REVIEW ARTICLE

Antifungal lock therapy: an eternal promise or an effective alternative therapeutic approach?

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Significance and impact of the study: Antifungal lock therapy is a promising alternative therapeutic approach for the treatment of Candida-related central line infections without catheter removal. This review summarizes the most relevant in vitro, in vivo and clinical data, published in the last two decades, regarded as antifungal lock therapy.

Keywords
antifungal lock therapy, biofilm, Candida, Candida auris, candidaemia, catheter-associated infection.

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Abstract
Each year, millions of central venous catheter insertions are performed in intensive care units worldwide. The usage of these indwelling devices is associated with a high risk of bacterial and fungal colonization, leading to the development of microbial consortia, namely biofilms. These sessile structures provide fungal cells with resistance to the majority of antifungals, environmental stress and host immune responses. Based on different guidelines, colonized/infected catheters should be removed and changed immediately in the case of Candida-related central line infections. However, catheter replacement is not feasible for all patient populations. An alternative therapeutic approach may be antifungal lock therapy, which has received high interest, especially in the last decade. This review summarizes the published Candida-related in vitro, in vivo data and case studies in terms of antifungal lock therapy. The number of clinical studies remains limited and further studies are needed for safe implementation of the antifungal lock therapy into clinical practice.

Introduction
Based on the last published data, an estimated 5 million central venous catheters (CVCs) are inserted in patients annually in the United States alone, associated with nearly 250,000 bloodstream infections (O’Grady et al. 2011). Central line-associated bloodstream infections (CLABSI) are defined as a central line-related laboratory-confirmed bloodstream infection occurring more than 48 h following central line placement (Haddadin et al. 2021). The CLABSI pose a serious problem to healthcare systems as they usually require a complex therapeutic approach and a prolonged length of hospital stay (13-13 ± 9-53 days) (Alotaibi et al. 2020). The International Nosocomial Infection Control Consortium (INICC) surveyed 703 intensive care units from 50 countries between 2010 and 2015; the CLABSI rate was 4.1 per 1000 central line days (Rosenthal et al. 2016). Mortality rates for diagnosed CLABSI range from 12 to 25%, according to the National Healthcare Safety Network (Norris et al. 2017). It is noteworthy that the CLABSI rates increased by 51% during the first 6 months of the coronavirus disease 2019 (COVID-19) pandemic compared to the 12 months prior at 78 hospitals in the United States (Fakih et al. 2021). Although most episodes are preventable with appropriately applied aseptic techniques, continuous surveillance and local hospital-specific therapeutic strategies, increased incidences have been reported worldwide with regard to CLABSI (Haddadin et al. 2021). In addition, the widespread use of intravascular devices, such as central venous and haemodialysis catheters, maintains this worrisome trend. The number of reported CLABSI in non-intensive care units is variable ranging from 0-9 infections per 1,000 central-line days to 5-2 episodes per 1000 catheter
days (Rhee et al. 2015). In the past decade, an important epidemiological trend was noticed where the non-intensive care unit associated CLABSI rate increased compared to concurrent intensive care unit rate (Tedja et al. 2014). Notably, a considerable proportion of CLABSI patients (70 out of 104 patients) outside the intensive care unit had underlying hematologic malignancy and nearly 92% of patients were neutropenic (Rhee et al. 2015).

Based on the epidemiological data derived from the past decade, Candida species are the fourth and seventh leading cause of bloodstream infections in the United States and Europe, respectively (Wisplinghoff et al. 2004). Additionally, the current incidence of candidaemia is significantly higher among COVID-19-infected patients compared to the non-COVID-19 group (Kayaaslan et al. 2021). Candida-related bloodstream infections are associated with the highest overall mortality of all nosocomial bloodstream infections in intensive care units, ranging from 30 to 60% depending on the species, which are comparable to that of Pseudomonas aeruginosa (Wisplinghoff et al. 2004). Data from the centres for disease control and prevention (CDC) revealed that most pathogen-specific CLABSI rates decreased over time in acute care hospitals between 2011 and 2017, except Candida species in adult intensive care units (Novosad et al. 2020). Based on this comprehensive study, these pathogens were the most common CLABSI-related microorganisms in 2017 (Novosad et al. 2020).

Candida cells can adhere to the surface of indwelling devices and produce an extensive extracellular polysaccharide matrix that will further facilitate adhesion, thickening the developed biofilm (Cavalheiro and Teixeira 2018). In such a sessile community, Candida cells display increased resistance to traditional antifungal agents; in addition, cells may disperse from these sources into the bloodstream, leading to a life-threatening infection (Cavalheiro and Teixeira, 2018; Vitális et al. 2020). Based on recent guidelines, immediate catheter replacement must be applied in the case of proven Candida-related catheter infections (Mermel et al. 2009; O’Grady et al. 2011). However, changing the CVC may be complicated; furthermore, the exchange significantly increases the risk of bloodstream infection and complications, depending on the catheter location (e.g., pneumothorax, arterial puncture) (O’Grady et al. 2011). In addition, catheter replacement is not feasible for all patients, such as premature neonates or critically ill patients who may be thrombocytopenic, coagulopathic or have limited venous access (Walraven and Lee 2013).

