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Hypersensitivity reactions to biologics (part II): classifications and current diagnostic and treatment approaches

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Abstract
Purpose Biotechnological substances (BS) have rapidly expanded their clinical use. In parallel, there is an increase in expected or unexpected immunological or non-immunological adverse effects. In this part of the review, the current nomenclature of BSs, the classification of hypersensitivity reactions (HSR), as well as diagnostic and treatment approaches are documented to provide the tools to understand the nomenclature used throughout the databases and the need to harmonize it where applicable.
Methods Detailed searches were performed on Pubmed, Web of Science, and Google Scholar to include all available publications. The search terms, such as specific BS, allergy, anaphylaxis, hypersensitivity, reactions, classification, diagnosis, grading, management, and desensitization, were determined for the search. Case reports, articles, and reviews on this subject were included.
Results Today, a variety of non-standardized methods are used to support the clinical diagnosis. These include prick-to-prick tests and intradermal tests with the drug itself and its potentially allergenic ingredients. More rarely, anti-drug antibodies are detected and basophil activation tests are used by centers with research facilities. Although the treatment protocols for acute conditions vary, the overall approach is the same.
Conclusion HSRs to BS are gradually increasing with the widening of their clinical use and indications. It is very important to prevent HSRs and to know the degree of severity as well as the emergency treatment algorithm. This review summarizes the diagnostic tests that should be applied: (a) immediately during/after a reaction, and (b) subsequently, and in the case that a switch of BS is not possible, desensitization is an option.

Keywords Allergy · Anaphylaxis · Anti-drug antibodies · Biologicals · Desensitization

Abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
α-Gal	Galactose-α-1,3-galactose
ARCN	Airway Research Center North
BAT	Basophil activation test
BMBF	Federal Ministry for Science and Education
BS	Biotechnological substances
BWH	Brigham and Women's Hospital
CD	Cluster of differentiation
CDR	Complementarity-determining region
CRS	Cytokine release syndrome
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
Erb	Eukaryotic ribosome biogenesis protein
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HSR	Hypersensitivity reaction
IFN	Interferon
Ig	Immunoglobulin

Part I see https://doi.org/10.1007/s40629-020-00126-6

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IL	Interleukin
INN	International nonproprietary names
mAb	Monoclonal antibody
RDD	Rapid drug desensitization
SPT	Skin-prick test
TGF	Transforming growth factor
TNF-α	Tumor necrosis factor α
USAN	United States' adopted names

Introduction

Biotechnological substances (BS) have rapidly expanded their clinical use since the years they were first defined. In parallel, there is an increase in expected and unexpected side effects and various adverse drug reactions (ADR) [1]. These reactions can be acute infusion reactions, anaphylaxis, hypersensitivity reactions (HSR), cytokine release syndrome due to intravenous injection, and local injection site reactions, HSRs and anaphylaxis due to subcutaneous administration.

Moreover, BSs are different from most drugs in that they do not contain prodrugs or small chemical compounds, but are produced to make them as similar to human proteins as possible. Unlike other drugs, they are not metabolized classically, but have functions like other proteins and can be digested from the gastrointestinal tract. Therefore, ADRs are also quite different. The adverse effects can be either immunological or non-immunological, as well as due to the excessive response of the immune system depending on the pharmacological properties of the drug [2].

In this part of the review, the current nomenclature of BSs, the classification of hypersensitivity reactions, as well as diagnostic and treatment approaches will be discussed.

Material and methods

Detailed searches were performed on Pubmed, Web of Science, and Google Scholar to include all available publications. The search terms, such as specific BS, allergy, anaphylaxis, hypersensitivity, reactions, classification, diagnosis, grading, management, and desensitization, were determined for the search. Case reports, articles, and reviews on this subject were retrieved.

Classification of biotechnological substances

Biologics include fully human and humanized monoclonal antibodies (mAb), chimeric (human + murine) antibodies, and recombinant fusion proteins that affect specific functions of the immune system. The three most common classes of biologics are mAbs, fusion proteins, and cytokines (Table 1).

Currently approved mAbs target immunoglobulin (Ig)-E antibodies, cell surface molecules, soluble mediators, cytokines, viral proteins, and tumor antigens.

Table 1 Classification of biotechnological substances[a]

Group	Example substances/targets
Monoclonal antibodies	
Towards IgE antibodies	Omalizumab, ligelizumab, quilizumab
Towards cell surface molecules	Rituximab (anti-CD20)
	Basiliximab (anti-IL-2 receptor)
	Efalizumab (anti-LFA-1)
Towards soluble mediators and cytokines	Infliximab, adalimumab (anti-TNFα)
	Daclizumab (anti-IL-2 R alpha)
	Lanadelumab (plasma kallikrein)
Towards tumor antigens	Cetuximab (EGFR)
	Trastuzumab (HER2/neu/ErbB2)
Fusion proteins	
Soluble receptors for cytokines	Etanercept (TNFα-RII)
Soluble cellular ligands	Anakinra (IL-1 receptor)
Soluble receptor constructs	Ritanercept (IL-1 β receptor)
Cytokines	Interferon-α
	Interferon-β
	GM-CSF
	Interleukin-2

CD cluster of differentiation, *IL* interleukin, *LFA* lymphocyte function-associated antigen, *TNF* tumor necrosis factor, *EGFR* endothelial growth factor receptor, *HER* human epidermal growth factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor

[a]Adapted from http://biologics.clinimmsoc.org (WEBbook of Biologic Therapies) and Scherer et al. [1] with permission

Fusion proteins include soluble cytokine receptors, soluble cellular ligands, and soluble receptor constructs, and immunoglobulin fragments. Recombinant cytokines, including interferon-α, interferon-β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin (IL)-2, may also be effective treatments for various conditions.

Biologics that neutralize tumor necrosis factor α (TNF-α), interferons, and ILs, or receptor blockers targeting receptors such as epidermal growth factor receptor (EGFR), eukaryotic ribosome biogenesis protein (Erb) 1, Erb2, and human clusters of differentiation (CD) 125 are currently available [3–5].

International nomenclature of biotechnological substances

Systems of nomenclature most commonly used are the World Health Organization's International Nonproprietary Names (INN) and the United States' Adopted Names (USAN) for biologicals [6, 7]. The syllables used in naming have various meanings.

The first one to two syllables have no specific meaning.

The second or third syllable defines the target or indication of the drugs. As used herein, -li/-lim designates the immune system, -tu/-ti designates tumors, -ki designates cytokines, -vi designates viruses, and -ci designates the cardiovascular system. Thus, oma-

Table 2 Internationally accepted nomenclature of biotechnological substances[a]

Syllable	Explanation	Syllable	Explanation
First	There is no specific meaning	–	–
Second or third	Target of the biological agent	*-ci*	Cardiovascular system
		-ki	Cytokine, interleukin
		-li/-lim	Immune system
		-tu/-ti	Tumor
		-vi	Viral
		-ba	Bacterial
Third or fourth	Source of the biological agent	*-mo/-mu*	Murine, mouse (0% human)
		-xi	Chimeric (75% human)
		-zu	Humanized (>90% human)
		-u	(Fully) human (100% human)
Last	Mechanism of action	*-mab*	Monoclonal antibody
		-cept	Soluble receptor
		-inib	Receptor blocker

[a]Adapted from World Health Organization [6] and American Medical Association [7]. The nomenclature process is adequately dynamic

li-zumab targets the immune system, ce-*tu*-ximab is an approved antitumor drug, pali-*vi*-zumab is used to prevent viral infections, ab-*ci*-ximab has a cardiovascular indication, and secu-*kin*-umab acts on IL-17a.

