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Recent advances in the understanding of severe cutaneous adverse reactions

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Abstract

Severe cutaneous adverse reactions (SCARs) encompass a heterogeneous group of delayed hypersensitivity reactions, which are most frequently caused by drugs. Our understanding of several aspects of SCAR syndromes has evolved considerably over the previous decade. This review explores evolving knowledge on the immunopathogenic mechanisms, pharmacogenomic associations, *in-vivo* and *ex-vivo* diagnostics for causality assessment and medication cross-reactivity data related to SCAR syndromes. Given the rarity and severity of these diseases, multidisciplinary collaboration through large international, national and/or multicentre networks to collect prospective data on patients with SCAR syndromes should be prioritized. This will further enhance a systematised framework for translating epidemiological, clinical, and immunopathogenetic advances into preventive efforts and improved outcomes for patients.

What's already known about this topic?

- Severe cutaneous adverse reactions (SCARs) encompass a heterogeneous group of delayed hypersensitivity reactions, which are most frequently caused by drugs.
- The designation SCAR most commonly includes Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS-TEN overlap, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS or HSS) and acute generalised exanthematous pustulosis (AGEP).
- The pathogenesis underlying T-cell mediated delayed hypersensitivity reactions involves interactions between small molecule drugs, HLA Class I molecules and T-cell receptors.

What does this review add?

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- The rapid evolution of pharmacogenomic discoveries associating severe T-cell mediated drug hypersensitivity syndromes have created the promise of prevention. This has led either to universal HLA screening prior to drug prescription (*e.g.* HLA-B*57:01 and abacavir) or specific recommendations regarding HLA genotyping before prescription of drugs in susceptible populations (*e.g.* HLA-B*15:02 and carbamazepine).
- Knowledge of the immunopathogenesis of SCAR and key novel and non-mutually exclusive mechanisms by which drugs activate T-cells has evolved.
- *In-vivo* and *ex-vivo* diagnostics are being increasingly employed to aid causality assessment.
- Knowledge of cross-reactivity between structurally-related medications is still rudimentary; however, this knowledge may avoid precipitating subsequent severe episodes and minimise unwarranted restriction of therapeutic options.

Introduction

Severe cutaneous adverse reactions (SCARs) encompass a heterogeneous group of delayed hypersensitivity reactions, most frequently caused by drugs, which are associated with significant morbidity and mortality.[1,2] SCARs include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS or HSS) and acute generalised exanthematous pustulosis (AGEP).[3] The clinical, biochemical and histological characteristics of these syndromes are summarised in Table 1.

Our understanding of several aspects of SCAR syndromes has evolved considerably over the previous decade. The recent 2016 UK guidelines on the management of SJS/TEN in adults highlighted many areas of evolving research.[4] The aim of this review article is to provide a complementary review of emerging immunopathogenic mechanisms, established pharmacogenomic associations, *in-vivo* and *ex-vivo* causality assessment tools and medication cross-reactivity data related to SCAR syndromes.

Immunopathogenesis of SCAR

Medications are the causative agents in greater than 85% of SCARs in adults,[5] with frequently implicated drugs being antimicrobials, aromatic antiepileptic drugs and antimetabolite agents, particularly, allopurinol and its derivatives.[4,5] Regardless of the causal medications, T-cell mediated delayed hypersensitivity reactions, triggered by interactions between small molecule drugs, human leucocyte antigen (HLA) Class I molecules and T-cell receptors (TCR), underlie the pathogenesis of most SCARs. Increasing knowledge suggests that carriage of specific HLA risk allele(s) are necessary but not sufficient factors in initiating the immunopathogenesis cascade.[6] Currently three non-mutually exclusive models have been proposed: the hapten/pro-hapten, the pharmacologic interaction (PI) and the altered peptide repertoire models (Fig. 1). The resultant effector immune mechanisms (*e.g.*,

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eosinophil-mediated injury in DRESS[7], CD8+ cytotoxic T-cell mediated injury in SJS/TEN[4] and the cytotoxic peptide 15kdal granulysin that has been identified as a key molecule produced by CD8+ T cells, natural killer (NK) T cells and NK cells that is responsible for the disseminated keratinocyte death in SJS/TEN[8]) in turn contribute to characteristic clinical manifestations of each condition (Table 1). Of note, Bellon *et al.*'s study suggests that the overexpression of endogenous damage-associate molecular patterns (DAMPs) or alarmins in SJS/TEN support the involvement of the innate immune system in the pathogenesis of delayed hypersensitivity reactions, suggesting an extension of the T-cell mediated hypothesis.[9] Indeed, several innate immune components have been investigated in the aetiopathogenesis of SJS/TEN. Morel and colleagues' study revealed that the innate receptor CD94/NKG2C is expressed by NK cells and cytotoxic T lymphocytes and might be involved in triggering degranulation in response to HLA-E in patients with SJS/TEN.[10] A further study by the same authors determined that upregulation of the innate immune molecules, α-defensins 1-3 in T cells, may be involved in the pathogenesis of SJS/TEN.[11] There is accumulating data to suggest that humoral and cellular components of the innate immune response may be involved in the pathogenesis of delayed cutaneous hypersensitivity reactions.[12]

