

CLINICAL REPORT

Evaluation of a Clinical Guideline for the Diagnoses of Physical and Chronic Urticaria and Angioedema

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In this retrospective study, the feasibility and implementation of a clinical guideline was evaluated in 130 consecutive patients with chronic urticaria. We analysed how often a questionnaire was used, how often routine laboratory tests were performed and on what information (history-taking, detailed questionnaire, laboratory or provocation tests) the diagnosis was made. In this validation sample, the number of identified diagnoses was compared with the number of identified diagnoses of a prospective study previously performed in the same hospital. A cause was identified in 58 patients (45%); 43 of these had physical urticaria and 15 had chronic urticaria. In 50 of the 58 patients (86%) the cause was identified by history-taking and in 8 patients by additional use of the questionnaire. In 38 patients the questionnaire was not in the patient's file. In 89 of 130 patients (68%), laboratory tests were performed without a reason suggested by the patients' history. This did not reveal a cause in any patient. In general, the diagnostic guideline was followed reasonably well. In identifying a cause of urticaria, careful history-taking was important; routine laboratory tests were not helpful. A detailed questionnaire is presented in an appendix. Key words: study; history-taking; laboratory tests; questionnaire; retrospective study.

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In many patients with chronic urticaria, the aetiology remains unclear (1). Symptomatic treatment with antihistamines is not successful in all patients (2) and is a cause of frustration for both patient and physician. In the past, many attempts have been made to discover underlying diseases by performing extensive diagnostic work-ups, but studies including large numbers of patients have shown that diagnostic work-ups are of little value in patients with chronic urticaria (2–5). Large clinical studies have shown that it is safe to omit routine laboratory screening if thorough history-taking is performed (3–5). Current recommendations limit the number of routine laboratory tests; they suggest

performing additional laboratory tests only if history-taking provides an indication (6–11).

There is a growing interest in the development of practice guidelines for clinical care in dermatology (12). Guidelines are developed to improve medical care, to control variations in medical practice and to make more effective use of health care resources (13). After the introduction of a clinical guideline, there is no guarantee that it will be used by clinicians, no matter how well designed it is, and more guidelines have been made than have been implemented (14). Obstacles for actual implementation and maintenance may be related to a lack of resources, a relapsing into old routines, or dissatisfaction with the results of the new guideline (15). Obviously, guidelines are not self-implementing (16). Continued motivation of clinicians and a continued evaluation of the process of implementation are necessary.

The purpose of this study was to investigate the use of the clinical guideline for patients with chronic urticaria and to find out how often and why clinicians deviate from it. In addition, we wanted to confirm the earlier performed prospective study (3) and analyse whether a comparable number of causes could be identified in this retrospective study, which represents the diagnostic process in daily clinical practice.

MATERIAL AND METHODS

Study population

All patients with urticaria and/or angioedema for at least 6 weeks, and who consulted our outpatient department of dermatology between January 1998 and February 2000, were included. The study was performed at the Academic Medical Center of the University of Amsterdam and was approved by the Medical Ethics Committee.

Description of the guideline

During the first visit, the following action was recommended: history-taking (see appendix) (the questionnaire had to be filled in at home); inspection of hives (if present) and a dermatography test. Only five laboratory tests were to be requested (haemoglobin level, haematocrit, erythrocyte sedimentation rate, white blood cell count and differential blood cell count). No other routine laboratory screening was to be performed. A (non)-sedating antihistamine could be prescribed. During subsequent visits, the guideline recommended: re-evaluation of the patient's history, discussion of the questionnaire, confirmation of suspected causes with laboratory or provocation tests (if necessary), stopping or replacing

suspected drugs, asking (again) for "over-the-counter" drugs, and prescribing an antihistamine (same or different).

