67.6)	5 (83.3)	0.65
Polimicrobial	14 (50)	11 (47.8)	3 (60)	1
Enterobacterales	16 (57.1)	14 (60.9)	2 (40)	0.62
Pseudomonas spp.	9 (32.1)	5 (21.7)	4 (80)	0.03
Enterococci	10 (35.7)	9 (39.1)	1 (20)	0.63
Baseline BDG >80 pg/mL	9 (22.5)	6 (17.6)	3 (50)	0.12
Baseline BDG >200 pg/mL	6 (17.6)	4 (11.8)	2 (33.3)	0.22
Median BDG among positive values (pg/mL) [median (IQR)]	216 (86–358)	–	–	
Days of antibiotic treatment [median (IQR)]	8 (4–14)	8 (5–15)	5 (3–9)	0.15
Confirmed abdominal invasive candidiasis	2 (5)	2 (5.9)	0 (0)	1
L-AmB confirmed after loading dose	14 (35)	11 (32.4)	3 (50)	0.65
Days of L-AmB administration [median (IQR)]	1 (1–4)	1 (1–4)	1 (1–13)	0.73
Outcome				
SAE within 30 days of L-AmB start	6 (15)	–	–	
New antifungal treatment after L-AmB discontinuation	2 (5)	–	–	
Length of hospital stay (days) [median (IQR)]	29 (16–49)	32 (16–52)	17.5 (14–29)	0.12
Length of ICU stay (days) [median (IQR)]	3 (2–13)	3 (2–8)	11 (2–28)	0.3
Death within 30 days	6 (15)	–	–	
Time from last L-AmB administration to death (days) (median)	7.5 (2–28)			
Time from surgery to death (days) [median (IQR)]	10 (3–28)	–	–	

IQR, interquartile range; ICU, intensive care unit; CRRT, continuous renal replacement therapy; BDG, beta-D-glucan; SAE, severe adverse event.

vs. 5.9%; *P*=0.02). The likelihood of a positive BDG result was higher among non-survivors (50% vs. 17.6%; *P*=0.12). Finally, patients without IAC were compared with patients with probable and proven IAC (Table 2). No differences in empirical antibiotic treatment and median number of blood products at baseline were observed. L-AmB was stopped after the loading dose in almost 80% of patients in whom IAC was excluded. The median duration of L-AmB administration ranged from 1 day in patients without IAC to 14 days in patients with proven IAC. The length of ICU stay was significantly higher in patients without IAC, but none of the patients with proven IAC died at the end of the study.

4. Discussion

This study highlights several aspects in the management of critically ill patients at high risk of IAC. Firstly, a novel approach based on a pre-emptive high dose of L-AmB seems to be feasible and safe in this population, as no adverse events related to drug administration and no deaths were reported in patients with IAC. Despite the selection of high-risk patients in this study, the incidence of IAC was fairly low (5%), and similar to previous studies. None of the patients with a negative baseline BDG result developed an invasive fungal disease, suggesting that a BDG-driven approach could be useful to avoid unnecessary antifungal overexposure, potentially representing a feasible principle of antimicrobial stewardship.

Current guidelines recommend pre-emptive antifungal therapy among critically ill patients with inherent risk factors, based on high mortality rates in cases of delayed treated or untreated IC in retrospective surveillance studies [15]. Nevertheless, a prospective clinical trial of critically ill patients managed with pre-emptive antifungal therapy compared with placebo did not show a net benefit on fungal-infection-free short-term survival (3–5). Thus, the selection of appropriate patients, especially in ICUs, is not well defined, and the prescription of prophylaxis in critically ill patients with risk factors may lead to antifungal overuse. Recent abdominal surgery is one of the main risk factors for IAC [1]. Nevertheless, the diagnosis is challenging as culture-based methods have scarce sensibility, and the pathogenic role of *Candida* spp. in polymicrobial peritonitis is still a matter of debate [16]. For these reasons, the use of BDG for the prediction of invasive fungal infections has been explored. A recent randomized clinical trial evaluated the impact of a BDG-guided strategy, with antifungal therapy adminis-

Table 2
Rates of probable and proven invasive abdominal candidiasis (IAC) according to baseline beta-D-glucan (BDG) and intraoperative results.