Higher plasma concentrations of the drug and/or its metabolites, caused by the individual's *in-vivo* absorption, distribution, metabolism and elimination enzyme (ADME) activities, or by way of drug-drug interactions, increase the risk for many hypersensitivity reactions.[13,14] This apparent dose-dependency seen in severe T-cell mediated adverse drug reactions (ADRs) supports that small molecules are non-covlaently interacting with an immune receptor. For instance, elevated serum levels of oxypurinol, an active metabolite of allopurinol, which has a long plasma half-life, increases the risk of allopurinol hypersensitivity.[14] Impaired renal function leading to high plasma concentrations of oxypurinol is also directly correlated with disease severity and mortality.[14] Historically, certain types of trimethoprim-sulfamethoxazole hypersensitivity reactions were more likely in those with N-acetyl transferase (NAT) 2 slow-acetylator genotypes.[15] Collectively, the paradigm has been shifting towards an interplay between ADME enzymatic activities and immunologic mechanisms being responsible for the initiation of hypersensitivity responses,[16] further triggered by yet-to-be-determined insults (such as viral infections), leading to polarisation toward distinct cytokine profiles and effector pathways. Further studies are required to explore this evolving concept of hypersensitivity and drug concentration-dependent relationships.

The role of herpes virus reactivation

Heterologous immunity is a longstanding concept that has recently gained renewed interest to explain both individual susceptibility and tissue specificity of SCAR. In this model, the effector memory T-cells generated during the course of a remote infection and maintained by latency or re-exposure to the infectious agent cross-react with drug modified proteins, thereby highlighting the role of

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infectious agents, such as chronic persistent DNA viruses including Human Herpes viruses (HHV), in SCAR pathogenesis.[16]

The concept of heterologous immunity in the immunopathogenesis of SCAR should not be confused with the reactivation of HHV, in particular human herpes virus 6 (HHV-6), which is known to be associated with DRESS.[17-20] Reactivation of Epstein-Barr virus (EBV), cytomegalovirus (CMV), HHV-6 and human herpes virus 7 (HHV-7) has been reported to occur in DRESS syndrome typically 2-3 weeks following the original syndrome and in the absence of re-exposure to the drug. It appears to correlate with the immune dysregulation occurring during DRESS syndrome and in particular, regulatory T-cell dysfunction. The reported proportion of patients with HHV-6 reactivation in DRESS varies according to the specific implicated drug and is between 36% and 62%.[18,21] HHV-6 reactivation, as measured by a rise in HHV-6 IgG titres and plasma HHV-6 DNA levels, typically occurs 2-3 weeks after the onset of the rash.[22] This temporal association suggests a complex interaction between HHV and the immunopathogenesis of DRESS.[22] Furthermore, reactivation of HHV have also been associated with the development of more severe disease.[19,21-24] The development of autoimmune diseases, such as systemic lupus erythematosus, type 1 diabetes mellitus and autoimmune thyroiditis, is a late complications of DRESS that has been associated with herpes virus reactivation.[20,25-27]

Reactivation of the other herpes viruses, which include HHV-7, EBV and CMV have also been reported to occur in association with DRESS.[22,28,29] Indeed, sequential reactivation of herpes viruses during the course of DRESS has been described in a similar sequence to that in graft-versus-host disease (GVHD): HHV-6 and/or EBV, followed by HHV-7 and subsequently by CMV.[29] Viral reactivation may also explain the prolonged clinical symptoms, multi-organ involvement and systemic inflammation following discontinuation of the offending drug.[22,29-31]

DRESS has been reported in the setting of immune reconstitution inflammatory syndrome (IRIS). IRIS describes an inflammatory processes that occurs soon after the initiation of highly active antiretroviral therapy (HAART) in patients with Human Immunodeficiency Virus (HIV) and is associated with an increase in CD4+ cell count and/or decrease in HIV viral load.[32] IRIS occurs as a result of immune recovery and it results in the host recognising pre-existing or latent infections.[33] DRESS may be considered a form of immune constitution whereby unregulated immune activation occurs against reactivated herpes viruses.[32]

For SJS/TEN however, there is weaker evidence, only at case report level, for its association with HHV-6 reactivation and this could also be secondary to phenotype misattribution of viral reactivation associated with the profound immunosuppression secondary to the protracted clinical course and significant courses of immunosuppressants, such as ciclosporin used in SJS/TEN.[34,35] The role of CMV has been proposed in the development of AGEP,[36] however evidence from European Study of Severe Cutaneous Adverse Reactions (EuroSCAR) study failed to find such an association.[37] Testing

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for herpes virus reactivation in SCAR syndromes may assist in clarifying the diagnosis in cases where the cutaneous and other clinical findings are non-specific, and may also be of prognostic value.[31,21,38]

Recent advances in pharmacogenomics in SCAR

Individuals with certain HLA genotypes carry higher risks of developing SCAR syndromes. Over the last decade, clinically significant pharmacogenomics associations have been discovered, leading to specific recommendations regarding HLA genotyping before prescription of drugs to reduce the risks in susceptible populations. However, for common causal medications, in particular, antibiotics, very few clinically meaningful HLA associations exist.[39] Medications that are considered to have strong pharmacogenomic associations with severe T-cell mediated ADRs, of which routine genetic screening prior to their prescription have already or in future may soon become the standard of clinical practice are presented herein (Table 2).

