# Liposomales Amphotericin B – Der Retter in der Not?

Giftiger Live-Stream
Pilzinfektionen bei schwer kranken PatientInnen
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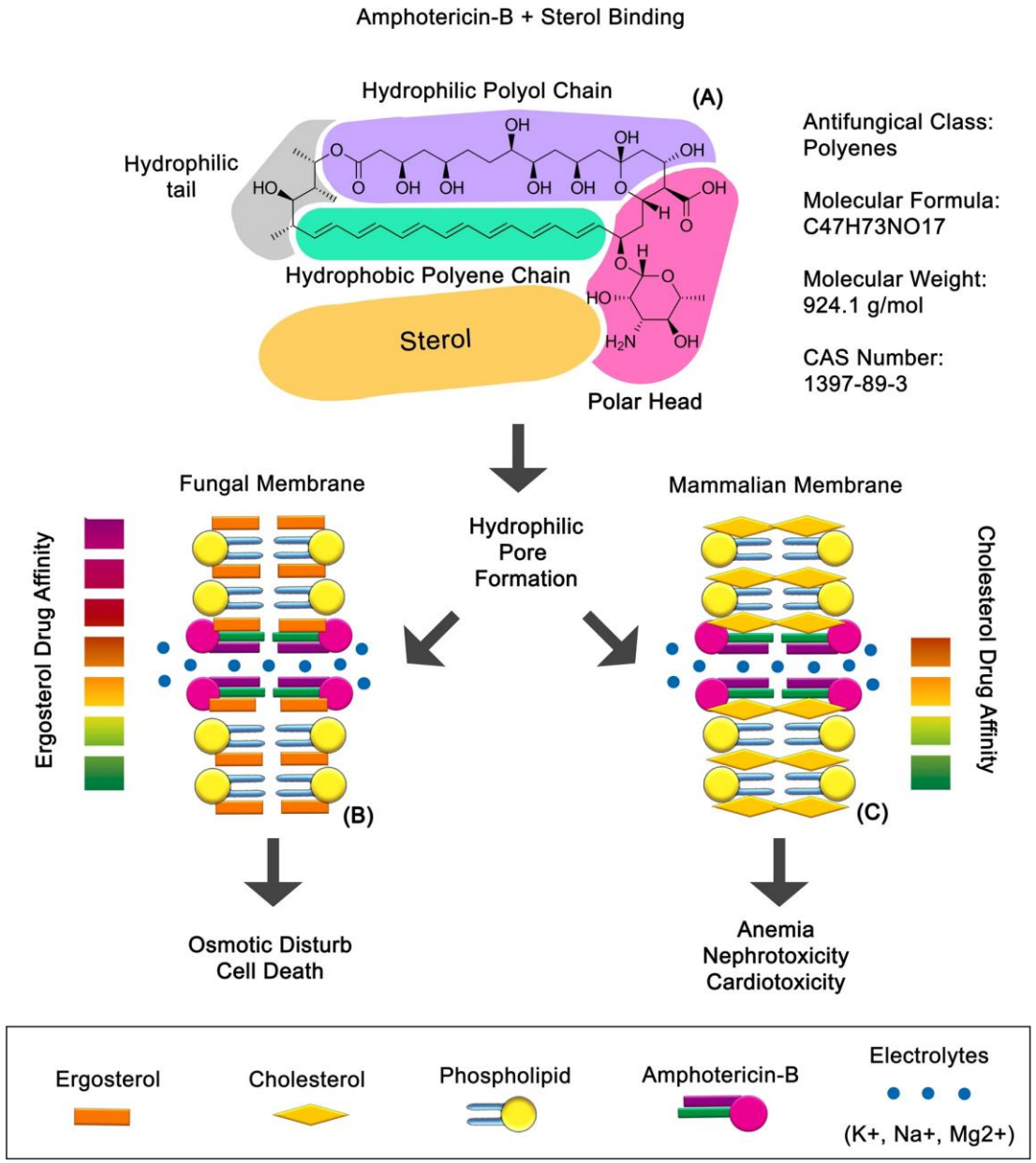
# Der Retter in der Not?

- Imaging non-specific
- Diagnosis?
- Biomarkers not available for a broad spectrum of fungal diseases
- Azoles: drug-drug interactions, side effects, azole resistance
- Principles of management?

- The polyene class of antifungal agents are important option for the prevention and treatment of invasive fungal diseases
- Broad spectrum
- Less resistance induction
- Concentration-dependent fungicidal pharmacodynamics
- Potent, dose-dependent activity in a large number of animal models
- Well-documented clinical efficacy
- Deoxycholate amphotericin B (D-AmB) has been the cornerstone for the management of life-threatening fungal infections
- D-AmB: its clinical utility is hampered by dose-dependent renal toxicity and infusion-associated reactions, thereby limiting therapeutic efficacy.
- LAmB can be given at much higher doses, resulting in enhanced plasma exposure and increased drug disposition in the lungs and the central nervous system, equal or improved antifungal efficacy, reduced nephrotoxicity, and the absence of relevant new toxicities.
- LAmB has become the polyene of choice in most situations where treatment with AmB is clinically indicated.

*Clinical Infectious Diseases*, 68:S4; 2019, S260–S274

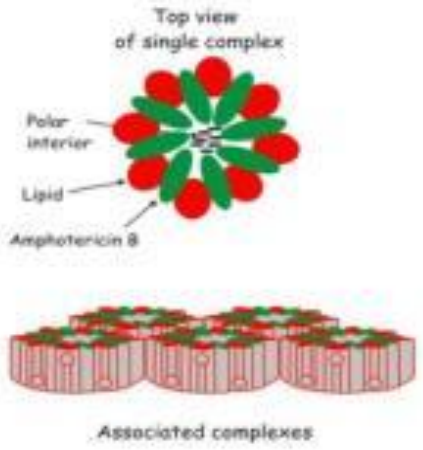



Lipid formulations…
….to reduce  nephrotoxicity

Infectious Diseases and Therapy, 10: 115–147 (2021)