Several randomized clinical trials proved that the use of extremely high local concentrations of antibacterial compounds (100–1000 times planktonic MIC) alone or in combination can eradicate the difficult-to-treat intraluminal sessile bacterial communities and can significantly reduce the risk of catheter-associated bacterial infections (Justo and Bookstaver 2014). The ideal lock solution should possess several characteristics such as a relatively wide spectrum, the ability to penetrate biofilms, compatibility with anticoagulant, prolonged stability, low risk of adverse effects, the low potential of resistance and cost-effectiveness (Justo and Bookstaver 2014). Based on the last Infectious Disease Society of America (IDSA) practice guideline for the management of intravascular catheter-related infections, the lock therapy is recommended as adjunctive therapy specifically for catheter salvage in certain clinical situations where the catheter is not removed, especially in the case of coagulase-negative staphylococci (Mermel et al. 2009). Despite these relatively widely used antibacterial approaches, there is, so far, no approved antifungal lock therapeutic protocol in clinical practice.

This review focuses on the in vitro, in vivo and clinical data of the antifungal lock therapy available in the literature to summarize the current status of this promising antifungal treatment approach.

**Traditional antifungal agents related in vitro results**

Over the last decade, the number of in vitro studies dealing with potential antifungal lock solutions against Candida biofilms has steadily increased (Walraven and Lee 2013; Imbert and Rammaert 2018). Most studies have used a static 96-well static microplate model with or without frequently used catheter material (e.g., silicone, polyvinyl chloride, etc.). On the one hand, these results are easy to use and to interpret; however, on the other hand, several limitations can be observed, such as the static nature, the total lack of host response and cellular components and different culturing media, which may influence the observed antifungal effect. Moreover, the metabolic activity changes of biofilms following antifungal drug exposure do not correlate linearly with the living cell number (Ramage 2016).

In one of the earliest study, Kuhn et al. (2002) reported that lipid formulations of amphotericin B (4 mg l⁻¹) and the echinocandins (4 mg l⁻¹) have a remarkable anti-biofilm effect against C. albicans (n = 2) and C. parapsilosis (n = 2), significantly higher than that of azoles (Katragkou et al. 2008). Miceli et al. (2009a) and Ku et al. (2011) demonstrated that anidulafungin (AN1), caspofungin (CAS) and micafungin (MICA) produced comparable high anti-biofilm effects against C. albicans (SC5314 reference strain) and C. tropicalis (n = 5), using an XTT assay-based static microplate model. The possible observed differences may be explained by the occurrence
of paradoxical growth at high dosages, which was most significant in the case of CAS, followed by ANI (Simitsopoulou et al. 2013; Prażyska and Gospodarek-Komkowska 2019). Furthermore, the susceptibility of Candida biofilms to echinocandins may influence the metabolic activity of sessile cells. Marcos-Zambrano et al. (2014) reported that MICA is more active against C. albicans biofilms (n = 265) with high metabolic activity, whereas the efficacy of CAS and ANI is not affected by the metabolic activity of biofilms (Marcos-Zambrano et al. 2016). Regarding early studies, Cateau et al. (2008) examined the potential role of CAS (2 mg l⁻¹) and MICA (5 mg l⁻¹) as a lock solution against early (12 h) and mature (5 days) biofilms formed by C. albicans reference strains (n = 2), using sections of 100% silicone catheters. Biofilm growth inhibition was observed after the end of a 12-h antifungal treatment period. The catheter was incubated without echinocandins for 24, 48 or 72 h after the lock therapy. Significant metabolic activity reduction was observed, irrespective of the maturation stage; moreover, this observed metabolic activity decrease was maintained even after 2 days (Cateau et al. 2008). Simitsopoulou et al. (2014) examined the activity of CAS at catheter lock concentration against two rarely isolated Candida species, C. guilliermondii (n = 5) and C. lusitaniae (n = 6). This study showed that CAS and L-AMB had the highest activity against the tested biofilms, although the activity of L-AMB was significantly lower than that exerted by CAS (512–2048 mg l⁻¹) (Simitsopoulou et al. 2014). Kovács et al. (2019) reported that nikkomycin Z may be a possible adjuvant in lock therapy in combination with echinocandins. In these experiments, nikkomycin Z enhanced the activities of CAS and MICA against 1-day-old biofilms formed by echinocandin-susceptible (n = 5) and echinocandin-resistant C. albicans (n = 1) strains (Kovács et al. 2019).

