In the Literature

**Mechanism of Action of Amphotericin B: Another Dogma Falls**


It has long been generally accepted that amphotericin B kills yeast by the formation of ion channels that result in permeabilization of the fungal cell membrane. The initial interaction of amphotericin with the membrane requires its preferential binding to ergosterol, the predominant membrane sterol of fungi and plants. The C19 mycosamine structure of amphotericin B is necessary for its ability to bind ergosterol. Its elimination results in a derivative molecule that is unable to bind this sterol, fails to form ion channels, and has no antifungal activity. For Gray and colleagues, this suggested either that ergosterol binding is a necessary first step leading to downstream fungistatic/fungicidal events or that such downstream events, including ion channel formation, are secondary and that ergosterol binding by itself is the critical mechanism causing antifungal activity. Consistent with the latter construct is the finding that the polyene antifungal natamycin binds ergosterol and has antifungal activity despite an inability to form ion channels.

The investigators probed these hypotheses by developing a derivative of amphotericin B that bound to ergosterol but was unable to form ion channels. The derivative retained the C19 mycosamine and lacked a hydroxyl group at C35, while retaining the anionic carboxylate group at C41. The former is necessary for ion channel formation, while the latter appears to be necessary for the ion channel activity of the C35 hydroxyl group. This derivative molecule, like natamycin, binds ergosterol but does not form ion channels. It nonetheless retains potent fungicidal activity against Saccharomyces cerevisiae in a standard broth microdilution assay.

Ergosterol has been demonstrated to be necessary for a number of critical functions in yeast cell physiology, such as vacuole fusion, endocytosis, and endocytosis. Decreased expression or structural modification of ergosterol markedly reduces fungal virulence. The investigation summarized here demonstrates that the critical element in the killing of yeast by amphotericin B is its binding to ergosterol and that membrane permeabilization by ion channel formation is a secondary phenomenon that, nonetheless, adds to the potency of amphotericin B.

As the investigators point out, improved understanding of the mechanism of action of this important antimycotic agent, which has retained its potency against pathogenic fungi despite a half century of use, has the potential to lead to enhanced versions of the molecule. Improving the therapeutic-toxic ratio of this drug would represent an important clinical advance.

**Treatment of Infections Due to Methicillin-Susceptible Staphylococcus aureus (MSSA): Cephalosporins Versus Semisynthetic Penicillins**


Cephalosporins are commonly used in the treatment of infections due to methicillin-susceptible Staphylococcus aureus (MSSA). Approximately 90% of MSSA produce β-lactamase, of which 4 types, A–D, vary both in substrate profile and in the amounts that are produced. One of these, type A, sufficiently hydrolyzes cefazolin when the enzyme is present in a high concentration to result in an increased minimal inhibitory concentration (MIC) for S. aureus. A subset of type A β-lactamase–producing MSSA strains, which seem to be hyperproducing strains, may, when present in high inocula, have MICs as high as 128 μg/mL [1].

This phenomenon has been implicated as a potential cause of the failure of cefazolin in the treatment of high-inoculum infections, particularly endocarditis, in which the bacterial density in vegetations may reach 10^10 colony-forming units per gram. Overall, approximately 20% of MSSA isolates are reported to have cefazolin MICs ≥16 μg/mL when tested at a high inoculum [1]. Observations such as these have led some to recommend the preferential use of a semisynthetic penicillin (SSP) rather than cefazolin or other cephalosporins for the treatment of MSSA infection.

Lee and colleagues at the Seoul National University College of Medicine have examined the postulated superiority of SSP therapy over cefazolin therapy in a retrospective, propensity score-matched, case-control study. The study was facilitated by the unavailability of nafcillin at their institution over a 2-year...
period, during which cefazolin was used to treat MSSA infections. There were 40 patients in each treatment group. By use of a composite definition of treatment failure that included clinical failure, relapse, and mortality, no significant difference in outcomes was found at either 4 weeks (10% vs 10%) or 12 weeks (15% vs 15%). Drug-related adverse events resulting in interruption of therapy, however, occurred more frequently in nafcillin recipients (17%) than in cefazolin recipients (0%). The reasons for interruption of nafcillin therapy included drug-induced fever in 4, cytopenia in 2, and phlebitis in one.

A retrospective study of 267 patients with MSSA bacteremia confirmed the previously observed superiority of β-lactam therapy, with either nafcillin or cefazolin, over vancomycin therapy, although statistical significance was only achieved with the cephalosporin [2]. Thus, the hazard ratio for mortality, relative to vancomycin therapy, was 0.45 (95% confidence interval [CI], .18–1.15) for nafcillin therapy and 0.25 (95% CI, .09–.66) for cefazolin therapy.

These findings also raise a question regarding the relative efficacy of cephalosporins other than cefazolin in the treatment of serious MSSA infection, with ceftriaxone being of particular interest given the convenience of its use, particularly in the outpatient setting. A recent retrospective review of 541 patients with MSSA bacteremia in whom β-lactam therapy was initiated within 48 hours after blood was drawn for culture found that administration of cloxacillin or cefazolin was associated with significantly lower 30-day mortality, compared with ceftriaxone or cefotaxime or with β-lactam/β-lactamase inhibitors [3]. In analyzing only definitive therapy in the 498 patients still alive after 7 days, there was, however, no statistically significant difference in 90-day mortality between patients treated with cloxacillin and those treated with cefazolin or between patients treated with cloxacillin and those treated with other β-lactam antibiotics.

If, as suggested by these retrospectively collected data, ceftriaxone therapy is inferior to SSP therapy or cefazolin therapy, it does not appear to be the result of reduced in vitro activity at high organism inocula, since Nannini and colleagues found no such effect in 98 MSSA isolates, 25 of which produced type A β-lactamase [4]. While there is a large amount of clinical experience with use of ceftriaxone therapy for MSSA infection in the outpatient setting, little of it has been published. Recently, however, Wieland and colleagues reviewed their experience with 124 patients with osteoarticular infections due to MSSA and found no difference in treatment success between ceftriaxone and oxacillin [5]. It was, however, less necessary to discontinue ceftriaxone therapy because of toxicity, which occurred in only 3 of 74 patients (4%), compared with 9 of 50 patients (18%) who received oxacillin (P = .01).

In the absence of prospective randomized trials, it may not be possible to reach definitive conclusions regarding the efficacy of cefazolin and other cephalosporins, relative to that of SSP, in the treatment of MSSA infections. However, it appears that cefazolin has at least similar efficacy and is better tolerated but that caution may be considered in the initial therapy of patients with endocarditis because of the high inoculum often present in valvular vegetation. Unless contradictory data become available, it may be best to treat MSSA endocarditis with an SSP until the inoculum has been reduced, after which cefazolin may be used. Ceftriaxone would also appear to be effective as definitive therapy of bacteremia and osteoarticular infections and provides the convenience of once-daily infusion. Once-daily administration of cefazolin together with probenecid, which has been used in the treatment of cellulitis, also offers convenience [6]. In addition to issues of convenience (and of cost—nafcillin is significantly more expensive than either cephalosporin), treatment with cephalosporins is associated with significantly fewer adverse reactions and thus provides some advantages over SSP therapy in many circumstances.

References