

PREVENTION OF ALLERGIC REACTIONS IN ANESTHETIZED PATIENTS

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Hypersensitivity reactions during perioperative period are increasing and may be potentially life-threatening. Therefore, major emphasis is given to prevention. We perform a review to examine which measures should be taken to prevent reactions to products used in elective and emergency surgery. Any patient with a history of previous anaphylaxis or severe reaction during anaesthesia should be referred to allergist for detection of the offending compound. However, the identification of the triggering agent is not always feasible because of the low accuracy of diagnostic tests. In these cases and when emergency surgery is required, it should be considered to replace all drugs administered before the onset of the reaction with alternatives. Furthermore, any cross-reacting agent and latex, especially in patients belonging to populations at-risk for latex allergy should be avoided. In susceptible patients, premedication with antihistamines and corticosteroids might reduce the severity of reaction to drugs or contrast material while it is unclear whether pre-treatment decreases incidence of anaphylactic reactions. There is no evidence that premedication prevents allergic reactions to latex. Overall, physicians should not rely on the efficacy of premedication.

Immediate allergic and pseudo-allergic reactions during anesthesia are of great concern because they may be severe and life-threatening. Strategies focusing on identification of patients at risk are needed for preventing perioperative reactions. Clinical history is the most important tool for screening these subjects. Patients who are at high risk are those who have allergy to latex or to other products used during anesthesia, and those who experienced previous anaphylaxis or severe reactions during anesthesia (1, 2). Therefore, patients with a positive or unclear clinical history of perioperative allergic reactions should be referred by the anesthetist to an allergist with drug testing competence for a thorough investigation, including interpretation of skin tests and drug challenge, and recognition of the offending product before the surgical procedure (Figure 1).

When this is unavailable an appropriate documentation

on the products used, including time of onset of reaction or type of symptoms, and laboratory tests for muscle relaxants and latex that are common causes of perioperative reactions should be performed.

When record of previous reaction exists, patients should undergo IgE tests for suspected agents (Figure 1). IgE-mediated reactions usually occur after previous administration of the allergen. The causative role of the agent is associated with positive IgE tests in about 60% of cases. Skin prick testing permits to investigate more types of drugs than blood tests for specific IgE antibodies. Hypersensitivity tests have low diagnostic value which is also a consequence of different pathophysiologic mechanisms (often unknown) involved in the reactions. Some agents may induce reactions through a direct non IgE-mediated activation of mast cells or complement

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activation that occurs without previous exposure. These reactions are generally not predictable and skin test results can be falsely positive or negative (Figure 1).

PATIENTS WITH REACTIONS TO SPECIFIC PRODUCTS

The only effective secondary preventive measure for patients with allergy to known products is obviously the complete avoidance of the triggering allergen and the replacement with alternatives. In this way, further allergic reactions are likely to be avoided.

When an alternative drug is not available, patients with anaphylaxis can be desensitized (3-9).

The induction of tolerance is achieved through incremental exposure to the relevant drug to the therapeutic dose. The desensitization allows a temporary tolerance through immune modulation and persists only with a daily maintenance dose of the drug (9).

Neuromuscular blocking agents (NMBA)

The tertiary or quaternary ammonium group, common to all muscle relaxants, is likely to be responsible of the cross-reactivity between NMBAs that occurs in up to 60% of patients (10-12). Therefore, patients who react to an NMBA should avoid all NMBAs when it is feasible. After assessing the cost-benefit ratio, local anesthetics, local regional anesthesia and inhaled anesthetics may be valuable alternatives.

When it is mandatory to administer an NMBA, an incremental challenge with an NMBA different from that which elicited the reaction and to which skin test result is negative should be given (2). However, on one hand it is unclear whether an NMBA with a positive skin prick test result elicits allergic reactions. On the other hand, there is no warranty against a repeated reaction since serious reactions to these agents can occur at the first known exposure. Fisher MM and coworkers described a patient who had perioperative anaphylaxis from pancuronium. During subsequent anesthesia, the same patient had an anaphylactoid reaction to alcuronium to which skin tests were negative (13). For this reason the prevention of primary sensitization to muscle relaxants is not possible. Furthermore, screening of the general population for NMBA sensitivity is not helpful since the positive predictive value of the test is poor (14, 15).