Study design

All clinical records were examined for the following items: history-taking performed, questionnaire in patient's file, dermatography test performed, limited set of laboratory tests requested, and whether any other laboratory tests were requested. All clinical records were analysed by an expert committee that had to select the most probable cause of the urticaria. All laboratory tests were analysed to find out whether the test confirmed a diagnosis already suspected by history or whether the laboratory test revealed a diagnosis by itself, not suspected by history. Deviations from the study protocol were counted and analysed.

RESULTS

Patient population, diagnoses and expert committee

The diagnosis of every patient is recorded in our department and is available for research purposes. On searching the computerized diagnosis registration system for (subtypes of) urticaria and angioedema, 159 patients (49 males and 110 females; mean age 37.2; range 1–71) were identified. All records were available for analysis. Nineteen patients had acute urticaria and were excluded. Ten hospital workers with a contact urticaria to natural rubber were directly referred by the company doctor to the allergy department. They, too, were excluded. The distribution of identified diagnoses is given in Table I.

Whenever the suspected cause of the physician was not confirmed with laboratory or provocation tests or no convincing information was mentioned in the patient's file, the expert committee decided that the cause of the urticaria was unknown. This occurred in 23 patients. Sometimes a member of the expert committee asked the patient a few months later whether a specific intervention had been helpful in decreasing the urticaria.

To validate our prospective study (3), we compared the identified causes of both studies. Almost equal percentages were found (Table I). The number of identified causes is high (45%) because a large number of patients with physical urticaria (33%) were referred to our hospital.

Implementation and guideline deviations

Before the introduction of the guideline, the diagnostic actions performed by each physician were different and

Table I. Diagnoses found (in %) in the retrospective study compared with the diagnoses found in the prospective study (3)

	Retrospective study (n = 130)	Prospective study (n = 220)
Diagnoses	45	46
Physical urticaria	33	33
Adverse drug reactions	3.1	5.0
Adverse food reactions	5.4	4.0
Contact urticaria	0.8	0.9
Infection	0	1.4
Internal diseases	2.3	1.4
Aetiology unknown	55	54

less complete. In this study, one or more guideline deviations occurred in 100 of the 130 patients (77%). During the study, no effort was made to interfere with the clinical decisions of physicians, and use of the flow chart was voluntary. A thorough history-taking and an examination of the hives (if visible) were performed in all patients. Protocol deviations were measured per patient, and more than one deviation occurred in many patients. The guideline deviations are presented below:

Extended laboratory tests: In 89 patients, routine laboratory tests were performed at the first visit. In most patients, liver- and/or kidney function tests (55 patients), radioallergosorbent tests (RASTs) for inhalation and/or food allergens (59 patients), and/or an epi- or intracutaneous allergy test (20 patients) were requested. In 23 of these 59 patients the RAST resulted positive. In one patient an additional laboratory test (RAST to shrimps) confirmed the cause of the urticaria, which was an adverse reaction to food with complaints of the oral allergy syndrome. In 12 patients, epicutaneous patch tests, and in 30 patients, an elimination diet, were performed. In 130 patients, 88 additional laboratory tests (except those mentioned above) were requested: mainly level of glucose and proteins, bacterial or parasite cultures and serum tests for autoimmune diseases.

Questionnaire: Most of the patients already knew from their general practitioners that very often no cause for their complaints would be found; they appreciated the thorough search with the questionnaire. In 38 of 130 patients, the questionnaire, which was the same as in the previous prospective study (3), was not in the patient's file. In the following patients the questionnaire seemed superfluous, because during history-taking the cause seemed to be clear: physical urticaria (13 cases), an adverse reaction to food or drugs (4 cases) and one contact allergy. In 12 patients the questionnaire was handed out, but the patient did not return.

Dermatography test and limited laboratory tests: The dermatography test was not performed in 45 patients (35%). Explanations were other identified causes; namely, other physical urticarias (11 cases), adverse reaction to drugs or food (5 cases), contact allergy (1 case), use of antihistamines or oral corticosteroids (10 cases), and having angioedema only (1 case). In 32 patients (25%), no limited laboratory tests were performed. These were patients with physical urticarias (20 cases), and one patient each with a contact allergy, an adverse reaction to a drug and young age.

