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Generalized fixed drug eruption to piperacillin/tazobactam and review of literature

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Abstract
Fixed drug eruption (FDE) is an adverse drug reaction characterized by the development of well-circumscribed, round, dusky erythematous macules and plaques on cutaneous or mucosal surfaces. The reaction occurs on the same mucosal or cutaneous site with subsequent exposures to the offending drug. Although FDE usually manifests as a single lesion, in rare instances, more than one lesion may arise and this is referred to as a generalized eruption. Herein, we present a 31-year-old man with history of cystic fibrosis who developed a generalized fixed drug eruption to piperacillin/tazobactam (Zosyn, Pfizer). We discuss our patient’s course and review causes and outcomes of generalized fixed drug eruptions in the literature.

Keywords: fixed drug eruption, generalized fixed drug eruption, piperacillin/tazobactam

Introduction
Fixed drug eruption (FDE) is an adverse drug reaction characterized by the development of well-circumscribed, round, dusky erythematous macules and plaques on cutaneous or mucosal surfaces [1-5]. This reaction is often accompanied by a sensation of burning or pruritus and occurs in the same mucosal or cutaneous site with each subsequent exposure to the offending agent [1, 2]. Although the exact pathophysiology has not been elucidated, CD8+ T cells are believed to play a role in causing the epidermal damage [1, 2, 6]. Although FDE usually manifests as a single lesion, in rare instances more than one lesion may arise, which is referred to as a generalized eruption [2-4]. Although FDE to piperacillin/tazobactam has been reported in the literature [7], herein we report a case of generalized FDE to piperacillin/tazobactam and review reported causes of generalized FDE in the literature.

Case Synopsis
A 31-year-old man with a past medical history of patent foramen ovale, cystic fibrosis, diabetes mellitus type II, and pancreatic insufficiency was admitted for a cystic fibrosis flare. The patient received piperacillin/tazobactam and developed several non-pruritic dusky, grey two-toned macules and patches <3cm in size on the hands, arms, legs, and abdomen (Figure 1). The patient reported that when he was previously treated with piperacillin/tazobactam two months prior, he developed a similar solitary asymptomatic patch on his dorsal hand, which was persistent at the time of presentation. Biopsy from the dorsal hand revealed junctional vacuolar alteration and necrotic keratinocytes along the dermal-epidermal junction and superficial, predominantly lymphocytic infiltrates with sparse eosinophils and neutrophils. The presence of melanophages around superficial vessels supported the clinical impression of a fixed drug reaction (Figure 2). The offending medication
was continued and the patient was treated with triamcinolone 0.1% ointment with improvement.

**Discussion**

Although antibiotics are one of the most common culprits of FDE, to our knowledge, this is the first known case of generalized FDE to piperacillin/tazobactam in the literature. Generalized FDE comprise only a small subset of FDE [2]; we therefore set out to review cases of generalized FDE is in the literature, the agents implicated, and the timing of the drug eruptions (Table 1). We conducted a PubMed search using the term “generalized fixed drug eruption” spanning January 2001 though November 2017. Only case reports and case-control studies written in English were eligible for inclusion. Our search yielded 27 articles containing 45 cases [1-28]. Three articles were excluded because one was not written in English [26] and two were not case reports or case-control studies [15, 17].

Our findings from this review correlate with information concerning FDE elsewhere in the literature. NSAIDS and antibiotics are two of the most common types of pharmacologic agents implicated

![Figure 1. Generalized Fixed Drug Eruption: A), B) distribution of the dusky lesions on the upper and lower extremities, respectively. C) Shows the biopsy site of the primary lesion on the left dorsal hand](image)

![Figure 2. Histopathologic findings of fixed drug eruption. Biopsy findings include a vacuolar interface dermatitis and melanin pigment around superficial vessels, supporting the impression of a generalized fixed drug eruption. H&E, A) 4x, B) 20x.](image)
in FDE [3, 5, 6, 29]. This was also the case for our review of generalized FDE in which 22 (50%) of the cases implicated antibiotics [4-6, 10, 12, 13, 20, 21, 28], and 16 (36%) implicated NSAIDs [1-3, 9, 11, 14, 16, 20, 25]. FDE tends to occur within 30 minutes to 24 hours after exposure [29]. Most of the generalized FDE cases included in our review also occurred within this interval [2-6, 8-10, 12-14, 16, 21, 23-25]. Additionally, it has been noted that the number of sites affected may increase with re-exposure to a given drug, meaning an FDE can present as generalized FDE upon re-exposure [3, 6, 29]. This correlates with our patient’s account and several cases in our review [1-3, 9, 10, 12, 18, 21, 23, 28]. In the majority of cases in our review, the offending drug was discontinued [1, 4-6, 9, 11, 13, 14, 16, 18, 21-25, 27, 28]. In our patient’s case, piperacillin/tazobactam was considered critical for his long-term prophylactic management, so this medication was continued. The patient was treated with triamcinolone 0.1% ointment with improvement.

