



Review

Allopurinol-Related Severe Cutaneous Adverse Reactions: A Narrative Review

Edoardo Cipolletta ^{1,2,*} , Satveer K. Mahil ³, Catherine H. Smith ³ and Abhishek Abhishek ¹

¹ Academic Rheumatology, University of Nottingham, Nottingham NG5 1PB, UK

² Department of Internal Medicine, Marche University Hospital, 60126 Ancona, Italy

³ St. John's Institute of Dermatology, King's College London and Guy's & St Thomas' NHS Foundation Trust, London SE1 7EH, UK; satveer.mahil@kcl.ac.uk (S.K.M.); catherine.smith@kcl.ac.uk (C.H.S.)

* Correspondence: edoardocipolletta@gmail.com; Tel.: +44-7821-284881

Abstract

Allopurinol, the most used urate-lowering drug for the treatment of gout, is associated with rare but life-threatening severe cutaneous adverse reactions (SCARs) such as Stevens–Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, but not Acute Generalised Exanthematous Pustulosis (AGEP). They are characterised by severe skin and systemic involvement and are associated with substantial morbidity and a high risk of mortality. This narrative review summarises evidence on the clinical presentation, epidemiology, risk factors, and preventive strategies for allopurinol-induced SCARs. Key risk factors include the presence of the *HLA-B*58:01* allele, renal impairment, older age, female sex, heart disease, higher starting doses of allopurinol, and certain ethnicities, e.g., South Asian, Han Chinese, and African populations likely due to the higher prevalence of the *HLA-B*58:01* allele. Risk mitigation strategies include genetic testing for *HLA-B*58:01* in high-risk ethnic groups and avoiding allopurinol in those that are positive for the *HLA-B*58:01* allele, starting allopurinol at a low-dose (e.g., 50–100 mg/day) and up-titrating it gradually at 4-week intervals, and avoiding high-dose allopurinol in those with risk factors (e.g., chronic kidney disease stage ≥ 3). In addition, risk stratification using prediction tools may enable a safer use of allopurinol.

Keywords: allopurinol; severe cutaneous adverse reactions; side effects; epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms syndrome; Stevens–Johnson syndrome; gout; hyperuricaemia



Academic Editor: David Mount

Received: 15 December 2025

Revised: 15 February 2026

Accepted: 24 February 2026

Published: 27 February 2026

Copyright: © 2026 by the authors.

Published by MDPI on behalf of the Gout, Hyperuricemia and Crystal Associated Disease Network. Licensee MDPI, Basel, Switzerland. This article

is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Allopurinol is a widely prescribed medication primarily used to manage gout, prevent tumour lysis syndrome in people with cancer, and treat recurrent uric acid nephrolithiasis in people with hyperuricosuria. Allopurinol remains the first-line urate-lowering drug for gout worldwide [1]. Emerging evidence suggests potential cardiovascular and renal benefits in this population, further emphasising the clinical importance of this drug in gout [2,3].

Despite its therapeutic benefits, allopurinol has been associated with rare but potentially fatal severe cutaneous adverse reactions (SCARs) [4–6]. SCARs include a spectrum of life-threatening conditions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens–Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis

(TEN). These reactions are characterised by extensive skin/mucosal involvement and systemic symptoms that can lead to substantial morbidity and mortality [7–9].

The risk of SCARs due to allopurinol is an important concern for both prescribing physicians and patients [10,11]. The mortality rate associated with SJS/TEN can be as high as 25–35% [7,12–14]. DRESS syndrome, while less common, is also associated with up to 10% risk of mortality, including multi-organ failure [8,9]. Given the seriousness of these conditions, it is crucial to understand risk factors, mechanisms, clinical presentation, risk mitigation and management of allopurinol-induced SCARs. This narrative review aims to synthesise the existing literature on the subject, providing a comprehensive overview that can guide clinicians in mitigating risks and improving patient outcomes.

2. Mechanism of Action and Pharmacokinetics of Allopurinol

Allopurinol reduces serum urate by inhibiting xanthine oxidase, the enzyme responsible for converting hypoxanthine to xanthine and subsequently to uric acid [15].

Allopurinol is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 1.5 h [15]. It is primarily metabolised in the liver into oxypurinol, which retains the ability to inhibit xanthine oxidase, contributing to its therapeutic effects [15,16]. Oxypurinol is renally excreted. Due to its long half-life (23 h), oxypurinol can accumulate in the presence of renal impairment, increasing the risk of SCARs [15,16].

3. Severe Cutaneous Adverse Reactions—Definition and Clinical Manifestations

SCARs encompass a range of hypersensitivity reactions that can occur in response to medications, including allopurinol. Their clinical manifestations vary depending on the type and severity of the reaction. The types of SCARs are:

- Stevens–Johnson Syndrome (SJS);
- Toxic Epidermal Necrolysis (TEN);
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome;
- Acute Generalised Exanthematous Pustulosis (AGEP).

Only SJS/TEN and DRESS syndrome have been associated with allopurinol [9,17,18], while there is only weak evidence supporting its role as a trigger of AGEP, and this is not discussed in the current review [19,20]. Table 1 summarises the main clinical characteristics of these syndromes.

Table 1. Main clinical characteristics of SJS/TEN and DRESS syndrome.

	SJS	SJS–TEN Overlap	TEN	DRESS Syndrome
General description	Severe mucocutaneous reaction with epidermal necrosis			Multisystem drug-induced hypersensitivity with skin rash, systemic involvement, and eosinophilia
Type of lesions	Ill-defined erythematous macules, flaccid bullae, epidermal detachment with positive Nikolsky sign (i.e., slight rubbing of the skin results in epidermal detachment)			Maculopapular rash progressing to coalescing erythema; purpura, plaques, pustules, target-like lesions; facial oedema
Distribution	Begins on face and chest, spreads symmetrically. Both skin and mucosae are involved			Trunk and extremities; symmetric; facial oedema is common (70% of cases). Mucosal involvement occurs in ≤50% of patients and it is usually mild
BSA involved	≤10%	11–30%	>30%	Often >50% of BSA; however, skin detachment is rare

Table 1. Cont.

	SJS	SJS–TEN Overlap	TEN	DRESS Syndrome
Histopathological features	Full-thickness epidermal necrosis, separation at dermo-epidermal junction; mild T-cell predominant dermal infiltrate			Spongiosis, interface dermatitis, lymphocytic and eosinophilic infiltrate; variable systemic involvement
Systemic involvement	Fever, myalgia, conjunctivitis, mucosal erosions, risk of multiorgan failure			Fever, lymphadenopathy, hematologic abnormalities (eosinophilia, leucocytosis), liver, kidney, or lung involvement
Onset after drug exposure	1–3 weeks (rarely up to 2 months)			2–8 weeks (up to 12 weeks)

BSA: Body Surface Area; **SJS:** Stevens–Johnson Syndrome; **TEN:** Toxic Epidermal Necrolysis; **DRESS:** Drug Reaction with Eosinophilia and Systemic Symptoms.

3.1. SJS/TEN

SJS and TEN are characterised by epidermal detachment and mucosal involvement [21–24]. The main distinction between SJS and TEN is the body surface area (BSA) involved [25]: $\leq 10\%$ SJS, 11–30% SJS–TEN overlap, and $>30\%$ TEN.

Early nonspecific symptoms of SJS/TEN include fever, myalgia, sore throat, cough, and conjunctivitis, often mistaken for a viral infection [21,22]. Lesions typically start on the face and chest before spreading to other areas and are symmetrically distributed. Within days, a painful rash develops. Early lesions typically begin with ill-defined, coalescing, erythematous macules, which rapidly evolve into flaccid bullae, skin detachment, and epidermal necrosis. Mucosal involvement is common, leading to painful lesions in the eyes, mouth, nose, genitals, respiratory tract and gastrointestinal system. The Nikolsky sign—pressure on the skin resulting in its detachment—is often positive [21,22]. Skin tenderness is prominent in SJS/TEN, and the diagnosis must be suspected in anyone who presents with a painful, mucocutaneous eruption with an attributable drug exposure history. The acute phase lasts for 7–9 days from initial symptoms, and the skin re-epithelizes over 1–3 weeks [24].

The overall mortality rate for SJS/TEN during the acute episode is 23%, varying from 12 to 49% across the spectrum of SJS/TEN severity [7]. TEN has a higher mortality rate than SJS due to the extensive skin loss, which can lead to severe dehydration, infections, and systemic complications such as multiorgan failure [23]. At one year, the overall mortality for SJS/TEN increased to 34% [7]. Among survivors, mucocutaneous and psychological sequelae are frequently reported [23,26].

Most cases of SJS/TEN are drug-induced, and it usually occurs within 5 to 28 days (less often up to two months) of initiation of a new treatment [18,21,22,27]. Allopurinol is classified among high-risk drugs (Table 2).

Table 2. Medications with a significant association with the development of a severe cutaneous adverse reaction according to the EuroSCAR-Study [18].

Drug Class	Drug Name
Non-steroidal anti-inflammatory drugs (NSAIDs)	Acetic acid NSAIDs (e.g., Indomethacin, Etodolac, Ketorolac), Oxicam-NSAIDs (e.g., Meloxicam, Piroxicam)
Urate-lowering drugs	Allopurinol
Antibiotics	Amino-penicillin (e.g., amoxicillin), Cephalosporins, Macrolides, Quinolones, Tetracycline, Co-trimoxazole and other Sulfonamides
Anticonvulsants	Carbamazepine, Phenytoin, Lamotrigine
Antiretroviral drugs	Nevirapine
Antidepressants	Sertraline

The diagnosis of SJS/TEN is primarily clinical, based on the extent of skin detachment and mucosal involvement, systemic symptoms, and a recent history of new drug initiation.

Skin biopsy can aid in the diagnosis, revealing characteristic findings such as full-thickness epidermal necrosis and separation of the epidermis at the dermo-epidermal junction as the disease progresses [28,29] and excluding other causes of bullous diseases. The dermal inflammatory infiltrate is typically mild and consists primarily of T lymphocytes, and direct immunofluorescence is negative [28,29].

