Emerging Dermatophytes

Sarah Kidd *PhD FASM FECMM*

National Mycology Reference Centre

SA Pathology, Adelaide

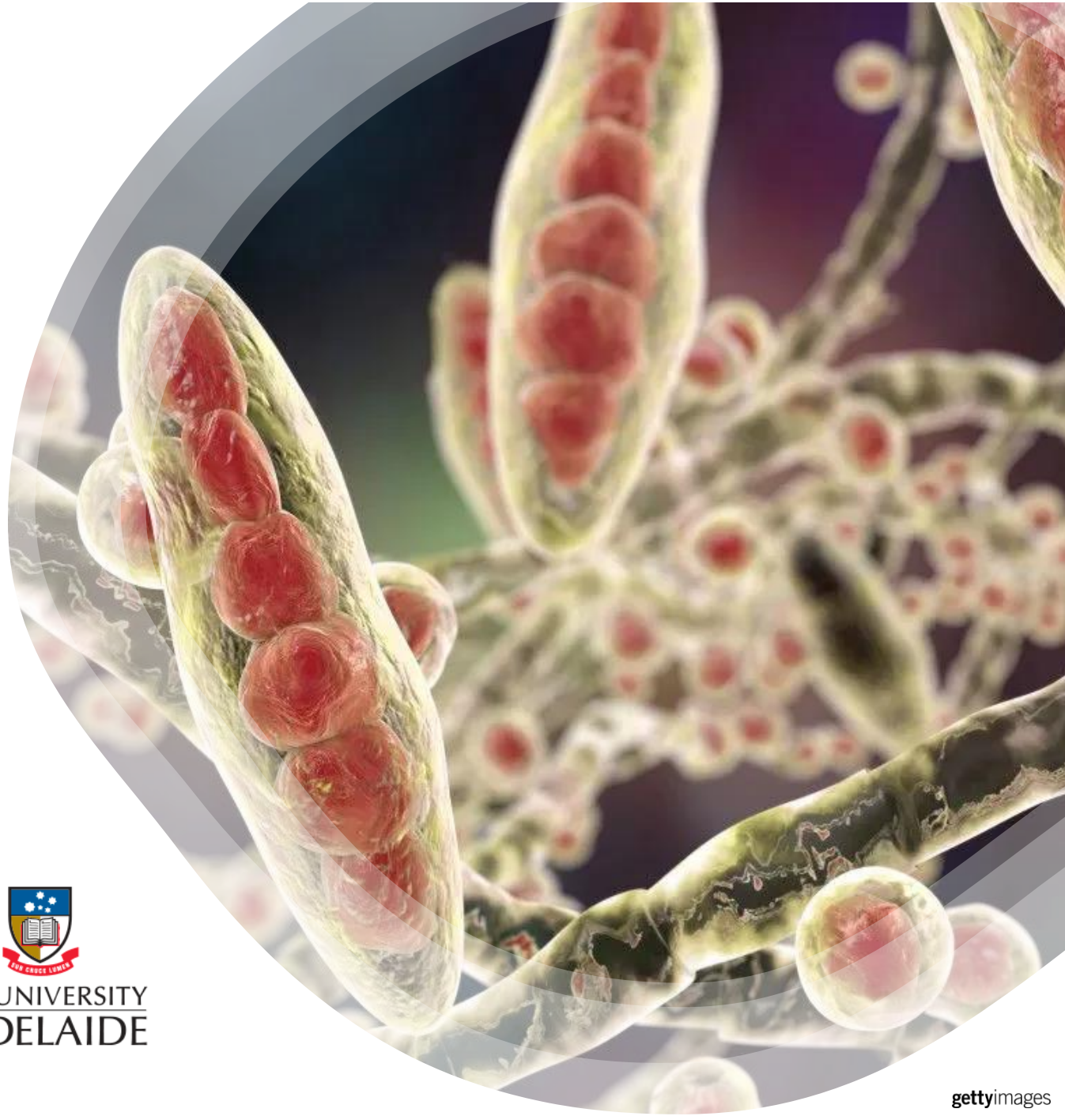
sarah.kidd@sa.gov.au

www.mycology.adelaide.edu.au

@thefunguskidd.bsky.social

SA PATHOLOGY

THE UNIVERSITY of ADELAIDE



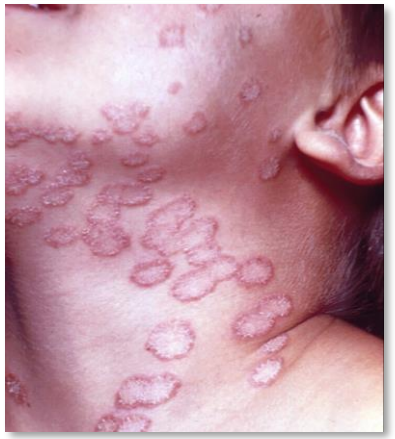
Disclosures

Conference & travel	Pfizer, AusDiagnostics
Advisory boards/consulting	Pfizer, Gilead Sciences, Mayne Pharma, Merck Sharp & Dohme
Honorariums/speaker fees	Pfizer, Gilead Sciences
Royalties	Kidd et al., Descriptions of Medical Fungi 4th Ed 2023
Relevant committees	CLSI M38, WHO FPPL, WHO fungal diagnostics landscape

Images are from Mycology Online or my own, except where otherwise credited

Dermatophyte infections

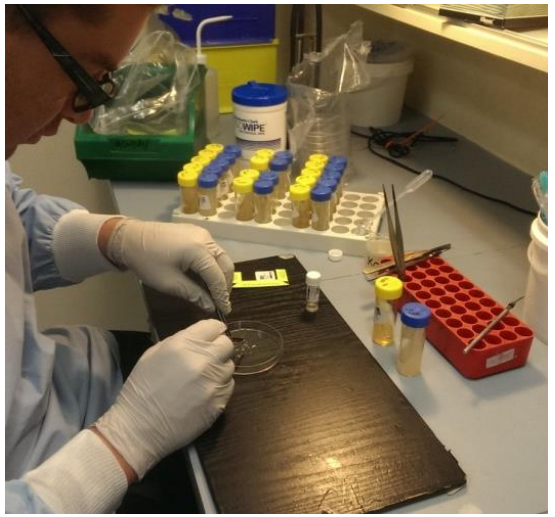
- A group of fungi that colonise and invade keratinised tissue
  - Unique ability among fungi to produce keratinases
  - Infections of skin, nails and hair
- Infections typically superficial but can be debilitating. Rarely invasive.
- Global prevalence of infection ~20%
- Common presentations: tinea pedis, tinea capitis, tinea corporis, onychomycosis
- Most commonly caused by *Trichophyton rubrum* and *T. interdigitale* (*T. mentagrophytes* complex).
  - Regional variability in presentation, and prevalent species
  - Typically treated with topical and/or oral terbinafine, or itraconazole. Historically, resistance is rare.

