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Evaluating Drug Fever to Beta Lactam Antibiotics

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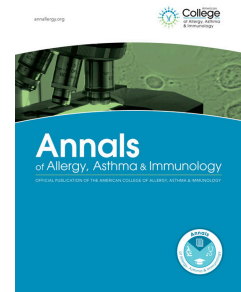
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Title: ~~A Case of~~ Evaluating Drug Fever to Beta Lactam Antibiotics

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Drug fever is a rare and frequently overlooked reaction to medications. Drug fever is often missed, as fever is commonly miscategorized as infectious, and drug fever is a diagnosis of exclusion. Drug fevers typically occur within days to weeks after starting the culprit medication and cease after stopping the medication.¹ Patients are otherwise well with no other symptoms. Many different medications have been implicated in drug fever.¹⁻⁵ The true incidence of drug fever is unknown, but it is likely underreported. Drug challenges reproducing drug fever are rarely reported, particularly in the outpatient setting, likely due to concern over the safety of such challenges.^{2,4}

Our patient is a 63-year-old male with a history of diabetes, hypertension, and hyperlipidemia presenting with a history of febrile reaction to penicillin. He has no diagnosed autoimmune conditions but has a history of positive ribosomal P antibody and nuclear antibody. At 50 years of age, he took amoxicillin and developed fever with chills approximately 6 hours after. He had no cutaneous or mucosal involvement nor other systemic symptoms. His fever self-resolved within 24 hours. After this febrile reaction, he avoided all penicillins and cephalosporins; however, he tolerated meropenem and multiple non-beta-lactam antibiotics. The patient was seeking drug allergy evaluation to clarify which antibiotics he could receive if ill.

An in office single dose oral challenge to amoxicillin was administered. The patient was monitored in clinic for 8 hours and then discharged home. Oral temperature readings were taken hourly with the same thermometer. The patient had a baseline temperature of 97.8°F, though his temperature slowly rose to a maximum of 102.5°F approximately 14 hours after taking amoxicillin. (Figure 1). He exhibited joint pain, chills, and flu-like symptoms that started

approximately 8 hours after taking amoxicillin. Temperature and symptoms resolved within 24 hours and responded to acetaminophen. Laboratory analysis at baseline and approximately 24 hours after administration of amoxicillin showed mild increase in tryptase, C-reactive protein, urea nitrogen, creatinine, bilirubin, absolute eosinophil count, and neutrophil percentage (Table 1). The patient subsequently passed home challenges to penicillin VK, cefadroxil, and cefdinir without fever, clinical symptoms, or significant laboratory changes. Penicillin VK challenge was performed to determine if the patient had a reaction to naturally occurring penicillin. Cefadroxil was chosen as it shares an identical R1-group side chain to amoxicillin.^{6,7} Cefdinir challenge was undertaken to confirm the patient could tolerate this commonly used third generation cephalosporin in case needed if ill. The patient was counseled that he should only avoid amoxicillin and could take all other beta-lactams.

There are five categories in which drug fever reactions can be classified: altered thermoregulatory mechanisms, administration-related reactions, fevers relating to drug pharmacologic action, idiosyncratic reactions, and hypersensitivity reactions.⁸ Due to the relatively rapid onset of fever and change in laboratory values in our patient, we believe our patient had a hypersensitivity reaction specific to amoxicillin. Granulocytes release pyrogens causing fever in the presence of circulating antibody-antigen immune complexes.⁸ Amoxicillin or a metabolite of amoxicillin could be a part of such immune complex. Allergy Practice Parameters list drug fever as an example of drug idiosyncrasy.⁹ This implies that drug fever is not related to drug pharmacologic action, has an unknown mechanism, is not mediated by immune response, and is reproducible on re-administration. We cannot rule out that the patient had an idiosyncratic reaction as opposed to hypersensitivity.

