

## Meropenem tolerance in a patient with probable fulminant piperacillin-induced immune hemolytic anemia

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### Clinical Implications

- Piperacillin-induced immune hemolytic anemia is a rare but often severe cause of hemolysis. Little is known about the cross-reactivity of related antibiotics in patients with piperacillin-induced hemolytic reactions; however, treatment with carbapenems may be a possibility.

### TO THE EDITOR:

Drug-induced immune hemolytic anemia (DIIHA) is a severe cause of hemolysis, first described in the 1950s. Currently, at least 125 different drugs have been reported to cause immune-mediated hemolysis, with cephalosporin and penicillin antibiotics being the most common agents.<sup>1</sup> There are several proposed mechanisms of DIIHA, summarized in a recent review,<sup>2</sup> with most involving the formation of drug-induced antibodies that lead to red blood cell (RBC) destruction. When DIIHA is suspected on the basis of clinical history, a diagnosis is confirmed with *in vitro* studies to assess for drug-dependent antibodies with or without the addition of the suspected drug.<sup>3</sup> The primary treatment of DIIHA is discontinuation of the causal drug, with blood transfusions to correct anemia. Because the cross-reactivity of related medications is not well known and limited testing exists to predict future reactions, avoidance of similar classes of medications is generally recommended.<sup>4</sup>

Herein, we describe the case of a 41-year-old woman with cystic fibrosis who developed fulminant piperacillin-induced immune hemolytic anemia (PIIHA). On admission, piperacillin/tazobactam and tobramycin were started to treat an acute exacerbation of bronchiectasis due to *Pseudomonas aeruginosa*. Five days into the antibiotic course, her hemoglobin dropped from 9.8 to 5.6 g/dL. Stool guaiac, nasogastric lavage, and computed tomography scan of the abdomen and pelvis showed no signs of bleeding. After becoming hypotensive and delirious, she was resuscitated with 2 L of crystalloid solution and transferred to the medical intensive care unit. A repeat hemoglobin was 2.7 g/dL, and she was noted to have an elevated lactate dehydrogenase and bilirubin, an undetectable haptoglobin, and a positive direct antiglobulin test (DAT) result. Because of a negative DAT result before starting therapy, piperacillin/tazobactam was suspected as a cause of hemolysis and was discontinued. The patient received 8 units of packed RBCs over the next few days and her hemoglobin stabilized. Further testing showed the DAT result to be strongly positive (3+) with anti-IgG and negative with anti-C3. An eluate from the patient's RBCs was weakly positive with all cells in the absence of piperacillin. The patient's serum was tested in the presence of piperacillin and piperacillin/tazobactam and was

TABLE I. Meropenem graded dose challenge protocol

| Day | Meropenem dose  |
|-----|-----------------|
| 1-3 | 1 mg IV q24h    |
| 4-6 | 10 mg IV q24h   |
| 7-8 | 100 mg IV q24h  |
| 9   | 200 mg IV q24h  |
| 10  | 400 mg IV q24h  |
| 11  | 600 mg IV q24h  |
| 12  | 800 mg IV q24h  |
| 13  | 1000 mg IV q24h |
| 14  | 1500 mg IV q24h |
| 15  | 2000 mg IV q24h |
| 16  | 2000 mg IV q12h |
| 17  | 2000 mg IV q8h  |

IV, Intravenous; q, every.

negative. A diagnosis of PIIHA was made by 2 independent hematologists given the patient's clinical course and *in vitro* testing. Avoidance of piperacillin and all related antibiotics was recommended by the Allergy-Immunology service.

Two years later, the patient was hospitalized with worsening productive cough and shortness of breath. Despite treatment with tobramycin, aztreonam, and azithromycin, she continued to clinically deteriorate, and her sputum cultures grew *P aeruginosa* that was sensitive only to piperacillin/tazobactam and meropenem. Because of her history of PIIHA, Allergy-Immunology was consulted for antibiotic recommendations. Given the severity of her cystic fibrosis exacerbation, meropenem was deemed medically necessary and informed consent was obtained. A graded dose challenge was performed with serial monitoring of the patient's complete blood cell counts, bilirubin, and lactate dehydrogenase. Meropenem 1 mg intravenously every 24 hours was started and slowly increased over 17 days until a target dose of 2 g intravenously every 8 hours was reached without any adverse reactions (Table I). Testing performed during the challenge showed a weakly positive anti-IgG and anti-C3 DAT result with a negative eluate and an absence of meropenem-dependent RBC antibodies. After initiating meropenem treatment, the patient clinically improved and was discharged home. She has continued to tolerate subsequent courses of full-dose meropenem without hemolysis.