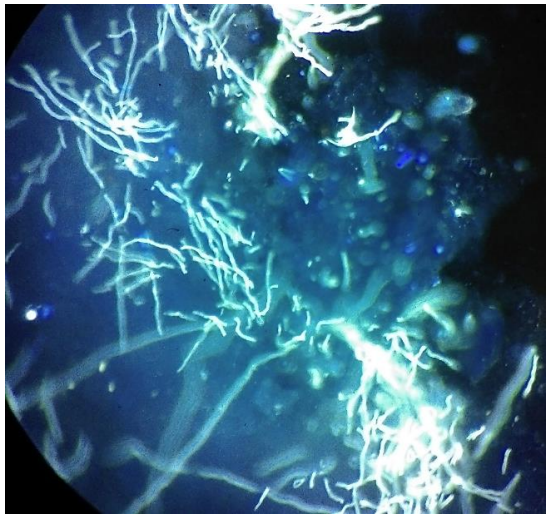


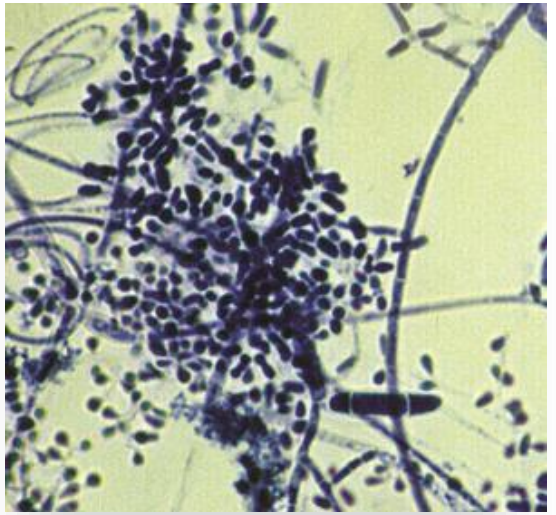
Havlickova et al *Mycoses* 2008; Weitzman et al *Clin Microbiol Rev* 1995

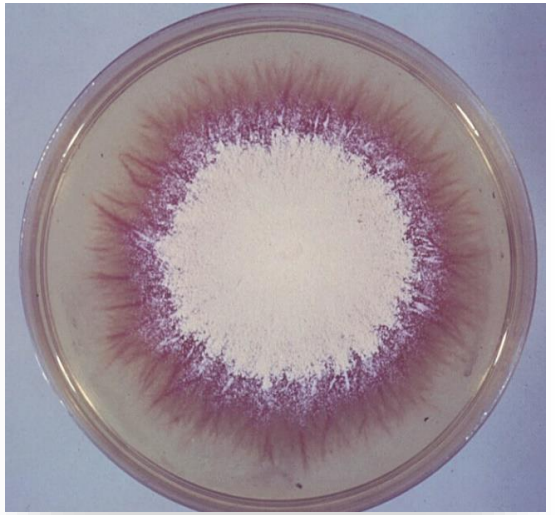
Traditional diagnostics

- Gold standard: microscopy and culture of skin scrapings, nail scrapings, hair plucks, etc.
- Direct microscopy of KOH digested tissue stained with optical brightener (e.g. calcofluor white)
  - Sensitivity 82–91%, specificity poor
- Culture requires specialised media, e.g. Lactritmel agar, containing antibiotics and cycloheximide
  - Limit overgrowth of bacteria and saprophytic fungi
  - Up to 4 weeks incubation time.
  - Sensitivity 40–60%, specificity excellent
  - Identification of fungi requires sig. expertise









PCR detection of dermatophytes

- Sensitivity of PCR 20–30% higher than culture
  - Dermatophytes often overgrown with saprophytes in culture
  - Detects non-viable fungal elements, e.g. post treatment
- TAT significantly reduced compared to culture
- Range of species detected varies between commercial assays
  - Some assays have pan-dermatophyte detection ±
  - Detection of common species e.g. *T. rubrum, T. interdigitale* (*T. mentagrophytes* complex)
  - Often identify only to genus or species complex level
  - May not differentiate emerging species of interest

Arabatzis et al *Br J Dermatol* 2007; Ghannoum et al *Int J Dermatol* 2018; Spiliopoulou et al *J Med Microbiol* 2015; Ross et al. *Pathology* 2020; Lin et al *Diagn Microb Infect Dis* 2021

Case: 27F

- Recently emigrated from Ireland (Nov 23). Now living in Western Australia.
- Presented with 12 mo. widespread plaque lesions to face, chest, groin and thighs
- Previous skin scraping grew *Trichophyton mentagrophytes*
  - 6 weeks oral terbinafine 250 mg/day, rash got worse
  - Switched to itraconazole but was taking “on and off” due to photosensitivity. Little improvement of lesions
  - Still taking itraconazole when she presented to Australian GP

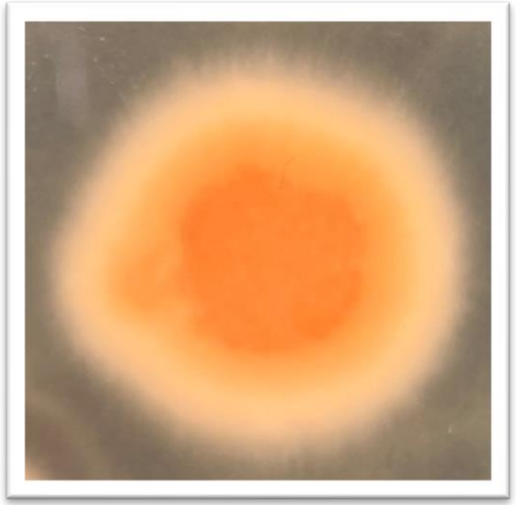
Images courtesy Dr. Catriona Hayes

Lab investigations

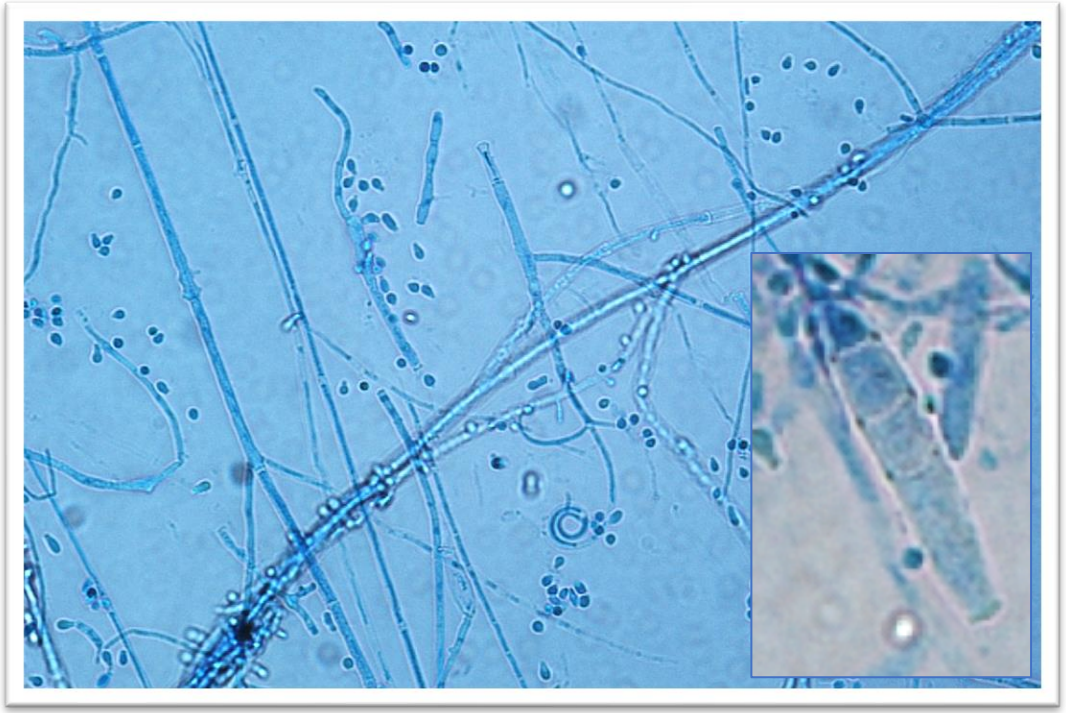
- Skin scraping collected by GP and submitted to a laboratory for fungal MC&S:
  - Microscopy: “++ fungal hyphae typical of a dermatophyte”
  - Culture: “*Trichophyton interdigitale* isolated”
- Referred to Adelaide for susceptibility testing

KOH-blankophor direct microscopy (not this patient’s specimen)

