

Drug Clues for the Treatment of Fungal Catheter-Related Bloodstream Infection With Antifungal Lock Therapy

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Background: Biofilm formation often represents significant challenges in managing of bloodstream infections associated with catheter use.

Objective: Antimicrobial lock therapy serves as an adjunctive treatment for catheter-related infections, effectively eradicating or inhibiting biofilm growth.

Methods: This review synthesizes the current knowledge on antifungal lock therapy (ALT) targeting clinically common fungi, primarily *Candida* species, based on both in vitro and in vivo studies (animals and patients) from the past decade.

Results: Amphotericin B (AmB) and echinocandins are identified as the most promising antifungal agents for ALT. Combinations of antifungal agents with other compounds, such as farnesol, *Neosartorya fischeri* antifungal protein 2, 8-hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide, and polyurethane, have also shown efficacy in ALT. Additionally, ethanol, doxycycline, tigecycline, and minocycline lock solutions can be effective in treating fungal infections.

Conclusion: More comprehensive investigations and additional rigorous clinical trials are essential to thoroughly understand the safety and efficacy of ALT. This will facilitate the development of novel treatments for catheter-related fungal infections, thereby improving clinical outcomes.

Keywords: antifungal lock therapy, catheter-related bloodstream infections, *Candida*

Introduction

Central venous catheters (CVCs) are widely utilized in patients undergoing chemotherapy, hemodialysis, or parenteral nutrition. The use of CVC is associated with an increased risk of catheter-related bloodstream infections (CRBSIs), which contribute to higher morbidity and mortality rates.¹ A meta-analysis of 18 studies involving 1,976 cases of central line-associated bloodstream infections demonstrated that patients with CRBSIs have a significantly higher risk of mortality compared to those without CRBSIs.² During the early months of the coronavirus disease 2019 (COVID-19) pandemic, the incidence of CRBSIs notably escalated; a study across 78 hospitals within a single healthcare system spanning 12 US states reported a 51% increase in CRBSI rates.³ Antimicrobial lock therapy represents a promising approach to addressing the challenges of CRBSIs. Antimicrobial lock therapy enhances intravenous therapy by delivering antimicrobial agents directly to the site of infection, thereby increasing local drug concentration and improving therapeutic efficacy.⁴ Moreover, antimicrobial lock therapy minimizes systemic drug distribution, consequently reducing potential side effects.



Fungal infections represent an escalating challenge, and the scarcity of antifungal agents has spurred interest in antifungal lock therapy (ALT). However, a comprehensive synthesis of the categories utilized in ALT has been lacking.⁵ This review consolidates data from the past decade's publications on ALT drugs used in both in vitro and in vivo settings (animals and patients), encompassing specific drugs, concentrations, and effects; isolate concentration and environmental conditions for biofilm formation and maturation; models and methodologies (patient data and catheter types); treatment duration; and strains. The synthesized information aims to provide a robust evidence base for the judicious use of these drugs in ALT, thereby enhancing the efficacy of antifungal therapy, reducing treatment costs, and fostering advancements in medical technology.

Drugs and Compounds Used for Antifungal Lock therapy

Azoles

Ten years ago, numerous studies investigated the efficacy of azoles as tube sealing solutions. For instance, fluconazole, itraconazole, and voriconazole were found to be effective against *Candida (C). albicans*, *C. glabra*, *C. tropicalis*.⁶ However, other studies indicated that these azoles were either ineffective or less effective compared to alternative antifungal agents.^{7,8} Over the past decade, research has increasingly focused on the combined use of azoles in sealing fluids. A study observed a synergistic effect of fluconazole + 8-hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide in 77.8% of the isolates.⁹ Nagy et al reported clear synergistic interactions between fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole + farnesol against one-day-old biofilms, with fractional inhibitory concentration indexes ranging from 0.038 to 0.375.¹⁰ Additionally, a combination of fluconazole (10 mg/mL) + polyurethane (50 mg/mL) reduced biofilm biomass by 4 logs, while coating catheters with this mixture decreased the accumulation of *C. albicans* on subcutaneous catheters in mice.¹¹ A film-forming system (FFS), a non-solid dosage form composed of drug and film-forming excipients, has also shown promise. Myricetin (MY) extracted from variety plants possesses antioxidant, antitumor, and antibacterial properties. Miconazole nitrate (MN) is a commonly used clinical antifungal agent. MN +MY@FFS demonstrated an excellent preventive effect against percutaneously inserted *C. albicans* catheter-related infection (CRI).¹²

Polyenes

Polyenes demonstrate potent inhibitory activity against *C. albicans* biofilm formation in vitro. The polyene antifungal agent amphotericin B (AmB) exhibits broad-spectrum efficacy against a wide array of fungal pathogens. AmB specifically binds to sterols, particularly ergosterol, disrupting cell membrane integrity by inducing pore formation and subsequent leakage of cellular components. AmB is available in multiple formulations, including deoxycholate-AmB (d-AmB) and lipid-based formulations such as liposomal AmB (L-AmB), amphotericin B colloidal dispersion (ABCD), and amphotericin B lipid complex (ABLC).

Recent studies have provided experimental evidence demonstrating that relatively low doses of AmB effectively inhibit biofilm formation by *C. species (spp)*. Consequently, AmB is commonly employed as a positive control in research aimed at exploring novel antifungal strategies.¹³ Specifically, AmB inhibits mature biofilms of *C. albicans*, *C. tropicalis* and *C. parapsilosis* by over 90% at concentrations ranging from 1 to 40 µg/mL in 96-well polystyrene microtiter plates.¹⁴ Additionally, AmB completely inhibits mature biofilms of *C. albicans*, *C. tropicalis* and *C. glabrata* at concentrations between 0.5 and 8 µg/mL.⁹ Sidrim et al reported that AmB achieves 100% inhibition of mature biofilms of *C. albicans* and *C. tropicalis* at concentration of 0.5 to 4 µg/mL.¹⁵ Given the increasing incidence of infections caused by *C. auris*, it has been observed that both 0.1 mg/mL AmB and 1 mg/mL L-AmB exhibit significant inhibitory effects against *C. auris* biofilms.¹⁶ Furthermore, L-AmB reduces the metabolic activity of biofilms formed by *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* by more than 96% after 72 h of exposure at a concentration of 2 mg/mL in flat-bottomed microtiter polystyrene plates.¹⁷ Notably, approximately 90% of biofilm cells of *C. spp.* were eliminated after 48 h of exposure to L-AmB at concentration of 32 mg/mL (*C. glabrata* CG334), 64 mg/mL L-AmB (*C. albicans* CA180 and *C. glabrata* CG171), or 128 mg/mL L-AmB (*C. albicans* CA176).¹⁸

