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Drug Allergy (MJ Torres Jaén, Section Editor)

How to Manage Antibiotic Allergy in Cystic Fibrosis? Epidemiologic, Diagnostic, and Therapeutic Aspects

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Abstract

Purpose of study Cystic fibrosis (CF) is a complex genetic disease with high mortality, of which 85% is a result of lung disease characterized by serious endobronchial infections.
Recent findings Antibiotic therapy is one of the main treatments of CF, both during acute exacerbations and as chronic maintenance medications, contributing to a prolonged survival. Since neonatal CF screening programs have been implemented universally and the longevity of patients with CF steadily increases, antibiotic hypersensitivity reactions (HSRs) are becoming more important. HSR to antibiotics in CF has been reported since the 1980s and was estimated to occur up to three times more frequently in these patients, probably owing to high rates of antibiotic exposure and boosting stimuli such as infections and inflammation. However, recent studies including large groups of CF patients with a suspicion of antibiotic allergy have used diagnostic algorithms including skin tests and drug provocation tests and showed that true incidence was much lower. The mechanism of the reactions and the clinical presentations are not different in CF than in the general population. Both the immediate and nonimmediate type HSRs are seen, and among the latter, drug fever and drug-induced hemolytic anemia are distinctive presentations. Beta-lactam (BL) agents are the most common cause, with higher rates for ureidopenicillins (piperacillin, mezlocillin, and piperacillin/tazobactam) and cephalosporins (especially ceftazidime), intermediate rates for carbapenems, and lowest rates for aztreonam, and also HSRs to aminoglycosides, macrolides, and quinolones are encountered. Since the available choices for antibiotic therapy are limited due to relevant organisms, management becomes a challenge. It is essential to evaluate the patients according to the mechanism of the HSR

and determine the risk of repeat administration of the culprit drug and also safety of alternative drugs with prior skin and provocation tests. The chemical structure and side chains must be taken into account when selecting a safe alternative drug.
Summary Contrary to what was previously thought, recent data on cross-reactions between BL antibiotics showed that some BLs can be an option of treatment for patients allergic to other BLs. Desensitization is a useful procedure in immediate and some delayed reactions, if a suitable alternative antibiotic is not available.

Introduction

Cystic fibrosis (CF) is the most common autosomal-recessive disease causing early mortality in Caucasians worldwide [1]. Cystic fibrosis is a complex genetic disease affecting many organs, although 85% of the mortality is a result of lung disease. CF lung disease begins early in life with inflammation and consequent chronic infection of the airways as a result of mutational dysfunction of the CF transmembrane conductance regulator (CFTR) gene [2, 3]. The age period of diagnosis of CF has changed dramatically over the past decade, as universal newborn screening for CF has been implemented in many countries with almost half of new diagnoses in the USA being detected by newborn screening [4].

Progressive lung disease including chronic endobronchial infections and pulmonary exacerbations is the major source of morbidity and mortality for people with CF. Data revealed by the Cystic Fibrosis Foundation and other studies showed that *Staphylococcus aureus* is generally the first and most common infectious agent, particularly detected among young children, whereas *Pseudomonas aeruginosa* was most common in adults. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. aureus* small-colony variants (SCVs) are associated with antibiotic resistance and higher lung disease severity [5–7]. Antibiotic therapy is one of the main treatments of CF, both during acute exacerbations and as chronic maintenance medications, contributing to a better nutritional and respiratory status and a prolonged survival. The most frequently recommended antimicrobial agents are penicillins, cephalosporins (especially ceftazidime), carbapenems, aminoglycosides, fluoroquinolones, aztreonam, and colistin, generally in combinations, for *Pseudomonas* infections and vancomycin or linezolid for MRSA [8, 9]. Acute respiratory exacerbations are usually treated with a combination of two intravenous (i.v.) antibiotics. The treatment course is classically at least 14 to 21 days and given in higher doses. Inhaled antibiotics are recommended as chronic maintenance medications for patients with CF with persistent *Pseudomonas aeruginosa*. Tobramycin is used most frequently, followed by aztreonam and then colistin [10, 11••]. Control of inflammation in CF may be important to prevent lung function decline. Long-term oral azithromycin is recommended and used as a chronic therapy to reduce inflammation, rather than act as an antibiotic [12••]. Over the last 30 years, there have been steady increases in the prevalence and life expectancy of adult patients with CF as a result of improvements in antimicrobial and other chronic therapies. Moreover, neonatal CF screening programs have been implemented universally which led to an increase in the incidence of CF [5, 13, 14]. Hence, hypersensitivity reactions (HSR) to antibiotics are becoming more important and reported more frequently among a growing population of CF patients [4, 5, 8, 14, 15]. However, overdiagnosis is a common problem in HSRs to drugs in general, and it has been increasingly reported that only 5 to 30% of the initial antibiotic HSR suspicions are actually confirmed after thorough allergological investigations among both adults and children [16•, 17]. Unless these reactions are appropriately recognized, evaluated, and managed, the choice of suitable antibiotics may be severely restricted.

Epidemiologic aspects

Adverse drug reactions (ADRs) which occur in approximately 10 to 15% of hospitalized patients and 1 to 5% of outpatients in the general population

result in substantial morbidity and risk of mortality [18, 19]. They are classified as predictable type A and unpredictable type B reactions, and the latter includes dose-independent hypersensitivity reactions and comprises 15–20% of all ADRs. Type B reactions are classified into immunologically mediated drug hypersensitivity reactions, which is called drug allergy, and nonimmune-mediated hypersensitivity/idiosyncratic reactions [20•].

The true incidence of drug HSRs is controversial since the majority of currently available epidemiologic studies have been on ADRs rather than true hypersensitivity reactions. The estimated incidence ranged between 0.018 and 4.2 per 1000 hospitalizations. The most common agents causing drug HSRs were antimicrobials, radiocontrast media, antineoplastic drugs, and anti-epileptic drugs [17, 21, 22]. The overall incidence of HSRs to antibiotics varies from 0.1 to 8% in the general population [23••, 24–26]. In a population-based study, the prevalences of HSRs to specific antibiotics were as follows: penicillins 7.9%, sulfonamides 4.3%, macrolides 1.2%, cephalosporins 1.1%, tetracyclines 0.70%, quinolones 0.46%, nitrofurantoin 0.24%, clindamycin 0.20%, and metronidazole 0.15%, with only rare reports to other antibiotics [27]. Although parent-reported drug HSR prevalence values are 2.8 to 5.4% in children, after a detailed diagnostic workup, the true population-based prevalence of immediate type drug hypersensitivity was only 0.11% among school children [28–30]. Hence, overdiagnosis of drug allergies is a major problem. A substantial number of studies conducted in children and adults have shown that when antibiotic allergy reports or suspicions are evaluated by in vivo and in vitro tests, only about 1 to 20% can be confirmed [16•, 29–34].

Polypharmacy is regarded as an important risk factor for ADRs [35, 36]. In accordance with this, it has been expected that chronic diseases necessitating polypharmacy such as CF are associated with an increased risk of HSR to antibiotics [15, 23••, 37]. Antibiotics are delivered intravenously at high doses, for prolonged periods, and on a repeated basis in CF. In addition to these factors, increased risk of sensitization emerges when additional endogenous "danger" factors from cells that have been damaged by the drug or a metabolite, or from the immune activation that follows infections or nonspecific "cellular stress" act as boosting stimuli [38•, 39].

