

Diagnosis of drug-induced skin reactions: a future role for computer-aided systems?

Guido J. Burbach and Torsten Zuberbier

Department of Dermatology and Allergy, Charité
Universitätsmedizin Berlin, Berlin, Germany

Correspondence to Torsten Zuberbier, Department of
Dermatology and Allergy, Charité Universitätsmedizin
Berlin, Charitéplatz 1, 10117 Berlin, Germany
Tel: +49 30 518135; fax: +49 30 518919;
e-mail: torsten.zuberbier@charite.de

**Current Opinion in Allergy and Clinical
Immunology** 2011, 11:000–000

Purpose of review

The diagnosis of drug-induced hypersensitivity reactions is a common clinical challenge and the skin is considered a signal organ for a large percentage of these reactions. In order to assure clinical improvement of the patient, nondermatologists in primary or intensive care settings attending to patients receiving several drugs are often confronted with the need for an immediate decision which drug to stop and which drug to continue. As reliable allergological tests are missing for most drugs and are not available for immediate interventions, computer-aided diagnostic systems might be of assistance.

Recent findings

This review highlights the evolution of automated diagnostic aides in dermatology, emphasizes prerequisites for the development of appropriate computational algorithms and discusses the specific requirements and chances for the development of computer-aided diagnostic systems as a supportive approach in the diagnosis of culprit drugs for putative drug-induced hypersensitivity reactions.

Summary

As complex computational algorithms have to be created integrating both image and data analysis, the development of a computer-aided system for supporting nondermatologists in the diagnosis of drug-related hypersensitivity reactions is an ambitious task but might represent an achievable goal for the medium-term future.

Keywords

cutaneous hypersensitivity reactions, decisional algorithms, European database, standardization

Curr Opin Allergy Clin Immunol 11:000–000
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

The identification of the causal relationship between certain drugs and suspected hypersensitivity reactions is often vital and the key to clinical improvement of the patient. The skin is the signal organ for most drug-induced hypersensitivity reactions and due to its apparent accessibility, thus, often a signpost for this diagnosis. Approximately 30% of drug-induced reactions are cutaneous and occur in 2–3% of hospitalized patients [1–5]. However, the large number of drugs, the multitude of possible clinical symptoms, and the variety of different underlying mechanisms frequently complicate the initiation of correct diagnostic procedures and therapeutic decisions. Especially in ICUs where patients mostly receive a considerable number of drugs, the decision which drug to stop and which to continue might be vitally important. This decision might even be complicated by the fact that skin diseases are a common finding in ICUs [6] and other differential diagnosis apart from drug-induced hypersensitivity reactions must be considered. Also, in primary care settings in which gen-

eral practitioners are confronted with chronically ill patients taking several drugs, not only the diagnosis of a drug-induced hypersensitivity reaction but also the identification of the causative medication might be difficult.

In these situations, in which the physician has to decide immediately which drug to stop and which to continue in order to assure clinical improvement of the patient, computer-aided diagnosis (CAD) systems could be a logical alternative especially if a dermatologist is not available instantaneously. However, given the wide spectrum of polymorphous skin eruptions in cutaneous drug-induced hypersensitivity reactions, do automated diagnostic aides in fact represent a realistic future goal?

Algorithms and automated diagnostic aides in dermatology

A good example of how diagnostic tools can evolve is demonstrated by the evolution of melanoma diagnosis: before the 1980s, macroscopic features of peculiar

pigmented lesions were clinically identified in a non-standardized way, and melanomas were, thus, often only recognized when they were large and ulcerated [7]. Later, the asymmetry, border irregularity, color, diameter mnemonic and other clinical algorithms like the 'ugly duckling' sign have added to a significant increase in diagnostic accuracy over time [8–10]. In the 1990s, dermoscopy usually facilitating a 10-fold magnification of the skin then enabled the recognition of new subsurface features. Here, also several clinical algorithms have been developed and successfully applied like the asymmetry, border, colors, and dermatoscopic structure (ABCD) rule of dermoscopy [11], the Menzies method [12], the seven-point checklist [13], or the color, architecture, symmetry, homogeneity algorithm [14]. Nowadays, clinical melanoma differential diagnosis incorporates the combination of 'macro' signs, that is a whole body screen by the naked eye as well as a dermoscopic whole body screen identifying dermoscopic patterns with 'micro' signs, that is an individual lesion assessment by the naked eye as well as a dermoscopic individual lesion assessment.