The activity, biomass, and proteinase and phospholipase activities of biofilms were significantly reduced following the combination treatment with AmB and poly(lactic-co-glycolic acid) (PLGA) nanoparticles under 42 kHz ultrasound irradiation at an intensity of 0.30 W/cm² for 15 min ($P < 0.01$).¹⁹ Additionally, AmB (1–40 µg/mL) and AND (0.125–2 µg/mL) inhibited over 90% of mature biofilms formed by *C. albicans*, *C. tropicalis*, and *C. parapsilosis* in 96-well polystyrene microtiter plates.¹⁴

In addition to evaluating the antifungal efficacy of diverse formulations of AmB in vitro, an increasing number of in vivo studies have assessed the effectiveness of AmB in rabbits and mice. Basas et al investigated the anti-biofilm effect of lower concentrations (5–5.5 mg/mL) and shorter exposure times (2 days) of L-AmB in CVC treatment in rabbits. The rates of catheter tip negativity ranged from 21% to 29% for two *C. glabrata* strains, from 17% to 30% for two *C. parapsilosis* strains, and from 50% to 83% for two *C. albicans* strains.^{13,18} Fujimoto and Takemoto combined systemic L-AmB administration (5 mg/kg) with intraluminal L-AmB lock therapy (2 mg/mL) in mice with CVC infections. They found that this combined therapy achieved cure rates ranging from 98.1% to 100% in mice infected with *C. albicans*, *C. tropicalis*, *C. Parapsilosis*, or *C. glabrata*.¹⁷

Combined treatment with AmB-NPs and continuously ultrasound for 7 days effectively eliminated *C. albicans* biofilms on catheters.¹⁹ In 7 out of 11 episodes (64%), a regimen consisting of AmB (0.1 mg/mL) combined with systemic therapy using flucytosine (500 mg BID) and fluconazole (150 mg every 48 h during the night exchange) for 4 weeks resulted in successful outcomes without the need for PD catheter removal.²⁰ DiMondi et al treated a 64-year-old woman with *C. albicans* double-lumen catheter-related fungemia using L-AmB lock therapy (2.67 mg/mL) for 6 days, along with intravenous MFG for 6 days followed by oral fluconazole.²¹

Echinocandins

Echinocandins represent a pioneering class of antifungals that target the fungal cell wall, marking a major breakthrough in antifungal chemotherapy. Four semisynthetic derivatives of echinocandins are currently available for clinical use: caspofungin (CAS), micafungin (MFG), anidulafungin (AND), and rezafungin. These compounds share a cyclic hexapeptide antibiotic core structure with modified N-linked acyl lipid side chains, which facilitate the anchoring of the hexapeptide nucleus to the fungal cell membrane. This interaction is crucial for the drug's engagement with the target enzyme complex responsible for cell wall synthesis.²² Echinocandins constitute a valuable addition to the antifungal arsenal due to their potent fungicidal activity against significant human pathogenic fungi, including azole-resistant strains of *C. spp.*

The MFG lock solution effectively inhibited biofilm formation by seven *C. albicans* strains (mean inhibition rate: 17.7%), two *C. tropicalis* strains (mean inhibition rate: 62.8%) and one *C. parapsilosis* strain (inhibition rate: 87.6%). Notably, lower concentrations of the MFG lock solution demonstrated greater efficacy compared to higher concentrations against six *C. glabrata* strains.¹⁷ Additionally, MFG completely inhibited biofilm formation by one *C. albicans* strain at a concentration of 16 µg/mL.²³ Furthermore, AND (2 µg/mL) inhibited biofilm formation by two *C. parapsilosis* strains by over 50% in polystyrene plates. At concentrations of 4–8 µg/mL in polystyrene plates and 1 µg/mL in silicone discs, AND inhibited biofilm formation by all tested strains by more than 90%. Moreover, AND at concentrations ranging from 0.03 to 2 mg/L eradicated more than 90% of biofilms for both *C. albicans* and *C. glabrata* strains (two *C. albicans*, two *C. glabrata*).^{13,18} AND (0.125–2 µg/mL) also inhibited biofilm maturation by more than 90% for all tested strains (three *C. albicans*, three *C. tropicalis*, and three *C. parapsilosis*) in 96-well polystyrene microtiter plates.¹⁴ Sumiyoshi et al reported that CAS dissolved in 5% glucose solution rapidly and effectively inhibited the growth of multidrug-resistant (MDR) *C. albicans*, *C. auris*, and bacterial cells, whereas 0.9% NaCl, other ion-containing solutions, and other echinocandins were ineffective.²⁴ CAS (0.125–2 µg/mL) inhibited 100% of mature biofilms of all tested strains (three *C. albicans*, three *C. tropicalis*, and three *C. glabrata*).⁹

Nikkomyacin Z, CAS, and MFG exhibit inhibitory effects on biofilms and demonstrate greater efficacy against *C. albicans* compared to *C. parapsilosis*.²⁵ Additionally, *Neosartorya fischeri* antifungal protein 2 (128 mg/L) + echinocandins (32 mg/L) significantly inhibited biofilm formation across all tested strains.²⁶

Echinocandins demonstrate superior antimicrobial efficacy against *C. catheter-related* infections in animal models. Basas et al evaluated the anti-biofilm activity of AND at a concentration of 3.33 mg/mL. The rates of catheter tip

negativity following AND treatment ranged from 64% to 100% for two *C. glabrata* strains, from 63% to 73% for two *C. parapsilosis* strains, and from 40% to 83% for two *C. albicans* strains.^{13,18} Fujimoto and Takemoto investigated the effects of combining L-AmB (2 mg/mL lock solution with 5 mg/kg intravenous) and MFG (2 mg/mL lock solution with 15 mg/kg intravenous) to treat CVC infections in mice. The combined therapy resulted in cure rates ranging from 10.8% to 88.6% for one *C. albicans* strain, one *C. tropicalis* strain, one *C. parapsilosis* strain, and two *C. glabrata* strains.¹⁷ Additionally, combining MFG lock treatment (16 µg/mL) with systemic therapy reduced the frequency of *C. albicans*-positive catheters by 75%.²³

Piersigilli et al reported the successful salvage of a CVC in a 2-year-old infant with a catheter-related *C. albicans* bloodstream infection. The treatment regimen included an intraluminal lock solution composed of a 1:1 mixture of 70% ethanol (EtOH) and 5 mg/L MFG, combined with systemic intravenous therapy using L-AmB (5 mg/mL) and MFG (10 mg/mL) for a duration of 21 days.²⁷

