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SYSTEMATIC REVIEW

Allopurinol Hypersensitivity: A Systematic Review of All Published Cases, 1950–2012

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Abstract

Background Allopurinol is the primary therapy for the management of chronic gout. Utilization of allopurinol has increased in tandem with the growing prevalence of gout globally. This exposes more patients to the risk of allopurinol hypersensitivity (AH), a rare adverse reaction characterised by a spectrum of cutaneous reactions and systemic manifestations. Severe forms of AH have been associated with high mortality. The pathophysiology underlying this reaction remains unknown, but several risk factors have been proposed.

Objective The aim of this study was to review all published cases of AH documented in the literature in order to better understand the constellation of factors predisposing to this reaction, building on previous reviews by Lupton and Odom [163], Singer and Wallace [8]) and Arellano and Sacristan [9]).

Methods A literature search was conducted in MEDLINE and EMBASE to identify relevant articles published between January 1950 and December 2012, with no language restrictions imposed. Articles that were included reported either allopurinol-induced cutaneous manifestations alone or satisfied the diagnostic criteria for AH as defined by Singer and Wallace.

Results Nine hundred and one patients (overall AH cohort) were identified from 320 publications. Of these patients, 802 satisfied the Singer and Wallace criteria ('Singer and Wallace' cohort) while 99 patients had only mild cutaneous manifestations ('non-Singer and Wallace' cohort). Data were often incomplete; hence the results reported reflect the fractions of the subsets of the cohort where the data in question were available. In the overall AH cohort, 58 % (416/722) were male. The majority (73 %; 430/590) of patients were Asian. Renal impairment (48 %; 182/376) and hypertension (42 %; 160/376) were the most common chronic conditions; accordingly, diuretics (45 %; 114/252) and antihypertensives (39 %; 99/252) were the most prevalent concomitant medications. Allopurinol was prescribed for approved indications (chronic gout and chemoprophylaxis) in only 40 % (186/464) of patients. The median allopurinol dose was 300 mg/day (range 10–1,000 mg/day) and was taken by 50 % (168/338). There was no significant association between a higher dose (>300 mg/day) and an increased risk of severe cutaneous manifestations [odds ratio (OR) 1.76; 95 % CI 0.73–4.22; $p = 0.23$]. Approximately 90 % (489/538) of patients developed AH within 60 days of initiating allopurinol therapy. Serum oxypurinol (the active metabolite of allopurinol) concentration was only recorded in six patients, four of whom had levels within the putative therapeutic range of 30–100 μmol/L. The HLA-B*5801 allele was present in 99 % (166/167) of patients tested, with the majority (147/166) being of Asian ancestry. The all-cause mortality rate was 14 % (109/788) with 94 AH-related deaths, all of which occurred in the cohort meeting the Singer and Wallace criteria.

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Limitations The publications included in this review utilized different laboratory reference ranges to classify the non-cutaneous manifestations of AH; this may have introduced some variation in the cases identified as AH. A majority of the articles included in this analysis consisted of case reports and series—publication types that are not recognized as best-quality evidence; this thus limited the conclusions we could draw about the many risk factors we were interested in evaluating.

Conclusions Risk factors associated with AH, such as concomitant diuretic use, pre-existing renal impairment and recent initiation of allopurinol, were commonly present in AH patients; however, their role in the mechanism of AH remains to be established. A clear risk factor was the HLA-B*5801 status; this was especially relevant in Asian populations where there is a higher carriage rate of the allele. High allopurinol dose, previously suggested to be a risk factor, was not confirmed as such. The paucity of well-documented case reports and studies of AH render it difficult to draw more concrete conclusions or construct a meticulous profile of patients at risk of AH. Future case reports of AH need to be better documented to contribute to understanding the risks for, and mechanisms of, AH.

1 Background

Allopurinol, the primary therapy for the management of chronic gout, hyperuricaemia associated with the treatment of malignancies, and renal stones accompanied by hyperuricosuria, has been widely used since its introduction in the early 1960s [1, 2].

Allopurinol and its major metabolite oxypurinol directly inhibit uric acid synthesis by inhibiting xanthine oxidase (oxidoreductase), an enzyme that catalyzes the conversion of the purine derivative hypoxanthine to xanthine and, subsequently, xanthine to uric acid [3, 4]. The longer half-life of oxypurinol (approximately 23 h) compared with allopurinol (1.2 h) indicates that it is the former that is largely responsible for the urate-lowering effect of allopurinol [4].

Allopurinol is generally well tolerated, with approximately 1–5 % of patients reporting minor side effects such as gastrointestinal intolerance, mild fever and/or a mild rash [5, 6]. Allopurinol hypersensitivity (AH), a rare adverse reaction to allopurinol, is characterised by a combination of cutaneous manifestations [which may range in severity, from relatively benign maculopapular rashes to more lethal forms, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)], fever, hepatic dysfunction, renal impairment, eosinophilia and leukocytosis [7]. Although the precise incidence of AH is not known, it has been estimated to be approximately 0.1 %, and the resulting mortality for the severest forms of AH, such as SJS and TEN, has been reported to be as high as 27 % [8–10].

Despite case reports dating back to 1970, the precise pathogenesis underlying this syndrome remains largely unknown. Early studies implicated the accumulation of oxypurinol, in particular because of renal impairment, as a primary factor for the development of AH [11]. Several other risk factors for AH have been proposed including concomitant diuretic use, renal insufficiency itself, recent allopurinol initiation, high allopurinol dose, and the HLA-B*5801 genotype [12]. The starting dose of allopurinol has also been recently proposed as a risk factor by Stamp and colleagues [13], who found that patients commenced on $\geq$1.5 mg of allopurinol per unit estimated glomerular filtration rate (eGFR) were more likely to develop AH.

Epidemiological data suggest that the prevalence of gout is increasing in both Western and Asian countries, with higher rates observed in specific ethnic groups (such as the Taiwanese Han Chinese, New Zealander Maoris and Pacific Islanders and Australian Aborigines) [14–21]. Coinciding with the rising prevalence of gout is the increasing number of prescriptions for allopurinol being dispensed globally. In the US alone, approximately 12 million prescriptions for allopurinol were dispensed by outpatient retail pharmacies in 2008, representing a 47 % increase since 2002 [22]. In Australia, allopurinol remains the foremost urate-lowering therapy, accounting for more than 98 % of all dispensed medications for gout [23]. A large number of patients are, therefore, at risk of developing AH, which is particularly problematic as so little is known about this syndrome. Although the incidence of AH is low, allopurinol has been found to be the leading drug-induced cause of SJS and TEN in Europe and Israel, overtaking other well-known drugs associated with such reactions, including carbamazepine, phenytoin and the sulphonamides [24, 25]. Consequently, there is some urgency to better understand the factors that predispose to AH.

A previous review on AH by Arellano and Sacristan [9] identified 101 cases documented in the literature between 1970 and 1990 based on the criteria previously employed by Singer and Wallace [8]. We herein review all cases reported in the literature between 1950 and 2012 utilizing the same criteria but broadened to include cases of cutaneous manifestations only which, we believe, better encompass the spectrum of hypersensitivity reactions to allopurinol. The aim was to better define a risk factor profile for AH.

2 Methods

2.1 Search Strategy

A literature search was performed in MEDLINE and EMBASE to identify potentially relevant articles published between January 1950 and December 2012. The search string employed to search the two databases is presented in Table 1. No language restrictions were imposed. While our search string algorithm may not have captured every published case of AH, we are confident that any that were missed would not alter the results of this review.

2.2 Selection Criteria

References retrieved from the MEDLINE and EMBASE search were cross-checked against each other to remove duplicate records. Literature that was not formally published (such as conference proceedings and dissertations) was excluded. The resulting articles were assessed by two independent reviewers (CSK, SNR) who screened the titles and abstracts for eligibility for inclusion. Where abstracts were not available, the complete articles were assessed for inclusion. Eligibility for inclusion in this review was based on fulfilment of the 1986 Singer and Wallace [8] diagnostic criteria for AH outlined below:

(1) Clear history of exposure to allopurinol
(2) Clinical picture, including:
    a. at least two of the following *major* criteria:
        i. worsening renal function
        ii. acute hepatocellular injury
        iii. rash (including diffuse maculopapular rash, exfoliative dermatitis, erythema multiforme or toxic epidermal necrolysis);

OR

    b. one of the major criteria plus at least one of the following *minor* criteria:
        i. fever
        ii. eosinophilia
        iii. leukocytosis
(3) Lack of exposure to another drug which may have caused a similar clinical picture.

As noted, in order to obtain a more complete picture of reactions to allopurinol, cases in which only a cutaneous manifestation was present were included in the dataset.

The full text of selected articles deemed to be potentially relevant were then evaluated. Articles were excluded at this stage if (i) there was only mean or population data available instead of individual patient data; (ii) there was a lack of clinical data which had originally been alluded to in the abstract; or (iii) the imputability of allopurinol as the causative agent of the hypersensitivity reaction was inadequate due to the involvement of other suspect drugs. Discrepancies between the reviewers concerning the inclusion and/or exclusion of studies were resolved by adjudication by two independent reviewers (KMW, ROD).

Table 1 Search strategy to identify cases of allopurinol hypersensitivity indexed in MEDLINE and EMBASE

String	Search terms
1.	(Allopurinol or oxypurinol or gout suppressants).sh. or (315-30-0 or 2,465-59-0).rn or (allopurinol or allopurinoli or allopurinolum or alopurinol or alopurinolis or oxypurinol or oxipurinol).af.
2.	(Kidney failure or kidney diseases or kidney/ci,im,pa,pp or renal insufficiency or nephritis or glomerulonephritis).sh. or (renal failure or kidney failure or renal impairment or kidney impairment or nephropathy or nephritis or glomerulonephritis).af.
3.	(Liver diseases or hepatitis or liver failure, acute or liver/ci,im,pa,pp or granuloma).sh. or (hepatitis or hepatic failure or liver failure).af.
4.	(Epidermal necrolysis, toxic or Stevens–Johnson syndrome or drug eruptions or skin diseases or skin ulcer or skin).sh. or (toxic epidermal necrolysis or TEN or Lyell's or Lyells or erythema multiforme or Stevens–Johnson or Stevens Johnson or SJS or erythematous or maculopapular or exfoliative dermatitis or severe cutaneous adverse reaction or SCAR or rash).af.
5.	Fever.sh. or fever.af.
6.	Eosinophilia.sh. or eosinophilia.af.
7.	Leukocytosis.sh. or (leukocytosis or leucocytosis).af.
8.	(Drug toxicity or drug hypersensitivity or vasculitis).sh. or (toxicity or hypersensitivity or vasculitis or DRESS or (drug rash with eosinophilia and systemic symptoms) or AHS or allopurinol hypersensitivity syndrome).af.
9.	(2 and 3) or (2 and 4) or (3 and 4)
10.	(2 and 5) or (2 and 6) or (2 and 7) or (3 and 5) or (3 and 6) or (3 and 7) or (4 and 5) or (4 and 6) or (4 and 7)
11.	1 and (4 or 8 or 9 or 10)

2.3 Data Extraction

Data extracted by six authors (CSK, SNR, NW, DMR, MWHS, DRWK), where available, were age, sex, ethnicity, medical history, concomitant medications, and pertinent baseline laboratory markers, allopurinol usage (daily dose, duration and indication), hypersensitivity manifestations (cutaneous, renal, hepatic and haematological abnormalities, fever and mucosal involvement), significant laboratory tests (oxypurinol concentrations, lymphocyte stimulation test [LST] and HLA-B*5801 allele screening), hypersensitivity treatment and outcome (recovery, mortality and other sequelae). Other atypical symptoms and

unique observations (such as raised viral titres) were also recorded. Renal function was assessed by calculating the eGFR, using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula [26], where serum creatinine concentrations were available. Authors of the studies included in this review were not contacted for additional information; only the data that were already available in the publications were extracted.

2.4 Reference Ranges

For hypersensitivity manifestations that could be quantified by their respective laboratory markers, the presence or absence of such manifestations was established by utilizing the reference ranges in Table 2.

2.5 Statistical Analysis

Descriptive data are presented as mean (SD), median, proportions (%) or range where appropriate. Odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) were calculated to evaluate the associations between allopurinol dose and the development of severe cutaneous reactions, allopurinol dose and mortality, allopurinol indication and mortality, as well as AH manifestation and mortality. Differences between groups were analysed using the χ^2 test, Fisher's exact test and paired *t* test. A *p*-value of 0.05 or less was considered statistically significant. All calculations were performed using the statistical software program GraphPad Prism, Version 5.04 (GraphPad Software, Inc., San Diego, CA, USA).

It should be noted that complete datasets for the variables were not available, as these data were not always reported in the publications (e.g. not all patients had concomitant medications recorded). Thus, each variable investigated in this review is quantified relative to a different '*n*', often a small figure in comparison to the total number of cases in the overall AH cohort.

Table 2 Reference ranges utilised for determination of the allopurinol hypersensitivity (AH) manifestations [463]

AH manifestation	Laboratory parameter	Abnormal range
Renal	Serum creatinine (sCr)[a]	>120 μmol/L
	Creatinine clearance (CrCL)	<60 mL/min
	Estimated glomerular filtration rate (eGFR)	<60 mL/min/1.73 m^2
	Blood urea nitrogen (BUN)	>6.7 mmol/L
Hepatic	Aspartate aminotransferase (AST)	>35 IU/L
	Alanine aminotransferase (ALT)	>35 IU/L
	Alkaline phosphatase (ALP)	>35 IU/L
	Total bilirubin (TBIL)	>17 μmol/L
Haematological	White blood cell (WBC) count	>11.0 × 10^9/L
	Eosinophils	>6.0 % of WBC
Fever	Temperature	>37.5 °C

[a] The upper limit for serum creatinine concentration was chosen to be 120 μmol/L (instead of 150 μmol/L as indicated in the Oxford Clinical Handbook of Medicine) so as to be concordant with standard clinical practice

3 Results

A total of 320 articles [1, 5, 7, 8, 11, 27–341] were retrieved from records identified in the MEDLINE and EMBASE databases. The flow diagram (Fig. 1) delineates the literature search results, indicating the exclusions at each step, leading to the final cohort of 901 cases.

Of the 901 cases of AH, 624 (69.2 %) satisfied the Singer and Wallace criteria. In addition, there were 178 patients who were reported as having only severe cutaneous manifestations [erythema multiforme (EM), SJS and TEN] and did not have sufficient data recorded about the presence or absence of other manifestations. As SJS and TEN rarely occur without fever [342], the 178 patients were included in the Singer and Wallace cohort, giving a total of 802 Singer and Wallace AH cases. The remaining 99 patients who did not meet the Singer and Wallace criteria were reported to have mild cutaneous reactions. Some authors refer to the latter as maculopapular erythema (MPE) and suggest a different mechanism to that causing AH [279].

Only 278 of the 802 Singer and Wallace patients had laboratory parameters reported to validate the systemic manifestations and, hence, be definitively identified as cases of AH.

3.1 Demographics and Baseline Clinical Parameters

The demographic features of the overall AH cohort are summarised in Table 3. There was a preponderance of patients aged 50 years and above, constituting more than 74 % of the AH cohort. The majority of patients (73 %) were of Asian ancestry, with a quarter of these patients reported as Han Chinese from Taiwan, Hong Kong and China.

Surprisingly, clinical parameters relevant to AH were reported only for a small minority of patients (Table 4). Of the 72 patients with serum urate values available, only one was not hyperuricaemic. Data on renal function, such as serum creatinine concentration, creatinine clearance (CrCL) and eGFR were also available only for a limited number of patients. Of these, 93 % of patients had renal impairment (eGFR ≤60 mL/min).

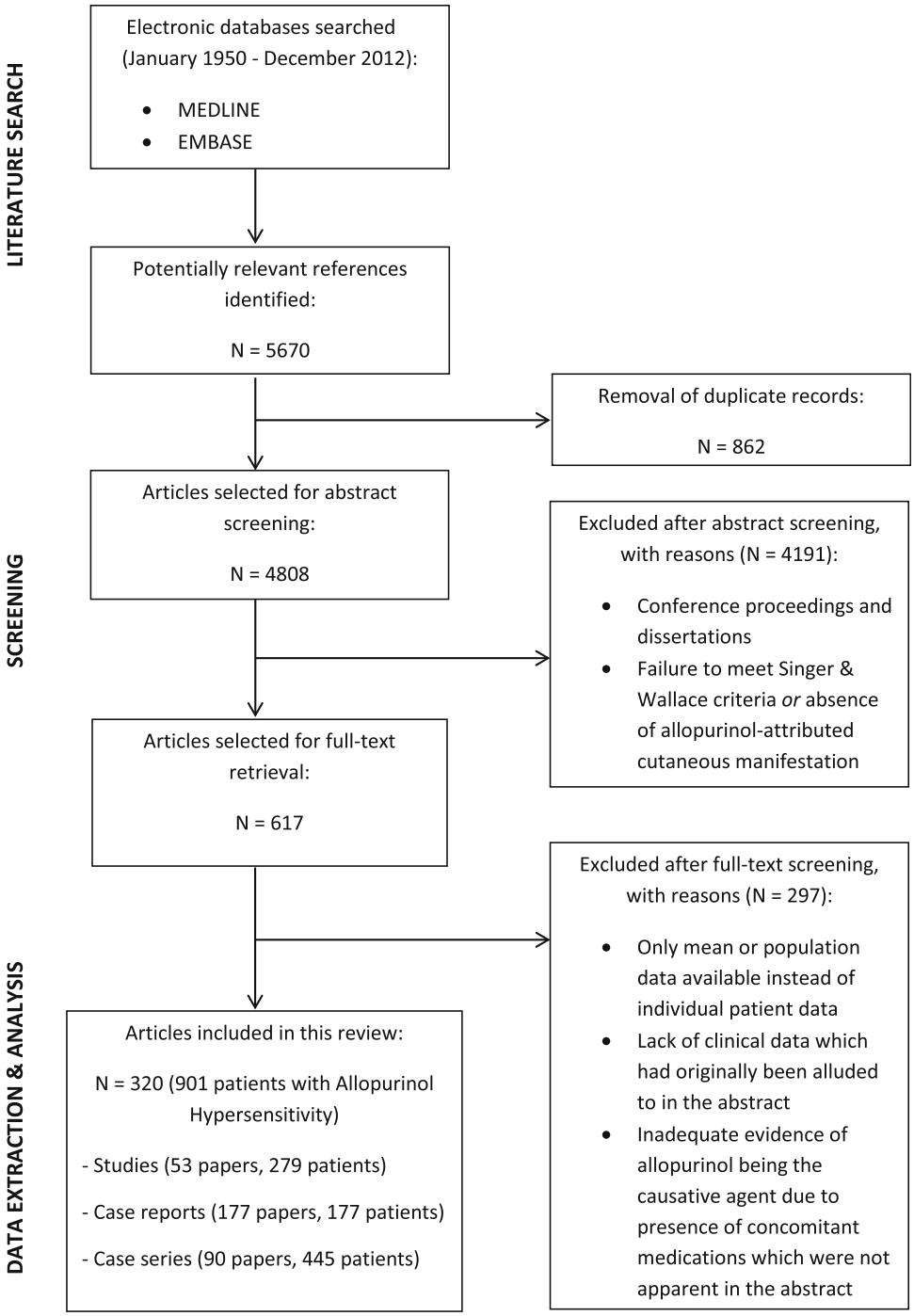

Fig. 1 Flow diagram illustrating the search strategy used to identify relevant studies from the literature

3.2 Comorbidities and Concomitant Therapies

Data on pre-existing chronic conditions and medication history were available for 376 and 252 patients, respectively (Table 5). Renal impairment and hypertension were the two most prominent comorbidities. More than a quarter of patients had a history of multiple (i.e. three or more) comorbidities.