Since SJS/TEN is primarily a drug-induced disease, the identification of the offending drug is a crucial part of the diagnostic process. Even though this step is often straightforward, sometimes it may not be easy in patients who have started multiple medications or in those with a concurrent infection. The algorithm of drug causality for epidermal necrolysis (ALDEN) has been developed as a tool for assessing drug causality [30]. It considers six parameters:

- Drug notoriety for causing SCARs;
- Drug half-life (i.e., drug present in the body at symptoms' onset);
- Latency (i.e., delay from initial drug intake to onset of symptoms);
- Pre-challenge/rechallenge and de-challenge results;
- Absence of alternative explanations.

The cumulative score ranges from −12 to 10. Five levels of certainty regarding the diagnosis are available: very unlikely (<0), unlikely (0–1), possible (2–3), probable (4–5), and very probable (≥6) SJS/TEN. For cases with no attributable drug exposure (10–15%), other investigations are needed. These include: 1) toxicological analysis because occult drug intake may have occurred; 2) tests for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* and Enterovirus; 3) antinuclear, anti-DNA, and anti-ENA autoantibodies for connective tissue disease; and 4) anti-epidermal-specific antibodies if an autoimmune bullous disease is suspected [31].

The extent of skin involvement is the most important parameter to assess the severity of SJS/TEN. The Lund–Browder chart is commonly used to estimate the extent of skin detachment total body surface area (BSA). Alternatively, the “rule of nines” can be used: the head and each upper limb represent 9% of BSA, and each lower limb and the anterior and posterior trunk each represent 18% of BSA.

Other prognostic tools can be used to predict the risk of mortality:

- **SCORTEN**: The standard prognostic tool, based on seven clinical/lab variables (including age, affected BSA > 10%, tachycardia, malignancy, urea, bicarbonate, and glucose) [32]. It predicts mortality on days 1 and 3.
- **ABCD-10**: A simpler five-factor score (Age ≥ 50, Bicarbonate < 20 mmol/L, active Cancer, Dialysis, and affected BSA > 10%) [33]. Points correlate with increasing mortality.

3.2. Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

DRESS syndrome—also known as drug-induced hypersensitivity syndrome (DIHS)—is a multisystem disorder that includes severe skin rash, fever, eosinophilia, leucocytosis, and internal organ involvement, such as hepatitis, nephritis, acute lung injury, and myocarditis [34,35]. DRESS syndrome can develop after weeks or months of allopurinol therapy—usually within 2–8 weeks, but up to 12 weeks [9,34–36].

DRESS syndrome may initially present with a prodromal phase characterised by non-specific findings such as fever, malaise, and lymphadenopathy followed by cutaneous manifestations [9,34,37]. Typically, there is a maculopapular rash that progresses to coalescing erythema with or without accompanying features such as purpuric lesions, infiltrated plaques, pustules, exfoliative dermatitis, and target-like lesions. Lesions are symmetrically distributed on the trunk and the extremities [28,29]. Facial oedema is striking and present in most cases. Nearly 80% of patients have a >50% involvement of the BSA. Mucosal

involvement can be seen in up to 50% of cases. However, it is typically mild, in contrast with SJS/TEN, and skin detachment is rarely seen [9,34,35,37].

Characteristically, skin features are accompanied by systemic symptoms such as fever, lymphadenopathy, and hematologic abnormalities such as eosinophilia, leucocytosis, neutrophilia, or lymphocytosis [9,34,37]. The extent of other organ involvement varies. Involvement of at least one internal organ system occurs in approximately 90% of patients [9,34,37], and up to 20% of patients may have multi-organ involvement [9,34,37].

Of note, the clinical course of the cutaneous manifestations may not parallel that of internal organs [9,34,37], thus increasing the complexity of diagnosing DRESS syndrome. DRESS syndrome is often misdiagnosed as atypical systemic lupus erythematosus, lymphoma, and infectious diseases, depending on which organ involvement is dominant in the clinical presentation. Therefore, DRESS should be suspected in a patient who has received a new drug in the previous 2 to 8 weeks and presents with an acute cutaneous eruption associated with systemic involvement, such as fever, lymphadenopathy, eosinophilia, or abnormal organ function tests. Early recognition is critical, as delays in diagnosis and treatment can lead to fatal outcomes.

The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system is one of the most adopted diagnostic criteria for DRESS syndrome [9]:

- Fever $>38.5^{\circ}\text{C}$ (core) or $>38^{\circ}\text{C}$ (axillary);
- Enlarged lymph nodes in at least two different body areas;
- Eosinophilia $\geq 0.7 \times 10^9$ or $\geq 10\%$ if leukopenia;
- Atypical lymphocytes;
- Skin involvement (extent $\geq 50\%$ of BSA, rash suggestive of DRESS);
- Skin biopsy suggestive of DRESS;
- Organ involvement (e.g., >2 -fold elevation of liver enzymes on at least 2 different days);
- Resolution >15 days;
- Exclusion of other causes.

The cumulative score ranges from -4 to 9 . Four levels of certainty regarding the diagnosis are available: excluded (<2), possible ($2-3$), probable ($4-5$), and definite (≥ 6) DRESS syndrome.

Confidence in the diagnosis may be further supported by positive patch tests and/or in vitro tests such as a positive lymphocyte proliferation assay [38,39].

Relapses are common, often triggered by other unrelated medications, so unnecessary drug exposure should be avoided in patients with a prior history of DRESS syndrome.

The mortality rate among individuals with DRESS is between 2 and 10% [8,37]. Older age, severe organ involvement, and multiorgan failure are the main predictors of mortality [8]. The extent of skin involvement and internal organ involvement are the most important parameters to evaluate the severity of DRESS syndrome [40].

- Mild DRESS syndrome can be defined as a modest elevation of liver enzymes (AST/ALT <4 -fold the upper normal limit) without evidence of renal, pulmonary, or cardiac involvement;
- Moderate DRESS syndrome is defined as non-life threatening organ involvement such as cytopenias (i.e., haemoglobin $7-10$ g/dL, neutrophils count between 500 and 1500 cells/mcl, platelets between 50,000 and 100,000 units/mcl), non-severe acute kidney injury (creatinine <3 mg/dL or <1.5 the upper normal limit), and elevation of liver enzymes (AST/ALT $>4-15$ -fold the upper normal limit or alkaline phosphatase $>3-5$ -fold the upper normal limit);
- Severe DRESS syndrome is characterised by life threatening organ involvement such as severe cytopenias, haemophagocytosis syndrome, severe acute kidney injury, acute liver failure, pulmonary or cardiac involvement, and multiorgan involvement.

4. Epidemiology of Allopurinol-Induced SCARs

The incidence of allopurinol-induced SJS/TEN varies globally, mainly influenced by genetic predisposition. In populations with a high prevalence of the *HLA-B*58:01* allele, such as the Han Chinese, the incidence of allopurinol-induced SJS/TEN can be as high as 4–5 per 1000 new allopurinol users per year [14], while it is estimated to be 0.7 per 1000 new allopurinol users per year in the USA [13] and 0.4 per 1000 allopurinol users in the UK [41].

The epidemiology of allopurinol-related DRESS syndrome is less clear-cut. DRESS syndrome is estimated to occur in 1–2 per 100,000 patients per year [42,43]. The risk of developing DRESS syndrome varies from drug to drug [9,44,45]. Allopurinol is among high-risk medications, and therefore the incidence of DRESS syndrome is estimated to range between 1 in 1000 to 1 to 10,000 new users, as for other high-risk medications [46].

5. Pathophysiology of Allopurinol-Induced SCARs

SCARs are type IV hypersensitivity adverse drug reactions. As such, they are mediated by the activation and expansion of T cells. They are typically delayed in onset by at least 48 to 72 h and up to several weeks following exposure to the culprit drug. Although SCARs are primarily driven by T-cell-mediated immune mechanisms, the pathological processes are complex and not fully elucidated. In addition to established immunological pathways, non-immunologic factors and the potential role of remote or latent infections may contribute to disease onset and severity, indicating a multifactorial pathogenesis [47]. A brief description of SCAR pathogenesis is described below, while Cadot et al. provide an up-to-date and in-depth review of these pathways [47].

5.1. Pathogenesis of SJS/TEN

Many studies have reported an association of certain HLA haplotypes such as *HLA-B*58:01* with an increased risk of SJS/TEN among allopurinol initiators [48–50]. Individuals with this genetic marker are more likely to experience hypersensitivity reactions due to differences in how their immune system processes the drug and its metabolites.

In susceptible people, allopurinol and its metabolites trigger an immune response against HLA self-peptides [50–52]. The main effectors in SJS/TEN are CD8+ cytotoxic T cells, with the subsequent release of cytotoxic proteins such as perforin and granzymes. Granulysin expressed and released by cytotoxic T cells has a direct cytotoxicity against keratinocytes. Fas ligand tumour necrosis factor (TNF)-alpha contributes to the inflammatory response and promotes keratinocyte apoptosis [51–54].

5.2. Pathogenesis of DRESS Syndrome

The pathogenesis of DRESS syndrome is not fully understood. The role of drug-specific immune response in the pathogenesis of DRESS syndrome has been proven based on the patch test positivity to causative drugs, as well as the in vitro demonstration of drug-specific T cells. The main effectors of DRESS syndromes are lymphocytes CD4+ Th1/Th2 and eosinophils, which produce large amounts of TNF-alpha and interferon (IFN)-gamma, interleukin (IL)-4 and IL-5 [51,55].

6. Risk Factors

Multiple studies have identified key risk factors contributing to allopurinol-related SCARs [12–14,16,17,49,56–62] such as age, sex, ethnicity, *HLA-B*58:01* genotype, kidney impairment, and allopurinol starting dose. Table 3, Table 4, and Table 5 summarise the results of a scoping literature review informing the development of a model to predict allopurinol-induced SCARs among people newly prescribed allopurinol [41].

Table 3. Articles included in the scoping review.

