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Advancements In Amphotericin B: A Comprehensive Review Of Mechanisms, Formulations, And Clinical Applications

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Abstract
Amphotericin B, a polyene macrolide antifungal, has been a cornerstone in the treatment of systemic fungal infections for decades. Its unique mechanism of action, involving the binding to ergosterol and disruption of fungal cell membranes, ensures a broad spectrum of antifungal activity. Despite its efficacy against life-threatening mycoses, the clinical utility of Amphotericin B is often limited by significant adverse effects, particularly nephrotoxicity and infusion-related reactions. Advances in pharmaceutical formulations, such as liposomal Amphotericin B, have addressed these challenges to some extent by improving its safety profile. This paper reviews the history, pharmacology, clinical applications, and limitations of Amphotericin B, highlighting recent innovations and future directions for enhancing its therapeutic potential. While its legacy as a life-saving antifungal remains uncontested, ongoing research is crucial to overcome resistance and optimize its clinical use in a rapidly evolving therapeutic landscape.

Keywords: Amphotericin – B, Antifungal therapy, Systemic fungal infection, Lipid formulation, Nephrotoxicity

Introduction

Fungal infections, ranging from superficial conditions like candidiasis to life-threatening systemic diseases such as invasive aspergillosis and cryptococcosis, have become a major global health concern. These infections are particularly prevalent among immunocompromised individuals, including those undergoing chemotherapy, organ transplantation, or living with HIV/AIDS. Despite the increasing incidence of invasive fungal infections, effective antifungal therapies remain limited. Among the existing options, Amphotericin B, a polyene macrolide antifungal agent discovered in 1955, has stood out as a critical therapeutic agent due to its broad-spectrum efficacy.

Amphotericin B targets ergosterol, a key component of fungal cell membranes, forming pores that lead to cell membrane disruption and fungal death. This unique mechanism of action has made Amphotericin B a cornerstone in antifungal therapy, particularly for severe and resistant infections. However, its clinical application is often overshadowed by significant limitations, including dose-dependent toxicities such as nephrotoxicity, hypokalemia, and infusion-related reactions. These adverse effects have necessitated the development of alternative delivery systems, such as liposomal formulations and lipid complexes, which have successfully reduced toxicity while maintaining therapeutic efficacy. [1]

Despite these advancements, the use of Amphotericin B is still challenged by issues such as cost, accessibility, and emerging fungal resistance. Moreover, its role is often limited in resource-poor settings, where conventional formulations with higher toxicity profiles are more commonly used. This paper provides a comprehensive review of Amphotericin B, discussing its pharmacological properties, mechanism of action, clinical applications, and associated challenges. Additionally, the paper highlights recent innovations and future prospects aimed at overcoming its limitations and optimizing its role in antifungal therapy.

Background and History

Amphotericin B, a polyene macrolide, was first isolated from *Streptomyces nodosus*, a soil-dwelling actinomycete, in 1955 by researchers at Squibb Institute for Medical Research. It was initially introduced as a treatment for systemic fungal infections at a time when therapeutic options were severely limited. Named after its amphiphilic structure—having both hydrophilic and lipophilic regions—Amphotericin B revolutionized antifungal therapy by providing effective treatment for life-threatening mycoses.

Its molecular structure comprises a large lactone ring with alternating conjugated double bonds, enabling its unique interaction with ergosterol, a sterol exclusive to fungal cell membranes. This property distinguished Amphotericin B from other antimicrobials of its time, as it provided a broad-spectrum antifungal effect while sparing human cells, albeit with notable toxicity.

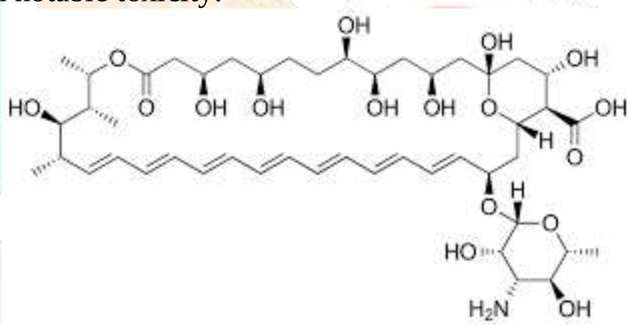

Fig 1: Structure of Amphotericin – B

The initial formulation of Amphotericin B (deoxycholate formulation) gained widespread use despite its significant side effects, including severe nephrotoxicity and infusion-related reactions. Over the decades, advancements in pharmaceutical technology led to the development of lipid-based formulations such as liposomal Amphotericin B (AmBisome) and Amphotericin B lipid complex (ABLC), which improved its tolerability and safety.

