HHS Public Access

Author manuscript

Lancet. Author manuscript; available in PMC 2019 June 13.

Published in final edited form as:

Lancet. 2019 January 12; 393(10167): 183–198. doi:10.1016/S0140-6736(18)32218-9.

Antibiotic allergy

Kimberly G Blumenthal[1], **Jonny G Peter**[2], **Jason A Trubiano**[3], and **Elizabeth J Phillips**[4]

[1]Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA.

[2]Division of Allergy and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa; Allergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa.

[3]Department of Infectious Diseases, Austin Health, Melbourne, VIC, Australia; Department of Medicine, University of Melbourne, Melbourne, VIC, Australia; The National Centre for Infections in Cancer, Peter McCallum Cancer Centre, Melbourne, VIC, Australia.

[4]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA, Australia; Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

Abstract

Antibiotics are the commonest cause of life-threatening immune-mediated drug reactions that are considered off-target, including anaphylaxis, and organ-specific and severe cutaneous adverse reactions. However, many antibiotic reactions documented as allergies were unknown or not remembered by the patient, cutaneous reactions unrelated to drug hypersensitivity, drug-infection interactions, or drug intolerances. Although such reactions pose negligible risk to patients, they currently represent a global threat to public health. Antibiotic allergy labels result in displacement of first-line therapies for antibiotic prophylaxis and treatment. A penicillin allergy label, in particular, is associated with increased use of broad-spectrum and non-β-lactam antibiotics, which results in increased adverse events and antibiotic resistance. Most patients labelled as allergic to penicillins are not allergic when appropriately stratified for risk, tested, and re-challenged. Given

Corresponding author: Prof Elizabeth J Phillips, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232–2582, USA, elizabeth.j.phillips@vanderbilt.edu.

Contributors

KGB performed the literature search and drafted the first report of this Review. All authors contributed equally to the development of visuals included in this Review and participated in the critical revision of the manuscript.

Declaration of interests

The authors declare no competing interests. KGB receives research funding and career development support from the National Institutes of Health, USA and the American Academy of Allergy, Asthma and Immunology Foundation, USA; has authored copy-written material and an electronic decision support tool and app used institutionally at Partners Health Care System for hospitalised patients with historical β-lactam allergies; has received royalties from Up To Date (Waltham, MA, USA) and honorarium from the New England Society of Allergy, USA. JGP is supported by a grant from the National Institutes of Health, USA (K43 TW011178-01). JAT is supported by a National Health and Medical Research Council (NHMRC) of Australia Early Careers Fellowship and a post-doctoral scholarship from the National Centre for Infections in Cancer (NCIC, Australia). EJP reports grants from NHMRC of Australia; grants from the National Institute of Health, USA (1P50GM11530501, 1P30AI110527-01A1, R21AI139021, and R34AI136815); grants from the Australian Centre for HIV and Hepatitis Virology Research (all paid to the institution); personal fees from Up To Date and Biocryst; consulting fees not directly received from Aicuris, outside the submitted work; and is co-director of IIID Pty Ltd that holds patent for HLA-B*57:01 testing for abacavir hypersensitivity, without any financial remuneration and not directly related to the submitted work. Funders played no role in any aspect of this Review.

the public health importance of penicillin allergy, this Review provides a global update on antibiotic allergy epidemiology, classification, mechanisms, and management.

Introduction

Antibiotics can result in adverse drug reactions (ADRs) and hypersensitivity reactions (HSRs) through a variety of mechanisms. Antibiotic allergies are frequently documented in the electronic health record, which results in changes to the care of future infectious diseases. Inaccurately determined allergies might result in the use of unnecessarily broad-spectrum or inferior antibiotics, posing a threat to patient safety and public health. Despite these threats, the histories associated with documented allergies are rarely reconciled, or acted on, by the health care team. Ideally, patients at low risk for allergy would have their allergy evaluated without specialist intervention, and high-risk patients would be referred for allergy diagnostic testing and have potential reaction mechanism(s) implicated. Although some allergy investigations are validated diagnostic tests approved by governing bodies globally, many tests for immunologically mediated drug hypersensitivity remain under investigation.

In this Review, we provide a global perspective on antibiotic allergies, with a focus on updated classification, epidemiology, effect on public health, diagnosis, and management. We also advise on the crucial steps required to appropriately combat unverified penicillin allergy labels as an emergent threat for individuals and public health.

Classification, presentation, and mechanism

ADRs include any untoward medication effect experienced at normal therapeutic doses of the drug, and HSRs are ADRs that are immunologically mediated. As our mechanistic understanding of ADRs improves, limitations of previous ADR classifications have become apparent. Consequently, a high-level classification of on-target and off-target reactions, with further categorisation of off-target immune and non-immune reactions has been proposed (figure 1).[2,3] Both on-target and off-target effects can show concentration-exposure relationships that can differ between individuals, due to acquired or genetic host factors. The type and intensity of interaction between the drug and target may relate to both the dose and duration of treatment. This classification recognises that in many ADRs, for example drug-induced liver injury, the aetiopathogenesis is not due to a singular mechanism. The targeting of eukaryotic and prokaryotic cellular differences by antibiotics means that there are few, true on-target antibiotic ADRs, which are due to an augmentation of the known therapeutic and pharmacological action of a drug. The negative consequences of disrupting commensal microbial communities, such as antibiotic-associated diarrhoea or *Clostridioides difficile* infection, are perhaps an exception. Some off-target ADRs are both directly immune-mediated and associated with immunological memory of varied duration (drug hypersensitivity), whereas others without immunological memory might have an immunological phenotype, such as non-IgE-mediated mast-cell activation seen with the use of fluoroquinolones. In this scheme, immunologically mediated drug hypersensitivity comprises the antibody-mediated and T-cell-mediated off-target ADRs.

Other HSR frameworks, including Gell and Coombs hypersensitivity mechanisms (eg, types I through IV HSRs) and reaction chronology and onset (immediate vs delayed), remain clinically important. Immediate antibiotic HSRs may either be mediated by IgE or by other factors (figure 1, table). The pathways of IgE-mediated reactions are well described.[6] Recently a mechanism for some reactions not driven by IgE, previously called pseudoallergic or anaphylactoid, has been further elucidated. A receptor on murine mast cells, Mrgprb2, the orthologue of the human G-protein-coupled receptor MRGPRX2, was necessary for certain non-IgE-mediated drug reactions.[5] Vancomycin and fluoroquinolones are the most commonly recognised mast-cell activators that cause non-IgE-mediated reactions to antibiotics,[8],[9] thus producing a reaction with an immunological phenotype, but without immunological memory. Typically, non-IgE reactions have less cardiovascular symptomatology and hypotension, but are otherwise not easily distinguished from IgE-mediated allergy (table).[10]

Delayed HSRs are mediated by T cells or antibodies other than IgE (table). Antibody-mediated cytopenias, such as haemolytic anaemia, neutropenia, and thrombo-cytopenia (Gell and Coombs Type II), and serum sickness (Gell and Coombs Type III), are uncommon. Organ-specific HSRs to antibiotics often involve the liver (eg, drug-induced liver injury), kidney, or both (eg, acute interstitial nephritis).[3] The commonest T-cell-mediated reaction to antibiotics is maculopapular rash, considered to be a type IVb HSR (table).[11] This is the mechanism of the drug rash observed with aminopenicillin use. Other specific cutaneous HSRs from antibiotics include fixed drug eruptions, reported from tetracyclines, sulphonamides, β-lactams, vancomycin, and fluconazole.[2] Generalised fixed drug eruptions can have bullae and mimic Stevens-Johnson syndrome or toxic epidermal necrolysis.[7] Vancomycin is the most common antibiotic cause of linear IgA bullous disease, a blistering cutaneous adverse reaction that can also mimic Stevens-Johnson syndrome and toxic epidermal necrolysis.[12] The major severe cutaneous adverse reaction (SCAR) phenotypes include Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction eosinophilia and systemic symptoms (DRESS) syndrome, and acute generalised exanthematous pustulosis, which are detailed in the table.[1,2]

In addition to causing HSRs through immunologic mechanisms, drugs can also be implicated as the cause through coincidential association with a viral exanthem or through drug-infection interactions.[13] A notable example of a drug-infection interaction is the rash observed with Epstein-Barr virus and amino-penicillin treatment, present in at least 30% of such patients.[14] Bacterial (eg, rash and mucositis associated with Mycoplasma pneumoniae) and viral (eg, herpes simplex virus) infections are directly linked to the onset of erythema multiforme mimicking Stevens-Johnson syndrome.[13] A more traditional illness that resembles Stevens-Johnson syndrome and toxic epidermal necrolysis has also been associated with viruses such as Coxsackie A6.[15] Viral reactivation to human herpesvirus (HHV) 6 and 7, cytomegalovirus, and Epstein-Barr virus has been described and thought to occur as a consequence of regulatory T-cell expansion and the immune dysregulation associated with DRESS, rather than as a trigger of DRESS syndrome.[13]

