

## Pathology of Infectious Diseases and Oncology 2019: The Azole Menace: The dark side of azoles revealed - Sidharth Sonthalia - The Skin Clinic and Research Centre

**Sidharth Sonthalia**

The Skin Clinic and Research Centre, India

**Background:** The Epidemic of antifungal therapeutic failures against superficial mycotic infections, especially dermatophytosis is expanding at a rapid pace across South Asia and beyond. Although the abuse of topical steroids, inadequate dose/duration of therapy, and ignorance of other important epidemiological and personal factors are contributory, perhaps the strongest reason is the AZOLE MENACE, relatively unknown and ill-understood phenomenon. In this lecture, I shall dwell upon objectively on how the indiscriminate use of azoles, in particular, oral itraconazole is responsible for this regional epidemic that is threatening to become a pandemic lest urgent rectification is undertaken.

**Unknown Facts Revealed:** In this lecture some of the many azole-related issues will be revealed with evidence-backed data. Patients with tinea visiting a dermatologist are not naive, rather polypharmacy-abused in more than 90% cases, having received multiple antifungals especially oral itraconazole/ topical azoles. Oral itraconazole is often injudiciously prescribed by primary care physicians in an inadequate dose/ duration or as multiple intermittent/ prolonged courses. The new report uncovered that 18 microorganisms cause right around 3 million anti-infection safe diseases and 35,000 passing's every year. For the primary time, this report includes several antibiotic resistant fungi: organisms: *Candida Auris*, other medication safe *Candida* (as in my patient above) and azole-safe *Aspergillus fumigatus*. These safe growths are particularly compromising on the grounds that solitary three classes of antifungal medications are as of now accessible. Fungi incorporate yeasts, which develop as circular cells; and molds, which develop as stretched, rounded cells. Both yeasts and molds are more closely related genetically to humans than they are to bacteria.

Therefore, it is hard to develop antibiotics that attack fungi without damaging human cells. The bioavailability/ serum levels of itraconazole are influenced by at least 15+ inconsistent factors Around 54.3% Indians above the age of 45 years are on antacid medications like PPI's, resulting in reduced bioavailability of itraconazole when co-administered. The effects of longer acting PPI's like esomeprazole may persist up to 4-5 days. Dependent on intake post meals and the effect of aerated drinks. Serum levels affected by drug brand and pellet size. The sub-inhibitory concentrations of itraconazole achieved in patient's serum significantly increase the likelihood of secondary azole resistance by selection pressure, since azoles being fungistatic allow persistence of organisms. The selection pressure-induced secondary resistance resulting from oral

itraconazole is also seen to perpetuate pan-triazole and partial terbinafine and amorolfine resistance. Ciclopirox olamine is the only drug without a propensity to develop resistance. Itraconazole-resistant strains show high levels of cross resistance to multiple triazoles including voriconazole and Posaconazole, and often to six triazole fungicides used extensively in agriculture, qualifying for multi-triazole resistance). Azole-resistant fungi are more virulent because of the differences in cell wall composition, increased filamentation and adherence, and enhanced biofilm formation. Once acquired, resistance is maintained even in the absence of drug. Primary azole resistance due to their widespread use as agricultural fungicides, further adds to the azole menace.

This phenomenon, which started from the Netherlands and rapidly engulfed majority of the European Union, has now reached the shores of the Indian Ocean. As per the statistics available from the website of Indian Ministry of Agriculture, in the 4-year period from 2012 to 2016, there was an estimated 29.5% decrease and 34.2% increase in the consumption of insecticides and fungicides, respectively. The spreading azole resistance in superficial fungal infections resulting in selection of a population of mutants that do not respond to any drug is likely to have graver ramifications in invasive dermatophytosis in immunocompromised individuals.

### Practical Guidelines to contain and reverse the epidemic:

Majority of patients with complicated tinea (recurrent/ relapsed/recalcitrant/chronic) who visit dermatologists have already taken multiple/prolonged courses of oral itraconazole, rendering them resistant to any further course of itraconazole; thus, they should not be given oral itraconazole. Resistance to terbinafine on the other hand, acquired through a rare mechanism, is infrequent, shows restoration of susceptibility after drug removal and has not been reported to confer cross-resistance to other antifungal agents. The dosing of oral TERBINAFINE should be as per body weight, 6mg/kg/day and it should be given for a duration of 8 (minimum) to 12 weeks (preferred), taking into consideration the dermatophytic involvement of vellus hair. For topical application, NO AZOLES should be used. Only three anti-fungal seem fit for topical use in current scenario – CICLOPIROX > TERBINAFINE > AMOROLFINE. Non-pharmaceutical means, such as low-dose UV-B therapy, LLLT, apple cider vinegar and other herbal substances capable of breaking the BIOFILM should be used as adjuvants.