**Conclusion**

Although there are many reported cases of FDE in the literature, there are few cases of generalized FDE [2]. To help address this gap, we describe the first reported case to our knowledge of a patient who developed a generalized FDE to piperacillin/tazobactam.

### Table 1. Reported Cases of Generalized Fixed Drug Eruption.

<table>
<thead>
<tr>
<th>Source Article (year) [Reference]</th>
<th>Offending drug</th>
<th>Timing of eruption after drug initiation</th>
<th>Was the drug stopped?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Doval et al. (2001) [8]</td>
<td>Influenza Vaccine</td>
<td>12-24 hours</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Leivo et al. (2004) [9]</td>
<td>Naproxen</td>
<td>Within 24 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Ada et al. (2008) [10]</td>
<td>Ciprofloxacin</td>
<td>“a few hours”</td>
<td>Yes</td>
</tr>
<tr>
<td>Hager et al. (2009) [12]</td>
<td>Levofoxacin &amp; Ciprofloxacin</td>
<td>12 hours</td>
<td>Not stated</td>
</tr>
<tr>
<td>Rho et al. (2010) [1]</td>
<td>Piroxicam</td>
<td>48 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Sawada et al. (2011) [13]</td>
<td>Paufoxacin</td>
<td>1 hour</td>
<td>Yes</td>
</tr>
<tr>
<td>Biliti et al. (2012) [2]</td>
<td>Diclofenac potassium Naproxen</td>
<td>6 hours</td>
<td>Not stated</td>
</tr>
<tr>
<td>Chen &amp; Chiang (2012) [14]</td>
<td>Ibuprofen</td>
<td>6 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Nitya et al. (2013) [5]</td>
<td>Doxycycline</td>
<td>Within 24 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Rubegni et al. (2013) [16]</td>
<td>Nimesulide</td>
<td>12 hours</td>
<td>Yes</td>
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<td>Balta et al. (2014) [3]</td>
<td>Flurbiprofen</td>
<td>6 hours</td>
<td>Not stated</td>
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<tr>
<td>Can et al. (2014) [6]</td>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>30 minutes- 1 hour</td>
<td>Yes</td>
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<td>Kaku et al. (2014) [18]</td>
<td>Tranexamic acid</td>
<td>Not stated</td>
<td>Yes</td>
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<td>Ozkol et al. (2014) [19]</td>
<td>Ursodeoxycholic acid</td>
<td>5 days</td>
<td>Not stated</td>
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<tr>
<td>Kavoussi et al. (2015) [20]</td>
<td>Cotrimoxazole (6)* Metronidazole (4)* Ibuprofen (3)* Doxycycline (2)* Nitrofurantoin Azithromycin Mefenamic acid Meloxicam Novafen</td>
<td>Not stated</td>
<td>Not stated</td>
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<tr>
<td>Kim et al. (2015) [4]</td>
<td>Cefaclor</td>
<td>Within 24 hours</td>
<td>Yes</td>
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<td>Podder et al. (2016) [21]</td>
<td>Doxycycline</td>
<td>Within 24 hours</td>
<td>Yes</td>
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<td>Vide et al. (2016) [22]</td>
<td>Bromhexine</td>
<td>Not stated</td>
<td>Yes</td>
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<td>Garcia &amp; Cohen (2017) [28]</td>
<td>Dapsone</td>
<td>Not stated</td>
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<td>Fukuda et al. (2017) [23]</td>
<td>Pseudoephedrine hydrochloride</td>
<td>6 hours</td>
<td>Yes</td>
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<td>Georgesen et al. (2017) [24]</td>
<td>Mycophenolate</td>
<td>Within 24 hours</td>
<td>Yes</td>
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<td>Malviya et al. (2017) [25]</td>
<td>Ibuprofen</td>
<td>24 hours</td>
<td>Yes</td>
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<tr>
<td>Ramirez-Bellver et al. (2017) [27]</td>
<td>Metformin</td>
<td>Not stated</td>
<td>Yes</td>
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References