Epidemiology

Adverse drug reactions and hypersensitivity reactions

ADRs account for more than 3% of hospital admissions[16] and complicate the inpatient care of 10–20% of hospitalised patients.[17,18] Drug HSRs comprise up to 20% of ADRs and are reported in approximately 8% of general populations.[19,20] Cutaneous reactions, including rash and hives, are the most commonly reported HSRs.[21,22] Although most patients are labelled with an antibiotic allergy at the time of hospital admission, new onset cutaneous HSRs were found to affect approximately 2% of inpatients.[11] Severe, immediate allergies are infrequent; however, anaphylaxis comprised 3% of reactions documented in a US electronic health record repository of allergy.[21]

Early studies identified antibiotics, particularly β-lactams, as the most common HSR culprits.[11] However, antibiotic HSRs are easily misdiagnosed because alternative explanations for rashes exist (eg, infections from viruses such as Herpesviridae, or bacteria such as Streptococcus pyogenes, and drug-infection interactions).[14,22],[23] Antibiotic allergy labels, which are those documented in health records but unverified, might also be recorded incorrectly in patients' charts after a non-immunological reaction, such as gastrointestinal upset, headache, or fatigue.[21]

β-Lactams, which include penicillins, cephalosporins, carbapenems, and monobactams (figure 2), are the most common antibiotic classes reported to cause HSRs.[24,25] β-Lactam ADRs are documented in 5–15% of patients' charts.[25,26] Sulphonamide antibiotics are another commonly reported antibiotic allergy, with ADRs documented in 2–10% of cases.[24–26] Patients labelled as sulfa allergic could have had a reaction previously to sulphonamide antibiotics or a non-antibiotic sulphonamide, and notably there is no cross-reactivity between sulphonamide antibiotics and non-antibiotic sulphonamides.[27] Sulphonamide antibiotics are implicated in benign T-cell-mediated rashes and SCARs.[1,28] A third of reported cases of Stevens-Johnson syndrome and toxic epidermal necrolysis documented in electronic health records is attributed to sulphonamide antibiotics.[25,29]

Other notable antibiotic allergies reported to cause HSRs are fluoroquinolones, macrolides, tetracyclines, and glycopeptides.[25,30] Although these antibiotic classes generally cause cutaneous reactions, the glycopeptide vancomycin is also the commonest antibiotic implicated in non-IgE-mediated reactions and up to 40% of DRESS syndrome cases.[12,29,31–34]

β-Lactam antibiotics

Penicillin was first widely used in the 1940s, with reports of immediate drug hypersensitivity surfacing soon thereafter.[34] Early reported allergies to penicillins included injection reactions, serum sickness-like reactions, and delayed T-cell-mediated cutaneous eruptions. Studies confirm an approximate penicillin reaction rate from 0·5% to 5·0% of administrations.[8,11] Today, from 5% to 15% of patients in developed countries carry a penicillin allergy label.[24–26,35] Aminopenicillins, largely administered orally, have been used since the 1970s. Although they are recognised as the most common cause of drug-

induced delayed rashes and drug viral interactions,[14] they infrequently cause true IgE-mediated reactions.

In the USA, cephalosporin ADRs are documented in 1–2% of patients' charts,[36] with rash being the most commonly reported reaction. The use of carbapenems is uncommon globally and is often restricted by antimicrobial stewardship programmes, because of the drugs' broad-spectrum activity and formulation as parenteral and intramuscular antibiotics. As such, ADRs and HSRs reported from carbapenems are substantially lower than those reported from penicillins and cephalosporins.[24,25]

β-Lactam IgE-mediated HSRs

Although IgE-mediated reactions are not uncommon in patients treated with penicillin, anaphylaxis is rare (approximately 0·001% for parenteral exposures and 0·0005% for oral exposures).[37,38] IgE-mediated penicillin HSRs are less frequent today than described previously, and the prevalence of penicillin anaphylaxis has also declined over time.[39] There was one fatal amoxicillin reaction in the UK during the period from 1972 to 2007.[37] The changing epidemiology of IgE-mediated penicillin allergy might be attributed to newer, less allergenic formulations and changes in administration route.[40,41] Penicillin antibiotics commonly prescribed today are used orally, such as for bacterial pharyngitis, sinusitis, lower respiratory tract infections, or skin and soft tissue infections. In addition to oral administration, cephalosporins are vital intramuscular (eg, ceftriaxone) and parenteral (eg, cefazolin, cefepime, ceftriaxone) anti- biotics. The cephalosporin cefazolin is identified as a common causative agent in perioperative anaphylaxis in countries where it is available and frequently used (USA, Canada, UK, France, Australia, South Africa, and parts of Southeast Asia and South America).[8]

Other β-lactam HSRs

The most common β-lactam reaction is a delayed-type rash, often a T-cell-mediated eruption. β-Lactams are also key culprits in serum sickness-like reactions observed that are due to cephalosporins, often cefaclor, and penicillins, typically with high-dose parenteral penicillin therapy.[8]

SCARs are the most severe non-immediate HSRs and can be attributed to antibiotics in a quarter to half of cases.[33,42] A recent USA-based study calculated an annual incidence per million inhabitants of 8·61–9·69 cases for Stevens-Johnson syndrome, 1·46–1·84 cases for Stevens-Johnson syndrome and toxic epidermal necrolysis overlap, and 1·58–2·26 cases for toxic epidermal necrolysis.[43] Antibiotics, including penicillins, are reported as SCAR culprits but are also common drugs started at the first sign of the Stevens-Johnson syndrome and toxic epidermal necrolysis prodrome that mimics an infection.[32] Illnesses similar to Stevens-Johnson syndrome and not induced by drugs, such as erythema multiforme, are often mis-classified as Stevens-Johnson syndrome, and the anti-biotics and non-steroidal anti-inflammatory drugs introduced during the prodromal stage of illness may be implicated as causative.[7] Patients with antibiotic-associated SCAR are often treated with more than one antimicrobial at the time of diagnosis. Aminopenicillins and cephalosporins uncommonly cause SCARs but may be implicated when drug causality is unclear.[28] In a

US study of over 800 000 patients exposed to over 1 million cephalosporins, there were three cases of cephalosporin-associated SCARs documented, but patients were on other drugs that could also have caused the SCAR.[44]

Special patient groups

The frequency of documented drug allergy is higher in women, those of self-reported European ancestry, adults, and in inpatients.[20,24] Female predominance has been stable across multiple studies for reported allergies, especially for antibiotic allergies, but no sex effect has been demonstrated in children.[24,25,45] Patients whose self-determined ancestry is European report more IgE-mediated HSRs.[39] Genetic associations for SCAR risk to specific drugs are more relevant in certain populations in which allele frequencies are higher, for example self-reporting Han Chinese or Black African (table).[1] Adults have more self-reported drug allergy because of more cumulative drug exposures (ie, the strongest drug allergy risk factor). Almost a quarter of patients admitted to hospital have an antibiotic ADR documented in the allergy section of their electronic health records.[46] Both penicillin and cephalosporin allergy labels are more common among inpatients and those linked to ongoing ambulatory care, compared with single-visit outpatients.[24,44] Internationally, a penicillin allergy label among patients admitted to hospital ranges from 6% (Netherlands) to 19% (Canada), although data from low-income and middle-income countries are scarce.[35,46–48]

Patients with documented allergies to multiple unrelated drugs or antibiotics are considered to have multiple drug allergy syndrome, which affects 1–5% of patients seeking health care.[22,49] Such patients might have more depression, anxiety, and somatic illnesses, but this syndrome could have a biological basis in differential histamine-releasing factors, tolerances of small chemicals, drug-induced interferon gamma release, or pre-activated CD4 T cells.[49] Patients with multiple drug allergy syndrome have allergy labels that interfere with optimal medical care and they often have subjective symptoms when drug allergies are formally evaluated.[24,49]

A high prevalence (23–35%) of reported antibiotic allergy is observed in patients with cancer.[50,51] Patients with HIV/AIDS also have a high frequency of reported drug allergy (up to one in four); these patients have 10–100 times more cutaneous reactions caused by drugs (including SCARs) than individuals without HIV/AIDS, especially from sulphonamide antibiotics.[52,53] Over 10% of patients with HIV have a reported sulphonamide antibiotic allergy or intolerance,[54] although data from endemic populations are insufficient. Compared with patients without cystic fibrosis, patients with cystic fibrosis have a threefold higher incidence of antibiotic allergy, with approximately a third of patients reporting an antibiotic allergy.[55] Although this high frequency might be related to high drug-infection interactions or a need for high-dose parenteral antibiotic treatment, most reactions in patients with cystic fibrosis are not IgE-mediated.[56]

Unverified antibiotic allergy labels

Most patients labelled with a β-lactam allergy are not allergic (ie, they tolerate penicillin and related drugs).[57] This mislabel occurs for a variety of reasons. First, the original reaction might not have been an allergy (there could be intolerance, a viral exanthem, or a drug-

infection interaction). Even if the original reaction were immunological, it might not recur with re-challenge. IgE-mediated reactions to β-lactams can wane over time; approximately 80% of patients who are positive for a penicillin skin test and 60% of those positive for a cephalosporin skin test are no longer sensitive, as measured by skin testing after a period of 10 and 5 years, respectively.[58,59] Mild delayed reactions that in many cases were T-cell-mediated do not reliably occur with re-challenge;[60–62] such reactions, therefore, either did not represent adaptive immune responses or were immune responses that were lost in the absence of ongoing drug exposure.

