

# Anaphylaxis During the Perioperative Period

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Anesthesiologists use a myriad of drugs during the provision of an anesthetic. Many of these drugs have side effects that are dose related, and some lead to severe immune-mediated adverse reactions. Anaphylaxis is the most severe immune-mediated reaction; it generally occurs on reexposure to a specific antigen and requires the release of proinflammatory mediators. Anaphylactoid reactions occur through a direct non-immunoglobulin E-mediated release of mediators from mast cells or from complement activation. Muscle relaxants and latex account for most cases of anaphylaxis during the

perioperative period. Symptoms may include all organ systems and present with bronchospasm and cardiovascular collapse in the most severe cases. Management of anaphylaxis includes discontinuation of the presumptive drug (or latex) and anesthetic, aggressive pulmonary and cardiovascular support, and epinephrine. Although a serum tryptase confirms the diagnosis of an anaphylactic reaction, the offending drug can be identified by skin-prick, intradermal testing, or serologic testing. Prevention of recurrences is critical to avoid mortality and morbidity. (Anesth Analg 2003;97:1381-95)

The term "anaphylaxis" was coined by Nobel prize recipients Portier and Richet (1) in 1902, when they described a dog that had tolerated a previous injection of actinotoxin, a jellyfish toxin, but reacted with bronchial spasm, cardiorespiratory arrest, and death to a smaller dose 14 days later. Whereas prophylaxis in Greek means "protection," anaphylaxis means "opposite protection" or "against protection" (2). Anaphylaxis generally occurs on reexposure to a specific antigen and requires the release of proinflammatory mediators, but it can also occur on first exposure, because there is cross-reactivity among many commercial products and drugs.

Immune-mediated allergic reactions are classified, according to their mechanism, on the basis of the Gell and Coombs classification. Whereas anaphylaxis is a Type I immunoglobulin (Ig)E-mediated hypersensitivity reaction involving mast cells and basophils, contact dermatitis is a Type IV T-lymphocyte cell-mediated delayed-type hypersensitivity reaction. Other immune-mediated reactions include Type II reactions in which IgG, IgM, and complement mediate cytotoxicity and Type III

reactions in which immune-complex formation and deposition leads to tissue damage (3). Anaphylactoid reactions occur through a direct nonimmune-mediated release of mediators from mast cells and/or basophils or result from direct complement activation, but they present with clinical symptoms similar to those of anaphylaxis (3,4).

Anaphylaxis is generally an unanticipated severe allergic reaction, often explosive in onset, that can occur perioperatively, especially during a surgical procedure when multiple drugs are administered during the conduction of an anesthetic. Because patients are under drapes and mostly unconscious or sedated, the early cutaneous signs of anaphylaxis are often unrecognized, leaving bronchospasm and cardiovascular collapse as the first recognized signs of anaphylaxis. A survey of anaphylaxis during anesthesia demonstrated that cardiovascular symptoms (73.6%), cutaneous symptoms (69.6%), and bronchospasm (44.2%) were the most common clinical features (5).

The incidence of anaphylaxis and anaphylactoid reactions during anesthesia is very difficult to estimate but has been calculated to range from 1 in 3,500 to 1 in 13,000 cases (6,7). Another report from Australia estimated the incidence to be between 1 in 10,000 and 1 in 20,000 (8), whereas the most recent report, from Norway, estimated the incidence to be 1 in 6,000 (9). Muscle relaxants are associated with the most frequent incidence of anaphylaxis, and over the last two decades, natural rubber latex (NRL, or *cis*-1,4-polyisoprene) has emerged as the second most common cause of anaphylaxis (5,10). However, one report (5) found that the incidence of cases of

Supported by the Department of Anesthesiology, Perioperative and Pain Medicine and by the Department of Medicine, Brigham and Women's Hospital, Harvard Medical School.

Accepted for publication June 6, 2003.

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DOI: 10.1213/01.ANE.0000082993.84883.7D

latex anaphylaxis is decreasing as a result of identification of at-risk patients and preventive measures. Antibiotics and anesthesia induction drugs account for the next group of drugs more likely to lead to an anaphylactic reaction (5,10). Table 1 outlines the common drugs involved in perioperative anaphylaxis in France (5).

Serious problems are unusual during surgery (0.4% of cases), but anesthesia contributes to a third of these cases (9). Allergic reactions are among the major factors that contribute to morbidity and mortality during an anesthetic and to changes in postoperative care (9). A recent review of serious intraoperative problems highlighted a case of fatal anaphylactic shock and suggested that preventive strategies are needed for anaphylaxis (9). Because anaphylaxis is a rare event that is not the first consideration for the anesthesiologist, its management in a full-scale anesthesia simulator has been suggested (11). In one study, none of 42 anesthesiologists tested on a simulator made the correct diagnosis during the first 10 min of anaphylaxis, and most of them failed to have a structured plan for its treatment (11).

Earlier review articles focused on the definition, diagnosis, and management of anaphylaxis (12,13). Other review articles highlight drugs involved in anaphylactic and anaphylactoid reactions but concentrate only on the most common causative drugs (14). Even recent reviews on anaphylaxis during anesthesia devote a limited portion to drugs likely to induce anaphylaxis (15). This review will identify most drugs implicated in anaphylaxis and will discuss its diagnosis and management. A MEDLINE literature search with the key words "anesthesia" plus "anaphylaxis" or "hypersensitivity" or "allergy" produced 491 articles from 1966 until October 2002. These articles were reviewed, and the common drugs associated with perioperative anaphylaxis were identified. Then a search of each specific drug and the key words "anaphylaxis," "hypersensitivity," or "allergy" was conducted. In addition, the references of relevant articles were reviewed to identify other articles missed in the original search. Finally, additional references were identified from the book *Drug Allergy* (16) and from the most recent survey of anaphylaxis during anesthesia (5).

## Pathophysiology

Anaphylaxis is a clinical syndrome that affects multiple organ systems. The clinical manifestations of anaphylaxis are derived from the acute release of mediators from mast cells and possible basophils. On initial exposure to an antigen in susceptible individuals, IgE is produced and binds to mast cells and basophils. On reexposure, the multimeric antigen cross-links two IgE receptors, inducing the tyrosine phosphorylation of

their cytoplasmic immune tyrosine activation motifs by Lyn and Syk tyrosine kinases. This initiates a signal-transduction cascade, which culminates in the increase of intracellular calcium and the release of preformed mediators such as histamine, proteases (tryptases), proteoglycans, and platelet-activating factor (3,17). Phospholipid metabolism then leads to the generation of potent inflammatory leukotrienes (LTC<sub>4</sub>, LTE<sub>4</sub>, and LTD<sub>4</sub>) and prostaglandins (PGD<sub>2</sub>). Histamine, PGD<sub>2</sub>, and LTC<sub>4</sub> are potent vasoactive mediators implicated in vascular permeability changes, flushing, urticaria, angioedema, hypotension, and bronchoconstriction (Fig. 1).

Histamine receptors are present in the skin, gastrointestinal tract, heart, vascular bed, and bronchial smooth muscle. Whereas histamine 1 receptors are responsible for increases in mucous production, heart rate, and flushing, histamine 2 receptors lead to an increase in vascular permeability, gastric acid secretion, and airway mucus production. PGD<sub>2</sub> and LTC<sub>4</sub> receptors are present in the skin, bronchial smooth muscle, and vascular bed and cause bronchoconstriction, a wheal and flare response, and increased vascular permeability. Proteases prevent local coagulation and degrade bronchodilating peptides. Heparin and platelet-activating factor can produce local and systemic anticoagulation.

Anaphylactoid reactions are derived from the activation of the complement and/or bradykinin cascade and the direct activation of mast cells and/or basophils (Fig. 1). Clinical manifestations of anaphylactoid reactions are indistinguishable from anaphylactic reactions. These reactions are rapid in onset and start within seconds to minutes of exposure to the allergen. Symptoms progress rapidly and can affect most organ systems, including the skin (pruritus, flushing, urticaria, and angioedema) and eyes (conjunctivitis), the upper (rhinitis and angioedema) and lower (bronchoconstriction with wheezing and dyspnea, and cyanosis) airway, the intestinal tract (abdominal pain, nausea, vomiting, and diarrhea), and the cardiovascular system (tachycardia, hypotension, and shock), and can lead to cardiovascular collapse and death (4) (Table 2). The onset and type of symptoms depend on the allergen concentration, although minute amounts of allergen have been shown to produce severe and even fatal reactions. The patient's sensitivity and the route of administration are determining factors, and IV infusion of allergen can trigger rapid cardiovascular symptoms.

## Diagnosis

Whereas the initial diagnosis of perioperative anaphylaxis relies on the history and physical examination, the retrospective diagnosis is based on serologic and

**Table 1.** Drugs Involved in Perioperative Anaphylaxis (5)

Substance	Incidence of perioperative anaphylaxis (%)	Most commonly associated with perioperative anaphylaxis
Muscle relaxants	69.2	Succinylcholine, rocuronium, atracurium
Natural rubber latex	12.1	Latex gloves, tourniquets, Foley catheters
Antibiotics	8	Penicillin and other $\beta$ -lactams
Hypnotics	3.7	Propofol, thiopental
Colloids	2.7	Dextran, gelatin
Opioids	1.4	Morphine, meperidine
Other substances	2.9	Propacetamol, aprotinin, chymopapain, protamine, bupivacaine

skin tests (Fig. 2). Serum tryptase is a mast cell protease that is increased in cases of anaphylaxis, signaling an immune-mediated mechanism. An increase in human  $\alpha$  and  $\beta$  tryptase, the predominant mast cell proteases, can be measured in serum and plasma 30 min after the first signs of anaphylaxis and correlate with the presence of hypotension. Tryptase's half-life is 2 h, and the levels gradually decrease over time. Tryptase may not be increased in the absence of hypotension (18,19), or it may remain increased for days in cases of late-onset, biphasic, and protracted anaphylaxis (20,21). Mast cell tryptase can also be released by pharmacologic drugs that cause direct nonimmunologic mast cell activation (22). An increase of serum tryptase does not differentiate an anaphylactic from an anaphylactoid reaction (23). Similarly, an absence of serum tryptase does not eliminate an anaphylactic reaction, because there have been reports of anaphylaxis with positive tests for IgE antibodies in the setting of an absence of serum tryptase. In conclusion, although serum tryptase is a helpful indicator of an anaphylactic reaction, it does not differentiate an anaphylactic from an anaphylactoid reaction. Histamine in serum is not measured routinely because of its half-life of only a few minutes (20,24). Collections of urine histamine for 24 h after the anaphylactic episode will reflect the release from mast cells and basophils (20,24).

