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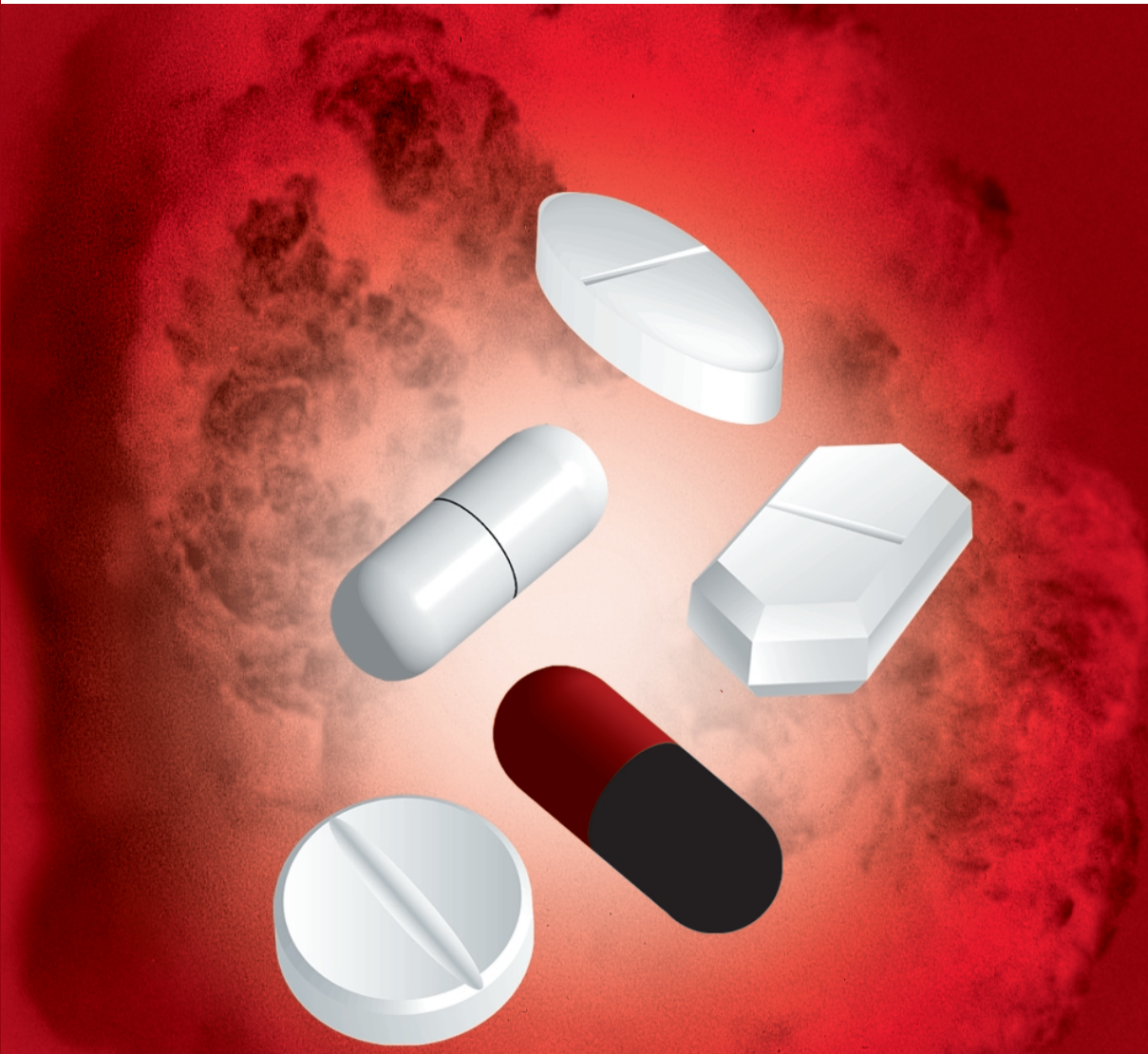
COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

REPORTING ADVERSE DRUG REACTIONS

DEFINITIONS OF TERMS AND CRITERIA FOR THEIR USE



CIOMS

REPORTING ADVERSE DRUG REACTIONS

Definitions of Terms and Criteria for their Use

Geneva

Book and CD-Rom

ISBN 92 9036 071 2

Printed in Switzerland
Reprinted 2000

The Council for International Organizations of Medical Sciences (CIOMS) is a nongovernmental organization established jointly by the World Health Organization and UNESCO in 1949, with a mandate to collaborate with the United Nations and its specialized agencies. Its international membership, consisting of international unions and federations of national associations and societies, represents a substantial proportion of the world's biomedical scientific community. Its secretariat is located in Geneva in offices made available by the World Health Organization.

A dominant theme of CIOMS for some time has been the ethical aspects of biomedical technology and the bioethical considerations to be taken into account in determining and implementing health policy.

A particular aspect of biomedical technology, the development and use of drugs, has been a second major theme. The independent status of CIOMS has permitted it to coordinate the contributions of research-based pharmaceutical companies, national drug regulatory authorities, and representative bodies of medical specialties to harmonizing and strengthening drug-safety surveillance measures.

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ACKNOWLEDGMENTS

The Council for International Organizations of Medical Sciences (CIOMS) gratefully acknowledges the contribution of over 160 individuals to the work that has resulted in this publication, by their participation in working groups, providing consultant advice or preparing background papers, as representatives of pharmaceutical companies, drug regulatory authorities or international medical societies, or as medical experts from universities, clinics, and hospitals in 15 countries (Appendix II).

CIOMS acknowledges especially the contribution of the core group of pharmaceutical companies at whose request the project was undertaken and which largely funded it. These were, from Germany, seven members of Verband Forschender Arzneimittelhersteller e.V., Bonn (Bayer AG, Leverkusen; Boehringer Ingelheim GmbH, Ingelheim; Boehringer Mannheim GmbH, Mannheim; Hoechst AG, Frankfurt; Knoll AG, Ludwigshafen; F. Merck AG, Darmstadt; Schering AG, Berlin); from Switzerland, three companies associated in INTERPHARMA, Basel [Ciba-Geigy AG and Sandoz AG (now Novartis AG), Basel; F. Hoffmann-La Roche AG, Basel]; and from France, Sanofi Synthelabo SA, Gentilly. Particularly appreciated was the enthusiastic support of Dr Eberhard Baumbauer, Head of the Secretariat of Verband Forschender Arzneimittelhersteller e.V., and of Dr Jürg Schrank, Head, Research and Development, INTERPHARMA.

Apart from this core group, the following pharmaceutical companies were represented in one or more groups: ICI Pharmaceuticals ZENECA, United Kingdom; Organon International BV, Netherlands; Rhone-Poulenc Rorer, Inc., France; Roussel Uclaf, France; Byk Gulden GmbH, Konstanz, Germany; Dr. K. Thomae GmbH, Biberach, Germany; Schwarz Pharma AG, Monheim, Germany.

The project depended crucially on the input of national drug regulatory authorities, from eight countries: Denmark (Danish Medicines Agency), France (Commission Nationale de Pharmacovigilance), Germany (Bundesinstitut für Arzneimittel und Medizinprodukte, Berlin); Italy (Pharmaceutical Department, Ministry of Health, Rome); Netherlands (Netherlands Centre for Monitoring of Adverse Reactions to Drugs); Sweden (the Medical Products Agency); Switzerland (Intercantonal Office for the Control of Medicines, Bern); the United Kingdom (Medicines Control Agency); and the United States of America (Food and Drug Administration).

The Commission of the European Communities, Brussels, funded a working group on cardiovascular disease terms. The European Agency for the Evaluation of Medical Products, London, hosted and assisted with the meeting of the working group on gastro-intestinal disorder ADR terms. The International Federation of Pharmaceutical Manufactures Associations, Geneva, contributed enthusiastically and was represented in several working groups.

Several individuals merit special mention. Dr Ronald D. Mann, chaired most of the working-group meetings; participants appreciated his skill in distilling the essence of definitions and requirements. As editor of *Pharmacoepidemiology and drug safety*, he guided the publication of the working-group reports. Professor Gottfried Kreutz chaired several meetings and provided valuable support. Professor Ralph Edwards of the Uppsala Monitoring Centre provided data on the frequency of reporting of different adverse drug reactions. The late Dr Susan Wood and Dr Louise Wood of the United Kingdom Medicines Control Agency made available preliminary versions of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Dr Gerhard Kremer and Ms Isolde Crusius, of Boehringer Ingelheim GmbH, Germany, prepared the computerized text of this publication.

CIOMS has highly appreciated the consistent support of the World Health Organization, Geneva, represented particularly by its Division of Drug Management and Policy, and its Directors, first Dr John Dunne and then his successor until the end of the project, Dr Juhana Idänpään-Heikkilä. Dr Martijn ten Ham of the Drug Safety section gave valuable technical and administrative support throughout. Other divisions also made essential contributions, notably in respect of psychiatric and cardiovascular-disease terms.

At CIOMS, Jan Venulet managed the project; James Gallagher edited and prepared for publication the working-group reports and the text of the present publication; and Kathryn Chalaby-Amsler and Christine Dübendorfer provided the essential administrative and secretarial support throughout the project.

FOREWORD

The thalidomide disaster, which struck in 1961, stimulated national and international action towards assuring the safety of medicinal drugs and reducing the risk of adverse reactions to them. The response of the World Health Assembly culminated in a few years in an international system of drug safety monitoring. One effect of this system was that the pharmaceutical industry overcame its mistrust of drug regulatory authorities, becoming with them, and with experts in university medical faculties and international medical societies, an essential and valued partner in the pursuit of drug safety. A way had to be found of associating the industry with the World Health Organization (WHO), and it was here that the Council for International Organizations of Medical Sciences (CIOMS), as a nongovernmental organization with a mandate to cooperate with WHO, was in a position to play a particular role. Under its auspices, the industry could cooperate with regulatory authorities, medical experts and WHO in projects for promoting drug safety.

This publication, in the form of a book and CD-ROM, is a product of that cooperation. It is the outcome of a series of international working groups convened by CIOMS over the past decade, in which representatives of regulatory bodies and pharmaceutical companies, together with clinical experts and staff members of WHO and CIOMS, agreed on standard definitions of selected terms for adverse drug reactions and on minimum requirements for the use of the terms in international reporting, in the framework of post-marketing surveillance. Those definitions and requirements have been collated from the published reports of the working groups.

A system of international pharmacovigilance requires efficient communication between people of diverse cultural and linguistic backgrounds and from different medical care and education systems. Such communication depends on the common use of a terminology that is simple, precise and unambiguous. This publication is designed primarily to meet the needs in this respect of drug regulatory authorities and the drug safety departments of pharmaceutical companies, as their participant representatives have perceived those needs in their day-to-day work. It is intended also for medical or other reporters of adverse drug reactions, to help them document their case reports and communicate them to regulatory authorities or drug manufacturers. It has wider educational potential also.

This novel initiative is one facet of a movement geared to the international harmonization of drug safety procedures. Its applicability to other languages and cultures is worth consideration. It presupposes an adequate infrastructure for post-marketing surveillance of drug safety, which is characteristic of developed countries but, in general, lacking in developing countries. Any contribution that this publication and the process of which it is the product can make to the efforts of WHO to reduce the public health consequences of poor drug safety in developing countries will be in some part a repayment for the support and encouragement which the project has consistently received from WHO.

PERSPECTIVES

The World Health Organization

J.E. Idänpään-Heikkilä [a]

After the discovery and synthesis of a new drug, and parallel to product development, it undergoes toxicological and pharmacological tests in animals, followed by clinical trials in humans. Although the pre-marketing investigation, preclinical and clinical, of a new medicinal product is carefully performed and critically assessed, it does not always reveal all possible effects, side-effects or adverse reactions. A product which the drug regulatory agency authorizes for marketing still requires intensive post-marketing monitoring. Many adverse reactions can be detected only after the medicinal product has been prescribed to, and used by, a large number of patients. This environment, with multiple potential new co-factors of real life, cannot be replicated in clinical trials. The introduction of a new medicinal product, therefore, always carries unknown risks, as numerous instances during the past decades have demonstrated. In this situation the alertness of the prescribing physician and the quality of the operational system for reporting adverse reactions are crucial.

Verification of a new potential and harmful reaction often requires the collection and review of reports from different countries, and these reports must be properly assessed and validated. One major problem has been that concepts of diagnosis and the terms used to designate adverse reactions vary from country to country. For some years the Council for International Organizations of Medical Sciences (CIOMS), with the collaboration of the World Health Organization (WHO), medical experts, drug regulatory authorities and the pharmaceutical industry, has worked on harmonization of reporting of adverse drug reactions. The terms concerned have been mainly those liable to be misinterpreted and those that designated serious adverse reactions.

The outcome of the project is now being published as a cumulative volume and a CD-ROM, designed to facilitate common understanding and the uniform use of terms for the monitoring of drug safety. The established definitions and basic requirements for the proper use of adverse-drug-reaction terms will undoubtedly assist practising physicians in their reporting of adverse reactions. Single case reports by physicians still represent the most important source of information for raising suspicions,

[a] Former Director, Division of Drug Management and Use, World Health Organization, Geneva, Switzerland.

generating early signals and confirming the occurrence of new adverse drug reactions. The more these reports conform to the established definitions and requirements, the easier it will be to monitor drug safety, and for drug regulators to carry out comparative assessment and verification of adverse reactions to new drugs. Pharmaceutical companies also will be assisted in assessing and reporting adverse reactions notified to them from different countries with varying medical cultures. Even scientists concerned with drug-safety issues and engaged in research will benefit from this work.

Further consideration must be given to means of ensuring that the end-users in all countries will have access to this publication. Evidently, translation into internationally used languages, and even into national languages, is essential; otherwise the reporting of adverse reactions on a national level will not benefit. Vigorous efforts must be made to distribute and promote it to physicians and other users, including drug regulators and the pharmaceutical industry. Ideally, all reporting physicians and drug safety officers should have this material available in their offices.

As science and our knowledge of drug safety develops, the definitions and requirements will need periodic updating and adaptation. Harmonization should not be forced too far, however. New, unknown adverse drug reactions, often a type of syndrome with multiple symptoms, should be easily recognized and verified. Symptoms of a potential syndrome should not be split into separate adverse - reaction terms. Physicians, therefore, should still report adverse events in words that describe the findings as they observe and detect them in patients. This should not inhibit them from using harmonized terms whenever such terms properly describe an observed event.

CIOMS is to be congratulated on developing and finalizing this project on definitions and requirements for the use of adverse-drug-reaction terms. This will contribute in a valuable way to the WHO Drug Monitoring Programme at both national and international levels. It represents an important step in promoting the safe use by patients of medicinal products.

Drug Regulatory Authorities

G. Kreutz[a] *and M.M. Lumpkin*[b]

Quality assurance and quality control are integral components of most aspects of the study, production, regulatory oversight, and marketing of pharmaceutical products. Specific standards of quality have been agreed in many of these areas of a product's "life". There is still, however, great diversity and inconsistency in the use of various specific medical terms used

[a] Professor and Director, Federal Institute for Drugs and Medical Devices, Berlin, Germany

[b] Director, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA.

to record suspected adverse reactions to drugs. Agreed quality assurance and quality control standards in this domain have been particularly lacking. Both lack of acknowledged definitions and translational errors by those whose usual language of practice is not medical English accentuate this continuing problem.