Antibiotics

A decade ago, research indicated that high concentration of doxycycline and tigecycline exhibited antifungal activity against mature *C. albicans* biofilms.^{28,29}

Certain antibiotics have also demonstrated anti-biofilm effects either independently or as potentiators of other antifungal agents. Sidrim et al reported that cefepime, meropenem, piperacillin + tazobactam (TZB), and vancomycin significantly diminished the cellular activity of mature *C. albicans* and *C. tropicalis* biofilms grown on polystyrene plates at various concentrations: MIC/10 ($P < 0.05$), MIC ($P < 0.01$), 10× MIC ($P < 0.0001$), and 50× MIC ($P < 0.0001$).¹⁵

Furthermore, a combination of doxycycline (800 µg/mL), micafungin (0.01565 µg/mL), and ethanol (20%) reduced the metabolic activity of mature *C. albicans* biofilms by more than 90%.³⁰

Ethanol

The application of EtOH as an ALT in vitro and in vivo is detailed in Table 1 and Table 2, respectively. A treatment with 20% EtOH significantly diminished the metabolic activity of *C. albicans* biofilms by 98%.³⁰ Mature *C. albicans* biofilms (48-hour old) on silicone elastomer disks were entirely inhibited after exposure to a combination of 25% EtOH, 5 mg/mL trimethoprim and 3% calcium EDTA for 4 h.³¹ Furthermore, for MDR *C. auris* biofilms grown on silicone discs for 24 h, a lock solution containing 0.003% nitroglycerin, 4% disodium citrate, and 22% EtOH administered for 2 h resulted in excellent antifungal efficacy, eradicating all replicates of 10 strains. In contrast, lock therapy with L-AmB at 1 mg/mL eliminated only 1 out of 10 strains, while d-AmB at 0.1 mg/mL eradicated 3 out of 10 strains.¹⁶ Alonso et al assessed the effectiveness of a heparinized 40% EtOH-based lock solution against four bacterial species and various clinical isolates using an in vitro model. They discovered that a 72-hour treatment with the heparinized 40% EtOH lock solution substantially reduced the biomass and metabolic activity of clinical isolates from patients with CRBSIs. However, the 40% EtOH solution could not completely eradicate biofilms in vitro due to their rapid renewal rate.³² A combination of 0.1% minocycline hydrochloride, 3% EDTA, and 25% EtOH fully eradicated ten *C. auris* biofilms within 1 h.³³

Chandra et al examined the impact of combination lock therapy applied for 2 h daily over 7 days against *C. albicans*-infected CVCs in rabbits. This lock therapy successfully cleared fungal cells in 8 out of 16 catheters (0 CFUs in each).³¹ Clinical studies have also utilized EtOH lock solutions.

Taurolidine

Taurolidine is a broad-spectrum antibacterial agent with a non-specific mechanism of action, functioning through interaction with the cell walls of microorganisms. It is utilized in several catheter lock solutions globally.^{43,44} In 2023, DefenCath, a catheter lock solution, containing 13,500 mg/L taurolidine and 1,000 units/mL heparin, received approval from the US Food and Drug Administration (FDA). This marks the first FDA-approved catheter sealing solution designed to reduce the risk of CRBSIs in adult patients with kidney failure undergoing chronic hemodialysis via CVCs.⁴⁵ Numerous studies have demonstrated taurolidine's efficacy in preventing CRBSIs,^{46–48} although data on its therapeutic use as a lock solution remain limited. The application of taurolidine as an ALT in vitro and in vivo is summarized in Table 1 and Table 2, respectively. Jakub Visek evaluated the effectiveness of various taurolidine solutions

Table 1 Drugs Used in Antifungal Lock Therapies Tested in Vitro

Drug Category	Agents (Dosage)	Fungal	Biofilm Age	Duration of Drug Treatment	Results	Reference
Azoles	Fluconazole (8 µg/mL) +8-Hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide (0.5 µg/mL)	<i>C. albicans</i> (1×10^6 CFU/mL), n=3; <i>C. tropicalis</i> (1×10^6 CFU/mL), n=3; <i>C. glabrata</i> (1×10^6 CFU/mL), n=3	48 h	48 h	Synergistic interactions were observed when 8-hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide was combined with fluconazole in 77.8% of isolates.	[9]
	Fluconazole (64 mg/L) +farnesol (75 µM)	<i>C. auris</i> (1×10^6 cells/mL), n=3	24 h	24 h	Farnesol (300 µM) significantly decreased the metabolic activity of biofilms of all strains. Combinations of farnesol with fluconazole, itraconazole, voriconazole, posaconazole, or isavuconazole had obvious synergistic effects on <i>C. auris</i> biofilms.	[10]
	Voriconazole (0.5–1 mg/L)+ farnesol (4.69–9.38 µM)					
	Itraconazole (0.5 mg/L) +farnesol (4.69–9.375 µM)					
	Posaconazole (0.25 mg/L) +farnesol (2.34–4.69 µM)					
	Isavuconazole (0.125–0.5 mg/L) +farnesol (4.69–18.75 µM)					
	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL)	<i>C. albicans</i> (10^6 CFU/mL), n=1	60 h	24 h, 48 h, 72 h	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL) led to 4-log reduction in biofilm biomass.	[11]

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Table I (Continued).

