Introduction
The past decade has witnessed a significant increase in the prevalence of resistance to antibacterial and antifungal agents. Resistance to antimicrobial agents has important implications for morbidity, mortality and health care costs in hospitals, as well as in the community. Hence, substantial attention has been focused on developing a more detailed understanding of the mechanisms of antimicrobial resistance, improved methods to detect resistance when it occurs, new antimicrobial options for the treatment of infections caused by resistant organisms, and methods to prevent the emergence and spread of resistance in the first place. Most of this attention has been devoted to the study of antibiotic resistance in bacteria for several reasons: (i) bacterial infections are responsible for the bulk of community-acquired and nosocomial infections; (ii) the large and expanding number of antibacterial classes offers a more diverse range of resistance mechanisms to study; and (iii) the ability to move bacterial resistance determinants into standard well-characterized bacterial strains facilitates the detailed study of molecular mechanisms of resistance in bacterial species.

The study of resistance to antifungal agents has lagged behind that of antibacterial resistance for several reasons. Perhaps most importantly, fungal diseases were not recognized as important pathogens until relatively recently (Anaissie and Bodey, 1989, Wey Mori. Pfaller et al., 1998). For example, the annual death rate due to candidiasis was steady between 1950 and about 1970. Since 1970, this rate increased significantly in association with several changes in medical practice, including more widespread use of therapies that depress the immune
system, the frequent and often indiscriminate use of broad-spectrum antibacterial agents, the common use of indwelling intravenous devices, and the advent of chronic immunosuppressive viral infections such as AIDS. These developments and the associated increase in fungal infections (Beck Sague, and Jarvis, 1993) intensified the search for new, safer, and more efficacious agents to combat serious fungal infections.

For nearly 30 years, amphotericin B, which is known to cause significant nephrotoxicity, was the sole drug available to control serious fungal infections. The approval of the imidazoles and the triazoles in late 1980s and early 1990s were major advances in our ability to safely and effectively treat local and systemic fungal infections. The high safety profile of triazoles, in particular fluconazole, has led to their extensive use. Fluconazole has been used to treat in excess of 16 million patients, including over 300,000 AIDS patients, in the United States alone since the launch of this drug (Sheehan, 1999) Concomitant with this widespread use, have been increasing reports of antifungal resistance (Rex and Rinaldi, 1995) The clinical inspect of antifungal resistance has been recently reviewed (Rex and Rinaldi, 1995) also, three excellent reviews concentrating on various aspects of antifungal resistance including clinical implications have been published recently (Espinel-Ingrof, 1997). Therefore, the clinical impact of resistance is not covered in this review. Instead, our goal is to focus on the molecular mechanisms of antifungal resistance. Since mechanisms of antibacterial resistance are characterized in considerably more detail than those of antifungal resistance, we have chosen to use well-described mechanisms of bacterial resistance as a framework for understanding fungal
mechanisms of resistance, insofar as such comparisons can be logically applied. In so doing, we hope to make an understanding of antifungal resistance mechanisms accessible to those who use these agents clinically, as well as those who may wish to study them in the future.

Structures of available antifungal agents

![Structures of available antifungal agents](image)

