

The search of latex sensitization in spina bifida: diagnostic approach

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Summary

Background Sensitization to latex has become a major problem in children with spina bifida. Life-threatening reactions may occur in these patients, therefore the search of latex sensitization must be an active task in all of these children.

Objective To design an approach for the diagnosis of latex sensitization in children with spina bifida.

Methods We studied 100 consecutive unselected patients. Skin prick tests with a commercial latex extract were performed, latex-specific serum immunoglobulin (Ig) E was determined by CAP test, and risk factors were studied. Originally, patients with an area of latex skin test >50% of the area of histamine and/or CAP class ≥ 3 were considered sensitized to latex. Diagnostic tests were also performed in a control group of 51 atopic and nonatopic children.

Results After performing a receiver-operating characteristics curve for both tests we recommend skin tests >25% of the area of histamine (sensitivity – SEN = 79%, specificity – SPE = 100%, positive predictive value – PPV = 100%, negative predictive value – NPV = 90%), or CAP class ≥ 2 (SEN = 88%, SPE = 100%, PPV = 100%, NPV = 94%) as diagnostic cut-off points. The anamnesis had a SEN of 44% for diagnosis, and a SPE of 100%. Latex sensitization was associated with more than 5 operations (OR = 8, 95% CI = 3–21.3), a personal history of atopy (OR = 11.5, 95% CI = 2.3–57.1), and serum total IgE ≥ 2 z-units (OR = 4, 95% CI = 1.6–10).

Conclusion For the routine evaluation of children with spina bifida, we propose a diagnostic algorithm with skin prick tests as a first step and CAP second.

Keywords: diagnosis, diagnostic tests, latex allergy, risk factors, sensitization, spina bifida

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Introduction

Since 1979, when urticaria to latex was described by Nutter [1], immunoglobulin (Ig) E-mediated allergy to latex is increasingly being reported. First mild cases of urticaria have been followed by severe anaphylactic reactions during surgical and diagnostic procedures [2–4], in which there is a direct contact of latex with mucosas and blood vessels. Some of the allergic reactions formerly attributed to anaesthetic agents and contrast media have been proved to be caused by latex [4].

Populations with professional contact with latex are at risk of developing latex allergy [5], and, what concerns the paediatric field, multi-operated patients, such as children with spina bifida and other malformations [2,6–8], constitute a distinct high risk group, whose pattern of sensitization differs from that of adult patients [9,10]. Thus, results of diagnostic tests in adults are not readily applicable to children.

Those involved in the care of children with spina bifida must be aware of the high frequency of latex allergy, and know how to manage and advise these patients. Simple procedures, such as dental care or rectal examination with latex gloves, may elicit potentially harmful reactions in sensitized patients.

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Sensitization to latex must be present before the onset of symptoms, so the search for latex hypersensitivity should be warranted in all children with spina bifida. The aim of this work was to measure, in a large group of unselected children with spina bifida, the value of commercial tests used for the diagnosis of latex allergy, and to study the associated risk factors, in order to design a diagnostic approach in these patients.

Patients and methods

We studied 100 consecutive unselected patients with spina bifida, who had been followed from birth in the Paediatric Urology Section of a tertiary reference centre. Data were recorded about sex, age, familial and personal history of atopy, history of intermittent bladder catheterization, number of operations and cystourethrograms, serum total IgE both in U/mL and in z units, and patients were questioned about undue reactions to latex. These included urticaria, oedema of face and lips, tongue itching, rhinitis, cough, and anaphylactic shock in one patient. A positive familial or personal history of atopy was that of asthma, atopic dermatitis, rhinitis, conjunctivitis or urticaria not related to latex.

A control group of non-spina bifida children, comprising 35 atopic patients, with demonstrated sensitization to common foods and aeroallergens, and 16 children without allergic diseases, was used to study specificity of latex skin prick tests and serum-specific IgE. None of these children had reactions to latex.

In vivo tests

After informed consent was obtained from parents, skin prick tests with commercial latex antigen (ALK-Abello Laboratories, Madrid, Spain) were done in all the patients. This antigen is obtained from an ammoniated preparation of latex, but ammonium is eliminated during the process of extraction. The final product is a glycerinated solution with a 2-mg/mL concentration of proteins, which include a 14 kDa antigen, corresponding with the rubber elongation factor (information provided by the manufacturer). Skin tests were graded 0–4+ compared with saline solution and 1% glycerinated histamine, according to a method similar to that of Turjanmaa [11]. No weal was graded as 0+, weals with an area up to 25% of the weal elicited by histamine were graded as 1+, 2+ when the area was between 25 and 50%, 3+ when the area was between 50 and 75%, and 4+ when it exceeded 75%. The skin tests did not cause adverse reactions in any of the patients.