Today, Amphotericin B remains an essential drug listed by the World Health Organization (WHO) for the treatment of fungal infections, particularly in resource-limited settings where lipid formulations are often inaccessible. However, the development of newer antifungal agents and increasing concerns about toxicity have necessitated a reevaluation of its role in modern medicine.

Mechanism of Action

Amphotericin B exerts its potent antifungal activity by targeting the integrity of fungal cell membranes. Its mechanism is primarily based on its high affinity for ergosterol, a sterol uniquely present in fungal cell membranes, which distinguishes fungal cells from mammalian cells that contain cholesterol instead.

1. **Binding to Ergosterol**
   - Amphotericin B integrates into the fungal cell membrane and binds to ergosterol through its hydrophobic side. This binding disrupts the organization of the membrane, weakening its structural integrity.
2. **Pore Formation**
   - Following ergosterol binding, Amphotericin B self-associates to form transmembrane pores or channels. These pores increase membrane permeability, leading to the uncontrolled efflux of essential ions, such as potassium (K^+) and magnesium (Mg^{2+}), and other small molecules. [2]
   - This ion leakage disrupts intracellular homeostasis, ultimately causing cell death.
3. **Selectivity**
   - Amphotericin B preferentially targets fungal cells due to its higher affinity for ergosterol compared to cholesterol, the equivalent sterol in mammalian membranes. However, it still interacts weakly with cholesterol, which contributes to its dose-dependent toxicity, particularly nephrotoxicity.
4. **Oxidative Damage**
   - In addition to pore formation, Amphotericin B is thought to induce oxidative stress within fungal cells by generating reactive oxygen species (ROS). This exacerbates cellular damage and promotes apoptosis in fungal cells.
5. **Fungicidal vs. Fungistatic Activity**
   - The effect of Amphotericin B can be fungicidal (killing fungal cells) or fungistatic (inhibiting fungal growth), depending on its concentration and the fungal species being targeted. [9]
   -

Mechanism of Resistance

- Resistance to Amphotericin B is rare but can occur through alterations in fungal cell membrane composition. For example:
  - **Reduced Ergosterol Content**: Some fungi modify their sterol biosynthesis pathways, reducing the amount of ergosterol in the membrane, which decreases Amphotericin B binding.
  - **Substitution of Ergosterol**: Altered sterol molecules with reduced Amphotericin B affinity may be incorporated into the membrane.

This unique and multifaceted mechanism of action underpins Amphotericin B's broad-spectrum antifungal activity and its enduring role in treating systemic fungal infections. However, its interaction with mammalian cell membranes remains the basis for its toxicity, highlighting the need for continued advancements in formulation and delivery strategies. [7]

Spectrum of Activity

Amphotericin B is renowned for its broad-spectrum antifungal activity, making it a versatile therapeutic agent in treating a wide range of fungal infections. Its efficacy encompasses many pathogenic fungi and some protozoa, positioning it as a critical drug in clinical settings.

1. Fungi Targeted by Amphotericin B

- **Yeasts**:
  - *Candida* species (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*).
  - *Cryptococcus neoformans*: Commonly associated with cryptococcal meningitis, particularly in immunocompromised patients.
- **Molds**:
  - *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. niger*), although less effective than newer azoles for some invasive aspergillosis cases.

    - Agents of mucormycosis (*Rhizopus*, *Mucor*, *Rhizomucor*).
- **Dimorphic Fungi**:
    - *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Paracoccidioides brasiliensis*. These fungi cause systemic mycoses, often in endemic regions.

2. Protozoal Activity

- Amphotericin B also demonstrates efficacy against certain protozoa, including *Leishmania* species, where it is used in liposomal formulations to treat visceral leishmaniasis (kala-azar).

3. Clinical Indications

- **Systemic Fungal Infections**: Often used as first-line therapy for life-threatening mycoses, especially in immunocompromised patients (e.g., HIV/AIDS, cancer patients).
- **Empirical Therapy**: Administered empirically in febrile neutropenic patients when fungal infections are suspected but not confirmed.
- **Fungal Meningitis**: Highly effective in penetrating the central nervous system (CNS), making it crucial for conditions like cryptococcal meningitis.
- **Opportunistic Infections**: Used to treat infections in patients undergoing chemotherapy or organ transplants.

