Evaluation of a Guideline for Etiological Diagnosis of Chronic Urticaria

Kronik Ürtikerin Etiyolojik Tanısı İçin Geliştirilen Rehberin Değerlendirilmesi

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ABSTRACT Background: Exhibiting potential causes of chronic urticaria in routine daily practice is a complex procedure. A guideline, developed by the researchers, investigating the etiology of chronic urticaria was evaluated in this study. In this guideline erythrocyte sedimentation rate, complete blood count, urine analysis and direct microscopic examination of stool for parasites were routine and other diagnostic procedures were requested according to clinical findings of potential causes. **Objective:** The purpose of the study was to determine the rate of implementation of the guideline considering a daily practice. **Material and Methods:** Following diagnosis of chronic urticaria, patients were interrogated with a standard questionnaire form, and were examined in order to determine the clinical findings of possible causes of the disease. The records of 903 patients in total were retrospectively evaluated. During the evaluation process, the necessary and unnecessary diagnostic procedures regarding the guideline were determined by using computerized algorithms. During evaluation some parameters such as age and gender of patients, duration and severity of the disease, and numbers and types of diagnostic procedures affecting the grade of the request and completion were also taken into account. **Results:** The total number of necessary procedures was 4070, less than one third of which were requested by the physicians. However, the patients completed more than three fourths of the requested procedures. Moreover, the physicians requested some unnecessary procedures in almost one third of the patients. **Conclusion:** According to clinical findings, lower threshold for necessity of investigation leads to more failure in implementation of a guideline. Guidelines developed for the etiological diagnosis of chronic urticaria should be evaluated retrospectively on data from daily practices to evaluate the utility of a guideline.

Key Words: Urticaria; retrospective studies; guideline; etiology

ÖZET Giriş: Günlük uygulamada kronik ürtikerin olası nedenlerini ortaya çıkarmak karmaşık bir işlemdir. Bu çalışmada kronik ürtikerin nedenini araştırmak için araştırmacılar tarafından geliştirilmiş olan bir rehber değerlendirildi. Bu rehberde eritrosit sedimantasyon hızı, tam kan sayımı, tam idrar tetkiki ve gaitada parazit incelemesi rutin olarak, diğer tanısal işlemler ise klinik bulgulara göre istendi. **Amaç:** Çalışmanın amacı günlük uygulamayı göz önünde bulundurarak oluşturduğumuz rehberimizi ne oranda tamamladığımızı saptamaktı. **Gereç ve Yöntemler:** Kronik ürtiker tanısı konulduktan sonra hastalığın olası nedenini saptayabilmek için hastalar, standart anket formu ile sorgulandı ve muayene edildi. Toplam 903 hastanın kayıtları retrospektif olarak incelendi. Değerlendirme sürecinde, rehbere göre tanıya yönelik olarak yapılan gerekli ve gereksiz işlemler, bilgisayarlı algoritimler kullanılarak saptandı. Değerlendirme kapsamında tetkiki istemenin ve tamamlamanın derecesini etkileyebilen, hastaların yaşı, cinsiyeti, hastalığın süresi ve şiddeti, tanıya yönelik işlemlerin sayısı ve tipi gibi bazı parametreler de göz önünde bulunduruldu. **Bulgular:** Gerekli işlemlerin toplam sayısı 4070 idi. Bunların üçte birinden daha azı doktorlar tarafından istenmişti. Bununla birlikte hastalar istenilen tetkiklerin dörtte üçünden daha fazlasını tamamlamışlardı. Dahası, doktorlar hastaların yaklaşık üçte birinde bazı gereksiz tetkikler de istemişlerdi. **Sonuç:** Klinik bulgulara göre istenilen tetkiklerin eşiğini düşük tutmak rehberlerimizin tamamlanmasında daha çok başarısızlığa neden olmaktadır. Kronik ürtikerin tanısına yönelik olarak geliştirilen rehberlerin yararını ve kullanılabilirliğini değerlendirmek için bu rehberler retrospektif olarak günlük uygulamalardaki bilgiler ile incelenmelidir.