Abacavir

Abacavir (ABC), an antiretroviral drug used in combination therapy to treat HIV, is associated with hypersensitivity syndrome (HSS) in 5% (range 0 – 14%) of patients.[40] The hypersensitivity syndrome associated with ABC is differentiated from DRESS/DIHS in that the median time to presentation with fever and malaise is 8 days with latency periods as short as 1 day and rash, which does not occur in up to 30%, is often a late feature of the presentation. The skin involvement in ABC HSS is typically a mild to moderate exanathem without evidence of blistering or epidermal detachment. De-challenge after withdrawal of drug occurs rapidly with disappearance of the fever, malaise and even skin rash within 72 hours of abacavir withdrawal. HLA-B*57:01 was found to be a significant risk allele for ABC-HSS by two independent groups.[41,42] The lack of specificity of clinical symptoms and signs associated with ABC HSS in HIV positive individuals led to a high clinical false positive rate and an apparent lack of sensitivity of HLA-B*57:01 for ABC HSS. This was particularly apparent in ethnicities with a lower prevalence of HLA-B*57:01 such as African Americans. ABC patch testing was found to be a sensitive and specific means to identify true immunologically-mediated ABC HSS.[43,44] A randomised double-blind controlled trial with a co-primary endpoint of clinically and immunologically (patch-test) confirmed ABC HSS demonstrated the clinical utility of HLA-B*57:01 screening to completely eliminate immunologically-mediated cases of ABC-HSS in those of European ancestry.[45] A case-control study confirmed the generalizability of this utility to African Americans.[46] Several factors favoured successful translation of HLA-B*57:01 screening into routine clinical practice including: 100% negative predictive value, low numbers (n=30) needed to test to prevent one case of true-immunologically mediated ABC HSS, generalisability of the test across all ethnic groups and availability of cost-effective quality-assured laboratory methods with rapid turn-around times.[46-48]

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Carbamazepine

Carbamazepine is an aromatic amine anticonvulsant and is associated with cutaneous adverse reactions in up to 10% of patients.[49] Although two digit HLA associations had been previously described between allopurinol SJS/TEN and sulfa antimicrobial SJS/TEN, the association between HLA-B*15:02 and carbamazepine SJS/TEN in a Taiwanese population was the first four digit association for SJS/TEN and the strongest overall for SJS/TEN in the literature to-date.[50] A recent meta-analysis showed that HLA-B*15:02 is strongly associated with carbamazepine-induced SJS/TEN in Han Chinese and Southeast Asians who carry high allele frequency (pooled Odds Ratio (OR) 113.4, 95% CI 51.2 – 251.0, $p<1\times10^{-5}$).[51] However, such association was lacking in Japanese,[52-54] Koreans,[55] and Caucasians,[56,57] in whom the allele carrier frequency was estimated to be <1%[58]. HLA-B*15:02 testing provides positive predictive value (PPV) of 1.8% and negative predictive value (NPV) of 100% respectively in susceptible populations, with proven cost-effectiveness for screening.[51,59,60]

Although HLA-B*15:02 is a risk variant strongly associated with carbamazepine SJS/TEN, there is no evidence to suggest that it is associated with hypersensitivity syndrome (HSS) or maculopapular exathems.[51,58]

Unlike HLA-B*15:02, HLA-A*31:01 is common with allele carrier frequencies >3% across many ethnic groups[58]. HLA-A*31:01 was shown to be associated with all SCAR phenotypes across populations including Han Chinese, Japanese, Koreans and Caucasians.[52,55,58,61,62] However, HLA-A*31:01 showed a stronger association with DRESS (pooled OR 13.2, 95% CI 8.4 – 20.8, p<0.001) over SJS/TEN (pooled OR 3.94, 95% CI 1.4 – 11.5, p=0.01).[58,63] This effect was particularly noted in populations where HLA-B*15:02 carriage is prevalent where it is likely that the strong association between HLA-B*15:02 and carbamazepine SJS/TEN overshadows that of HLA-A*31:01. . In contrast, in Europeans, the higher frequency of the HLA-A*31:01 allele appears to overshadow the effect of the uncommon HLA-B*15:02 allele. [47,51]

Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency have issued recommendations regarding genotyping before initiation of carbamazepine in certain at-risk populations.[64] Genetic testing for HLA-B*15:02 is recommended in Han Chinese, Southeast and South Asians or in patients whose ethnic origin is unknown (Level A). HLA-A*31:01 testing may be considered in patients of all ancestries (level B); however, there is no current recommendation for routine screening for HLA-A*31:01 before initiation of carbamazepine therapy. In patients who are positive for HLA-B*15:02, alternatives to carbamazepine should be used, preferably avoiding all aromatic amine anticonvulsants since SJS/TEN has been more weakly associated with HLA-B*15:02 with these drugs in Southeast Asians. In the case of HLA-A*31:01 positivity, ideally, alternative first-line medication to carbamazepine should be used in carbamazepine naïve individuals unless there are no identifiable alternatives, in which case patients should be followed with extremely close monitoring for the first signs of evolving SCAR. [58]