# Lipid Amphotericin B Formulations

## Abelcet ® ABLC

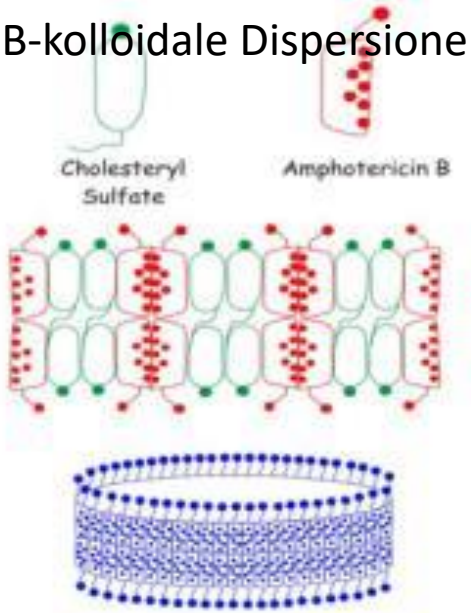



Lipid-Komplex

**Ribbon-like particles**
**Carrier lipids: DMPC, DMPG**
**Particle size (µm): 1.6-11**

## Amphotec ® ABCD

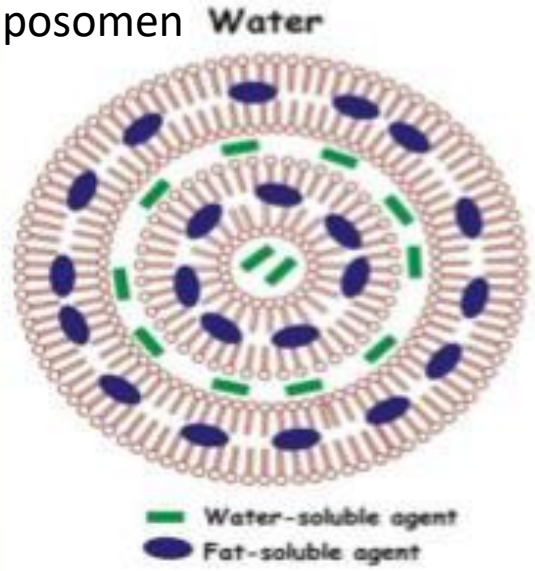
AmB-kolloidale Dispersionen




**Disk-like particles**
**Carrier lipids: Cholesteryl sulfate**
**Particle size (µm): 0.12-0.14**

## Ambisome ® L-AMB

Liposomen




**Unilaminar liposome**
**Carrier lipids: HSPC, DSPG, cholesterol**
**Particle size (µm) : 0.08**

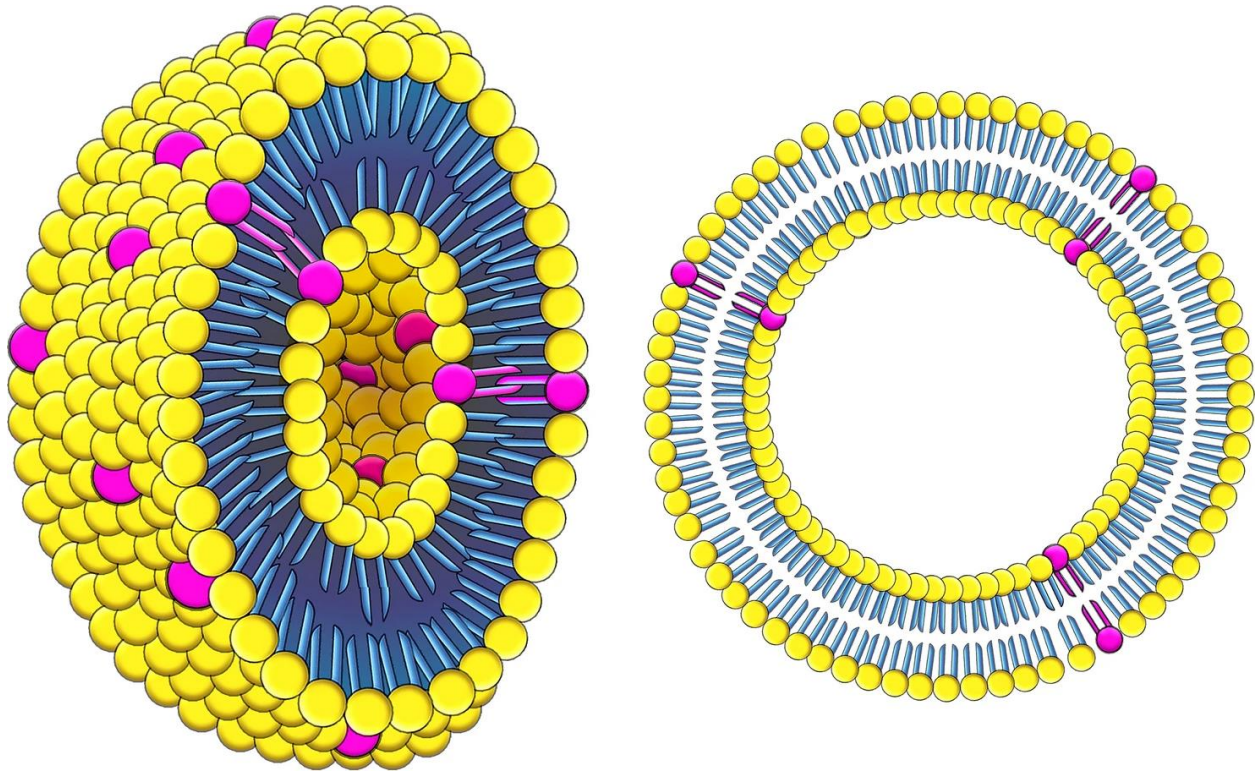
DMPC-Dimyristoyl phospitidylcholine
DMPG- Dimyristoyl phospitidylcglycerol
HSPC-Hydrogenated soy phosphatidylcholine
DSPG-Distearoyl phosphitidylcholine

| Property | Amphotericin B formulation | | | |
|---|---|---|---|---|
| | Amphotericin B deoxycholate | L-AmB | ABLC | ABCD |
| Composition | – | HSPC:cholesterol:DSPG 10:5:4 | DMPC:DMPG 7:3 | Cholesteryl sulfate |
| Structure | Micelles | Unilamellar spherical liposomes | Ribbons | Discs |
| Amphotericin B:lipid ratio | NA | 1:9 | 1:3 | 1:1 |
| Size (nm) | 0.035 | 80 | 1,600–11,000 | 122 × 4 |
| Dose (mg/kg) | 1.0 | 5.0 | 5.0 | 4.0 |
| $C_{max}$ (μg/mL) | 1.5–2.9 | 83 ± 35.2 | 1.7 | 2.9 |
| AUC (μg · h/mL) | 17.1–36 | 555 ± 311 | 14.0 ± 7.0 | 36 |
| Half-life (h) | 24 | 8.6 ± 3.1 | 173.4 | 28.2 |
| $V_d$ (L/kg) | 5.0 ± 2.8 | 0.16 | 131 ± 57.7 | 4.1 |
| Cl (mL/h/kg) | 38.0 ± 15.0 | 11.0 ± 6.0 | 436 ± 188 | 112 |

Data derived predominately from package inserts

± indicates range of values

*ABCD* amphotericin B colloidal dispersion, *ABLC* amphotericin B lipid complex, *AUC* area under the concentration–time curve, *Cl* clearance, $C_{max}$ peak plasma concentration, *DMPC* dimyristoyl phosphatidylcholine, *DMPG* dimyristoyl phosphatidylglycerol, *DSPG* distearoyl phosphatidylglycerol, *HSPC* hydrogenated soy phosphatidylcholine, *L-AmB* liposomal amphotericin B, *NA* not applicable, $V_d$ volume of distribution

