Update on the Management of Antibiotic Allergy

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Drug allergy to antibiotics may occur in the form of immediate or non-immediate (delayed) hypersensitivity reactions. Immediate reactions are usually IgE-mediated whereas non-immediate hypersensitivity reactions are usually non-IgE or T-cell mediated. The clinical manifestations of antibiotic allergy may be cutaneous, organ-specific (e.g., blood dyscrasias, hepatitis, interstitial nephritis), systemic (e.g., anaphylaxis, drug induced hypersensitivity syndrome) or various combinations of these. Severe cutaneous adverse reactions manifesting as Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) may be potentially life-threatening. The management of antibiotic allergy begins with the identification of the putative antibiotic from a detailed and accurate drug history, complemented by validated in-vivo and in-vitro allergological tests. This will facilitate avoidance of the putative antibiotic through patient education, use of drug alert cards, and electronic medical records with in-built drug allergy/adverse drug reaction prescription and dispensing checks. Knowledge of the evidence for specific antibiotic cross-reactivities is also important in patient education. Apart from withdrawal of the putative antibiotic, immunomodulatory agents like high-dose intravenous immunoglobulins may have a role in TEN. Drug desensitization where the benefits outweigh the risks, and where no alternative antibiotics can be used for various reasons, may be considered in certain situations. Allergological issues pertaining to electronic drug allergy alerts, computerized physician prescriptions and decision support systems, and antibiotic de-escalation in antimicrobial stewardship programmes are also discussed.

Key Words: Anaphylaxis; desensitization; drug hypersensitivity; Stevens Johnson syndrome; toxic epidermal necrolysis

INTRODUCTION

Antibiotics are one of the most common causes of drug allergy in most epidemiological studies, both among adults and children. Among the various classes of antibiotics, beta-lactam antibiotics (penicillins and cephalosporins), cotrimoxazole and quinolones are some of the most common causes of antibiotic allergy. Antibiotic allergy may occur in the form of immediate or non-immediate (delayed) hypersensitivity reactions. Immediate reactions are usually IgE-mediated whereas non-immediate hypersensitivity reactions are usually non-IgE or T-cell mediated. The clinical manifestations of antibiotic allergy may be cutaneous, organ-specific (e.g., blood dyscrasias, hepatitis, interstitial nephritis), systemic (e.g., anaphylaxis, drug induced hypersensitivity syndrome) or various combinations of these. Severe cutaneous adverse reactions (SCAR) manifesting as Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) may be potentially life-threatening.

DIAGNOSIS OF ANTIBIOTIC ALLERGY

The management of antibiotic allergy begins with the identification of the putative antibiotic from a detailed and accurate drug history. Not infrequently, the drug history may need to be obtained from a combination of sources other than the patient, including care-givers, records from other prescribing physicians and both non-electronic and electronic medical records. With the use of digital photography, instructing patients to take digital photographs of the initial rash may become increasingly important in helping the allergist to diagnose a drug eruption, especially when the rash is likely to have resolved by the time the patient sees the allergist.

In the diagnosis of immediate allergic reactions to antibiotics, the in-vivo tests available are skin prick tests (SPT) and intradermal tests (IDT). However, these have been well validated mainly for beta-lactam antibiotics and less so for other classes of antibiotics. For in-vitro tests, commercially available assays include fluorescent enzyme immunoassays (FEIA) (Immuno-
CAP, Phadia) which are less sensitive and specific compared to skin tests. Again, these tests are available mainly for penicillins and cephalosporins. Radioimmunoassays previously used mainly for the diagnosis of penicillin allergy (including the radioallergosorbent test, RAST) have over the years been replaced with the FEIA assays. Flow-cytometric based basophil activation tests (BAT) (flow assay stimulation test, FAST/FlowCAST, Buhlmann Laboratories) which measure CD69 or CD203c on drug-specific activated basophils may have a role in the diagnosis of antibiotic allergy, with studies so far mostly focused on beta-lactam allergy.