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Allopurinol

Allopurinol accounts for up to 5% of all cases with SCAR.[65] An association between allopurinol induced SCAR (SJS/TEN and HSS phenotypes) and HLA-B*58:01 genotype was first described in Taiwanese Han Chinese population.[66] Thereafter, studies in other ethnic groups including, Han Chinese from mainland China[67,68] and Hong Kong,[69] Thai,[70] Koreans,[71,72] Japanese,[54] and Europeans[73,74] have replicated similar associations, although the strength of association was much weaker with a lower negative predictive value in Japanese and Europeans, likely owing to different allele frequencies across ethnic groups. The NPV of HLA-B*58:01 screening for allopurinol induced SCAR in Southeast Asian populations is 100%.[75]A modelling study from Singapore showed that routine genetic screening to prevent an episode of SCAR, even in high risk populations, did not appear to be cost-effective.[76] The extreme short and long-term morbidity and mortality that is in particular associated with SJS/TEN, the lack of comparably inexpensive treatment options to allopurinol, the development of newer and less expensive molecular assays for HLA-B*58:01 and the availability of a prospective screening study suggesting a significantly reduced incidence of allopurinol SCAR with HLA-B*58:01 screening in Taiwan suggest that further attention and implementation of HLA-B*58:01 screening may be warranted.

Causality assessment through clinical, *in vivo* and *ex vivo* testing

Assigning drug causality is often difficult in SCAR syndromes, especially when multiple agents are implicated, in particular, antimicrobials.[78] Conversely, in situations of a single implicated drug (*e.g.* carbamazepine, allopurinol), utilisation of appropriate clinical algorithms is often sufficient to assign causality,[5,79] especially in histologically confirmed cases.[80,81] Drug causality may be clinically established through several different validated methods/algorithms, each with own strengths and limitations (Table 3). Nonetheless, *in vivo* and *ex vivo* diagnostics are being increasingly employed to aid causality and management of patients with SCAR.[82] Guidelines exist for the recommended concentrations of drugs to be used in *in vivo* testing for delayed hypersensitivity,[83,84] although universal consensus has not been established.

Patch testing

Patch testing (PT) involves the application of an implicated and/or potentially cross-reactive drug with a control vehicle (petroleum jelly) to skin for 48 hours[82] and subsequently read after 48-96 hours and if possible 7 days. The safety of PT in SCAR has been increasingly demonstrated.[85-91] Systemic (but non-life threatening) reactions have been reported infrequently with PT, although mostly for anti-tuberculosis drugs in HIV patients.[92-96] The recommendations have been to perform skin testing at least 6 weeks post-resolution of SCAR.[97] The sensitivity of patch testing appears highest for ABC HSS (87%)[43,44] and DRESS (31.6%-58%) and lowest for SJS/TEN (20%-24%) and AGEP

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(18%).[85,86,90] The sensitivity also appears to be affected by the investigated drug, highest for abacavir, anticonvulsants and beta-lactam antibiotics,[87] in particular for abacavir (87%), amoxicillin (up to 44.4%), and lowest for vancomycin (9.1%), trimethoprim-sulfamethoxazole (8.6%), macrolides (4.8%), hepatitis C antivirals[98] and cephalosporins (4.4%).[85] The use of oral provocation after a negative PT should be used with caution in patients with SCAR, considering the low sensitivity of PT.

Intradermal testing

Intradermal testing (IDT) utilising 0.02-0.05 ml of the highest non-irritant concentration of drug, has been reported in DRESS and other SCAR phenotypes in a number of small series.[86,99-101] IDT with delayed readings has been utilised extensively for T-cell mediated hypersensitivity, in particular for non-SCAR phenotypes related to beta-lactams.[102,103] IDT avoids the inconvenience of patch testing and reactions will often occur within 6-24 hours. Barbaud *et al*. demonstrated in a small cohort of predominately beta-lactam SCAR that IDT appeared to have a greater sensitivity than PT when performed following negative PT and was not associated with adverse events.[86] Guidelines also support the use of IDT following negative PT in patients with SCAR, outside of SJS/TEN.[83] IDT is often limited by the availability of a sterile injectable formulation of the investigated drug. Like PT, oral provocation testing after a negative IDT should be undertaken with caution.

Ex vivo diagnostics

The stimulation of patient peripheral blood mononuclear cells (PBMCs) to measure T-cell responses in the setting of drug-associated SCAR has been increasingly investigated in research and clinical settings. Whilst responses have been detected out to 20 years post-index event, a blood sample from 'acute bleeds' or in the early recovery phase is likely to display greater sensitivity.[104-106] The lymphocyte transformation test (LTT),[99,107] which typically incubates investigated drugs with PBMCs for 5-7 days or longer, measures T-cell responses to a variety of drugs (*e.g.* antimicrobials, anticonvulsants, analgesics and diuretics) via a stimulation index.[104,107-117] Enzyme-linked immunospot assay (ELISpot) has been primarily employed for antiretroviral and antimicrobial hypersensitivity and SCAR syndromes,[118-121] especially when *in vivo* testing has been negative.[94,99,113,122,123] Variability in testing methods, incubation periods (1 vs. 2 vs. 5 days), co-stimulation factors (*e.g.* IL-7/IL-15) and measured outputs (*e.g.* granulysin, IFN-γ, TNF-α) make comparison within and between testing modalities difficult.[8,106,124,125] The known drug epitopes are unknown for most T-cell mediated hypersensitivity syndromes[126,127] Currently LTT or ELISpot should not be employed to exclude a suspected drug due to low sensitivity (24-70%[125,128] and 60%-80%,[125] respectively.) Whilst LTT has demonstrated a higher sensitivity in other types of anticonvulsant hypersensitivity (70-90%),[129] lower rates have still been noted in lamotrigine-SJS.[130]