PROBLEMS WITH COMPARING ANTIFUNGAL AND ANTIBACTERIAL RESISTANCE

Although it is our premise that a comparison between mechanism of resistance to antifungal and antibacterial is a useful way of developing a perspective on antimicrobial resistance in the two kingdoms, the comparison is necessarily limited by several factors. First; the structures of fungi and bacteria differ in very significant ways (such as the diploid nature of most fungi and the longer generation time...
of fungi compared to bacteria), and the available antibacterial and antifungal agents target structures and functions most relevant to the organisms to be inhibited. For example, many antibacterial agents inhibit steps important for the formation of peptidoglycan, the essential component of the bacterial cell wall. In contrast, most antifungal compounds target either the formation or the function of ergosterol, an important component of the fungal cell membrane. Nevertheless, there are important parallels between the mechanisms by which fungi develop resistance to ergosterol biosynthesis inhibitors and bacteria develop resistance to antibacterial agents. Regarding other types of bacterial resistance, comparisons are limited by the fact that antifungal analogues of many classes of antibacterial agents (protein synthesis inhibitors such as aminoglycosides, macrolides, and tetracyclines; topoisomerase inhibitors such as fluoroquinolones; and metabolic pathway inhibitors such as trimethoprim-sulfamethoxazole) do not exist. Conversely, antifungal nucleoside analogues such as 5-fluorocytosine (5FC) have no counterparts among clinically available antibacterial agents (although they are represented among the antiviral compounds). As such, the capacity for fungi to develop ribosomal resistance or topoisomerase mutations is unknown, as is the capacity for bacteria to develop resistance to nucleoside analogues. Interestingly, the antibacterial RNA polymerase inhibitor rifampin, which demonstrates no intrinsic activity against fungi, appears quite active against several fungal species when used in combination with amphotericin B (Beggs et al., 1976). This synergistic activity has been attributed to increased uptake of the rifampin into the fungal cell resulting from the action of amphotericin B on the fungal membrane. Similar synergism has been demonstrated
between amphotericin B and 5FC by Polak et al., (1982), using murine models of candidiasis. The mechanism for this synergism has been postulated by some investigators to be improved uptake of the 5FC as a result of membrane disorganization due to amphotericin B-ergosterol interaction (Medoff Comfort, 1971). This synergistic effect resembles the postulated mechanism of bactericidal synergism between cell wall active agents and aminoglycosides against enterococci, in which increased intracellular concentrations of streptomycin are detectable when streptomycin is combined with penicillin in vitro against Enterococcus faecalis (Moellering and Weinberg, 1971). In contrast to the notion that Amp-B improves the uptake of 5FC, data obtained by Beggs et al., (1981) suggest that these two agents act sequentially and not in combination against Candida albicans to affect synergy.

The second limitation to the comparison between antifungal and antibacterial resistance mechanisms is that some general classes of resistance mechanisms have not yet been identified in fungi. Resistance to antibacterial agents results from modification of the antibiotic, modification of the antimicrobial target, reduced access to the target, or some combination of these mechanisms. Antibiotic modification is arguably the most important mechanism of resistance to the β-lactamas) and aminoglycoside (aminoglycoside-modifying enzymes) classes of antibacterials. In contrast, although there has been a single, unconfirmed report of degradation of nystatin by dermatophytic fungi (Capek and Simek, 1971), there are no data to suggest that antibiotic modification is an important mechanism of antifungal resistance. On the other hand, accumulating evidence suggests that both target alterations
and reduced access to targets (sometimes in combination) are important mechanisms of resistance to antifungal agents. These mechanisms have important parallels in antibacterial resistance.

The third limitation to the comparison is that our knowledge of genetic exchange mechanisms in bacteria is far more advanced than our knowledge of exchange mechanisms; if they exist, in fungi. Bacteria employ an extensive repertoire of plasmids, transposons, and bacteriophages to facilitate the exchange of resistance and virulence determinants among and between species. As a result, the opportunity for rapid emergence of high-level resistance and the potential for emergence and dissemination of resistance even in the absence of direct selection by specific antimicrobial pressure abound. Conversely, antifungal resistance described to date generally involves the emergence of naturally resistant species (as in the increasing importance of Candida Krusei in areas of extensive use in certain medical centers) or the progressive, stepwise alterations of cellular structures or functions to avoid the activity of an antifungal agent to which there has been extensive exposure.

