A Guide on Severe Cutaneous Adverse Reactions

Updated from the version published in 2016

This guide features the various types of severe cutaneous adverse reactions (SCAR), the drugs commonly associated with SCAR and an analysis of SCAR reports received by HSA in the last decade (2014 – 2023). It also includes 1) "SCAR Watch", an infographic guide to aid doctors in mitigating potential SCAR in their patients; 2) a patient education guide for healthcare professionals to counsel patients on recognising early signs and symptoms of SCAR and what to do if SCAR is suspected; and 3) a poster of laboratories in Singapore providing HLA-B*15:02 and HLA-B*58:01 genotyping services should doctors wish to consider genotyping tests for at-risk patients prescribed carbamazepine and/or allopurinol.

About SCAR

SCAR are a group of uncommon and life-threatening skin conditions associated with medication use. They include acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).[1] SCAR are of significant concern due to their high morbidity and mortality rates. Mortality rates range from around 4% for AGEP, 5 – 10% for DRESS and 10 – 40% for SJS/TEN.[1,2] Patients often require intensive care and may suffer from long-term complications such as scarring, visual impairment and organ damage. Early recognition and discontinuation of culprit drugs are associated with better prognoses.

Apart from SCAR associated with drugs, HSA has also received reports due to adulterated health products and those obtained from illicit / unknown sources such as modafinil /armodafinil.

Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)[3,4]

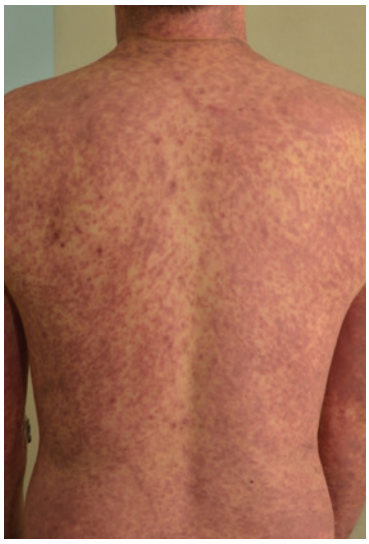


Figure 1. SJS: Diffuse non-blanchable dusky areas on the back with erosions.

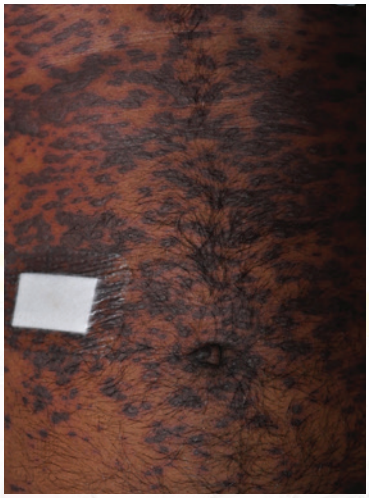


Figure 2. SJS: Multiple flaccid blisters arising from dusky patches on the trunk of a dark-skinned patient.

Commonly implicated drugs

- Antiepileptics (carbamazepine, phenytoin, lamotrigine)
- Antibiotics and antivirals (co-trimoxazole, nevirapine)
- Non-steroidal anti-inflammatory drugs
- Allopurinol
- Sulfasalazine
- Immune checkpoint inhibitors (pembrolizumab, nivolumab)

Onset

- Usually within 4 weeks of drug initiation
- May be delayed up to 8 weeks

Clinical characteristics

- Prodromal symptoms (flu-like illness with sore throat and conjunctivitis) may develop 1 to 3 days before development of mucocutaneous and skin lesions
- Poorly defined, coalescing, erythematous macules with atypical target lesions. As disease progresses, vesicles and bullae form, and skin starts to slough within days. Rash usually covers at least 1% body surface area (BSA); mild cases may be <1%
- Mucosal involvement (ocular, oropharyngeal, urogenital), commonly in the form of painful crusts or erosions, may precede or follow skin eruption
- Epidermal detachment – SJS: <1-10%; SJS-TEN overlap: 10-30%; TEN: >30%
- Systemic involvement (intestinal or pulmonary manifestations; haematological abnormalities, especially anaemia and lymphopenia)

Long term sequelae

- Cutaneous, ocular (corneal scarring, visual impairment), mucosal, pulmonary and urogenital complications
- Chronic pain
- Psychosocial complications and psychiatric disorders (post-traumatic stress disorder, anxiety, depression)

References:

1. *Lancet. 2017;390(10106):1996-2011*
2. *Front. Pharmacol. 2023;14:1117391*
3. *UpToDate Stevens-Johnson syndrome and toxic epidermal necrolysis: pathogenesis, clinical manifestations, and diagnosis; accessed 1 Aug 2024*
4. *UpToDate Stevens-Johnson syndrome and toxic epidermal necrolysis: management, prognosis and long term sequelae; accessed 1 Aug 2024*

Drug reaction with eosinophilia and systemic symptoms (DRESS)*[5]

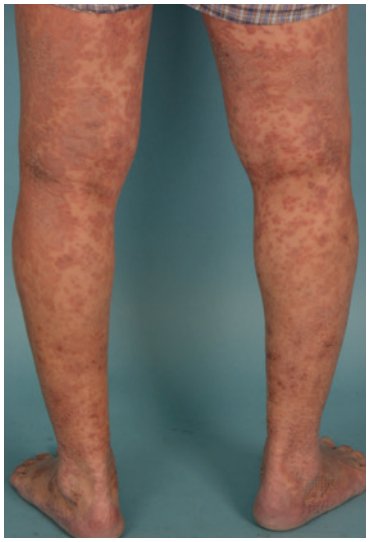


Figure 3. DRESS: Indurated erythematous patches on the thighs with desquamative scaling.

