Ceftaroline Desensitization Procedure in a Pregnant Patient With Multiple Drug Allergies

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Validated skin testing is lacking for many drugs, including ceftaroline. The cross-reactivity between ceftaroline and other β-lactam antibiotics is unknown. We report a case of a pregnant patient with cystic fibrosis and multiple drug allergies who required ceftaroline for methicillin-resistant *Staphylococcus aureus* pneumonia and underwent an uncomplicated empiric desensitization procedure.

Keywords. β-lactam; ceftaroline; cross-reactivity; desensitization procedure; drug allergy.

Adverse drug reactions (ADRs) account for 3%–6% of all hospital admissions and occur in 10%–15% of hospitalized patients [1]. Adverse drug reactions can be costly, life threatening, and result in morbidity, prolonged hospitalization, and increased risk of mortality [1]. Approximately one quarter of all ADRs are attributed to drug hypersensitivity [2], with antibiotics representing the most frequently reported class of drugs causing hypersensitivity reactions (HSR). Penicillin (PCN) allergy alone is documented in up to 15% of hospitalized patients [3–5]. When evaluating an inpatient with a history of multiple drug allergies to antibiotics, exonerating a reported drug allergy is challenging. Validated skin testing for immediate, type I HSR exists only for PCN, where the antigenic determinants have been identified [3–5]. Skin testing to most other drugs, although not validated, may be performed using a nonirritating concentration (NIC) [5, 6] when this value has been previously established. A drug graded challenge, or test dose, can be performed when the reaction is unlikely to have an immunoglobulin (Ig)E-mediated mechanism or if skin testing is negative [5–7]. A desensitization protocol can be used to safely administer a drug if there is a history of IgE-mediated HSR, positive skin testing, or if cross-reactivity within a drug class is unknown and no reasonable alternative treatment options are available [5, 6, 8, 9].

Given the lack of validated tools available to evaluate drug allergies, we report the case of a patient with history of multiple β-lactam antibiotic allergies and methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia treated with ceftaroline. She reported a history of HSR to both PCN and an advanced-generation cephalosporin and was managed safely using a desensitization procedure to ceftaroline. We discuss the chemical structure of ceftaroline and how this might result in cross-reactivity with PCN and other cephalosporins.

CASE PRESENTATION

A 29-year-old female G1P0 in her 12th week of pregnancy with a history of cystic fibrosis (CF) presented with cough and increased sputum production. She reported dyspnea on exertion, productive cough, sore throat, nasal congestion, and postnasal drip. In addition to CF, her medical history was notable for allergic rhinitis, chronic rhinosinusitis with nasal polyposis, diabetes mellitus, gastroesophageal reflux disease, pancreatic insufficiency, and vitamin D deficiency. She had documented drug allergies to amoxicillin, piperacillin-tazobactam, cefepime, and vancomycin. On exam, she was tachycardic and hypoxemic but hemodynamically stable. Auscultation identified crackles over the bilateral upper lung fields; radiographic images were not obtained given the patient's pregnancy. Laboratory evaluation included normal renal function. A sputum Gram stain revealed abundant polymorphonuclear lymphocytes and few squamous cells with a culture growth of few *Pseudomonas aeruginosa* and abundant MRSA. The Infectious Diseases service was consulted and recommended ceftaroline as the optimal

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treatment given the predominance of MRSA and ceftaroline's presumed safety in pregnancy (class B), compared with that of vancomycin and linezolid (both class C), and the patient's reported allergy to vancomycin [10]. Given the patient's multiple allergies to β-lactam antibiotics, Allergy/Immunology (AI) was consulted. The patient reported 3 prior reactions to PCN and cephalosporins. Her first reaction was in childhood, characterized by immediate respiratory distress requiring an emergency room treatment after receiving amoxicillin. At age 21, she experienced diffuse urticaria after piperacillin-tazobactam administration. Four months before her admission, she developed diffuse urticaria after cefepime administration while hospitalized for a CF exacerbation. From the allergy history, AI consultation determined these reactions were most likely IgE-mediated and felt that the patient was at high risk for subsequent PCN and cephalosporin allergic reactions. In light of the clinical urgency to treat the MRSA pneumonia with associated hypoxemia aggressively in the setting of pregnancy, the lack of data on a NIC for ceftaroline, and the unknown cross-reactivity between cefepime and ceftaroline, the patient was treated with ceftaroline using a 12-step drug desensitization procedure that took approximately 5 hours to complete (Supplementary Table 1) [3]. Before the desensitization, written informed consent was obtained. According to hospital policy, the patient's desensitization procedure was conducted in an intensive care unit bed with orders for as-needed antiallergic medications including antihistamines, oral and parenteral steroids, and epinephrine. The patient tolerated the desensitization procedure without adverse effects. She completed 14 days of intravenous ceftaroline (600 milligrams twice daily) without complications and returned to her baseline pulmonary status. A full-term healthy male child was born 6 months after her admission.