Antibiotics

Patients with allergy to a particular antibiotic should be given drugs with a different chemical structure. When the antibiotic to which the patient is allergic is substituted with another that belongs to a cross-reacting class, a change of agent does not ensure that a renewed reaction

may occur. The predictive value of IgE tests is useful for IgE-mediated allergic reactions induced by a small group of antibiotics. Therefore, controlled challenges may be required to determine whether the alternative antibiotic is clinically safe.

Allergic reactions to β -lactam drugs are the most frequent and more studied. In patients with a high documented probability of clinical history of immediate reaction to penicillin a positive skin prick test result was found in 70% of cases (16). However, it should be taken into account that patients with negative penicillin skin tests can often have positive challenge test to penicillin (17). Therefore, patients with positive clinical history and negative skin tests should undergo provocation test to ascertain the diagnosis. The safest therapeutic approach to patients who are allergic to penicillin is to administer antibiotics that do not contain a β -lactam ring, however this can reduce the efficacy of the treatment and increase costs. From a practical viewpoint, patients with immediate reactions and positive skin tests to penicillin should avoid cephalosporins to which skin test result is positive while cephalosporins to which skin test is negative seem to be safe given in a graded challenge (18). Only about 3% of patients with delayed non IgE-mediated reactions to penicillin reacted to cephalosporin (19).

Anesthetic induction drugs

The clinical meaning of laboratory tests showing cross-reactivity among barbiturates is unclear. It has been suggested to avoid other barbiturates in patients with allergy to thiopental since immunologic cross-reactivity may occur (20). Cross-reactivity does not occur between drugs used for anesthetic induction belonging to different pharmaceutical classes. Therefore, propofol can be helpful in patients with sensitivity to barbiturates. A lipid vehicle containing soybean oil and egg lecithin is used in the preparation of propofol. There is no convincing evidence that patients with egg allergy or soy allergy are at risk of developing reactions to propofol (2).

Desmetyldiazepam seems to be responsible for the cross reactivity of diazepam with other benzodiazepines. It is noteworthy that patients with a history of allergy to products such as medications, vaccines, cosmetics, and foods containing propylene glycol solvent should avoid diazepam that also contains this solvent.

Opioids

Morphine may commonly induce a cutaneous rash, urticaria, and rarely hypotension or bronchospasm through a non IgE-mediated mechanism (21).

When analgesia is required in patients who experienced an adverse reaction, a non opioid alternative drug should be given. When this drug does not control

pain, it is recommended to perform a graded challenge with a drug belonging to a different class of opioids (phenanthrones (morphine, codeine), phenylpiperidines (alfetanyl, fentanyl, remifentanyl, sufentanyl, meperidine), or andihetylheptanes (methadone, propoxyphene). They have distinct chemical structures and clinical cross-reactivity has not been reported. However, this is not firmly established since the mechanism of the reaction is usually non IgE-mediated (22, 23).

Non-steroidal anti-inflammatory drugs (NSAID)

Blood or skin allergy tests are not useful for ascertaining sensitivity to NSAID. The diagnosis can be established only by a graded challenge under medical supervision. Clinical reactions to inhibitors of the cyclo-oxygenase-1 enzyme (COX 1) are a risk factor for developing reactions to COX 2 inhibitors.

Cross-reactivity occurs among members of COX 1 inhibitor class as well as among COX 2 inhibitor class, while it is uncommon between COX 1 and COX 2 inhibitors. IgE tests to NSAID are almost always not reliable (24). This implies that a diagnostic challenge test for the suspected drug is needed when the history is not convincing.

Furthermore, in patients with previous reactions to NSAID, tolerance to any other drug belonging to this group must be ascertained by a challenge test in order to prevent further reactions.

Local anesthetics

Local anesthetics are classified as amides or esters. Cross-reactivity (25, 26) may take place among members of the ester class and rarely among drugs belonging to the amide class. Esters generally do not cross-react with amides.

In the rare cases of children with positive skin test result to the responsible amide, it is generally not recommended to perform a challenge test. A reasonable approach would be to perform skin test to another amide and when the result is negative, proceed to the graded challenge test, in order to establish whether the drug is safe (27). Alternatively, skin testing and incremental challenge with the other class of local anesthetics can be performed (27). In children with allergy to local anesthetics, general anesthesia is a possible option.

Dyes

Blue dyes are used particularly in lymphangiography and lymphatic mapping in sentinel lymph node biopsy. There is an immunologic cross reactivity between Patent Blue V (also called E131, Acid Blue 3, and disulfine blue) and isosulfan blue (also called Patent Blue violet or Lymphazurin), which share the same formula (28).

