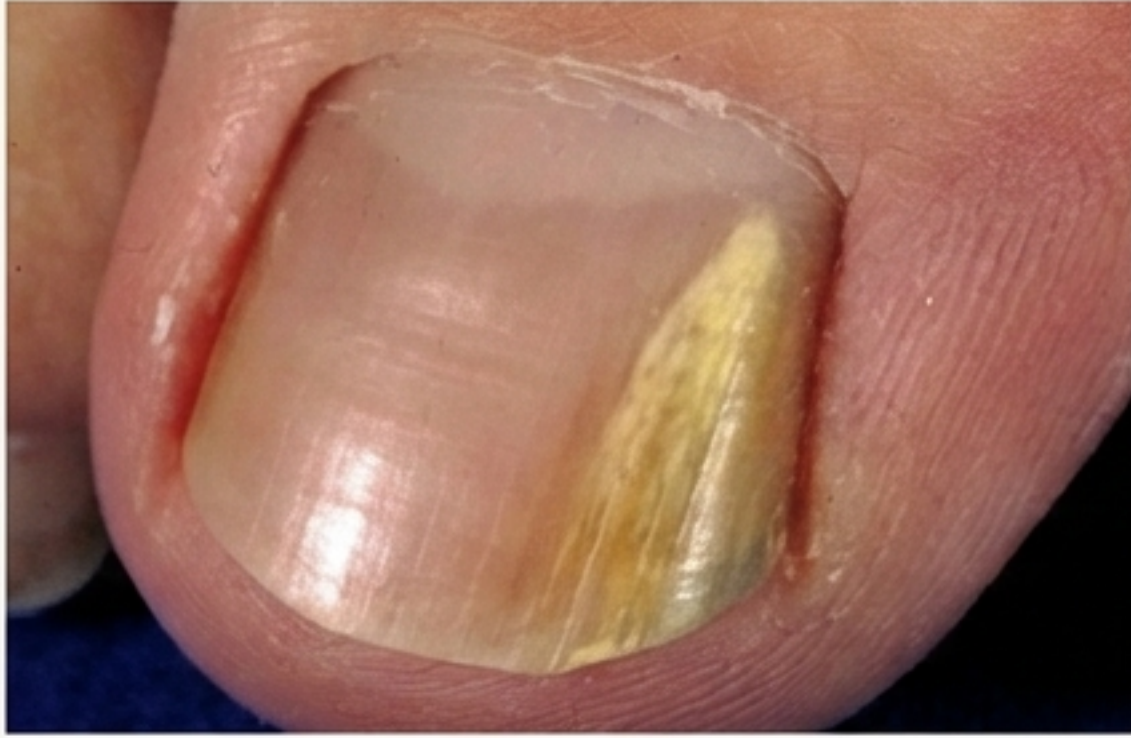


# Fungal Nail Infection is More Than a Cosmetic Concern

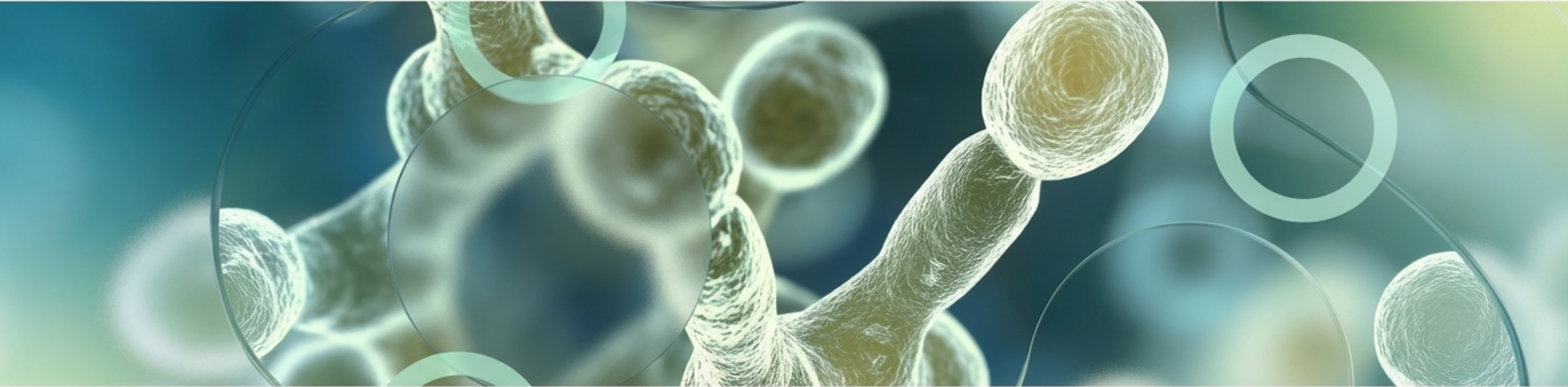


**Affects up to 6% of the global population, with prevalence rising to over 50% in people aged over 70.**



Onychomycosis, or fungal nail infection, is a common and persistent clinical problem. While often dismissed, it can significantly impact quality of life, causing pain when walking, psychosocial distress, and embarrassment. Untreated, it can lead to permanent nail damage, spread to other nails, and increase the risk of secondary bacterial infections like cellulitis, especially in patients with diabetes or immunosuppression.

# The Investigation Begins: Identifying the Causative Agents



- Dermatophytes, fungi that degrade keratin, are the primary cause in 60-90% of all cases.
  - ***Trichophyton rubrum***: The most frequently identified organism.
  - **Yeasts (e.g., *Candida albicans*)**: Responsible for 10-20% of cases, more commonly affecting fingernails.
  - **Non-dermatophyte moulds**: Account for approximately 10% of infections.

## Key Clinical Insight

Laboratory confirmation is crucial before starting treatment. Empiric therapy can lead to false negative cultures later, complicating diagnosis if the initial treatment fails.

# The Two Main Contenders: Terbinafine vs. Itraconazole

## Terbinafine (Lamisil)

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- **Class:** Allylamine
- **Mechanism:** Inhibits squalene epoxidase, a crucial enzyme in fungal cell membrane synthesis.
- **Action:** Primarily **fungicidal** (kills the fungus).
- **Typical Regimen:** Continuous daily dosing (e.g., 250 mg/day for 12 weeks for toenails).

## Itraconazole (Sporanox)

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- **Class:** Triazole
- **Mechanism:** Inhibits cytochrome P-450 14 $\alpha$ -demethylase, disrupting ergosterol synthesis at a later stage.
- **Action:** Primarily **fungistatic** (inhibits fungal growth).
- **Typical Regimen:** Intermittent "pulse" dosing (e.g., 400 mg/day for 1 week per month).

Both are potent, but which provides a more effective and durable cure?

The clinical evidence holds the answer.

# The LION Study: A Head-to-Head Comparison

A prospective, randomised, double-blind, multicentre study to find the superior treatment for toenail onychomycosis.