In vitro tests

Serum total and latex-specific IgE (Pharmacia CAP System, Uppsala, Sweden), according to the manufacturer's

instructions, were measured in all cases. Total serum IgE was evaluated in absolute units/mL, and to account for age, it was also converted into standard deviations from the mean for age (z units), following the values published by Kjellman *et al.* [12]. Values lower than 2 units/mL (sensitivity of the technique) were treated as 2 U/mL for analysis. Latex-specific IgE was graded, as suggested by the manufacturer, as class 0 for values lower than 0.35 U/mL, class 1 for values between 0.35 and 0.7, class 2 between 0.7 and 3.5, class 3 between 3.5 and 17.5, class 4 between 17.5 and 50, class 5 between 50 and 100, and class 6 for values above 100 U/mL.

Classification of patients

Spina bifida patients were classified according to responses to both *in vivo* and *in vitro* tests. Patients with strong responses (skin test 3+, CAP class 3) in any of the tests were considered sensitized to latex. One patient with a skin test of 2+ and latex-specific IgE of class 2, concordant with each other, was also classified as sensitized. Patients with both tests negative, or with only one of them with a very weak response (skin test 1+, CAP class 1) were classified as non-sensitized. The rest (patients with responses 0 and 2, 1 and 1, 1 and 2 in the tests) were considered inconclusive.

Statistical study

A stepwise logistic regression analysis was performed using sensitization as the dependent variable, and the factors listed above as independent variables. The independent variables thus selected were crossed with the variable sensitization to calculate their odds ratio. The statistical analysis was performed with the commercial package SPSS-PC (SPSS Inc., Chicago, IL, USA).

Once the patients were classified using the above described criteria, a receiver-operating characteristics (ROC) curve was performed for each separate diagnostic test, skin prick tests and CAP. Through the use of these curves, we selected the best cut-off points to choose the final diagnostic criteria, and according to these, we recalculated sensitivity, specificity and positive and negative predictive values of the tests. These values were also calculated for the combined use of the selected risk factors.

Results

The control group of atopic and nonatopic children comprised 51 children (33 male), with a mean $\pm$ SD age of 8.2 ± 3.9 years (range 3 months–14.7 years). Skin tests were graded as 0+ in 49 of them, and 1+ in the other two. CAP test was done in 39 patients. Values <0.35 U/mL (class 0) were found in 36 cases, values in class 1 (0.36 and 0.41

U/mL) in two cases, and a value of 17.8 U/mL (class 4) in one patient, who was a highly atopic girl, with serum total IgE over 2000 U/mL. Two other patients with serum total IgE over 1000 U/mL (1330 and 1415) had undetectable levels of specific IgE. The results yielded a specificity of 100% for skin tests, and 97.5% for CAP.

The study group of spina bifida children comprised 100 children (51 male) with a mean $\pm$ SD age of 7.5 ± 4.9 years (range 2 months–17.5 years).

According to the original aforementioned criteria, we classified 29 patients as sensitized, 63 as non-sensitized, and eight as inconclusive. The cut-off points originally selected for diagnosis of sensitization to latex was 3+ in skin tests, and class 3 in CAP. Once the patients were classified, we performed a ROC curve for each test, CAP and skin prick tests, which had an area under the curve of 0.95 and 0.96, respectively. According to these curves, we identified 2+ for skin tests, and CAP class 2 as the best cut-off points. These values were used as new diagnostic criteria; patients with results of at least 2+ in skin tests and/or CAP class ≥ 2 were considered to be sensitized to latex. Thus, 34 patients were classified as sensitized, and the other 66 as currently non-sensitized. With this classification, we performed new ROC curves for both tests, and areas under the curve were 0.91 for skin tests and 0.97 for CAP. The same best cut-off points, 2+ for skin tests, and class 2 for CAP were identified in the new curves, so we calculated their sensitivity, specificity and predictive values, which are shown in Tables 1 and 2.

Among the 34 patients newly classified as sensitized, 15 (44%) presented adverse reactions in relation to latex, which ranged from mild urticaria when inflating balloons to anaphylactic shock while undergoing a cystourethrogram.