Anahtar Kelimeler: Ürtiker; retrospektif çalışma; rehber; etiyoloji

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Numerous and various factors can cause chronic urticaria.[1] Investigation of these factors as potential causes are very exhausting both for physicians and patients. Considering this, two different approaches are usually recommended: a) performing all diagnostic investigations for all possible causes, and b) limiting investigations according to clinical findings.[2,3] Of both, the latter seems to be more advantageous as it excludes some unnecessary investigations and reduces consumption of time and cost. Nevertheless, this approach seems to be more complex as the physician first should fulfill the requirements such as taking a detailed history, doing a detailed physical examination, and then properly analyze and synthesize clinical findings in order to determine further investigations. In this study, we looked into to what extent such an approach could be completed successfully in a daily practice.

MATERIAL AND METHODS

The data for this study was collected from computerized records of 903 patients with chronic urticaria who were admitted to the outpatient clinic (Department of Dermatology, Faculty of Medicine, Çukurova University) from January 1996 to July 2002. In order to get reliable information, a special program was developed by the researchers aiding in decision-making in the determination of investigations of possible causes of chronic urticaria, and was later applied in the clinic, with findings elicited from patients being evaluated in a computerized platform during the patients' visits.

When a patient with urticaria first applied to the outpatient clinic, s/he was interrogated and examined for characteristics of individual urticarial lesions, duration and severity of the disease, and effects of physical factors leading to complaints. Patients with lesions occurring only by physical factors were excluded. Following the diagnosis of chronic urticaria, the patient was interrogated with a standard questionnaire form and examined in order to determine the clinical findings of possible causes of the disease, such as drugs, foods, additives, inhalants, focal pyogenic infections, parasitoses, connective tissue disease, malignancies, thyroid diseases and psychological stress. All patients were requested to fulfill routine laboratory tests, such as erythrocyte sedimentation rate, complete blood count, urine analysis and direct microscopic examination of stool for parasites and ova. Additionally, diagnostic procedures were requested only for patients with clinical findings of possible causes. These procedures were presented in Table 1.

In this study, three conditions for investigating each possible cause were determined for each patient. The first condition was whether or not clinical findings were suggestive of a possible cause, and thus diagnostic procedures for this cause were necessary. The first "necessity of investigation" condition was valued with "no" or "yes" by a computerized algorithm running on the records of the patients. The second condition "request for investigation" was whether or not the physician requested a diagnostic procedure for a possible cause when necessary. The third condition "completion of investigation" was whether or not the patient had completed a diagnostic procedure for a possible cause when the physician requested it. The second and third conditions were also valued with "no" or "yes" by reviewing the records of the patients. During this process, two rates were calculated for each patient, first of which was the ratio of the total number of requested procedures to the total number of necessary procedures and was called "rate of request". The ratio of the total number of completed procedures to the total number of requested procedures, the second rate was called "rate of completion". Finally, two grades, "grade of request" and "grade of completion," were determined in terms of the rate of request and completion, respectively. It was rated "poor" if the rate was equal to or less than one third; rated "moderate" if it was more than one third and equal to or less than two thirds; and "good" if the rate was greater than two thirds.

Effects of some parameters on the grade of request and completion were also examined regarding age and gender of the patients, duration and severity of the disease, and numbers and types of diagnostic procedures. The patients were divided into four subgroups according to duration of the di-

TABLE 1: Diagnostic procedures according to clinical findings in our guideline.