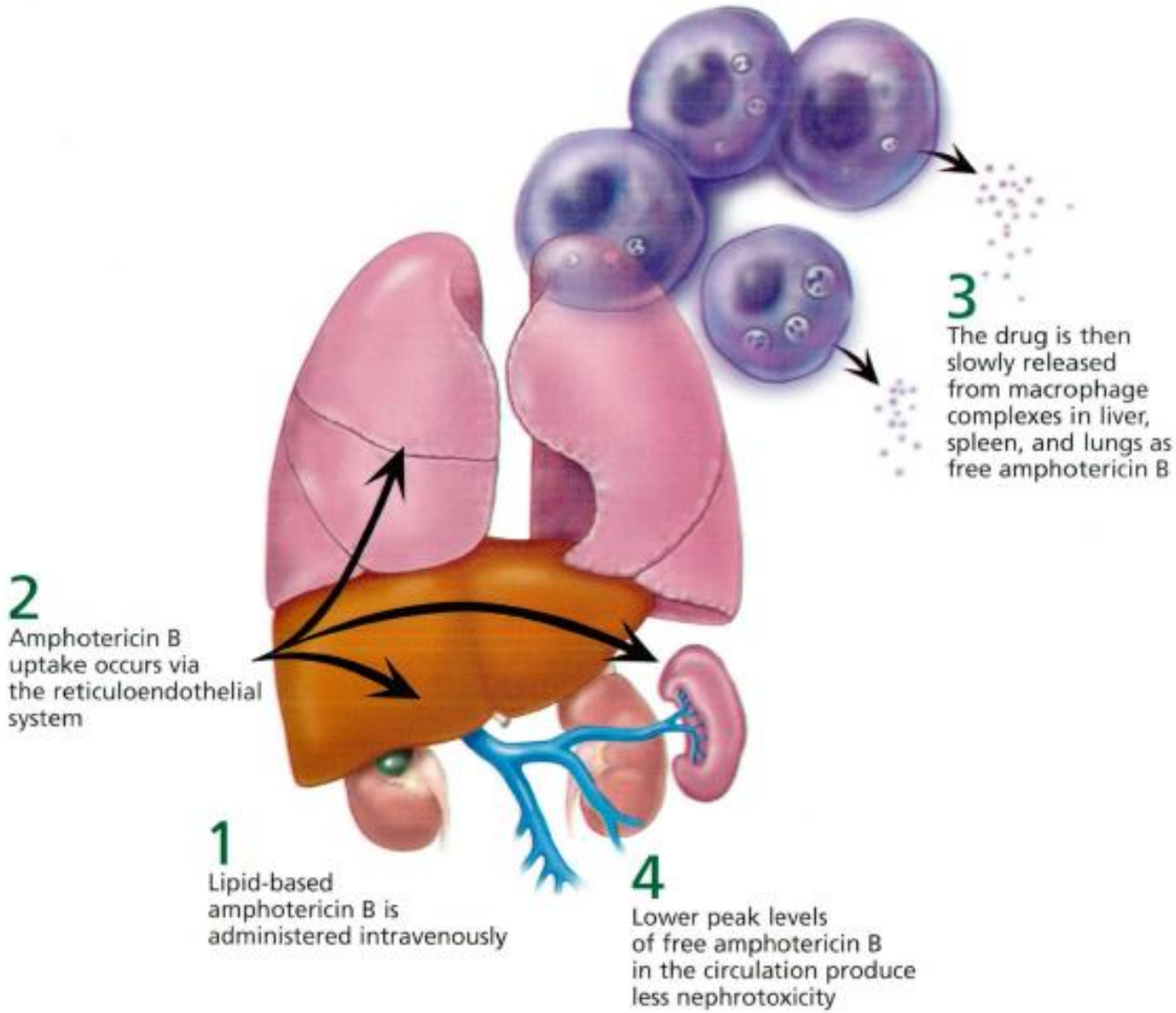


Liposomal amphotericin B (L-AMB). Amphotericin B Phospholipid

- Small sperical unilamellar liposomes
- AmB encapsulated in liposomes consiting of hydrogenated soyphosphatidylcholine, cholersterol, and dimyristoylphosphatidylglycerol
- Size: < 100nm
- No substrate inhibition of CytP450
- Not metabolized
- Unchanged in faeces and urine
- Standard dosage: 3-5mg/kg
- LD50 175 mg/kg
- Distribution: Spleen>liver>lung=kidney
- Blood–brain barrier overpass
- PD in vivo: Cmax/MIC

*Infect Dis Ther* 10:115-147, 2021

# Distribution of lipid-based amphotericin B



# Table 1

Overview on pharmacokinetics of amphotericin B preparations

| Preparation | Amphotericin B deoxycholate | Liposomal amphotericin B AmBisome® |
|---|---|---|
| $C_{max}$ (µg/mL) | 1.7–2.8 | 14–29 (90) |
| AUC (µg h/mL) | 14–29 | 423 |
| $V_d$ (L/kg) | 0.5–2.0 | 0.05–2.2 |
| Protein binding (%) | 95–99 | 95–99 (of amphotericin B, liberated from lipid encapsulation) |
| $t_{1/2}$ (h) | 15–27 | 13–24 |
| CL (mL/h/kg) | 10–30 | 1–23 |
| Elimination | Bile, kidney; no metabolites identified | Bile, RES long-term disposition, final elimination not yet clear; no metabolites identified |
| Renal impairment | Contra-indicated in reversible renal impairment | No dose adjustment, consider nephrotoxicity |
| Hepatic impairment | No dose adjustment, consider hepatotoxicity and renal toxicity | No dose adjustment, consider hepatotoxicity |
| Remark | $T_{inf} \geq 4$ h mandatory, continuous infusion reduces toxicity, but may decrease the efficacy | $T_{inf} \geq 4$ h recommended |

Details and references are displayed in the text

$C_{max}$ amphotericin B peak level; *AUC* total area under the concentration–time curve; $V_d$ apparent volume of distribution; $t_{1/2}$ half-life; *CL* clearance; *RES* reticuloendothelial system; $T_{inf}$ infusion time

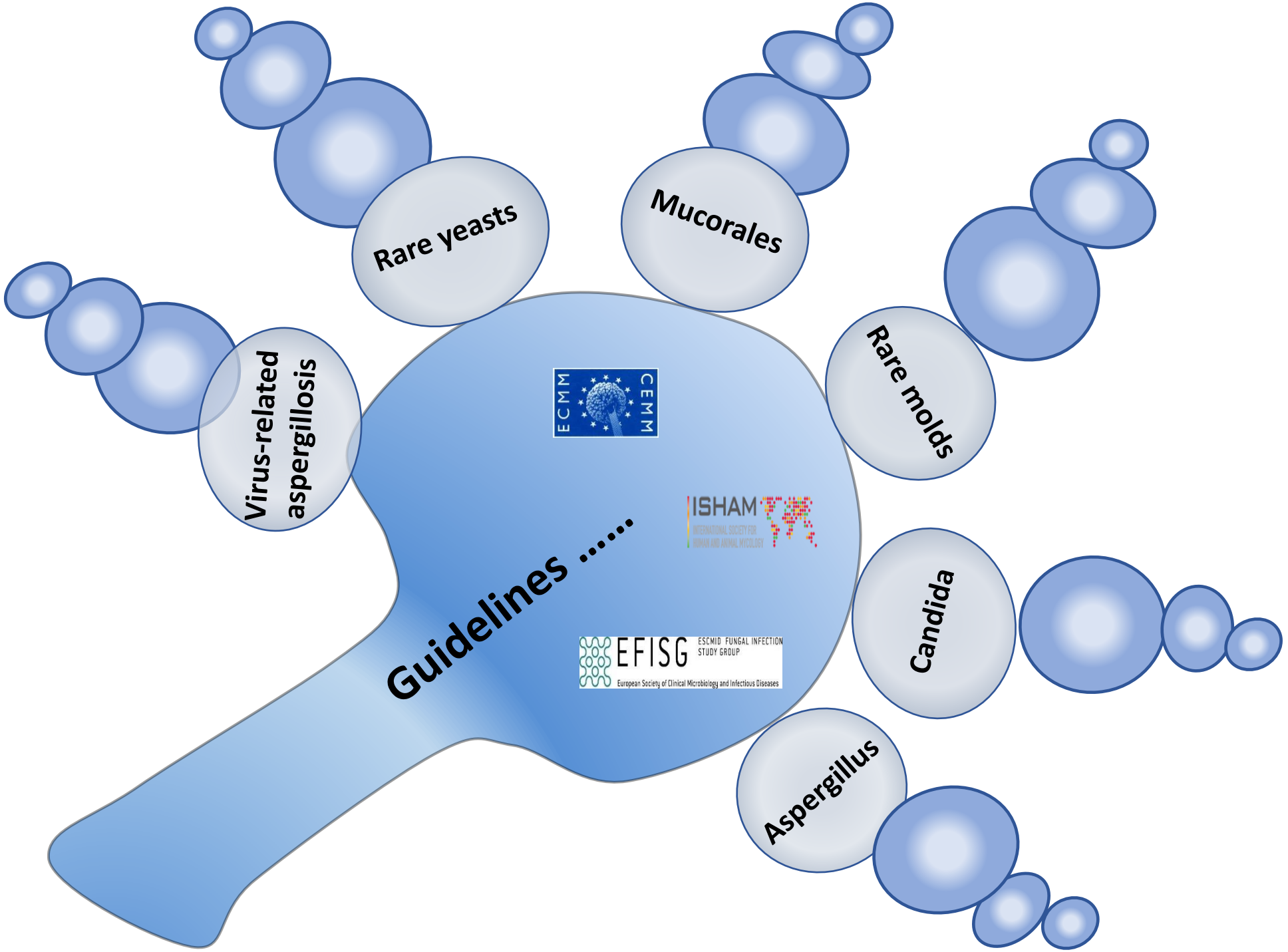
| The pathogen | | | Comments (the spectrum of activity of liposomal amphotericin B (L-AmB) is similar to amphotericin B deoxycholate (AmB) | CLSI | | EUCAST | |
|---|---|---|---|---|---|---|---|
| | | | | CBP | ECV | CBP | ECV |
| **Fungi** | Yeasts | *C. albicans* | *Candida* species are usually considered to be susceptible to AmB; some report show resistance for *C. tropicalis* and *C. krusei*; *C. glabrata, C. parapsilosis,* C*. kefyr*, *C. famata, C. lusitaniae* and C*. guilliermondii* [a] are usually considered to be susceptible, although occasional resistant strains may exist<br>*C. auris* and species of the *C. haemulonii* complex are frequently observed to be AmB resistant (intrinsic/acquired)<br>*Saccharomyces cerevisiae*[a] are usually considered to be AmB susceptible<br>*Trichosporon* species are usually AmB susceptible, *T. asahii* may demonstrate resistance<br>*Malassezia* spp. are difficult to culture, but are considered to be AmB susceptible; *M. furfur* may demonstrate AmB resistance | | ≥ 2 | > 1 | ≤ 1 |
| | | *C. glabrata* | | | ≥ 2 | > 1 | ≤ 1 |
| | | *C. parapsilosis* | | | ≥ 2 | > 1 | ≤ 1 |
| | | *C. tropicalis* | | | ≥ 2 | > 1 | ≤ 1 |
| | | *C. krusei* | | | ≥ 2 | > 1 | ≤ 1 |
| | | *C. dubliniensis* | | | | > 1 | ≤ 0.25 |
| | | other *Candida* species & yeasts | | | | | (≤ 0.5) [a] |
| | | *Cryptococcus neoformans* | Both representatives are usually susceptible to AmB, resistance is rare | | | > 1 | (1)[a] |
| | | *C. gattii* [a] | | | | | (0.5) [a] |
| | Molds | *A. fumigatus* | Overall, reports show a low incidence of AmB resistance in *Aspergillus* spp.; for *A. fumigatus,* the most common cause of invasive aspergillosis, resistance is rarely described; intrinsic resistance is well known for *A. terreus;* however, susceptible variants do exist; intrinsic resistant isolates exist within *A. flavus*[b] and *A. lentulus.*<br><br>*A. nidulans* and *A. niger* [a] are in principle susceptible to AmB | | | > 1 | ≤ 1 |
| | | *A. flavus* | | | | | ≤ 4 |
| | | *A. niger* | | | | > 1 | (0.5) [a] |
| | | *A. terreus* | | | | | 8 |
| | | other *Aspergillus* species | | | | | (4) [b] |
| | | *Mucorales* | Generally consider to be susceptible to AmB; some *Rhizopus* and *Cunninghamella* strains show decreased AmB susceptibility | No cut-off values defined | | | |
| | | *Fusarium* species | AmB is recommended to treat fusariosis, members of the genus *Fusarium* are generally susceptible to AmB; primary resistance may be seen *Fusarium fujikuroi* [a] and *Fusarium solani SC* [a]*,* yet is quite variable | | | | (8) [a] |
| | | *Scedosporium* species | Members of the genus *Scedosporium* are generally susceptible to AmB; primary resistance may be seen in *P. bodyii*, *S. apiospermum* and *Lomentospora prolificnas*, the latter representatives are in general multidrug-resistant pathogens | No cut-off values defined | | | |
| | | Others | *Penicillium marneffei* is considered to be susceptible to AmB; *Paeciliomyces spp., Bipolaris* spp., *Exophiala* spp. and *Cladophialophora* spp. demonstrate intermediate susceptibility to AmB, depending upon the species | | | | |
| | Dimorphic | *Histoplasma capsulatum*<br>*Blastomyces dermatitidis*<br>*Coccidioides immitis*<br>*Paracoccidioides brasiliensis* | Dimorphic fungi are usually susceptible to AmB, some strains of *Sporothrix schenckii* may show primary resistance | No cut-off values defined | | | |
| **Protozoa** | | *Leishmania species*<br>*L. donovani* complex<br>*L. tropica*<br>*L. major*<br>*L. mexicana* | L-AmB is an alternative for the treatment of cutaneous and mucosal leishmaniasis including old and new world *Leishmania* strains;<br>MIC values obtained show a parasitical concentration of 0.5 µg/ml for AmB and the various *Leishmania* spp; resistance seems to be varable, an altered membrane composition, ATP-binding cassette transporters, and an upregulated thiol metabolic pathway have a role in AmB resistance in clinical isolates of *L. donovani*. | No cut-off values defined | | | |
| **Virus** | Enveloped and non-enveloped | *Human immunodeficiency virus*<br>*Rubella virus*<br>*Japanese encephalitis virus (JEV)*<br>*Vesicular stomatitis virus* | In vitro, AmB may affect cholesterol structures in viral envelopes, cellular membranes, and intracellular organelles of various viruses. In JEV, AmB reduced both plaque size and number of infected cells in a dose-dependent manner. A 200-fold reduction of infectious virus titer was observed by treatment of infected cells with 5 mg/ml of AmB;<br>AmB methyl-ester was found to inhibit the replication of a highly divergent panel of HIV-1 isolates in various T-cell lines and primary cells irrespective of clade or target cell tropism. | No cut-off values defined | | | |