During the past decade, some of these noncomputational clinical algorithms have been translated into computational algorithms and integrated into CAD systems. These new computer-based technologies have finally significantly optimized the selection of skin lesions for biopsy and pathology review [7]. A meta-analysis in 2009 reviewing manual dermoscopy and computer-assisted dermoscopy systems demonstrated that the pooled specificity for manual dermoscopy was still better than for CAD systems but that the pooled sensitivity for the artificial intelligence systems was slightly higher than for manual dermoscopy [15]. Artificial intelligence systems will most probably further significantly improve and some experts believe that they might soon exceed the assessment of a trained dermatologist. However, the presence of an expert dermatologist is nowadays still considered necessary for a final confirmation of the diagnosis and the discussion of treatment options with the patient [16].

Naturally, there was not only an evolution from a non-standardized clinical assessment of pigmented lesions to a professional use of CAD systems but also an evolution of the artificial intelligence systems themselves over time, which nicely demonstrates which aspects have to be recognized in the process of developing CAD systems: a most logical approach towards developing a CAD system for differentiating benign and malignant melanocytic lesions is to mimic human evaluation by reproducing clinical algorithms like the ABCD rule of dermoscopy [17]. However, for each part of the rule, that is asymmetry, border, and so on or any other feature in question, a different algorithm has to be developed.

Key points

- A mandatory prerequisite for the development of computer-aided diagnosis (CAD) systems supporting the diagnosis of drug-induced cutaneous hypersensitivity reactions is the standardized collection of the biggest variety of skin rashes, in which the causative agent has already been identified.
- The separation and clear definition of distinct subgroups in the wide confusing spectrum of nonlife-threatening exanthematous skin reactions will facilitate diagnostic procedures.
- CAD systems for diagnostic support require standardization of image acquisition, translation of clinical decisional algorithms into computational algorithms as well as integration and combination of drug and host-related clinical data.
- A novel European initiative is now concentrating on the highly ambitious goal of realizing a CAD system for the diagnosis of drug-induced skin reactions in the medium-term future.

Nonetheless, by detecting, quantifying and grading patterns and their relationship to each other, algorithms only covering one single aspect of clinical mnemonics can already by itself be a helpful diagnostic aide. Computational algorithms used for CAD systems in melanoma diagnosis include, for example, image segmentation algorithms for differentiating or partitioning objects from background or other objects [18,19], color characteristics algorithms for quantifying variation and distribution of colors [20], and border detection algorithms for revealing asymmetry, border irregularity and abrupt border cut-off [21]. Still, each of these single clinician-related algorithms might alone have significant shortcomings. Interestingly, in 2009, one group suggested the analysis of lacunarity, that is a measure of heterogeneity or gaps in multitextured structures of an object [22,23], as part of an artificial neural network in dermoscopy [24]. This feature was identified by computer scientists as additional data beyond which the naked eye can see and might point out functional characteristics of future systems.

Noteworthy, the algorithms applied for image analysis are not necessarily dependent on the quality of the images taken [25] and commercially available digital cameras can be used [26]. However, a correct implementation of computational algorithms is only possible if a minimum of standardization procedures is warranted. Standardization for efficient image analysis first of all has to consider exposure settings like the use of a ring flash for consistent lighting. In order to optimize the image calibration procedure, so-called MacBeth color checker charts (X-Rite, Regensdorf, Switzerland) are now more frequently included in the image close to the region of interest during exposure. It contains a number of color squares

with known colorimetric properties [26]. Thereby, the digital image can be normalized, that is converted into relative colors in order to accommodate any variations caused by lighting, photographic or digitization processes and variations in healthy skin color between individuals [27].

Computer-aided diagnostic systems for the differential diagnosis of benign melanocytic nevi versus malignant melanoma, in summary, have significantly improved over time and nowadays already represent a helpful diagnostic tool for the clinician. However, the diagnosis of cutaneous drug-induced hypersensitivity reactions not only relies on visual information about the skin lesion but also significantly depends on several data, for example regarding the time frame of drug intake, the application route or concomitant diseases.

