

the rapid degradation of SMX-NO as suggested by Naisbitt et al.¹

This discussion refers to the role of reactive metabolites in drug hypersensitivity. Decades ago, it was proposed that alterations in the detoxification pathways and increased production of reactive metabolites were key factors, with most medications small, inert compounds considered not capable of inducing an immune response. Actually, the list is already long of human T-lymphocyte clones that react to the parent form of drugs.³ For example, Naisbitt et al.⁵ demonstrated that T-lymphocyte clones from patients hypersensitive to lamotrigine recognized lamotrigine and none of several metabolites tested.

We obviously have a different interpretation of the results of Schnyder et al.³ on the role of reactive metabolites. We invite those interested to read that article. The introduction states, "The majority of drug-reactive T cells from allergic individuals recognize the noncovalently bound sulfamethoxazole directly and do not respond to SMX-NO-modified APC. This pattern of Ag reactivity suggests that in sulfamethoxazole hypersensitivity the major part of the primary stimulation may be directed to the noncovalently bound sulfamethoxazole."³

These discussions should not obscure the most important finding of our study. Until now, the demonstration of drug-reactive T lymphocytes in humans was based on clones derived from the blood or from positive skin tests of hypersensitive patients. Because these clones had been obtained after several reactivations by the drug in culture, their clinical relevance remained questionable. By finding a specific reactivity in T cells obtained directly at the site of active lesions without rechallenge, our results provide strong support to these previous studies on immune reactivity to medications.

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The study to which this correspondence refers was supported by the Institut National de la Santé et de la Recherche Médicale and the French Ministry of Health (grant #4CH09G), and by the 5th PCRD of the European Union (contract QLG1-CT-2002-01738).

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doi:10.1016/j.jaci.2005.01.012

Laboratory diagnostics for hereditary angioedema: An economic, evidence-based standpoint

To the Editor:

We commend the principle of the Canadian 2003 International Consensus for providing a working algorithm for the diagnosis, therapy, and management of hereditary angioedema (HAE).¹

We have compared the economic impact of this diagnostic approach with that used within our center from a health economics viewpoint. Our diagnostic algorithm undertakes a primary screen of serum complement factor 4 (C4) and quantitation of C1 inhibitor antigenic protein (C1-Inh) for all individuals presenting with the clinical features mentioned in Figure 2 of the Canadian 2003 International Consensus article. Both of these tests are normal in the vast majority of individuals presenting with isolated angioedema. For such individuals, no further testing is undertaken, and HAE/acquired angioedema (AAE) is excluded. We are aware that a minority of patients with HAE^{2,3} may have normal C4 and C1-Inh levels outside of an attack (approximately 1 per 1 × 10⁶ population), and we undertake a C1-Inh functional assay if clinical suspicion remains high despite normal primary screening tests (ie, family history, poor response to antihistamines, good response to C1-Inh, and so forth). For those with a low C4, in particular those below 30% of the lower limit of the reference range,³ we would strongly consider a C1-Inh pathway abnormality. In these circumstances, we repeat the test with an additional C1 functional assay. If the functional test C4 and C1-Inh are low, we diagnose type I HAE, and if the C1-Inh is normal or elevated, we diagnose the less common (1 in 0.25 × 10⁶) type II HAE. If in either of these circumstances the clinical presentation is suggestive of an AAE (ie, age of onset, pre-existing autoimmune or malignant disease), we undertake C1q testing to establish a diagnosis of AAE. Because the laboratory reference ranges for both C4 and C1-Inh are set to 2 SD of the mean of a normal population, 2.5% of patients will have a C4 and C1-Inh below the normal limit. For such individuals, we undertake secondary screening with C1 functional assay and repeat C4 and C1-Inh assay, recognizing that most of these patients will not have HAE/AAE.