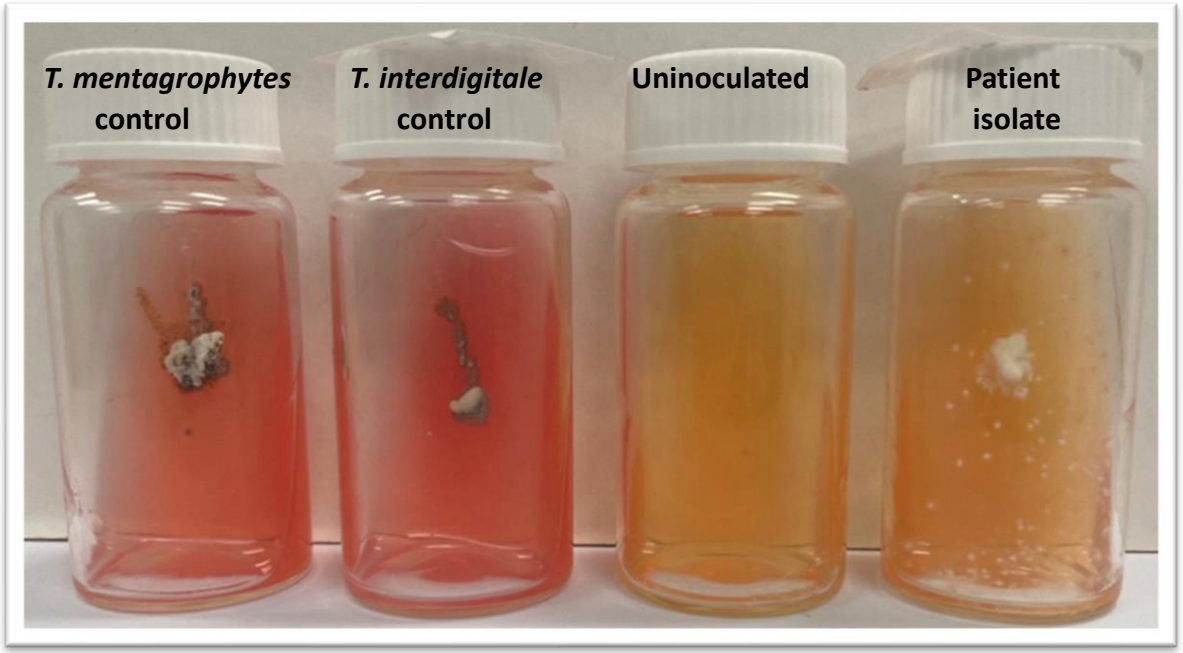
Colony surface



Colony reverse



Microscopic morphology



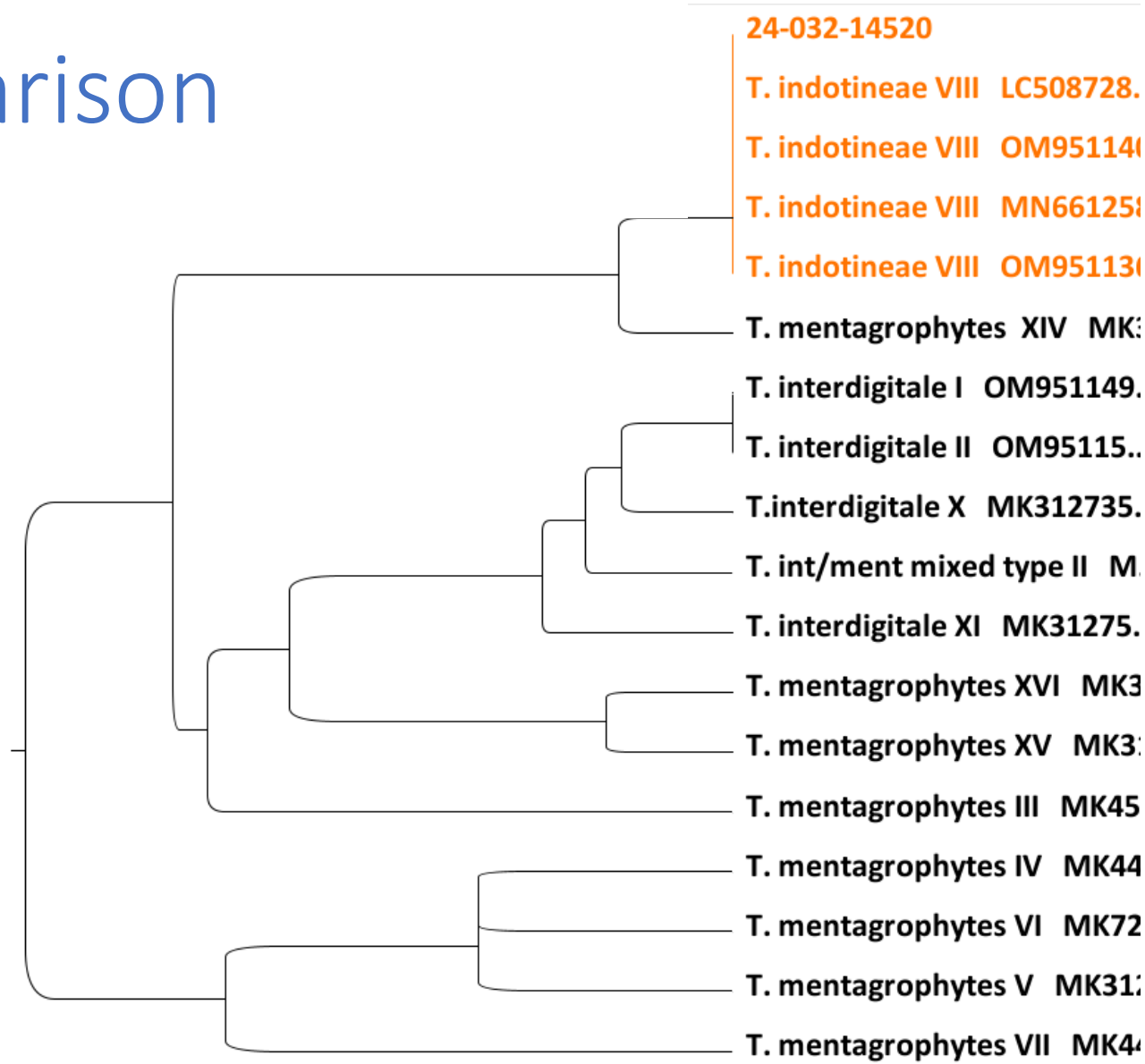
Urease test – 7 days, 26°C

- Morphologically resembling *T. interdigitale* and *T. mentagrophytes*
- Nil urea hydrolysis at 7 days, unlike *T. interdigitale/ mentagrophytes*
- Molecular identification/confirmation required