Indeed, Polak and colleagues' study compared the lymphocyte proliferation assay (LPA) against combination INF-γ and IL-4 drug ELISpot assays in patients with delayed-type drug hypersensitivity

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reactions in the acute phase. In their study, the assays demonstrated a test specificity of 95%, 83% and 92% for LPA, INF-γ and IL-4, respectively. During acute drug hypersensitivity reactions, the sensitivity of combined measurement of drug-specific INF-γ and IL-4 cytokines was greater than that of LPA (82% *vs*. 50%). Thus, these investigators determined that *in vitro* assays of drug-specific INF-γ and IL-4 production may be more sensitive than LPA for the detection of drug-specific T-cells in the acute setting.[131] Further, a recent study by Haw *et al.* concluded that cytokine assays (INF-γ and IL-4) are superior to LPA in identifying the causative drug in the paediatric population; however, these investigators suggested that when combined, they offer even greater utility in the diagnosis and post-recovery of delayed-type hypersensitivity reactions.[132]

The sensitivity and hence NPV of *ex-vivo* testing in the future is likely to be enhanced by co-utilisation of flow cytometry and intracellular cytokine staining methods.[118,133-136]

The importance of drug cross-reactivity between structurally-related drugs

Structurally-related drugs can cause cross-reactions with SCAR. Although the specific epitopes remain elusive with regards to drug-self peptide responses, it is recognized that the immune system may recognise structural similarities Knowledge regarding the likelihood of cross-reactivity between drugs is important as exposure to structurally similar compounds after an index reaction can precipitate another severe episode. On the contrary, excessive avoidance of medications with low risk of cross-reactivity can lead to unwarranted restriction on therapeutic options that can adversely impact upon clinical care.

Beta-lactams

All beta-lactams (penicillins, cephalosporins, carbapenems and monobactams) share the core beta-lactam structure but with differing side-chains (Fig. 2). Evolving evidence to date suggests that side chain structures are commonly implicated in beta-lactam cross-reactivity for most immediate and delayed reactions. Table 4 further provides a list of commonly prescribed beta-lactams which share similar side chain structures.

Cephalosporins

R1 side-chains of cephalosporins (Fig. 2) are highly conserved and have been demonstrated to promote cross-reactions with penicillins containing similar structures. This is particularly true between aminopenicillins (amoxicillin, ampicillin and bacampillin) and aminocephalosporins (cephalexin and cefaclor), with recent studies demonstrating that the cross-reactivity rates between the amino compounds may be as high as 18.7%.[137,138] On the contrary, patients with delayed aminopenicillin allergy have recently been shown to have complete absence of cross-reactivity and good tolerance to therapeutic challenge to non-amino cephalosporins (cefuroxime and ceftriaxone).[137]

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Overall, low rates of cross-reactivity exist between penicillins and third and fourth generation cephalosporins of dissimilar side chain structures (1.1% vs. 10.9% for first and second generation cephalosporins which share similar side chains).[138]

Further, an interesting *in vitro* study by El-Ghaiesh *et al.* in eight cystic fibrosis patients with delayed hypersensitivity reactions to piperacillin, compared to five tolerant controls, demonstrated the critical role of drug-specific CD4+ and CD8+ T-cell clones in pathogenesis, which did not cross-react to a multitude of penicillins and cephalosporins including those that share similar side chain to piperacillin (*e.g.* cefoperazone). This study highlights the drug-specific nature of T-cell mediated hypersensitivity reactions as well as the highly complex nature of cross-reactivity to other beta-lactams, with some unknown mechanisms in addition to 'structural similarities,' likely further contributing to its pathogenesis.[113]

Carbapenems and monobactams

Although a cross-reactivity rate of 5.5% to imipenem has been previously reported in penicillin-allergic patients.[139] A more recent study involving 204 patients demonstrated that none of the patients with delayed penicillin hypersensitivity cross-reacted to imipenem, meropenem or ertapenem, and all tolerated therapeutic doses of drug challenge.[140] In view of the reportedly low (<1%) rates of cross-reactivity to carbapenems in patients with immediate penicillin hypersensitivity reactions,[141,142] the true cross-reactivity rates in delayed reactions are likely very low (<1%) and therefore, carbapenems may be judiciously considered in patients who have limited therapeutic options.

In contrast, virtually zero percent cross-reactivity to aztreonam has been consistently demonstrated in patients with delayed penicillin hypersensitivity reactions.[137,143] The only caveat is that aztreonam should be avoided in patients with ceftazidime allergy due to side-chain similarities.

It should also be noted that although cross-reactivity rates between penicillins and later generation cephalosporins or carbapenems are low, the vast majority of patients included in these studies had benign skin reactions and few patients with definitive SCAR phenotypes were represented. As such, considerable caution should be taken when prescribing beta-lactam antibiotics to patients with SCAR.

