

ANTIBIOTIC ALLERGY IN THE INTENSIVE CARE UNIT

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ABSTRACT

Drug allergy in an intensive care unit (ICU) may be more common than realised. Antibiotics are the main drug involved and few patients have a previous history of drug reaction. Of all drug and antibiotic allergic reactions, allergy to beta-lactams is the most common reaction. Beta-lactam allergy is common enough for most clinicians to have an approach to this condition but since other drug allergies are less common, less often diagnosed, and often lack validated diagnostic tests, they are usually managed poorly. Based on the risk factors, the most important statement regarding clinical presentation of drug allergy is that a high index of suspicion is the most useful clue to suspected allergy. Testing strategies need to confirm allergy and skin-prick testing is useful in many circumstances. Treatment of a proven antibiotic allergy may include avoidance, but because the ICU patient frequently harbours an organism that has multiple antibiotic resistance patterns and demands use of a drug despite suspected allergy, methods of desensitisation should be known.

INTRODUCTION

The incidence of adverse drug reactions is widely quoted as about 15% of all hospitalised patients.^{1,2} However, this total includes many non-allergic reactions in both susceptible and non-susceptible individuals. At most 5% of individuals have allergic drug reactions, of which antibiotic allergy is by far the most frequent event. Few studies of the incidence of adverse drug reactions in intensive care units (ICUs) are available. However, a recent report of cutaneous adverse drug reactions in an ICU has been published.³ The authors report on an 8-month period in an adult ICU. The incidence of adverse drug reactions of a cutaneous nature was 11.6%. Risk factors identified were female gender, obesity, age over 60 and immune dysregulation (systemic lupus, dysthyroidism and anti-phospholipid antibody syndrome). Antibiotics were the main drug involved and few patients had a previous history of drug reaction. Patients who had anaphylactic events had a poor prognosis. The risk factors are commonly reported (Table I).

Of all drug and antibiotic allergic reactions, allergy to beta-lactams is the most common reaction.⁴ Penicillin reactions are usually explained by either IgE or T-cell dependent responses. Benzylpenicillin is no longer the most frequently prescribed antibiotic, especially in the

Table I. Risk factors for antibiotic allergy

Increasing age – uncommon in children
Female sex
Intravenous administration
Obesity
Immune disorders including HIV-positive individuals
Cystic fibrosis
Multiple adverse events to many drugs
Atopy is not generally a risk factor
Previous reactions are uncommon

ICU, and therefore newer antibiotic allergies have evolved.

Immediate hypersensitivity reactions to antibiotics are IgE mediated and characterised by the immediate release of inflammatory mediators from mast cells resulting in anaphylaxis, urticaria and angio-oedema.⁵

Beta-lactam allergy is common enough for most clinicians to have an approach to this condition but other drug allergies are less common, less often diagnosed, often lack validated diagnostic tests and are usually managed poorly.

This review focuses on the various diagnostic tests as well as therapeutic strategies to deal with antibiotic allergy in the ICU setting.

SUSPECTING ANTIBIOTIC ALLERGY

Based on the risk factors, the most important statement regarding clinical presentation of drug allergy is that a high index of suspicion is the most useful clue. Nearly every clinical sign or abnormal laboratory test has drug allergy in its differential. A useful clinical guide is that IgE-mediated reactions usually present within 30 minutes of drug administration and usually have skin (urticarial, angio-oedema), gastro-intestinal (diarrhoea or vomiting), respiratory (bronchospasm) or systemic (shock, hypotension) features. Delayed reactions suggest another immune mechanism for allergy.

Testing for suspected antibiotic allergy

Many clinical features of drug allergy in patients in an ICU setting may be attributable to other causes, or drugs other than antibiotics, and hence the approach of trying to confirm allergy is useful. Wohrl and colleagues⁶ reported on a cohort of 291 individuals with suspected drug allergy. All patients had a detailed history, skin-prick testing (SPT) or specific IgE and provocation testing. Although this was not an ICU study they were able to offer clear-cut recommendations on drug allergy, avoidance and alternatives to 82.1% of patients, clearly showing the usefulness of testing strategies. In addition the ICU patient frequently harbours an organism that has multiple antibiotic resistance patterns and demands use of a drug despite suspected allergy. In addition some disease states have few or no alternative drug selections.

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Today a wider selection of tests are available for testing for antibiotic allergy. The four main tests are specific RAST testing, specific CAST testing, skin-prick testing and measurement of serum tryptase.

Specific radio-allergosorbent test (RAST)

While RASTs are available to a wide range of inhalant and food allergens only a few antibiotic tests are offered. They are reflected in Table II.

