

Diagnosing Cutaneous Adverse Reactions to Drugs

Erythema multiforme (EM) develops in a patient on the 10th day of therapy with sulfamethoxazole and trimethoprim. The therapy was initiated for the treatment of an upper respiratory tract infection. The drug treatment was stopped and the patient's condition improved over the subsequent week.

See also p 48.

For a dermatologist, the above scenario is all too familiar. I will build on this sample clinical problem in the following review; but first, what is the challenge? Ask yourself the following question (as I am sure the patient and referring physician will): Did the drug cause this patient's skin problem? Before we move on, we must establish some facts about the case: let us assume the patient is a 12-year-old boy (if the patient were an adult, would that change your opinions?), the diagnosis is EM without a doubt, and there are no other complicating factors hidden from us. Your opinion could be a clear yes (100% certainty or probability of 1), no (probability of 0), or somewhere in between. To really focus your thinking, I would ask you to record your response to the challenge with an X on the line in Fig 1.

MAKING A CLINICAL DIAGNOSIS

It is critical to commit yourself. The question is straightforward: Did the patient have a drug reaction? There is no other information available; you must use your clinical judgment or what others have called "global introspection"¹ to make your decision. That is, you as an expert collect the relevant information in your head, run the data through a mixture of processes, and just decide what the answer must be. Unfortunately, this method has drawbacks. Most of these relate to the unstandardized method of solving the problem; others will unfold as we continue.

What if the patient we just considered was one of the patients in the study by Halevy et al in this issue of the ARCHIVES?² Presumably if your X was to the right of center, the patient would be considered to

have had a drug reaction. This then becomes the gold standard to which the macrophage migration inhibition factor (MIF) test is compared. How far to the right was your mark? Would you consider it a gold standard? But it must be that way. The in vitro test needs a bench mark for comparison, something to help us determine the true positives and the false negatives, and to quantify the predictive capabilities of the test.

Another clinical approach is the "better-safe-than-sorry" tactic. Briefly, if the X is anywhere, except at the extreme left of the line, it is safer to assume the patient had an adverse reaction or at least to tell that patient that he or she might be sensitive to the drug and should never receive that particular medication again. This would seem to be a practical conclusion and the advice sound. The consequences, however, are not always desirable. First, patients may be needlessly deprived of an important drug and all drugs in its class for the rest of their lives. Second, patients may begin to accumulate a list of "drug allergies" that result in a narrowing of therapeutic choices and this is problematic for both the patient and physician. Both start to believe, perhaps incorrectly, that the patient is "allergic to everything."

Third, and I believe most important, the "safe" diagnosis may not have been the thoughtful diagnosis. Perhaps a correct differential diagnostic possibility has been missed during a hasty guilty decision against the drug.³

Some approaches attempt to formalize the clinical thought process. Several specific algorithms have been developed and used to help solve individual problems of drug-induced disease. Some authors have

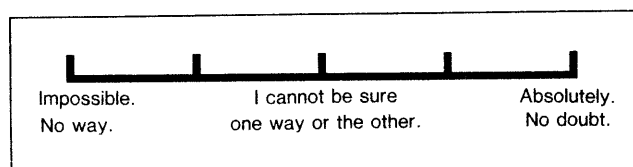


Figure 1.

believed their algorithms result in consistent decisions among different diagnosticians. Other authors disagree.^{4,5} If one applies a modification of one algorithm to the case in question, points are accumulated (+1), subtracted (-1), or equivocal (0) depending on what features are present.⁶ A selected summary of the score for this case would be as follows:

Adverse effect is well established	+1
Alternative candidates exist (ie, EM could be postinfectious)	-1
Timing is suitable for drug eruption	+1
Drug levels are not helpful	0
Adverse effect improves after drug therapy is stopped	+1
No rechallenge attempted	-0
Total	+2

The score is then converted to a judgment of likelihood that the drug caused the reaction. The choices are familiar: definite, probable, possible, and unlikely. The definitions are variable, but for this algorithm a +2 score is interpreted as "possible." This could be visualized on our line as in Fig 2.

Does this agree with your decision? Of course, the obvious limitation of this approach, even if we could imagine it was incredibly accurate, is making something of possible results. In our use of algorithms this is where most results fall. That is because the unlikely and probable drug reactions do not need a diagnostic tool. We already believe in our clinical judgment and it is unlikely an algorithm can shake that belief. We need something to move us from the possible zone to the left or to the right. This is what we demand of our diagnostic test.

