Antibiotic allergy in cystic fibrosis

J S Parmar, S Nasser

Allergic reactions to antibiotics are more common in cystic fibrosis (CF) than in the general population. This 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.

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. 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. 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.

A major cornerstone of the improvements in patient survival achieved in CF has been through the use of high dose and long duration intravenous antibiotic courses. 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. 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%. Other cases 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. 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%. Other antibiotics such as mezlocillin (17%), carbenicillin (7%), and imipenem (3%) had lower rates of reactions. The incidence of allergic reactions was antibiotic-dependent and increased with the number of courses of antibiotic administered.

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. 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. The mono-bactam 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
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.20–22 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.21
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 aminoglyco-

sides.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.23

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.21–25

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 hypersen-
sitivity reactions to a penicillin increase the risk of
subsequent reactions by sixfold to other penicillin antibiot-
ics.3 4 Beta-lactams have been shown to be highly immuno-
genic and may undergo accelerated haptenisation in the
presence of infection.5 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.7 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 pyrexia, nausea,
vomiting, diarrhoea, arthralgia, myalgia, cosinophilia,
derangement of liver function, haematological abnormalities,
and lethargy. These delayed reactions are unlikely to be IgE
mediated, so are not classically associated with an anaphy-
lactic 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.

**MECHANISMS**

Immediate reactions to antibiotics such as urticaria, angio-
edema, 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
al29 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 cephalo-
sporin 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 cephalo-
sporin 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 alkyl 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. This relies on a graded reintroduction of the antibiotic starting with 10^2–10^5 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). A single case report of desensitisation for meropenem has also been published, but this method has not been rigorously examined. 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. 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.

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/or the previous clinical response. In clinical 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. 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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www.thoraxjnl.com
REFERENCES


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Online supplement

Table 1  Standard desensitisation regime for ceftazidime using log$_{10}$ increments of ceftazidime

<table>
<thead>
<tr>
<th>Dose of ceftazidime (mg)</th>
<th>Cumulative dose (mg)</th>
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<tbody>
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<td>0.004</td>
<td>0.004</td>
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<tr>
<td>0.04</td>
<td>0.044</td>
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<tr>
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<td>4</td>
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<tr>
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Each dose is diluted in 50 ml normal saline and delivered in 20 minutes. A delay of 10 minutes should be observed before introducing the next dose. Careful assessment of pulse rate, blood pressure and saturations should be taken before dose escalation. A persistent tachycardia (>120 bpm or fall in BP >20 mmHg) should halt any further dose escalation.[33] Any features suggestive of anaphylaxis should prompt immediate treatment.
<table>
<thead>
<tr>
<th>Dose of tobramycin (mg)</th>
<th>Cumulative dose (mg)</th>
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<td>64.023</td>
</tr>
<tr>
<td>16.000</td>
<td>80.023</td>
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</table>

Each dose is diluted in 10 ml of normal saline and delivered in 20 minutes. A delay of 10 minutes should be observed before introducing the next dose escalation. The final dose is reduced to 16 mg to ensure that 80 mg in total is received. Careful assessment of pulse rate, blood pressure and saturations should be taken before dose escalation. A persistent tachycardia (>120 bpm or fall in BP >20 mm Hg) should halt any further dose escalation. Any features suggestive of anaphylaxis should prompt immediate resuscitation.[34]
Table 3 Standard desensitisation regime for ciprofloxacin using incremental doses of ciprofloxacin

<table>
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<tr>
<th>Concentration (mg/ml)</th>
<th>Absolute amount given (mg)</th>
<th>Cumulative dose (mg)</th>
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<tr>
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<tr>
<td>2</td>
<td>80</td>
<td>160.231</td>
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</table>

Each dose is diluted in 5 ml of normal saline and delivered over 20 minutes. The last three increments in total dose are achieved by increasing the volume of the infusion. A delay of 10 minutes should be observed before introducing the next dose escalation. Careful assessment of pulse rate, blood pressure and saturations should be taken before dose escalation. A persistent tachycardia (>120 bpm or fall in BP >20 mm Hg) should halt any further dose escalation. Any features suggestive of anaphylaxis should prompt immediate resuscitation.[35]
Table 4 Evidence from the major CF papers contributing to this review

<table>
<thead>
<tr>
<th>Source</th>
<th>Design and sample</th>
<th>Observations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wills et al[3]</td>
<td>Retrospective analysis. 53 consecutive courses of antibiotic treatment.</td>
<td>33% (18/53) experienced a reaction. Reactions most common in IV courses with 9.5% provoking a reaction.</td>
<td>Life threatening anaphylaxis was rare. Piperacillin associated with the highest frequency of reactions</td>
</tr>
<tr>
<td>Jensen et al[19]</td>
<td>Prospective open trial of aztreonam in 15 patients who had hypersensitivity reactions to beta-lactams and were skin prick test positive to penicillin.</td>
<td>56 courses of aztreonam successfully delivered. No type 1 reactions. Two late drug fevers developed.</td>
<td>Aztreonam can be used successfully in beta-lactam sensitive patients.</td>
</tr>
<tr>
<td>Koch et al[6]</td>
<td>Retrospective analysis of 121 CF case notes.</td>
<td>Total of 2793 courses given to 121 patients. 53 immediate reactions in 34 patients. 72 late reactions. Piperacillin reaction rate was 51%. Lowest rates of reactions were seen with ceftazidime (6.5%) and imipenem (4%).</td>
<td>Drug hypersensitivity common in CF. Piperacillin associated with the highest reaction rate. Immediate reactions were evenly distributed across the seven antibiotics used. Late reactions are common and often non-specific.</td>
</tr>
<tr>
<td>Pleasants et al[7]</td>
<td>Retrospective analysis of 90 case notes from 111 admissions for IV antibiotics.</td>
<td>26 patients had one or more allergic reaction to beta-lactams. Reactions seen with all antibiotics. Reaction rates for piperacillin 35%, imipenem 25%, and eftazadine 4%</td>
<td>Piperacillin and other acyl-aminopenicillins associated with the highest frequency of allergic reactions.</td>
</tr>
<tr>
<td>Moss et al[20]</td>
<td>20 patients with documented allergic reactions and skin prick test positive to penicillin but negative for aztreonam were treated with aztreonam.</td>
<td>4 patients had evidence of sensitisation to aztreonam by exposure on repeat skin prick testing. One patient developed bronchospasm and two patients with anaphylaxis on subsequent re-exposure.</td>
<td>Aztreonam can be used safely in patients who are beta-lactam allergic with positive skin prick reactions. There is a small risk of cross reaction between the two antibiotics.</td>
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<tr>
<td>Source</td>
<td>Design and sample</td>
<td>Observations</td>
<td>Conclusions</td>
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<td>Burrows et al[37]</td>
<td>Retrospective analysis of 19 patients who had undergone single or multiple desensitisations.</td>
<td>62 drug allergic reactions with a mean of 3.3 per patient. Desensitisation successful in 54/71 attempts. Desensitisation successful in 18/35 patient/drug combinations. Reactions in 16 patient/drug combinations of which 3 were mild and 13 necessitated halting treatment.</td>
<td>Desensitisation may allow successful use of an antibiotic to which a patient has previously reacted. It was less successful in this study if there was a clear history of allergy. The use of concomitant steroids and antihistamines may improve the success rate.</td>
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