Hot Topics In Podiatric Dermatology
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Disclosures

Advisory Board Member:
UCB Pharmaceuticals

Consultant:
UCB Pharmaceuticals
Unilever
Podiatrists & Dermatologists
General Outline

Bumps
Stripes
Collimated Lights
The Power of Observation
Robert Ryman, Untitled 1960-1961
Outline

Common Podiatric Rashes
Keys To Differential Diagnosis
Uncommon Presentations
Bumps
Classic Psoriasis

Well-demarcated
Erythematous plaque
Silvery scale

Classic locations:
Scalp, elbows, knees, buttocks

3% of the population

Nail, joint involvement common

Dx: clinical +/- biopsy

Tx: topical steroids, nbUVB, immunomodulators
Psoriasis of the Foot & Lower Leg

May appear like classic plaque psoriasis

However may have different presentation

Patchy or generalized thickening and scaling of nearly entire surface of palms / soles without redness
  • Keratoderma

Greater associations with nail and joint psoriasis

Chronic, difficult to treat
Palmoplantar Pustulosis

Different presentation

Palms and soles, especially lateral
Localized or entire surface

Sterile pustules admixed with
yellow-brown macules +/- scaly
erythematous plaques

No longer considered psoriasis

10-25% of patients with
palmoplantar pustulosis also have
plaque psoriasis
SAPHO Syndrome

May be associated with sterile inflammatory bone lesions

Synovitis
Acne
Pustulosis
Hyperostosis
Osteitis

AKA chronic recurrent multifocal osteomyelitis, pustulotic arthro-osteitis

Misdiagnosis, mistreatment common

Dermatology referral
Psoriasis / Palmoplantar Pustulosis

Important differential diagnosis

Tinea pedis
• Pustular or bullous variant

Eczematous dermatitis
• Dyshidrotic
• Contact (allergic or irritant)

Scabies

Uncommon diagnoses:
• Bazex syndrome
• Bullous disorders
Common Differential Diagnoses
Tinea pedis

Pruritic
Macular
Scaly (thin)
Erythematous
Leading edge of scale

KOH+
Eczematous dermatidites

**Dyshidrotic:**

Tense, deep-seated vesicles of palms +/- soles

Intensely pruritic
Eczematous dermatidites

Contact:
Well-demarcated
Erythematous
Diffuse scale
+/-Serous drainage
+/-Vesicobullae

Distribution of contactant: e.g. cream, sandal

• May need patch testing
• History is relevant
Scabies

Interdigital _burrows_: fingers > toes
Severe pruritus
Not restricted to palms and soles
History is relevant

When widespread / on feet, think crusted
Crusted scabies

- Thick, crusted plaques
- Typically acral, may be generalized
- Dystrophic nails
- May not see burrows
- Severe pruritus
- Socioeconomic considerations
Uncommon Diagnoses
Bazex Syndrome

Assoc with UGI or respiratory malignancies
Medical referral is mandatory

Sator PG et al, 2006
Bullous Pemphigoid
• Erythematous wheals → tense bullae (lower abdomen, thighs, forearms)

• May result in milia with healing

• May have underlying systemic illness or medication trigger
Blistering Disorders

Epidermolysis Bullosa Acquisita
• Erosions of feet / hands, tense vesicobullae that may be hemorrhagic

• May also result in milia with healing

• May be associated with IBD
Take Home Points

Sometimes scaly red plaques are just psoriasis

Lower leg psoriasis may have an atypical presentation

Sometimes the differential diagnosis is broad

Observation of key clinical features can be very helpful in events when diagnosis is uncertain

Dermatologic +/- medical referral to rule out atypical syndromes or underlying systemic disease
Stripes

(Longitudinal) Melanonychia
Outline

Non-Melanocytic
Melanocytic

Tips for Diagnosis
Common & Rare Conditions

Image via regionalderm.com
Melanonychia

Non-Melanocytic
- Nail staining
- Fungal Melanonychia
- Subungual hemorrhage

Melanocytic
- Melanocyte activation
  - Single
    - Trauma-induced
    - Periungual tumor-induced
    - Nail apparatus lentigo
  - Multiple
    - Drug/systemic dz-induced
    - Ethnic type nail pigmentation
    - Laugier-Hunziker syndrome
    - Peutz Jeghers syndrome