The third or fourth *syllable* names the source of the BS. Murine biologicals take -mo/-mu. They are produced from 100% murine genes and are the most potentially allergenic biologics (e.g., muro-*mo*-nab, blinatu-*mo*-mab). Chimeric antibodies (-xi) are only murine in their variable region, consisting of approximately 30% mouse protein (e.g., infli-*xi*-mab, cetu-*xi*-mab). Humanized antibodies' (-zu) variable regions are mostly human, consisting of mouse protein only in their complementarity-determining regions (CDR). These antibodies (e.g., omali-*zu*-mab, trastu-*zu*-mab) contain approximately 5% non-human protein. Human biologicals (-u) contain 100% human protein sequences (e.g., golim-*u*-mab, dupil-*u*-mab) and are the least allergenic. Human homologies are 0%, 75%, >90%, and 100%, respectively [1]. The risk of allergic reactions decreases proportionally with the increase in human homology [8]. Many BSs have been abandoned due to the fact that they caused intolerable immunological/allergic reactions or lacked efficacy [9].

The last syllable defines the mechanism of action. MAbs are designated -mab, receptor-derived biologics are designated -cept, and receptor blockers are designated -inib (omalizu-*mab*, etaner-*cept*, and imat-*inib*) (see Table 2).

Classification of allergic reactions to biotechnological substances

As clinical use and approved indications for BSs increase, reports of BS-associated adverse events increase in proportion. Five types of adverse side effects (alpha, beta, gamma, delta, and epsilon) were described by W.J. Pichler in 2006 (Table 3; [10]). The

Table 3 Classification of adverse drug reactions to biotechnological substances[a]

Features	Type alpha (α)	Type beta (β)	Type gamma (γ)	Type delta (δ)	Type epsilon (ε)
Nomenclature	Cytokine release syndrome	Hypersensitivity	Immune or cytokine imbalance syndromes	Cross-reactivity	Non-immunological side effects
Effect	Pharmacological-toxic reaction	Immune-mediated reactions	Immune deviation	Appear after some time of treatment (up to several years)	Unexpected physiological effects and functions of BS
Dose	Dose-dependent	Dose-independent	–	–	–
Mechanism	Direct effect by cytokine release	Induction of antibodies; T-cell involvement	Immunosuppression or autoimmunity	Reactions with structurally similar protein or antigen	–
Example	Infusion reactions	Aspirin-induced asthma, maculopapular exanthema, hypersensitivity reactions and anaphylaxis	*De novo* induction of a SLE, TBC under TNF-α-blocking therapy	Acneiform eruptions observed during anti-EGFR treatment	Role of TNF-α in heart failure, neuropsychiatric side effects and retinopathies observed during IFN-α treatments

TNF tumor necrosis factor, *TBC* tuberculosis, *HF* Heart failure, *EGFR* epidermal growth factor receptor, *SLE* systemic lupus erythematosus, *BS* biotechnological substance, *IFN* interferon
[a]Quoted and modified from Pichler [10] with permission

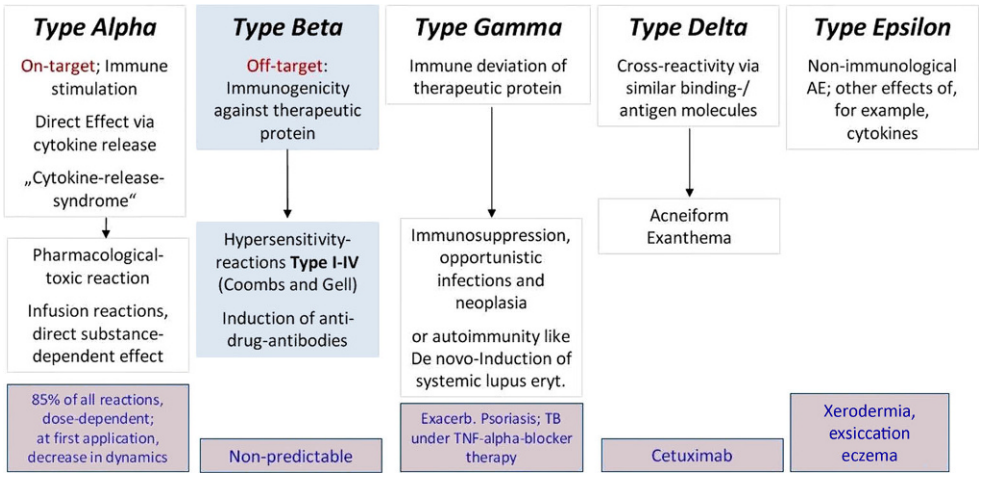

Fig. 1 Classification of adverse drug reactions to biotechnological substances. (Modified from Scherer et al. [1] and Pichler [10] with permission)

classification scheme of W.J. Pichler [10] has been accepted internationally and provides a useful framework for a better understanding of ADRs induced by BSs. This approach has helped define pathogenic mechanisms and manage/minimize broadband side effects (Fig. 1; [1, 10]). It has been stated that classifying and learning these HSRs is important for managing acute conditions [11].

Type-alpha (α) ADRs are also referred to as cytokine release syndrome and cytokine storm. These ADRs occur in response to high systemic concentrations of circulating cytokines or to sudden high rates of cytokine release into the circulation during treatment [10, 12]. Cytokine release syndrome (CRS) can produce gastrointestinal symptoms (nausea, vomiting, diarrhoea), headache, myalgia, pulmonary edema, encephalopathy, aseptic meningitis, fever, arthralgia, and systemic capillary leak syndrome [12]. CRS can result in acute respiratory distress syndrome, cardiovascular shock, and multi-organ failure owing to systemic inflammatory responses [12–14]. These side effects usually occur during infusion at first administration and are dose-dependent [10].

Type-α reactions are divided into five levels by severity (referenced in [15]):

- Grade I: Mild reaction, no need to discontinue treatment, no additional intervention required
- Grade II: Intervention or termination of treatment required, responds quickly to pharmacological intervention
- Grade III: Long-term reaction, slow response to pharmacological intervention and/or treatment interruption; recurrence of symptoms; hospitalization
- Grade IV: Life-threatening reaction, requires vasopressor drug support and mechanical ventilation
- Class V: Death

Acute and delayed infusion reactions

Most BSs are administered intravenously, and thus may induce IRs. These reactions may be IgE- or non-IgE mediated [10, 14, 15]. There is no consistent terminology in the literature that distinguishes acute IR from type-α or type-β HSR [15]. Acute IRs typically appear during the first 15 min of the infusion, or as delayed IRs between 1 h to 14 days after the infusion (referenced in [14]). However, acute IRs occur in 3–5% of treatments with chimeric BSs within 1 h after the first infusion, and clinical manifestations can vary widely, ranging from mild to life-threatening [10–15]. Delayed IRs are usually accompanied by symptoms such as muscle and joint pain, pruritus, facial edema, fever, dysphagia, skin rash, and exanthema [10, 14].