Aromatic anticonvulsants

Commonly prescribed aromatic anticonvulsants include carbamazepine, oxcarbazepine, lamotrigine, phenytoin and phenobarbital.[144] Cross-reactivity between these structurally related aromatic anticonvulsants was originally thought to be mediated by arene oxides, toxic metabolites produced through cytochrome P450 pathway.[145,146] However, it is now clear that poor metabolisers (*e.g.* CYP2C9*3) are at higher risk for SCAR associated with some anticonvulsants such as phenytoin.[147] Earlier studies suggested that approximately 70% will experience some degree of cross-reactivity between aromatic anticonvulsants.[146,148-150] There is also evidence suggesting that HLA-B*15:02 and other B75 serotype HLA alleles confer risk of developing SJS/TEN to other aromatic anticonvulsants,

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however, to a much lesser degree compared to carbamazepine.[151,152] What is currently unclear is the extent to which HLA cross-reactivity occurs since cases of HLA-B*15:02 positive individuals who have reacted to one aromatic amine anticonvulsant but tolerated another (despite the association of HLA-B*15:02 with all aromatic amine anticonvulsant SCAR) have been well-described. Additionally Seitz *et al.* also noted that 21.7% of patients with carbamazepine hypersensitivity also displayed cross-reactivity to tricyclic antidepressants.[150] However, this has not been substantiated as an effect that is seen *in-vivo* and in the case of HSS to carbamazepine, recommendations would not dictate avoidance of tricyclic antidepressants. In patients with SCAR to aromatic anticonvulsants, valproate, gabapentin, pregabalin and levetiracetam are safe alternatives.[153,154]

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Conclusion and Future Directions

Recent advances in the knowledge of SCAR syndromes have provided us with a better understanding of immunopathogenic mechanisms, including the potential role of pre-existing cross-reactive T cell responses to viral infections, the discovery of important pharmacogenomic associations, which have become the standard of care, the use of clinical and laboratory methods for causality assessment and the knowledge of drug cross-reactivity mechanisms. Further knowledge on how precisely drugs activate T-cells, the pathomechanism for the generally very low positive predictive value of an HLA risk allele for a specific drug toxicity, more specific pharmacogenomic associations and future mechanistic information including cellular and molecular signatures will be key for pre-clinical prediction and prevention of drug toxicity as well as for enabling personalised approaches to prevention, early intervention and treatment of high morbidity and mortality diseases such as SJS/TEN. As highlighted in this review, numerous aspects of SCAR syndromes merit further interdisciplinary research. Finally, given the overall rarity but high morbidity and mortality of SCAR, collaboration through large international, national and multicentre networks to collect prospective data and biobank samples will further enhance a systematised framework for translating discovery into prevention and improved outcomes for patients.

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Table 1. **Summary of the clinical manifestations and histopathological features of SCAR syndromes.**

SCAR syndrome	Effector mechanisms	Clinical manifestations	Investigation findings	Histopathological features	Latency period	Common causal drugs

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SJS/TEN	CD8+ cytotoxic T lymphocyte mediated Fas-FasL and granulysin-mediated apoptosis.[4,8,155]	SJS and TEN are a disease continuum; the differentiation is based upon the percentage of body surface area of skin detachment.[156-158] Acute onset of blisters and erosions affecting the skin, and mucous membranes; often associated severe systemic complications with significant morbidity and long-term sequelae.[159]	Abnormal liver, renal and respiratory function. Haematological, metabolic, fluid & electrolyte complications.	Subepidermal blister; spectrum of changes ranging from lichenoid reaction pattern with apoptotic keratinocytes, partial to full thickness epidermal necrosis.[158]	1-4 weeks.[156,159]	Carbamazepine Phenytoin Lamotrigine Allopurinol Nevirapine NSAID* Sulfonamides Sulfasalazine[159]
DRESS	T-cell mediated perforin-granzyme B as well as Fas/Fas L-dependent cell death.[7,160]	Clinical presentation is heterogeneous: widespread exanthematous eruption, facial oedema, fever and lymphadenopathy.[18,160,161] High variability in disease severity; some patients have modest systemic symptoms, while others develop significant morbidity due to internal involvement.[160]	Haematological abnormalities, most commonly eosinophilia and atypical lymphocytes. Abnormal liver, renal, respiratory and other organ function.[18,160,161]	Multiple histological patterns including: interface reaction, apoptotic keratinocytes, parakeratosis, spongiosis.[161]	2-6 weeks.[79]	Carbamazepine Phenytoin Lamotrigine Allopurinol Sulfonamides Vancomycin Minocycline Amoxicillin[79]
AGEP	Activation and proliferation of specific CD4 and CD8 T-cells, perforin/granzyme B and Fas ligand	Acute onset of widespread non-follicular sterile pustules overlying erythematous oedematous skin, starting in the intertriginous areas,	Neutrophilia +/- eosinophilia, abnormal renal/liver function, hypocalcaemia.[162-164]	Spongiform subcorneal and/or intradermal pustules with marked oedema of the papillary dermis and	1–5 days.[163]	Amoxicillin Quinolones Sulfonamides Terbinafine Hydroxychloroquine Diltiazem[166]

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	mechanisms to induce apoptosis.[162]	often associated with fever.[162-164]		polymorphous perivascular infiltrate.[165]		

AGEP: acute generalised exanthematous pustulosis, CD: cluster of differentiation, DRESS: drug rash with eosinophilia and systemic symptoms, NSAID: Non-steroidal anti-inflammatory drug, SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis.

Table 2. Therapeutic recommendations where evidence exists for strong HLA associations for various adverse drug reaction phenotypes[†].