Melanocytic hyperplasia
- Benign
  - Nail matrix nevus
- Malignant
  - Subungual melanoma
Non-Melanocytic

Nail staining

Fungal Melanonychia

Subungual hemorrhage
A patient presents for a routine exam and you see yellow discoloration of multiple fingernails. How can this help you meet your Clinical Quality Measures (CQM) for meaningful use?

**Recording** smoking status for patients 13 years or older is a core objective.

Smoking cessation **medical assistance** is an additional set CQM.
Nail Staining

**Location:** Bilateral thumbnails, 2\textsuperscript{nd} & 3\textsuperscript{rd} fingernails of dominant hand

**Causes:**
- Brown: hobbies, occupational exposure to foods, clothing dyes
- Yellow: smoking, nail polish (red)

**Dermoscopy of Pigment:**
- Irregularly shaped
- Well-demarcated border, may be parallel to PNF

**Tx:** Easily removed w/ 15 blade

Nail Staining

Huang Guofu

A 39yo man presents with 1 month of discoloration of multiple toenails. He is concerned about melanoma. He has no personal or family h/o of skin cancer.

What questions are important to ask this patient?
- Medication history
- Trauma

Most appropriate next steps?
- PAS, fungal culture, +/- PCR
- Dermoscopy

A Word On Dermoscopy

Non-invasive diagnostic test for evaluation of lesions of skin, hair, & nails

Low-powered microscope with contact or polarized light to reduce surface light-scatter interference

A Word On Dermoscopy

Helpful tool, low cost, portable

Eliminates biopsies

Pilot study of pigmented lesions shows that old dogs can learn new tricks

Pigmented lesions are much more difficult to assess than nails

Terushkin et al 2010

<table>
<thead>
<tr>
<th>Table. Histopathologic Diagnoses and BMRs of Biopsied Pigmented Lesions*</th>
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<td>Diagnosis</td>
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<td>Dysplastic nevus, severe</td>
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Abbreviations: BMR, benign to malignant ratio; PL3, pigmented lesion specialist.
*Cases restricted to lesions removed where the differential diagnosis on the pathology requisition form included melanoma and/or dysplastic nevus. Unless otherwise indicated, all data are reported as number of lesions.
Fungal Melanonychia

**Location:** toenails > fingernails
- Men > Women

**Causes:** Most common
1) Non-Dermatophyte, dematiaceous fungus: *Scytalidium dimidiatum*

2) Dermatophyte, nondematiaceous fungus: *Trichophyton rubrum*
Fungal Melanonychia

Clinical clue: often **spares** matrix

**Dermoscopy of pigment:**
- Pigment streak w/ **distal widening**
- Yellowish streaks w/ jagged borders composed of spikes

**Dx:** KOH, fungal Cx  
*(cycloheximide-free media)*

**Tx:** Azole (Fluconazole, Itraconazole)  
Allylamine (Terbinafine)
Fungal Melanonychia: Dermoscopy

- Pigmented streak
- Distal widening
- Yellowish streaks
- Jagged borders
- Spikes

Ohn et al, JAAD 2017
A 35yo construction worker presents to your clinic after slamming his hand in a door. You notice that the nail bed edges are disrupted. Would you perform a nail bed trephination for evacuation of the subungual hematomas? Are there any additional exams that you would order?