Type-beta (β) is an immediate (IgE-mediated) or delayed (IgG- and T-cell-mediated)-type HSR [10, 11]. Immediate (acute) reactions occur within 20–30 min after injection, and are most common in response to intravenous infusion. These reactions can disappear when the treatment is discontinued or the infusion rate is reduced. Consequently, tolerance can be induced. Delayed-type reactions may occur from 6 h after the start of treatment. They are usually mediated via T-cells or immunoglobulins and are drug dose-independent [10]. Examples include maculopapular exanthema and hypersensitivity reactions. The occurrence of these reactions depends on the immunogenicity of the BS. Risk is reduced in proportion to the BS's degree of humanization [8, 10]. Murine and chimeric antibodies are the most immunogenic due to the high percentage of foreign protein they contain. Humanized and (fully) human antibodies can still elicit systemic immune responses, but the risk is reduced considerably when compared to chimeric ones. They can also cause other ADRs by different mechanisms. Various other factors, such as the addition of adjuvants, route of administration (intravenous or subcutaneous), treatment protocol (intermittent or continuous), and simultaneous use of immunosuppressive drugs, also influence the risk of HSR. Organic compounds with adjuvant activity in the vehicle are believed to contribute to immunogenicity in cases of pure red cell aplasia associated

Table 4 Pathomechanisms of hypersensitivity reactions[a]

	Antibody-mediated hypersensitization			Cell-mediated hypersensitization (Delayed)			
	Type I	Type II (a and b)	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Mediator	IgE; non-IgE	IgG or IgM, complement	IgG/IgM; complement	T-helper 1	T-helper 2	T-cells ($CD8^+$)	T-cells
Mechanism	Mast cell activation	Antibody- and/or complement-mediated; cytotoxic	Immune complexes	Macrophage activation	Eosinophil activation	Cytotoxic reactions	Neutrophilic inflammation
Clinical presentation	Allergic rhinitis	Autoimmune haemolytic anemia	Immune complex vasculitis	Contact dermatitis	Chronic asthma	Contact dermatitis	AGEP
	Anaphylaxis	Antibody-mediated glomerulonephritis	Serum sickness-like reaction	Type I Diabetes	Chronic allergic rhinitis	SJS	Behcet disease
	Angioedema	Chronic urticaria (idiopathic)	Arthus reaction			TEN	Pustular psoriasis
	Asthma	Drug-induced cytopenia	Arthritis				
	Urticaria	Graves Disease	Nephritis				
		Penicillin allergy	SLE				

AGEP acute generalized exanthematous pustulosis, *Ig* immunoglobulin, *SLE* systemic lupus erythematosus, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis
[a]According to Gell and Coombs [23], modified and updated by Uzzaman and Cho, 2012 [24]

with erythropoietin injections [16]. In addition, it is a well-known fact that combining infliximab therapy with methotrexate reduces sensitivity, immunogenicity, and the formation of anti-infliximab antibodies [17, 18].

Delayed or non-IgE-mediated reactions can cause local reactions at injection sites, or generalized urticaria and anaphylaxis. These types of allergic reactions are often mild, but more severe reactions such as IgE-mediated anaphylaxis have been described [19]. Formation of (mostly neutralizing) antibodies against BSc occur in a wide variation of frequency, depending on the BS structure, serum-drug levels, concomitant teatment and patient-related factors [20]. TNF-alpha inhibitors also induce autoimmune phenomena including autoantibodies, lupus-like syndrome and direct antigen-mediated hypersensitivity vasculitis [21], the latter probably due to immune complexes.

- Hypersensitivity reactions (type-β) are graded according to severity as follows [15, 22]:
- Grade I: Transient flush, rash, drug-induced fever <38 °C
- Grade II: Flush, rash, exanthema, urticaria, and dyspnea, drug-induced fever ≥38 °C
- Grade III: Symptomatic bronchospasm with or without urticaria, hypotension, and angioedema
- Grade IV: Anaphylaxis (is not consistently clarified in the literature, probably grade III/grade IV)
- Grade V: Death

Classical grading of hypersensitivity reactions by Gell and Coombs

The immune system responds in various ways to different factors. These factors include bacteria, viruses, fungi, and allergens. The primary goal of each response is to protect the host. Sometimes, the immune system produces an excessive response. This is called hypersensitivity. The classical Gell and Coombs classification system [23] divides HSRs into four subtypes according to factor, type of immunological response, as well as cell and tissue damage (Table 4; [23, 24]):

- Type I, due to mast cell activation, immediate, IgE-mediated
- Type II, associated with antibodies, cytotoxic, IgG-/IgM-mediated, complement
- Type III, mediated by immune complexes and IgG/IgM, complement
- Type IV, delayed-type hypersensitivity reactions, mediated by T-helper and T-cytotoxic cells

Penicillin can cause any of these HSR types, for example: type I, anaphylaxis, angioedema, and urticaria; type II, hemolytic anemia, cytopenia; type III, serum sickness-like reaction; and type IV, delayed type skin rash or contact dermatitis [24]. In clinical practice, the anaphylactic reaction to contrast agents used in radiology is a non-IgE-mediated HSR, a pseudoallergy, and can be prevented by pretreatment with corticosteroids and antihistamines, whereas IgE-mediated anaphylaxis cannot be prevented by pharmacological pre-treatment alone.

Ring and Messmer's anaphylaxis grading system

The term "anaphylaxis" refers to an acute reaction that affects specific organ systems or the entire organism. Anaphylactic reactions can affect skin and mucous membranes, the respiratory system, the gastrointestinal system, the cardiovascular, and the nervous system and can trigger specific symptoms. The term, "anaphylactic shock" was coined to describe a condition characterized by life-threatening symptoms including sudden respiratory distress, hypotension, as well as cardiac and circulatory failure within a few minutes of contact with the allergen. The grading sys-

Table 5 Grading of anaphylaxis[a]

Systems	Grade I	Grade II	Grade III	Grade IV
Skin and subjective symptoms	Pruritus, flush urticaria, angioedema	Pruritus, flush urticaria, angioedema	Pruritus, flush urticaria, angioedema	Pruritus, flush urticaria, angioedema
Abdominal	–	Nausea, abdominal cramps, vomiting	Vomiting, defecation	Vomiting, defecation
Respiratory	–	Rhinorrhea, hoarseness, dyspnea	Laryngeal edema, bronchospasm, cyanosis	Respiratory arrest
Cardiovascular	–	Tachycardia[b], blood pressure change,[c] arrhythmia	Shock	Cardiac arrest

[a]According to the Guideline for acute therapy and management of anaphylaxis [26]
[b]Δ >20 beats/min
[c]Δ >20 mm Hg systolic

tem was suggested by Ring and Messmer in 1977 [25] and is still valid, based on the severity of the clinical manifestations and organ involvement (Table 5; [26]). Anaphylaxis is an example of type I hypersensitivity according to Gell and Coombs [23].