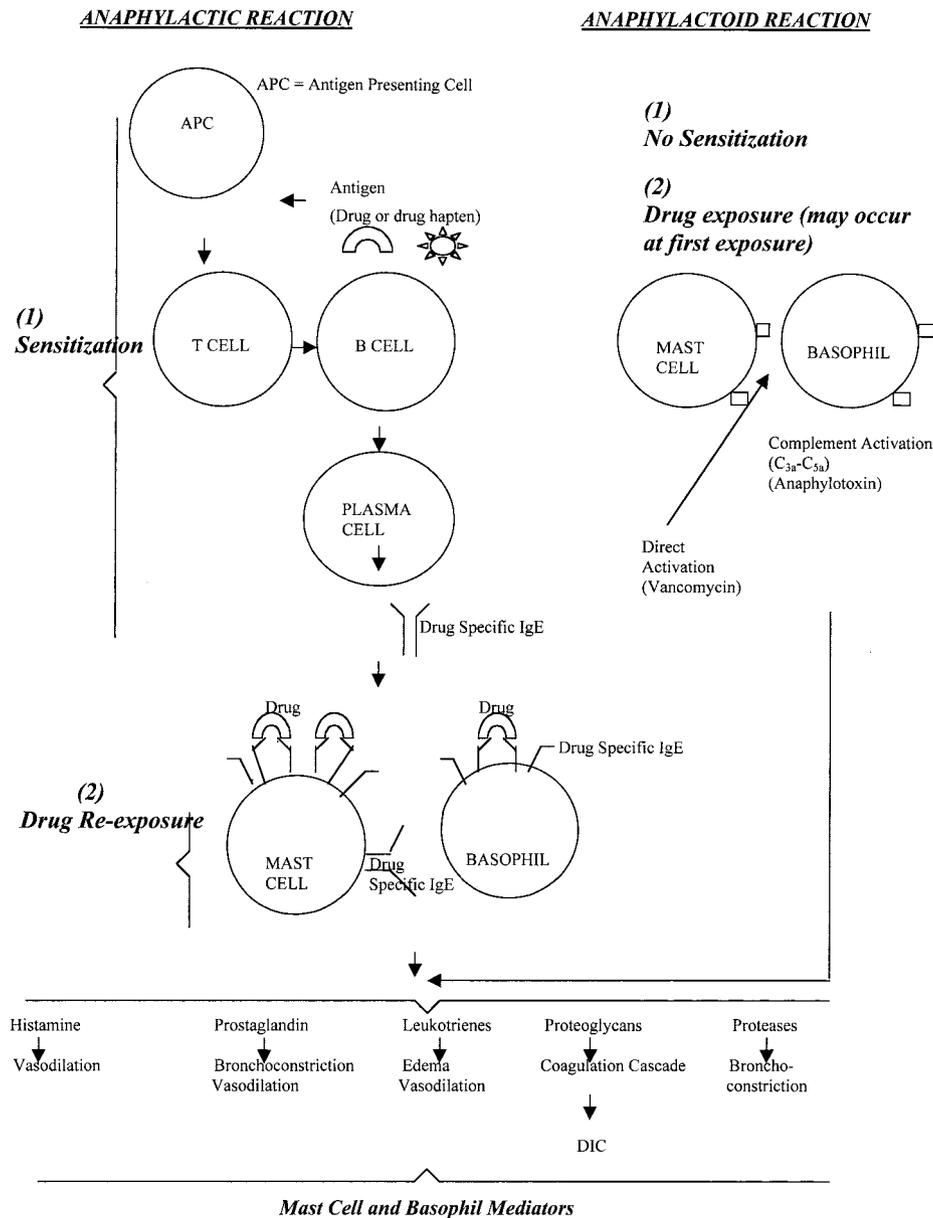
*In vitro* tests available in clinical practice detect the presence of IgE antibodies by the radioallergosorbent test (RAST, Pharmacia CAP system). This test measures the presence of specific IgE antibodies in serum that bind to a disk coupled with the specific drug and can be performed if the patient has extensive skin lesions, is receiving drugs such as antihistamines, or has presented with a recent episode of anaphylaxis. RAST tests are highly specific, but the sensitivity is low for most drugs. Subjects may remain sensitized for up to 30 yr after exposure to muscle relaxants, unlike other drugs, such as  $\beta$ -lactam antibiotics, for which individuals lose sensitization over time (6,16). Basophil histamine release is a research assay not commercially available in the United States and not approved by the US Food and Drug Administration

(FDA). It is performed *in vitro* by exposing the patient's basophils to the drug suspected of inducing anaphylaxis (25). It can be used for the detection of IgE reactions to muscle relaxants and propofol.

*In vivo* testing includes skin testing, which is performed by prick and intradermal techniques. Routine skin testing of all patients undergoing anesthesia in the absence of prior adverse reactions to anesthetic drugs is not recommended because of the presence of subclinical IgE sensitization (26,27). In the general population, 9.3% have a positive skinprick test to one or more muscle relaxants, and specific IgE to quaternary ammonium ions is found in the absence of clinical symptoms (26). Superficial dermal mast cells are triggered by the prick technique, and nonspecific irritation is its major limitation. A positive test has a high predictive value in the setting of a history of anaphylaxis. Prick tests are usually negative with local anesthetics, and in the setting of a positive clinical history, there is the need for an evaluation with a graded challenge (28). Intradermal skin testing is performed by diluting the concentration of the prick test by 1:10 and is used for local anesthetics, muscle relaxants, and propofol. At least 0.2–0.3 mL is introduced intradermally, eliciting a response from a deeper mast cell population. The risk of anaphylaxis induced by skin testing is small (<0.1% for antibiotics). Skin testing should be done 4–6 wk after the anaphylactic episode because of mast cell and basophil-mediator depletion. Because of the risk of inducing a systemic reaction, skin tests should be performed only by trained physicians in a setting with adequate resuscitative equipment.

## Management of Perioperative Anaphylaxis

The management of anaphylaxis consists of withdrawing the offending drug, interrupting the effects of the preformed mediators that were released in response to the antigen, and preventing more mediator release (Fig. 3). Management must be immediate, because anaphylaxis is life threatening and may produce cardiovascular collapse (Table 3). Immediate discontinuation of the anesthetic and of drugs and early



**Figure 1.** Anaphylactic and anaphylactoid reactions. Anaphylaxis is a clinical syndrome that affects multiple organ systems and occurs after the sudden release of chemical mediators from tissue mast cells or circulating basophils mediated by the cross-linking of immunoglobulin E (IgE) antibodies. Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions but occur through a direct non-IgE-mediated release from mediators of mast cells or from complement activation. DIC = disseminated intravascular coagulation.

administration of epinephrine are the cornerstones of treatment. Epinephrine is the drug of choice in the treatment of anaphylaxis, because its  $\alpha_1$  effects help to support the blood pressure while its  $\beta_2$  effects provide bronchial smooth-muscle relaxation. Epinephrine is used at 5- to 10- $\mu$ g IV bolus (0.2  $\mu$ g/kg) doses for hypotension and at 0.1- to 0.5-mg IV doses in the presence of cardiovascular collapse (2). Failure to recognize anaphylaxis and treat it promptly with epinephrine may result in biphasic or protracted anaphylaxis or in a fatal outcome (29,30).

Airway support with 100% oxygen will increase oxygen delivery and compensate for the increased oxygen consumption. IV crystalloid (2-4 L) replacement will compensate for the peripheral vasodilation that often accompanies anaphylaxis. Histamine 1

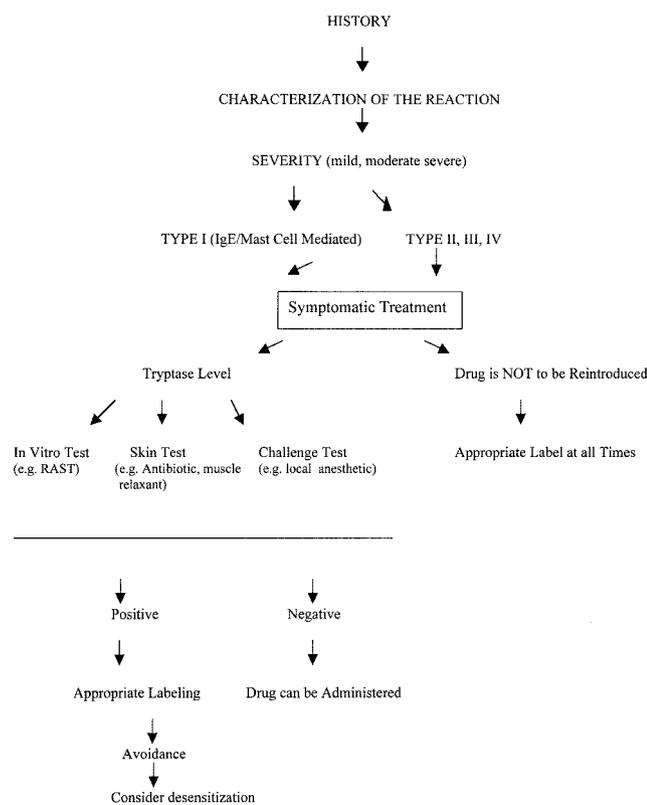
blockers (e.g., diphenhydramine 0.5-1 mg/kg), histamine 2 blockers (e.g., ranitidine 150 mg or cimetidine 400-mg IV bolus), bronchodilators (e.g., albuterol and ipratropium bromide nebulizers), and corticosteroids (e.g., hydrocortisone 1-5 mg/kg) should be given (2,31,32). Histamine 1 blockers are used in the early phases of anaphylaxis, but once cardiovascular collapse occurs, their role is controversial (33). Corticosteroids can decrease the airway swelling and prevent recurrence of symptoms, as seen in biphasic or protracted anaphylaxis (31). Hydrocortisone is the preferred steroid because it has a fast onset. Extubation should be delayed, because airway swelling and inflammation may continue for 24 h (2). An epinephrine infusion may be necessary to maintain the blood pressure, and bronchodilators should be continued during

**Table 2.** Clinical Manifestations of Anaphylaxis (4)

Organ system	Signs and symptoms	Signs during anesthesia
Cutaneous	Flushing, pruritus, urticaria, angioedema	Flushing, <sup>a</sup> urticaria, angioedema
Gastrointestinal	Nausea and vomiting, abdominal cramping, diarrhea	Absent or difficult to appreciate in patients receiving general anesthesia. May be present in patients under regional anesthesia or monitored anesthesia care
Respiratory	Rhinitis, laryngeal edema, shortness of breath, wheezing, respiratory arrest	Increased peak inspiratory pressure, increased end-tidal carbon dioxide, decreased oxygen saturation, wheezing, bronchospasm
Cardiovascular	Tachycardia, hypotension, cardiac arrhythmias, cardiovascular collapse	Tachycardia, hypotension, cardiac arrhythmias, cardiac arrest
Renal	Decreased urine output	Decreased urine output secondary to acute tubular necrosis
Hematologic	DIC	DIC

DIC = disseminated intravascular coagulation.

<sup>a</sup> The skin is often covered, and it may be difficult to appreciate any cutaneous manifestations.



