Sudarshan Publications

Available online at https://s-epub.in/index.php/trp/index

Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2021.v13.i01.pp11-20

CUTANEOUS ADVERSE DRUG REACTIONS: CAUSALITY AND SEVERITY ASSESSMENT IN A DERMATOLOGY UNIT

MATHILDE GUILLEMOT[1]*, CALLUM PENGELLY[2], KYLE OKAFOR[3]

Affiliation

[1]Department of Pharmacovigilance, Loire Valley Institute of Pharmacy, Saumur, France
[2]Department of Clinical Pharmacology, Exmoor Institute of Pharmaceutical Sciences, Taunton, United Kingdom
[3]Department of Pharmacy Practice, Shenandoah Valley College of Pharmacy, Harrisonburg, USA

*Corresponding author: Mathilde Guillemot, m.guillemot@lvip.fr
ORCID iD: Mathilde Guillemot 0000-0001-0976-8380; Callum Pengelly 0000-0001-1653-2341; Kyle Okafor 0000-0001-4320-2356

Article info

Received date:05-08-2020
Accepted date:30-11-2020
Published date:26-02-2021
ISSN;0975-8216

Keywords:

Cutaneous adverse drug reactions, Causality assessment, Severity assessment, Pharmacovigilance, Dermatology

Abstract

Skin reactions are among the most frequent and most visible adverse effects of medicines, and a small fraction are life-threatening. This review, which reports no new data, brings together published literature on how cutaneous adverse drug reactions are recognised, how the link between drug and rash is judged, and how severity and preventability are graded in a dermatology setting. It compares the commonly used causality algorithms, the Stevens–Johnson syndrome and toxic epidermal necrolysis tools, and the scoring used for drug reaction with eosinophilia and systemic symptoms. Agreement between methods is only moderate, and few tools were built for the delayed reactions that dermatologists see most. Prospective validation and shared reporting standards remain the main gaps.

1. INTRODUCTION

Ask a hospital dermatologist which patients are hardest to deal with and many will name the ones whose rash appeared on day nine of a new antibiotic. The drug seems an obvious suspect, but so do the viral illness it was given for, the three other medicines on the chart and the sun-exposed holiday last week. Cutaneous adverse drug reactions (CADRs) are common, and in most patients they are mild and settle once the culprit is stopped. Population studies of hospital inpatients put the frequency of drug-related skin reactions at a few per cent [1, 2]. A small group, however, develop severe disease with blistering, organ involvement and a real risk of death [3, 4].

Two questions follow every suspected reaction. How likely is it that the drug caused the eruption, and how bad is it? Causality assessment answers the first, and severity

grading the second; the answers drive different decisions. Causality decides whether a drug is labelled as an allergy, avoided in future and reported to the pharmacovigilance centre. Severity decides whether the patient goes home with a topical steroid or to a burns unit [5, 6]. Both rely on structured tools whose strengths and weaknesses are not always appreciated by the clinicians who apply them every week.

This review covers the published evidence on the tools used to assess causality and severity of CADRs, with particular attention to the work done in dermatology units. It starts from classification and mechanisms, which determine what a tool needs to capture, then summarises epidemiology and drugs commonly implicated, and goes on to causality, severity and preventability assessment. A short section looks at how the tools fit into day-to-day practice. The article reports no new patient data and no unit audit; it describes what others have published and where the gaps lie.

The terminology is itself a source of trouble. Edwards and Aronson defined an adverse drug reaction as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, and distinguished it from an adverse event, which may or may not be caused by the drug [5]. In dermatology the word reaction is often used loosely for any eruption in a patient taking medicines. Studies that count every rash as a reaction will report higher rates than those that require a documented assessment, and this alone explains some of the spread between published incidences [1, 7].

2. CLASSIFICATION AND MECHANISMS

The classic Gell and Coombs scheme divides hypersensitivity into four types, and its fourth category, the T-cell mediated reaction, covers most of what dermatology sees [8]. Pichler later refined it by describing how T cells recognise drugs, through direct binding to receptor or peptide-presenting molecules, and by subdividing type IV reactions according to the cytokines and effector cells involved [9]. The practical consequence is timing. Immediate IgE-mediated urticaria and anaphylaxis appear within minutes to an hour of exposure; T-cell reactions usually need days to weeks of sensitisation, and may appear after the drug has been stopped [9, 10].

