Recurrent and recalcitrant tinea corporis / cruris infection – management approach

Background
There is currently an epidemic of terbinafine-resistant *Trichophyton interdigitale/menagrophytes* in India, which causes recurrent and recalcitrant tinea corporis and cruris, with increasing numbers of cases being seen in Dermatology clinics and GP practices in the UK. The extent of this problem is likely wider than is currently described. There is currently no consensus about the best way to manage patients with recurrent and recalcitrant tinea corporis and cruris.

Aim
To propose an approach for managing patients with recurrent or recalcitrant tinea corporis and cruris.

Definition
Of recalcitrant tinea corporis / cruris: "no or limited response (<50% reduction) after 3 weeks of first-line systemic antifungal therapy, with terbinafine 250mg od"

Actions for GP or Dermatology team

Investigation
All patients with clinically suspected tinea corporis or cruris that has failed to adequately respond to first-line treatment should have a sample submitted for mycological analysis, to confirm the diagnosis and to help determine the most effective antifungal agent.

Collect skin scrapings from the edge of the lesion(s) into a Dermatophyte Collection Kits (MycoTrans, Dermapak or similar). On tQuest or CRS; request 'Mycology MC&S', stating the sample type as 'skin scraping' and in clinical details state 'recalcitrant tinea'.
email microbiology.bartshealth@nhs.net to alert re incoming sample
email Jonathan.Lambourne@nhs.net (microbiology consultant) who will collate cases and follow-up lab results
See appendix for more information re sampling, requesting & packaging.

Treatment approach
- Increase terbinafine to 250mg bd (if terbinafine not already tried, then consider terbinafine 250mg po od for 3 weeks before increasing to 250mg bd if no response at 3 weeks)
- Review at 3 weeks
    - If >50% clinical clearance was achieved
        - continue terbinafine 250mg bd until clinical cure
    - If response is <50% (or if clinical cure with terbinafine 250 bd takes >9 weeks)
        - switch to itraconazole (200mg bd)
        - for at least 6 weeks to clinical cure
    - if response on itraconazole at week 6 is sub-optimal
        - consider checking trough levels & switching to liquid preparation of itra
        - consider referring to dermatology

Adjunctive treatments to consider
Ensure the patient is not using any topical steroids a these may impede eradication of the infection.
Consider screening, and treating, household contacts (50% of household contacts affected in case series).
When undertaking household treatment, this should be undertaken simultaneously, rather than sequentially.
Consider high temperature wash of shared household items such as bed linen and towels.
Consider adjunctive topical therapy such as Whitfield's ointment.
Consider adjunctive therapies for symptom control:
Anti-histamines
Anti-inflammatories
Moisturisers / emollients

Points to bear in mind & monitoring for antifungal prescribing
Terbinafine
Side effects to be aware of: change in taste, depression, hepatitis, exacerbation of lupus
Cautions / avoid:
Pregnancy - 'avoid'
Breast-feeding – 'risk-benefit'

Advanced hepatic impairment – 'avoid'
SLE – discuss with rheumatology or dermatology team responsible for their SLE care via A&G or email
Renal impairment - use half normal dose if eGFR < 50 mL/minute/1.73 m2

Monitoring LFTs:
LFTs before starting (especially if known pre-existing liver disease, alcohol excess, abnormal LFTs)
Repeat LFTs at week 4-6 if terbinafine needs to be continued beyond this point
Repeat LFTs sooner if symptoms arise suggesting hepatotoxicity (e.g nausea, abdo pain, jaundice)
If LFTs at baseline abnormal, use terbinafine with caution, and consider more frequent monitoring

Itraconazole
Side effects to be aware of: GI upset (nausea, diarrhoea), exacerbation of heart failure, hepatotoxicity, QTc prolongation with co-administration of other agents, liquid preparation tastes unpleasant (to some)

Cautions / avoid:
Pregnancy- 'avoid' in first trimester
consider contraception during and for 2/12 post-treatment
Breast feeding - 'risk-benefit'
Heart failure – 'risk-benefit' (and close monitoring)
Grapefruit juice – avoid
Check interactions (QTc & CYP3A4)
Do not take either form with Gaviscon or alginates

Dosing 200mg bd
Start with capsule formulation (which can be opened and mixed into food for children).
Take immediately after food or with acidic liquid e.g. orange juice, cola drink, ginger ale
If on antacid take 2hrs pre or post antacid

Monitoring – baseline
ECG if history of arrythmia and/or if already on a medication known to prolong the QTc
LFTs if known pre-existing liver disease, alcohol excess, abnormal LFTs)

Monitoring – on treatment
ECG at around day 10-14 if baseline QTc prolonged and/or if history of arrythmia or if co-prescribed a medication known to prolong the QTc

LFTs at week 4-6 if itraconazole needs to be continued beyond this point
repeat LFTs sooner if symptoms arise suggesting hepatotoxicity (e.g nausea, abdo pain, jaundice)
consider itraconazole serum levels if side effects (as may need to reduce dose), see below
If LFTs at baseline abnormal, use itraconazole with caution & consider more frequent monitoring

Failure to respond to itraconazole
Absorption of itraconazole in capsule form is variable, and can be poor, so inadequate absorption may be a reason for poor clinical response.