Clinical findings	Diagnostic procedures (one of the following)
Concurrent use of drugs associated with one of the following: - Previous drug allergy - Increase in urticarial symptoms at a special time within a day - Gastrointestinal symptoms accompanying urticarial symptoms	Prohibition of drugs A diary of drugs
Increase in urticarial symptoms after ingestion of a special food	A diary of foods Dietary restrictions Prick tests with foods
Increase in urticarial symptoms after ingestion of foods with additives	Dietary restrictions Provocation tests with food additives
One of the following: - Ocular, nasal or pulmonary symptoms accompanying urticarial symptoms - Increase in urticarial symptoms after exposure to an aeroallergen - Asthma or allergic rhinitis - Previous immunization - Seasonal increases in urticarial symptoms	Prick tests with inhalants
Symptoms or signs of sinusitis, tonsillitis, pharyngitis or otitis	Clinical examination by an otorhinolaryngologist
Symptoms or signs of dental infections	Clinical examination by a dentist
Symptoms or signs of cholecystitis	Clinical examination by a gastroenterologist or a general surgeon Abdominal ultrasonography
Symptoms or signs of vulvovaginitis	Clinical examination by a gynecologist
One of the following: - Photosensitivity - Arthritis	Clinical examination by a rheumatologist Antinuclear antibody
One of the following: - Heliotrope rash, poikiloderma or Gottron's sign - Muscular weakness (only if determined in physical examination)	Clinical examination by a rheumatologist Muscle enzymes
Long-lasting cough or hemoptysis	Clinical examination by a pneumologist or an oncologist Chest X-ray
A mass in the breast	Clinical examination by a general surgeon or an oncologist
Lymphadenomegaly, hepatomegaly or splenomegaly	Clinical examination by a hematologist or an oncologist
A mass in the abdomen or gastrointestinal bleeding	Clinical examination by a gastroenterologist, a general surgeon or an oncologist
Prostatism	Clinical examination by an urologist or an oncologist Prostate specific antigen
Goiter, hyperhidrosis, tremor, tachycardia, weight loss or irritability Thyroid function tests	Clinical examination by an endocrinologist
At least two of the following: - Irritability - Boredom - Use of drugs such as sedatives and hypnotics - Decrease in urticarial symptoms during vacation	Clinical examination by a psychiatrist

sease: those who suffered from the disease for ≤3 months; those, for >3 months and ≤12 months; those, for >1 year and ≤3 years; and those, for >3 years. For simplicity, these durations were also called "a few months", "many months", "a few years" and "many years", respectively. Severity of the disease was graded as mild, moderate, or severe according to statements of the patients. Since physicians following patients with chronic urticaria rotated for intervals of two months in the outpatient clinic, the

grades of request and completion were also determined for each period of two months from January 1996 to July 2002. All physicians were aware of the guidelines beforehand and their training was standardized.

Unnecessary diagnostic procedures were also determined for each patient. For instance, in case a patient displayed no clinical findings necessitating a diagnostic procedure, this procedure was considered unnecessary. In this evaluation, some diagnostic procedures were excluded since they might have been acting as possible causes for not only chronic urticaria but also for other health problems. Since we requested routine laboratory tests for all patients with chronic urticaria and we did not take conditions of diagnostic procedures for routine laboratory tests into consideration when we were determining the grade of request and the grade of completion.

Chi-square tests were used in order to compare subgroups. For goodness of fit, binomial exact tests were carried out instead of chi-square, if expected values were less than 5.

Written approval of the ethic review board of the Faculty of Medicine was obtained for the retrospective review of the records of the patients.

RESULTS

Six hundred thirty two (70.0%) patients were females; and 271 (30.0%), males. The mean age of the patients was 34.1 years (standard deviation ± 13.8, range 2 to 76). One hundred twenty nine patients (14.3%) were children (younger than 19 years); 569 (63.0%), adults (aged 19 to 44 years); and 205 (22.7%), middle aged or elderly (older than 44 years). The duration of the disease was "a few months" in 181 patients (20.0%), "many months" in 224 (24.8%), "a few years" in 310 (34.3%), and "many years" in 188 (20.8%). Only 824 patients had stated the severity of their disease, which was mild in 95 patients (11.5%), moderate in 457 (55.5%), and severe in 272 (33.0%).

According to the computerized algorithm running on the records of the patients, a total of 4070 diagnostic procedures were necessary and only 1255 (30.8%) of the necessary procedures were requested. On the other hand, 963 (76.7%) of the requested procedures were completed.

Diagnostic procedures were necessary for at least one possible cause in 881 (97.6%) patients. The number of necessary procedures ranged from 1 to 12, and its median was 4. Among these 881 patients, the grade of request was "poor" in 556 (63.1%) patients, "moderate" in 255 (28.9%), and "good" in only 70 (7.9%). In another point of view, the physicians requested some diagnostic procedures in only 653 (74.1%) patients for whom these were necessary. The number of requested procedures ranged from 1 to 9, and its median was 2. Among these 653 patients, the grade of completion was "poor" in 105 (16.1%) patients, "moderate" in 92 (14.1%), and "good" in 456 (69.8%). With the exception of 22 patients (2.4%) for whom diagnostic procedures were not necessary, only 30 out of 903 (3.3%) patients completed all of the diagnostic procedures for the possible causes which were determined according to clinical findings.

