

## Bullous fixed drug eruption induced by fluconazole: Importance of multi-site lesional patch testing

Ky Lyn Tan<sup>1</sup>, Ilaria Bisconti<sup>1</sup>, Claire Leck<sup>1</sup>, Thippeswamy Billahalli<sup>1</sup>, Sheena Barnett<sup>1,3</sup>,  
Karalasingam Rajakulasingam<sup>1,3</sup>, Timothy J. Watts<sup>1,2\*</sup>

<sup>1</sup> Department of Respiratory Medicine & Allergy, Homerton University Hospital NHS Foundation Trust, London E9 6SR, United Kingdom

<sup>2</sup> National Heart & Lung Institute, Imperial College London, London SW7 2AZ, United Kingdom

<sup>3</sup> Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London, E1 2AD, United Kingdom

### \* Corresponding Author:

Timothy J Watts

Email: [t.watts@imperial.ac.uk](mailto:t.watts@imperial.ac.uk)

Phone: (+44) 020 8510 7769

Postal address: Dr Timothy J. Watts, Department of Respiratory Medicine & Allergy, Homerton University Hospital NHS Foundation Trust, London E9 6SR, United Kingdom

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Fluconazole, a triazole antifungal agent, is commonly used in the treatment of vulvovaginal candidiasis<sup>1</sup>. Whilst fluconazole is rarely associated with fixed drug eruptions (FDE), there have however been a growing number of cases reported in the literature<sup>1,2</sup>. In FDE, patch testing has reported utility<sup>3</sup>, and is conventionally performed on residual pigmented lesional sites<sup>4</sup>. In this case report of bullous FDE induced by fluconazole, we report on the value of multi-site lesional patch testing in safely establishing the diagnosis.

### Case Report

A 39-year old-lady with recurrent vaginal candidiasis was referred to the allergy clinic for investigation into episodic erythematous vesicular-bullous lesions, affecting her lower lip, wrist, knee and elbow regions. These all developed following ingestion of a single fluconazole 150mg tablet, always at the same skin sites. The acute lower lip area bullous lesion (Figure 1a) typically started to emerge 30 minutes after drug ingestion, and left only temporary pigment change, which vanished entirely within a few weeks. The bilateral knee eruptions left persisting residual hyperpigmentation (Figure 1b). She had since tolerated topical clotrimazole, although this was not clinically effective. The clinical presentation was deemed to be in keeping with a likely bullous FDE.

Intradermal testing was later performed with fluconazole (1:10 dilution of 2 mg/ml) on the unaffected forearm and this was entirely negative at 48 hour reading. Lesional patch testing using IQ Ultra chambers was then performed on the only remaining residual pigmented skin sites (knees bilaterally) to fluconazole (30% in petrolatum (pet)), itraconazole (30% pet), ketoconazole cream 2% and clotrimazole cream 1%.

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These readings and control site duplicate testing (unaffected back) were entirely negative at Day 2 (D2) and Day 4 (D4). Additional (open) lesional patch testing to fluconazole (30% pet) was then undertaken on the lower lip adjacent skin (which lacked residual pigmentation), and this produced within 24 hours a strong positive vesicular-bullous reaction (+++) (Figure 2). All other prior FDE sites remained quiescent as expected.

The patient was diagnosed with an oral fluconazole-induced bullous FDE following the lesional patch testing confirmation. We additionally later on also conducted further open lesional patch testing to itraconazole (oral solution neat) to the lower lip adjacent skin, which was entirely negative at D2 & D4 readings. This was followed by an oral provocation test to itraconazole 200mg twice a day (single day course) which was fully tolerated and was recommended as the safe triazole antifungal alternative for future use.

## Discussion

FDE are erythematous, violaceous or vesicular-bullous lesions that recur at the same site typically 30 minute to 8 hours after re-exposure to a causative drug<sup>5</sup>. It is a specific CD8 T-cell mediated delayed type IV hypersensitivity (DTH), where the drug causes reactivation of resident cutaneous memory T lymphocytes<sup>3,6</sup>. Patch testing in general is an effective and safe diagnostic tool for the investigation of DTH (including FDE)<sup>7,8</sup>. However, the sensitivity of drug patch testing is variable<sup>7</sup>, and often oral provocation tests are required, which can fully reactivate the eruption<sup>6</sup>. To date there are a total of 28 previously published case reports on fluconazole-induced FDEs

listed on MEDLINE<sup>1,6</sup>. However, fluconazole patch reactivity rate in FDE is low at only 27%, accordingly to recent reports<sup>1</sup>.

Our report describes a novel and interesting finding, whereby we successfully elicited a positive patch test on a previously affected site that lacked any residual hyperpigmentation; suggesting that pigmented lesions should not be the only locations used when considering lesional patch testing in FDE. We therefore propose that in FDE multiple prior lesional sites (hyperpigmented and normal) should be patch tested, especially in cases where preliminary results are negative, to increase the overall detection rate. This may reduce the need for oral challenge studies, which carry the risk of generalised FDE reactivation<sup>6</sup>. The (false) negative patch test result on the pigmented knee lesions may hypothetically be related to increased stratum corneum thickness and poor percutaneous penetration of the drug<sup>9</sup>. It is also important to note, that the same lesional testing approach combined with an oral challenge (both of which were negative), also excluded cross-reactivity to itraconazole.

In conclusion, our report highlights the value of multi-site lesional patch testing in FDE, including affected areas without residual hyperpigmentation, to improve the chance of detection and avoid systemic reactivation from oral provocation testing.

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## Figure Legends:

**Figure 1:** Acute fixed drug eruption ruptured bullae 24 hours after taking oral fluconazole on lower lip region **(a)** and persisting residual hyperpigmentation on right knee **(b)**.

**Figure 2:** Strong positive vesicular-bullous reaction (+++) on lower lip region, after open lesional patch testing with fluconazole (photo taken at 24 hours post testing)

**Figure 1**

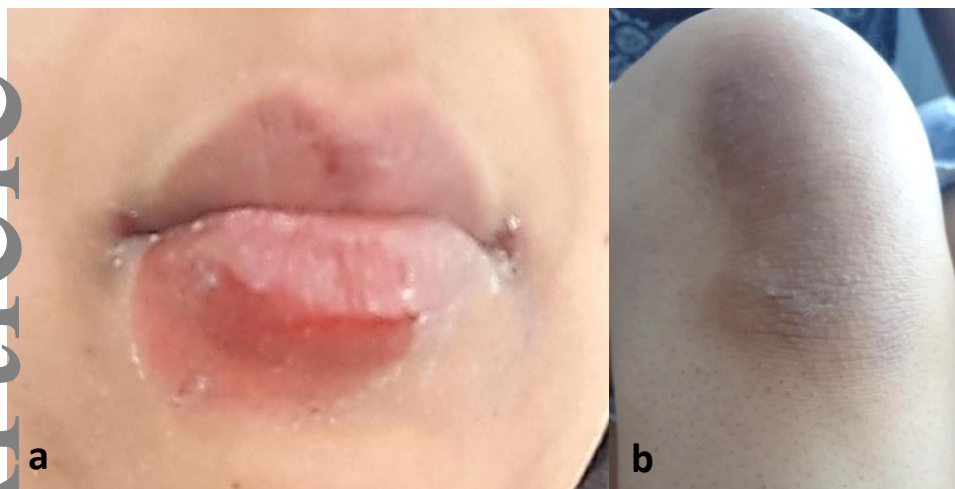


Figure 2