Clinical patterns matter as much as mechanisms. Maculopapular exanthem is the commonest, followed by urticaria and angioedema. Fixed drug eruption, photosensitivity, vasculitis and acneiform eruptions are less frequent, and each has its own typical drugs and timing [7, 11]. The severe patterns are Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS). Bocquet and colleagues described the latter as a hypersensitivity syndrome with fever, rash, lymphadenopathy and visceral involvement [12]. Latency differs sharply across these entities: AGEP typically develops within a couple of days of the drug, SJS and TEN over one to three weeks, and DRESS often two to eight weeks after starting [13, 14, 15].

Not every pattern behaves like the exanthem. Fixed drug eruption is the notable exception: the lesion recurs at the same site each time the drug is taken, and this stereotyped behaviour makes it one of the few reactions where a history of repeat exposure is itself near-diagnostic. Urticaria and angioedema with an IgE or bradykinin basis appear within hours, so the culprit is usually among the most recently started drugs, while vasculitic reactions and serum-sickness-like illnesses cluster in the second week [7, 11]. The assessor therefore needs a pattern-specific idea of what a plausible interval looks like before scoring the timing item in any algorithm, and that idea comes from experience and from the case series rather than from the algorithm itself [9, 16].

Genetics has added a further layer. Chung and colleagues reported a strong association between carbamazepine-induced SJS and the HLA-B*1502 allele in Han Chinese patients [17]. Hung and co-workers found that HLA-B*5801 was a genetic marker for severe cutaneous reactions to allopurinol [18], and the PREDICT-1 trial showed that screening

for HLA-B*5701 cut the incidence of abacavir hypersensitivity [19]. Phillips and colleagues reviewed these and related findings, stressing that the associations are allele-, drug- and population-specific [10]. A positive HLA result alone does not establish causality in a given patient, and its absence does not exclude it, which is why genotype sits beside clinical assessment rather than replacing it [10, 17].

Viral infection often travels with drug reactions, and the two can be hard to separate. Reactivation of herpesviruses, particularly human herpesvirus 6, has been described in DRESS, and Shiohara and Kano discussed how drug allergy and viral infection may amplify each other [20]. For the assessor this blurs the question of causality, because the rash may be driven by the virus, by the drug, or by both acting together. Patients on antibiotics for a viral-like illness are the classic trap, since the drug may be blamed for an eruption the infection would have produced on its own [9, 20].

3. EPIDEMIOLOGY AND IMPLICATED DRUGS

The Boston Collaborative Drug Surveillance Program followed consecutive inpatients in the 1970s and 1980s and reported skin reactions in a little over 2 per cent of those exposed [2]. Bigby later reviewed rates across studies and arrived at a similar figure, in the region of 2 to 3 per cent of hospitalised patients [1]. Prospective hospital surveys from Europe gave comparable numbers, with Fiszenson-Albala and colleagues recording reactions in a modest fraction of patients over six months and finding that most were mild exanthems [11]. Hunziker and co-workers analysed twenty years of comprehensive hospital drug monitoring in Switzerland, which provides one of the longest series available [21].

Spontaneous report systems give a different picture. Naldi and colleagues analysed reports from four Italian regions and found that antibiotics, anti-inflammatory drugs and anticonvulsants accounted for much of the reported cutaneous burden [7]. Such data come with the usual caveats: reports reflect prescribing volume, clinician attention and reporting habits, so the proportion of reports is not the risk of reaction per exposure. Hazell and Shakir, in a systematic review, found under-reporting to be widespread across settings and countries, with a median in the region of 94 per cent for all adverse reactions [22]. Rates derived from reports alone should therefore be read as signals, not incidences.