[a] ECV (in brackets): these are proposed cut-off values

Dtsch Arztebl Int 2019; 116: 271-8

| Class | Substance | Candida | | | | | Aspergillus | | | Mucorales | | | Fusarium spp. | Application | | | Interactions/ *1 | Common adverse effects*1 | Treatment of neurological infections | Dosage (i. v.) | Licensed/recommended indications | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | albicans | dubliniensis | glabrata | krusei | parapsilosis | fumigatus | flavus | terreus | Lichtheimia spp. | Mucor spp. | Rhizopus spp. | | i. v. | p.o. | Other | | | | | Prophylaxis Aspergillus | Prophylaxis Candida | Therapy Aspergillus | Therapy Candida | Therapy: other fungal species | Empirical treatment |
| Polyenes | **Liposomal Amphotericin B** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | + | – | Local, intraocular, intrathecal, nebulized | No | ≥ 1/10 hypokalemia, gastrointestinal symptoms ≥ 1/100 to <1/10 electrolyte imbalances, headache, tachycardia, hypotension, dyspnea, raised liver enzymes, skin rash, backache, raised creatinine levels | ● | 3–10 mg/kg | ● | ● | ● | ● | ● | ● |

*Resistance: Aspergillus terreus, Candida lusitaniae, Scedosporium* spp, and some *Fusarium* spp


Rare yeasts
Mucorales
Virus-related aspergillosis
Rare molds
Guidelines .....
ECMM CEMM
ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY
EFISG
ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases
Candida
Aspergillus

| Study/Design | Endpoints of Efficacy | Main Results |
|---|---|---|
| ***Proven or probable invasive aspergillosis*** | | |
| Open-label, randomized, multicenter trial comparing the efficacy of 2 doses of LAmB (1 and 4 mg/kg/day) for the treatment of proven or probable invasive aspergillosis in 120 neutropenic patients | Complete/partial responses and stable disease at end of therapy in patients receiving ≥1 dose; overall mortality at 2 months after start of therapy. | Response rates were 64% in the 41 eligible LAmB 1 mg/kg/day recipients and 48% in the 46 eligible LAmB 4 mg/kg/day recipients; overall, mortality was 42% and 49% in the 2 cohorts, respectively. The rate of patients with AEs was slightly higher in the LAmB 4 mg/kg/day cohort. |
| Double-blind, randomized, multicenter trial in 201 patients with proven or probable invasive mold infection, comparing LAmB as first-line therapy at either 3 or 10 mg/kg/day for 14 days, followed by 3 mg/kg/day | Complete or partial response at the end of study drug treatment in patients receiving ≥1 dose. Overall mortality at 12 weeks after start of therapy. | A complete or partial response was achieved in 50% and 46% of patients in the 3 and 10 mg/kg/day groups, respectively. Mortality at 12 weeks was 28% and 41% in the 3 and 10 mg/kg/day arms, respectively. The rates of nephrotoxicity and hypokalemia were significantly higher in the high-dose group. |
| ***Invasive* Candida *infections*** | | |
| Double-blind, randomized, multicenter, non-inferiority trial comparing the efficacy of LAmB (3 mg/kg/day) and micafungin (100 mg/day) as first-line treatment of candidemia and invasive candidiasis in 531 patients | Clinical (complete or partial resolution of symptoms) and mycological (eradication or presumed eradication) response at the end of treatment in the per protocol analysis. | Treatment success was observed for 170 patients (89.5%) treated with LAmB and 181 patients (89.6%) treated with micafungin. Efficacy was independent of the *Candida* species, site of infection, neutropenic status, APACHE II score, and catheter removal/replacement. Fewer treatment-related AEs and discontinuations were observed with micafungin. |
| ***Cryptococcal meningoencephalitis*** | | |
| Double-blind, randomized, multicenter trial comparing efficacy and safety of LAmB at either 3 or 6 mg/kg/day to DAmB at 0.7 mg/kg/day in 267 patients with AIDS and acute cryptococcal meningitis | Mycological success (conversion of cerebrospinal fluid culture results) at Week 2 (14 ± 4 days), protocol-defined therapeutic success at Week 10, and survival at Week 10 among the modified intent-to-treat population. | Efficacy was similar among all 3 treatment groups; overall mortality at 10 weeks was 11.6%, with no significant differences among treatment groups. Infusion-related reactions were significantly less frequent in LAmB-treated patients and fewer patients receiving the 3 mg/kg/day dose of LAmB developed a doubling of the serum creatinine value. |
| ***Disseminated histoplasmosis*** | | |
| Double-blind, randomized, multicenter trial comparing LAmB at 3 mg/kg/day with DAmB at 0.7 mg/kg/day for 2 weeks in 81 patients with AIDS and moderate-to-severe disseminated histoplasmosis | Clinical success, conversion of baseline blood cultures to negative, survival during induction therapy, and acute toxicities that necessitated discontinuation of treatment. | Clinical success was achieved in 45/51 patients (88%) receiving LAmB and 14/22 patients (64%) treated with DAmB ($P = .014$). Culture conversion rates were similar. Fewer patients receiving LAmB died during induction ($P = .04$). Infusion-related side effects and nephrotoxicity were less frequent in patients treated with LAmB (25% vs 63% and 9% vs 37%; $P = .002$ and $P = .003$, respectively). |

