A GUIDE ON SEVERE CUTANEOUS ADVERSE REACTIONS

This guide highlights the key features of various forms of severe cutaneous adverse reactions (SCAR), the drugs that are most commonly associated with each form of SCAR as well as the risk factors associated with two drugs commonly associated with SCAR: allopurinol and carbamazepine (CBZ).

- SCAR, namely, SJS and TEN, DRESS as well as AGEP are rare, idiosyncratic disorders that are most often induced by drugs.
- They are associated with significant morbidity, usually leading to hospitalisation. Some forms of SCAR may lead to long term sequelae such as ocular, mucosal, pulmonary and urogenital complications, or fatality.[1]
- The initial presentation of SCAR may include constitutional symptoms of fever, sore throat and conjunctivitis. Subsequently, the patient may develop eye redness, mucositis and rash which may be pruritic or painful. Healthcare professionals need to recognise these early signs and to educate their patients on the early recognition of such features, the importance of prompt withdrawal of the drug and early medical attention.
- Risk factors, including genetic markers associated with CBZ-induced SJS/TEN and allopurinol SCAR have been identified. Apart from clinical vigilance, genotyping for HLA-B*1502 in new patients of Asian ancestry is recommended as standard of care to prevent CBZ-induced SJS/TEN, while a low starting dose, gradual titration and close monitoring are key factors in mitigating allopurinol-induced SCAR. Genotyping for HLA-B*5801 may be considered for patients who have other pre-existing risk factors for allopurinol-induced SCAR, such as renal impairment.

Severe cutaneous adverse reactions (SCAR) are rare, idiosyncratic disorders that are most often induced by drugs and associated with significant morbidity, usually leading to hospitalisation.[2] This article addresses three types of SCAR, namely, (1) Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), (2) drug reaction with eosinophilia and systemic symptoms (DRESS); also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS) and (3) acute generalised exanthematous pustulosis (AGEP).

From January 2006 to December 2015, HSA received reports of 810 cases of SJS/TEN, 246 cases of DIHS/DRESS and 20 cases of AGEP. Of these, 53 cases of SJS/TEN and 12 cases of DRESS were fatal. The seriousness of these rare adverse drug reactions (ADRs) underscores the importance of healthcare professionals' awareness, prompt diagnosis, and withdrawal of the suspected drug upon first recognition of the reactions.

Stevens-Johnson Syndrome/ Toxic epidermal necrolysis

Fig 1: Toxic epidermal necrolysis
Discrete and confluent blisters with sheet-like detachment and erosions

Most commonly implicated drugs[3,4]: CBZ, phenytoin, lamotrigine; allopurinol; co-trimoxazole; non-steroidal anti-inflammatory drugs (NSAIDs); nevirapine.

Onset[3,5]: SJS and TEN usually occur within four weeks of commencement of the implicated drug, but may occasionally be delayed for up to 8 weeks.

Clinical characteristics[6]: The classical prodromal features of SJS and TEN include "flu" like illness with sore throat, conjunctivitis and erythematous macular rash, with purpuric centres, covering at least 1% of the body surface area (BSA). The macular rash may progress to blisters and bullae within hours to days. The rash is typically very painful. Presentations with epidermal detachment involving <10% of body surface area (BSA) are classified as SJS, those with >30% BSA involvement as TEN and those with 10 to 30% BSA involvement as SJS/TEN overlap. Mucosal involvement (e.g. on ocular, oropharyngeal and urogenital surfaces), in the form of painful crusts or erosions, is common and can precede or follow the skin eruption. Other manifestations indicating systemic involvement may be present. These include but are not limited to intestinal and pulmonary manifestations, or the presence of haematological abnormalities, particularly anaemia and lymphopenia. Patients who survive may suffer from long-term sequelae, such as cutaneous, ocular, mucosal, pulmonary, and urogenital complications. Ocular sequelae may be serious, leading to corneal scarring and visual impairment.

Drug reaction with eosinophilia and systemic symptoms; Drug induced hypersensitivity syndrome; hypersensitivity syndrome

Most commonly implicated drugs: Phenytoin, CBZ, lamotrigine; allopurinol; dapsone; co-trimaxazole; antiretrovirals (nevirapine and abacavir).