For severe reactions the most informative data come from case-control work. Roujeau and colleagues identified sulphonamide antibacterials, anticonvulsants, oxicam non-steroidal anti-inflammatory drugs, allopurinol and thiacetazone as strongly associated with SJS and TEN [23]. The EuroSCAR study extended the analysis to newer drugs, confirming allopurinol, carbamazepine, lamotrigine, phenobarbital, nevirapine and several others and noting that the risk was concentrated in the first weeks of use [24]. Auquier-Dunant and co-workers examined the link between clinical pattern and cause, and found that drugs were implicated in a large majority of SJS and TEN cases, though infections and other causes accounted for some of the remainder [15].

Severe reactions are rare in absolute terms. SJS and TEN occur at roughly a few cases per million people per year in the general population, so even a drug with a strong association will cause a reaction in only a small proportion of the people who take it [3, 23]. Relative risk and absolute risk need to be kept apart. A drug that raises the risk many-fold may still be a sensible choice when the baseline is tiny and the alternative is untreated epilepsy or gout, a trade-off that EuroSCAR made explicit by reporting that the excess risk for most newer drugs was concentrated in the first weeks of use [24]. For the dermatology unit the practical message is to ask when the drug was started before asking what it was.

Hospital studies also show that adverse reactions of all kinds carry a cost. In a meta-analysis of prospective studies Lazarou and colleagues estimated that serious reactions occurred in a meaningful minority of hospital admissions [25], and Pirmohamed and colleagues found that reactions caused a substantial number of admissions in a large UK prospective analysis [26]. Skin reactions

form only part of these totals, but they are among the easiest to detect, which is one reason dermatology units have been fertile ground for pharmacovigilance work.

4. CAUSALITY ASSESSMENT

Why not rely on clinical judgement alone? Because experienced clinicians looking at the same case reach different conclusions more often than they would like to admit. Meyboom and colleagues made this point in discussing the role of causality assessment in pharmacovigilance, arguing that the aim is not to prove causation but to classify the likelihood in a way that others can follow [6]. Structured methods fall into three broad families: expert judgement or global introspection, algorithms (decision tables or scored questionnaires), and probabilistic approaches. Agbabiaka and colleagues counted dozens of published methods and found that none had a clear gold-standard validation [16].

Algorithms in clinical use trace back to the late 1970s. Karch and Lasagna proposed a set of operational criteria that asked about temporal sequence, response to withdrawal, response to rechallenge and alternative causes [27], and Kramer and colleagues built on them with an algorithm of structured questions [28]. The Naranjo scale, published in 1981, reduced the exercise to ten weighted questions covering previous reports, timing, dechallenge, rechallenge, alternative causes, placebo response, drug levels, dose-response, previous similar reaction and objective confirmation [29]. Total scores place the reaction in one of four bands: definite, probable, possible or doubtful. Its popularity comes from simplicity, though that same simplicity is the source of its limits.

The WHO-UMC system, in contrast, uses categories described in words rather than a score: certain, probable or likely, possible, unlikely, conditional or unclassified, and unassessable. It asks the assessor to consider timing, dechallenge, rechallenge and the plausibility of alternative explanations, but does not weight them numerically [6, 16]. Comparison studies are instructive. Théophile and colleagues compared consensual expert judgement, an algorithmic method and a probabilistic one on reports from a French pharmacovigilance centre, and found that agreement between methods was only moderate [30]. Agbabiaka and co-workers drew a similar conclusion from their review, noting poor reproducibility between assessors for several algorithms [16].

General tools were not designed with skin reactions in mind. Their questions about rechallenge, drug levels and placebo response rarely apply, and they give little weight to latency, which is often the most informative feature for a delayed rash. The ALDEN algorithm was built to fill this gap for SJS and TEN. Sassolas and colleagues scored six items, covering the delay from first intake to onset, the presence of the drug in the body at onset, prior exposure and rechallenge, dechallenge, the notoriety of the drug based on case-control data, and other possible causes, to yield a score from −12 to 10 and a category from very unlikely to very probable [31]. Compared with case-control analysis, it performed better than previous general algorithms for SJS and TEN [24, 31].