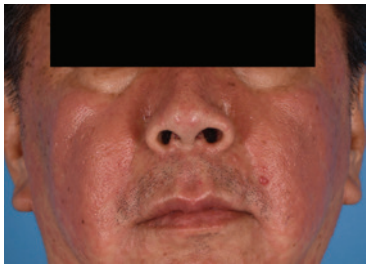


Figure 4. DRESS: Oedematous erythematous plaques on the face, with earlobe oedema. The periorbital area was spared.

Commonly implicated drugs

- Antiepileptics (carbamazepine, phenytoin, lamotrigine)
- Antibiotics and antivirals (co-trimoxazole, dapsone, vancomycin, anti-tuberculosis drugs, abacavir, nevirapine)
- Allopurinol
- Protein kinase inhibitors / Tyrosine kinase inhibitors (imatinib, sorafenib)

Onset

- Usually within the first 3 months of treatment
- Peaks in 2 to 8 weeks

Clinical characteristics

- Prodromal symptoms (fever, malaise, lymphadenopathy)
- Rash starts as a maculopapular eruption that may progress to a coalescing erythema and may include purpura, infiltrated plaques, pustules, exfoliative dermatitis, and target-like lesions
- Facial oedema
- Systemic involvement (haematological abnormalities such as eosinophilia, lymphopenia, presence of atypical lymphocytes, thrombocytopenia; hepatitis; interstitial kidney and lung disease; myocarditis)

Long term sequelae

- Autoimmune thyroiditis, vitiligo, alopecia areata / universalis, autoimmune haemolytic anaemia, systemic lupus erythematosus and type 1 diabetes which may appear months to years after the acute phase

**also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome*

Acute generalised exanthematous pustulosis (AGEP)[6]

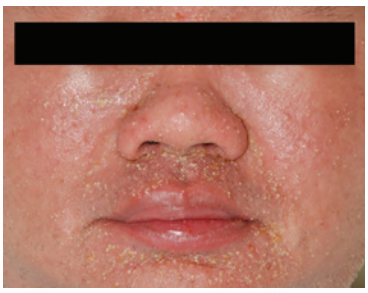


Figure 5. AGEP: Facial oedema with pinpoint non-follicular pustules.

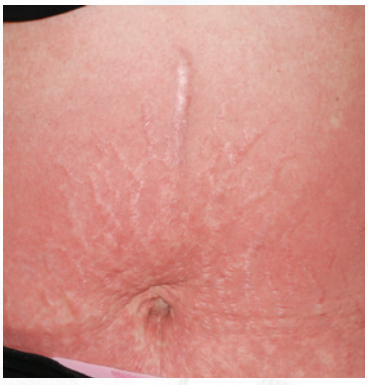


Figure 6. AGEP: Diffuse bright red erythema on the abdomen with non-follicular pinpoint pustules on the flanks.

Commonly implicated drugs

- Antibiotics (sulphonamides, beta-lactam antibiotics, macrolides, quinolones)
- Antifungals (terbinafine)
- Hydroxychloroquine
- Calcium-channel blockers

Onset

- Usually within hours to a few days (average 3 days) of drug initiation

Clinical characteristics

- Skin eruptions are often accompanied by fever > 38.0°C, leucocytosis and eosinophilia
- Acute onset of widespread non-follicular, sterile, pinhead-sized pustules on a background of oedematous erythema
- Eruption generally begins on face or intertriginous areas and rapidly extends to the trunk and limbs with a diffuse or patchy distribution
- Mucosal involvement is unusual and if present, is usually limited to lip erosions