Onset[3]: This reaction typically occurs within the first 3 months of drug treatment (peak occurs in two to six weeks) and the recovery phase is often prolonged despite withdrawal of the drug.

Clinical presentation[2,7]: DRESS is a complex syndrome commonly characterised by fever, rash, lymphadenopathy, haematological findings (eosinophilia, leucocytosis and/or thrombocytopenia), abnormal liver function tests and renal dysfunction. The cutaneous manifestations typically consist of a morbiliform exanthematous and oedematous rash, with occasional pustules, vesicles and purpura. Hepatitis may be severe and peripheral eosinophilia is usually prominent. The rash and hepatitis may persist for weeks to months after drug withdrawal. Mortality from DRESS is usually due to fulminant hepatitis, hence the importance of recognising this syndrome. Autoimmune sequelae such as autoimmune thyroid disease may develop several months to years after clinical resolution of DRESS.[8]

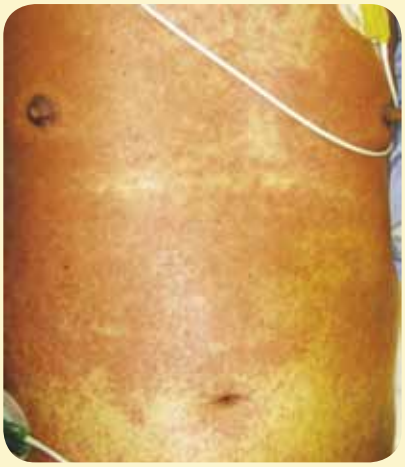


Fig 2: DRESS
Confluent erythematous patches and plaques in a patient with DRESS

Acute generalised exanthematous pustulosis

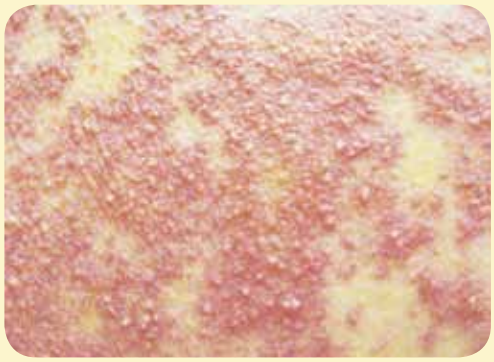


Fig 3: AGEP
Multiple pinpoint pustules studded on an erythematous base.

Most commonly implicated drugs[3,4,5,9]: Sulfonamides; beta-lactam antibiotics, macrolides, hydroxychloroquine, calcium channel blockers, terbinafine, quinolones

Onset[10]: The eruption may begin within three to five days after the administration of the offending drug.

Clinical presentation[2,6]: AGEP typically manifests with the acute widespread non-follicular, sterile, pinhead-sized pustules on a background of edematous erythema. The eruption generally begins on the face or intertriginous areas and rapidly extends to the trunk and limbs with a diffuse or patchy distribution. Mucous membranes may be involved. During the acute phase, fever, leukocytosis, and mild eosinophilia are usually present. The prognosis is usually good, with spontaneous resolution of skin symptoms through desquamation within two to three weeks. The main clinical differential diagnosis is generalised pustular psoriasis.

Risk factors associated with CBZ- and allopurinol-induced SCAR

Allopurinol-induced SCAR

Identified risk factors:

- High starting dose of allopurinol
- Renal impairment
- Carriage of the HLA-B*5801 allele

Risk minimisation measures

- Use allopurinol according to approved indications only
- Start at low dose, titrate gradually and monitor closely
- Consider HLA-B*5801 screening for patients at high risk, e.g. renal impairment

Allopurinol was first licensed locally in 1989, and there are currently ten registered allopurinol-containing products, including Zyloric® (A. Menarini) and six other generic brands. Allopurinol is indicated as first-line therapy for reducing urate formation in chronic gout and other conditions such as nephrolithiasis.