All 15 patients with clinical reactions to latex in anamnesis had skin tests with values of 3+, and all of them had a CAP class ≥ 2 . In these 15 patients, the anamnesis was supported by the tests. Thus, sensitivity of the anamnesis for diagnosis of sensitization to latex was 44%, specificity was 100%, positive predictive value was 100% and negative predictive value was 78%.

Table 1 Sensitivity, specificity and predictive values for the selected cut-off point of 2+ (>25% of area of histamine) for latex skin prick tests in children with spina bifida

Skin prick test	Sensitized patients	Non-sensitized patients
$\geq 2+$	27	0
<2+	7	66

Sensitivity: 79%. Positive predictive value: 100%. Specificity: 100%. Negative predictive value: 90%.

Table 2 Sensitivity, specificity and predictive values for the selected cut-off point of latex CAP class ≥ 2 in children with spina bifida

CAP	Sensitized patients	Non-sensitized patients
Class ≥ 2	30	0
Class <2	4	66

Sensitivity: 88%. Positive predictive value: 100%. Specificity: 100%. Negative predictive value: 94%.

Three of the potential risk factors (number of operations, personal history of atopy and serum total IgE) were selected by a multivariate logistic regression analysis as synergistic-independent variables to predict sensitization to latex. More detailed information has been published elsewhere [13]. These three factors were chosen for the evaluation algorithm shown in Fig. 1, and their separate odds ratios and diagnostic values for the diagnosis of sensitization to latex are displayed in Table 3.

The combination of more than five operations and/or a positive personal history of atopy and/or 2 z units of serum total IgE may be used in some instances as a diagnostic test to predict sensitization to latex, with a sensitivity of 88%, specificity of 70%, and positive and negative predictive values of 60% and 92%. If we only use the combination of the first two risk factors (more than five operations and/or a positive personal history of atopy), their values would be 67, 85, 70 and 84%, respectively.

Discussion

The natural rubber or latex, used in widespread products, may contain up to 240 polypeptides [9]. After extraction by industrial manufacturing some of them remain [14] and act as very potent antigens [15]. The list of identified allergens implied in latex allergy keeps growing [16,17], making difficult the standardization of reagents for diagnostic tests.

Our work was aimed at the clinical diagnosis of sensitization to latex, not only to the diagnosis of allergy or symptomatic sensitization to latex. The risk of anaphylactic reactions to latex is highest in patients who have experienced previous severe reactions; nevertheless there are descriptions in adult patients on the gradual progress from minor symptoms (itching, urticaria) to anaphylactic reactions [3,18], and there are reports of patients in whom the onset of clinical symptoms was a life-threatening event [2–4]. In some of these, previous minor reactions to latex were identified retrospectively [2,4], but these data are not available in others [4]. Identification of asymptomatic patients who are sensitized to latex, as demonstrated by a

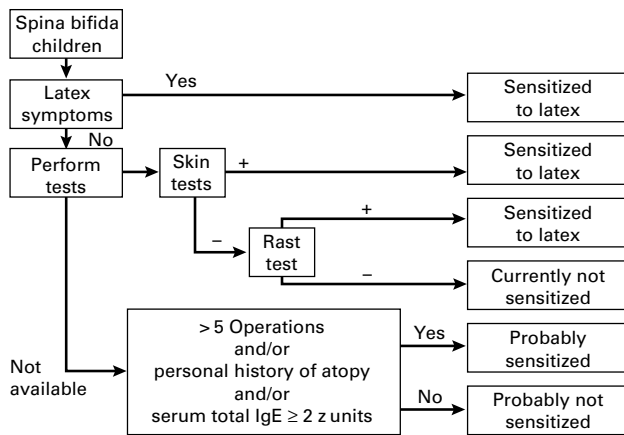


Fig. 1. Algorithm for the routine evaluation of sensitization to latex in children with spina bifida. When tests are not available, risk factors may be used for a tentative diagnosis

positive RAST or skin prick test, is essential as they remain at risk for clinically significant latex reactions. Formerly, the routine search for latex allergy was not recommended in children with spina bifida, and diagnostic approaches in risk groups other than spina bifida did not recommend diagnostic tests in asymptomatic patients [19]. However, with present evidence the tests are particularly indicated in asymptomatic children with spina bifida, to identify those ones who are already sensitized.