Subungual Hemorrhage

**Location:** single or multiple nails; toes > fingers (great toe)

**Causes:** trauma (overt episode, exercise)

**Dermoscopy of pigment:** purple-black: homogenous, globular & peripheral fading patterns
Subungual Hemorrhage

**Dx:** Serial dermoscopy (color fading & distal movement of features), does not involve matrix

**Radiology:** X-Ray of affected digit to r/o:
- Fracture of distal phalanx
- Extensor tendon avulsion of distal phalanx

**Tx:** Drainage indicated when:
- 1) Pain present & 2) Nail edges intact
  - Previously: nail bed trephination only for subungual hematomas <25-50% of nail surface (>25-50%, tx avulsion with repair of any underlying nail bed laceration)
  - More recently: if nail plate is partially adherent, not displaced out of PNF → may leave nail plate in place and subungual hematoma may be trephined
Not all brown discoloration of the nail is due to melanin.

Dermoscopy and non-invasive diagnostic testing may be of utility.

Nail bed trephination may be indicated for hematomas of any size if the nail edges are not disrupted.

• If edges are disrupted → higher likelihood of nail bed injury & associated distal phalanx fx → may lead to a secondary nail deformity if not surgically repaired.

Summary: Non-Melanocytic
Melanonychia

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Melanonychia: Melanocytic

**Melanocyte activation:**
- Normal # of melanocytes with *increased production of melanin* → epithelial hyperpigmentation

**Melanocyte hyperplasia:**
- Increased # of melanocytes (proliferation)
Dermoscopy: Melanocytic Activation v Proliferation

Melanocyte activation: thin, regular gray lines on grayish background

v

Melanocyte proliferation: homogenous brown color of background band with:

- regular pattern of brown lines: longitudinal parallel lines w/ regular spacing & thickness

- irregular pattern of brown to black lines: w/ irregular spacing & thickness, disruption of parallelism


2007 Feb 22.
Melanocytic Melanocyte activation

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Trauma-induced:

- **Location**: fingernails > toes (thumb, 2\textsuperscript{nd} nail)

- **Causes**: occupational trauma, onychotillomania, overt trauma w/ nail plate deformity, repeated minor trauma to toe/s (may involve multiple digits)

- **Dermoscopy of pigment**: thin, regular \textit{gray} lines on \textit{grayish} background; \textit{abnormal surface} of nail plate; (+) \textit{blood spots}
Trauma-induced Melanonychia

Photo courtesy: Dr. Shane Meehan
Periungual tumor-induced:

• **Location**: fingernails, toenails

• **Causes**: digital mucous cyst, warts, fibromas, SCC, onychomatomatricoma

• **Dermoscopy of pigment**: thin, regular gray lines on grayish background; abnormal surface of nail plate; (-) blood spots

Melanocyte activation: single nail involved
Nail apparatus lentigo:

- **Location**: fingernails (L thumb/2\textsuperscript{nd}), toenails (R great toe)

- **Cause**: epithelial hyperpigmentation

- **Dermoscopy of pigment**: thin, regular gray lines on grayish background

Melanocyte activation: single nail involved
Nail apparatus Lentigo

Photos courtesy of: Dr. Jennifer Stein
Melanocytic Melanocyte activation

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Drug/Systemic disease-induced:

- **Location**: fingernails > toenails

- **Causes**:
  - Medications:
    - Antiretrovirals (Zidovudine, Lopinavir)
    - Chemotherapeutics (5-FU, MTX)
    - Antimalarials (Hydroxychloroquine)
  - Systemic Disease:
    - Scleroderma, SLE, HIV, Addison’s Dz (Bissell’s lines)
Drug-induced melanonychia

Ethnic type nail pigmentation:

- **Location**: fingernails > toenails
  - dark-skinned (Type V, VI) > light-skinned patients

- **Dermoscopy of pigment**: thin, regular gray lines on grayish background
Ethnic type nail pigmentation

Photo courtesy: Dr. Jennifer Stein
Laugier-Hunziker syndrome:
• **Adult** onset; sporadic, AD

• **Location**: fingernails, oral mucosa (lips, buccal mucosa, tongue), genitals

• **Dermoscopy of pigment**: thin, regular gray lines on grayish background

Melanocyte activation: Multiple nails involved
Peutz Jeghers syndrome:
• Congenital/Childhood onset; AD (STK11 mutation)

• Location: oral mucosa + genital + digits (rarely)