**Figure 2.** Simple algorithm for the diagnosis of perioperative anaphylaxis. The initial diagnosis of perioperative anaphylaxis relies on the history and physical examination. Whereas *in vitro* tests are used to confirm the diagnosis (serum tryptase) and to identify the offending drug or substance (radioallergosorbent test; RAST), *in vivo* tests (e.g., skin test) are used to identify the offending drug or substance with more sensitivity and specificity. IgE = immunoglobulin E.

bronchospasm. Histamine 1 receptor antagonists should be continued in the presence of urticaria and angioedema, and a histamine 2 receptor antagonist should be added to a histamine 1 receptor antagonist in the setting of hypotension.

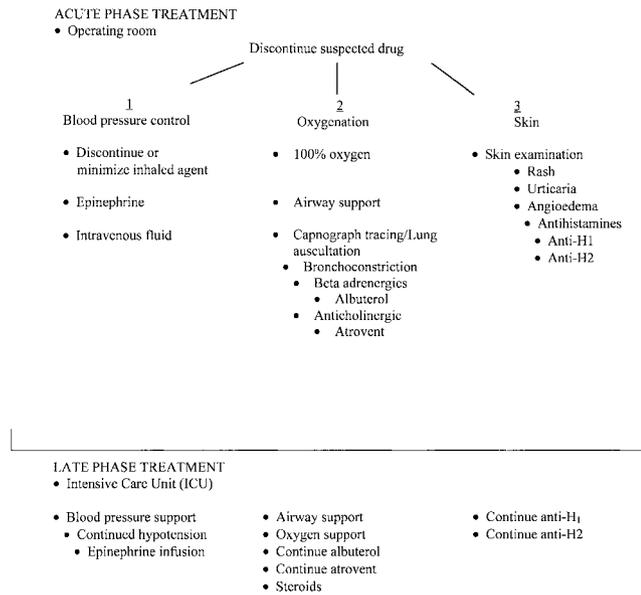
Preliminary work has demonstrated that the histamine 3 receptor is also involved in anaphylaxis (34). These receptors have been identified on presynaptic terminals of the sympathetic nervous system that innervates the heart and systemic vasculature, and they inhibit endogenous epinephrine release from the sympathetic nerves (35). Histamine 3 receptor blockade has been shown to improve left ventricular systolic function and heart rate in canine anaphylaxis when compared with controls (34).

## Prevention of Perioperative Anaphylaxis

A careful history regarding adverse drug reactions and allergies should be conducted before any surgical procedures requiring anesthesia. Identification of at-risk patients will lead to avoidance of a particular drug and is likely to prevent anaphylaxis. Atopic individuals with increased IgE are at risk for allergic reactions to propofol and latex (36,37). Health-care workers and patients with multiple prior surgical procedures can be sensitized to latex and may develop anaphylaxis when exposed to latex (37). Females are more likely than males to have anaphylaxis during anesthesia, with a 3:1 ratio (5). Avoidance of drugs that produced anaphylaxis and positive tests during a prior anesthetic has been demonstrated to prevent an episode of anaphylaxis from recurring (38,39).

There is little benefit in premedicating allergic patients with histamine 1 and histamine 2 blockers or corticosteroids before surgery or anesthesia (40,41). Although they could minimize the severity of anaphylaxis, these drugs may also blunt the early signs of anaphylaxis, leaving a full-blown episode as the presenting sign. These drugs should be reserved for the early treatment of anaphylaxis.

Patients with anaphylaxis who have no alternative drug available can be desensitized (42-47). Eligible



**Figure 3.** Step-by-step approach to the management of perioperative anaphylaxis. Treatment of the acute phase of perioperative anaphylaxis relies on blood pressure maintenance and airway support. Treatment of the late phase of perioperative anaphylaxis relies on drug support measures, including histamine 1 (H<sub>1</sub>) and histamine 2 (H<sub>2</sub>) blockers and corticosteroids.

patients have an IgE mechanism with mast cell activation and mediator release (46). The desensitization mechanism allows for the incremental introduction of the specific drug to the targeted doses. Patients transiently lose the skin-test positivity after desensitization. There is temporary tolerance as long as there are continued systemic levels of the allergen. The mechanism is unknown, but signal transduction in mast cells is abolished during the process (47).

## Specific Drugs

### Local Anesthetics

Local anesthetics belong to the amide or ester groups. Ester local anesthetics, such as procaine, chlorprocaine, tetracaine, and benzocaine, have a lipophilic or aromatic group, an intermediate ester linkage, and a hydrophilic quaternary amine side chain. Amide local anesthetics, such as lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, and ropivacaine, differ in that they have an intermediate amide linkage. The metabolism of amide local anesthetics is primarily in the liver, whereas that of esters is via plasma cholinesterases to paraaminobenzoic acid.

Anaphylactic reactions to amide local anesthetics are extremely rare, and true allergic reactions to esters account for <1% of all drug reactions to local anesthetics (28,48,49). True Type I IgE-mediated allergic

reactions are usually due to the paraaminobenzoic acid metabolite from esters or methylparaben (a preservative). Epinephrine and metabisulfite, often present in local anesthetics, can also cause adverse drug reactions. Vasovagal responses, tachycardia, lightheadedness, metallic taste, and perioral numbness can result from intravascular injection of the local anesthetic, epinephrine, or both (28). The most common immune-mediated reaction to local anesthetics is a delayed hypersensitivity reaction (Type IV reaction), or contact dermatitis (49).

Skin and challenge tests are used for diagnosis, and it is important to use preservative-free local anesthetics. There is no cross-reactivity between amide and ester local anesthetics, except in cases in which a preservative is the allergen. Although cross-reactivity occurs among esters, it is very unusual among amides.

### Muscle Relaxants

Muscle relaxants are the most common cause of anaphylaxis during anesthesia. Whereas the overall incidence is 1 in 6500 patients undergoing anesthesia with a muscle relaxant (7), muscle relaxants account for 69.2% of anaphylactic reactions during an anesthetic (5). IgE antibodies to the two quaternary or tertiary ammonium ions mediate anaphylaxis. Succinylcholine contains a flexible molecule that can cross-link two mast cell IgE receptors and, thus, induce mast cell degranulation. Succinylcholine is more likely to cause anaphylaxis than nondepolarizing muscle relaxants with a rigid backbone between their two ammonium ions (e.g., pancuronium or vecuronium) (6). The incidence of anaphylaxis is also more frequent with benzylisoquinolinium compounds than with aminosteroid compounds. Many over-the-counter drugs, cosmetics, and food products contain quaternary or tertiary ammonium ions that could sensitize people (50). Therefore, anaphylaxis may develop on the first exposure to a muscle relaxant in a sensitized patient. Cross-sensitivity between muscle relaxants occurs in up to 60% of patients (50-52). Furthermore, neostigmine and morphine also contain ammonium ions that may cross-react with muscle relaxants.

Another mechanism involved in adverse reactions to muscle relaxants, independent of and more common than IgE-mediated reactions, is direct mast cell degranulation that causes the release of histamine and other mediators (17). This histamine release is not immune mediated and does not require prior exposure. Benzylisoquinolinium compounds, such as D-tubocurarine, metocurine, doxacurium, atracurium, and mivacurium, are more likely to cause direct mast cell degranulation than aminosteroid compounds such as pancuronium, vecuronium, rocuronium, and

**Table 3.** Treatment of Perioperative Anaphylaxis

Management <sup>a</sup>	Action
Discontinuation of anesthetic or drug	Decreased vasodilation, decreased antigen delivery
100% Oxygen airway support	Increase oxygen delivery, maintain airway
IV fluids	Compensate for systemic vasodilation
Epinephrine	
5–10- $\mu$ g initial bolus up to 100–500 $\mu$ g for vascular collapse	Alpha <sub>1</sub> agonist
Start drip with 1 $\mu$ g/min for refractory hypotension	Beta <sub>2</sub> agonist
Diphenhydramine 25–50 mg	H1 receptor blocker (antihistamine)
Ranitidine 150-mg bolus or cimetidine 400-mg bolus	H2 receptor blocker
Albuterol 0.3% and ipratropium bromide 0.03% nebulization	Bronchial smooth-muscle relaxation
Corticosteroids	
0.5–1.0 mg/kg methylprednisolone	Prevent late and delayed symptoms
1–5 mg/kg hydrocortisone	

H1 = histamine 1; H2 = histamine 2.

<sup>a</sup> All doses are given for IV administration.

pipecuronium. Cisatracurium, a benzyliisoquinolinium compound and an isomer of atracurium, and succinylcholine have the lowest potency of direct mast cell activation (17,53,54).

Current controversy revolves around the potential for an increased incidence of anaphylaxis to rocuronium when compared with other muscle relaxants (7,55–57). The increased number of allergic reactions to rocuronium in Norway—55 reactions and 3 deaths over 4 yr—led to a “dear doctor letter” from the Norwegian Medicines Agency that recommended rocuronium’s withdrawal from routine practice and its use reserved for urgent intubations (57). There is a discrepancy between the reported incidence of anaphylaxis due to rocuronium in Norway (1 in 3,500 anesthetics) and the incidence noted in the United States (1 in 445,000 anesthetics; 80% of worldwide use) (57). This discrepancy has been attributed to multiple factors, including false-positive testing, increased use of the drug, statistical challenge, and, possibly, population genotype differences (58–60). Rocuronium may cause a wheal and flare response independent of mast cell degranulation. Levy et al. (58) demonstrated that intradermal skin testing with rocuronium at concentrations larger than  $10^{-4}$  M (609.70 g/L = 1 M) produced a positive wheal or flare response in 29 of 30 volunteers in the absence of mast cell degranulation. These authors suggest that skin testing with concentrations larger than  $10^{-4}$  M may account for some of the reported cases of rocuronium allergy reported in Europe (58). A report from Australia, using a 1:1000 dilution for intradermal skin testing, demonstrated that rocuronium is intermediate in its potential to cause anaphylaxis (59). This study also demonstrated that the increased incidence of anaphylaxis due to rocuronium in Australia is a result of its increased use (59). Statistical challenges, such as small sample size and biased reporting of newer drugs, may account for the increased incidence of rocuronium anaphylaxis (60).

Routine testing of muscle relaxants is not recommended because of a small positive predictive value (26,27). However, testing is recommended in patients with a history of anaphylaxis to muscle relaxants, and in these cases, intradermal skin tests and prick tests with undiluted muscle relaxants have a high predictive value (16). Skin testing with rocuronium should be performed at concentrations  $<10^{-4}$  M, whereas cisatracurium testing should be performed at concentrations  $<10^{-5}$  M (929.2 g/L = 1 M) (58). Cross-reactivity between muscle relaxants can be assessed by nonirritant intradermal titration. IgE radioimmunoassay (RIA) can be helpful, especially when intradermal tests are negative in the presence of a positive history of an allergic reaction to a muscle relaxant (61,62). The sensitivity of IgE RIA has been improved by coupling an analog of choline to a polymer (Sepharose) via an ether linkage (63). The morphine radioimmunoassay (RIA) has been found to be more sensitive than muscle-relaxant RIA for the detection of IgE antibodies to muscle relaxants (64).