Now, with the availability of the series of "Definitions and Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions", CIOMS continues its special effort to address this concern. Reporters of adverse reactions can be assured that, when they choose to use a specific term contained in this publication, it indeed conveys the medical concept they wish to convey. They can examine their selection of a specific term against specific minimum definitional criteria and thus decrease observational and linguistic biases in the assignment of certain terms. This can be a first and very important step in improving the quality of the data accumulated and reported on suspected adverse drug reactions.

It is important to realize, however, that the confirmation of an event observed as being consistent with a given definition and minimum criteria applied to the use of a term does not constitute proof or add to the probability of a causal relationship between the event and the pharmaceutical product or any of its effective substances or its excipients.The process of causality assessment has to be based on a complex judgement that takes into account a full evaluation founded on thorough knowledge of the pharmacological properties of a product, added to a validated description of the observed event, and including all observations that may support causes of the event other than a suspected pharmaceutical product.

What is the main advantage of this publication?

The main advantage is the opportunity to reduce observational and linguistic biases in the assignment of terms. Also, from the experience gained from the guidance given here, it will be possible to determine what alterations will be needed in future editions.

What are its limitations?

Only a limited number of adverse-drug-reaction terms are covered and the criteria may not be applicable in each single case. Also, not uncommonly, not all the minimum criteria will be met, yet one will be convinced that the suspected reaction nonetheless qualifies as an instance of a particular term. It must be possible to use the term in certain cases, even when all criteria are not met, in order to group adequately single cases that one believes should be grouped together for various analytical purposes.

Who should use these definitions and apply the criteria?

Though these definitions and criteria offer the possibility of improving the quality of recording and reporting suspected adverse drug reactions, they are not yet fully validated or tested in "real world" experience. They will at first be primarily of use to pharmaceutical companies but all who report, record and assess adverse drug reactions should become aware of, and use, them, irrespective of their professional or organizational backgrounds.

What is needed in the future?

All experience from using this set of definitions and criteria should be reported to CIOMS or to a designated person to allow a comprehensive assessment of experience with the definitions and criteria. This will make it possible to determine what changes will need to be made in the future to ensure that the original goals of the project can be met.

Much effort has gone into this project; the challenge now is to determine whether use of such an instrument indeed improves the public health by improving the quality of recording and reporting individual reports of suspected adverse drug reactions.

The View of a Clinician

Ronald D. Mann[a]

Words are in many ways different from numbers. Words are more affected by problems concerned with differences between languages and changes over periods of time than are numbers. The definitions given in this book aim to resolve at least in part those problems concerned with words and our need to communicate medical information by written and verbal exchanges.

Clinicians and academicians communicate verbally with one another and with their patients and peers. In relation to reporting of adverse drug reactions, the language problem is very real and persistent.

Clinicians and academicians, in connection with the reporting of adverse drug reactions or events, can be involved in a number of ways. They can be reporters of suspected adverse drug reactions, assessors of adverse drug reactions (when they are working within regulatory bodies or drug companies), responders to enquiries when adverse drug reaction reports are being validated, and finally, critical reviewers or readers of papers and other communications.

[a] Former Director, Drug Safety Research Unit, University of Southampton, Southampton, United Kingdom

When reporting adverse drug reactions, or their suspicions regarding such reactions, clinicians are often confronted by difficulties. Sometimes, although relatively seldom, they will be reporting a clearly defined and well-known disease or syndrome. The difficulty is that many of the terms used in reporting have different meanings in different medical cultures; the definitions given in this book aim to cross those cultural differences. Clinicians are very well advised to frame their initial reports of a suspected adverse drug reaction or event in the words in which the patients describe them unless a very clear and precise and well-established definition can be given. It is important not to corrupt the data at source by using terms different from those the patient used, unless there is good reason to do so. In the Prescription-Event Monitoring Program, for example, there was a very clear difference between the terms that the patients used and those that clinicians tended to impose upon the patients' complaint of 'persistent dry cough'.

The character of the clinical complaint and its nature can be lost, and the data corrupted at source, by the careless use of words other than those that the patients use in talking to their physicians. When, as reporters, we are using terms other than those that the patients used, we need to be careful that we are using a term that is somewhere sensibly defined. This book provides definitions of many such terms. Textbooks of medicine and dictionaries define many other well-established terms and it is very helpful when clinicians in the field use a term and say what they mean by it, and name their source or definition of the term.

The practising clinician can also be involved when a report is being validated by the authority to which the suspicion of an adverse drug reaction has been reported. Validators may be either medically or scientifically qualified or both, and have received other appropriate training. Validation is the very essence of dealing with suspected adverse drug reactions. Seven reports of serious hepatic dysfunction may look very alarming when a new drug has just been marketed and such reports are unexpected from previous experience. They will look very different if, upon validation or follow-up, it is found that two of the patients to whom these reports relate are now known to have had carcinoma of the head of the pancreas, two are known to have suffered bile-stone problems, one has received a blood transfusion, and another was subsequently shown to have glandular fever. It then appears that only one case of the condition is possibly attributable to the drug given to all seven patients. Clinicians, therefore, need to be aware that, if they report a happening which leads to a serious suspicion of iatrogenic disease, their collaboration in the process of validation is important. When collaborating in such an exercise it is crucial to know what the terms the different participants are using mean and to avoid semantic confusion.

Clinicians and academicians can also be assessors of reports of adverse drug reactions. They may be working within one of the drug regulatory bodies or one of the pharmaceutical companies concerned, or they may be

experts whose opinion is sought by those with public responsibilities. Assessors always need to make sure that they understand what the words being used by the different participants mean. When this meaning crosses language barriers, or barriers resulting from different schools of medicine, and when the term being used crosses cultural divides, then it becomes even more necessary to ensure that everyone knows what all the others concerned mean by the terms they are using. Textbooks of medicine and surgery and medical science help enormously, but not always. A good example is to look at the different meanings given in different medical cultures to the terms 'phlebothrombosis' and 'thrombophlebitis'. If one just indiscriminately joins together reports of these conditions from different countries, then the outcome can be totally confusing. By joining together superficial thrombophlebitis (an inflammatory process which virtually never gives rise to pulmonary embolism) and phlebothrombosis (which does give rise to pulmonary embolism) one can show by semantic imprecision that all forms of venous thrombosis cause embolism.

Finally, the clinician and academician becomes concerned with this issue as a critical reader of published papers and reports of suspected adverse drug reactions or events. Are the different reports homogeneous in the meaning of the terms used? Have reports which really mean different things been lumped together as though they have a consistent and uniform meaning? Have the statisticians done something very sophisticated with the numbers without noticing or realizing that they have grouped together terms with heterogeneous meanings? The thinking critical reader will be keenly aware of the problems raised by such issues and will, it is hoped, find this present volume informative and useful.

The Pharmaceutical Industry

W. Aellig[a], *R. Bruppacher*[b], *G. Kremer*[c], *W. Pfeiffer*[d], *W. Spiegl*[e], *and D. Tancrede*[f].

Drug-safety physicians are often confronted, especially in relation to spontaneous reporting, with incomplete information on observed adverse events. To make the best use of the information received, they need medical commonsense, experience and — when collecting additional information — communication skills.

Having collected all the needed information available, the drug-safety physician is supposed to write a medical evaluation — including a

[a] Novartis Pharma AG, Clinical Safety and Epidemiology, Basel, Switzerland

[b] Institute for Social and Preventive Medicine, University of Basel; Department of Clinical Pharmacology, University Clinics Basel, Switzerland;

[c] Boehringer Ingelheim GmbH, Ingelheim-am-Rhein, Germany

[d] Bayer AG, Pharma Research Centre, Wuppertal, Germany

[e] F. Hoffmann-La Roche AG, Basel, Switzerland

[f] Direction internationale de la Pharmacovigilance, Sanofi-Synthelabo SA, Gentilly, France

diagnosis, a comment on the causal role of the drug in question, and alternative explanations — and a discussion of any action that needs to be taken.

This evaluation, to be of use in the international pharmacovigilance process, must be based on definitions that are internationally consistent. In general, terms used to designate adverse events have not been defined specifically for purposes of drug safety, but, rather, for much broader use within the academic environment. Normally, therefore, in connection with drug safety, already existing definitions are used.

Not uncommonly, however, different countries use different definitions of the same term. For this reason, especially in an international drug-safety network, where an issue raised in one country has an impact on regulatory decision-making in all others, it is necessary to agree upon definitions that are equally understood in all countries.

An even more important issue than unique definitions of terms, which are mostly provided by medical science, is the proper use of these terms in real-life situations.

A medical textbook describes diseases in detail, including all the signs and symptoms of a given condition. The drug-safety physician in the pharmaceutical industry is in a completely different position. There is normally no direct access to the patient. The information available is often scanty, and often all efforts to collect additional information fail.

Whenever a report of an adverse event is received, it must be documented and forwarded to regulatory authorities, as required by national law. In addition, however, the case must be evaluated appropriately, which includes a logical diagnosis together with possible differential diagnoses, on the basis of the information available.

Spontaneous reports cannot be expected to contain a complete set of findings to support our diagnoses. A diagnosis cannot be made without facts to support it, however. Consequently, it is necessary to determine the minimum set of signs and symptoms that will allow a specific diagnosis to be made. The drug-safety physician is always in the position of having to make an accurate diagnosis from scanty data, without resort to mere speculation.

For this reason, industry physicians mainly in Germany and Switzerland discussed in the late 1980s how to establish a set of "Basic Requirements for the Use of Terms". These would be requirements which, though insufficient to the needs of a practitioner making a bed-side diagnosis, would reflect a common understanding of what facts must be available in order to validate a diagnosis based upon a spontaneous report. It was felt that, to be widely accepted, the process of preparing such definitions and requirements should be undertaken only by an international, widely respected, neutral forum.

We are grateful, therefore, to the Council for International Organizations of Medical Sciences (CIOMS) and its Secretary General, Dr Zbigniew Bankowski, and to Dr Jan Venulet, Senior Adviser to CIOMS, who recognized this need and instituted a project accordingly. It brought together a series of dedicated international working groups of academics, regulators and industry experts, who over the past decade have cooperated effectively to accomplish the objective.

We are sure that all drug-safety colleagues who participated in the project for the pharmaceutical industry are satisfied that its results will contribute to better common understanding of terminology and diagnosis of adverse events, and — the ultimate goal of our efforts — to continuous improvement in the safety of our drugs.

INTRODUCTION

Jan Venulet and Zbigniew Bankowski

The advent of international drug monitoring in the late 1960s[1] and the directions that drug monitoring took in the following years led to the creation of large data-bases of heterogeneous origins. The data had been collected not only by international organizations such as the World Health Organization (WHO), but also by major pharmaceutical companies with world-wide activities.

Although suspected adverse drug reactions (ADRs) are reported mostly by physicians trained in what is called Western medicine, countries differ considerably in their use and interpretation of certain medical terms. Even within a country, physicians differ in knowledge and type of experience, sometimes because they have been trained in one country and practise in another. This may result in the use of different terms for the same event. Though practising physicians are the main beneficiaries of ADR data, they also generate most of the original observations and are thus largely responsible for the quality of the ADR data they transmit. Reported ADR data are, in general, incomplete and of poor quality[2, 3, 4, 5].

In 1986, the Council for International Organizations of Medical Sciences (CIOMS), which since 1977 had functioned as a forum for discussion between international drug regulatory authorities and pharmaceutical companies[6], set up a working group on International Reporting of Adverse Drug Reactions to explore means of coordinating and standardizing the reporting of ADRs. The group devised and pilot-tested a method and a reporting form — the so-called CIOMS Form — for the reporting by manufacturers to regulatory authorities of suspected adverse drug

[1] Venulet J. The WHO drug monitoring programme: The formative years (1968 -1975). In: Bankowski Z, Dunne JF, eds. Drug Surveillance: International Cooperation Past, Present and Future. Geneva: CIOMS, 1994:13-21.

[2] Venulet J. The practising physician as generator and user of adverse reaction data. International Journal of Clinical Pharmacology Therapy and Toxicology 1986; 24:385-9.

[3] Venulet J et al. How good are articles on adverse drug reactions. BMJ 1982; 284:252-4.

[4] Venulet J. Informativity of adverse drug reaction data in medical publications. Drug Information Journal 1985; 19: 357-65.

[5] Venulet J. Incomplete information as a limiting factor in causality assessment of adverse drug reactions and its practical consequences. Drug Information Journal 1986: 20:423-31.

[6] Venulet J., Bankowski Z. Harmonizing adverse drug reaction terminology: The role of the Council for International Organizations of Medical Sciences. Drug Safety 1998 Sep;19(3): 16572.

reactions[7]. Subsequent working groups, known as CIOMS II[8], III[9], IV[10] and V[11], have dealt with other matters relating to drug safety, while a separate project was instituted, in 1989, to standardize definitions and basic requirements for the use of ADR terms.

A CIOMS meeting in 1994 decided that the Medical Dictionary for Drug Regulatory Affairs (MedDRA)[12] would be the basis for the further development of an international medical terminology for drug regulatory purposes. Entries from both the WHO Adverse Reaction Terminology (WHO-ART) and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) would be included to facilitate transfer of recorded data. The meeting also recommended that the CIOMS project on definitions of preferred terms, already under way, be continued, to establish an unambiguous international medical terminology for regulatory purposes.

Standardization of definitions and basic requirements for the use of terms

Health professionals from different countries differ considerably in their use of medical terminology, including that used for ADRs, and in the exact meanings attributed to terms. In some European countries, for example, in contrast to the United Kingdom, the term 'thrombophlebitis' is used for a group of conditions, including deep venous thrombosis.

Pharmaceutical companies receive numerous reports of suspected ADRs from medical practitioners and other prescribers of drugs. Each company is required to transmit these reports to the drug regulatory agency of the country in which the report originated. When the reports are of particularly important or severe ADRs, companies are often also required to transmit them to the regulatory authorities of other countries in which the suspected product is marketed.

Variability in reporting ADRs is sometimes due to different codes or abbreviations used for drug forms, for example, or for dosage regimens or names of drugs. These can be streamlined with simple translating procedures built into computer programs. More difficult to handle internationally is information that requires more detailed medical knowl-

[7] International Reporting of Adverse Drug Reactions. Final Report of a CIOMS Working Group. Geneva: CIOMS, 1990.

[8] International reporting of periodic drug-safety update summaries. Final report of CIOMS Working Group II. Geneva: CIOMS, 1992.

[9] Guidelines for preparing core clinical-safety information on drugs. Final report of CIOMS Working Group III. Geneva: CIOMS, 1995.

[10] Benefit-risk balance for marketed drugs: evaluating safety signals. Report of CIOMS Working Group IV. Geneva: CIOMS, 1998.

[11] Current challenges in pharmacovigilance: Pragmatic approaches. Report of CIOMS Working Group V. Geneva: CIOMS (in preparation).

[12] Wood KL. The Medical Dictionary for Drug Regulatory Affairs (MedDRA). Pharmacoepidemiology and Drug Safety 1994; 3: 7-13.

edge, such as reasons for taking a drug or the attribution of adverse events to drug treatment. The International Classification of Diseases (ICD)[13] helps with reporting the reasons for taking a drug. For purposes of drug safety a correct diagnosis and assessment of causality of a suspected ADR are of particular importance.

The need to establish requirements for the diagnosis of a suspected ADR and to describe it with the correct term is particularly evident in the case of spontaneous monitoring of single case reports, for the following reasons:

- Single case reports still represent the most important type of information for raising suspicions, generating signals and, frequently, for taking action. Single case reports frequently lack details usually contained in clinical studies.
- Single case reports are by definition a collection of suspicions concerning both the occurrence of an ADR and the causal relationship between the reaction and the treatment.
- Single case reports, as a rule, are transmitted by the reporting doctor to a collecting centre at either the drug regulatory agency or a pharmaceutical company, and quite often between these organizations as well. They are thus assessed by people at some distance from the patient.