Dechallenge, the observation that a reaction improves when the drug is withdrawn, is where delayed skin reactions most often confuse the scoring. In a T-cell mediated eruption the rash may keep spreading for several days after the last dose and may take weeks to clear, so a patient who gets worse after stopping has not necessarily shown that the drug is innocent [9, 29]. Drugs with long half-lives stay in the body well beyond the last tablet, which is why ALDEN asks whether the drug was still present at onset, not merely whether it had been prescribed [31]. Assessors who score improvement within a fixed number of days, as some general algorithms implicitly do, will penalise exactly the reactions that follow this slower course [16, 29].

Polypharmacy is the other practical obstacle. Hospital patients typically take several drugs at once, and an algorithm scored for each would often give the same rating to two or three of them. ALDEN handles this by comparing each drug on notoriety and timing, so that a drug with a strong case-control record and an appropriate delay scores above one with a weak record and an implausible

interval [24, 31]. A high score is a probability, not a verdict, so assessors are encouraged to keep a short list of suspects, not a single one, and to avoid all of them until the picture is clear [31, 32].

Dermatology adds its own evidence. Patch, prick and intradermal tests with drugs can support causality for some delayed reactions, and the European Network for Drug Allergy has published guidance on how and when to perform them [32, 33]. Sensitivity varies by drug and by reaction pattern, and skin tests are not recommended in the acute phase of the most severe reactions. Histology helps to distinguish patterns such as AGEP from pustular psoriasis. Rechallenge is the strongest single piece of evidence but is generally unethical for severe reactions, so the dermatologist must usually decide without it [29, 32]. The main instruments for causality, severity, classification and prevention are set side by side in table 1.

Counting the tools by purpose gives four groups (fig. 1). Causality instruments are the most numerous, which reflects the long history of the field. Severity tools and classification schemes follow, while prevention tools, including genetic screening and preventability criteria, make up the smallest group. The count says little about quality: a tool used in thousands of reports may be less well validated than one used in a handful of careful studies. It does say where the effort has gone, and that is mostly towards the question of whether the drug did it, with less on what to do next [16, 34].

A practical point about timing. Assessors often apply the algorithm after the event, working from notes. Entries made at the time, including the date each drug was started and stopped, the date of the first skin change and whether the reaction improved after withdrawal, are what make a score reliable. Missing dates are the commonest reason for a case to end up as possible or unassessable. Several authors recommend a standard reaction form that prompts for dates and concomitant medicines [6, 22]. Electronic prescribing records now make some of this retrospective reconstruction easier, though administration times, patient-held medicines and over-the-counter products still have to be asked about directly [22, 32].

Table 1: Tools used to assess causality, severity, classification and prevention of cutaneous adverse drug reactions

Tool	Reported features and use	Ref.
Naranjo scale	Ten weighted questions giving a total score in four bands from doubtful to definite; simple, but several items rarely apply to skin reactions.	[16, 29]
WHO-UMC system	Verbal categories from certain to unassessable based on timing, dechallenge, rechallenge and alternative causes, without numerical weighting.	[6, 16]
Karch–Lasagna and Kramer algorithms	Early operational criteria and structured questions on timing, withdrawal, rechallenge and other causes.	[27, 28]
ALDEN	Six-item score for SJS and TEN including delay, drug notoriety and other causes; compared against case-control data.	[24, 31]
Hartwig scale	Seven levels of severity from no change in treatment to death; works across specialities.	[34]
SCORTEN	Seven risk factors scored at admission to predict mortality in SJS and TEN.	[35, 36]
Bastuji-Garin classification	Separates SJS, overlap and TEN by the extent of skin detachment and lesion type.	[3, 37]
RegiSCAR DRESS score	Combines fever, eosinophilia, lymph nodes, skin features and organ involvement into four diagnostic categories.	[12, 14]
Schumock–Thornton criteria	Short questionnaire that labels a reaction preventable if prescribing, monitoring or allergy history was inadequate.	[38]
HLA screening	Allele testing (B*5701, B*5801, B*1502) lowered or flagged risk for abacavir, allopurinol and carbamazepine in defined populations.	[17, 18, 19]