Publication Year	Authors	Study Design	Country	Population	Sample Size	Outcome Definition	Diagnosis Based on
2008	Halevy S et al. [17]	Case–control	European Union + Israel	Hospitalised patients with allopurinol-induced SCARs vs. hospitalised patients that were representative of the general population	94	SJS, TEN	Manual adjudication
2012	Stamp LK et al. [57]	Case–control	New Zealand	Hospitalised patients with gout and allopurinol-induced SCARs vs. allopurinol-tolerant users	211	Allopurinol hypersensitivity reactions (ICD9 codes 693.0 695.1 974.7, ICD10 codes L27.0 L27.1 L51.0 L51.1 L51.2 T50.4)	Diagnostic codes
2013	Kim SC et al. [13]	Cohort study	USA	New allopurinol users without solid tumours, hematologic malignancies, myelodysplastic syndromes, or chemotherapy	90,358	SCAR (ICD9 codes 695.1) within 99 days after allopurinol initiation	Diagnostic codes
2015	Chung WH et al. [16]	Case–control	Taiwan	Hospitalised patients with allopurinol-induced SCARs vs. allopurinol-tolerant users (>6 months)	244	SJS, TEN, DRESS syndrome	Manual adjudication
2015	Yang CY et al. [14]	Cohort study	Taiwan	New allopurinol users without a history of SCARs; 3-year lookback period	1,613,719	SCAR (ICD9 codes 693.0, 695.1 695.9 695.89) within 90 days after allopurinol initiation and no further use of allopurinol afterwards. Comedications were excluded as the cause if the drugs had been used for longer than 3 months or continued to be used after the hypersensitivity reaction	Diagnostic codes
2016	Ng CY et al. [49]	Case–control	Taiwan	Hospitalised patients with allopurinol-induced SCARs vs. allopurinol-tolerant users	431	SJS, TEN, DRESS syndrome	Manual adjudication
2017	Saksit N et al. [58]	Case–control	Thailand	Hospitalised patients with allopurinol-induced SCARs vs. allopurinol-tolerant users (>6 months)	268	SJS, TEN, DRESS syndrome	Manual adjudication
2018	Keller SF et al. [12]	Cohort study	USA	New allopurinol users without a history of SCARs	400,401	SCAR (ICD9 codes 693.0, 695.1 695.9 695.89) within 90 days after allopurinol initiation	Diagnostic codes
2019	Yokose C et al. [56]	Cohort study	Canada	New allopurinol users without a history of SCARs; 3-year lookback period	130,325	SCAR (ICD9 codes 693.0, 695.1 695.9 695.89) within 90 days after allopurinol initiation and no further use of allopurinol afterwards. Comedications were excluded as the cause if the drugs had been used for longer than 3 months or continued to be used after the hypersensitivity reaction	Diagnostic codes

Table 3. Cont.

Publication Year	Authors	Study Design	Country	Population	Sample Size	Outcome Definition	Diagnosis Based on
2020	Do MD et al. [60]	Case-control	Vietnam	Hospitalised patients with allopurinol-induced SCARs vs. allopurinol-tolerant users (>6 months)	500	SJS, TEN, DRESS syndrome	Manual adjudication
2021	Lee SC et al. [61]	Case-control	Malaysia	Hospitalised patients with gout and allopurinol-induced SCARs vs. allopurinol-tolerant users vs. allopurinol users	1747	SJS, TEN, DRESS syndrome, AGEP	Manual adjudication
2022	Bathini L et al. [62]	Cohort study	Canada	New allopurinol users aged ≥ 66 years with CKD (defined as an eGFR <60 mL/min/1.73 m ² but not on dialysis and without a kidney transplant)	47,315	SCAR within 180 days from allopurinol initiation (ICD10 codes L270, L271, L539, L538, L26, L510, L511, L512, L518, L519)	Diagnostic codes

CKD: Chronic kidney disease, DRESS: Drug Rash with Eosinophilia and Systemic Symptoms, eGFR: estimated glomerular filtration rate, SCAR: severe cutaneous adverse reaction, SJS: Stevens–Johnson’s syndrome, TEN: Toxic epidermal necrolysis, USA: United States of America. Adapted from Ref. [41].

Table 4. Allopurinol-induced SCARs: definite risk factors.

Authors	Allopurinol Starting Dose (≤ 100 mg/Day Reference)	Age, Years	Gender (Male Reference)	CKD	CVD (Ischemic Heart Disease and Heart Failure)	Ethnicity (White/Hispanic Reference)	HLA-B*58:01
Halevy S et al. [17]	36 (17–76) Reference (<200 mg/day)						
Stamp LK et al. [57]	16.7 (5.7–47.6) Reference (allopurinol dose $\leq$ creatinine clearance-based dose)						
Kim SC et al. [13]	1.30 (0.31–5.36) Reference (≤ 300 mg)	1.03 (1.01–1.06)					
Chung WH et al. [16]			6.9 (3.2–15.1)	8.0 (3.9–16.8)			109 (24.8–481)
Yang CY et al. [14]	1.27 (1.18–1.37)	40–59 y 1.02 (0.91–1.14) 60–79 y 5.54 (2.84–10.80) ≥ 80 y 12.37 (6.24–24.53) Reference (0–39 y)	1.45 (1.35–1.56)	1.49 (1.38–1.61)	1.13 (1.04–1.22)		
Ng CY et al. [49]		1.03 (1.00–1.05)	4.71 (2.36–9.70)	4.30 (1.96–9.62)			17.42 (9.1–33.0)
Saksit N et al. [58]			4.6 (1.4–15.6)	3.2 (0.6–16.8)			228.5 (58.1–899.1)
Keller SF et al. [12]	1.85 (1.36–2.51)	1.66 (1.23–2.24) Reference (<60 y)	2.49 (1.83–3.38)	2.33 (1.44–3.77)		Black 3.0 (2.18–4.14), Asian 3.03 (1.72–5.34), Pacific Islander 6.68 (4.37–10.22)	

Table 4. Cont.

Authors	Allopurinol Starting Dose (≤100 mg/Day Reference)	Age, Years	Gender (Male Reference)	CKD	CVD (Ischemic Heart Disease and Heart Failure)	Ethnicity (White/Hispanic Reference)	HLA-B*58:01
Yokose C et al. [56]	2.79 (1.75–4.45)	1.02 (1.00–1.04)	2.48 (1.67–3.70)	1.86 (1.16–2.99)	1.60 (1.04–2.44)		
Do MD et al. [60]	316 (101–1224) Reference (≤150 mg)	>65 y 15.1 (5.8–40.1) ≤40 y 0.28 (0.05–0.91) Reference (40–65 y)	333 (40–43,453)	100 (32–353)			147 (45–746)
Lee SC et al. [61]	1.72 (1.38–2.15) Reference (<300 mg)	1.31 (1.04–1.64) Reference (<65 y)	1.54 (1.24–1.93)	2.02 (1.36–3.00)		Chinese 1.19 (0.96–1.48), Indian 0.98 (0.51–1.91) Reference (Malay)	
Bathini L et al. [62]	2.25 (1.50–3.37)						

CKD: Chronic kidney disease, CVD: cardiovascular diseases, SCAR: severe cutaneous adverse reactions, y: years. Significant associations are highlighted in grey. Adapted from Ref. [41].

Table 5. Allopurinol-induced SCARs: potential risk factors.

Authors	Indication for Allopurinol: Asymptomatic Hyperuricemia (Reference: Gout)	Diuretics Use (Reference: No Use)	Diabetes Mellitus (Reference: Absence of the Disease)	Cancer (Reference: Absence of the Disease)	History of ALLOPURINOL- Induced Skin Reaction (Reference: Absence of the Disease)	Charlson Comorbidity Index (Reference: no Comorbidities)	Antibiotics Use (Reference: no Use)	Angiotensin- Converting Enzyme Inhibitors Use (Reference: no Use)
Halevy S et al. [17]								
Stamp LK et al. [57]								
Kim SC et al. [13]		1.49 (0.77–2.90)				1.18 (1.05–1.33)		
Chung WH et al. [16]	4.34 (2.0–10.0)							
Yang CY et al. [14]	2.08 (1.94–2.24)	1.02 (0.78–1.32)	0.92 (0.85–0.99)	0.97 (0.88–1.07)			1.03 (0.77–1.38)	0.88 (0.74–1.06)
Ng CY et al. [49]								
Saksit N et al. [58]								
Keller SF et al. [12]	1.21 (0.91–1.60)	1.38 (0.99–1.92)						
Yokose C et al. [56]	1.20 (0.86–1.82)	1.27 (0.84–1.94)	0.96 (0.63–1.46)					
Do MD et al. [60]		304 (35–40,018)			78 (6–10,808)			
Lee SC et al. [61]	1.87 (1.29–2.70)							
Bathini L et al. [62]								

Significant associations are highlighted in grey. Adapted from Ref. [41].

6.1. Genes and Ethnicity

One of the most prominent risk factors is the presence of the *HLA-B*58:01* allele. This has been strongly associated with an increased risk of SCARs across different populations, with an odds ratio ranging between 17.4 and 228.5 [16,49,58,60]. For instance, the strong association between the *HLA-B*58:01* allele and SCARs has been highlighted not only in Asian countries [16,49,58,60], but also in Portugal and the USA [63,64]. A national prospective cohort study in Taiwan further emphasised the clinical relevance of the *HLA-B*58:01* allele [65]. Conducted across 15 medical centres, the study involved 2926 allopurinol-naïve individuals who had an indication for allopurinol. None of the 2339 participants who tested negative for *HLA-B*58:01* and were subsequently treated with allopurinol developed SCARs, compared to the historically expected incidence of SCARs [65].

Ethnicity has been shown to be a significant risk factor for allopurinol-induced SCARs [12,56]. Indeed, *Asian* (adjusted hazard ratio: 3.0 and 5.6), *Chinese* (adjusted hazard ratio: 5.4), *Indian/Pakistani/Bangladeshi* (adjusted hazard ratio: 5.4), and *Black* (adjusted hazard ratio: 3.0 and 1.4) ethnicities have been associated with higher risk of SCARs compared to *White* and *Hispanic* ethnicities [12,41]. This association is explained, at least in part, by the different prevalence of the *HLA-B*58:01* allele in these ethnic groups. Other ethnic groups have shown conflicting results. Indeed, *Pacific Islander* ethnicities have been associated with an increased risk of SCARs in an observational study [12]. On the other hand, the prevalence of *HLA-B*58:01* was significantly lower in indigenous people of French Polynesia (<1%) in contrast to people reporting *Chinese* ancestry who lived there [66] and in Hawaiian people with *Filipino* ancestry [67]. This may be explained by the large genetic heterogeneity of this ethnic group.