Percentages of patients subjected to poor, moderate or good request in different subgroups are presented in Table 2. There was no effect of gender and age of the patients and duration and severity of the disease on the grade of request. On the other hand, good request was significantly more common in the patients requiring a fewer number of procedures ($p< 0.001$).

Percentages of patients with poor, moderate or good completion of the requested procedures are shown in Table 3. As observed in the table, there is no effect of gender and age of the patients and severity of the disease on the grade of completion. Percentages of patients with good completion gradually increase as the duration of the disease is prolonged. Upon consideration of good request, good completion is seen significantly more common in patients subjected to a fewer number of procedures ($p< 0.001$).

Percentages of patients subjected to good request and percentages of patients with good completion are given in Table 4 for each possible cause. Both rates seem to be lower for drugs; and the for-

TABLE 2: Percentages of patients subjected to poor, moderate or good request for the necessary diagnostic procedures in different subgroups.

Parameters	Subgroups	Number of patients	Grade of request (Percentages of patients)			Significance of difference
			Poor	Moderate	Good	
Gender	Females	619	61.7	30.9	7.4	p> 0.05
	Males	262	66.4	24.4	9.2	
Age	Children	125	64.0	32.0	4.0	p> 0.05
	Adults	553	60.8	30.7	8.5	
	Middle-aged or elderly	203	69.0	22.2	8.9	
Duration of urticaria	A few months	175	61.1	29.7	9.1	p> 0.05
	Many months	218	67.0	26.1	6.9	
	A few years	303	65.3	28.1	6.6	
	Many years	185	56.8	33.0	10.3	
Severity of urticaria	Mild	91	69.2	28.6	2.2	p> 0.05
	Moderate	447	62.6	28.0	9.4	
	Severe	266	62.4	30.5	7.1	
Number of necessary procedures	≤ 4	458	63.1	25.3	11.6	p< 0.001
	> 4	423	63.1	32.9	4.0	

TABLE 3: Percentages of patients with poor, moderate or good completion of the requested diagnostic procedures in different subgroups.

Parameters	Subgroups	Number of patients	Grade of request (Percentages of patients)			Significance of difference
			Poor	Moderate	Good	
Gender	Females	470	14.7	13.4	71.9	p> 0.05
	Males	183	19.7	15.8	64.5	
Age	Children	90	20.0	12.2	67.8	p> 0.05
	Adults	420	13.8	16.0	70.2	
	Middle-aged or elderly	143	20.3	9.8	69.9	
Duration of urticaria	A few months	130	19.2	16.9	63.8	p> 0.05*
	Many months	158	17.7	13.9	68.4	
	A few years	215	17.2	10.7	72.1	
	Many years	150	10.0	16.7	73.3	
Severity of urticaria	Mild	58	8.6	17.2	74.1	p> 0.05
	Moderate	330	16.7	14.2	69.1	
	Severe	211	16.6	14.2	69.2	
Number of requested procedures	≤ 2	486	16.3	10.9	72.8	p< 0.001
	> 2	167	15.6	23.4	61.1	

mer, for foods and additives. Both are apparently higher for inhalants and thyroid diseases; and the latter, for connective tissue disease.

When periods of two months from January 1996 to July 2002 were examined, there were 35 periods, in which at least 10 patients with chronic urticaria was followed. In these periods, percentages of patients subjected to good request ranged from 0% to 23.8%. However, this rate is significantly different from the general rate of 7.9% in only two periods. In both, it is seen higher. In these 35 periods, percentages of patients with good

TABLE 4: Percentages of patients subjected to good request and percentages of patients with good completion for each possible cause.

Possible causes	Number of patients requiring procedures	Percentage of patients subjected to good request	Number of patients subjected to procedures	Percentage of patients with good completion
Drugs	446	16.8	75	18.7
Foods and additives	463	8.4	104	48.1
Inhalants	481	47.2	227	93.4
Focal pyogenic infections	682	24.0	315	74.3
Connective Tissue Disease	119	25.2	31	90.3
Malignancies	114	25.4	32	65.6
Thyroid diseases	693	44.3	307	89.6
Psychological stress	308	27.6	85	72.9

completion range from 35.3% to 100%. However, this rate is significantly different from the general rate of 69.8% in only four periods. In all of them, it is observed lower. Moreover, in all of these four periods with poorer completion, percentages of patients subjected to good request are higher than 10%.

