OCCASIONAL REVIEW

Antibiotic allergy in cystic fibrosis

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Allergic reactions to antibiotics are more common in cystic fibrosis (CF) than in the general population. This in part is due to the improving survival in adults with CF and the increased use of high dose intravenous antibiotics. While some are immediate anaphylaxis type (IgE mediated) reactions, the majority are late onset and may have non-specific features such as rash and fever. Piperacillin has consistently been found to have the highest rate of reported reactions (30–50%). There is a low risk of cross reactions between penicillins and other non-β-lactam classes of antibiotics in penicillin skin prick positive patients. Carbapenems should only be used with extreme caution in patients with positive skin prick tests to penicillin. However, aztreonam can be used safely in patients who are penicillin allergic with positive skin prick reactions. The aminoglycosides are a relatively uncommon cause of allergic reactions, but patients who react to one member of the family may cross react with other aminoglycosides. Desensitisation relies on the incremental introduction of small quantities of the allergen and has been used for penicillins, ceftazidime, tobramycin and ciprofloxacin and must be repeated before each course. Personalised cards should be regularly updated for patients who develop allergic reactions. Written instructions on the emergency treatment of allergic reactions should be provided to patients self-administering intravenous antibiotics at home. Further research is required to identify risk factors and predictors for antibiotic allergy.

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Cystic fibrosis (CF) is the most common lethal recessive genetic disease in the western world. Over 1000 mutations of the cystic fibrosis transmembrane receptor (CFTR) have been described which contribute to the complex relationship between genotype and phenotype.[1] The major mortality and morbidity results from the expression of CFTR in the airways leading to a failure of chloride transport and the production of thick secretions, bronchial stasis, and chronic bacterial colonisation causing recurrent infective pulmonary exacerbations.[2] Typically, these infective episodes are caused initially by staphylococcal species but, as the severity of the disease progresses, *Pseudomonas aeruginosa* becomes more common. The resulting chronic bronchial sepsis leads to a high requirement for oral, intravenous, and nebulised antibiotics. While reactions to antibiotics given orally and by the nebulised routes are well recognised, they are less sensitising and thus this review will focus on allergic reactions to intravenous antibiotics.[3]

A major cornerstone of the improvements in patient survival achieved in CF[4] has been through the use of high dose and long duration intravenous antibiotic courses.[5] As a consequence, hypersensitivity reactions are seen commonly in the CF population and are predicted to increase. Unless these reactions are appropriately recognised and managed, the choice of suitable antibiotics may be severely restricted leading to suboptimal bacterial clearance and a consequent decline in lung function.

INCIDENCE

Acute allergic reactions are up to three times more common for beta-lactam antibiotics in patients with CF than in the general population.[5] The Danish adult CF centre reported 53 immediate reactions in 121 patients receiving nearly 2800 courses of intravenous antibiotics for *Pseudomonas aeruginosa* infections, equivalent to a rate of 1.9%. These immediate reactions were evenly distributed among the seven antibiotics used in this retrospective analysis. When the data were analysed for all adverse reactions the frequency of reactions rose to 4.5%.[6] Other smaller case series which failed to distinguish between immediate and late reactions have reported much higher frequencies with overall adverse reaction rates of 9.5% in children and up to 25% in adults.[3 7] Piperacillin has consistently been found to have the highest risk of reaction in a number of case series with rates of reaction of between 30% and 50%.[3 6 8] Other antibiotics such as mezocillin (17%), carbenicillin (7%), and imipenem (3%) had lower rates of reactions.[3 6 8] The incidence of allergic reactions was antibiotic-dependent and increased with the number of courses of antibiotic administered.[6]

CROSS REACTIONS BETWEEN ANTIBIOTICS

Cross reactivity among the beta-lactam antibiotics in CF appears to be less of a problem than would be predicted from a study of their structures.[9] When all nine studies of cephalosporin administration in penicillin skin test positive non-CF patients are considered, the incidence of cross reactivity is 4.5% with the majority reacting to cephalosporins with an identical or similar side chain.[10–18] 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 skin prick positive patients. However, aztreonam