ITS sequence comparison

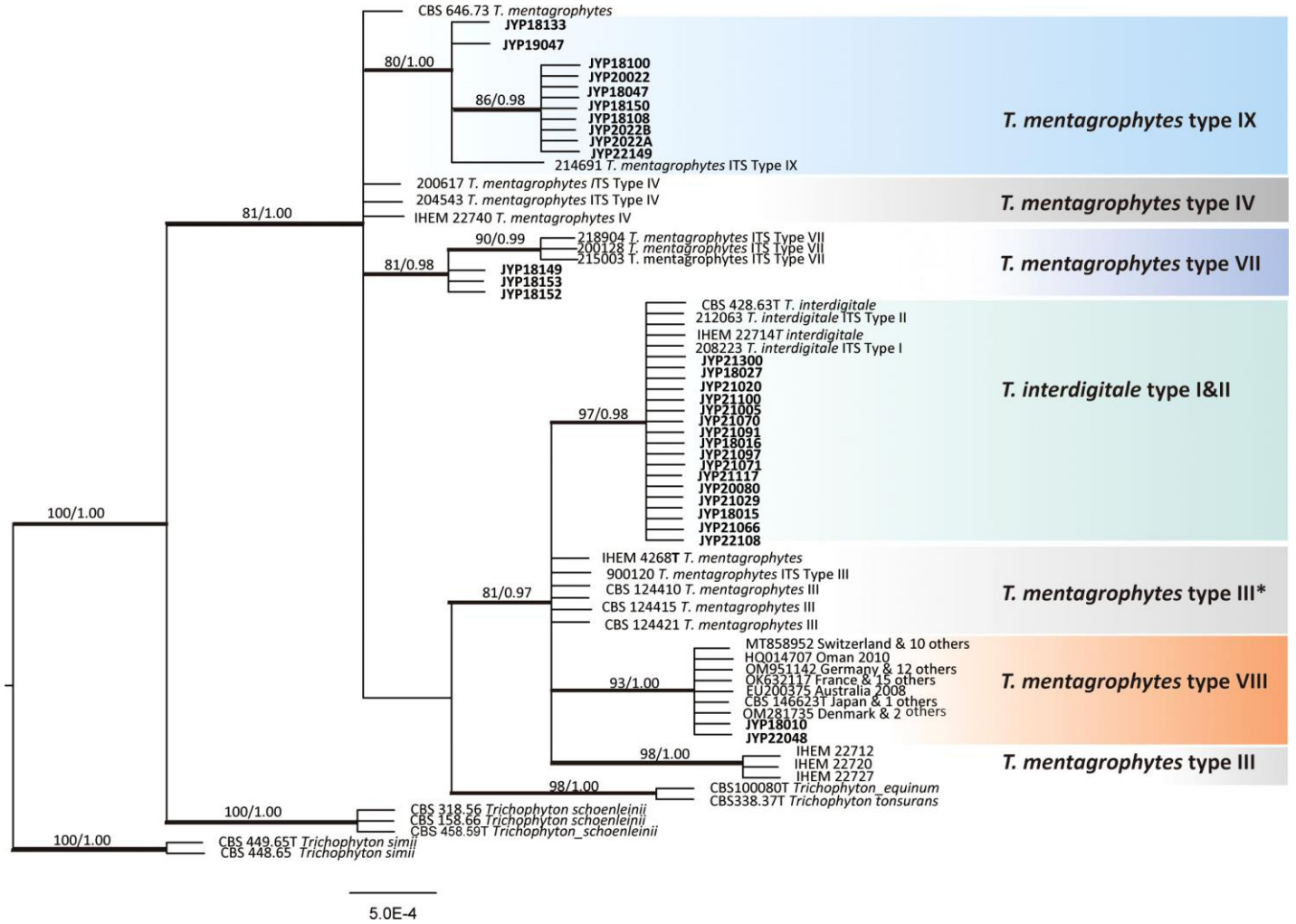
Comparison of ITS1-5.8S-ITS2 sequence with those of *Trichophyton* reference sequences revealed clustering with ***Trichophyton indotineae*** (previously *T.men* genotype VIII).

Note: use of reference sequences for identification is critical due to errors and misidentifications in Genbank



Reference sequences: Uhrlaß et al *J Fungi* 2022

Trichophyton mentagrophytes complex



Trichophyton mentagrophytes

Trichophyton interdigitale

Trichophyton mentagrophytes

Trichophyton indotineae

(Elevated to species level in 2020)

Kano et al *Mycopathologia* 2020; Jia et al *Front Immunol* 2023; Jabet et al *EID* 2023

Trichophyton indotineae

- Commonly presents as extensive pruritic annular lesions on the trunk, face, groin, buttocks.
  - Hallmark is greater severity and frequent relapse, compared to other dermatophyte infections
- Transmission via skin-to-skin contact and fomites
- Associated with terbinafine-resistance (but not intrinsic resistance)
  - ~72% Terb-R.
  - Regional variability in India (North 76%-R vs. South 16%-R)
- Azole resistance observed in ~10% of isolates.

Image: Uhrlaß et al, *J Fungi* 2022

Image: Khurana et al, *JAAD* 2024

Ebert et al, *Mycoses* 2020; Brasch et al, *J Dtsch Dermatol Ges.* 2021; Kong et al, *AAC* 2021; Yamada et al, *AAC* 2022; 2023; Spivack et al, *Emerg Infect Dis.* 2024; Kumar et al., *J Mycol Med*. 2022; Khurana et al, *JAAD* 2024

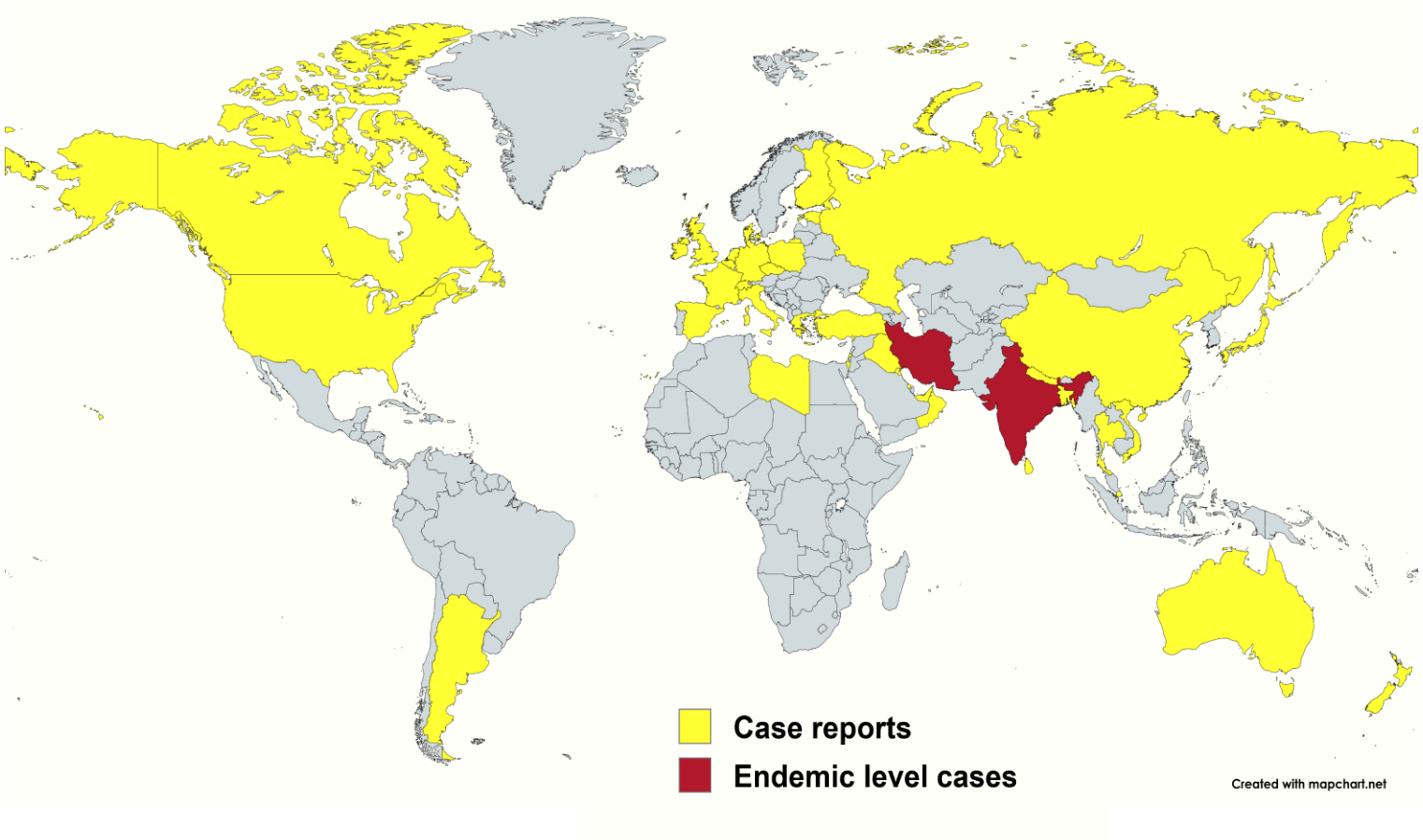
Uhrlaß et al *J Fungi* 2022

Why has resistance exploded?