Diagnosis of drug-induced skin reactions

Cutaneous drug-induced hypersensitivity reactions are a source of confusion even among dermatologists. Conclusive diagnostic tests are often not available leading to a lack of clarity about how to describe, classify and approach them [28[•]]. Common patterns of this wide variety of polymorphous drug-induced hypersensitivity reactions include, for instance, the classical maculo-papular eruptions (MPEs), fixed drug eruptions (FDEs), and urticarial reactions. The differential diagnosis of these reactions often includes para-infectious exanthematous rashes and a clear diagnosis might even be more complicated, if drugs are taken to treat the infection. Although newer studies utilizing large databases have already identified high-risk culprit drugs for some of these clinical entities [29], a clear definition of high or low-risk drugs for drug-induced exanthematous rashes is mostly lacking. Only for very few drug-induced skin reactions, for example bleomycin-induced flagellate dermatitis [30] or epidermal growth factor receptor (EGFR)-related acneiform dermatitis [31] the culprit drug can basically be identified by looking at the clinical picture. The remaining spectrum of nonlife-threatening cutaneous drug-induced reactions, however, remains confusing because there is still a great variety of cutaneous drug-induced eruptions which are not yet clearly defined neither clinically nor with regard to high or low-risk causative agents. These include, for example psoriasiform, pustular, lichenoid, erythema multiforme-like, and urticaria-like eruptions. From these typically nonlife-threatening reactions, drug rashes with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndromes (DIHS) have to be differentiated [32,33]. However, a clear diagnosis of DRESS is also often complicated by the fact that the associated rashes show wide variations including maculopapular, lichenoid and erythema multiforme-like eruptions.

In order to intensify an efficient search for causative drugs in the large spectrum of drug-induced exanthematous rashes, we believe that there is a need for separating and clearly defining distinct subgroups. This 'splitter' versus 'merger' attitude which was originally described for severe cutaneous adverse reactions (SCAR) [34] is believed to better allow the development of diagnostic criteria and, thus, significantly facilitate the identification of culprit drugs. For instance, the clear differentiation of SCARs as distinct clinical entities which were originally considered similar with regard to their putative drug-related cause revealed that only Stevens–Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN) but not erythema multiforme majus (EMM) had an elevated probability of being drug-induced and high-risk drugs could be clearly identified [35–37].

The accurate diagnosis of a drug-induced hypersensitivity reaction and the identification of the causative drug, however, still relies on the correct allergological approach. For that purpose, a detailed history with careful evaluation of the temporal relationship between drug intake and appearance of skin lesion, as well as a thorough physical examination, is fundamental [38]. Unfortunately, there are no universally reliable tests for proving a suspected drug allergy. However, in case of positive reactions, tests can provide important information. For immediate reactions prick tests, intradermal tests, and serum-specific IgE assays are used and in some cases, basophil activation tests may prove useful. Patch tests and delayed-reading intradermal tests are used for non-immediate reactions and lymphocyte transformation tests may prove useful as an additional tool in selected cases. If the allergological test results are negative, not available or not validated, drug provocation tests with the suspected drug in question are necessary and still represent the 'gold standard' for both immediate and nonimmediate reactions [2,39,40,41[•]]. A fairly new development is the identification of genetic markers for distinct drug-induced entities. For instance, a strong association of allopurinol or carbamazepine-induced SJS and TEN with the genetic markers HLA-B*1502 and HLA-B*5801 was demonstrated in distinct ethnicities [42,43,44[•]]. An association between HLA-B*5701 and abacavir hypersensitivity has now even been used for the widespread implementation of genetic screening procedures before abacavir prescription [44[•],45,46].

Taken together, the diagnosis of cutaneous drug-induced hypersensitivity reactions is a challenging task for clinicians even with the help of supporting allergological tests, which can only be applied after the hypersensitivity reaction has already healed. An ideal CAD system for cutaneous drug-induced hypersensitivity reactions, however, would be able to suggest a diagnosis without the need for allergological tests because its purpose would be

to suggest which drug to stop and which drug to continue as an immediate intervention measure at the time the hypersensitivity reaction occurs.

Computer-aided diagnosis systems for drug-induced skin reactions?

Similar to the development of artificial intelligence systems for melanoma diagnosis, the logical approach for developing a CAD system for cutaneous drug-induced hypersensitivity reactions is to mimic human evaluation by reproducing clinical algorithms.