The final important limitation in comparing mechanisms of resistance to antifungals and antibacterials lies in the availability of standardized bacterial strains and plasmids for use in the study of antimicrobial resistance in bacteria. This availability allows the isolation of resistance determinants in well-characterized backgrounds; so that the specific contribution of different resistance mechanisms can be assessed. The availability of well-characterized strains and systems for DNA delivery allows a much more rigorous approach to the study of the
genetics and physiology of bacterial resistance mechanisms, in comparison to fungal mechanisms of resistance. For example, the first step in analyzing plasmid-mediated β-lactamases in bacteria is the transfer of the plasmid to a well-characterized strain, generally Escherichia coil. In this way, complicating mechanisms such as membrane alteration can be controlled and reasonable comparisons of the level of resistance conferred by different β-lactamases can be made. The fact that similar standardized systems are not available in fungi means that the study of resistance almost always occurs in the clinical strains themselves, making an assessment of the precise contribution of individual resistance mechanisms to the phenotypic expression of resistance difficult and often impossible.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>MIC (µg/ml) for:</th>
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<tr>
<td></td>
<td>Susceptible Strains</td>
<td>Susceptible (dose-dependent) strains</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>≤ 8</td>
<td>16-32</td>
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<tr>
<td>Itraconazole</td>
<td>≤ 0.125</td>
<td>0.25 – 0.5</td>
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Treatment of fungal infections have increased considerably over the last four decades and the pharmacological principles of antifungal therapy are only partially understood (Trincy and Riley, 1984). Fungal diseases, both local and intestinal, are common, but systemic fungal infections have become more frequent and important as a consequence of the lowering of host resistance following the increasing use of immunosuppressive drugs and the spread of AIDS. The antifungal agents in current use include some antibiotics as well as synthetic drugs. The antifungal agents are:
Those employed locally: These include many synthetic drugs. Antibiotics used include nystatin and other polyene antibiotics.

Those used systemically: Amphotericin B (Amp B) selected by the author for the present study is an antibiotic with no antibacterial action, but is highly effective against many yeast-like and filamentous fungi and is one of the few antifungal antibiotics that can be given by injection. It is of value in the treatment of deep fungal infections such as Cryptococcosis, histoplasmosis and systemic candidiasis and is given in doses of 250 mg/kg daily by slow intravenous injection, often preceded by a test dose of 1 mg. The injection solution should be freshly prepared and protected from light during administration. The dose is slowly increased up to 1 mg/kg daily, but treatment for months may be required, with frequent changes of the injection site, as Amphotericin B is an irritant and may cause local pain and thrombophlebitis.

The dose of Amp B is normally limited by the nephrotoxic effects of the drug and the development of renal insufficiency. The risk of toxicity has recently been reduced within introduction of two new presentations of Amphotericin for intravenous infusion, Ambisome and Amphocil. Ambisome is a liposome encapsulated preparation of amphotericin, from which the drug is slowly released; Amphocil is a complex of amphotericin with sodium cholesterol sulphate.

**History and Source of Amphotericin B**

Amp B was discovered by Gold et al., (1956), who were studying a strain of Streptomyces nodosus, an aerobic actinomycete, obtained
from the Orinoco River Valley of Venezuela. The antibiotic was isolated by Vandeputte et al., (1956).

Chemistry

Amp B is one of a family of some 200 polyene macrolide antibiotics. Those studied to date share the characteristics of four to seven conjugated double bonds, an internal cyclic ester, poor aqueous solubility, substantial toxicity on parenteral administration and a common mechanism of antifungal action. Amp B is a haptaeene macrolide, containing seven conjugated double bonds in the transposition and 3-amino-3, 6-dideoxymannose (mycosamine) connected to the main ring by a glycosidic bond. The amphoteric behavior for which the drug is named derives from the presence of a carboxyl group on the main ring and a primary amino group on mycosamine; these groups confer aqueous solubility at extremes of pH. X-ray crystallography has shown the molecule to be rigid and rod-shaped, with the hydrophilic hydroxyl groups of the macrolide ring forming an opposing face to the lipophilic polyenic portion (Kerridge and Whelan, 1984).