Long term sequelae

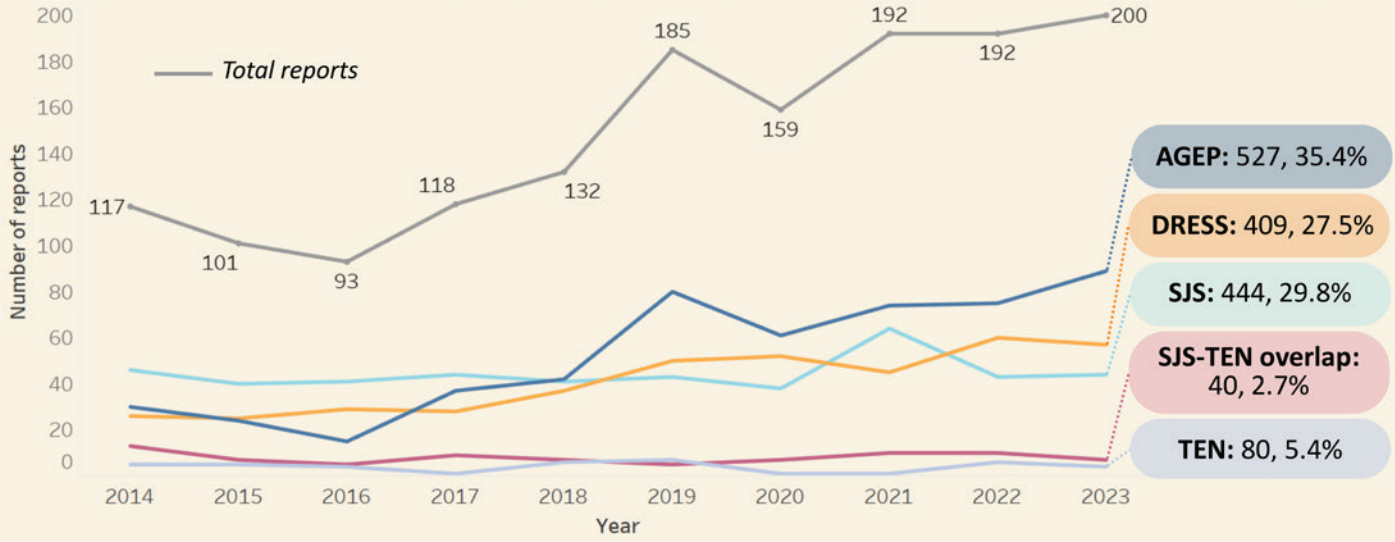
- Spontaneous resolution of cutaneous reactions through desquamation within 2 to 3 weeks upon drug discontinuation

References:
5. UpToDate DRESS; accessed 1 Aug 2024
6. UpToDate AGEP; accessed 1 Aug 2024

Review of SCAR reports received by HSA (2014 – 2023)

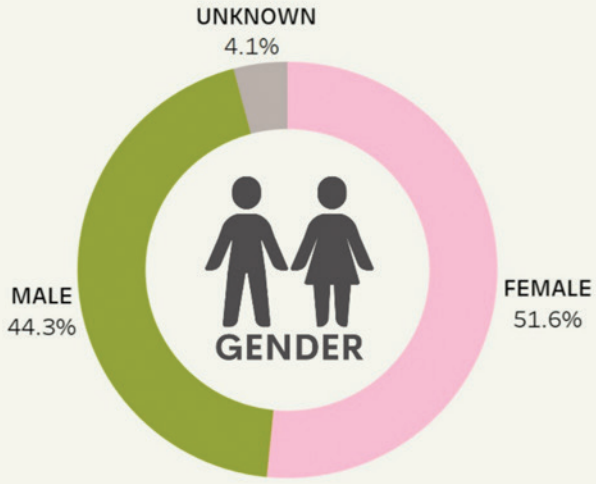
1,489 REPORTS OF SCAR^ RECEIVED OVER THE PAST 10 YEARS

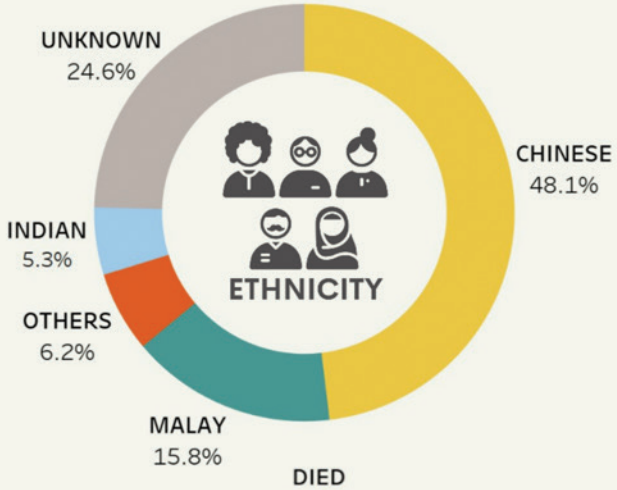
SCAR reports have increased over the years, mainly driven by an increase in the number of AGEP and DRESS reports.