Among patients admitted to hospital with a documented penicillin allergy who were skin tested and challenged, 95% were not allergic and were de-labelled.[63] Outpatients with documented penicillin allergies have also been largely (>98%) tolerant to penicillin.[64,65] However, notable global variation in the frequency of confirmed IgE-mediated penicillin allergy exists. Although some international variation might be tied to differential antibiotic prescribing patterns, other variations could be explained by differences in patient selection or demographic and genetic differences. For example, European studies confirm penicillin allergy in 18%–30% of evaluated patients, although confirmed allergy could include diagnostics in vitro.[66,67]

Children might have an even lower incidence of true β-lactam allergy because the observed allergy could have been confused with a viral exanthem. Most children with documented β-lactam allergies presenting to a US emergency department (76%) were determined to have low-risk allergy histories, unlikely to represent true allergy.[68,69] Protocols in children have recently included one-step amoxicillin challenge without preceding skin testing and more than 90% had no immediate reactions.[61,70]

Although validated skin tests do not exist for non-penicillin antibiotics, skin testing with non-irritating concentrations and challenge procedures have identified that 11% of US patients in one study[71] and less than 1% in another[72] were allergic to the drug reported to cause an allergy that prompted specialist evaluation. In European studies, less than 20% of patients with reported reactions have their allergy confirmed.[73] Therefore, more than 80% of patients seen by allergy specialists for evaluation of non-penicillin antibiotic allergies are likely tolerant. Although such patients could also benefit from drug allergy evaluations to confirm them or rule them out, to date, there are no direct data supportive of the need for such evaluations for improved quality, safety, and public health.

Effect of antibiotic allergy labels

Precise assessment and subsequent documentation of antibiotic allergies is a key mechanism to ensure patients do not receive a medication to which they are allergic. However, most allergy labels are untrue and less than 1% of reported antibiotic allergies globally are interrogated through allergy evaluation methods, despite known negative consequences of allergy mislabels for patients, health-care systems, and communities.

Effect on patients

Patients with only a penicillin allergy documented receive alternative antibiotics that are more broad-spectrum and have lower efficacy or increased side effects, such as vancomycin, clindamycin, gentamicin, and fluoro- quinolones.[47] Alternatives are used even when β-lactams are indicated.[74,75] Canadian inpatients with a β-lactam allergy label had a three-fold increased risk of adverse events, compared with patients without a documented β-lactam allergy.[48]

Effect on health-care associated infections

Antibiotic allergies have a strong impact on the development of health-care associated infections, which are globally and uniformly important to patients, hospitals, and health-care systems. These infections are monitored for quality, safety, and public health purposes.[76]

The US Centers for Disease Control and Prevention consider C difficile infections an urgent threat to public health with over half a million cases annually.[77] Prevalence of this infection type was increased by 23% in US patients admitted to hospital with penicillin allergy labels compared with those without a penicillin allergy label.[78] Patients with penicillin allergy in a UK cohort had a 26% increased incidence of C difficile infection, compared to matched comparators after adjustment for other known C difficile risk factors.[79] Over a third of the heightened C difficile risk in patients with penicillin allergy was attributable to subsequent β-lactam alternative antibiotic use, with subsequent fluoroquinolone use alone responsible for more than 10% of the increased risk.[79]

Infections that occur postoperatively, termed surgical site infections, represent almost half of health-care associated infections[80] and result in substantial patient morbidity.[81] When patients with penicillin allergy labels get surgical site infections, inferior perioperative prophylactic antibiotic choice may be the cause.[82] For most surgical procedures, the β-lactams cefazolin or cefoxitin are the preferred perioperative antibiotics.[83] For patients who report a previous penicillin allergy, the non-β-lactam antibiotics clindamycin, vancomycin, or teicoplanin are often administered, even though there is very limited and unproven cross-reactivity between penicillins and cefazolin in patients with a documented IgE-mediated allergy to penicillin (figure 2).[84] Among 8385 perioperative patients in the USA, penicillin allergy labels resulted in 50% increased odds of surgical site infections attributed to perioperative antibiotic choice or timing, compared with patients without a penicillin allergy label.[82] Alternative non-β-lactam antibiotics such as clindamycin and vancomycin can also confer additional negative sequelae, including postoperative C difficile infections[85] and non-IgE-mediated reactions respectively, even when used sparingly in the perioperative setting.[86,87]

Effect on antibiotic resistance

Each year in the USA, at least 2 million people become infected with bacteria that are resistant to antibiotics, with at least 50 000 Americans and Europeans dying annually as a direct result of these infections.[77,88] A UK report predicted that 10 million people globally could die from antimicrobial resistance per year by 2050.[88] Some of the most common resistant pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA) and

vancomycin-resistant Enterococci (VRE). One previous study documented a 14% increased prevalence of MRSA and 30% increased prevalence of VRE in hospital inpatients with a penicillin allergy matched to those without a penicillin allergy label.[78] A UK study identified that a penicillin allergy label conferred a 69% increased incidence of MRSA[79] and 55% of the increased risk was attributable to administration of β-lactam alternative antibiotics.

One of the core actions recommended to prevent antibiotic resistance is improving antibiotic prescribing and stewardship,[89] which includes penicillin allergy evaluations as a method to reclaim narrow-spectrum β-lactams.[90] International guidelines have begun to recommend penicillin allergy assessments as part of antibiotic stewardship interventions.91

Diagnosis and management of suspected hypersensitivity

The evaluation of patients with antibiotic allergies begins with an allergy history that includes symptom details, timing of reaction, timing since reaction, treatment of the reaction, and relevant ingestions concurrent with, and since, the reaction. When relevant, review of historical details, such as: rash description, photos, and biopsy; concomitant medication list; concomitant diagnoses; laboratory; and imaging details should be obtained. Although allergy specialists widely agree on these important history components, limited drug allergy history tools have been developed, endorsed, and validated.[92] Further, tools have largely been for specialist use, although a practical history risk tool that uses low-risk and high-risk signals from the salient history is needed (figure 3). Drug allergy history tools for general use have included clinical decision support for inpatient providers[93,94] and a history tool for perioperative patients implemented by pharmacists.[95]

Potentially IgE-mediated reactions

Patients with reactions that are, by history, immediate and potentially IgE-mediated can undergo further evaluation (figure 4). Although it is appropriate for this initial evaluation and risk-stratification to be performed by non-specialists, patients with severe immediate or delayed reactions should be evaluated by the relevant specialist, such as an allergist or dermatologist.

For reactions that could be IgE-mediated, skin testing can be considered (figure 4, appendix). See online for appendix). Antibiotic skin testing for immediate reactions uses both epicutaneous (ie, prick, puncture, or scratch) testing and intradermal skin testing (if the epicutaneous step is negative). For penicillin skin testing, the major antigenic determinant penicilloylpolylysine (also known as PPL) injection is used[8,96,99] and is available as the PRE-PEN[97] or Diater DAP-kit.[98] Skin tests for drugs and drug antigens are performed and compared with a positive control (histamine phosphate) and a negative control (normal saline). Penicillin skin testing has been successfully implemented by internists,[100] infectious diseases physicians,[101] and pharmacists,[102] largely in patients with non-severe allergy phenotypes.

To skin-test patients for immediate reactions to anti-biotics other than penicillin, non-irritating concentrations are used.[103] Antibiotics that typically cause non-IgE- mediated

reactions, such as fluoroquinolones and vancomycin, have measurable non-specific mast-cell activation that renders immediate hypersensitivity skin testing challenging to interpret.[8]

Drug challenge procedures, whereby a therapeutic dose of the culprit drug is administered under medical observation, are the current standard for excluding IgE-mediated allergy. Challenge procedures are often performed using escalating drug doses in one, two, or three steps, and 30–60 min of observation in between steps. A common challenge to disprove IgE-mediated penicillin allergy is a two-step amoxicillin challenge, for example administering 50 mg of amoxicillin orally with an observation period of 30–60 min. If there is no reaction, then 500 mg is administered orally, followed by another period of observation of 60–90 min. A common one-step amoxicillin challenge for patients at low risk of allergy is simply the administration of 250–500 mg of amoxicillin to a patient and observing them for 60–120 min. In patients at high risk for IgE-mediated allergy, skin testing should precede drug challenge, when available. The skin test and challenge together have more than 99% negative predictive value for excluding IgE-mediated penicillin allergy.[8] Drug challenge procedures for patients labelled with penicillin allergy have been implemented in pediatric outpatients,[61,104] military recruits,[65] hospitalised patients,[93] and allergy outpatients.[60,71,72]

Cross-reactivity between β-lactam antibiotics has been described for IgE-mediated HSRs (figure 2).[84] Early cephalosporin formulations were likely to be contaminated with penicillin, leading to high estimates of β-lactam cross-reactivity (10%).[105] Although the cross-reactivity rate is currently calculated to be lower than these initial estimates (2%),[8] European allergy referral populations have documented high rates of β-lactam cross-reactivity in skin tests, predicted by shared side-chain structures.[106,107]