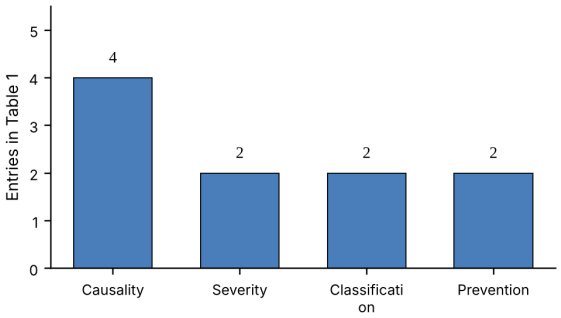


Fig. 1: Number of entries in table 1 by assessment purpose

5. SEVERITY AND PREVENTABILITY ASSESSMENT

General severity scales grade the clinical consequences of a reaction regardless of the organ system. Hartwig and colleagues proposed a seven-level scale running from a reaction needing no change in treatment, through levels requiring withdrawal of the drug, antidote or treatment, to prolonged hospitalisation, intensive care, permanent harm and death [34]. Levels 1 and 2 are generally treated as mild, 3 and 4 as moderate and 5 to 7 as severe. The scale is quick to use and works across specialities, which is why it is common in hospital pharmacy audits. It does not capture the pattern-specific prognostic information that dermatologists need [5, 34].

For SJS and TEN, the first requirement is correct classification. Bastuji-Garin and colleagues proposed that cases be separated by the extent of skin detachment: below 10 per cent of body surface area for SJS, 10 to 30 per cent for overlap, and above 30 per cent for TEN, with the lesion type and distribution distinguishing these from erythema multiforme [37]. Extent of detachment is a strong predictor of outcome but is not, by itself, a prognostic score. SCORTEN was developed for that purpose. Bastuji-Garin and co-workers identified seven independent risk factors: age over 40 years, malignancy, heart rate above 120 per minute, initial detachment above 10 per cent, serum urea above 10 mmol/L, serum glucose above 14 mmol/L and bicarbonate below 20 mmol/L, with mortality rising as the count increases [35].

Reported mortality for TEN has been put at around a third in older series, and lower for SJS [3, 4]. An Asian case series of SJS and TEN described the ocular complications that follow the acute illness, noting that survivors often have long-term eye problems [39]. SCORTEN is calculated at admission and ideally repeated on the third day, because the score changes as the illness evolves. Validation studies since its original publication have generally supported its discrimination but suggest it may overestimate or underestimate mortality in particular settings, a reminder that scores reflect the population in which they were derived [4, 35].

Severity does not end at discharge. Survivors of SJS and TEN commonly report chronic dry eyes, scarring of the eyelids and conjunctivae, nail and pigmentation changes, and mucosal strictures, and ocular involvement in the acute phase is the strongest clinical pointer to later eye disease [39, 40]. Scales built around mortality, such as SCORTEN, say nothing about this burden, and a patient with a low score may still carry serious morbidity for years. The Hartwig levels capture permanent harm only crudely. Several authors have argued that long-term outcome measures should accompany acute scores in follow-up clinics, although no agreed instrument has emerged [34].

DRESS lacks a single severity scale. The RegiSCAR group developed a scoring system that combines fever, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin extent and features, organ involvement, resolution time and exclusion of other causes, classifying cases as no, possible, probable or definite [14]. Kardaun and colleagues in the prospective RegiSCAR study described DRESS as a multisystem reaction in which the liver is most often involved, followed by the kidney and lung [14]. The score is a diagnostic aid, not a severity gauge, but in practice organ involvement and duration of illness serve as markers of severity, and clinicians use them alongside it [12, 14]. Viral reactivation, discussed by Shiohara and Kano, can prolong the course and is worth looking for when a patient relapses on steroid withdrawal [20].

AGEP is the mildest of the three severe patterns in most series, but it is easily mistaken for something else. Sidoroff and

colleagues, in the EuroSCAR case-control study, found that antibiotics, particularly aminopenicillins, macrolides and some others, were associated with AGEP, and that the interval between starting the drug and the eruption was short, often within a few days [13]. Fever and a raised neutrophil count accompany the sterile pustules, which usually dry and desquamate within about two weeks of stopping the drug. Severity grading here relies on extent of skin involvement, organ dysfunction in the minority who have it, and the general Hartwig scale [13, 34]. The distinction from pustular psoriasis matters because the long-term plan differs, and drug history is one of the few clues that separates them.