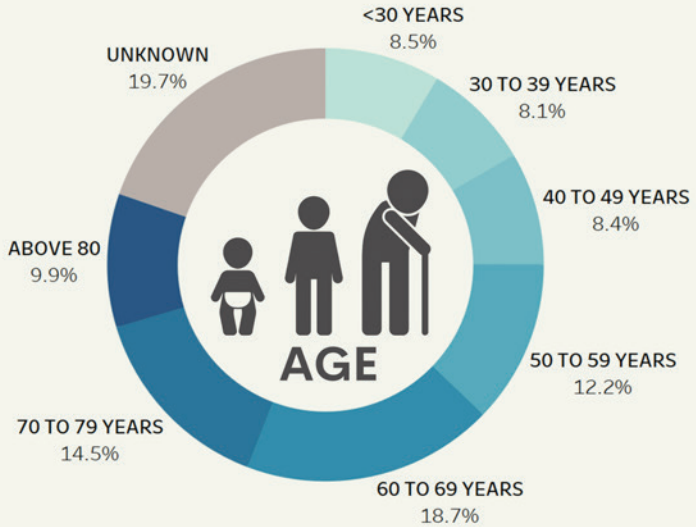


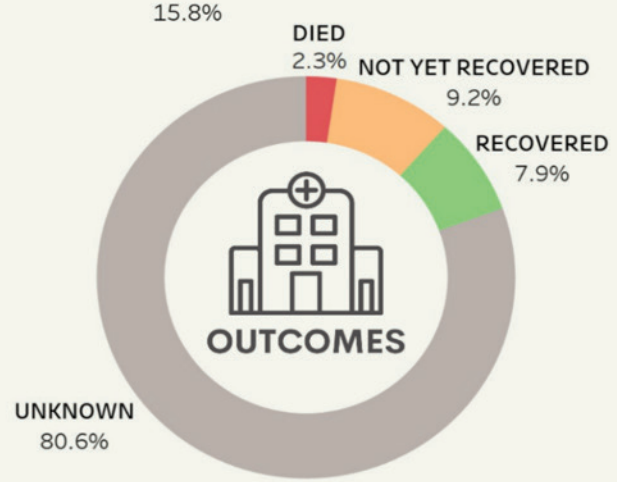
^Some reports may include more than one type of SCAR e.g., DRESS and SJS.

PATIENT DEMOGRAPHICS AND OUTCOMES









Outcomes at the time of reporting were provided in only 289 (19.5%) reports.

TOP 5 DRUG CLASSES

1. **Antibiotics**

2. **Antiepileptics**

3. **Anti-gout preparations**

4. **Drugs for acid-related disorders**

5. **Non-steroidal anti-inflammatory drugs (NSAIDs)**

This trend has remained relatively consistent over the past 10 years, except in 2021 and 2022.

In 2021, **vaccines** were one of the top five drug classes associated with SCAR, which was largely attributed to heightened awareness of adverse event reporting and the high number of COVID-19 vaccines administered. As at 31 December 2023, HSA received 12 reports of SCAR following administration of 17.6 million doses of COVID-19 vaccines. This comprised four reports of AGEP, three reports of DRESS, two reports of SJS and one report of AGEP-DRESS with Pfizer-BioNTech/Comirnaty Original COVID-19 (tozinameran) vaccine; one report of SJS with Moderna/Spikevax Original COVID-19 (elasomeran) vaccine; and one report of SJS with Moderna/Spikevax Bivalent Original/Omicron COVID-19 (elasomeran / imelasomeran) vaccine.

In 2022, **antineoplastic monoclonal antibodies** were one of the top five drug classes associated with SCAR, contributed by reports associated with immune checkpoint inhibitors (ICI) such as pembrolizumab (n=6) and nivolumab (n=2). Over the past decade, majority of the reports in this drug class were ICI-induced SJS/TEN (n=23/29, 79.3%), affecting patients aged 45 to 81 years. Of these, nine reports had other concomitant suspected drugs, including omeprazole (n=6). SJS/TEN occurred at a median of 102 days (Interquartile range, IQR: 12.5-160 days) following initiation of ICIs. As reported in the literature, ICI-triggered SJS/TEN can have a delayed onset, manifesting weeks to months after initiation, unlike the usual drug-induced SJS/TEN which commonly occurs within 5 to 28 days after exposure.[7,8] The mechanism of ICI resulting in SJS/TEN is unclear; it is postulated that cytotoxicity induced by ICI can result in T-cells targeting keratinocytes, leading to apoptosis.[9] ICI-induced cases could also be severe immune-mediated bullous eruptions which mimic SJS.