In summary, we report a patient who developed life-threatening hemolysis after receiving piperacillin and subsequently tolerated meropenem without any adverse reactions. The patient's clinical course of severe hemolysis with piperacillin/tazobactam that resolved after its discontinuation is consistent with PIIHA. One limitation of this case was the inability to confirm the presence of piperacillin-specific antibodies. Although the presence of drug-specific antibodies would have been supportive of DIIHA, a negative result should not exclude the diagnosis. Tazobactam has been reported to cause a positive DAT result secondary to nonimmunologic red cell adsorption of proteins,<sup>5</sup> and there are reports of decreased RBC survival in patients taking beta-lactamase inhibitors<sup>6</sup>; however, it is unlikely to be the cause of this patient's severe hemolysis.

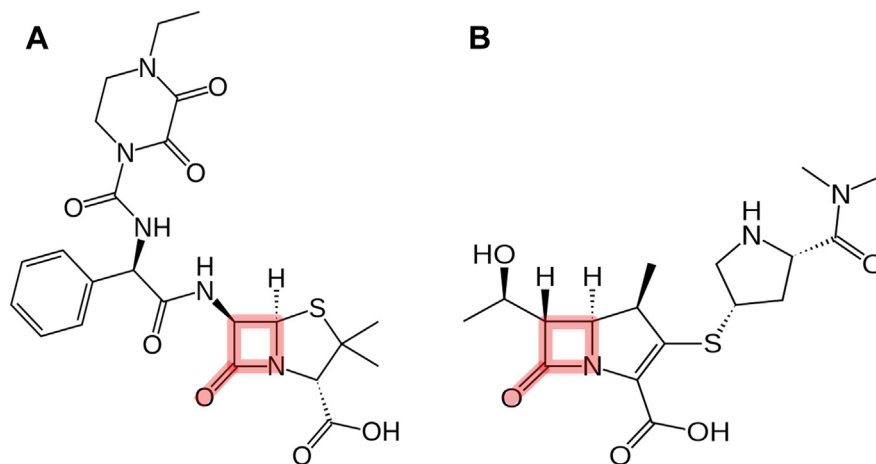


**FIGURE 1.** The chemical structure of (A) piperacillin and (B) meropenem with their common beta-lactam rings highlighted in red.

Piperacillin is a semisynthetic penicillin that is often combined with tazobactam to achieve broad activity against Gram-positive and Gram-negative bacteria. It was reported as the third most common cause of DIIHA in a review of cases from 1979 to 2008.<sup>4</sup> It is well documented in the literature that a second course of a drug that previously caused DIIHA can result in a more severe hemolytic reaction, but there is limited information on the cross-reactivity of DIIHA reactions within similar classes of medications. Only 1 case report of PIIHA was identified in the literature in which the authors show negative indirect agglutination testing with a panel of antibiotics, including meropenem; however, it is not known whether this patient subsequently received and tolerated these antibiotics.<sup>7</sup> Because of an absence of this information, patients diagnosed with DIIHA are often limited in the antibiotics that they can safely tolerate. This becomes particularly important in patients who are at risk of developing infections with resistant strains of bacteria as described in this case.

Carbapenems have a similar beta-lactam ring as penicillins (Fig 1) and thus a possibility of allergic cross-reactivity between the 2 drug classes exists. Some studies suggest that there is shared skin test reactivity<sup>8</sup>; yet, the risk of IgE-mediated clinical cross-reactivity between these antibiotics is thought to be low,<sup>9</sup> possibly because carbapenems and other later-generation beta-lactam antibiotics have larger, more bulky side chains that are more often the target of IgE binding instead of the shared beta-lactam ring. IgM, IgG, and complement have been implicated in the pathogenesis of DIIHA, and a similar mechanism of steric hindrance could explain a lack of clinical cross-reactivity between penicillin and carbapenem antibiotics. A fourth-generation cephalosporin may have been another treatment option; however, cephalosporins are more commonly associated with DIIHA than are carbapenems.<sup>1</sup> This is the first known report of a patient with PIIHA who was subsequently shown to tolerate meropenem. Although more studies investigating the cross-reactivity of DIIHA reactions are necessary, carbapenems may be a viable treatment option in patients with a history of PIIHA.

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