Allopurinol is an effective urate-lowering therapy in patients who can tolerate it well (notably, there are limited therapeutic options for chronic gout). It is also one of the leading causes of drug-induced SCAR reported to HSA, with an average of approximately 14 cases per year. Hence, it is important for healthcare professionals to take note of ways to minimise the risk of SCAR in patients who are being initiated allopurinol. Risk factors of allopurinol-induced SCAR include high starting dose,[11] renal impairment and carriage of the HLA-B*5801 allele. Allopurinol should be started at a low dose, and titrated accordingly to minimise the risk of allopurinol-induced SCAR.[12,13]

Genetic association of HLA-B*5801 and allopurinol-induced SCAR

A strong association between the HLA-B*5801 allele and allopurinol-induced SCAR has been reported in people of Korean, Chinese and Thai ancestry. Genotyping for the allele in these Asian subpopulations prior to initiation of allopurinol has been recommended by the American College of Rheumatology,[14] but the clinical utility has not been well established. Routine genotyping for the HLA-B*5801 allele prior to initiating allopurinol therapy is currently not required as standard of care in Singapore,[15] based on the low Positive Predictive Value of HLA-B*5801 for allopurinol-induced SCAR (PPV~2%), limited alternative urate-lowering therapies, and unfavourable cost-effectiveness analysis based on current data.[16] Nonetheless, doctors may consider genotyping patients who have other pre-existing risk factors for allopurinol-induced SCAR, notably renal impairment, to facilitate identifying and monitoring patients who are at a greater risk of allopurinol-induced SCAR. While patients who have tested negative for the HLA-B*5801 allele are at lower risk of developing allopurinol-induced SCAR, they can still develop SCAR.

Regardless of knowledge of the genotype status, healthcare professionals are advised to use allopurinol according to approved indications, to communicate to patients to be alert for signs of allergic skin reactions, and to monitor patients starting allopurinol treatment for possible SCAR development.

CBZ-induced SJS and TEN

Identified risk factor:

- Carriage of the HLA-B*1502 allele

Risk minimisation measures:

- HLA-B*1502 screening for all new patients of Asian ancestry before initiation
- Clinical vigilance in HLA-B*1502-negative patients who are prescribed CBZ as SJS/TEN can develop in these patients, although the occurrence is rare

CBZ was first licenced locally in 1988, and there are currently nine registered CBZ-containing products, including Tegretol® (Novartis) and four other generic brands. It is indicated for the treatment of epilepsy and other conditions such as bipolar disorders, alcohol-withdrawal syndrome, trigeminal neuralgia, diabetic neuropathy and diabetes insipidus centralis.

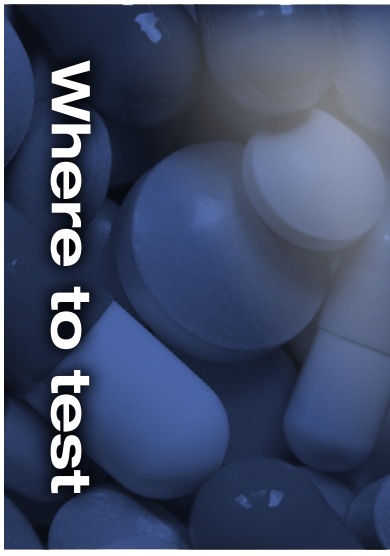
Genetic association of HLA-B*1502 and CBZ-induced SJS and TEN

A genetic association between HLA-B*1502 and CBZ-induced SJS and TEN has been established based on strong local and international data. In April 2013, a Dear Healthcare Professional Letter was jointly issued by the Ministry of Health (MOH) and HSA to inform that genotyping for HLA-B*1502 allele prior to initiation of CBZ therapy in new patients of Asian ancestry[15] is considered the standard of care in Singapore. Since April 2013, more than 2,700 patients have been genotyped for HLA-B*1502, of which 11% were found to carry the at-risk allele. The implementation of genotyping of HLA-B*1502 in new CBZ patients of Asian ancestry has significantly reduced the number of CBZ-induced SJS/TEN received by HSA.

Although rare, patients negative for HLA-B*1502 could still develop SJS/TEN as the role of other factors such as drug dose, concomitant medications and co-morbidities have not been studied. Patients

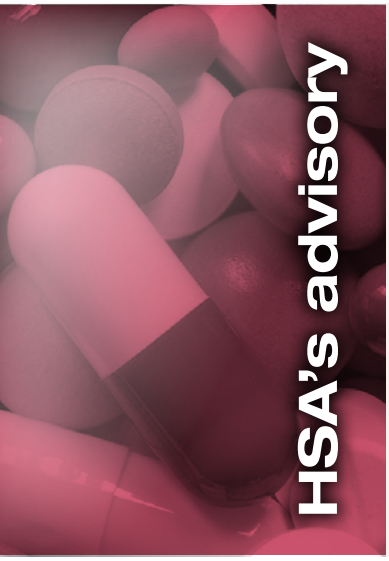
negative for HLA-B*1502 may also develop CBZ-DRESS, which cannot be predicted by HLA-B*1502. Healthcare professionals are reminded that genetic testing for HLA-B*1502 should not substitute appropriate clinical vigilance and patient management.