### Opioids

Anaphylactic reactions to opioids are rare. Morphine is a tertiary amine that causes nonimmunological histamine release, and meperidine causes nonimmunological histamine release more often than any other opioid (16). There are reported cases of IgE-mediated reactions to these opioids (6,65,66). Fentanyl belongs to the phenylpiperidine group and does not cause nonimmunological histamine release (16), but there are a few reported cases of IgE-mediated anaphylaxis to fentanyl (67). There is cross-reactivity between different opioids of the same family, but not between phenylpiperidine derivatives (6,16).

IgE antibodies (IgE RIA or RAST) to morphine and meperidine have been detected, and skin tests

have been reported to be positive (6,65,66). However, morphine and meperidine cause histamine release when applied to the skin and may confound the results of positive skin tests. The few cases of anaphylaxis that have been reported with fentanyl have been confirmed with intradermal skin testing (67).

### Induction Drugs

**Barbiturates.** The incidence of anaphylaxis to thiopental is estimated to be 1 in 30,000 administrations, and previous exposure and female sex are associated with an increased incidence (68). Although IgE-mediated hypersensitivity reactions to thiopental, a thiobarbiturate, have been described, no reports of IgE-mediated hypersensitivity reactions to methohexital, an oxybarbiturate, have been described (16). Diagnosis is via the detection of thiopentone-reactive IgE antibodies by the RAST method (6,69,70). Alternative diagnosis is via skinprick or intradermal tests to thiopental with a dilution of 1:1000 to 1:10 of 2.5% thiopental (16).

**Propofol.** Propofol was originally formulated with the surfactant Cremophor EL, but a series of hypersensitivity reactions prompted a change in the formulation (36,71,72). Propofol (2,6-diisopropylphenol) is currently formulated in a lipid vehicle containing soybean oil, egg lecithin, and glycerol. The incidence of anaphylactic reactions with the new formulation is 1 in 60,000, although it has been reported to cause 1.2% of cases of perioperative anaphylaxis in France (73). A more recent report from the same group in France demonstrated that 2.1% of cases of intraoperative anaphylaxis are due to propofol (5). In a report of 14 patients with documented propofol allergy on first exposure, the 2 isopropyl groups of the propofol were thought to be the sensitizing epitopes (36). Isopropyl groups are present in dermatologic products and may account for anaphylactic reaction to propofol on the first exposure. In addition, there is a report of an anaphylactic reaction to propofol at the time of the third exposure to the drug (72). Phenol may have acted as an antigen and produced sensitization that led to an episode of anaphylaxis on reexposure. Most cases of drug allergy to propofol are IgE mediated, and specific IgE RIA and intradermal skin tests have been reported (36).

Propofol is formulated in a lipid emulsion containing 10% soybean oil, 2.25% glycerol, and 1.2% egg lecithin. The egg lecithin component of propofol's lipid vehicle is a highly purified egg yolk component (74). Ovalbumin, the principal protein of eggs, is present in the egg white. Skinprick and intradermal testing with propofol and with its lipid vehicle (Intralipid) were negative in 25 patients with documented egg allergy (74). The measles-mumps-rubella

vaccine does contain small amounts of egg-related antigens (ovalbumin), which are grown in cultures of chick-embryo fibroblasts. However, the measles-mumps-rubella vaccine has been given to egg-allergic children without any episodes of anaphylaxis (75). Therefore, current evidence suggests that egg-allergic patients are not more likely to develop anaphylaxis when exposed to propofol.

**Etomidate and Ketamine.** Allergic reactions to these two drugs are exceedingly rare (5,16). The most recent review of anaphylaxis during anesthesia did not include any cases related to these two drugs. Etomidate is perhaps one of the most immunologically safe anesthetics (76). Although there is a report of an anaphylactoid reaction with etomidate (77), no *in vivo* or *in vitro* diagnostic method is currently available (16). There are reports of IgE-mediated reactions to ketamine (78,79), and an intradermal skin test has been used in one patient (78).

**Benzodiazepines.** Allergic reactions to benzodiazepines are extremely rare. The Cremophor EL solvent was responsible for most reactions to benzodiazepines (80). Diazepam is more likely than midazolam to cause an anaphylactic reaction because of the propylene glycol solvent that replaced Cremophor EL. The active metabolite desmethyldiazepam may be responsible for the cross-reactivity with other benzodiazepines (16). Midazolam is a safe drug, because it does not have any active metabolites. Although anaphylactoid reactions to midazolam have been reported, no serologic or cutaneous testing was performed (81). In addition, midazolam has been used safely for the induction of anesthesia in patients with drug allergy (82,83). Cutaneous testing to benzodiazepines has been negative, and no serologic tests are clinically available.

### Inhaled Anesthetics

There are no reports of anaphylaxis related to volatile anesthetics. However, these drugs have been associated with hepatic injury due to an immune-mediated toxicity (84). Patients generate an antibody response (IgG antibodies) toward a covalently bound metabolite (trifluoroacetyl metabolite) of halothane, as detected by an enzyme-linked immunosorbent assay (ELISA) (85), and can present with a rash, fever, arthralgia, eosinophilia, and increased liver enzymes (86). Prior administration of halothane increases the incidence and severity of hepatitis. Although volatile anesthetic immune-induced hepatitis is much more common with halothane, other volatile anesthetics with trifluoroacetyl metabolites can induce immune hepatitis (87). Enflurane and isoflurane have been associated with an immune-mediated hepatic injury without prior exposure to halothane (84,88). Two reports support desflurane-induced hepatotoxicity

(89,90), but because of its decreased metabolism, desflurane is less likely to cause immune-mediated hepatitis. Sevoflurane is not metabolized to trifluoroacetyl metabolites and does not cause immune-mediated hepatitis.

### *Drugs Affecting Coagulation*

*Aprotinin.* Aprotinin is a naturally occurring polybasic polypeptide serine protease inhibitor used in cardiac surgical procedures to decrease blood loss and blood transfusions. Aprotinin is derived from bovine lung and is antigenic in humans. The incidence of allergic reactions to aprotinin given for cardiac surgery is 0.5% but may be as frequent as 2.5%–2.8% on repeat exposure (16,91,92). The risk of an allergic reaction on repeat exposure is increased when it occurs within 6 mo of the last aprotinin use. However, IgG and IgE antibodies take 10–14 days to form, and, therefore, reexposure to aprotinin in the first 24–36 h is less likely to lead to an adverse reaction (91,92). IgE and IgG antibodies have been demonstrated in patients exposed to aprotinin for the first time and are necessary for developing an anaphylactic reaction, but they lack specificity for predictive purposes (91). IgE antibodies are detected with RAST, whereas IgG antibodies are detected with ELISA (91,93). Although there are a few positive cases of cutaneous testing with aprotinin prick or intradermal tests after an allergic reaction, one study demonstrated that a preoperative aprotinin prick test was not predictive of an adverse reaction (91).

*Heparin.* Heparin is a strongly acidic, anionic, sulfated mucopolysaccharide, and it has a large molecular weight. It is derived from bovine or porcine lung or intestine and is antigenic in humans. Type I IgE-mediated hypersensitivity reactions to heparin are exceedingly rare, and skin tests are used for their diagnosis (94). Although there are no reported cases of anaphylaxis to low-molecular-weight heparin, low-molecular-weight heparin has *in vitro* and *in vivo* cross-reactivity with unfractionated heparin (16). Cross-reactivity has been demonstrated with delayed-type hypersensitivity reactions after performing patch, intradermal, and subcutaneous tests to unfractionated and low-molecular-weight heparin (95,96). The most common reaction to heparin is heparin-induced thrombocytopenia (HIT), a nonanaphylactic reaction mediated via IgG and IgM antibodies, and it occurs in up to 5% of patients receiving heparin for >5 days (16). HIT is less common with low-molecular-weight heparin, but there is also cross-reactivity with unfractionated heparin. Heparin-coated catheters and heparin in arterial and central venous catheters are best avoided in patients with a history of HIT or heparin-induced anaphylaxis.

*Protamine.* Protamine sulfate is a strongly alkaline, polycationic, small molecule extracted from salmon sperm and used to reverse the anticoagulant effects of heparin. Exposed patients (0.4%–0.76%) can develop an allergic reaction to protamine, and the risk is increased in patients previously exposed to protamine (97,98). Some forms of insulin, such as neutral protamine hagedorn and protamine-zinc insulin, contain protamine, and there is an increased risk for a protamine reaction in diabetic patients exposed to neutral protamine hagedorn and protamine-zinc insulin (99). There is a theoretical risk that patients allergic to fish or those who are infertile or vasectomized are more likely to develop an allergic reaction to protamine (100), because protamine is extracted from salmon sperm. Whereas earlier reports suggest that autoantibodies to sperm may develop after it is reabsorbed in infertile or vasectomized men (101,102), more recent reports have failed to demonstrate an association between protamine allergy and vasectomy, infertility, or fish allergy (16,103). Others have demonstrated the presence of protamine-specific IgG antibody in 29% of vasectomized men and the absence of these antibodies in control patients (104). However, although the presence of these antibodies is more common in patients who have a protamine reaction, it does not imply a cause-and-effect relationship (105).

IgE- and IgG-mediated hypersensitivity, complement activation, nonimmunologic histamine release, and augmentation of thromboxane leading to an increase of the pulmonary artery pressure have been documented (99,106,107). Reactions to protamine include urticaria and systemic hypotension with pulmonary vasoconstriction. Protamine can cause a nonimmunologic dose-related decrease in blood pressure, which is worse when the drug is given rapidly. Cutaneous testing will identify IgE-mediated sensitivity (99). Protamine-specific IgE and IgG antibodies can be measured by solid-phase immunoassay, ELISA, and RAST.

### *Antibiotics*

*Penicillin, Cephalosporins, and Other  $\beta$ -Lactam Antibiotics.* These are the most commonly used antibiotics during the perioperative period and perhaps some of the most commonly used drugs overall. Penicillin is the most common cause of anaphylaxis in the general population and may account for as many as 75% of anaphylactic deaths in the United States (108). Although most allergic reactions to penicillin occur in patients with a history of a prior reaction to penicillin, one review of the literature found that only 10%–20% of patients who report a penicillin allergy have a documented allergy (109). Most patients usually refer to side effects such as gastrointestinal symptoms or do

not remember exactly why they are "allergic" to penicillin. They may remember that a health-care provider or family member told them not to take penicillin or that someone in their family had a reaction when they received penicillin. Taking a detailed history of the reaction to penicillin will remove most of the questionable cases.

