

1 **TITLE: “Red man syndrome” adverse reaction following intravenous infusion of cefepime**

2 **RUNNING TITLE: Cefepime-induced “red man syndrome”**

3 George Panos^{1†*}, MD, PhD, DTM&H(Lon), FRCP; Dionysios C Watson^{1*}, MD; Maria

4 Sargianou^{1*}, MD; Dionysios Kampiotis¹, MD; Paraskevi Chra², MD.

5 1. Department of Internal Medicine, Division of Infectious Diseases, Patras University

6 General Hospital, Greece.

7 2. Department of Microbiology, Kogialenio-Benakio Hospital, Athens, Greece.

8 *These authors contributed equally.

9 †Corresponding author: Patras University General Hospital

10 University Campus at Rio

11 26500 Patras, Greece

12 Tel: +30(693)222-0766

13 Email: panmedix@otenet.gr ; George.panos@upatras.gr

14

15 Funding and conflicts of interests: Nothing to declare.

16

17

18 ABSTRACT

19 We report the first case of cefepime-induced "red-man syndrome," which appeared 30
20 minutes following drug infusion and was confirmed with a rechallenge test. This syndrome is
21 classically associated with vancomycin infusion and is the result of non-IgE mediated mast
22 cell degranulation. While this adverse effect can be easily managed with drug withdrawal
23 and antihistamine administration, it is unknown whether it can be prevented with slower
24 cefepime infusion and pre-infusion antihistamines, as is the case with vancomycin.

25

26

27

28 INTRODUCTION

29 Cefepime, a 4th generation cephalosporin, is a broad-spectrum antibiotic with activity
30 against Gram-negative nosocomial pathogens (e.g. *Pseudomonas aeruginosa*) [5], and often
31 against streptococcus and staphylococcus species [8]. It is generally reserved for the
32 treatment of nosocomial infections, especially pneumonias, while it is also approved for
33 treatment of complicated and uncomplicated urinary tract infections, skin and soft-tissue
34 infections, intra-abdominal infections, and febrile neutropenia [10].

35 Cefepime is administered via the intravenous or intramuscular route, with suggested
36 dosages of 0.5, 1, and 2 g. Each intravenous dose is diluted in 50 or 100 ml of compatible
37 fluid and is then infused over 30 minutes. Moderately severe infections, such as pneumonia
38 due to *Pseudomonas* [3], are among the recommended indications for cefepime, where it is
39 administered at dosages of 1-2 g , every 12h, for 10 days [10].

40 The most frequently reported adverse effects of cefepime are local reactions (3%), phlebitis
41 (1.3%), and pain or inflammation (0.6%). Nausea, colitis, diarrhea, vomiting, headache, and
42 fever have been described in less than 1% of the patients; less often, encephalopathy,
43 myoclonus, and seizures have also been observed [1]. Furthermore, cefepime is known to
44 cause dermatological adverse effects, such as rash (1.1% when lower doses are administered
45 versus 4% for the 2g dosage), pruritus (1-10%), urticaria, and anaphylaxis in less than 1% [1].

46 We report the first case of “red man” (or “red neck”) syndrome, presenting as an adverse
47 reaction related to intravenous cefepime administration.

48 CASE REPORT

49 A 25-year-old man suffering from meningoencephalitis was admitted to the Intensive Care
50 Unit (ICU) due to the acute appearance of seizures and cardiac arrest. During his one-month
51 hospitalization in the ICU he acquired nosocomial infections, such as venous catheter and
52 respiratory infections, which were treated with various antibiotics. During his recovery
53 period at the Internal Medicine Department, he developed intense pruritus, and an
54 erythematous-fine maculopapular rash covering the neck and upper torso 30 minutes after
55 cefepime intravenous infusion (see Figure 1), without any local, infusion site erythema; this
56 reaction appeared on the twelfth day of cefepime's administration (2g over 30 minutes,
57 three times daily) as part of the treatment regimen. Other symptoms, such as dyspnea,
58 tachycardia, and hypotension, were not present. The patient was completely relieved by
59 intravenous antihistamine administration (dimetindene; 0.1mg/kg). Given the temporal
60 association of this reaction with cefepime infusion, the antibiotic was suspected as the
61 underlying cause. In order to assess this hypothesis, all other antibiotics were held while we
62 rechallenged him with intravenous cefepime (alone) eight hours later; the same symptoms
63 reappeared and then quickly resolved after the administration of intravenous dimetindene.
64 Thus, we concluded that the observed reaction was an adverse effect induced by cefepime.
65 The patient did not report any past history of drug allergy or atopic disease.

66 DISCUSSION

67 The adverse effect of cefepime observed in this patient corresponds with the "red man
68 syndrome," a combination of pruritic erythematous rash (affecting the face, neck, and upper
69 torso) and possible anaphylaxoid symptoms, classically associated with vancomycin infusion
70 [9]. A few cases have also been reported following administration of infliximab [2],
71 teicoplanin, and amphotericin B, but not cefepime [9]. The reaction observed in our patient
72 occurred five days after the last dose of vancomycin (per os) was administered for suspected

73 *C. difficile* colitis, making any contribution of this antibiotic to the adverse event described
74 exceptionally implausible.

