Small molecules, used as drugs, can induce immune reactions by binding covalently as haptens to a carrier protein, which is thereby modified and immunogenic. In addition, drugs bind to proteins via hydrogen bonds, electrostatic force, and van der Waals forces, and may directly interact with immune receptors such as T cell receptors or major histocompatibility complex molecules (pharmacologic interaction with immune receptors, so-called p-i concept). Even this noncovalent interaction may stimulate T cells. The ensuing immune response based on hapten-peptide presentation or direct drug-receptor interaction results in many distinct clinical situations. Based on progress in T cell immunology, this heterogeneity of T cell reaction is now also reflected in a subclassification of type IVa to IVd reactions.

Clinicians commonly encounter patients who report to have drug allergy. In a large part, such allergy corresponds to adverse drug reactions, which are not immune mediated. The incriminated drug need not always be avoided for further therapy. On the other hand, drug allergy may manifest in many unexpected clinical pictures and thus not be recognized. There is no single standardized diagnostic test to confirm the immune-mediated mechanism and to identify the causative drug. Therefore, immune-mediated drug hypersensitivity reactions and their causative drugs have to be considered by the constellation of exposure, timing, and clinical features, including the pattern of organ manifestation. Prior experience with the drug is also an important feature. An allergologic workup with additional investigation may provide some help. Patients should be informed carefully about their drug allergy, whereby symptoms, drug that elicits reaction, modes of diagnosis of drug allergy, and possibly alternatives should be indicated in their allergy passport.

Adverse drug reactions (ADRs) are a frequent problem in clinical routine, affecting 10% to 15% of all patients receiving pharmacotherapy. Approximately 2% to 3% of hospitalized patients develop cutaneous ADRs. The skin is an important herald organ and may display early signs that may indicate a severe course of the cutaneous reaction or the potential
involvement of internal organs or circulating blood cells. Timely recognition of such cutaneous lesions and the correct differential diagnosis with prompt withdrawal of the putative culprit drug are essential to reducing morbidity and preventing mortality. This article discusses risk factors, early symptoms, and danger signs indicating a possibly severe course of an ADR and advises on early actions.

Acute Symptoms of Drug Hypersensitivity (Urticaria, Angioedema, Anaphylaxis, Anaphylactic Shock) 691
Ticha Limsuwan and Pascal Demoly

Drug hypersensitivity reactions (HSRs) are the adverse effects of drugs which, when taken at doses generally tolerated by normal subjects, clinically resemble allergy. Immediate-reaction of drug HSRs are those that occur less than 1 hour after the last drug intake, usually in the form of urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, and anaphylaxis or anaphylactic shock. Acute urticarial and angioedema reactions are common clinical problems frequently encountered by internists and general practitioners. They are not specific to drug allergic reaction, and can be caused by various pathogenic mechanisms. Despite the benign course of urticaria and angioedema, a mucocutaneous swelling of the upper respiratory tract could be life-threatening by itself or a feature of anaphylaxis. This article reviews acute symptoms of drug HSR-related urticaria, angioedema, anaphylaxis, and anaphylactic shock, and how clinicians should approach these problems.

Delayed Cutaneous Manifestations of Drug Hypersensitivity 711
Andreas J. Bircher and Kathrin Scherer

Drugs may elicit a considerable variety of clinical signs, often affecting the skin and the mucous membranes. The most common are maculopapular exanthemas and urticaria, more rarely pustules, bullae vasculitic lesions, and lichenoid lesions may also be observed. Apart from the morphology, the chronology of the occurrence and the evolution of single skin lesions and exanthema are also paramount in the clinical diagnosis of cutaneous drug hypersensitivity. Often, the skin represents the only organ manifestation; however, it may be the herald for a systemic involvement of internal organs, such as in severe drug-induced hypersensitivity syndromes or anaphylaxis.

Severe Cutaneous Adverse Reactions: Acute Generalized Exanthematous Pustulosis, Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome 727
Thomas Harr and Lars E. French

Most drug hypersensitivity reactions show skin symptoms. The most severe cutaneous manifestations include pustular and bullous skin eruptions. These 2 manifestations can lead to acute generalized exanthematous pustulosis or Stevens-Johnson syndrome and toxic epidermal necrolysis. These complications are rare, but should be known to any doctor prescribing drugs because they are life threatening and early stoppage of treatment is mandatory.
Visceral Involvements and Long-term Sequelae in Drug-induced Hypersensitivity Syndrome 743

Yoko Kano, Tadashi Ishida, Kazuhisa Hirahara, and Tetsuo Shiohara

Drug-induced hypersensitivity syndrome (DIHS) is a severe systemic reaction with several herpesvirus reactivations. Multiple organ failures appear during the course of the disease. The severity of DIHS is determined by the degree of visceral involvement. Autoimmune diseases also develop several months to years after the apparent clinical resolution of DIHS.

Perioperative Anaphylaxis 761


The incidence of immune-mediated anaphylaxis during anesthesia ranges from 1 in 10,000 to 1 in 20,000. Neuromuscular blocking agents are most frequently incriminated, followed by latex and antibiotics, although any drug or substance used may be a culprit. Diagnosis relies on tryptase measurements at the time of the reaction and skin tests, specific immunoglobulin E, or basophil activation assays. Treatment consists of rapid volume expansion and epinephrine administration titrated to symptom severity.

