Cutaneous Fungal Infections (Excluding Onychomycosis)

Ted Rosen, MD
Professor of Dermatology
Baylor College of Medicine
Houston, Texas
Cutaneous Fungal Infection

• Please be patient with me.....there is a lot to cover
• I promise we will be done before you are mummified
Fungi

• Kingdom Eumycota (1969)

• Four Phyla
  Chytridiomycota (chytrids)
  Zygomycota (bread moulds)
  Basidiomycota (mushrooms)
  Ascomycota (yeast and sac)

• Candida and Dermatophytes are classified as ascomycetes
Fungi

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• Candida and Dermatophytes are classified as **ascomycetes**
Fungi: Unique Organisms

- Reproductive mechanisms
- Dimorphic growth
- Nutritional requirements
- Cell wall containing chitin
- Cell membrane rich in ergosterol
- Size (larger than virus/bacteria)
- No photosynthesis
- No response to antibiotics
Fungi: Unique Organisms Therapeutic Targets

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Antifungal Therapy

**Azoles:** Cell membrane
Lanosterol demethylase

**Allylamines:** Cell membrane
Squalene epoxidase

**Candins:** Cell wall
Glucan synthase complex
Fungal Infections Are Important

- Over 600 species of fungi routinely cause human infection, varying from trivial and common to potentially fatal
- As many people die from fungal infection yearly as from TB or malaria
- Modern medical interventions increase risk of serious fungal infection
- Needs: rapid diagnostics, more drugs and ? vaccines for endemic mycoses
- US ID research funding: 2% on mycoses

Science 336:647, 2012
Fungal Disease

• Superficial
• Deep
Fungal Disease

- Superficial (skin, hair & nails)
  - Dermatophytosis
  - Tinea versicolor
  - Some Candidiasis

All may be treated topically EXCEPT tinea capitis, which requires systemic therapy, and onychomycosis, where systemic therapy is much better than topical therapy, at present.
Fungal Disease

- Deep (structures beneath skin or visceral organs)
- N. and S. American Blastomycosis
- Coccidioidomycosis
- Cryptococcosis
- Histoplasmosis
- Some Candidiasis
- Rarely: zygomycetes and others

All are treated with systemic medications
Fungi are ubiquitous!
Fungal Disease: Pathogenesis

- Colonization
- Defense Mechanisms
Fungal Disease

- **COLONIZATION**
- Ecologic changes
- Ambient factors
- Inoculum size/frequency
- Host status
Fungal Disease

- **DEFENSE MECHANISMS**
- Keratinase inhibitor
- Complement activation
- Humoral (IgG, IgM, IgE)
- Cell-mediated (Th1)
- Unsaturated transferrin
- Epidermal desquamation
Fungal Disease

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Most important: Defects hereditary or acquired
Autosomal Dominant Trait

Acute disease management
Recurrence prevention

JEADV 19(S1):17, 2005
Genetic predictors of susceptibility to cutaneous fungal infections: A pilot genome wide association study to refine a candidate gene search

Susan M. Abdel-Rahman a,b,*, Barry L. Preuett a

a Division of Pediatric Clinical Pharmacology and Medical Toxicology, The Children’s Mercy Hospital and Clinics, Kansas City, MO, USA
b Department of Pediatrics, University of Missouri-Kansas City, School of Medicine, Kansas City, MO, USA