Ko et al. (2010) examined the efficacy of 1 mg ml⁻¹ amphotericin B deoxycholate (d-AMB), CAS, fluconazole (FLU), itraconazole (ITRA) and voriconazole (VOR) against a one-one clinical strain of C. albicans, C. glabrata and C. tropicalis, using a polyurethane segment colonization model. The biofilm killing patterns of antifungal agent tested were assayed after lock periods of 1, 3, 5, 7, 10 or 14 days, where the antifungal lock solutions were replaced every 2 days. Interestingly, the obtained results suggested that ITRA, FLU and VORI may be potential lock agents, whereas the efficacy of d-AMB and CAS was questionable at the tested concentration (Ko et al. 2010). Öncü (2011) tested the potential use of d-AMB, CAS, FLU, ITRA and VOR as a lock solution against one-one clinical C. albicans and C. parapsilosis isolates, using the silicone catheter segment model. The examined concentrations were 300, 500 and 1000 times higher than the MIC values. Different drugs were assayed after lock periods of 1, 3, 5 and 7 days, where lock solutions were replaced every 2 days. The d-AMB and CAS lock treatment showed complete inhibition, whereas FLU, ITRA and VOR had no effect (Öncü 2011), although the authors used azole-based lock solutions at significantly lower concentrations. C. albicans (n = 8) and C. glabrata (n = 6) clinical isolates were examined against MICA, CAS and posaconazole (POSA) (10 mg l⁻¹) lock solutions, using a silicone catheter segment model by Cateau et al. (2011). Lock efficacy was examined against early (12 h) and mature (5 days) biofilms following exposure to CAS (5 and 25 mg l⁻¹), MICA (5 and 15 mg l⁻¹) and POSA (10 mg l⁻¹) for 12 h. The results showed that MICA had the highest inhibitory efficacy against early and mature C. albicans and C. glabrata biofilms. Moreover, this activity appeared to persist for up to 3 days. Toulet et al. (2012) tested the efficacy of L-AMB-based lock solution (200 and 1000 mg l⁻¹) against early (12 h) and mature (5 days) biofilms formed by six clinical C. albicans, C. glabrata and C. parapsilosis isolates, using a silicon segment model. The lock solution at the highest concentration strongly inhibited early and mature biofilms for up to 48 h after the end of the lock. However, total eradication of the sessile cells was not obtained using 1000 mg l⁻¹ L-AMB as a single lock.

**Drug repurposing and alternative potential lock solutions**

Miceli et al. (2009b) combined high-dose doxycycline (128 512 and 2028 mg l⁻¹) with different concentrations of FLU, CAS and d-AMB (2–1024 mg l⁻¹) and determined their antifungal efficacy against C. albicans SC5314 reference strain, using the XTT-assay. It is noteworthy that doxycycline alone (at 2048 and 1024 mg l⁻¹) demonstrated up to an 85% decrease of the metabolic activity of the C. albicans biofilm following 24 h of drug exposure. Doxycycline at 128 mg l⁻¹ in combination with FLU demonstrated synergistic interaction. Furthermore, the combination of doxycycline at 2048 or 512 mg l⁻¹ and d-AMB was superior to d-AMB alone at low concentrations (0.25–1.25 mg l⁻¹). The same group examined the efficacy of pure heparin and its two preservatives methylparaben and propylparaben against C. albicans clinical isolates (n = 5) (Miceli and Chandrasekar 2012). Pure heparin, methylparaben and propylparaben caused up to 75, 85 and 60% decreases in the metabolic activity of mature C. albicans biofilms. Complete inhibition of biofilm formation was observed with a heparin sodium preparation at 5000 U ml⁻¹ and higher. Furthermore, the authors demonstrated that the combination of high concentrations (5× or higher) of pure heparin,
methylparaben and propylparaben in the proportions contained in heparin sodium solution had a synergistic effect on C. albicans SC5314 mature biofilms (Miceli and Chandrasekar 2012).

Tigecycline was tested by Ku et al. (2010) against SC5314 C. albicans biofilms; the data indicated that tigecycline at high doses is highly active in vitro against C. albicans biofilms. Tigecycline inhibited the formation of biofilms from 128 mg l⁻¹. Against mature biofilms, 2048 mg l⁻¹ tigecycline reduced metabolic activity by 84.2%. It could also enhance the activity of FLU and d-AMB against sessile cells; however, the observed effect was not superior to that of 512 mg l⁻¹ tigecycline alone, which could significantly inhibit (more than 50%) the metabolic activity of C. albicans biofilms (Ku et al. 2010).

Regarding further antibiotics, the antibacterial drugs cefepime, meropenem, piperacillin/tazobactam and vancomycin, at concentrations from MIC/10 to 50 × MIC, decreased the in vitro viability of mature C. albicans (n = 10) and C. tropicalis (n = 10) biofilms (Sidrim et al. 2015).