- Over >1 year, this patient reported:
  - erratic use of topical and oral antifungal drugs
  - using >100 tubes OTC fixed-dose combination steroid/antifungal/antibacterial creams
- Sub-optimal dosing & low efficacy brands
- Steroids suppress local cellular immunity

> "Tinea has become an Indian Frankenstein's monster, nurtured by the same pharmaceutical industry that continues to manufacture existing [fixed drug combinations], i.e. topical antifungals with steroid."
>
> Shyam Verma, *Lancet Infect Dis* 2018

Global expansion of *Trichophyton indotineae*

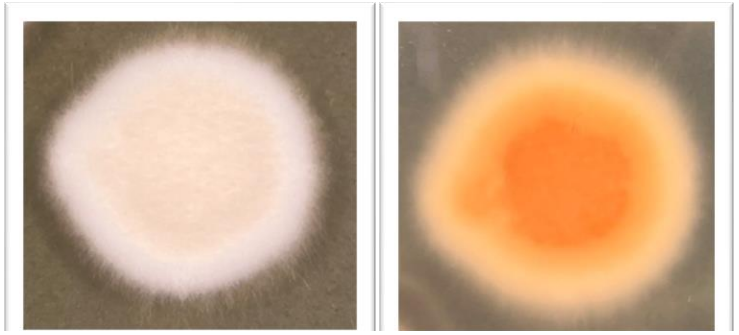


- Proliferation across Indian subcontinent over past decade
- Epidemic-levels reported from India, Iran
- Now the most common cause of dermatophytosis in India (78%)
- Expanding throughout rest of the world

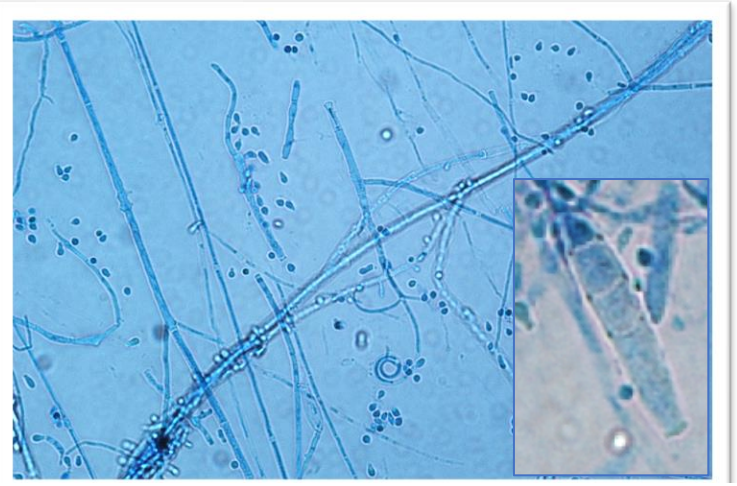
Created in MapChart.net; adapted from Jia et al, *Front Immunol* 2023 & Lock hart et al., Nature Rev Microbiol 2023; other published case reports

Lab identification

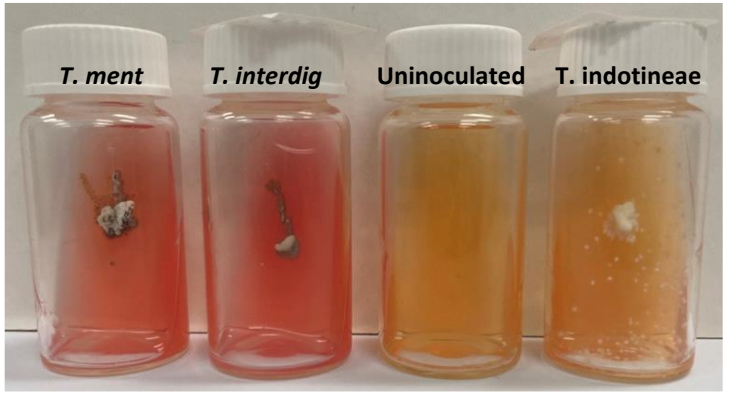
- Morphologically similar to *T. interdigitale* and *T. mentagrophytes*
- MALDI-ToF can differentiate *T. indotineae,* but not yet represented in commercial databases
- Currently detected but not differentiated in dermatophyte PCR assays (e.g. AusDiagnostics)
- Definitive identification is by ITS1-5.8S-ITS2 sequencing with comparison to reference sequences
- High index of suspicion required, clinical notes important
  - Travel? Recalcitrant infection?
- Most *T. indotineae* isolates nil urea hydrolysis at 7 days