Relevance of history-taking and the questionnaire

All identified causes of this study were suspected during history-taking or during discussion of the questionnaire. In most patients the suspected causes were later confirmed by laboratory or provocation tests. Forty-three patients had physical urticaria (urticaria factitia 26,

pressure urticaria 10, cholinergic urticaria 7). In 35 of these patients, the cause could be identified during history-taking, and in 8 of them after using the questionnaire. In 4 patients an adverse reaction to a specific drug was confirmed by elimination and oral provocation. In 7 patients an adverse reaction to food was suspected during history-taking. This was confirmed in 3 patients by intracutaneous allergy tests, and in 3 other patients the decrease or absence of hives during the elimination diet and the increase of the symptoms during the reintroduction period made the diagnosis of an adverse food reaction likely. In one patient the diagnosis was based on history only. One patient had a contact allergy to a nasal spray containing fluticasone. This was suspected during history-taking and confirmed by epicutaneous patch-testing. Three patients had an internal disease. A 34-year-old woman was developing a not yet identified autoimmune disorder (joint pain, fever without any infection and antinuclear antibodies), one patient had hypocomplementemic urticarial vasculitis and one had an IgM-paraproteinaemia. In the latter two patients the hives persisted for longer than 48 h.

Relevance of the dermatography test and the limited laboratory tests

The dermatography test was performed in 94 patients. All 26 patients with dermatographic urticaria were identified during history-taking. In 23 of them it was confirmed with the dermatography test. In no case was the cause of urticaria found from the results of the limited set of laboratory tests.

DISCUSSION

The purpose of this study was to evaluate the implementation of a clinical guideline for the diagnosis of chronic and physical urticaria. Although the number of guideline deviations was high (77%), in most cases a reasonable explanation could be found. Deviations were that 20% of the patients did not receive the questionnaire and in 68% unnecessary laboratory tests were performed. Forty-three patients had physical urticarias. The remaining 87 patients had chronic urticaria and in only 15 of these could a cause be identified (17%).

This study was performed 4 to 5 years after completion of a prospective study (3) and showed almost identical percentages of identified diagnoses (Table I). With this study, we enhanced the generalizability of our hypothesis, namely that with thorough history-taking routine laboratory screening does not substantially disclose more causes of chronic urticaria, and we proved that history-taking is the most important diagnostic instrument in identifying the causes of chronic urticaria. The results of both studies show that the recommendations given fulfil the criteria of reproducibility and partly of transportability (historical and methodologic

transportability) (17). This study tested the accuracy of the guideline in data collected after its development (prospective validation), evaluated reproducibility and tested its susceptibility to mild differences in a historical time frame (17). Because this study was performed in the same care centre we cannot provide information on the geographic transportability.

To improve the quality of clinical care, our department is developing clinical guidelines. During the prospective study (3), all possible efforts were made to find an underlying cause. For this validation sample, a retrospective design was chosen to prevent the dermatologists from being more precise than they would have been in daily clinical practice had they known that the patients' files were to be analysed for guideline deviations.

Fifty out of 58 diagnoses (86%) were found by history-taking only. In the remaining 8 patients, the cause (all physical urticarias) was found thanks to the questionnaire. The high percentages of causes identified by history-taking in this patient cohort can be related partly to a learning or training effect of the clinicians. The introduction of this guideline has proved to be a valuable educational instrument in our department. If thorough history-taking is performed, the questionnaire may not yield that many additional data. The importance of the questionnaire is that it gives the patient the opportunity to provide relevant information and to participate actively in the diagnostic process by suggesting possible causes. Without this participation it is difficult to find underlying causes because of the diversity of causes of urticaria. The questionnaire should be regarded not as a replacement for careful history-taking, but as another useful instrument to search together with the patient. The patient is requested to provide the physician with a list of drugs used, which reduces the time-consuming search for the patient's drug-intake during visits. The large number of questions related to different causes and diseases allows for more possible causes to be evaluated by the physician and this may decrease the patient's concerns.