Given the prevalence of compromised renal function and hypertension in the patient cohort, unsurprisingly, diuretics and antihypertensives were the most common therapeutic agents that patients were taking prior to commencing allopurinol. At least 62 patients were on both medications. Three or more medications were used by 54 patients (21 %).

3.3 Indications for Allopurinol Prescription and Dosage

Reasons for initiating allopurinol were identifiable in 464 patients (Table 6). More than 45 % of patients were being

Table 3 Characteristics of patients in the overall allopurinol hypersensitivity patient cohort ($n = 901$)

Patient demographics	[*n* (%)]
Sex[a]	
Males	416 (57.6)
Females	306 (42.4)
Age (years)[b]	
Mean ± SD	59.8 ± 16.1
Median	61
Range	8–96
Geographical ancestry[c]	
Europe	83 (14.1)
Africa	40 (6.78)
Americas	31 (5.25)
Oceania	6 (1.02)
Asia	430 (73.0)
Taiwan[d]	112 (26.0)
China[d]	79 (18.4)
Japan	42 (9.77)
Thai	35 (8.14)
Korea	27 (6.28)
Hong Kong[d]	21 (4.88)
India/Sri Lanka	4 (0.93)
The Philippines	3 (0.70)
Cambodia	3 (0.70)
Indonesian	1 (0.23)
Singapore	1 (0.23)
Laos	1 (0.23)
Vietnam	1 (0.23)
Pakistan	1 (0.23)
Not further defined	99 (23.0)

[a] Sex was specified for 722 of the 901 subjects

[b] Age was specified for 701 of the 901 subjects

[c] Ancestry was specified for 590 of the 901 subjects

[d] Of the 112 Taiwanese patients, 52 were identified as Han Chinese. Of the 79 Chinese patients, 39 were identified as Han Chinese. Of the 21 Hong Kong patients, 20 were identified as Han Chinese

Table 4 Baseline clinical parameters [relevant to allopurinol hypersensitivity (AH)] of patients in the overall AH patient cohort ($n = 901$)

Baseline (pre-AH) clinical parameters	
Serum urate (μmol/L)[a]	
Mean ± SD	639 ± 124
Median	636
Range	370–960
Serum creatinine (μmol/L)[b]	
Mean ± SD	239 ± 141
Median	177
Range	87–672
Reported creatinine clearance (mL/min)[c]	
Mean ± SD	39 ± 26
Median	30
Range	1–100
Calculated estimated glomerular filtration rate (eGFR) by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) [mL/min/1.73 m^2][d]	
Mean ± SD	31 ± 18
Median	29
Range	6–99

[a] Pre-AH serum urate concentrations were only available for 72 of the 901 patients

[b] Pre-AH serum creatinine concentrations were only available for 71 of the 901 patients

[c] Pre-AH creatinine clearances were only available for 38 of the 901 patients

[d] Pre-AH eGFR values were only able to be derived (using the CKD-EPI formula) [26] for 69 of the 71 patients who had serum creatinine concentrations available; age was not stated for the remaining two patients, hence we were unable to determine the pre-AH eGFR of these patients

treated with allopurinol for asymptomatic hyperuricaemia, whilst 13 % were taking the drug to treat an acute attack of gout.

Data on allopurinol dosing were available for 339 patients (Table 6). The median allopurinol dose was 300 mg/day (range 10–1,000 mg/day). Five patients were on 50 mg/day while one patient was on 10 mg/day [119, 241, 279, 286, 334]. Fifteen patients received allopurinol doses 500 mg or greater daily. There was one patient each on 500, 900 and 1,000 mg/day, eight patients on 600 mg/day and four patients on 800 mg/day [1, 5, 27, 64, 234, 238, 261, 271, 276, 295, 321, 324, 333]. Renal function prior to AH was available for only one of these 15 patients; the patient who was on a dose of 900 mg/day had pre-existing moderate kidney disease (eGFR of 40 mL/min/1.73 m^2) [234].

Of the 339 patients for whom allopurinol dosage was known, 23 had pre-AH CrCL values available [31, 32, 41, 80, 81, 87, 111, 121, 129, 145, 155, 163, 170, 178, 184, 207, 250, 340]. Only two patients were receiving doses recommended (R) for their renal function. One patient received a dose 100 mg lower than recommended ($R - 100$), while the remainder (20 patients) were receiving higher than recommended doses. Of this latter subset, seven received doses 150 mg above the recommended ($R + 150$), five received $R + 100$, two patients each received $R + 200$ and $R + 50$, respectively, and the other four patients received $R + 250$, $R + 270$, $R + 300$ and $R + 350$. There were five fatalities out of the 23, with two occurring in the $R + 50$ group and one each in the $R + 100$, $R + 150$ and $R + 200$ groups. Severe cutaneous reactions were only observed in five of the 23 patients, two

Table 5 Chronic conditions and common concomitant therapies noted in the overall allopurinol hypersensitivity patient cohort ($n = 901$)

	n (%)
Chronic illnesses[a]	
Renal impairment	182 (48.4)
Hypertension	160 (42.5)
Neoplasm/malignancy	39 (10.4)
Diabetes type II	44 (11.7)
Chronic heart failure	29 (7.7)
Others[b]	294 (78.2)
Concomitant medications[c]	
Diuretics	114 (45.2)
Antihypertensives	99 (39.3)
Digoxin	31 (12.3)
Colchicine	35 (13.9)
Probenecid	4 (1.6)
Others[d]	155 (61.5)

[a] Data on co-existing chronic illnesses were available for 376 of the 901 subjects

[b] Other conditions include, but are not limited to, renal disorders other than renal impairment ($n = 54$), cardiac or cardiovascular diseases other than chronic heart failure ($n = 53$), rheumatic diseases other than gout ($n = 26$), metabolic disorders ($n = 24$), infections ($n = 24$), autoimmune disorders ($n = 19$), respiratory disorders ($n = 14$), neurological disorders ($n = 13$), other haematological disorders ($n = 10$), other hepatic diseases ($n = 10$), gastrointestinal disorders ($n = 10$), ocular diseases ($n = 6$), allergies ($n = 6$) and immunological disorders ($n = 4$)

[c] Data on the use of medications commonly observed in the gout population were available for 252 of the 901 subjects. Patients were usually on more than one medication

[d] Authors may be contacted for the full list of medications

of whom developed fatal EM ($R + 150$ group and $R + 200$ group, respectively). The remaining three patients developed SJS ($R - 100$ group), EM ($R + 150$ group) and TEN ($R + 200$ group), all with non-fatal outcomes.

3.4 Time to Onset of Allopurinol Hypersensitivity (AH)

The latency period to the onset of the hypersensitivity reaction was chronicled in 538 patients (Fig. 2). The mean (SD) time to reaction was 10 (46) weeks, with the median being 3 weeks; however, this period of quiescence was exceedingly variable, with some patients ($n = 15$) developing hallmark features of the reaction as early as 1 day after allopurinol initiation, whereas in other patients ($n = 15$) symptoms only manifested more than 1 year after commencement of therapy. However, over 90 % of patients developed AH within 8–9 weeks of commencing allopurinol treatment.

Table 6 Patterns of allopurinol dosing and indication in the overall allopurinol hypersensitivity patient cohort ($n = 901$)

Allopurinol usage	*n* (%)
Dose (mg/day)[a]	
<100	6 (1.8)
100	68 (20.1)
150	2 (0.6)
200	70 (20.7)
300	168 (49.7)
400	9 (2.7)
≥500	15 (4.4)
Indication[b]	
Diagnosis of gout[c]	164 (35.3)
Asymptomatic hyperuricaemia	210 (45.3)
Chemoprophylaxis	22 (4.7)
Acute gout attack[c]	62 (13.4)
Other[d]	6 (1.3)

[a] Daily dose of allopurinol was known for 339 of the 901 patients. One patient (8-year-old female) was given a dose of 8.5 mg/kg bodyweight but patient's weight was not reported in the paper; thus, this patient was excluded from the final allopurinol dose analysis ($n = 338$)

[b] Indication for allopurinol use was known for 464 of the 901 patients

[c] A diagnosis of gout and an acute attack of gout in patients were accepted as such if stated in the publications; no attempts were made to verify the validity of the gout diagnosis or the classification of an 'acute' attack as the very first attack

[d] Other (non-approved) indications included worsening leg pain ($n = 2$), and back pain, ureterolith, cystitis and stage II essential hypertension ($n = 1$ each) [64, 86, 143, 215, 261, 287]

3.5 Hallmark Clinical Manifestations and Laboratory Findings during AH

A summary of the clinical features documented during the course of AH in the Singer and Wallace cohort ($n = 802$) is presented in Tables 7 and 8.

3.5.1 Major Criteria

Cutaneous manifestations were recorded in 787 (98 %) Singer and Wallace patients, with no further details available (vis-à-vis the type of skin alteration) for 196 (25 %) of these patients. The most frequent cutaneous lesion reported, occurring in 314 (40 %) patients, were the severe cutaneous reactions of SJS and TEN. MPEs occurred in 187 (24 %) patients. Exfoliative dermatitis (ED) and EM were far less common.

Mucosal involvement was also described frequently, with ulceration of the ocular, oral, oesophageal and genital mucosae being the most prevalent.

Although acute renal and hepatic injury were reported in 325 (40 %) and 308 (38 %) patients, respectively, only 188 and 153 of these patients, correspondingly, had the relevant

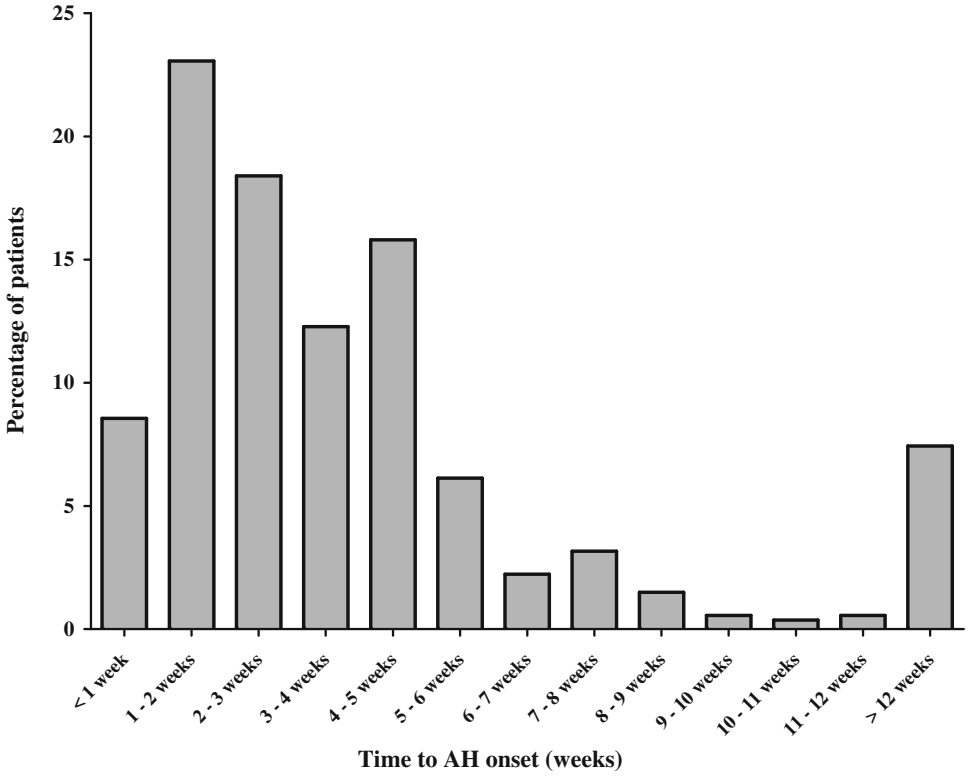

Fig. 2 Duration of allopurinol therapy prior to onset of allopurinol hypersensitivity (AH) reaction ($n = 538$)

laboratory parameters reported. The data from the 188 patients indicated quite severely compromised renal function (Table 8).

There were only 10 matched pairs for CrCL and 54 pairs for eGFR comparing baseline pre-AH values with values during AH. CrCL declined by an average of 31 % and eGFR by 54 % ($p < 0.001$ and $p < 0.0001$, respectively). Similarly, markers of hepatic function were grossly elevated compared with normal reference ranges (Table 8).

In the non-Singer and Wallace cohort ($n = 99$), all patients were reported to have had only a mild cutaneous reaction to allopurinol and no systemic symptoms. Approximately 45 % of patients were simply noted to have a rash or skin eruption. MPEs were reported in 36 patients, while ED was observed in five patients. Other cutaneous changes included urticaria ($n = 4$), bullous exanthema and fixed drug eruptions ($n = 2$ each), and eczematous rash, lupus erythematosus, erythema annulare centrifugum, acute generalised exanthematous pustulosis and eosinophilic pustular folliculitis ($n = 1$ each).

3.5.2 Minor Criteria

Fever was common; of 347 (43 %) patients reported with fever, only 134 patients had values recorded, with the mean (SD) temperature being 38.9 (0.7)°C and range 37.6–41.5°C. Presence of leukocytosis and eosinophilia was noted in 182 and 250 patients, respectively, with actual laboratory parameters available for confirmation for 118 and 141 patients, correspondingly. Leukocyte and eosinophil counts were exceedingly raised, with the mean (SD) leukocyte count being 18.0 (7.5) $\times$ 10^9/L and the mean (SD) eosinophil count being 20.9 (12.8) % (Table 8).

3.6 Other Aspects of AH

Non-specific symptoms observed in several patients included diarrhoea, nausea, anorexia, malaise, chills, dizziness, myalgia and sore throat. Other clinical manifestations such as lymphadenopathy, leukopenia, thrombocytopenia, neutropenia, agranulocytosis, interstitial pneumonitis, metabolic acidosis, tachycardia, hypovolaemia, tachypnoea and hypotension were also recorded.

Immunoglobulin G (IgG) antibody titres against various viruses such as human herpesvirus (HHV)-6, HHV-7, Epstein–Barr virus (EBV) and cytomegalovirus (CMV) were markedly elevated in some patients, indicating reactivation of latent viral infections. These patients tended to be diagnosed with Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) or Drug-Induced Hypersensitivity Syndrome (DIHS) [94, 97, 105, 108, 122, 138], with DRESS and DIHS being subsets of AH [279].

Isolated findings of autoantibodies were documented in two patients; one developed antinuclear antibodies (ANA) and antiribonucleoprotein (anti-RNP) antibodies after 3 years of allopurinol therapy, while the other

Table 7 Clinical manifestations of allopurinol hypersensitivity (AH)[a] reported in the Singer and Wallace cohort of 802 patients

		n (%)	Laboratory data available[b] (% of *n*)
Major criteria	Worsening renal function	325 (40.5)	188 (57.8)
	Acute hepatic injury	308 (38.4)	153 (49.7)
	Cutaneous change	787 (98.1)	–
	Simple rash	19 (2.41)	–
	MPE[c]	187 (23.8)	–
	ED	31 (3.94)	–
	EM	24 (3.05)	–
	SJS/TEN	314 (39.9)	–
	Other[d]	16 (2.03)	–
	Not specified[e]	196 (24.9)	–
Combinations of the major criteria	All three major criteria	186 (23.2)	107 (57.5)
	Cutaneous + renal	129 (16.1)	62 (48.1)
	Cutaneous + hepatic	111 (13.8)	40 (36.0)
	Renal + hepatic	6 (0.75)	3 (50.0)
Minor criteria	Fever	347 (43.3)	134 (38.6)
	Leukocytosis	182 (22.7)	118 (64.8)
	Eosinophilia	250 (31.2)	141 (56.4)
Combinations of the minor criteria	All three minor criteria	96 (12.0)	51 (53.1)
	Fever + leukocytosis	43 (5.36)	16 (37.2)
	Fever + eosinophilia	68 (8.48)	23 (33.8)
	Leukocytosis + eosinophilia	25 (3.12)	14 (56.0)
Strict fulfilment of Singer and Wallace criteria	Two major *OR* one major + one minor	624 (77.8)	278 (44.5)

[a] Manifestations of AH as defined by Singer and Wallace [8]

[b] Applicable to all manifestations, with the exception of cutaneous manifestations, which could be quantified by their respective laboratory markers (refer to Table 2)

[c] MPE, as noted in the methods, is used by some authors to indicate a simple rash without systemic manifestations and with a mechanism different from AH [279]; however, a simple rash of the MPE type in association with other Singer and Wallace criteria can make a diagnosis of AH

[d] Other cutaneous manifestations reported include petechial rash, haemorrhagic rash, eczematous rash, lupus erythematosus, bullous lesions/exanthema, urticaria, erythema annulare centrifugum, acute generalized exfoliative pustulosis, follicular toxic pustuloderma, blisters, skin lesions and fixed drug eruptions

[e] The presence of any skin manifestation, even if there were no further details as to the type of skin alteration, was accepted as such when indicated in the publications

developed peri-nuclear antineutrophil cytoplasmic antibodies (p-ANCA) within 3 weeks of allopurinol commencement [76, 87].

3.7 Serum Oxypurinol Concentrations

Serum oxypurinol concentrations were only available for 6 (herein referred to as patients A–F) of the 653 patients [11, 181, 185, 188, 203, 218]. Four patients (A, C, D and E) had concentrations that were within the putative therapeutic range of 30–100 μmol/L (A: 9.3 μmol/L; C: 50 μmol/L; D: 50 μmol/L; E: 86 μmol/L); serum samples, however, were drawn at different time points after the last allopurinol dose (A, E: 336 h; C, D: 8 h). As the putative therapeutic range refers to a 6–9 h window post-allopurinol dose, patient E was likely to have been above the therapeutic range initially, given the extensive time interval between the last allopurinol dose and the time point of blood sampling. The remaining two patients (B, F) had serum oxypurinol concentrations above the upper limit of the recommended therapeutic range (B: 126 μmol/L; F: 267 μmol/L); timing of the serum samples, however, was not stated.