• Dermoscopy of pigment: thin, regular gray lines on grayish background

• Malignancy risk: GI, breast, others
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- Subungual melanoma
Melanocytic

Melanocyte hyperplasia

Nail matrix nevus

Subungual melanoma
Nail matrix nevus:
• **Location**: fingernails > toenails; single nail > multiple nails

• **Dermoscopy of pigment**: homogenous brown color of background band w/ regular pattern of brown lines: longitudinal parallel lines w/ regular spacing & thickness
Nail Matrix Nevus


Melanocyte Proliferation

Subungual melanoma:
- **Location**: thumb > great toe > index finger
- (+) Hutchinson’s Sign, (+/-) nail dystrophy
- 50% of pts recollect **preceding trauma**
Worrisome features:
1) Pigment wider at the base
2) Multiple, variegated uneven bands
3) Destruction of nail plate/associated dystrophy
4) Pigment beyond nail/Hutchinson’s sign
Longitudinal Melanonychia Dermoscopy Summary

ABCDEFs of Subungual Melanoma

(A) Age: peak incidence in 5th to 7th decades of life, AA, Asians, Native Americans (in whom subungual melanoma accounts for ≤ 1/3 of all melanoma)

(B) Brown-black band w/ breadth greater than 3 mm with variegated borders

(C) Change in nail band or lack of change in morphology despite adequate tx

(D) Digit most commonly involved: thumb > great toe > index finger

(E) Extension of the brown-black pigment onto the proximal and/or lateral nailfold (+ Hutchinson’s sign)

(F) Family or personal history of dysplastic nevus or melanoma
Most melanonychias are benign, but it is essential to r/o subungual melanoma

Detailed history, clinical exam & medication review are important for diagnosis

Dermoscopy may aid in diagnosis & monitoring

If in doubt, perform a nail matrix biopsy
Collimated Lights

Lasers for Onychomycosis
Emerging Therapeutics in Nail Disease

Onychomycosis
• Lasers
• Photodynamic Therapy
• Iontophoresis

Psoriasis
• Lasers
• Intense Pulsed Light
Outline

Why lasers?
Mechanisms
Data
Future Directions

Lasers for Onychomycosis
Background

Onychomycosis: the most common nail disease affecting ~14% of the population
- Multiple modalities of treatment
  - Orals
  - Topicals
  - Multimodal treatment

Challenges:
- Nail plate
- Patient compliance
- Low cure rates
- High rates of relapse
- Uncertain follow-up time
- Potential adverse events (e.g. hepatotoxicity, drug-drug interactions)

Why Lasers?

Principle of Selective Thermolysis
• Selective targeting of fungus?
• Better penetration, reduced side effects, physician control

Six Lasers FDA Cleared for the “temporary increase of clear nail of patients with onychomycosis”
• Based on Equivalence Data
• Not on RCTs

• 5 are Nd:YAG (1064nm), 1 is a diode (635/405nm)
Mechanisms of Action

Ideally based on TRT of fungi or melanin

- Time required for heated tissue to lose 50% of heat through diffusion
- Related to size of target chromophore
- If time > TRT, target is not treated but collateral damage inflicted

In reality, most mechanisms are uncertain

Mechanisms of Action

Nd:YAG: bulk heating

Selective photothermolysis?
- $T \uparrow \rightarrow$ induced by energy absorption by lipids and moisture within fungal & host cells $\rightarrow$ heat shock response $\rightarrow$ affects transcription / translation $\rightarrow$ death by induced cell imbalance
- *T. rubrum* death within 15 min of exposure at 50$^{\circ}$C
- $T>45^{\circ}$C $\rightarrow$ pain, necrosis in humans
  - Theoretically**, pulses should alleviate this
  - Lower temperatures can lead to fungistasis, but later spore germination

Fungistasis or fungicide?

Mechanisms of Action

**QS lasers**: selective photothermolytic and photomechanical effects
- Which are target chromophores: melanin in cell wall or fungi?