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shares a common R-group side chain with ceftazidime and so a proportion of patients with ceftazidime allergy would be expected to cross react. In practice, however, aztreonam is generally well tolerated in these patients although there are case reports of individuals who react to both.[19 20] Caution should therefore still be exercised when using aztreonam in patients with a proven ceftazidime allergy with prior skin testing to both antibiotics before administration. In studies of non-CF patients the frequency of reactions to carbapenems in penicillin skin prick positive patients is significantly higher.[16] Thus, imipenem and meropenem should only be used with caution in patients with positive skin prick tests to penicillin.

While the aminoglycosides are generally well tolerated, there are case reports of adverse reactions to aminoglycosides after repeated administration.[21] In addition, there have also been case reports of cross reactivity with other aminoglycosides.[22] There is the potential to maintain immune tolerance in patients who have been desensitised to aminoglycosides by continuing treatment with nebulised therapy, however the efficacy of this approach has yet to be fully established.[21]

There are few data on the frequency and prevalence of reactions to the macrolides erythromycin, clarithromycin and azithromycin in patients with CF. This group of antibiotics is not commonly implicated in IgE mediated reactions. However, gastrointestinal upset with nausea, vomiting and abdominal discomfort with erythromycin commonly leads to discontinuation. Azithromycin has been increasingly used to successfully treat chronic *Pseudomonas* infection and has been the subject of a number of randomised controlled trials. In three randomised, double blind, placebo controlled studies the incidence of adverse drug reactions was not discernibly different from placebo.[23–25]

Sulphonamides are not commonly used in cystic fibrosis, except in patients with *Stenotrophomonas maltophilia*, so few data exist for the frequency and prevalence of reactions. However, severe cutaneous reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis precludes their subsequent use.

RISK FACTORS

There are no clear predictors of the risk of an initial hypersensitivity reaction in a CF patient. Previous hypersensitivity reactions to a penicillin increase the risk of subsequent reactions by sixfold to other penicillin antibiotics.[5 9] Beta-lactams have been shown to be highly immunogenic and may undergo accelerated haptenisation in the presence of infection.[9] It has been argued that atopic children with CF who are skin prick positive to aeroallergens are more likely to be colonised by *Pseudomonas* and, as a consequence, are more likely to need frequent high doses of IV antibiotics resulting in an increased incidence of allergic reactions.[26]

CLINICAL MANIFESTATIONS

Despite being more frequent, acute allergic reactions in CF are not clinically different from those in the general population.[5] Furthermore, CF patients are more likely to have late reactions up to 13 days because of the protracted length of each intravenous antibiotic course. In one case series the mean time to development of late reactions was 9.1 days.[7] These late reactions may present in a variety of ways including fixed drug eruptions, morbilliform rashes, other non-specific rashes, unexplained pyrexias, nausea, vomiting, diarrhoea, arthralgia, myalgia, eosinophillia, derangement of liver function, haematological abnormalities, and lethargy. These delayed reactions are unlikely to be IgE mediated, so are not classically associated with an anaphylactic picture and therefore cannot be diagnosed by skin prick or intradermal testing. Life threatening conditions such as Stevens-Johnson syndrome and toxic epidermal necrolysis both cause widespread desquamation, mucosal ulceration, high fevers, and prostration and require intensive treatment in specialised units. Both are most commonly associated with sulphonamides and penicillin.