Indications for Cephalosporins and Ceftaroline

Cephalosporins are first-line antimicrobial treatment for many common infections, including urinary tract infections, healthcare-associated pneumonia, methicillin-sensitive *S aureus* (MSSA) bacteremia, endocarditis, and osteomyelitis. Hypersensitivity reactions to cephalosporin antibiotics occur in 0.0001%–3% of administrations, with anaphylaxis comprising 0.0001%–0.1% of these HSR [4]. Patients with chronic or recurrent infections requiring repeat courses of antibiotics, such as those with CF, are at increased risk of HSR [9, 10].

Ceftaroline fosamil, a relatively new anti-MRSA "5th generation" cephalosporin, was approved in the United States in 2010 for treatment of complicated skin and soft tissue infections (SSTIs) and community-acquired pneumonia. Ceftaroline demonstrates activity against organisms including MRSA, MSSA, PCN-resistant *Streptococcus pneumoniae*, and *Haemophilus influenzae* [7, 11]. In addition to treating MRSA SSTIs, postmarketing experience in the treatment of invasive MRSA disease, including MRSA pneumonia, is accumulating [11–14].

Ceftaroline: Adverse Reactions, Structure, and Potential Cross-Reactivity

Cross-reactivity of ceftaroline with PCNs and other cephalosporins is reported; however, the exact risk of cross-reactivity is unknown [12]. Previously reported reactions to ceftaroline include the following: positive Coomb's test without hemolysis (11%); pruritus (3%–4%); rash (3%); vomiting (2%); elevated transaminases (2%); anaphylaxis (<2%); eosinophilia, thrombocytopenia, or neutropenia (<2%); and urticaria (<2%) [11, 13]. These reactions occur at a similar incidence compared with other advanced-generation cephalosporins [9, 13]. Prior studies evaluating allergy to β-lactam antibiotics have not included ceftaroline, and although NIC to many cephalosporins have been reported, there is no validated or published NIC for ceftaroline [14, 15]. Although ceftaroline has been in use for over 4 years with existing reports of HSR [13, 16], desensitization to ceftaroline has only recently been described [15].

In cephalosporin allergy, cross-reactivity exists; up to 37% of patients who react to one cephalosporin react to a different cephalosporin [16]. Data suggest that cephalosporin allergy is mediated by development of IgE antibodies against antigenic determinants that are unique to cephalosporins (side chains or R groups) or to determinants that are shared with other β-lactam drugs (eg, β-lactam ring) [17]. In later-generation cephalosporins, allergy is thought to be due to the R groups rather than the β-lactam ring [17]. This is supported by clinical data showing <1% cross-reactivity between PCNs and later-generation cephalosporins [18].

Ceftaroline contains a bicyclic ring with a 4-member β-lactam ring joined to a 6-member cephem ring (Figure 1) [12]. Ceftaroline's R1 group is defined by 2 parts: the 7-alpha-iminoethoxy group and an aminothiadiazole group [12]. Ceftaroline's R2 group is a 1,3-thiazole ring [12]. Structurally, ceftaroline's R groups are less likely to be cross-reactive with other cephalosporins with 2 key exceptions: ceftobiprole medocaril, the other 5th-generation cephalosporin, and cefclidine, a 4th-generation cephalosporin. Ceftobiprole medocaril is likely to be cross-reactive based on an identical R1 group. Cefclidine's R1 group differs from ceftaroline, containing 1 less carbon (7-α-iminomethoxyl group as opposed to iminoethoxy group), making cross-reactivity possible. More importantly, ceftaroline's R groups are dissimilar from those of the most commonly used cephalosporins in the United States, including cephalexin, cefazolin, ceftriaxone, ceftazidine, and cefepime, and is therefore less likely to cause a reaction when administered in patients with reported allergy to any of these antibiotics.

Although this structural information suggests that the patient would have likely tolerated ceftaroline, because of her poor