A R T I C L E  I N F O

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A B S T R A C T

Background: Trichophyton tonsurans is the foremost fungal pathogen of minority children in the U.S. Despite overwhelming infection rates, it does not appear that this fungus infects children in a non-specific manner.
Objective: This study was designed to identify genes that may predispose or protect a child from T. tonsurans infection.
Methods: Children participating in an earlier longitudinal study wherein infection rates could be reliably determined were eligible for inclusion. DNA from a subset (n = 40) of these children at the population extremes underwent whole genome genotyping (WGG). Allele frequencies between cases and controls were examined and significant SNPs were used to develop a candidate gene list for which the remainder of the cohort (n = 115) were genotyped. Cumulative infection rate was examined by genotype and the ability of selected genotypes to predict the likelihood of infection explored by multivariable analysis.
Results: 23 genes with a putative mechanistic role in cutaneous infection were selected for evaluation. Of these, 21 demonstrated significant differences in infection rate between genotypes. A risk index assigned to genotypes in the 21 genes accounted for over 60% of the variability observed in infection rate (adjusted $r^2 = 0.665$, $p < 0.001$). Among these, 8 appeared to account for the majority of variability that was observed ($r^2 = 0.603$, $p < 0.001$). These included genes involved in: leukocyte activation and migration, extracellular matrix integrity and remodeling, epidermal maintenance and wound repair, and cutaneous permeability.
Dermatophytosis

- 37 species in 3 genera
- Dermatophytosis = Tinea
- Considerable morbidity
- Anthropophilic (human)
- Zoophilic (animal)
- Geophilic (soil)
Dermatophytosis

- **Tinea capitis**  Scalp
- **Tinea corporis**  Body
- **Tinea cruris**  Groin
- **Tinea manum**  Hands
- **Tinea pedis**  Feet
- **Tinea unguium**  Nails
  *(Onychomycosis)*
Tinea Capitis

- **Scope of the problem**
- Major metropolitan areas
- 5% of all children grades K-3
- 14% ASx carriers (+culture)
- Given one index case, in 50% of families, a second sibling affected (overt or carrier)

JEADV 21:1061, 2007
Tinea Capitis

• Pediatric disorder (rare adults)
• Alopecia + pruritus
• Role of fomites (hats, combs)
• Anthrophilic fungi
  “Grey patch” scaly areas
  “Black dot” broken hairs
• Zoophilic or geophilic fungi
  “Kerion” highly inflammatory
Tinea Capitis

- Black Dot
- Grey Patch
- Kerion
Tinea Capitis

- **Differential Diagnosis**
  - Seborrhea, psoriasis
  - Alopecia areata
  - Trichotillomania

- **Diagnosis**
  - Culture plucked hairs
  - Toothbrush or swab test
Tinea Capitis: Wood’s Lamp

- Hand-held UV
- Energy absorbed
- Re-emitted as green fluorescence
- Not very useful as typical species no longer do this
Tinea Pedis

- “Athlete’s foot”
- **Subtypes:** clinical and mycologic
  - Dry, scaly (moccasin)
  - Interdigital
  - Vesicular (blisters)
- **Adult disease; rare before puberty**
- Shoes aid colonization (hot, humid)
- **Clinical:** Scaly and itchy
Tinea Pedis

- Interdigital scaling and itching
- Most common variety
- Check nails!
Tinea Pedis

- Scaling and itching on ventral surface
- May encircle foot like a moccasin
- Check nails!
Tinea Pedis

- Blisters/itching, ventral surface
- Least common variety
- Check nails!
Tinea Pedis

• In all cases of tinea pedis (athlete’s foot) CHECK THE NAILS for fungal infection, as this may be the source (reservoir) for recurrent disease!
Tinea Manum

- Palmar equivalent to t. pedis
- Subtypes: clinical and mycologic
  - Dry, scaly
  - Vesicular (animal/dirt/plant)
- Adult disease; rare before puberty
- Almost always associated with foot disease
Vesicular Tinea Manum
Tinea Cruris

- “Crotch rot”
- Men > women
- Intensely itchy
- Annular scaly patches
- Spares scrotal skin (?why)
- Common mimic: erythrasma
  Corynebacterium disease
Tinea: Annular Lesions

- Relative central clearing
- Active, raised and scaly border
- Due to centrifugal spread of organisms
Tinea Cruris
Tinea Cruris
Erythrasma mimics tinea cruris
Erythrasma mimics tinea cruris
Coral red fluorescence