The benefit of the five laboratory tests was nil in this patient cohort. In the prospective study (3), the results of these tests had been helpful in finding internal diseases (elevated erythrocyte sedimentation, ESR) and parasite infections (differential blood cell count). In both studies (including 350 patients), the results of the haemoglobin level and haematocrit were not helpful in finding any cause of urticaria. We therefore recommend the following laboratory tests: ESR, white blood cell count and differential blood cell count. The possibility of missing an important diagnosis motivated us to keep these laboratory tests in the guideline, but they may be superfluous in a large number of patients.

Although additional laboratory tests not based on the history were requested in 64% of the patients at the first visit, the number of tests was much lower compared to

the period before introduction of the flow-chart. It was disturbing that in 59 of 130 patients, investigations were performed to disclose an allergy. This implies an expensive misunderstanding by physicians, since allergen-specific IgE is unrelated to chronic urticaria in almost all patients (3–11).

Even if the test for dermatographism revealed that pressure on the skin is not the cause of all patient complaints, it is often an aggravating factor, and this information is helpful for patients in handling their urticaria. In some patients, history-taking can readily reveal dermatographism and that this test could be superfluous, and it is unnecessary to motivate patients to stop antihistamines. The test for dermatographism remained in the diagnostic procedure because if the relationship is clear the test can be omitted, but if the test is not mentioned in the guideline it can easily be forgotten.

In several papers, mostly opinion-based diagnostic recommendations (8, 10, 11), sometimes in flow-charts (5, 7, 9, 11) or in algorithms (6, 18, 19), have been presented for patients with chronic urticaria. Putting a flow-chart in the patient's file as a reminder is the simplest strategy to remind physicians (20).

Implementation of the guideline was only partly successful, despite the fact that the physicians knew of it. The deviations confirmed that guidelines should be regarded as flexible criteria that can be adjusted to suit specific circumstances, settings and patient preferences. Patients often request, or sometimes even demand, laboratory investigations because they fear having an underlying disease. It is important to assure these patients that the chance of finding an underlying disease is much higher by careful history-taking than by routine laboratory screening.

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REFERENCES

- Greaves MW. Chronic urticaria. *J Allergy Clin Immunol* 2000; 105: 664–172.
- Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. *Br J Dermatol* 1998; 138: 635–8.
- Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol* 1998; 134: 1575–1580.
- Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. *Br J Dermatol* 1981; 104: 369–81.
- Champion RH. Urticaria: then and now. *Br J Dermatol* 1988; 119: 427–436.
- Greaves MW. Chronic urticaria. *N Engl J Med* 1995; 332: 1767–1772.
- Champion RH, Hight AS. Investigation and management of chronic urticaria and angio-oedema. *Clin Exp Dermatol* 1982; 7: 291–300.
- Soter NA. Acute and chronic urticaria and angioedema. *J Am Acad Dermatol* 1991; 25: 146–154.
- Bindsvlev-Jensen C, Finzi A, Greaves M, Camarasa J, Ortonne JP, Schöpf E, et al. Chronic urticaria: diagnostic recommendations. *J Eur Acad Dermatol* 2000; 14: 175–180.
- Kobza Black A, Greaves MW, Champion RH, Pye RJ. The urticarias 1990. *Br J Dermatol* 1991; 124: 100–108.
- Friedmann PS. Assessment of urticaria and angio-oedema. *Clin Exp Allergy* 1999; 29 Suppl 3: 109–112.
- Ladhani S. The need for evidence-based management of skin diseases. *Int J Dermatol* 1997; 36: 17–22.
- Wolf SH. Practice guidelines: a new reality in medicine. III. Impact on patient care. *Ach Intern Med* 1993; 153: 2646–2455.
- Delamothe T. Wanted: guidelines that doctors will follow. *BMJ* 1993; 307: 218.
- Grol R. Beliefs and evidence in changing clinical practice. *BMJ* 1997; 315: 418–421.
- Grol R. Implementing guidelines in general practice care. *Quality in Health Care* 1992; 1: 184–91.
- Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Int Med* 1999; 130: 515–524.
- Cooper KD. Urticaria and angioedema: diagnosis and evaluation. *J Am Acad Dermatol* 1991; 25: 166–176.
- Zuberbier T, Henz BM. Diagnosis of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer-Verlag; 1998. p. 141.
- Grimshaw JM, Russell IT. Achieving health gain through clinical guidelines. II: Ensuring guidelines changes medical practice. *Quality in Health Care* 1994; 3: 45–52.
- Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Diagnostisch beleid bij patienten met chronische urticaria. *Ned Tijdschr Derm Vener Venereol* 2000; 10: 220–225.