Aqueous insolubility of Amp B at neutral pH renders intravenous infusion difficult. Bartner et al., (1958) found that Amp B could be solubilized as a colloidal dispersion in deoxycholate. Although this formulation has been in clinical use for more than 30 years, toxicity of the deoxycholate complex has prompted attempts to develop other formulations. N-acyl derivatives of Amp B or esters of the carboxyl group are generally less active in vitro but can be formulated as
water-soluble salts. For example, the methylester has been administered intravenously as the hydrochloride, ascorbate or aspartate salt (Hoeprich et al., 1988). The amphipathic property of Amp B also permits incorporation of the drug into liposomes. Preliminary clinical experience with two liposomal preparations indicated the neither caused azotemia, but the two differed profoundly in the drug concentrations that were achieved in plasma (Lopez-Berestein, 1988; Meunier et al., 1988). Formulations in lipid emulsions and as complexes with cholesterol have also been tested; there is reason to hope for improved formulations of this useful drug.

Current regulations in the United States require that Amp B for intravenous use be at least 75% pure and have no more than 5% amphotericin A, a tetraene. The amount of amphotericin A and of amphotericin X in the commercial product depends upon the strain of Streptomyces used for production and the purification process. Differences in pyrogenicity between lots of the drug and between manufacturers are probably attributable to variable composition and to technical problems in measuring contamination of preparations with endotoxin.

Antifungal Activity

Amp-B has useful clinical activity against Candida species, Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Torulopsis glabrata, Coccidioides immitis, Paracoccidioides braziliensis, Aspergillus species and the agents of mucomycosis.
Methods for determination of susceptibility of fungi to Amp B are still controversial, although efforts at standardization are in progress.

Amp-B has limited activity against the protozoa, Leishmania braziliensis and Naegleria fowleri. The drug has no antibacterial activity.

**Mechanism of Action**

The antifungal activity of Amp B is at least in part dependent on its binding to a sterol moiety, primarily ergosterol, present in the membrane of sensitive fungi. By virtue of their interaction with the sterols of cell membranes, polyenes appear to form pores or channels. The result is an increase in the permeability of the membrane, allowing leakage of a variety of small molecules (Hamilton-Miller, 1974). Additional mechanisms of action may include oxidative damage to fungal cells, at least in vitro (Sokol-Anderson *et al.*, 1986), and some capability to enhance cell mediated immunity in the host (Medoff *et al.*, 1983).

**Fungal Resistance**

Mutants with decreased susceptibility to Amp B have been isolated from several fungal species by passage in culture medium containing the drug. Many but not all of these mutants have decreased concentrations of ergosterol in their cell membranes. Some resistant strains have elevated concentrations of precursors of ergosterol with lower affinity for the polyene antibiotics. Isolation from blood or deep tissues of strains with decreased susceptibility has been reported (Powderly *et al.*, 1988). More commonly, species of Candida with
decreased susceptibility have been isolated only from the throat, stool or urine, with no evidence that infection with drug resistant organisms has occurred (Dutcher et al., 1989).

Absorption, Distribution and Excretion

Absorption of Amp B from the gastrointestinal tract is negligible. Repeated daily intravenous infusions to adults of 0.5 mg/kg results in concentrations in plasma of about 1.0 to 1.5 µg/ml at the end of the infusion, which falls to about 0.5 to 1.0 µg/ml 24 hours later (Bindschadler and Bennett, 1969). The drug is released from its complex with deoxycholate in the bloodstream and the Amp B that remains in plasma is more than 90% bound to proteins, largely lipoprotein. Approximately 2 to 5% of each dose appears in the urine when patients are on daily therapy. Elimination of the drug appears to be unchanged in anephric patients and in patients receiving hemodialysis. In dogs, biliary occlusion results in elevated concentrations of Amp B in blood (Craven et al., 1979), but hepatic or biliary disease have no known effect on metabolism of the drug in man. At least a third of the injected doses can be recovered unchanged by methanolic extraction of tissue at autopsy; the highest concentrations are found in liver and spleen, with lesser amounts in kidney and lung (Christiansen et al., 1985; Collette et al., 1989). Concentrations of Amp B in fluids from inflamed pleura, peritoneum, synovium and aqueous humor are approximately two thirds of trough concentrations in plasma. The drug probably crosses the placenta readily (Bennett, 1990). Little Amp B penetrates into cerebrospinal fluid (CSF), vitreous humor or normal amniotic fluid.
Because of extensive binding to tissues, there is a terminal phase of elimination with a half-time of about 15 days.