*Clinical Infectious Diseases*, 68:S4; 2019, S260–S274

| Study/Design | Endpoints of Efficacy | Main Results |
|---|---|---|
| ***Empirical therapy in patients with fever and neutropenia*** | | |
| Combined analysis of 2 randomized, multicenter trials comparing LAmB at 1 or 3 mg/kg/day with DAmB at 1 mg/kg/day in a total of 338 adult and pediatric patients with fever and neutropenia who were not responding to broad-spectrum antibacterial treatment | Clinical success, defined by a minimum of 3 consecutive days with fever <38°C, continuing to study end (recovery of neutrophils to $0.5 \times 10^9$/L). Addition of systemic antifungals, development of systemic fungal infection, and persistent fever to study end were considered treatment failures. | Similar success rates in patients treated with LAmB (58% and 64%) and DAmB (49%), but fewer drug-related adverse effects and severe drug-related adverse effects with LAmB ($P < .01$). Nephrotoxicity, defined as doubling of the serum creatinine value from baseline, was less frequent in the LAmB arms versus DAmB (0% and 3%, respectively, vs 23%), as was hypokalemia ($P < .01$). |
| Double-blind, randomized, multicenter trial to compare LAmB at 3 mg/kg/day with DAmB at 0.6 mg/kg/day in a total of 687 adult and pediatric patients with fever and neutropenia who were not responding to broad-spectrum antibacterial treatment | Composite of 5 criteria: survival for 7 days after initiation of the study drug; resolution of fever during the period of neutropenia; successful treatment of any baseline fungal infection; the absence of breakthrough fungal infections during administration of the study drug or within 7 days after the end of treatment; and absence of premature discontinuation of the study drug because of toxicity or lack of efficacy. | The composite rates of successful treatment were similar (50% for LAmB and 49% for DAmB), as were survival rates (93% and 90%, respectively), resolution of fever (58% and 58%, respectively), and premature discontinuation of the study drug (14% and 19%, respectively). Fewer proved breakthrough fungal infections were observed in the LAmB group (3.2% vs 7.8%, respectively; $P = .009$). LAmB was associated with significantly fewer infusion-related reactions and fewer patients developed a serum creatinine level 2 times the upper limit of normal (19% vs 34%, respectively; $P < .001$). |
| ***Primary antifungal prophylaxis*** | | |
| Open-label, randomized, single-center trial of low-dose LAmB (50 mg every other day) versus no systemic antifungal therapy as antifungal prophylaxis in 219 neutropenic episodes in 132 patients with hematological malignancies and expected neutropenia for 10 days | Failure of antifungal prophylaxis, defined as occurrence of proven or probable invasive fungal diseases under prophylactic study treatment. Pneumonia without identification of a causative organism, mortality from any cause, and mortality related to invasive fungal disease were secondary endpoints. | In the first episode of each patient, the incidences of proven or probable invasive fungal diseases were 6.7% in LAmB-treated patients (5/75) and 35% in the control patients (20/57; $P = .001$). Invasive aspergillosis occurred less frequently in patients receiving LAmB ($P = .0057$). Pneumonia occurred in 6 vs 28 neutropenic episodes ($P < .001$), and there was no difference in overall and fungal-related mortality. |
| Double-blind, randomized, placebo-controlled trial of LAmB (2.5 mL of a 5 mg/mL solution) versus placebo inhalation twice a week in 271 adult patients with hematological disease with expected neutropenia for 10 days, studied during 407 neutropenic episodes | Occurrence of proven or probable invasive pulmonary aspergillosis, according to the European Organization for Research and the Treatment of Cancer/Mycoses Study Group definitions. Other endpoints were overall mortality and fungal infection-related mortality. | There were 18/132 patients in the placebo group versus 6/139 patients in the LAmB group who developed invasive pulmonary aspergillosis (odds ratio 0.26, 95% confidence interval 0.09–0.72; $P = .005$). There was no difference in overall and infection-related mortality rates. More patients in the LAmB group versus the placebo group discontinued the inhalation therapy for at least 1 week (45% vs 30%, respectively; $P = .01$). |
| Double-blind, randomized, multicenter trial to compare prophylactic LAmB at 5 mg/kg intravenously or placebo twice weekly in a 2:1 random allocation during remission-induction treatment in 355 adult patients undergoing remission induction therapy for acute lymphoblastic leukemia | Development of proven or probable invasive fungal diseases. Secondary endpoints included those focused on the safety and tolerability of prophylactic LAmB. | Rates of proven and probable invasive fungal diseases were 7.9% (18/228) in the LAmB group and 11.7% (13/111) in the placebo group ($P = .24$). Overall mortality rates were similar between the groups: 7.2% (17/237) for LAmB and 6.8% (8/118) for placebo. There were no differences in premature, treatment-related discontinuations. Hypokalemia and creatinine increase were significantly more frequent with LAmB ($P < .001$). |