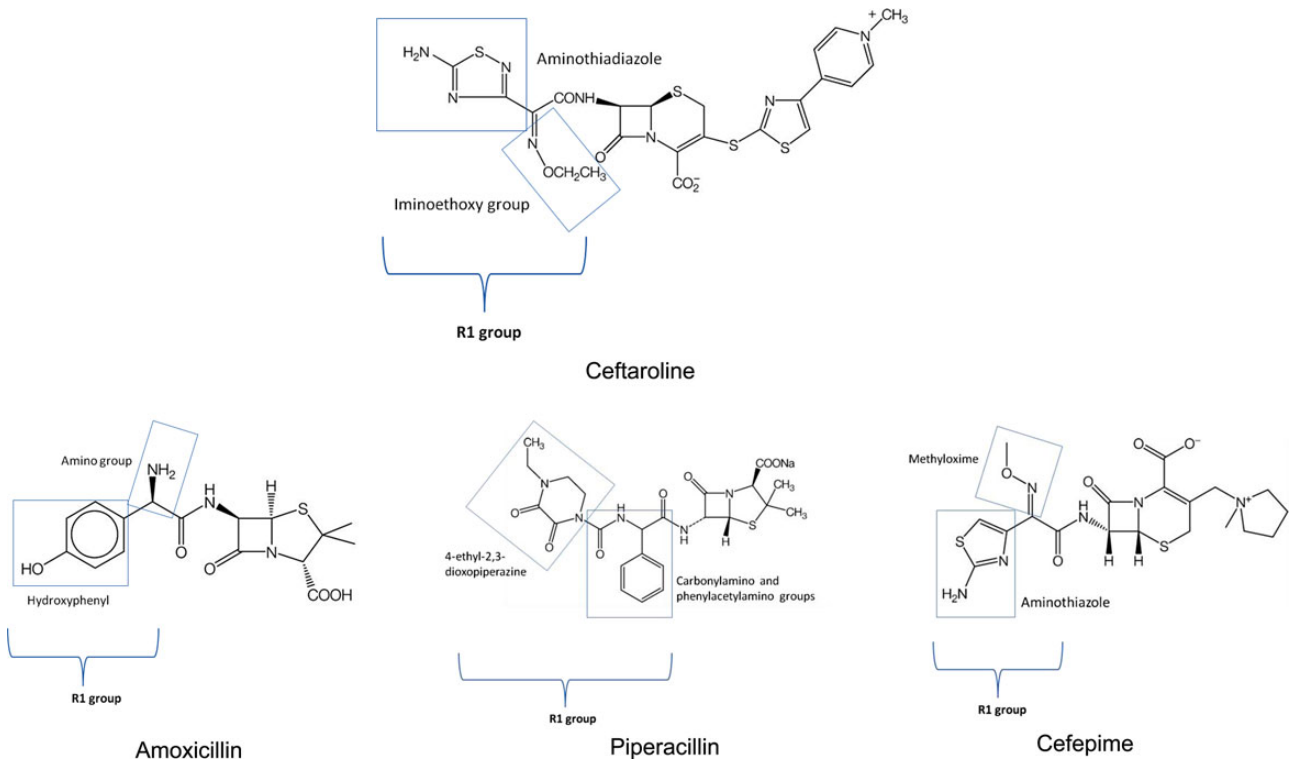

Figure 1. Chemical structure of β-lactam antibiotics. The chemical structures of ceftaroline as well as other β-lactam antibiotics to which the patient was allergic (amoxicillin, piperacillin, and cefepime). All structures contain a central β-lactam ring with distinct R groups.

respiratory status and pregnancy, we determined that the safest approach was administration of ceftaroline by desensitization.

CONCLUSIONS

We report a case of ceftaroline desensitization in a patient with multiple β-lactam antibiotic allergies. The patient's antibiotic treatment plan was complicated by a well documented PCN and cephalosporin allergy, lack of validated skin testing to ceftaroline, poor respiratory status, and need for aggressive therapy with no reasonable alternative treatment options. Ceftaroline was considered the optimal therapy given the patient's diagnosis of MRSA pneumonia. Although the literature supports the safety of vancomycin in pregnancy despite its class C classification [19–23], our patient additionally had a reported allergy to vancomycin, which led to the selection of ceftaroline as the preferred therapy. Without knowing the cross-reactivity of ceftaroline and cefepime or ceftaroline and PCN, drug desensitization was recommended and tolerated. Similar to another recent report of ceftaroline desensitization [15], we were unable to tell whether the patient's tolerance of ceftaroline was due to lack of cross-reactivity or the result of a successful desensitization procedure.

The patient's desensitization protocol was similar to previously published desensitizations [5, 8, 9], using a 12-step protocol beginning with a dilution of 1:100 000 of the therapeutic dose (for ceftaroline, 0.0002 mg/mL). The only other published ceftaroline desensitization protocol used 14 steps, initiated at 0.0004 mg/mL, and took 3.75 hours to complete [15]. Protocols are chosen based on a patient's risk of HSR, with the slowest protocols recommended for patients at highest risk of HSR.

Based on its structural properties, we hypothesize that ceftaroline may be tolerated in patients with a PCN or cephalosporin allergy, although clinical data are needed to confirm these hypotheses. In addition, more research to define a skin-testing protocol should be established and validated to improve the care of patients with multiple allergies to PCN and cephalosporin antibiotics.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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