Preventability is the third axis. Schumock and Thornton framed a short set of questions: was the drug inappropriate for the patient's condition, were dose, route and frequency wrong, was the required monitoring missing, was there a documented history of allergy or previous reaction, was a drug interaction involved, or was a toxic serum level documented [38]. A yes to any of them classifies the reaction as preventable. Applied to skin reactions, the allergy history question is the most relevant, along with prescribing of known high-risk drugs without genotype testing where this is recommended [19, 38]. Preventability results are less often published for CADRs than causality scores.

Taken separately, each score is simple. In a busy dermatology unit, three scores may be recorded for one patient: Naranjo or WHO-UMC for causality, a severity level, and preventability. Where they disagree, the severity usually drives action and causality drives labelling. A possible reaction of high severity still deserves strict avoidance, whereas a certain reaction that is trivial may only need a note in the record [6, 34].

6. PRACTICE IN A DERMATOLOGY UNIT

The published guidance for dermatology units follows a common sequence. First, build a timeline from the drug chart and, if necessary, the community prescription record, listing every medicine, supplement and topical product with start and stop dates. Second, describe the eruption by morphology, distribution, mucosal involvement and systemic features, since these determine which pattern and which tools apply. Third, stop the suspected drug or drugs, giving priority to those started in the window associated with that pattern. Fourth, apply the relevant causality algorithm and record the category and reasons [31, 32]. Where several drugs are suspect, each should be scored, not only the favourite.

Management of severe reactions is mostly supportive. The UK guidelines for adults with SJS and TEN recommend early transfer to a specialist unit, withdrawal of the culprit, fluid and nutritional support, wound care, and attention to the eyes, and they discuss immunomodulatory therapies with the observation that evidence for any single one is limited [36, 40]. For DRESS, systemic corticosteroids are commonly used when organs are involved, with slow tapering because relapse during withdrawal is well described [12, 14]. The causality category and severity grade are part of the record that travels with the patient, and they inform decisions about alternative drugs.

Training matters because the tools are applied by people. When different assessors score the same case, the Naranjo total can differ by several points, mainly on the questions about alternative causes and objective confirmation, which invite judgement [29, 30]. Short shared sessions in which a ward pharmacist and a dermatologist score a handful of past cases together and discuss the differences are a low-cost way of narrowing the spread. They also show which items are repeatedly misread. Meyboom and colleagues made the same point, that the process of discussion is as useful as the number it produces [6, 16].

Reporting closes the loop. Spontaneous reports to the national pharmacovigilance centre are the means by which rare reactions, and new drug associations, become known. Hazell and Shakir showed that most reactions are never reported, and that reports are more likely for serious or unexpected events [22]. Dermatologists have a disproportionate part to play because their patients provide well-documented cases. A concise report that states the causality category, the method used

and the key dates is more useful to the centre than a long narrative without them [6, 22]. Labelling the patient in the medical record with the drug and reaction type, as well as the category, prevents repeat exposure on the next admission [32, 33].

7. LIMITATIONS AND FUTURE DIRECTIONS

Three kinds of limitation apply here. The first concerns the tools: most were derived from expert opinion, tested on small samples and rarely validated against a reference standard, since none exists [16, 30]. Reproducibility between assessors is modest, and algorithms built for general adverse reactions handle delayed cutaneous reactions poorly. The second concerns the data: many dermatology publications are retrospective, from single centres, and use differing definitions of a reaction, which makes pooling hazardous [1, 11, 21]. The third concerns this review, which is narrative and was not designed to be exhaustive; important work may have been missed.

The most useful next steps are modest. Tools designed specifically for delayed cutaneous reactions, along the lines of ALDEN, deserve development for other patterns such as DRESS and AGEP, together with validation in prospective cohorts [13, 14, 31]. Shared reporting standards for dermatology units, covering dates, concomitant medicines and the tool used, would make local data easier to compare. Genotype-guided prescribing has worked where the association is strong and the test is affordable [17, 18, 19], and further population-specific data would help to extend it. None of this requires new drugs or new technology, only agreement on how to record what clinicians already see.