Information about renal function preceding the onset of AH was available for four of these six patients; all four had pre-existing severe renal impairment (as indicated by a low eGFR value) preceding the AH reaction (A: 11 mL/min/1.73 m^2; B: 11 mL/min/1.73 m^2; E: 12 mL/min/1.73 m^2; F: 28 mL/min/1.73 m^2).

Table 8 Laboratory parameters of allopurinol hypersensitivity (AH) manifestations[a] in the Singer and Wallace cohort ($n = 802$)

	Variable	*N*	Mean (SD)	Median	Range
Major criteria					
Hepatic	AST (IU/L)	124	357 (687)	135	36–5,595
	ALT (IU/L)	122	358 (396)	215	37–2,222
	ALP (IU/L)	26	518 (361)	387	116–1,366
	TBIL (mmol/L)	12	110 (83)	93	18–289
Renal	Serum Cr (μmol/L)	161	461 (338)	354	88–1,945
	CrCL (mL/min)	30	20.4 (15.6)	17.2	1–70
	BUN (mmol/L)	115	37.4 (27.6)	30.3	7–176
	eGFR (mL/min per 1.73 m^2)[b]	160	17.8 (13.6)	13.1	2–63
Minor criteria					
Fever	Temperature (°C)	134	38.9 (0.7)	39.0	37.6–41.5
Leukocytosis	WBC count ($\times 10^9$/L)	118	18.0 (7.5)	15.5	11.1–65.3
Eosinophilia	Eosinophils (%)	141	20.9 (12.8)	15.4	7.0–64.2

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CKD-EPI* Chronic Kidney Disease-Epidemiology Collaboration, *CrCL* creatinine clearance, *eGFR* estimated glomerular filtration rate, *Serum Cr* serum creatinine, *TBIL* total bilirubin, *WBC* white blood cell

[a] Manifestations of AH as defined by Singer and Wallace [8]

[b] The eGFR values were derived using the CKD-EPI formula [26]. There were 99 patients who had data on serum creatinine, age and sex but not race—they were assumed to be non-African American for purposes of eGFR calculation

Table 9 Clinical management of allopurinol hypersensitivity (AH) and outcome in the overall AH patient cohort ($n = 901$)

	n (%)
Treatment modality[a]	
None	60 (14.6)
Glucocorticosteroids	285 (69.2)
Intravenous immunoglobulin	37 (8.98)
Antibiotics	75 (18.2)
Dialysis	27 (6.55)
Outcome[b]	
Recovery	679 (86.2)
All-cause mortality	109 (13.8)
Mortality from AH	94 (86.2)
Mortality from unrelated complications	15 (13.8)

[a] Data on treatment strategies employed were available for 412 of the 901 patients. Several patients received combination therapy with those therapies listed

[b] Data on outcome subsequent to the AH reaction were available for 788 of the 901 patients

3.8 Results of Patch Tests and Lymphocyte Stimulation Tests (LSTs)

Of the ten patients in the AH cohort who underwent patch testing [64, 82, 87, 152, 167, 182, 233, 328], seven returned negative results (six of whom were tested with allopurinol, with the remaining patient being tested with oxypurinol), while three returned positive results with allopurinol.

LSTs were performed in 29 patients in the AH cohort, with 21 patients returning negative results with allopurinol. Of these 21, one patient also returned a negative LST to oxypurinol, while nine patients returned a positive LST to oxypurinol. Furthermore, 2 of the 21 patients underwent patch testing with allopurinol, returning a positive and negative result each. Of the eight patients with a positive LST to allopurinol, one patient returned a negative LST to oxypurinol while another patient had a negative patch test with allopurinol.

3.9 HLA-B*5801 Genotyping

The presence of the HLA-B*5801 allele was demonstrated in 166 patients [125, 241, 271, 276, 278, 279, 311, 327, 329], 160 of whom were from the Singer and Wallace AH cohort. The remaining six patients had only mild MPEs.

Of the 166 patients, 146 were of Asian background. Approximately 75 % of these Asian patients belonged to the Han Chinese ethnic group. The HLA-B*5801 allele was also confirmed in 20 non-Asian patients, of whom 16 were of European ancestry. There was one patient who returned a negative result for the allele; this patient was of Han Chinese ethnicity from Hong Kong and had developed EM after 28 days of 300 mg allopurinol therapy [276].

Table 10 Comparison table of mortality rates between and within cohorts

	Recovery [*n* (%)]	All-cause mortality [*n* (%)]	AH-related mortality [*n* (%)]	Odds ratio (95 % CI)	Fisher's exact test
Singer and Wallace ($N = 696$)[a]	590 (84.8)	106 (15.2)	94 (13.5)	5.33 (1.66–17.2)[†]	$p = 0.0006$[†]
				28.6 (1.76–466)[‡]	$p < 0.0001$[‡]
Non-Singer and Wallace ($N = 92$)[a]	89 (96.7)	3 (3.3)	0 (0)		
Severe Singer and Wallace ($N = 280$)[b]	217 (77.5)	63 (22.5)	57 (20.3)	2.52 (1.65–3.84)ƨ	$p < 0.0001$ƨ
				2.65 (1.69–4.14)ƨƨ	$p < 0.0001$ƨƨ
Mild Singer and Wallace ($N = 416$)[b]	373 (89.7)	43 (10.3)	37 (8.9)		

[a] Of the overall allopurinol hypersensitivity (AH) cohort of 901 patients, 802 belonged to the Singer and Wallace cohort while the remaining 99 patients were designated as the non-Singer and Wallace cohort. Outcome of AH was known for 696 of the 802 Singer and Wallace patients and 92 of the 99 non-Singer and Wallace patients

[b] In the Singer and Wallace cohort of patients where outcome was known (i.e. $n = 696$), 280 patients had severe cutaneous reactions (such as erythema multiforme, Stevens–Johnson Syndrome and toxic epidermal necrolysis) while the remaining 416 patients had milder cutaneous reactions (including maculopapular exanthema)

[†] The all-cause mortality rate in the Singer and Wallace cohort was compared against that of the non-Singer and Wallace cohort

[‡] The AH-related mortality rate in the Singer and Wallace cohort was compared against that of the non-Singer and Wallace cohort

ƨWithin the Singer and Wallace cohort, the all-cause mortality rate in the subset with severe cutaneous reactions was compared against that of the subset with milder cutaneous reactions

ƨƨWithin the Singer and Wallace cohort, the AH-related mortality rate in the subset with severe cutaneous reactions was compared against that of the subset with milder cutaneous reactions

Additionally, three Japanese patients were found to carry the HLA-B58 serotype; one developed the DIHS subset of AH while the other two patients developed the more severe reactions of SJS and TEN [247].

3.10 AH Treatment and Outcomes

Data on treatments were available for 412 patients (Table 9). Withdrawal of allopurinol, either immediately upon presentation with AH symptoms or as soon as a diagnosis of AH was established, was reported in 234 (57 %) patients. The majority of patients (69 %) received glucocorticosteroid therapy, in either the systemic, oral or topical form. Antibiotics, dialysis and intravenous immunoglobulin (IVIg) were also relatively common, indicative of the severity of AH. Multimodal treatment involving various combinations of the above-mentioned therapies was more prevalent than unimodal treatment options.

Patient outcome could be ascertained for 788 of the 901 patients (Table 9). The overall mortality rate was 14 %, with 94 deaths directly attributed to AH and its sequelae.

Results for mortality were similar in the Singer and Wallace sub-cohort ($n = 802$) (Table 10). Severe cutaneous involvement (EM, SJS and TEN) was found to be associated with significantly higher odds of both all-cause and AH-related mortalities, compared with milder cutaneous involvement (Table 10).

Complications were described in 94 patients, with pathogenic infections and/or accompanying septicaemia being the most common, occurring in 47 patients. Twenty-six of these 47 patients succumbed to their infections.

3.11 Statistical Analysis

There was no association between higher allopurinol dose (>300 mg/day) and the development of severe cutaneous reactions (EM, SJS and TEN), all-cause mortality or AH-related mortality. However, allopurinol indication was found to be associated with AH-related mortality, with prescription for non-approved indications carrying an almost fourfold increased risk of death, compared with prescription for approved indications (OR 3.85; 95 % CI 1.76–8.45; $p = 0.0003$). Of the various Singer and Wallace manifestations during AH, worsening renal function was found to carry the highest odds ratio for both all-cause mortality (OR 2.98; 95 % CI 1.97–4.51; $p < 0.0001$) and AH-related mortality (OR 3.11; 95 % CI 1.99–4.84; $p < 0.0001$). Other manifestations such as hepatic dysfunction (OR 1.59; 95 % CI 1.05–2.39; $p = 0.03$ for all-cause mortality) and fever (OR 1.69; 95 % CI 1.13–2.54; $p = 0.01$ for all-cause mortality, and OR 1.81; 95 % CI 1.17–2.79; $p = 0.009$ for AH-related mortality) were also found to be associated with mortality, although these were less significant.

4 Discussion

4.1 Relationship of AH to Dose of Allopurinol and Renal Function

It has been thought that patients who develop AH are more likely to be renally impaired and to be taking maintenance allopurinol doses of between 300 and 400 mg daily [11]. Thus, the most common risk factors proposed for AH have been the maintenance dose of allopurinol and renal function; both relate to the concentration of the primary and active metabolite, oxypurinol, which is excreted renally. Dosing in accordance with renal function has thus been advocated.

Consistent with a dose-association hypothesis, the majority (85 %) of patients who developed AH were being treated with a daily maintenance dose of allopurinol 50–300 mg above that recommended by the guidelines of Hande et al [11]. The modal daily maintenance dose of allopurinol for the AH cohort (300 mg/day) is, however, also the most common dose used to treat patients with gout [343–346]. The proliferation in allopurinol usage worldwide, particularly of affordable generics and higher-dose formulations (such as 200 and 300 mg dosages) may also account for the frequency with which these doses feature in AH cases [22, 24].

Many studies have drawn a link between the higher-than-recommended maintenance doses and the occurrence of AH [343, 345, 347, 348]. Results from the EuroSCAR project, for example, revealed that allopurinol doses ≥200 mg/day were associated with a significantly increased risk for SJS and TEN compared with lower doses (adjusted OR 36; 95 % CI 17–76) [24]. By contrast, our review revealed that daily doses of >200 mg were not associated with an increased risk of serious AH, namely SJS and TEN, compared with a lower dose (OR 0.58; 95 % CI 0.33–1.02). However, as dose appropriateness according to renal function (viz. the guidelines of Hande et al.) could not be ascertained for the majority of our AH cohort, we were not able to assess whether a higher-than-recommended maintenance dose as per the guidelines by Hande et al. [11] is an irrefutable risk factor for AH.

A recent study by Stamp and colleagues [13] identified the starting dose of allopurinol to be a significant risk factor for AH. They found that AH patients had initiated allopurinol at a higher dose than matched, unaffected controls (183.5 ± 14.0 mg/day vs. 112.2 ± 6.3 mg/day; $p < 0.001$). Stamp et al. suggested a very conservative allopurinol starting dose of 1.5 mg per unit eGFR to mitigate the risk of AH in new allopurinol users. We were not able to confirm this association in our review as the doses reported in the publications we analysed were largely maintenance doses (or assumed to be maintenance doses, if not stated explicitly). However, it should be noted that there is likely to be a difference in the risk for AH between low starting allopurinol doses which are gradually escalated and higher starting allopurinol doses. This important point should be explored further.

A lack of a dose-association for AH risk is supplemented by evidence from a spate of studies demonstrating that (i) a lower allopurinol dose does not diminish the risk of AH [10, 81, 241, 349]; (ii) hypersensitivity occurs despite dose adjustment for renal function [10, 251, 350, 351]; (iii) hypersensitivity can occur even with normal renal function [37, 153, 188]; (iv) no statistical difference in dose is usually observed between hypersensitive patients and tolerant patients [271, 276, 352]; and (v) doses above 300 mg/day (achieved by means of upward titration) are safe and tolerable [353–355]. We therefore speculate that AH is most likely not dose-associated, although the rate of increase of dose is not excluded as a risk factor [13].

4.2 Oxypurinol Concentrations

The published, putative therapeutic range of oxypurinol concentrations is 30–100 μmol/L, 6–9 h post allopurinol dose [356–359]. Studies that demonstrated strongly positive LST results with oxypurinol in patients with AH further implicated oxypurinol in the pathogenesis of AH [182, 198], while the significant inverse relationship between serum oxypurinol concentration and CrCL was the basis for dose adjustment according to renal function, mentioned above.

However, the paucity of serum oxypurinol measurements in case reports of AH, as unequivocally demonstrated in this review, makes it difficult to authenticate any relationship between serum oxypurinol concentration and the incidence of AH. Notably, only six cases of AH reported the associated oxypurinol concentrations; of these, four patients had serum concentrations of oxypurinol within the therapeutic range. Furthermore, serum oxypurinol concentrations above the therapeutic range are frequently reported in patients, including those with renal insufficiency, without serious adverse events ensuing [360, 361].

Unfortunately, the concerns of toxicity and, adherence to the dosing guidelines of Hande et al., have resulted in sub-optimal management of gout and hyperuricaemia in a majority of patients; up to 50 % of patients fail to achieve target serum urate concentrations. A revision of the therapeutic range and guidelines is now required [348, 360].

4.3 Hyperuricaemia, Gout and Quality of Care

Key quality-of-care indicators for the management of gout have been developed [362]. Asymptomatic hyperuricaemia, in the absence of (i) a prior history of gouty arthritis

or tophaceous deposits; (ii) a prior history of nephrolithiasis or hyperuricosuria; and (iii) ongoing treatment of malignancy, is not an indication for urate-lowering therapy (such as allopurinol). However, the current review found that indicators are rarely adhered to, with 45 % of the AH cohort receiving allopurinol for hyperuricaemia alone, a non-approved indication. Again, this finding is concordant with previous studies, with treatment rates of asymptomatic hyperuricaemia ranging from 21 to 57 % [271, 363, 364]. Four previous reviews of patients with AH found that allopurinol was prescribed for asymptomatic hyperuricaemia in 55, 67, 56 and 75 % of patients, respectively [8, 9, 11, 163].

Treatment of asymptomatic hyperuricaemia stemmed from the results of the Framingham Study, which found that hyperuricaemia was associated with a risk of developing acute gouty arthritis and nephropathy [365]. Despite later studies [366–368] demonstrating that hyperuricaemia did not impair renal function in either gouty and asymptomatic hyperuricaemic subjects, and that only an estimated 20 % of hyperuricaemic individuals would experience a gout attack [369], treating hyperuricaemia (by means of allopurinol) became prevalent and this practice appears to have continued. This is likely due to re-emerging data that proposes that hyperuricaemia is an independent risk factor for hypertension, cardiovascular and renal disease, and metabolic syndrome [370–380]. Additionally, there have been data demonstrating that hyperuricaemia correlates with future kidney injury in those with normal renal function [381], and allopurinol treatment of asymptomatic hyperuricaemic individuals with chronic kidney disease (CKD) can conserve renal function for up to 1 year [382]. As the strength of such associations grows, and given the rising prevalence of hyperuricaemia in several countries (US: 21.2 % in males and 21.6 % in females; Australia: 23 % in males; Thailand: 18.4 % in males and 7.8 % in females; China: 21.6 % in males, 8.6 % in females), it is conceivable that allopurinol may be indicated as prophylaxis for asymptomatic hyperuricaemia in those with cardiovascular or renal risk factors.

Apart from asymptomatic hyperuricaemia, approximately 15 % of AH cases were prescribed allopurinol inappropriately for acute attacks of gout and for other miscellaneous conditions. This is significantly higher than the rate reported by Neogi et al. [383], who found that 5 of 110 (4.5 %) patients who consulted a physician for recurrent attacks of gout were prescribed allopurinol acutely.

Another study which examined allopurinol prescribing habits in a teaching hospital observed that 47 % of patients without appropriate indications were prescribed allopurinol [350]. This could be partly because junior doctors often continue to prescribe whatever drugs the patient was on in the community. Similar results were seen in an Australian study which examined the prescribing patterns in gout, whereby 42 % of general practitioners and 7 % of rheumatologists initiated urate-lowering treatment after a single acute gout attack [291]. There are data suggesting that, after the first attack, approximately 38 % of patients do not experience a recurrent attack for 1 year, while there is no recurrence for at least 10 years in 7 % of patients [384]. Given this and a quality-of-care indicator which advocates commencing urate-lowering therapy only in hyperuricaemic patients who experience at least two attacks per year, allopurinol introduction following an initial attack of gout is unwarranted [362, 363].

4.4 Risk Factors

4.4.1 Ethnicity

The overwhelming majority of patients (82 %) who constitute the burden of ambulatory care of gout in the US are Caucasian; [385] African-Americans, and Asian and Pacific Islanders account for only 6 and 8 %, respectively. By contrast, Asians constituted the majority (73 %) of the AH cohort in our study. The general prevalence of gout in Asians has traditionally been lower than that of Caucasians [14–21]. Hence, the overwhelming representation of Asians in the AH cohort, in particular by those from East Asia, is striking. This observation mirrors that of Stamp et al. [13], who found that New Zealanders of Chinese origin had an increased propensity to develop AH, compared with New Zealanders of European ancestry (OR 70.8; $p = 0.005$).

This increased risk stems from the higher carriage rate of the HLA-B*5801 allele in the Chinese population (allelic frequency of 8.9 % from the dbMHC database) [386]. A genetic predilection to allopurinol-induced cutaneous reactions was initially identified in a study which found that 15/17 patients of southern Chinese descent who developed AH possessed the HLA-B17 serotype [relative risk (RR 15); 95 % CI 10.3–209.2; $p = 1.7 \times 10^{-5}$], of which the HLA-B58 serotype is a subtype [387]. This observation was later substantiated by Hung et al. [241], who identified the specific allele to be HLA-B*5801. In the latter study, all 51 patients (Han Chinese from Taiwan) with severe cutaneous adverse reactions (SCAR) due to allopurinol carried the HLA-B*5801 allele, compared with 15 % of allopurinol-tolerant controls (OR 580.3; 95 % CI 34.4–9,780.9; $p = 4.7 \times 10^{-24}$) and 20 % of healthy controls (OR 393.5; 95 % CI 23.2–6,665.26; $p = 8.1 \times 10^{-18}$). Polymorphisms in other alleles (HLA-C*0302, HLA-A*3303, HLA-C*0801 and HLA-DRB1*0301) were thought also to contribute to the pathogenesis of allopurinol-induced SCAR [241, 388]. Hung et al. [241] suggested that the HLA-B*5801 allele, while essential, was not

sufficient, as allopurinol-tolerant patients also possessed the allele; however, this conclusion has been disputed by Lonjou et al. [329], who found that only 61 % of allopurinol-induced SJS/TEN patients (most of whom were Europeans) carried the HLA-B*5801 allele and concluded that the allele was neither essential nor sufficient. The lower frequency (0.8 %) of the HLA-B*5801 allele in the European population [386] may explain the results of Lonjou and colleagues.