Table II. Antibiotic RASTs

Penicilloyl G	c1
Penicilloyl V	c2
Amoxicilloyl	c6
Ampicilloyl	c5
Cefachlor	Rc7

Unfortunately the RASTs for penicillin measure only the major determinant of penicillin. The minor determinant is an important cause of anaphylaxis and therefore anaphylactic reactions cannot be excluded by negative penicillin RAST. RAST testing has a useful negative predictive value in excluding future allergic reactions in negative patients. However positive predictive value is poor.

Cellular antigen stimulation test (CAST)

The CAST is useful for detecting non-IgE-mediated sensitivity to certain drugs. It can also confirm IgE-mediated sensitivity, but in general, specific IgE tests, such as SPTs and the CAP RASTs are more efficient in this regard.

Principle of the CAST

The CAST depends on the exposure of interleukin-3 primed fresh basophils to different concentrations of an allergen, drug or chemical. Basophils which are sensitive to such exposure release sulphido leukotrienes into the media. These released leukotrienes are measured by an enzyme-linked immunosorbent assay

(ELISA). The CAST thus measures both IgE- and non-IgE-mediated leukotriene release in the ELISA.

Cut-off values for non-specific leukotriene release have been determined by exposing (± 20) healthy (non-allergic and non-sensitive) adult individuals to the agents, determining background release in this way. Patients who are clinically sensitive release leukotrienes in levels above the normal controls.⁷

The technical cut-off values are listed in Table III.

Requesting a CAST

A limited number of laboratories conduct the CAST in South Africa. For a CAST a full history of specific exposure in relation to clinical symptoms should be provided to the laboratory to assist selection of the most likely 'allergen' in a cost-effective way.

A fresh sample of EDTA blood is required (2 x 4 ml specimens) and this should reach the laboratory in the morning on which the test is to be conducted, preferably within 3 hours of taking the blood sample. Patients should be off all oral steroids for 48 hours prior to the test. It is also preferable to investigate the patients 3 weeks after a severe adverse reaction.

Patients may be brought to the laboratory where blood is taken freshly and the patient can also be interviewed to assist intelligent selection of the most appropriate CAST reagent. It is also important to ensure that patients are not on oral or injected steroids within 2 weeks of conducting a CAST on their basophils.

The result of a CAST is usually available within 24 hours and it is our policy to discuss each result with the patient and to provide specific written information to facilitate avoidance of the allergen/preservative/additive/drug to which the patient is found to be sensitive.

This form of testing is becoming increasingly useful for patients with antibiotic reactions; however borderline or low values may not exclude patients with potential life-threatening reactions on challenge testing.

Skin-prick testing (SPT)

SPT is available only for beta-lactam antibiotics. Both major and minor determinants of penicillin should be tested.⁸ Currently the temporary commercial unavailability of Pre-Pen (penicilloyl polylysine) makes SPT to this major determinant difficult. Minor determinant

Table III. Technical cut-off values for CAST

Code	Allergen	Conc. in cell stimulation	Technical cut-off pg/ml sLT
ANTIBIOTICS			
BAG2-C1	Penicillin G	500 μ g	50
BAG2-C2	Penicillin V	500 μ g	40
BAG2-C11	PPL (Benzylpenicilloyl-polylysine)	5 μ g	110
BAG2-C12	MDM (Minor determinant mixture)	100 μ g	100
BAG2-C203	Ampicillin	2 mg	70
BAG2-C204	Amoxicillin	200 μ g	100
BAG2-C3	Cephalosporin C	20 μ g	40
BAG2-C31	Cefamandole	500 μ g	80
BAG2-C32	Cefazolin	500 μ g	80
BAG2-C33	Cefuroxime	500 μ g	40
BAG2-C61	Sulfamethoxazole	20 μ g	50
BAG2-C62	Trimethoprim	20 μ g	40
BAG2-C75	Tetracycline	20 μ g	90
BAG2-C81	Ciprofloxacin	20 μ g	90

testing is also important. MDM can be made by diluting fresh Penicillin G with 2-week-old penicillin, 10 000 U/ml. A protocol for penicillin SPT is described in Table IV. Other protocols are available from the authors.