For non-immediate reactions, delayed readings of IDT are done at 24 hours and 72 hours. Delayed reactions are considered positive when there is an infiltrated erythematous reaction. Patch tests are often done in Europe to assist in the diagnosis of non-immediate reactions to various antibiotics. The tests are read on day 2, day 4, and day 7 (if negative on days 2 and 4), and the vehicle used is usually petrolatum. The patch test allergens can be prepared in-house or using commercially available products (Chemotechnique Diagnostics, Sweden). However, the sensitivity of the test is usually drug- and reaction-specific. Patch tests have been described in the diagnosis of non-immediate reactions to amoxicillin, cefcapene pivoxil, clindamycin, ciprofloxacin, clarithromycin, cotrimoxazole, doxycycline, erythromycin, fluoroquinolones, isoniazid, metronidazole, minocycline, pristinamycin, rifampicin, spiramycin, teicoplanin and vancomycin. Patch tests are generally useful in maculopapular exanthema (MPE), eczema, acute generalized exanthematous pustulosis (AGEP), fixed drug eruptions (FDE) (when done on the lesional skin), symmetric drug-related intertriginous and flexural exanthema (SDRIFE, Baboon’s syndrome); but have not been shown to be very useful in SJS/TEN and vasculitis.

In-vivo tests available for non-immediate reactions include the lymphocyte transformation test (LTT) which is a proliferation assay which detects drug-specific T-cells. This test can be technically difficult to carry out and are thus often done in specialized centres, mostly in Europe. Like the patch test, the LTT is usually positive in a drug- and reaction-specific manner. Antibiotics which have been found to often test positive in LTT are beta-lactams, quinolones, macrolides, sulfonamides, tetracycline, isoniazid and rifampicin. Similar to patch tests, LTT are beta-lactams, quinolones, macrolides, sulfonamides, tetracycline, isoniazid and rifampicin. However, the sensitivity of the test is usually drug- and reaction-specific.

Definitive treatment involves cessation of the suspected antibiotic. In certain instances where the antibiotic is required because there are no better alternatives (e.g., infection with multi-resistant organisms, or when alternative drugs are more expensive), drug desensitization can be carried out. Desensitization is a method of reintroducing antibiotics into highly sensitized patients to induce tolerance. However such individuals are still considered as being allergic to the antibiotic. Recent studies of in vitro rapid antigen desensitizations implicate mast cells and basophils as cellular targets, as well as syk, a signal transducing molecule, and signal transducer and activator of transcription 6 (STAT6), which is responsible for the transcription of interleukin (IL)-4 and IL-13. Rapid desensitization results in patients achieving the target total dose of the drug through rapidly escalating doses usually within 24 hours, slow desensitization results in patients achieving the total target dose within a few days to weeks. Desensitization should be avoided should the initial reaction be potentially life-threatening reactions like immunobullous eruptions and SJS/TEN, with the exception of anaphylaxis. Various desensitization protocols are available for penicillin (benzylpenicillin, ampicillin), cephalosporins (cefazidime, cefotaxime), cotrimoxazole, ethambutol, imipenam, isoniazid, meropenam, metronidazole, rifampicin, streptomycin, vancomycin and fluoroquinolones.
Penicillin allergy

Allergic reactions to beta-lactam antibiotics are the most common cause of drug allergies in most epidemiological studies on adverse drug reactions. SPT and IDT using commercially available penicillloyl polylysine (PPL), minor determinant mix (MDM) and benzylpenicillin G or amoxicillin have been validated in various studies and shown to be useful in the evaluation of suspected immediate reactions to penicillin. In 2004, Allergopharma and Hollister-Stier announced their decision to stop the commercial production of penicillin reagents (AllergoGen® and PrePen® respectively). A Spanish product (Diater®) was subsequently found to be a reliable and consistent alternative and is presently used in many countries worldwide. In September 2009, Pre-Pen® was approved for marketing by the Food and Drug Administration (FDA) through ALK-Abello and Allerquest LLC. In countries where commercial PPL and MDM are not available, skin testing with benzylpenicillin may be used in lieu. However, this may miss patients who may have tested positive to PPL or MDM, and thus could result in potentially positive drug provocation tests being done.

In-vitro tests are often less sensitive and more expensive when compared to skin tests, with the FEIA currently being the most widely commercially available test. The determinants used in FEIA are benzylpenicillloyl and amoxicilloyl. However, the sensitivity (42-74%) and specificity (85-100%) reported varied among studies, depending on when the sample was taken from the time of the initial clinical reaction, and the outcomes of skin tests to PPL, MDM and/or amoxicillin in the respective studies.