Raad et al. (2008) determined the activity of the amphoterin B lipid complex (ABLC) (2 mg ml⁻¹) in the presence or absence of EDTA (30 mg ml⁻¹) against five-five C. albicans and C. parapsilosis biofilms, using the silicon disk colonization model. The disks were incubated for 6 and 8 h in lock solutions containing ABLC alone, EDTA alone and ABLC in combination with EDTA. The ABLC with EDTA was significantly more effective compared to the compounds used alone against C. parapsilosis at 6 h and C. albicans at 8 h. Martins et al. (2012) reported an improved efficacy of d-AMB when it was used in combination with DNase against C. albicans biofilm (SC5314 reference strain), using the XTT-assay and quantitative culturing, whereas DNase treatment did not significantly enhance the effect of CAS and FLU. Bergamo et al. (2015) examined the potential activity of imidazolium salt (C₁₆MImCl) against C. tropicalis biofilms (n = 6) formed by clinical isolates, using polyvinylchloride catheter segments. The tested imidazolium salt prevented the biofilm formation of C. tropicalis in concentrations as low as 0.028 mg l⁻¹. Similarly, cerium-nitrate also exhibited a considerable antifungal effect against developed biofilms of various Candida species at concentrations from 16 to 1000 mmol l⁻¹, resulting in a decrease in the biomass and metabolic activity of preformed sessile cells (Silva-Dias et al. 2015). In these experiments, C. glabrata isolates (n = 8) showed the highest resistance to cerium-nitrate treatment, whereas C. guilliermondii strains (n = 8) were the most susceptible ones (Silva-Dias et al. 2015). Rosenblatt et al. (2013) examined the effect of glyceryl-trinitrate in the presence of adjuvant compounds against bacterial and fungal biofilms to test for the eradication of biofilm within 2 h of lock exposure on low-surface-energy silicone rubber surfaces. The authors reported that the addition of 7% citrate to 0.1% glyceryl-trinitrate plus 6% ethanol plus 6% propylene glycol could totally eradicate biofilm formed by C. albicans (n = 1), showing synergy for this organism. In vitro data published by Alonso et al. (2018) revealed that an ethanol-based lock solution with 40% ethanol + 60 IU heparin, administered daily for 72 h, is sufficient to almost eradicate the metabolic activity of biofilms formed by a C. albicans reference strain. Based on the published data, heparin is a frequently used component of promising lock solutions. However, the addition of heparin to a lock solution has two major disadvantages. First, we have to consider the potential emergence of allergy- and heparin-associated thrombocytopenia, which may occur in 10–30% of patients receiving heparin (Shantsila et al. 2009). Second, heparin promotes the biofilm formation of Candida cells (Green et al. 2013). Reitzel et al. (2016) compared the efficacy of nitroglycerin-citrate-ethanol to (0.0015 to 0.003% nitroglycerine—4% citrate—22% EtOH) to 1.35% taurolidine—3.5% citrate—1000 U ml⁻¹ heparin. The tested nitroglycerin-citrate-ethanol was superior to taurolidine-citrate-heparin against C. glabrata biofilm (n = 1) (Reitzel et al. 2016). A recent study demonstrated the potential usage of aspirin as a lock component (Chan et al. 2021). In this study, C. albicans (n = 1) and C. tropicalis (n = 1) biofilms were most sensitive to aspirin exposure. The C. albicans biofilm was eradicated by aspirin at a concentration of 40 mg ml⁻¹ in 4 h. Moreover, C. glabrata (n = 1) C. krusei (n = 1) and C. tropicalis biofilms were eradicated by aspirin at a concentration of 40 mg ml⁻¹ in 24 h (Chan et al. 2021).

Based on in vitro data, ethanol-based lock solutions appear as some of the most promising antifungal lock strategies; however, more limitations may emerge in terms of the usage of this compound, such as its potential incompatibility with polyurethane catheters. Nonetheless, Raad et al. (2007) compared minocycline, EDTA and 25% ethanol against one C. parapsilosis strain, using silicone catheter segments. Both ethanol-EDTA and ethanol-EDTA-minocycline combinations eradicated 100% of the growth of the C. parapsilosis biofilm when tested for 1 day. Based on the results published by Balestrino et al. (2009), 60% ethanol eliminated C. albicans SC5314 biofilm from silicone catheter segments following 20 min of exposure. Venkatesh et al. (2009) found that 12.5% ethanol treatment significantly reduced the metabolic activity and living cell number of C. albicans biofilms. In addition, this ethanol concentration showed a synergistic interaction with d-AMB and FLU. Ghannoum et al. (2011) performed a comprehensive study in which 5 mg ml⁻¹ trimethoprim, 25% ethanol and 3% EDTA...
were combined, inhibiting all Candida isolates examined, namely C. albicans (n = 25), C. glabrata (n = 25), C. tropicalis (n = 25) and C. krusei (n = 25). A three component-based lock solution was tested by Lown et al. (2016). The solution containing 20% (v/v) ethanol, 0.01565 mg l⁻¹ MICA and 800 mg l⁻¹ doxycycline demonstrated a 98% reduction in metabolite activity; however, there was no advantage over 20% ethanol alone (Lown et al. 2016).