**Preparations, Routes of Administration and Dosage of Amp-B**

Amp B (FUNGIZONE) is available for injection. The sterile, lyophilized powder is marketed in vials containing 50 mg of Amp B plus 41 mg of sodium deoxycholate and sodium phosphate buffer. The contents of the vial should be dissolved, with shaking, in 10 ml of sterile water and then added to 5% dextrose in water. Solutions of some electrolytes, acidic solutions or solutions with preservatives should not be used because they cause precipitation of this antifungal agent (Jurgens et al., 1981). If fever and chills in response to administration of the drug are severe, the addition of 0.7 mg/kg of hydrocortisone may alleviate the symptoms in some patients. Meperidine is also effective (Burks et al., 1980). Topical preparations of Amp B are also marketed for use (Bennett, 1990).

Opinions vary as to the most effective dosage for administration of Amp B. To a certain extent, the dosage is dependent on the type and severity of infection. Most physicians agree that a small test dose (1 mg dissolved in 20 ml of 5% dextrose solution) should first be administered intravenously over 20 to 30 minutes. The temperature, pulse, respiratory rate and blood pressure should be recorded every 30 minutes for 4 hours. Fever, chills, hypotension and dyspnea are common. A patient with a severe, rapidly progressing fungal infection, good cardiopulmonary function and a mild reaction to the test dose can immediately receive 0.3 mg/kg of Amp B intravenously over a period
of 2 to 4 hours (Bennett, 1990). If the patient has a severe reaction to the test dose or cardiopulmonary impairment, a smaller dose is recommended for example, 0.1 mg/kg or 5 to 10 mg. This dose may then be increased by 5 to 10 mg per day. In severe or fulminant infections, dosage should be escalated rapidly until the patient is receiving 0.5 to 1.0 mg/kg daily incremental doses can be given every 6 to 8 hours if reaction in a fragile patient make immediate advancement to full dosage inadvisable. For example, a severe reaction to a 1 mg dose could be followed by 5, 15 and 25 mg given at 8 hour intervals, followed by 40 mg 24 hours later. The recommended maintenance dose for most deep mycoses is 0.4 to 0.5 mg/kg per day, infused over 2 to 4 hours. Adult doses of 10 to 15 mg/kg daily can be sufficient in Candida esophagitis. When used with flucytosine, the daily dose of Amp B is 0.3 mg/kg (Brajtburg et al., 1977& 1985).

The febrile reactions associated with the administration of Amp-B usually subside despite continued use of the drug and the concurrent use of hydrocortisone frequently can be stopped. Amp B may be administer every other day by doubling the recommended daily dose within sacrifice of therapeutic efficacy. The individual dose should not exceed 7 mg in the alternate day regimen, even if the daily dose was greater than 35 mg. There is a greater chance for toxicity and no proof of addition efficacy above this dose. Although this schedule decreases the number of venipunctures and allows more ambulation, the incidence of nephrotoxicity is not reduced and the severity of febrile reactions may increase (Lamy-Freund et al., 1985).
Intrathecal infusion of Amp B is necessary in patients with meningitis caused by Coccidioides. The drug can be injected into the CSP of the lumbar spine, cisterna magna or lateral cerebral ventricle Irrespective of site, the treatment is begun with 0.05 to 0.1 mg an, increased on a three times-a-week schedule to 0.5 mg, as tolerance permits. Therapy is then continued on a twice-a-week schedule. Fever and headache are common reactions and may be decreased by administration of 10 to 15 mg of hydrocortisone. Less common but more serious problems attend the use of intracheal injections; the nature of the problem depends on the injection site chosen. Local injections of Amp B into a joint or peritoneal dialysate fluid commonly produce irritation and pain. Intraocular injection following pars plana vitrectomy has been used successfully for fungal endophthalmitis, but retinal damage can occur (Bennett, 1990).