Such clinical decision algorithms for the clarification of adverse reactions in general might be drug-related or not were already developed in the early 1980s [47,48]. For instance, the so-called Naranjo algorithm, already published in 1981 [49], uses 10 simple yes/no questions to categorize adverse drug reactions in definite, probable, possible and doubtful. For SCARs, a clinical algorithm termed algorithm of drug causality for epidermal necrolysis (ALDEN) was recently developed to grade the probability of a drug being the causative agent for a severe cutaneous hypersensitivity reaction [50^{••}]. Studies have shown that the use of these algorithms does improve the inter-rater and intra-rater agreement significantly [47]. However, most clinical algorithms include the effects of re-challenge in the measurement of their semi-quantitative scores. Thus, if drug provocation tests are not applied which is often the case in clinical practice, the causality score can often not be graded more than 'possible'. Nonetheless, a translation of these clinical decisional algorithms into computational algorithms for CAD systems might prove useful.

Although the standardization of image acquisition is certainly a similar prerequisite to that described for CAD systems in melanoma detection, the translation of clinical decisional algorithms into computational algorithms for the development of CAD systems for cutaneous drug-induced hypersensitivity reactions is only a first step of many. In contrast to CAD systems for melanoma recognition which for the most part rely on the analysis of one single image, CAD systems for drug-induced hypersensitivity reactions have to combine information from overview and close-up pictures. Furthermore, a great amount of data regarding drug-related factors like route of administration and the exact time frame of drug intake, host-related factors like sex, age, concomitant diseases and infection, lab and allergological results, and in the future possibly even genetic information have to be integrated into the development process [51[•]]. Fusion algorithms for the integration of information from multiple data sources have already been developed [52] but would have to be adapted to the specific situation of drug-induced hypersensitivity reactions.

A prerequisite for the development of such a CAD system is, therefore, the standardized collection of the biggest possible variety of cutaneous drug-induced hypersensitivity reactions. These reactions should preferably be confirmed by appropriate allergological provocation tests as a gold standard. As the development of CAD systems aims at an application as immediate intervention measure at the time the hypersensitivity reaction occurs, the artificial intelligence systems would be able to 'learn' from such classical cases in large multinational databases. For the standardized collection of drug hypersensitivity reactions in general, the ENDA-DAHD (European Network for Drug Allergy-Drug Allergy and Hypersensitivity Database, [53]) and as a standardized registry for SCARs the RegiSCAR project (<http://regiscar.uni-freiburg.de>) were already created. However, a project focusing on the standardized collection of nonlife-threatening cutaneous drug-induced hypersensitivity reactions, which are the most frequent adverse events, was until recently still lacking. A new European initiative, the European network for cutaneous adverse reactions of drugs (ENCAD) concentrating on nonlife-threatening cutaneous drug-induced hypersensitivity reactions, is specifically designed to ensure a detailed dermatological description of skin lesions and assesses drug and host-related key factors.

An increasing challenge with large databases providing a huge amount of data, however, is the widening gap between data collection and data comprehension. Relevant information patterns have to be extracted from the wealth of data and have to be correlated to and connected with the information extracted by image analysis. For drug safety surveillance purposes, for instance, data mining, that is computational signal detection algorithms have already been successfully applied to detect unexpected adverse reactions in general which may have escaped manual reviews [54]. Also, so-called rule mining techniques for the identification of predictive if-then-rules have already proven their value in practice [55]. However, these algorithms were developed for a general postmarketing analysis of drugs and are not necessarily applicable to the analysis of cutaneous hypersensitivity reactions in the above-mentioned settings.

Conclusion

The unprecedented evolution of computational diagnostic aides which has taken place over the years for the differential diagnosis between benign melanocytic lesions and melanoma is a good example of how much potential the development of CAD systems might hold. Yet, the development of a CAD system for supporting nondermatologists in the diagnosis of drug-related hypersensitivity reactions and the identification of the respective culprit drug is an ambitious task because not only

image information but also the analysis of a wide array of clinical data has to be processed and integrated. However, a novel project namely the ENCAD initiative already explicitly pursues this goal. Therefore, the development of CAD systems aimed at the diagnostic support of cutaneous drug-related hypersensitivity reactions might represent an achievable goal in the medium-term future.

Acknowledgements

The authors wish to thank Ms Melanie May for excellent technical and administrative support. This work was supported by the European Fund for Regional Development (EFRE grant 20072013 2/24).