It is estimated that HSR to antibiotics are up to three times more common in patients with CF, although true incidence is controversial [8, 15]. Among adult and pediatric CF patients, 22 to 62% of cases were reported to have allergic reactions to BLs, with the highest rates for ureidopenicillins (mezlocillin, piperacillin, and piperacillin/tazobactam) and cephalosporins (especially ceftazidime) and others in decreasing rates [40–46]. Aztreonam had a higher risk of anaphylaxis especially in those hypersensitive to also ceftazidime. Twenty to 30% of patients had a history of multiple beta-lactam hypersensitivity [42, 43]. Bronchial reactions to inhaled antibiotics were also reported in other studies [47, 48]. However, in most of these studies, diagnosis of antibiotic HSR was solely based on clinical findings, probably leading to overdiagnosis. In the early reports, in vivo and in vitro evaluation studies were rarely performed [49, 50]. Recent studies including large numbers of adult and pediatric CF patients with a suspicion of BL allergy used standardized drug skin and provocation tests to evaluate the real prevalence of BL allergy among this population. The results have shown that only 0.7 to 4% of CF patients were truly allergic to BLs [51•, 52•, 53]. These figures were similar, even lower, when compared with

estimated antibiotic allergy prevalence in the general population [16•, 27–30]. Although it is expected that frequent exposure to drugs may lead to sensitization and allergic hypersensitivity, this may not be true for CF patients. Possible explanations are as follows: first, repeated or chronic exposure (as in prophylactic antibiotics) to antigens/allergens may also lead to immunological tolerance depending on the background [54, 55]. Second, most of the delayed type reactions to antibiotics more likely result from the presence or interaction of infectious diseases, which may play a role as "danger signals" or result in polyclonal activation [33••, 38•, 39, 56, 57]. A third explanation is that true immunoglobulin E (IgE)-mediated hypersensitivity to BLs decreases with time, with over half of skin test-positive patients losing sensitivity by 5 years and 80% with histories of BL allergy by 10 years [58, 59]. Hence, evaluation of cases after a long interval may decrease the number of real sensitivities.

Mechanisms and clinical presentations

Allergic reactions to antibiotics may be caused by a variety of immunologic hypersensitivity mechanisms including IgE-mediated (type I), cytotoxic (type II), immune complex (type III), and T cell-mediated (type IV) types and raise a considerable diagnostic challenge [60, 61••]. Clinically, HSRs to antibiotics are classified by the European Network of Drug HSR Group (ENDA) as immediate (IR) and nonimmediate (NIR) depending on their onset during treatment [61••, 62]. Immediate reactions are defined as those occurring within 1 h and up to 6 h after the last drug administration. They usually manifest as urticaria, angioedema, or rarely as anaphylaxis. The immunologic mechanism involved in most IRs is antigen-specific IgE-dependent mast cell activation. Also, nonimmunologic reactions such as direct mast cell activation (such as vancomycin, quinolones) present with immediate reactions. Nonimmediate reactions (NIRs) are defined as those occurring at any time greater than 1–6 h after the initial drug administration, often starting 2 to 5 days later. These reactions (also called delayed type reactions) are more heterogeneous and may occur as a result of type II, III, or IV mechanisms, mostly T cell mediated [60–62]. The most common NIRs are maculopapular or morbilliform exanthems (MPE) and delayed-appearing urticaria/angioedema. Other T cell-mediated reactions are fixed drug eruption (FDE) and, more rarely, severe cutaneous adverse reactions (SCARs), which include acute generalized exanthematous pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (drug eruption with eosinophilia and systemic symptoms [DRESS]), and severe bullous exanthems such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In addition, NIRs involving type II or type III mechanisms can rarely manifest by interstitial nephritis, pneumonitis, hemolytic anemia, cytopenias, hepatitis, vasculitis, drug fever, and serum sickness-like reaction occurring from few hours up to several weeks after the first dose [61••, 63] (Table 1). Most drug allergies occur in the first 2 weeks; some drugs, particularly those causing systemic involvement, may cause symptoms within the first 1 to 3 months of treatment. Drugs taken for years are very improbable causes for drug allergies [61••, 63]. However, some reactions may appear after intermission or dose increase.

Table 1. Classification of drug hypersensitivity reactions and choice of tests

Reaction type/mechanism	Clinical pattern	Tests
Type I, immediate (IgE)	Anaphylaxis Flushing/erythema Urticaria/angioedema Rhinitis Conjunctivitis Bronchospasm	In vivo: Prick and intradermal skin test (early reading) Drug provocation test In vitro: Specific IgE testing BAT
Nonimmunologic (pseudoallergic)	Anaphylaxis Flushing/erythema Urticaria/angioedema Rhinitis Conjunctivitis	In vivo: Drug provocation test In vitro: BAT
Tip II, cytotoxic (IgG and complement)	Hemolytic anemia Thrombocytopenia Neutropenia	Full blood count Coombs test
Tip III, immune complex	Serum sickness, serum sickness-like reaction Drug fever(?) Vasculitis	C3, C4, ANA, ANCA Histology CIC assay
Tip IV (a–d), T cell mediated	Contact dermatitis Photoallergic reactions Maculopapular exanthem Erythema multiforme Fixed drug eruption Exfoliative dermatitis* Acute generalized exanthematous pustulosis (AGEP)* Stevens-Johnson syndrome* Toxic epidermal necrolysis* DRESS (drug reaction with eosinophilia and systemic symptoms)*	In vivo: Patch test Delayed reading of intradermal tests Drug provocation test In vitro: Lymphocyte transformation test Cytokine assays

BAT basophil activation test; *CIC* Circulating immune complexes
*Only patch tests should be performed

The clinical reports of HSR to antibiotics among adult and pediatric CF patients included both IRs and NIRs, the latter was more frequent (> 50%) in all reports [42–45, 51•, 52•]. CF patients are more likely to have late reactions up to 13 days because of the protracted length of each intravenous antibiotic course [43, 44]. The most common presentations were cutaneous reactions such as pruritus, MPE, erythema, flushing, urticaria/angioedema, and FDE, bronchospasm, anaphylaxis, drug fever, serum sickness-like reaction, and drug-induced immune hemolytic anemia (DIIHA) [40–46, 51•, 52•, 53, 64, 65]. DRESS and TEN were rarely reported as isolated cases [66, 67]. There was no report of AGEP caused by antibiotics among CF patients. Additional late reactions reported include malaise, myalgia, arthralgia, and/or frank arthritis and, rarely, lymphadenopathy, organomegaly, and vasculitic rash [40, 42–44]. However, the

true mechanism of these reactions and whether they should be included among immune-mediated HSRs is not known. High fever, malaise, polyarthralgia or polyarthritis, and lympadenopathy may also be manifestations of underdiagnosed serum sickness-like reaction or DRESS. Relative rarity of SCARs to antibiotics among CF patients is interesting in spite of very high antibiotic exposure among these patients. The probable explanation is that some of these severe reactions such as DRESS and SJS/TEN are mostly caused by a certain number of drugs such as antiepileptics, cotrimoxazole, NSAIDs, allopurinol, and anti-HIV drugs, especially among genetically predisposed persons [68••, 69••]. Also, partial tolerance development as a result of chronic exposure may be another explanation [54].

Several studies have reported that the incidence of drug-induced fever in patients with CF is usually considerably higher than in non-CF patients, especially with high-dose prolonged penicillins [41–46, 70, 71]. Drug fever is a febrile response that coincides temporally with the administration of a drug and disappears after discontinuation of the offending agent. However, it is difficult to diagnose and the mechanism is obscure. The mechanisms proposed include HSR, altered thermoregulation, pyrogenic contaminants, idiosyncratic reactions, and Jarisch-Herxheimer reaction. Various immune mechanisms can cause fever, including the formation of circulating antibody-antigen complexes and/or a T cell immune response provoked by a drug or its metabolites [72, 73]. In most nonsensitized cases, fever appears several days to 3 weeks after the drug has been started. On the other hand, fever can arise within hours of a reprovocation, intentional or otherwise, in a previously sensitized patient. Withdrawal of the offending drug usually results in improvement within 72 to 96 h, which helps to confirm the diagnosis, but delays of 5 to 7 days have been observed [41, 44, 50, 71].

Cystic fibrosis is among a number of diseases that are more frequently associated with DIIHA which is a type II HSR. Among patients with CF, piperacillin is the most frequently reported antibiotic for causing DIIHA [70, 71, 74–77]. An explanation has been offered by Bandara, who proposed that the altered function of the CFTR decreases the nitric oxide available for vasodilation, thereby increasing the risk of red blood cell sequestration in the microcirculation [77]. DIIHA presents with nonspecific signs and symptoms that are related to a decrease in hemoglobin in the range of 1.6 to 10 g/dl. The symptoms generally occur 7 to 13 days after the initiation of therapy [75].