Medications	**HLA**	**Phenotype**	**Populations studied**	**Therapeutic recommendation**	**Selected references**
Abacavir	HLA-B*57:01	HSS	All	HLA-B*57:01 testing prior to abacavir prescription and avoid abacavir use in HLA-B*57:01 positive individuals	41,42,45-48
Carbamazepine	HLA-B*15:02[§]	SJS/TEN	Han Chinese (China, Hong Kong, Taiwan), Thai, Malaysian, Indian (South Asians)	Avoid carbamazepine in all HLA-B*15:02 positive individuals[††] Screening currently recommended for at risk populations (Han Chinese, southeast and south Asians) or unknown ethnicity	51,58,64,167,168
Carbamazepine	HLA-A*31:01	DRESS/HSS >SJS/TEN	Han Chinese, Japanese, Korean, Caucasian	If alternative therapeutic agent exists, avoid carbamazepine in all carbamazepine naïve HLA-A*31:01 positive individuals	51,58,63 52,55,61 ,62,64

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Allopurinol	HLA-B*58:01	DRESS/HSS and SJS/TEN	Han Chinese (China and Hong Kong), Thai, Korean, Japanese, European	Avoid allopurinol use in the setting of allopurinol naïve HLA-B*58:01 posivite individuals Widespread guidelines for screening prior to use have not been issued[¶]	[54,66-74]

SCAR: severe cutaneous adverse reactions, HLA: human leucocyte antigen, HSS: hypersensitivity syndrome, SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis, DRESS: drug reaction with eosinophilia and systemic symptoms.

[†] For any individual carrying an HLA risk allele, if they have already tolerated the drug for ≥ 12 continuous weeks currently or in the past, then it is safe for them to continue the drug or for the drug to be reinstituted in the future.

[§] Carbamazepine SJS/TEN is also associated with other B75 serotype HLA alleles such as HLA-B*15:21, B*15:08, B*15:11 and potentially B*15:30 and B*15:31, therefore additional caution should be exerted for carbamazepine use if these HLA types are identified.

[††] Although a much weaker association exists between HLA-B*15:02 and other aromatic amine anticonvulsants, such as oxcarbamazepine, eslicarbamzepine, lamotrigine, phenytoin and fosphenytoin, consideration should be given to choosing an alternative non-aromatic anticonvulsant in the case of identified HLA-B*15:02+.

[¶] The American College of Rheumatology Guidelines for Management of Gout (2012) have recommended HLA-B*58:01 testing prior to allopurinol prescription in specific popualtions including 1) those of increased risk (Southeast Asian) and 2) Subpopualtions with increase risk based on advanced chronic renal failure (stage 3).[169]

Table 3. Three major approaches to drug causality assessment in severe cutaneous adverse drug reactions.

Method	**Description**	**Strengths**	**Weaknesses**	**Selected references**
Global introspection	Inference of causality by expert clinical judgement.	Consensus opinion by a group of experts. Often serves as the gold standard in causality assessment.	Subjective, influenced by the experience, knowledge and biases of the assessor(s). Poor reproducibility.	[5,170,171]

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Bayesian approach	Uses clinical and epidemiological data to transform a prior into a posterior probability.	Allows simultaneous assessment of multiple causes. Previous knowledge of the culprit drug profile is not required.	Time consuming and highly technical.	[172]
Drug causality algorithms (see A & B)	Collection of specific data points followed by problem solving operations resulting in an objective assessment of probability.	Structured and standardised method. Reproducible and transparent.	Clinical utility may be limited in cases where more than one drug is administered. Clinical judgement may be required at various stages. Some algorithms may not be able to identify novel ADRs or first cases of ADRs.*	[5,172]
(A) Naranjo Scale	Consists of 10 questions and yields a final assessment of causality as: 'definite', 'probable', 'possible' or 'doubtful' that a drug administered in therapeutic doses caused an adverse event.	Well-validated. Widely used and quick/simple tool.	Classifies >90% of suspected adverse drug reactions as 'possible.' Does not take into account drug-drug interactions.	[173]
(B) ALDEN	Specific algorithm for assessing drug causality in SJS and TEN. The final assessment of causality is expressed as 'very probable'. 'probable', 'possible', 'unlikely' or 'very unlikely.'	Developed by experts in SJS/TEN. Validated on cases enrolled in the EuroSCAR study in a case-control analysis.	Only validated for SJS/TEN.	[5]

ADR: Adverse drug reaction, ALDEN: Algorithm for drug causality for epidermal necrolysis, SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis.

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Table 4. Beta-lactams with similar R1 side-chain structures (adapted from Trubiano *et al.*[174])

Penicillin G	Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Ceftamandole	Ceftazidime
Cephaloridine	Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cephalothin	Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefoxitin	Cefatrizine	Cephadrine	Cefditoren			
	Cephalexin	Cephaloglycin	Ceftizoxime			
		Loracarbef	Cefmenoxime			
			Cefepime			

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Figure 1. Proposed models of T-cell receptor (TCR), major histocompatability complex (MHC), drug interactions**:** In the **hapten/prohapten model (i)** a drug (e.g., penicillin) binds covalently to an endogenous peptide (e.g., albumin), forming a new molecule. Antigen presenting cells process and present it as short peptide fragments within the MHC binding cleft, some of which (peptide A) include drug epitopes (purple pentagon). If recognized by a TCR, a drug-specific immune response can ensue. In the **pharmacological-interaction (P-I) model (ii)** the drug binds non-covalently to certain MHC molecules or TCRs, stimulating specific TCR and thus generating drug-reactive T-cells. In the **altered peptide repertoire model (iii)** a drug (e.g., abacavir) binds non-covalently to the binding pocket of a MHC molecule (e.g. HLA-B*57:01), altering its conformation and allowing a new array of self-peptides (peptide B) to stably occupy it and stimulate T-cells. This can lead to drug-induced activation of autoimmunity (e.g., abacavir hypersensitivity reaction.) Adapted from Pavlos *et al.*[175]

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Figure 2. Basic structures of beta-lactams (adapted from Trubiano *et al.*[174]). R denotes side chains. Cephalosporins have two side chains, R1 and R2. However, R2 is lost during hydrolysis.