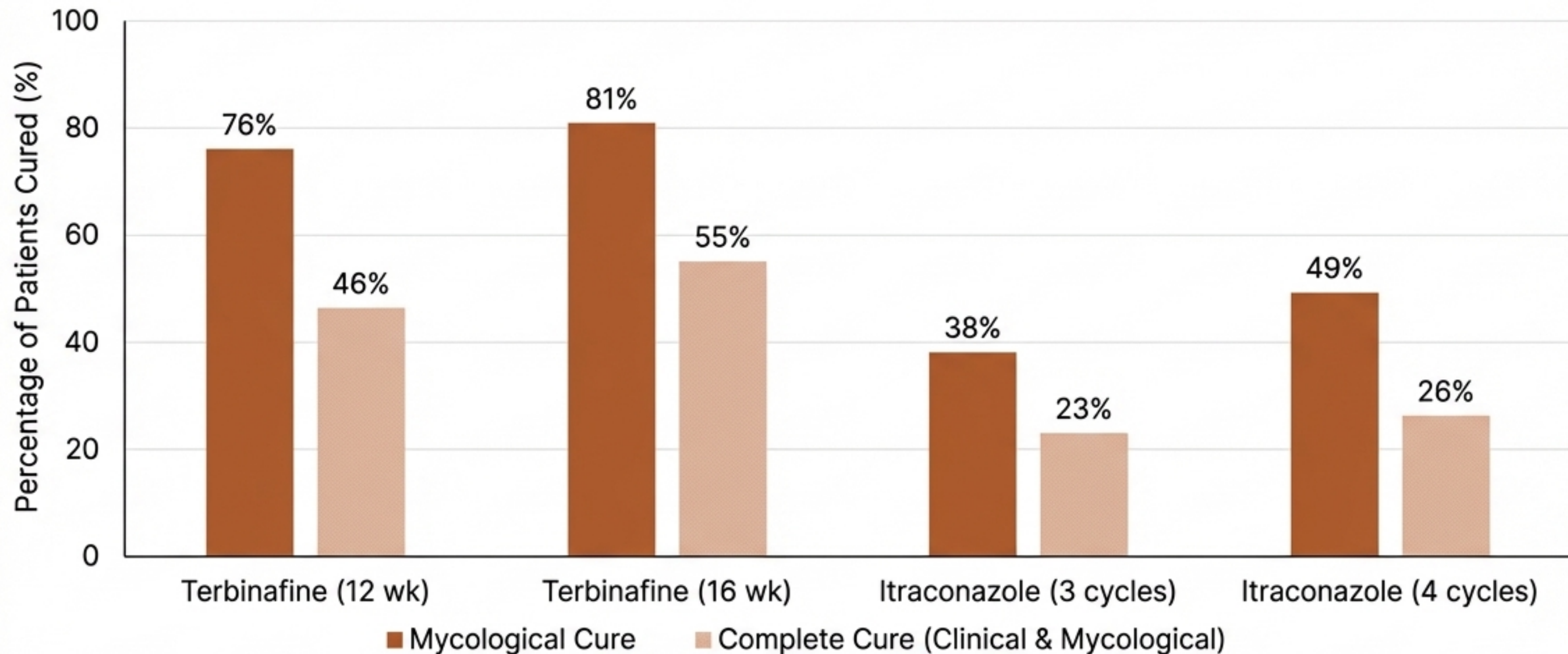
## Key Study Parameters

- **Objective:** To compare the efficacy and safety of continuous **terbinafine** with intermittent **itraconazole**.
- **Duration:** **72 weeks**.
- **Population:** **496 patients** with confirmed dermatophyte toenail onychomycosis.
- **Interventions:**
  - **Group T12/T16:** Terbinafine **250 mg/day** for **12 or 16 weeks**.
  - **Group I3/I4:** Itraconazole **400 mg/day** for **1 week/month**, for **3 or 4 cycles**.
- **Primary Outcome:** **Mycological Cure at Week 72** (negative microscopy and culture).

*“We conducted the first large scale, double blind comparison of continuous terbinafine with intermittent itraconazole in the treatment of toenail onychomycosis.”*

# The Evidence at 72 Weeks: A Clear Winner Emerges

## Cure Rates at Week 72 (LION Study)



All comparisons showed significantly higher cure rates in the terbinafine groups ( $P < 0.0001$ ). For itraconazole, there was no significant improvement in clinical cure beyond week 48.

# Beyond the Initial Cure: The 5-Year Follow-Up

A prospective study reveals significant differences in long-term effectiveness and relapse rates.

## Long-Term Mycological Cure (without re-treatment)

**46%**

Terbinafine

**13%**

Itraconazole

(P<.001)

## Mycological Relapse Rates

**23%**

Terbinafine group

**53%**

Itraconazole group

“In the treatment of onychomycosis, continuous terbinafine provided superior long-term mycological and clinical efficacy and lower rates of mycological and clinical relapse compared with intermittent itraconazole.”

# The Financial Verdict: Cost-Effectiveness and Disease-Free Time

A pharmacoeconomic analysis from a government payer perspective in Canada.

Although older drugs like Griseofulvin have lower acquisition costs, Terbinafine's shorter treatment duration and higher success rate make it the most cost-effective choice.

## Expected Cost for Toenail Onychomycosis

Treatment	Expected Total Cost
<b>Terbinafine</b>	<b>\$1,049.77</b>
Griseofulvin	\$1,388.54
Ketoconazole	\$1,936.48

## Maximizing Healthy Days

**1,073** **disease-free days** for toenails provided by Terbinafine.

This compares to 798 days for Ketoconazole and only 569 days for Griseofulvin.