- Light absorption peak for *t. rubrum* is 415nm

- Chitin, xanthomegnin, and melanin produced by *t. rubrum*
- Pigments are virulence factors that protect fungi from host immune responses and ROS → with destruction there could be an antifungal effect

- At 532nm QS Nd:YAG can suppress *t. rubrum* due to large amounts of xanthomegnin it contains
- However only wavelengths 750 – 1300nm can penetrate the nail plate
- At 1064nm, wavelength is beyond absorption spectrum

Mechanisms of Action

Nd:YAG Outstanding Issues

• TRTs of mycelia and spores are not precisely known
• Are short pulses sufficient for fungicide or only fungistasis?
• How long do elevated temperatures need to be sustained to kill spores without damaging surrounding tissues?
• Is there a mismatch between the wavelength needed to penetrate the nail plate and that required to target necessary chromophores?

Mechanisms of Action

**Diode**: antimicrobial plus increased immune response?
- **Dual wave, Non-thermal or “low level laser”**

- **Antimicrobial**
  - 405nm (blue) light: antimicrobial, antibacterial, antifungal effects

- **Increased immune response**
  - 635nm (red) light: increase immune response by increasing circulation

**Theory of photomodulation to increase immune activation:**
- Light exposure → target chromophore (iron and copper-containing enzyme cytochrome C oxidase in the mitochondrial respiratory chain) → increased production of mitochondrial products → PMNs stimulated to generate additional ROS → increased fungicidal capacity

Gupta & Versteeg, 2017; Bhatta et al, 2017
Mechanisms of Action

Erbium and CO$_2$: ablative v fractionated
- Vaporization of nail bed +/- enhanced topical drug delivery

fCO$_2$ Photothermal effects
On fungus
- ↑ tissue T $\rightarrow$ direct fungicide as H$_2$O converted to steam $\rightarrow$ swelling, pressure $\rightarrow$ microexplosions in fungi
On microenvironment
- Exfoliation and vaporization of target tissues $\rightarrow$ remodeling and destruction of fungal growth environment

Enhanced topical drug delivery
- Enhanced absorption via microscopic holes in nail bed

Fraught with limitations
Most reports are case series, uncontrolled trials without placebo or randomization
Numbers of subjects are low
Treatment numbers range from 1 – 12 sessions
Follow-up ranges from 0 – 12 months
Few pure laser studies: often use concomitant antifungals
Measurements: no consistency
  • Type of onychomycosis
  • Species
  • Diagnosis (Culture / PAS)
  • Clinical measurements
  • How cure and clinical improvement defined
  • Fingers v toenails

47% of 1064nm device trials reported a positive response
60% reported clinical and mycologic cure in >50% of treated subjects

Francuzik et al 2016
### Randomized Studies With A Comparison Group

<table>
<thead>
<tr>
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<th>Year</th>
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<th>No. of nails</th>
<th>Follow-up (mo)</th>
<th>CRR (%)</th>
<th>MCR (%)</th>
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CRR - Clinical Response Rate; Defined by linear clearing of the nail unless otherwise noted
MCR - Mycologic Cure Rate; Defined by negative fungal culture unless otherwise noted
* Fingernails
** At 3 months
M Reported as mean proximal nail plate clearance in millimeters
C Reported as clinical clearance rate
P Placebo-controlled
S Subjects served as their own controls
A Nd:YAG with half the number of treatments served as control group
B Fingernails and toenails served as control groups for each other
T1 Oral terbinafine served as control group
T2, T3, T4 Topicals served as control group (T2 – terbinafine, T3 – naftifine, T4 – amorolfine)