A relatively novel and innovative lock strategy is the usage of gas plasma-activated disinfectants (Bhatt et al. 2018). It is noteworthy that viable cells of C. albicans in mature biofilms decreased by 6–8 orders of magnitude with a novel antifungal-free lock solution formed from gas plasma-activated disinfectant for 60 min. For comparison, the usage of a minocycline-EDTA-ethanol lock solution for 60 min resulted in a significant regrowth of 100% biofilms (Vargas-Cruz et al. 2021). A promising alternative therapeutic approach is the treatment disrupting quorum-sensing by the usage of quorum-sensing molecules at supraphysiologcal concentrations, which may enhance the activity of traditional antifungal agents (Kovács and Majoros 2020). Regarding C. auris biofilms, Nagy et al. (2020a, 2020b) examined the effects of echinocandins and triazole in the presence of farnesol as potential lock solutions against 1-day-old C. auris biofilms (n = 7). According to the FIC index determination, farnesol could significantly enhance the activities of ANI, CAS and MICA (FICI range 0.133–0.5). Additionally, the interaction between FLU, ITRA, VOR, POSA, isavuconazole (ISA) and farnesol showed clear synergism (FICI range from 0.038 to 0.375) against 1-day-old biofilms. A further alternative lock solution contained small cysteine-rich cationic antifungal protein, Neosartorya fischeri antifungal protein 2 (NFAP2), which exerted synergistic interactions with FLU, AMB, ANI, CAS and MICA, with FICIs ranging between 0.064 and 0.5 against C. auris biofilms (n = 5). Moreover, sessile cells exposed to three echinocandins (32 mg l⁻¹) exhibited significant cell death in the presence of NFAP2 (128 mg l⁻¹) (Kovács et al. 2021).

**Promising antifungal lock solutions against Candida auris in vitro**

*Candida auris* is posing a continuous global public health threat due to its ability to cause nosocomial outbreaks of invasive infections in healthcare environments worldwide (Du et al. 2020). The biofilm-forming ability of this species and its role in catheter-associated infections are known phenomena (Horton and Nett 2020; Sayeed et al. 2020). However, the treatment of this central line infection is a particularly hard task due to the multiresistant phenotype of *C. auris*, justifying this separate section within this review. Recently, several studies focusing on potential lock solutions against *C. auris* have been published. Vargas-Cruz et al. (2019) compared the efficacy of traditional antifungal agents to nitroglycerine-citrate-ethanol catheter lock solution. Testing was performed on 1-day-old C. auris biofilms followed by 2 h of exposure to the lock solutions. In their study, L-AMB (1 mg ml⁻¹), d-AMB (0.1 mg ml⁻¹), FLU (2 mg ml⁻¹), VOR (0.5 mg ml⁻¹), MICA (0.5 mg ml⁻¹), CAS (0.5 mg ml⁻¹) and ANI (0.5 mg ml⁻¹) failed to completely eradicate all 10 tested C. auris biofilms (Vargas-Cruz et al. 2019). Conversely, nitroglycerine (0.003%), citrate (4%), ethanol (22%) lock solution completely eradicated all *C. auris* biofilms examined (Vargas-Cruz et al. 2019). Reitzel et al. (2020) examined the effect of amoxicillin (0.1%) -EDTA (3%) -ethanol (25%) lock against *C. auris* biofilms. This three-component solution was able to fully eradicate all 10 tested isolates of *C. auris* biofilms following 60 min of exposure (Reitzel et al. 2020). A promising alternative therapeutic approach is the treatment disrupting quorum-sensing by the usage of quorum-sensing molecules at supraphysiologi cal concentrations, which may enhance the activity of traditional antifungal agents (Kovács and Majoros 2020).