4. Resistance Spectrum

- Amphotericin B retains activity against most fungi, but some species exhibit intrinsic or acquired resistance:
    - **Resistant Species**:
        - *Candida auris*: Emerging pathogen with varying susceptibility.
        - *Scedosporium* and *Fusarium* species: Known for reduced susceptibility.
        - *Agalactomyces* and some *Trichosporon* species.
- Resistance remains rare compared to other antifungal drugs, partly due to its unique mechanism targeting ergosterol.

5. Comparison with Other Antifungals

- While azoles and echinocandins are less toxic alternatives for many infections, Amphotericin B is preferred for severe, refractory, or rapidly progressive infections due to its unparalleled fungicidal potency.

Formulations of Amphotericin B

The clinical use of Amphotericin B has evolved significantly due to its high efficacy against systemic fungal infections and the development of various formulations to mitigate its dose-limiting toxicity. Each formulation has unique characteristics, offering a balance between efficacy, safety, and cost.

1. Conventional Amphotericin B (C-AMB)

- **Description**: Amphotericin B deoxycholate is the original and most widely used formulation.
- **Advantages**:
    - Broad-spectrum antifungal activity.
    - Cost-effective and accessible in resource-limited settings.
- **Limitations**:
    - High incidence of nephrotoxicity (dose-dependent).
    - Infusion-related adverse reactions, including fever, chills, and thrombophlebitis.
    - Poor solubility, necessitating intravenous administration with strict precautions.

2. Lipid-Based Formulations

These formulations were developed to reduce toxicity while preserving the antifungal efficacy of Amphotericin B.

a. Liposomal Amphotericin B (L-AmB)

- **Description**: Amphotericin B encapsulated within liposomes (e.g., AmBisome).
- **Advantages**:
    - Significantly reduced nephrotoxicity due to preferential uptake by the mononuclear phagocyte system (MPS).

  - Enhanced distribution to infection sites, including the central nervous system.
  - Better tolerability with reduced infusion-related reactions. [12]
- **Limitations**:
  - High cost limits widespread use, particularly in low-income regions. [5]

b. Amphotericin B Lipid Complex (ABLC)

- **Description**: A lipid complex formulation (e.g., Abelcet) where Amphotericin B is embedded in a ribbon-like lipid structure.
- **Advantages**:
  - Lower nephrotoxicity compared to C-AMB.
  - Higher drug delivery to fungal infection sites.
- **Limitations**:
  - Infusion-related reactions are more common compared to L-AmB.

c. Amphotericin B Colloidal Dispersion (ABCD)

- **Description**: Amphotericin B is complexed with cholesterol sulfate.
- **Advantages**:
  - Reduced nephrotoxicity compared to C-AMB.
- **Limitations**:
  - High rate of infusion-related side effects like hypoxia and chills.
  - Less commonly used due to the superiority of other lipid formulations.

3. Novel and Experimental Formulations

Emerging formulations aim to further optimize the therapeutic index of Amphotericin B:

- **Nanoparticle-Based Amphotericin B**: Offers targeted delivery to infected tissues, improving efficacy and reducing systemic toxicity.
- **Inhalable Amphotericin B**: Designed for the prophylaxis or treatment of pulmonary fungal infections, such as aspergillosis in immunocompromised patients.
- **Amphotericin B Emulsions**: Under development to improve solubility and reduce toxicity.

Table 1: Comparision of Formulation

Formulation	Nephrotoxicity	Infusion Reactions	Cost	Clinical Use
Conventional (C-AMB)	High	High	Low	Resource-limited settings, last resort.
Liposomal (L-AmB)	Very Low	Low	Very High	Severe infections, CNS penetration.
Lipid Complex (ABLC)	Moderate	Moderate	High	Systemic fungal infections.
Colloidal Dispersion (ABCD)	Low	High	High	Rarely used today.

The advent of lipid-based formulations has significantly enhanced the clinical utility of Amphotericin B by reducing its toxic side effects. However, challenges like cost and accessibility still limit their widespread adoption, underscoring the need for continued research into affordable and effective delivery methods.