Clearly, therefore, collecting and evaluating centres, whether they are part of a regulatory agency or of a pharmaceutical company, need to be provided with both the name of the ADR and sufficient supporting data to be convinced that what is reported was what was actually observed, and that the ADR term used designates correctly the observed event. Assessment of causality is a different matter and requires various kinds of additional information.

In setting requirements for the use of ADR terms for spontaneous reporting, the level of detail that a case report should include to convince an evaluator that the reported reaction occurred must not be set either too high or too low. If it is too high, too few reports will meet the requirements, thus seriously limiting the practical value of the whole effort. If it is too low, too many will qualify, though no report is discarded for lack of sufficient detail. In practice, the level of detail will depend to a certain extent on the structure and requirements of the ADR terminology for which the reports are prepared.

The aim should be a level of detail normally at the disposal of an average reporting physician. As a rule, it should be sufficient to transcribe into the ADR report certain details usually contained in patients' records. In reporting hypertension, for example, the physician will have taken the patient's blood pressure, but only rarely are readings included in

[13] International Statistical Classification of Diseases and Related Health Problems (ICD-10). Geneva: World Health Organization, 1992.

spontaneous case-reports. It is the inclusion of such additional details that allows the evaluator, either with a regulatory agency or in the industry, to accept this essential part of a report, not at its face value, but in an informed way.

Unlike spontaneous reporting, clinical studies are by design subject to strict protocols, validation procedures and other safeguards so that, generally, the needed details are already included.

The lack of standardized definitions of ADRs has hampered the work of those concerned with drug safety. To designate an adverse event, medical reporters use terms derived from their medical education or from their conceptions of the mechanisms of reactions to drugs. The regulatory authority or the pharmaceutical firm records this information in the reporters' terms or in other terms that the evaluator considers equivalent, chosen from an internationally agreed terminology. There are, however, several international terminologies (mainly WHO-ART, COSTART, and the forthcoming MedDRA) and they are difficult to compare since the terms they contain have not been formally defined. Medical-dictionary or textbook definitions of ADRs are often contradictory and difficult to use in practice. Nevertheless, an accurate term must be used for each ADR in order to record, report or list it, and to comply with regulatory requirements concerning its labelled or unlabelled nature or severity.

In practice, a standardization of definitions and of basic requirements for their use in reporting would result in data-bases of two types of case-report: those that met the basic requirements and those that did not. Case reports could then be tagged correspondingly to facilitate their retrieval.

The CIOMS project

Because of the obvious interest of pharmaceutical companies in the proper assessment of their products and of drug regulatory authorities in that of case reports in general, the need arose to avoid misunderstandings and to streamline communication between all users of ADR data. In 1987 the first attempts to meet this need were initiated by the Roussel-Uclaf group[14], which organized in France a series of consensus meetings of pharmacovigilance and clinical experts. The activities that CIOMS had already initiated on drug safety prompted the French group, aware of an interest in continuing the project on an international basis, to propose that it be continued under the auspices of CIOMS.

At about the same time, in 1990, at the request of a group of seven German pharmaceutical companies, members of Verband Forschender Arzneimittelhersteller e.V. in Bonn, Germany (Bayer AG, Leverkusen; Boehringer Ingelheim GmbH, Ingelheim; Boehringer Mannheim GmbH,

[14] Bénichou C, Danan G. Réunion de consensus sur les définitions en pharmacovigilance. Thérapie 1987; 42: 347 350.

Mannheim; Hoechst AG, Frankfurt; Knoll AG, Ludwigshafen; F. Merck AG, Darmstadt; Schering AG, Berlin) and three Swiss companies associated with INTERPHARMA, Basel [Ciba-Geigy AG, Basel; Sandoz AG, Basel (now Novartis AG); F. Hoffmann-La Roche AG, Basel], CIOMS, with the continuing financial support of this group, initiated a project for defining selected ADR terms employed in spontaneous reporting of single cases of suspected ADRs, and for proposing basic requirements for their use. This made it possible for pharmaceutical manufacturers, under the aegis of CIOMS, to collaborate in the project with national drug regulatory authorities and bodies representative of medical specialties. In 1996 Sanofi-Synthelabo SA, Gentilly, France, joined the group.

Reporters of ADRs use thousands of terms, which in turn are incorporated in ADR terminologies. Not all need to be defined or made subject to particular requirements for their use in reporting. One of the first tasks, therefore, was to establish criteria for deciding which terms should be considered.

The following criteria were established:

- Terms liable to be misinterpreted, or that designate conditions that tend to be misdiagnosed, or that may be understood differently in different medical-care or medical-education systems. This is the principal criterion.
- Terms that designate serious adverse reactions. Serious reactions are those that are fatal, life-threatening, cause hospitalization, result in persistent or significant disability or incapacity, require intervention to prevent permanent damage, or cause congenital anomalies. If a term designates a serious and diagnostically complex ADR it is especially important that the basic requirements for its use in a report be clear. For these types of reaction there must be a high degree of certainty that what was reported was what actually occurred.
- Terms that are used frequently in reporting adverse reactions. Information on the frequency of reporting of a particular ADR is obtained from the WHO Collaborating Centre for International Drug Monitoring, at Uppsala, Sweden (now the Uppsala Monitoring Centre).

The steering committee of the project grouped ADRs into system-organ classes, according to the WHO-ART terminology. A group of experts selected terms that met the agreed criteria, consulting both the latest version of WHO-ART and the preliminary version of MedDRA. To overcome, at least in part, difficulties raised by differences between these terminologies, care was taken to ensure that each defined term would remain valid irrespective of the terminology used.

Meetings of working groups were organized to process lists of selected terms. The groups consisted of representatives of drug regulators (from drug safety units); independent experts, mainly from university medical faculties and international medical societies; drug safety experts from

pharmaceutical companies; members of the steering committee of the project; and representatives of the WHO Division of Drug Management and Policies, Geneva and the WHO Collaborating Centre for International Drug Monitoring, Uppsala.

For each meeting, ADR experts from the pharmaceutical industry were designated to prepare background papers on the selected terms, according to the following layout:

- Preamble (comments that may be of help to validators of reports of ADRs)
- Proposed definition of the term (including a list of published definitions)
- Basic requirements for use of the term (for validating the reported ADR diagnosis)
- Additional comments, if any

The working group reviewed the background papers and reached agreement on definitions of the terms and basic requirements for their use in reporting. In determining those requirements, account was taken of the conditions of spontaneous reporting, with its shortcomings and frequent lack of detail, and the need to be practical rather than exhaustive.

After each meeting, a draft text was circulated for comments and approval to the authors of the background papers, independent experts and the chairperson of the working group. On receipt of their comments, CIOMS prepared the final version for publication in *Pharmacoepidemiology and Drug Safety*.

A consolidated publication

This book and the accompanying CD-ROM are compilations of the definitions and basic requirements for the use of over 180 terms for reporting adverse drug reactions, as agreed by the 16 working groups and published in a series of papers.

The wording of the operative sections of the papers (**Preamble, Definition,** and **Basic requirements for use of the term**) has not been changed. The chapters show a certain variability, to be expected from the variety of the working groups with independent experts from different fields, and due in part also to minor modifications introduced as the project progressed. Some chapters begin with an introduction, for instance. Two chapters represent the outcome of two meetings held at the initiative of Roussel-Uclaf, Paris, and resulting in two papers published in *International Journal of Clinical Pharmacology Therapy and Toxicology*.

For each term defined and explained, the reference meeting is indicated. The meetings held and the corresponding publications are listed in Appendix I.

The terms are grouped by chapters given the title of the WHO-ART system/organ class from which they were selected. Definitions of terms of more than one system/organ class are contained in only one chapter but are cross-referenced.

No ADR reporting scheme formally requires the use of the definitions and basic requirements presented here; health professionals are not obliged to use them. Much dedicated effort has gone into their preparation, however, by medical experts from different countries, representatives of international medical societies, and members of national drug surveillance authorities and drug safety units of pharmaceutical companies. They are offered for everyday use by practising physicians when they fill in ADR reporting forms, and also for use in the validation of reported ADR diagnoses by regulatory authorities and the pharmaceutical industry. They may also serve educational purposes and thus improve the quality of reporting of adverse drug reactions.

Comments are invited and should be addressed to the Council for International Organizations of Medical Sciences (CIOMS), c/o World Health Organization, CH-1211 Geneva, Switzerland.

DEFINITIONS AND BASIC REQUIREMENTS FOR THE USE OF TERMS FOR REPORTING ADVERSE DRUG REACTIONS

Skin and Appendages Disorders (SOC 0100)

Introduction

In diagnosing a cutaneous eruption that may be an adverse drug reaction it is important to decide whether the eruption is due to the disease, primarily due to the drug, or due possibly to an interaction between the disease and the drug. Cutaneous reactions frequently occur when patients are receiving a number of drugs, and thus etiological relationship may be difficult to assess. When patients take drugs for a febrile disorder that ultimately proves to be an infection, an eruption may be due to the underlying disorder or the prescribed drug. Some cutaneous drug reactions may be dose-dependent or due to exacerbation of underlying disease.

The terms considered here refer to adverse drug reactions that affect the skin prominently and are at times severe. Systemic disorders such as serum sickness may have skin manifestations but do not involve the skin primarily and are therefore discussed under different organ-systems. Other terms not considered are those that refer to such disorders as psoriasis, scleroderma, and systemic lupus erythematosus, disorders occasionally reported as drug-related but already clearly defined in the medical literature. However, when patients present with atypical signs and symptoms of such conditions as scleroderma and systemic lupus erythematosus, drugs as etiological factors should be considered; an example is the eosinophilia-myalgia syndrome, associated with l-tryptophan. Also not considered are terms for disorders of the hair and sweat glands and acneiform eruptions; these disorders are usually easy to describe and the terms used are not liable to misinterpretation.

Bullous reactions, i.e., reactions characterized by blisters, frequently reported in association with drugs include erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Bullae may also be a feature of photosensitivity reactions and fixed drug reactions. In assessing patients with blisters it is important to distinguish the condition from primary bullous diseases such as pemphigus and pemphigoid. The latter is seen mainly in the elderly, who may be taking multiple medications. It is important to be aware that many common skin disorders, e.g. insect-bite reactions and pompholyx eczema, may present with localized blisters.

Drug-induced alterations in the pigmentation of the skin usually take the form of hyperpigmentation; it may be due to excess melanin, as in melasma due to estrogen-containing drugs, or to other pigments — e.g. associated

with the use of minocycline or amiodarone. Drug-induced pigmentation is usually most marked in parts of the skin exposed to sun.

Rash is an undesirable term for reporting a cutaneous drug reaction. *Rash* is essentially a lay term, usually implying sudden onset of skin lesions and therefore encompassing virtually all cutaneous adverse reactions.

As a general rule, in reporting cutaneous drug reactions specific terms should be used, but only when the criteria for their use are fulfilled. If minimum criteria for a specific diagnosis cannot be met it is better to provide a description of the features of the case, including distribution, physical appearance, associated signs and symptoms, and laboratory findings. It is also important to give the evolutionary history of the reaction in relation to administration of the drug and final outcome.

Validation of reports of cutaneous adverse reactions will usually require expert opinion.

Terms

Dermatitis (Eczema)

Preamble

The terms *dermatitis* and *eczema* are synonyms. The term *contact dermatitis* is used to describe dermatitis produced by direct contact with a causative agent, which may be an irritant or an allergen.

Definition

Dermatitis or eczema is a superficial skin inflammation. In the acute phase it is characterized by vesicles, redness, oedema, oozing and crusting. In the chronic phase there is marked scaling and thickening of the epidermis. There is usually itching.

Basic requirements for use of the term

Skin eruptions as defined.

Reference 7b

Dermatitis exfoliative

Preamble

The terms *erythroderma* and *exfoliative dermatitis* are used synonymously. Preference should be given to *exfoliative dermatitis*.

Definition

Exfoliative dermatitis is a potentially life-threatening inflammation of the entire skin, characterized by redness of the skin and scaling, with acute onset.

Basic requirements for use of the term

Presence of skin eruption as defined. Cutaneous lymphoma, eczema and psoriasis have to be excluded.

Reference 7b

Fixed drug eruption

Preamble

The term *fixed drug eruption* is preferred to *fixed drug reaction*.

The term *drug eruption (drug rash)* should not be used as a synonym of *fixed drug eruption* or *fixed drug reaction*. The diagnosis should be differentiated from erythema multiforme.

Definition

Fixed drug reaction is a skin or mucosal eruption characterized by solitary or multiple oval erythematous patches, initially with dark-coloured centres, which may progress to bullous formation, and tending to involve the face, hands, feet and genitalia. With each drug challenge the eruption rapidly occurs in the areas initially affected but new areas can also be affected.

Eruptions may be followed by residual pigmentation.

Basic requirements for use of the term

An eruption satisfying the above definition.

Reference 7b

Lichenoid drug eruption

Preamble

Lichenoid drug eruption is a skin reaction with some features of lichen planus. For reporting purposes the term *lichenoid drug eruption* should replace the term *dermatitis lichenoid* used in several terminologies.

Definition

Lichenoid drug eruption is a subacute violaceous papular/plaque eruption. Wiekham's striae and polygonal configuration, characteristic of lichen planus, are not present, and the eruption does not always involve the sites most likely to be affected by lichen planus (i.e., the flexures of the wrists and ankles, and the oral mucosa).

Basic requirements for use of the term

Skin reaction as defined. Eosinophils in the infiltrate support a drug-induced reaction but do not prove it. Characteristic biopsy findings help to confirm the diagnosis.

Reference 7b

Pustular eruption

Preamble

Acute pustular eruptions are uncommon but often serious enough to merit hospitalization. The characteristic lesions are sterile pustules in the superficial part of the epidermis. The eruption resembles pustular psoriasis. The condition is a specific syndrome. Synonyms of *pustular eruption* are *pustuloderma, pustular rashes*, and *acute generalized exanthemic pustulosis*.

Definition

Pustular eruption is a sudden, symmetrical and widespread eruption consisting of numerous small sterile pustules arising on oedematous painful erythema. Lesions usually predominate in intertriginous areas. Fever, leukocytosis and eosinophilia are usual.

Basic requirements for use of the term

Presence of pustules as defined. Spontaneous regression of the eruption in less than two weeks is an important feature helping to differentiate pustular eruption from pustular psoriasis.

Reference 7b

Urticaria / Angioedema

Preamble

Urticaria is a very common skin reaction with many possible causes, including insect stings, food and drugs. The basic lesions of urticaria are wheals, which are swellings of the skin originating in the dermis and having a white centre with a red edge. Characteristically, the lesions of urticaria may come and go. Individual lesions are of short duration.

The term *angioedema* is used to describe a condition similar to urticaria but involving the deeper dermal and subcutaneous tissues. In everyday clinical use *angioedema* is a synonym of *Quincke's oedema* and *angioneurotic oedema*.

Urticaria and angioedema may be part of a life-threatening anaphylaxis.

Definition

Urticaria is a skin eruption consisting of multiple transient wheals, usually with itching.

Angioedema is an eruption similar to urticaria but with larger, oedematous wheals involving dermal, subcutaneous or submucosal tissues. It is sometimes associated with severe respiratory distress due to oedema of the upper airways.