75 Vancomycin-related "red man syndrome" is usually associated with a high infusion rate and
76 appears soon after the initiation of infusion; however, it has been observed with slower
77 infusion rates and following several days of treatment, as well [9]. Correspondingly, our
78 patient presented this adverse reaction shortly after high-dose cefepime infusion, but was
79 asymptomatic during the first 12 days of treatment.

80 The underlying mechanism of "red man syndrome" has been found to be IgE-independent
81 degranulation of mast cells brought about by vancomycin, with mast cell-derived histamine
82 being a significant mediator of the observed adverse effect [11]. As a result, the established
83 effectiveness of antihistamines in the prevention and treatment of "red man syndrome [7],"
84 as observed in our patient, is not surprising.

85 Unlike our description of cefepime-related "red man syndrome," two cases of IgE-mediated
86 anaphylaxis with prominent angioedema, airway compromise, and/or circulatory symptoms
87 following cefepime have been previously reported [4] [6].

88 *Conclusion:* Cefepime can cause an anaphylaxoid reaction, similar to the non-IgE-mediated,
89 vancomycin-related "red man syndrome." The relative incidence of "red man syndrome"
90 among the rashes commonly associated with cefepime is not known. Although this adverse
91 effect can be managed with drug-withdrawal and antihistamines, prevention with the latter
92 (along with a slower infusion rate of cefepime) has not been assessed; this may be important
93 in those critically ill patients for whom cefepime is considered a critical antimicrobial.

94

95

96 **Bibliography**

- 97 1. Endimiani A, Perez F, Bonomo R. Cefepime: a reappraisal in an era of increasing
98 antimicrobial resistance. Expert Rev Anti Infect Ther. 2008;6(6):805-24.
- 99 2. Lobel E, Korelitz B, Warman J. Red man syndrome and infliximab. J Clin Gastroenterol.
100 2003;36(2):186.
- 101 3. Mandell LA, Wunderink RG, Anzueto A, Barlett JG, Campbell GD, Dean NC, et al.
102 Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines
103 on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis.
104 2007;44(Suppl 2):S27-72.
- 105 4. Moreno E, Dávila I, Laffond E, Macías E, Isidoro M, Ruiz A, et al. Selective immediate
106 hypersensitivity to cefepime. J Investig Allergol Clin Immunol. 2007;17(1):52-4.
- 107 5. Mutnick AH, Rhomberg PR, Sader HS, Jones RN. Antimicrobial usage and resistance
108 trend relationships from the MYSTIC Programme in North America (1999-2001). J
109 Antimicrob Chemother. 2004;53(2):290-6.
- 110 6. Orhan F, Odemis E, Yaris N, Okten A, Erduran E, Durmaz M, et al. A case of IgE-
111 mediated hypersensitivity to cefepime. Allergy. 2004;59(2):239-41.
- 112 7. Renz C, Thurn J, Finn H, Lynch J, Moss J. Antihistamine prophylaxis permits rapid
113 vancomycin infusion. Crit Care Med. 1999;27(9):1732-7.
- 114 8. Sader HS, Fritsche TR, Jones RN. Potency and spectrum trends for cefepime tested
115 against 65746 clinical bacterial isolates collected in North American medical centers:

- 116 results from the SENTRY Antimicrobial Surveillance Program (1998–2003). Diagn
117 Microbiol Infect Dis 2005;52:265–73.
- 118 9. Sivagnanam S, Deleu D. Red man syndrome. Crit Care. 2003;7(2):119-20.
- 119 10. U.S. Food and Drug Administration, Center for Drug Evaluation and Research.
120 Maxipime, NDA no. 050679/S032. Drug label, September 30, 2009. Retrieved August
121 22, 2012, from
122 http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050679s032lbl.pdf
- 123 11. Williams P, Laska D, Shetler T, McGrath J, White S, Hoover D. Vancomycin-induced
124 release of histamine from rat peritoneal mast cells and a rat basophil cell line (RBL-1).
125 Agents Actions. 1991;32(3-4):217-23.
- 126
- 127

128

129

130

131 **Table 1: Drug administration times, prior to reaction-inducing infusion of cefepime**

Drug	Dosage (route)	Time (hospitalization day)
cefepime	2g (i.v.)	0600 (51), 1800 (51), 0600 (52) [*] , 1400 (52) [†]
atenolol	25mg (p. os)	0600 (51), 0600 (52)
citalopram	20mg (p. os)	0600 (51), 0600 (52)
lorazepam	2.5mg (p. os)	0600 (51), 1800 (51), 0600 (52)
miconazole	(oral gel)	0600 (51), 1200 (51), 1800 (51), 0000 (52), 0600 (52)
omeprazole	40mg (i.v.)	0600 (51), 0600 (52)
pregabalin	75mg (p. os)	0600 (51), 1800 (51), 0600 (52)
risperidone	1mg (p.os)	0600 (51), 0600 (52)
tinzaparin	4500 IU (s.c.)	0600 (51), 0600 (52)
venlafaxine	75mg (p. os)	0600 (51), 0600 (52)

Notes: Initial reaction-associated infusion (*). Drug rechallenge infusion (†). Abbreviation: intravenous (i.v.), per os (p. os), subcutaneous (s.c.).

132

133

134

135



Fig. 1: Cefepime-induced red man syndrome in 25-year-old male