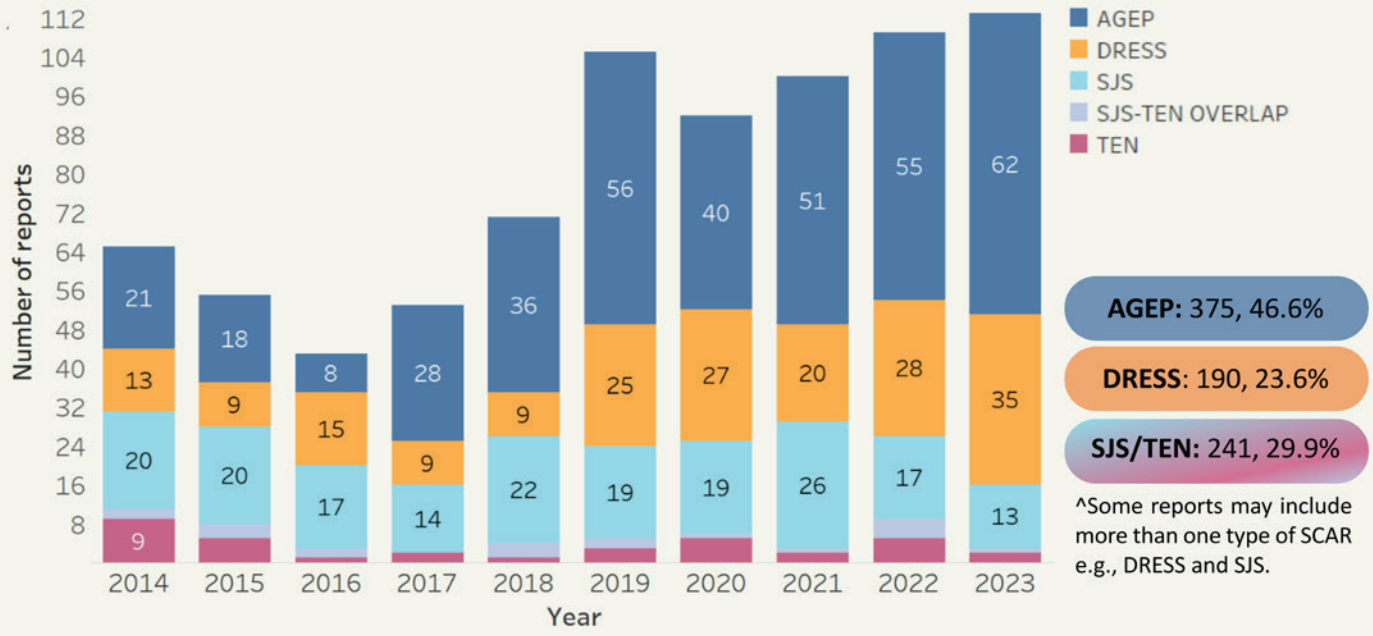
TOP 10 CULPRIT DRUGS

	AGEP	DRESS	SJS, SJS-TEN overlap and TEN
1	Co-amoxiclav	Allopurinol	Allopurinol
2	Amoxicillin	Co-trimoxazole	Co-trimoxazole
3	Piperacillin-Tazobactam	Omeprazole	Omeprazole
4	Clindamycin	Vancomycin	Etoricoxib
5	Omeprazole	Phenytoin	Co-amoxiclav
6	Meropenem	Rifampicin	Piperacillin-Tazobactam
7	Co-trimoxazole	Piperacillin-Tazobactam	Ciprofloxacin
8	Ceftriaxone	Meropenem	Lamotrigine
9	Cefazolin	Sulfasalazine	Phenytoin
10	Benzylpenicillin	Co-amoxiclav	Amoxicillin

References:
7. *Dermatol Online J. 2020 Aug 15;26(8):13030/qt8fc428f6*
8. *J Am Acad Dermatol. 2020 Oct;83(4):1130-1143*
9. *J Cutan Med Surg. 2021 Jan-Feb;25(1):59-76*

SCAR REPORTS WITH ANTIBIOTICS

Antibiotics were implicated in 805 SCAR reports^ and made up most of the top 10 culprit drugs for AGEP.

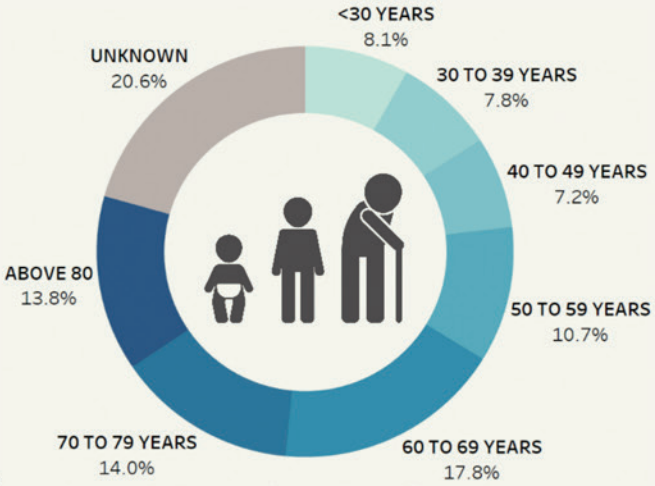


GENDER

Females 52.4% | Males 44.0% | Unreported 3.6%

LATENCY (MEDIAN)

AGE



The median age of patients affected was 63 years (IQR: 44 – 75 years).