Inhaled antibiotics are recommended as chronic maintenance medications for patients with CF with persistent *Pseudomonas aeruginosa* infection [8, 9, 12••, 78]. Tobramycin is used most frequently, followed by aztreonam and then colistin. Some patients complained of bronchial irritation such as cough or tightness of the chest and bronchoconstriction after inhalation of some antibiotics [47, 48, 79]. Bronchial hyperreactivity and/or irritation of inhaled solutions inducing mucociliary clearance and small airway obstruction were the possible explanations for the airway obstruction after the inhalation of different antibiotics [78].

Evaluation and diagnosis

The diagnosis of antibiotic allergy is complex and usually overestimated. This has led to use of alternative drugs that may be less effective, or more

toxic, potentially leading to a suboptimal or failed therapeutic outcome. Importantly, alternative antibiotics may lead to increased bacterial resistance. A cohort study on over 100,000 patients revealed that simply being labeled penicillin allergic was associated with higher incidences of *Clostridium difficile*, vancomycin-resistant *Enterococcus* spp., and methicillin-resistant *Staphylococcus aureus* infections along with an increased number of hospital days when compared to nonallergic controls [80••]. Along with these reports, a policy statement jointly published by different societies in 2012 called for broad adoption of antimicrobial stewardship nationwide [81]. This was followed up by a 2016 recommendation to incorporate penicillin allergy testing, where possible, as part of antimicrobial stewardship protocols [82].

Therefore, the appropriate evaluation and management of suspected antibiotic allergy is essential in achieving good medical care of CF patients whose survival is mostly dependent on rational, evidence-based, and effective antimicrobial treatments on time. Patients with CF are frequently treated with multiple drugs, especially when hospitalized. Hence, polypharmacy is an important diagnostic challenge for drug hypersensitivities in these patients. In case of a suspicion of a HSR, it is essential to identify the underlying mechanism(s) and the causative drug(s) [60, 61••]. Although antibiotics and NSAIDs are the mostly incriminated drugs for DHRs in general, every drug has the potential to cause immune-mediated reactions [83]. Patients generally develop allergic reactions when reexposed to an antibiotic they had received before, or during the second week of a course of treatment with an antibiotic they have never received in the past [63, 84••]. However, it should be kept in mind that rare cases of severe reactions on the first encounter to a drug, that have never been exposed, are reported (direct T cell receptor interaction) [57, 60]. On the other hand, it is unusual for a patient to have an allergic reaction to an antibiotic she/he has been receiving continuously for months [62, 84••]. Drug-induced reactions can mimic a large variety of diseases, including viral and bacterial infections, superantigen stimulations, collagen vascular disease, chronic urticaria, neoplasia, psoriasis, and autoimmune blistering disease. In children, viral-induced exanthema, food allergy, and nonimmune reactions to excipients are the most important differential diagnosis [23••, 33, 37, 63]. A detailed and standardized history is the most essential first step toward an accurate diagnosis of a suspected antibiotic HSR [23••, 37, 83, 84••, 85]. The essential elements that should be included in the query are as follows:

- Which active drug substances and xenobiotics are in use in the last 8 weeks or had been used and stopped within the last 2 weeks?
- What are the ingredients (active substance, excipients) of the drug(s)?
- Since when the drug(s) has been taken?
- Chronology of the reaction: What is the temporal relationship between exposure to the last dose of each drug and onset of the reaction? (exposure analysis by a timeline chart is useful)
- What is the presentation of the reaction? Which systems are involved? Does it look similar to known HSRs?
- Are other drugs or herbal medicines administered concurrently that could have caused the reaction?

- Are there any underlying conditions of the patient that could explain the reaction (e.g., intercurrent infections, food)?
- If the reaction occurred in the past, did the reaction resolve after cessation of the drug and reproduced after new exposure?
- Is there any history of allergic reactions to similar or different drugs in the patient?
- What is the genetic background of the patient? Is there any history of drug allergies in the family?

The answers to these questions may help reasoning with regard to mechanism and causative drugs [61••, 63, 83]. In the setting of acute reaction, a careful physical examination, in addition to history, can help better classify possible mechanisms underlying the reaction. In the physical examination, vital signs and skin examination including the nature, localization, and extension of lesions and associated symptoms such as pruritus, burning, or pain have utmost importance. Involvement of oral, conjunctival, and genital mucosa should be searched for and a thorough systemic examination, especially the lymph nodes and liver and respiratory system, should be performed [23••, 37, 83]. Manifestations such as malaise, polyarthralgia, or polyarthritis may accompany in some instances [23••, 53, 83]. The suspected diagnosis can be supported by laboratory investigations in the acute setting. In immediate reactions and especially anaphylactic episodes, measurements of total tryptase in serum 60 to 240 min after onset of symptoms is helpful in demonstration of mast cell degranulation [23••, 37, 84••]. During the acute phase of nonimmediate reactions, the finding of an eosinophilia supports the diagnosis of an immune-mediated HSR, especially drug fever and DRESS [69••, 73]. Additional laboratory investigations such as complete blood counting, peripheral blood smear for atypical lymphocytosis, acute phase reactants, liver and renal function tests, and urinalysis may determine the severity of reaction and the systemic or organ-specific involvement [37, 83]. For atypical skin lesions, photodocumentation and a biopsy with histologic examination may help in the diagnosis. In rare cases in which an IgG-mediated mechanism (type II or III reaction) is suspected, the direct antiglobulin test (Coombs test) may support diagnosing immune hemolytic anemia, and complement levels (C3, C4, CH50) and immune complexes (C1q binding or Raji cell assays) can support the diagnosis in cases with serum sickness-like syndrome [23••, 53].

Danger signs in antibiotic allergy

Various signs and symptoms of drug HSR are described as potential early danger signals for severe reactions, and these should be carefully monitored during the acute phase [86].

A) Danger signs for severe IR

a. Sudden onset of extensive pruritus, in particular palmoplantar and scalp

b. Flush on face and neck with conjunctivitis and rhinitis

c. Angioedema of the oral mucosa, in particular the pharynx and larynx

d. Severe urticaria

e. Dyspnea and bronchospasm, especially in known asthmatics

f. Hypotension

B) Cutaneous danger signs for severe NIR

a. Centrofacial edema (diffuse erythematous swelling)

b. Involvement of large body surfaces or erythroderma

c. Extensive, confluent infiltrated exanthema

d. Painful skin, skin tender to touch

e. Atypical target lesions

f. Nikolsky sign positive, vesiculobullous lesions, epidermolysis

g. Erosive stomatitis; mucositis, especially if affecting more than one mucosa

h. Hemorrhagic necrotizing lesions

i. Purpura

C) Systemic danger signs for severe NIR

a. High fever, malaise

b. Continuation of symptoms after stopping the drug

c. Lymphadenopathy

d. Eosinophilia ($> 1500/mm^3$)

e. Atypical lymphocytosis

f. Elevation in hepatic enzyme or renal function tests

g. Arthralgia/arthritis

h. Cytopenias

If any of these is present, the suspected drugs should be stopped immediately [61••, 83, 86].

Allergy workup

In some drug HSR, especially immediate or severe forms in association with single drug exposure, the diagnosis and the culprit drug is so obvious that no further testing is necessary, apart from evaluation for alternative drugs. However, the history is often not sufficient because of difficulties in recall and different drugs are frequently taken simultaneously [61••, 83]. Even a drug reaction in a hospitalized patient may be imprecise in many cases because of polypharmacy and coexisting infections [63, 83]. Reexposure to the causative and cross-reactive drugs has to be avoided to prevent the recurrence of HSR. Thus, the identification of the causative and cross-reactive drugs is essential by performing an algorithmic diagnostic study depending on the underlying immune mechanism (Fig. 1) [37, 61••, 63, 84••]. In vivo tests include skin prick test (SPT), early and late reading of intradermal test (IDT), patch tests, and drug provocation test (DPT) [23••, 84••, 87]. In vivo and in vitro tests are not generally recommended during the active reaction phase. The allergy workup should ideally be carried out between 6 weeks and 12 months after the index reaction [37, 61••, 87]. In vitro tests also should be performed after 1 to 6 months after the acute event [88, 89]. However, data from Japan suggest that in bullous skin diseases lymphocyte transformation tests (LTT) are more frequently positive in the first weeks of disease [63, 90].