Type-gamma (γ) responses are also called immune or cytokine imbalance syndromes [10]. These ADRs include immune system depression or autoimmunity caused by the immune system and cytokine imbalances. Skin-prick tests (SPT) and *in vitro* assays for anti-drug antibodies (ADA) are generally negative [10]; ADA might be detectable but are of no relevance for type-gamma reactions. BSs can cause immunodeficiencies that are beneficial in treating a condition, but will facilitate invasion by or activation of opportunistic pathogens that have remained under control such as tuberculosis, fungal infections, or herpes zoster. BSs can also result in imbalances in the immune system by mechanisms that are not fully understood. The use of BSs may trigger autoimmune diseases such as lupus-like syndrome, autoimmune thyroid disease, Guillain-Barre syndrome, vasculitis, psoriasis, idiopathic thrombocytopenic purpura, and systemic sclerosis [10]. One possible mechanism of action is the alteration of the T-helper 1 (Th1)/Th2 balance by alteration of central and peripheral tolerance mechanisms. Other possibilities include alteration of regulatory T cells and change in levels of certain cytokines such as transforming growth factor (TGF-β) and IL-10 [27].

Type-delta (δ) ADRs are also called cross-reactions. These side effects may be caused by antibodies produced in response to an antigen expressed on the targeted cells, which may cross-react with an antigen on normal host cells [10, 28]. For example, some publications indicate that the EGFR is strongly expressed in various carcinomas and plays a role in tumor progression [29]. However, this receptor also plays an important role in epidermal homeostasis. Therapeutic antibodies against EGFR (e.g., cetuximab) are used to treat various tumors. Acneiform eruptions are quite common during these treatments, probably owing to the effects of anti-EGFR antibodies on the epidermal cells [28]. Some antibodies used as treatments may cause unexpected side effects by interacting with structurally similar proteins.

Type-epsilon (ε) ADRs represent non-immunologic side effects. This newly defined type tries to explain BS-mediated impairment of other physiological functions in the body. The promotion of heart failure by anti-TNF-α agents, as well as the neuropsychiatric side effects and retinopathy caused by IFN-α, may represent type ε ADRs [30–32]. Such unexpected and interesting side effects of BSs offer researchers opportunities to detect new functions of established drugs.

Diagnostic measures

So far, no established and approved routine (allergy) diagnostic test exists for the diagnosis of the different immune reactions to BSs. Today, a variety of non-standardized methods are used to support the clinical diagnosis (Fig. 2; [33]). These are SPT applied as prick-to-prick tests and intradermal tests with the drug itself and its potentially allergenic ingredients. *In vitro* diagnostic tests are established in routine diagnostic laboratories for the detection of ADA, a test basically used for the detection of anti-drug-IgG antibodies that are associated with the loss of efficacy to a biological.

Some laboratories also provide tests for the detection of anti-drug IgE, which has not yet been routinely established. Serum tryptase concentration, which increases during anaphylactic reactions, is a very helpful parameter to support the clinical diagnosis of anaphylaxis to a BS in its acute state. It is, however, rarely used by the physicians in charge of the patients while the event occurs, and when the patients are subsequently referred to an allergy outpatient clinic for detailed exploration, serum tryptase is within its normal range again. The authors strongly recommend using this diagnostic tool regularly in cases of HSR. Basophil activation tests or lymphocyte stimulation tests have also been shown to add valuable informa-

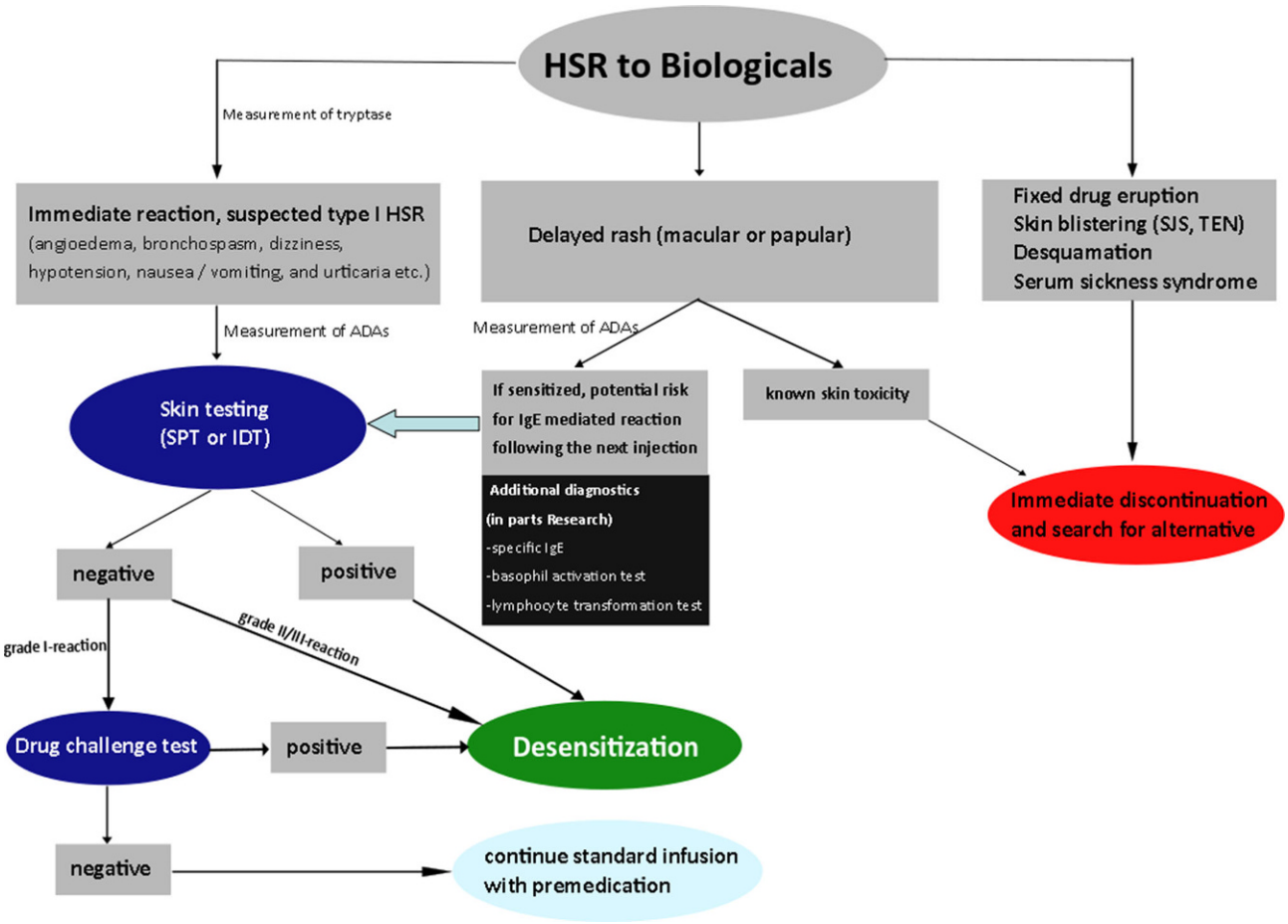

Fig. 2 Diagnostic algorithm after a hypersensitivity reaction[a]. (*HSR* hypersensitivity reactions, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *SPT* skin prick test, *IDT* intradermal test. [a]Adapted from Hsu Blatman et al. [33] with permission and modified)

tion, but have not yet been studied on large patient groups.