Drug Category	Agents (Dosage)	Fungal	Biofilm Age	Duration of Drug Treatment	Results	Reference
Polyenes	Liposomal amphotericin B (0.015–1024 mg/L)	<i>C. parapsilosis</i> (1×10^6 cells /mL), n=2	2 d	2 d	Liposomal amphotericin B (2 mg/L) inhibited >50% of biofilms of both strains on polystyrene plates; Liposomal amphotericin B (8–16 mg/L) inhibited >90% of biofilms of all strains on polystyrene plates; Liposomal amphotericin B (1024 mg/L) inhibited >90% of biofilms of all strains on silicone discs.	[13]
	Amphotericin B (1–40 µg/mL)	<i>C. albicans</i> ($1.0\text{--}5.0 \times 10^6$ CFU/mL), n=3; <i>C. tropicalis</i> ($1.0\text{--}5.0 \times 10^6$ CFU/mL), n=3; <i>C. parapsilosis</i> ($1.0\text{--}5.0 \times 10^6$ CFU/mL), n=3	48 h	24 h	Amphotericin B (1–40 µg/mL) inhibited >90% of mature biofilms of all strains in 96-well polystyrene microtiter plates.	[14]
	Amphotericin B (0.03125–16 µg/mL)	<i>C. albicans</i> (1×10^6 CFU/mL), n=3; <i>C. tropicalis</i> (1×10^6 CFU/mL), n=3; <i>C. glabrata</i> (1×10^6 CFU/mL), n=3	48 h	48 h	Amphotericin B (0.5–8 µg/mL) inhibited 100% of mature biofilms of all strains.	[9]
	Amphotericin B (0.5–2 µg/mL)	<i>C. albicans</i> (1×10^6 cells/mL), n=10	48 h	48 h	Amphotericin B (0.5–2 µg/mL) inhibited 100% of mature biofilms of all strains.	[15]
	Amphotericin B (0.5–4 µg/mL)	<i>C. tropicalis</i> (1×10^6 cells/mL), n=10	48 h	48 h	Amphotericin B (0.5–4 µg/mL) inhibited 100% of mature biofilms of all strains.	
	Liposomal amphotericin B (1 mg/mL)	<i>C. auris</i> (5.5×10^5 CFU/mL), n=10	24 h	2 h	Liposomal amphotericin B (1 mg/mL) significantly inhibited biofilms of one strain.	[16]
	Amphotericin B (0.1 mg/mL)				Amphotericin B (0.1 mg/mL) significantly inhibited biofilms of three strains.	
	Liposomal amphotericin B (2 mg/mL)	<i>C. albicans</i> (10^7 CFU /mL), n=7; <i>C. tropicalis</i> (10^7 CFU /mL), n=2; <i>C. parapsilosis</i> (10^7 CFU /mL), n=1; <i>C. glabrata</i> (10^7 CFU /mL), n=6	2 d	3 d	Liposomal amphotericin B (2 mg/mL) inhibited >96% of biofilms of all strains.	[17]
Liposomal amphotericin B (0.015–1024 µg/mL)	<i>C. albicans</i> (1×10^7 blastoconidia/mL), n=2; <i>C. glabrata</i> (1×10^7 blastoconidia/mL), n=2	48 h	48 h	Liposomal amphotericin B (32–128 mg/L) eradicated >90% of biofilms of all strains.	[18]	

Echinocandins	Anidulafungin (0.015–1024 µg/mL)	<i>C. parapsilosis</i> (1×10^6 blastospores/mL), n=2	2 d	2 d	Anidulafungin (2 µg/mL) inhibited >50% of biofilms of all strains on polystyrene plates. Anidulafungin (4–8 µg/mL) inhibited >90% of biofilms of all strains on polystyrene plates. Anidulafungin (1 µg/mL) inhibited >90% of biofilms of all strains on silicone discs.	[13]
	Anidulafungin (0.125–2 µg/mL)	<i>C. albicans</i> ($1.0\text{--}5.0 \times 10^6$ CFU/mL), n=3; <i>C. tropicalis</i> ($1.0\text{--}5.0 \times 10^6$ CFU/mL), n=3; <i>C. parapsilosis</i> ($1.0\text{--}5.0 \times 10^6$ CFU/mL), n=3	48 h	24 h	Anidulafungin (0.125–2 µg/mL) inhibited >90% of mature biofilms of all strains in 96-well polystyrene microtiter plates.	[14]
	Caspofungin (0.000375–2 µg/mL)	<i>C. albicans</i> (1×10^6 CFU/mL), n=3; <i>C. tropicalis</i> (1×10^6 CFU/mL), n=3; <i>C. glabrata</i> (1×10^6 CFU/mL), n=3	48 h	48 h	Caspofungin (0.125–2 µg/mL) inhibited 100% of mature biofilms of all strains.	[9]
	Micafungin (2 mg/mL)	<i>C. albicans</i> (10^7 CFU /mL), n=7; <i>C. tropicalis</i> (10^7 CFU /mL), n=2; <i>C. parapsilosis</i> (10^7 CFU /mL), n=1; <i>C. glabrata</i> (10^7 CFU /mL), n=6	2 d	3 d	Micafungin (2 mg/mL) inhibited 17.7%–87.6% of biofilms of all strains.	[17]
	Anidulafungin (0.015–1024 µg/mL)	<i>C. albicans</i> (1×10^7 blastoconidia/mL), n=2; <i>C. glabrata</i> (1×10^7 blastoconidia/mL), n=2	48 h	48 h	Anidulafungin (0.03–2 mg/L) eradicated >90% of biofilms of all strains.	[18]
	Micafungin (16 µg/mL)	<i>C. albicans</i> (1×10^6 CFU/mL), n=1	24 h	3 d	Micafungin (16 µg/mL) inhibited 100% of biofilms.	[23]
	Caspofungin (500 µg/mL)	<i>C. albicans</i> (5×10^6 CFU/mL), n=1	2 d	5 min, 30 min, 60 min	Caspofungin (125–500 µg/mL) in 5% glucose inhibited >99% of biofilms of all strains in 5 min.	[24]
	Caspofungin (125 µg/mL)	<i>C. auris</i> (5×10^6 CFU/mL), n=1				
Antibiotics	Cefepime (0.01–100 mg/mL)	<i>C. albicans</i> (1×10^6 cells/mL), n=10; <i>C. tropicalis</i> (1×10^6 cells/mL), n=10	48 h	48 h	Cefepime, piperacillin + tazobactam, and vancomycin (0.01–100 mg/mL) significantly inhibited biofilms of all strains. Meropenem (1–50 mg/mL) significantly inhibited biofilms of all strains.	[15]
	Piperacillin + tazobactam (0.01–100 mg/mL)					
	Meropenem (0.01–50 mg/mL)					
	Vancomycin (0.01–100 mg/mL)					

(Continued)

Table I (Continued).