Positive associations between HLA-B*5801 and allopurinol-induced SCAR have also been reported in Hong Kong Han Chinese, Japanese, Koreans, Thai and Europeans [141, 276, 311, 327, 329, 351, 388, 389]. The strength of these associations correlate with the frequency with which the HLA-B*5801 allele occurs in these populations [390].

In this review, HLA-B*5801 was reported in 166 patients, 109 of whom were reported to be of Han Chinese ethnicity from Taiwan, Hong Kong and China [241, 271, 276, 278]. Of the remaining 57 HLA-B*5801 positive patients, 37 were from other Asian countries such as Thailand ($n = 27$) and Japan ($n = 4$); 16 were of European ancestry, two of African ancestry and one from Oceania [125, 279, 311, 327, 329]. Additionally, three Japanese patients were positive for the HLA-B58 serotype [247]. This is not surprising, given the HLA-B*5801 allele frequencies observed in these populations (Han Chinese: 7.3–10.4 %; Thailand: 8.6 %; North-East Asia: 6.1 %; Europe: 0.8 %; Africa: 2.9 %; and Oceania: 2.5 %, from the dbMHC database) [386]. Despite the higher carriage rate of the HLA-B*5801 allele in Asian populations in general than in European populations, a recent meta-analysis demonstrated that the strength of the association between HLA-B*5801 and allopurinol-induced SJS/TEN was as strong in the non-Asian population (OR 101.45; 95 % CI 44.98–228.82) as it was in the Asian population (OR 74.18; 95 % CI 26.95–204.14), indicating that HLA-B*5801 screening prior to allopurinol commencement could be useful in different populations [391].

To date, there has been no formal evaluation of the cost-effectiveness of HLA-B*5801 screening to prevent cases of AH. A small study from Thailand utilized a decision analytical model to determine the cost price threshold for HLA-B*5801 genotyping that would be economical from a healthcare provider's point of view. They estimated that, to be cost effective, an HLA-B*5801 test would need to be in the range of $US13–$35 [392]; however, one must note that since this is not a routine test, it is not widely available. Furthermore, it is also time-consuming (turnover times are reported to be 3–4 weeks) and, currently, it is in the vicinity of $US150.00, based on private laboratory estimates. [393] The HLA-B*5801 allele has a low-to-moderate sensitivity but high specificity in cases of allopurinol-induced SJS/TEN; however, the positive predictive value of the allele for the development of AH is low, because of the very low incidence of AH and the reasonably high carriage rate of the HLA-B*5801 allele in Asian sub-populations (e.g. approximately 10 % in the Han Chinese). Thus, HLA-B*5801 as a *population screening tool* on its own does not appear to be an effective preventive measure against AH, even in high-risk populations which have a higher carriage rate of the allele, such as the Han Chinese and Thai. [279] However, at this stage of our knowledge, HLA-B*5801 genotyping might be beneficial in individual patients who are about to initiate allopurinol, if they are of certain Asian ethnic backgrounds; these patients should be advised about the availability of such a test so that they can choose to be genotyped if they are concerned about the risk (although small) of AH.

4.4.2 Age, Comorbidities and Polypharmacy

Older age, pre-existing multiple comorbidities and polypharmacy were characteristic of the AH cohort, associations which are reflective of the clinical profiles of primary users of allopurinol. Gout increases in prevalence with age and occurs 3–4 times more frequently in men than women, although this difference disappears when women reach menopause [394–398]. Therefore, given that the median age of male patients was 60 years and that of female patients was 65 years, the sex discrepancy usually seen in gout was not observed in the AH cohort, with females as likely to be affected by AH as males.

Patients with gout and/or hyperuricaemia manifest several types of comorbidities, with hypertension, cardiovascular disease, CKD, hyperlipidaemia and diabetes being the most prevalent [13, 399–402]. The results of this review are in line with the afore-mentioned studies, whereby renal impairment, hypertension, diabetes and heart failure were the most commonly reported pre-existing conditions in AH patients. Secondary hyperuricaemia as a consequence of chemotherapy is also an accepted indication for allopurinol treatment. It was then unsurprising that malignancies were reported in more than 10 % of AH patients. Approximately 10 % of the AH cohort had four or more co-existing comorbidities; however, the majority (54 %) had a minimum of two comorbidities.

The prevalence of comorbidities in the AH cohort was paralleled by the prevalence of prescription medication use. Polypharmacy is frequent in patients with gout and/or hyperuricaemia [399, 403–410]. Prescription medication use in the AH cohort (where known) was common, with the use of antihypertensives (including diuretics) being documented in over 84 % of patients. Although polypharmacy was observed on a smaller scale in the AH cohort, with only approximately one-fifth of patients using three or more

concomitant medications, this could have been due to the tallying of medications according to drug class, e.g. antihypertensives, instead of counting each single medication.

4.4.3 Reactivation of HHV-6

Reactivation of HHV-6 occurs exclusively in patients with DRESS/DIHS. This association is such that it is now included as a diagnostic criterion sensitive and specific for DRESS/DIHS [411–413]. It has been proposed that reactivation of HHV-6 or EBV triggers a sequential reactivation cascade of other herpes viruses, namely HHV-7 and CMV [411]. This is consistent with the detection of these viruses in some of the DRESS/DIHS patients in the AH cohort but not in patients with other drug eruptions.

The functional role of herpes virus reactivation in the pathogenesis of DRESS/DIHS remains uncertain. It has been suggested that certain drugs can interact with T cells which have retained the virus from an antecedent infection. Activation of these T cells causes reactivation of the viral genome, triggering a cellular and humoural response, thus leading to the onset of the DRESS/DIHS syndrome [414]. A recent study by Hirahara and colleagues [415] showed that EBV DNA was more prevalent in SJS/TEN patients than in DRESS/DIHS patients (78 vs. 30 %); SJS/TEN patients also had significantly higher titres of anti-herpes simplex virus IgG than DRESS/DIHS patients. Although we did not encounter any cases of SJS/TEN with virus reactivation, this is probably because studies of viral loads were not conducted.

4.4.4 Time to Onset of AH

In terms of risk mitigation, knowing the time after commencing treatment that a patient is most likely to develop AH is useful. The mean time has been reported to range from 3.5 to 6 weeks [8, 9, 163]. For our AH cohort, the mean (±SD) time to onset was longer (10 ± 46 weeks). More appropriately, we found a median time to onset of 3 weeks, similar to that seen previously [13, 276, 279, 351]. However, approximately 90 % of cases in our AH cohort occurred within 8.6 weeks (or 60 days), a rather shorter period than the 25.7 weeks (or 180 days) recently reported by Stamp et al. [13].

Sub-analysis revealed that SJS and TEN patients had a median time to onset of 21 days, which is comparable to the 20 days observed in the EuroSCAR study [416]. Another finding of EuroSCAR and that of its predecessor, the SCAR study, was that allopurinol therapy beyond 8 weeks posed no significant risk for the development of SJS and TEN (EuroSCAR study: univariate RR 1.4; 95 % CI 0.7–3.0. and SCAR study: crude RR 0.5; 95 % CI 0.1–4) [417] compared with therapy duration ≤8 weeks (EuroSCAR study: univariate RR 261; 95 % CI 36–∞, and SCAR study: crude RR 52; 95 % CI 16–167) [25]. A similar association was found in this study, whereby the risk of developing SJS and TEN was significantly higher when the duration of allopurinol therapy was 8 weeks or less compared with a longer duration (RR 6.6; 95 % CI 2.2–20.0; $p < 0.0001$).

Fifteen patients who developed AH did so 1 year or more after commencing allopurinol. We suggest that a possible explanation for this delay could be the short episodic use of allopurinol. Several studies have documented the exceptionally poor compliance to medication in patients with gout [346, 418–421]. Reasons for allopurinol non-compliance include (i) disenchantment with treatment when gout flares are not averted; (ii) a mistaken belief that allopurinol can be ceased once gouty symptoms subside, resulting in intermittent use when symptoms recur; (iii) aversion to the notion of lifelong therapy; (iv) failure to remember to take the medication; (iv) concerns about potential adverse effects; and (v) inability to afford the drug due to financial duress [346, 422–425].

4.5 Laboratory Tests for AH

Both in vivo (e.g. patch test) and in vitro (e.g. LST) tests can be employed to determine the culpable agent in drug hypersensitivity reactions [426]; however, the sensitivity and specificity of these tests vary depending on the drug being investigated, the type of cutaneous reaction being elicited, as well as the timing of the tests [427–429]. One study reported that all allopurinol-induced DRESS patients ($n = 19$) returned negative patch tests with allopurinol, while nine were also negative when tested with oxypurinol, leading the authors to conclude that patch testing was unhelpful where allopurinol was implicated [265]. Similar results have been found in other studies [430, 431]. While patch testing of the AH cohort returned mostly negative results, the mixed results perhaps reflect the different reagents used under varying conditions, such as drug exposure time and choice of vehicle, which are known to affect the sensitivity of patch tests [265, 429, 431]. Similarly, the majority of LSTs performed in the AH cohort were negative, which is concordant with other studies where LSTs were frequently negative [265, 430]. In a proportion of the AH cohort, both patch tests and LSTs were performed simultaneously; however, results were inconsistent, with only one of the two tests being positive.

It should be acknowledged that while a positive in vivo or in vitro test is usually a useful indicator of the culpability of a drug in a hypersensitivity reaction, a negative test does not exclude the role of the drug in the reaction [426, 432, 433]. The conflicting results of both tests seen in the AH cohort suggest that diagnostic testing for AH is

unreliable; instead, drug provocation (or drug rechallenge) is the gold standard for identifying the perpetrator drug in an adverse reaction, but whether this should be attempted in cases of possible AH needs very careful consideration.

4.6 Manifestations of Allopurinol Hypersensitivity

The skin is often the primary site of manifestation of drug hypersensitivity reactions; occasionally it may be the only organ displaying evidence of an adverse reaction [434, 435]. Hence, in order to obtain a more complete representation of the various types of hypersensitivity reactions induced by allopurinol, cutaneous-only reactions were also incorporated into this review. Thus, while we adopted the diagnostic criteria for AH as previously defined by Singer and Wallace [8], we also included cases where only a cutaneous manifestation was reported.

4.7 Mortality Rates

The overall mortality rate for the AH cohort was 13.8 %, considerably lower than that reported in previous reviews (26.3, 27.5 and 26.7 %) [8, 9, 163]. Similarly, a mortality rate of 25 % was found in Han Chinese patients diagnosed with allopurinol-SCAR [276], while a study of AH in new allopurinol users found a mortality rate of 26.7 % [436]. The multicentre EuroSCAR study revealed a mortality rate of 32 % in allopurinol-SCAR patients [24]. The high mortality rates observed in these studies were attributable to the higher proportion of patients with severe reactions (SJS and TEN) than those with milder hypersensitivity reactions. In the present cohort, Singer and Wallace patients diagnosed with EM, SJS or TEN, had a significantly higher mortality rate than Singer and Wallace patients with milder hypersensitivity reactions (20.3 vs. 8.9 %; $p < 0.0001$). This is in line with the findings of Atzori et al. [351] who reported that while the overall allopurinol-related mortality rate was 12 %, it was much higher (32 %) in the sub-population of patients with SJS and TEN. As expected, a low all-cause mortality rate (3 %) was observed in patients with mild cutaneous reactions and none of the deaths were directly attributable to AH. A few studies have also reported lower mortality rates in patients with AH, ranging from 5.3 to 12 %; these studies tended to have more patients with milder forms of AH [13, 351, 437].

4.8 Clinical Management of AH

There is no specific treatment for AH. The general management of drug hypersensitivity reactions involves immediate cessation of the causative agent, supportive care (which encompasses aggressive skin care and re-establishment of fluid and electrolyte balance), as well as a range of drug therapies, including corticosteroids in most patients. Immunoglobulin, ciclosporin (cyclosporine), cyclophosphamide, plasmapheresis and a number of other exotic choices, dictated more by the desperation of the clinicians rather than reasonable evidence of effect, have been reported [414, 438–441].

Despite appearing to be a first-line choice in the treatment of drug hypersensitivity reactions, controversy continues to dog the use of corticosteroids, with some studies reporting increased mortality or lack of efficacy, while other studies demonstrate a mortality benefit, especially if administered early on in the reaction as a high dose, short course and with appropriate tapering [413, 440–442]. Treatment of the AH cohort was dominated by the use of corticosteroids, with more than two-thirds of patients receiving this agent. This is similar to the previous report that 65 % of patients were treated with corticosteroids [9]. The same review identified a substantially higher mortality rate in corticosteroid-treated patients compared with those who did not receive corticosteroids (30.3 vs. 9.1 %). By contrast, mortality rates of patients treated with only corticosteroids did not differ significantly from that of patients treated with other agents (overall mortality: 11.9 vs. 10.9 %; $p = 0.7$, and AH-mortality: 9.5 vs. 10.0 %; $p = 1.0$). These data, again, are most likely explained by the severity of the condition of the patient driving the prescribing decisions.

Studies have reported conflicting results on the use of IVIg, with some showing no effect on mortality or progression of epidermal sloughing [443–446] while others found earlier cessation of epidermal detachment, lower mortality and a faster time to re-epithelialization [336, 447–451]. In the present AH cohort, IVIg was used almost exclusively in patients with SJS and TEN. The overall mortality rate for patients treated with IVIg was 27 %, substantially higher than that of the corticosteroid-treated group (12 %). This is similar to the figures reported in the EuroSCAR study; mortality rate of IVIg-treated patients was 34 %, while that of corticosteroid-treated patients was 18 % [452]. It must be noted, however, that the EuroSCAR study comprised patients with hypersensitivity reactions to several classes of drug, only one of which was allopurinol. Although the use of IVIg remains controversial, studies that have used IVIg suggest that high doses of IVIg ($\geq$2 g/kg) commenced early in the course of the disease do confer a survival benefit [440, 441, 453–455].

Antibiotics have also been frequently administered as empirical treatment preceding diagnosis of AH due to suspicion of an infection underlying the hypersensitivity reaction. However, prophylactic antibiotic use has been deemed unnecessary, as it may confound or exacerbate the clinical picture as a result of unforeseen cross-reactivity between drugs, or their use may lead to the advent of resistant pathogens [413, 441].

5 Limitations

There are several caveats in this study. Firstly, as the publications included in this analysis utilized different laboratory reference ranges to classify the manifestations of AH, this may have introduced some variation in the definition of AH; however, this was dealt with by adopting standardized reference ranges across all publications to standardize the manifestations. Secondly, a majority (over 80 %) of the articles included in this analysis consisted of case reports and series, publication types that are not recognized as best-quality evidence; the conclusions we could draw about the many risk factors for AH we were interested in evaluating were, accordingly, limited. As with most retrospective studies, an inherent limitation of this study was the quality and accuracy of data extraction; however, as the data collected from the publications for this study were mostly quantitative, there was little potential for variability in recording the data. Where qualitative data, such as descriptions of cutaneous manifestations, non-specific symptoms of AH and complications, were concerned, the study authors who were involved in data extraction entered the information into a pre-designed spreadsheet, which allowed consistent coding and cataloguing of the data.

6 Conclusions and Recommendations

AH is a relatively rare adverse event; however, when it occurs, the mortality rate is not insignificant. The clearest risk factor is ethnicity (Han Chinese, notably) and, more specifically, those possessing the HLA-B*5801 allele. Greater risk with elevated serum oxypurinol concentrations due to higher doses of allopurinol and/or impaired renal function remains unproven. As the mechanism is a hypersensitivity response, classically, dose-independence would be expected. The rate of increase of dose as suggested recently by Stamp et al. [13] remains to be established as a risk factor but the data are suggestive of this association. Concomitant diuretic use, pre-existing renal impairment and prescribing for an inappropriate indication are commonly present but might represent the prevalence of these factors in the population sample prescribed allopurinol. Again, whether these indeed are risk factors remain to be proven. The risk of AH is greatest in the first few months after initiation of allopurinol.

Our understanding of AH and details of its underlying pathophysiological mechanisms remain poor. Advances have been made in the identification of risk factors for AH; however, the absence of complete and important data in most case reports continues to hinder our ability to draw more concrete conclusions. The incompleteness of adverse drug reaction (ADR) case reports in general is well-documented [456–461] and is not confined to AH.

We recommend that all future case reports of AH should adhere to, or as a minimum, incorporate crucial elements of, the ADR reporting guidelines proposed by the International Society for Pharmacoepidemiology (ISPE) and International Society of Pharmacovigilance (ISoP) [462]. Importantly, HLA-B*5801 status should also be reported. This would facilitate the uniform reporting of cases, thus allowing both direct comparisons of cases as well as systematic reviews, which may assist in elucidating the underlying pathophysiology of AH.

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References

1. Rundles RW, Metz EN, Silberman HR. Allopurinol in the treatment of gout. Ann Intern Med. 1966;64:229–58.
2. Bradlow A. Adverse reactions profile: allopurinol. Prescr J. 1997;37:29–33.
3. Pacher P, Nivorozhkin A, Szabo C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev. 2006;58:87–114.
4. Day RO, Graham GG, Hicks M, et al. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet. 2007;46:623–44.
5. McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalised patients. Ann Rheum Dis. 1981;40:245–9.
6. Aubock J, Fritsch P. Asymptomatic hyperuricaemia and allopurinol induced toxic epidermal necrolysis. BMJ. 1985;290:1969–70.
7. Lang PG Jr. Severe hypersensitivity reactions to allopurinol. South Med J. 1979;72:1361–8.
8. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome: unnecessary morbidity and mortality. Arthritis Rheum. 1986;29:82–7.
9. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother. 1993;27:337–43.
10. Dalbeth N, Stamp L. Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. Semin Dial. 2007;20:391–5.
11. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency. Am J Med. 1984;76:47–56.
12. Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. Curr Rheumatol Rep. 2009;11:135–40.
13. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum. 2012;64:2529–36.
14. Chang HY, Pan WH, Yeh WT, et al. Hyperuricemia and gout in Taiwan: results from the Nutritional and Health Survey in Taiwan (1993–96). J Rheumatol. 2001;28:1640–6.