In 297 out of 903 (32.9%) patients, some unnecessary diagnostic procedures were requested. In most of them, the number of unnecessary procedures was one. The most common unnecessary procedure was a prick test with inhalants. It was requested in 107 patients having no clinical findings suggesting that inhalants were possible causes of the disease.

Although erythrocyte sedimentation rate, complete blood count, urine analysis and direct microscopic examination of stool for parasites and ova were requested in all of the 903 patients, only 628 (69.5%) patients completed the first investigation; 809 (89.6%), the second; 793 (87.8%), the third; and 723 (80.1%), the fourth.

DISCUSSION

In this study, we evaluated how often the diagnostic procedures which were necessary according to clinical findings, were completed in 903 patients with chronic urticaria. Only less than one fourth of the necessary procedures (963/4070) were completed. In other words, only less than six percent of the patients (52/903) required no procedures or completed all of the necessary procedures. Moreover, some unnecessary procedures were requested in one third of the patients. So, adherence to the researchers' guideline for investigation of possible causes of chronic urticaria was very low, particularly because of the failure in implementation. Deviation from a guideline was also observed in a study of Kozel et al.[4] They retrospectively evaluated the feasibility and implementation of their guideline in 130 patients with chronic urticaria. While, according to their guideline, the questionnaire should be handed out to all of the patients, in almost 30% of them, it was not found in the patient's file. They also found that in almost 70% of the patients' laboratory tests were performed without a reason suggested by the patient's history.

However, the rate of failure in the implementation of guidelines was higher in this study than it was in Kozel et al's.[4] This difference could be explained with different thresholds for necessity of investigation. In the study of Kozel et al, history-taking, even without handing out of the questionnaire was found to be enough for acceptance of a drug as the cause of chronic urticaria. However, according to the guideline in this study, further diagnostic procedures, such as prohibition of drugs or a diary of drugs should be done even if clinical findings suggested that drugs might be the cause of chronic urticaria. One may suggest that the threshold here for necessity of investigation was exaggeratedly low. Nevertheless, it has recently been emphasized that the arguments for an important role of underlying causal infections in chronic urticaria are weak from an evidence-based view-

point, and chronic urticaria is not statistically associated with malignancy in general.[5,6] Even though the purpose of this study is not to determine the scope of investigation of possible causes of chronic urticaria, we wish to remind the reader that in some of the most recent textbooks of dermatology, infections and malignancies have still been listed among the main causes of chronic urticaria.[7]

It is obvious that request for diagnostic procedures according to clinical findings is the physician's work, whereas their completion is mainly dependent on the patient's attitude. In this study, the routine laboratory tests requested from all patients were completed by almost 70-90% of the patients. Moreover, good completion of the necessary diagnostic procedures, which had been requested according to clinical findings, was found in almost 70% of the patients. On the other hand, the necessary diagnostic procedures with a good grade were requested in only less than 8% of the patients although a computer program- helpful in decision-making- was available. Hence, it is obvious that the physicians were mainly responsible for the failure in the implementation of the guideline. In this respect, the question of "Were our physicians negligent?" is likely to presume that our physicians were negligent, which would be an ordinary and superficial explanation for this failure. However, in the disclaimer of the guidelines for urticaria, which was prepared for dermatologists on behalf of the British Association of Dermatologists, it was stated that deviation from the guidelines should not be deemed negligence.[8] Grattan et al. also stated that it may be necessary even desirable to depart from guidelines in the interests of specific patients and special circumstances.[2]

The failure in requesting the necessary diagnostic procedures was not affected by age or gender of the patients, or by the duration and severity of the disease. Rather, the more procedures were required, the higher were the chances of encountering failure. One may suggest that if more than one diagnostic procedure was necessary, the physician may have put the procedures in an order of priority by taking primarily some problems into consideration such as those possibly life-threatening or those having a more causal relationship to chronic urticaria. The physician may have requested simple procedures immediately by leaving long lasting or possibly life-threatening ones to be performed later. Therefore, if the disease healed or if the physician somehow found it hard to remember how necessary the procedures were, such procedures may not have been performed at all. This suggestion has been supported with our observation that diagnostic procedures for drugs, foods and additives were poorly requested, and, among these procedures, diaries of drugs or foods were long lasting ones, and, provocation tests with food additives have a life-threatening potential.