Testing can often be able to distinguish a non-IgE-mediated reaction from an IgE-mediated reaction. If a serum mast-cell tryptase was drawn at the time of a reaction and elevated, an IgE (rather than non-IgE) mechanism is likely.[8] For clear non-IgE-mediated mast-cell activation, future administrations require pre-medications, slowed infusions, or altering drug choice (table). When an IgE mechanism is excluded, future antibiotic use is considered safe; however, few longer-term studies exist. We know that patients with previous penicillin allergy who had negative penicillin allergy evaluation received a subsequent series of parenteral courses of penicillin without difficulty.[108] However, despite a negative IgE allergy evaluation, approximately 3% of adult patients and up to 10% in pediatric patients[61] could have a benign, delayed, possibly T-cell-mediated eruption to the drug.[109] These reactions are nevertheless considered to be close to their baseline incidence in the general population.[11] Although some allergists advocate for prolonged multiple-day oral challenges of 3, 5, or 7 days to ensure there is no evidence of delayed hypersensitivity,[110] general antibiotic stewardship principles caution against unnecessary antibiotic usage. Therefore, prolonged multiple drug challenges need to only be employed in carefully selected patients.[62]

When IgE-mediated allergy is confirmed by skin testing or drug challenge, patients can only receive the drug in question by an induction of tolerance or desensitisation procedure (appendix).[111] For patients whose clinical history alone is high-risk for true, IgE-mediated

allergy (eg, severe or recurrent immediate reactions), or in situations in which anaphylaxis would pose an unacceptable risk (eg, those with unstable coronary or respiratory status or pregnancy), desensitisation procedures can be used without skin testing to safely administer a first-line antibiotic therapy despite the allergy.[112] Desensitisations are particularly beneficial to facilitate use of β-lactam antibiotics when alternatives have inferior efficacy (eg, methicillin-sensitive *Staphylococcus aureus* endocarditis or bacteraemia, streptococcal or enterococcal endocarditis and syphilis in pregnancy).[8,74]

Non-immediate reactions

For non-immediate reactions, delayed intradermal testing or patch testing can be used (figure 4). Delayed intradermal testing is more convenient for patients than patch testing, as multiple reads are not required and positives can be identified within 24 h. It also appears more sensitive than patch testing for DRESS and acute generalised exanthematous pustulosis. For Stevens-Johnson syndrome and toxic epidermal necrolysis, in which delayed intra-dermal testing is contraindicated despite a low risk of provoking a systemic reaction, the sensitivity of patch testing is less than 30% and is therefore not recommended unless the benefit outweighs any risk. Patch testing is generally avoided when the culprit drug can be identified with high likelihood on the basis of clinical history alone.[113–115] Patch testing is performed by applying a drug in a soluble base (usually petroleum), with subsequent patch removal after 48 h and taking readings for erythema, induration, and vesiculopapular eruption at 48 h, 96 h, and 7 days to maximise sensitivity. Patch testing has proved clinically useful for specific drug hypersensitivity phenotypes (eg, acute generalised exanthematous pustulosis, intra-lesional fixed drug eruptions) and culprit drugs (eg, abacavir hypersensitivity syndrome).[116,117]

For non-SCAR T-cell-mediated hypersensitivity, re-challenge is safe and cross-reactivity is less defined.[8] Administration of small, escalating doses over hours, days, and weeks have also been successfully used in patients with reported non-SCAR T-cell-mediated hypersensitivity, typically for delayed rashes from a sulphonamide antibiotic.[112,118]

For severe T-cell-mediated reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, DRESS, and organ-specific reactions, there are few long- term antibiotic re-challenge or cross-reactivity data to guide future therapy.[32] However, since ex-vivo and in-vitro studies have demonstrated long-lived immune responses,[119] patients with severe T-cell-mediated allergies associated with antibiotics should refrain from re-exposure to the same drug and, ideally, all potentially cross-reactive drugs. The exception to this is when SCAR occurs in the setting of multiple drug therapy for tuberculosis, in which the benefit of selective drug re-challenges might outweigh the risk of death from an inadequately treated infection.[53] The SCAR should remain a permanent part of the patients' allergy history.[3]

New and investigational allergy tools

Advancing diagnostic testing for drug HSRs requires distinguishing patients who are reportedly allergic from those who are truly allergic with subsequent phenotyping and translational studies. To date, this research has been hampered by the disproportionate

labelling of allergy, lack of standard time from HSR to clinical presentation to allergy specialists, and lack of known antigens for most drug allergens. Despite this, new investigational tools are being evaluated for both immediate and non-immediate HSRs (appendix, figure 4).

A global call for action

Although penicillin allergy evaluations are recognised as important by a variety of government bodies, foundations, and professional organisations,[91,120–122] there is no standard approach to penicillin allergy evaluation or documentation. However, a systematic approach to remove the penicillin allergy label is now warranted.

Global implementation of penicillin allergy evaluations must be supported on an international scale to improve the quality and safety of health care delivered to patients with documented penicillin allergies. The simplest intervention might be a universal drug allergy history tool aimed at improving allergy documentation and identifying patients with penicillin allergy histories that should undergo further investigation. Even when there are limited allergy details, most patients will describe low-risk history elements (figure 3). Patients at low risk are most appropriate for de-labelling with direct re-challenge procedures. For patients at moderate risk for IgE-mediated allergy by history, de-labelling can be accomplished by first using penicillin skin testing, followed by a drug challenge for those with negative skin test results. Although penicillin skin testing was developed in the 1960s, and the primary reagent penicilloylpolylysine is commercially available, no clear guidance for its use exists on a global scale. Non-allergists need instruction and training on how to perform and interpret skin tests.

Given the large numbers of patients with documented penicillin allergy, evaluation programmes must prioritise immunocompromised, preoperative, or actively infected patients first and use different methods to remove the penicillin allergy label in low-risk patients, such as history alone, direct re-challenge, and skin testing. Variation by treatment setting must also be encouraged, since there are limitations in the inpatient setting that could make skin testing less desirable than drug challenges,[93,123] whereas in preoperative settings skin testing might be preferable to direct challenges.[124–126] There are existing treatment algorithms, questionnaires, and electronic clinical decision support systems for patients with β-lactam allergies, some of which consider direct cephalosporin use in patients reporting penicillin allergy (figure 5).[61,94,123,127,128] Similar treatment algorithms have increased first-line antibiotic therapy and increased use of β-lactam antibiotics overall.[57,74,127]

Although allergists have unique expertise that make them suited to evaluate patients with suspected drug allergy, there is an inadequate supply of allergy specialists to address this problem alone.[129,130] A quarter of US infectious diseases specialists describe not having any local options for antibiotic allergy testing,[131] with similar deficiencies noted in Australia and New Zealand.[132] In the UK, wait time to see an allergist exceeds 3 months.[87] When straightforward, investigations for low-risk penicillin allergy can be accomplished by generalists throughout the world, then the complex cases can be appropriately triaged to allergists and specialist centres.

There are many examples of penicillin allergy evaluations led by trained non-allergists with various specialist medical backgrounds.[95,100,101,133,134] The most impactful multidisciplinary antibiotic allergy testing programmes have been those embedded in antimicrobial stewardship services.[57,102,127,128] However, barriers to engaging non-allergists in penicillin allergy evaluations remain, as drug allergy is not universally taught in medical school, and Allergy and Immunology rotations for postgraduate trainees are not required in most centres outside of Europe.[135] Most survey studies of general provider knowledge identified substantial educational gaps in the knowledge of drug allergy.[136,137] Thus, any intervention must include appropriate, multi-dimensional education for health-care team members on the importance of penicillin allergy verification, drug allergy history taking, testing indication and methods, electronic health record documentation, and the implications of negative testing.

The education of patients and the general public is similarly crucial to advance penicillin allergy evaluations. Patients often use the term allergy interchangeably with side-effects, and most electronic health records contain missing, erroneous reactions that are inconsistently and incompletely documented[138,139] or entirely discrepant with the patient report.[140] Educating and empowering patients to define and manage their drug allergies and intolerances might improve allergy documentation generally and lead to more penicillin allergy evaluations and de-labelling. Patient education must also focus on the harms of unverified penicillin allergies, since patients can be resistant to allergy testing. Previous studies have shown that more than 15% of patients decline penicillin evaluation with skin testing when offered.[127,141] Multimedia educational materials might also serve to assuage fear of future reactions in those found not allergic. For example, 18% of parents refused penicillins for their child because of continued fear of a penicillin reaction, despite a negative penicillin allergy evaluation.[142] Patient education has the potential to affect the uptake and effectiveness of any penicillin allergy evaluation programme.