Methylene blue is structurally unrelated with Patent Blue V and has been recommended as a safe alternative (29).

However, immunologic cross-reactivity between these dyes has been reported. Thus in patients who react to Patent Blue V, skin testing with methylene blue should be routinely performed. It has been suggested that methylene blue should be given when skin test result is negative (30).

Reactions to blue dyes can be both IgE-mediated and non IgE-mediated. Patients can react to dyes at first known exposure. Therefore, IgE tests are not helpful in predicting clinical reaction (30, 31).

Radiographic contrast material (RCM)

After a severe allergic reaction to RCM, the patient should not be exposed to a RCM again. Safe alternative procedures such as magnetic resonance imaging or ultrasound imaging should be performed. When patients who have previously experienced a reaction to high osmolality RCM, require a new RCM administration, a low osmolality RCM should be given. Low osmolality RCMs are associated with a decreased incidence of severe repeated reaction up to 10-fold in comparison with high osmolality RCM (32-34). However, this option does not guarantee that allergic reactions will not occur. For the above reason, patients with risk factors for having a reaction after RCM administration are usually given a low osmolality RCM (32). Such risk factors include food allergy, bronchial asthma (35), cardiac diseases, β -blockers (36), serum creatinine > 2 mg/ml, history of allergy (37) and therapy with Interleukin-2 (38). Mastocytosis, viral infection at the time of RCM administration and autoimmune diseases, such as LES have been reported to influence the severity but not the onset of the reactions to RCM (39, 40). Further larger studies are required to clarify whether allergy tests are useful in identifying safe alternative RCM in patients with RCM reactions (32). A previous allergic reaction to iodinated contrast agent is a risk factor for having an adverse reaction to gadolinium.

Latex

The main purpose in the management of latex allergy is the primary prevention of sensitization. In children with spina bifida, the prevalence of latex allergy is significantly reduced by the elimination of contact with latex from the first surgical operation (41). Therefore, a latex-free environment is recommended for each procedure performed on children at risk. These children include those requiring multiple surgeries especially because of spina bifida and genitourinary malformations and those with allergy to fruit, particularly banana, kiwi, or avocado, that cross-react with latex allergens (42). In

workers with occupational exposure to latex, primary prevention is achieved by reducing contact with latex products. Health-care workers should avoid exposure to aerosolization of latex antigens adherent to the cornstarch powder of latex glove by using non-powered latex gloves or latex-free gloves.

In patients with latex allergy, secondary prevention has been shown to be effective for avoiding anaphylactic reactions. Patients with asymptomatic sensitization to latex (43), such as those suffering from pollinosis (42) or those monosensitized to latex profilin (Hev b 8) (44), even if they safely undergo surgery, they should follow a prophylaxis program because of the possible risk of developing clinical hypersensitive reactions following multiple intra-operative exposures to latex.

A secondary prevention strategy must include a latex-safe environment, that should be established not only in the room or surgical suite but also in the pediatric ward and in all clinical settings. In a latex-safe environment the use of latex gloves and latex accessories (catheters, adhesives, tourniquets, and anesthesia equipment or devices) should be banned. It is recommended to have a "check-list" providing information on latex free products and a supply of them. The list of latex-free medical and surgical material should be updated regularly by anesthetists, allergists and pharmacists. The anesthetic and surgical areas should be prepared the day before to avoid the release of latex particles and the patient should be the first on the list (45).

Others products

Washed red blood cells should be given to subjects with IgA deficiency who rarely develop IgE or IgG antibodies against IgA and react to *blood transfusions*.

Antiseptics. In patients with reactions to chlorhexidine, povidone iodine should be used.

Colloids. Clinical cross-reactions between colloids [gelatin, albumin, hydroxyethyl starch (HES), dextrans] have not been reported. Therefore, one class can be substituted with another if necessary. Among colloids, there is increasing awareness of the frequency of allergic reactions to gelatin solutions. Intravenous gelatin solutions should be avoided in patients with a positive history of allergic reactions to products containing gelatin such as foods, vaccines, pharmaceuticals and cosmetics (2). Dextran may provoke serious allergic reactions. The apten inhibition with dextran 1 before exposure to dextran has been found to be useful in dramatically reducing the risk of potentially life-threatening reactions. When 3 g of dextran 1 are preinjected dextran-induced anaphylactoid reactions rarely occur in patients with extremely high titers of antibodies to dextran. Pre-treatment with dextran 1 does not prevent occasional mild, anaphylactoid, non

antibody-dependent reactions (46).