Basic requirements for use of the terms

Presence of skin eruptions as defined. If individual wheals remain fixed for more than 48 hours or there is unexplained fever, alternative diagnoses, including vasculitis, should be considered.

Reference 7b

Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis

Preamble

(See Introduction to Skin and Appendages Disorders)

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are conditions characterized by blisters (bullous reactions); they have traditionally been regarded as related disorders, with occasionally overlapping signs and symptoms. Similar disorders include necrosis of keratinocytes, leading to blisters and epidermal detachment.

Recent evidence suggests that erythema multiforme should be separated from Stevens-Johnson syndrome and toxic epidermal necrolysis: erythema multiforme is usually not caused by drugs, while Stevens-Johnson syndrome and toxic epidermal necrolysis in general are adverse drug reactions.

In some countries, the term *erythema exudativum* or *erythema exudativum multiforme* is used as a synonym of *erythema multiforme*.

The term *Lyell's syndrome* is considered a synonym of *toxic epidermal necrolysis* but its use is not recommended.

Definitions

Erythema multiforme is an acute disease characterized by symmetrically distributed papular lesions affecting mainly the extremities, often with mucosal erosions. The typical lesion is target-shaped: it is concentrically organized with three different-coloured zones, often with a blister in the centre, and it is clearly demarcated from the surrounding skin. There may be general symptoms such as fever and malaise.

Reference 7b

Stevens-Johnson syndrome (formerly also called erythema multiforme of major type) shows widespread skin lesions, which may either be target-shaped or consist of erythematous macules with epidermal detachment, together with severe mucosal erosions. Erosions of the skin do not exceed 10 per cent of body surface area. The general symptoms are more marked than in erythema multiforme.

Reference 7b

Toxic epidermal necrolysis is characterized by widespread erythematous areas with epithelial necrosis and epidermal detachment (> 10 per cent body surface area), leaving bare dermis. Initially there are often also small erythematous or purpuric lesions with or without blisters. Extensive mucosal erosion is frequent. General symptoms, usually severe, include high fever, malaise and painful skin.

Basic requirements for use of the terms

Presence of typical skin lesions. Physical causes and autoimmune blistering diseases may have to be excluded; skin biopsy and clinical photographs are helpful.

Reference 7b

Photosensitivity reaction, Phototoxic reaction, Photoallergic reaction

Preamble

All forms of photosensitivity refer to exaggerated or abnormal responses to ultra-violet radiation or to light, and most commonly occur on exposed parts of the skin. Photosensitivity reactions may be pleomorphic and include dermatitis-like reactions.

Phototoxic reactions, which are non-immunological events caused by drugs or chemicals, are far more common than photoallergic reactions, which do signify an immunological response.

The terms *phototoxic reaction* and *photoallergic reaction* are considered more suitable than *photosensitivity toxic reaction* and *photosensitivity allergic reaction*, respectively.

The terms *phototoxic* and *photoallergic* are specific and should be used with caution in the absence of expert investigation.

Definitions

Photosensitivity reaction is an exaggerated 'sunburn' reaction.

Reference 7b

Phototoxic reactions are exaggerated sunburn-like reactions resulting directly from the photosensitizing substance.

Reference 7b

Photoallergic reactions are pleomorphic, immunologically mediated, skin reactions.

Basic requirements for use of all three terms

Cutaneous drug reactions satisfying the defined criteria, with special reference to the effects of exposure to light or ultra-violet radiation. Phototoxic reactions occur up to two days after exposure and are clearly limited to exposed areas of the skin. Photoallergic reactions occur only after a period of sensitization, and the skin reaction may extend beyond the exposed areas and may recur with re-exposure to sunlight even without further use of the drug (rechallenge).

Reference 7b

Musculo-Skeletal System Disorders (SOC 0200)

Dystonia

(see SOC 0410: Central and Peripheral Nervous System Disorders)

Fracture pathological

Preamble

A pathological fracture can occur in association with inflammatory, metabolic or neoplastic bone lesions or otherwise altered bone structure.

Definition

Pathological fracture is fracture of damaged or diseased bone by a cause that would not fracture a normal bone.

Basic requirements for use of the term

Clinical and X-ray findings consistent with the definition.

Reference 12

Myopathy

Preamble

Myopathy can be due to a number of causes and the underlying pathological mechanism should be elucidated. Myopathy may occur as a result of drug-induced disease.

The level of serum creatine kinase (CK) activity is of special value in the diagnosis of myopathy.

Patients often present with renal failure, as a secondary effect of myositis. Myopathy should be considered in cases of acute renal failure, which may be due to rhabdomyolysis.

Definition

Myopathy is a disorder of striated muscle, with or without changes in muscle mass. It may be accompanied by muscle pain (myalgia) or tenderness.

Basic requirements for use of the term

A clinical diagnosis supported by appropriate investigations and a search for the cause is necessary. The condition should not be called a myopathy if

the relevant electromyographic, clinical-chemistry, histological, and histochemical findings are normal.

Reference 4

Myositis

Preamble

Myositis is a frequently misused term and should not be used as a synonym of *myalgia*. Myositis generally involves striated muscle and only rarely cardiac muscle.

Polymyositis is characterized by inflammatory changes with a predominant lymphocytic infiltration. Dermatomyositis is a polymyositis associated with a characteristic heliotropic rash. Both polymyositis and dermatomyositis are associated with myositic-specific auto-antibodies.

Infectious myositis (interstitial focal myositis) is caused by such infectious agents as mycoses, parasites, bacteria or viruses.

Definition

Myositis is inflammation of striated muscle, producing muscle weakness, elevated muscle enzymes in the serum, and electromyographic abnormalities.

Basic requirements for use of the term

The clinical picture plus elevated serum creatine kinase (CK). If the CK level is not elevated the diagnosis will normally be confirmed by electromyography and biopsy.

Reference 12

Osteoporosis

Preamble

Osteoporosis results from an accelerated rate of bone loss or a reduced rate of bone formation. Apart from age-related osteoporosis, risk factors include genetic, lifestyle (smoking, excessive alcohol consumption, low physical activity), and nutritional (calcium, vitamin D and protein intake) factors. Women are predominantly affected, owing to post-menopausal deficiency of estrogen.

Secondary osteoporosis can be due to immobilization (e.g., from spinal-cord injury), disease (e.g., hyperthyroidism, hyperparathyroidism, rheumatoid arthritis) or drugs, especially glucocorticoid therapy.

The cause of osteoporosis can usually be determined by a careful diagnostic work-up that includes clinical history, physical examination, laboratory measurements, bone densitometry and radiographic imaging.

Definition

Osteoporosis is a bone disorder characterized by low bone-mass and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture.

Basic requirements for use of the term

The diagnosis is established by proof of systemic osteopenia (T-score value at lumbar spine more than 2.5 standard deviations below the mean for a young adult population) with osteodensitometry, such as dual-energy X-ray absorptiometry, with or without vertebral fracture. Bone turnover can be determined by biochemical markers of bone formation and bone resorption (e.g., osteocalcin, bone-specific alkaline phosphatase, collagen-telopeptide, deoxypyridinoline).

Other osteopenic conditions should be excluded.

Reference 12

Collagen Disorders (SOC 0300)

LE syndrome (Lupus erythematosus syndrome)

Synonym: *Systemic lupus erythematosus*

Preamble

LE syndrome (lupus erythematosus syndrome) is a classical auto-immune disease. Over a period it may produce variable combinations of fever, skin lesions (in typical cases a butterfly malar rash), hair loss, arthritis, pleuritis, pericarditis, nephritis, anaemia, leukopenia, thrombocytopenia and disorders of the central nervous system. Hormonal factors, environmental toxins, infectious agents, genetic predisposition and certain medications have all been considered risk factors. The clinical course is characterized by periods of remission and relapse.

Drugs may trigger symptoms of the disease in predisposed individuals or exacerbate existing symptoms. Such symptoms may continue for some months after the drug is withdrawn.

A drug-induced LE syndrome may differ from the idiopathic condition; only rarely does the drug-induced syndrome involve the kidney. The antinuclear antibodies (ANA) in the drug-induced syndrome are directed mostly against histones and rarely against double-stranded (ds) DNA.

Definition

Lupus erythematosus syndrome is a collagen-vascular disease with a wide range of rheumatic manifestations and affecting multiple organ systems. It is characteristically associated with auto-immune abnormalities, especially auto-antibodies to a number of antigens, most specifically antinuclear antibodies and their sub-specificities (e.g., anti-double-stranded DNA).

Basic requirements for use of the term

The American Rheumatism Association has specified 11 criteria for the classification of lupus erythematosus syndrome (listed below). To establish the diagnosis, at least four of these criteria, including the presence of antinuclear antibodies (ANA), must be met.

American Rheumatism Association Criteria for Classification of Systemic Lupus Erythematosus

1. Malar rash	Fixed erythema, flat, or raised, over the malar eminences, tending to spare the basolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging

3.	Photosensitivity	Skin rash as a result of unusual reaction to sunlight
4.	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5.	Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6.	Serositis	a) Pleuritis
	or	b) Pericarditis
7.	Renal disorder	a) Persistent proteinuria
	or	b) Cellular casts
8.	Neurologic disorder	a) Seizures
	or	b) Psychosis
9.	Haematologic disorder	a) Haemolytic anaemia
	or	b) Leukopenia
	or	c) Lymphopenia
	or	d) Thrombocytopenia
10.	Immunologic disorder	a) Positive LE cell preparation
	or	b) Anti-DNA: antibody to native DNA in abnormal titre
	or	c) Anti-Sm: presence of antibody to Sm nuclear antigen
	or	d) False-positive serologic test for syphilis
11.	Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay.

Reference 12

Retroperitoneal fibrosis

Preamble

Retroperitoneal fibrosis (also called Ormond's disease) is a rare disorder, with an incidence in males about three times that in females, and peaking in the sixth and seventh decades. Fibrous tissue is deposited extensively throughout the retroperitoneal space, compressing the ureters, the great vessels, the bile duct and other structures. In most cases the disorder is idiopathic. It may be malignant. The condition has been reported in association with several drugs: methysergide (for migraine), ergotamine, various beta-adrenergic blocking agents, hydralazine and methyldopa.

Associated diseases have included systemic lupus erythematosus, vasculitis, scleroderma, eosinophilic fasciitis, biliary cirrhosis, rubella-associated arthritis, and renal or uterine or other cancers.

There is accumulating evidence that the condition is an autoimmune periaortitis. *Peri-aortitis* or *chronic peri-aortitis* could thus be regarded as a synonym of *retroperitoneal fibrosis*.

As the symptomatology is vague and the clinical presentation non-specific, the diagnosis of retroperitoneal fibrosis is commonly delayed. It relies on radiological or other imaging findings.

In the differential diagnosis a tumour of a different origin should be excluded.

Definition

Retroperitoneal fibrosis is fibrosis of organs or tissues in the retroperitoneal space, compressing the ureters, the great vessels, the bile duct or other structures.

Basic requirements for use of the term

The demonstration of fibrotic tissue by imaging techniques, such as ultrasonography, computed tomographic (CT) scan, or magnetic resonance imaging (MRI).

Reference 12

Vasculitis

Preamble

Vasculitis comprises a heterogeneous group of inflammatory vascular lesions that can involve any kind of blood vessel, irrespective of its lumen or location. Vasculitis gives rise to such conditions as ischaemia or thrombosis, which may cause serious organ-damage and be life-threatening.

Definition

Vasculitis is a necrotizing inflammatory lesion of blood vessels, leading to their occlusion or disruption, with clinical sequelae.

Basic requirements for use of the term

Clinical or biopsy findings satisfying the definition.

The clinico-pathological diagnosis of vasculitis is supported by the demonstration of elevated levels of acute-phase reactants (demonstrated

by, e.g., erythrocyte sedimentation rate, differential blood count showing thrombocytosis and leukocytosis, and C-reactive protein), high levels of rheumatoid factors and cryoglobulins, hypocomplementaemia, anti-nuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA) especially those ANCAs directed against proteinase 3 or myeloperoxidase.

Reference 12

Central and Peripheral Nervous System Disorders (SOC 0410)

General Introduction to Terms Designating Central and Peripheral Nervous System Disorders and Psychiatric Disorders

There have been notable advances in knowledge about the function and role of neurotransmitters in the processing of information in the brain. Numerous neurotransmitter systems have been identified. Among the most significant are those that contain gamma-aminobutyric acid (GABA), glutamate, noradrenaline, serotonin, dopamine and acetylcholine.

Many drugs may cause disturbances in the neurotransmission or other processes in the brain. They are manifested in disturbances of affect, behaviour, psychomotor activity or centrally controlled somatic functions. Some drugs may exert non-specific effects — e.g., a general toxic effect on neurones, or impairment of membrane conduction; others, by contrast, may affect specifically one or other neurotransmitter system, such as the dopaminergic or GABA-ergic system. Specific effects of drugs on a particular neurotransmission system may be intended therapeutic effects in certain patients but adverse effects in others. An example is the sedative and muscle-relaxant effects of benzodiazepines, which are therapeutic in various conditions but considered as adverse in patients treated for anxiety states.

Drug-induced adverse reactions reflecting brain dysfunctions are in many cases similar to spontaneous, physiological fluctuations in brain functioning or to symptoms and signs of mental or neurological disorders, which the drugs may trigger or exacerbate. Moreover, without specific diagnostic criteria or techniques, a variety of centrally induced drug-related symptoms cannot be differentiated from those of peripheral origin. Also, in some cases, a central origin of an adverse reaction can be only inferred from the known pharmacological action of the drug on the central nervous system.

A factor that has to be considered in the use of terms and classifications of, particularly, psychiatric adverse events is that the symptoms can rarely be assessed by objective methods. They are prone to individual interpretation, therefore, and the diagnosis often depends upon special clinical experience. In reporting such adverse reactions, the observed event should be precisely described and it is often necessary to take into account the current state and clinical course of the condition.

In reporting psychiatric or neurological adverse events, terms precisely describing the observed signs, symptoms or states should always be preferred to the general term *disorder*. A precise description often indicates the site of action of the drug. In the classification of diseases, *disorder* usually denominates a common, higher nosological category (for example: mood disorders, personality disorders, eating disorders, sleep disorder) to which a particular disease or disturbance belongs. It gives no information

about the specific type of event or the phenomenon observed. Therefore, the use of the term in reporting carries many risks of misinterpretation or misrepresentation of drug-induced adverse-event profiles.

Introduction to Terms Designating Disorders of the Central and Peripheral Nervous System

Motor, sensory and autonomic (vegetative) functions are controlled by the central nervous system. Many drugs may affect nerve conduction. The type of drug action and localization of its effect will determine whether or how one or several motor, sensory or autonomic functions may be affected.

The status of the central and peripheral nervous system, since it is expressed in motor, sensory and vegetative functions, can be more or less objectively assessed by clinical examination as well as by neuroradiological and electrophysiological techniques. These techniques are important aids to differential diagnosis but they have no place in determining whether a condition is caused by, or related to, a drug.

Symptoms and signs of drug-induced neuronal dysfunctions may require differentiation from those of other neurological disorders. Drugs may exacerbate signs of pre-existing disorders (e.g., convulsions in epilepsy). Sometimes drugs induce specific and typical patterns of dysfunction related to particular pharmacological properties (e.g., neuroleptic malignant syndrome or anticholinergic syndrome), often with symptoms that occur also with conditions not caused by drugs, such as influenza or acute infectious disease, or with intoxication of other origin (e.g., poison, alcohol delirium). The diagnosis of such events calls for particular attention to, and consideration of, current status and time course. Some symptoms of body dysfunctions (motor, sensory or other) suspected of being drug-related may not be due to drug-induced peripheral or central nervous system conditions, but may be indirect effects of other, even physiological, reactions (e.g., tremor, muscular tension or increased muscular tone in acute fear) or symptoms of pre-existing motor, autonomic, mental or sensory malfunctions.