Drug Category	Agents (Dosage)	Fungal	Biofilm Age	Duration of Drug Treatment	Results	Reference
Ethanol	Nitroglycerin (0.003%) + disodium citrate (4%) + ethanol (22%)	<i>C. auris</i> (5.5×10^5 CFU/mL), n=10	24 h	2 h	Nitroglycerin (0.003%) + disodium citrate (4%) + ethanol (22%) inhibited biofilms of all strains.	[16]
	Ethanol (20%, v/v)	<i>C. albicans</i> (1×10^7 CFU/ mL), n=3	24 h	24 h	EtOH (20%, v/v) inhibited 98% of biofilms of all strains.	[30]
	Trimethoprim (5 mg/mL) + ethanol (25%) + calcium EDTA (3%)	<i>C. albicans</i> (10^7 CFU/mL), n=1	48 h	4 h	Trimethoprim (5 mg/mL) + ethanol (25%) + calcium EDTA (3%) eradicated 100% of biofilms.	[31]
	Ethanol (40%) + heparin (60 IU)	<i>C. albicans</i> (1×10^8 CFU/mL), n=20	24 h	24 h, 72 h	Ethanol (40%) + heparin (60 IU) decreased the biofilm biomass of 7 strains by 50%.	[32]
					Ethanol (40%) + heparin (60 IU) decreased the metabolic activity of biofilms of 8 strains by 83%.	
Minocycline hydrochloride (0.1%) + EDTA (3%) + ethanol (25%)	<i>C. auris</i> , n=10	24 h	60 min	Minocycline hydrochloride (0.1%) + EDTA (3%) + ethanol (25%) eradicated 100% mature biofilms of all strains.	[33]	

Combination strategies	Amphotericin B (2.5 µg/mL) + anidulafungin (0.5 µg/mL)	<i>C. albicans</i> (1.0–5.0 × 10 ⁶ CFU/mL), n=3; <i>C. tropicalis</i> (1.0–5.0 × 10 ⁶ CFU/mL), n=3; <i>C. parapsilosis</i> (1.0–5.0 × 10 ⁶ CFU/mL), n=3	48 h	24 h	Amphotericin B (1–40 µg/mL) and anidulafungin (0.125–2 µg/mL) inhibited >90% mature biofilms of all strains in 96-well polystyrene microtiter plates.	[14]
	8-Hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide (0.5 µg/mL) + fluconazole (8 µg/mL)	<i>C. albicans</i> (1 × 10 ⁶ CFU/mL), n=3; <i>C. tropicalis</i> (1 × 10 ⁶ CFU/mL), n=3; <i>C. glabrata</i> (1 × 10 ⁶ CFU/mL), n=3	48 h	48 h	Synergistic interactions were observed when 8-hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide was combined with fluconazole in 77.8% of isolates.	[9]
	Caspofungin (0.25 µg/mL) + nikkomycin Z (8 µg/mL)	<i>C. albicans</i> (1 × 10 ⁶ CFU/mL), n=5	24 h	24 h	Caspofungin (0.25 µg/mL) + nikkomycin Z (8 µg/mL) and micafungin (0.25 µg/mL) + nikkomycin Z (8 µg/mL) inhibited mature biofilms of all strains by >50%.	[25]
	Micafungin (0.25 µg/mL) + nikkomycin Z (8 µg/mL)					
	Caspofungin (128 µg/mL) + nikkomycin Z (8 µg/mL)	<i>C. parapsilosis</i> (1 × 10 ⁶ CFU/mL), n=5			Caspofungin (128 µg/mL) + nikkomycin Z (8 µg/mL) and micafungin (128 µg/mL) + nikkomycin Z (8 µg/mL) inhibited mature biofilms of all strains by >50%.	
	Micafungin (128 µg/mL) + nikkomycin Z (8 µg/mL)					
Ultrasound (0.30 W/cm ² , 15 min) + amphotericin B-NPs (4 µg/mL)	<i>C. albicans</i> (10 ⁷ CFU/mL), n=1	48 h	24 h	Ultrasound + AmB-NPs (4 µg/mL) inhibited mature biofilms by 74.64%.	[19]	

(Continued)

Table I (Continued).

Drug Category	Agents (Dosage)	Fungal	Biofilm Age	Duration of Drug Treatment	Results	Reference
	Farnesol (75 μ M) + fluconazole (64 mg/L)	<i>C. auris</i> (1×10^6 cells/mL), n=3	24 h	24 h	Farnesol (300 μ M) significantly decreased the metabolic activity of biofilms of all strains. Combinations of farnesol with fluconazole, itraconazole, voriconazole, posaconazole, or isavuconazole had obvious synergistic effects on <i>C. auris</i> biofilms.	[10]
	Farnesol (4.69–9.38 μ M) + voriconazole (0.5–1 mg/L)					
	Farnesol (4.69–9.375 μ M) + itraconazole (0.5 mg/L)					
	Farnesol (2.34–4.69 μ M) + posaconazole (0.25 mg/L)					
	Farnesol (4.69–18.75 μ M) + isavuconazole (0.125–0.5 mg/L)					
	Neosartorya fischeri antifungal protein 2 (128 mg/L) + echinocandins (32 mg/L)	<i>C. auris</i> (1×10^6 cells/mL), n=5	24 h	24 h	Neosartorya fischeri antifungal protein 2 (128 mg/L) + echinocandins (32 mg/L) significantly inhibited biofilms of all strains.	[26]
Fluconazole (10 mg/mL) + polyurethane (50 mg/mL)	<i>C. albicans</i> (10^6 CFU/mL), n=1	60 h	24 h, 48 h, 72 h	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL) led to 4-log reduction in biofilm biomass.	[11]	
Taurolidine	Taurosept Taurolock Taurolock 1:1 3.5% Taurolidine	<i>C. albicans</i> (1×10^7 cells /mL), n=3 <i>C. glabrata</i> (1×10^7 cells /mL), n=3	24 h	30, 60, and 120 min	Taurosept, Taurolock and Taurolock 1:1 all inhibited >50% of CFU of both strains; 3.5% Taurolidine was not tested.	[34]
	2% taurolidine 1.34% taurolidine 1.34% taurolidine +4%Citrate+500 IU/mL Heparin	<i>C. glabrata</i> (1×10^6 cells /mL), n=1	–	–	2% taurolidine, 1.34% taurolidine and 1.34% taurolidine+4%Citrate+500 IU/mL Heparin inhibited <i>C. glabrata</i> growth.	[35]
	Taurolock	<i>C. albicans</i> (1×10^7 cells /mL)	18–24 h	2 or 24 h	Taurolock biofilms eradication rate was 100%.	[36]
	1.35% taurolidine +3.5% disodium citrate +1,000 IU/mL heparin	<i>C. auris</i> (1×10^7 cells/mL), n=10	24 h	60 min	Taurolidine lock partially eradicated all of the <i>C. auris</i> biofilms	[33]