PATIENTS WITH SEVERE REACTIONS DURING ANESTHESIA TO AN UNKNOWN AGENT

Any patient with a convincing history of previous anaphylaxis or severe reaction (i.e. cardio-respiratory collapse) during anaesthesia in which the causative agent was investigated but not identified is matter of concern during surgery (Figure 1).

When emergency surgery is required, if previous record is available, it should be considered to avoid all drugs administered before the onset of the reaction. Furthermore any cross-reacting agent, especially when the skin test result is positive should be avoided (2).

It would be advisable to avoid triggers that epidemiological studies have shown to commonly cause reactions during operation. If it is unclear from history whether the patient is allergic to latex or if he belongs to a risk group for latex allergy, all surgical procedures should be conducted in a latex-free environment. It is appropriate to avoid NMBAs, if feasible (2). Alternatively, drugs used in local and regional anaesthesia should be used since they rarely cause allergic reactions. Inhalational agents are also generally safe. The fast injection of histamine-releasing drugs (e.g., morphine, d-tubocurarine, vancomycin, muscle relaxants) particularly in subjects with asthma or cardiopulmonary disease may enhance the rate of histamine release and may favor the onset of the reaction. A slow administration usually reduces the rate of histamine release and prevents the severity of the reactions. If allergy tests to drugs are performed with negative results, it may be hypothesized that the previous reaction may have been the result of non-allergic mechanisms. Therefore, it is better to avoid releasing-histamine drugs, such as morphine (2). It is better to use povidone iodine as a disinfectant.

PREMEDICATION

A prophylactic treatment with corticosteroids alone or in combination with H1 antihistamines and/or H2 antihistamines is largely used in clinical practice even if the benefit remains a matter of debate. Administering premedication in patients who need surgery or in patients who previously had perioperative reactions to an unknown substance should be considered. Moreover, in patients with allergy to a product used during the perioperative period, pre-treatment may be an option when a cross-reacting agent is given (Figure 1).

Generally, premedication does not prevent an anaphylactic reaction but in some instances has been useful in reducing the severity of hypersensitivity

Table 1. *Prevention of intra-operative reactions to offending agents*

Offending agents	Prevention
NMBA	- Local anesthetics, local regional anesthesia or inhaled anesthetics should be used after assessing the cost-benefit ratio. - When a NMBA must be administered, patients should be given a graded challenge with a NMBA different from that which elicited the reaction and to which skin test result is negative for ascertaining the tolerance.
Latex	A latex-safe environment is recommended for each procedure performed on children at high risk for latex allergy or allergic to latex.
Local anesthetics	Patients with allergy to local anesthetics should be given an incremental challenge with a different drug belonging to the same class or with a drug belonging to another class of local anesthetics to which skin test result was negative.
Radiographic contrast material	In patients with allergic immediate reactions to contrast media, safe alternative procedures such as magnetic resonance imaging or ultrasound imaging should be used. When this is not feasible, a low osmolarity contrast media should be given and premedication should be administered.
Antibiotics, NSAIDs, anesthetic induction drugs, narcotics or other agents	- An alternative product should be administered. - When a cross reacting agent is given, an incremental challenge is advisable.

events. However, this may depend on clinical conditions and on the pathogenic mechanism of the reaction. Therefore, physicians should not rely on the efficacy of premedication.

There is no evidence that pre-treatment (2, 47) can effectively prevent the onset or reduce the severity of anaphylaxis to latex (47). Moreover, pre-treatment could delay the reaction and make it more difficult to recognize early signs of latex anaphylaxis. Therefore, anaphylaxis is treated only when systemic manifestation occurs (47, 48).

Regarding anesthetics, it is unclear whether the prophylactic administration of steroids is beneficial. In patients with anaphylaxis to NMBA, Moneret-Vautrin and coworkers (49) demonstrated that pretreatment with H1 and H2 receptor antagonists could decrease skin reactivity. This may suggest that premedication may reduce non specific histamine release but not the incidence of anaphylaxis or its severity. Pre-treatment

with combined H1 and H2 antagonists has been found to reduce histamine-mediated adverse effects such as hypotension or rash related to high doses of mivacurium (50, 51) or high doses of atracurium (52, 53). However, despite of pretreatment with corticosteroids, anti H1 and anti H2 anaphylactic reactions to NMBA have been reported (54).