Conflicts of interest

None declared.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

- 1 Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005; 209:123–129.
- 2 Mirakian R, Ewan PW, Durham SR, *et al.* BSACI guidelines for the management of drug allergy. *Clin Exp Allergy* 2009; 39:43–61.
- 3 Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev* 2001; 53:357–379.
- 4 Drake LA, Dinehart SM, Farmer ER, *et al.* Guidelines of care for cutaneous adverse drug reactions. *American Academy of Dermatology. J Am Acad Dermatol* 1996; 35:458–461.
- 5 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. *J Am Med Assoc* 1986; 256:3358–3363.
- 6 Badia M, Trujillano J, Gasco E, *et al.* Skin lesions in the ICU. *Intensive Care Med* 1999; 25:1271–1276.
- 7 Rigel DS, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. *CA Cancer J Clin* 2010; 60:301–316.
- 8 Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *CA Cancer J Clin* 1985; 35:130–151.
- 9 Rigel DS, Friedman RJ. The rationale of the ABCDs of early melanoma. *J Am Acad Dermatol* 1993; 29:1060–1061.
- 10 Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. *Arch Dermatol* 1998; 134:103–104.
- 11 Stolz W, Riemann A, Cognetta AB, Pillet L. ABCD rule of dermatoscopy: a new practical method for early recognition of malignant melanoma. *Eur J Dermatol* 1994; 4:521–527.
- 12 Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. *Arch Dermatol* 1996; 132:1178–1182.
- 13 Argenziano G, Fabbrocini G, Carli P, *et al.* Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Arch Dermatol* 1998; 134:1563–1570.
- 14 Henning JS, Dusza SW, Wang SQ, *et al.* The CASH (color, architecture, symmetry, and homogeneity) algorithm for dermatoscopy. *J Am Acad Dermatol* 2007; 56:45–52.
- 15 Rajpara SM, Botello AP, Townend J, Ormerod AD. Systematic review of dermatoscopy and digital dermatoscopy/artificial intelligence for the diagnosis of melanoma. *Br J Dermatol* 2009; 161:591–604.
- 16 Rahman MM, Bhattacharya P. An integrated and interactive decision support system for automated melanoma recognition of dermoscopic images. *Comput Med Imaging Graph* 2010; 34:479–486.
- 17 Pellacani G, Grana C, Seidenari S. Algorithmic reproduction of asymmetry and border cut-off parameters according to the ABCD rule for dermatoscopy. *J Eur Acad Dermatol Venereol* 2006; 20:1214–1219.
- 18 Wighton P, Sadeghi M, Lee TK, Atkins MS. A fully automatic random Walker segmentation for skin lesions in a supervised setting. *Med Image Comput Comput Assist Interv* 2009; 12:1108–1115.
- 19 Kockara S, Mete M, Chen B, Aydin K. Analysis of density based and fuzzy c-means clustering methods on lesion border extraction in dermatoscopy images. *BMC Bioinformatics* 2010; 11 (Suppl 6):S26.
- 20 Stanley RJ, Stoecker WV, Moss RH, *et al.* A basis function feature-based approach for skin lesion discrimination in dermatology dermatoscopy images. *Skin Res Technol* 2008; 14:425–435.
- 21 Mete M, Sirakov NM. Lesion detection in dermatoscopy images with novel density-based and active contour approaches. *BMC Bioinformatics* 2010; 11 (Suppl 6):S23.
- 22 Plotnick RE, Gardner RH, Hargrove WW, *et al.* Lacunarity analysis: a general technique for the analysis of spatial patterns. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics* 1996; 53:5461–5468.
- 23 Mandelbrot BB. The fractal geometry of nature. Basel: Birkhäuser; 1987.
- 24 Gilmore S, Hofmann-Wellenhof R, Muir J, Soyer HP. Lacunarity analysis: a promising method for the automated assessment of melanocytic naevi and melanoma. *PLoS One* 2009; 4:e7449.
- 25 Christensen JH, Soerensen MB, Linghui Z, *et al.* Prediagnostic digital imaging prediction model to discriminate between malignant melanoma and benign pigmented skin lesion. *Skin Res Technol* 2010; 16:98–108.
- 26 Vander HY, Naeyaert JM. Consistent cutaneous imaging with commercial digital cameras. *Arch Dermatol* 2006; 142:42–46.
- 27 LeAnder R, Chindam P, Das M, Umbaugh SE. Differentiation of melanoma from benign mimics using the relative-color method. *Skin Res Technol* 2010; 16:297–304.
- 28 Friedmann PS, Pickard C, Ardern-Jones M, Bircher AJ. Drug-induced exanthema: a source of clinical and intellectual confusion. *Eur J Dermatol* 2010; 20:255–259.