Even though genetic factors play an important role, approximately 50% of people with allopurinol-induced SCARs did not carry the *HLA-B*58:01* allele in ethnicities with a low prevalence of this allele (e.g., *Caucasians/Hispanics*) [68]. This emphasises the importance of other genetic and non-genetic risk factors in the pathogenesis of allopurinol-induced SCARs. Indeed, in a recent US study, allele *HLA-A*34:02* was found to be an independent genetic risk factor for allopurinol-related SCARs [69]. However, the clinical relevance of this additional risk factor is yet to be defined.

6.2. Previous SCARs

A history of allopurinol-induced skin reaction has shown to be a significant risk factor for the development of SCARs in those previously exposed to allopurinol with an odds ratio of 78 in a case–control study [60]. However, it is quite unusual to re-prescribe allopurinol to people with a severe cutaneous reaction to allopurinol in their medical records, and it is not advised to do so.

6.3. Chronic Kidney Disease

Chronic kidney disease (CKD) has been identified as another critical risk factor for SCARs [14,16,49,56,58,60,61]. Patients with CKD have a 1.5/2-fold increased risk of SCAR compared to those without any renal impairment in cohort studies [12,14]. In an UK cohort study, there was a dose–response effect, with higher risk of allopurinol-induced SCARs among people with CKD stage 5/dialysis (adjusted hazard ratio: 18.9) compared to those with stage 4 (adjusted hazard ratio: 6.7), stage 3 (adjusted hazard ratio: 2.2), or stage 0–2 (reference category) [41]. The higher risk of SCARs in people with CKD seems to be related to increased exposure to oxypurinol, a key allopurinol metabolite, due to reduced renal clearance [16].

6.4. Allopurinol Starting Dose

Another particularly important risk factor is the allopurinol starting dose, as a higher starting dose of allopurinol is associated with an elevated risk of SCARs (adjusted hazard ratio ranging between 1.30 and 2.25) [14,62]. A potential explanation for this association is that higher starting doses may increase the circulating levels of oxypurinol abruptly. It is not clear whether the allopurinol starting dose or the dose required to achieve target serum urate is more important in the risk for allopurinol-induced SCARs. However, there is initial evidence supporting the hypothesis that the starting dose is more relevant in this context. First, most allopurinol-induced SCARs typically occur within the first weeks to months after starting allopurinol (up to 8 weeks in SJS/TEN and 12 weeks in DRESS syndrome) [17,18]. In addition, in a randomised controlled trial of allopurinol dose escalation there were no cases of SCARs and similar cutaneous adverse events between those who maintained a creatinine clearance-based dose and those who increased the dose above this threshold [70,71]. Even though these studies were underpowered to evaluate a rare outcome such as SCARs, they support the current recommendations from some specialist societies such as the ACR and the EULAR [72,73] on starting with a low dose and gradually titrating the dose up to achieve target serum urate levels.

6.5. Sex

Female sex is also associated with an increased risk of allopurinol-induced SCARs [12–14,16,49,56,58,60,61]. For instance, a population-based cohort study in British Columbia, Canada, which analysed data from 130,325 allopurinol initiators between 1997 and 2015, found that women had a two-fold higher risk of SCARs compared to men [56].

6.6. Age

Age is another factor influencing the risk of SCARs to allopurinol [12–14,16,49,56,60,61], with an increased risk of 2–3% per year [13,56]. The increased susceptibility in older adults can be attributed to several factors, including decreased renal function, polypharmacotherapy, and the accumulation of comorbidities such as heart disease, which, in turn, may decrease renal perfusion.

6.7. Cardiovascular Diseases

Heart disease has recently emerged as an independent risk factor for allopurinol-associated SCARs, with a study from British Columbia reporting 55% higher risk of hospitalisation in those with heart disease [56], potentially related to reduced clearance of oxypurinol.

6.8. Other Potential Risk Factors

However, not all parameters show consistent evidence as risk factors for SCARs. For example, the indication for allopurinol use—whether for gout or asymptomatic hyperuricaemia—has shown conflicting results in different studies [12,14,16,56,61] (Table 5). Two case-control studies and a cohort one, carried out in Asia, reported a significant association between the indication for allopurinol use and the risk of SCARs [14,16,61]. On the other hand, two North American studies did not [12,56]. This discrepancy may be attributable to differences in genetic susceptibility, prescribing patterns, and patient characteristics across populations, which could modify the effect of allopurinol indication on SCAR risk.

Similarly, the concomitant use of diuretics and/or angiotensin-converting enzyme inhibitors with allopurinol, which are commonly prescribed in people with gout, has been implicated in a few studies as increasing the risk of SCARs, but the evidence remains inconclusive, as all cohort studies have reported a non-significant association. Furthermore,

these studies may be biased by confounding by indication, as the severity of renal function decline was not considered [12–14,56,60] (Table 5).

7. Treatment of SCARs

SCARs require rapid recognition and coordinated multidisciplinary care. Immediate withdrawal of the offending drug is the cornerstone of management, as it improves outcomes and reduces mortality [74].

7.1. SJS/TEN

Detached–detachable skin surface $\geq 10\%$, hypotension, shock, lactic acidosis, acute respiratory failure, hypoxemia, anuria, uncontrolled pain, and severe ocular involvement are the most important reasons to transfer a patient to an intensive care unit with expertise in the management of SJS/TEN [31].

Progressive skin detachment occurs over 7–9 days, with major risk of fluid/electrolyte imbalance, sepsis, multiorgan failure, and death [24]. Therefore, in the acute phase of the disease, management focuses on comprehensive supportive care and prevention of complications [31]. Patients with SJS/TEN require immediate hospitalisation. Management in highly specialised centres has shown to improve survival and reduce complications and is recommended for patients with $\geq 10\%$ BSA detachment or rapidly progressive disease [31].

Supportive care is another key aspect of acute management of SJS/TEN. This involves wound care, fluids and temperature balance, nutritional support, pain control, management of mucous involvement, and close monitoring of infectious complications [31]. Prophylactic antibiotic therapy is generally avoided [31].

No pharmacological treatment is definitely established, as supporting evidence remains limited, heterogeneous, and largely influenced by centre expertise [31]. Data from randomised controlled trials are scarce, and the overall quality of available evidence remains limited [31]. Compared with the best supportive care alone, immunosuppressants such as cyclosporin, etanercept, systemic glucocorticoids, and intravenous immunoglobulin have not proven their efficacy in reducing mortality, stopping skin detachment, or accelerating skin/mucosal healing [31]. Although immunosuppressants could be effective in stopping disease progression, infectious risks possibly outweighed the potential benefits [31]. In addition, as the acute phase is self-limited to 8 days, these drugs are most likely to be effective when started early; the critical importance of this narrow therapeutic window may, in part, explain the conflicting results reported across studies [31].

7.2. DRESS Syndrome

Management is guided by the severity of skin and organ involvement [40,75].

All patients require prompt discontinuation of the causative drug and avoidance of unnecessary new medications (particularly antibiotics). As in SJS/TEN, supportive care includes fluid and electrolytes balance, nutritional support, skin care, and careful monitoring of infectious complications [40,75].

Patients without significant organ involvement or only mild liver enzyme elevation are usually treated with high-potency topical corticosteroids. Patients with moderate/severe organ involvement are usually treated with systemic corticosteroids (0.5–1 mg/kg/day) tapered gradually over a few months [40,75].

As in SJS/TEN, immunosuppressants such as cyclosporin, JAK-inhibitors, and anti-IL5 agents can be considered in most severe cases [40,75]; however, evidence supporting their use is mainly based on case reports and case series. In patients with high serum cytomegalovirus viral load, antiviral treatment can be considered [40,75].

8. Prevention Strategies

8.1. Allopurinol Starting Dose

To reduce the risk of SCARs, allopurinol should be initiated at a low dose, particularly in patients with renal impairment or other risk factors [72,73]. To mitigate this risk, both the EULAR and the ACR have provided guidelines emphasising the importance of starting allopurinol at a low dosage [72,73]. Both guidelines highlight the critical role of individualised dosing in preventing SCARs, considering factors such as renal function and the need for gradual dose escalation.

The EULAR guidelines recommend initiating allopurinol at a low dose of 100 mg per day in patients with normal kidney function, followed by a gradual increase in the dose by 100 mg increments every two to four weeks [72]. For patients with renal impairment, the EULAR guidelines underscore the need for adjusting the maximum dosage of allopurinol according to the patient's creatinine clearance [72]. The rationale behind this recommendation is linked to the fact that renal dysfunction can lead to decreased clearance of allopurinol metabolites. Although some studies suggest that dose escalation beyond the creatinine clearance limits may not necessarily result in SCARs [70,71,76], the EULAR task force acknowledged that these studies may be underpowered to detect such associations due to the rarity of the outcome [72]. Given the severity of SCARs and the availability of alternative therapies such as febuxostat, the EULAR guidelines adopt a conservative stance, recommending adhering to a creatinine clearance-based dosing strategy [72]. This approach has been criticised, as it could lead to a situation where patients may be exposed to allopurinol side-effects, without the benefits of achieving the serum urate target [77]. Indeed, a creatinine clearance-based dosing strategy resulted in suboptimal control of hyperuricaemia in most (81%) patients with gout [78].

The ACR guidelines emphasise the importance of starting allopurinol at a low dose of 100 mg/day in patients with normal renal function, or even lower (≤ 50 mg/day) in patients with CKD, followed by gradual dose titration [73]. However, the ACR acknowledges that while patients with CKD may require dose escalation above the creatinine clearance-based dose (and above 300 mg/day) to achieve the desired serum urate target. Since the risk of allopurinol-induced SCARs significantly decreases after six months of drug exposure [5,57], and untreated/undertreated gout is associated with significant musculoskeletal and systemic complications, the ACR recommend increasing allopurinol dose beyond the renal dosing limits proposed by Hande et al. Nevertheless, such escalation should be done cautiously and under close supervision [77]. Alternate ULT such as Febuxostat may be considered in this setting.