The prevalence of sensitization to latex in children with spina bifida ranges from 18 to 72% [20–26]. Reasons for this wide range include the different diagnostic techniques, the different diagnostic criteria, and whether diagnosis

includes asymptomatic or just symptomatic sensitization. Among the methods used for diagnosis, there have been surveys [20,27], skin tests [4,22], RAST tests [21,25] or a combination of these [2,3,6,7,22,24,28–30]. In our case, for diagnosis and to avoid false positive responses, we originally chose a strong positive response in any of the tests we used, skin prick tests or CAP.

We used the combination of these tests as the gold standard diagnostic criterion to calculate their separate sensitivity and specificity. This may seem misleading, but to date they are the best available methods to detect latex-specific IgE antibodies. In some studies the diagnostic value of tests has been calculated for latex-symptomatic sensitization, using a history of clinical reactions as the gold standard [27,29–32], and patients with positive tests but with a negative history are considered false positive. This carries the risk to label some patients as nonallergic, when they are in fact sensitized, and might present adverse reactions to latex in subsequent exposures. To study the value of diagnostic tests comparing them to a gold standard makes sense when they are easier, faster, cheaper, or safer. The clinical use of tests for the diagnosis of latex allergy seems to be superfluous if this can be accomplished by the simple questioning of patients or the inspection of medical records.

In published studies, including ours, skin tests yield positive results in nearly all the patients who have previous symptoms, using antigens of different origins [3,7,22,24–27,29–33]. RAST tests, from different laboratories, confirm the results of the skin tests in most patients who have symptoms and are considered very specific [3,7,21,24–26,29,32–34]. The presence of clinical reactions to latex in anamnesis is, by itself, enough to diagnose sensitization to latex. The indication to perform tests in these symptomatic patients would be for investigation or legal purposes. Moreover, adverse reactions with skin tests have only appeared in patients with a positive history [23,35,36], while they have not been described in asymptomatic patients.

We have developed the diagnostic algorithm shown in Fig. 1. No tests are needed for the clinical diagnosis of latex sensitization in children with previous reactions to latex, but tests must be done in spina bifida children without latex symptoms. The sensitivity was better for CAP (88%) than for skin tests (79%), but in the routine study, as the first step, we recommend skin tests. They are fast, cheap and we have found them to be safe. We, like other authors [3,27–29], have not had adverse reactions in children, and those which have been published happened in patients usually with some previous symptoms [23,31,35,36], and sometimes with a highly concentrated antigen [35]. Next step would be the *in vitro* quantification of specific IgE, which is slower and more expensive, although more sensitive than the commercial reagent we used in skin tests. Sensitivity of

Table 3 Risk factors for sensitization to latex. Diagnostic values for the diagnosis of sensitization to latex, and odds ratio with 95% confidence interval for each separate factor are shown

	Sensitized Yes/No	SEN/SPE PPV/NPV (%)	Odds ratio (95% CI)
<i>No. of operations</i>			
> 5	19/9	56/86	8
≤ 5	15/57	68/79	(3–21.3)
<i>Personal history of atopy</i>			
Yes	9/2	26/97	11.5
No	25/64	82/72	(2.3–57.1)
<i>Serum total IgE (z units)</i>			
≥ 2	16/12	47/82	4
< 2	18/54	57/75	(1.6–10)

SEN: sensitivity. PPV: Positive predictive value. SPE: specificity. NPV: negative predictive value.

this reagent rated third of four commercial extracts, and lower than a natural latex extract in a study on adult patients [32]. By definition, specificity was considered to be 100% in both tests for our children with spina bifida, and this figure was supported by testing a control group of atopic and nonatopic children. Nevertheless, CAP would not be so reliable when serum total IgE is very high (> 2000 U/mL), as found in a very atopic patient of the control group. The differences of sensitivity and specificity of tests between other studies and our own are explained by the fact that we diagnosed sensitization to latex. When applied for the diagnosis of latex allergy, specificity has been graded between 69 and 100% [26,27,29,30,32].

When tests are not available, the presence of risk factors such as a personal history of atopy, more than five operations and serum total IgE ≥ 2 z units is very often associated with sensitization to latex, so these patients should be managed as if they were sensitized. The 'use test' has recently been studied in children with spina bifida, and 54 of 55 positive results appeared in patients in whom sensitization could be demonstrated by skin or CAP tests [29], so its role remains to be determined.