	No IAC (*n*=33, 85%)	Probable IAC (*n*=5, 12.5%)	Proven IAC (*n*=2, 5%)	*P*-value
Demographic data				
Age (years) [median (IQR)]	63 (39–75)	73 (58–80)	58 (55–61)	0.51
Sex, male	12 (36.4)	1 (20)	2 (100)	0.20
Charlson Comorbidity Index [median (IQR)]	2 (0–4)	2 (1–4)	4 (4–4)	0.37
Underlying disease				
Secondary/tertiary peritonitis	18 (54.5)	2 (40)	2 (100)	0.21
Crohn's disease	8 (24.2)	1 (20)	0	
Colorectal cancer	4 (12.1)	0	0	
Previous surgery (within 30 days)	17 (51.5)	2 (40)	1 (50)	1
Postoperative variables				
Apache II score at ICU admission (median, IQR)	12 (10–14)	15 (13–19)	11 (7–13)	0.22
Mechanical ventilation	27 (81.8)	4 (80)	2 (100)	1
CRRT	2 (6.1)	2 (40)	1 (50)	0.04
Septic shock	3 (9.1)	2 (40)	0	0.20
Blood product transfusion during surgery (median, IQR)	1 (0–1)	0 (0–0)	0 (0–0)	0.86
Microbiological data				
Documented bacterial cIAI	21 (63.6)	5 (100)	0	0.22
Monomicrobial *Candida* spp. growth	0	0	2 (100)	
C. albicans	0	0	1 (50)	
C. glabrata	0	0	1 (50)	
Baseline BDG value [median (IQR)]	0 (0–49)	358 (234–686)	200 (184–216)	<0.001
Empirical antibiotic treatment				
Beta-lactam treatment	16 (48.5)	3 (60.0)	1 (50.0)	1
Glycopeptide treatment	3 (9.1)	1 (20.0)	1 (50.0)	0.20
Carbapenem treatment	7 (21.2)	2 (40.0)	1 (50.0)	0.34
Days of antibiotic treatment [median (IQR)]	7 (3–15)	11 (8–14)	14 (8–22)	0.47
Antifungal management				
L-AmB only LD	26 (78.8)	0	0	<0.001
L-AmB started after LD	7 (21.2)	5 (100)	2 (100)	<0.001
Days of L-AmB administration [median (IQR)]	1 (1–1)	8 (4–11)	14 (12–16)	0.002
Outcome				
Length of hospital stay (days) [median (IQR)]	25 (15–46)	42 (30–56)	56 (48–73)	0.10
Length of ICU stay (days) [median (IQR)]	2 (2–7)	30 (9–48)	16 (4–29)	0.03
Death within 30 days	4 (12.1)	2 (40)	0	0.28

IQR, interquartile range; ICU, intensive care unit; CRRT, continuous renal replacement therapy; cIAI, complicated intra-abdominal infection; L-AmB, liposomal amphotericin B; LD, loading dose.

Table 3
Comparison according to negative (<80 pg/mL), borderline (80–200 pg/mL) and positive (>200 pg/mL) baseline beta-D-glucan (BDG) results.

	Overall, *n*=40
Laboratory tests	
Baseline creatinine (mg/dL) (median, IQR)[a]	0.95 (0.64 to 1.4)
Creatinine difference during treatment (median, IQR)[a]	-0.03 (-0.15 to 0.16)
RIFLE criteria for AKI classification	
Stage 1	3 (8.6)
Stage 2	2 (5.7)
Baseline BUN (mg/dL) (median, IQR)	18.7 (11.2 to 38.3)
BUN difference during treatment (median, IQR)	0 (-2.8 to 3.3)
Hypokalaemia during treatment	3 (8.6)
Adverse events	
Overall	6 (15)
CTC grade 3	0
CTC grade 4	6 (15)
Death within 30 days of L-AmB discontinuation	6 (15)
SAE related to study drug	0
L-AmB last dose to death (days) (median, IQR)	6 (2 to 16)
L-AmB discontinuation due to SAE onset	0

[a] Patients needing CRRT at enrolment were excluded.IQR, interquartile range; AKI, acute kidney injury; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CTC, Common Toxicity Classification criteria; L-AmB, liposomal amphotericin B; SAE, severe adverse event.

tered in the case of a positive BDG result [2]. This study demonstrated an increase in antifungal therapy prescription but did not improve short-term mortality. As various factors has been associated with false-positive BDG results, some authors have suggested that serum BDG should be used mainly to rule out IAC by harnessing its elevated NPV [17]. In addition, open gut surgery itself may result in a high serum BDG level, especially in the first postoperative days, ideally impacting the results. Thus, a recent randomized clinical trial among patients with sepsis with risk factors for IC was conducted based on these assumptions [7]. In the intervention arm, empirical antifungal therapy was stopped promptly in patients with a negative BDG result. The authors did not find differences in terms of mortality, IC rates or length of ICU stay, despite a significant reduction in antifungal prescription (2 days in BDG-

guided group vs. 10 days in control group). This approach seems to be effective and feasible based on the present results, considering that none of the BDG-negative patients were diagnosed with IAC.