Untoward Effects of Amp-B Administration:

Intravenous administration of Amp B can cause a large number of adverse effects; the two most common are fever and azotemia. Fever and chills are most common at the beginning of therapy; they tend to subside later in the course. The reaction often begins an hour or two after start of the infusion and lasts 2 to 4 hours. Dyspnea and tachycardia may precede fever. Bronchospasm and true anaphylaxis are rare. The capacity of the drug to release interleukin -1 and tumor necrosis factor from human monocytes and murine macrophages in vitro suggests a mechanism for pyrogenicity. Although administration of Amp B following leukocyte transfusion was, at one time, thought to cause pulmonary infiltrates and hypoxemia, this observation has not been
confirmed. Amp B can, however, cause leukocyte aggregation in vitro, an action that could lead to trapping of leukocytes in the pulmonary capillary bed if it occurred in vivo (Berliner et al., 1985; Cutaia et al., 1993).

Azotemia occurs in 80% of patients who receive Amp B for deep mycoses. Toxicity is dose-dependent, transient and increased by concomitant therapy with other nephrotoxic agents such as aminoglycosides or cyclosporine (Kennedy et al., 1983). Although permanent histologic damage to renal tubules occurs even during short courses, permanent functional defects are uncommon in patients whose renal function was normal prior to treatment unless a total dose in excess of 3 to 4 g is given (to an adult). Renal tubular acidosis and renal wasting of K+ and Mg²⁺ may also be seen during and for several weeks after therapy. Supplemental K+ is required in a third of patients on prolonged therapy. An increase in intrarenal vascular resistance is the major cause of nephrotoxicity in Amp B treated rats (Tolins an Rail, 1988). In patients and experimental animals, loading with sodium chloride has decreased nephrotoxicity, even in the absence of water or salt deprivation. Administration of one liter of saline intravenously on the day that Amp B is to be given has been recommended for adults who are able to tolerate the Na+ load and who are not already receiving that amount in intravenous fluids (Branch, 1988).

Hypochromic, normocytic anemia is usual; the average hematocrit declined to 27% in one study. Decreased production of erythropoietin is the probable mechanism. Anemia reverses slowly following therapy. Headache, nausea, vomiting, malaise, weight loss
and phlebitis at peripheral infusion sites are common side effects. Thrombocytopenia or mild leukopenia is observed rarely.

In cell systems, the most important known mechanisms of Amp-B toxicity are an increase in cell membrane permeability to small ions or oxidant-induced membrane damage or both (Brajtburg et al., 1985; Bolard, 1986). The fact that this agent produces an increase in membrane permeability and ultimately cell lysis. Possibly related to oxidant-induced membrane damage - suggests that it might be a useful model for the study of cell injury (Cutaia et al., 1993).

**Therapeutic Uses of Amp-B:**

Intravenous administration of Amp B is the treatment of choice for mucormycosis, invasive aspergillosis, extracutaneous sporotrichosis and cryptococcosis. Although imidazoles or triazoles are useful in many patients with blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis, Amp B is preferred when these mycoses are rapidly progressive, occur in an immunosuppressed host or involve the central nervous system. Amp B can also be useful in selected patients with profound neutropenia and fever that is unresponsive to broad spectrum antibacterial agents. Amp B given once weekly has been used to prevent relapse in patients with acquired immunodeficiency syndrome (AIDS) who have been treated successfully for cryptococcosis or histoplasmosis. Topical Amp B is useful only in cutaneous candidacies. Oral tablets are commercially available in Europe for decreasing colonization of the intestine by Candida.
Review of Literature:

It is hypothesized Amp B and its side-effects (e.g. nephrotoxicity and hemolytic action) are suggested to be associated with its prooxidant effects in target cells (Osaka et al., 1977). The same authors have showed that Amp B does not produce any prooxidant effects but rather acts as an intercellular anti-oxidant. The experiments of Mullen et al., (1997) showed that the efficacy of Amp B as anti parasitic agent is associated with its degree of aggregation in the presence of serum, ESA treatment was reported as successful against deep candida infection but during treatment, a rise in serum creatinine, hypokalemia and metabolic acidosis B like side effects are known to occur (Beovic et al., 1997). Mernar and Mieles (1997) stated that enhancement of nitric oxide synthesis by macrophages represents an additional mechanism of action of this agent.

Cleary et al., (1993) have observed cardiac complications in five pediatric patients who received between 4.6 and 40.8 mg/kg/d of Amp B. Cardiac arrest occurred in all patients and four patients died. The same authors concluded that Amp B over dose can be fatal in children and infants. The presentation in humans appears similar to that in dogs; where cardiac arrhythmias occurred at doses of 5-15 mg/kg. The authors Cleary et al., (1993) are of the view that animal studies are necessary for understanding of Amp B toxic effects.

Cutaia et al., (1993) have demonstrated that Amp-B directly injurious endothelial cells in a dose and time defendant manner and they further demonstrated the importance of the Na/K ATPase for the

Sivak et al., (2004) by way of studying the dose related effects of AmpB on rat serum creatinine and aspartate aminotransferase levels have reported this agent as to cause renal and hepatic toxicity. Francois et al., (2006) in their summation article regarding azoles toxicity have cited that these agents induce Ros production and this probably is caused by inhibition of the enzymes implicated in breakdown of peroxide radicals and hydrogen peroxide, ie peroxidase and catalase. Vanessa et al., (2005) reported that exposure of candida albicans to antifungal agents affects expression of SAP2 and SAP9 secreted proteinase genes. Edundo (2001) stated that AmpB continues to be the treatment of choice in many severe disseminated mycosis cases but problems with toxicity. In contrary to the above Mehta et al., (1984) reported that Amp-B is toxic to fungal cells but not to mammalian cells.

Tolerance of Amphotericin-B is limited by its acute and chronic toxicities. In addition to fungal ergosterol the drug also interact with
cholestrol in human cell membranes. Which likely accountes for its toxicity Depauw et al., (2000). Up to 80% of patients receiving AmpB develop either in fusion –related toxicity or Nephrotoxicity Gallis et al., (1990) especially with concomuant therapy with nephrotoxicity drugs such as aminoglycosidase, vancomycin, cyclosporins or tacrolimus Paterson et al., (1997). Finquelievich et al., (2000) and Walsh et al., (1998). Renal function usually returns to normal after cessation of Amphotericin-B although permanent renal impairment is common after larger doses 65 Kullberg et al.,(1999), Risk factor associated with AmpB related nephrotoxcity include a total dose of > 4g, sodium depletion age > 30 years and concomitant therapy with nephrotoxicity drug Walsh et al.,(1998). Sodium supplementation has decreased nephrotoxicity and it has been recommended to infuse 500ml of 0.9% saline before admenstration of AmpB Kelly et al., (1994) and Levy (1990).

Takemoto et al., (2003); Sorkine et al., (1996); Van Etten et al., (2000); Heidermann et al., (1992); Sanchez-brunete et al., (2004); Bartlett et al., (2004) summarize the mode of action of AmpB and possible toxic side effects in laboratory clinical based experiments. Recently from our laboratory we have demonstrated that AmpB at doses of 1.0 or 1.5 mg/kg impairs the after all nitric oxide pathway parameters and induce the production of NO (Poornima 2002) excepting to these to the best knowledge of the author there is little or no experimental basis that supports how Amp-B interacts with the basic metabolism of experimental animals to bridge this gap, the author attempted to study the invivo effects of certain doses of Amp-B as selected metabolic parameters of the rat tissues and the work submitted forms the Ph.D. thesis part of the author.