IN VIVO TESTING

All current diagnostic tests are forms of rechallenge. The classic rechallenge would be to give the index patient sulfamethoxazole and trimethoprim again after he recovers. If he gets EM, we have a positive result. This would certainly help move our *X* out of the possible zone to the far right, at the cost of severe morbidity. What if the result is negative? Perhaps we need to re-create the full 10 days of therapy before we can accept a negative result. Differing views of the utility of rechallenge have been published for further review.^{7,8}

Penicillin skin testing has been widely used to confirm allergy to penicillin that is IgE mediated. A positive challenge is very convincing in this instance as well. Negative tests can be very helpful for reassessing patients who have been inappropriately labeled as allergic to penicillin. Another method of rechallenging the skin is by patch testing and this has been reviewed.^{9,10}

IN VITRO TESTING

Rechallenging the cells from a patient in the laboratory has tremendous appeal. In vitro models allow one not only to have a diagnostic test but also to investigate pathogenic mechanisms and cross-reactivity with other drugs at a cellular level. Two tests are appropriate to discuss in this context: the MIF and

the lymphocyte toxicity assay. Others have been widely used but will not be discussed herein (eg, the lymphocyte transformation test, the basophil degranulation test).

The MIF test of Halevy et al² takes lymphocytes from the patient, adds the drug in question, and incubates these with guinea pig macrophages. Increased MIF in the presence of drug relative to that produced in the absence of drug is considered a positive result. Let us imagine that this test is available to you and is performed on the cells from our patient in the challenge case. If the results are positive, what do you think the likelihood of the drug being the cause of the EM to be now? Record your answer on the line in Fig 1 with a *P*. If the MIF test result is reported as negative, what would the likelihood of a drug reaction be? Mark this on the line with an *N*.

To answer these latter questions you need to know how "good" the diagnostic test is. To determine the sensitivity and specificity of the test, a 2 × 2 table should be employed and this is shown in Table 1.

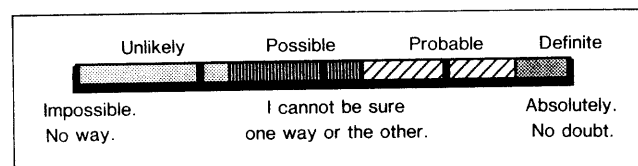


Figure 2.

Table 1.—2 × 2 Table for Migration Inhibition Factor Assay*

	Clinical Positive (Drug Eruption)	Clinical Negative	Row Totals
MIF positive	35	5	40
MIF negative	15	105	120
Column Totals	50	110	160

*MIF indicates migration inhibition factor. The true-positive rate is 35/50 or 70%; the false-positive rate is 5/110 or 5%. If pretest probability is 50%, then effect of a positive test is to raise posttest probability to 85% and a negative test lowers the probability to 20% (calculations are approximate and are based on Sox et al¹¹). The probability of a drug reaction given a positive test is 35/40 or 88%; the probability of a drug reaction given a negative test is 15/120 or 13%.

Table 2.—2 × 2 Table for Lymphocyte Toxicity Assay*

	Clinical Positive (Drug Eruption)	Clinical Negative	Row Totals
LTA positive	35	5	40
LTA negative	15	105	120
Column Totals	50	110	160

*LTA indicates lymphocyte toxicity assay. The true-positive rate is 35/50 or 70%; the false-positive rate is 5/110 or 5%; If pretest probability is 50% then the effect of a positive test is to raise posttest probability to 85% and a negative test lowers the probability to 20% (calculations are approximate and are based on Sox et al¹¹). The probability of a drug reaction given a positive test is 35/40 or 88%; the probability of a drug reaction given a negative test is 15/120 or 13%.

At the University of Toronto (Canada) Center for Drug Safety Research, we have been working with the lymphocyte toxicity assay. This lymphocyte toxicity assay is based on the hypothesis that hypersensitivity reactions to drugs (ie, the syndrome of skin rash, fever, hepatitis) are associated with a genetic defect in the detoxification of toxic drug metabolites. In this test, the drug and a metabolizing system are incubated with representative cells from the patient (usually peripheral blood lymphocytes). Cells from patients are unable to detoxify the oxidative metabolites generated in vitro, as compared with cells from controls. The drug eruptions associated with this syndrome include exanthema, erythroderma, EM, and toxic epidermal necrolysis. The drugs used in the assay have primarily been sulfonamide antibiotics and the aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine). Several important observations have resulted from this work. The detoxification defect is inherited and siblings of patients who had reactions are at greatly increased risk for toxic reactions compared with the general population. Seventy-five percent of patients who have had reactions to an anticonvulsant are likely to react to all three of the major anticonvulsants.¹²⁻¹⁴

Let us assume we have data from this assay based on a population of patients who have had adverse cutaneous reactions to sulfonamides (ie, clinical positive) and patients who have taken sulfonamides without consequence (ie, clinical negative). Possible results are tabulated in the 2×2 table to further develop the concept of in vitro testing (Table 2). The results are hypothetical and approximate for ease of calculation. The interested reader is referred to a recent article for further details.¹³

Let us not forget our patient. What if we studied his cells with this assay and had a positive result? Mark your likelihood of a drug reaction on the line in Fig 1 with a plus sign. Consider the test result is negative. Put down a minus sign on the line for your postnegative test result.