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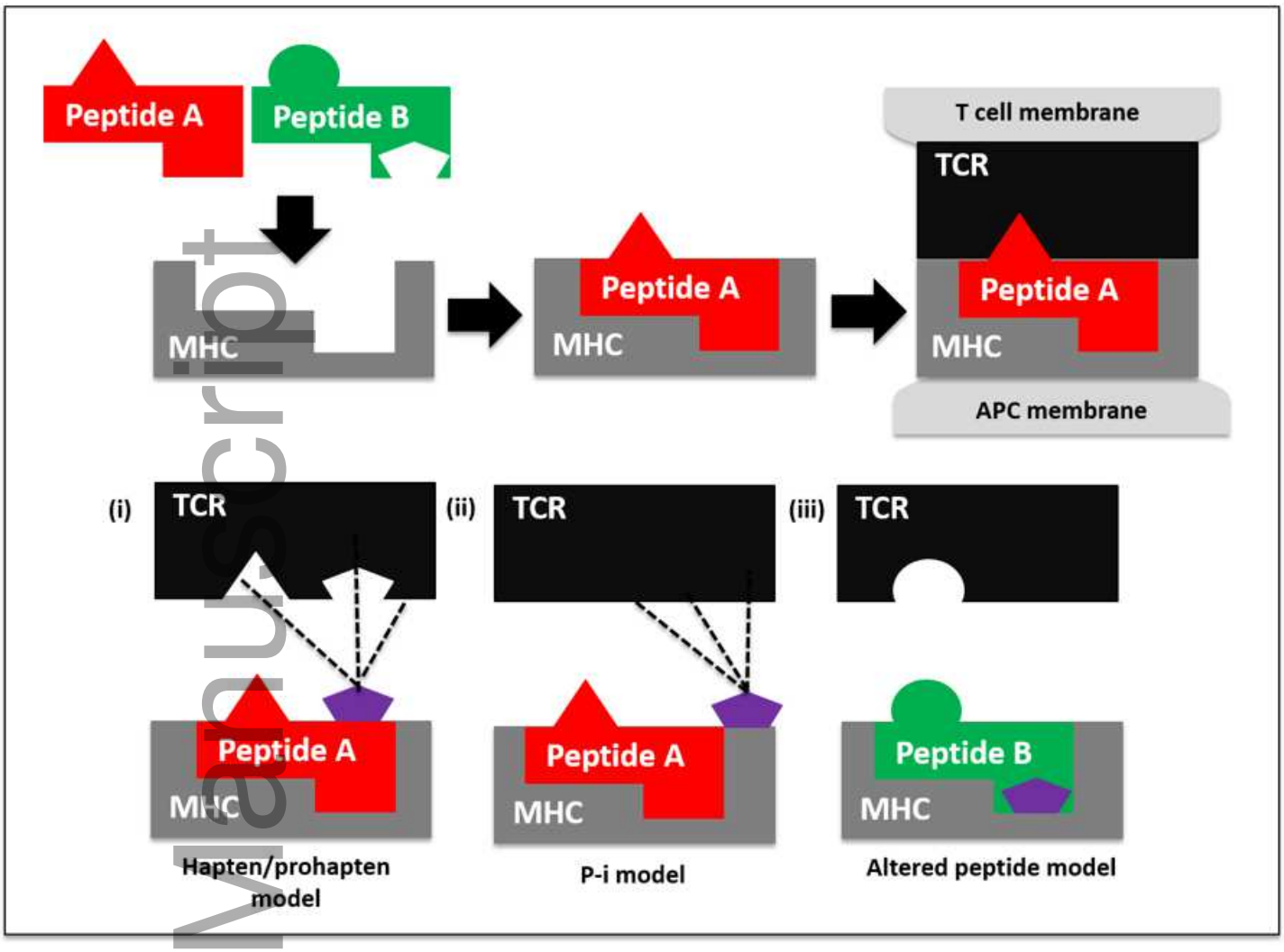

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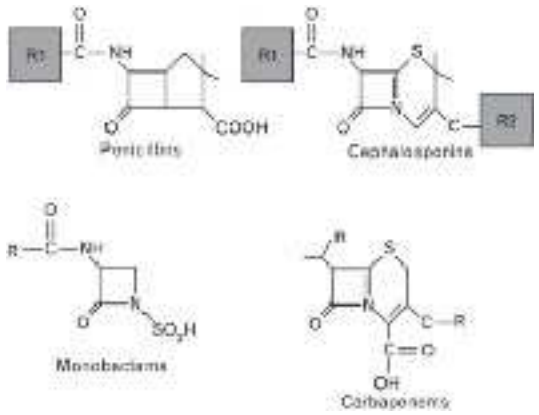

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