For sustaining the diagnosis of sensitization to latex we originally chose strong responses in the tests, 3+ in skin tests and CAP class ≥ 3 . We performed a ROC curve for these tests and, in view of the gains obtained in sensitivity with smaller losses in specificity, we now recommend to lower the cut-off point for diagnosis to 2+ in skin tests and CAP class ≥ 2 . Furthermore, all the cases thus included in the sensitized group belonged to the original 'inconclusive group'. Patients in this group were considered to probably be in the earlier stages of sensitization [13], and we have recently verified that four out of six patients studied evolved to the clearly sensitized group (submitted).

The Task Force on allergic reactions to latex [37] recommends a latex-free environment for procedures on all patients with spina bifida. This way adverse reactions will not appear, and it will prevent the development of sensitization to latex. Avoidance of latex, the best policy, is encouraged, and all efforts should be made to achieve this goal. But we acknowledge that it is often difficult to arrange, and while the generalized extent of these measures is not possible, the diagnostic evaluation of these children is needed. Thus, we recommend diagnostic tests for all children with spina bifida. The use of risk factors for a tentative diagnosis of sensitization to latex would be restricted to instances where there is no time for a scheduled study. Whenever the medical record of a patient is not available, as in emergency visits, and a latex-free environment is not arranged, the knowledge of two risk factors (personal history of atopy and number of operations) would be helpful for a better evaluation of the risk/benefit ratio of medical procedures in these children.

References

- 1 Nutter AF. Contact urticaria to rubber. *Br J Dermatol* 1979; 101:597–8.
- 2 Kelly KJ, Pearson ML, Kurup VP et al. A cluster of anaphylactic reactions in children with spina bifida during general anesthesia: epidemiologic features, risk factors and latex hypersensitivity. *J Allergy Clin Immunol* 1994; 94:53–61.
- 3 Sussman GL, Tarlo S, Dolovich J. The spectrum of IgE-mediated responses to latex. *JAMA* 1991; 265:2844–7.
- 4 Moneret-Vautrin DA, Laxenaire MC, Bavoux F. Allergic shock to latex and Ethylene oxide during surgery for spina bifida. *Anesthesiology* 1990; 73:556–8.
- 5 Lagier F, Vervloet D, Lhermet I, Poyen D, Charpin D. Prevalence of latex allergy in operating room nurses. *J Allergy Clin Immunol* 1992; 90:319–22.
- 6 Bode CP, Füllers U, Röseler S, Wawer A, Bachert C, Wahn V. Risk factors for latex hypersensitivity in childhood. *Pediatr Allergy Immunol* 1996; 7:157–63.
- 7 Michael T, Niggemann B, Moers A, Seidel U, Wahn U, Scheffner D. Risk factors for latex allergy in patients with spina bifida. *Clin Exp Allergy* 1996; 26:934–9.
- 8 Banta JV, Bonanni C, Prebluda J. Latex anaphylaxis during spinal surgery in children with myelomeningocele. *Dev Med Child Neurol* 1993; 35:543–8.
- 9 Alenius H, Kurup V, Kelly KJ, Palosuo T, Turjanmaa K, Fink JN. Latex allergy: frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. *J Lab Clin Med* 1994; 123:712–20.
- 10 Tomazic VJ, Withrow TJ, Hamilton RG. Characterization of the allergens in latex protein extracts. *J Allergy Clin Immunol* 1995; 96:635–42.
- 11 Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Alenius H, Palosuo T. Natural rubber latex allergy. The European experience. *Immunol Allergy Clin N Amer* 1995; 15:71–88.
- 12 Kjellman NIM, Johansson SGO, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). *Clin Allergy* 1976; 6:51–9.
- 13 Nieto A, Estornell F, Mazón A, Reig C, Nieto A, García-Ibarra F. Allergy to latex in spina bifida: a multivariate study of associated factors in 100 consecutive patients. *J Allergy Clin Immunol* 1996; 98:501–7.
- 14 Hamilton RG, Charous BL, Adkinson NF Jr, Yunginger JW. Serologic methods in the laboratory diagnosis of latex rubber allergy: study of nonammoniated, ammoniated latex, and glove (end-product) extracts as allergen reagent sources. *J Lab Clin Med* 1994; 123:594–604.
- 15 Kurup VP, Kumar A, Choi H et al. Latex antigens induce IgE and eosinophils in mice. *Int Arch Allergy Immunol* 1994; 103:370–7.
- 16 Breiteneder H, Scheiner O. Molecular and immunological characteristics of latex allergens. *Int Arch Allergy Immunol* 1998; 116:83–92.
- 17 Posch A, Chen Z, Raulf-Heimsoth M, Baur X. Latex allergens. *Clin Exp Allergy* 1998; 28:134–40.
- 18 Morales C, Basomba A, Carreira J, Sastre A. Anaphylaxis produced by rubber glove contact. Case reports and immuno-