Pharmacokinetics and Pharmacodynamics of Amphotericin B

Understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of Amphotericin B is crucial for optimizing its use while minimizing toxicity. The drug's unique properties, including poor solubility and extensive tissue distribution, influence its efficacy and safety profile.

Pharmacokinetics

1. **Absorption**
   - Amphotericin B is poorly absorbed from the gastrointestinal tract due to its high molecular weight and hydrophobic nature.
   - It is administered intravenously for systemic infections. Oral formulations are not suitable for treating systemic mycoses.

2. **Distribution**
   - After intravenous administration, Amphotericin B rapidly binds to plasma proteins, particularly lipoproteins (95–99%).
   - It distributes widely to tissues, especially those rich in mononuclear phagocytes, such as the liver, spleen, and lungs.
   - Penetration into the cerebrospinal fluid (CSF) is minimal (~2–4%), making liposomal formulations preferable for treating fungal meningitis.

3. **Metabolism**
   - Amphotericin B is not extensively metabolized. Its degradation occurs slowly, and the exact pathways remain unclear.

4. **Excretion**
   - The drug is excreted very slowly, primarily via the bile and feces, with minimal renal excretion (<5%).
   - The terminal half-life is long, ranging from 15 to 48 hours for C-AMB and up to 100 hours for lipid-based formulations, contributing to its prolonged effects. [8]

Pharmacodynamics

1. **Concentration-Dependent Killing**
   - Amphotericin B exhibits concentration-dependent fungicidal activity. Higher drug concentrations result in faster and more effective fungal cell killing.
2. **Post-Antifungal Effect (PAFE)**
   - Amphotericin B has a significant PAFE, meaning it continues to suppress fungal growth even after plasma concentrations fall below the minimum inhibitory concentration (MIC).
3. **Spectrum of Activity**
   - Amphotericin B is active against a broad range of fungi, including *Candida*, *Aspergillus*, *Cryptococcus*, and dimorphic fungi, as previously discussed.
4. **Toxicity and Selectivity**
   - Selectivity is based on its preferential binding to ergosterol in fungal membranes over cholesterol in mammalian cells. However, weak binding to cholesterol contributes to toxicity, particularly nephrotoxicity.

Table 2: Pharmacokinetic Variations Across Formulations

Parameter	Conventional (C-AMB)	Liposomal (L-AmB)	Lipid Complex (ABLC)	Colloidal (ABCD)
Protein Binding	~95%	~90%	~90%	~90%
Volume of Distribution	High	Lower tissue binding	High tissue uptake	Intermediate
Half-Life	24–48 hours	100–150 hours	~50–90 hours	~24–48 hours
Renal Excretion	Minimal	Negligible	Minimal	Minimal
Nephrotoxicity	High	Very low	Moderate	Moderate

Clinical Implications

- **Dosing**: Optimizing dose regimens based on concentration-dependent activity can improve efficacy while minimizing toxicity. Lipid-based formulations allow for higher doses with reduced adverse effects.
- **Therapeutic Drug Monitoring (TDM)**: Although rarely required, TDM may be considered in special populations (e.g., renal impairment, pediatrics).
- **Resistance**: Amphotericin B maintains low resistance rates due to its unique mechanism of action, but emerging resistant strains necessitate careful monitoring.

Toxicity and Adverse Effects of Amphotericin B

Despite its remarkable efficacy, Amphotericin B is associated with significant toxicity, which can limit its use, particularly in conventional formulations. The severity of adverse effects varies across its formulations, with lipid-based variants offering improved safety profiles.

1. Nephrotoxicity

- **Mechanism**:
  - Amphotericin B binds to cholesterol in renal tubular cells, disrupting cell membranes and causing renal vasoconstriction, leading to ischemia and tubular damage.
- **Manifestations**:
  - Acute kidney injury (AKI), characterized by increased serum creatinine and reduced glomerular filtration rate (GFR).
  - Electrolyte imbalances, such as hypokalemia (low potassium) and hypomagnesemia (low magnesium).
- **Mitigation**:
  - Lipid-based formulations significantly reduce nephrotoxicity by altering tissue distribution.
  - Adequate hydration with normal saline before and after infusion reduces renal damage. [3]

2. Infusion-Related Reactions

- **Symptoms**:
  - Fever, chills, rigors, nausea, vomiting, headache, and hypotension.
- **Mechanism**:
  - Triggered by the release of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukins from mononuclear cells.
- **Mitigation**:
  - Premedication with antipyretics (e.g., paracetamol), antihistamines (e.g., diphenhydramine), or corticosteroids. [6]
  - Slowing the infusion rate or using lipid-based formulations.