Skin prick test and intradermal test

Skin tests are generally recommended to be performed 2–4 weeks after a suspected HSR has occurred. Specific IgE antibodies may be depleted in the first days/weeks after the reaction, and this may lead to a false negative result. Generally known non-irritant concentrations for SPT and intradermal testing are given in Table 6 [33–37]. Unfortunately, there is no specific test concentration, sensitivity, or specificity for all BSs. Whenever the drug itself is used for diagnostic purposes, it is considered "off-label-use," to which the patients should declare their informed consent in writing. According to Cox et al. [38], no irritant reactions, adverse events, or IgG antibodies developed after SPT with omalizumab. An intradermal test with, for example, omalizumab at a concentration of 1:100,000 (~1.25 µg of omalizumab per ml) could be safely applied without inducing irritant reactions [39].

Serum tryptase level

Tryptase is an enzyme produced from mast cells that reflects anaphylactic reactions and mast cell diseases. The most accurate time for serum sampling is 30–120 min after the start of the reaction (referenced in [40]). However, it should be kept in mind that normal tryptase levels can be observed, and basophil mediators may play a role in immediate type HSRs. Nonetheless, the authors strongly recommend using this diagnostic tool regularly in cases of HSR.

Drug challenge test

The drug challenge test can be performed if skin tests are negative, tryptase levels are within normal range, and clinical findings are not indicative for a true IgE-mediated allergic reaction [33, 40]. This test is performed in cases of previous immediate reactions, administering between 1/10,000 and 1/10 of the total dose of the drug under medical supervision. If the patient tolerates the drug, the regular infusion is continued. In addition, it should be noted that the initial dose of the test should not exceed 1/100 of the therapeutic dose in patients that had previously developed non-immediate reactions during medical treat-

Table 6 Non-irritant concentrations of biotechnological substances for skin prick test (SPT) and intradermal test (IDT)[a]

Drug	SPT	IDT	References
Abciximab	0.2–2.0 mg/mL	0.2–2.0 mg/mL	Referenced in Corominas et al., 2014 [35]
Abatacept	25 mg/mL	0.025–0.25–2.5 mg/mL	Referenced in Hsu Blatman et al., 2014 [33]
Anakinra	As is	–	Referenced in Corominas et al., 2014 [35]
Adalimumab	40.0 mg/mL	0.4 mg/mL	Referenced in Isabwe et al., 2017 [34], and in Picard et al., 2017 [36]
	50.0 mg/mL	5–50.0 mg/mL	Referenced in Corominas et al., 2014 [35]
Basiliximab	4 mg/mL	0.4–400 μg/mL	Referenced in Corominas et al., 2014 [35]
Bevacizumab	25 mg/mL	0.25–2.5–25.0 mg/mL	Castels et al., 2017 [37]
Cetuximab	2 mg/mL	0.2 mg/mL	Referenced in Isabwe et al., 2017 [34], and in Picard et al., 2017 [36]
	20 mg/mL	0.2–2.0–20.0 mg/mL	Castels et al., 2017 [37]
	500 μg/mL	5–50–500 μg/mL	Referenced in Corominas et al., 2014 [35]
Etanercept	25 mg/mL	5 mg/mL	Referenced in Corominas et al., 2014 [35]
	50 mg/mL	0.5 mg/mL	Referenced in Isabwe et al., 2017 [34], and in Picard et al., 2017 [36]
	50 mg/mL	0.05–0.5–5.0 mg/mL	Referenced in Hsu Blatman et al., 2014 [33]
Infliximab	10 mg/mL	0.1–1.0 mg/mL	Referenced in Corominas et al., 2014 [35]
	10 mg/mL	0.1–1.0–10.0 mg/mL	Castels et al., 2017 [37]
Natalizumab	20 mg/mL	2 mg/mL	Referenced in Corominas et al., 2014 [35]
Omalizumab	12.5–125 mg/mL	1.25 μg/mL	Referenced in Corominas et al., 2014 [35]
Pertuzumab	1.6 mg/mL (1/20)	0.16 mg/mL	Referenced in Picard et al., 2017 [36]
Rituximab	10 mg/mL	0.01–0.1–1.0 mg/mL	Referenced in Hsu Blatman et al., 2014 [33]
	10 mg/mL	0.10–1.0 mg/mL	Referenced in Corominas et al., 2014 [35]
	10 mg/mL	0.10–1.0–10.0 mg/mL	Castels et al., 2017 [37]
Tocilizumab	20 mg/mL	0.2–2.0–20.0 mg/mL	Castels et al., 2017 [37]
Trastuzumab	21 mg/mL	0.21–2.1 mg/mL	Referenced in Corominas et al., 2014 [35]
	21 mg/mL	0.21–2.1–21.0 mg/mL	Castels et al., 2017 [37]

[a]Quoted and adopted from Corominas et al. [35] with permission, modified

ment [41]. A positive test result indicates that the patient may profit from desensitization to the drug. Drug challenge should also not be performed in severe forms of delayed-type hypersensitivity.

Anti-drug antibodies

BSs are potentially immunogenic drugs that technically affect and alter the immune system. As a result, ADAs are produced and may cause various HSRs and side effects. The majority of ADAs comprise the IgG class, as well as IgG subclasses (IgG 1–4), which are mainly investigated in cases of reduced efficacy (neutralizing effect) [20]. However, multiple isotypes (IgE, IgM, and IgG) can be detected during HSR [14, 42, 43] and are involved in severe HSR to certain BSs, such as infliximab, where they can be effective in predicting the reaction [42, 43].

Two types of HSR related to antibodies have been identified: acute and delayed, but many do not appear to be IgE-mediated/anaphylactic [44]. However, non-IgE ADAs represented by IgG can lead to acute infusion reaction via complement activation, and – shown in animal models – involving Fc gamma RIII, neutrophils, macrophages, and basophils [45]. It has been reported that the antibody concentrations decrease with the concomitant use of immunosuppressants together with BSs [1]. Some ADA testing for various BSs (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, natalizumab, nivolumab, omalizumab, rituximab, tocilizumab, trastuzumab, ustekinumab, and vedolizumab) is commercially available in the European Union through a Dutch company (www.sanquin.org).

An enzyme-linked immunosorbent assay (ELISA; ImmunoCAP, Thermofisher Scientific), which can detect anti-cetuximab IgE, has been developed to identify treatment-associated IgE-mediated cases of HSR, and possibly identifies patients with increased risk of allergic side effects. Own investigations on potential allergenic peptide epitopes on infliximab and adalimumab, both TNF-α-inhibitors, revealed some allergenic epitopes that are recognized by patients' Ig antibodies (IgG and IgE). In a proof of principle study, we could show that neutralizing ADAs bind to epitopes in the pharmacologically relevant TNF-α binding site [46], providing the elucidation of the mechanism for the loss of efficacy of the drug in patients with ADA. In subsequent investigations, we could show that these epitopes were not cross-reactive between both biologicals [47]. These results confirmed a clinical observation by Steenholdt and co-authors, who described a patient with Crohn's disease and acute non-IgE-mediated but ADA-positive anaphylactoid reaction to infliximab [48]. The patient was subsequently treated with adalimumab and developed a delayed reaction based on rapidly

Table 7 Additional mostly inactive ingredients of biotechnological substances[a]