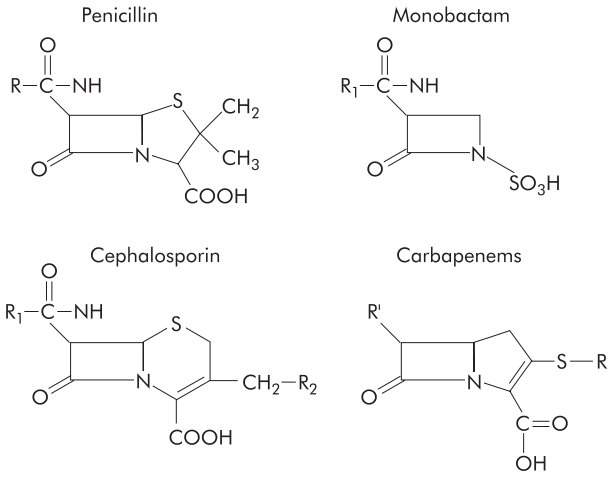


Figure 1 Schematic diagram of the common core structures of four major antibiotic classes used in CF. Penicills, cephalosporins and carbapenems share a similar bicyclic core. This in part may help to explain the incidence of cross rections between these antibiotic families. Monobactams have a single central cyclic structure.

MECHANISMS

Immediate reactions to antibiotics such as urticaria, angio-oedema, bronchospasm and anaphylaxis are most likely to be mediated by IgE. The variety of clinical presentations for late reactions indicates that a number of distinct non-IgE mediated mechanisms are involved. These are likely to involve T cell mediated mechanisms, with drug specific memory T cells as the effector cells.[27] Other components of intravenous antibiotic preparations including pH buffers and stabilising agents may also be involved in the development of late reactions.

While both penicillins and cephalosporins share a beta-lactam ring, there is a relatively low level of clinical cross reactivity to cephalosporins in patients who are penicillin skin prick positive.[28] It has therefore always been assumed that the major antigenic component responsible for allergic reactions resides in the side chains. Although this may be true for the majority of patients, a recent report by Romano *et al*[29] suggests that other antigenic determinants may also be important. In this study about half of 30 cephalosporin allergic non-CF patients who underwent skin testing with several different cephalosporins reacted only to the cephalosporin that caused the reaction whereas the other half reacted to a variety of cephalosporins including those with different R-group side chains (fig 1). Although none of the patients was challenged, this suggests that some cephalosporin allergic patients form cross reacting antibodies. Therefore, although in a cephalosporin allergic individual a different cephalosporin may be tolerated, it is still advisable to be cautious with the use of cephalosporins in patients who have previously exhibited allergic reactions to penicillins or other cephalosporins. The emergence of multiple allergies can be a very difficult management problem, particularly in the late stages of CF. Recently, the multiple allergy syndrome has been described in a non-CF population in which patients displayed allergic sensitisation to a variety of drugs caused by cross reaction of IgE antibodies to small akyl groups on the side chains of beta-lactam antibiotics.[30]

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DIAGNOSIS

A keen index of suspicion is necessary when patients with CF are treated with antibiotics. An awareness of the possible adverse drug reactions with each administered drug is mandatory. The possibility that an unusual or unexpected symptom has resulted from drug use should always be considered. If a reaction is suspected, a careful history examining the temporal sequence of each drug administration is critical in determining which drug is responsible. This is often complex in CF patients because of the large number of co-administered drugs.

If the patient has been on a beta-lactam, skin prick testing should be undertaken to ampicillin, amoxicillin, the major and minor antigenic determinants of penicillin, and to an intravenous preparation of the implicated drug. If the skin prick test is negative, an intradermal test should be considered. However, a negative skin test only excludes an IgE mediated reaction and caution must still be exercised on re-introduction as other non-IgE mediated mechanisms may be relevant.

Degranulation of mast cells with the release of tryptase occurs in anaphylactic or anaphylactoid reactions. Mast cell tryptase appears in the circulation at the time of the reaction with a half life of a few hours and is routinely measured by NHS immunology laboratories. A definitive diagnosis of anaphylactic or anaphylactoid reactions may therefore be advanced by taking a clotted blood sample for serum mast cell tryptase at the time of the reaction, 1 hour later, and a baseline measurement at 24 hours. A rise in serum tryptase levels should confirm that the mechanism of the reaction involves mast cell degranulation and increases the likelihood of an IgE mediated reaction. If doubt remains about the cause of the reaction because of the number of co-administered drugs, these patients should be referred to an allergy department for skin testing and challenge if clinically indicated.