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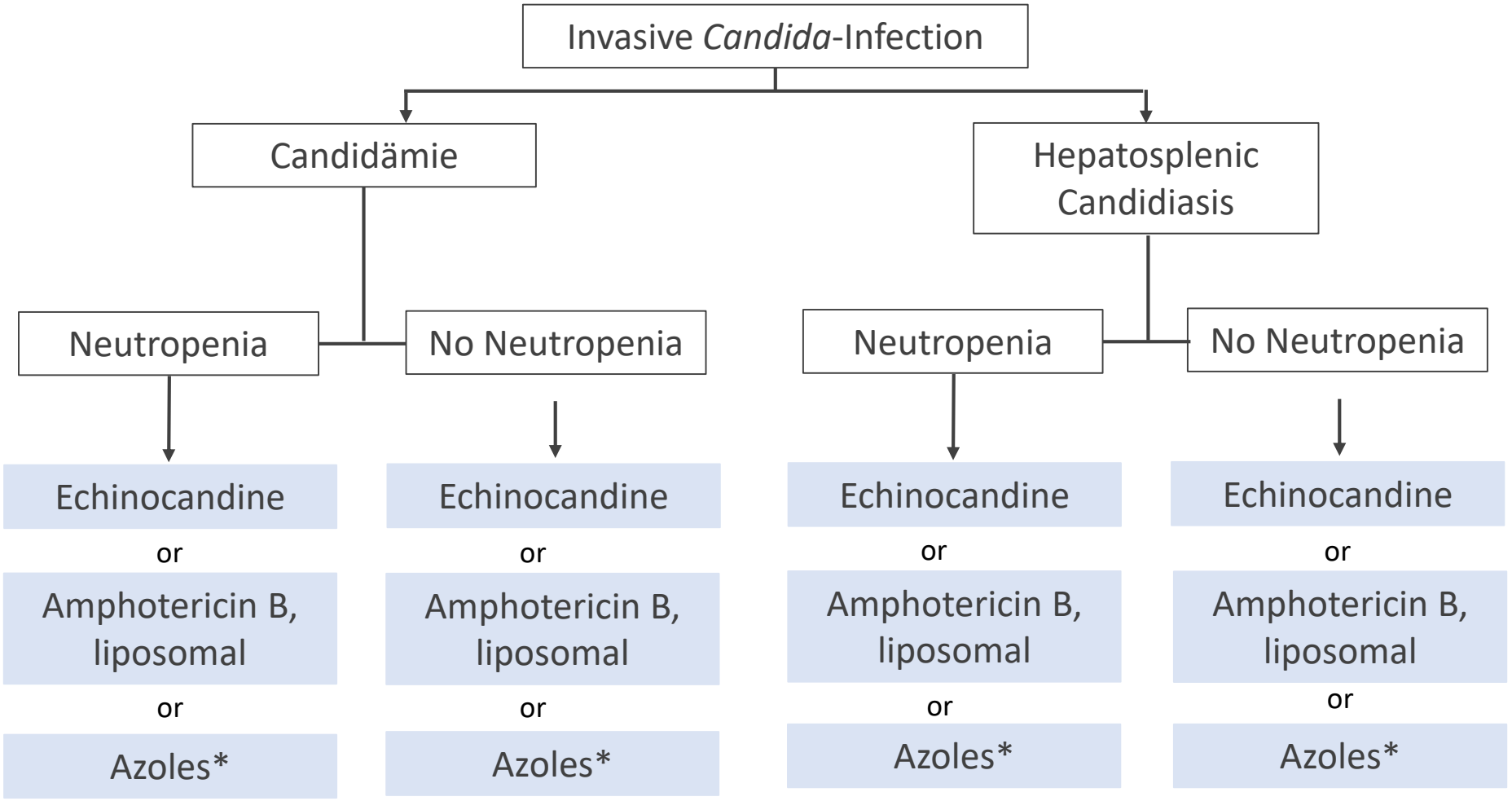
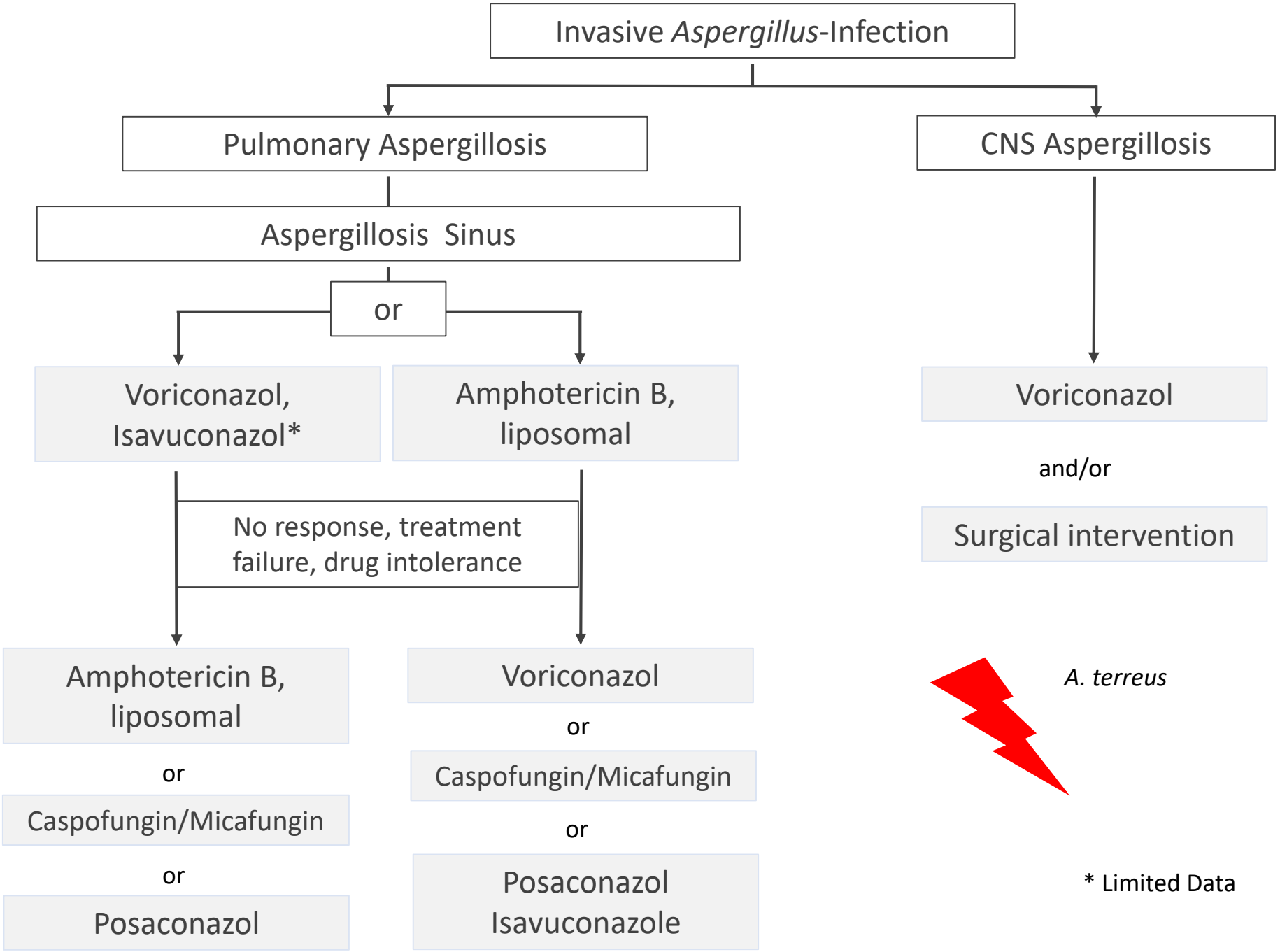