8.2. Avoiding Allopurinol in Those with the HLA-B*58:01 Allele

The HLA-B*58:01 allele is the strongest risk factor for allopurinol-induced SCARs [16,49,58,60]. The prevalence of the HLA-B*58:01 allele varies significantly across different ethnic groups, with particularly high frequencies ranging from 5% to 20% among Asian populations [79]. In contrast, the prevalence is much lower among Caucasians and Hispanics (approximately 1%) [79].

Several international recommendations have been issued regarding HLA-B*58:01 testing before initiating allopurinol treatment:

- Asia Pacific League of Associations for Rheumatology (APLAR): Recommends HLA-B*58:01 testing in populations with a high prevalence ($\geq 5\%$) of the allele and avoiding allopurinol in patients who have tested positive for HLA-B*58:01 [80].
- American College of Rheumatology (ACR): Conditionally recommends testing for patients of Southeast Asian descent (including Han Chinese, Korean, and Thai) and African American patients before starting allopurinol. Universal testing is conditionally

recommended against for patients of other ethnic backgrounds, such as *Caucasians* and *Hispanic* patients [73].

- Hong Kong Society of Rheumatology: Suggest considering screening for the allele in *Asian* patients and those with risk factors such as advanced age (≥ 60 years) or chronic kidney disease (CKD stage ≥ 3) [81].

The cost-effectiveness of *HLA-B*58:01* screening: In ethnicities with a high prevalence of the allele, such as certain *Asian* and *African* ethnicities, genetic testing is generally considered cost-effective [65,82–84]. However, the cost-effectiveness diminishes in ethnicities with lower allele frequencies [64], and it is not believed to be cost-effective in *Caucasian* populations [64] as approximately 1 in 2 people with allopurinol-induced severe cutaneous adverse reactions did not carry the *HLA-B*58:01* allele in countries with low prevalence of this allele [68]. Nonetheless, the continued reduction in the cost of genomic testing—together with national initiatives aimed at large-scale population genomic profiling (e.g., emerging national biobank programmes)—is likely to enhance the cost-effectiveness of *HLA-B*58:01* screening over time.

8.3. Prediction Tools

We have recently performed a scoping literature review on risk factors for allopurinol-induced SCARs and developed and validated a prognostic model to predict the 100-day risk of SCARs in new allopurinol initiators using the UK's linked primary care, secondary care and mortality data [41]. Using readily ascertainable clinical variables—age, sex, ethnicity, chronic kidney disease stage, cardiovascular comorbidity, and initial allopurinol dose—the model demonstrated good discrimination, calibration, and clinical utility. The model is expected to enable more precise individual-level SCAR risk estimation than existing population-level figures in populations where *HLA-B*58:01* screening is not routinely available or cost-effective and support personalised-risk assessment to guide the choice of a urate-lowering drug. Indeed, the population-level risk of allopurinol-induced SCARs ranges from 1 in 10,000 to 1 in 1000 in the British National Formulary. Our prognostic model represents a substantial improvement as it provides individual-risk estimates that ranges from less than 1 in 1,000,000 to more than 1 in 100.

Table 6 reports the equation to predict the risk of allopurinol-induced SCARs within 100 days after allopurinol initiation, while Table 7 shows a worked example of our prediction model in different clinical scenarios.

We believe that this model will allow for better informed decision making about urate-lowering drug choice, as knowledge about individual risk might improve the adherence to allopurinol by reducing concerns about this rare but severe side effect when the risk is predicted to be very low. On the other hand, it will reduce the potential for serious harm by avoiding allopurinol when the risk is predicted to be high. Before implementing the model into routine clinical care, several steps need to be undertaken. First, we must develop risk thresholds at which alternate urate-lowering drugs should be considered. Second, we aim to validate our model in other countries. Third, future studies should consider whether including results of pre-treatment genetic screening rather than ethnicity categories would improve the performance of the developed prediction model.

Importantly, the allopurinol starting dose was the only modifiable risk factor included in this prognostic model. Therefore, to minimise the risk of SCARs among new allopurinol initiators, it is essential that allopurinol is initiated at a daily dose of ≤ 100 mg/day, as recommended by the ACR and the EULAR and detailed in the next section.

Table 6. Equation to predict the risk of severe cutaneous adverse reactions to allopurinol within 100 days after allopurinol initiation.

Risk Probability = $1 - \exp(-\exp(\alpha + \gamma(\delta * \beta X)^\epsilon))$	
$\beta X =$	0.033 * age in years
	+0.360 * female sex
	+0.3667 * Black ethnicity
	+1.685 * Chinese ethnicity
	+1.678 * South Asian (Indian/Pakistani/Bangladeshi) ethnicity
	+1.728 * other Asian ethnicities
	+0.488 * other/Unknown ethnicity
	+1.062 * allopurinol starting dose 101–299 mg
	+1.790 * allopurinol starting dose ≥ 300 mg
	+0.805 * chronic kidney disease stage 3
	+1.894 * chronic kidney disease stage 4
	+2.936 * chronic kidney disease stage 5/dialysis
	+0.103 * ischaemic heart disease
	+0.225 * heart failure

All variables were coded 0/1 if absent/present, respectively, except for age in years. The other numbers are the estimated regression coefficients for the predictors, which indicate their mutually adjusted relative contribution to the outcome risk. $\alpha = 3.085$, $\gamma = -22.608$, $\delta = 0.96$, $\epsilon = -0.5$. α , γ , and ϵ derived from the recalibration of Cox's original linear predictors using multifractional polynomial analysis. α was then re-estimated after penalisation to ensure that the calibration-in-the-large is correct (i.e., that the sum of predicted probabilities equals the overall proportion of observed events). δ is the shrinkage factor obtained from the internal validation using bootstrapping. Adapted from Ref. [41].

Table 7. Worked example of the individual risk probability using the proposed risk prediction model.

Age	Sex	Ethnicity	Allopurinol Starting Dose	CKD Stage	IHD	HF	Individual Risk Probability
20	Female	Caucasian	≤ 100 mg/day	0–2	No	No	<0.000001
67	Female	Caucasian	≥ 300 mg/day	3	No	No	0.00085
52	Male	Black	101–299 mg/day	3	Yes	No	0.00023
72	Male	Indian	≤ 100 mg/day	4	Yes	Yes	0.0025
91	Female	Black	101–299 mg/day	3	No	Yes	0.0015
48	Female	Chinese	101–299 mg/day	3	No	No	0.0012

CKD: chronic kidney disease, HF: heart failure, IHD: ischaemic heart disease.

9. Management of Hyperuricaemia in Patients with a History of SCARs

In patients with a history of SCARs attributed to allopurinol, re-exposure is contraindicated, given the high risk of recurrence and potential fatality. Alternative urate-lowering strategies should be selected cautiously, balancing efficacy against residual hypersensitivity risk. Non-pharmacological measures should be optimised in all patients, including dietary modification, weight reduction, and alcohol limitation. Current treatment should be evaluated and, if possible, medications able to lower serum urate (i.e., SGLT2-inhibitors, losartan, calcium channel blockers) preferred over those which raise serum urate levels (i.e., diuretics and calcineurin inhibitors).

9.1. Desensitisation

In late 90s, desensitisation regimens for people with mild allopurinol-induced skin rash had been proposed [85]. They were used when there was no or little alternative to use in the presence of allopurinol hypersensitivity. They consist of oral administration of very small doses of allopurinol, i.e., 50 mcg/day, slowly up-titrated over a month up to

100 mg/day [85]. Even though they have been shown to reduce the recurrence of such side effects, with the availability of other urate-lowering drugs, such desensitisation is rarely performed nowadays.

9.2. Switch to Other Urate-Lowering Agents

Switching from allopurinol to other urate-lowering agents is thought to be generally safe. Nationwide data from Taiwan show that allopurinol carries a substantially higher risk of SCARs, since febuxostat has a 16-fold lower risk of SCARs than allopurinol.

A retrospective hospital-based French study comparing sequential treatment with allopurinol and febuxostat in patients found a modestly higher proportion of febuxostat-associated skin reactions among those with a prior allopurinol reaction compared to those without prior skin reaction to allopurinol (9.1% vs. 2.5%) [86]. However, this increase was not statistically significant, and the overall evidence did not support a strong cross-reactivity between the two drugs.

Together, these findings suggest that switching from allopurinol to a structurally distinct xanthine oxidase inhibitor (febuxostat) or to other classes such as uricosurics or pegloticase, depending on the local availability of alternatives, can reduce the risk of recurrent SCARs in susceptible patients, but careful monitoring for this side effect remains essential.

10. Future Directions

Despite substantial progress in understanding the risk factors and pathophysiology underlying allopurinol-induced SCARs, important knowledge gaps remain.

Further studies are needed to elucidate additional genetic determinants of risk, as it is increasingly recognised that *HLA-B*58:01* alone does not fully account for susceptibility to allopurinol-induced SCARs in populations with a low prevalence of this allele. Other genetic risk factors are emerging (i.e., *HLA-A*34:02*); however, their clinical relevance needs to be elucidated.

The safety of allopurinol dose escalation beyond the initial 12-week period in high-risk individuals who do not develop cutaneous reactions remains uncertain and warrants further studies.

The identification and validation of biomarkers and prognostic models represent another key research priority. Such tools could enable personalised risk stratification, supporting clinicians in selecting optimal urate-lowering drugs—allopurinol or alternatives such as febuxostat or uricosuric agents. In this context, further external validation of our prognostic model in diverse populations is essential to assess its generalisability. Furthermore, specific risk thresholds at which alternate drugs such as febuxostat or uricosurics should be preferentially considered as an alternative to allopurinol should be defined.

11. Conclusions

Allopurinol-induced SCARs—including DRESS syndrome and SJS/TEN—represent significant clinical challenges due to their potential for poor outcomes and high mortality rates. Understanding the genetic, pharmacokinetic, and immunological factors that contribute to these reactions is critical for improving patient safety. Genetic screening, appropriate dosing, avoidance of allopurinol in high-risk patients, early recognition of symptoms, mapping drug timelines, and early dermatological assessment are key strategies in preventing and managing these conditions. Ongoing research and the development of new tailored treatment strategies are needed to further reduce the burden of allopurinol-induced SCARs and improve patient outcomes. Importantly, the potential for serious side effects should not discourage clinicians or patients from treating gout to the target serum urate. Allopurinol remains a cornerstone of

urate-lowering therapy and should be prescribed using a “start-low go-slow” approach, in accordance with international recommendations.