Morphine administered during the perioperative period can produce cardiovascular effects attributed to non IgE mediated histamine release. The use of anti H1 (diphenhydramine) and anti H2 (cimetidine) may have hemodynamic protection (blood pressure, systemic vascular resistant and cardiac index). The combination of these drugs might give better protection than one given alone (55). Anti H1 plus anti H2 (promethazine/pethidine) administration reduces the histamine release due to fentanyl or nalbuphine (56). The infusion of polygeline (Haemaccel) can provoke cutaneous anaphylactoid

reactions; it has been proved that these effects can be abolished by premedication with diphenhydramine and cimetidine (57). The rapid vancomycin administration can induce the onset of the "red man syndrome". Pretreatment with intravenous H1 and H2 antihistamines has been found to prevent hypotension and to reduce skin rash. Antihistamine prophylaxis permits rapid vancomycin infusion (58). There is some evidence that in patients at risk, life-threatening events but not incidence of first-time anaphylactoid reactions to blue dyes may be reduced by pre-treatment with corticosteroids and anti H1 (59).

Pretreatment regimens may reduce incidence and severity of non IgE mediated reactions to RCM. The administration of steroids may reduce the incidence and severity of respiratory symptoms and the combination of respiratory and hemodynamic symptoms (bronchospasm, laryngeal edema, and hypotension). Anti H1 with/without anti H2 may reduce the risk of urticaria, flushing and pruritus (60). However, it has been reported that premedication does not prevent recurrence of anaphylaxis due to RCM (61).

A recommended pre-treatment for RCM reactions in patients at risk (3) consists of 1 mg/kg up to 50 mg of prednisone given orally 13, 7, and 1 hour before administration of RCM and 50 mg of diphenhydramine given orally or intramuscularly 1 hour before the administration of RCM. Modifications to this regimen have included addition of 25 mg of ephedrine given orally 1 hour before RCM and of H2 antihistamines, 4 mg/kg of cimetidine (62). Lower doses of glucocorticosteroids, oral diphenhydramine, and the use of new oral H1 antihistamines have also been suggested.

In emergency conditions, a regimen of 200 mg of hydrocortisone administered intravenously immediately and every 4 hours until the RCM is administered, and 50 mg of diphenhydramine given intramuscularly 1 hour before RCM is used (62).

In high risk subjects a longer treatment with higher doses, and an intravenous administration of a methylprednisolone bolus one hour before the induction of anesthesia has been proposed (63). For delayed reactions to RCM an effective pretreatment consists in 40 mg per day of 6-methyl-prednisolone and 100 mg bid of oral cyclosporine given 1 week before and 2 weeks after RCM (64).

Another issue of debate is whether pretreatment should be routinely used in the absence of risk factors for perioperative reactions. In the general population premedication does not completely prevent a severe intraoperative reaction, but it may be useful in reducing the severity of unpredictable reactions (63). There are also some data that prophylaxis reduces both the severity and the incidence of reactions to RCM in subjects not at

risk (65). However, cost, delay in diagnosis of adverse events, risk of adverse effect caused by steroids or antihistamines, delay in performing radiologic or surgical procedures, and possible lack of attention for the necessity of a prompt treatment of reactions may limit the use of premedication (60).

PREOPERATIVE IGE SCREENING

When clinical history is negative, even in patients with drug allergy and in those that are atopic, IgE tests have not been reported to be helpful in predicting anaphylactic reactions to substances used in the perioperative period. Moreover, the predictive assessments of IgE-mediated reactions may not estimate the risk of reaction due to nonspecific release of anaphylactic mediators in response to future exposure to anesthetics. Therefore, it is not recommended to perform screening IgE tests in patients undergoing operations.

CONCLUSIONS

A careful clinical history has a critical role in identifying patients at increased risk of developing reactions during anesthesia. Prevention of perioperative allergic reactions relies on the identification of the offending agent by allergist. This is of paramount importance in order to avoid further hypersensitivity reactions since they cannot effectively be prevented by premedication. Furthermore, patients should be provided with drugs likely to be safe for future anesthesia. However, a complete prevention is not possible to achieve, due to the relatively high rate of sensitization to anesthetics in the absence of prior exposure or risk factors and to the low diagnostic accuracy of IgE tests.