The impact of the positive result is clear. The patient is at a high risk of developing an adverse reaction to sulfonamides, and EM is a potential consequence. Absolute certainty is still not possible. The negative test result does not help as much in reality as the 2×2 table would suggest. The test is based on a single postulated pathogenesis (ie, abnormal detoxification of reactive metabolites). Just because that is not present (or more exactly, was not observed in vitro

Table 3.—Steps in the Approach to a Suspected Adverse Reaction

Steps Involved	The Case in Point
1. Clinical diagnosis of an adverse event An accurate diagnosis is critical; help from laboratory tests and consultations is often necessary; the role of the specialist is key; the differentiation between pityriasis versicolor and erythroderma will have a dramatic impact on the ultimate conclusion	Erythema multiforme
2. Analysis of drug exposure Obviously, an accurate drug history is needed; this may be guided by the nature of the diagnosis, but the drug exposure list should be as complete as possible; as much detail as possible about timing, rechallenge, dechallenge, and the form of drug used is needed	Sulfamethoxazole and trimethoprim; adverse event on day 10
3. Differential diagnosis There are many possible causes for each diagnosis generated; each of these must be considered; this is the most common step in which the diagnostician is led astray	Postinfectious or idiopathic erythema multiforme
4. Literature search There are many sources of information about drug reactions; if the diagnosis and drug list are firm, then the literature may have a profound influence on deciding if a drug reaction has occurred and which drug is the cause	Erythema multiforme is well described in association with sulfamethoxazole and trimethoprim therapy
5. Confirmation It is imperative to try to confirm the drug-disease connection; there are many approaches and all have limitations and pitfalls; the most common ones used by us are penicillin skin testing, in vitro lymphocyte toxicity assay, and rechallenge using an N-of-1 protocol	In vitro testing?
6. Advice to the patient The conclusions and implications of the drug reaction must be communicated to the patient (and referring physician); issues to be addressed include the diagnosis, the suspected drug, and cross-reacting drugs, and if there is an increased risk in family members	Avoid sulfa antibiotics; avoid trimethoprim? avoid other aromatic amine drugs (procainamide, hydralazine, etc)?
7. Reporting Spontaneous reporting to local and national organizations is encouraged	

for this patient) does not really alter the odds that this may be a drug eruption because the pathogenesis of cutaneous adverse reactions to drugs is varied and multifactorial.

STEPWISE APPROACH

All of the above considerations come into play in what I call the stepwise approach. This is an attempt to organize a complete evaluation of a drug-induced eruption. The components are listed and described in Table 3. The patient is discussed in this context as well.

But the stepwise approach really just organizes our thinking. To bring all of the facts gathered together into a neat and, hopefully, quantitative package, we need to attach likelihood probabilities to each factor. We also need to know what the likelihood is that a drug caused the reaction compared with an alternate cause. Applying numbers and probabilities to the variables is the basis behind a Bayesian approach to adverse reactions, or BARDI. This concept is discussed elsewhere in detail.¹⁵ BARDI takes all clinical and laboratory data together and the answer is a probability between 0 (ie, very unlikely) and 1 (certainty). There are many vagaries with this method as well and it requires time to understand it. Applying BARDI to our problem, we might get a pretest probability of approximately .87.¹⁶

Decision analysis is another more exhaustive approach that can take into account the utilities (pros and cons) of each decision made in the management of the diagnosis of an adverse reaction. The development of the decision tree is quite involved and the interested reader is referred to the text by Sox et al.¹¹

MEETING THE CHALLENGE

An attempt must be made to try to diagnose drug eruptions. The rash may clear but the consequences never do. The more precise we can be, the better. The basic problem is that except for fixed drug eruptions, virtually all cutaneous manifestations of drug toxic reactions have alternate causes. The other issue addressed by Halevy et al² is the situation when patients are receiving multiple drugs. In vitro tests hold great promise for sorting these out. No test can be ideal. False positives and false negatives will have a great impact on the outcome of our decision making. The meaning and utility of tests such as the MIF test need further investigation in a wide variety of clinical settings and over time.

There is no doubt we have a long way to go and the focus must be on the pharmacologic, immunologic,

and genetic factors involved in the pathogenesis of drug eruptions. Drug eruptions are the great mimickers of our era and it is unlikely that with such protean manifestations one diagnostic test will meet the challenge alone. In the meantime, clinicians will need to use an assortment of approaches and recognize their limitations.

NEIL H. SHEAR, MD
Dermatology A#
Sunnybrook Medical Center
2075 Bayview Ave
Toronto, Ontario
Canada M4N 3M5

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