3. Hepatotoxicity

- **Manifestations**:
  - Elevated liver enzymes, which may rarely progress to hepatocellular injury.
- **Risk Factors**:
  - Concurrent use of other hepatotoxic drugs.
- **Management**:
  - Monitor liver function tests regularly during therapy.

4. Hematologic Effects

- **Manifestations**:
  - Anemia due to suppression of erythropoietin production by renal tubular cells.
- **Mitigation**:
  - Regular monitoring of hemoglobin levels and red blood cell counts.

5. Neurotoxicity (Rare)

- **Symptoms**:
  - Headache, dizziness, and, in rare cases, seizures.
- **Associated Conditions**:
  - Intrathecal administration for fungal meningitis can exacerbate neurotoxic effects.

6. Lipid-Based Formulations and Toxicity

- **Liposomal Amphotericin B (L-AmB)**:
  - Significantly reduces nephrotoxicity and infusion-related reactions by sequestering the drug in liposomes and delivering it preferentially to infected tissues.
- **Amphotericin B Lipid Complex (ABLC)** and **Colloidal Dispersion (ABCD)**:
  - Both formulations reduce toxicity to varying extents but are less effective than L-AmB in reducing infusion reactions.

7. Dose-Dependent vs. Idiosyncratic Reactions

- **Dose-Dependent**:
  - Includes nephrotoxicity and anemia, which are directly related to cumulative doses.
- **Idiosyncratic**:
  - Includes rare hypersensitivity reactions and neurotoxicity, which occur unpredictably.

Management of Adverse Effects

- **Prevention**:
  - Adequate hydration and electrolyte replacement before treatment.
  - Use of lipid formulations in high-risk patients.
- **Monitoring**:
  - Frequent assessments of renal and liver function, as well as serum electrolytes, during therapy.
- **Intervention**:
  - Adjust or discontinue therapy in severe cases of toxicity, switching to alternative antifungals if necessary.

Clinical Applications of Amphotericin B

Amphotericin B remains a cornerstone in the treatment of severe and life-threatening fungal infections, particularly in immunocompromised patients. Its clinical applications span a variety of systemic fungal infections, both common and rare, where it serves as the drug of choice or an essential option in managing treatment-resistant infections.

1. Systemic Mycoses

- **Candidiasis**:
  - Amphotericin B is used for invasive *Candida* infections, including candidemia, endocarditis, and infections of deep tissues, particularly in patients with neutropenia, diabetes, or organ transplants.
  - Liposomal formulations are preferred for treating systemic candidiasis due to their reduced nephrotoxicity and improved tissue penetration.
- **Cryptococcosis**:
  - *Cryptococcus neoformans* causes cryptococcal meningitis, especially in HIV/AIDS patients. Amphotericin B, often in combination with flucytosine, is the first-line therapy for severe cases, particularly those involving the central nervous system (CNS).
- **Aspergillosis**:
  - Amphotericin B is effective against invasive *Aspergillus* species, including *A. fumigatus*, a common cause of pulmonary and disseminated infections. Although less effective than newer agents (e.g., voriconazole), it is used in life-threatening cases, particularly when resistance or intolerance to other antifungals occurs.
- **Mucormycosis (Zygomycosis)**:

- Amphotericin B is a first-line treatment for mucormycosis, a rapidly progressive and often fatal fungal infection caused by molds like *Rhizopus*, *Mucor*, and *Rhizomucor*. Early intervention with Amphotericin B is crucial for improving outcomes. [4,11]

2. Dimorphic Fungal Infections

- **Histoplasmosis**:
  - Caused by *Histoplasma capsulatum*, this infection can cause severe pulmonary or disseminated disease in immunocompromised individuals. Amphotericin B is often used for disseminated or refractory cases, especially in HIV-positive patients.
- **Blastomycosis**:
  - *Blastomyces dermatitidis* causes blastomycosis, which can lead to pulmonary, cutaneous, or systemic infections. Amphotericin B is employed in severe or disseminated infections.
- **Coccidioidomycosis**:
  - *Coccidioides immitis* causes coccidioidomycosis, commonly referred to as Valley fever. Amphotericin B is indicated for severe, disseminated, or CNS involvement.

