Appendix B – Reference Letters

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October 8, 1999

Judit Nyirady, M.D.
Director
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Dear Dr. Nyirady,

You have asked for my comments on the risk of azole-resistance development that might result in fungi from the topical use of miconazole nitrate for the treatment of *Candida*-associated diaper dermatitis.

Decades of experience with the use of antimicrobial compounds teach us that resistance to any agent is almost certain to emerge when that agent comes into routine clinical, agricultural or other use. The important issue is really one of statistics: how fast will resistance emerge and how much of a problem will it be?

The most important factors that govern emergence of resistance to antimicrobial agents are frequency of exposure, level of exposure, growth rate of the microbe concerned, and time. Fungi such as *C. albicans* grow more slowly than most bacteria, for example, so it should take longer for resistance to an antifungal agent to emerge than for antibacterial resistance. Treatment courses with an agent such as topical miconazole tend to be relatively short, and do not need to be repeated in most cases. Therefore frequency, level and duration of exposure are low. All this would predict that resistance to miconazole should appear only slowly in the course of a long period of time.

Topical antifungal treatment in diaper dermatitis further confines the exposure of fungus to drug to a single, external site, which is not the principal location for *C. albicans* in the body (the digestive tract from mouth to anus is the main reservoir for *Candida* species). This again suggests that the pressure for resistance development at the level of the whole commensal microflora is low: indeed the fungi exposed externally to the agent would need to re-colonize the digestive tract by ascending spread of the bowel to produce a reservoir of resistant organisms. This is not a likely scenario.

An additional situation that favors resistance development among many organisms is the possibility of host-to-host transmission of resistant strains. With an organism such as *Staphylococcus aureus* shed into the air in a hospital the chances of spreading resistant strains is high: with *C. albicans* at a diaper site the chance of host-to-host spread is much lower.

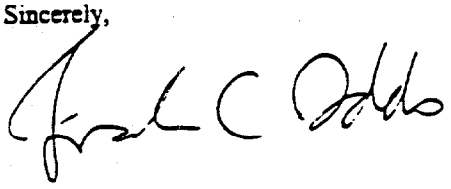
In my opinion, therefore, one would not expect to see resistance to miconazole emerge either rapidly or with high frequency if it is used topically to treat *Candida*-associated diaper dermatitis.

The only way to monitor adequately for general resistance development to an antifungal agent is to perform *very* large-scale prospective studies, or to do repeated (every two years or so) cross-sectional studies in a fixed group of clinics with a wide geographical distribution. In the case of miconazole usage in all indications, we are really far too late to detect changes. We needed baseline surveys (and maybe frozen cultures of *Candida* isolates) from around 1970. By now, we may have already reached a sort of equilibrium where the limitation of person-to-person spread means those few strains that might have developed resistance remain with a single patient rather than becoming a community threat.

I have done a rapid survey of my database of MIC values for miconazole against *C. albicans*, built up since 1994 and involving mostly isolates from Belgium. There is no official breakpoint for resistance to miconazole from the NCCLS or any other organization, but on the basis of long experience I would choose a value of 2 µg/ml or higher as almost certainly indicating resistance. Of 693 MIC test results in my database, 21 (3%) were at this level of "non-susceptibility". Just 11 (1.6%) results were at the unequivocally resistant level of 16 µg/ml or higher. This prevalence is far lower than the usual rate of clinical failure in trials of topical miconazole for the treatment of vaginitis, suggesting that strains with overt resistance to the agent are a very minor clinical problem. I regret I do not have any *C. albicans* isolates from cases of dermatitis, and therefore no statistics directly related to the indication that concerns you.

One final comment. Miconazole is one of very many antifungal agents of the azole class. Antifungal azoles are all inhibitors of the enzyme 14α-demethylase in fungi. These compounds have not only been used extensively in human medicine: members of the same chemical class are also sprayed regularly and on a huge scale as plant fungicides. It therefore seems inevitable that humans are often exposed at least to small quantities of azole antifungals through the food chain, which might represent another environmental pressure towards resistance development. Yet the only known circumstances in which resistance to azole antifungal agents has developed conspicuously, unequivocally and measurably is among HIV-infected individuals treated with fluconazole for oral *Candida* infections. I regard the topical treatment of diaper dermatitis with miconazole nitrate as a trivial setting in terms of the potential for development of antifungal resistance.

Sincerely,



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Judit Nyirady, M.D.
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20 September 1999

Dear Dr. Nyirady:

Per our recent phone discussion, I am happy to provide my thoughts regarding resistance and azole antimycotic agents; more specifically to your concerns, resistance development to the imidazole drug miconazole nitrate by Candida albicans when this antifungal is employed to treat diaper dermatitis caused by this species.