The Complex Clinical Picture of Side Effects to Biologicals 791

Oliver V. Hausmann, Michael Seitz, Peter M. Villiger, and Werner J. Pichler

Biologicals are proteins used as drugs. Biologicals target clearly defined molecular structures, being part of established pathogenetic pathways. Therefore, their focused mode of action seems to render them superior to classic small molecular drugs regarding “off-target” adverse drug reactions (ADR). Nevertheless, the increasing use of biologicals for the treatment of different diseases has revealed partially unexpected adverse reactions. The often direct interaction of a biological with the immune system provides a clue to most side effects, which have consequently been subclassified, based on pathogenetic principles, into 5 subtypes named α, β, γ, δ, and ε, reflecting overstimulation (high cytokine values, type α), hypersensitivity (type β), immune deviation (including immunodeficiency, type γ), cross-reactivity (type δ), and nonimmune mediated side effects (type ε). This article presents typical clinical manifestations of these subtypes of ADR to biologicals, proposes general rules for treating them, and provides a scheme for a thorough allergological workup. This approach should help in future handling of these often very efficient drugs.

The Complex Clinical Picture of β-Lactam Hypersensitivity: Penicillins, Cephalosporins, Monobactams, Carbapenems, and Clavams 805

Maria J. Torres and Miguel Blanca

β-Lactam antibiotics are the drugs most frequently involved in drug hypersensitivity reactions that are mediated by specific immunologic
mechanisms. In addition to benzylpenicillin, several chemical structures belonging to 5 major subgroups can induce reactions. The most relevant structure is that of the amoxicillin molecule. Reactions belong to the 4 major mechanisms described by Coombs and Gell, whereby type IV reactions have recently been further subclassified. The most frequent reactions are type I, which are IgE mediated, and type IV, which are nonimmediate and T-cell dependent. IgE-specific antibodies may recognize the benzylpenicilloyl structure or another part of the molecule, such as the side chain, as antigenic determinants. Depending on specific recognition, subjects can be either cross-reators or selective responders. A variety of entities exist in T-cell reactions, ranging from mild exanthema to life-threatening, severe reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Diagnostic tests for IgE-mediated reactions can be done in vivo by testing skin with different penicillin determinants or in vitro by quantitating specific IgE antibodies. For nonimmediate reactions, there are also in vitro and in vivo tests, with variable degrees of sensitivity and specificity. The natural history of IgE-mediated reactions indicates that the count of specific IgE antibodies decreases over time and that results of diagnostic tests can become negative.

The Complex Clinical Picture of Side Effects to Anticoagulation 821
Axel Trautmann and Cornelia S. Seitz

Inflammatory plaques at injection sites are frequent side effects of heparin treatment and a clinical symptom of delayed-type hypersensitivity (DTH) to heparin. In most cases, changing the subcutaneous therapy from unfractionated to low-molecular-weight heparin or treatment with heparinoids does not provide improvement because of extensive cross-reactivity. Because of their completely different chemical structure, hirudins are a safe alternative for anticoagulation. Despite DTH to subcutaneously injected heparins, patients tolerate heparin intravenously. Therefore, in case of therapeutic necessity and DTH to heparins, the simple shift from subcutaneous to intravenous heparin administration is justified. Skin necrosis is a rare complication of anticoagulation. Heparin-induced skin necrosis is 1 of the symptoms of immune-mediated heparin-induced thrombocytopenia and should result in the immediate cessation of heparin therapy to prevent potentially fatal thrombotic events. This is in contrast to coumarin-induced skin necrosis, where therapy may be continued or restarted at a lower dose.

The Complex Clinical Picture of Presumably Allergic Side Effects to Cytostatic Drugs: Symptoms, Pathomechanism, Reexposure, and Desensitization 835
Mauro Pagani

The number of drugs used for the treatment of different types of cancers is constantly increasing and actually exceeds 100 distinct chemical formulations. The use of most cytotoxic agents is associated with potential hypersensitivity reactions, and the constant increase of their administration has caused an increase in incidence of these adverse effects, thus becoming a relevant problem for clinicians. Hypersensitivity reactions are common with platinum compounds, L-asparaginase, taxanes, procarbazine, and epipodophyllotoxins, whereas they are unusual, but always possible,
with the other chemotherapeutic drugs. Reactions associated with individual drugs are discussed in detail. The mechanism underlying these hypersensitivity reactions involves IgE-mediated hypersensitivity reactions, nonallergic hypersensitivity reactions, and a few pathogenetically unclear reactions. More studies are needed to better understand, diagnose, treat, and prevent these reactions. To achieve this goal, a multidisciplinary approach to treat patients with cancer who have potential allergies is needed.

NSAID Hypersensitivity (Respiratory, Cutaneous, and Generalized Anaphylactic Symptoms) 853

Mario Sánchez-Borges

Adverse reactions to drugs have been classified as predictable (related to the pharmacologic actions of the drug) and unpredictable (related to the individual’s immunologic response or genetic susceptibility). The term “drug hypersensitivity” refers to the symptoms or signs initiated by an exposure to a drug at a dose normally tolerated by nonhypersensitive persons. In this article, the current knowledge on hypersensitivity reactions to nonsteroidal antiinflammatory drugs is discussed.

Index 865