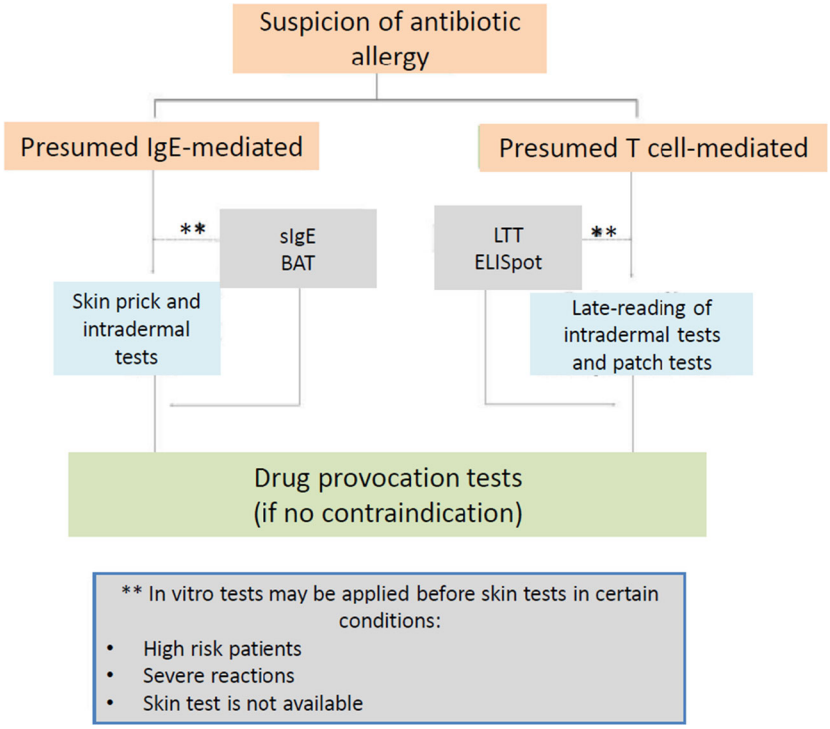

Fig. 1. Diagnostic algorithm for suspected antibiotic hypersensitivity. sIgE: serum drug-specific IgE, BAT: basophil activation test, LTT: lymphocyte transformation test, ELISpot: enzyme-linked immunosorbent spot assay.

According to the clinical presentation and time course, a hypothesis on pathogenesis should be generated in order to select appropriate testing procedures (Table 1) [37, 61••, 63, 87]. A suspected IgE-mediated reaction should be assessed by immediate reading (at 15–20 min) of SPT and IDTs [61••, 87, 89]. In vitro tests such as serum-specific IgE assays and flow cytometric basophil activation test (BAT) can aid diagnosis in IRs [88]. Skin tests have no value for nonimmunologic HSRs, but DPT and BAT can be employed [63, 84••]. When a T cell-mediated reaction is suspected, delayed reading (at 24–72 h) of SPT and IDT and patch tests is indicated [87, 89, 91]. In cases with urticaria, both early and late readings should be done, since it may appear both immediately or late [62••, 83, 87]. Other tools such as LTT and determination of cytokines/cytotoxic molecules by ELISpot, flow cytometry, and/or ELISA can be valuable diagnostic aids in some T cell-mediated reactions, especially when DPT cannot be performed [88, 90]. For severe reactions, such as SJS, TEN and DRESS skin tests, especially IDTs, can reproduce the reactions resulting in severe manifestations and their use should be limited. Patch tests should be the preferred method but in higher dilutions [37, 63, 84••, 87].

In case of a suspected BL allergy, the recommended procedure is skin testing with major and minor determinants, penicillin G, aminopenicillins, and the culprit BL, such as ureidopenicillin, cephalosporin, carbapenem, aztreonam, or clavulanic acid [92••, 93, 94••]. PPL (Pre-Pen™, AllerQuest LLC, USA) and benzylpenicilloyl-octa-L-lysine (BP-OL, DAP™, Diater, Spain) are the commercially available major determinants in use today [89, 92••]. With regard to the minor determinants, in the USA, the only minor determinant commercially

available is benzylpenicillin and thus most US allergists do not routinely test with a complete minor determinant mixture (MDM) [23••, 89]. In Europe, the commercially available minor determinants are benzylpenicillin and sodium benzylpenilloate (MD, 0.5 mg/ml, DAP®). It should be emphasized that the formulation for the previous MDM has changed in Diater kits and no longer contains a mixture of benzylpenicillin, benzyl penicilloic acid, and sodium benzylpenicilloate. The reagent is renamed as MD but now only comprises benzylpenicilloate (MD, 0.5 mg/ml, DAP®). Hence, skin testing to penicillin G, an important minor determinant, should be included in the BL panel in addition to MD (DAP®) reagent [87, 89, 92••, 93, 94••]. In Europe, amoxicillin and ampicillin for parenteral administration are also recommended in the routine panel of SPT and IDT at concentrations up to 20 mg/ml, in addition to PPL, MD, and benzylpenicillin, owing to high rates of HSRs to aminopenicillins [87, 92••, 93]. When β-lactams are used in combination with a β-lactamase inhibitor (e.g., amoxicillin and clavulanic acid), the European guidelines recommend STs with the original drug and individual components of the antibiotic combination, since clavulanic acid can be the responsible component [58, 92••, 93, 94••, 95] (Table 2).

Skin tests are not standardized and have low sensitivity for non-beta-lactam antibiotics (NBLAs), and the definitive diagnosis of NBLA HSR frequently relies upon provocation tests both in adults and children [61••, 84••, 87, 91, 96]. Nevertheless, nonirritating SPT and IDT concentrations have been evaluated and reported for the parent drug of some of NBLAs, which may provide useful information in clinical studies [96–100] (Table 2). These are maximum nonirritant concentrations and the starting concentrations should be 10 to 1000 times more diluted, according to the severity of index reaction [87, 96, 99••]. However, macrolide and quinolone skin testing is generally not useful due to the potential for false-positive skin test results, even at concentrations below the published nonirritating concentrations [96, 97, 100].

In patch tests, pure or commercialized forms of antibiotics, except major and minor determinants of BLs, are used in concentrations up to 10% for pure drugs and up to 30% for commercialized drugs [92••, 101••, 102–104, 105•]. Although there is not enough data on the best vehicle to perform patch testing, most chemicals react when prepared in petrolatum (pet) and should be preferred, but for some specific drugs, water or ethanol may be better [102]. Optimal patch test concentrations and vehicle for some antibiotics are reported [91, 93, 95, 102, 104]. Among CF patients with a suspicion of antibiotic allergy, a limited number of evaluation studies revealed 0 to 31% positivity rates for SPT and IDTs [51•, 52•, 53]. There have been no large published studies evaluating the role of delayed reading IDT or patch tests for NIRs in CF patients.

If skin tests with these concentrations are positive, a drug hypersensitivity is likely and accepted as positive (but not proven) and the drug should be avoided [37, 61••, 63, 87]. On the other hand, a negative skin test result does not exclude drug hypersensitivity, because the sensitivity of skin tests may be suboptimal or unknown and it is possible that a drug metabolite not used in the test may be the relevant allergen [61••, 63, 87–91]. In skin test-negative patients who have mild to moderate reaction histories, a DPT should be performed (Fig. 1) [37, 61••, 84••]. DPT, also referred to as graded challenge, or test dosing in US terminology, is the gold standard to establish or exclude the diagnosis of hypersensitivity to a certain drug [23••, 63, 89, 106, 107••].