Tetrasodium EDTA	Tetrasodium EDTA (0.004–4.0%)	<i>C. albicans</i> (3.0×10^6 CFU/mL), n=2	24 h	1 h, 3 h, 6 h, 24 h	After 1% tetrasodium EDTA treatment for 24 hours, the number of cells in the biofilm decreased by 1.7–2.7 log ₁₀ .	[37]
		<i>C. glabrata</i> (2.0×10^7 CFU/mL), n=2	48 h			
Repurposed agents and adjunctive agents	8-Hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide (0.125–64 µg/mL)	<i>C. albicans</i> (1×10^6 CFU/mL), n=3; <i>C. tropicalis</i> (1×10^6 CFU/mL), n=3; <i>C. glabrata</i> (1×10^6 CFU/mL), n=3	48 h	48 h	8-Hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide (1–4 µg/mL) inhibited mature biofilms of all strains by 100%.	[9]
	Farnesol (10, 50, 100 and 300 µM)	<i>C. auris</i> (1×10^6 cells/mL), n=3	24 h	24 h	Farnesol (300 µM) significantly decreased the metabolic activity of biofilms of all strains.	[10]
	Auranofin (3 mg/mL) + polyurethane (50 mg/mL)	<i>C. albicans</i> (10^6 CFU/mL), n=1	60 h	24 h, 48 h, 72 h	Auranofin (3 and 10 mg/mL) + polyurethane (50 mg) led to 3-log reduction of biofilm biomass.	[11]
	Cerium nitrate (0.5 mM–1 M)	<i>C. albicans</i> (1×10^6 cells/mL), n=8; <i>C. parapsilosis sensu stricto</i> (1×10^6 cells/mL), n=8; <i>C. glabrata</i> (1×10^6 cells/mL), n=8; <i>C. tropicalis</i> (1×10^6 cells/mL), n=8; <i>C. krusei</i> (1×10^6 cells/mL), n=8; <i>C. guilliermondii</i> (1×10^6 cells/mL), n=8	24 h	24 h, 48 h	Cerium nitrate (0.5 mM–1 M) reduced the metabolic activity and biomass of biofilms of all strains.	[38]
	Aspirin (30, 35, 40 and 45 mg/mL)	<i>C. albicans</i> ($1–5 \times 10^6$ CFU/mL), n=1; <i>C. glabrata</i> ($1–5 \times 10^6$ CFU/mL), n=1; <i>C. krusei</i> ($1–5 \times 10^6$ CFU/mL), n=1; <i>C. tropicalis</i> ($1–5 \times 10^6$ CFU/mL), n=1	48 h	2h, 4 h, 24 h	Aspirin (40 mg/mL) eradicated biofilms of all strains in 4–24 hours.	[39]
	Hypochlorous acid (0.002–12.61 mM)	<i>C. albicans</i> (1.0×10^7 CFU/mL), n=1; <i>C. glabrata</i> (1.0×10^7 CFU/mL), n=1; <i>C. parapsilosis</i> (1.0×10^7 CFU/mL), n=1	48 h	48 h	Hypochlorous acid (8.84 mM) inhibited mature biofilms of all strains by 100%.	[40]

Notes: *C. albicans*; *C. tropicalis*; *C. glabrata*; *C. parapsilosis*; *C. auris*; *C. krusei*; *C. guilliermondii*: They are all conditionally pathogenic bacteria that can cause diseases in humans, with *C. albicans* being the most virulent.

Table 2 Drugs Used in Antifungal Lock Therapies Tested in Vivo

Drug Category	Agents (Dosage)	Animals Models or Catheter type	Fungal	Biofilm Age	Duration of Therapy	Results (Curative Ratios)	Reference
Azoles	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL)	Mice, subcutaneous catheter model	<i>C. albicans</i> (10^6 CFU), n=1	60 h	24 h, 48 h, 72 h	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL) led to a 1.5-log reduction in biofilm biomass.	[11]
	Miconazole nitrate (20 μ mol/L)+ Myricetin (1250 μ mol/L)	Mice,CRI model	<i>C. albicans</i> (1.0×10^7 CFU/mL), n=1	–	–	Myricetin + miconazole nitrate in film-forming system exhibited excellent preventive effects against percutaneously inserted <i>C. albicans</i> CRI.	[12]
Polyenes	Liposomal amphotericin B (5.5 mg/mL)	Rabbits,CVC model	<i>C. parapsilosis</i> (1.0×10^7 CFU/mL), n=2	48 h	2 days	17%-30%	[13]
	Liposomal amphotericin B (2 mg/mL) with systemic 5 mg/kg	Mice,CVC model	<i>C. albicans</i> (1×10^7 CFU/mL), n=1; <i>C. tropicalis</i> (1×10^7 CFU/mL), n=1; <i>C. parapsilosis</i> (1×10^7 CFU/mL), n=1; <i>C. glabrata</i> (1×10^7 CFU/mL), n=2	48 h	3 days	98.1%-100%	[17]
	Liposomal amphotericin B (5 mg/mL)	Rabbits,CVC model	<i>C. albicans</i> (1×10^7 CFU/mL), n=2 <i>C. glabrata</i> (1×10^7 CFU/mL), n=2	48 h	2 days	50%-83% 21%-29%	[18]
Echinocandins	Anidulafungin (3.3 mg/mL)	Rabbits,CVC model	<i>C. parapsilosis</i> (1.0×10^7 CFU/mL), n=2	48 h	2 days	63% (5/8)-73% (8/11)	[13]
	Micafungin (2 mg/mL) with systemic 15 mg/kg	Mice,CVC model	<i>C. albicans</i> (1×10^7 CFU/mL), n=1; <i>C. tropicalis</i> (1×10^7 CFU/mL), n=1; <i>C. parapsilosis</i> (1×10^7 CFU/mL), n=1; <i>C. glabrata</i> (1×10^7 CFU/mL), n=2	48 h	3 days	10.8%-86.6%	[17]
	Anidulafungin (3.33 mg/mL)	Rabbits,CVC model	<i>C. albicans</i> (1×10^7 CFU/mL), n=2 <i>C. glabrata</i> (1×10^7 CFU/mL), n=2	48 h	2 days	40%-83% 64%-100%	[18]
	Micafungin (16 μ g/mL) with systemic 1 mg/kg	Wistar rats, CVC model	<i>C. albicans</i> (1×10^4 CFU/mL), n=1	24 h	7 days	Lock therapy: 65%;systemically treated:37.5%;systemically treated and lock therapy: 75%	[23]