APPENDIX: Questionnaire for patients with chronic urticaria and/or angioedema. Published with permission (21)

(In the original layout of the questionnaire, space is left for answers and there are many yes/no answers.)

- How long have you had hives and/or deep swellings? (Please give the date)
- How frequently do you have a bout of hives and/or deep swellings? (Continuously, daily, weekly, monthly or different, namely ...)
- How long does an individual hive persist before it disappears? (You can determine this by marking an individual hive with a ballpoint when it first appears and noting the time elapsed when the hive is gone.)
- Did you ever have a hive or swelling which lasted more than 24 hours?
- What is the average size of your hives?
- Where are your hives located? (All over the body, mostly on the arms and/or legs, on pressure sites (e.g. under the belt or the bra), or on the following parts of my body ...)
Where are your swellings located? (On the eyelids, lips, hands and/or fingers, feet, tongue and/or throat, or on the following parts of my body ...)
- Do your hives frequently leave blue, purple or brownish spots or red dots after disappearing?
- Do you experience itchiness where you have the hives and/or swellings?
- Did you scratch? Is your skin dry and scaly where you have the hives or swellings?

10. Do you feel any other sensation(s) besides itch in the affected skin? (Pain, burning sensation, tense sensation, or another sensation, namely ...)
 11. Have you experienced any of the following symptoms during or shortly after a bout of hives or swellings? (Runny nose, tearing eyes, asthma or shortness of breath, hoarseness, swollen tongue, palate or throat, headache, dizziness, fainting, gastric pain or abdominal spasm, nausea or vomiting, diarrhoea, fever or fatigue)
 12. When during the day do you have the most complaints? (In the morning, during the day, in the evening, during the night, do you wake up during the night because of itchiness, not predictable)
 13. When or where do you have more hives and/or swellings? (Inside the house, outside the house, at work, at home, during the weekend, during the week, on vacation less complaints, or on vacation more complaints)
 14. Did your symptoms start after a particular infection or disease? (e.g. after an infected tooth, sinus infections, worm infections, pneumonia, bladder infection, or other infections, namely ...)
 15. Did your symptoms start after the following? (An X-ray with radio contrast media, taking a particular tablet or injection, vaccinations, or other events, namely ...)
 16. Does a change in season or weather affect your symptoms? When do your symptoms aggravate?
 17. Have you ever been in a tropical area? If yes, where and when?
Sometimes bouts of hives and/or swellings are related to particular circumstances. We described some of them in the following questions. If you recognize one or more of the circumstances, please mark the question.
 18. Did your hives start approximately 15 minutes after any of the following: rubbing or scratching of the skin, wearing tight clothing, leaning against something (for example a chair)?
 19. Did your hives or the swellings occur after prolonged pressure on your skin? This type of hives occurs 4–12 hours after the prolonged pressure. If this happened, what kind of activities precipitated your symptoms? (Staying or walking for a long period could result in swelling of the soles, sitting or riding bicycle could result in swelling of the buttocks, working with tools (like pliers or a hammer), carrying heavy things, or other circumstances, namely ...).
 20. Did the hives occur after exposure to: cold weather (snow, cold wind or rain), cold water (shower, swimming pool, lake), cold objects or food (eating ice-cream or cold drinks with ice cubes)?
 21. Have you experienced hives after any of the following: exposure to hot or warm weather, after physical exercise or during sports, after sexual intercourse, after taking a hot shower or bath, after consuming spicy or hot foods or drinks, after contact of your skin with warm objects, if you are excited, frightened or under stress, or if you are perspiring?