Author Contributions: Conceptualization: A.A., C.H.S., E.C. and S.K.M.; formal analysis: A.A., C.H.S., E.C. and S.K.M.; writing—original draft preparation: E.C.; writing—review and editing: A.A., C.H.S. and S.K.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflicts of Interest: The authors declare that they have no conflict of interest related to the present manuscript.

Abbreviations

The following abbreviations are used in this manuscript:

ACR	American College of Rheumatology
AGEP	Acute Generalised Exanthematous Pustulosis
ALDEN	Algorithm of Drug causality for Epidermal Necrolysis
APLAR	Asia Pacific League of Associations for Rheumatology
CD	Cluster of Differentiation
CKD	chronic kidney disease
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EULAR	European Alliance of Associations for Rheumatology
HLA	Human Leukocyte Antigen
IL	Interleukin
INF	Interferon
NSAID	Non-Steroidal Anti-Inflammatory Drug
RegiSCAR	Registry of Severe Cutaneous Adverse Reactions
SCAR	severe cutaneous adverse reaction
SJS	Stevens–Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
TNF	Tumour Necrosis Factor

References

1. Son, C.-N.; Stewart, S.; Su, I.; Mihov, B.; Gamble, G.; Dalbeth, N. Global patterns of treat-to-serum urate target care for gout: Systematic review and meta-analysis. *Semin. Arthritis Rheum.* **2021**, *51*, 677–684. [[CrossRef](#)] [[PubMed](#)]
2. Cipolletta, E.; Sandström, T.Z.; Rozza, D.; Leyrat, C.; Nakafero, G.; Drivelegka, P.; Avery, A.J.; Mamas, M.A.; Tata, L.J.; Dehlin, M.; et al. Treat-to-Target Urate-Lowering Treatment and Cardiovascular Outcomes in Patients with Gout. *JAMA Intern. Med.* **2026**, e257453. [[CrossRef](#)]
3. Wang, Y.; Dalbeth, N.; Terkeltaub, R.; Zhang, Y.; Li, X.; Zeng, C.; Lei, G.; Wei, J. Target Serum Urate Achievement and Chronic Kidney Disease Progression in Patients With Gout and Kidney Disease. *JAMA Intern. Med.* **2024**, *185*, 74–82. [[CrossRef](#)]
4. Stamp, L.K.; Barclay, M.L. How to prevent allopurinol hypersensitivity reactions? *Rheumatology* **2018**, *57*, i35–i41. [[CrossRef](#)]
5. Stamp, L.K.; Day, R.O.; Yun, J. Allopurinol hypersensitivity: Investigating the cause and minimizing the risk. *Nat. Rev. Rheumatol.* **2016**, *12*, 235–242. [[CrossRef](#)]
6. Stamp, L.K.; Chapman, P.T. Allopurinol hypersensitivity: Pathogenesis and prevention. *Best Pract. Res. Clin. Rheumatol.* **2020**, *34*, 101501. [[CrossRef](#)] [[PubMed](#)]
7. Sekula, P.; Dunant, A.; Mockenhaupt, M.; Naldi, L.; Bavinck, J.N.B.; Halevy, S.; Kardaun, S.; Sidoroff, A.; Liss, Y.; Schumacher, M.; et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J. Investig. Dermatol.* **2013**, *133*, 1197–1204. [[CrossRef](#)]

8. Kridin, K.; Brüggen, M.; Walsh, S.; Bensaid, B.; Ranki, A.; Oppel, E.; Meyersburg, D.; Chua, S.; Seeli, C.; Sandberg, H.; et al. Management and treatment outcome of DRESS patients in Europe: An international multicentre retrospective study of 141 cases. *J. Eur. Acad. Dermatol. Venereol.* **2023**, *37*, 753–762. [[CrossRef](#)]
9. Kardaun, S.; Sekula, P.; Valeyrie-Allanore, L.; Liss, Y.; Chu, C.; Creamer, D.; Sidoroff, A.; Naldi, L.; Mockenhaupt, M.; Roujeau, J.; et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br. J. Dermatol.* **2013**, *169*, 1071–1080. [[CrossRef](#)] [[PubMed](#)]
10. Singh, J.A. Challenges faced by patients in gout treatment: A qualitative study. *J. Clin. Rheumatol.* **2014**, *20*, 172–174. [[CrossRef](#)]
11. Spragg, J.C.J.; Michael, T.J.F.; Aslani, P.; Coleshill, M.J.; Chan, J.S.; Day, R.O.; Stocker, S.L. Optimizing adherence to allopurinol for gout: Patients' perspectives. *Br. J. Clin. Pharmacol.* **2023**, *89*, 1978–1991. [[CrossRef](#)]
12. Keller, S.F.; Lu, N.; Blumenthal, K.G.; Rai, S.K.; Yokose, C.; Choi, J.W.J.; Kim, S.C.; Zhang, Y.; Choi, H.K. Racial/ethnic variation and risk factors for allopurinol-associated severe cutaneous adverse reactions: A cohort study. *Ann. Rheum. Dis.* **2018**, *77*, 1188–1194. [[CrossRef](#)]
13. Kim, S.C.; Newcomb, C.; Margolis, D.; Roy, J.; Hennessy, S. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: A population-based cohort study. *Arthritis Care Res.* **2013**, *65*, 578–584. [[CrossRef](#)]
14. Yang, C.Y.; Chen, C.H.; Deng, S.T.; Huang, C.S.; Lin, Y.J.; Chen, Y.J.; Wu, C.Y.; Hung, S.I.; Chung, W.H. Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan. *JAMA Intern. Med.* **2015**, *175*, 1550–1557. [[CrossRef](#)]
15. Day, R.O.; Graham, G.G.; Hicks, M.; McLachlan, A.J.; Stocker, S.L.; Williams, K.M. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin. Pharmacokinet.* **2007**, *46*, 623–644. [[CrossRef](#)]
16. Chung, W.-H.; Chang, W.-C.; Stocker, S.L.; Juo, C.-G.; Graham, G.G.; Lee, M.-H.H.; Williams, K.M.; Tian, Y.-C.; Juan, K.-C.; Wu, Y.-J.J.; et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: The impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann. Rheum. Dis.* **2015**, *74*, 2157–2164. [[CrossRef](#)]
17. Halevy, S.; Ghislain, P.-D.; Mockenhaupt, M.; Fagot, J.-P.; Bavinck, J.N.B.; Sidoroff, A.; Naldi, L.; Dunant, A.; Viboud, C.; Roujeau, J.-C. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J. Am. Acad. Dermatol.* **2008**, *58*, 25–32. [[CrossRef](#)] [[PubMed](#)]
18. Mockenhaupt, M.; Viboud, C.; Dunant, A.; Naldi, L.; Halevy, S.; Bavinck, J.N.B.; Sidoroff, A.; Schneck, J.; Roujeau, J.-C.; Flahault, A. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J. Investig. Dermatol.* **2008**, *128*, 35–44. [[CrossRef](#)]
19. Creadore, A.; Desai, S.; Alloo, A.; Dewan, A.K.; Bakhtiar, M.; Cruz-Diaz, C.; Femia, A.; Fox, L.; Katz, K.L.; Micheletti, R.; et al. Clinical Characteristics, Disease Course, and Outcomes of Patients with Acute Generalized Exanthematous Pustulosis in the US. *JAMA Dermatol.* **2022**, *158*, 176–183. [[CrossRef](#)] [[PubMed](#)]
20. Sidoroff, A.; Dunant, A.; Viboud, C.; Halevy, S.; Bavinck, J.B.; Naldi, L.; Mockenhaupt, M.; Fagot, J.-P.; Roujeau, J.-C. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). *Br. J. Dermatol.* **2007**, *157*, 989–996. [[CrossRef](#)] [[PubMed](#)]
21. Duong, T.A.; Valeyrie-Allanore, L.; Wolkenstein, P.; Chosidow, O. Severe cutaneous adverse reactions to drugs. *Lancet* **2017**, *390*, 1996–2011. [[CrossRef](#)]
22. Roujeau, J.C.; Stern, R.S. Severe adverse cutaneous reactions to drugs. *N. Engl. J. Med.* **1994**, *331*, 1272–1285. [[CrossRef](#)]
23. Morales, M.E.; Purdue, G.F.; Verity, S.M.; Arnoldo, B.D.; Blomquist, P.H. Ophthalmic Manifestations of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis and Relation to SCORTEN. *Am. J. Ophthalmol.* **2010**, *150*, 505–510.e1. [[CrossRef](#)]
24. Heng, Y.K.; Lee, H.Y.; Roujeau, J.C. Epidermal necrolysis: 60 years of errors and advances. *Br. J. Dermatol.* **2015**, *173*, 1250–1254. [[CrossRef](#)] [[PubMed](#)]
25. Bastuji-Garin, S.; Rzany, B.; Stern, R.S.; Shear, N.H.; Naldi, L.; Roujeau, J.C. Clinical Classification of Cases of Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, and Erythema Multiforme. *Arch. Dermatol.* **1993**, *129*, 92–96. [[CrossRef](#)] [[PubMed](#)]
26. Hoffman, M.; Chansky, P.B.; Bashyam, A.R.; Boettler, M.A.; Challa, N.; Dominguez, A.; Estupinan, B.; Gupta, R.; Hennessy, K.; Huckell, S.N.; et al. Long-term Physical and Psychological Outcomes of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. *JAMA Dermatol.* **2021**, *157*, 712–715. [[CrossRef](#)] [[PubMed](#)]
27. Frey, N.; Jossi, J.; Bodmer, M.; Bircher, A.; Jick, S.S.; Meier, C.R.; Spoendlin, J. The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK. *J. Investig. Dermatol.* **2017**, *137*, 1240–1247. [[CrossRef](#)]
28. Rzany, B.; Hering, O.; Mockenhaupt, M.; Chröder, W.; Goertler, E.; Ring, J.; Schöpf, E. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens—Johnson syndrome and toxic epidermal necrolysis. *Br. J. Dermatol.* **1996**, *135*, 6–11. [[CrossRef](#)] [[PubMed](#)]
29. Côté, B.; Wechsler, J.; Bastuji-Garin, S.; Assier, H.; Revuz, J.; Roujeau, J.C. Clinicopathologic Correlation in Erythema Multiforme and Stevens-Johnson Syndrome. *Arch. Dermatol.* **1995**, *131*, 1268–1272. [[CrossRef](#)]
30. Sassolas, B.; Haddad, C.; Mockenhaupt, M.; Dunant, A.; Liss, Y.; Bork, K.; Hausteine, U.F.; Vieluf, D.; Roujeau, J.C.; Le Louet, H. ALDEN, an Algorithm for Assessment of Drug Causality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Comparison with Case-Control Analysis. *Clin. Pharmacol. Ther.* **2010**, *88*, 60–68. [[CrossRef](#)]