Type I IgE-mediated sensitivity is the most common mechanism in patients with a documented anaphylactic episode or allergy workup. Diagnosis is performed with prick and intradermal skin testing by using minor and major determinants. It has been recommended to skin-test those patients with clinical symptoms consistent with a Type I IgE-mediated reaction (109). The predictive value of a negative penicillin test is 97% because only 3% of patients with a negative skin test who are given penicillin will develop a limited skin rash. Serologic testing with RAST and ELISA do not detect IgE antibodies to minor determinants (16,108). Although Pharmacia has recently introduced a test for specific IgE against penicillin minor determinants in their UniCap system, it is not available in the United States (110,111). Cephalosporin skin testing is available in Europe but not in the United States. Cutaneous testing to cephalosporins indicates that, in some patients, side-specific chain IgE can develop in the absence of penicillin allergy (112).

Some allergy books still quote an 8%–10% risk of cross sensitivity between penicillins and cephalosporins and attribute it to the  $\beta$ -lactam ring that is shared by both (16). However, most of the reported reactions of cross-sensitivity consist of rashes that are not immunologic in origin. In addition, earlier generations of cephalosporins contained trace amounts of penicillin, and this may account for some of the adverse reactions (113). A review of this subject found that patients with an allergy to penicillin were more likely (threefold) to experience an anaphylactic reaction to any other drug (113). Although some experts state that it is safe to administer cephalosporins to penicillin-allergic patients and that penicillin skin tests are not indicated (113), others have recommended avoidance of cephalosporins in those with positive penicillin skin tests or anaphylaxis (109,114,115). Goodman et al. (115) performed a retrospective chart review of intraoperative anesthesia records over a 14-mo period and demonstrated that cephalosporins can be given to patients who claim to be allergic to penicillin. However, a limitation of this study is that patients who reported anaphylaxis to penicillin were excluded.

*Vancomycin.* Vancomycin is a complex tricyclic glycopeptide and is often the antibiotic used in cases of penicillin resistance or allergy. The classic "red man syndrome" consists of flushing, pruritus with an erythematous rash, and hypotension and occurs in 5%–14% of adults. It usually occurs during rapid vancomycin injection, is due to nonimmunologic histamine

release, and accounts for most reactions (116). Management of the red man syndrome includes the use of antihistamines, a slow infusion rate, and division of the total dose. Although it is extremely rare, there are reported cases of IgE-mediated hypersensitivity reactions to vancomycin (16,117). Skinprick tests are usually negative, and there are a few reported positive intradermal skin tests (16). There is a report of successful desensitization after an episode of anaphylaxis (117).

*Bacitracin.* Bacitracin is a polypeptide complex antibiotic that is used topically or as an irrigation solution. Although contact dermatitis is the most common reaction to this drug, there are reports of intraoperative anaphylaxis due to bacitracin irrigation of surgical sites (118,119). A Type I IgE-mediated reaction is diagnosed by skinprick tests.

*Others.* Other antibiotics that are often used in the operating room and that may rarely trigger an anaphylactic reaction include clindamycin, gentamicin, and metronidazole. Clindamycin is used against Gram-positive and anaerobic bacteria and usually causes a contact dermatitis. No specific IgE antibody has been found, and skinprick and intradermal skin tests are negative (16). Gentamicin is a broad-spectrum aminoglycoside often used in patients at risk for endocarditis, whereas metronidazole is a nitroimidazole derivative used against anaerobic infections. IgE-mediated hypersensitivity, although previously reported, is extremely rare in both cases (16).

### *Other Potential Antigens*

*Povidone-Iodine.* Povidone-iodine (betadine) is the most common topical antiseptic solution used in the United States, and there are only a few reports in the literature of anaphylaxis to this drug (120). A positive skinprick test to povidone-iodine and povidone extract and the presence of serum-specific IgE to povidone demonstrate a Type I IgE-mediated hypersensitivity. Allergic contact dermatitis, a Type IV cell-mediated hypersensitivity reaction, is more common with povidone-iodine. Patch testing to diagnose this type of reaction is best done with dried 10% povidone-iodine solution, because long exposure to povidone-iodine in the aqueous state may yield a false-positive result due to direct skin irritation (121).

*Iodinated Contrast Material.* Contrast drugs do not undergo substantial metabolism and contain small amounts of free iodine. Whereas povidone-iodine contains a loose complex of iodine and surfactant (polyvinylpyrrolidone), iodinated contrast drugs contain covalently bound iodine (122). Patients with adverse reactions to povidone-iodine are not at risk for adverse reactions to iodinated contrast dyes. Reactions to contrast drugs have been attributed to ionic side

groups, osmolality, protein binding, partition coefficients, and pi electron density. Most reactions to non-ionic contrast drugs are minor events such as flushing or skin rashes, appear in a significant number of patients, and are preventable by premedication with antihistamines and steroids (123). These reactions are due to nonspecific histamine release and are not immune in origin.

Anaphylactoid reactions to hyperosmolar, ionic, iodinated contrast material (ICM) are rare but are more common than those to nonionic material. These reactions account for 2.4%–3.1% of all adverse reactions, are more frequent in patients who have experienced a previous reaction, and are not prevented by premedication with steroids (124,125). Other important risk factors include asthma, atopy, cardiac disease, and  $\beta$ -blocker use (126). Female sex and age increase the severity of anaphylactoid reactions to ICM (126). Specific IgE (IgE RIA) against ICM has been detected in a few patients with positive skin tests (127).

*Chlorhexidine.* Chlorhexidine is widely used all over the world as a skin disinfectant before surgery or invasive procedures and in the general population in mouthwash or for disinfecting minor scratches (128). Therefore, patients may become sensitized before a surgical procedure. A report in the literature describes four patients with a history of minor rashes or faints in connection with previous chlorhexidine exposure who developed severe hypotension requiring epinephrine after subsequent exposure (128,129). Skin testing (prick test with 0.5% or intradermal test with 0.0002% chlorhexidine) was positive for chlorhexidine, demonstrating a Type I IgE-mediated reaction (129).

*Latex.* NRL is the milky, white fluid derived from the *Hevea brasiliensis* tree and is a component of most sterile and nonsterile gloves used in the perioperative period. NRL is often contained in other operating room products, including tourniquets, face masks, Ambu bags, and Foley catheters. The use of universal precautions, implemented by the US FDA in the 1980s in response to the human immunodeficiency virus, led to a dramatic increase in the use of latex gloves. The high demand for latex gloves led to a decrease in manufacturing time, which in turn led to an increased protein content in gloves. This led to a dramatic increase in the incidence of latex anaphylaxis, a Type I IgE-mediated reaction. It is beyond the scope of this article to provide a complete review of latex allergy, because other publications have done so (130).

It has been reported that close to 20% of cases of intraoperative anaphylaxis are due to latex, and the incidence of cases of anaphylaxis due to latex has been increasing in the past few years (6,16). However, one report suggests that the incidence of intraoperative anaphylaxis cases due to latex may be decreasing (12.1%), in part because of an increased awareness of the problem and the avoidance of latex gloves (5).

High-risk groups include health-care workers or other workers with occupational exposure; patients with multiple surgical procedures, including those with spina bifida; atopic individuals; and those with a history of fruit or food allergies (37,130). Common fruits or foods that cross-react with latex include mango, kiwi, chestnut, avocado, passion fruit, and banana. Latex exposure is more likely with parenteral or mucous membrane exposure but can also occur with cutaneous contact or via latex aeroallergens. In a study of anesthesiologists exposed to NRL, 12.5% presented with positive latex allergen-specific IgE antibody levels (Pharmacia-Upjohn CAP system) or skinprick test (nonammoniated NRL reagent pending approval by the FDA), and they had a prevalence of contact dermatitis of 24% (131). Although latex sensitization (asymptomatic latex allergy) was present in 12.5% of anesthesiologists, latex allergy with clinical symptoms was present in only 2.4% of anesthesiologists (131).

No standardized antigens for skin testing are currently available in the United States, but these are available in Europe and are considered the gold standard test. Latex-specific IgE can be detected in the patient's serum by RAST and the enzyme-allergosorbent test (37,130). Avoidance is the only effective treatment at the present time and consists of latex-free gloves and operating room equipment (132,133). It has also been recommended to perform surgical procedures in latex-allergic patients as the first case of the day to decrease the levels of latex aeroallergens (6). Two reports describe subcutaneous desensitization to latex, but some of these patients developed serious anaphylactic reactions (42,43). More recently, there have been reports of latex allergy desensitization by a repeated contact exposure protocol (44) or by rush (4-day) sublingual desensitization (45). None of these patients developed any signs of latex anaphylaxis.

*Colloids.* Colloids are plasma expanders used to restore intravascular fluid volume and for distension and irrigation during gynecologic endoscopic procedures (dextran 70). Albumin, dextran, hetastarch, and gelatin are colloids often used in the operating room. The incidence of allergic reactions to colloids seems to be increasing. Whereas earlier reports from the 1980s described an incidence of 0.03% for dextran and hetastarch (134,135), a French study from 1994 (136) demonstrated an overall frequency of 0.22%. Gelatins (0.34%) and dextrans (0.27%) were more likely to cause an allergic reaction than albumin (0.1%) or hetastarch (0.06%) (136). Individuals with prior drug allergies were three times more likely to develop anaphylaxis, and males were more likely than females to develop an allergic reaction (136). Egg allergy does not appear to be a contraindication to the use of albumin, because the principal egg protein, ovalbumin (45 kd), is different from human serum albumin (67 kd) (137).

A report from France demonstrated that 2.9% of intraoperative anaphylaxis cases were due to colloids (5).

IgE-mediated anaphylaxis has been proven by demonstrating IgE antibodies and positive intradermal tests against gelatins (136). Increased circulating IgG dextran-reactive antibodies are found in most adults with dextran anaphylaxis, and ELISA is used for detecting hetastarch- and dextran-reactive antibodies (IgG and IgM) in human sera (138). Hetastarch appears to be the safest colloid, because the incidence of IgG antibodies against hetastarch is very rare in the general population (139,140). There is no known cross-reactivity between the different colloids, so a particular allergy to one should not preclude the use of a different colloid.

**Isosulfan Blue Dye.** Isosulfan blue, a rosaniline dye of the triphenylmethane type, is the 2,5-disulfonated isomer of patent blue dye and is the only dye of its type approved for lymphatic visualization by the FDA (141). Intraoperative lymphatic mapping and sentinel lymph node biopsy, often used for breast cancer and melanoma, are made possible with intradermal or intraparenchymal 1% isosulfan blue dye, which traces the lymphatic drainage of the cancer for the detection of occult nodal metastases. The drug circulates through the venous system after lymphatic uptake, and it is common for some patients to turn blue temporarily or to have a transient decrease in the oxygen saturation. Allergic reactions to isosulfan blue dye were first reported in 1985 (142) but are more common today because of the increased use of this dye for lymphatic mapping. The incidence of allergic reaction ranges from 1% to 2% (143,144), and severe anaphylactic reactions requiring vigorous resuscitation have been reported 15–30 min after injection of isosulfan blue (143).