Viewed under Woods’s light
Tinea Corporis

• “Ringworm”
• Annular, scaly
• Sharp borders
• Solitary or multiple
• Localized or......
• Disseminated
Tinea Corporis

Active peripheral border

Relative central clearing
New kitten .......
Tinea corporis: Localized
Tinea Corporis: Extensive
Tinea Faciei

- Variant t. corporis
- Facial lesions
- Annular, red, scaly
- Almost always zoophilic fungi
- Kitten, puppy
- Treat patient
- Treat animal
Routine domestic pets.....
.....when in close proximity
Can cause Tinea Faciei!
Treatment

MY PET

MY DAUGHTER

MICROWAVE THE CAT
Animal Dermatophyte: Rx

Miconazole spray shampoo

Conofite cr/spray

Dermazole

Miconazole products
Should You Find Fungi?

- For every illness that is fungal, there are one or more almost exact clinical mimics
- Failing to seek fungi and then treating as fungal infection is, therefore, tantamount to mere guesswork
Fungal Infection: Diagnosis

- KOH prep
- Chlorazol Black Schwarz-Lampkin
- Calcofluor white
- Culture
- Tissue PAS stain
- Tissue biopsy
- (PCR)
Diagnosis

KOH

Culture
Tinea and Systemic Disease

- Cushing’s Disease
- Diabetes mellitus
- Leukemia/Lymphoma
- AIDS
Dermatophytosis: Rx

- Any topical azole QD-BID
  - Econazole, Ketoconazole, Oxiconazole, Sertaconazole, or Luliconazole

- Any topical allylamine QD-BID
  - Terbinafine, Naftifine, Butenafine

- Any topical hydroxypyridone
  - Cicloprirox olamine

- Widespread: Terbinafine 250mg/day
  - Itraconazole, Fluconazole off-label

- Tinea capitis: Terbinafine granules dosed by weight or Griseofulvin
Efficacy and safety of topical antifungals in the treatment of dermatomycosis: a systematic review

I. Rotta, A. Sanchez, P.R. Gonçalves, M.F. Otuki and C.J. Correr*

Pharmaceutical Sciences Postgraduate Program, and *Department of Pharmacy, Federal University of Paraná, Av. Pref. Lothario Meissner 632, Curitiba, Paraná 80210170, Brazil

Summary

The analysis of comparative efficacy and safety of topical antifungals in the literature is restricted to the treatment of tinea pedis and onychomycosis. Therefore our objective was to evaluate and compare the efficacy and safety of topical antifungals used in the treatment of dermatomycosis, we performed a comprehensive search for randomized controlled trials (RCTs) in the following databases: Medline, Cochrane Central Register of Controlled Trials, EMBASE, Lilacs and International Pharmaceutical Abstracts, we identified studies that compared the use of topical antifungals with other antifungals or with placebo published up to July 2010 in English, Spanish or Portuguese. The quality of reporting was assessed according to the Jadad scale; only studies with a score of 3 or more were included. The outcomes evaluated were mycological cure at the end of treatment.
Meta-analysis: Topical Antifungal Agents

- Allylamine, Benzylamine, Imidazole, Hydroxypyridone
- Active vs Placebo and Active vs Active studies
- 135 studies, 15,795 subjects
- All agents are CLEARLY superior to placebo; all future studies should be active vs active comparative
- No statistical difference in efficacy is detectable between the different classes, although rapidity of effect favors allylamines
- No differences in safety or tolerability

Br J Dermatol 166:927, 2012
Luliconazole 1% QD x 7
Extensive Dematophytosis

- Itraconazole 200mg BID x 7d
- Terbinafine 250mg/d x 14d
- Fluconazole 50mg/d x 14-30d

Drugs 58:179, 1999
Am J Clin Dermatol 5:225, 2004
J Dtsch Dermatol Ges 7:11, 2009
Terbinafine Granules