Drugs	Components
Abciximab	Polysorbate 80, sodium chloride, sodium phosphate
Adalimumab	Polysorbate 80, mannitol, sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium, phosphate dihydrate, sodium citrate, citric acid monohydrate
Aflibercept	Polysorbate 20, sucrose, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium hydroxide and/or hydrochloric acid
Alefacept	Citric acid monohydrate, glycine, sodium citrate, sucrose
Alemtuzumab	Polysorbate 80, dibasic sodium phosphate, disodium edetate dihydrate, potassium chloride, potassium dihydrogen phosphate, sodium chloride
Anakinra	Polysorbate 80, sodium hydroxide, anhydrous citric acid, sodium chloride, disodium edetate
Atezolizumab	Polysorbate 20, sucrose, L-histidine, glacial acetic acid
Basiliximab	Potassium phosphate monobasic, sodium phosphate dibasic anhydrous, sodium chloride, sucrose, mannitol, glycine
Belatacept	Monobasic sodium phosphate, sodium chloride, and sucrose
Belimumab	Polysorbate 80, citric acid, sodium citrate, sucrose for IV infusion. Polysorbate 80, L-arginine hydrochloride, L-histidine, L-histidine monohydrochloride, and sodium chloride for SC injection
Benralizumab	Polysorbate 20, L-histidine, L-histidine hydrochloride monohydrate, α-trehalose dihydrate
Bevacizumab	Polysorbate 20,trehalose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate
Blinatumomab	Polysorbate 80, citric acid monohydrate, lysine hydrochloride, trehalose dihydrate, sodium hydroxide
Canakinumab	Polysorbate 80, histidine, histidine hydrochloride monohydrate, sucrose and mannitol
Certolizumab	Polysorbate 20, lactic acid, sucrose for injection. The prefilled syringe contains sodium acetate and sodium chloride
Cetuximab	Sodium chloride, sodium phosphate, sodium hydroxide, hydrochloric acid or citric acid
Daclizumab	Polysorbate 80, sodium succinate, succinic acid, sodium chloride
Dupilumab	Polysorbate 80, L-arginine hydrochloride, L-histidine, sodium acetate, sucrose
Durvalumab	Polysorbate 80, L-histidine, L-histidine hydrochloride monohydrate, α-trehalose dihydrate
Eculizumab	Polysorbate 80, sodium chloride, sodium phosphate monobasic and dibasic
Efalizumab	Polysorbate 20, L-histidine hydrochloride, L-histidine, sucrose
Etanercept	Sodium chloride, L-arginine hydrochloride, sodium phosphate, and sucrose
Gemtuzumab ozogamicin	Dextran 40, sodium chloride, sodium phosphate dibasic anhydrous, sodium phosphate monobasic, sucrose
Golimumab	Polysorbate 80, L-histidine, L-histidine monohydrochloride monohydrate, and sorbitol
Ibritumomab tiuxetan	Sodium chloride
Imatinib	Colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, red iron oxide (E172), talc, titanium dioxide (E171) and yellow iron oxide (E172) for tablets. Crospovidone, sodium stearyl fumarate, gelatin, water, sodium lauryl sulfate, titanium dioxide, iron oxide yellow for capsules
Infliximab	Polysorbate 80, dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, and sucrose
Ipilimumab	Polysorbate 80 (vegetable origin), diethylene triamine pentaacetic acid, mannitol, sodium chloride, tris hydrochloride
Ixekizumab	Polysorbate 80, citric acid anhydrous, sodium chloride, sodium citrate dihydrate
Lanadelumab	Polysorbate 80, citric acid monohydrate, disodium phosphate dehydrate, L-histidine, sodium chloride
Lebrikizumab	No information
Ligelizumab	No information
Mepolizumab	Polysorbate 80, sodium phosphate dibasic heptahydrate, and sucrose. In addition, citric acid monohydrate, EDTA disodium dihydrate for prefilled syringe
Muromonab	Polysorbate 80, monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride
Natalizumab	Polysorbate 80, sodium chloride, sodium phosphate, monobasic, monohydrate; sodium phosphate, dibasic
Necitumumab	Polysorbate 80 (E433), sodium citrate dihydrate (E331), citric acid anhydrous (E330), sodium chloride, glycine (E640), mannitol (E421)
Nivolumab	Polysorbate 80, sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, sodium hydroxide, hydrochloric acid
Omalizumab	Polysorbate 20, L-arginine hydrochloride, L-histidine hydrochloride, L-histidine
Panitumumab	Sodium chloride, sodium acetate
Palivizumab	Chloride, glycine, and histidine
Pembrolizumab	Polysorbate 80, L-histidine, L-histidine hydrochloride monohydrate, sucrose
Pertuzumab	Polysorbate 20, L-histidine, sucrose
Ramucirumab	Polysorbate 80, histidine, histidine monohydrochloride, sodium chloride, glycine
Reslizumab	Sodium acetate, sucrose, glacial acetic acid
Rituximab	Polysorbate 80, sodium chloride, sodium citrate dihydrate

Table 7 (Continued)

Drugs	Components
Secukinumab	Polysorbate 80, α-trehalose dihydrate, L-histidine hydrochloride-monohydrate, L-histidine, L-methionine
Tocilizumab	Polysorbate 80 and sucrose for IV infusion. In addition; L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, and L-methionine for SC injection
Trastuzumab	Polysorbate 20, α-trehalose dihydrate, L-histidine HCl monohydrate, L-histidine
Ustekinumab	Polysorbate 80, L-histidine and L-histidine monohydrochloride monohydrate, and sucrose for SC injection. In addition; EDTA disodium salt dihydrate, and L-methionine for IV infusion

[a]According to the summary of product characteristics (prescribing information) and https://dailymed.nlm.nih.gov/dailymed/. There may be slight differences in some brands
IV intravenous, *SC* subcutaneous

developing ADA to adalimumab; however, no cross-reactivity could be proven *in vitro*.

It is still too early to postulate that no cross-reactions may occur, and further epitopes will need to be identified and be made available for diagnostic tests. Some investigations have been performed on the subject of ADA to omalizumab in different formulations (lyophilized and in pre-filled syringes). No ADA were detectable [49]. No correlation between anaphylaxis and ADA (IgE, IgG) was demonstrated [50].

Alpha-gal-specific IgE test

Allergen-specific IgE assays may be useful to confirm allergic reactions to certain chimeric BSs containing the galactose-α-1,3-galactose (α-gal) component, such as cetuximab, infliximab, and reslizumab. Although its clinical relevance is not fully understood due to the fact that it is different for α-gal-containing biologicals, it may be useful in predicting allergic reactions and, subsequently, monitoring the potential development of IgE-mediated reactions. In the case of cetuximab, pre-existing IgE to α-gal, e.g., due to sensitization via tick bites, were detected [51]. In order to perform useful treatment monitoring, the

Table 8 Potentially allergenic excipients in biotechnological substances[a]