Ethanol	Trimethoprim (5 mg/mL), Ethanol (25% v/v) and calcium EDTA (3%)	Rabbits, CVC model	<i>C. albicans</i> (10^7 CFU/mL), n=1	24 h	2 h/d×7 days	50%	[31]
Combination strategies	Ultrasound (0.30 W/cm ² , 15 min) + AmB-NPs (4 µg/mL)	Rats, subcutaneous catheter model	<i>C. albicans</i> (10^7 CFU/mL), n=1	48 h	3 days, 7 days	After 7 days of continuous treatment, the biofilms on the catheters were basically eliminated.	[19]
	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL)	Mice, subcutaneous catheter model	<i>C. albicans</i> (10^6 CFU), n=1	60 h	24 h, 48 h, 72 h	Fluconazole (10 mg/mL) + polyurethane (50 mg/mL) led to a 1.5-log reduction in biofilm biomass.	[11]
	Myricetin (1250 µmol/L) + miconazole nitrate (20 µmol/L)	Mice, CRI model	<i>C. albicans</i> (1.0×10^7 CFU/mL), n=1	–	–	Myricetin + miconazole nitrate in film-forming system exhibited excellent preventive effects against percutaneously inserted <i>C. albicans</i> CRI.	[12]
	Liposomal amphotericin B (2.67 mg/mL) + systemic therapy (intravenous micafungin for 6 days then changed to oral fluconazole)	64-year-old woman, double-lumen catheter	<i>C. albicans</i>	–	6 days	100% (1/1)	[21]
	Amphotericin B (0.1 mg/mL) + systemic therapy flucytosine (500 mg BID) fluconazole (150 mg every 48 h in the night exchange)	Women (6) and men (5), peritoneal dialysis catheter	<i>C. spp.</i>	–	4 weeks	64% (7/11)	[20]
	Ethanol (70%) + micafungin (5 mg/L) + systemic liposomal amphotericin B (5 mg/kg) and micafungin (10 mg/kg)	2-year-old boy, CVC	<i>C. albicans</i>	–	21 days	100% (1/1)	[27]

(Continued)

Table 2 (Continued).

Drug Category	Agents (Dosage)	Animals Models or Catheter type	Fungal	Biofilm Age	Duration of Therapy	Results (Curative Ratios)	Reference
Taurolidine	2% taurolidine	21 neonates with CRBSI	<i>C. albicans</i> , n=2	–	Taurolidine was injected and locked for at least 120 min every 24 h	85.7% (18/21)	[41]
	2% taurolidine	A boy with CRBSI	<i>C. glabrata</i> , n=1	–	–	100%(1/1)	[42]
Repurposed agents and adjunctive agents	Auranofin (3 and 10 mg/mL) + polyurethane (50 mg/mL)	Mice, subcutaneous catheter model	<i>C. albicans</i> (10 ⁶ CFU), n=1	60 h	24 h, 48 h, 72 h	Auranofin (10 mg/mL) + polyurethane (50 mg) led to a 1-log reduction in biofilm biomass.	[11]

Notes: *C. albicans*; *C. tropicalis*; *C. glabrata*; *C. parapsilosis*: They are all conditionally pathogenic bacteria that can cause diseases in humans, with *C. albicans* being the most virulent.

in the preventing and treating CRBSIs caused by *C. albicans* or *C. glabrata* in patients receiving parenteral nutrition over a short period. The results indicated that Taurosept, Taurolock, and Taurolock 1:1 all inhibited both strains.³⁴ Similarly, E.D. Olthof et al found that taurolidine completely prevented the growth of *C. glabrata* and *C. albicans*.^{35,36} Taurolidine lock therapy was also shown to partially eradicate *C. auris* biofilm.³³

Savarese et al confirmed the feasibility and direct outcomes of prophylactic and therapeutic taurolidine locks in term and preterm neonates through a descriptive retrospective study. Among the 21 cases, clinical symptom resolution and bacteremia clearance were achieved without catheter removal in 18 cases (85.7%). This high success rate underscores the efficacy of taurolidine locks in this patient population.⁴¹ Additionally, Antonella Diamanti et al reported the successful treatment of a 3-years-old boy with CRBSI caused by *C. glabrata* using 2% taurolidine.⁴²

Tetrasodium EDTA

Liu et al reported that following a 24-hour treatment with 1% tetrasodium EDTA, the cell counts in the biofilms of *C. albicans* and *C. glabrata* were reduced by 1.7 to 2.7 log₁₀ units.³⁷

Repurposed Agents and Adjunctive Agents

Table 1 summarizes the adjunctive agents and biocides utilized for the treatment of *C.*-related catheter infections. Silva-Dias et al examined the antifungal efficacy of cerium nitrate (CN), a lanthanide compound, against various *C. spp.* CN demonstrated significant inhibition of biofilm formation in both in vitro and in vivo models using polyurethane catheters segments. Furthermore, at higher concentrations, CN effectively disrupted and nearly eradicated preformed biofilms.³⁸ Nagy et al explored the impact of farnesol, a quorum-sensing molecule known to inhibit yeast-to-hyphae transition and promote reverse morphogenesis, on *C. auris*. Their study revealed that 300 μM farnesol treatment for 2 to 24 h significantly reduced the metabolic activity of one-day-old biofilms ($P < 0.001$).¹⁰ It has been demonstrated that adding 3 mM farnesol at the initial stage of biofilm formation can achieve approximately 50% inhibition.⁴⁹ Additionally, farnesol synergistically enhances the effectiveness of fluconazole against *C. albicans* biofilms.⁵⁰ Chan et al evaluated the anti-biofilm effects of aspirin on *C.* biofilms, including those formed by *C. albicans*, *C. glabrata*, *C. krusei*, and *C. tropicalis* on surgical catheters. At a concentration of 40 mg/mL, aspirin eradicated *C. albicans* biofilms within 4 h. However, it required 24 h to effectively eradicate biofilms of the other tested *C. spp.*³⁹ The 8-hydroxyquinoline derivative 8-hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide (1–4 μg/mL) completely inhibited biofilm growth in three strains each of three *C. albicans*, three *C. glabrata*, and three *C. tropicalis*.⁹ Palau et al assessed the efficacy of hypochlorous acid (HClO) against biofilm-producing strains on silicone discs. HClO was generated via direct electric current (DC) pulses at specified amperages and durations. For the three *C.* strains examined (CA176, CG171, and CP54), a DC pulse of 20 mA for 20 min (equivalent to 8.84 mM HClO) was required to completely eradicate the biofilms.⁴⁰ In another study, mouse catheters coated with polyurethane and 3 mg or 10 mg of auranofin accumulated 1.6×10^5 and 7.8×10^5 CFU, respectively, compared to 2.0×10^8 CFU on catheters exposed to THF solvent alone. Consequently, the auranofin coating resulted in a 3-log reduction in *C. albicans* cells ($P=0.0229$ and $P=0.023$).¹¹

Additionally, auranofin-coated catheters achieved a 3-log reduction in *C. albicans* within a dual-microbe biofilm compared to uncoated catheters.¹¹