15. Minaur N, Sawyers S, Parker J, et al. Rheumatic disease in an Australian Aboriginal community in North Queensland, Australia. A WHO-ILAR COPCORD survey. J Rheumatol. 2004;31:965–72.
16. Zeng QY, Chen R, Darmawan J, et al. Rheumatic diseases in China. Arthritis Res Ther. 2008;10:R17.
17. Anagnostopoulos I, Zinzaras E, Alexiou I, et al. The prevalence of rheumatic diseases in central Greece: a population survey. BMC Musculoskelet Disord. 2010;11:98.
18. Cea Soriano L, Rothenbacher D, Choi HK, et al. Contemporary epidemiology of gout in the UK general population. Arthritis Res Ther. 2011;13:R39.
19. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum. 2011;63:3136–41.
20. Robinson PC, Taylor WJ, Merriman TR. Systematic review of the prevalence of gout and hyperuricaemia in Australia. Intern Med J. 2012;42:997–1007.
21. Winnard D, Wright C, Taylor WJ, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. Rheumatology (Oxford). 2012;51:901–9.
22. Zineh I, Mummaneni P, Lyndly J, et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. Pharmacogenomics. 2011;12:1741–9.
23. Chung Y, Lu CY, Graham GG, et al. Utilization of allopurinol in the Australian community. Intern Med J. 2008;38:388–95.
24. Halevy S, Ghislain PD, Mockenhaupt M, et al. 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.
25. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128:35–44.
26. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
27. Klinenberg JR. The effectiveness of allopurinol in the treatment of gout. Arthritis Rheum. 1965;8:891–5.
28. Scott JT, Hall AP, Grahame R. Allopurinol in treatment of gout. Br Med J. 1966;2:321–7.
29. Blechman WJ, Rosenberg DG, Hilf P. Use of allopurinol in gout, hyperuricemia and uric acid lithiasis. South Med J. 1967;60:215–8.
30. Muggia FM, Ball TJ Jr, Ultmann JE. Allopurinol in the treatment of neoplastic disease complicated by hyperuricemia. Arch Intern Med. 1967;120:12–8.
31. Wilson JD, Simmonds HA, North JD. Allopurinol in the treatment of uraemic patients with gout. Ann Rheum Dis. 1967;26:136–42.
32. Manahan LA, Portes JC. Allopurinol in the treatment of gout. Acta Medica Philipp. 1968;4:189–97.
33. Kantor GL. Toxic epidermal necrolysis, azotemia, and death after allopurinol therapy. JAMA. 1970;212:478–9.
34. Bailey RR, Neale TJ, Lynn KL. Allopurinol-associated arteritis. Lancet. 1976;2:907.
35. Espiritu CR, Alalu J, Glueckauf LG, et al. Allopurinol-induced granulomatous hepatitis. Am J Dig Dis. 1976;21:804–6.
36. Butler RC, Shah SM, Grunow WA, et al. Massive hepatic necrosis in a patient receiving allopurinol. JAMA. 1977;237:473–4.
37. Gelbart DR, Weinstein AB, Fajardo LF. Allopurinol-induced interstitial nephritis. Ann Intern Med. 1977;86:196–8.
38. Medline A, Cohen LB, Tobe BA, et al. Liver granulomas and allopurinol. Br Med J. 1978;1:1320–1.
39. Burkle WS. Allopurinol hypersensitivity. Drug Intell Clin Pharm. 1979;13:218–23.
40. Fam AG, Paton TW, Chaiton A. Reinstitution of allopurinol therapy for gouty arthritis after cutaneous reactions. Can Med Assoc J. 1980;123:128–9.
41. Hamilton DV, Shah PJR, Pryor JS, et al. Acute vasculitis and exacerbation of renal failure secondary to allopurinol hypersensitivity. Dial Transpl. 1980;9:78.
42. Link F, Mueller-Fassbender H. Drug-induced lupus erythematodes (DILE): minor tranquillizers and allopurinol as general inducers of the DILE syndrome? [German] Medikamentos Induzierter Lupus Erythematodes. Minor-Tranquilizers Und Allopurinol Als 'General Inducers' Des Di-Le Syndroms. Munchener Medizinische Wochenschrift. 1980;122:1099–100.
43. Daul AE, Graben N, Anlauf M, et al. Generalized vasculitis as potentially fatal side effect of allopurinol. [German] Generalisierte Vaskulitis Als Lebensbedrohliche Nebenwirkung Von Allopurinol. Verhandlungen der Deutschen Gesellschaft fur Innere Medizin. 1981;87:1235–8.
44. Gotz VP, Salem R. Bullae associated with allopurinol. Drug Intell Clin Pharm. 1981;15:490–1.
45. Lee EJ, Kueh YK. Allopurinol-induced skin reactions and agranulocytosis. Singap Med J. 1982;23:178–80.
46. Ramond MJ, Nouel O, Degott C, et al. Allopurinol-induced hepatitis: report of a case and review of the literature (author's transl). Gastroenterol Clin Biol. 1982;6:138–42.
47. Bruguera M, Libre J, Aubia J, et al. Allopurinol-induced cholestasis. [Spanish] Colestasis Por Alopurinol. Gastroenterologia y Hepatologia. 1983;6:253–5.
48. Halebian P, Corder V, Herndon D, et al. A burn center experience with toxic epidermal necrolysis. J Burn Care Res. 1983;4:176–83.
49. Dan M, Jedwab M, Peled M, et al. Allopurinol-induced toxic epidermal necrolysis. Int J Dermatol. 1984;23:142–4.
50. Fong PH, Ratnagopal P, Wong KL. Drug induced toxic epidermal necrolysis. Singap Med J. 1984;25:184–6.
51. Ebel V, Baumann R, Czechanowski B. Five cases of drug-induced Lyell's syndrome. [German] Funf Falle Mit Medikamenten-Induziertem Lyell-Syndrom. Innere Medizin. 1985;12:280–4.
52. Renwick IG. Asymptomatic hyperuricemia and allopurinol induced toxic epidermal necrolysis. Br Med J. 1985;291:485 (Clinical Research Ed).
53. Zakraoui L, Daly L, Hamza M. Lyell's syndrome happened to a patient treated by allopurinol. [French] Syndrome De Lyell Survenant Chez Une Patiente Traitee Par L'allopurinol. Tunisie Medicale. 1985;63:167–70.
54. Durst UN, Muller E, Pfister T. Toxic epidermal necrolysis (Lyell's syndrome). [German] Toxische Epidermale Nekrolyse (Lyell-Syndrom). Schweiz Med Wochenschr. 1986;116:713–20.
55. Johnston JB, Glazer RI, Pugh L, et al. The treatment of hairy-cell leukaemia with 2′-deoxycoformycin. Br J Haematol. 1986;63:525–34.
56. Kumar L. Allopurinol induced toxic epidermal necrolysis. Indian J Dermatol. 1986;31:53–4.
57. Rayle RT. 5 nursing lessons from a patient with T.E.N. Am J Nurs. 1986;86:300–2.
58. Balacco-Gabrieli C, Palmisano C, Lorusso V, et al. Lyell's syndrome caused by allopurinol. Clinical case. Ophtalmologie. 1988;2:123–6.
59. Sauve C, Pinquier JL, Boissonnad A, et al. Systemic allopurinol toxicity. Eur J Intern Med. 1992;3:78–81.
60. Yu RC, Chu TC. Allopurinol-induced toxic pustuloderma. Br J Dermatol. 1993;128:95–8.
61. Carsuzaa F, Pierre C, Morand JJ, et al. Allopurinol hypersensitivity syndrome: Erythema annulare centrifugum. [French]

Syndrome D'hypersensibilite a L'allopurinol a Type D'erytheme Annulaire Centrifuge. Nouvelles Dermatologiques. 1994;13:670–1.
62. Ioannides D, Vakali G, Chrysomallis F, et al. Toxic epidermal necrolysis: a study of 22 cases. J Eur Acad Dermatol Venereol. 1994;3:266–75.
63. Richter G, Blasum C. Allopurinol hypersensitivity syndrome. [German] Allopurinol-Hypersensitivitatssyndrom. Aktuelle Dermatologie. 1994;20:217–9.
64. Bang HD, Chung JH, Cho KH, et al. Three cases of allopurinol hypersensitivity syndrome. Korean J Dermatol. 1995;33:130–4.
65. Baroni T, Bocor M. Erythemato-maculo-papular eruption induced by allopurinol. [Italian] Eruzione Eritemato-Maculo-Papulosa Da Allopurinolo. Giornale Italiano di Dermatologia e Venereologia. 1995;130:45–7.
66. Domingues-Costa A, Marques P, Vaz-Da-Silva M. The allopurinol hypersensitivity syndrome: A case report. [Portuguese] Sindrome De Hipersensibilidade Ao Alopurinol. A Proposito De Um Caso Clinico. Arquivos de Medicina. 1996;10:48–54.
67. Kruppa A, Smola H, Scharffetter-Kochanek K, et al. Allopurinol-induced allergic vasculitis. [German] Vasculitis allergica auf Allopurinol. H+G Zeitschrift fur Hautkrankheiten. 1996; 71:868–9.
68. Gimbel Moral LF, De Miguel Sanchez C, Mugarza Hernandez MD, et al. Erupcion Fija Medicamentosa Causada Por Alopurinol. Medicina Clinica. 1996;106:119.
69. Sabaris Ma CF, Duran EP, Garcia-Patos PE, et al. Generalized acute exanthematic pustulosis due to allopurinol. [Spanish] Pustulosis exantematica aguda generalizada por alopurinol. Actas Dermo-Sifiliograficas. 1996;87:471–4.
70. Akriditis NK, Sakkas LI. Leukocytoclastic vasculitis. Consultant. 1997;37:1414.
71. Higuchi S, Yamamoto M. A case of Stevens–Johnson syndrome associated with allopurinol hypersensitivity [Japanese]. Acta Dermatologica Kyoto. 1997;92:367–73.
72. Schnyder B, Zanni MP, Pichler WJ. Drug-induced hypersensitivity syndrome. A review and presentation of 2 personal cases. Schweiz Med Wochenschr. 1997;127:355–9.
73. Calvino JA, Burgos RR, Mardaras J, et al. Hypersensitivity syndrome and granulomatous interstitial nephritis associated with allopurinol. [Spanish] Sindrome de hipersensibilidad y nefritis intersticial granulomatosa aguda asociada al alopurinol. Nefrologia. 1998;18:238–42.
74. Choquet-Kastylevsky G, Intrator L, Chenal C, et al. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. Br J Dermatol. 1998;139:1026–32.
75. Kluger E. Fatal outcome in allopurinol hypersensitivity syndrome. Ugeskr Laeger. 1998;160:1179–80.
76. Torralba FJ, Sanchez-Carbayo M, Gil MT, et al. Allopurinol hypersensitivity. [Spanish] Hipersensibilidad a alopurinol. Nefrologia. 1998;18:81–5.
77. Voets AJ, Joesoef KS. Allopurinol toxicity after coronary artery bypass grafting. Clin Intensive Care. 1998;9:88–9.
78. Wooten MD, Lipsmeyer E. Gout accompanying rheumatoid arthritis: a comparison of affected women and men. J Clin Rheumatol. 1998;4:220–4.
79. Hari Y, Urwyler A, Hurni M, et al. Distinct serum cytokine levels in drug- and measles-induced exanthema. Int Arch Allergy Immunol. 1999;120:225–9.
80. Buna D. Allopurinol hypersensitivity syndrome: a case report and review. Can J Hosp Pharm. 2000;53:36–9.
81. Vazquez-Mellado J, Morales EM, Pacheco-Tena C, et al. Relation between adverse events associated with allopurinol and renal function in patients with gout. Ann Rheum Dis. 2001;60:981–3.
82. Hari Y, Frutig-Schnyder K, Hurni M, et al. T cell involvement in cutaneous drug eruptions. Clin Exp Allergy. 2001;31:1398–408.
83. Ortega JD, Trindade C, Llamazares A, et al. Hypersensitivity to allopurinol. Efficacy of a desensitization procedure in three cases. [Spanish] Hipersensibilidad al alopurinol. Eficacia de un protocolo de desensibilizacion en tres casos. Anales de Medicina Interna. 2001;18:27–8.
84. Hoffman LA. My gout and allopurinol desensitization. J Clin Rheumatol. 2002;8:354–7.
85. Joshi A, Verma A, Gulati A, et al. Toxic epidermal necrolysis in a patient of chronic myeloid leukemia treated successfully with high dose steroids. J Inter Med India. 2002;5:40–2.
86. Maejima H, Mukai H, Hikaru E. Eosinophilic pustular folliculitis induced by allopurinol and timepidium bromide. Acta Derm Venereol. 2002;82:316–7.
87. Nishimura S, Shinoda T, Suzuki Y, et al. Drug-induced MPO-ANCA-positive necrotizing crescentic glomerulonephritis preceded by granulomatous hepatitis. Clin Exp Nephrol. 2002;6:118–20.
88. Posadas SJ, Padial A, Torres MJ, et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. J Allergy Clin Immunol. 2002;109:155–61.
89. Sommers LM, Schoene RB. Allopurinol hypersensitivity syndrome associated with pancreatic exocrine abnormalities and new-onset diabetes mellitus. Arch Intern Med. 2002;162: 1190–2.
90. Chubar Y, Bennett M. Cutaneous reactions in hairy cell leukaemia treated with 2-chlorodeoxyadenosine and allopurinol. Br J Haematol. 2003;122:768–70.
91. Hirashima N, Misago N, Nakafusa J, et al. Two cases of drug-induced hypersensitivity syndrome [Japanese]. Nishinihon J Dermatol. 2003;65:365–9.
92. Kim BJ, Kim MN, Ro BI, et al. A case of allopurinol hypersensitivity syndrome [Korean]. Korean J Dermatol. 2003;41: 251–4.
93. Nitti F, Fumagalli M, Incorvaia C. Rush desensitization to allopurynol. Allergy. 2003;58:690.
94. Koizumi H, Tsunoda T, Ito O, et al. A case of drug-induced hypersensitivity syndrome (DIHS) caused by allopurinol [Japanese]. Nishinihon J Dermatol. 2004;66:37–9.
95. Takayasu S, Nasu N, Hoshino T, et al. Drug eruption associated with allopurinol and vancomycin in a patient undergoing continuous ambulatory peritoneal dialysis (CAPD). A case report [Japanese]. Nishinihon J Dermatol. 2004;66:479–81.
96. Cho WI, Yoon YH, Kim MN, et al. Two cases of allopurinol hypersensitivity syndrome due to use of allopurinol for the patient with asymptomatic hyperuricemia [Korean]. Korean J Dermatol. 2005;43:961–4.
97. Kim JW, Kim JS, Kim KJ. A clinical observation of drug hypersensitivity syndrome and serologic and molecular genetic analyses of human herpesvirus-6 reactivation [Korean]. Korean J Dermatol. 2005;43:143–50.
98. Kwon KS, Kim BS, Jang BS, et al. Clinical study of drug rash with eosinophilia and systemic symptoms (DRESS) on drug eruption patients over the last 10 years (1995–2004) [Korean]. Korean J Dermatol. 2005;43:1164–9.
99. Lin MS, Dai YS, Pwu RF, et al. Risk estimates for drugs suspected of being associated with Stevens–Johnson syndrome and toxic epidermal necrolysis: a case-control study. Intern Med J. 2005;35:188–90.
100. Lissia M, Figus A, Rubino C. Intravenous immunoglobulins and plasmapheresis combined treatment in patients with severe toxic epidermal necrolysis: preliminary report. Br J Plast Surg. 2005;58:504–10.