This overview about drug-induced skin rashes discusses the problem of categorizing these entities.

- 29 Brahimi N, Routier E, Raison-Peyron N, *et al.* A three-year-analysis of fixed drug eruptions in hospital settings in France. *Eur J Dermatol* 2010; 20:461–464.
 - 30 Ziemer M, Goetze S, Juhasz K, Elsner P. Flagellate dermatitis as a bleomycin-specific adverse effect of cytostatic therapy: a clinical-histopathologic correlation. *Am J Clin Dermatol* 2011; 12:68–76.
 - 31 Ehmann LM, Ruzicka T, Wollenberg A. Cutaneous side-effects of EGFR inhibitors and their management. *Skin Ther Lett* 2011; 16:1–3.
 - 32 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; 22:1044–1049.
 - 33 Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am* 2009; 29:481–501.
 - 34 Valeyrie-Allanore L, Roujeau JC. Denominations and classification of severe cutaneous adverse reactions to drugs: splitters versus mergers. *Eur J Dermatol* 2007; 17:359–360.
 - 35 Auquier-Dunant A, Mockenhaupt M, Naldi L, *et al.* 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; 138:1019–1024.
 - 36 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.
 - 37 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.
 - 38 Przybilla B, Aberer W, Bircher AJ, *et al.* Allergological approach to drug hypersensitivity reactions. *J Dtsch Dermatol Ges* 2008; 6:240–243.
 - 39 Romano A, Demoly P. Recent advances in the diagnosis of drug allergy. *Curr Opin Allergy Clin Immunol* 2007; 7:299–303.
 - 40 Aberer W, Bircher A, Romano A, *et al.* Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; 58:854–863.
 - 41 Romano A, Torres MJ, Castells M, *et al.* Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; 127:S67–S73.
- This article summarizes recent advances in diagnosis and management of drug-induced hypersensitivity reactions in general.

- 42 Chung WH, Hung SI, Hong HS, *et al.* Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004; 428:486.
- 43 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 U S A* 2005; 102:4134–4139.
- 44 Phillips EJ, Chung WH, Mockenhaupt M, *et al.* Drug hypersensitivity: pharmacogenetics and clinical syndromes. *J Allergy Clin Immunol* 2011; 127:S60–S66.
An overview about current advances in pharmacogenomics with the focus on severe cutaneous adverse reactions.
- 45 Mallal S, Nolan D, Witt C, *et al.* Association between presence of HLA-B*5701; HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; 359:727–732.
- 46 Hetherington S, Hughes AR, Mosteller M, *et al.* Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002; 359:1121–1122.
- 47 Doherty MJ. Algorithms for assessing the probability of an adverse drug reaction. *Respir Med CME* 2009; 2:63–67.
- 48 Benahmed S, Picot MC, Hillaire-Buys D, *et al.* Comparison of pharmacovigilance algorithms in drug hypersensitivity reactions. *Eur J Clin Pharmacol* 2005; 61:537–541.
- 49 Naranjo CA, Busto U, Sellers EM, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239–245.
- 50 Sassolas B, Haddad C, Mockenhaupt M, *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; 88:60–68.
This article introduces a new tool for causality assessment in drug-induced severe cutaneous adverse reactions.
- 51 Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol* 2011; 71:684–700.
A review of evidence-based knowledge about prevalence, incidence, risk factors, and genetic associations of drug allergy in general.
- 52 Madabhushi A, Agner S, Basavanahally A, *et al.* Computer-aided prognosis: predicting patient and disease outcome via quantitative fusion of multiscale, multimodal data. *Comput Med Imaging Graph* 2011. [Epub ahead of print]
- 53 Bousquet PJ, Demoly P, Romano A, *et al.* Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GALEN platform. The Galenda project. *Allergy* 2009; 64:194–203.
- 54 Hauben M, Horn S, Reich L. Potential use of data-mining algorithms for the detection of 'surprise' adverse drug reactions. *Drug Saf* 2007; 30:143–155.
- 55 Batal I, Hauskrecht M. Mining clinical data using minimal predictive rules. *AMIA Annu Symp Proc* 2010; 2010:31–35.