 22. Did you ever experience hives or swellings after exposure to sunlight?
 23. Did you ever experience white, blue, painful or numb fingers after exposure to cold?
 24. Do you think that your hives worsen with stress or bad 'nerves', or if you have problems?
 25. Did you ever notice that contact of your skin with one of the following objects caused itching, redness or swelling of the skin? I have hives after contact of the skin with: wool or other clothes, animals or plants, cosmetics or perfume, drugs or particular food (e.g. meat, fish, vegetables, fruits), chemical or other products, namely ...)
 26. Has any member of your family ever had hives or swellings?
 27. Has any member of your family or have you ever had one of the following diseases? (Hay fever, attacks of sneezing (allergic rhinitis), allergic conjunctivitis, allergic asthma, childhood eczema, eczema in the arm pits or on the back of the knees (atopic dermatitis)).
 28. Are you allergic to house dust mite, pollen, animals, wasp- or bee venom, rubber (e.g. in latex gloves or condoms), or to other things? If yes, to what? Is this confirmed by allergy testing?
 29. Did you ever observe that your symptoms are related to or become worse after consuming certain foods? (e.g. fish, mussels, crustaceans, celery, strawberries, pears, banana, peanuts, nuts, soy, cheese, alcohol, chocolate, juices with quinine, eggs, milk products, ice-cream, conserved food or deep frozen food products, artificial sweetener, or others)
 30. Did you ever experience one of the following complaints after eating certain foods? (Tingling or a burning sensation of the tongue, swelling of the tongue or the lips, cramps of the intestine or diarrhoea)
 31. Do you have an aversion to certain foods? Are you allergic to certain foods?
 32. Did you ever follow a diet to alleviate your symptoms? Was the diet effective? Did you have professional help from a dietician? Did you constantly follow the diet?
 33. Do you have animals at home? If so, what kind of animals and since when?
 34. Do you have much contact with any of the following? (Plants, flowers, cosmetics, cleaning or washing products, paints or glues, or other certain products, namely ...)
 35. What is your job/profession?
 36. What leisure activities/hobbies do you have?
 37. Are you exposed to any airborne chemicals or industrial products in your profession? (e.g. fluids, steam, vapours or dust, namely ...)
 38. Do you have any metallic object (e.g. pacemaker, artificial joints, metallic screws, dental implants) or other type of implant in your body?
 39. Women only: Do you take contraceptives (e.g. birth control pill) or other hormones?
Did you ever experience more symptoms during certain times of your menstrual cycle?
 40. Please list the drugs you used to treat your hives or angioedema in the past year:
 41. If you used antihistamines to prevent hives or swellings, please indicated when you last used them?
 42. Please name all the medication (prescription and non-prescription) and vaccinations you have used in the last year. You can also asked your pharmacy to provide a list of the medications you used in the last year. Please mention antibiotics, pain medication (like aspirin), medication against the flue, anti-rheumatics, sleeping pills, sedatives, psycho-pharmacologic drugs, drugs related to epilepsy, laxatives, cough medications, hormones (like oral contraceptives, estrogen, insulin), vitamins, homeopathic drugs or other drugs?
 43. Are you allergic to certain drugs? If so, which ones and what kinds of allergic reaction have you had?
 44. Have you ever been hospitalized or put under the care of a medical specialist? If so, for what?
 45. Do you have any other physical complaints at the moment?
 46. Do you have any ideas or suggestions about the possible cause of your hives or angioedema, or have you found any relationship between certain circumstances or certain surroundings and your symptoms?
- A list of medical questions follows the original questionnaire which informs about the general health of the patient.