101. Mantha S, Jacobs MI, Savage DG. Unusual leukemia presentations. Case 3. Type I IgGlambda cryoglobulinemia associated with chronic lymphocytic leukemia. J Clin Oncol. 2005;23: 5841–3.
102. Marie E, Fournier C, Bautin N, et al. Ultra-rush desensitization to allopurinol. [French] Accoutumance ultrarapide a l'allopurinol. Revue Francaise d'Allergologie et d'Immunologie Clinique. 2005;45:498–500.
103. Park MW, Kim SS, Lee JJ. Two cases of allopurinol hypersensitivity syndrome [Korean]. Korean J Dermatol. 2005;43: 114–7.
104. Song HJ, Kim CO, Lee KS. Two cases of allopurinol hypersensitivity syndrome in patients receiving thiazide therapy due to hypertension [Korean]. Korean J Dermatol. 2005;43:1426–9.
105. Stingeni L, Zeppa L, Lisi P. Allopurinol induced DRESS syndrome: Clinical and pathogenetic remarks. [Italian] Sindrome da ipersensibilita ad allopurinolo: Considerazioni clinicopatogenetiche. Annali Italiani di Dermatologia Allergologica Clinica e Sperimentale. 2005;59:115–7.
106. Wang D, Xhu XJ. Gouty patient hypersensitive to allopurinol: an intractable case. J Dermatol. 2005;32:64–5.
107. Das R. Allopurinol-associated angitis. J Pharm Pract Res. 2006;36:77.
108. Seishima M, Yamanaka S, Fujisawa T, et al. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. Br J Dermatol. 2006;155:344–9.
109. Torres MJ, Mayorga C, Fernandez TD, et al. T cell assessment in allergic drug reactions during the acute phase according to the time of occurrence. Int J Immunopathol Pharmacol. 2006;19:119–30.
110. Vahid B, Wildemore B, Lin T, et al. What caused diffuse alveolar hemorrhage in a patient with gout? J Respir Dis. 2006;27:441–3.
111. Wung DC, Cheng MF, Huang JJ, et al. Corticosteroid therapy in allopurinol hypersensitivity syndrome: a case report [Chinese]. J Intern Med Taiwan. 2006;17:133–40.
112. Calogiuri G, Muratore L, Congedo M, et al. Alternative treatments in allopurinol hypersensitivity syndrome: a case report. [Italian] Alternative terapeutiche nella sindrome da ipersensibilita all'allopurinolo: Descrizione di un caso clinico. Italian. J Allergy Clin Immunol. 2007;17:66–70.
113. Cornejo-Garcia JA, Fernandez TD, Torres MJ, et al. Differential cytokine and transcription factor expression in patients with allergic reactions to drugs. Allergy. 2007;62:1429–38.
114. Gravante G, Delogu D, Marianetti M, et al. Toxic epidermal necrolysis and Steven–Johnson syndrome: 11-years experience and outcome. Eur Rev Med Pharmacol Sci. 2007;11:119–27.
115. Nishio D, Izu K, Kabashima K, et al. T cell populations propagating in the peripheral blood of patients with drug eruptions. J Dermatol Sci. 2007;48:25–33.
116. Paquet P, Jacob E, Quatresooz P, et al. Delayed reepithelialization and scarring deregulation following drug-induced toxic epidermal necrolysis. Burns. 2007;33:100–4.
117. Yamane Y, Aihara M, Ikezawa Z. Analysis of Stevens–Johnson syndrome and toxic epidermal necrolysis in Japan from 2000 to 2006. Allergol Int. 2007;56:419–25.
118. Fortunati M, Dewulf V, Jouret F, et al. "DRESS syndrome"or systemic allopurinol hypersensitivity syndrome. [French] «DRESS syndrome» ou syndrome d'hypersensibilite systemique a l'allopurinol. Louvain Med. 2008;127:376–9.
119. Roche Gamon E, Carazo JLS, Argente CL, et al. Delayed allopurinol hypersensitivity syndrome. [Spanish] Sindrome de hipersensibilidad retardada a alopurinol. Piel. 2008;23:166–8.
120. Koike M, Kanno Y, Tomori K, et al. Viruses may trigger allopurinol hypersensitivity syndrome. NDT Plus. 2008;1:273–4.
121. Tausche AK, Aringer M, Schroeder HE, et al. The Janus faces of allopurinol-allopurinol hypersensitivity syndrome. Am J Med. 2008;121:e3–4.
122. Tohyama M, Shirakata Y, Sayama K, et al. A marked increase in serum soluble Fas ligand in drug-induced hypersensitivity syndrome. Br J Dermatol. 2008;159:981–4.
123. Asano Y, Kagawa H, Kano Y, et al. Cytomegalovirus disease during severe drug eruptions: report of 2 cases and retrospective study of 18 patients with drug-induced hypersensitivity syndrome. Arch Dermatol. 2009;145:1030–6.
124. Gratton SB, Scalapino KJ, Fye KH. Case of anakinra as a steroid-sparing agent for gout inflammation. Arthritis Rheum. 2009;61:1268–70.
125. Kemen C, Lemke J, Hoeger PH, et al. Human leukocyte antigen-related risk factors for toxic epidermal necrosis. Pediatr Infect Dis J. 2009;28:552.
126. Tamzaourte M, Errabih I, Krami H, et al. Acute cytolytic hepatitis induced by allopurinol in a patient treated for hepatitis C. [French] Hepatite aigue cytolytique induite par l'allopurinol chez un patient traite pour hepatite virale C. Journal Africain d'Hepato-Gastroenterologie. 2009;3:160–2.
127. Ang CC, Wang YS, Yoosuff EL, et al. Retrospective analysis of drug-induced hypersensitivity syndrome: a study of 27 patients. J Am Acad Dermatol. 2010;63:219–27.
128. Bellon T, Alvarez L, Mayorga C, et al. Differential gene expression in drug hypersensitivity reactions: induction of alarmins in severe bullous diseases. Br J Dermatol. 2010;162:1014–22.
129. Bennett S, Mitsides N, Dhaygude A, et al. A pilot in distress. NDT Plus. 2010;3:84–8.
130. Chaabane A, Aouam K, Fredj NB, et al. DRESS syndrome: 11 Case reports and a literature review. [French] DRESS syndrome: Etude de 11 cas et revue de la litterature. Therapie. 2010;65:543–50.
131. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010;146:1373–9.
132. Cooksley T, Iqbal J, Robertson C, et al. DRESS syndrome caused by allopurinol. Acute Med. 2010;9:122–3.
133. Elia F, Apra F. A potentially fatal cause of rash. Int J Emerg Med. 2010;3:491–2.
134. Flores SM, Hidalgo LG, Topete RO. Erithrodermia as presentation of DRESS syndrome associated with allopurinol. A report of a case. [Spanish] Eritrodermia como presentacion del sindrome DRESS asociado con alopurinol. Comunicacion de un caso. Dermatologia Revista Mexicana. 2010;54:104–7.
135. Ben Fredj N, Aouam K, Chaabane A, et al. Hypersensitivity to amoxicillin after drug rash with eosinophilia and systemic symptoms (DRESS) to carbamazepine and allopurinol: a possible co-sensitization. Br J Clin Pharmacol. 2010;70:273–6.
136. Lee T, Bae YJ, Park SK, et al. Severe pneumonia caused by combined infection with *Pneumocystis jiroveci*, parainfluenza virus type 3, cytomegalovirus, and *Aspergillus fumigatus* in a patient with Stevens–Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol. 2010;90:625–9.
137. Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E, et al. Amoxicillin-induced flare in patients with DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on human herpesvirus 6 replication in vitro. Eur J Dermatol. 2010;20:68–73.
138. Peppercorn AF, Miller MB, Fitzgerald D, et al. High-level human herpesvirus-6 viremia associated with onset of Stevens–Johnson syndrome: report of two cases. J Burn Care Res. 2010;31:365–8.
139. Cardoso CS, Vieira AM, Oliveira AP. DRESS syndrome: a case report and literature review. BMJ Case Rep. 2011. doi:10.1136/bcr.02.2011.3898.

140. Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. J Rheumatol. 2011;38:1957–9.
141. Jung JW, Song WJ, Kim YS, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. Nephrol Dial Transpl. 2011;26:3567–72.
142. Natkunarajah J, Goolamali S, Craythorne E, et al. Ten cases of drug reaction with eosinophilia and systemic symptoms (DRESS) treated with pulsed intravenous methylprednisolone. Eur J Dermatol. 2011;21:385–91.
143. Ranu H, Jiang J, Ming PS. A case series of allopurinol-induced toxic epidermal necrolysis. Indian J Dermatol. 2011;56:74–6.
144. Teo WL, Pang SM, Koh HY. Allopurinol hypersensitivity syndrome with acute generalized exanthematous pustulosis manifestations. Cutan Ocul Toxicol. 2011;30:243–4.
145. Aach R, Kissane J. Hypertension, hyperuricemia and iatrogenic disease. Am J Med. 1970;49:242–9.
146. Jarzobski J, Ferry J, Wombolt D, et al. Vasculitis with allopurinol therapy. Am Heart J. 1970;79:116–21.
147. Mills RM Jr. Severe hypersensitivity reactions associated with allopurinol. JAMA. 1971;216:799–802.
148. Simmons F, Feldman B, Gerety D. Granulomatous hepatitis in a patient receiving allopurinol. Gastroenterology. 1972;62:101–4.
149. Young JL Jr, Boswell RB, Nies AS. Severe allopurinol hypersensitivity. Association with thiazides and prior renal compromise. Arch Intern Med. 1974;134:553–8.
150. Ellman MH, Fretzin DF, Olson W. Toxic epidermal necrolysis associated with allopurinol administration. Arch Dermatol. 1975;111:986–90.
151. Boyer TD, Sun N, Reynolds TB. Allopurinol-hypersensitivity vasculitis and liver damage. West J Med. 1977;126:143–7.
152. Lockard O Jr, Harmon C, Nolph K, et al. Allergic reaction to allopurinol with cross-reactivity to oxypurinol. Ann Intern Med. 1976;85:333–5.
153. McMenamin RA, Davies LM, Craswell PW. Drug induced interstitial nephritis, hepatitis and exfoliative dermatitis. Aust N Z J Med. 1976;6:583–7.
154. Utsinger PD, Young WJ. Allopurinol hypersensitivity. Granular deposition of IgM at the dermal-epidermal junction. Am J Med. 1976;61:287–94.
155. Chan HL, Ku G, Khoo OT. Allopurinol associated hypersensitivity reactions: cutaneous and renal manifestations. Aust N Z J Med. 1977;7:518–22.
156. Devulder B, Plouvier B, Francois M, et al. Zeek's angiitis during combination treatment with allopurinol and a thiazide diuretic. Lille Med. 1977;22:798–800.
157. Calin A. Allopurinol toxicity masquerading as malignancy. JAMA. 1978;239:497.
158. Korting HC, Lesch R. Acute cholangitis after allopurinol treatment. Lancet. 1978;1:275–6.
159. Lindsey SW, Evans EF. Allpurinol hypersensitivity syndrome: effects and treatment. Va Med. 1978;105:297–9.
160. Male PJ, Schaer B, Posternak F. Hypersensitivity reaction to allopurinol. Schweiz Med Wochenschr. 1978;108:681–3.
161. Swank LA, Chejfec G, Nemchausky BA. Allopurinol-induced granulomatous hepatitis with cholangitis and a sarcoid-like reaction. Arch Intern Med. 1978;138:997–8.
162. Haughey DB, Lanse S, Imhoff T, et al. Allopurinol sensitivity: report of two cases. Am J Hosp Pharm. 1979;36:1377–80.
163. Lupton GP, Odom RB. The allopurinol hypersensitivity syndrome. J Am Acad Dermatol. 1979;1:365–74.
164. McKendrick MW, Geddes AM. Allopurinol hypersensitivity. Br Med J. 1979;1:988.
165. Phanichphant S, Boonpucknavig V. Allopurinol associated hypersensitivity. J Med Assoc Thai. 1980;63:155–63.
166. Al-Kawas FH, Seeff LB, Berendson RA, et al. Allopurinol hepatotoxicity. Report of two cases and review of the literature. Ann Intern Med. 1981;95:588–90.
167. Grussendorf M, Andrassy K, Waldherr R, et al. Systemic hypersensitivity to allopurinol with acute interstitial nephritis. Am J Nephrol. 1981;1:105–9.
168. Irino S, Sanada H, Maesako N, et al. A case of angio-immunoblastic lymphadenopathy with dysproteinemia related to allopurinol. Acta Med Okayama. 1981;35:263–72.
169. Earll JM, Saavedra M. Oxipurinol therapy in allopurinol-allergic patients. Am Fam Physician. 1983;28:147–8.
170. Ohsawa T, Ohtsubo M. Hepatitis associated with allopurinol. Drug Intell Clin Pharm. 1985;19:431–3.
171. Stein CM. Allopurinol hypersensitivity. A case report. S Afr Med J. 1985;67:935–6.
172. Webster E, Panush RS. Allopurinol hypersensitivity in a patient with severe, chronic, tophaceous gout. Arthritis Rheum. 1985;28:707–9.
173. Guerin C, Genin C, Toulon J, et al. Allopurinol toxicity. Apropos of 1 case. Nephrologie. 1986;7:47–9.
174. Handa SP. Drug-induced acute interstitial nephritis: report of 10 cases. CMAJ. 1986;135:1278–81.
175. Magner P, Sweet J, Bear RA. Granulomatous interstitial nephritis associated with allopurinol therapy. CMAJ. 1986;135:496–7.
176. Mousson C, Justrabo E, Tanter Y, et al. Acute granulomatous interstitial nephritis and hepatitis caused by drugs. Possible role of an allopurinol-furosemide combination. Nephrologie. 1986;7:199–203.
177. Pan HY, Glazener FS. The mackerel was in fact a red herring. Drug Intell Clin Pharm. 1986;20:687–9.
178. Schillinger F, Montagnac R, Milcent T. A new case of severe allopurinol toxicity. Nephrologie. 1986;7:214.
179. Vanderstigel M, Zafrani ES, Lejonc JL, et al. Allopurinol hypersensitivity syndrome as a cause of hepatic fibrin-ring granulomas. Gastroenterology. 1986;90:188–90.
180. Arbeteta J, Ledo L, Teruel JL, et al. Severe adverse reaction to allopurinol. Med Clin (Barc). 1987;88:125–6.
181. Pewsner D, Bachmann C, Muller U. Allopurinol-induced kidney failure with hepatitis and squamous dermatitis in pre-existing kidney insufficiency. Schweiz Med Wochenschr. 1987;117:139–41.
182. Emmerson BT, Hazelton RA, Frazer IH. Some adverse reactions to allopurinol may be mediated by lymphocyte reactivity to oxypurinol. Arthritis Rheum. 1988;31:436–40.
183. Foucault V, Pibouin M, Lehry D, et al. Severe drug accidents and allopurinol. Ann Dermatol Venereol. 1988;115:1169–72.
184. McDonald J, Fam AG, Paton T, et al. Allopurinol hypersensitivity in a patient with coexistent systemic lupus erythematosus and tophaceous gout. J Rheumatol. 1988;15:865–8.
185. Casas E, Puig JG, Mateos FA, et al. The allopurinol hypersensitivity syndrome: its relation to plasma oxypurinol levels. Adv Exp Med Biol. 1989;253A:257–60.
186. Coutellier P, Delgrange B. Fatal toxic epidermolysis following administration of allopurinol. Acta Clin Belg. 1989;44:196–8.
187. Gram JT, Gundersen T. Allopurinol hypersensitivity syndrome. Tidsskr Nor Laegeforen. 1989;109:3102–4.
188. Puig JG, Casas EA, Ramos TH, et al. Plasma oxypurinol concentration in a patient with allopurinol hypersensitivity. J Rheumatol. 1989;16:842–4.
189. Stricker BH, Blok AP, Babany G, et al. Fibrin ring granulomas and allopurinol. Gastroenterology. 1989;96:1199–203.
190. Chong RS, Ng HS, Teh LB, et al. Hepatic granulomas: an experience over the last 8 years. Singap Med J. 1990;31:422–6.
191. Collins CE, Thomas DJ, Gumpel JM. Catatonia in the allopurinol hypersensitivity syndrome. BMJ. 1991;302:970.

192. Marazuela M, Moreno A, Yebra M, et al. Hepatic fibrin-ring granulomas: a clinicopathologic study of 23 patients. Hum Pathol. 1991;22:607–13.
193. Walz-LeBlanc BA, Reynolds WJ, MacFadden DK. Allopurinol sensitivity in a patient with chronic tophaceous gout: success of intravenous desensitization after failure of oral desensitization. Arthritis Rheum. 1991;34:1329–31.
194. Fam AG, Lewtas J, Stein J, et al. Desensitization to allopurinol in patients with gout and cutaneous reactions. Am J Med. 1992;93:299–302.
195. San Andres Rebollo FJ, Gonzalez Rubio M, Postigo C, et al. Hypersensitivity syndrome caused by allopurinol: report of 2 cases and review of the literature. Rev Clin Esp. 1992;191:426–9.
196. Huang RY, Liu HN, Wong CK. Stevens–Johnson syndrome: a review of 42 cases. Zhonghua Yi Xue Za Zhi (Taipei). 1993;51:225–30.
197. Berbegal J, Morera J, Andrada E, et al. Syndrome of allopurinol hypersensitivity. Report of a new case and review of the Spanish literature. Med Clin (Barc). 1994;102:178–80.
198. Braden GL, Warzynski MJ, Golightly M, et al. Cell-mediated immunity in allopurinol-induced hypersensitivity. Clin Immunol Immunopathol. 1994;70:145–51.
199. Fitzgerald DA, Heagerty AH, Stephens M, et al. Follicular toxic pustuloderma associated with allopurinol. Clin Exp Dermatol. 1994;19:243–5.
200. Hanger HC, Pillans PI. Death following allopurinol hypersensitivity syndrome. N Z Med J. 1994;107:229.
201. Lee SS, Lin HY, Wang SR, et al. Allopurinol hypersensitivity syndrome. Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi. 1994;27:140–7.
202. Salinas Martin A, Mendez Abad M, Miguelez M, et al. Hypersensitivity reaction to allopurinol. Aten Primaria. 1994;14:694.
203. Elasy T, Kaminsky D, Tracy M, et al. Allopurinol hypersensitivity syndrome revisited. West J Med. 1995;162:360–1.
204. Gonzalez U, Reyes E, Kershenovich J, et al. Hypersensitivity syndrome caused by allopurinol. A case of massive hepatic necrosis. Rev Invest Clin. 1995;47:409–13.
205. Parra E, Gota R, Gamen A, et al. Granulomatous interstitial nephritis secondary to allopurinol treatment. Clin Nephrol. 1995;43:350.
206. Urban T, Maquarre E, Housset C, et al. Allopurinol hypersensitivity: a possible cause of hepatitis and mucocutaneous eruptions in a patient undergoing antitubercular treatment. Rev Mal Respir. 1995;12:314–6.
207. Kumar A, Edward N, White MI, et al. Allopurinol, erythema multiforme, and renal insufficiency. BMJ. 1996;312:173–4.
208. Rothwell PM, Grant R. Cerebral vasculitis following allopurinol treatment. Postgrad Med J. 1996;72:119–20.
209. Andrade RJ, de la Mata M, Lucena MI, et al. Severe acute hepatitis due to allopurinol in a patient with asymptomatic hyperuricemia and kidney failure. A review of the literature and an analysis of the risk factors. Gastroenterol Hepatol. 1997;20:353–6.
210. Carpenter C. Allopurinol hypersensitivity syndrome. Tenn Med. 1997;90:151–2.
211. Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. Intensive Care Med. 1997;23:1237–44.
212. Choi HK, Merkel PA, Niles JL. ANCA-positive vasculitis associated with allopurinol therapy. Clin Exp Rheumatol. 1998;16:743–4.
213. Gillott TJ, Whallett A, Zaphiropoulos G. Oral desensitization in patients with chronic tophaceous gout and allopurinol hypersensitivity. Rheumatology (Oxford). 1999;38:85–6.
214. Grahame R, Simmonds HA, McBride MB, et al. How should we treat tophaceous gout in patients with allopurinol hypersensitivity? Adv Exp Med Biol. 1998;431:19–23.
215. Hamanaka H, Mizutani H, Nouchi N, et al. Allopurinol hypersensitivity syndrome: hypersensitivity to oxypurinol but not allopurinol. Clin Exp Dermatol. 1998;23:32–4.
216. Jappe U, Franke I, Wendekamm U, et al. Allopurinol as an inducer of acute graft-versus-host-like drug reaction. Case report with review of the literature. Hautarzt. 1998;49:126–30.
217. Pereira S, Almeida J, Silva AO, et al. Fatal liver necrosis due to allopurinol. Acta Med Port. 1998;11:1141–4.
218. Pluim HJ, van Deuren M, Wetzels JF. The allopurinol hypersensitivity syndrome. Neth J Med. 1998;52:107–10.
219. Suzuki Y, Inagi R, Aono T, et al. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. Arch Dermatol. 1998;134:1108–12.
220. Woss E, Neyer U. Hypersensitivity angiitis following allopurinol therapy. Fortschr Med. 1988;106(730–1):29.
221. Morel D, Guez S, Merville P, et al. Recurrent renal failure associated with hypersensitivity to allopurinol. Nephrol Dial Transpl. 1999;14:780–1.
222. Tanna SB, Barnes JF, Seth SK. Desensitization to allopurinol in a patient with previous failed desensitization. Ann Pharmacother. 1999;33:1180–3.
223. Aoki S, Kotooka N, Yokoyama M, et al. Recurrence of rapidly progressive glomerulonephritis probably associated with two different kinds of drugs. Clin Nephrol. 2000;54:249–51.
224. Brand R, Rohr JB. Toxic epidermal necrolysis in Western Australia. Australas J Dermatol. 2000;41:31–3.
225. Khoo BP, Leow YH. A review of inpatients with adverse drug reactions to allopurinol. Singap Med J. 2000;41:156–60.
226. Arakawa M, Kakuto Y, Ichikawa K, et al. Allopurinol hypersensitivity syndrome associated with systemic cytomegalovirus infection and systemic bacteremia. Intern Med. 2001;40:331–5.
227. Benito-Leon J, Porta-Etessam J. Guillain–Barre syndrome and allopurinol-induced hypersensitivity. Eur Neurol. 2001;45:186–7.
228. Hammer B, Link A, Wagner A, et al. Hypersensitivity syndrome during therapy with allopurinol in asymptomatic hyperuricemia with a fatal outcome. Dtsch Med Wochenschr. 2001;126:1331–4.
229. Rivas Gonzalez P, Calvo Hernandez R, Molinelli Barranco M, et al. Allopurinol hypersensitivity syndrome. Rev Clin Esp. 2001;201:493.
230. Anderson BE, Adams DR. Allopurinol hypersensitivity syndrome. J Drugs Dermatol. 2002;1:60–2.
231. Descamps V, Mahe E, Houhou N, et al. Drug-induced hypersensitivity syndrome associated with Epstein–Barr virus infection. Br J Dermatol. 2003;148:1032–4.
232. Fine P, Savrinski B, Millodot M. Contact lens management of a case of Stevens–Johnson syndrome: a case report. Optometry. 2003;74:659–64.
233. Masaki T, Fukunaga A, Tohyama M, et al. Human herpes virus 6 encephalitis in allopurinol-induced hypersensitivity syndrome. Acta Derm Venereol. 2003;83:128–31.
234. Mete N, Yilmaz F, Gulbahar O, et al. Allopurinol hypersensitivity syndrome as a cause of hepatic centrilobular hemorrhagic necrosis. J Investig Allergol Clin Immunol. 2003;13:281–3.
235. Dia D, Ba-Fall K, Bouldouyre M, et al. DRESS syndrome to allopurinol: a case in Dakar. Dakar Med. 2004;49:114–5.
236. Marrakchi C, Kanoun F, Kilani B, et al. Allopurinol induced DRESS syndrome. Rev Med Interne. 2004;25:252–4.
237. Chao SC, Yang CC, Lee JY. Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. Ann Pharmacother. 2005;39:1552–6.