Polysorbate 80	**Polysorbate 20**	**Sucrose**	**Mannitol**	**Trehalose**	**Glycine**
Abciximab	Aflibercept	Aflibercept	Adalimumab	Benralizumab	Alefacept
Adalimumab	Atezolizumab	Alefacept	Basiliximab	Bevacizumab	Basiliximab
Alemtuzumab	Benralizumab	Atezolizumab	Canakinumab	Blinatumomab	Necitumumab
Anakinra	Bevacizumab	Basiliximab	Etanercept	Durvalumab	Palivizumab
Belimumab	Certolizumab	Belatacept	Ipilimumab	Secukinumab	Ramucirumab
Blinatumomab	Efalizumab	Belimumab	Interferon β-1a	Trastuzumab	
Canakinumab	Omalizumab	Canakinumab	Interferon β-1b		
Daclizumab	Pertuzumab	Certolizumab	Interferon γ-1b		
Dupilumab	Trastuzumab	Dupilumab	Lenograstim		
Durvalumab		Efalizumab	Necitumumab		
Eculizumab		Etanercept	Nivolumab		
Golimumab		Gemtuzumab	Palivizumab		
Infliximab		Infliximab			
Ipilimumab		Mepolizumab			
Ixekizumab		Pembrolizumab			
Lanadelumab		Pertuzumab			
Mepolizumab		Reslizumab			
Muromonab		Ustekinumab			
Natalizumab					
Necitumumab	**Latex**	**Albumin**	**Sodium acetate**	**Dextran 40**	**Trometamol**
Nivolumab	Adalimumab	Interferon β-1a	Panitumumab	Gemtuzumab	Etanercept
Pembrolizumab	Anakinra	Interferon β-1b	Certolizumab		
Ramucirumab	Etanercept	Interferon α-2b	Dupilumab		**Sorbitol**
Rituximab			Reslizumab		Golimumab
Secukinumab					
Tocilizumab					**Papain**
Ustekinumab					Abciximab

[a]Quoted and adopted from Corominas et al. [35] with permission, and modified by addition of further substances

Table 9 Classification of the severity of infusion reactions and infusion center protocols[a]

Grade	Description	Therapy protocol
I—Mild	Mild and transient response, no indication for interruption of the infusion, no indication for intervention	No indication for intervention
II—Mild to moderate	Indication for therapy or discontinuation of the infusion, but with no immediate response to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids), prophylactic medications indicated for ≤24 h	Temporary interruption of the infusion, use of rescue medication, if necessary; infusion resumed after complete resolution of symptoms
III—Moderate	Brief or prolonged interruption of the infusion (e.g., no rapid response to symptomatic medications); recurrence of symptoms after initial improvement: hospitalization indicated for other clinical sequelae	Temporary interruption of the infusion and use of rescue medication; infusion resumed after complete resolution of symptoms. Discontinuation of the procedure considered
IV—Severe	Life-threatening consequences; urgent intervention indicated	Interruption of the infusion and use of rescue medication and hemodynamic support. Discontinuation of the procedure
V—Severe	Death	Death

[a]According to National Institutes of Health National Cancer Institute, 2017 [65, 66]

serum of patients treated with biologicals should be investigated before, under, and after treatment (monitoring for Ig development). With regard to α-gal, an IgE detection assay, the ImmunoCAP (Thermo Fisher Scientific) is available for routine allergy diagnostics. However, it may not always be sensitive enough [52].

Inactive substances and potentially allergenic ingredients in biotechnological substances

BSs contain additional inactive components or substances such as albumin, arginine, citric acid, glycine, histidine, latex, polysorbate, mannitol, methionine, papain, sodium acetate, sodium chloride, sodium citrate, sodium phosphate, sorbitol, trehalose, trometamol, and sucrose ([35, 53]; Table 7). Polysorbates, emulgators and stabilizers of the active ingredients of BSs, can cause HSRs by activating the complement system. In addition, as a result of degradation of polysorbates, A. oxidation of the mAb may occur, thereby increasing its immunogenicity; B. a number of reactive products may develop, functioning as haptens, interacting with proteins at the injection site, followed by ISRs [54]. Many drugs and BSs that we use in our daily clinical practice contain polysorbate. However, in a recently published case report, polysorbate was shown to be the cause of anaphylaxis the patient had developed to corticosteroids [55]. In addition, syringe needle protectors of some BSs such as adalimumab, etanercept, and anakinra contain latex, so that they may be responsible for some reactions ([35]; Table 8).

The importance of these other substances for the allergic reactions is not yet fully understood and further research is needed. Detailed information about

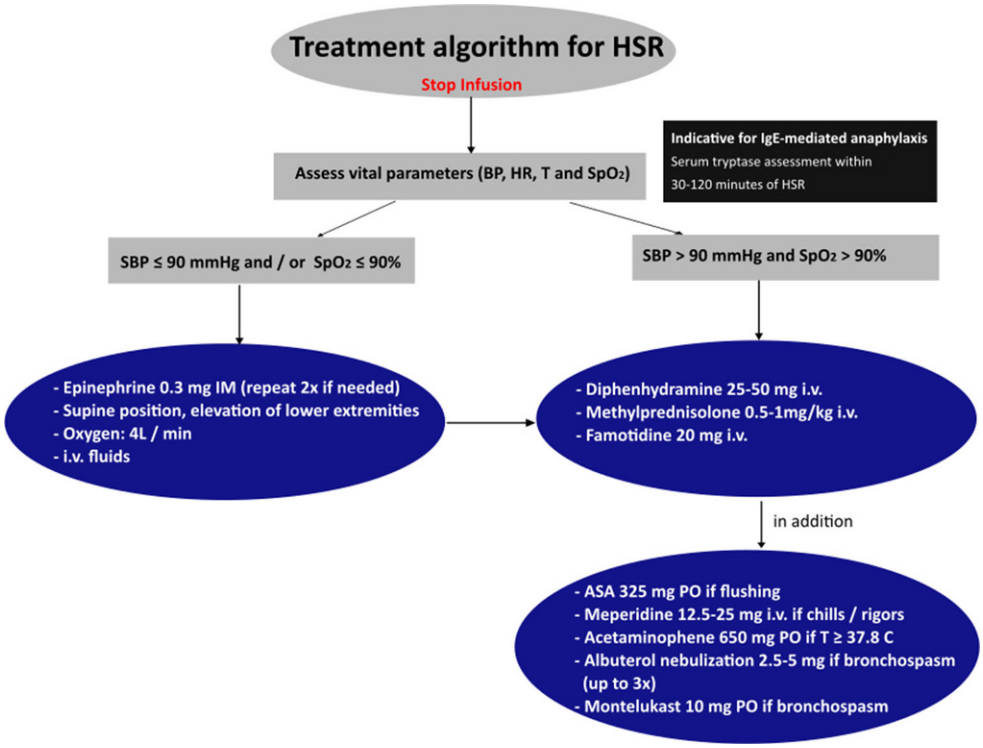

Fig. 3 Algorithm for the management of hypersensitivity reactions. (*BP* blood pressure, *HR* heart rate, *T* temperature, *SBP* systolic blood pressure, *SpO2* peripheral oxygen saturation, *IM* intramuscular, *i.v.* intravenous, *PO* per os, *ASA* acetylsalicylic acid. Adapted from Galvão et al. [40] with permission)

Table 10 An example of desensitization protocols: rituximab i.v. (Ritux® 851 mg), solution preparation [76]

Bags	Volume (mL)	Concentration (mg/mL)	Total amount of drug per solution (mg)
Solution 1	250	0.034	8.51
Solution 2	250	0.34	85
Solution 3	250	3.40	851
i.v. intravenous			

the components of BSs and potentially allergenic excipients is given in Tables 7 and 8.

Basophil activation test

Basophils play an important role in allergic reactions and diseases by releasing their own mediators.