Table 2. Nonirritating maximal concentrations for skin testing with beta-lactam and some non-beta-lactam antibiotics

Hapten	Maximum skin prick test concentration	Maximum intradermal test concentration
Major determinant Diater® (benzylpenicilloyl-octa-L-lysine-BP-OL)	8.64×10^{-5} mol/l (0.04 mg/ml) (5×10^{-5} mol/l for PPL)	8.64×10^{-5} mol/l (0.04 mg/ml) (5×10^{-5} mol/l for PPL)
Minor determinant Diater® (sodium benzylpenilloate)	1.5×10^{-3} mol/l (0.5 mg/ml) (2×10^{-2} mol/l for MDM)	1.5×10^{-3} mol/l (0.5 mg/ml) (2×10^{-2} mol/l for MDM)
Benzylpenicillin	10.000 IU/ml	10.000 IU/ml
Amoxicillin	20 mg/ml	20 mg/ml
Ampicillin	20 mg/ml	20 mg/ml
Particular cephalosporins (cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefozolin, cephalexin, cefaclor, and cefatrizine)	2 and 20 mg/ml	2 and 20 mg/ml
Cefepime and other cephalosporins	2 mg/ml	2 mg/ml
Amoxicillin/clavulanate	20/4 mg/ml	20/4 mg/ml
Other penicillins	20–25 mg/ml	20–25 mg/ml
Imipenem/cilastatin	0.5/0.5 mg/ml	0.5/0.5 mg/ml
Meropenem	1 mg/ml	1 mg/ml
Aztreonam	2 mg/ml	2 mg/ml
Tobramycin	Full strength	4 mg/ml (1/10 dilution)
Levofloxacin*	5 mg/ml	0.025 mg/ml (1/1000 dilution)
Azithromycin*	Full strength	0.01 mg/ml (1/10,000 dilution)
Vancomycin	Full strength	0.005 mg/ml (1/10,000 dilution)

These are maximum nonirritant concentrations. The starting concentrations should be 10 to 1000 times more diluted, according to the severity of index reaction

*Drugs with high nonspecific irritation potential PPL: Benzylpenicilloyl poly-L-lysine; MDM: Minor Determinant Mixture including Sodium benzylpenicillin, Benzylpenicilloic acid, and Sodium benzylpenicilloate (modified from refs. [92–98]

Moreover, preceded by skin testing, it can be used to provide alternative drugs [93, 106]. DPTs have the highest sensitivity but should only be performed under the most rigorous surveillance conditions [84••, 107••]. In the following situations, DPT is contraindicated: severe anaphylaxis, SJS, TEN, DRESS, AGEP, organ-specific reactions such as nephritis, hepatitis, vasculitis and cytopenias, and severe concurrent illness or pregnancy (unless the drug is essential for the concurrent illness) [23••, 61••, 63, 107••]. The route of administration depends on the suspected drug, which should in principle be administered in the same way as it was given when the initial reaction occurred. However, all the guidelines agree that the oral route is preferred whenever possible [23••, 37, 61••]. Although the optimal doses and intervals between provocation doses is controversial, in IR history, the starting dose is 1/10,000–1/1000 of the therapeutic dose and the intervals between 3- and 5-fold increasing doses are 30–60 min [92••, 106, 108]. In NIR, an initial dose is 1/100 and the intervals between 10-fold increasing doses are 3 days and 1 week depending on the time interval between the drug intake and the index reaction [92••, 93,

106, 108]. The duration of drug provocation remains controversial with some groups using 1-day DPT and others extending the provocation for several days [89, 92••, 93, 106, 108–110]. A positive DPT confirms the existence of hypersensitivity to the culprit drug and a negative result excludes it in most of the cases [92••, 106, 108]. Recently, the Pediatric Task Force of the EAACI Drug Hypersensitivity Interest Group proposed a general diagnostic algorithm for DHR evaluation in children depending on some relevant studies that, in the case of nonimmediate reactions manifesting as mild cutaneous exanthemas such as MPE or nonimmediate urticaria, a DPT without previous skin tests can be considered, since late skin tests have low sensitivity and procedures are painful in children [111••, 112, 113]. However, it is emphasized that the physician must be sure about the benign nature of the previous reaction. However, some authors still prefer a more conservative approach that SPT and IDTs must precede DPT, even in mild reactions [33••, 93].

Management

Management in the acute reaction phase

Once symptoms and signs compatible with drug HSR have emerged during antibiotic treatment in a CF patient, drug causality assessment and immediate withdrawal of the most likely implicated drug(s) are mandatory in the acute setting [23••, 63, 83, 84••]. Common offenders such as BLs, quinolones, glycopeptides, and macrolides should be considered initially, but all drug exposures including antipyretics and other drugs should be regarded as potential sources and the relevant literature and online sources reviewed for unusual drugs (http://www.drugeruptiondata.com/). An exposure analysis by a timeline chart is recommended [84••]. Potential early danger signals for severe reactions should be carefully monitored during the acute phase, and if suspected, all drugs should be stopped immediately (see relevant section) [61••, 86]. In addition to stopping suspected drugs, acute HSR caused by the culprit drug(s) should be treated accordingly, mainly by antihistamines, adrenaline, steroids, intravenous immunoglobulin (IVIG) infusions, and even plasmapheresis in very severe cases, according to the type of reaction [23••, 37, 83, 114, 115]. However, there are no randomized controlled trials for their use. Excellent reviews and position papers on the management of acute drug reactions are reported [37, 114, 115].

Strategies for finding suitable treatment options

Once it is suspected or determined that a specific antibiotic (or antibiotics) is responsible for an allergic reaction in a CF patient, the following strategies may be applied [15, 23••, 37, 61••, 84••, 111••, 116]:

1. A safe alternative agent based on the antibiotic sensitivities of the infectious agent and cross-reactivity potential of the culprit drug may be considered (Fig. 2). Cross-reactivity patterns of different antibiotic groups are given in the following section. For some alternative agents, it is prudent to perform first skin and, if negative, provocation/graded challenge tests in the hospital setting to permit the use of the drug [83, 96, 113, 116, 117].
2. If an alternative agent is not available or is not as effective, the following options with the culprit drug may be considered:

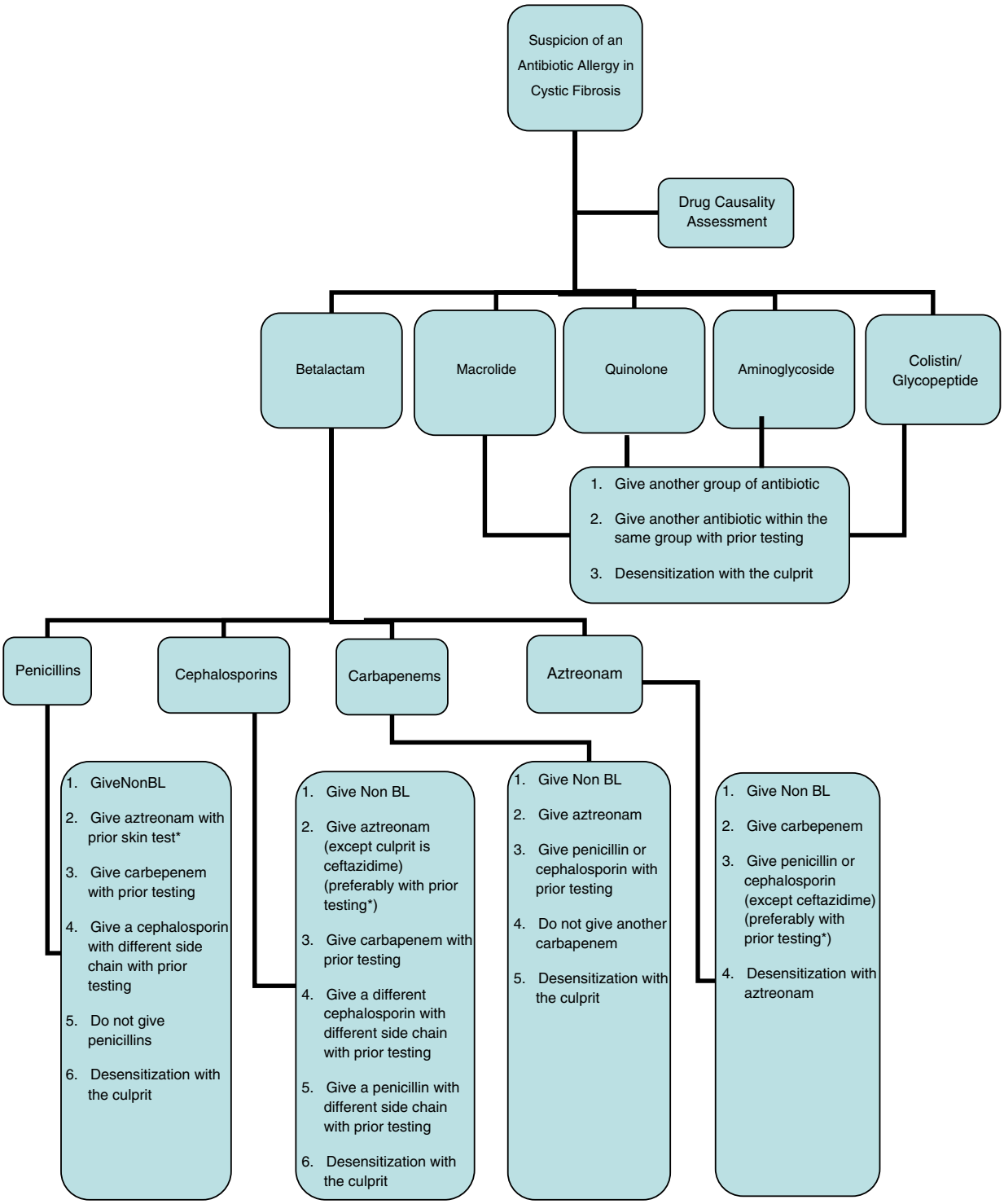

Fig. 2. Choice of alternative antibiotics and evidence-based management of a patient with suspected/confirmed antibiotic allergy in cystic fibrosis. Testing includes skin tests first and, if negative, graded provocation procedure. The rank of recommendations on management is given according to safety. *Higher cross-reaction risk in CF.

(a) The second option is an acute drug desensitization, in which the goal is induction of drug tolerance. Desensitization is performed in patients who either have an IgE-mediated or a presumed IgE-mediated response to a drug when no alternative choice exists. The procedure involves the gradual administration of incremental concentrations of the drug, starting with a very low concentration. Desensitization also has been useful in some non-IgE-mediated delayed immune responses, but it is contraindicated in severe delayed reactions [23••, 37, 61••, 64, 114–117].

(b) Premedicating the patient with antihistamines and corticosteroids prior to administering the antibiotic is another option. Premedication is reserved for nonimmunological reactions that are believed to be due to mast cell degranulation (for example vancomycin, quinolones), and does not help in immunologic reactions [23••, 115].

(c) Inhaled antibiotics may cause bronchoconstriction. Some authors recommend that lung function tests should be performed at the first nebulization with high-dose tobramycin. If lung function testing reveals significant bronchial reactions, beta-agonists should be used in combination with the nebulization of high-dose tobramycin preparations [44, 47].

Special antibiotic groups and cross-reactivity

Chronic endobronchial infections and frequent exacerbations necessitating effective antimicrobial treatment, increasing prevalence of bacterial resistance, and the limited number of antibiotics available make the assessment of antibiotic cross-reactivity and finding the safe alternative treatments crucial for the management of infectious episodes complicated by antibiotic HSRs in CF (Fig. 2).

Beta-lactams

Beta-lactam antibiotics, which are the most frequent cause of DHRs in the general population and also among patients with CF, are classified into different classes: penicillins, cephalosporins, monobactams, carbapenems, and clavams, according to chemical structure. BLs have a common antigenic four-member BL ring. Except monobactams, this BL ring is connected to another different ring in other BLs. Moreover, all of these antibiotics, except clavams, have different R side chain substituents. In all cases, a side chain (R or R1) is bound to the BL ring, and cephalosporins and carbapenems contain additional side chains (R2 and/or R3) associated with the second ring. While penicillins have only one side chain (at position 6), cephalosporins have two, one in position 7 and one at position 3 [117–120]. The beta-lactam ring, other rings, and side chains are all potentially immunogenic and therefore may cause allergy and cross-reactivity [117, 119, 120] (Fig. 3).

Theoretically, all BLs possess cross-reactivity potential with each other because of the common BL ring. However, clinical reactivity is variable and lower than expected [120]. The cross-reactivity related to the recognition by IgE or T lymphocytes of only the BL ring appears to be rare, in which case all the BLs have a high risk of DHR [117]. More frequently, cross-reactivity relates to BL class or side chain similarity.

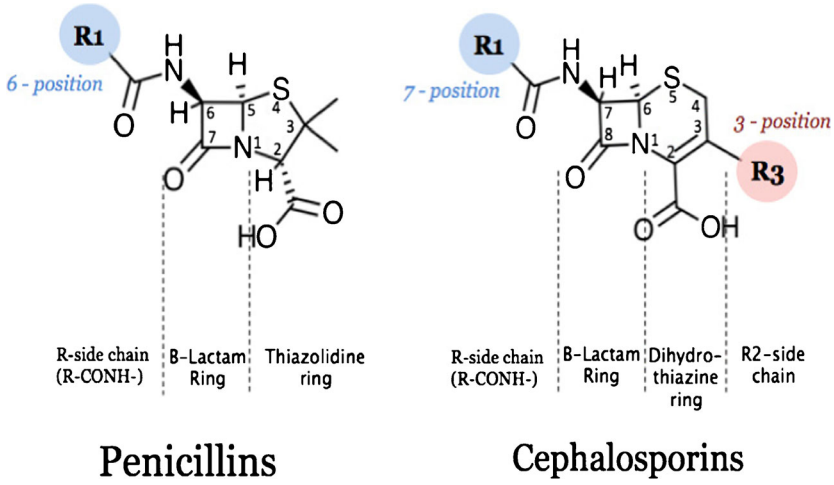

Fig. 3. Common and different ring and side chain structures of penicillins and cephalosporins.

Penicillins (benzylpenicillins such as penicillin G and V, aminopenicillins such as ampicillin, amoxicillin, ureidopenicillins such as mezlocillin and piperacillin, carboxypenicillins such as carbenicillin and ticarcillin, and beta-lactamase-resistant penicillins such as methicillin and oxacillin) as a group carry a higher risk of within-group cross-reactions owing to more similar structures [117, 119]. In the last years, there have been a body of reports that described a group of patients who developed severe anaphylactic reactions to only side chain structures of aminopenicillins, especially amoxicillin [92••, 93, 121]. Clavulanate may be the sole responsible molecule in some cases [92••, 95, 117]. Piperacillin is among the most often used antibiotics in CF patients. In addition to nonselective penicillin reactions, immediate type and delayed type selective reactions to piperacillin have also been reported for a limited number of cases [122, 123]. Taken together, these results indicate that it is important to explore whether patients that are allergic to one penicillin can tolerate others, since clinical reactivity changes.