Conclusions

Although antibiotic ADRs are commonly reported, immunologically mediated hypersensitivity is uncommon and true IgE-mediated antibiotic allergy is verified in only a small minority. For those with true antibiotic HSRs, appropriate specialty assessment is indicated to prevent future ADR-related morbidity and mortality. This assessment includes defining the most likely drug implicated in the allergic reaction, the probable mechanism(s), and the potential cross-reactive drugs that should be avoided in the future. Despite the threat associated with true antibiotic allergy, the highest burden lies with those reporting a penicillin allergy who do not have one. These patients have multiple lifelong negative sequelae that begin with inferior and unnecessarily broad-spectrum infection prophylaxis and treatment. Given the associations between unverified penicillin allergy and health-care associated infections and multidrug-resistant organisms, the capacity to appropriately address penicillin and other antibiotic allergy labels must increase globally across health-care settings. To address this threat, international efforts might better define risk groups, determine optimal use and method of penicillin allergy evaluations, and identify a workforce to spread evaluations to environments in which the epidemiology of antibiotic allergy differs. Along with a strategic implementation plan, health-care provider and patient

education materials and support are required. Despite the anticipated barriers to penicillin allergy de-labeling programmes, the benefits of reclaiming β-lactams are to improve infectious disease care and antibiotic stewardship, while unmasking drug hypersensitivity phenotypes to advance drug hypersensitivity discovery, outcomes that are desirable, feasible, and imminently necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Yu Li for her research assistance and Karen Adamson for her design expertise.

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Search Strategy and Selection Criteria

We searched MEDLINE from January 1, 2005 through April 30, 2018, but did not exclude commonly referenced landmark articles published prior to 2005. Primary search terms included: “drug” “antibiotics” “drug-induced” “penicillin” “beta-lactam” “sulfonamide” “nevirapine” “abacavir” “antiretroviral” “rifampin” “rifamycin” “vancomycin” “fluoroquinolone” “anesthesia” “itch” “erythema” “pruritus” “rhinitis” “wheezing” “urticaria” “hive” “angioedema” “edema” “swelling” “anaphylaxis” “serum sickness” “fever” “rash” “eczema” “contact” “dermatitis” “maculopapular” “interstitial” “nephritis” “erythema multiforme” “exfoliative dermatitis” “drug reaction with eosinophilia and systemic symptoms” “drug-induced hypersensitivity syndrome” “severe cutaneous adverse reaction” “Stevens-Johnson syndrome” “toxic epidermal necrolysis” “liver” “DILI” “hepatotoxicity” “acute generalized exanthematous pustulosis” “fixed drug reaction” “linear IgA exanthem” “allergy” “hypersensitivity” “cross-reactivity.” Priority review was given to studies with more rigorous study designs, those with more numbers or diversity of patients, and those published in higher-quality journals. We excluded clinical drug trials, case reports, and animal model studies. Additional articles were identified through review of all reference lists from relevant articles identified by this search strategy. Review articles, practice parameters, and position statements were included to provide readers with additional resources on this topic. Detailed sources on primary severe cutaneous adverse reaction (SCAR) data were excluded given a recent Seminar.[1]

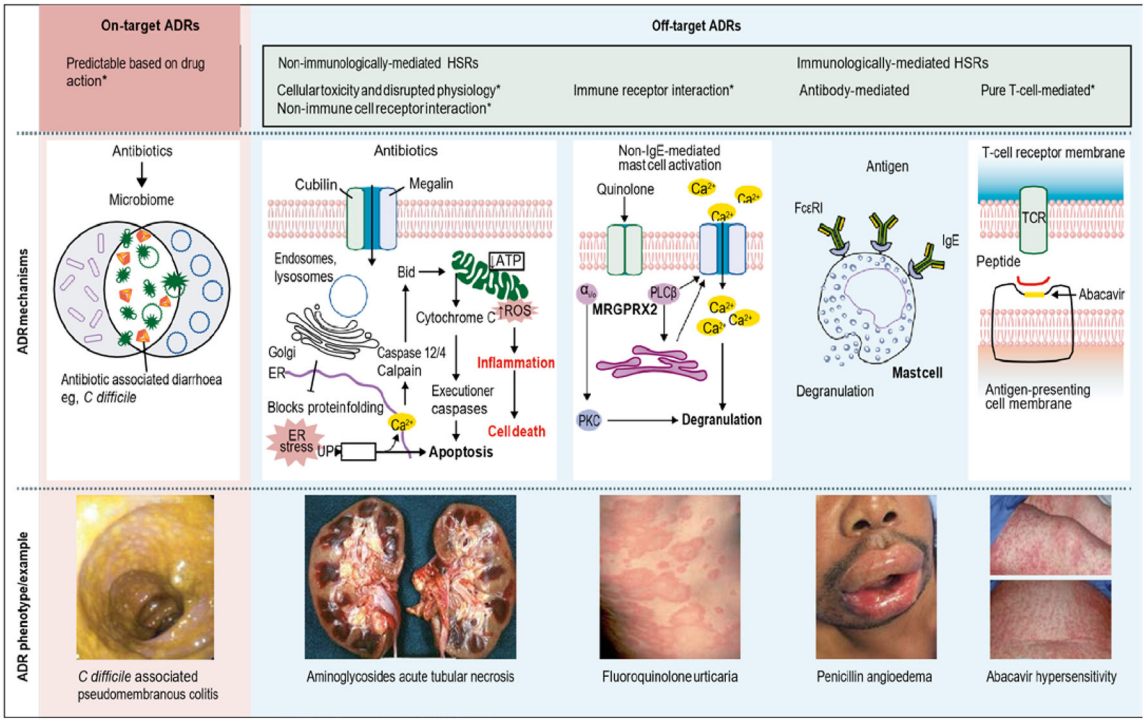

Figure 1:

Classification of on-target and off-target ADRS Pink panel illustrates an example of an on-target ADR. Blue panel (left) illustrates non-immunologically-mediated off-target effects: direct cellular toxicity or disruption of normal physiology, interaction with non-immune receptors, and interaction with immune receptors (eg, non-IgE-mediated mast-cell activation via G-protein coupled receptors). Blue panel (right) shows immunologically mediated adaptive immune responses (antibody-mediated [eg, IgE] immediate reactions or T-cell-mediated delayed reactions). Predisposition to both on-target and off-target reactions is driven by genetic variation, but also ecological factors that can vary over the course of an individual's lifetime. ADR=adverse drug reaction. Bid=BH3 interacting-domain death. C difficile=*Clostridioides difficile*. ER=endoplasmic reticulum. FcεR1=high-affinity IgE receptor. HSR=hypersensitivity reaction. MRGPRX2=MAS-related G-protein coupled receptor member X2. PKC=protein kinase C. PLCβ=phospholipase C β. ROS=reactive oxygen species. TCR=T cell receptor. UPR=unfolded protein response. *Dose-dependent. Reproduced from Peter et al.[2]

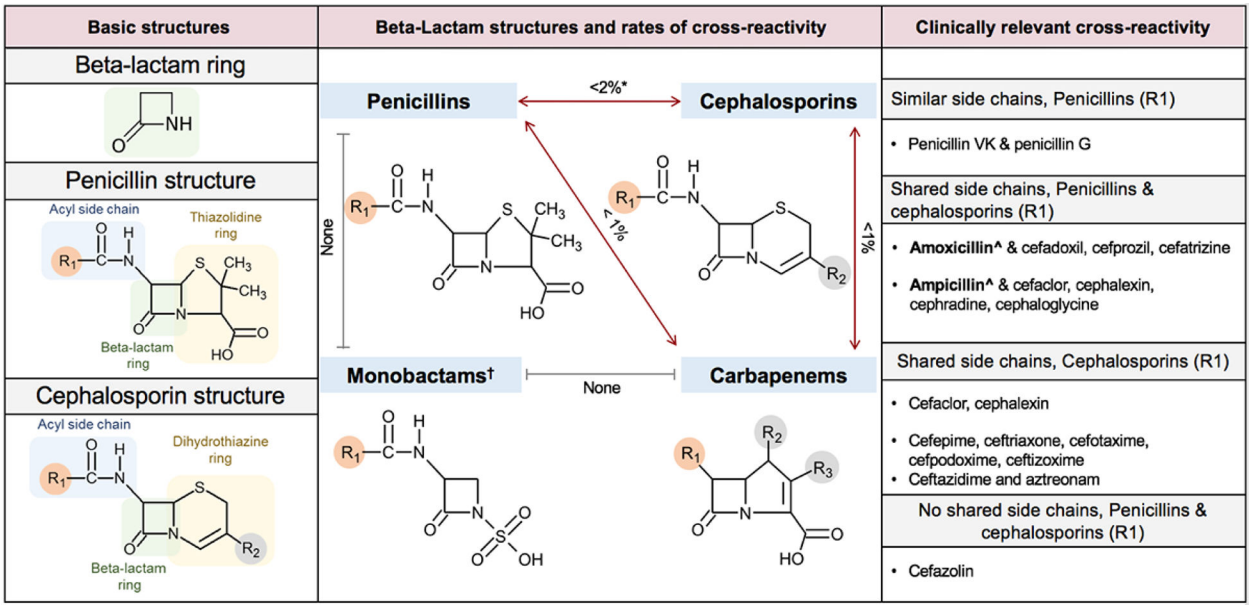

Figure 2:

β-Lactam structure and cross-reactivity β-Lactam antibiotics include penicillins, cephalosporins, carbapenems, and monobactams. Cross-reactivity is possible through the core β-lactam ring, adjacent thiazolidine (penicillin) or dihydrothiazine (cephalosporin) ring, and also from a side chain, R1, or R2 group (left panel). Cephalosporins have both an R1 and R2 group and penicillins only an R1. Despite varied mechanisms, true cross-reactivity is largely based on R1 side chains. Identical side chains in patients with IgE-mediated allergy pose the highest risk. However, cross-reactivity from side chains that are similar, but not identical, and from R2 group similarity is possible and reported. The centre panel demonstrates the structure and rates of cross-reactivity between penicillins, cephalosporins, carbapenems, and monobactams. The right panel details the most clinically important cross-reactivity considerations. *Except for shared group aminopenicillins and cephalosporins. †Monobactams have no shared cross-reactivity with other β-lactams, with the exception for aztreonam and ceftazidime, which share an identical R1. ‡Amoxicillin and ampicillin are structurally similar aminopenicillins and should be considered clinically cross-reactive with each other and the respective cephalosporins with shared R1 groups listed in the figure. Similar considerations exist for the aminocephalosporins.