The flow cytometric BAT assay, when used in the diagnosis of beta-lactam allergy, has a sensitivity of 50%, and specificity of 93%. However, the test is unable to differentiate between selective reactors and cross-reactors, and tests become negative the longer the duration from the initial reaction. Using a combination of skin tests, specific IgE assays, followed by cellular tests in negative patients, can facilitate confirmation of beta-lactam allergy, avoiding DPT in up to two-thirds of patients. Using an alternative marker like CD203c may increase the sensitivity of these tests.

Patch tests when used, should be carried out with benzylpenicillin, amoxicillin, ampicillin, and any suspect penicillins and/or cephalosporins. LTT for beta lactam allergy has a low sensitivity of 60-70%, hence a positive test is useful in confirming beta lactam allergy but a negative test does not rule it out. The LTT is often positive in AGEP and DRESS, but rarely positive (<10%) in blood dyscrasias and TEN associated with drug allergy.

Cephalosporin allergy

The reported cross-reactivity for IgE-mediated hypersensitivity between cephalosporins and penicillins in patients with IgE-mediated penicillin allergy of 5-10%, were based on early studies from the 1970s on patients with a history of penicillin allergy who developed allergic reactions to cephalaxin, cefalothin and cephaloridine. In addition, early cephalosporin antibiotics contained traces of penicillin. Although the practice parameters of the AAAAI in 1999 did not advocate the use of cephalosporin skin testing, this is recommended by the British Society of Allergy and Clinical Immunology (BSACI) and the European Academy of Allergy and Clinical Immunology (EAACI). The R1 side chain rather than the beta-lactam structure, shared by penicillins and cephalosporins, seems to play a dominant role in determining the specificity of immunologic reactions to cephalosporins. Thus, penicillin can be administered safely to patients allergic to cephalosporins and with a negative skin test result to penicillin determinants. Similarly, this may be the reason why the penicillin allergic individuals appear to be able to tolerate most third and fourth generation cephalosporins.

The flow cytometric BAT assay appears to be a promising in-vitro test in the diagnosis of cephalosporin allergy as well as penicillin allergy.

Carbapenem allergy

Earlier studies from the late 1980s showed that cross-reactivity between penicillin and imipenem allergy was 50% based on 10 of 20 patients with penicillin allergy being skin test positive to one or more penicillin or imipenem determinants. Recent prospective studies in adults and children with penicillin (predominantly amoxicillin) IgE-mediated allergy have shown that the cross-reactivity based on positive skin tests to imipenem-cilastatin and meropenem was 0.9%, and that patients who were SPT/IDT negative to imipenem-cilastatin and meropenem were able to tolerate a graded, challenge dose of intravenous imipenem-cilastatin and meropenem respectively. For delayed reactions to carbapenems, the cross-reactivity with penicillins was 5.5% based on patients with cell-mediated allergy to penicillins showing positive patch tests at least one penicillin reagent and imipenem-cilastatin. All patients with negative patch test and delayed IDT reading to imipenem-cilastatin tolerated an intramuscular provocation test.

Cotrimoxazole allergy

Cotrimoxazole is an immunogenic drug which may cause both immediate and non-immediate reactions. Non-immediate reactions range from mild MPE and FDE to serious SJS and TEN, and are more common than immediate reactions. This is especially prevalent in HIV-infected individuals where cotrimoxazole is used for the treatment and prophylaxis for Pneumocystis jiroveci infection and toxoplasmosis. Slow acetylator phenotype and genotype, and major histocompatibility complex (MHC) polymorphisms have not been shown to be major predisposing risk factors for cotrimoxazole hypersensi-
tivity in HIV-infected individuals. Rapid and slow desensitization to cotrimoxazole especially in the setting of HIV infection, has been shown to be effective and safe.60

**FLUOROQUINOLONE ALLERGY**

Fluoroquinolone allergy may present in the form of immediate and non-immediate reactions. The immediate reactions may be IgE mediated or non IgE mediated, with non-IgE mediated reactions occurring after the first dose with no previous history of sensitization.61,62 Although previous studies had shown that skin tests to quinolones lack sensitivity and specificity,63 a negative skin test could predict a negative challenge test in 94% of the challenged cases.64 Cross-reactivity has been demonstrated for immediate reactions through positive skin tests to a range of quinolones,65 and delayed reactions through generation and analysis (flow cytometry and proliferation assays) of quinolone-specific T cell clones respectively.65 Thus, patients with allergy to a fluoroquinolone should avoid other fluoroquinolones.