Table IV. Penicillin SPT protocol

1. Pre-Pen in increasing quantities of diluted concentrations 1:1 000, 1:100, 1:10 followed, if negative, by intradermal test
2. MDM in increasing quantities of diluted concentrations as above
3. Reaction measurement: positive if > 5 mm wheal size
4. Always use a positive (histamine) and negative (saline) control
5. SPT should be performed in an ICU setting even for non-ICU patients

Serum tryptase

The patient who has a sudden severe episode of shock in the ICU or theatre is often considered to have had an anaphylactic reaction to a drug. However, many causes exist and these complicate the diagnosis especially in patients who have been ill with various conditions prior to drug administration. A useful test to separate out anaphylactic from other 'anaphylactoid' events is serum tryptase. This measurement should be done immediately following the reaction, when a peak in levels is expected, and then some 6 hours later when return to baseline should occur. Tryptase seems not to be a useful measure after drug-provocation test reactions.⁹

Oral provocation testing

Some antibiotics have no gold-standard diagnostic testing available and oral provocation may serve as the gold standard. Such agents include metronidazole and erythromycin.¹⁰

TREATING ANTIBIOTIC ALLERGY IN THE ICU

The diagnostic work-up suggested above is important for the ICU patient with suspected antibiotic allergy because often that antibiotic is the last antibiotic to

Table V. Principles of managing anaphylactic drug reactions

1. Stop the antibiotic administration immediately
2. Treat the patient for the circulatory collapse and bronchospasm by standard means.
3. Intramuscular or intravenous adrenaline remains the mainstay of treatment.
4. Advise drug avoidance where possible
5. Advise cross-reacting drug avoidance where possible
6. On discharge the patient should receive a Medic-alert disc.
7. Desensitise if the drug is absolutely required

which highly resistant organisms may still be sensitive or alternatives may not be available.

General principles of management of anaphylactic drug reactions are listed in Table V.¹

A frequent question in practice is the use of cephalosporins in patients with penicillin allergy. This topic was the subject of a recent meta-analysis.¹¹ These authors reviewed 219 articles and commented on 9. Although the description of penicillin allergy diagnosis varied among studies they found a significant cross-allergy between penicillins and first-generation cephalosporins but this is negligible with second- and third-generation cephalosporins. They concluded with the statement that in selecting such a substitute antibiotic, particular emphasis should be placed on the chemical structure similarities between the reacting drug and proposed substitute. A third- or fourth-generation cephalosporin may be an acceptable substitute in the ICU setting for penicillin-allergic patients who have minor reactions but should be considered only in special situations in individuals who have had a documented anaphylactic reaction to penicillin. A recommendation is that before using any cephalosporin in a penicillin-sensitive patient, SPT to the proposed cephalosporin should be used at concentrations of 25 mg/ml (with positive and negative controls) to confirm that the patient is not sensitive. There is a 95% negative predictive value to this test. This could have medicolegal significance as some would argue that no patient with penicillin allergy is completely safe from reactions to any generation of cephalosporin.

Other antibiotics containing beta-lactam rings, such as monobactams (aztreonam), have no significant cross-reactivity with penicillins, and recently imipenem has been shown to be tolerated by penicillin and beta-lactam allergic patients.¹²

Desensitisation for antibiotic allergy

Desensitisation for drug allergy is the induction of temporary clinical unresponsiveness to drug allergens.¹² Gradual re-introduction of small doses of drug allergen at fixed time intervals allows the delivery of full therapeutic doses protecting against anaphylaxis. The cellular and molecular inhibitory mechanisms are not well understood but the suggestion is that intracellular signalling pathways within mast cells and basophils become inhibited.¹²

Such protocols are available for common drugs (Tables VI-IX) including penicillin, cephalosporins, carbapenems, vancomycin and sulphas. Most of these protocols apply to adult patients while the techniques are seldom employed in children.

Only immediate type I reactions to penicillin and beta-lactams are amenable to rapid desensitisation. Other reactions such as maculopapular rashes, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, bullous erythema, erythroderma, serum sickness, haemolytic anaemia, neutropenia, thrombocytopenia, and acute interstitial nephropathy are not amenable to rapid desensitisations.¹²

Table VI. Penicillin desensitisation protocol

A typical protocol for desensitisation to intravenous penicillin and cephalosporins starts at 1:10 000 to 1:100 the target dose, and doubling doses are delivered every 15-20 minutes over the course of several hours until the target dose is reached.¹²

Table VII. Ceftazidime desensitisation protocol

1. 50 mg over 6-8 hours IV infusion
2. 750 mg over 6-8 hours IV infusion
3. 1 g over 6-8 hours IV infusion
4. Full dose (100 mg/kg/day) over 24 hours

Table VIII. Piperacillin/tazobactam desensitisation protocol

1. 100 mg over 6 hours IV infusion
2. 500 mg over 6 hours IV infusion
3. 2 g over 6 hours IV infusion
4. Full dose (10 mg/kg/day) over 24 hours

All patients should be given an H1-antihistamine during the desensitisation process. The role of steroids is controversial.

Sulfa hypersensitivity in patients with HIV infection

Sulfamethoxazole/trimethoprim (SMX-TMP) is the most effective medication for treatment and prevention of *Pneumocystis jirovecii* pneumonia (PCP) in patients with AIDS. In many sectors of practice in South Africa it is the only available agent. However, adverse events are frequently reported. In most patients using SMX/TMP skin reactions occur. In most patients the drug is stopped but there is new evidence that this drug needs to be stopped only in severe cases (Table X).