31. Ingen-Housz-Oro, S.; Matei, I.; Gaillet, A.; Gueudry, J.; Zaghib, K.; Assier, H.; Wolkenstein, P.; de Prost, N.; Hua, C.; Bensaid, B.; et al. Diagnosing and Managing Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Adults: Review of Evidence 2017–2023. *J. Investig. Dermatol.* **2025**, *145*, 1589–1603. [\[CrossRef\]](#)
32. Bastuji-Garin, S.; Fouchard, N.; Bertocchi, M.; Roujeau, J.C.; Revuz, J.; Wolkenstein, P. Scortten: A severity-of-illness score for toxic epidermal necrolysis. *J. Investig. Dermatol.* **2000**, *115*, 149–153.
33. Noe, M.H.; Rosenbach, M.; Hubbard, R.A.; Mostaghimi, A.; Cardones, A.R.; Chen, J.K.; Cotliar, J.; Davis, M.D.P.; Dominguez, A.; Fox, L.P.; et al. Development and Validation of a Risk Prediction Model for In-Hospital Mortality Among Patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis-ABCD-10. *JAMA Dermatol.* **2019**, *155*, 448–454. [\[CrossRef\]](#)
34. Wei, B.M.; Fox, L.P.; Kaffenberger, B.H.; Korman, A.M.; Micheletti, R.G.; Mostaghimi, A.; Noe, M.H.; Rosenbach, M.; Shinkai, K.; Kwah, J.H.; et al. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Part II diagnosis and management. *J. Am. Acad. Dermatol.* **2024**, *90*, 911–926. [\[CrossRef\]](#)
35. Wei, B.M.; Fox, L.P.; Kaffenberger, B.H.; Korman, A.M.; Micheletti, R.G.; Mostaghimi, A.; Noe, M.H.; Rosenbach, M.; Shinkai, K.; Kwah, J.H.; et al. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Part I. Epidemiology, pathogenesis, clinicopathological features, and prognosis. *J. Am. Acad. Dermatol.* **2024**, *90*, 885–908. [\[CrossRef\]](#)
36. Soria, A.; Bernier, C.; Veyrac, G.; Barbaud, A.; Puymirat, E.; Milpied, B. Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: A retrospective study. *J. Am. Acad. Dermatol.* **2020**, *82*, 606–611. [\[CrossRef\]](#)
37. Chu, C.Y.; Chen, Y.C.; Chiu, H.C. Drug reaction with eosinophilia and systemic symptoms: A retrospective study of 60 cases. *Arch. Dermatol.* **2010**, *146*, 1373–1379.
38. Kano, Y.; Hirahara, K.; Mitsuyama, Y.; Takahashi, R.; Shiohara, T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: Dependence on its timing and the type of drug eruption. *Allergy* **2007**, *62*, 1439–1444. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Barbaud, A.; Collet, E.; Milpied, B.; Assier, H.; Staumont, D.; Avenel-Audran, M.; Grange, A.; Amarger, S.; Girardin, P.; Guinnee, M.-T.; et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br. J. Dermatol.* **2013**, *168*, 555–562. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Brügger, M.C.; Walsh, S.; Ameri, M.M.; Anasiewicz, N.; Maverakis, E.; French, L.E.; Ingen-Housz-Oro, S.; Abe, R.; Arderon-Jones, M.; Assier, H.; et al. Management of Adult Patients With Drug Reaction With Eosinophilia and Systemic Symptoms: A Delphi-Based International Consensus. *JAMA Dermatol.* **2024**, *160*, 37–44. [\[CrossRef\]](#)
41. Cipolletta, E.; Nakafero, G.; Rozza, D.; Mahil, S.K.; Smith, C.H.; Riley, R.D.; Abhishek, A. Development and validation of a prognostic model for predicting the risk of allopurinol-induced severe cutaneous adverse reactions: A retrospective new-user cohort study using linked primary care, hospitalisation, and mortality data. *Lancet Rheumatol.* **2025**, *7*, e840–e850. [\[CrossRef\]](#)
42. Muller, P.; Dubreil, P.; Mahé, A.; Lamaury, I.; Salzer, B.; Deloumeaux, J.; Strobel, M. Drug Hypersensitivity Syndrome in a West-Indian population. *Eur. J. Dermatol.* **2003**, *13*, 478–481.
43. Wolfson, A.R.; Zhou, L.; Li, Y.; Phadke, N.A.; Chow, O.A.; Blumenthal, K.G. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module. *J. Allergy Clin. Immunol. Pract.* **2019**, *7*, 633–640. [\[CrossRef\]](#)
44. Chiou, C.; Yang, L.; Hung, S.; Chang, Y.; Kuo, T.; Ho, H.; Hu, S.; Hong, H.; Chung, W. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: A study of 30 cases in Taiwan. *J. Eur. Acad. Dermatol. Venereol.* **2008**, *22*, 1044–1049. [\[CrossRef\]](#)
45. Hiransuthikul, A.; Rattananupong, T.; Klaewsongkram, J.; Rerknimitr, P.; Pongprutthipan, M.; Ruxrungtham, K. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS): 11 years retrospective study in Thailand. *Allergol. Int.* **2016**, *65*, 432–438. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Papp, Z.; Török, L. Anticonvulsant hypersensitivity syndrome: Incidence, prevention and management. *Drug Saf.* **1999**, *21*, 1665–1668.
47. Cadot, R.; Gery, P.; Lenief, V.; Nicolas, J.F.; Vocanson, M.; Tauber, M. Exploring recent advances in drugs severe cutaneous adverse reactions immunopathology. *Allergy Eur. J. Allergy Clin. Immunol.* **2025**, *80*, 47–62. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Lonjou, C.; Borot, N.; Sekula, P.; Ledger, N.; Thomas, L.; Halevy, S.; Naldi, L.; Bouwes-Bavinck, J.-N.; Sidoroff, A.; de Toma, C.; et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet. Genomics* **2008**, *18*, 99–107. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Ng, C.Y.; Yeh, Y.-T.; Wang, C.-W.; Hung, S.-I.; Yang, C.-H.; Chang, Y.-C.; Chang, W.-C.; Lin, Y.-J.; Chang, C.-J.; Su, S.-C.; et al. Impact of the HLA-B*58:01 Allele and Renal Impairment on Allopurinol-Induced Cutaneous Adverse Reactions. *J. Investig. Dermatol.* **2016**, *136*, 1373–1381. [\[CrossRef\]](#)
50. Gibson, A.; Deshpande, P.; Campbell, C.N.; Krantz, M.S.; Mukherjee, E.; Mockenhaupt, M.; Pirmohamed, M.; Palubinsky, A.M.; Phillips, E.J. Updates on the immunopathology and genomics of severe cutaneous adverse drug reactions. *J. Allergy Clin. Immunol.* **2023**, *151*, 289–300.e4. [\[CrossRef\]](#)
51. Chung, W.-H.; Pan, R.-Y.; Chu, M.-T.; Chin, S.-W.; Huang, Y.-L.; Wang, W.-C.; Chang, J.-Y.; Hung, S.-I. Oxypurinol-Specific T Cells Possess Preferential TCR Clonotypes and Express Granulysin in Allopurinol-Induced Severe Cutaneous Adverse Reactions. *J. Investig. Dermatol.* **2015**, *135*, 2237–2248. [\[CrossRef\]](#)