- Approved 9/28/07
- Ages 4-12 years of age
- Once daily dosage x 6 weeks
- Granules sprinkled on non-acidic food
- Weight-based dosage:
  - <25 kg: 125 mg/day
  - 25-35 kg: 187.5 mg/day
  - >35 kg: 250 mg/day
- Supplied: box of 14 packets, each packet with 30 or 45 granules, and each granule contains 4.6875 mg
Tinea Versicolor

- Versicolor means “many colored”
- Salmon to white to brown
- Slight scale, itch
- Normal flora
- Favors the back and chest
- Summer months
Tinea Versicolor
Tinea Versicolor
Tinea Versicolor - KOH
Spaghetti & Meatballs
Tinea versicolor Rx

- Any topical azole or ciclopirox
  - Ketoconazole shampoo 2%
- Allylamines not optimum
- Selenium sulfide may work
- Oral azole or triazole
- Ketoconazole works well but recent warnings mitigate against oral use
Oral ketoconazole should not be used as first-line therapy for ANY fungal infection. Ketoconazole should be used only for treatment of life-threatening mycoses when the potential benefits outweigh the risks and alternative therapeutic options are not available or not tolerated.

Oral ketoconazole is no longer indicated for dermatophyte or Candida infections.

Oral ketoconazole is not indicated for fungal infections of the skin or nails.

Contraindicated in any individual with liver disease.
Systemic Rx Tinea Versicolor

• **Itraconazole**
  • 400mg/day x 3
  • 200mg/day x 5
• **Fluconazole**
  • 300mg/week
• Two consecutive weeks

J Dermatol Treat 13:185, 2002
Mycoses 50:311, 2007
Candida (Monilia)

• Normal in small numbers
• Multiplies in warm, moist areas under certain optimal conditions
• Diabetes, immunosuppression, immobility/sweating, antibiotics
• Can become blood-borne
• Bright red with satellite pustules
• Control predisposing factors (like hyperglycemia); Rx: Topicalazole antifungals; Fluconazole
Candida (Monilia)

- Groin, axilla, inframammary (Intertrigo)
- Interdigital (Erosio interdigitale blastomycetica)
- Labial commissure (Perleche)
- Nail cuticle (Paronychia)
Candida Intertrigo

Groin

Axilla
Erosio interdigitale blastomycetica
Erosio interdigitale blastomycetica

Excess water exposure
Bartenders, Maids
Rx: Reduce exposure
Topical azole antifungal
Candida: Perleche
Candida: Perleche
Candida: Paronychia

Same predisposing factors as erosio interdigitale
Candida

- May cause diaper dermatitis in infants
- Differentiate from simple maceration, allergic contact dermatitis, seborrhea and psoriasis
Deep Fungi

- Rarely pathognomonic clinical
- Exception: sporotrichosis
  Linear nodules follow lymphatics
- Usually disseminate to skin, bones and organs from primary focus in lung
- Increased: immunocompromised
- Systemic symptoms
- Systemic therapy required
Deep Fungi: Skin + Internal Organs

- NAB
- Lungs
- Cocci
- Bone marrow
- Liver
- Crypto
- Bone
- Lungs
- Brain
- Histo
- Spleen
- Adrenal
Sporotrichosis
Sporotrichosis

Dermatol Online J 17(6):2, 2011
Int J Dermatol 48:1198, 2009
Smog Rosen 1994-2014
Sporotrichosis
Terbinafine v. Itraconazole

- Terbinafine 250mg/d (n = 55)
- Itraconazole 100mg/d (n = 249)
- Ages 18-70, all culture positive
- Rx duration to healing: ~3 months
- Cure rate: Terb 92.7% Itra 92.0%
- Two patients in each group required dose escalation (500mg/d, 200mg/d)
- Adverse events nearly identical 7%

Mycopathologia 179:349, 2011
The End
Thanks for your attention