Studies in the last 15 years have reported that the BAT is useful in the diagnosis of allergic reactions to various drugs (betalactams, quinolones, H2 blockers, neuromuscular blocking agents), foods (egg, milk, peanut), venoms (bee, wasp), and pollens (birch, timothy grass), and *D. pteronyssinus* (referenced in [56]).

Piva et al. [57] investigated the importance of the basophil activation test (BAT) in five patients with an anaphylactic reaction (angioedema, bronchospasm, hypotension, and urticaria) to rituximab. In this study, the percentage of CD63 expression in basophils was reported to be higher than in healthy controls. Therefore, it was emphasized that BAT (using CD63 as measurement for their activation status) may be helpful in cases with HSR against rituximab, when standard diagnostic tests are not available and diagnosis is difficult [57]. In addition, Iwamoto et al. [58] emphasized that further advanced tests targeting the interactions and bindings of IgE–cetuximab on basophils can be useful in predicting severe HSRs for cetuximab. BATs using CD63 and/or CD203c to measure basophil activation have been reported to be a fast and reliable test with diagnostic benefits in patients that develop life-threatening anaphylaxis induced by various drugs [59]. Further large scale studies with various BSs are needed to establish the BAT as a diagnostic tool for this entity.

Management of reactions to biotechnological substances

Today, the use and indications of biological treatments in different medical fields continue to increase. Therefore, the management of drug-related reactions has become important for the sustainability of treatment and safety for patients in daily practice. Algorithmic approaches should be developed and optimized to identify patients potentially at risk and in order to minimize the risk beforehand. Loss of immune tolerance causes problems such as the development of cancers and susceptibility to infections in some patients.

The risk for the development of HSRs to BSs depends on several factors: The degree of humanization of BSs, the additional ingredients, the type of administration (intravenous, subcutaneous, and intramuscular), the treatment intervals (and treatment pauses), the development of ADAs, and the clinical characteristics of the patients.

Premedication/concomitant medication/prophylaxis

There is still controversial data regarding the administration of premedication before treatment with BSs [14]. However, premedication for potential IRs and HSRs is recommended in FDA labels of many intravenously administered BSs. Low infusion rate, avoidance of long intervals between infusions and pretreatment with antihistamine and prednisone may prevent immediate and avoid delayed reactions [60]. In addition, H1 antihistamines plus acetaminophen or high-dose corticosteroid administration is recommended as prophylaxis for CRS induced by mAbs used in some cancer treatments and can significantly reduce the incidence and severity of CRS [61]. In rheumatoid arthritis patients, it has been reported that combination therapy with an anti-TNF-α and methotrexate reduces the development of ADA, thereby reducing the neutralization of the drug and reducing the risk of immunological reactions [17, 18, 62]. Further research is needed on the use of concomitant drugs with BSs. The literature describes desensitization protocols to reduce the risk of anaphylactic reactions to BSs, for example, for adalimumab [63]. In addition, adalimumab is the treatment alternative for patients with severe anaphylactic reactions to infliximab, another anti-TNF-α mAb [64].

Acute infusion reactions

An example approach in infusion centers according to the severity of acute infusion reactions is given in Table 9; [65, 66]. The management of acute infusion reactions is generally achieved by premedication with antihistamines, analgesics, corticosteroids, and slowing infusion rates [15, 65, 66].

Prevention of acute hypersensitivity reactions

Galvao et al. proposed an algorithmic treatment approach for HSRs [40]. This recommends treatment according to the vital parameters of the patients after the reaction, and offers treatment options for subsequent reactions (Fig. 3; [40]).

Desensitization protocols

Rapid drug desensitization (RDD) is a highly important treatment option that may protect patients from

Table 11 An example of a 12-step rapid drug desensitization protocol: Rituximab i.v. (Ritux® 851 mg): administration [76]

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.5	0.017	0.017
2	1	5	15	1.25	0.042	0.059
3	1	10	15	2.5	0.085	0.145
4	1	20	15	5	0.17	0.315
5	*2*	*5*	*15*	*1.25*	*0.42*	*0.740*
6	*2*	*10*	*15*	*2.5*	*0.85*	*1.59*
7	*2*	*20*	*15*	*5*	*1.70*	*3.29*
8	*2*	*40*	*15*	*10*	*3.40*	*6.69*
9	3	10	15	2.5	8.51	15.20
10	3	20	15	5	17.0	32.23
11	3	40	15	10	34.0	66.27
12	3	80	172.89	230.53	784.732	851.000
Total time: 338 min (5.63 h)						

severe reactions and anaphylaxis and ensures that their treatment continues. However, this treatment option is absolutely contraindicated in delayed onset cases such as toxic epidermal necrolysis, Stevens-Johnson syndrome, serum sickness, exfoliative or bullous dermatitis, acute generalized exanthematous pustulosis, erythema multiforme, vasculitis, and systemic drug reactions with eosinophilia [14, 40]. There are different approaches for RDD in various centers, and the protocols are not fully standardized and harmonized for the BSs.

There are many BSs (such as adalimumab, alemtuzumab, anakinra, bevacizumab, brentuximab, cetuximab, etanercept, infliximab, nivolumab, ofatumumab, panitumumab, rituximab, tocilizumab, and trastuzumab) in which RDD has been successfully applied, and new ones are added to the literature on a daily basis [40, 67–75]. An example for the 12-step RDD with rituximab is given in Tables 10 and 11 (for calculation see Ref. [76]). If any reaction occurs during RDD, the infusion and the application should be stopped. Additional medications should be administered according to the clinical condition observed in the patient.

The 12-step RDD protocol developed at Brigham and Women's Hospital (BWH; Boston, MA, USA) has been recognized worldwide [77, 78]. In general, the standard RDD protocol includes a three-step process. This includes three 250-mL solutions with 10-fold increasing concentrations and a total of 12 steps in which the dose is doubled every 15 min by increasing speed and/or concentration [40, 76, 79]. The treatment dose starts at a dilution of 1/1000 to 1/10,000. The first bag and second bag contain a 1/100 and a 1/10 dilution solution, respectively [40]. The third bag is calculated by subtracting the cumulative dose from steps 1 to 8 from the targeted dose, and is administered over a relatively long period of time compared to the first two steps (calculation in Ref.[76]). There are also 16-step protocols in the literature, which are used for patients with severe anaphylactic reactions such as cardiac arrest [78].

Brown et al. classified acute systemic HSRs with a simpler and more useful grading system [80]. Accordingly, reactions are divided into three groups.

- Grade 1: Only cutaneous reactions
- Grade 2: Reactions involving symptoms of the respiratory, cardiovascular system, or gastrointestinal tract
- Grade 3: Loss of consciousness, hypoxia or hypotension, and cardiovascular collapse

Some experienced centers desensitize 3rd degree reactions according to this classification in the intensive care unit [33]. Patients that tolerate the first desensitization and those with 1–2 degree reactions receive desensitization treatments in outpatient infusion centers.

Conclusion

HSRs to BS are gradually increasing with the widening of clinical use and indications. It is very important to prevent HSRs, to know the degree of severity and the emergency treatment algorithm, as well as to apply desensitization when necessary. In this review, the authors have sought to extract information from the literature containing all these issues and provide some structures that help to classify the reactions that may have occurred in their daily practice. They have summarized the diagnostic tests that should be applied: (a) immediately during/after a reaction, and (b) subsequently, and in the case that a switch of BS is not possible, desensitization is an option.

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