In general, immunocompetent individuals resist infections by most fungi.

- infections which do occur in immunocompetent individuals tend to be mild, follow a predictable course and are self-limited.

Depending on the form of immunodeficiency, immunodeficient individuals may be at no increased risk of infection or may develop severe localized or disseminated infections.

- increased risk of severe fungal infection is associated with neutropenia, defects in neutrophil function or defects in cell-mediated immunity.
- infections in immunocompromised individuals follow an unpredictable course in which any or all tissues may be affected.

Specific immune responses induced by fungal infections:
1. anti-fungal antibody
2. fungus-specific T cells (both CD4+ and CD8+)

Effective immune response to fungal infections in most cases are:

1. acute inflammatory response (control of initial infection by neutrophil killing)

2. activated macrophages which restrict intracellular growth of phagocytized fungi.

NOTE: In most cases, antibody response against fungal infections has little or no effect on elimination of the organism.

* There is a dose effect, however

Neutrophils: * has little effect on fungal replication

Defect in Th1 & Th2 (normal role Th1 activate MDC and Th2 activate MDC)

* High DTH has better prognosis, be more important than fungal infection.
Generalized sequence of immune response against pulmonary fungal infections.

(Model for pulmonary infections by Cryptococcus neoformans, Histoplasma capsulatum
and Coccidioides immitis.) → Systemic

1. Alveolar macrophages ingest some of the inhaled conidia, but do not kill effectively. Fungal growth proceeds.

2. Invasion of interstitial tissue ensues. Alternative pathway of complement is activated, which leads to C3b deposition on the fungi. Opsonization leads to enhanced phagocytosis by alveolar and tissue macrophages. Killing still ineffective, so growth proceeds.

3. Complement components and tissue damage induce acute inflammatory response and influx of neutrophils. Yeast forms phagocytized and killed more effectively. Hyphae forms incompletely phagocytized, leading to release of hydrolytic enzymes and additional tissue damage. Infection becomes stationary.

4. Specific immune response develops: both antibody and cellular immunity.

5. Antibody allows for neutrophil opsonization against both yeast and hyphae forms.

6. Th1 cells release IFNγ, leading to macrophage activation. Killing most effective and may lead to sterile or nonsterile immunity. Sterile: complete elimination Nonsterile: walled off, but not totally clear → granuloma

7. Granulomas may develop to wall off the fungi.
Coccidioides immitis:

Infections are usually asymptomatic in healthy, immunocompetent individuals.

- 60% of infections are asymptomatic
- 40% have flu-like symptoms
  - 5 - 10% develop granulomas in the lungs
  - <1% develop disseminated disease

Immune response during infections by Coccidioides:

- >90% of infected individuals develop specific antibody. (demonstrate w/ skin test)
- most infected individuals develop cutaneous hypersensitivity to fungal antigens
  - strong DTH reactions in asymptomatic infections
  - weak DTH reactions during active pulmonary infections
  - no DTH (anergy) during disseminated infections

NOTE: skin test negative in individuals most likely to have severe disease

- antibody responses: disseminated > pulmonary > asymptomatic cases
  (sometimes see elevated IgE in disseminated infections)

- infection pattern suggests that strong Th1 response leads to recovery
  and that a strong Th2 response may lead to uncontrolled infections.

![Diagram showing relative immune response with cellular and Ab (High) peaks](image)