Our tertiary practice serves a population of 1.5 million and reviews approximately 300 cases of isolated angioedema per year with a cohort of 18 patients with type I HAE. We diagnose most of our patients with HAE from family studies of an index case and identify a new case of HAE within our isolated angioedema population approximately once every 5 years. A 5-year cost analysis using the diagnostic algorithms is shown in Tables I and II with

TABLE I. International algorithm*

Primary screen

1500 × £45 = £67,500

Secondary screen

Results	Normal (N)		↓C4 and N/↓C1-Inh		↓C4 and N/↓C1-Inh		Total
	C4 and N C1-Inh	↓C4 and N/↓C1-Inh	N/↓C4 and ↓C1-Inh	↓C4 (<30%) and ↓C1-Inh			
Number	1425	37	37	1			
Cost	1425 × £25	37 × £40	37 × £40	1 × 40			
Total	£35,625	£1480	£1480	£40			£38,625

*Total for primary and secondary screen = £106,125.

N, Normal.

TABLE II. Southampton, United Kingdom, algorithm*

Primary screen

1500 × £15 = £22,500

Secondary screen

Results	Normal		↓C4 and N/↓C1-Inh		↓C4 and N/↓C1-Inh		Total
	C4 and N C1-Inh	↓C4 and N/↓C1-Inh	N/↓C4 and ↓C1-Inh	↓C4 (<30%) and ↓C1-Inh			
Number	1425	37	37	1			
Cost	—	37 × £40	37 × £40	1 × 40			
Total	—	£1480	£1480	£40			£3000

*Total for primary and secondary screen = £25,500.

the costing of tests as follows (all in pounds sterling): C4 and C1-Inh @ £15/test, C1 functional @ £25/test, and C1q @ £5/test.

The price for both the detection of the single case of HAE/AEE and the exclusion of this disorder in all other cases of isolated angioedema is £106,125 for the International Consensus (Table I) and £25,540 for the Southampton approach (Table II). If the International Consensus approach is applied across the National Health Service within the United Kingdom, the total projected excess expenditure per annum for screening for 1 rare disease would amount to approximately £600,000.

We believe that our approach is cost-effective and no less evidence-based than that of the International Consensus panel and that it would be more easily accepted from an economic standpoint in most laboratories and health economies.

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doi:10.1016/j.jaci.2004.12.1126

Reply

To the Editor:

We thank Krishna et al¹ for their comments regarding the cost implications of the algorithm we proposed.² We stated in figure and in text that suspicion for C1-INH deficiency requires at least the presence of “recurrent angioedema without urticaria, abdominal pain, etc.” These scenarios may be different from those of isolated angioedema, which are considered in the Southampton protocol and for which C1-INH measurement may be questionable. The finding of 1 positive every 5 years out of 300 screenings per year (1 positive every 1500 tests) confirms the questionable appropriateness of the screening. Using our algorithm, we make the diagnosis of hereditary angioedema (HAE) in 1 to 2 cases out of the approximately 300 patients with isolated angioedema tested annually. In their letter, they stated that the costs of both the detection of a single case of HAE/acquired angioedema (AAE) and the exclusion of this disorder in all other cases of angioedema are higher if performed using our consensus recommendations compared with their Southampton approach. However, if one reviews our text, one sees that our approaches are essentially the same. The confusion may come from our Fig 2, the line diagram algorithm, but is clarified in the text beneath the figure, Section 3.a, and we use the indication of recurrent angioedema. In the text of our article, we stated that the screening is first performed only with C4 and C1-INH protein measurements (p. 632, 3.a), as they also propose. If the test results are low and AAE is not suspected, the diagnosis is likely type I HAE. If the C4 and C1-INH antigenic proteins are both normal but clinical suspicion is strong, then we recommend testing C1-INH functional level. If low, this is suggestive of type II HAE. We recommend C1q testing only when AAE is suspected, again in agreement with Krishna et al.¹ We described that repeated testing of C4 and C1-INH antigenic level during an acute attack is necessary only in a small percentage of cases in which these parameters are both normal but clinical suspicion is strong (<1% of patients with HAE have normal C4 between attacks; see p. 632, 3.a.ii). We appreciate the clarification of Krishna et al¹ of our line diagram algorithm by confirming what we have outlined in our text, Section 3.a, and what could have been more clearly outlined in a larger line diagram algorithm.

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