For these reasons it is essential in reporting suspected drug-induced events of neurological origin to describe precisely the signs observed and the symptoms reported. General terms such as *disorder* and *abnormal* should be avoided.

Terms

Anticholinergic syndrome

Preamble

The anticholinergic syndrome is a rare complication of treatment with drugs having anticholinergic properties. The typical clinical picture is one

of symptoms of a blockade of central and peripheral cholinergic (parasympathetic) neurones. The form that the syndrome takes should correspond with known anticholinergic properties of the drug in question. Other possible causes of anticholinergic syndrome must be considered before it is diagnosed as an adverse drug reaction. For reporting a single symptom of anticholinergic nature, a term precisely describing it (e.g., *blurred vision*, *dry mouth*) should be used.

Definition

Anticholinergic syndrome is a confusional state with characteristic features related to dysfunction of the autonomic parasympathetic (cholinergic) system.

Basic requirements for use of the term

The presence of fixed and dilated pupils is essential. Additionally, there must be a cluster of symptoms of the autonomic-dysfunction type (e.g., tachycardia, fever, vasodilation, constipation, urinary retention, dry mouth), or of the mental type (e.g., anxiety, delirium, disorientation, hallucinations, confusion), or of the motor type (e.g., seizures, agitation).

Reference 9

Apathy (See SOC 0500: Psychiatric Disorders)

Choreoathetosis

Preamble

Choreoathetosis usually indicates dysfunction of the extrapyramidal system. Chorea or athetosis may occur separately in a variety of neurological diseases and syndromes. When choreoathetosis is drug-induced (as in hyoscine chorea after acute scopolamine intoxication) it should be called *chorea-like* or *choreiform movements*. For movements that are so sustained that they appear as abnormal posture the term *dystonia* is commonly used, and the terms *athetosis* and *dystonia* are often used interchangeably. In reporting such abnormal movements as suspected adverse drug reactions, causes other than drug-related should be excluded (e.g., cerebral palsy, focal intracranial diseases, hepatic encephalopathy, hepatic cirrhosis). Whenever possible, the cause of the movement abnormality should be specified (e.g., levodopa-induced or lithium-induced chorea). In reporting an adverse event that appears similar to only one of these types of abnormal movement, the terms *choreiform movements* and *athetosis/dystonia-like* should be used instead of *chorea* and *athetosis*.

Definition

Choreoathetosis is a common term used to describe abnormal movements having characteristics of chorea and athetosis, and usually accompanied by abnormal gait and speech difficulties.

Chorea denotes the ceaseless occurrence of a variety of apparently well-coordinated involuntary, arrhythmic, rapid, highly complex and unpredictable jerky movements of different, mostly distal, parts of the body (limbs, face muscles, tongue).

Athetosis denotes abnormal, slow, sinuous, writhing-type movements that may be generalized or restricted in distribution, and tend to occur more in the distal than in the proximal parts of the body.

Basic requirements for use of the term

According to the definition.

Reference 9

Convulsions

Preamble

'A convulsion is but a symptom ...' (Writings of Dr. Hughlings Jackson).

Temporary or persistent structural or functional disorders of the cerebral tissue are involved in the pathogenesis of convulsions.

Drugs may directly or indirectly cause convulsions in epileptic patients or in persons with a low convulsion-threshold, or even in healthy subjects. Convulsions may also be precipitated by discontinuation of drug use. The nature and sequence of related symptoms may give important diagnostic information.

The electroencephalogram (EEG) is the most important diagnostic adjunct available in the clinical assessment of convulsions. However, a normal EEG does not preclude a diagnosis of convulsions.

For present purposes, convulsions have been defined in a way that excludes absence seizures (petit mal); hysterical seizures also need to be differentiated from convulsions.

A convulsion can be an isolated event or part of a convulsive syndrome for example, of an epileptiform state. The underlying cause needs to be discovered whenever possible.

Definition

Convulsions are the motor component of cerebral seizures. Convulsions are of cerebral origin and are characterized by contractions of skeletal

muscles, appearing abruptly and involuntarily. These contractions may be tonic or clonic and they may be focal or generalized.

Basic requirements for use of the term

Verification of convulsions involves a clinical description satisfying the definition. The type and cause of the convulsion should be explored to the degree possible.

Reference 4

Delirium (see SOC 0500: Psychiatric Disorders)

Dyskinesia

Preamble

The term *dyskinesia* has been used to describe abnormal patterns of movement in which voluntary control is impaired and which are due to extrapyramidal dysfunction, as in Parkinson's disease. In clinical practice the term is commonly but imprecisely used as a synonym of *hyperkinesia*.

Reports of dyskinesia should be qualified by using a more exact term, by describing its exact clinical characteristics, and by assigning it to a clinical syndrome or a disease entity. Careful consideration should be given to the possible place of drugs in the cause or modification of dyskinesia.

Muscle fibrillations, fasciculations and myokymia have to be excluded, since they are caused by lesions of the anterior horn cells or the peripheral nerve.

Definitions

The term *dyskinesia* is used to describe abnormal movement related to extrapyramidal function and in which voluntary control is impaired.

Hyperkinesia refers to excessive involuntary, uncontrolled, recurring, nonrhythmic but occasionally stereotyped movements, of extrapyramidal origin, of striated muscles, resulting in altered patterns of movement of the affected body parts.

The terms *hypokinesia* and *akinesia* refer to diminished and ultimately absent movement; *bradykinesia* is used to designate slow movement, and (as above) *hyperkinesia* to designate excessive movements.

Tremor, though not always due to extrapyramidal disorders, is similar to hyperkinesia but is rhythmic.

Basic requirements for use of the term

The term *dyskinesia* has a general clinical meaning that lacks precision regarding the specific type of movement and the parts of the body involved.

Well-defined and commonly used clinical expressions that describe the condition and type of movement are preferred for reporting purposes — for instance, choreiform movements of the head, limbs and trunk; or grimacing contractions of facial muscles, etc.

Care should be taken to differentiate drug-induced effects from neurological manifestations of disease of other etiology.

Reference 4

Dysphonia

Preamble

Drugs may impair the voice and thereby produce difficulties in speech. Impaired voice may occur for many other reasons, however (e.g., a cold, tumours of the vocal cords). In reporting dysphonia as an adverse event, other causes of voice impairment need to be excluded and the type of impairment should be specified — e.g., hoarseness. Usually voice impairment can be clearly differentiated from speech difficulties due to impaired articulation or other neurological conditions.

Definition

Dysphonia denotes any impairment of voice.

Basic requirements for use of the term

The presence of any impairment of voice.

Reference 9

Dystonia

Preamble

Dystonia occurs as an occasional complication of treatment with neuroleptic and dopaminergic drugs and many others. Drug-induced dystonia may be early (onset within one week of commencement of treatment) or late (onset after several weeks, months or years of treatment). Late persistent dystonia is usually termed *tardive dyskinesia*. In reporting dystonia as an adverse drug reaction, pre-existing conditions and other underlying causes such as ischaemia or anoxia should be excluded. Drugs may aggravate pre-existing disorders.

Definition

Dystonia denotes abnormal movements that are slow or so sustained that they may appear as abnormal postures.

Basic requirements for use of the term

The presence of abnormal movements of groups of muscles or body segments (grimacing, torticollis, blepharospasm, limb torsions), which are sustained or slow, or appear as change in posture. Generally, they are absent during sleep and exacerbated by emotional stress or voluntary activity.

Reference 9

Encephalopathy

Preamble

Encephalopathy is a generic term that encompasses all diseases — especially all chronic degenerative diseases of the brain. For reporting an adverse drug reaction the term is uninformative as to the actual condition or event and therefore should not be used. Instead, the observed signs/symptoms should be described.

Definition

Encephalopathy is any disease of the brain — in particular, any chronic degenerative disease of the brain.

Basic requirements for use of the term

The unqualified term *encephalopathy* should not be used in reporting adverse drug reactions.

Reference 9

Extrapyramidal disorder

Preamble

Extrapyramidal and movement disorders encompass a variety of disturbances of motor functions caused by lesions or dysfunctions of the extrapyramidal motor system. In the nosology of disorders, therefore, the term *extrapyramidal disorder* only globally denominates a common anatomical basis for a variety of motor or movement disorders that may present in a number of different ways — e.g., a hyperkinetic-hypotonic or an akinetic-rigid type of disorder. Some drugs, particularly those that affect dopaminergic systems, may induce extrapyramidal motor dysfunctions. *Extrapyramidal disorder*, however, is an imprecise and uninformative term with regard to type of dysfunction; it can also be misleading since the event or condition to which it refers (e.g., tremor) may not be of extrapyramidal origin. The term should not be used, therefore, in reporting adverse drug reactions. Instead, the reporter should use the term for the actual sign observed — e.g., tremor, rigidity, akinesia, hypokinesia,

dystonia, and as far as possible describe precisely the type of disorder — e.g., postural tremor, intention tremor.

Definition

Extrapyramidal disorder is a disturbance of motor function caused by lesions or dysfunctions of the extrapyramidal motor system.

Basic requirements for use of the term

As *extrapyramidal disorder* is a global term that does not indicate the actual dysfunction or motor disorder that is present, the term should not be used for reporting adverse drug reactions.

Reference 9

Gait abnormal

Preamble

Gait is a complex function dependent on the normal functioning of different parts of the nervous system. Abnormal gait is a dysfunction within this complex system. The term *abnormal* is imprecise and should be replaced whenever possible by a term that describes precisely the type of impaired gait (e.g., *festinating gait*, *ataxia, anteropulsia)*.

Definitions

Abnormal gait is impaired posture and movement when walking.

Basic requirements for use of the term

According to the definition.

Reference 9

Hypertonia

Synonym: *Increased muscular tone* (Included terms: *spasticity*, *rigidity*)

Preamble

Some drugs can increase muscular tone and the increase may be of variable severity and short-lasting or comparatively long-lasting. There are two types of hypertonia: spasticity and rigidity.

Spasticity is a velocity-dependent increase in muscular tone, which affects different muscle groups to a different extent. Rigidity is increased resistance to passive movement, independent of the direction of movement.

Definition

Hypertonia is pathological increase in muscular tone.

Basic requirements for use of the term

Demonstration of increased muscular tone, severe enough to impair motor functioning, and, whenever possible, of the type of hypertonia (spasticity or rigidity).

Reference 9

Hypotonia

Synonyms: *Flaccidity; Diminished tone; Floppiness*

Preamble

Many drugs may decrease muscular tone and this can be a desired or undesired effect. Decrease of muscular tone is usually the consequence of a specific action of a drug either on muscle or motor-nerve function or, not rarely, on general arousal (e.g., sedative-hypnotic action). Hypotonia of various degrees may be physiological (e.g., reduced wakefulness, sleep) or associated with various neurological diseases. In reporting an adverse reaction the possible origin of the decrease in muscle tone should be considered, and the term *hypotonia* preferably replaced by *muscular relaxation* if the condition is secondary to sedative, tranquillizing or hypnotic action and a relationship to pharmacological action of a non-toxic nature is obvious.

Definition

Hypotonia is decrease or loss of muscular tone, manifested by a decrease or loss of resistance to passive movement.

Basic requirements for use of the term

The presence of decrease or lost muscular tone is verified by physical examination.

Reference 9

Neuroleptic malignant syndrome

Preamble

Neuroleptic malignant syndrome is a rare complication of treatment with neuroleptic drugs or drugs having neuroleptic properties. Other diseases with similar clusters of signs must be excluded — e.g., septic shock (toxic

sepsis), septic encephalopathy, spontaneous pernicious catatonia with malignant hyperthermia, and infectious diseases.

Definition

Neuroleptic malignant syndrome is a life-threatening condition associated with treatment with neuroleptic drugs.

Basic requirements for use of the term

The presence of a cluster of signs, which should include at least the triad of hyperthermia, rigidity, and increased creatinine phosphokinase activity, associated with neuroleptic treatment. The presence of other signs outside this triad supports the diagnosis; they include impaired consciousness and signs of disturbed autonomic function (labile blood pressure or increase in blood pressure, tachycardia and sweating) and leukocytosis, polynucleosis and increase in liver enzymes.

Reference 9

Neuropathy

Preamble

Polyneuropathy is usually a manifestation of an underlying disease. The underlying cause, including the possibility of a drug reaction, should always be sought. Mononeuropathy is, in most cases, a manifestation of a mechanical lesion. Investigation should include a complete neurological and general medical examination, and the obtaining of a family, environmental, occupational, and drug-exposure history.

Definition

Neuropathy is an impairment of the peripheral motor, sensory and autonomic nervous system.

Basic requirements for use of the term

The diagnosis is usually made on clinical grounds, supplemented by electrophysiological investigation. At least one of the following features should be present:

1. Muscular weakness with diminished tone, or flaccid paralysis (diminished tendon reflexes and wasting)
2. Sensory disturbances, including pain.
3. Impairment of autonomic function.

Reference 4

Oculogyric crisis

Synonyms: *Oculogyric spasms*; *Eye spasms*

Preamble

Oculogyric crisis may occur as a complication of treatment with drugs that affect the extrapyramidal system (dopaminergic antagonists/agonists and a number of other drug-groups). Similar symptoms may be related to Parkinson's disease.

Definition

Oculogyric crisis denotes abrupt involuntary upward or sideward torsion of the eyeballs and elevation of the upper eyelids associated with torsion of the head in the same direction as that of the eyeballs.

Basic requirements for use of the term

According to the definition.

Reference 9

Paralysis

Preamble

Paralysis can be caused by a variety of diseases, injuries, or pharmacological or noxious agents. A distinction should be made between peripheral, central and psychogenic paralysis. Investigation should include a complete neurological and general medical examination, and the obtaining of a family, environmental, occupational, and drug-exposure history.

The term *paresis* indicates incomplete paralysis.

Definition

Paralysis is transient or permanent complete loss of muscle function. This may be due to a neural, muscular, or psychological mechanism.

Basic requirements for use of the term

A clinical diagnosis of loss of muscle function, established by appropriate investigations, and a determination of the cause.

Reference 4

Respiratory arrest (see SOC 1100: Respiratory System Disorders)

Respiratory depression (see SOC 1100: Respiratory System Disorders)

Serotonin syndrome

Preamble

The serotonin syndrome is a rare complication of treatment with drugs with serotonergic properties. lt is characterized by clusters (at least four signs) of associated, comparatively severe, signs of motor (tremor, myoclonus, convulsions), autonomic (hyperthermia, headache, profuse sweating, tachycardia, hypertension/hypotension, diarrhoea, gastrointestinal cramps), and mental (agitation, confusion, disorientation, hypomania, logorrhoea) dysfunctions. They may be present in any combination or develop successively over a period of 24 to 48 h. Single symptoms are non-specific and may have different causes (gastrointestinal infections, influenza). For reporting a single symptom of suspected serotonergic nature, a term that describes it precisely should be used.

Definition

The serotonin syndrome is a cluster of signs of motor, autonomic and mental disturbances indicative primarily of excessive serotonergic function.

Basic requirements for use of the term

Essential signs are agitation, hyperthermia and myoclonus. Impaired consciousness and other signs of disturbed autonomic functions confirm the diagnosis.