**In vivo studies of antifungal lock strategies**

The number of valid *in vivo* experiments dealing with potential antifungal lock solutions is strongly limited (Table 1). Most studies tested various formulations of AMB alone or in combination with another traditional antifungal drug. In one of the earliest studies, Mukherjee et al. (2009) used a rabbit CVC model of *C. albicans* to examine the efficacy of ABLC (5 mg ml⁻¹ for 4 and 8 h per day, respectively). On day 11 of the lock treatment, both arms completely sterilized the ABLC-locked catheters (Mukherjee et al. 2009). In another study, Schinabeck et al. (2004) compared the efficacy of L-AMB (10 mg ml⁻¹) with that of FLU (10 mg ml⁻¹) against *C. albicans* using a rabbit CVC model, where the L-AMB lock solution could completely sterilize the catheters. Shufford et al. (2006) observed a superior effect of CAS lock (6-67 mg ml⁻¹) compared to d-AMB (3-33 mg ml⁻¹) in a 7-day lock model of a *C. albicans* catheter infection. Fujimoto and Takemoto (2018) compared the *in vivo* activity of 2 mg l⁻¹ L-AMB lock to that of 2 mg l⁻¹ MICA lock solution against *C. albicans*, *C. glabrata*, *C. parapsilosis* and *C. tropicalis*. The L-AMB lock showed a superior effect against *C. parapsilosis* using the murine
| Reference                  | Candida species/strain | Animal/Model                | Lock solution              | Duration of therapy | Therapeutic success |
|----------------------------|------------------------|-----------------------------|----------------------------|---------------------|--------------------|
| Schinabeck et al. (2004)   | C. albicans (M61 strain) | Rabbit CVC model           | 10 mg ml⁻¹ L-AMB, 10 mg ml⁻¹ FLU | 8 h per day for 7 days | 7/7 (100%)         |
| Shuford et al. (2006)      | C. albicans (IDRL-5319) | Rabbit CVC model           | 6.67 mg ml⁻¹ CAS, 3.33 mg ml⁻¹ d-AMD | 7 days              | 16/16 (100%)       |
| Mukherjee et al. (2009)    | C. albicans (M61 strain) | Rabbit CVC model           | 5 mg ml⁻¹ ABLC             | 4 h per day for 7 days | 6/6 (100%)         |
| Lazell et al. (2009)       | C. albicans (SC5314 strain) | Murine CVC model           | 0.25 mg l⁻¹ CAS            | 24 h                | 4/6 (67%)          |
| Basas et al. (2016)        | C. parapsilosis (CP12 strain) | Rabbit CVC model           | 5.5 mg ml⁻¹ L-AMB, 3.3 mg ml⁻¹ ANI | 48 h                | 3/10 (30%)         |
|                            | C. parapsilosis (CP54 strain) |                       | 5.5 mg ml⁻¹ L-AMB, 3.3 mg ml⁻¹ ANI |                     | 5/8 (63%)          |
|                            |                        |                             |                            |                     | 8/11 (73%)         |
| Fujimoto and Takemoto (2018) | C. albicans (SP-20012) | Murine CVC model           | 2 mg l⁻¹ daily lock L-AMB + 5 mg kg⁻¹ daily i.p. L-AMB | 72 h                | 7/7 (100%)         |
|                            | C. glabrata (SP-20040) |                             | 2 mg l⁻¹ daily lock MICA + 15 mg kg⁻¹ daily i.p. MICA |                     | 7/7 (100%)         |
|                            | C. glabrata (SP-20040) |                             | 2 mg l⁻¹ daily lock L-AMB + 5 mg kg⁻¹ daily i.p. L-AMB |                     | 8/7 (88%)          |
|                            | C. parapsilosis (SP-20137) |                        | 2 mg l⁻¹ daily lock MICA + 15 mg kg⁻¹ daily i.p. MICA |                     | 8/8 (100%)         |
|                            | C. tropicalis (SP-20047) |                             | 2 mg l⁻¹ daily lock L-AMB + 5 mg kg⁻¹ daily i.p. L-AMB |                     | 6/5 (83%)          |
|                            |                        |                             | 2 mg l⁻¹ daily lock MICA + 15 mg kg⁻¹ daily i.p. MICA |                     | 6/4 (67%)          |
|                            |                        |                             | 2 mg l⁻¹ daily lock L-AMB + 5 mg kg⁻¹ daily i.p. L-AMB |                     | 8/7 (88%)          |
|                            |                        |                             | 2 mg l⁻¹ daily lock MICA + 15 mg kg⁻¹ daily i.p. MICA |                     | 8/4 (50%)          |
|                            |                        |                             | 2 mg l⁻¹ daily lock L-AMB + 5 mg kg⁻¹ daily i.p. L-AMB |                     | 6/6 (100%)         |
|                            |                        |                             | 2 mg l⁻¹ daily lock MICA + 15 mg kg⁻¹ daily i.p. MICA |                     | 6/6 (100%)         |
| Salinas et al. (2019)      | C. albicans (SKCA23-ACτLuc) | Murine CVC model           | 16 mg l⁻¹ daily lock MICA + 1 mg kg⁻¹ daily i.p. MICA | Treatment started at day 1, lasted 7 days, and was followed by 7 days of surveillance with no treatment | 8/6 (75%) |
| Basas et al. (2019)        | C. albicans (CA176)    | Rabbit CVC model           | 5 mg ml⁻¹ L-AMB, 3.3 mg ml⁻¹ ANI | 48 h                | 10/5 (50%)         |
|                            | C. albicans (CA180)    |                             | 5 mg ml⁻¹ L-AMB, 3.3 mg ml⁻¹ ANI |                     | 10/4 (40%)         |
|                            | C. glabrata (CG171)    |                             | 5 mg ml⁻¹ L-AMB, 3.3 mg ml⁻¹ ANI |                     | 6/5 (83%)          |
|                            | C. glabrata (CG334)    |                             | 5 mg ml⁻¹ L-AMB, 3.3 mg ml⁻¹ ANI |                     | 6/5 (83%)          |
CVC model; however, the efficacy of the two tested lock solutions was comparable to those of *C. albicans*, *C. glabrata* and *C. tropicalis* (Fujimoto and Takemoto 2018). In another study, ANI (3.3 mg ml\(^{-1}\)) exerted a significant decrease relative to L-AMB (5.5 mg ml\(^{-1}\)) for *C. parapsilosis* isolates in vivo. In addition, only ANI achieved negative catheter tip cultures (Basas et al. 2016). In the case of *C. albicans*, both L-AMB (5 mg ml\(^{-1}\)) and ANI (3.3 mg ml\(^{-1}\)) produced significant reductions compared to growth control recovered from the catheter tips, whereas ANI lock solution achieved significant reductions compared to other treatments in the case of *C. glabrata* (Basas et al. 2019). Lazzell et al. (2009) examined the efficacy of CAS (0.25 mg l\(^{-1}\)) lock for the treatment and prevention of biofilms formed by a *C. albicans* reference strain. The 24-h-long lock time significantly reduced the fungal burden derived from catheters when used for either treatment or prevention in a murine CVC model (Lazzell et al. 2009). A comparable therapeutic success was observed in another study (Salinas et al. 2019), where a 16-mg l\(^{-1}\) daily lock treatment was examined with 1 mg kg\(^{-1}\) daily systemic MICA therapy. The treatment started on day 1, lasted for 7 days and was followed by 7 days of surveillance without treatment. In this study, the therapeutic success was 75% compared to the results reported by Lazzel et al. (2009), who observed 67% (Salinas et al. 2019).