MANAGEMENT

Where a clear allergic reaction has occurred, that antibiotic should be withheld from the treatment regime or desensitisation considered if appropriate. There have been a number of case reports of anaphylactic reactions to ceftazidime and this has led to the development of desensitisation regimes.[32 33] This 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 immune tolerance. This method has been successfully used for penicillin, ceftazidime, tobramycin and ciprofloxacin (see online supplement available at the *Thorax* website http://www.thoraxjnl.com/supplemental).[33–35] A single case report of desensitisation for meropenem has also been published, but this method has not been rigorously examined.[36] In a recent retrospective analysis over a 7 year period of desensitisation for a range of nine different antibiotics in 19 different patients, the success rate was found to be 73% for patients who had late reactions but only 50% in those with a well documented allergic reaction to the antibiotic.[37] The duration of this induced immune tolerance is not known and therefore it is recommended that desensitisation is undertaken each time the antibiotic is used.[20]

Desensitisation

When desensitisation protocols are used they should be carefully supervised at all times, and it is mandatory to have immediate access to full resuscitation facilities. Practices vary across the world but in North America it is routine to admit patients to the ICU for desensitisation, although in the UK it is usually performed with careful supervision in a ward environment. Where the patient is then discharged on home therapy, careful consideration needs to be given to the timing of discharge from hospital and it is prudent to ensure that they have access to and education in the use of devices for self-administration of adrenaline. This should be given in the form of supervised teaching by a health professional and, in addition, a written treatment plan should be provided for self-treatment of allergic reactions.

Where a reaction has occurred, the subsequent choice of antibiotics is usually dictated by information from microbiological sensitivities and on the previous clinical response. In critical situations where an alternative antibiotic is not suitable, pretreatment with antihistamines and steroids may be helpful. Where oral steroids have failed to control reactions and the clinical imperative has remained for intravenous treatment, three pulses of methylprednisolone (500–1000 mg) on consecutive days with intravenous antihistamines have been used.[9] Personalised cards detailing drug allergies and current treatment must be used in CF in order to avoid administration of antibiotics to which there has been an allergic reaction.

FUTURE RESEARCH

Drug reactions in CF represent a major challenge which will only be further amplified by the continuing improvements in mortality rates. Advances in pharmacogenetics with identification of the risk factors to hypersensitivity reactions in patients with CF would represent a major evolution in clinical management. Do certain CF mutations predispose to a higher frequency of reactions or do other modifier genes have a significant role in reactions? Does the frequency of antibiotic treatment increase the risk of reactions to the same antibiotic and is there evidence of cross class sensitisation?

Further research is required on the altered drug metabolism in CF that not only leads to high dose requirements but may be also responsible for the formation of novel metabolites leading to adverse reactions. Just as patients with EBV or CMV infection develop drug rashes with antibiotics such as amoxicillin, it is possible that there is a similar modulating effect of infection on the processing of antibiotics administered in CF and their metabolites may predispose to the development of hypersensitivity reactions. Further research is also required for improving diagnostic reagents used for skin prick testing and in vitro tests developed for both IgE and non-IgE mediated reactions to the major antibiotics. However, above all, there is an immediate requirement for careful documentation of each adverse reaction in every CF patient so that accurate data on the nature and prevalence of adverse drug reactions in CF can be used to assist clinical decisions and direct future research. The eventual aim should be to have an antibiotic specific classification of clinical syndromes with an understanding of the underlying mechanisms and likely cross reactivity with other drugs.



Desensitisation protocols for ceftazidime, tobramycin and ciprofloxacin are shown in tables 1–3 and the major papers on CF used to provide evidence for this review are shown in table 4 in the online supplement available at the *Thorax* website http://www.thoraxjnl.com/supplemental

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