Colony surface Colony reverse



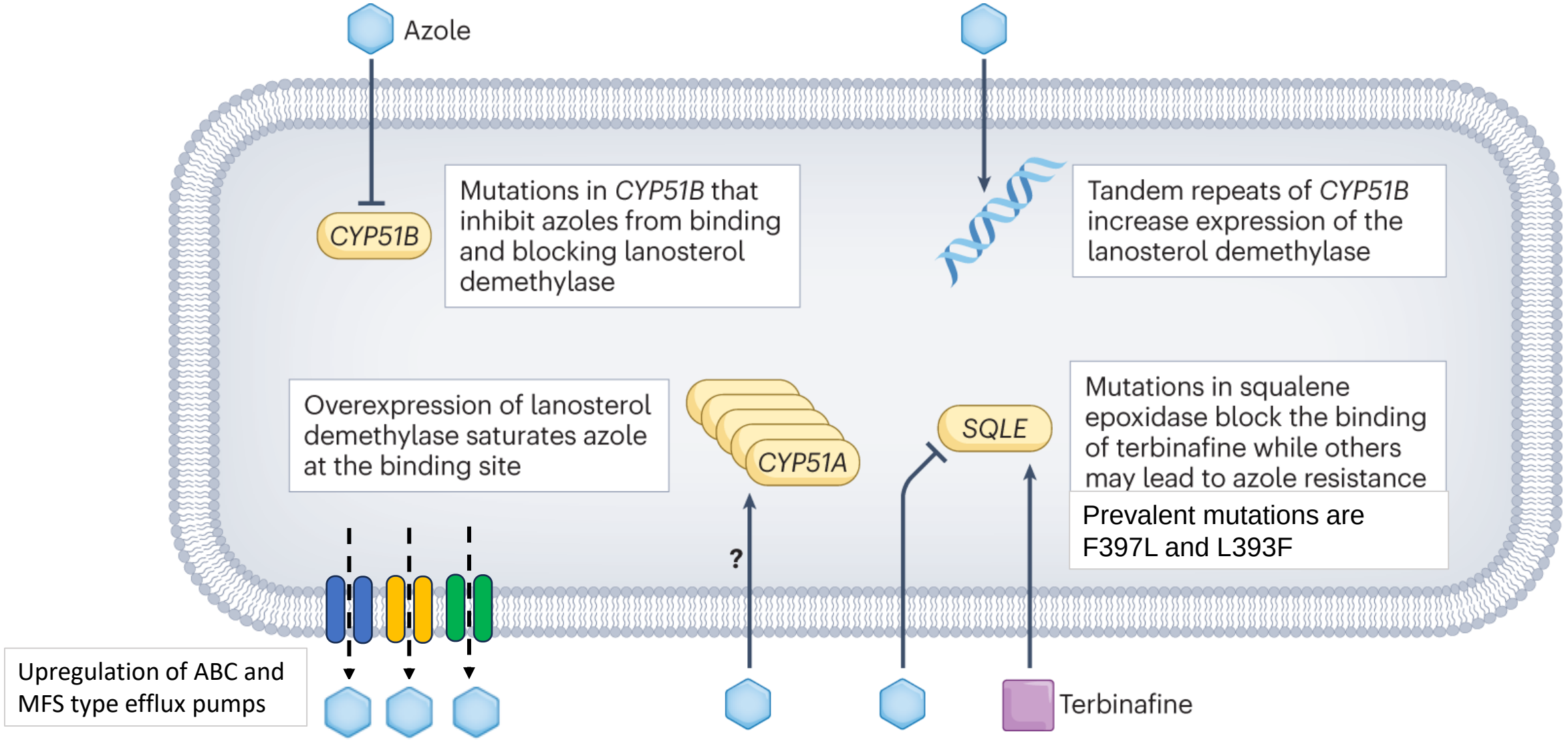
Microscopic morphology



Urease test – 7 days, 26°C

Tang et al *Mycopathologia* 2021; Tang et al *Front Microbiol* 2022; Chowdhary et al *PLoS Pathogens*, 2022; Uhrlaß et al *J Fungi* 2022

T. indotineae resistance mechanisms



Adapted from Lockhart et al *Nature Rev Microbiol* 2023

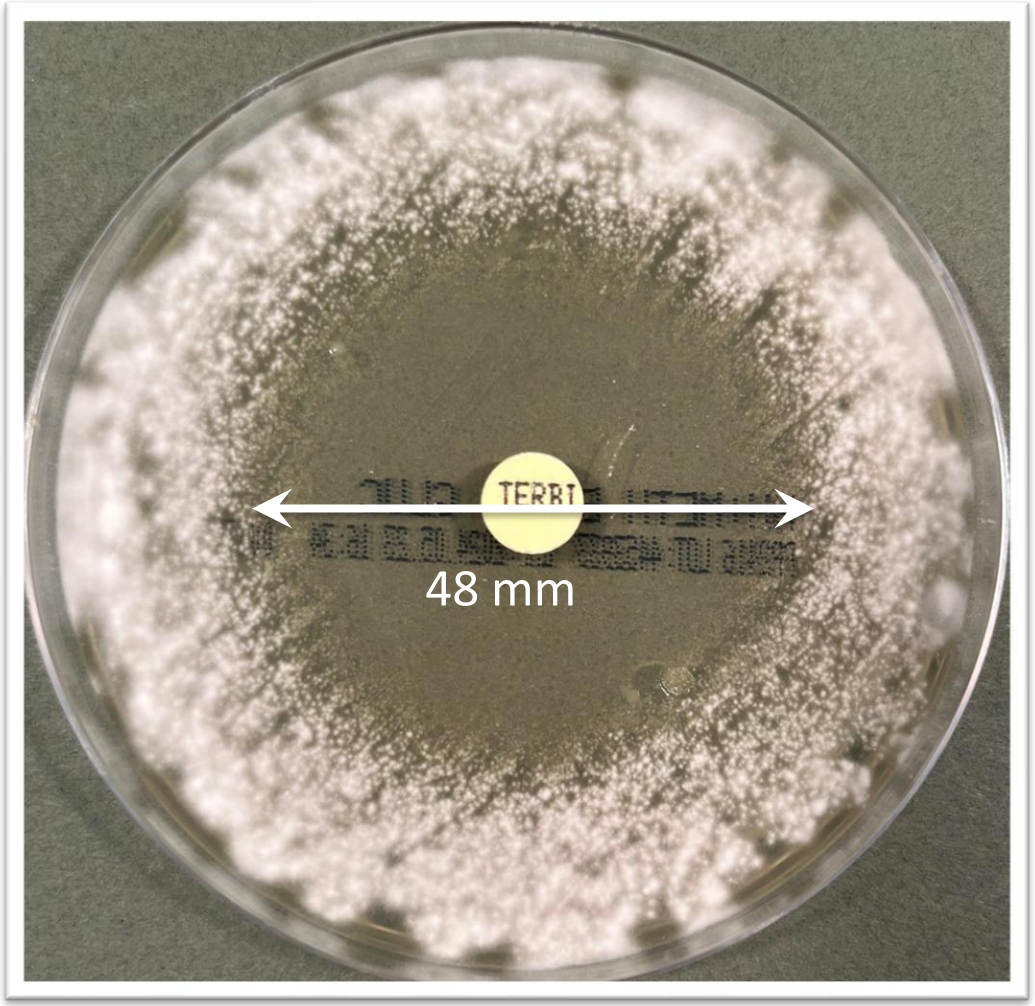
Antifungal susceptibility testing

- CLSI and EUCAST BMD methods endorsed for dermatophyte AFST
  - Very labour intensive
  - No lab in Australia has resources for this – not even the reference labs!
- Limited commercial assays for terbinafine
- Terbinafine Neosensitab discs available (Rosco Diagnostica) but there are no interpretive criteria for dermatophytes.
- Terbinafine Ezy MIC gradient strips now available in Australia (HiMedia/WishMed).
- No validated/endorsed MIC breakpoints for dermatophytes, but some studies have suggested:
  - Terb ≥0.5 µg/mL associated with resistance

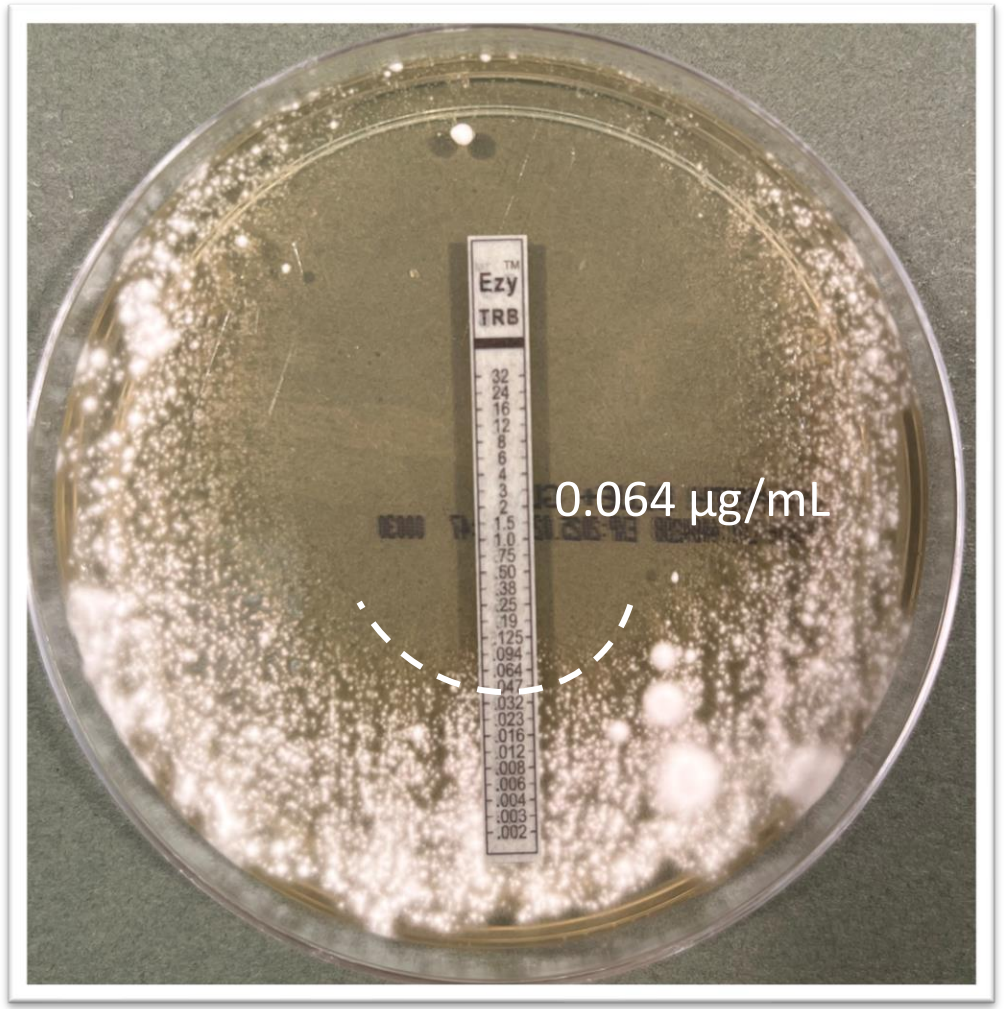
Not to be used for interpreting MICs on lab reports, but could be used to discuss appropriate treatment with GPs