In patients with defined allergy, desensitisation can be performed. In ICUs that treat PCP in HIV-positive children this method is sometimes important to be able to continue life-saving therapy (Table XI). Desensitisation can restore tolerability in approximately two-thirds of patients who use it.¹⁵

Table IX. Vancomycin desensitisation protocol¹³

Day	Time (min)	Concentration (mg/ml)	Infusion rate (mg/min)	Cumulative dose from the start (mg)
Rapid desensitisation				
1	0-10	0.0001	0.0001	0.001
	10-20	0.001	0.00033	0.004
	20-30	0.001	0.001	0.014
	30-40	0.01	0.0033	0.047
	40-50	0.01	0.01	0.15
	50-60	0.1	0.033	0.48
	60-70	0.1	0.1	1.48
	70-80	1	0.33	4.8
	80-90	1	1	14.8
	90-100	10	2.2	36.8
	100-110	10	4.4	80.8
Slow desensitisation				
1	110-215	10	4.4	500
2	0-300	1	1.7	500
3	0-300	1	1.7	500
4	0-300	1	1.7	500
5	0-300	1	1.7	500
6	0-300	2	3.3	1000
7	0-300	2	3.3	1000
8	0-300	2	3.3	1000
9	0-300	3	5.0	1500
10	0-300	3	5.0	1500
11	0-300	3	5.0	1500
12	0-300	3	5.0	1500
13	0-300	3	5.0	1500
14	0-300	4	6.7	2000
15	0-300	4	6.7	2000
16	0-300	4	6.7	2000
17	0-300	4	6.7	2000
18	0-300	4	6.7	2000
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21	0-300	4	6.7	2000
22	0-300	4	6.7	2000
23	0-300	4	6.7	2000
24	0-300	4	6.7	2000
25	0-300	4	6.7	2000
26	0-300	4	6.7	2000
27	0-300	4	6.7	2000
28	0-300	4	6.7	2000

Table X. Indications to stop SMX-TMP¹⁴

Persistent rash or fever > 5 days
Absolute neutrophil count < 500/mm³
Hypotension/dyspnoea
Blistering desquamation/mucus membrane involvement

Table XI. SMX-TMP desensitisation

Day	Dose SMX-TMP
1	1 ml of 1:20 paediatric suspension of SMX-TMP 0.4 mg/2 mg
2	2 ml of 1:20 paediatric suspension of SMX-TMP 0.8 mg/4 mg
3	4 ml of 1:20 paediatric suspension of SMX-TMP 1.6 mg/8 mg
4	8 ml of 1:20 paediatric suspension of SMX-TMP 3.2 mg/16 mg
5	1 ml of paediatric suspension of SMX-TMP 8 mg/40 mg
6	2 ml of paediatric suspension of SMX-TMP 16 mg/80 mg
7	4 ml of paediatric suspension of SMX-TMP 32 mg/160 mg
8	8 ml of paediatric suspension of SMX-TMP 64 mg/320 mg
9	1 tablet of SMX-TMP 80 mg/400 mg
10	1 tablet of double-strength (DS) SMX-TMP 160 mg/800 mg

Thereafter 1 tablet of DS SMX-TMP on Monday, Wednesday, and Friday for PCP prophylaxis or 2 tablets a day for the treatment of isosporiasis.

CONCLUSION

Antibiotic allergy in the ICU is becoming an important topic with the emergence of multiresistant organisms and limitations in antibiotic selections. We should have an approach to confirming suspected allergy and not

simply stop or change antibiotics without proof. In addition protocols are now available to restore tolerance to antibiotics in patients with severe allergic reactions. These however should in the main be employed in an ICU setting to limit the possibility of adverse reactions.

Declaration of conflict of interest

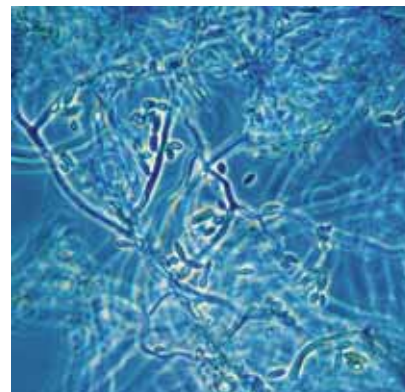
The authors declare no conflict of interest.

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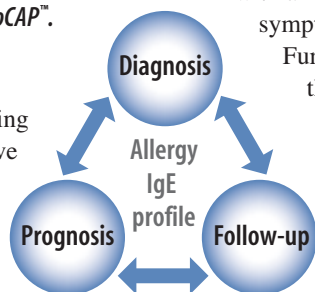
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