

OPTIMIZATION OF A GUINEA PIG MODEL TO EVALUATE ANTIFUNGAL DRUGS AGAINST ASPERGILLUS INFECTIONS

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Immunosuppressed guinea pigs have been used as models for evaluating the efficacy of itraconazole against *Aspergillus fumigatus*, but little has actually been reported on the relationship of immunosuppression and *A. fumigatus* burden. In an effort to better understand this relationship, leukocyte counts in *A. fumigatus*-infected guinea pigs were assessed using several immunosuppressive regimens and *A. fumigatus* kidney burdens were assessed using a novel quantitative PCR (qPCR) method. Results showed that a loading dose of 300 ug/kg of cyclophosphamide administered one day prior to *A. fumigatus* challenge (3.8×10^3 colony forming units/animal) did not suppress the leukocyte count by the time of infection; subsequent maintenance doses of cyclophosphamide combined with either triamcinolone or prednisolone did lead to lower leukocyte counts by day 4 post infection (p.i.), but qPCR analysis indicated minimal *A. fumigatus* colonization up to 7 days p.i. Conversely, a protocol in which 300 ug/kg of cyclophosphamide was given only once 3 days prior to challenge resulted in leukopenia at time of challenge and a modest *A. fumigatus* burden by day 4 p.i., but both were reversed in animals evaluated at day 8 p.i. The protocol which allowed the best establishment of *A. fumigatus* infection in the kidneys employed a 300 ug/kg dose of cyclophosphamide 3 days prior to challenge, such that leukocytes were suppressed at challenge, and maintenance doses of 50 ug/kg once or twice more were given throughout the week of observation to maintain suppression. All animals received ceftazidime daily after challenge to protect from bacterial infections. Consequently, optimization of the cyclophosphamide regimen to maintain suppression of leukocytes at challenge and throughout the observation period provided for greater establishment of *A. fumigatus* kidney colonization. This regimen of immunosuppression provides a useful model for studying the effect of itraconazole, alone and in combination with other antifungal agents, on *A. fumigatus* burden in guinea pigs.