- logical identification of the antigens involved. *Clin Exp Allergy* 1989; 19:425–30.
- 19 Kelly KJ, Kurup VP, Reijula KE, Fink JN. The diagnosis of natural rubber latex allergy. *J Allergy Clin Immunol* 1994; 93:813–6.
- 20 Pearson ML, Cole JS, Jarvis WR. How common is latex allergy? A survey of children with myelodysplasia. *Dev Med Child Neurol* 1994; 36:64–9.
- 21 Tosi LL, Slater JE, Shaer C, Mostello LA. Latex allergy in spina bifida patients: Prevalence and surgical implications. *J Pediatr Orthop* 1993; 13:709–12.
- 22 Moneret-Vautrin DA, Beaudouin E, Widmer S et al. Prospective study of risk factors in natural rubber latex hypersensitivity. *J Allergy Clin Immunol* 1993; 92:668–77.
- 23 Kelly KJ, Kurup V, Zacharisen M, Resnick A, Fink JN. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol* 1993; 91:1140–5.
- 24 Ellsworth PI, Merguerian PA, Klein RB, Rozycki AA. Evaluation and risk factors of latex allergy in spina bifida patients: Is it preventable? *J Urol* 1993; 150:691–3.
- 25 Konz KR, Chia JK, Kurup VP, Resnick A, Kelly KJ, Fink JN. Comparison of latex hypersensitivity among patients with neurologic defects. *J Allergy Clin Immunol* 1995; 95:950–4.
- 26 De Swert LFA, Van Laer KMIA, Verpoorten CMA, Van Hoeyveld EM, Cadot P, Stevens EAM. Determination of independent risk factors and comparative analysis of diagnostic methods for immediate type latex allergy in spina bifida patients. *Clin Exp Allergy* 1997; 27:1067–76.
- 27 Hamilton RG, Adkinson NF Jr. Multi-Center Latex Skin Testing Study Task Force. Diagnosis of natural rubber latex allergy: multicenter latex skin testing efficacy study. *J Allergy Clin Immunol* 1998; 102:482–90.
- 28 Mathew SN, Melton AL Jr, Wagner WO. Latex hypersensitivity: a case study. *Ann Allergy* 1993; 70:483–6.
- 29 Niggemann B, Buck D, Michael T, Wahn U. Latex provocation tests in patients with spina bifida: Who is at risk of becoming symptomatic? *J Allergy Clin Immunol* 1998; 102:665–70.
- 30 Shah S, Cawley M, Gleeson R, O'Connor J, McGeedy S. Latex allergy and latex sensitization in children and adolescents with meningomyelocele. *J Allergy Clin Immunol* 1998; 101:741–6.
- 31 Turjanmaa K, Palosuo T, Alenius H et al. Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. *Allergy* 1997; 52:41–50.
- 32 Blanco C, Carrillo T, Ortega N, Alvarez M, Domínguez C, Castillo R. Comparison of skin-prick test and specific serum IgE determination for the diagnosis of latex allergy. *Clin Exp Allergy* 1998; 28:971–6.
- 33 Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M. Latex allergy: clinical features and cross-reactivity with fruits. *Ann Allergy* 1994; 73:309–14.
- 34 Niggemann B, Michael T, von Moers A et al. Comparison of three immunoassays for diagnosing sensitization to latex in children with spina bifida. *Pediatr Allergy Immunol* 1996; 7:164–6.
- 35 Bonnekoh B, Merk HF. Safety of latex prick skin testing in allergic patients (letter). *JAMA* 1992; 267:2603.
- 36 Spaner D, Dolovich J, Tarlo S, Sussman G, Butto K. Hypersensitivity to natural latex. *J Allergy Clin Immunol* 1989; 83:1135–7.
- 37 Task Force on Allergic Reactions to Latex. American Academy of Allergy and Immunology. Committee report. *J Allergy Clin Immunol* 1993; 92:16–8.