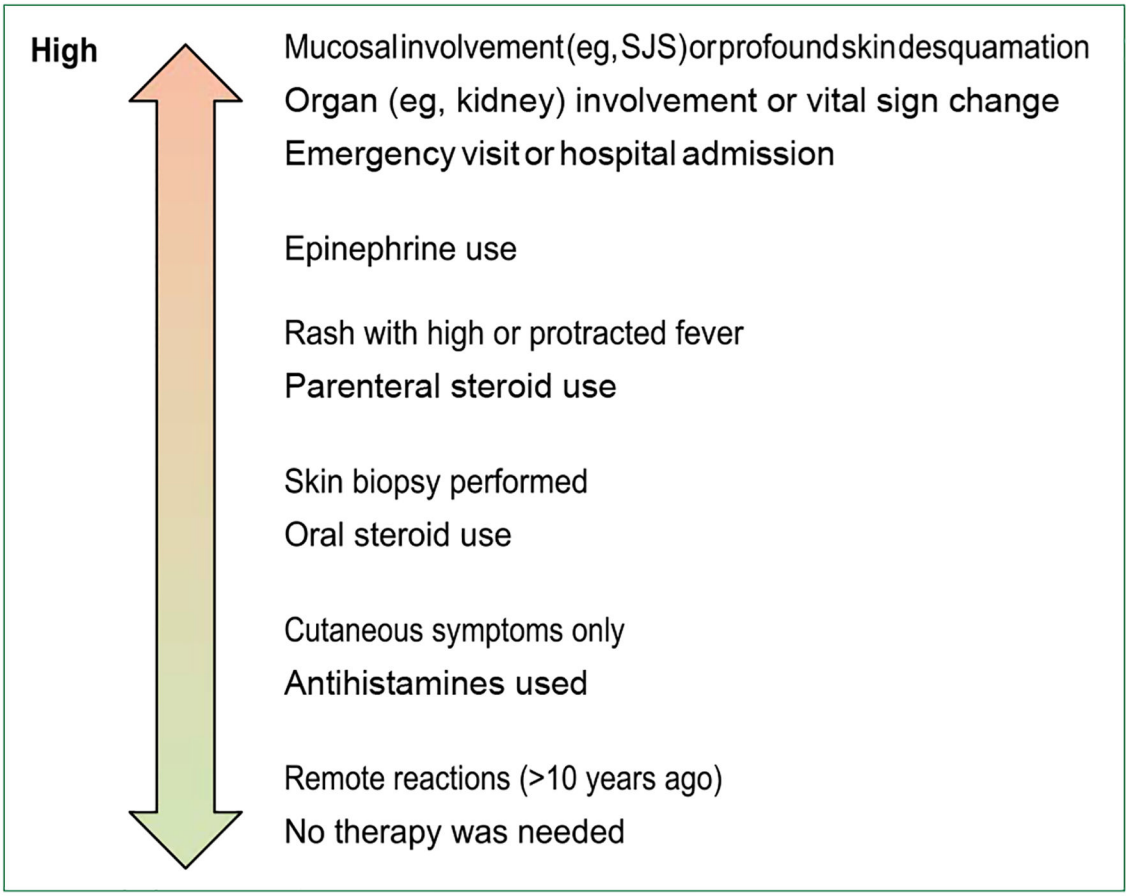

Figure 3:

Patient-reported history for risk stratification When limited allergy details are available, patient-reported historical details can be used to distinguish patients at high and low risk. In the case of penicillin allergy, patients with low risk histories are unlikely to be allergic and could be referred on large scales for allergy evaluations. When details are available about the purported reaction, the following questions are important components of the drug allergy history. (1) What were the symptoms? (raised, red, itchy spots with each lesion lasting less than 24 h [hives or urticaria]; swelling of the mouth, eyes, lips, or tongue [angioedema]; blisters or ulcers involving the lips, mouth, eyes, urethra, vagina, or peeling skin [severe type IV HSRs, SCARs]; respiratory or haemodynamic changes [anaphylaxis]; joint pains [serum sickness and serum-sickness like reaction]; organs involvement such as kidneys, lungs, or liver [severe type IV HSRs]). (2) What was the timing of the reaction after taking penicillin [minutes, hours, or days later]? Was it after the first dose or after multiple doses? (3) How long ago did the reaction happen? (4) How was the reaction treated? Was there a need for urgent care or was epinephrine administered? (5) Has the patient tolerated similar medications, such as ampicillin, amoxicillin, or cephalexin since the penicillin reaction?

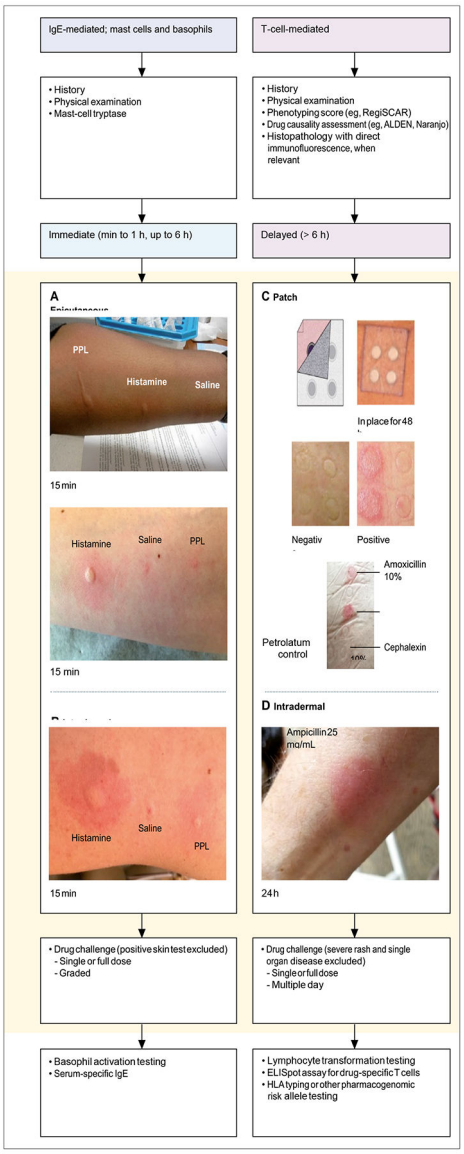

Figure 4:

Diagnostic approach to antibiotic allergy Immediate reactions commonly occur within 1 h but can occur up to 6 h after drug administration. Serum tryptase drawn 30–90 min after reaction onset is a useful biomarker to help differentiate anaphylaxis from non-IgE-mediated mast-cell activation. Drug-specific diagnostic tests for immediate reactions include (A) epicutaneous skin testing (ie, prick, puncture, or scratch) and (B) intradermal skin testing. The definition of a positive penicillin skin test varies globally.[96–98] Delayed reactions typically occur in more than 6 h and up to 8 weeks after drug exposure and can occur after drug discontinuation. Testing for delayed reactions varies geographically and is not standardised. In-vivo testing for delayed reactions can include (C) patch testing, in which non-irritant drug concentrations in a base vehicle are applied by a Finn chamber and adhesive tape for 48 h and are read at 96 h and 1 week, or (D) delayed intradermal testing, in which results are read 24 h and 48 h after the drug solution is injected. Drug challenge, when

safe to perform, is often the final step to confirm or exclude a drug allergy, after negative epicutaneous, immediate or delayed intradermal, or patch testing. In immediate reactions, drug challenges can feature a single full dose or be graded, with 2 to 3 dosing increments. In delayed reactions, dosing can be continued for multiple days but might be considered to be an unnecessary exposure to antibiotics. Drug challenge is contraindicated for SCAR and single-organ disease. Several additional ex-vivo and in-vitro diagnostic options are available in some subspecialty centres but are currently at the level of research tools that require further validation. See appendix. ALDEN=an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis. ELISpot=enzyme-linked immunosorbent assay. Naranjo=an adverse drug reaction probability scale that can be used to assess causality for any adverse drug reaction.
PPL=penicilloyl-polylysine. RegiSCAR=the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples group.
SCAR=severe cutaneous adverse reaction.