Recent studies have shown that early dogma about the high degree of cross-reactivity between penicillins and cephalosporins has changed [118, 124, 125, 126••]. In meta-analysis it was revealed that first-generation cephalosporins have a modest cross-allergy with penicillins, but cross-allergy is much lower with second-, third-, and fourth-generation cephalosporins [126••]. Clinical studies point to the spectacular importance of similarities in side chain structure, especially R1 side chain, to predict cross-allergy between cephalosporins and penicillins, although other shared epitopes may also account for cross-reactions in both IgE-mediated and T cell-mediated reactions (Table 3). Studies of cephalosporin administration in penicillin skin test-positive non-CF patients with immediate reactions showed that the incidence of cross-reactivity was 0 to 22%, with the majority reacting to cephalosporins with an identical or similar side chain [120, 125, 126••, 127]. Few studies performed in adults with T cell-mediated hypersensitivity to penicillins have found a rate of cross-reactivity with cephalosporins ranging from 2.8 to 20%, especially between aminopenicillins and aminocephalosporins [128•]. Piperacillin has a high potential to cross-react

Table 3. Cross-reactivity between penicillins and cephalosporins based on 7-position (R1) side chain structure

Similar side chain/ cross-reactivity possible within the group	Similar side chain/ cross-reactivity possible with the group	Similar side chain/ cross-reactivity possible with the group	Completely dissimilar side chains/unlikely cross-reactivity with each other	
Cephaloridine (1st)	Cefaclor (2nd)	Cefepime (4th)	Cefoperazone (3rd)	Cefixime (3rd)
Cephalothin (1st)	Cephradine (1st)	Ceftizoxime (3rd)	Cefotetan (2nd)	Cefprozil (2nd)
Penicillin G	Cephalexin (1st)	Cefpirome (4th)	Cefazolin (1st)	Cefmetazole (2nd)
	Cefadroxil (1st)	Cefotaxime (3rd)	Cefuroxime (2nd)	Ceftibuten (3rd)
	Amoxicillin	Cefpodoxime (3rd)	Cefdinir (3rd)	Ceftazidime (3rd)
	Ampicillin	Ceftriaxone (3rd)	Cefditoren (3rd)	Cefoxitin (2nd)

with other penicillins and first- and second-generation cephalosporins, but also cross-reactivity to some third-generation cephalosporins (e.g., cefaperazone and cefbuperazone) due to similar side chain structures [126••, 127]. Although side chain similarity accounts for an important proportion of cross-reactions between penicillins and cephalosporins, it is still risky to treat penicillin allergic patients even with cephalosporins selected on the basis of side chain differences. For this reason, it is advisable to avoid cephalosporin treatment in patients with positive skin tests for penicillins. In patients who especially require cephalosporin treatment, first skin tests with the required cephalosporin followed with a graded provocation are recommended, even if it has a different side chain [121, 127] (Figure 2).

Cross-reactions between cephalosporins include general BL hypersensitivity, selective reactions to side chains, and co-reactions to other cephalosporins. Hence, in subjects with cephalosporin allergy who especially require alternative cephalosporins, compounds that have side chain determinants different from those of the responsible cephalosporins should be chosen and should undergo skin testing with the new cephalosporin before administration [118, 121, 129] (Table 3 and Figure 2). To aid in choosing a penicillin or cephalosporin drug based on a subject having had an allergic reaction to one of these drugs, charts that list whether the R1 or R2 side chains are identical or similar can be used [130–133].

Although penicillins and carbapenems possess a structural similarity of their bicyclic core including the BL ring, prospective cross-reactivity studies including skin tests and provocations showed very low cross-reactivity rates (0 to 1%) between the members of carbapenems and penicillins for IR and NIRs [134–137, 138•]. A systematic review analyzed all published data on children and adults reported to have a clinical history of IgE-mediated hypersensitivity to a penicillin and/or cephalosporin who were subsequently given a carbapenem. The results showed that the cross-reactivity between penicillins and carbapenems for IgE-mediated reactions was very low (< 1%), but caution was still advised [139••]. However, cross-reactivity rates were found to be higher between cephalosporins and carbapenems, but data were limited [139••]. Hence, although most data indicate the tolerability of carbapenems

in penicillin allergic patients, pretesting with carbapenems are still advised because of rare cases of immediate cross-reactions [121, 139••] (Figure 2).

The monobactam aztreonam does not have a bicyclic core structure unlike the penicillins, cephalosporins, or carbapenems and, thus, does not lead to an increased frequency of reactions in penicillin SPT-positive patients [117, 120, 130, 133]. Recent studies found that all of the penicillin allergy-proven patients had negative skin tests and DPTs to aztreonam [135, 140, 141]. However, aztreonam shares a common R-group side chain with ceftazidime, and so a proportion of patients with ceftazidime allergy would be expected to cross-react [117, 130, 142]. When using aztreonam in patients with a proven ceftazidime allergy, prior skin testing and DPT with aztreonam should be performed before administration. SPT, IDT, and patch tests with aztreonam establish tolerability in other BL allergic patients with both immediate and NIRs [128•]. It is important to emphasize that in patients with CF cross-reactivity between aztreonam and other BLs seems to be higher, probably reflecting repeated administration of both aztreonam and ceftazidime for pseudomonal infections. In studies performed among CF patients, 5 to 20% of cases with allergy to antipseudomonal semisynthetic penicillins and cephalosporins had a positive skin test result to aztreonam and a few patients developed systemic reactions [43, 143]. Hence, in BL allergic CF patients, in vivo tests should be conducted with aztreonam, before administering the drug.

In conclusion, in spite of being in the same family, some BLs can be an option of treatment for patients allergic to other BLs taking into account the chemical structure and side chains when selecting an alternative. In the case of a patient with a proven BL allergy and a mandatory need for an alternate BL, skin tests should be performed with the latter; if skin test results are negative, the alternate BL can be given with a graded provocation [120, 121, 128•, 132•, 137]. This approach has proven to be safe in administering cephalosporins, aztreonam, and carbapenems to subjects allergic to penicillin as well as in administering penicillins, aztreonam, and carbapenems to individuals allergic to cephalosporin.

Quinolones

Quinolones can be classified according to their generation: first (cinoxacin and nalidixic acid), second (ofloxacin, norfloxacin, ciprofloxacin, and enoxacin), third (levofloxacina), and fourth (gemifloxacin and moxifloxacin). Quinolones have been increasingly used in children and adults, particularly in those with CF, and immediate and nonimmediate allergic reactions have become more commonly reported [64, 144, 145]. Skin testing and in vitro tests are not considered a completely reliable tool for diagnosing HSR to quinolones, mainly because it can induce both false-positive and false-negative results [87, 97, 98, 101, 102, 104, 146]. Therefore, DPT is considered the gold standard in the diagnosis of nonsevere HSR to quinolones [146–148]. A broad pattern of cross-reactivity among quinolones was demonstrated in patients with IgE-mediated and non-IgE-mediated DHR [144, 147, 148]. The best approach is to avoid all quinolones in cases with suspected quinolone allergy. Alternatively, if a quinolone is required, it is prudent to perform skin tests and especially DPT thereafter

with the other quinolones, in order to find a safe one [146–148].

Macrolides

Macrolides are classified according to the number of carbon atoms in their lactone ring: 14 membered (erythromycin, troleandomycin, roxithromycin, dirithromycin, and clarithromycin), 15 membered (azithromycin), and 16 membered (spiramycin, rokitamycin, josamycin, and midecamycin) [149]. HSR to macrolides is relatively uncommon but mild and severe IRs and NIRs have been reported in children and adults [149, 150]. The sensitivity of skin tests is low, false-positive reactions are common, and DPT is the only reliable method to predict macrolide hypersensitivity as well as to detect cross-reactivity between macrolides [100, 150–153]. Cross-reactivity among 14-membered macrolides (erythromycin, clarithromycin, and roxithromycin) and between different macrolide groups has been reported in patients with either IR and NIR in approximately 25% of cases [149, 151, 153]. Hence, when there is a suspicion of HSR to a macrolide, it is prudent to perform DPT with the other macrolides, in order to find a safe one. In situations where a macrolide is a desirable or inevitable treatment option, desensitization may be necessary [152].