Adapted from Wiznia et al, 2016; Karsai et al; Park et al; Kim et al

Nd:YAG n = 352
CRR = 0-100%
MCR = 0-84%
f/u = 0-12 mo

Lasers for Onychomycosis
## Compelling (?) Data: Erbium & CO₂

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Fractionated</th>
<th>Wavelength (nm)</th>
<th>Fluence (J/cm²) or Power (W)</th>
<th>No. of patients</th>
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<th>CRR (%)</th>
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<td>10-15mJ</td>
<td>60</td>
<td>233</td>
<td>6</td>
<td>73^</td>
<td>57^</td>
<td>Yes***</td>
</tr>
<tr>
<td>Shi et al.</td>
<td>2017</td>
<td>Yes</td>
<td>10600</td>
<td>15mJ</td>
<td>31</td>
<td>124</td>
<td>3</td>
<td>69*</td>
<td>74**</td>
<td>No</td>
</tr>
</tbody>
</table>

CRR - Clinical Response Rate; Defined by linear clearing of the nail unless otherwise noted

A Greater than 60% clear  
B Less than 5% nail affected

MCR - Mycologic Cure Rate; Defined by negative fungal culture unless otherwise noted

**Negative fungal microscopy (KOH)

***CO₂ arm served as control v CO₂ + topical

Adapted from Wiznia et al; Shi et al; Zhang et al; Zhou et al

**Fractionated CO₂**

n = 190

CRR = 69-90%

MCR = 50-80%

3-12 tx, q2-4 wk
daily antifungal
Adverse Effects

• Pain
• Necrosis, especially in diabetics
• Risk of anesthesia

Leverone et al, 2015
How to Approach This?

Assume that lasers do not work and do not use them
• A recent "real-world" study (Rivers et al)

Use lasers for only selected indications
• DLSO, in patients intolerant / unwilling to use prescriptions, those with better prognosis

Employ multimodal treatment
• Time, money

Attempt fractionally ablative methods

Consider the language that is being used

Rivers et al 2016
Education

Dispel the notion of treatment of onychomycosis
• Temporary increase in clear nail
• Offer treatment for cosmesis only
• Analogous to botulinum toxin, hyaluronic acid fillers

Set expectations

Recognize your own moral compass

Image via greaterspringfield.nimbledeals.com
Future Studies: Standardization

Lasers as monotherapy

How best to identify controls
• Untreated digit of contra foot v untreated individuals

Follow-up times

Treat all affected nails to control for reinfection

Separate by onychomycosis subtype, location (fingers v toes)
• Growth rates differ between fingers and toes as will time to treatment endpoints and measurements

Methods for quantifying clinical improvement
• Cure rates – clinical and mycological
• Cosmesis
• Treatment
  
  Gupta et al 2016
Lasers: The Bottom Line

Studies generally of poor quality, without standardization
Comparisons difficult to make

The optimal non-ablative laser needs
• Activity against melanin/fungal elements AND pulse duration matching TRT
• Adequate nail penetration

Fractionated Erbium and CO$_2$
• Initial data look promising
• Mechanism makes sense
Conclusions

The differential diagnosis of podiatric rashes is broad and includes uncommon systemic conditions.

Careful clinical examination can help narrow differentials.

Most melanonychias are benign.

Following an algorithm helps to demystify these conditions.

Detailed history and examination, including dermoscopy, can help.

Lasers hold promise for the cosmetic / medical treatment of onychomycosis.

Data are early, methodologies are unsound, improved standards will help.
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All other clinical information and photos obtained from:

UpToDate
VisualDx
Dermnetnz.com
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Novel Therapeutics: Photodynamic Therapy

• Mechanism: free radicals

• Treatment parameters varied: 1-22 sessions, q1-8wks, wavelengths of light 470 – 750nm, fluence 18 – 228J/cm²

• Recent meta-analysis: 17 studies, 214 patients total, one RCT

• Strengths: minimal side effects, targeted, may work where other treatments have failed, across dermatophytes, molds, yeast; endonyx

• Weaknesses: early data, impractical – time intensive – requires significant debridement / avulsion / nail softening / nail drilling or fractionation

Bhatta et al, 2016
Novel Therapeutics: Iontophoresis

- Mechanism: application of small current to increase transport of molecules via co-transport with water or ion flux
- May hold promise for enhancing absorption of topical antifungals
- Data: *in vitro* and one pilot study with questionable results

Sotiriou et al, 2010; Amichai et al, 2010