The failure of patients in completing the requested diagnostic procedures was markedly less than the failure of the physicians. This failure of patients cannot be due to inability to pay for diagnostic costs, since more than 90% of the patients admitted to the hospital had health insurance covering all diagnostic expenses related to possible causes of chronic urticaria. As was the rate of the physicians' failure, that of the patients' was not affected by patients' age, gender or severity of the disease; failure increased when the number of requested diagnostic procedures was higher; and it varied according to the degree of complexity of the diagnostic procedures. When the disease was prolonged, the success of patients in completing the requested diagnostic procedures increased. One may suggest that if a patient has suffered from chronic urticaria for many months or years, s/he realizes that the medications have only symptomatic or suppressive effects in this disease. In this case, s/he would want to reach its roots in order to uproot it. If a physician requested a thorough investigation, such a patient would complete the procedures with pleasure.

When we examined the periods of two months, we found that good completion by the patients was at a significantly lower frequency in all four periods, where percentages of the patients subjected to good request were higher than the general rate of approximately 8%. In other words, the patients did their work poorly whereas the

physicians did their work well. This condition may be explained by the fact that the higher workload is a significant cause of patients' failure. Another explanation is that if physicians did not take notes about the diagnostic procedures on patient's records immediately after they requested them, and if patients did not complete these procedures, the physicians, rather than the patients, would appear unsuccessful in a retrospective evaluation. Only if physicians were to take notes completely, the real rate of success or failure of patients could accurately be calculated. Therefore, if the physicians recorded their data incompletely, as is not uncommonly encountered in a daily practice, the real rate of failure of patients would be higher than the rate which was calculated in this study.[9,10]

In chronic urticaria, in order to determine the possible cause, good diagnostic investigation based on detailed history is necessary. Nowadays, arguments about "to what extent these diagnostic procedures should be" have still been continuing.[11] In chronic urticaria, to reach diagnostic accuracy, implementation of investigation is as important as the proper investigation itself. Further research about chronic urticaria should also focus on implementation of diagnostic procedures in routine daily practice. In our study, we found that the lower threshold for necessity of investigation according to clinical findings leads to more failure in implementation of a guideline. As was also suggested by Kozel et al., all diagnostic guidelines for chronic urticaria should be evaluated retrospectively on data from daily practices.[4]

REFERENCES

1. Aytekin S, Türkmen H. [Investigation of autologous serum skin test andetiological factors in 31 patients wıth chronic urticaria]. Turkiye Klinikleri J Dermatol 2001;11(3):141-5.
2. Grattan CE, Humphreys F; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. Br J Dermatol 2007;157(6):1116-23.
3. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM, et al. EAACI/GA2LEN/EDF. EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. Allergy 2006;61(3):316-20.
4. Kozel MM, Ansari Moein MC, Mekkes JR, Meinardi MM, Bossuyt PM, Bos JD. Evaluation of a clinical guideline for the diagnoses of physical and chronic urticaria and angioedema. Acta Derm Venereol 2002;82(4): 270-4.
5. Wedi B, Raap U, Kapp A. Chronic urticaria and infections. Curr Opin Allergy Clin Immunol 2004;4(5):387-96.
6. Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. Br J Dermatol 1990;123(4):453-6.
7. James WD, Berger TG, Elston DM. Erythema and urticaria. Andrews' Disease of the Skin Clinical Dermatology, 10th ed. Philadelphia: Saunders Elsevier; 2006. p.139-56.
8. Grattan C, Powell S, Humphreys F; British Association of Dermatologists. Management and diagnostic guidelines for urticaria and angioedema. Br J Dermatol 2001;144(4):708-14.
9. Rubin G, George A, Chinn DJ, Richardson C. Errors in general practice: development of an error classification and pilot study of a method for detecting errors. Qual Saf Health Care 2003;12(6):443-7.
10. Dovey SM, Phillips RL, Green LA, Fryer GE. Types of medical errors commonly reported by family physicians. Am Fam Physician 2003;67(4):697.
11. Thomas P, Perkin MR, Rayner N, Cox H, Fox AT, Leech S, et al. The investigation of chronic urticaria in childhood: which investigations are being performed and which are recommended? Clin Exp Allergy 2008;38(6): 1061-2.