Isosulfan blue dye anaphylaxis is an IgE-mediated event, as confirmed by positive skin tests in patients with an episode of intraoperative anaphylaxis after the injection of the dye (144). Allergic reaction to isosulfan blue is mediated by histamine release, and intradermal testing with 0.02 mL of 1% isosulfan blue dye (from 1:10,000 to 1:100 dilutions) produces a pruritic wheal and flare response (144,145). Undiluted prick tests are also positive in cases of anaphylaxis to isosulfan blue (144). It has been recommended to avoid this dye in the future after an episode of anaphylaxis or to use pretreatment if no alternative is available (145). Further studies are recommended to evaluate the effectiveness of pretreatment with histamine 1 and histamine 2 blockers and corticosteroids in patients with a prior episode of anaphylaxis due to isosulfan blue dye. The decrease in the oxygen saturation after the use of 1% isosulfan blue dye is a common finding and should not preclude its future use.

## Summary

Adverse drug reactions or side effects are usually expected, are dose dependent, and occur at therapeutic doses. Anaphylactic and anaphylactoid reactions are unexpected and dose independent and can occur at the first exposure to drugs used during anesthesia. The presentation of anaphylactic and anaphylactoid reactions is clinically indistinguishable. Anaphylaxis is IgE dependent and is detected by the presence of positive *in vitro* and *in vivo* tests and the release of tryptase, a mast cell protease, during the reaction. Anaphylactoid reactions occur through a direct nonimmune-mediated release of mediators or complement activation and are IgE independent but can be associated with mast cell and/or basophil activation and increased tryptase.

Although anaphylaxis is a rare intraoperative event, most drugs used in the perioperative period can lead to anaphylaxis. Unfortunately, documentation of anaphylaxis is often lacking because the cause and effect relationship is often hard to prove and because the diagnosis is not easy to make with the patient under anesthesia. Furthermore, only a minority of patients get referred for allergy testing to confirm the offending drug. Muscle relaxants and NRL are the most common anesthetic drugs or substances that may lead to anaphylaxis. Prevention is the most important component to decrease the incidence of anaphylaxis. Documentation of anaphylaxis during anesthesia, referral to an allergist for identification of the causative drug, and appropriate labeling of the patient are essential to prevent future episodes of anaphylaxis.

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## REVIEW ARTICLE

# Ankylosing spondylitis: recent developments and anaesthetic implications

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### Summary

Ankylosing spondylitis can present significant challenges to the anaesthetist as a consequence of the potential difficult airway, cardiovascular and respiratory complications, and the medications used to reduce pain and control the disease. There is also an increased risk of neurological complications in the peri-operative period. Awake fiberoptic intubation is the safest option in those patients with a potentially difficult airway as it allows continuous neurological monitoring while achieving a definitive airway. Neurophysiological monitoring (somatosensory and motor evoked potentials) should be considered in patients undergoing surgery for cervical spine deformity. The medical management of the disease has improved with the use of anti-tumour necrosis factor- $\alpha$  agents. There is potential for increased wound infection in patients taking these drugs. This article reviews the anaesthetic issues in patients with ankylosing spondylitis. The challenge to the anaesthetist is in the understanding of these issues so that appropriate management can be planned and undertaken.

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Accepted: 19 October 2008

Ankylosing spondylitis (AS; also known as Bechterew disease; Marie Strumpell disease), an autoimmune seronegative spondyloarthropathy, is a painful chronic inflammatory arthritis punctuated by exacerbations ('flares') and quiescent periods. It primarily affects the spine and sacroiliac joints and eventually causes fusion and rigidity of the spine ('bamboo spine'). Ankylosing spondylitis varies widely in prognosis and outcome. It is also associated with ulcerative colitis, Crohn's disease, psoriasis and Reiter's syndrome (uveitis). Recent experience with anti-tumour necrosis factor  $\alpha$  agents clearly indicates that these biological agents are effective in treating ankylosing spondylitis.

AS can present significant challenges to the anaesthetist as a consequence of the potential difficult airway, cardiovascular and respiratory complications, and the medications used to reduce pain and control the disease.

This article aims to provide an overview of AS and the recent advances in its management with anti-tumour necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) agents and to highlight the key practical issues of relevance to the anaesthetist.

### Epidemiology

Ankylosing spondylitis occurs in 1% of men and 0.5% of women in Caucasians [1–4]. It is more prevalent in males with a peak age onset of 20–30 years [5, 6]. Men tend to have more severe spinal and pelvic disease, whereas women have peripheral joint (knees, wrists, ankles, hips) involvement [7]. Symptoms develop before the third decade of life in 80% of patients with AS. Less than 5% of patients develop AS in the fourth decade. Juvenile onset (age 10–16 years) AS is a more severe disease and occurs in 4% of AS.

### Pathogenesis

The initiating cause of AS is not known but environmental factors (unidentified bacterial or viral agents), susceptibility genes (HLA-B27), gender, age and ethnicity play a role [8]. Overall, sporadic AS is more severe than familial disease. Although only 5% of HLA-B27 positive individuals develop AS, 90–95% of patients with AS possess HLA-B27 alleles. HLA-B60, MHC genes

including MICA, HLADRB1/MHC Class II alleles, tumour necrosis factor- $\alpha$ , IL-1ra and low molecular weight proteasome are all implicated [9]. In 2007, an international collaborative research team reported the discovery of two genes (ARTS1 and IL23R) that are associated with AS. Together with HLA-B27, these two genes account for roughly 70% of the overall incidence of the disease [10]. The presence of HLA-B27 is estimated to account for no more than 50% of the genetic susceptibility to AS. One study showed that onset of symptoms of AS was earlier in HLA-B27 positive patients compared with HLA-negative patients [11, 12]. Genes in the chromosomes 18, 20 and 21 are responsible for increased severity of disease in sporadic AS, whilst susceptibility genes in chromosomes 1, 2, 9, 10, and 16 are implicated in familial AS. There are at least 23 subtypes of HLA-B27 (B\*2701–B\*2723). Some subtypes have a protective role, for example, HLA-B\*2709 is found in healthy individuals from Sardinia, and HLA-B\*2706 is negatively associated with AS [12].

Two hypotheses, the arthrogenic peptide hypothesis and the HLA-B27 folding hypothesis have been proposed [9]. The arthrogenic peptide hypothesis postulates that when an individual with HLA-B27 is exposed to an antigenic pathogen (e.g. Epstein–Barr virus protein, human vasoactive intestinal peptide receptor-1 and a peptide derived from type VI collagen), a cytotoxic T cell mediated autoimmune response occurs in the joints [13]. The HLA-B27 folding hypothesis suggests that abnormal conformation or misfolding of the HLA-B27 heavy chains results in the accumulation of unfolded proteins in the endoplasmic reticulum. This generates pro-inflammatory cytokines and chemokines that activate nuclear factor  $\kappa\beta$ , resulting in transcription of genes encoding cytokines, tumour necrosis factor  $\alpha$ , and interleukins IL-1 and IL-6, that are responsible for the inflammation in the joints. Synovial fluid mononuclear cells of patients with spondyloarthropathy provide evidence of this process [14].

Gram negative bacteria such as *Campylobacter*, *Salmonella*, *Shigella flexneri* and *Yersinia* cause reactive arthropathy. Of these patients who have reactive arthritis and possess HLA-B27, approximately 10–20% develop AS 10–20 years later. In patients with Crohn's disease, 54% of HLA positive patients develop AS whilst only 2–6% of HLA negative patients develop AS. It is postulated that leakage of gut mucosa causes an interaction between the immune system with gut bacteria [15]. However, there is no clear evidence as to the role of bacteria in development of AS.

Both innate and adaptive immune responses play a role in spondyloarthritis. CD4+ and CD8+ T cell infiltrates are found in synovial fluid, sacroiliac joint biopsies and in

peripheral blood of patients with AS. TNF- $\alpha$  is over-expressed in sacroiliac joints of patients with AS and this provides the basis of the use of anti TNF- $\alpha$  agents in the treatment of AS [16].

### Clinical features

Ankylosing spondylitis is characterised by sacroilitis, peripheral arthropathy, enthesopathy (pathological changes at the sites of insertion of ligaments and tendons), and the absence of rheumatoid factor. The symptoms of AS usually begin between the ages of 15 and 40 years with persistent pain and morning stiffness (worse at rest but improves with exercise) in the lower spine and the sacroiliac joints. The mortality of patients with AS is 1.5–4 times higher than the general population [17].

Histologically, granulomatous inflammatory tissues in the affected joints are infiltrated by plasma cells, lymphocytes, mast cells, macrophages and chondrocytes. These are gradually replaced by fibrocartilage and progress to bony fusion in about 70% of patients. The absence of any specific pathognomonic clinical feature or laboratory test tends to delay the diagnosis by 7–10 years from onset of symptoms. Extensive ectopic bone formation occurs within the inflamed vertebral ligaments, leading to syndesmophyte formation. This is compounded further by the increased incidence of osteoporosis in patients with AS, which, in the long term, can lead to compression fractures resulting in a rigid hyperkyphotic deformity ('hump'). This greatly increases the iatrogenic risk of spinal cord injury when transferring patients or performing fracture reduction manoeuvres. The rigid, kyphotic spinal deformity and peripheral arthritis cause an unsteady gait, and an increased susceptibility to falls leading to fracture.

Complications of severe spinal disease include fractures with little or no history of trauma, collapse of vertebral end-plates (spondylodiscitis) and spinal nerve root compression. Cervical fractures which occur commonly at C5–6 are often overlooked because they occur with minimal trauma or hyperextension. Clinically significant atlanto-axial subluxation occurs in 21% of patients with AS. About 47% of AS patients with vertebral compression fractures have a neurological complication ranging from paraesthesia to loss of muscle strength [17–19].

The most common joints affected are the hips and shoulders. End stage hip disease requiring hip replacements occurs in 20% of patients with juvenile onset AS, in about 10% of patients with onset in late teens, and rare when the onset is in the late 20–30s. Peripheral joint involvement occurs in 50% of patients and is more common in patients with concomitant psoriasis [12].

Temporomandibular joint involvement causes limited mouth opening in 10% of patients and this increases to 30–40% patients with long standing disease. The disease rarely causes arthritis of the cricoarytenoid joint, but can lead to dyspnoea, hoarseness and vocal cord fixation. AS often affects costovertebral and costo-transverse joints (less commonly the manubriosternal and costochondral joints) causing local tenderness and pain on coughing or sneezing. Other features include plantar fasciitis and Achilles tendonitis [7].