8. CONCLUSION

Cutaneous reactions to drugs are common, mostly mild and occasionally deadly, and the published literature offers a reasonably full toolkit for judging them. Causality can be graded by general algorithms such as Naranjo and the WHO-UMC categories, or by ALDEN where SJS or TEN is suspected; severity can be graded with the Hartwig levels, the extent of detachment and SCORTEN; and preventability can be checked against the Schumock and Thornton criteria [6, 29, 31, 34, 35, 38]. Each tool answers a different question, and the choice should follow the question.

The weak points are agreement and validation. Methods disagree more often than clinicians expect, and most were not built for delayed, T-cell mediated eruptions [9, 16, 30]. For practice, the sensible course is to record dates carefully, use one named causality method consistently, grade severity at once, report to the pharmacovigilance centre and update the allergy record with the category as well as the drug [22, 32, 33]. For research, prospective validation of pattern-specific tools is the clear priority [14, 31].

9. ABBREVIATIONS

ADR-Adverse drug reaction, AGEP-Acute generalised exanthematous pustulosis, ALDEN-Algorithm of drug causality for epidermal necrolysis, CADR-Cutaneous adverse drug reaction, DRESS-Drug reaction with eosinophilia and systemic symptoms, HLA-Human leukocyte antigen, SCORTEN-Severity-of-illness score for toxic epidermal necrolysis, SJS-Stevens–Johnson syndrome, TEN-Toxic epidermal necrolysis, WHO-UMC-World Health Organization–Uppsala Monitoring Centre

10. FUNDING

Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol 2001;137:765–70.
2. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 1986;256:3358–63.
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–85.

4. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol 2013;69:173.e1–13.

5. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255–9.

6. Meyboom RHB, Hekster YA, Egberts ACG, Gribnau FWJ, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997;17:374–89.

7. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, *et al.* Cutaneous reactions to drugs: an analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol 1999;48:839–46.

8. Gell PGH, Coombs RRA. Clinical aspects of immunology. Oxford: Blackwell Scientific; 1963.

9. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med 2003;139:683–93.

10. Phillips EJ, Chung WH, Mockenhaupt M, Roujeau JC, Mallal SA. Drug hypersensitivity: pharmacogenetics and clinical syndromes. J Allergy Clin Immunol 2011;127:S60–6.

11. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, *et al.* A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol 2003;149:1018–22.

12. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). Semin Cutan Med Surg 1996;15:250–7.

13. Sidoroff A, Dunant A, Viboud C, Halevy S, Bouwes Bavinck JN, Naldi L, *et al.* Risk factors for acute generalized exanthematous pustulosis (AGEP): results of a multinational case-control study (EuroSCAR). Br J Dermatol 2007;157:989–96.

14. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013;169:1071–80.

15. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol 2002;138:1019–24.

16. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf 2008;31:21–37.

17. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, *et al.* Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.

18. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, *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.

19. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568–79.

20. Shiohara T, Kano Y. A complex interaction between drug allergy and viral infection. Clin Rev Allergy Immunol 2007;33:124–33.

21. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. Allergy 1997;52:388–93.

22. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006;29:385–96.

23. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600–7.

24. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, *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.

25. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200–5.

26. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. BMJ

2004;329:15–9.

27. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther 1977;21:247–54.
28. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. JAMA 1979;242:623–32.
29. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
30. Théophile H, Arimone Y, Miremont-Salamé G, Moore N, Fourrier-Réglat A, Haramburu F, *et al.* Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Saf 2010;33:1045–54.
31. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, *et al.* ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther 2010;88:60–8.
32. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001;45:321–8.
33. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, *et al.* Skin test concentrations for systemically administered drugs: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013;68:702–12.
34. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229–32.
35. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000;115:149–53.
36. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.
37. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92–6.
38. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27:538.
39. Yip LW, Thong BY, Lim J, *et al.* Ocular manifestations and complications of Stevens-Johnson syndrome and toxic epidermal necrolysis: an Asian series. Allergy 2007;62:527–31.
40. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JKG, *et al.* UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. J Plast Reconstr Aesthet Surg 2016;69:e119–53.