Clinical studies of antifungal lock therapies

The available case studies with regard to antifungal lock therapies against *Candida* species are summarized in Table 2. Most case studies dealing with antifungal lock therapies focused on paediatric patients, and the number of adult-related studies is strongly limited (Table 2). Regarding the traditional antifungal agents, until recently, the AMB-based lock solutions were the most frequently tested compounds. Overall, d-AMB locks (2–2.5 mg ml\(^{-1}\)) produced an 89% therapeutic success (100, 75 and 100% therapeutic success for *C. albicans*, *C. glabrata* and *C. parapsilosis*, respectively). The L-AMB showed efficacy comparable to that of d-AMB, where 83% overall therapeutic success was reported (75, 100 and 100% for *C. albicans*, *C. glabrata* and *C. guilliermondii*, respectively) (Table 2). Two reports of an echinocandin lock monotherapy can be found in the literature (Özdemir et al. 2011; Isgüder et al. 2017). In these cases, CAS lock solution was used with systemic CAS treatment for the treatment of *Candida lypolitica* catheter-related bloodstream infections (Özdemir et al. 2011). The lock used a portion of a 3 ml solution of 10 mg CAS and 5% dextrose with 200 units of heparin in lines for 12 h per day for 14 days. The obtained cultures were negative after day 4 of treatment (Özdemir et al. 2011). Isgüder et al. (2017) followed the previous lock protocol for the treatment of a catheter-related bloodstream infection caused by *C. parapsilosis*; however, the therapy was unsuccessful. Regarding alternative lock compounds, Blackwood et al. (2011) reported 100% lock efficacy of a heparin-free 70% ethanol in three paediatric patients against two *C. albicans* isolates and one *C. parapsilosis* isolate. In a case study published by Piersigilli et al. (2014), systemic antifungal treatment (5 mg kg\(^{-1}\) L-AMB) did not resolve the candidaemia. Lock therapy with 70% ethanol combined with 5 mg l\(^{-1}\) MICA was added to the therapy, which resulted in sterile blood cultures (Piersigilli et al. 2014). Recently, a total of 123 ethanol lock therapy episodes among 95 patients were analysed (including *Mycobacterium*, *Staphylococcus aureus*, *Candida* episodes) (Ashkenazi-Hoffnung et al. 2021). Overall, successful catheter salvage was observed in 78% compared to episodes where systemic antimicrobials were used alone (54%). Multivariate analysis revealed four major predisposing factors in the case of ethanol lock therapy failure, such as the presence of Gram-positive bacteria, elevated C-reactive protein, signs of tunnel infection, low neutrophil count (Ashkenazi-Hoffnung et al. 2021). In addition, the usage of ethanol as a lock solution may be associated with potential risks. Ethanol locks with concentrations above 28–30% have been related to clotting, dizziness, protein precipitation and compromised catheter integrity in polyurethane catheters (Mermel and Alang 2014; Schiller et al. 2014).