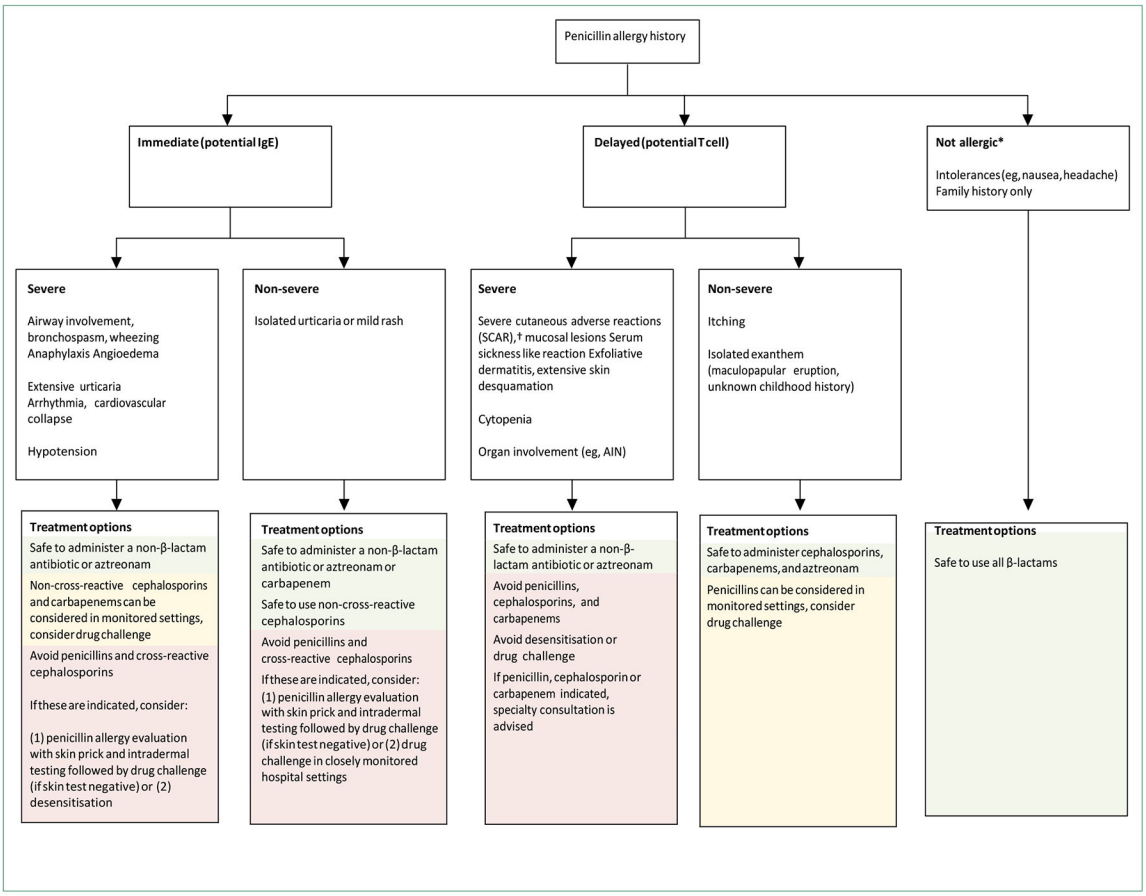

Figure 5:

Treatment algorithm for patients with penicillin allergy histories This algorithm, adapted from expert opinion, published studies, and guidelines,[93,127,128] can be used to identify how to optimally prescribe β-lactam antibiotics acutely to patients with prior penicillin allergies. Reactions are divided into those with immediate and delayed onset, with reactions subsequently grouped as severe and non-severe. ADR=adverse drug reaction. AGEP=acute generalised exanthematous pustulosis. AIN=acute interstitial nephritis. DRESS=drug reaction with eosinophilia and systemic symptoms. SJS/TEN=Stevens-Johnson syndrome and toxic epidermal necrolysis.

*Non-immune mediated ADRs are typically pharmacologically predictable side effects which do not preclude penicillin usage. †SCARS include DRESS, SJS/TEN, and AGEP (table 2).

Table 1.

Non-IgE-mediated Reactions*

	Phenotype(s)	Mechanism	Presentation	Chronology/Onset	Antibiotic Examples	Diagnosis	Treatment	Future Antibiotic Recommendations
Non-IgE-Mediated	Flushing, itching, urticaria, angioedema Occasionally can present like anaphylaxis	Direct mast cell stimulation or basophil activation MRGPRX2 implicated for certain direct mast cell degranulators	Cutaneous symptoms>>>respiratory symptoms >> cardiovascular symptoms	Minutes to <1 hour (typically during infusion)	Vancomycin, fluoroquinolones	History and physical exam, serum mast-cell tryptase post reaction usually normal Drug challenge typically negative with lower dose (dose-dependent reaction)	Antihistamines alone typically suffice Epinephrine for those meeting anaphylaxis criteria Adjunctive treatment with corticosteroids and inhaled beta-agonists, as needed	Slow infusion and/or premedication with antihistamines and/or corticosteroids Use fewer associated drugs with similar mast cell effects (e.g., opioids)

*Previously called pseudoallergic or anaphylactoid reactions.

Abbreviations: IgE, immunoglobulin E; MRGPRX2, MAS-related G-protein coupled receptor member X2.

Table 2.

Hypersensitivity Reactions and Clinical Phenotypes

A. Antibody-Mediated								
	Phenotype(s)	**Mechanism**	**Presentation**	**Chronology/Onset**	**Antibiotic Examples**	**Diagnosis**	**Treatment**	**Future Antibiotic Recommendations**
IgE-mediated (Type I)	Urticaria, angioedema, bronchospasm, anaphylaxis	Mast cell and basophil degranulation via IgE-crosslinking bound to FcεR1[48]	Itching, palmar erythema, rhinitis, wheezing, urticaria, angioedema, anaphylaxis	<1 hour typical, but can be considered within 6 hours of exposure	Penicillins Cephalosporins	History, physical exam, serum tryptase (measured within 30 minutes to 1.5 hours of reaction), skin testing, drug challenge	Antihistamines Epinephrine for those meeting anaphylaxis criteria Adjunctive treatment with corticosteroids and inhaled beta-agonists, as needed	Desensitization protocol for same drug; Caution with use of drugs in the same class and cross-reactive drugs†
IgG-mediated (Type II)	Cytopenias	Antigen-antibody interactions/IgG and complement- mediated phagocytosis or cytotoxicity	Hemolytic anemia, thrombocytopenia, vasculitis	Often <72 hours, but can be up to 15 days	Penicillins, cephalosporins, sulfonamides, dapsone, rifampin	History, physical exam, targeted laboratory evaluation, biopsies as indicated	Corticosteroids	Avoidance of same drug; caution with use of same class and cross-reactive drugs†
Serum sickness-like reaction (Type III)	Serum sickness	High antibody titers and circulating immune-complexes/IgM or IgG and complement*	Fever, rash, arthralgia Uncommon in adults	Days to weeks (typically 1–3 weeks)	Penicillin, amoxicillin, cefaclor* trimethoprim-sulfamethoxazole	History, physical exam, laboratory evaluation including differential blood count, sedimentation rate, C-reactive protein, total complement, C3, and C4), urinalysis to assess for proteinuria, skin biopsy	Antihistamines, corticosteroids (systemic for severe cases only)	Avoidance of same drug; caution with use of same class and cross-reactive drugs†
*Serum sickness reaction largely relates to interactions of large molecules (nonhuman protein) with antibodies and immune complex formation. Serum sickness-like reaction associated with cefaclor and likely other small molecule antibiotics, does not involve immune complexes, so C3 and C4 are normal and nephritis is not observed. These drugs associated with serum sickness-like reaction from drug or reactive metabolites with an alternative, potentially directly toxic or T-cell-mediated mechanism.								
†See Figure 3.								
Abbreviations: Ig, immunoglobulin; FcεR1, the high-affinity IgE receptor; C3, complement C3; C4, complement C4.								