Discussion and Conclusion

The incidence of fungal infections has escalated significantly in recent years, necessitating the development of clinical solutions for catheter-related fungal infections. When a CRBSI occurs, deciding whether to remove or salvage the catheter is a critical component of interdisciplinary management discussions involving both the patient and healthcare team. Many guidelines advocate for prompt catheter removal upon diagnosis of CRBSI as a key measure to prevent further infection spread.^{51–53} However, some conservative approaches suggest attempting to salvage the catheter, particularly for pediatric patients requiring it for chemotherapy, hemodialysis, and parental nutrition, where alternative venous access can be challenging to establish.^{54,55} Indeed, catheter removal has been associated with potential increases in costs and significant delays in treatment, especially in cancer patients. Therefore, if there is any possibility of catheter salvage, alternative methods such as ALT should be considered as part of the treatment strategy. Given that ALT is a relatively

new concept for treating catheter-related fungal infections, this review focuses on in vitro studies, animal experiments, and clinical studies of ALT over the past decade.

This review encompasses numerous in vitro studies of antifungal lock solutions (Table 1). Collectively, various formulations of AmB lock solutions exhibit robust antifungal biofilm activities in vitro. Echinocandin lock solutions also demonstrate antifungal efficacy, particularly against azole-resistant *C. albicans* and *C. Parapsilosis*, with notable anti-biofilm effects lasting up to 48–72 h in vitro.²³ However, a paradoxical phenomenon has been observed: the antifungal effectiveness of echinocandin drugs in lock solutions against *C. albicans* biofilms decreases as the concentration of the drug increases in vitro.⁵⁶ This paradoxical effect is evident for both CAS and AND lock solutions but not for MFG lock solutions.²⁴ Additionally, when CAS is dissolved in low ionic strength solutions, it rapidly and effectively inhibits the growth of MDR *C. albicans*, *C. auris*, and bacterial cells in vitro.

Cefepime, meropenem, TZB, and vancomycin exhibit antifungal activity against *C. albicans* and *C. tropicalis* biofilms in vitro.¹⁵ EtOH demonstrates effective antifungal properties against biofilms in vitro when utilized as a standalone lock solution or as part of a combination lock solution. Specifically, EtOH shows significant anti-biofilm efficacy against *C. albicans* in vitro at a concentration of 20% when used alone, or in combination solutions such as EtOH (40%) + heparin (60 IU), minocycline hydrochloride (0.1%) + EDTA (3%) + EtOH (25%), and EtOH (25%) + trimethoprim (5 mg/mL) + calcium EDTA (3%).^{30–33} Additionally, the combination lock solution of EtOH (22%) + nitroglycerin (0.003%) + disodium citrate (4%) has been shown to effectively inhibit MDR *C. auris* biofilms in vitro.¹⁶

Drug combinations represent a viable strategy against *C.* biofilms, including dual-drug regimens such as AmB in conjunction with echinocandins. Furthermore, the combination of antifungal agents with other compounds, for instance, farnesol paired with triazoles (fluconazole, itraconazole, voriconazole, posaconazole, or isavuconazole),¹⁰ or nikkomycin Z combined with echinocandins (CAS or MFG), has demonstrated efficacy in inhibiting *C.* biofilms.²⁵

In addition to using EtOH, numerous studies have evaluated the efficacy of antifungal lock solutions based on non-antimicrobial drugs or compounds in vitro. Compounds such as CN, aspirin, farnesol, and 8-hydroxyquinoline-5-(N-4-chlorophenyl) sulfonamide demonstrate varying degrees of effectiveness against fungal biofilm.^{9,38,39} Farnesol exhibits synergistic effects with other antifungal agents, including fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole, in combating *C. auris* biofilms.¹⁰ Furthermore, a combination of auranofin (3 mg/mL) and polyurethane (50 mg/mL) has been shown to reduce biofilm biomass by 3 log units.¹¹

This review also summarizes in vivo studies of antifungal lock solutions, encompassing both animal experiments and clinical cases (Table 2). Animal studies have demonstrated that L-AmB lock solution, as well as MFG and AND lock solutions, exhibit significant antifungal biofilm activity. The efficacy is further enhanced when these lock solutions are combined with systemic therapy. Combination regimens include L-AmB lock solution paired with systemic L-AmB, and MFG lock solution paired with systemic MFG.^{17,23} Given the severity and complexity of CRBSIs, antifungal lock solutions are frequently used in conjunction with systemic therapies. For instance, a case report describes how a 64-year-old woman with a catheter fungal infection was successfully treated with an L-AmB lock solution combined with a 6-day course of systemic MFG and fluconazole.²¹

The reviewed studies possess certain limitations. First, we did not examine the choice of catheter removal, despite it being the traditionally preferred treatment. This omission is due to our comprehensive review's primary objective of providing alternative drug options aimed at preserving catheters. Second, ALT still faces challenges in treating catheter-related fungal infections. For instance, in vitro test conditions do not always accurately reflect in vivo biofilm development conditions for *C. spp.* Additionally, laboratory and reference strains can exhibit significant differences in growth rates and biomass.⁵⁷ Randomized clinical trials are necessary to evaluate ALT further. Although single or combination ALT solutions have demonstrated efficacy against antifungal biofilms both in vitro and in vivo, more clinical data on their efficacy and safety across diverse patients populations are required. A critical concern regarding ALT is the stability and safety of relatively high drug concentrations used in lock solutions. Further research into the stability and safety of ALT agents is imperative. Established appropriate indications and standardized formulations for ALT solutions will maximize therapeutic efficacy and health economic benefits. Continued ALT research will address current challenges in treating fungal infections and promote medical technology innovation and development. Optimizing ALT and antifungal drug formulations will enhance treatment effectiveness, mitigate risks, and improve patient care.

Abbreviations

ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; ALT, antifungal lock therapy; AmB, amphotericin B; AND, anidulafungin; CAS, caspofungin; CN, cerium nitrate; COVID-19, coronavirus disease 2019; CRBSIs, catheter-related bloodstream infections; CRI, catheter-related infection; CVCs, Central venous catheters; d-AmB, deoxycholate-AmB; DC, direct electric current; EtOH, ethanol; FFS, film-forming system; HClO, hypochlorous acid; L-AmB, liposomal AmB; MDR, multidrug-resistant; MFG, micafungin; MN, Miconazole nitrate; MY, Myricetin; TZB, tazobactam; US, the United States.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Consent for Publication

The Author confirms that the work described has not been published before.

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Disclosure

The authors declare that they have no competing interests.

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