**MACROLIDE ALLERGY**

Macrolides are classified according to the number of carbon atoms in the chemical structure: 14 membered (erythromycin, roxithromycin, dirithromycin, clarithromycin) and 16 membered (spiramycin, josamycin, midemycycin) macrolides. Allergic reactions to macrolide antibiotics appear to be relatively uncommon (0.4% to 3% of treatments).66 Cases of immediate reactions in the form of anaphylaxis,67 and non-immediate reactions like fixed drug eruptions, toxic epidermal necrolysis and leukocytoclastic vasculitis have been reported, in children and adults, for clarithromycin and azithromycin. Successful desensitization has also been reported.68

**TETRACYCLINE ALLERGY**

Minocycline can cause serious adverse reactions including drug hypersensitivity syndrome, serum sickness and drug-induced lupus. These occur on average within 4 weeks of therapy, whereas minocycline-induced lupus occurs on average 2 years after the initiation of therapy.69 Apart from photodermatoses and photo-onycholysis which are usually phototoxic in nature, adverse drug reactions, in particular drug allergies to doxycycline and tetracycline are relatively rare.70

**CLINDAMYCIN ALLERGY**

Clindamycin may be associated with both immediate and non-immediate allergic reactions.71 However, the prevalence of such reactions is rare.72 Apart from exanthematous eruptions, cases reported in the literature include contact dermatitis, AGEP73 and TEN.74 The use of a combination of skin prick tests, patch tests and oral challenges if skin tests are negative, appear to be more useful compared to SPT and IDT alone as negative skin tests may still result in positive challenges.75,76 Clindamycin desensitization has been reported in the literature in particular in HIV-infected individuals.77,78

**VANCOMYCIN AND TEICOPOLAN ALLERGY**

Vancomycin, a glycopeptide, has rarely been reported to be associated with allergic drug reactions including exfoliative dermatitis and maculopapular rash. This is in contrast to vancomycin red man syndrome, which is commonly associated with too rapid an infusion of vancomycin resulting in direct mast cell histamine release.79

Anaphylaxis from vancomycin may be through IgE mediated allergic mechanisms or non-IgE mediated non-allergic mechanisms. Various effective desensitization regimes have been described in the treatment of vancomycin anaphylaxis.80-83

Linear IgA bullous dermatosis (LABD) is an autoimmune, subepidermal, vesiculobullous disease that has been commonly associated with the use of vancomycin.84,85 Lesions typically appear during vancomycin therapy, 24 hours to 15 days after the first dose. Histopathologic examination and immunofluorescence studies are diagnostic, showing linear IgA and C3 deposits at the basement membrane zone on direct immunofluorescence. Withdrawal of vancomycin is all that is required.

Teicoplanin, another glycopeptide, has fewer side effects compared to vancomycin.79 Red man syndrome is very unusual with teicoplanin because this compound does not cause histamine release even at faster infusion rates than those of vancomycin. Immediate reactions [anaphylaxis,86,87] and non-immediate reactions [rash,88 AGEP89 and DHS90] are infrequent. Although there have been reports of cross-reactivity between individuals with vancomycin and teicoplanin allergy,91-93 there have also been reports of patients with teicoplanin who tolerated vancomycin.94,95

Pre-operative allergy clinic assessment together with penicillin skin testing has been shown to be an effective intervention in reducing unnecessary use of prophylactic vancomycin perioperatively.96,97 This would be helpful in the long-term in reducing the spread of vancomycin resistant infections in hospitals and within the community, and the need for potentially expensive antibiotics like linezolid and tigecycline.