Consider
1: Checking trough itraconazole levels
Take serum sample at least 6 hours after the last dose (and ideally as close to pre-dose as possible).
Target trough = >0.5mg/L. Levels >4mg/L are associated with higher risk of toxicity.

2: If trough itraconazole level is low, then try switching to the liquid preparation of itraconazole.
Same dose, 200mg bd. Take on empty stomach (1 hour pre or post food).
This preparation is more expensive (£4/100mg).

Actions for microbiology laboratory
Any dermatophytes that grow from samples sent with a request indicating recurrent / recalcitrant tinea corporis or cruris should be sent to both the PHE Mycology Reference Lab (Bristol) and to Sue Howell, mycologist at St John's in order to:
confirm the identification of the dermatophyte
undertake susceptibility testing (MICs +/- epidemiological cut-offs) to the following:

first line: terbinafine, itraconazole, voriconazole
second line: griseofulvin, posaconazole, olorofilm

save & store the isolate (at St John's) in anticipation of future work (e.g. sequencing)

Please email Jonathan Lambourne (microbiology consultant, Jonathan.Lambourne@nhs.net) when an isolate has been sent to PHE & to St John's in order to maintain the log of cases & isolates.

Actions for microbiology medics

If validating or authorising any results from Winpath that report the growth of a dermatophyte, where the clinical details suggest the possibility of ecurrent and recalcitrant tinea corporis or cruris then please:

Alert the mycology bench to send isolates to Mycology Ref Lab & St Johns (as above)
Email Jonathan.lambourne@nhs.net (who will maintain the log of cases & isolates)

Useful refences

Public Health England guidance: Fungal skin and nail infections: Diagnosis and laboratory investigation. Quick reference guide for primary care
https://www.gov.uk/government/publications/fungal-skin-and-nail-infections-diagnosis-and-laboratory-investigation

Alarming India-wide phenomenon of antifungal resistance in dermatophytes: A multicentre study. Ebert A et al. Mycoses. 2020 Jul;63(7):717-728. doi: 10.1111/myc.13091.

Appendix- How to take a skin scraping

Collection Instructions

1. Clean the infected site with 70% alcohol (or sterile water if inflamed) to eliminate body bacteria. Allow to air dry.
2. Remove the black paper provided in the Dermatophyte Collection Kit (e.g. MycoTrans, Dermapak or similar).
3: Using a scalpel blade, scrape the active periphery of the infected site onto the black paper.
4: Carefully fold the paper so the skin scrapings are enveloped inside.

Requesting and labelling Instructions

1: On tQuest (GP) or CRS (Dermatology)
request Mycology MC&S
record the sample type as 'skin scraping'
in clinical details state 'recalcitrant tinea'.

2. Affix the request sticker to the outside of the folded black paper
3. Place the folded black paper into the envelope provided.
4: Handwrite the patient details in the envelope
5: Place the envelope inside the plastic bag provided with the kit and seal.
6. Store and transport at room temperature – do not refrigerate

Informing the microbiology team re incoming samples

email microbiology.bartshealth@nhs.net to alert re incoming sample (as samples from patients with recurrent & recalcitrant tinea corporis / cruris require more work than routine samples)
email Jonathan.Lambourne@nhs.net (microbiology consultant) who will collate cases and follow-up lab results

How to obtain Dermatophyte Collection Kits

For GP surgeries: Dermatophyte Collection Kits (e.g. MycoTrans) can be ordered from Pathology Reception at the Royal London Hospital using the GP pathology stock order form (same form is used for blood tubes, urine containers etc) and write on the form the number of MycoTrans collection kits required.

For Dermatology clinics: Dermatophyte Collection Kits (e.g. MycoTrans) can be ordered from Pathology Reception at the Royal London Hospital using the current ordering process, or can be collected from the microbiology department in the Pathology & Pharmacy Building at the Royal London Hospital (email microbiology.bartshealth@nhs.net to arrange)