B. Cell-Mediated								
i. Primarily Single Organ Disease								
Phenotype*	**Mechanism[47]**	**Presentation**	**Chronology/Onset**	**Antibiotic Examples**	**Diagnosis**	**Genetic (HLA) Association[145]**	**Treatment**	**Future Antibiotic Recommendations**
Acute interstitial nephritis	CD4/monocyte immune injury to the renal tubulointerstitium	Rash, acute kidney injury, white cell casts in urinary sediment, peripheral blood eosinophilia, eosinophiluria	3 days to 4 weeks	Semi-synthetic anti-staphylococcal penicillins (e.g. nafcillin, oxacillin) fluoroquinolones, rifampin	History, physical exam, laboratory, urinalysis, renal biopsy (severe cases)		Antihistamines, topical corticosteroids, systemic corticosteroids, mycophenolate mofetil or cyclophosphamide (for renal failure not responsive to systemic corticosteroids)	Avoidance of culprit drug, and same class drugs advisable. Limited data to support or negate cross-reactivity within same family (e.g., cephalosporins often tolerated with semi-synthetic penicillin acute interstitial nephritis)
Drug-induced liver injury	CD4 then CD8 T cell activation and FasL, TNF-alpha, perforin to hepatocyte cell death	Transaminitis (cholestatic or mixed picture). Hepatitis is main presentation, but some cases are accompanied by rash, fever, and eosinophilia	From 5 days to 12 weeks (typically more than 4 weeks)	Amoxicillin-clavulanate, flucloxacillin, rifampin, trimethoprim-sulfamethoxazole, nevirapine, efavirenz, nitrofurantoin,* minocycline*	History, physical exam, laboratory,† liver biopsy (severe cases)	HLA-B*57:01 (flucloxacillin) HLA-A*02:01;HLA-DRB1*15:01;HLA-DQB1*06:02 (amoxicillin-clavulanate) HLA-DRB1*01:01 and 01:02 (nevirapine)	Corticosteroids (after toxic or viral etiology excluded), antihistamines and topical corticosteroids (if concurrent rash)	Avoidance of culprit drug, drugs in same class, and structurally related drugs
*Autoimmune drug-induced hepatitis.								
†Most autoimmune hepatitis is Type 1 (96%). Drug-induced autoimmune hepatitis is often associated with ANA, anti-LKM, and anti-SMA (>1:80); however, these will often only be present acutely and not after drug withdrawal or clinical resolution. Drug-induced autoimmune hepatitis patients also have a polyclonal gammopathy, making IgG levels a useful laboratory evaluation with IgG > 1.5 times the upper limit of normal.								
Abbreviations: HLA, human leukocyte antigen; CD, cluster of differentiation; FasL, Fas ligand or CD95; TNF, tumor necrosis factor; ANA, antineutrophil antibody; ant-LKM, anti-liver-kidney microsomal antibody; anti-SMA, anti-smooth muscle antibody; Ig, immunoglobulin.								

ii. Isolated Cutaneous Disease

Phenotype	Mechanism[47]	Presentation*	Chronology/Onset	Antibiotic Examples	Diagnosis	Treatment	Future Antibiotic Recommendations
Maculopapular rash	Eosinophilic inflammation/CD4/Th2 via IL-4, IL5, IL-13, eotaxin (type IVb)	Morbilliform ("measles-like") rash, often with peripheral blood eosinophilia	Days to weeks (typically in second week of therapy)	Amoxicillin, sulfonamide antibiotics	History, physical exam, laboratory evaluation (eosinophilia, no organ involvement), biopsy (severe cases only) with eosinophilic infiltrate in the dermis or variable nonspecific picture	Antihistamines, topical corticosteroids, systemic corticosteroids (severe cases only)	Repeat exposure to same drug may not result in same reaction, especially after a period of unexposed time; cross-reactivity is less of a concern. Data exists on a "treat-through" approach for patients requiring therapy who develop this reaction with monitoring for signs of SCAR
Fixed drug eruption†	Activated intraepidermal CD8 T cells release IFN-gamma and cytotoxic granules	Erythematous/edematous plaques of a round shape with gray/dusky center at same sites (often lip, tongue, face, genitalia) with each exposure. Burning, and pain at involved sites	Days to weeks (on rechallenge, within minutes)	Sulfonamide antibiotics, vancomycin	History, physical exam, biopsy with basal cell degeneration, pigmentary incontinence dermal melanophages, patch testing (topical provocation), drug challenge (systemic provocation)	Antihistamines, topical corticosteroids, systemic corticosteroids (severe cases only)	Avoidance of the same drug advisable. Cross-reactivity is less of a concern
Contact dermatitis/eczema‡	Monocytic inflammation/Th1 and IFN-gamma	Erythema and edema with vesicles or bullae	Days to weeks	Bacitracin, ampicillin‡	History, physical exam, biopsy (mixed superficial perivascular inflammation), patch testing, drug challenge	Treatment similar atopic dermatitis (mild cleansers, emollients, topical corticosteroids, and antihistamines), systemic corticosteroids (severe cases only)	Avoidance of same drug advisable. Cross-reactivity is less of a concern

*All phenotypes present with itching and rash.

†Generalized bullous fixed drug eruption can be severe and associated with systemic features.

‡Can occasionally be more extensive, symmetrical drug-related intertriginous and flexural exanthem (SDRIFE), formerly termed baboon syndrome, presenting with sharply demarcated erythema of buttock and inner thighs (in a "V-shape").

Abbreviations: CD, cluster of differentiation; Th, T helper cell; IL, interleukin; SCAR, severe cutaneous adverse reaction; IFN, interferon.

iii. Systemic or Multisystem Disease

Phenotype	Mechanism[47]	Presentation	Chronology/Onset	Antibiotic Examples	Genetic (HLA) Association[145]	Diagnosis	Treatment	Future Antibiotic Recommendations
Drug rash eosinophilia and systemic symptoms syndrome	CD4/Th2 via IL-4, IL5, IL-13, eotaxin (eosinophilic inflammation)	Fever, rash, peripheral blood eosinophilia, lymphadenopathy, organ involvement (often liver or kidney)	2–6 weeks (typically 4 weeks)	Vancomycin, rifamicin, sulfonamide antibiotics, dapsone, all beta-lactam antibiotics	HLA-B*13:01 (dapsone in Southeast Asians) HLA-B*35:05 (nevirapine in Southeast Asians) HLA-B*53:01 (raltegravir in African ancestry)	History, physical exam, laboratory (assessment of absolute eosinophil count and organ involvement), biopsy, clinical scoring RegiSCAR,* causality assessment Naranjo,† patch testing (may identify culprit)	Antihistamines, corticosteroids (severe cases only)	Avoidance of same drug and related drugs by chemical structure, although no demonstrable cross-reactivity
Abacavir Hypersensitivity Syndrome	CD8 T cells, non-covalent binding to floor of antigen blinding cleft with altered peptide repertoire of endogenous peptides bound to HLA-B*57:01	Fever, malaise, gastrointestinal or respiratory symptoms. Rash is mild to moderate, occurs late, and is absent in 30%	From days to 3 weeks (typically 1 week)	Abacavir (no other drugs to-date cause identical syndrome)	HLA-B*57:01 (screening is guideline-based therapy in developed world)	History, physical exam, patch test (to confirm culprit)	Immediate removal of drug	Avoidance of abacavir only
Stevens-Johnson syndrome/toxic epidermal necrolysis	CD4/CD8 cytotoxic T cells via granulysin, perforin, granzyme B, FasL (keratinocyte death, Type IVc)	Rash with desquamation, mucosal lesions (mouth, eyes, genitals) with mucositis, fever SJS: < 10% BSA SJS/TEN overlap: 10–30% BSA TEN: >30% BSA	4 days to 4 weeks (For many antimicrobials, shorter latency is typical)	Trimethoprim/ sulfamethoxazole, nevirapine, antimycobacterials, macrolides, quinolones	HLA-C*04:01 (nevirapine in Africans)	History (tender, painful skin), physical exam (Nikolsky and/or Asboe-Hansen signs), skin biopsy with keratinocyte necrosis, ranging from partial to full-thickness necrosis of the epidermis, clinical scoring SCORETEN,* causality ALDEN§ or Naranjo†	Immediate removal of drug Aggressive supportive care in ICU/Burn unit setting Pulse corticosteroids, etanercept, cyclosporine	Avoidance of same drug and related drugs by chemical structure, although no demonstrable cross-reactivity
Acute generalized exanthematous pustulosis	T cells via IL8 and GM-CSF (neutrophilic inflammation, type IVd)	Acute pustular eruption characterized by widespread nonfollicular sterile pustules with fever, facial edema,	<48 hours (typically within 24 hours) longer latency for pristinamycin and hydroxychloroquine	Aminopenicillins, clindamycin, other beta-lactams, fluoroquinolones, and sulfonamides antimicrobials, pristinamycin, terbinafine,		History, physical exam, fever, laboratory evaluation showing neutrophilic leukocytosis with mild eosinophilia; skin biopsy	Topical corticosteroids; systemic corticosteroids (severe cases, widespread involvement)	Avoidance of same drug and related drugs by chemical structure, although no demonstrable cross-reactivity. Drugs introduced may be guided by patch testing

iii. Systemic or Multisystem Disease

Phenotype	Mechanism[47]	Presentation	Chronology/Onset	Antibiotic Examples	Genetic (HLA) Association[145]	Diagnosis	Treatment	Future Antibiotic Recommendations
		neutrophilia. Oral involvement in 25%		hydroxychloroquine (anti-malarial)		(subcorneal pustules or intraepidermal pustules filled with neutrophils); patch testing (to help identify culprit)		

*From the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples group.[34]

†An adverse drug reaction probability scale that can be used for any adverse drug reaction to assess causality.[34]

‡A severity of illness score for toxic epidermal necrolysis.[34]

§An algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis[34]

Abbreviations: HLA, human leukocyte antigen; CD, cluster of differentiation; Th, T helper cell 2; IL, interleukin; FasL, Fas ligand or CD95; BSA, body surface area; IVIG, intravenous immunoglobulin.