Another important issue regards the very low incidence of IAC in the study cohort (5%), confirming previous results conducted among high-risk patients and underlining the possible overuse of antifungal therapy in this specific setting. In fact, despite a large number of patients with common risk factors, the incidence rate of IC/IAC is estimated to be approximately 20 cases per 10,000 hospital discharges. According to the 77.5% negative baseline BDG result, this approach allowed pre-emptive antifungal therapy to be discontinued promptly in 26 of 40 (65%) high-risk patients, saving drug-related costs and reducing the ecological impact of prolonged antifungal exposure.

Regarding the choice of antifungal agent for IAC, there is only indirect evidence from studies on IC. Despite favourable PK/PD behaviour in abdominal tissues, fluconazole has been associated with higher rates of treatment failure compared with fungicidal agents [8]. Conversely, only limited data are available regarding the penetration of echinocandins and L-AmB into the peritoneal fluid. Pharmacological and clinical studies suggest that echinocandin penetration in the abdomen is poor, potentially leading to treatment failure and emergence of resistance [18]. Weiler et al. reported that, in patients with cirrhosis-associated ascites, a standard dose (3 mg/kg) of L-AmB was associated with higher free drug concentrations in peritoneal fluid compared with conventional AmB-deoxycholate [10]. Therefore, it could be assumed that inflammation in the peritoneal cavity may lead to a higher degree of L-AmB accumulation [10]. Considering that L-AmB has concentration-dependent antifungal activity, an initial higher dose in high-risk patients could be feasible and cost-saving compared with the standard dosage. The PK/PD principle, according to which the total dose infused over a lower number of administrations is more effective than a daily low dose, has been demonstrated in visceral leishmaniasis [19]. In this setting, a single dose of 10 mg/kg was as effective as the standard dose, with similar adverse events. In addition, a prospective phase II trial demonstrated that a prophylactic weekly high dose of L-AmB was a safe effective strategy in liver transplant recipients at high risk of invasive fungal infections, with a rate of adverse events $<$10% [20]. In another multicentre trial, patients diagnosed with probable or proven invasive mould infection were randomized to receive a 14-day course of L-AmB at 3 mg/kg or 10 mg/kg daily [21]. Although no differences in survival were reported, patients in the 10 mg/kg group had significantly higher rates of nephrotoxicity and grade 3 hypokalaemia. The authors concluded that a daily regimen of 10 mg/kg did not demonstrate a net benefit compared with the standard dose. In the present study cohort, none of the enrolled patients experienced severe adverse events related to L-AmB administration. Specifically, only three (8.6%) cases of reversible moderate hypokalaemia and five (12.5%) cases of acute kidney injury occurred, with the latter attributed to underlying conditions. In the two cases of IAC, L-AmB was confirmed on day 3 at the standard dose, according to the study protocol, with clinical success, suggesting that an initial pulse dose followed by a daily standard dose at 72 h seems to be feasible from a PK/PD point of view. Furthermore, it is important to note that deaths during the follow-up period were notified as severe adverse events in accordance with the study protocol, but none of the deaths in this study were considered to be related to the study drug, considering that they occurred a median of 7.5 (IQR 2–28) days after L-AmB discontinuation.

This study has some limitations. First, the lack of a control group managed with standard care hampers any conclusions about the efficacy of this new approach. In addition, the relatively low number of confirmed cases of IAC did not enable evaluation of the sensitivity, specificity, positive predictive value and NPV of BDG for diagnosing IC/IAC. However, none of the patients with confirmed IAC had a negative BDG value, highlighting the importance of this tool to rule out IC. Finally, an accurate evaluation of cost-saving and further ecological impact of this novel approach was not performed, although it allowed early discontinuation of pre-emptive antifungal treatment.

5. Conclusion

This pilot study found that a single high dose of L-AmB in critically ill patients with severe abdominal disease was safe, and when coupled with a BDG-guided strategy to rule out IC/IAC may lead to a reduction in antifungal exposure. Further larger randomized controlled studies are needed to confirm these results.

Funding: This study received a grant from Gilead Sciences (Grant No. IN-IT-131-2085).

Competing interests: MB has received speaker fees from Pfizer, Gilead and MSD, and sat on advisory boards for Pzifer, Gilead, MSD and AstraZeneca. PV has received research grants from Shionogi, Gilead and MSD, and sat on advisory boards for Pfizer, Gilead, MSD, Mundipharm, Viatris, bioMérieux and Astrazeneca.

Ethical approval: This study was approved by the Ethics Committee of Comitato Etico Indipendente di Area Vasta Emilia Centro (Ref. No. 645/2018/Farm/AOUBo). Informed signed consent was obtained from all enrolled patients.

Availability of data and materials: The dataset analysed during the current study is available from the corresponding author on reasonable request.

Author contributions: MR – patient enrolment and major contributor to writing the paper. MB – study ideation and writing the paper. CB, MG, BT and CSH – patient enrolment. NC – data management. MG – paper revision. PV – study ideation and paper revision. All authors read and approved the final manuscript.

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