3. Fungal Meningitis

- **Cryptococcal Meningitis**:
  - As noted, Amphotericin B is the first-line treatment for cryptococcal meningitis, typically in combination with flucytosine to reduce the risk of resistance and improve outcomes.
- **Candida Meningitis**:
  - For Candida-associated meningitis, particularly in patients with CNS involvement, Amphotericin B (often in liposomal form) is used in combination with other antifungals.
- **Other Fungal CNS Infections**:
  - It may be used in treating infections from *Aspergillus*, *Mucor*, or other mold pathogens that involve the brain or spinal cord, especially when other therapies fail. [10]

4. Prophylactic Use

- **Neutropenic Patients**:
  - Amphotericin B is used for prophylaxis in high-risk patients, such as those undergoing chemotherapy for hematologic malignancies or those with bone marrow suppression, where fungal infections like *Candida* or *Aspergillus* are common. [13]
- **Solid Organ Transplantation**:
  - Post-transplant patients are also at risk for fungal infections, particularly *Candida* and *Aspergillus*. Prophylactic use of Amphotericin B may be employed, especially in those at high risk for systemic fungal infections.
- **HIV/AIDS**:
  - Amphotericin B is often used for fungal prophylaxis, particularly in patients with CD4 counts <50 cells/mm^3, who are at increased risk for opportunistic fungal infections like *Cryptococcus* and *Aspergillus*.

5. Leishmaniasis

- **Visceral Leishmaniasis (Kala-Azar)**:
  - *Leishmania* species cause visceral leishmaniasis, a protozoal infection that is often fatal if untreated. Liposomal Amphotericin B (e.g., AmBisome) is considered one of the most effective treatments for this disease, especially in areas where it is endemic.
- **Cutaneous and Mucocutaneous Leishmaniasis**:
  - Amphotericin B can also be used for cutaneous forms, although milder cases are typically managed with oral antifungal agents (e.g., miltefosine).

6. Treatment of Resistant Fungal Infections

- **Refractory Infections**:
  - Amphotericin B is often considered for fungal infections resistant to azoles or echinocandins. In particular, it may be used in cases of multidrug-resistant *Candida* or *Aspergillus* species.
- **Refractory Cryptococcosis**:
  - For cryptococcal infections that do not respond to standard antifungal therapy, Amphotericin B, often in combination with other antifungals, can be used as a salvage treatment.

7. Role in Polycystic Kidney Disease (PKD) and Renal Cystic Infections

- While not a primary indication, Amphotericin B may be considered for managing fungal infections in patients with polycystic kidney disease who develop renal cyst infections, as they are particularly prone to fungal infections due to cystic fluid cultures.

8. Administration Strategies

- **Dosing Regimens**:
  - The typical dosing regimen of conventional Amphotericin B is 0.5–1 mg/kg/day, while lipid formulations may require a reduced dose (3–5 mg/kg/day) to minimize nephrotoxicity.
- **Combination Therapy**:
  - Amphotericin B is often used in combination with other antifungal agents (e.g., azoles, echinocandins) to enhance efficacy and prevent resistance. [14]

Conclusion

Amphotericin B continues to be one of the most effective antifungal agents for treating severe and life-threatening systemic fungal infections. Its broad-spectrum activity, including efficacy against *Candida*, *Aspergillus*, *Cryptococcus*, and other pathogenic fungi, makes it a cornerstone in clinical practice. Despite its potent antifungal action, the drug's use is often limited by significant toxicity, particularly nephrotoxicity and infusion-related reactions.

The development of lipid-based formulations, such as liposomal Amphotericin B, has significantly reduced the drug's adverse effects, improving its safety profile and allowing for its use in higher doses and for longer durations. These advancements have broadened its clinical utility, particularly in immunocompromised patients who are at heightened risk for fungal infections.

Amphotericin B remains the gold standard for many severe fungal infections, including mucormycosis, cryptococcal meningitis, and certain dimorphic fungal infections. However, emerging resistance and the complexity of managing its side effects necessitate careful monitoring and an individualized treatment approach. [15]

Despite newer antifungal agents being available, Amphotericin B's role remains indispensable, particularly in treating infections caused by resistant or difficult-to-treat fungi. Understanding its pharmacology, therapeutic indications, and safety considerations is crucial for optimizing patient outcomes and minimizing the risks associated with this powerful antifungal agent.

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