Extra-articular manifestations are associated with more severe AS and those relevant to anaesthesia involve the cardiovascular system, lungs and skin. Cardiovascular complications associated with AS are seen infrequently. Fibrous proliferation of the intima of the aorta can result in aortic insufficiency. It occasionally affects the mitral valve [20]. Involvement of the Purkinje fibres causes conduction defects and there is an increased risk of myocardial infarction. Respiratory complications include upper lobe fibrosis and reduced chest expansion due to involvement of the costovertebral joints. In patients with restricted chest movement, vital capacity and functional residual capacity are decreased. Owing to lung fibrosis, chest X-rays may show apical fibrosis while pulmonary function testing may reveal a restrictive lung defect. Anterior uveitis (iridocyclitis) occurs in 20–40% of AS patients, psoriasis in 9% and inflammatory bowel disease in up to 6% of patients with AS. Anterior uveitis classically presents with sudden onset of blurred vision associated with eye pain, redness and photophobia. Some can progress to become chronic uveitis with permanent visual impairment [21]. Neurological effects include spinal cord compression, cauda equina syndrome, cervical spine fracture, focal epilepsy, vertebrobasilar insufficiency and peripheral nerve lesions. Spinal fractures can lead to acute epidural haematoma. Other systemic effects include fatigue, weight loss and fever. Most (85%) male patients complain of symptoms of prostatitis at some point in the disease [22].

## Diagnosis

The diagnosis of AS is made on clinical and radiological criteria [23]. Radiological evidence of sacroiliitis is a late feature of the disease. Earlier diagnosis and treatment may reduce the severity of the effects of the disease [24]. In 2006, Rudwaleit et al. [25] proposed diagnostic criteria for inflammatory back pain in patients < 50 years with chronic back pain that may lead to an earlier diagnosis of AS. These included morning stiffness > 30 min, improvement in back pain with exercise but not rest, awakening because of back pain during the second half of the night only, and alternating buttock pain. The criteria

**Table 1** Modified New York criteria for AS [23]. Diagnosis of AS requires one radiological criterion with at least one clinical criterion. Probable AS > 3 clinical criteria present or radiological criteria.

<b>Clinical criteria</b>	
Low back pain > 3 months duration, improves with exercise and is not relieved by rest	
Limitation of motion of the lumbar spine in sagittal and coronal planes	
Limitation of chest expansion relative to normal values corrected for age and sex	
<b>Radiological criteria</b>	
Bilateral sacroiliitis – grade 2 (sclerosis with some erosions) or higher	
Unilateral sacroiliitis – grade 3 (severe erosions, pseudodilatation of joint space and partial ankylosis) or grade 4 (complete ankylosis)	

required for diagnosis of AS are summarised in Table 1. Mild normochromic anaemia and raised IgA serum levels may be present. ESR is elevated in 50% of patients but may be normal even in severe disease. A raised alkaline phosphatase is found in severe disease. The correlation between inflammatory markers and AS is poor with only half of patients with AS having a raised CRP [26]. HLA-B27 may be useful in diagnosis of early spondyloarthritis. Most patients with AS are HLA-B27 positive with a 50% chance of transmitting the antigen to their children. Children who are HLA-B27 positive have a 33% risk of developing AS.

Radiographs of the sacroiliac spines appear normal in the early phase of the disease and structural changes only become apparent after many years. As the disease progresses, interspinous ligaments become ossified and bony bridges form between the vertebrae of the lumbar spine giving the classic bamboo spine appearance on X-ray. The characteristic bamboo spine and fused sacroiliac joints on radiographs are a late presentation. Magnetic resonance imaging (MRI) is useful in the early diagnosis of AS because it can show inflammation, bone marrow oedema and erosions at the sacroiliac joints and at cartilage/bone interphase before they can be observed on plain radiographs. It is a highly specific and sensitive tool that can detect active inflammatory axial disease, especially in combination with scintigraphy used to screen for other affected sites. MRI is useful for monitoring the progression of the disease and can predict the development of structural radiographic change 3 years before they occur (positive predictive value of 60%). In a prospective study of the role of MRI, quantitative sacroiliac scintigraphy and plain radiography in detecting active sacroiliitis in 44 patients, MRI was found to be the most sensitive imaging technique (95% sensitive vs 48% sensitive for scintigraphy and 19% sensitive for plain radiographs) [27, 28].

## Management

The main aims of the management of AS patients are to relieve pain, reduce inflammation and maintain good posture and function. Early diagnosis and treatment may prevent spinal deformity. Traditionally, non-steroidal-anti-inflammatory-drugs (NSAIDs), education, exercise and physical therapy are the cornerstones of management for AS. Anti-TNF- $\alpha$  agents are novel drugs that are relatively efficacious in the management of patients who have failed conventional treatment. Joint replacement and spinal surgery is considered in patients with severe advanced disease associated with refractory pain and disability. Daily hydrotherapy and swimming can improve general fitness while protecting the joints. Although a Cochrane review concluded that there is little evidence for the effectiveness of non-pharmacological management, expert opinion and clinical experience suggest that individuals benefit from intensive physiotherapy [29].

### Conventional drug therapy

Randomised controlled trials demonstrated that NSAIDs and cyclooxygenase-2 specific inhibitors were useful in controlling spinal pain [30]. In addition, NSAIDs may have a protective role against structural damage in the spine because they inhibit the synthesis of prostaglandin E2 which promotes bone growth.

Disease-modifying antirheumatic drugs such as methotrexate, sulfasalazine and leflunomide may provide symptomatic relief of symptoms of synovitis in peripheral joints but not spinal pain (caused by enthesitis) in axial joints [22]. Bisphosphonates may have a beneficial effect on underlying osteoporosis, the inflammatory process and spinal symptoms [31]. Thalidomide has also been used with some success but its toxic side effects has prevented its widespread use.

Intra-articular corticosteroid injection (guided by arthrography, CT or MRI) of an inflamed joint is safe and can provide rapid and long-lasting relief. Oral steroid therapy is less effective in patients with AS compared to patients with rheumatoid arthritis [32]. Pulsed intravenous methylprednisolone (0.5 mg) may provide short-term benefits by enabling the patient to obtain more benefit from physiotherapy [12].

### Novel drugs

Anti-TNF- $\alpha$  drugs are the first drugs that have been shown in large randomised, placebo controlled, double blind trials to benefit patients with AS. Other cytokine based therapies in various stages of clinical development include PEG-sTNFR1 and CDP-870 [33]. TNF- $\alpha$  is a multifunctional cytokine involved in acute and chronic inflammation, antitumour responses and infection. TNF

messenger RNA is found in synovial biopsies of sacroiliac joints of patients with AS. TNF- $\alpha$  binds to cell membrane receptors and this results in adhesion molecule expression for leucocytes and vascular cell adhesion, chemoattraction, monocyte chemotactic protein and tissue degradation. It also promotes the generation of T cells and plays an important role in antigen presenting cell function and in regulating apoptosis of T cells. TNF- $\alpha$  increases inflammation in AS as well as other related spondyloarthropathies, psoriasis, and inflammatory bowel disease. Anti-TNF- $\alpha$  agents render TNF- $\alpha$  biologically inactive and diminish their biological responses. These drugs are also approved for severe and active rheumatoid arthritis that is refractory to conventional treatment, active juvenile idiopathic arthritis, psoriatic arthritis, severe Crohn's disease with inadequate response to conventional therapies, and severe psoriasis.

The three anti TNF  $\alpha$  agents available for clinical use are infliximab (Remicade<sup>TM</sup>; Centocor Inc., Malvern, PA, USA), adalimumab (Humira<sup>TM</sup>; Abbott Laboratories, Abbott Park, IL, USA) and etanercept (Enbrel<sup>TM</sup>; Immunex Corporation, Seattle, WA, USA). Infliximab and adalimumab are monoclonal antibodies that bind specifically to human TNF- $\alpha$  and inhibit it binding to its receptors, neutralising its biological activity. These two monoclonal antibodies also inhibit TNF- $\alpha$  production by binding to TNF expressing cells such as macrophages. Etanercept is a fusion protein that binds to TNF- $\alpha$  and TNF- $\beta$  and neutralises these two cytokines but does not inhibit production from the cells. Patients usually improve within 2 weeks of commencing therapy [33].

Large-scale randomised, double blind, placebo controlled trials demonstrated that the TNF- $\alpha$  blockers suppress disease activity, improve physical function, slow disease progression and may achieve remission of the disease. MRI studies showed reduced spinal inflammation [34]. The erythrocyte sedimentation rate and C-reactive protein levels decrease following treatment with anti-TNF- $\alpha$  agents. Symptoms relapse when treatment with infliximab and adalimumab is ceased. Unlike infliximab and adalimumab, etanercept is not effective for the treatment of gastrointestinal symptoms and uveitis associated with AS. Recent international experience with anti-TNF- $\alpha$  agents suggests that these drugs are effective in treating patients with AS. Short term benefits include significant improvements in the control of the disease, function and quality of life. Younger patients with a shorter disease duration respond better to anti-TNF- $\alpha$  agents [35]. The pharmacological properties of the anti-TNF- $\alpha$  agents are summarised in Table 2 [36–39].

There is a twofold increase in the risk of bacterial infections in patients taking TNF- $\alpha$  blockers especially

**Table 2** Anti TNF- $\alpha$  agents [49, 52].

Drug	Comments
Infliximab	Chimeric monoclonal antibody (human and murine proteins) Dose: 5 mg.kg <sup>-1</sup> intravenous infusion every 6–8 weeks Half life: 8–10 days Effective in AS and concomitant IBD, uveitis and psoriasis
Adalimumab	Human monoclonal antibody Dose: 40 mg subcutaneous injection every other week Half life: 10–20 days Effective in AS, psoriasis and IBD
Etanercept	Human fusion protein Dose: Subcutaneous injection weekly (50 mg) or biweekly (25 mg) Half life: 5 days Effective in psoriasis but less efficacious for uveitis and IBD

IBD, immune bowel disease.

with adalimumab, which causes a longer period of immunosuppression. *Mycobacterium tuberculosis* (TB) is reported most frequently, with a preponderance of extrapulmonary tuberculosis. Patients should therefore be screened (Mantoux test and chest X-ray) for tuberculosis before starting treatment. Active or latent TB must be treated prior to commencing a TNF- $\alpha$  blocker. TNF- $\alpha$  blockers can reactivate chronic hepatitis B if concurrent antiviral therapy is not administered. Preliminary data suggest it may be safe and even beneficial in patients with chronic hepatitis C. The increased risk of serious infection in patients taking TNF- $\alpha$  blockers has implications for those patients undergoing surgery.