Conclusions

Antifungal lock strategies have been introduced in clinical practice in the late 1980s and have been recommended for the prevention and treatment of certain catheter-associated infections by the IDSA and the CDC. Until recently, there was no officially approved antifungal lock therapeutic strategy, despite the fact that the majority of *Candida* bloodstream infections in long-term CVCs are associated with a prominent intraluminal *Candida* colonisation, serving as a continuous source of life-threatening candidaemia. Based on the available *in vitro*, *in vivo* and clinical data, the ethanol-based lock solutions show the highest activity. Nevertheless, the ethanol-associated risks and limiting factors are well-defined, impeding its widespread clinical use. There are *in vitro* data regarding echinocandin- and amphotericin B-based lock solution alone or in combination with promising adjunctive compounds with various mechanisms; however, the number of valid *in vivo* studies dealing with these combinations is scarce. In summary, the forthcoming introduction of antifungal lock therapy into clinical practice remains questionable because several randomized
Table 2 Case reports of antifungal lock therapy against Candida species

| Reference               | Patient(s)       | Species       | Lock solution | Systemic therapy            | Duration of therapy                  | Therapeutic success |
|-------------------------|------------------|---------------|---------------|-----------------------------|--------------------------------------|---------------------|
| Johnson et al. (1994)   | 4-yr-old sex is unknown | C. albicans  | 2 mg ml⁻¹ d-AMB | Unknown                     | 12 h twice a day for 10–14 days       | 2/2 (100%)          |
|                         | 18-yr-old sex is unknown | C. albicans  | 2 mg ml⁻¹ d-AMB | Unknown                     | 12 h twice a day for 10–14 days       |                    |
| Benoit et al. (1995)    | 30-yr-old female | C. glabrata   | 2:5 mg ml⁻¹ d-AMB | d-AMB for three days then FLU for 4 days | 8–12 h/day for 15 days            | 2/1 (50%)           |
| Viale et al. (2001)     | 40-yr-old female | C. glabrata   | 2:5 mg ml⁻¹ d-AMB | d-AMB for 7 days            | 12 h per day for 14 days             | 2/2 (100%)          |
| Castagnola et al. (2005)| Infant           | C. parapsilosis | 2:67 mg ml⁻¹ L-AMB | FLU for 7 days              | 12 h per day for 14 days             |                    |
| Angel-Moreno et al. (2005)| 40-yr-old male | C. glabrata   | 5 mg ml⁻¹ d-AMB | Systemic FLU (no duration and dosage) | 6 h per day for 14 days          | 1/1 (100%)          |
| Wu and Lee (2007)       | 13-yr-old female | C. parapsilosis | 2:5 mg ml⁻¹ d-AMB | d-AMB for 6 days then FLU (no duration and dosage) | 24 h per day for 20 days        | 1/1 (100%)          |
| Buckler et al. (2008)   | 17-mo-old female | C. albicans   | 2:67 mg ml⁻¹ L-AMB | Systemic FLU for 5 days, which was changed to L-AMB | 8 h per day for 7 to 16 days       | 4/2 (50%)           |
|                         | 7-yr-old female | C. glabrata   |               |                             | 8 h per day for 17 days            |                    |
|                         | 6-mo-old male   | C. parapsilosis |               |                             | 8 h per day for 15 days            |                    |
|                         | 1-yr-old female | C. guilliermondii |               |                             | 8 h per day for 14 days            |                    |
| Özdemir et al. (2011)   | 9-yr-old male   | C. lypolitica | 3:3 mg ml⁻¹ CAS | CAS + meropenem and teicoplanin | 12 h per day for 14 days       | 1/1 (100%)          |
| Blackwood et al. (2011) | 8-mo-old male   | C. albicans   | 70% ethanol   | Systemic FLU                | 14 days                            |                    |
|                         | 8-mo-old female | C. parapsilosis |               | Systemic VOR                |                                    |                    |
|                         | 5-yr-old male   | C. albicans   |               | Systemic FLU                |                                    |                    |
| Paul DiMondi et al. (2014)| 64-yr-old female | C. albicans  | 2:67 mg ml⁻¹ L-AMB | MICA for 14 days         | 24 h per day, change every 12 h, for 6 days | 1/1 (100%)          |
| Persigilli et al. (2014)| Infant male    | C. albicans   | 70% ethanol combined with 5 mg l⁻¹ MICA | MICA for 14 days         | 12 h                                | 1/1 (100%)          |
| Isgüder et al. (2017)   | 1-5-yr-old male | C. parapsilosis | 3:33 mg ml⁻¹ CAS | Systemic CAS                | 12 h per day for 14 days          | 1/0 (0%)            |
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