Adverse drug reactions are either related to their pharmacologic activity or to idiosyncratic or immune-mediated reactions.

Adverse drug reactions are sometimes life-threatening because of various organ injuries leading to organ (or multiple-organ) failure.

Many drugs used in dermatologic diseases are involved in such severe manifestations.

Adverse drug reactions and severe outcome of drug-induced adverse effects are partly preventable.

Almost all drugs can induce life-threatening reactions, but these manifestations are unfrequent.

There is a lack of information about the risks of new marketed products.

29.1 Adverse Effects of Drugs

Adverse drug reactions are a major cause of morbidity and mortality world-wide. A marked increase was found between 1998 and 2005 in deaths and serious injuries associated with drug therapy reported to the US Food and Drug Administration [1]. Despite some limitations or alternative explanations, this increase seems to be related to a real increase in the numbers of patients experiencing serious injuries from drug therapy.

During clinical trials, only a small number of patients are exposed to a new drug, over a limited period of time, compared to the number that might use it once a marketing authorisation has been granted. Thus, when a drug is first marketed, much may be known about its efficacy while relatively little may be known about its safety. Rare and possibly serious adverse reactions, occurring in only a small percentage of cases, may not be detected during clinical trials.

Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects of drugs, especially by means of post-marketing surveillance. Spontaneous adverse drug reaction reporting or large-scale databases are useful to generate hypotheses and signals about potential risks of marketed drugs that require further investigation. Spontaneous reporting of suspected adverse drug reactions is particularly useful in identifying serious, rare and/or delayed reactions.

Establishing a diagnosis of drug-induced disease (i.e., imputability processes) may be difficult. Imputability relies upon the elimination of other causes and a compatible or a suggestive time-relationship between drug ingestion (onset and withdrawal) and the evolution of the adverse event. In addition, it is important to consider the nature of the reaction and the relationship to the dose administered.

Healthcare professionals must be aware of the benefit–risk ratio before prescribing. They should be particularly aware that some situations related to the patient may favour drug-induced reactions: children, elderly patients, pregnant women, and patients with liver or renal failure are susceptible to adverse reactions.
and it is therefore important to monitor drug safety in these patient populations.

The risk of adverse effect may increase in situations related to the status of drugs:

– Newly marketed drugs or established products with a new indication or route of administration
– New combinations of established drugs or new targeted patient populations
– Drugs with a narrow therapeutic index
– Drugs known to interact

Drug reactions can be classified into immunologic and non-immunologic mechanisms.

– The majority of adverse drug reactions are caused by non-immunologic effects, which are either predictable (due to pharmacologic action, thus often dose-related), or unpredictable (idiosyncratic) such as pseudo-allergic reactions.
– Predominant mechanisms that lead to clinical symptoms of immune-mediated reactions (or allergy) are commonly described in the Gell and Coombs classification system. A revised nomenclature for allergy, including drug reactions, was proposed in 2004 [2]. Immune-mediated reactions are unpredictable and not clearly related to the dose.

This review will focus on the most severe and life-threatening adverse reactions to the common drugs or therapies used in dermatology. It is not meant to be exhaustive because of the number and the variety of agents prescribed by dermatologists, in inpatients as well as in outpatients.

29.2 Anaphylaxis

Anaphylaxis is a severe and potentially lethal immediate-type generalised hypersensitivity reaction affecting multiple organ systems. Severe anaphylaxis includes such serious symptoms as cardiovascular collapse, cardiac arrhythmia, severe bronchospasm, circulatory failure, cardiac and/or respiratory arrest, and finally lethal anaphylaxis.

Drugs are a frequent cause of anaphylaxis identified in epidemiological studies conducted in both hospital and emergency units [3]. Antibiotics were the more common cause of life-threatening drug anaphylaxis, as registered by the French Allergy Vigilance Network over 2003/2004, with amoxicillin involved in 40% of cases, cephalosporins in 15% and other antibiotics in 5% [3]. Injectable antibiotics (penicillin, cephalosporin, vancomycin, quinolones, macrolides) were responsible for 15% of anaphylaxis during anaesthesia among 502 patients referred to an allergo–anaesthesia centre between January 2001 and December 2002, taking the third position after curare and latex [4]. Local anaesthetics (articaine, lidocaine, mepivacaine) were involved in less than 1% of cases.

Death from an allergic reaction to penicillin occurs at an incidence of about 1 per 50,000 treatment courses of parenteral penicillin in the general population [5].

All routes of administration are potentially involved, even in topical skin application (antibiotics or antiseptics) [6] and prick-tests [7].

Urticaria may be a non-severe manifestation of anaphylaxis, but is more often a manifestation of pseudo-allergic reaction. In a prospective study including 350 patients who presented with immediate hypersensitivity (urticaria, angioedema, anaphylactic shock) suspected of being drug-induced, only 22 had definite allergy defined as positive tests for the suspected drug. Among these 22 patients, 20 had severe effects such as major angioedema, hypotension, bronchospasm or anaphylactic shock. The other 328 patients suffered from pseudo-allergic or not drug-related urticaria without severe manifestation, which made re-challenge of the suspected drug possible [8].

29.3 Life-Threatening Cutaneous Drug Reactions

A separate chapter in this book is devoted to severe cutaneous drug reactions such as toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and acute generalized exanthematous pustulosis (AGEP).

More than 100 drugs have been suspected to be a possible etiologic agent of SJS/TEN in case reports or retrospective studies. Among drugs used in dermatology, according to results of prospective case-control studies, anti-infective sulfonamides were the most strongly associated with SJS/TEN; a significant but lower risk was found with other antibiotic drugs (aminopenicillins, cephalosporins, quinolones, tetracyclines, macrolides) [9, 10].