Genotyping for HLA-B*1502 allele prior to initiation of CBZ therapy in new patients of Asian ancestry is considered the standard of care in Singapore. CBZ should not be prescribed prior to the return of HLA-B*1502 test results due to the possibility of development and progression of SJS/TEN in susceptible patients even after prompt discontinuation of the drug. The use of CBZ should be avoided and treatment alternatives are recommended in patients who are found to be positive for HLA-B*1502. As a precaution, these patients should also not be prescribed phenytoin, as there is preliminary data suggesting a suspected association between HLA-B*1502 and phenytoin-induced SJS/TEN.



HLA-B*1502	HLA-B*5801
1. DNA Diagnostic & Research Laboratory (DDRL) at KK Women's and Children's Hospital (KKH). ◆ $205.70 (w/o GST)* ◆ Turnaround time (TAT) 1-2 working days*	1. DNA Diagnostic & Research Laboratory (DDRL) at KK Women's and Children's Hospital (KKH). ◆ $220 (w/o GST)* ◆ Turnaround time (TAT) 1-2 working days*
2. Molecular Diagnosis Centre (MDC) at National University Hospital ◆ $187 (w/o GST)* ◆ Turnaround time (TAT) 2-4 working days*	Subsidy not available
75% subsidy is available for subsidised patients at MOH-funded restructured hospitals.	

**Prices and TAT quoted are based on current information and may be subjected to changes over time. Healthcare professionals may wish to contact the respective laboratories to obtain the latest information*



Early signs of rash and skin reactions may be indicative of a more serious reaction such as SCAR. Hence, it is important to recognise cutaneous drug reactions as early as possible. All drugs introduced within 4-12 weeks before the onset of the adverse reaction should be considered as possible causative agents. The management of the condition will differ depending on the clinical diagnosis. Regardless of the specific condition, the suspected drug should be promptly withdrawn.

- Healthcare professionals are advised to educate their patients on early recognition of allergic reactions, the importance of prompt withdrawal of the drug at the first sign of rash and the early seeking of medical advice.
- Healthcare professionals are encouraged to continue reporting suspected cutaneous adverse drug reactions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority

Phone: (65) 6866 1111
Fax: (65) 6478 9069
Email: HSA_productsafety@hsa.gov.sg
Online Reporting:
http://www.hsa.gov.sg/ae_online

1. *J Am Acad Dermatol 2013 Aug 69: 187. E1-16*
2. *Dermatol Sinica Dec 2009; 27: 203-9*
3. *Fernando S. Skin Biopsy- Perspectives, Chapter 4, Severe cutaneous adverse reactions. 2013. doi:http://dx.doi.org/10.5772/54820*
4. *Clin Pharmacol Ther. 2011; 89: 896-901*
5. *http://www.hsa.gov.sg/content/dam/HSA/HPRG/Safety_Alerts_Product_Recalls_Enforcement/Cutaneous%20drug%20reactions_Report_Guide.pdf*
6. *Stevens Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis in Uptodate®, accessed on 20 July 2016*
7. *J Clin Aesthet Dermatol 2013: 6; 31-7*
8. *Dermatol Sinica Dec 2013; 31, 211-6*
9. *Int J Dermatol. 2010 May;49: 507-12*
10. *Acute generalized exanthematous pustulosis (AGEP) in Uptodate®,accessed on 20 July 2016*
11. *Arthritis and Rheumatism. 2012; 64: 2529-36*
12. *Arthritis Care & Research 2012; 64, 1431-46*
13. *Ann Rheum Dis 2006; 65:1312-1324*
14. *http://www.ncbi.nlm.nih.gov/books/NBK127547/*
15. *http://www.hsa.gov.sg/DHCPL*
16. *Pharmacogenomics, 2015 16: 1781-93*

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