Reference 9

Speech disorder

Synonym: *Impaired speech*

Preamble

Drugs may affect speech in various ways: through their effects on the central nervous system or on the muscular control of speech performance. The term *speech disorder* covers dysphonia and disorders of articulation, and should be distinguished from *language disorder*. The term should be avoided as far as possible and used only when a more precise description of speech abnormality (such as dysarthria or stuttering) cannot be used.

Definition

Speech disorder is any impairment in fluidity, rhythm, tone, or articulation of words.

Basic requirements for use of the term

In accordance with the definition.

Reference 9

Thinking abnormal (see SOC 0500: Psychiatric Disorders)

Urinary retention (see SOC 1300: Urinary System Disorders)

Vision Disorders (SOC 0431)

Introduction

The eye is a highly developed sense organ in which minimal impairment can produce a substantial effect upon function. The field is difficult with regard to ADR reporting, for many non-specific terms have to be used if special methods of investigation are not available.

The following descriptors are unsatisfactory as clinical or ADR reporting terms, and further development of this terminology is necessary.

Terms

Cataract

Preamble

Cataracts may result from a number of processes and are mainly age-related. Cataract is responsible for about 35 per cent of cases of visual impairment and is one of the largest single causes of blindness world-wide. Cataracts usually progress slowly, but are frequently only detected when they reach a certain extent. Thus, even a "sudden appearance" could result from a pre-existing condition. Care should be taken in evaluating apparent association between these lesions and drug therapy. Symptoms may include glare, blurred vision, altered colour perception, change of refraction, and monocular diplopia.

Definition

A cataract is a congenital or acquired lack of clarity of the lens.

Basic requirements for use of the term

Demonstration of lack of lens clarity, normally by ophthalmoscopy with dilation of the pupil. For confirmation, characterization and localization of a cataract, slit-lamp examination of the lens is usually required.

Reference 5

Keratitis

Preamble

The term *keratitis* without qualification is undesirable in ADR reporting. Keratitis may be caused by many factors, including physical exposure of the cornea; bacterial, viral or fungal infection; toxic agents or foreign

bodies; and local exposure of the eye to drugs or the concentration of drugs in the lachrymal fluid. lt may be associated with decreased corneal sensitivity.

Definition

The non-specific term *keratitis* is used to describe a wide variety of lesions of the cornea.

Basic requirements for use of the term

The demonstration of corneal appearances satisfying the definition. Specific terms describing the pathological nature of the lesion are to be preferred.

Reference 5

Retinal disorder

Preamble

Many retinal disorders, especially those of the macula, lead to visual impairment, which may ultimately be irreversible. Drugs have been implicated in a wide variety of retinal lesions. Macular lesions may include degeneration, oedema, and pigmentary changes. Other retinal lesions may include detachment, vascular disorders (e.g., hypertensive, diabetic, and other forms of retinopathy) inflammation, haemorrhage, deposits, degeneration, and pigmentary changes. An exact diagnosis should be established whenever possible.

Definition

All abnormalities of the retina are included in the term *retinal disorder*.

Basic requirements for use of the term

Fundoscopy, usually with dilation of the pupil, is necessary.

Reference 5

Vision abnormal

Preamble

The term *vision abnormal* is non-specific and therefore undesirable in ADR reporting. If the use of the term is unavoidable, then careful follow-up or referral should be considered in order to establish a definitive diagnosis.

Definition

Vision abnormal is a change, usually a deterioration, in visual function or perception.

Basic requirements for use of the term

A report of vision abnormal should lead to the establishment and reporting of a specific diagnosis.

Reference 5

Hearing and Vestibular Disorders (SOC 0432)

Ototoxicity

Preamble

Ototoxic drugs can act selectively on the cochlea or the vestibular apparatus, or on both. Hearing loss, tinnitus and vertigo are three major clinical manifestations of drug-induced damage to the inner ear. They can occur separately or in combination, develop suddenly or gradually, and may be temporary or permanent. Cochlear dysfunction may range from minor elevations of hearing threshold, detectable only by audiometry, to deafness. Hearing loss may be accompanied by transient or permanent tinnitus. Clinically, cochlear-function deficits give rise to symptoms much earlier than vestibular toxicity, which must be asymmetrical or bilaterally severe before vertigo occurs. A reliable quantitative measure of vestibular function is difficult to establish.

Definition

Ototoxicity is an adverse drug reaction affecting the inner ear, characterized by cochlear or vestibular dysfunction.

Basic requirements for use of the term

Development of hearing loss, tinnitus or vertigo in connection with drug treatment.

While an ototoxic lesion may be suspected from the case history, an ototoxic hearing loss can be verified only by audiograms taken before and after the drug treatment. Audiometry should be performed under standardized conditions in a sound-proof test box. The criterion for establishing a diagnosis of drug-induced hearing loss is an increase in pure-tone threshold from a baseline audiogram >15 dB (decibels) at one or more frequencies. Without audiograms taken before and after the treatment, however, the imputation of the condition to a drug is difficult to sustain.

Reference 13

Psychiatric Disorders (SOC 0500)

Introduction

See General Introduction to Terms Designating Central and Peripheral Nervous System Disorders and Psychiatric Disorders (SOC 0410)

Introduction to Terms Designating Psychiatric Disorders

With few exceptions there are no fully objective qualitative or quantitative measures of mental functions; their assessment is usually based on criteria established and agreed upon by experts. Also, the definition of abnormal states depends largely on the definition of normality, which obviously can be neither fully precise nor absolute for every individual. Usually the assessment and diagnosis of psychiatric disorders are based on various rating scales, which often include semi-quantification of the severity of symptoms. Operational criteria for symptom definitions, diagnosis and classification are found in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994) of the American Psychiatric Association and the International Classification of Diseases and Related Health Problems (Chapter V: Mental and behavioural disorders) (ICD-10, 1992) of the World Health Organization. In practice, however, the assessment and diagnosis of psychiatric abnormalities rely heavily upon clinical experience and are prone to subjectivity. In general, drugs may stimulate or inhibit central nervous functions, with corresponding signs and symptoms of increased or decreased mental processes and body reactions, or stimulation and inhibition may occur together. In any case, in assessing drug-induced changes it is essential to take into consideration the baseline condition and often also the evolution of the changes over time.

Terms

Anorexia

Synonym: *Lack* or *loss of appetite for food*

Preamble

Drugs may have inhibitory effects on appetite and food intake. Anorexia, or loss of appetite, should be differentiated from hyporexia, which is decrease of appetite. Also, it should be differentiated from lack of appetite associated with adverse effects on gastrointestinal functions (e.g., nausea, vomiting or diarrhoea). A lasting loss of appetite is accompanied by loss of weight, which may go on to emaciation, which the physician should measure and document. In anorexia, limitation of food-intake and loss of weight are not deliberate. Anorexia may be a symptom of many acute and

chronic organic as well as mental disorders. The term *anorexia nervosa* for a drug-induced adverse effect on appetite should be discouraged. Anorexia nervosa is a well-defined mental disorder characterized by refusal to maintain body weight at or above a minimally normal weight for age and height. For the diagnosis of anorexia nervosa, operational criteria should be applied.

Definition

Anorexia is loss of appetite for food.

Basic requirements for use of the term

In accordance with the definition.

Reference 9

Apathy

Synonyms: *Indifference*; *Lack of feelings*; *Emotional unresponsiveness*; *Emotionlessness*

Preamble

Apathy is a term frequently used to describe impaired emotional reactivity. Signs of psychomotor inhibition or retardation, or reduced wakefulness, or hypomimia may be mistaken for apathy. Mostly, drug-induced signs of apathy are secondary to the effects of drugs on alertness. The term should therefore be used with caution and not used for signs of drug-induced central-depressant effects.

Definition

Apathy is absence of emotional responsiveness or of feelings, or indifference to one's surroundings, or reduced reactivity to stimuli normally eliciting a positive or negative reaction.

Basic requirements for the use of the term

According to the definition.

Reference 9

Delirium

Synonym: *Acute confusional state*.

Preamble

Delirium is usually a consequence of acute or chronic intoxication caused by drugs or by withdrawal of drugs or of alcohol, or due to causes other

than drugs (infection, fever, metabolic disorders, cerebrovascular disorders). The cause can usually be clearly determined.

Definition

Delirium is a confusional state of acute onset, characterized by distorted or reduced attention, delusions or hallucinations, disorientation, and clouded consciousness.

Basic requirements for use of the term

The presence of clusters of signs and symptoms, of fluctuating intensity, such as brief illusions and brief unsystematized delusions, hallucinations, incoherence, psychomotor agitation or inhibition, and many physical symptoms, including those of impaired autonomic functions. These clusters may develop progressively and in a variety of combinations, and may last from several days to weeks.

Reference 9

Depersonalization

Preamble

Depersonalization occurs in a variety of neurological and psychiatric disorders. Transient episodes of depersonalization may occur in states of excessive fatigue or acute distress, or after sleep deprivation. Drugs with hallucinogenic properties may induce depersonalization, often associated with psychotic reactions. Usually the individual retains insight and recognizes the abnormal nature of the experience. The term *depersonalization* should be used only if the individual clearly recognizes the most basic level and the key components of self-awareness — e.g., the reality and integrity of the self ('I am one person'), the continuity of the self ('I am I now, I was I in the past and I will be I in the future', 'I see myself from outside my body as in a movie') and the activity of the self ('I move mechanically', 'My movements are automatic and mechanical', 'I feel like a robot').

Definition

Depersonalization is alteration in the experience and awareness of self, leading to a feeling of being unreal and detached from one's own mind and body.

Basic requirements for use of the term

According to the definition.

Reference 9

Depression

Preamble

Depression is a term used in everyday language to denote a state of gloom, despondency or sadness. Depression is not necessarily pathological if the decline in mood is appropriate to the circumstances.

Mild transient changes in mood should not be confused with medically significant depressive syndromes, which can be severe and life-threatening.

Definition

Depression is a morbid mental state dominated by a lowering of mood and it often includes a variety of associated symptoms, particularly anxiety, agitation, feelings of unworthiness, suicidal ideas, alteration of appetite and sexual function, psychomotor retardation (slowness), sleep disturbance and various somatic symptoms and complaints.

Basic requirements for use of the term

Clinical diagnosis. Organic brain conditions, such as Alzheimer's disease, need to be considered and eliminated.

Reference 4

Personality disorder

Preamble

Personality is a term used to describe the ingrained patterns of thought, feeling and behaviour characterizing an individual's unique lifestyle and mode of adaptation, and resulting from constitutional factors, development and social experience. The term *personality disorder* is used to describe heterogeneous conditions in which a disturbance of some aspects of behaviour is present. The term should not be used to report an adverse drug reaction; rather, the report should indicate the specific change that has occurred. In reporting the adverse effects of a drug, the baseline personality type, trait, or disorder should be taken into consideration, and only those changes deviating from the baseline reported.

Definition

See Preamble.

Basic requirements for use of the term

See Preamble.

Reference 9

Psychosis

The term *psychosis* is still sometimes used in reporting adverse drug reactions. It is an imprecise term, however, which does not denote a specific mental disorder and has little nosological value; it is used less and less, therefore, in the medical/psychiatric literature. The recommended term for reporting an adverse drug reaction is *psychotic reaction*.

Reference 9

Psychotic reaction

Preamble

Certain drugs may provoke a psychotic reaction, aggravate an existing reaction, or exacerbate a psychotic episode in patients with pre-existing disorders characterized by recurrent psychotic phases. Psychotic reactions may be brief or lasting; the symptoms of drug-induced psychotic reactions are usually the same as those that characterize psychotic episodes of other origins. If the psychotic reaction lasts more than four weeks the term *psychotic state* is preferred. Usually, psychotic reactions do not occur with normal doses of drugs. In reporting adverse reactions the type of reaction should be specified — e.g., delusional, hallucinatory, confusional, or other.

Definition

Psychotic reaction is a general term for any major mental disturbance characterized by loss of contact with reality, impaired insight and awareness, impairment of judgement and abstract thinking, or grossly disorganized or bizarre behaviour.

Basic requirements for use of the term

According to the definition.

Reference 9

Thinking abnormal

The use of the term *thinking abnormal* is to be discouraged; it should be replaced by *thought disturbances*.

Reference 9

Thought disturbances

Synonym: *Thought disorder*

Preamble

Drugs may affect thought processes, but this occurs usually in addition to other effects on mental and brain functions. Also, drugs may exacerbate thought disturbances associated with mental disorders such as schizophrenia and mood disorder, and thought disturbances may occur with organic diseases of the brain (e.g., tumours or degenerative disorders). Underlying mental or organic disease should be excluded, therefore, in reporting adverse events. Slowness of the cognitive processes, secondary to central-nervous-system depressant effects, should be differentiated from primary thought disturbances.

In reporting suspected adverse drug reactions, it is preferable to specify signs or symptoms rather than use the term *thought disturbances*.

Definition

Abnormal thought processes are changes in the speed of ideation and association processes, which are reflected in changes of formal organization and content of thoughts and their verbal expression.

Basic requirements for use of the term

According to the definition.

Reference 9

Withdrawal syndrome / Rebound effect

(see SOC 1810: Body as a Whole — General Disorders)

Gastro-Intestinal System Disorders (SOC 0600)

Abdominal pain

Preamble

The term *abdominal pain* is a very undesirable term for reporting adverse drug reactions but its use is also unavoidable. Abdominal pain may be of pelvic origin or it may be referred pain of extra-abdominal origin. Back pain (i.e., non-abdominal) may arise from abdominal viscera. If the term is used for reporting an adverse reaction it should be qualified in relation to anatomical site, severity, duration and nature of the pain.

Definition

Abdominal pain is pain in the topographical area of the abdomen.

Basic requirements for use of the term

The patient complains of abdominal pain. Every effort should be made to establish an anatomical and pathological diagnosis.

Reference 10

Anorexia (see SOC 0500: Psychiatric Disorders)

Colitis

Preamble

The term *colitis* should be used only when the diagnosis has been confirmed by endoscopy. When this is not feasible it is advisable to use descriptive terms such as *diarrhoea*.

Endoscopy with biopsy establishes the type of colitis.

Definition

Colitis, which is inflammation of the colon, is a condition manifested by such symptoms as diarrhoea and faecal blood or leukocytes, and may be associated with abdominal pain. The inflammation may be diffuse or limited to certain segments of the colon. When it is confined to the rectum, the term *proctitis* is usually employed.

Basic requirements for use of the term

Endoscopy is the basic requirement for establishing the diagnosis. However, the diagnosis of clostridium-associated colitis can be made with

high probability by demonstrating the presence of the specific toxin in addition to the clinical signs and symptoms.

Reference 2

Colitis collagenous

Preamble

Collagenous colitis is a condition that affects females predominantly; it is associated with chronic watery diarrhoea and sometimes also with cramping abdominal pains. It was first recognized in 1976. It can be diagnosed only by colonoscopic biopsy, as colonoscopic and radiological appearances are normal. It has been associated with the use of non-steroidal anti-inflammatory drugs and also with other medications.

Definition

Collagenous colitis is a widening of the sub-epithelial collagen layer of the colon.

Basic requirements for use of the term

Chronic watery diarrhoea accompanied by colonoscopic-biopsy demonstration of a subepithelial collagen layer wider than 10 m.

Reference 10

Constipation

Preamble

As an adverse drug reaction, constipation often presents as reduced frequency in an individual's defecation pattern associated with exposure to a drug. For reporting purposes, the reporter should specify the change and how it was related to exposure to the drug.