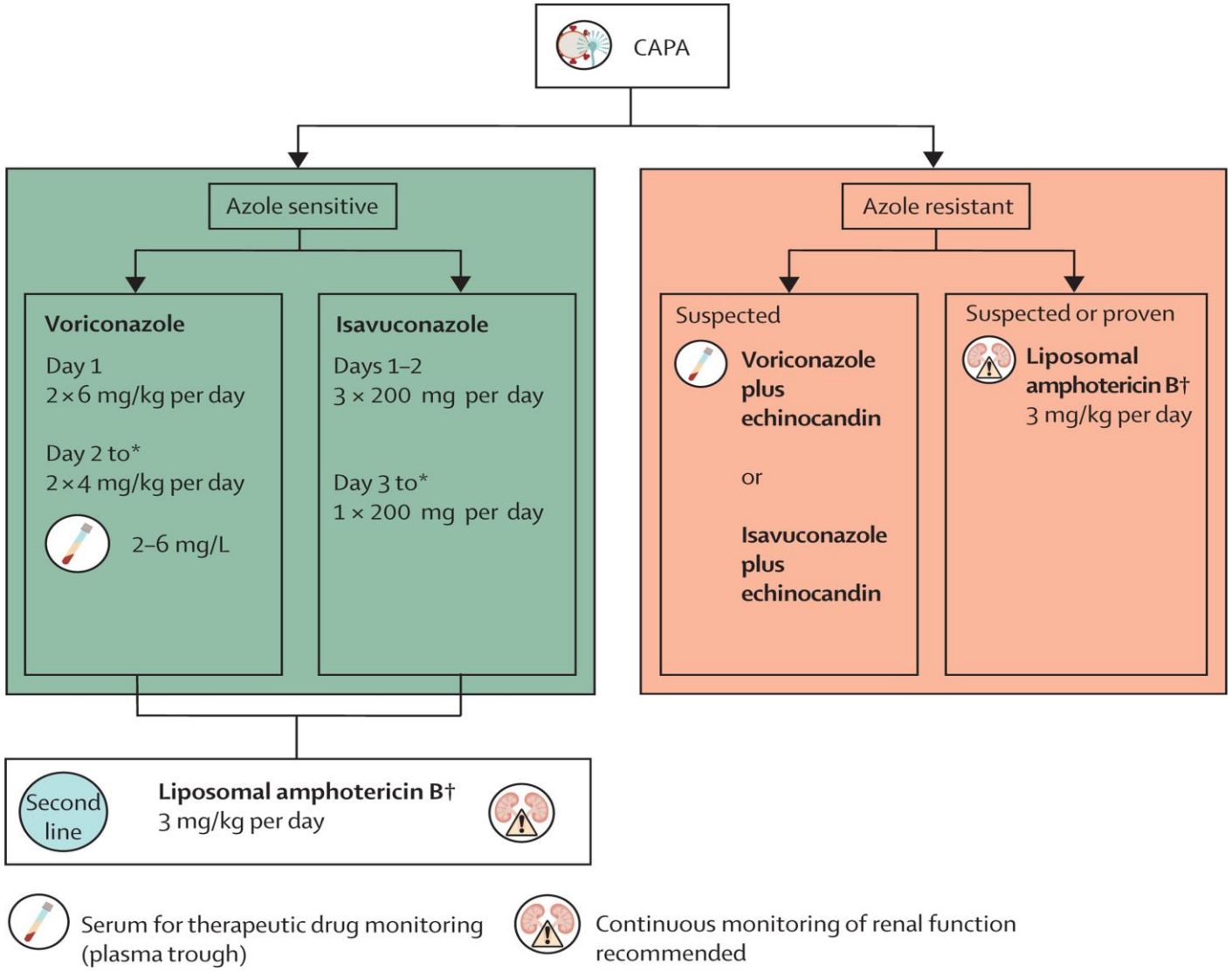

Remove intravascular devices - if clinically feasible - after diagnosis of candidemia.

* based on species and MICs

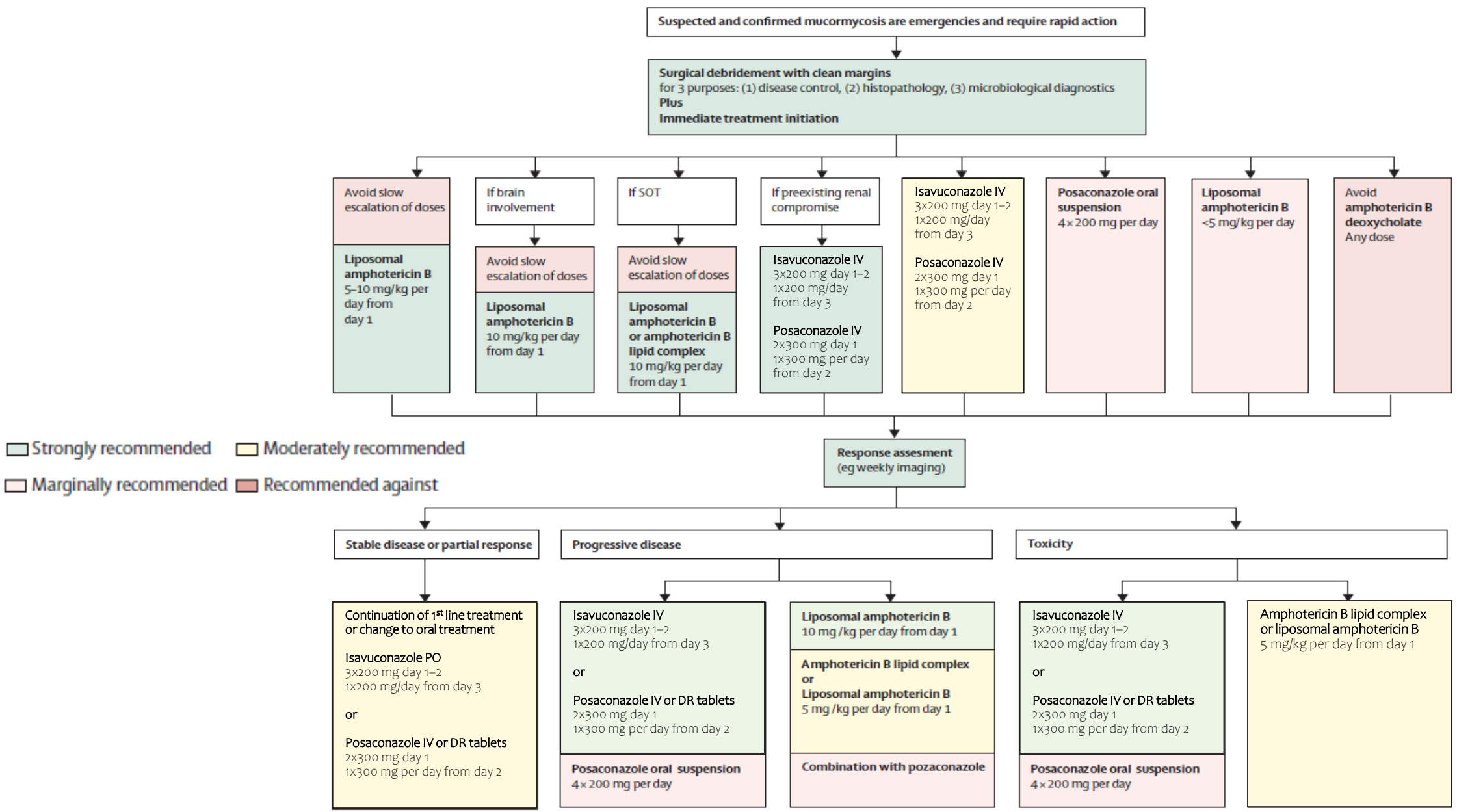
Med Mycol. 2019;57(Supplement2):S155-S160
ESCMID & ECIL Guidelines, update 2018




Med Mycol. 2019;57(Supplement2):S155-S160




*The Lancet Infectious Diseases* DOI: (10.1016/S1473-3099(20)30847-1)




Posaconazole is not indicated for the treatment of mucormycosis.
Please give consideration to your local guidelines.
DR, delayed-release; IV, intravenous; PO, *per os*; SOT, solid organ transplantation

Cornely OA, *et al. Lancet Infect Dis*. 2019;19(12):e405–e421.

GCMA code PP-CRB-GLB-0545; Date of preparation February 2021.

Strongly recommended | Moderately recommended | Marginally recommended | Recommended against

| | First-line | First-line alternative | Second-line | Treatments to avoid | Salvage treatments |
|---|---|---|---|---|---|
| Fusariosis | Voriconazole, or voriconazole plus L-AmB, or voriconazole plus ABLC | L-AmB, or ABLC | Isavuconazole, or posaconazole | D-AmB | Posaconazole |
| Lomentosporosis | Voriconazole plus terbinafine | Voriconazole | Isavuconazole, or posaconazole | L-AmB | Voriconazole |
| Scedosporiosis | Voriconazole | Voriconazole in combination with L-AmB, ABLC, echinocandins, or terbinafine | Isavuconazole, or posaconazole, or itraconazole | L-AmB | Voriconazole echinocandins, or posaconazole |
| Phaeohyphomycosis: localised infection | Voriconazole | L-AmB with or without echinocandins, or triazole | Isavuconazole | D-AmB | Isavuconazole, or posaconazole, or voriconazole |
| Phaeohyphomycosis: cutaneous or subcutaneous infection | Itraconazole or voriconazole | L-AmB with or without echinocandins, or triazole | Isavuconazole | D-AmB | Isavuconazole, or posaconazole, or voriconazole |
| Phaeohyphomycosis: disseminated infection | Posaconazole, or voriconazole plus echinocandins, or voriconazole plus terbinafine | L-AmB with or without echinocandins, or triazole | Isavuconazole | D-AmB | Isavuconazole, or posaconazole, or voriconazole |
| Phaeohyphomycosis: *Exserohilium rostratum* | Voriconazole with or without L-AmB | .. | L-AmB plus triazoles other than voriconazole | D-AmB | .. |

www.thelancet.com/infection Published online February 16, 2021 https://doi.org/10.1016/S1473-3099(20)30784-2