## The Plot Twist: A Warning from the FDA

**ADVISORY**

**The US Food and Drug Administration (FDA) issued warnings about rare but serious side effects associated with both drugs.**

### **Itraconazole (Sporanox)**

- Physicians warned against prescribing for fungal nail infections in patients with congestive heart failure (CHF) or a history of CHF, as the drug may weaken heart contractions.

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### **Both Itraconazole and Terbinafine (Lamisil)**

- Have been associated with rare cases of serious liver problems, including liver failure.

Regulatory Mandate: The FDA advises physicians to obtain lab specimens to confirm diagnosis before prescribing either medication.

# A Closer Look at Hepatotoxicity Risk



While antifungal-induced acute liver failure is rare, it is a known risk that requires clinical vigilance.

## Comparative Risk (from a Taiwanese cohort study)

- The study identified **58 cases** of drug-induced liver injury (DILI).
- Longer treatment duration may increase risk, especially for ketoconazole, where the DILI rate increased from **49 per 100,000** to **1,286 per 100,000** for courses >30 days.

## Most Serious Potential Side Effects

- **Terbinafine:** Liver damage, severe skin reactions, blood issues.
- **Itraconazole:** Heart failure, liver problems, pancreatitis.

## Clinical Recommendation (from systematic review)

Liver function evaluation before treatment and periodic monitoring every three to six weeks after commencement of treatment is suggested.

# Voices from the Front Lines: The Patient Experience

“Terbinafine won't turn the affected nail back to normal, it kills the fungus in place... It allows for the new nail to grow fungus free from the base. you just clip away the already damaged nail as it grows.

“I get frustrated when I hear toe nail fungus is just cosmetic... mine hurts too. So I am trying hard to treat this.

“I am 6 weeks terbinafine and no results either i am so discouraged... Toenails only grow approximately 1 mm per month. Give it time.

# The Verdict: Terbinafine is the Evidence-Based First-Line Choice



## Superior Efficacy & Durability

Consistently higher mycological and complete cure rates in large-scale, double-blind trials (**76-81% vs. 38-49%** mycological cure).

Significantly lower long-term relapse rates (**23% vs. 53%**), leading to a more durable cure.



## Greater Cost-Effectiveness

Lowest overall expected cost when factoring in treatment success and duration.

Provides the greatest number of disease-free days post-treatment.



## The Critical Caveat - Safety

The choice is not without risk. Rare but **serious hepatotoxicity** is a known side effect.

This necessitates baseline laboratory confirmation of fungus and **monitoring of liver function** during therapy.

# A Practical Guide to Management

A three-step approach to optimizing outcomes and ensuring patient safety.

1

## Confirm the Diagnosis Before Treatment

- Use potassium hydroxide (KOH) preparation, fungal culture, or PAS stain.
- This prevents unnecessary exposure to oral antifungals and their potential side effects.
- Remember: Prior antifungal use can inhibit culture growth, leading to false negatives.



2

## Assess the Patient & Select Therapy

- Oral terbinafine is first-line for dermatophyte onychomycosis.
- Consider patient factors: liver disease, heart failure (contraindication for itraconazole), and potential drug-drug interactions.
- Topical therapy is a less effective alternative for mild-to-moderate cases without matrix involvement.



3

## Monitor and Manage

- Obtain baseline liver function tests (LFTs) before starting oral therapy.
- Re-check LFTs four to six weeks after treatment initiation.
- Advise patients to report any symptoms of hepatotoxicity (nausea, fatigue, jaundice) immediately.



# Setting Expectations and Preventing Recurrence

## The Long Road to a New Nail

# 18 months

Full regrowth of a toenail can take up to 18 months.

- **Patience is Key:** Healing is slow, at about 1 mm per month.
- **Healing is Growth:** The damaged, infected nail will **not** revert to normal. The goal is the growth of a new, healthy nail from the base.