**TUBERCULOUS DRUG ALLERGY**

*Mycobacterium tuberculosis* (MTC) infection remains endemic in certain parts of Asia. Treatment of MTC infections involves combinations of anti-tuberculous drugs including isoniazid, rifampicin, ethambutol and pyrazinamide. Non-immediate reactions are much more common than immediate reactions to
anti-tuberculous drugs. Drug eruptions in the form of MPE and lichenoid drug eruptions, haematological reactions, hepatitis, DHS, SJS/TEN have all been reported in the literature. Diagnosis using LTT have not been useful to date. Patch tests are also not consistently useful as they are dependent on the type of cutaneous drug eruption. In practice, it is often not clinically feasible to leave MTC infection untreated for 6 weeks pending evaluation using LTT or patch tests, which in the end may not be helpful. Diagnosis using LTT have not been useful to date. In DHS, systemic corticosteroids (0.5 to 1 mg/kg/day) tapered over 6-8 weeks rapidly improves symptoms and laboratory measurements, but its impact on the long term disease course is not known. Controlled clinical trials are lacking on the use of systemic corticosteroids in DHS. Relapses of rash and hepatitis may occur as corticosteroids are tapered. Sequential reactivation of herpes viruses (e.g., human herpes virus 6, Ebstein Barr virus, cytomegalovirus) and subsequent triggering of autoimmunity may explain these relapses, and hence the effectiveness of systemic corticosteroids.

In SJS, the use of systemic corticosteroids has been supported by case reports and series (prospective and retrospective) which showed positive outcomes with the early use of corticosteroids (prednisolone 1 mg/kg/day or methylprednisolone 1-2 mg/kg/day) within 72 hours was beneficial in arresting the progression of SJS. However, there were also other studies which showed harm or no benefit.

TEN is defined as the detachment of the epidermis affecting more than 30% body surface area of skin involvement. In early TEN, between 10-30% of epidermal detachment occurs which can sometimes be diagnosed clinically from a positive Nikolsky’s sign or histological evidence of epidermal necrolysis. Apart from prompt withdrawal of the suspected drug, supportive measures including specialized nursing, early referral to a specialized unit, nutritional and respiratory care and support, skin care including the use of Biobrane dressings, are standard of care for which there are no controlled trials. Systemic corticosteroids should not been used as most series have suggested that the risks outweigh the benefits. The use of oral and intravenous cyclosporine 3-5 mg/kg/day, of duration of up to 3 weeks in case series of patients with severe TEN suggest that the risks of infection outweighed the benefits. The only double-blind placebo-controlled trial to date in the management of TEN, using thalidomide was stopped because there was excessive mortality in the thalidomide group. Other therapies like cyclophosphamide and plasmapheresis have not been shown to be useful.

In the last decade, several case series have described the use of high dose intravenous immunoglobulins (IVlg) from 0.8-3 g/day in the treatment of TEN. The rationale for the use of IVlg is based on the inhibition of Fas-mediated keratinocyte apoptosis in TEN by naturally occurring Fas-blocking antibodies within the IVlg. Although there were wide variation in patients and treatment protocols, different brands of IVlg used with different dosing regimens, the overall mortality rate was around 20% with earlier re-epithelialization demonstrated in some of the studies.

The prevalence of acute ocular complications ranges from 6% to 100%, and long-term sequelae from 1% to 50%. The most common long-term sequelae is sicca syndrome. Others include corneal ulceration, corneal epithelial defect, symblepharon and fornix foreshortening. Treatment modalities for ocular complications include topical antibiotics, topical corticosteroids, lubricants, and fornix sweeping. High-dose IVlg did not appear to reduce the severity of visually significant ocular complications. Early intervention with cryopreserved amniotic membrane transplantation was shown in a recent study to suppress inflammation and promote epithelial healing at the acute stage. Significant dry eye problems and photophobia may also be avoided with this intervention.