238. Chen IH, Kuo MC, Hwang SJ, et al. Allopurinol-induced severe hypersensitivity with acute renal failure. Kaohsiung J Med Sci. 2005;21:228–32.
239. Choi SH, Yang SH, Song YB, et al. A case of vanishing bile duct syndrome associated with hypersensitivity to allopurinol. Korean J Hepatol. 2005;11:80–5.
240. Gutierrez-Macias A, Lizarralde-Palacios E, Martinez-Odriozola P, et al. Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. BMJ. 2005;331:623–4.
241. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA. 2005;102:4134–9.
242. Kakeda M, Tohyama M, Iwasaki J, et al. A case of histopathologically typical toxic epidermal necrolysis despite no visible blisters or erosive lesions. J Dermatol. 2005;32:654–60.
243. Saxena R, Loghmanee F. Fatal drug reaction due to allopurinol therapy in a 72-year-old man. Arch Pathol Lab Med. 2005;129:e183–4.
244. Almirall J, Orellana R, Martinez Ocana JC, et al. Allopurinol-induced chronic granulomatous interstitial nephritis. Nefrologia. 2006;26:741–4.
245. Kokunai A, Azusawa H, Murota H, et al. Hypersensitivity reactions to multiple drugs during the course of hairy cell leukemia treated with 2-chlorodeoxyadenosine. Arerugi. 2006;55:662–6.
246. Rodevand E, Sletvold O, Kvande KT. Side effects off allopurinol. Tidsskr Nor Laegeforen. 2004;124:2618–9.
247. Dainichi T, Uchi H, Moroi Y, et al. Stevens–Johnson syndrome, drug-induced hypersensitivity syndrome and toxic epidermal necrolysis caused by allopurinol in patients with a common HLA allele: what causes the diversity? Dermatology. 2007;215:86–8.
248. Tohyama M, Hashimoto K, Yasukawa M, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol. 2007;157:934–40.
249. Chiou CC, Yang LC, Hung SI, et al. 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;22:1044–9.
250. Fagugli RM, Gentile G, Ferrara G, et al. Acute renal and hepatic failure associated with allopurinol treatment. Clin Nephrol. 2008;70:523–6.
251. Lee HY, Ariyasinghe JT, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? Singap Med J. 2008;49:384–7.
252. Shalom R, Rimbroth S, Rozenman D, et al. Allopurinol-induced recurrent DRESS syndrome: pathophysiology and treatment. Ren Fail. 2008;30:327–9.
253. Suzuki HI, Asai T, Tamaki Z, et al. Drug-induced hypersensitivity syndrome with rapid hematopoietic reconstitution during treatment for acute myeloid leukemia. Haematologica. 2008;93:469–70.
254. Yoon JY, Min SY, Park JY, et al. A case of allopurinol-induced granulomatous hepatitis with ductopenia and cholestasis. Korean J Hepatol. 2008;14:97–101.
255. Eshki M, Allanore L, Musette P, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol. 2009;145:67–72.
256. Gyotoku E, Iwamoto T, Ochi M. A fatal case of drug-induced hypersensitivity syndrome due to allopurinol. Arerugi. 2009;58:560–6.
257. Hung CC, Liu WC, Kuo MC, et al. Acute renal failure and its risk factors in Stevens–Johnson syndrome and toxic epidermal necrolysis. Am J Nephrol. 2009;29:633–8.
258. Hsieh HJ, Chan AL, Lin SJ. Stevens–Johnson syndrome induced by combination of imatinib and allopurinol. Chemotherapy. 2009;55:197–9.
259. Reinders MK, van Roon EN, Jansen TL, et al. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. Ann Rheum Dis. 2009;68:51–6.
260. Sackesen C, Dut R, Gucer S, et al. Allopurinol-induced DRESS syndrome in a 13-year-old girl. J Investig Allergol Clin Immunol. 2009;19:65–7.
261. Dewan AK, Quinonez RA. Allopurinol-induced DRESS syndrome in an adolescent patient. Pediatr Dermatol. 2010;27:270–3.
262. Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2010;49:834–41.
263. Fathallah N, Ben Salem C, Slim R, et al. Fatal allopurinol-induced hypersensitivity syndrome associated with pancreatic abnormalities. J Clin Rheumatol. 2010;16:170–1.
264. Hamaguchi Y, Fujimoto M, Enokido Y, et al. Intractable genital ulcers from herpes simplex virus reactivation in drug-induced hypersensitivity syndrome caused by allopurinol. Int J Dermatol. 2010;49:700–4.
265. Santiago F, Goncalo M, Vieira R, et al. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Dermat. 2010;62:47–53.
266. Ventura F, Fracasso T, Leoncini A, et al. Death caused by toxic epidermal necrolysis (Lyell syndrome). J Forensic Sci. 2010;55:839–41.
267. Yang DC, Chang CM. Allopurinol-induced drug reaction with eosinophilia and systemic symptoms syndrome with recurrence. J Am Geriatr Soc. 2010;58:2043–4.
268. Taylor TH, Mecchella JN, Larson RJ, et al. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. Am J Med. 2012;125:1126 e7–34 e7.
269. Sekine A, Saito T, Ito S, et al. Two cases of tuberculosis with multiple drug hypersensitivity after drug-induced hypersensitivity syndrome. Respir Investig. 2012;50:70–5.
270. Agnes K, Anna L, Anita V, et al. Allopurinol-induced hypersensitivity syndrome. Orvosi Hetilap. 2012;153:586–91.
271. Cao ZH, Wei ZY, Zhu QY, et al. HLA-B*58:01 allele is associated with augmented risk for both mild and severe cutaneous adverse reactions induced by allopurinol in Han Chinese. Pharmacogenomics. 2012;13:1193–201.
272. Comparin C, Hans Filho G, Takita LC, et al. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin: a series of three cases. An Bras Dermatol. 2012;87:477–81.
273. Kamal T, Elnikety S, Mashaly H, et al. Acute compartment syndrome of the forearm as a rare complication of toxic epidermal necrolysis: a case report. J Med Case Rep. 2012;6:84.
274. Biagioni E, Busani S, Rinaldi L, et al. Acute renal failure and liver necrosis associated to allopurinol therapy. Anaesth Intensive Care. 2012;40:190–1.
275. Botelho LF, Higashi VS, Padilha MH, et al. DRESS: clinicopathological features of 10 cases from an University Hospital in Sao Paulo. An Bras Dermatol. 2012;87:703–7.
276. Chiu ML, Hu M, Ng MH, et al. Association between HLA-B*58:01 allele and severe cutaneous adverse reactions with allopurinol in Han Chinese in Hong Kong. Br J Dermatol. 2012;167:44–9.
277. Gordon K, Miteva M, Torchia D, et al. Allopurinol-induced palisaded neutrophilic and granulomatous dermatitis. Cutan Ocul Toxicol. 2012;31:338–40.
278. Huang YC, Shih PY, Chin SY, et al. Allopurinol-induced drug rash with eosinophilia and systemic symptoms mimicking acute

generalized exanthematous pustulosis. J Dermatol. 2012;39: 1077–8.
279. Lee MH, Stocker SL, Anderson J, et al. Initiating allopurinol therapy: do we need to know the patient's human leucocyte antigen status? Intern Med J. 2012;42:411–6.
280. Martinez-Aranguren R, Gamboa PM, Garcia-Lirio E, et al. In vitro cytokine production after in vivo desensitization in an allopurinol-induced delayed allergic reaction. Ann Allergy Asthma Immunol. 2012;108:280–1.
281. Yaylaci S, Demir MV, Temiz T, et al. Allopurinol-induced DRESS syndrome. Indian J Pharmacol. 2012;44:412–4.
282. Wongkitisophon P, Chanprapaph K, Rattanakaemakorn P, et al. Six-year retrospective review of drug reaction with eosinophilia and systemic symptoms. Acta Derm Venereol. 2012;92:200–5.
283. Onuma H, Tohyama M, Imagawa A, et al. High frequency of HLA B62 in fulminant type 1 diabetes with the drug-induced hypersensitivity syndrome. J Clin Endocrinol Metab. 2012;97:E2277–81.
284. Laguna C, Martin B, Torrijos A, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis. Actas Dermo-Sifiliograficas. 2006;97:177–85.
285. Raymond JZ, Goldman HM. An unusual cutaneous reaction secondary to allopurinol. Cutis. 1988;41:323–6.
286. Fonseka MM, Sathischandra H, Jayamanne SF, et al. Successful desensitisation of allopurinol-induced erythema multiforme. Ceylon Med J. 1999;44:190–1.
287. Edwards R, Ridder M. Stevens–Johnson syndrome: a multisystem case. Dimens Crit Care Nurs. 1985;4:335–48.
288. Teo L, Tay YK, Liu TT, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: efficacy of intravenous immunoglobulin and a review of treatment options. Singap Med J. 2009;50:29–33.
289. Turki H, Walha N, Boudaya S, et al. Le syndrome de Lyell (nécrolyse épidermique toxique). Étude de 8 cas. Sem Hôp Paris. 1998;74:953–8.
290. Gil Gonzalez I, Gimenez Garcia RM, Diez Gonzalez G, et al. Toxic epidermal necrolysis caused by allopurinol. Anales de Medicina Interna. 1988;5:649.
291. Quintas S, Do Carmo G, Gama R, et al. Lyell's syndrome in a patient with AIDS. Acta Medica Portuguesa. 1997;10:509–16.
292. Cid Conde L, Novoa Fernandez E, Padron Rodriguez B. Toxic epidermal necrolysis (Lyell's syndrome) secondary to alopurinol. Farmacia Hospitalaria. 2009;33:229–30.
293. Knezevic A, Frkovic A, Francetic I, et al. Toxic epidermal necrolysis (Lyell's syndrome) caused by allopurinol. Lijecnicki Vjesnik. 1987;109:272–4.
294. Dicle Ö, Yilmaz E, Alpsoy E. Stevens–Johnson syndrome and toxic epidermal necrolysis: a retrospective evaluation. Türkderm Deri Hastaliklari ve Frengi Arsivi. 2009;43:15–20.
295. Assaad D, From L, Ricciatti D, et al. Toxic epidermal necrolysis in Stevens–Johnson syndrome. Can Med Assoc J. 1978;118:154–6.
296. Paquet P, Nikkels A, Arrese JE, et al. Macrophages and tumor necrosis factor alpha in toxic epidermal necrolysis. Arch Dermatol. 1994;130:605–8.
297. Gambert SR. Medication-induced Stevens–Johnson syndrome in elders. Clin Geriatr. 2012;20:8.
298. Stenton SB, Dalen D, Wilbur K. Myocardial infarction associated with intravenous immune globulin. Ann Pharmacother. 2005;39:2114–8.
299. Bennett TO, Sugar J, Sahgal S. Ocular manifestations of toxic epidermal necrolysis associated with allopurinol use. Arch Ophthalmol. 1977;95:1362–4.
300. Cheriyan S, Patterson R, Greenberger PA, et al. The outcome of Stevens–Johnson syndrome treated with corticosteroids. Allergy Proc. 1995;16:151–5.
301. Chaidemenos GC, Chrysomallis F, Sombolos K, et al. Plasmapheresis in toxic epidermal necrolysis. Int J Dermatol. 1997;36:218–21.
302. Tan SK, Tay YK. Profile and pattern of Stevens–Johnson syndrome and toxic epidermal necrolysis in a general hospital in Singapore: treatment outcomes. Acta Derm Venereol. 2012;92:62–6.
303. Patterson R, Cheriyan S, Greenberger PA. Recurrent dermopathy after remission of Stevens–Johnson syndrome secondary to mild dermal trauma. Allergy Proc. 1995;16:115–8.
304. Struck MF, Illert T, Schmidt T, et al. Secondary abdominal compartment syndrome in patients with toxic epidermal necrolysis. Burns. 2012;38:562–7.
305. Yun SJ, Choi MS, Piao MS, et al. Serum lactate dehydrogenase is a novel marker for the evaluation of disease severity in the early stage of toxic epidermal necrolysis. Dermatology. 2008;217:254–9.
306. Trautmann A, Klein CE, Kampgen E, et al. Severe bullous drug reactions treated successfully with cyclophosphamide. Br J Dermatol. 1998;139:1127–8.
307. Arevalo JM, Lorente JA. Skin coverage with Biobrane biomaterial for the treatment of patients with toxic epidermal necrolysis. J Burn Care Rehabil. 1999;20:406–10.
308. Moniz P, Casal D, Mavioso C, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: a 15-year retrospective study. Acta Med Port. 2011;24:59–70.
309. Ziemer M, Kardaun SH, Liss Y, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: a descriptive study of 17 cases from a national registry and review of the literature. Br J Dermatol. 2012;166:575–600.
310. Davies P, Ryan DW. Stevens–Johnson syndrome managed in the Clinitron bed. Intensive Care Med. 1983;9:87–9.
311. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics. 2009;19:704–9.
312. Kelso JM, Keating RM. Successful desensitization for treatment of a fixed drug eruption to allopurinol. J Allergy Clin Immunol. 1996;97:1171–2.
313. Teraki Y, Shiohara T. Successful desensitization to fixed drug eruption: the presence of CD25+CD4+T cells in the epidermis of fixed drug eruption lesions may be involved in the induction of desensitization. Dermatology. 2004;209:29–32.
314. Yeung CK, Lam LK, Chan HH. The timing of intravenous immunoglobulin therapy in Stevens–Johnson syndrome and toxic epidermal necrolysis. Clin Exp Dermatol. 2005;30:600–2.
315. Ying S, Ho W, Chan HH. Toxic epidermal necrolysis: 10 years experience of a burns centre in Hong Kong. Burns. 2001;27:372–5.
316. Prins C, Kerdel FA, Padilla RS, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. Arch Dermatol. 2003;139:26–32.
317. Fania L, Giannico MI, Fasciani R, et al. Ocular mucous membrane pemphigoid after Lyell syndrome: occasional finding or predisposing event? Ophthalmology. 2012;119:688–93.
318. Sakellariou G, Koukoudis P, Karpouzas J, et al. Plasma exchange (PE) treatment in drug-induced toxic epidermal necrolysis (TEN). Int J Artif Organs. 1991;14:634–8.
319. Marra LM, Wunderle RC. Oral presentation of toxic epidermal necrolysis. J Oral Maxillofac Surg. 1982;40:59–61.
320. Carmona AF, Redondo AD, Pena LO, et al. Toxic epidermal necrolysis treated with cyclosporin A. Med Intensiva. 2011; 35:442–5.

