



ISSUES & ANSWERS

FROM THE DESKS OF

DIANNE I. MAWBY, DVM, MVSc, DACVIM, &
JACQUELINE C. WHITTEMORE, DVM, PhD, DACVIM
UNIVERSITY OF TENNESSEE

Amphotericin B: Is It Still “Ampho-terrible” or Should I Include It in My Therapeutic Armamentarium?

The cost of triazole therapy can be substantial, as the length of treatment for systemic mycoses generally must continue for ≥ 90 days.¹

CSF = cerebrospinal fluid,
GI = gastrointestinal



ISSUE

RATIONAL USE OF ANTIMICROBIAL THERAPY IS DETERMINED BY PHARMACOKINETICS AND PHARMACODYNAMICS, method

of administration, cost, and adverse effects. Triazole antifungals (eg, itraconazole, fluconazole) are common first-line therapies for systemic mycoses. Efficacy depends on adequate drug absorption and delivery to the infection site. The cost of triazole therapy can be substantial, as the length of treatment for systemic mycoses generally must continue for ≥ 90 days.¹

- Fluconazole is well absorbed after oral administration and is widely distributed throughout the body.²
- Itraconazole, in contrast, is poorly absorbed, with bioavailability highly dependent on formulation and gastric pH.³⁻⁵ Although trademark and generic formulations of itraconazole had similar bioavailability in 1 study, compounded itraconazole had almost zero bioavailability.⁶ Compounded itraconazole, therefore, should *never* be used. After absorption, itraconazole has relatively wide distribution throughout the body.⁵ Although minimal concentrations of itraconazole are found in privileged sites such as cerebrospinal fluid (CSF), measured concentrations do not appear to equate with low efficacy.⁷

ADVERSE EFFECTS OF TRIAZOLE AGENTS INCLUDE REVERSIBLE GI UPSET, hepatotoxicity, and cutaneous vasculitis. Triazole agents also act by altering fungal cell membranes and are thus fungistatic, not fungicidal. Newer triazoles (eg, voriconazole, posaconazole) that require less frequent dosing in animals and have promise against refractory systemic mycoses are being investigated, but costs are substantially greater than for traditional triazole agents.⁸

SOME PATIENTS DO NOT TOLERATE TREATMENT WITH TRIAZOLE AGENTS.

Additionally, systemic fungal and protozoal infections often have high morbidity rates and mortality. Animals with pulmonary, neurologic, or disseminated disease can rapidly decompensate, and severe infiltrative GI disease (eg, histoplasmosis) can compromise absorption of orally administered drugs.⁹ In these patients, use of amphotericin B may be considered.

MORE ►



Amphotericin B remains an ideal choice for some patients, primarily because of its fungicidal activity and rapid onset of action, as well as the availability of parenteral dosing regimens.

BUN = blood urea nitrogen,
CSF = cerebrospinal fluid,
GI = gastrointestinal



ANSWERS

The ideal antifungal drug depends on disease process, concurrent disorders, individual risk for developing adverse effects, convenience, and cost. Amphotericin B should be considered for first-line therapy in patients with meningoencephalitis, severe pulmonary disease, or GI infiltration severe enough to compromise enteral antifungal absorption and in patients that cannot tolerate oral therapies because of adverse effects or instability. Combination therapy can be particularly helpful in stabilization of critical patients. For example, humans with fungal meningoencephalitis are typically treated with a combination of amphotericin B and flucytosine, voriconazole, or itraconazole.¹⁰ With further studies, voriconazole might become an additional or first-line treatment for animals. However, amphotericin B remains an ideal choice for some patients, primarily because of its fungicidal activity and rapid onset of action, as well as the availability of parenteral dosing regimens.

MECHANISMS OF ACTION & EFFICACY

Amphotericin B binds to ergosterol in fungal cell membranes, thereby causing membrane leakage.

- Can be fungicidal at higher tissue concentrations⁵
- Has good efficacy against systemic mycoses and some protozoal diseases^{5,11}

After injection, it is widely distributed into most tissues in the body.

- Inflammation associated with active disease likely improves penetration into otherwise privileged sites.⁵
—Although concentrations in CSF have reportedly been much lower than in other organ systems of healthy dogs,¹² amphotericin B remains a key agent for managing fungal meningoencephalitis in animals and humans.
- Newer formulations that incorporate lipid complexing or encapsulation of amphotericin B achieve higher serum concentrations and have less nephrotoxicity due to hydrophobicity, allowing greater delivery to inflamed sites and decreased delivery to the kidneys.¹³

ADMINISTRATION

Amphotericin B is not absorbed orally and must be administered parenterally.

- Conventional amphotericin B can be administered IV or SC¹⁴ and alternative formulations (eg, lipid complexed, liposomal encapsulated) by IV.^{15,16}

- All formulations are administered 2 to 3 times a week until either a cumulative target dose is reached (varies by infection and formulation) or the patient develops clinicopathologic evidence of renal tubular damage.
- With use of any of the formulations, patients should be euvolemic at administration and monitored for renal injury (eg, urinalysis for proteinuria and casts, serum BUN, creatinine) before each treatment.
- For IV infusion of conventional amphotericin B, diluted infusion over 4 to 6 hours is less toxic than rapid infusion.¹⁷

COST

The cost of conventional amphotericin B is approximately one-eighth to one-tenth that of other formulations.

- Additional costs for all formulations include administration and monitoring of renal function.
- Alternatively complexed formulations are the most expensive of the available treatment options.
 - However, these formulations are associated with an 8- to 10-fold decreased risk for nephrotoxicity, allowing for higher cumulative dose targets than possible for conventional amphotericin B.¹⁸
- SC administration of conventional amphotericin B is generally well tolerated and is less expensive than the other treatment protocols.¹⁴
 - There are no data proving superiority of one protocol over the others, but because of lower administration costs, the SC regimen is typically reserved for owners with financial constraints.

ADVERSE EFFECTS

Nephrotoxicity is the most significant adverse effect.⁵

- However, use in patients with kidney dysfunction is not necessarily contraindicated.
- Inflammation at the injection site and systemic signs (eg, nausea, vomiting, hypokalemia, cardiac arrhythmias, fever) can also occur.⁵
- Use of lipid-complexed formulations might increase the risk for infusion-related reactions, while liposomal formulations appear to have lower reaction rates.¹⁹
- Use of amphotericin B is generally limited by the necessity of parenteral administration combined with the risk for nephrotoxicity, but it has a valuable role in management of life-threatening infections.

DIANNE I. MAWBY, DVM, MVSc, DACVIM, is a clinical professor of small animal medicine at University of Tennessee, where she is also involved with daytime emergency and medicine services in the veterinary teaching hospital. She earned her DVM and MVSc and completed an internship and residency in small animal medicine at University of Saskatchewan. Dr. Mawby's current research interests are pharmacokinetics of antifungal drugs in dogs and cats.

JACQUELINE C. WHITTEMORE, DVM, PhD, DACVIM, is an associate professor at University of Tennessee, where she also manages the minimally invasive procedures service. She earned her DVM from University of California, Davis, and spent 2 years in small animal general practice before completing a residency in small animal internal medicine and earning her PhD at Colorado State University. Dr. Whittemore's active research foci include antifungal therapies and gastroenterology.

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