REFERENCES

1. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, Demoly P; Working Group for the SFAR; ENDA; EAACI Interest Group on Drug Hypersensitivity. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol.* 2005;15:91-101.
2. Harper NJN, Chairman N, Dixon T, Dugue' P, Edgar DM, Fay A, Gooi HC, Herriot R, Hopkins P, Hunter JM, Mirakian R, Pumphrey RSH, Seneviratne SL, Walls AF, Williams P, Wildsmith JA, Wood P. Ex Officio: Nasser AS, Powell RK, Mirakur R, Soar J, Executive Officers, AAGBI. *Suspected anaphylactic reactions associated with anaesthesia.* Association of Anaesthetists of Great Britain and Ireland. Suspected anaphylactic reactions associated

- with anaesthesia. *Anaesthesia* 2009;64:199-211.
3. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM. The diagnosis and management of anaphylaxis practice parameter: 2010 Update. *J Allergy Clin Immunol* 2010;126:477-80.
 4. Pereira C, Rico P, Lourenco M, Lombardero M, Pinto-Mendes J, Chieira C. Specific immunotherapy for occupational latex allergy. *Allergy* 1999;54:291-3.
 5. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. *J Allergy Clin Immunol* 2000;106:585-90.
 6. Patriarca G, Nucera E, Buonomo A, Del Ninno M, Roncallo C, Pollastrini E, De Pasquale T, Milani A, Schiavino D. Latex allergy desensitization by exposure protocol: five case reports. *Anesth Analg* 2002;94:754-8.
 7. Patriarca G, Nucera E, Pollastrini E. Sublingual desensitization: a new approach to latex allergy problem. *Anesth Analg* 2002;95:956-60.
 8. Sanford JP. The technique of penicillin desensitization: how to reduce anaphylaxis risk when only penicillin will do. *J Crit Illness* 1992;7:791-5.
 9. Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol* 1987;80:314-9.
 10. Baldo BA, Fisher MM. Substituted ammonium ions as allergic determinants in drug allergy. *Nature* 1983;306:262-6.
 11. Matthey P, Wang P, Finegan BA, Donnelly M. Rocuronium anaphylaxis and multiple neuromuscular blocking drug sensitivities. *Can J Anaesth* 2000;47:890-3.
 12. Fisher MM, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983;62:559-64.
 13. Fisher MM, Bowey CJ. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. *Br J Anaesth* 1997;79:59-63.
 14. Porri F, Lemièrre C, Birnbaum J, Guilloux L, Lanteaume A, Didelot R, Charpin D, Vervloet D. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy* 1999;29:72-5.
 15. Porri F, Pradal M, Rud C, Charpin D, Alazia M, Gouin F, Vervloet D. Is systematic preoperative screening for muscle relaxant and latex allergy advisable? *Allergy* 1995;50:374-7.
 16. Torres MJ, Romano A, Mayorga C, Moya MC, Guzman AE, Reche M, Juarez C, Blanca M. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy* 2001; 56: 850-856.
 17. Bousquet PJ, Kvedariene V, Co-Minh HB, Martins P, Rongier M, Arnoux B, Demoly P. Clinical presentation and time course in hypersensitivity reactions to betalactams. *Allergy* 2007; 62:872-6.
 18. Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
 19. Trcka J, Seitz CS, Brocker EB, Gross GE, Trautmann A. Aminopenicillin induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin. *J Antimicrob Chemother* 2007;60:107-111.
 20. Harle DG, Baldo BA, Smal MA, Wajon P, Fisher MM. Detection of thiopentone-reactive IgE antibodies following anaphylactoid reactions during anaesthesia. *Clin Allergy* 1986;16:493-498.
 21. Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology* 1982;56:93-6.
 22. Baumann TJ. Analgesic selection when the patient is allergic to codeine. *Clin Pharm* 1991;10:658.
 23. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; 62: 471-487.
 24. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G, Kowalski ML, Setkowicz M, Ring J, Brockow K, Bachert C, Wöhrl S, Dahlén B, Szczeklik A. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111-8.
 25. Seng GF, Kraus K, Cartwright G, Nerone R, Pacione R. Confirmed allergic reactions to amide local anesthetics. *Gen Dent* 1996;44:52-4.
 26. Phillips JF, Yates AB, Deshazo RD. Approach to Patients With Suspected Hypersensitivity to Local Anesthetics. *Am J Med Sci* 2007;334:190-196.
 27. Executive summary of disease management of drug hypersensitivity: a practice parameter. Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1999;83:665-700.
 28. Scherer K, Studer W, Figueiredo V, Bircher AJ. Anaphylaxis to isosulfan blue and cross-reactivity to patent blue V: case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol* 2006;96:497-500.