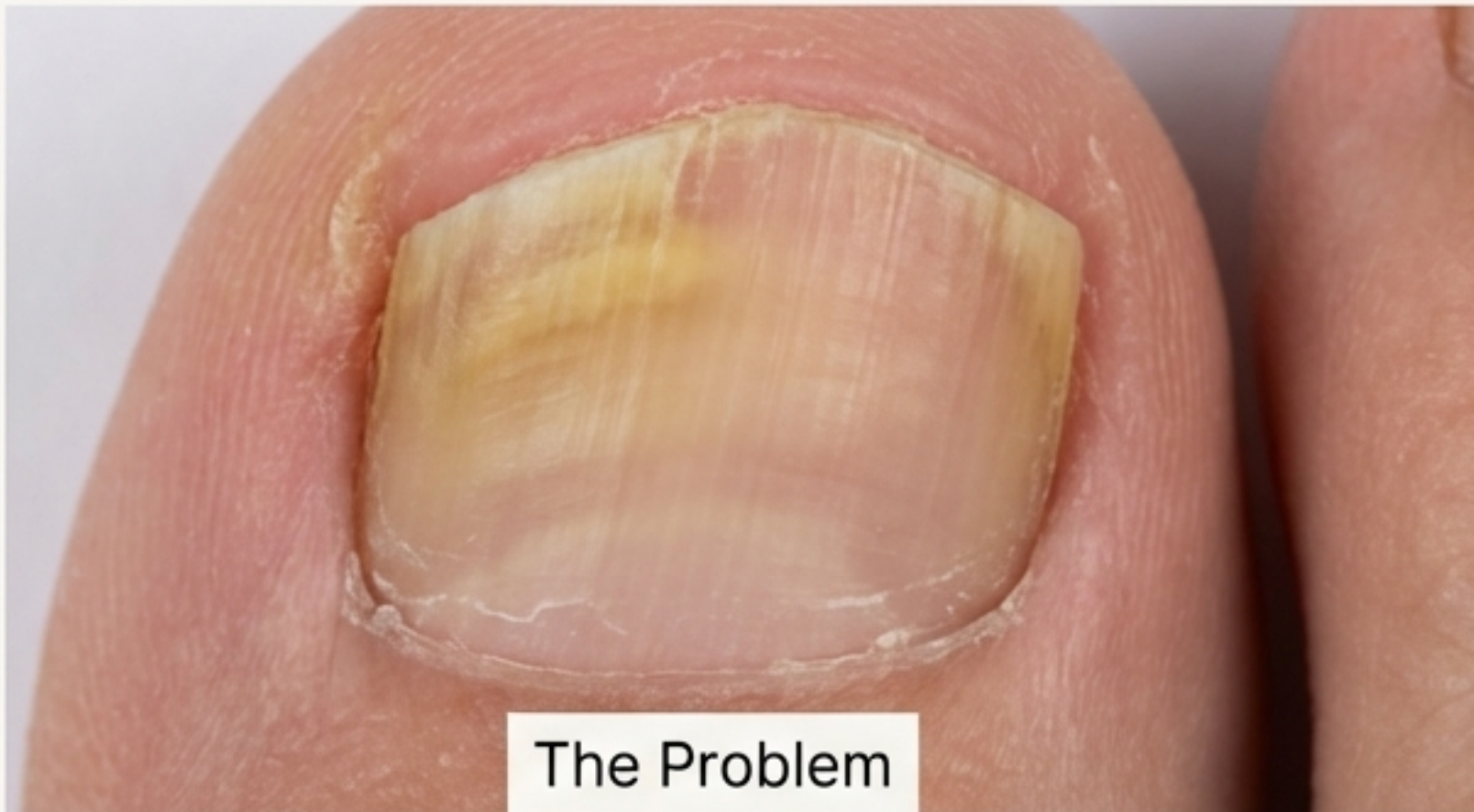
## Preventing a Relapse

## The relapse rate is as high as 25%

- Keep feet cool and dry with cotton socks and breathable footwear.
- Treat co-existing tinea pedis (athlete's foot), which can act as a fungal reservoir.
- Wear footwear in communal areas like pools and gyms.
- Disinfect shoes and socks regularly with antifungal powders or sprays.



# The Journey to a Cure: A Matter of Evidence, Patience, and Vigilance



- **Evidence:** Choosing the right therapy is based on robust clinical data showing superior efficacy and durability.
- **Patience:** Success requires understanding that visible results take months as a new, healthy nail slowly grows out.
- **Vigilance:** Safety is paramount, requiring pre-treatment confirmation and careful monitoring, followed by proactive prevention of recurrence.