52. Gibson, A.; Ram, R.; Gangula, R.; Li, Y.; Mukherjee, E.; Palubinsky, A.M.; Campbell, C.N.; Thorne, M.; Konvinse, K.C.; Choshi, P.; et al. Multiomic single-cell sequencing defines tissue-specific responses in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat. Commun.* **2024**, *15*, 8722. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Nassif, A.; Bensussan, A.; Boumsell, L.; Deniaud, A.; Moslehi, H.; Wolkenstein, P.; Bagot, M.; Roujeau, J.-C. Toxic epidermal necrolysis: Effector cells are drug-specific cytotoxic T cells. *J. Allergy Clin. Immunol.* **2004**, *114*, 1209–1215. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Chung, W.-H.; Hung, S.-I.; Yang, J.-Y.; Su, S.-C.; Huang, S.-P.; Wei, C.-Y.; Chin, S.-W.; Chiou, C.-C.; Chu, S.-C.; Ho, H.-C.; et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat. Med.* **2008**, *14*, 1343–1350. [\[CrossRef\]](#)
55. Shiohara, T.; Mizukawa, Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. *Allergol. Int.* **2019**, *68*, 301–308. [\[CrossRef\]](#)
56. Yokose, C.; Lu, N.; Xie, H.; Li, L.; Zheng, Y.; McCormick, N.; Rai, S.K.; Aviña-Zubieta, J.A.; Choi, H.K. Heart disease and the risk of allopurinol-associated severe cutaneous adverse reactions: A general population-based cohort study. *CMAJ* **2019**, *191*, E1070–E1077. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Stamp, L.K.; Taylor, W.J.; Jones, P.B.; Dockerty, J.L.; Drake, J.; Frampton, C.; Dalbeth, N. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: A proposed safe starting dose of allopurinol. *Arthritis Rheum.* **2012**, *64*, 2529–2536. [\[CrossRef\]](#)
58. Saksit, N.; Tassaneeyakul, W.; Nakkam, N.; Konyoung, P.; Khunarkornsiri, U.; Chumworathayi, P.; Sukasem, C.; Suttisai, S.; Piriychananusorn, N.; Tiwong, P.; et al. Risk factors of allopurinol-induced severe cutaneous adverse reactions in a Thai population. *Pharmacogenet. Genom.* **2017**, *27*, 255–263. [\[CrossRef\]](#)
59. Lu, N.; Rai, S.K.; Terkeltaub, R.; Kim, S.C.; Menendez, M.E.; Choi, H.K. Racial disparities in the risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis as urate-lowering drug adverse events in the United States. *Semin. Arthritis Rheum.* **2016**, *46*, 253–258. [\[CrossRef\]](#)
60. Do, M.D.; Mai, T.P.; Do, A.D.; Nguyen, Q.D.; Le, N.H.; Le, L.G.H.; Hoang, V.A.; Le, A.N.; Le, H.Q.; Richette, P.; et al. Risk factors for cutaneous reactions to allopurinol in Kinh Vietnamese: Results from a case-control study. *Arthritis Res. Ther.* **2020**, *22*, 182. [\[CrossRef\]](#)
61. Lee, S.C.; Wo, W.K.; Yeoh, H.S.; Mohamed Ali, N.; Hariraj, V. Allopurinol-Induced Severe Cutaneous Adverse Drug Reactions: An Analysis of Spontaneous Reports in Malaysia (2000–2018). *Ther. Innov. Regul. Sci.* **2021**, *55*, 514–522. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Bathini, L.; Garg, A.X.; Sontrop, J.M.; Weir, M.A.; Blake, P.G.; Dixon, S.N.; McArthur, E.; Muanda, F.T. Initiation Dose of Allopurinol and the Risk of Severe Cutaneous Reactions in Older Adults With CKD: A Population-Based Cohort Study. *Am. J. Kidney Dis.* **2022**, *80*, 730–739. [\[CrossRef\]](#)
63. Gonçalves, M.; Coutinho, I.; Teixeira, V.; Gameiro, A.; Brites, M.; Nunes, R.; Martinho, A. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. *Br. J. Dermatol.* **2013**, *169*, 660–665. [\[CrossRef\]](#)
64. Jutkowitz, E.; Dubreuil, M.; Lu, N.; Kuntz, K.M.; Choi, H.K. The cost-effectiveness of HLA-B*5801 screening to guide initial urate-lowering therapy for gout in the United States. *Semin. Arthritis Rheum.* **2017**, *46*, 594–600. [\[CrossRef\]](#)
65. Ko, T.-M.; Tsai, C.-Y.; Chen, S.-Y.; Chen, K.-S.; Yu, K.-H.; Chu, C.-S.; Huang, C.-M.; Wang, C.-R.; Weng, C.-T.; Yu, C.-L.; et al. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: National prospective cohort study. *BMJ* **2015**, *351*, h4848. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Pascart, T.; A Wasik, K.; Preda, C.; Chune, V.; Torterat, J.; Prud'homme, N.; Nassih, M.; Martin, A.; Le Masson, J.; Rodière, V.; et al. The gout epidemic in French Polynesia: A modelling study of data from the Ma'i u'u epidemiological survey. *Lancet Glob. Health* **2024**, *12*, e685–e696. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Terashima, R.; Medina, A.J.P.; Del Mundo, H.J.F.; Briones, R.S.S.; Aquino, J.A.B.; Quiminiano, E.M.; Sin, Y.M.; Bautista, R.A.; Sonido, C.Y.; Yamada, S. Prevalence of Human Leukocyte Antigen (HLA)-B*58:01 and Allopurinol-Induced Adverse Reactions in Filipino Patients in Hawai'i: Implications for Genotyping. *Int. J. Rheum. Dis.* **2025**, *28*, e70127. [\[CrossRef\]](#)
68. Yu, K.H.; Yu, C.Y.; Fang, Y.F. Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: An updated systematic review and meta-analysis. *Int. J. Rheum. Dis.* **2017**, *20*, 1057–1071. [\[CrossRef\]](#)
69. Campbell, C.N.; Krantz, M.S.; Yu, A.; Phillips, E.J.; Gad, R.D.; Drucker, A.; Ergen, E.; Gangula, R.; Goh, M.; Kaffenberger, B.; et al. HLA-B*58:01 and Risk of Allopurinol-Induced Severe Cutaneous Adverse Reactions in the US. *JAMA Dermatol.* **2025**, *161*, 1258–1263. [\[CrossRef\]](#)
70. Stamp, L.K.; Chapman, P.T.; Barclay, M.L.; Horne, A.; Frampton, C.; Tan, P.; Drake, J.; Dalbeth, N. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. *Ann. Rheum. Dis.* **2017**, *76*, 1522–1528. [\[CrossRef\]](#)
71. Stamp, L.K.; Chapman, P.T.; Barclay, M.; Horne, A.; Frampton, C.; Tan, P.; Drake, J.; Dalbeth, N. Allopurinol dose escalation to achieve serum urate below 6 mg/dL: An open-label extension study. *Ann. Rheum. Dis.* **2017**, *76*, 2065–2070. [\[CrossRef\]](#) [\[PubMed\]](#)

72. Richette, P.; Doherty, M.; Pascual, E.; Barskova, V.; Becce, F.; Castañeda-Sanabria, J.; Coyfish, M.; Guillo, S.; Jansen, T.L.; Janssens, H.; et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann. Rheum. Dis.* **2017**, *76*, 29–42. [\[CrossRef\]](#)
73. FitzGerald, J.D.; Dalbeth, N.; Mikuls, T.; Brignardello-Petersen, R.; Guyatt, G.; Abeles, A.M.; Bardin, T.; Becker, M.A.; Brophy, J.L.; Burke, F.M.; et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Rheumatol.* **2020**, *72*, 879–895. [\[CrossRef\]](#)
74. Garcia-Doval, I.; LeCleach, L.; Bocquet, H.; Otero, X.L.; Roujeau, J.C. Toxic epidermal necrolysis and Stevens-Johnson syndrome: Does early withdrawal of causative drugs decrease the risk of death? *Arch. Dermatol.* **2000**, *136*, 323–327. [\[CrossRef\]](#)
75. Kuyucu, S.; Blanca-Lopez, N.; Caubet, J.; Moral, L.; Sousa-Pinto, B.; Topal, O.Y.; Mori, F.; Markovic, M.A.; Gomes, E. Clinical diagnosis and management of drug reaction with eosinophilia and systemic symptoms (DRESS) in children: An EAACI position paper. *Pediatr. Allergy Immunol.* **2025**, *36*, e70103. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Stamp, L.K.; Chapman, P.T.; Barclay, M.; Horne, A.; Frampton, C.; Tan, P.; Drake, J.; Dalbeth, N. The effect of kidney function on the urate lowering effect and safety of increasing allopurinol above doses based on creatinine clearance: A post hoc analysis of a randomized controlled trial. *Arthritis Res. Ther.* **2017**, *19*, 283. [\[CrossRef\]](#)
77. Neogi, T.; Dalbeth, N.; Stamp, L.; Castelar, G.; Fitzgerald, J.; Gaffo, A.; Richette, P.; Doherty, M.; Pascual, E.; Barskova, V.; et al. Renal dosing of allopurinol results in suboptimal gout care. *Ann. Rheum. Dis.* **2017**, *76*, e1. [\[CrossRef\]](#)
78. Dalbeth, N.; Kumar, S.; Stamp, L.; Gow, P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J. Rheumatol.* **2006**, *33*, 1646–1650.
79. Robinson, P.C.; Dalbeth, N. Advances in pharmacotherapy for the treatment of gout. *Expert Opin. Pharmacother.* **2015**, *16*, 533–546. [\[CrossRef\]](#)
80. Lorenzo, J.P.P.; Sollano, M.H.M.Z.; Salido, E.O.; Li-Yu, J.; Tankeh-Torres, S.A.; Manuaba, I.A.R.W.; Rahman, M.; Paul, B.J.; Mok, M.Y.; De Silva, M.; et al. 2021 Asia-Pacific League of Associations for Rheumatology clinical practice guideline for treatment of gout. *Int. J. Rheum. Dis.* **2022**, *25*, 7–20. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Yip, R.M.; Cheung, T.T.; So, H.; Chan, J.P.; Ho, C.T.; Tsang, H.H.; Yu, C.K.; Wong, P.C. The Hong Kong Society of Rheumatology consensus recommendations for the management of gout. *Clin. Rheumatol.* **2023**, *42*, 2013–2027. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Ke, C.-H.; Chung, W.-H.; Wen, Y.-H.; Huang, Y.-B.; Chuang, H.-Y.; Tain, Y.-L.; Wang, Y.-C.L.; Wu, C.-C.; Hsu, C.-N. Cost-effectiveness Analysis for Genotyping before Allopurinol Treatment to Prevent Severe Cutaneous Adverse Drug Reactions. *J. Rheumatol.* **2017**, *44*, 835–843. [\[CrossRef\]](#)
83. Park, D.; Kang, J.; Lee, J.; Lee, K.; Wen, L.; Kim, T.; Park, Y.; Park, S.; Lee, S. Cost-effectiveness analysis of HLA-B*58:01 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. *Arthritis Care Res.* **2015**, *67*, 280–287. [\[CrossRef\]](#)
84. Wong, C.S.-M.; Yeung, C.-K.; Chan, C.-Y.; Yap, D.Y.-H.; Tang, S.C.-W.; Cheung, B.M.-Y.; Kwok, J.S.-Y.; Chan, H.H.-L. HLA-B*58:01 screening to prevent allopurinol-induced severe cutaneous adverse reactions in Chinese patients with chronic kidney disease. *Arch. Dermatol. Res.* **2022**, *314*, 651–659. [\[CrossRef\]](#)
85. Fam, A.; Dunne, S.; Iazzetta, J.; Paton, T. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum.* **2001**, *44*, 231–238. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Bardin, T.; Chalès, G.; Pascart, T.; Flipo, R.-M.; Ea, H.K.; Roujeau, J.-C.; Delayen, A.; Clerson, P. Risk of cutaneous adverse events with febuxostat treatment in patients with skin reaction to allopurinol. A retrospective, hospital-based study of 101 patients with consecutive allopurinol and febuxostat treatment. *Jt. Bone Spine* **2016**, *83*, 314–317. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.