47
48 Suspected culprits for beta-lactam drug reactions are typically the beta-lactam ring and the R1
49 side chains. However, our patient tolerated other beta-lactam and identical R1-group side chain
50 antibiotics. Prior studies evaluating anaphylaxis to amoxicillin have shown that drug reactions
51 can be specific to amoxicillin and not to beta-lactam rings or R1 side chains, though there is
52 limited data on cross reactivity in cases of drug fever.⁷
53
54 There is limited research on drug fevers and particularly re-challenges and laboratory findings.
55 Vodovar et al. reviewed 167 patients with drug fever and found that antibiotics, including beta-
56 lactams, were the most common cause of the drug fever.⁴ In these 167 cases, the median time
57 from drug administration to fever onset was 2 days and the fever resolved within 3 days of onset.
58 This patient cohort rarely had laboratory abnormalities and the positive re-challenge rate was
59 38%. Oizumi et al. examined 390 cases of drug fever and similarly found that beta-lactams were
60 also the most common cause of drug fever.³ In this study, there was a higher incidence of drug
61 fever by newer derivatives of beta-lactams, which suggests that the side chain attached to core
62 moiety might be the etiology of the reaction as opposed to the beta-lactam ring itself. 51% of
63 these patients had a transient increase in lactic dehydrogenase, 23% in neutrophils, and 8% in
64 platelets. Yaita et al. studied 16 patients with drug fever and found that 25% had neutropenia and
65 eosinophilia during episodes.⁵ Yaita et al. also hypothesized that low or normal procalcitonin
66 levels might distinguish drug fever from infectious fever. Mackowiak et al. examined 142
67 reported cases of drug fever and found a range of fever patterns reported.² Only 15% of these
68 patients had leukocytosis and eosinophilia, while about half had reproducible re-challenges and 1
69 patient had a complication coinciding with re-challenge.

70

71 Drug fever is a commonly overlooked adverse drug reaction. There is significant cost associated
72 with reported penicillin allergy and de-labeling drug fever is important in minimizing cost.¹⁰

73 Early diagnosis may reduce inappropriate and expensive diagnostic and therapeutic interventions
74 and its consideration is worthwhile, particularly when fever does not correspond with infection.

75

76 The limitations to this case study are that this is only a single case report. The case we describe
77 demonstrates reproducible drug fever to amoxicillin with no demonstrable cross-reactivity to
78 beta-lactams with or without identical R1-group side chains. We suggest that in case of drug
79 fever, patients should undergo diagnostic challenges in a controlled environment that is equipped
80 to handle an adverse outcome of the challenge. The challenges should be to the suspected culprit
81 and/or to the potentially cross-reactive medications to widen the spectrum of the medications
82 available for use by the affected patients.

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Table 1. Laboratory analysis pre and post drug administration.

Laboratory Test		Baseline	Post-Amoxicillin	Post-Penicillin VK	Post-Cefadroxil	Normal Value
Temperature	0 hours	98.0°F	98.0°F	98.0°F	97.9°F	97-99°F
	3 hours		99.0°F	98.0°F	98.7°F	
	6 hours		98.2°F	98.6°F	98.6°F	
	11 hours		101°F	98.0°F	98.8°F	
	13 hours		102.5°F	99.0°F	N/A	
	21 hours		99.0°F	N/A	N/A	
Tryptase		9 ng/mL	13 ng/mL	10 ng/mL	10 ng/mL	<11 ng/mL
C3 complement		114 mg/dL	118 mg/dL	112 mg/dL	104 mg/dL	80-300 mg/dL
C4 complement		22 mg/dL	21 mg/dL	22 mg/dL	19 mg/dL	20-60 mg/dL
C-reactive protein		<0.5 mg/dL	4.1 mg/dL	<0.5 mg/dL	0.7 mg/dL	<0.8 mg/dL
Erythrocyte sedimentation rate		17 mm/h	19 mm/h	20 mm/h	15 mm/h	0-20 mm/h
Urea nitrogen		20 mg/dL	25 mg/dL	25 mg/dL	25 mg/dL	5-20 mg/dL
Creatinine		1.2 mg/dL	1.5 mg/dL	1.3 mg/dL	1.2 mg/dL	<1.5 mg/dL
Bilirubin (total/conjugated)		0.7/0.2 mg/dL	1.2/0.2 mg/dL	0.8/0.2 mg/dL	0.8/0.2 mg/dL	<1.2/<0.3 mg/dL
Alanine aminotransferase		18 U/L	16 U/L	19 U/L	18 U/L	<40 U/L
Aspartate aminotransferase		24 U/L	20 U/L	29 U/L	27 U/L	<50 U/L
WBC		7.1 k/uL	7.7 k/uL	7.1 k/uL	5.7 k/uL	4.8 - 10.8 k/uL
Eosinophils		0.1 k/μL 2%	0.4 k/μL 5%	0.3 k/μL 4%	0.3 k/μL 4%	0.1-0.3 k/μL 0-6%
Neutrophils		5.3 k/μL 74%	6.4 k/μL 83%	5.5 k/μL 77%	4.6 k/μL 80%	1.8-7.7 k/μL 40-75%
Platelets		279 k/μL	234 k/μL	318 k/μL	263 k/μL	150 - 400 k/uL