29. Simmons R, Thevarajah S, Brennan MB et al. Methylene blue dye as an alternative to isosulfan blue dye for sentinel lymph node localization. *Ann Surg Oncol* 2003;10:242–7.
30. Mertes PM, Malinovsky JM, Mouton-Faivre C, Bonnet-Boyer MC, Benhajjoub A, Lavaud F, Valfrey J, O'Brien J, Pirat P, Lalourcey L, Demoly P. Anaphylaxis to dyes during the perioperative period: Reports of 14 clinical cases. *J Allergy Clin Immunol* 2008;122:348–52.
31. Keller B, Yawalkar N, Pichler C, Braathen LR, Hunger RE. Hypersensitivity reaction against patent blue during sentinel lymphnode removal in three melanoma patients. *Am J Surg* 2007;193:122–124.
32. Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A, Dewachter P, Gueant JL, Rodriguez-Gueant RM, Mouton-Faivre C, Ring J, Romano A, Sainte-Laudy J, Demoly P, Pichler WJ. For ENDA and the EAACI interest group on drug hypersensitivity. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:150–8.
33. Morcos SK, Thomsen HS, Webb JAW. Prevention of generalized reactions to contrast media: a consensus report and guidelines. *Eur Radiol* 2001;11:1720–8.
34. Wolf GL, Mishkin MM, Roux SG, Halpern EF, Gottlieb J, Zimmermann J, Gillen J, Thellman C. Comparison of the rates of adverse drug reactions. Ionic contrast agents, ionic agents combined with steroids, and non ionic agents. *Invest Radiol*. 1991;26:404–10
35. Bettmann MA, Heeren T, Greenfield A, Goudey C. Adverse events with radiographic contrast agents: results of the SCVIR contrast agent registry. *Radiology* 1997;203: 611–620.
36. Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both β -blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993;153: 2033–2040.
37. Hosoya T, Yamaguchi K, Akutsu T, Mitsuhashi Y, Kondo S, Sugai Y, Adachi M. Delayed adverse reactions to iodinated contrast media and their risk factors. *Radiat Med* 2002;58: 1245–1251.
38. Choyke PL, Miller DL, Lotze MT, Whiteis JM, Ebbitt B, Rosenberg SA. Delayed reactions to contrast media after interleukin-2 immunotherapy. *Radiology* 1992;183: 111–114.
39. Pichler WJ, Yawalkar N, Britschgi M, Depta J, Strasser I, Schmid S, Kuechler P, Naisbitt D. Cellular and molecular pathophysiology of cutaneous drug reactions. *Am J Clin Dermatol* 2002;3:229–238.
40. Pichler WJ, Yawalkar N. Allergic reactions to drugs: involvement of T cells. *Thorax* 2000;55:561–565.
41. Cremer R, Kleine-Diepenbruck U, Hering F, Holschneider AM. Reduction of latex sensitization in spina bifida patents by a primary prophylaxis programme (five years experience) . *Eur J Pediatr Surg* 2002;12:519–21.
42. Haeberle HA, Lupic D, Midoro-Horiuti T, Kiefer RT, Schroeder TH, Unertl K et al. Role of cross-allergies to latex in clinical routine of anesthesia. *J Clin Anesth* 2003;15:495–504.
43. Liss GM, Sussman GL, Deal K Brown S, Cividino M, Siu S, Beezhold DH, Smith G, Swanson MC, Yunginger J, Douglas A, Holness DL, Lebert P, Keith P, Wasserman S, Turjanmaa K. Latex allergy: epidemiological study of 1351 hospital workers. *Occup Environ Med* 1997; 54: 335–42.
44. Quercia O, Stefanini GF, Scardovi A, Asero R. Patients monosensitized to Hev b 8 (Heveabraziliensis latex profilin) may safely undergo major surgery in a normal (non-latex safe) environment. *Eur Ann Allergy Clin Immunol* 2009; 41:112–116.
45. Joint Task Force on Practice Parameters. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005; 115:S483–523.
46. Ljungstrom KG. Dextran 40 therapy made safer by pretreatment with dextran 1. *Plastic & Reconstructive Surgery* 2007;120:337–40.
47. Weiss ME, Hirshman CA. Latex allergy. *Can J Anaesth* 1992;39:528–32.
48. Setlock MA, Cotter TP, Rosner D. Latex allergy: failure of prophylaxis to prevent a severe reaction. *Anesth Analg* 1993;76:650–2.
49. Moneret-Vautrin DA, Laxenaire MC, Mouton C, Widmer S, Pupil P. Change in skin reactivity in anaphylaxis to muscle relaxants and hypnotics after administration of anti H1, anti H2 and tritoqualine. *Ann Fr Anesth Reanim* 1985;4:225–30.
50. Doenicke A, Moss J, Lorenz W, Mayer M, Rau J, Jedrzejewski A, Ostwald P. Effect of oral antihistamine premedication on mivacurium-induced histamine release and side effects. *Br J Anaesth* 1996;77:421–3.
51. Mayer M, Doenicke A, Nebauer AE, Rosenberger C, Lorenz W, Peter K. Pharmacodynamics and clinical adverse effects of mivacurium. The effect of oral premedication with H1/H2 antagonists. *Anaesthesist* 1993;42:592–6.
52. Hosking MP, Lennon RL, Gronert GA. Combined H1 and H2 receptor blockade attenuates the cardiovascular effects of high-dose atracurium for rapid sequence endotracheal intubation. *Anesth Analg* 1988;67:1089–92.
53. Scott RP, Savarese JJ, Basta SJ, Sunder N, Ali HH,