Aminoglycosides

Aminoglycosides are classified into two groups: the streptidine group (e.g., streptomycin) and the desoxystreptamine group (e.g., kanamycin, amikacin, gentamicin, tobramycin, and neomycin). Aminoglycosides can cause both IRs and NIRs [44-48, 154–157]. With regard to the diagnosis, skin testing and, if negative, DPT can be useful in evaluating HSRs [83, 84••, 95, 156, 157]. Cross-reactivity among aminoglycosides is common, approaching 20 to 50% among those that belong to the desoxystreptamine group. However, streptomycin does not share common antigenic structures with other aminoglycosides that belong to the desoxystreptamine group, and cross-reactivity to the latter has not been reported [157–159]. Desensitization protocols for aminoglycoside antibiotics have been proposed for patients with CF [160]. There is the potential to maintain immune tolerance in patients who have been desensitized to aminoglycosides by continuing treatment with nebulized therapy; however, the efficacy of this approach has yet to be fully established [48].

Glycopeptides

Glycopeptides are especially important for the treatment of MRSA infection which is a serious thread in CF patients [8, 10, 12]. Important glycopeptide antibiotics include vancomycin, teicoplanin, bleomycin, ramoplanin, and decaplanin. The most frequent immediate reaction to vancomycin is the "red man syndrome", which is a nonimmunologic HSR and associated with rapid intravenous administration [45, 161]. It can be easily managed by decreasing the infusion rate/dose or premedication. However, immunologic anaphylactic reactions to glycopeptides are also reported [162, 163]. They can also can elicit a variety of nonimmediate reactions, including severe

ones, such as SJS, TEN, and DRESS [164–166]. Cross-reactivity between vancomycin and teicoplanin has been reported for different types of HSRs [165, 166].

Desensitization

If an antibiotic with a convincing history of allergy or a positive skin test result is clearly the drug of choice, or without other available options, desensitization should be considered [167••, 168••]. Desensitization represents a well-tolerated method of reintroducing the culprit drug and an established procedure in patients with or without CF for immediate and some nonimmediate antibiotic reactions [169–172]. Based on the position papers, obligatory requirements for drug desensitization are as follows: (1) Drug therapy is essential; (2) the drug concerned is irreplaceable or more effective than the potential alternatives; (3) the unavailability of a noncross-reacting pharmaceutical agent for treatment; (4) the previous drug reaction was compatible with a type I IgE-mediated reaction, immediate type nonimmunologic reaction, or not severe type IV T cell-mediated reaction such as maculopapular exanthem or fixed drug eruption; and (5) the potential benefit outweighs the potential risks [167••, 168••, 173••, 174].

Absolute contraindications are as follows:

- Severe or life-threatening nonimmediate drug-induced reactions like SJS/TEN, DIHS/DRESS, cutaneous or systemic vasculitis
- Drug-induced autoimmune disorders
- Drug-induced severe general symptoms, such as drug fever, arthritis, generalized lymphadenopathy
- Drug-induced organ involvement, such as hepatitis, nephritis, pneumonitis, or cytopenias, or severe eosinophilia

Relative contraindications (only after careful consideration) are as follows:

- AGEP
- Underlying autoimmune disorders
- Preexisting severe renal or hepatic impairment
- Severe cardiac disease/hemodynamically unstable patient
- Simultaneous treatment with potentially interfering drugs [168••, 173••].

Prior to the desensitization procedure, informed consent must be obtained after explaining the risks and benefits to the patients. The medical necessity for the drug must be documented, including the fact that there are no other suitable alternatives. Desensitization should be performed in the setting where personnel and equipment are readily available for resuscitation. Epinephrine 1:1000, i.v. diphenhydramine, and i.v. hydrocortisone must be available at the bedside, and the patient's vital signs must be monitored. A physician must be in attendance throughout the procedure. Oral desensitizations should be preferred whenever possible [167••, 168••, 173••].

Desensitization procedure relies on a graded reintroduction of the antibiotic starting with 10^{-5}–10^{-7} of the final dose with doubling or $\log_{10}$ increments, culminating in the full dose given as a single administration in order to induce a temporary state of immune tolerance to the offending drug [173••]. Castells

has developed a general protocol to be applied in parenteral antibiotic desensitizations [167••]. This flexible protocol includes 4 to 16 steps (typically 12) and escalating the dose 2 to 2.5 times every 15 min. Usually the starting concentration of the solution in a 4-bags/16-steps protocol is 1/1000 and in a 3-bags/12-steps protocol is 1/100, then with 10-fold higher concentrations up to a full concentration bag. The advances in dosing are made by increasing the rate of infusion [167••, 174]. If a reaction occurs during the desensitization, the reaction is treated and the patient is stabilized. Afterwards, the dose that was last tolerated is repeated, and the desensitization procedure is continued [173••]. It is very important to continue to administer the antibiotic after desensitization is completed, until the therapeutic course is completed. If a time interval of more than 5 half-lives of the antibiotic passes without antibiotic administration, then it will be necessary to repeat the desensitization [167••, 168••, 174]. In certain settings, reactions can be noted with delayed redosing after as little as 2 half-lives, but reactions are also common in desensitized individuals even with continual dosing. Most reported adverse reactions to a desensitization protocol occur in the final steps of desensitization and are mild to moderate, but severe breakthrough reactions occurring during the full-dose treatment and requiring termination of treatment also have been reported [167••, 171, 174]. In one study, an alternative method was suggested to treating patients with CF who cannot tolerate the following intravenous BL therapy after the desensitization procedure. In this new approach, an eight-step desensitization protocol was followed by a continuous infusion of the BL antibiotic for the full treatment course, instead of a regular intermittent-dose treatment course [175]. All procedures were completed successfully without any adverse events. This method has been offered to be used in all patients at high risk of developing severe life-threatening allergic reactions to BL antibiotics.

Many other protocols for antibiotic desensitization in CF have been reported in the literature with success rates between 55 and 100% [64, 160, 169–172, 175–178]. A study from Australia reported 57 desensitization procedures in 21 patients with CF and reactions suggestive of IgE-mediated immediate reactions. Desensitizations were performed to 12 different antibiotics. Desensitization protocol was performed by starting at 1/1,000,000 of the full therapeutic dose delivered by continuous intravenous infusion of 30 min duration and proceeding with 10-fold dose increases, until the full therapeutic dose was reached. Generally, patients were not pretreated with antihistamines or corticosteroids before desensitization. Of the 57 desensitizations, 43 (75%) were completed safely and successfully [172].

There are a few reports of CF cases involving desensitization to inhaled antibiotics. One report described a 9-year-old patient with CF who developed a severe rash after intravenous gentamicin and inhaled tobramycin. He underwent desensitization with inhaled high-dose tobramycin in an escalating dose regimen. The first dose was 0.3 mg in 5 ml normal saline. The dose in milligrams was gradually increased in a 5-ml normal saline total volume. Each dose was nebulized on an every 2-h schedule, until the full dose of 300 mg was given. He tolerated the procedure well and continued to be on tobramycin 9 months after desensitization [48].

Another report demonstrated successful desensitization of a 19-year-old patient with CF who was allergic to intravenous aztreonam. Rapid intravenous desensitization with aztreonam was performed followed by inhaled therapy without intolerance [179].

Conclusions

A major cornerstone of the improvements in survival of patients with cystic fibrosis has been through the use of high-dose and long duration intravenous antibiotic courses. As a possible consequence, HSRs are reported commonly in the CF population and are predicted to increase. However, overdiagnosis is a common problem in HSR to drugs in general. Recent studies comprising a detailed workup including skin tests and provocation tests revealed much lower confirmation rates among CF patients with a suspicion of antibiotic allergy. It is essential to perform in vivo tests including skin tests and DPT with both the culprit drug and cross-reactive drugs, in order to reveal safe treatment options. Unless these reactions are appropriately recognized, evaluated, and managed, the choice of suitable antibiotics may be severely restricted. This may lead to both suboptimal bacterial clearance and clinical improvement and an increase in resistant strains, which may pose a great problem for CF patients in terms of mortality and life expectancy. Once it is determined that a specific antibiotic is responsible for an allergic response, the strategies that may be applied are to use safe alternative drugs, or drug desensitization, if no alternative exists.

Compliance with Ethical Standards

Conflict of Interest
Semanur Kuyucu declares that she has no conflict of interest. Tugba Arıkoglu declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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