The most common side effects are injection site reactions to drugs administered subcutaneously and infusion reactions with infliximab. TNF- $\alpha$  blockers can induce a range of autoimmune neurological diseases such as Guillain–Barre syndrome and multifocal motor neuropathy. These drugs should be avoided in patients with pre-existing demyelinating diseases such as multiple sclerosis because of a risk of exacerbating demyelination in these patients. Vasculitis (a type III hypersensitivity reaction) is a very rare but serious complication associated with TNF- $\alpha$  targeted therapies. Paradoxically, anecdotal reports suggest that TNF- $\alpha$  blockers may be effective in the treatment of various types of vasculitis [40–42]. Large phase II and III trials have shown that TNF- $\alpha$  blockers should be avoided in patients with advanced cardiac failure (New York Heart Association class III–IV) because they may worsen the prognosis. The role of the anti-TNF agents in the incidence of lymphoma is debatable. The only study to investigate the rate of lymphoma in

**Table 3** Contraindications for the use of TNF- $\alpha$  blockers [49].

Absolute contraindications	Active infections (including joint infections, infected prosthesis within previous 12 months) or severe sepsis Indwelling catheter Previous, untreated tuberculosis Moderate to severe congestive heart failure Multiple sclerosis or optic neuritis Combination treatment with anakinra (IL-1 receptor antagonist) Active or history of malignancy in the last 10 years (except basal cell carcinoma)
Relative contraindications	Pregnancy Lactation HIV, hepatitis B, hepatitis C infection

**Table 4** Criteria for initiating anti-TNF therapy in ankylosing spondylitis [44].

Diagnosis	Modified New York criteria for definitive AS fulfilled
Active disease	Active disease > 4 weeks BASDAI $\geq$ 4 (range 0–10) and an expert opinion
Treatment failure after trial of:	Non steroidal anti-inflammatory drugs (NSAIDs) $\geq$ 2 NSAIDs for a minimum of 3 months at maximum recommended or tolerated dose or < 3 months if treatment withdrawal because of intolerance/toxicity/contraindications Disease Modifying Anti-rheumatic Drugs – no response to sulfasalazine in patients with persistent peripheral arthritis Corticosteroid injection – no response to at least one local corticosteroid injection in patients with symptomatic peripheral arthritis

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

If there are no contraindications, all three sections have to be fulfilled before treatment with TNF blockers is commenced.

rheumatoid arthritis patients on TNF- $\alpha$  blockers found no increased risk [43]. The contraindications for the use of TNF- $\alpha$  blockers are summarised in Table 3 [42].

Guidelines for the use of anti TNF agents in the management of patients with AS are summarised in the international assessment in ankylosing spondylitis consensus (Table 4) [44].

Anakinra is a recombinant human interleukin-1 receptor antagonist that has been investigated in the treatment of AS. Two open trials have reported conflicting results [45, 46].

### Anaesthetic considerations

In severe AS, knee and hip joint replacements and corrective spinal surgery for severe flexion deformities may be required to improve function and quality of life. Fixed cervical flexion resulting in chin on chest deformity

leads to difficulty with forward vision, swallowing and hygiene. Treatment of severe cervical kyphosis may ultimately require surgical correction. These surgical procedures present a wide range of challenges to the anaesthetist [47].

A thorough pre-operative assessment is essential to evaluate the severity of the disease, in particular airway involvement and the extra-articular manifestations of the disease. Peri-operative neurological deficits should be documented. The range of movement of all joints should be assessed to plan optimal positioning of the patient. The extent of pre-operative investigations depends on the severity of the disease and these include echocardiography, lung function tests, imaging of the cervical spine and arterial blood gas analysis. In view of the potential for conduction defects, a pre-operative ECG is mandatory. An echocardiogram is required to assess the severity of valvular disease associated with AS.

There is no clear consensus regarding the management of anti-TNF- $\alpha$  blockers in the peri-operative period. Giles et al. [48] showed a significant association between infectious complications following orthopaedic surgery and treatment with anti-TNF- $\alpha$  agents. Chang et al. [49] suggested that TNF- $\alpha$  blocker should be stopped pre-operatively in patients undergoing abdominal surgery to reduce the risk of infection and restarted when postoperative healing is established. The Dutch Society for Rheumatology advocated stopping the anti-TNF- $\alpha$  agents to allow the washout of the drug by the time of operation, i.e. 4.5 times the half-life of the particular agent. This recommendation is currently under debate [50]. However, in a retrospective study, den Broeder et al. [51] concluded that the peri-operative continuation of anti-TNF- $\alpha$  agents was not a significant risk factor for surgical wound infections. Other authors have also suggested that the infection risk is no reason to withhold therapy [52]. Prospective studies are needed to address this issue.

### Airway management

Difficult intubation is associated with AS involving the cervical spine and can be compounded further when the temporomandibular joint is involved. Neck movements in extension and flexion should be assessed by radiological screening. Pre-operative indirect laryngoscopy can be invaluable in assessing a patient to predict difficult intubation. There is significant risk of neurological injury with any excessive neck extension in patients with chronic cervical kyphosis. Neck extension can cause vertebral artery insufficiency as a result of bony encroachment on the vertebral artery. Injuries to the cervical spine and spinal cord such as dislocation of C6 vertebra and quadriplegia after an emergency intubation have been reported. Fixed cervical flexion deformities limit access to

the trachea and tracheostomy may be impossible. Neck supports should be used during anaesthesia and forcible movements of the neck in the presence of neuromuscular blockade avoided.

Death from a retropharyngeal abscess that resulted from multiple attempts at blind intubation has been reported [53]. Awake fiberoptic intubation is the safest option, especially in those patients where it is not possible to visualise the larynx on indirect laryngoscopy or those with severe chin on chest deformity. It also allows for constant neurological monitoring during placement of the tracheal tube. Retrograde intubation may also be considered.

The intubating laryngeal mask (ILM) and the classic laryngeal mask have been used during failed intubations in AS patients as alternatives or aids to tracheal intubation in the anaesthetised patient, and for awake insertion. An advantage of this technique is that the trachea can be intubated without head and neck movement or direct laryngoscopy and ventilation of the patient's lungs can be maintained during the procedure. However, it may be impossible to insert a laryngeal mask in patients with severe flexion deformities because the angle of the oropharynx axis can cause it to kink and hinder its placement over the trachea.

In elective surgical patients who refuse an awake fiberoptic intubation, the ILM may be a useful device in managing the airway in an anaesthetised patient. One case series demonstrated successful blind intubation through the ILM in 11 of the 12 patients with severe AS. The ILM was inserted and manual ventilation was achieved at first attempt in all 12 patients. The authors suggested that a precurved PVC tracheal tube in the reverse direction enabled higher success with a lower complication rate compared to the straight silicone tube [54]. The ILM may also be easier to insert in patients with an immobile neck and is a superior aid for fiberoptic intubations compared with a laryngeal mask [54–56].

The laryngeal mask is more appropriate in patients with restricted mouth opening of < 2 cm or in patients who do not require intubation. It may not be possible to place a laryngeal mask in patients with AS when the mouth opening is < 1.2 cm and if a fixed extension deformity and large cervical osteophytes are present [54].

Lai et al. [57] reported that the Glidescope<sup>®</sup> (GS) (Saturn Biomedical System Inc., Burnaby, BC, Canada) was a useful device that improved visualisation of the larynx and facilitated naso-tracheal intubation in anaesthetised patients with AS. In this study of 11 AS patients who were assessed to have difficult airways, the GS improved the laryngoscopic view in all patients and nasal intubation was successful in eight of the 11 patients. Awake fiberoptic intubation was performed in the other three patients who could not be intubated using the GS.

The main limitation of the GS is the resistance encountered during advancement of the tracheal tube.

### Regional or local anaesthesia

Spinal and epidural anaesthesia is technically difficult and may result in an increased risk of complications. Convulsions secondary to accidental intra-osseous injection of bupivacaine during a caudal block and spinal haematomas following insertion of an epidural anaesthetic have been reported. Subarachnoid block using a lateral approach has been advocated as an alternative when general anaesthesia is contraindicated [58].

The placement of epidural anaesthesia is technically difficult and is associated with an increased risk of an epidural haematoma. In a comprehensive review of spinal haematoma associated with epidural anaesthesia over a 30-year period (1966–1995), Wulf reported five out of 51 patients with spinal haematoma occurred in patients with AS. These were related to difficult or traumatic insertion [59]. Other predisposing factors included concurrent NSAID therapy and a narrow epidural space. Pre-operative coagulation studies may be prudent in these patients. Repeated neurological examination in these patients after neuraxial anaesthesia should be undertaken because they have an increased risk of developing a spinal haematoma [60].

The epidural space is narrow in AS patients and local anaesthetic solutions should be administered slowly in small doses to avoid total spinal anaesthesia. A recent case report described a total spinal anaesthetic following epidural test dose in an AS patient with anticipated difficult airway for a total hip replacement. Technical difficulty and multiple attempts of a combined spinal epidural were possible contributory causes [61].

### Corrective spinal surgery

Surgical correction of severe cervical spine deformity can significantly improve a patient's functional and psychological status. Airway problems and potential neurological injury are the main issues. A fixed thoracic deformity causes restrictive pulmonary function. The patient may be malnourished due to swallowing difficulties and may need pre-operative supplementation or parenteral nutrition. The surgical procedure itself is technically demanding and carries a potential risk of significant neurological injury. Peri-operative mortality as a result of pulmonary, cardiac and intestinal problems is approximately 4% [62]. Important anaesthetic considerations include neurophysiological monitoring, patient positioning, surgical approach and spinal instrumentation. The prone position allows surgical access for multilevel decompression and internal fixation.

General anaesthesia with controlled ventilation via tracheal intubation affords a secure airway, facilitates

cervical spine surgery by allowing a patient to be prone, eases placement of instrumentation, and reduces the risk of air embolism. Neurological function monitoring is essential because spinal cord injury can result from direct translational injury or from impingement from osseous compression. A wake-up test can allow assessment of patient's neurological function.

Motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) are used to monitor neurological function intra-operatively [63]. SSEPs primarily evaluate sensory function mediated by the dorsal columns of the spinal cord. Unlike intravenous anaesthetic agents, inhalational anaesthetics cause a dose related increase in latency and a decrease in the amplitude of SSEP. Several case reports of significant postoperative neurological deficits associated with normal intra-operative SSEPs have been published. [47]. MEPs are used to complement SSEP monitoring to detect potential damage to the corticospinal (motor) tracts of the spinal cord. The relatively large voltage of MEP enables instantaneous monitoring because signal averaging is not required. Following extension of the neck during corrective surgery decreases in the amplitude of MEPs actuates immediate corrective measures [47].

### Anaesthetic management of the parturient with AS

Most pregnant patients with AS have normal vaginal deliveries. However, manifestations of AS can interfere with labour, delivery and the administration of regional and general anaesthesia. Awake fiberoptic intubation in the left lateral position has been reported in a parturient with a history of a failed intubation at previous surgery [64]. These patients should be referred early on in the pregnancy to the obstetrician and anaesthetist so that together they can prepare a management plan.

### Postoperative management

The same precautions regarding patient positioning and neck movement apply at emergence from anaesthesia as with intubation. Physiotherapy, breathing exercises and early mobilisation should be instituted early because patients are at increased risk of respiratory complications. The effects of fluid shifts and the effects of medications on peri-operative fluid balance should be monitored.

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