- Gargarian M, Gionfriddo M, Batson AG. Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anaesth* 1985;57:550-3.
54. Laxenaire M, Mertes PM, GERAP: Anaphylaxis during anaesthesia: results of a 2-year survey in France. *Br J Anaesth* 2001;21:549-558.
 55. Philbin DM, Moss J, Akins CW, Rosow CE, Kono K, Schneider RC, VerLee TR, Savarese JJ. The use of H1 and H2 histamine antagonists with morphine anesthesia: a double-blind study. *Anesthesiology* 1981;55:292-6.
 56. Dick W, Lorenz W, Heintz D, Sitter H, Doenicke A. Histamine release during induction of combination anesthesia using nalbuphine or fentanyl. Modulation of the reaction by premedication with promethazine/pethidine. *Anaesthesist* 1992;41:239-47.
 57. Schöning B, Lorenz W, Doenicke A. Prophylaxis of anaphylactoid reactions to a polypeptidal plasma substitute by H1- plus H2-receptor antagonists: synopsis of three randomized controlled trials. *Klin Wochenschr* 1982;60: 1048-55.
 58. Renz, Cheryl L. MD; Thurn, John D. MD; Finn, Henry A. MD; Lynch, James P. BA; Moss, Jonathan MD, PhD. Antihistamine prophylaxis permits rapid vancomycin infusion. *Crit Care Med* 1999;27:1732-7.
 59. Raut CP, Hunt KK, Akins JS, Daley MD, Ross MI, Singletary SE, Marshall GD Jr, Meric-Bernstam F, Babiera G, Feig BW, Ames FC, Kuerer HM. Incidence of anaphylactoid reactions to isosulfan blue dye during breast carcinoma lymphatic mapping in patients treated with preoperative prophylaxis: results of a surgical prospective clinical practice protocol. *Cancer* 2005;95:962-9.
 60. Tramèr MR, Von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;333:663-4.
 61. Worthley DL, Gillis D, Kette F, Smith W. Radiocontrast anaphylaxis with failure of premedication. *Intern Med J* 2005;35:58-60.
 62. Greenberger PA, Halwig JM, Patterson R, Wallemark CB. Emergency administration of radiocontrast media in high-risk patients. *J Allergy Clin Immunol* 1986;77:630-4.
 63. Liccardi G, Lobefalo G, Di Florio E, Di Iorio C, Occhiochiuso L, Romano L, Savoia G, Massa RM, D'Amato G, Cardarelli Hospital radiocontrast Media and Anesthetic-Induced Anaphylaxis Prevention (CHRAIAP) Working Group. Strategies for the Prevention of Asthmatic, Anaphylactic and Anaphylactoid Reactions During the Administration of Anesthetics and/or Contrast Media. *J Investig Allergol Clin Immunol* 2008;18:1-11.
 64. Romano A, Artesani MC, Andriolo M, Viola M, Pettinato R, Vecchioli-Scaldazza A. Effective prophylactic protocol in delayed hypersensitivity to contrast media: report of a case involving lymphocyte transformation studies with different compounds. *Radiology* 2002;225:466-70.
 65. Marshall GD, Lieberman PL. Anaphylactoid reactions to radiocontrast agents. *Immunol Allergy Clin North Am* 1998;18:799-807.