Top culprit antibiotic

Co-trimoxazole was the top antibiotic associated with DRESS and SJS/TEN reports. Based on sales data and outpatient prescriptions from public healthcare institutions over the past five years, the local reporting rate of co-trimoxazole-associated SCAR was estimated at 1.3 per 1,000 new users. Risk factors for co-trimoxazole-induced SCAR include human immunodeficiency virus (HIV) infection, duration of therapy longer than 10 days and prophylactic use.[10] Various human leukocyte antigen (HLA) alleles have been associated with the risk of co-trimoxazole-induced SCAR, including HLA-B*38:02 and HLA-B*15:02 with SJS/TEN in Taiwanese and Thais, as well as HLA-B*13:01 with DRESS among Chinese, Thais and Malaysians.[11,12]

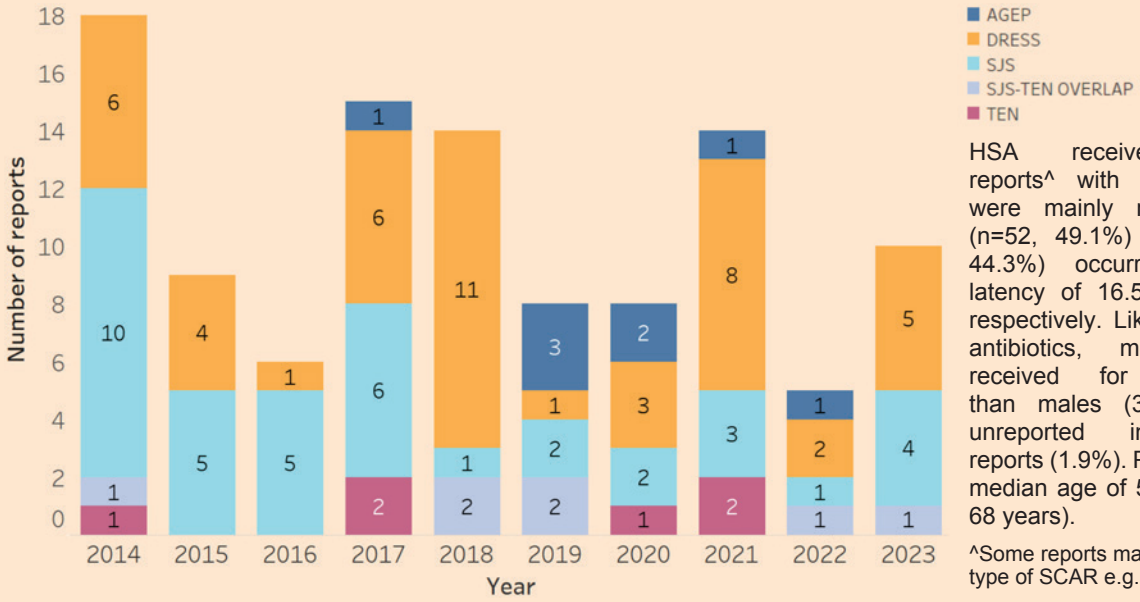
Local reporting rate
Co-trimoxazole-associated SCAR

1.3

per 1,000 new users

References:
10. *Dermatology. 2023;239(6):966-975*
11. *Clin Pharmacol Ther. 2020;108(5):1078-1089*
12. *Front Pharmacol. 2023;14:1183491*

SCAR REPORTS WITH ANTIEPILEPTICS



HSA received 106 SCAR reports^ with antiepileptics. These were mainly reports of SJS/TEN (n=52, 49.1%) and DRESS (n=47, 44.3%) occurring at a median latency of 16.5 days and 32 days respectively. Like SCAR reports with antibiotics, more reports were received for females (59.4%) than males (38.7%), with gender unreported in the remaining reports (1.9%). Patients affected had a median age of 52 years (IQR: 28.5 – 68 years).

^Some reports may include more than one type of SCAR e.g., DRESS and SJS.

Top 3 culprit antiepileptics for SJS, SJS-TEN overlap and TEN

1. Lamotrigine
2. Phenytoin
3. Carbamazepine

Based on the number of reports received over the past 10 years, the top 3 antiepileptics associated with SJS, SJS-TEN overlap and TEN were lamotrigine (LT), phenytoin (PT) and carbamazepine (CBZ), with estimated local reporting rates of 2.5, 3.3 and 3.9 per 1,000 new users respectively. The rate for LT is similar to a post-marketing surveillance study conducted in patients with bipolar disorder in Japan, where two out of 989 patients developed SJS within eight weeks of starting LT, whereas the incidence of CBZ-induced SJS/TEN in Taiwan has been cited to be around 2.5 per 1,000 new users.[13,14] In comparison, a matched case-control study conducted using a large-scale employment-based claims database in Japan found that the 90-day cumulative incidences of SJS/TEN per 1,000 new users were 0.843 (95% confidence interval, CI 0.317 – 2.25) for LT, 0.662 (95% CI 0.093 – 4.70) for PT and 0.938 (95% CI 0.469 – 1.88) for CBZ.[15] Incidence rates across studies may not be directly comparable due to different methodologies employed. CBZ and PT have also been associated with higher risks of SCAR among Asians as compared to Europeans due to different HLA allele frequencies.[16,17]