In discussing such resistance issues as regards azole antimycotics, the first concept to carefully define is what is meant by "resistance" - does one mean true microbiologic resistance in which the fungus is genetically resistant (either innately or via acquired means) to the antifungal in question, or does one mean "clinical resistance" in which a patient does not respond to a particular antifungal drug when employed at a dose and duration which is supposedly appropriate for the mycosis being treated. In almost every instance, resistance problems with antifungal drugs have been "clinical resistance"; microbiologic resistance, with some signficant exceptions, has been rare.

As relates to azole antimycotics, the most signficant resistance difficulties, both microbiologic and clinical have been with one fungus, one disease, one drug, and in one patient population - namely, C. albicans, oral-pharyngeal candidiasis, fluconazole, and HIV+ patients. In this instance, there is little doubt of both true genetic resistance and clinical resistance to fluconazole. The recent and current literature is replete with papers dealing with this topic. Even in this scenario, however, genuine microbiologic resistance represents a very small part of the resistance issue as contrasted to clinical resistance perhaps represented by using too low a dose of fluconazole.

To be certain, there are some species of yeast genera which are innately resistant to fluconazole, e.g., C. krusei (virtually all clinical isolates) and C. glabrata (many clinical isolates). From time-to-time, other species of Candida and other yeast species, are reported to demonstrate resistance to fluconazole, but on the whole, this is very uncommon. The above findings almost always result in the question of azole cross-resistance as well. That is, if a certain strain of C. albicans or C. krusei were resistant to fluconazole, is there cross resistance with other azole antimycotics as well? The answer is clearly yes, there is cross-resistance between azoles, but whether the resistance patterns (translated to higher minimum inhibitory concentrations = MIC) are clinically relevant is another matter. For example, a certain clinical isolate of C. albicans may have a pre-treatment MIC of 2 µg/ml to fluconazole and 0.2 µg/ml to miconazole, ketoconazole, or itraconazole. Following therapy with fluconazole, most likely at too low a dose, the patient develops worsening disease, and a post-therapy isolate demonstrates an MIC of 64 µg/ml (clearly resistant to fluconazole), and an MIC

of 2 µg/ml to miconazole, ketoconazole or itraconazole. There is little doubt that the MICs with miconazole, ketoconazole or itraconazole have increased, however, the amount of each of these agents achieveable in human biologic fluids or tissues still exceeds the MIC by a considerable amount. Hence, there is cross-resistance between fluconazole and the other azoles, but the resistance is probably of little consequence clinically. In fact, the Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards have developed "breakpoints" for interpretation of such MICs. In the above scenario, fluconazole would be called resistant, while the MICs generated for miconazole, ketoconazole, or itraconazole would be interpreted as a new term, "susceptible, dose-dependent or SDD. This new term indicates that the clinician should employ higher doses of the azole in order for optimal therapy to occur.

With the above in mind, the following can be discussed as relates to your particular concern of miconazole employed to treat diaper rash. As far as C. albicans and miconazole, resistance has generally been a non-issue. Some reports in the early literature involved resistance to miconazole by isolates of C. albicans from patients with chronic mucocutaneous candidiasis. These isolates were well-characterized at the time, but these aside few other reports demonstrated any resistance issues with yeasts of any species and miconazole. Over its decades of clinical use, both via prescription only and later across the counter, resistance of yeast-fungi to miconazole has not surfaced (nor has resistance surfaced as an issue with miconazole treatment of dermatophytosis). Even in the HIV+ patient with recurrent oral candidiasis, resistance to miconazole has not been perceived as the considerable clinical resistance problem as occurred with fluconazole. To my knowledge there have been virtually no resistance issues - either microbiologic or clinical - with miconazole when used to treat diaper rash.

Here at the Fungus Testing Lab, in reviewing the records of miconazole susceptibility testing against C. albicans obtained from diaper rash patients, over the last 15 years, none were judged in vitro as demonstrating resistance (from all C. albicans isolates tested from all clinical sources, 83% were judged susceptible to miconazole - if the new NCCLS breakpoint definitions are employed, the percentage is higher). As with the dermatophytic fungi and dermatophytosis, despite the long number of years of therapy with miconazole, ketoconazole, or itraconazole, resistance to these azoles has not developed as a clinical problem in candidal diaper dermatitis. I suspect a literature review would support this view as well.

In summary, based on past and contemporary findings, both in vitro and in vivo, it seems unlikely that deveopment of resistance to miconazole by clinical isolates of C. albicans causing diaper dermatitis is or will become a significant factor in clinical practice.

I am at your service to discuss this issue with you, your company colleagues, or any agency with which you may have interaction. All best wishes. I am

Sincerely yours,

Michael G. Rinaldi

MGR:mc

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