321. Bashir S, Shah SM, Babar I. Allopurinol induced Stevens–Johnson syndrome: a case report. J Pak Med Assoc. 2000;50:207–9.
322. Boffa MJ, Chalmers RJ. Allopurinol-induced toxic pustuloderma. Br J Dermatol. 1994;131:447.
323. Correia O, Chosidow O, Saiag P, et al. Evolving pattern of drug-induced toxic epidermal necrolysis. Dermatology. 1993;186:32–7.
324. Goldfarb E, Smyth CJ. Effects of allopurinol, a xanthine oxidase inhibitor, and sulfinpyrazone upon the urinary and serum urate concentrations in eight patients with tophaceous gout. Arthritis Rheum. 1966;9:414–23.
325. Guillaume JC, Roujeau JC, Revuz J, et al. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). Arch Dermatol. 1987;123:1166–70.
326. Hanken I, Schimmer M, Sander CA. Basic measures and systemic medical treatment of patients with toxic epidermal necrolysis. J Dtsch Dermatol Ges. 2010;8:341–6.
327. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics. 2008;9:1617–22.
328. Lee HJ, Kim HS, Park YM, et al. Fixed drug eruption due to allopurinol: positive oral provocation. Ann Dermatol. 2011;23:S402–3.
329. Lonjou C, Borot N, Sekula P, 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.
330. Lun K, Harley W. Allopurinol-induced pustular eruption: an unusually mild case. Australas J Dermatol. 2002;43:140–3.
331. Nasser M, Bitterman-Deutsch O, Nassar F. Intravenous immunoglobulin for treatment of toxic epidermal necrolysis. Am J Med Sci. 2005;329:95–8.
332. Ooi CG, Walker P, Sidhu SK, et al. Allopurinol induced generalized eosinophilic pustular folliculitis. Australas J Dermatol. 2006;47:270–3.
333. Stratigos JD, Bartsokas SK, Capetanakis J. Further experiences of toxic epidermal necrolysis incriminating allopurinol, pyrazolone and derivatives. Br J Dermatol. 1972;86:564–7.
334. Thomas J. Dermatologic complications of allopurinol treatment of gout. Rein et Foie. 1969;12:129–33.
335. Trent JT, Kirsner RS, Romanelli P, et al. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. Arch Dermatol. 2003;139:39–43.
336. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science. 1998;282:490–3.
337. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. Eye (Lond). 2005;19:846–53.
338. Becker D, Enk A, Brauninger W, et al. Granuloma anulare disseminatum as a rare side effect of allopurinol. Hautarzt. 1995;46:343–5.
339. Hara Y, Yoshioka M, Yoshiki R, et al. Increased human herpes virus 6 DNA detected by real-time PCR in the saliva of two patients with drug-induced hypersensitivity syndrome. Eur J Dermatol. 2012;22:418–9.
340. Pasero G, Riccioni N, Rizzo G. Prime esperienze con un inibitore della xantina-ossidasi (4-idrossi-pirazolo-(3,4-d)-pirimidina; allopurino) nel trattamento di soggetti gottosi con grave compromissione della funzione renale. La Settimana medica. 1966;54:63–8.
341. Cusido GVI, Aguilar JL. Exantema fijo medicamentoso inducido por alopurinol. Actas Dermo-Sifiliograficas. 1994;85:755–7.
342. Wolf R, Orion E, Marcos B, et al. Life-threatening acute adverse cutaneous drug reactions. Clin Dermatol. 2005;23:171–81.
343. Peterson GM, Boyle RR, Francis HW, et al. Dosage prescribing and plasma oxipurinol levels in patients receiving allopurinol therapy. Eur J Clin Pharmacol. 1990;39:419–21.
344. Stuart RA, Gow PJ, Bellamy N, et al. A survey of current prescribing practices of antiinflammatory and urate-lowering drugs in gouty arthritis. N Z Med J. 1991;104:115–7.
345. McClintock AD, Egan AJ, Woods DJ, et al. A survey of allopurinol dosage prescribing. N Z Med J. 1995;108:346–7.
346. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. Mayo Clin Proc. 2006;81:925–34.
347. Smith P, Karlson N, Nair BR. Quality use of allopurinol in the elderly. J Qual Clin Pract. 2000;20:42–3.
348. Stamp L, Gow P, Sharples K, et al. The optimal use of allopurinol: an audit of allopurinol use in South Auckland. Aust N Z J Med. 2000;30:567–72.
349. Dalbeth N, Kumar S, Stamp L, et al. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. J Rheumatol. 2006;33:1646–50.
350. Athisakul S, Wangkaew S, Louthrenoo W. Inappropriate prescription of allopurinol in a teaching hospital. J Med Assoc Thai. 2007;90:889–94.
351. Atzori L, Pinna AL, Mantovani L, et al. Cutaneous adverse drug reactions to allopurinol: 10 year observational survey of the dermatology department—Cagliari University (Italy). J Eur Acad Dermatol Venereol. 2012;26:1424–30.
352. Jung JW, Kim MH, Song WJ, et al. HLA-B58 does not increase allopurinol hypersensitivity among patients with hematologic malignancy. XXII World Allergy Congress; 2012 (4–8 December 2011); Cancun, Mexico: World Allergy Organization; 2012. p. S98.
353. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, et al. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia: a pathogenic approach to the treatment of primary chronic gout. Ann Rheum Dis. 1998;57:545–9.
354. Reinders MK, Haagsma C, Jansen TL, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. Ann Rheum Dis. 2009;68:892–7.
355. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011;63:412–21.
356. Elion GB, Kovensky A, Hitchings GH. Metabolic studies of allopurinol, an inhibitor of xanthine oxidase. Biochem Pharmacol. 1966;15:863–80.
357. Hande K, Reed E, Chabner B. Allopurinol kinetics. Clin Pharmacol Ther. 1978;23:598–605.
358. Rodnan GP, Robin JA, Tolchin SF, et al. Allopurinol and gouty hyperuricemia. Efficacy of a single daily dose. JAMA. 1975;231:1143–7.
359. Emmerson BT, Gordon RB, Cross M, et al. Plasma oxipurinol concentrations during allopurinol therapy. Br J Rheumatol. 1987;26:445–9.
360. Panomvana D, Sripradit S, Angthararak S. Higher therapeutic plasma oxypurinol concentrations might be required for gouty patients with chronic kidney disease. J Clin Rheumatol. 2008;14:6–11.
361. Stamp LK, Barclay ML, O'Donnell JL, et al. Relationship between serum urate and plasma oxypurinol in the management of gout: determination of minimum plasma oxypurinol

concentration to achieve a target serum urate level. Clin Pharmacol Ther. 2011;90:392–8.
362. Mikuls TR, MacLean CH, Olivieri J, et al. Quality of care indicators for gout management. Arthritis Rheum. 2004;50:937–43.
363. Bellamy N, Brooks PM, Emmerson BT, et al. A survey of current prescribing practices of anti-inflammatory and urate-lowering drugs in gouty arthritis in New South Wales and Queensland. Med J Aust. 1989;151:531–2 535–7.
364. Mikuls TR, Farrar JT, Bilker WB, et al. Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). Rheumatology (Oxford). 2005;44:1038–42.
365. Hall AP, Barry PE, Dawber TR, et al. Epidemiology of gout and hyperuricemia: a long-term population study. Am J Med. 1967;42:27–37.
366. Rosenfeld JB. Effect of allopurinol administration on serum GFR in normotensive and hypertensive hyperuricemia subjects. Adv Exp Med Biol. 1974;41B:581–96.
367. Fessel WJ. Renal outcomes of gout and hyperuricemia. Am J Med. 1979;67:74–82.
368. Yu TF, Berger L, Dorph DJ, et al. Renal function in gout. V. Factors influencing the renal hemodynamics. Am J Med. 1979;67:766–71.
369. McGill NW. Gout and other crystal arthropathies. Med J Aust. 1997;166:33–8.
370. Krishnan E. Hyperuricemia and incident heart failure. Circ Heart Fail. 2009;2:556–62.
371. Pater C. Hyperuricemia and hypertension: a causal relationship ignored for all too long. Curr Hypertens Rev. 2011;7:41–53.
372. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;41:1183–90.
373. Johnson RJ, Feig DI, Herrera-Acosta J, et al. Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension. 2005;45:18–20.
374. Johnson RJ, Segal MS, Srinivas T, et al. Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? J Am Soc Nephrol. 2005;16:1909–19.
375. Verdecchia P, Schillaci G, Reboldi G, et al. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension. 2000;36:1072–8.
376. Edwards NL. The role of hyperuricemia and gout in kidney and cardiovascular disease. Cleve Clin J Med. 2008;75(Suppl 5):S13–6.
377. Gaffo AL, Saag KG. Drug treatment of hyperuricemia to prevent cardiovascular outcomes: are we there yet? Am J Cardiovasc Drugs. 2012;12:1–6.
378. See LC, Kuo CF, Chuang FH, et al. Hyperuricemia and metabolic syndrome: associations with chronic kidney disease. Clin Rheumatol. 2011;30:323–30.
379. Goncalves JP, Oliveira A, Severo M, et al. Cross-sectional and longitudinal associations between serum uric acid and metabolic syndrome. Endocrine. 2012;41:450–7.
380. Lohsoonthorn V, Dhanamun B, Williams MA. Prevalence of hyperuricemia and its relationship with metabolic syndrome in Thai adults receiving annual health exams. Arch Med Res. 2006;37:883–9.
381. Avram Z, Krishnan E. Hyperuricaemia: where nephrology meets rheumatology. Rheumatology. 2008;47:960–4.
382. Siu YP, Leung KT, Tong MK, et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47:51–9.
383. Neogi T, Hunter DJ, Chaisson CE, et al. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. J Rheumatol. 2006;33:104–9.
384. Yu TF, Gutman AB. Efficacy of colchicine prophylaxis in gout. Prevention of recurrent gouty arthritis over a mean period of five years in 208 gouty subjects. Ann Intern Med. 1961;55:179–92.
385. Krishnan E, Lienesch D, Kwoh CK. Gout in ambulatory care settings in the United States. J Rheumatol. 2008;35:498–501.
386. Kitts A, Feolo M, Helmberg W. Allele and haplotype frequencies. dbMHC anthropology search results (HLA-B*58:01:01). National Center for Biotechnology Information (NCBI). http://www.ncbi.nlm.nih.gov/projects/gv/mhc/ihwg.cgi. Accessed 14 Dec 2012.
387. Chan SH, Tan T. HLA and allopurinol drug eruption. Dermatologica. 1989;179:32–3.
388. Cristallo AF, Schroeder J, Citterio A, et al. A study of HLA class I and class II 4-digit allele level in Stevens–Johnson syndrome and toxic epidermal necrolysis. Int J Immunogenet. 2011;38:303–9.
389. Kang HR, Jee YK, Kim YS, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. Pharmacogenet Genomics. 2011;21:303–7.
390. Phillips EJ, Chung WH, Mockenhaupt M, et al. Drug hypersensitivity: pharmacogenetics and clinical syndromes. J Allergy Clin Immunol. 2011;127:S60–6.
391. Somkrua R, Eickman EE, Saokaew S, et al. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet. 2011;12:118.
392. Somkrua R, Chaiyakunapruk N, Tassaneeyakul W. What cost of HLA-B*5801 genotyping would be cost-effective for the prevention of allopurinol-induced Stevens–Johnson syndrome/Toxic Epidermal Necrolysis in Thailand: analyses using a decision-analytic model. Value Health. 2010;13:A564–5.
393. Yeo SI. HLA-B*5801: utility and cost-effectiveness in the Asia-Pacific Region. Int J Rheum Dis. 2013.
394. Arromdee E, Michet CJ, Crowson CS, et al. Epidemiology of gout: is the incidence rising? J Rheumatol. 2002;29:2403–6.
395. Wallace KL, Riedel AA, Joseph-Ridge N, et al. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol. 2004;31:1582–7.
396. Singh JA, Hodges JS, Toscano JP, et al. Quality of care for gout in the US needs improvement. Arthritis Rheum. 2007;57:822–9.
397. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008;58:26–35.
398. Hak AE, Curhan GC, Grodstein F, et al. Menopause, postmenopausal hormone use and risk of incident gout. Ann Rheum Dis. 2010;69:1305–9.
399. Riedel AA, Nelson M, Wallace K, et al. Prevalence of comorbid conditions and prescription medication use among patients with gout and hyperuricemia in a managed care setting. J Clin Rheumatol. 2004;10:308–14.
400. Keenan RT, O'Brien WR, Lee KH, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med. 2011;124:155–63.
401. Fuldeore MJ, Riedel AA, Zarotsky V, et al. Chronic kidney disease in gout in a managed care setting. BMC Nephrol. 2011;12:36.
402. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. Am J Med. 2012;125(679–87):e1.
403. Sharpe CR. A case-control study of alcohol consumption and drinking behaviour in patients with acute gout. Can Med Assoc J. 1984;131:563–7.

404. Roubenoff R, Klag MJ, Mead LA, et al. Incidence and risk factors for gout in white men. JAMA. 1991;266:3004–7.
405. Emmerson BT. The management of gout. N Engl J Med. 1996;334:445–51.
406. Tikly M, Bellingan A, Lincoln D, et al. Risk factors for gout: a hospital-based study in urban black South Africans. Rev Rhum Engl Ed. 1998;65:225–31.
407. McGill NW. Gout and other crystal-associated arthropathies. Baillieres Best Pract Res Clin Rheumatol. 2000;14:445–60.
408. Fam AG. Gout, diet, and the insulin resistance syndrome. J Rheumatol. 2002;29:1350–5.
409. Mandell BF. Hyperuricemia and gout: a reign of complacency. Cleve Clin J Med. 2002;69:589–90 92–3.
410. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. Ann Rheum Dis. 2008;67:960–6.
411. Shiohara T, Iijima M, Ikezawa Z, et al. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156:1083–4.
412. Pritchett JC, Nanau RM, Neuman MG. The link between hypersensitivity syndrome reaction development and human herpes virus-6 reactivation. Int J Hepatol. 2012;2012:723062.
413. Shiohara T, Kano Y, Takahashi R, et al. Drug-induced hypersensitivity syndrome: recent advances in the diagnosis, pathogenesis and management. Chem Immunol Allergy. 2012;97:122–38.
414. Criado PR, Criado RF, Avancini Jde M, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS): a review of current concepts. An Bras Dermatol. 2012;87:435–49.
415. Hirahara K, Kano Y, Mitsuyama Y, et al. Differences in immunological alterations and underlying viral infections in two well-defined severe drug eruptions. Clin Exp Dermatol. 2010;35:863–8.
416. Mockenhaupt M. Allopurinol is the most frequent cause of Stevens–Johnson syndrome and toxic epidermal necrolysis. Expert Rev Dermatol. 2012;7:213–5.
417. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333:1600–7.
418. de Klerk E, van der Heijde D, Landewe R, et al. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. J Rheumatol. 2003;30:44–54.
419. Riedel AA, Nelson M, Joseph-Ridge N, et al. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. J Rheumatol. 2004;31:1575–81.
420. Solomon DH, Avorn J, Levin R, et al. Uric acid lowering therapy: prescribing patterns in a large cohort of older adults. Ann Rheum Dis. 2008;67:609–13.
421. Harrold LR, Andrade SE. Medication adherence of patients with selected rheumatic conditions: a systematic review of the literature. Semin Arthritis Rheum. 2009;38:396–402.
422. Bull PW, Scott JT. Intermittent control of hyperuricaemia in the treatment of gout. Adv Exp Med Biol. 1989;253A:251–5.
423. Luk AJ, Simkin PA. Epidemiology of hyperuricemia and gout. Am J Manag Care. 2005;11:S435–42 quiz S65–8.
424. Harrold LR, Mazor KM, Velten S, et al. Patients and providers view gout differently: a qualitative study. Chronic Illn. 2010;6:263–71.
425. Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a qualitative study. Ann Rheum Dis. 2012;71:1490–5.
426. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy. 2004;59:809–20.
427. Kano Y, Hirahara K, Mitsuyama Y, et al. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy. 2007;62:1439–44.
428. Romano A, Demoly P. Recent advances in the diagnosis of drug allergy. Curr Opin Allergy Clin Immunol. 2007;7:299–303.
429. Friedmann PS, Ardern-Jones M. Patch testing in drug allergy. Curr Opin Allergy Clin Immunol. 2010;10:291–6.
430. Lammintausta K, Kortekangas-Savolainen O. The usefulness of skin tests to prove drug hypersensitivity. Br J Dermatol. 2005;152:968–74.
431. Andrade P, Brinca A, Goncalo M. Patch testing in fixed drug eruptions: a 20-year review. Contact Dermat. 2011;65:195–201.
432. Barbaud A. Drug patch testing in systemic cutaneous drug allergy. Toxicology. 2005;209:209–16.
433. Waton J, Trechot P, Loss-Ayav C, et al. Negative predictive value of drug skin tests in investigating cutaneous adverse drug reactions. Br J Dermatol. 2009;160:786–94.
434. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions—new concepts. Clin Exp Allergy. 2007;37:989–99.
435. Bircher AJ, Scherer K. Delayed cutaneous manifestations of drug hypersensitivity. Med Clin N Am. 2010;94:711–25 x.
436. Kim SC, Newcomb C, Margolis D, et al. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. Arthritis Care Res (Hoboken). 2012.
437. Ryu HJ, Song R, Kim HW, et al. Clinical risk factors for adverse events in allopurinol users. J Clin Pharmacol. 2012.
438. Riedel MA, Casillas AM. Adverse drug reactions: types and treatment options. Am Fam Physician. 2003;68:1781–91.
439. Rieder MJ. Immune mediation of hypersensitivity adverse drug reactions: implications for therapy. Expert Opin Drug Saf. 2009;8:331–43.
440. Harr T, French LE. Toxic epidermal necrolysis and Stevens–Johnson syndrome. Orphanet J Rare Dis. 2010;5:39.
441. Worswick S, Cotliar J. Stevens–Johnson syndrome and toxic epidermal necrolysis: a review of treatment options. Dermatol Ther. 2011;24:207–18.
442. Michaels B. The role of systemic corticosteroid therapy in erythema multiforme major and Stevens–Johnson syndrome: a review of past and current opinions. J Clin Aesthet Dermatol. 2009;2:51–5.
443. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003;139:33–6.
444. Brown KM, Silver GM, Halerz M, et al. Toxic epidermal necrolysis: does immunoglobulin make a difference? J Burn Care Rehabil. 2004;25:81–8.
445. Shortt R, Gomez M, Mittman N, et al. Intravenous immunoglobulin does not improve outcome in toxic epidermal necrolysis. J Burn Care Rehabil. 2004;25:246–55.
446. Pasic S. Intravenous immunoglobulin in toxic epidermal necrolysis. Int J Dermatol. 2006;45:1117–8.
447. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens–Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. Pediatrics. 2003;112:1430–6.
448. Al-Mutairi N, Arun J, Osama NE, et al. Prospective, noncomparative open study from Kuwait of the role of intravenous immunoglobulin in the treatment of toxic epidermal necrolysis. Int J Dermatol. 2004;43:847–51.
449. Tan AW, Thong BY, Yip LW, et al. High-dose intravenous immunoglobulins in the treatment of toxic epidermal necrolysis: an Asian series. J Dermatol. 2005;32:1–6.

450. Mangla K, Rastogi S, Goyal P, et al. Efficacy of low dose intravenous immunoglobulins in children with toxic epidermal necrolysis: an open uncontrolled study. Indian J Dermatol Venereol Leprol. 2005;71:398–400.
451. Stella M, Clemente A, Bollero D, et al. Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS): experience with high-dose intravenous immunoglobulins and topical conservative approach. A retrospective analysis. Burns. 2007;33:452–9.
452. Schneck J, Fagot JP, Sekula P, et al. Effects of treatments on the mortality of Stevens–Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol. 2008;58:33–40.
453. French LE, Trent JT, Kerdel FA. Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens–Johnson syndrome: our current understanding. Int Immunopharmacol. 2006;6:543–9.
454. Trent J, Halem M, French LE, et al. Toxic epidermal necrolysis and intravenous immunoglobulin: a review. Semin Cutan Med Surg. 2006;25:91–3.
455. Momin SB. Review of intravenous immunoglobulin in the treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis. J Clin Aesthet Dermatol. 2009;2:51–8.
456. Ferguson JC, Carr RT, Chang EW, et al. Evaluation of endotracheal tube safety for CO_2 laser resurfacing. Laryngoscope. 2002;112:1239–42.
457. Aronson JK. Anecdotes as evidence. BMJ. 2003;326:1346.
458. Kelly WN. The quality of published adverse drug event reports. Ann Pharmacother. 2003;37:1774–8.
459. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385–96.
460. Loke YK, Price D, Derry S, et al. Case reports of suspected adverse drug reactions—systematic literature survey of follow-up. BMJ. 2006;332:335–9.
461. Impicciatore P, Mucci M. Completeness of published case reports on suspected adverse drug reactions: evaluation of 100 reports from a company safety database. Drug Saf. 2010;33:765–73.
462. Kelly WN, Arellano FM, Barnes J, et al. Guidelines for submitting adverse event reports for publication. Pharmacoepidemiol Drug Saf. 2007;16:581–7.
463. Longmore JM, Wilkinson IB, Rajagopalan SR. Oxford handbook of clinical medicine. 6th ed. New York: Oxford University Press; 2004.