Local reporting rates of SJS, SJS-TEN overlap and TEN

Lamotrigine	Phenytoin	Carbamazepine
2.5	3.3	3.9

per 1,000 new users

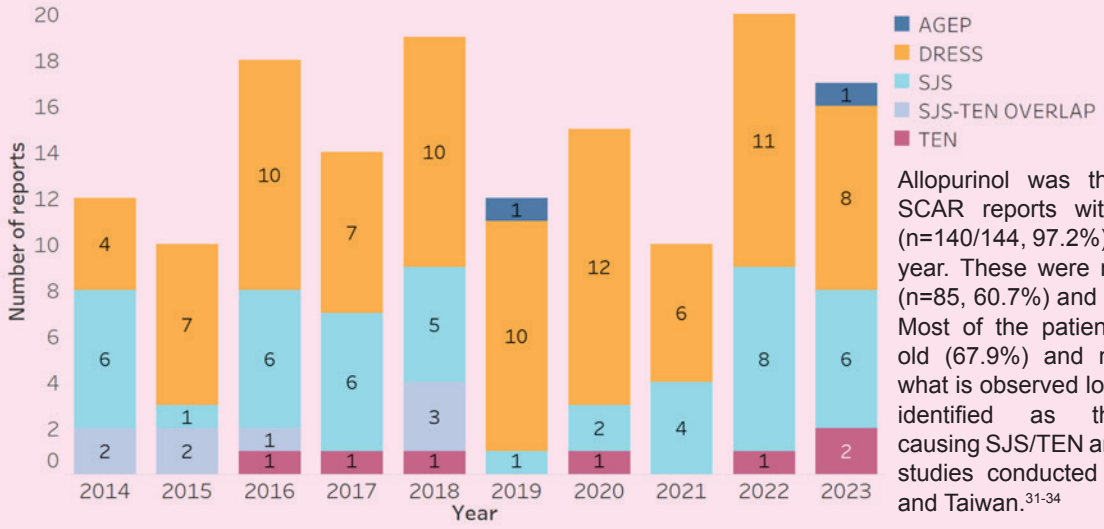
CBZ-induced SJS/TEN is associated with HLA-B*15:02 among Han Chinese and Southeast Asians, but not among Japanese or Europeans of non-Asian ancestry.[18-23] SJS/TEN with PT and oxcarbazepine, which are structurally similar to CBZ, were also found to be associated with HLA-B*15:02 among Han Chinese and Southeast Asians.[18,24-26] Since 2013, HLA-B*15:02 genotype testing prior to initiation of CBZ in new patients has been the standard of care in Singapore.[27] It was also recommended that phenytoin should not be prescribed to patients who are positive for the allele. **Since these developments, the number of CBZ-induced SJS/TEN has dropped dramatically to an average of 1.2 reports per year between 2014 and 2023 compared to 15 reports per year in the previous decade.** Five patients tested positive for the HLA-B*15:02 allele in the 12 SJS/TEN cases reported in the past 10 years.

Seventeen reports of **LT-induced SJS/TEN** were received in the past 10 years. Patients who developed SCAR with LT were younger, with 68.2% below 30 years old. One patient developed SJS 16 days after LT was initiated at a dose four times higher than recommended in the package insert[28] (i.e. 25 mg once daily as monotherapy) and three other patients developed SJS/TEN after rapid dose titration. **The risk of a severe rash from LT may be reduced by over 10-fold with a slow titration schedule such as 25 mg increments every fortnight.**[17] Higher reporting rates of fatal SCAR cases related to LT have been observed in Japan as compared to other countries worldwide, including France, Germany, India and China.[29] Majority (71%) of these cases in Japan showed evidence of non-compliance to the guidance for dosing regimen and dose escalation in the package insert. While several HLA alleles such as HLA-B*15:02 and HLA-A*24:02 have been identified as risk factors for LT-induced SJS/TEN in Asians, a case series conducted locally did not identify a single major HLA-related genetic risk factor for LT-induced SCAR.[30]

References:

13. *Neuropsychiatr Dis Treat. 2017;13:1441-1448.*
14. *Per Med. 2005;2(3):225-237*
15. *Allergol Int. 2021;70(3):335-342.*
16. *Seizure. 2021;91:332-338.*
17. *Seizure. 2019;72:61-70.*
18. *Nature. 2004;428(6982):486*
19. *Epilepsia. 2007;48(5):1015-1018*
20. *Epilepsia. 2008;49(12):2087-2091*
21. *Indian J Dermatol Venereol Leprol. 2009;75(6):579-582*
22. *Pharmacogenomics 2008; 9: 1617–22*
23. *Pharmacogenomics J 2006; 6: 265–8*
24. *Neurology. 2017;88(1):78-86*
25. *Pharmacogenomics J. 2017;17(2):170-173*
26. *Pharmacogenomics. 2010;11(3):349-356*
27. *https://www.hsa.gov.sg/announcements/safety-alert/recommendations-for-hla-b-1502-genotype-testing-prior-to-initiation-of-carbamazepine-in-new-patients*
28. *Singapore package insert for Lamictal®. Approved 26 Oct 2023*
29. *Ther Clin Risk Manag. 2017;13:897-903*
30. *Ann Acad Med Singap. 2021;50(12):915-918*

SCAR REPORTS WITH ALLOPURINOL



Allopurinol was the culprit for almost all SCAR reports with anti-gout preparations (n=140/144, 97.2%), averaging 14 reports per year. These were mainly reports of DRESS (n=85, 60.7%) and SJS/TEN (n=60, 42.9%)^. Most of the patients were above 60 years old (67.9%) and male (55.7%). Similar to what is observed locally, allopurinol has been identified as the top culprit drug causing SJS/TEN and DRESS across multiple studies conducted in Korea, Portugal, Italy and Taiwan.[31-34]

^Some reports may include more than one type of SCAR e.g., DRESS and SJS.