| | | | | | |
|---|---|---|---|---|---|
| *Rasamsonia* spp | Caspofungin, or micafungin | Caspofungin plus L-AmB or posaconazole, or micafungin plus L-AmB or posaconazole | -- | Azole monotherapy | -- |
| *Schizophyllum commune* | L-AmB; stepdown to posaconazole | -- | Voriconazole | -- | -- |
| *Schizophyllum* spp other than *S commune* and other basidiomycetes (eg, *Coprinopsi cinereal*, *Hormographiella aspergillata*) | L-AmB with or without inhaled L-AmB, or L-AmB with or without voriconazole | -- | Voriconazole | Echinocandins | L-AmB, or voriconazole |
| *Scopulariopsis* spp | Isavuconazole, or voriconazole | L-AmB with or without voriconazole | -- | -- | Posaconazole with or without micafungin with or without terbinafine |
| *Penicillium* spp: disseminated infection | L-AmB with or without other antifungals | -- | -- | -- | Voriconazole |
| *Penicillium* spp: lung infection | Posaconazole | -- | -- | -- | Voriconazole |
| Non-*marneffei Talaromyces* spp | L-AmB | -- | -- | -- | Voriconazole, or echinacondine plus terbinafine |
| *Paecilomyces* spp | L-AmB | -- | -- | -- | Itraconazole, or posaconazole |
| *Purpureocillium* spp | Voriconazole | -- | Itraconazole or L-AmB or posaconazole | -- | Itraconazole, or L-AmB, or posaconazole |
| *Purpureocillium* spp: cutaneous or subcutaneous infection | Voriconazole plus terbinafine | -- | Itraconazole or L-AmB or posaconazole | -- | Itraconazole, or L-AmB, or posaconazole |

Strongly recommended  Moderately recommended  Marginally recommended  Recommended against

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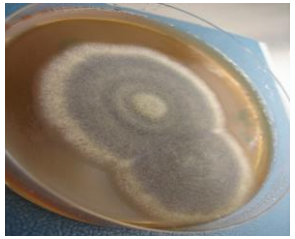
**Global guideline for the diagnosis and management of rare yeast infections: An initiative of the ECMM in cooperation with ISHAM and ASM[#]**

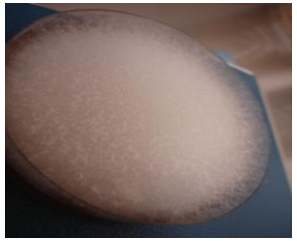
| Pathogen/ pathogen group | First line | First line alternative | Second line | Avoid | CVAD removal |
|---|---|---|---|---|---|
| *Geotrichum* spp. | L-AmB +/- 5-FC | VCZ | Drug class not used as first line therapy | Echinocandins | No specific data but moderately recommended |
| *Saprochaete/ Magnusiomyces* spp. | L-AmB +/- 5-FC | VCZ | _ | Echinocandins | Yes |
| *Trichosporon* spp. | VRC | FLU | L-AmB or D-AmB | Echinocandins | Yes |
| *Kodamaea ohmeri* | L-AmB or D-AmB | Echinocandins | VCZ or FLU or Azole or different formulation of AmB to that used as first line | _ | Yes |
| *Malassezia* spp.[ǂ] | L-AmB | D-AmB | - | - | Yes |
| *Pseudozyma* (*Moesziomyces/Dirkmeia)* spp. | L-AmB | VCZ | ABLC | FLU Echinocandins | Yes |
| *Rhodotorula* spp. | L-AmB _+/- 5-FC | D-AmB +/- 5-FC | _ | Triazoles Echinocandins | Yes |
| *Saccharomyces* spp. | L-AmB or D-AmB | FLU or Echinocandin (CASPO or MICA) | Drug class not used as first line therapy | - | Yes |
| *Sporobolomyces* spp. | L-AmB | VCZ | No data | FLU Echinocandins | Yes |

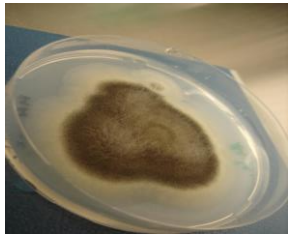
#Detailed recommendations regarding doses can be found in Appendix.
*Selection of salvage therapy is dependent on the drug class the patient has already been treated with; [ǂ] AmB lock therapy is weakly supported only
**Abbreviations:** 5-FC, 5-flucytosine; ABLC, amphotericin B lipid complex; AmB, Amphotericin B; D-AmB, Amphotericin B deoxycholate; CASPO, caspofungin; CVAD, central venous access device; FLU, fluconazole; L-AmB, liposomal amphotericin B; MICA, micafungin; POS, posaconazole; VCZ, voriconazole.

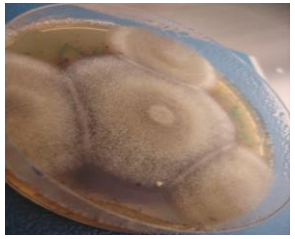
**Legend:**
strongly recommended
moderately recommended
marginally recommended
recommended against

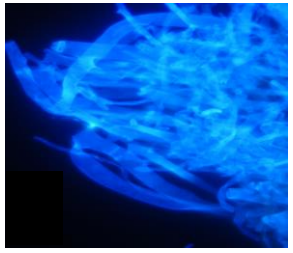
The Lancet, in press











# Beyond….

- Bladder irrigation
- Intraperitoneal
- Intrathecal
- Intravitreal
- Aerosolized/nebulized
- Antibiotic lock

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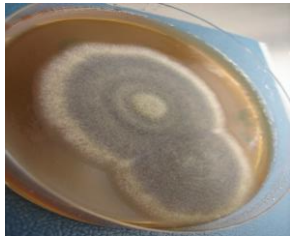
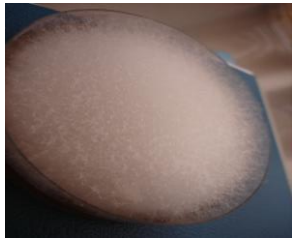
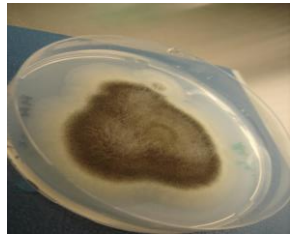
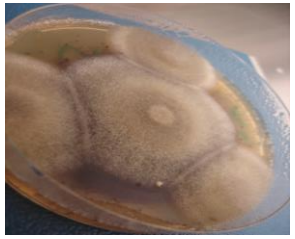
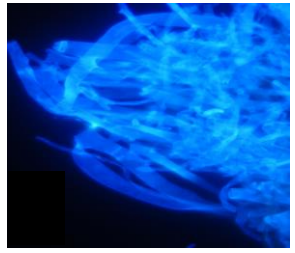




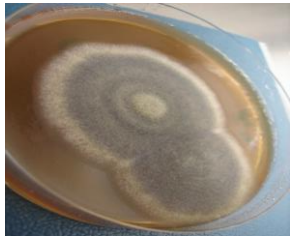


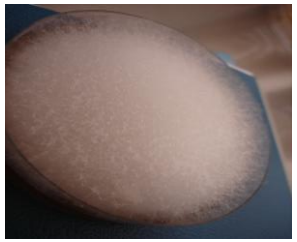


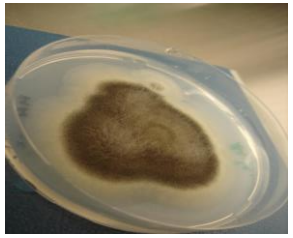


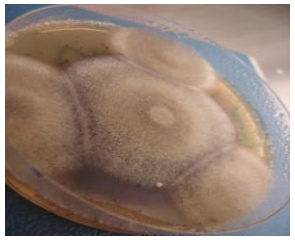
# Summary

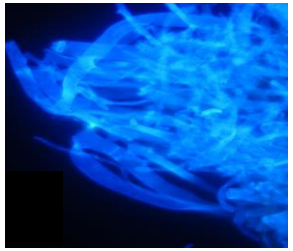
| |
|---|
| Broadest antifungal drug |
| Resistance induction is no issue |
| Excellent clinical data |
| Highly recommended in invasive fungal infections |
| Less side effects |
| Guidelines: L-amphotericin B has been recommended first-line +/- another antifungal |











# Liposomales Amphotericin B – Der Retter in der Not!