Definition

Constipation is either the passage of stools hard in consistency and difficult to expel, or less frequent defecation than is habitual for the patient.

Basic requirements for use of the term

According to the definition.

Reference 10

Diarrhoea

Preamble

Diarrhoea may be of infectious or non-infectious origin, and acute or chronic. It is usually considered chronic if it continues for more than two weeks.

Definition

Diarrhoea is the passage of loose, unformed stools.

Basic requirements for use of the term

Clinical appearances satisfying the definition.

Special remark

A particular instance of diarrhoea as an adverse drug reaction is diarrhoea associated with infection of the colon by *Clostridium difficile* related to the use of antibiotics. The most severe form of this condition is pseudomembranous colitis and its diagnosis requires endoscopic verification.

Reference 10

Dyspepsia

The term *dyspepsia* is used indiscriminately and imprecisely and should be avoided in reporting adverse drug reactions. It is often used to designate such complaints as abdominal pain, epigastric burning, heartburn, pyrosis, sour/bitter taste, nausea, retching, vomiting, bloating or belching. The actual terms for these conditions should be used instead. Reporters of adverse drug reactions sometimes employ the term *dyspepsia* to designate an isolated symptom or a group of symptoms of various disorders of the alimentary tract, and sometimes as a 'diagnosis' of a functional disturbance after they have excluded or failed to diagnose an organic condition.

Reference 10

Gastritis

Preamble

The term *gastritis* is used indiscriminately and imprecisely and should be avoided in reporting adverse drug reactions unless a histological diagnosis has been obtained. The term is commonly misapplied. It should not be used as a single term without qualification or further description. It is impossible to make a clinical diagnosis of gastritis. Erosions seen at gastroscopy should be termed *gastric erosion* and not *gastritis*.

Definition

Gastritis is inflammation of the gastric mucosa.

Basic requirements for use of the term

The use of the term requires establishment of the diagnosis by biopsy. It should be qualified if possible by site (antrum or fundus) and by presence or absence of *Helicobacter pylori* and of atrophy.

Reference 10

Gastrointestinal haemorrhage

Preamble

Gastrointestinal haemorrhage is a term representing a sign or symptom, not a diagnosis. Every effort should be made to establish a precise diagnosis reflecting the causative lesion. Bleeding from the nasopharynx should be excluded. Care should be taken to verify that blood (overt, microscopic or occult) is present and that dietetic changes are not erroneously reported as gastrointestinal haemorrhage.

The term *gastrointestinal haemorrhage* should not be used alone when the specific site of the bleeding is known.

Definition

Gastrointestinal haemorrhage is defined as bleeding of any degree occurring in the gastrointestinal tract (including the oesophagus and haemorrhoidal varices).

Basic requirements for use of the term

1. It is essential that true blood in or from the gastrointestinal tract be demonstrated before the term *gastrointestinal haemorrhage* is used.
2. In addition, every effort should be made to establish the origin of the bleeding and report the specific lesion as such.
3. Bleeding from haemorrhoids should be reported as such.

Reference 2

Gastrointestinal infarction, Gastrointestinal necrosis, Gastrointestinal gangrene

Preamble

The terms *gastrointestinal infarction, gastrointestinal necrosis* and *gastrointestinal gangrene* are equivalent for clinical purposes. The term *gangrene*, however, connotes infected necrosis. The condition may be a result of ischaemia or of the action of a toxic substance or enzyme.

Definition

Intestinal necrosis is death of intestinal tissue.

Basic requirements for use of the terms

Definitive diagnosis by angiography, laparoscopy, laparotomy, endoscopy or post-mortem examination.

Reference 10

Haematemesis

Preamble

Haematemesis generally follows bleeding from the oesophagus, stomach or duodenum, but occasionally nasopharyngeal, pulmonary or even pancreaticobiliary-tract bleeding is manifested initially by haematemesis. Severity can be assessed by evidence of low blood pressure, rise in pulse rate, low haemoglobin and low haematocrit.

Definition

Haematemesis is the vomiting of fresh or altered blood.

Basic requirements for use of the term

Evidence of vomiting blood. 'Coffee-ground' vomiting should be substantiated specifically by endoscopic evidence of a bleeding site-otherwise it should not be called *haematemesis*.

Reference 10

Haematochezia

Preamble

Haematochezia is usually a symptom of distal small-bowel or colonic haemorrhage. Brisk haemorrhage from the proximal gastrointestinal tract with accelerated transit may also result in haematochezia.

Definition

Haematochezia is the anal passage of bright red blood.

Basic requirements for use of the term

Evidence of the passage of blood by the anus.

Reference 10

Ileus

Preamble

Ileus is a consequence of inflammation, ischaemia, metabolic disturbance, neuromuscular damage or mechanical obstruction affecting the

bowel. It is not a primary diagnosis and the underlying cause should always be sought.

Definition

Ileus is lack of intestinal peristalsis.

Basic requirements for use of the term

The clinical findings of silent abdomen (or nearly silent abdomen) should be confirmed by X-ray of the abdomen showing dilated intestine.

Reference 10

Intestinal ischaemia

Preamble

Intestinal ischaemia occurs when, in the absence of irreversible damage, the oxygenation of the intestine is inadequate to allow normal function. It may result from partial occlusion of small or large vessels, reduced cardiac output or generalized hypoxia. Symptoms include weight loss and post-prandial pain (small-intestine ischaemia) and diarrhoea associated with pain (ischaemic colitis).

Definition

Intestinal ischaemia is inadequate oxygenation of the small intestine or colon, resulting in a reversible impairment of intestinal function.

Basic requirements for use of the term

The presence of characteristic local-tissue signs, including the absence of peristalsis, on visual inspection by laparoscopy, laparotomy or endoscopy; or a combination of characteristic symptoms with confirmatory evidence on angiography.

Reference 10

Intestinal obstruction

Preamble

Intestinal obstruction may be due to acute or chronic blockage of the intestine at one or more sites and may be partial or complete. Complete obstruction may eventually lead to ileus. Intestinal obstruction is distinguished from paralytic ileus by the presence of bowel sounds. The cause of the obstruction may be within the lumen or the wall of the intestine or external to the wall.

Definition

Intestinal obstruction is the occurrence of a mechanical impediment to the progression of the content of the intestinal lumen.

Basic requirements for use of the term

The clinical diagnosis of obstruction must be confirmed by X-ray.

Reference 10

Intestinal perforation

Preamble

Intestinal perforation may be uncovered (in direct contact with the whole peritoneal cavity) or covered (localized by the omentum or other organs).

Definition

Intestinal perforation is perforation of all the layers of the wall of the stomach or intestine.

Basic requirements for use of the term

The presence of typical clinical signs of perforation, including in uncovered perforation signs indicating a diffuse peritonitis, and in covered perforation signs of only a localized peritonitis. Uncovered perforation is confirmed by the demonstration of free gas in the abdominal cavity by X-ray of the diaphragmatic region. Covered perforation is confirmed at surgery. The anatomical site is established by surgery

Reference 10

Intestinal stenosis

Synonym: *Intestinal stricture*

Preamble

Stenosis in the gastrointestinal tract is a consequence of various inborn or acquired disease processes, such as anatomical abnormalities, inflammation, toxic injuries, ischaemia and malignancy, as well as drug use. It may result in partial or total obstruction of the lumen of the gastrointestinal tract.

Definition

Intestinal stenosis is pathological narrowing of the lumen of the intestine.

Basic requirements for use of the term

Endoscopic or radiological evidence of narrowing of the intestine

Reference 10

Melaena

Preamble

Melaena usually indicates bleeding in the upper gastrointestinal tract but may also be due to bleeding in the middle or distal small bowel or even the proximal colon.

Definition

Melaena is the passage of black stools.

Basic requirements for use of the term

According to the definition. Other causes of black stools, such as oral medication with iron or bismuth or dietary causes (e.g., dark beers or liquorice), should be excluded.

Reference 10

Pancreatitis

Preamble

Drug-induced pancreatitis is usually an acute condition. The clinically suspected diagnosis of acute pancreatitis should always be confirmed by biochemical investigations.

Definition

Acute pancreatitis is an inflammatory disease of the pancreas, characterized by abdominal pain, frequently severe and of sudden onset, and almost always accompanied by increased pancreatic enzymes in the blood and urine. Although in about 80% of cases the disease is mild, severe attacks may lead to shock with renal and pulmonary insufficiency, which may prove fatal. In non-fatal cases, clinical, morphological and functional recovery usually occurs.

Chronic pancreatitis is in most cases characterized by recurrent or persisting abdominal pain. The diagnosis cannot be satisfactorily established unless there is evidence of persistent morphological change or pancreatic insufficiency, manifested by, for example, steatorrhoea or diabetes mellitus. Pancreatic enzymes in blood or urine are usually

increased during attacks of acute pain, but usually to a less extent than in acute pancreatitis.

Basic requirements for use of the term "acute pancreatitis"

1. Upper abdominal pain, which is severe and sudden, usually accompanied by vomiting, and in more severe cases by abdominal guarding, rigidity, rebound tenderness and diminution or loss of bowel sounds;

AND

2. Increased pancreatic enzymes in the blood (amylase and lipase). Lipase is more specific than amylase, but an increase in either enzyme to at least twice the level of normal is significant.
3. Confirmatory investigations.

Whenever possible, the diagnosis should be confirmed by ultrasonography or computerized tomography (CT), or other imaging techniques.

Basic requirements for use of the term "chronic pancreatitis"

The presence of two of the following three manifestations:

1. Persistent impairment of pancreatic exocrine function (clinically suspected by weight loss and signs of malabsorption) as demonstrated by appropriate tests.
2. Confirmation of morphological change in the pancreas as demonstrated by imaging techniques.
3. Abdominal or referred pain with or without pancreatic-enzyme changes.

Reference 2

Peptic ulcer

See page 57: **Ulcer oesophago-gastro-intestinal or Ulcer of the alimentary tract**

Preamble

The generic term *peptic ulcer*, as used in English, has no exact equivalent in a number of other languages. Thus, more precise terms referring to the site of the lesion (oesophageal, gastric, duodenal or jejunal) are preferred. Ulceration should be distinguished from erosion of the mucosa. Erosion involves the mucosa only; ulceration signifies penetration deeper than the mucosal layer.

Unless endoscopy or radiological examination has established the diagnosis, the clinical findings — for example, abdominal pain — should be reported as such.

Definition

Peptic ulcer is a non-neoplastic, focal destructive lesion penetrating beyond the mucosal layer and occurring in regions of the gastrointestinal tract where there is acid and peptic activity. Such ulceration can be asymptomatic but is frequently associated with abdominal pain occurring in the fasting state, in relation to meals, or at night.

Basic requirements for use of the term

The findings of endoscopic or radiological examination are essential in order to establish the diagnosis. The indicators for these examinations include recurrent upper abdominal pain related to meals.

Reference 2

Peritonitis

Preamble

Peritonitis is most frequently an acute condition, either primary (of unknown etiology) or secondary (perforation of intra-abdominal and intra-pelvic organs, vascular events, pelvic infections, spontaneous infection of hepatic ascites, haemorrhage, foreign bodies or drainage — e.g., continuous ambulatory peritoneal dialysis). As an adverse drug reaction peritonitis may occur:

- after perforation of drug-induced ulcers
- after leakage through an intestinal perforation of X-ray contrast material — e.g., barium sulphate
- as sterile inflammation after certain drugs, and as pseudoperitonitis in drug-induced diabetes mellitus
- as a granulomatous reaction to foreign material e.g., talc from surgical gloves
- as a sterile or septic complication following the use of contaminated solutions
- (e.g., during continuous ambulatory peritoneal dialysis)

Peritonitis, unless localized, is characterized by generalized rigidity of the abdominal wall, severe pain and ileus.

Definition

Peritonitis is inflammation of the peritoneum.

Basic requirements for use of the term

Demonstration of peritoneal inflammation by imaging procedures (ultrasound examination, CT scan, MRI) or by examination of peritoneal fluid obtained by guided aspiration, or by visualization of macroscopic peritonitis during laparoscopy or laparotomy.

Reference 10

Stomatitis

Preamble

Stomatitis may occur in the following forms: angular (e.g., in vitamin-B2 deficiency); erythematous, in Kawasaki syndrome in children; membranous or pseudomembranous, due to bacteria or fungi (e.g., candidiasis); uraemic; buccal haemorrhage due to thrombocytopenia or other thrombocytic disorders; petechiae in the gum in infectious mononucleosis; or in lichen planus, lupus erythematosus, Behcet's disease or pemphigus.

As an adverse drug reaction stomatitis may occur in the following forms: membranous or pseudomembranous, due to chemical irritants (gold, iodine); due to heavy metals; as erythema and swelling due to allergens (allergic stomatitis); and erythematous or ulcerative ('mucositis') during chemotherapy. Stomatitis may occur also after radiotherapy or as a reaction to dental problems and dentures, and as a reaction to ethanol, tobacco or food (e.g., spices).

Definition

Stomatitis is a localized or generalized inflammation of the buccal mucosa.

Basic requirements for use of the term

Clinical findings according to the definition.

Reference 10

Stomatitis ulcerative

Preamble

Ulcerative stomatitis occurs as a symptom of erythema multiforme, which may be drug-induced; as ulceration of the oral mucosa induced by chemotherapy; as ulcerative or necrotizing gingivitis (Plaut-Vincent angina); as oral ulceration from mercury poisoning; as a complication of agranulocytosis, which may be drug-induced; as recurrent aphthous stomatitis; or as herpetic ulcers (usually of the gum).

Definition

Ulcerative stomatitis is the occurrence of single or multiple ulcers in the oral mucosa.

Basic requirements for use of the term

Clinical appearances according to the definition.

Reference 10

Ulcer oesophago-gastro-intestinal or Ulcer of the alimentary tract

Preamble

Ulceration may occur at any site in the oesophagus, stomach, duodenum, small intestine or colon. There are many possible etiological factors, including acid, drugs, infection (*Heliobacter pylori* in the stomach, viruses at any site, protozoa in the colon), inflammatory bowel disease, malignancy and ischaemia. The term *peptic ulcer* should be abandoned. Ulcers should be defined according to their site.

Definition

An ulcer of the alimentary tract is a break of >3 mm diameter in the mucosal lining. Smaller breaks are termed *erosions*.

Oesophageal ulcer. Oesophageal ulcer is an ulcer in the oesophagus, distinct from the linear ulceration seen in reflux oesophagitis.

Gastric ulcer. Gastric ulcer is an ulcer in the stomach. It may be superficial (not extending through the muscular mucosa) or deep. A superficial gastric ulcer is synonymous with gastric erosion. Malignancy can he excluded only by endoscopic biopsy.

Duodenal ulcer. Duodenal ulcer is an ulcer usually in the first part of the duodenum.

Intestinal ulcer. Intestinal ulcer is an ulcer of the small intestine distal to the first part of the duodenum.

Colon ulcer. Colon ulcer is an ulcer in the colon or rectum.

Basic requirements for use of the terms

Endoscopic or radiological demonstration of ulcer as defined.

Reference 10

Liver and Biliary System Disorders (SOC 0700)

Gastro-intestinal haemorrhage

(see SOC 0600: Gastro-Intestinal System Disorders)

Haematemesis (see SOC 0600: Gastro-Intestinal System Disorders)

Liver injury

Preamble

In the absence of a histologically established diagnosis, the term *liver injury* is to be preferred to *hepatocellular damage;* the latter should be used only when there is pertinent histological evidence.