Local reporting rate

2.6

per 1,000 new users

Comparable to rates reported in Taiwan (estimated at 3 per 1,000 users)[35] and Malaysia (2.5 per 1,000 new users)[36]

Risk factors for allopurinol-induced SCAR

- *Presence of HLA-B*58:01 (among Han Chinese, Koreans, Thais and Vietnamese)[37-40]*
- *Older age*
- *Female sex*
- *Chronic renal and cardiovascular diseases.[40-42]*
- *Initial dose of allopurinol >100 mg/day*

Drug-specific recommendations to mitigate the risk of SCAR

Allopurinol

- Initiate in patients with gout who meet the treatment criteria for urate lowering therapy[44]
- Start at a low dose (typically 50 – 100 mg/day) and slowly titrate upwards based on serum urate and clinical features in 50 – 100 mg increments every four to eight weeks
- While routine genotyping before initiation of allopurinol in all patients with gout is not recommended, consider HLA-B*58:01 genotyping in patients who are assessed to be at a higher risk of allopurinol-induced SCAR such as those with renal impairment or older age, taking cost of testing into consideration

Carbamazepine

- HLA-B*15:02 genotype testing prior to initiation of carbamazepine in new patients has been the standard of care in Singapore since 2013[27]
- Carbamazepine, even short courses, should not be prescribed before HLA-B*15:02 test results are obtained[27]
- Avoid use of carbamazepine and phenytoin in patients who are positive for HLA-B*15:02
- Genetic testing should not substitute appropriate clinical vigilance and patient management. Although rare, patients negative for HLA-B*15:02 could still develop SJS/TEN as the role of other factors such as drug dose, concomitant medications and co-morbidities have not been studied

Lamotrigine

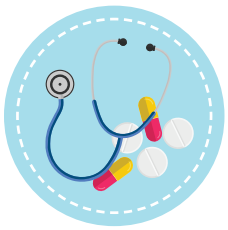
- Adhere to recommendations from the package inserts or drug information references to start at a low dose and slowly titrate upwards with close monitoring until the optimal response is achieved[28,45]
- Consider if dose adjustments are required when interacting medications, such as valproate, phenytoin or carbamazepine, are removed or added

References:

31. *J Allergy Clin Immunol Pract. 2021;9(2):929-936.e7*
32. *Expert Opin Drug Saf. 2020;19(6):763-769*
33. *Pharmacoepidemiol Drug Saf. 2016;25(2):196-203*
34. *J Formos Med Assoc. 2022;121(8):1397-1405*
35. *JAMA Intern Med. 2015;175(9):1550-1557*
36. *Br J Clin Pharmacol. 2022;88(8):3782-3788*
37. *BMJ. 2015;351:h4848*
38. *Pharmacogenet Genomics 2011;21:303-307*
39. *Pharmacogenet Genomics. 2017;27(7):255-263*
40. *Arthritis Res Ther. 2020;22(1):182*
41. *Ann Rheum Dis. 2018;77(8):1187-1193*
42. *CMAJ. 2019;191(39):E1070-E1077*
43. *Front Pharmacol. 2022;13:832048*
44. *https://www.go.gov.sg/acg-gout-achieving-management-goal*
45. *Psychopharmacol Bull. 2021;51(2):96-114*

SCAR WATCH

An infographic guide on mitigating the risk of SCAR



Prescribe medications

- Prescribe appropriate drug(s) and starting dose for patient's medical condition(s).

Consider risk factors for SCAR[43]

- Female
- History of drug allergy
- Family history of SCAR
- Comorbidities such as malignancy, human immunodeficiency virus (HIV), infection and systemic lupus erythematosus (SLE)
- Commonly implicated drugs for SCAR

Counsel patient on signs and symptoms of SCAR

- Fever
- Flu-like symptoms (sore throat, malaise, myalgia)
- Conjunctivitis
- Rash
- Lip/oral mucosa erosions
- Lymphadenopathy

Monitor patient for SCAR

- Stay vigilant for presenting symptoms of SCAR in patient.

If SCAR is suspected, identify and withdraw the offending drug

- The latency of SCAR differs depending on the type of SCAR and offending drug.
- Majority of SCAR occur within 8 weeks of drug initiation.
- Consider other health products taken by the patient which may contribute to SCAR.

Refer to a specialist or hospital for further review

- Early diagnosis of SCAR is associated with improved survival.

Acknowledgements

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