A recent retrospective study from China suggested that combination therapy with corticosteroid and high dose IVIG exhibited a tendency to reduce the mortality rate in comparison with administration of corticosteroid alone. The decrease in the mortality rate, however, was not statistically significant. Combination therapy also arrested progression earlier and decreased the hospitalization time, meaning that the total dose of corti-
corticosteroid may be reduced. Combination therapy, however, did not lead to earlier tapering of corticosteroid.136

**DRUG-INDUCED LUPUS**

Drug-induced lupus erythematosus (DILE) is defined as a lupus-like syndrome temporally related to continuous drug exposure which resolves after discontinuation of the offending drug. There are currently no standard diagnostic criteria for DILE and the pathomechanisms are still unclear. Among the antibiotics, minocycline and isoniazid are most often associated with DILE. Systemic DILE is characterized by typical lupus-like symptoms including skin signs, usually mild systemic involvement and a typical laboratory profile with positive antinuclear and anti-histon antibodies. In most cases of classic DILE, visceral involvement, low serum complement levels as well as anti-extractable nuclear antigen antibodies and anti-dsDNA antibodies are rarely present. In contrast, these are present in half the cases of anti-tumour necrosis factor (TNF) alpha inhibitor induced DILE. The diagnosis of DILE is based on a temporal association (months to years) of use of the putative drug with characteristic lupus-like symptoms, and resolution of symptoms upon withdrawal of the drug. Systemic corticosteroids and immunosuppressive drugs are only needed in refractory cases.137

**ANTIBIOTIC ALLERGY AND ANTIMICROBIAL STEWARDSHIP PROGRAMMES**

Antimicrobial stewardship programs in hospitals seek to optimize antimicrobial prescribing in order to improve individual patient care, reduce hospital costs and slow the spread of antibiotic resistant organisms. Such programs are often administered by multidisciplinary teams comprising infectious diseases physicians, clinical pharmacists, clinical microbiologists, and infection control practitioners. Strategies for changing antimicrobial prescribing behaviour include education of prescribers regarding proper antimicrobial usage, creation of an antimicrobial formulary with restricted prescribing of targeted agents, and review of antimicrobial prescribing with feedback to prescribers. De-escalation from broad-spectrum empirical antibiotics to narrow-spectrum, culture and sensitivity specific antibiotic is a supplemental strategy used in such programmes to minimize antimicrobial prescribing in order to improve individual antibiotic resistant organisms. Such programs are often administered by multidisciplinary teams comprising infectious diseases physicians, clinical pharmacists, clinical microbiologists, and infection control practitioners. Strategies for changing antimicrobial prescribing behaviour include education of prescribers regarding proper antimicrobial usage, creation of an antimicrobial formulary with restricted prescribing of targeted agents, and review of antimicrobial prescribing with feedback to prescribers. De-escalation from broad-spectrum empirical antibiotics to narrow-spectrum, culture and sensitivity specific antibiotic is a supplemental strategy used in such programmes to reduce antibiotic resistance from the use of broad-spectrum antibiotics.138 However, de-escalation in a patient with unconfirmed antibiotic allergy should be exercised with caution as drug provocation tests in the presence of negative skin tests, should be avoided in the presence of on-going sepsis unless no other alternative antibiotics are available.25 Similarly, in the patient with a high probability of allergy to a narrow spectrum antibiotic (e.g., penicillin G) who has been tolerating a broad-spectrum antibiotic (e.g., meropenem), it would be prudent to continue the broad-spectrum antibiotic rather than to consider skin testing and desensitization to penicillin G in the presence of on-going sepsis where alternative antibiotic choices remain available.

**ANTIBIOTIC ALLERGY ALERTS AND DECISION SUPPORT FOR COMPUTERIZED PHYSICIAN ORDERS**

Antibiotic stewardship programmes may also be complemented by electronic computerized physician prescriptions with decision support systems139 utilizing drug/antibiotic allergy checks.140 However, the data from electronic drug allergy physician reporting systems are often inaccurate or incomplete. Thus, using such electronic alerts in any type of electronic medication record system as a decision support tool to facilitate antibiotic prescribing has to be done very cautiously.

**CONCLUSIONS**

Antibiotics may cause various types of allergic drug reactions ranging from mild to serious cutaneous reactions, organ-specific or systemic reactions. A high index of clinical suspicion and immediate withdrawal of the suspected drug/drugs are the most important steps in the management of antibiotic allergy. Systemic immunomodulatory drugs may be required to suppress severe cutaneous/systemic reactions. Drug desensitization may be considered in cases where the risks of retrying the drug outweigh the benefits, in particular where no alternative medications are available or are as effective.

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