Cañete-Gibas et al *JCM* 2023; Ebert et al *Mycoses* 2020

Case: terbinafine susceptibility



Neosensitabs terbinafine (30 µg) (Rosco Diagnostica)



HiMedia Terbinafine Ezy MIC strip (WishMed, Sydney, Aust.)

Terbinafine zones/MICs vs. mutations

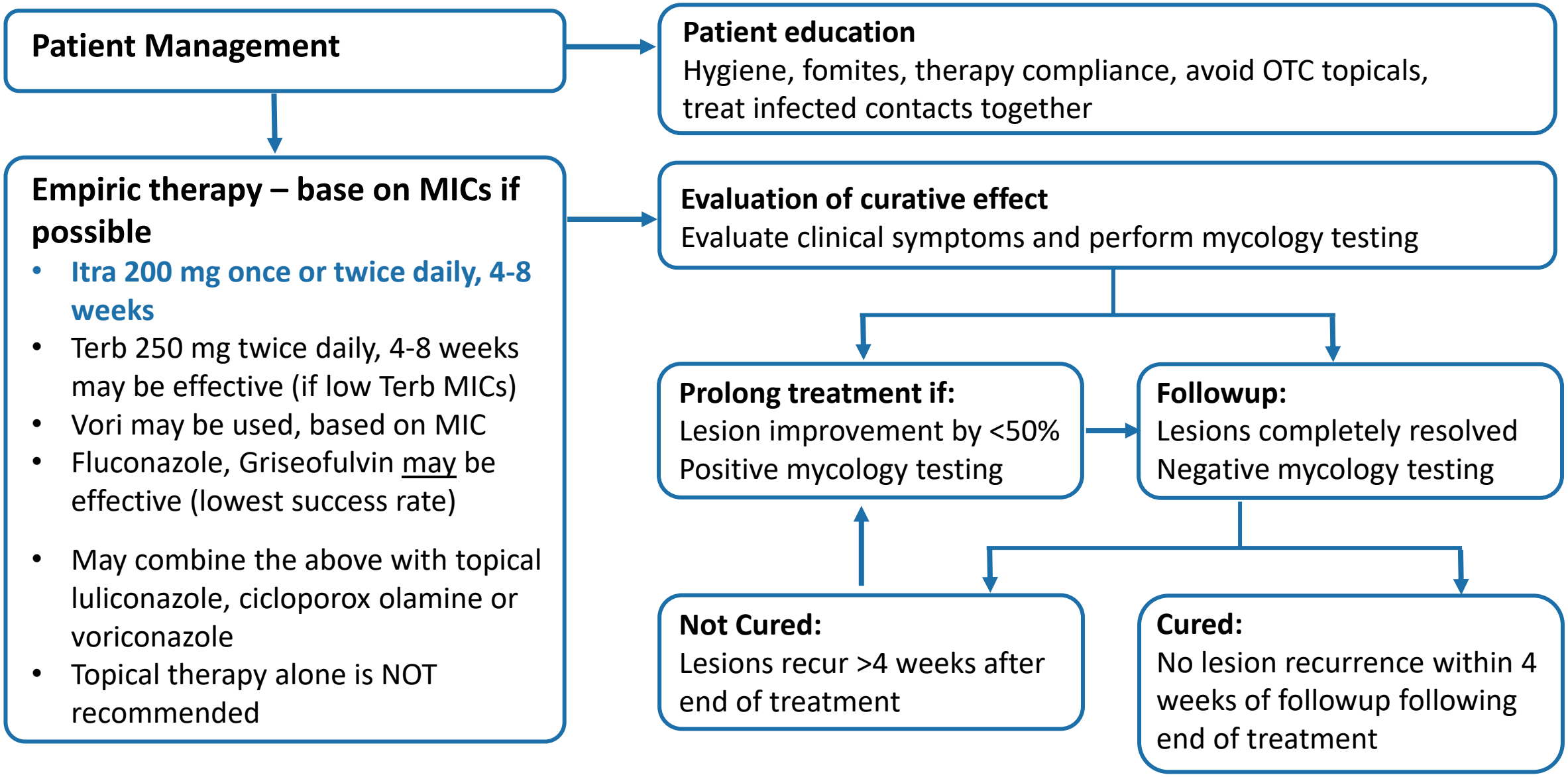
Species ID	Accession number	Terb disk zone	Terb gradient strip MIC	SQLE Mutations						
				E174D	L393S	L393F	F397L	Q408L	A448T	I483V
T. interdigitale	ATCC MYA-4439	not done	0.04-0.06	–	–	–	–	–	–	–
T. indotineae	2403214520	48 mm	0.064	–	–	–	–	–	–	–
T. indotineae	2402214787	50 mm	0.006	–	–	–	–	–	–	–
T. indotineae	2335408581	50 mm	0.023	–	–	–	–	–	–	–
T. indotineae	2220622462	50 mm	0.016	–	–	–	–	–	–	–
T. indotineae	2405814832	9 mm	4	–	–	–	+	–	–	–
T. indotineae	2402214796	9 mm	>32	–	–	–	+	–	–	–
T. indotineae	2403006224	9 mm	8	–	–	–	+	–	–	–
T. indotineae	2402214791	11 mm	8	–	–	–	+	–	–	–

Case: other antifungals

- Sensititre YeastOne panel (AUSNMRC1)
  - Inoculation, incubation and interpretation according to CLSI M38 standard
- No azole breakpoints, but the following MICs proposed as non-wild type:
  - Itraconazole MICs ≥0.5 µg/mL
  - Voriconazole MICS ≥ 0.25 µg/mL
- Other azole MICs also appear to be high

Antifungal	MIC (µg/mL)
Itraconazole	1
Isavuconazole	2
Posaconazole	1
Voriconazole	1
Fluconazole	>256
Amphotericin B	2

Cañete-Gibas et al *JCM* 2023

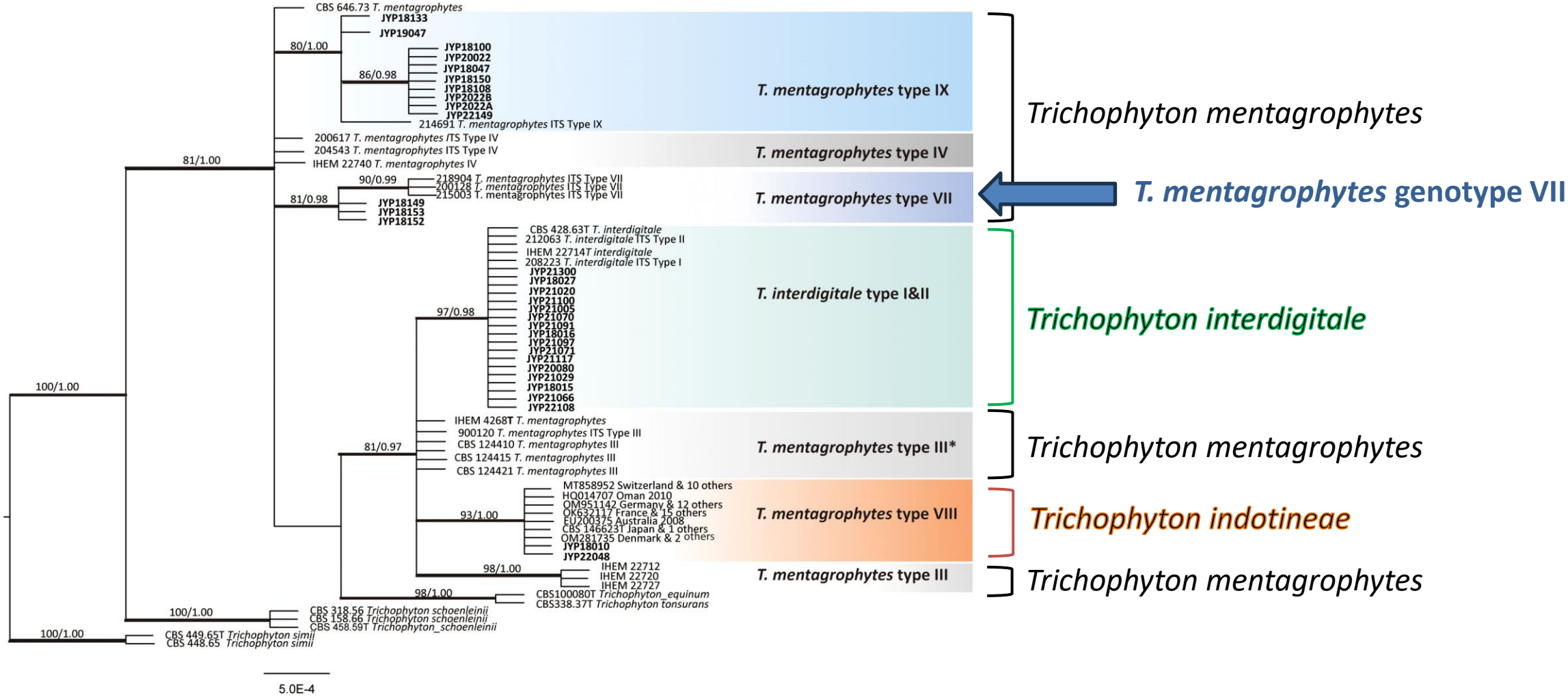


**Liang et al. Chinese expert consensus on management of antifungal-resistant dermatophytosis. *Mycoses* 2024
Singh et al *Indian J Dermatol* 2020; Lockhart et al *Nature Rev Microbiol* 2023

Case follow-up

- Confirmed *T. indotineae,* appearing to be susceptible to terbinafine, resistant to azoles.
- Switched back to terbinafine, but with increased dose, at 250 mg twice daily
  - Duration not clear, but was >8 weeks
- Lesions had significantly improved as at Oct 2024

Trichophyton mentagrophytes complex



Kano et al *Mycopathologia* 2020; Jia et al, *Front Immunol* 2023; Jabet et al *EID* 2023

T. mentagrophytes genotype VII (TMVII)

- Associated with painful, pruritic, annular lesions on buttocks, groin, genitals or face
- Often leading to scarring and secondary bacterial infection
- Predominantly transmitted through sexual contact

Jabet 2024

Kupsch 2019

Luchsinger 2015

Jabet 2023

Jabet et al *EID* 2023; Jabet et al *J Eur Acad Dermatol Venereol* 2024; Luchsinger et al *BMJ* 2015; Kupsch et al *J Dtsch Dermatol Ges* 2019

Reported TMVII cases

- 2016-2017 Berlin: 37 TMVII cases, 60% male, 40% female
- 2021-2022 Paris: 13 TMVII cases in men (12 MSM), 2/13 co-infected with Mpox
- 2022-2023 Paris: A further 32 cases, all in men (30 MSM)
  - 15 cases sporadic, including four among sex workers
  - 17 cases belonged to a cluster, traced to a “tantric masseur” who infected 16 people
  - Incubation period 16 days (2-52 days)
- 2024 USA: 1 male case with travel to Europe, sexual contact with several other men while travelling.
- 2024 USA: A further 4 cases in NYC, all MSM
- TMVII theorised to have emerged from Southeast Asia via travel for sex tourism, now expanding globally, largely via sexual transmission

Luchsinger *Sex Transm Infect* 2015; Kupsch *J Dtsch Dermatol Ges* 2019; Jabet *EID* 2023; Chromy *OFID* 2023; Jabet *J Eur Acad Dermatol Venereol* 2024; Caplan *JAMA Dermatol* 2024; Zucker *MMWR* 2024

Is TMVII the first fungal STI?

- Despite strong evidence for sexual transmission, TMVII doesn't fit the classical definition of STI, infections transmitted through exchange of body fluids during sexual activity

When is it a sexually transmitted infection? Intimate contact transmission of pathogens not traditionally defined as STIs

Angelo Roberto Raccagni[a], *Antonella Castagna*[a,b] *and Silvia Nozza*[a,b]

Curr Opin Infect Dis 2025, 38:65–70

"Clinicians should broaden their diagnostic considerations to include emerging STIs"

"Recognition that non-traditional pathogens can be spread through sexual contact allows for screening protocols and specific management strategies that go beyond the traditional focus on bacterial and viral STIs."

Raccagni *Curr Opin Infect Dis* 2025

Lab identification of TMVII

- Cannot be differentiated by morphology or phenotypes
- Cannot be differentiated by MALDI-ToF
- Currently only differentiated from other T*. mentagrophytes* complex species/genotypes by ITS sequence typing using reference strains
  - Beyond capabilities of most labs
- High index of suspicion needed
- Consider referring any isolate from tinea genitalis cases for sequence-based identification

Treatment of TMVII infections

- Generally susceptible to antifungals
- Oral terbinafine (250 mg/daily) an effective first line option.
- Some patients successful with itraconazole with topical adjuvant therapy
- Topical antifungals alone are not recommended
- Topical steroids should be avoided
- Take treatment until all lesions fully resolved, may take up to 3 months
- Education of patients on treatment compliance, and avoiding skin to skin contact and possible fomites until all lesions resolved

Zucker et al *MMWR* 2024

Final comments

- *T. indotineae* isolates are likely to exhibit antifungal resistance, but other dermatophyte species are sporadically resistant.
- Labs and clinicians need to have high index of suspicion for *T. indotineae*, and of dermatophytes as agent of STI.
- Global expansion of resistant pathogenic fungi and new transmission risks will continue in response to selective pressure from clinical antifungals, fungicide use, and climate change (see also *Candida auris*, azole-resistant *Aspergillus*)

With thanks

Dr. Lucy Crawford

A/Prof. David Ellis

Sonia Kralj

Dr. Ian Ross

Dr. Lex Leong

Dr. Jacob May

A/Prof. Morgyn Warner

Dr. Gerhard Weldhagen

SA PATHOLOGY

Dr. Catriona Hayes

Dr. Jonathon Chan

DSG
Dermatology Specialist Group
ARDROSS, WESTERN AUSTRALIA

Prof. Sharon Chen

Dr. Catriona Halliday

NSW GOVERNMENT
NSW Health Pathology

Dr. Shawn Lockhart

CDC
U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

A/Prof. Lars Westblade

Weill Cornell Medicine