Specific terms, e.g., *hepatitis, cholangitis*, should be used only when the conditions they designate have been confirmed by histological or other means. In the absence of confirmation of a specific liver lesion, such as hepatitis, descriptive clinical terms such as *jaundice* should be used. The term *liver injury* is appropriate in the presence of, e.g., jaundice, confirmed by blood enzyme changes.

Definition

Liver injury is an increase of over twice the upper limit of the normal range in alanine aminotransferase (ALT) or conjugated bilirubin (CB), or a combined increase in aspartate aminotransferase (AST), alkaline phosphatase (AP) and total bilirubin (TB), provided that one of these is present in excess of twice the normal level.

Symbols:

ALT = Alanine aminotransferase;
AST = Aspartate aminotransferase;
N = Upper limit of the normal range;
AP = Alkaline phosphatase;
CB = Conjugated bilirubin;
TB = Total bilirubin

$$\text{R (ratio)} = \frac{\text{Serum activity of ALT}}{\text{Serum activity of AP}}$$

Each activity is expressed as a multiple of N. Both should be measured together at the time of recognition of liver injury.

The ratio (R) is used most in the case of patients with jaundice. R may vary during the course of the liver injury.

The term *acute liver injury* is used when the increases specified for liver injury have lasted less than three months.

The term *chronic liver injury* is used when the increases have lasted more than three months. It should be distinguished from c*hronic liver disease*, which may be used only on the basis of histological findings.

The term *severe liver injury* is used in the presence of (in order of increasing severity):

- jaundice
- prothrombin* $<$ 50% (or equivalent)**
- hepatic encephalopathy

* valid only after parenteral administration of Vitamin K

** may be expressed as decrease in prothrombin concentration or prolongation of prothrombin time

Fulminant liver injury is the term used to designate rapid (days to weeks) development of hepatic encephalopathy and severe coagulation disorders.

Basic requirements for use of the terms

1. Demonstration of the enzyme changes as defined above.
2. Isolated but unconfirmed results of biochemical tests should be reported as such and confirmed by repetition of the tests.

Further investigation is essential to establish a specific diagnosis.

Reference pre 1

Cholestatic liver injury

Definition

Liver injury is designated *cholestatic* when there is an increase of over 2 N in AP alone or R 2.

Basic requirements for use of the term

According to the definition

Reference pre 1

Melaena (see SOC 0600: Gastrointestinal System Disorders)

Hepatocellular liver injury

Definition

Liver injury is designated *hepatocellular* when there is an increase of over 2 N in ALT alone or R $\geqslant$ 5.

Basic requirements for use of the term

According to the definition

Reference pre 1

Mixed liver injury

Definition

Liver injury is designated *mixed* when both ALT (above 2 N) and AP are increased *and* $2 < R < 5$.

Reference pre 1

Liver function tests abnormal

Isolated increase even over 2 N in AST, AP or TB should be considered only a biochemical abnormality and not necessarily a sign of liver injury.

When the increase in ALT, AST, AP or TB is between N and 2 N, the term a*bnormality of liver tests* should be used, not *liver injury*. (See the following overview summarizing the above material.)

Reference pre 1

Overview: Designations of drug-induced liver disorders on basis of abnormalities shown by liver function tests

Terms requiring histological data:	**Type of liver injury:**
Hepatitis *Hepatic necrosis* *Chronic liver disease* *Cirrhosis*	• Hepatocellular: increase of over 2 N in ALT alone, or $R > 5$ • Cholestatic: increase of over 2 N in AP alone, or $R < 2$ • Mixed: increase of both ALT over 2 N and AP, and $2 < R < 5$ • Acute: elevation of liver tests lasting less than 3 months • Chronic: elevation of liver tests lasting more than 3 months • Fulminant: rapid (days to weeks) development of hepatic encephalopathy and severe coagulation disorders • Severe: liver injury complicated by, in order of increasing severity, jaundice, prothrombin $< 50\%$, hepatic encephalopathy
In absence of histological data:	
Abnormality of liver tests: • any increase between N and 2 N in – ALT – or AST – or AP – or TB *Liver injury*: • increase over 2 N in ALT or CB • or combined increase in AST, AP and TB, providing one of them is above 2 N	

Metabolic and Nutritional Disorders (SOC 0800)

Acidosis

Preamble

The pH of blood is one of the most constant physiological parameters. It is maintained around pH 7.4, mainly by the bicarbonate—carbonic acid buffer system. Measurement of the blood PCO_2 and bicarbonate together with the pH will indicate the degree of metabolic or respiratory acidosis or alkalosis and the extent of compensation by the buffer system. Drugs may contribute to, but seldom cause, major disturbances of acid-base balance.

The causes of respiratory acidosis include:

1. Airways obstruction
2. Failure of bellows function, as in:
   - obesity
   - ankylosing spondylitis
   - poliomyelitis
   - chest injuries
   - relaxant drugs
4. Depression of respiratory centre, as in:
   - use of drugs (morphine, barbiturates)
   - cerebrovascular accident
   - encephalitis
   - coma.

The causes of metabolic acidosis include:

1. Ketosis due to diabetes or starvation
2. Shock
3. Cyclical vomiting in children
4. Severe dehydration
5. Ammonium chloride intake
6. Ingestion of large quantities of salicylates or other acidic compounds
7. Renal failure
8. Uretero-colonic anastomosis
9. Severe anoxia with accumulation of lactic acid (strenuous and prolonged exercise, biguanides)

Acidosis can only be suspected from clinical signs and symptoms, such as Kussmaul breathing. It must be substantiated by appropriate investigations and its cause determined.

Definition

Acidosis is an excess of hydrogen ion in the body. A respiratory acidosis is *primarily* an increase in the blood CO_2. A metabolic acidosis is *primarily* a fall in the blood bicarbonate.

Basic requirements for use of the term

In ADR reporting, the term *acidosis* should always be qualified: the results of biochemical studies, including the blood pH, bicarbonate, and CO_2 are essential to establish the diagnosis and determine the cause.

Reference 5

Dehydration

Preamble

Dehydration occurs with deficient intake of water or more commonly when excessive amounts of water and sodium are lost by the kidneys, the gastrointestinal tract or the skin. Water depletion may affect extracellular or intracellular volume or both.

Dehydration may be the consequence of abnormality of water intake (hypothalamic malfunction) or renal water wasting (diabetes insipidus). Hypernatraemia (Na > 145 mmol/l) is common. When both water and sodium are depleted, tachycardia, hypotension, and weight loss are common.

Definition

Dehydration is deficiency of body water.

Basic requirements for use of the term

Clinical appearances consistent with the definition.

Reference 13

Gout

Preamble

Gout is a manifestation of hyperuricaemia, typically in the form of acute mono-articular inflammatory arthritis induced by crystals of monosodium urate monohydrate. In some patients aggregated deposits of these crystals (tophi) occur, in and around the joints of the extremities, which can induce severe crippling. Many patients develop a chronic interstitial nephropathy. Uric-acid urolithiasis is also common.

These manifestations of gout can occur in different combinations. However, essential hyperuricaemia alone, even when complicated by uric-acid lithiasis, should not be called gout; gout signifies inflammatory arthritis or tophaceous disease.

Definition

Gout is a hyperuricaemic disease characterized by an acute or chronic inflammatory process, generally in the form of an arthritis induced by crystals of monosodium urate monohydrate.

Basic requirements for use of the term

1. Increase in serum urate values above 70 mg/L (0.42 mmol/L).
2. Signs and symptoms of a hyperuricaemic inflammation, typically affecting the basal joint of the big toe (podagra), but also other joints or bursae or tendon sheaths.

Reference 13

Osteoporosis (see SOC 0200: Musculo-Skeletal System Disorders)

Renal failure (see SOC 1300: Urinary System Disorders)

Cardiovascular Disorders, General (SOC 1010)

Arterial occlusive (occlusion) disease

(see SOC 1230: Platelet, Bleeding and Clotting Disorders)

Cardiac aneurysm

(see SOC 1020: Myocardial, Endocardial, Pericardial and Valve Disorders)

Cardiac failure

Synonyms: *Heart failure; Cardiac insufficiency; Myocardial failure; Myocardial insufficiency; Pump failure*[15]

Preamble

In establishing this diagnosis, special attention should be paid to the following:

1. Pre-existing cardiac failure.
2. Known cardiac disease.
3. Conditions predisposing to cardiac failure.
4. Detailed history of previous and concomitant drug therapy.

Definition

Cardiac failure is a condition in which the heart is unable to pump an adequate amount of blood to meet the metabolic and physiological needs of the body. Cases should be classified as follows, according to the classification used by the New York Heart Association:

Class I: no limitation of physical activity

Class II: slight limitation of physical activity

Class III: marked limitation of physical activity.

Class IV: inability to carry on any physical activity without discomfort.

Basic requirements for use of the term

Any three of the following:

- Dependent oedema.
- Raised jugular venous pressure or hepatomegaly in the absence of liver disease

[15] International Nomenclature of Diseases, Volume V, Cardiac and Vascular Diseases, CIOMS/ WHO, Geneva, 1989, p. 84.

- Signs of pulmonary congestion or effusion
- Rapid heart-rate (> 100 beats/min) or gallop rhythm
- Enlarged heart
- Dyspnoea in the absence of pulmonary disease
- Ejection fraction less than 35 per cent.

Reference 1

Circulatory failure

Preamble

In reporting circulatory failure as an adverse drug reaction the accompanying symptoms and, when known, the causes should be clearly described. A term more specific than *circulatory failure* should be used when possible. Acute severe circulatory failure, regardless of etiology, should be reported as shock and its origin should be indicated.

Definition

Circulatory failure is the inability of the cardiovascular system to provide sufficient oxygen and nutrients to vital organs and to remove metabolites at rates commensurate with metabolic requirements.

Basic requirements for use of the term

The presence of hypotension and one or more signs of organ dysfunction, such as diminished renal output.

Reference 11

Dyspnoea (see SOC 1100: Respiratory System Disorders)

Heart malformation (see SOC 1500: Fetal Disorders)

Hypertension

Preamble

In validating a report on hypertension as an adverse drug reaction, the following points should be kept in mind:

1. The number of measurements of blood pressure.
2. Whether the measurements were made with the patient at rest.
3. The presence or absence of pre-existing hypertension.
4. Any increase in blood pressure, within or above the normal range.

5. The presence of any underlying causes of hypertension.
6. The presence or absence of any known complication of hypertension in the eyes, heart, kidney or brain.

Definition

Hypertension is elevation of the systemic arterial blood pressure above an arbitrary dividing line, the one most commonly used for adults being 160 mmHg for the systolic pressure and 95 mmHg for the diastolic pressure.

Basic requirements for use of the term

Systolic pressure 160 mmHg or more, or diastolic pressure 95 mmHg or more, as indicated by the fifth sound (Korotkoff), except in pregnant women and in children

Reference 1

Hypertension pulmonary

Definition

Pulmonary hypertension is persistently elevated pulmonary arterial pressure.

Basic requirements for use of the term

Clinical findings according to the definition — either a pulmonary systolic pressure of 30 mmHg or more, or a pulmonary mean pressure of 20 mmHg or more.

Reference 11

Hypotension

Preamble

As an adverse drug reaction, hypotension should be reported as systolic rather than mean pressure.

Definition

Hypotension is a level of blood pressure below the usual for the individual and associated with attributable symptoms and signs

Basic requirements for use of the term

Clinical features according to the definition.

Reference 11

Hypotension postural

Synonym: *Hypotension orthostatic*

Definition

Postural hypotension is an excessive fall in blood pressure occurring upon sitting up or standing up.

Basic requirements for use of the term

Evidence of a fall of more than 20 mmHg in systolic and more than 10 mmHg in diastolic pressure on sitting up or standing up.

Reference 11

Pulmonary oedema (see SOC 1100: Respiratory System Disorders)

Shock (see Circulatory failure)

Acute severe circulatory failure, manifest as multi-organ failure and hypotension, is sometimes called shock. The word 'shock' sometimes appears in unrelated expressions (e.g., 'psychogenic shock', referring to strong emotional reaction), but these are misleading and should be avoided.

In reporting shock, the appropriate specific term (such as *anaphylactic shock, cardiogenic shock, hypovolaemic shock, septic shock, or spinal shock*) should be used instead of the more general term *shock*.

Reference 11

Syncope

Preamble

Syncope has many causes but it is most often due to cerebral hypoperfusion. The term *syncope* should not be used to describe the loss of consciousness associated with seizures or trauma.

Definition

Syncope is a temporary loss of consciousness — a fainting — not associated with seizures or trauma.

Basic requirements for use of the term

Confirmation that consciousness was temporarily lost.

Reference 11

Myocardial, Endocardial, Pericardial and Valve Disorders (SOC 1020)

Angina pectoris

Preamble

Angina pectoris is a frequent symptom of myocardial ischaemia, occurring when myocardial oxygen demand exceeds supply. It can be precipitated by increased oxygen demand (exercise) as well as by reduced supply (coronary vasoconstriction). It is associated with disturbed myocardial function. Anginal symptoms can be caused or aggravated by drugs, including vasodilating agents, which in the presence of coronary artery obstruction may lead to more marked dilatation of healthy vessels and thereby reduce blood flow in the diseased areas, thus leading to a so-called 'steal phenomenon'. Sometimes for the differential diagnosis, chest pain of non-cardiac origin — due to, e.g., pleuritis, pulmonary emboli, spasm of the oesophagus, gallbladder disease, gastro-oesophageal reflux — must be excluded.

Synonyms of angina pectoris include *anginal syndrome, angor pectoris, cardiac angina, effort angina, stenocardia, coronary spasm, coronary insufficiency, anginal pain, anginal attack*.

Variants of the term include the following:

Unstable angina. A subacute condition in which typical anginal attacks occur without precipitating factors such as exertion, last longer and cause more severe pain than in stable angina pectoris, and may occur more frequently. Synonyms: *acute coronary insufficiency; angina decubitus; crescendo angina; preinfarction angina.*

Coronary artery spasm. Temporary narrowing of the lumen of an epicardial coronary artery as a result of contraction of the mural smooth-muscle fibres, with reduction of blood flow giving rise to myocardial ischaemia. The contraction is ascribed to spasm occurring in angiographically normal or, more often, atherosclerotically stenosed coronary arteries at the site of atherosclerotic stenosis. It results in attacks of anginal pain occurring in most cases at rest (usually at night) and characterized, when the lumen is completely occluded, by elevation of the ST segments of the electrocardiogram; ST depression and/or T-wave inversion occur frequently, sometimes in the same individual in different attacks, and associated with incomplete occlusion of the artery. Attacks may occur also during exercise. The disorder is more frequently associated with atrioventricular block and ventricular arrhythmias than the classical form of angina.

Synonyms: *Prinzmetal angina; angina pectoris aggravated*

Definition

Angina pectoris is a symptom of myocardial ischaemia. It is characterized by attacks of precordial retrosternal pain or tightness, sometimes radiating into the back and often into the neck and the left shoulder and arm, and often precipitated by effort or excitement.

Basic requirements for use of the term

Presence of the typical symptoms, particularly pain, which is relieved by sublingual nitroglycerine, together with confirmation of myocardial ischaemia by appropriate tests such as ECG (with or without exercise testing), radionuclide tests, or coronary angiography.

Reference 6

Aortic coarctation (see SOC 1500: Fetal Disorders)

Aortic stenosis (see SOC 1500: Fetal Disorders)

Arteriosclerosis [see SOC 1040: Vascular (Extracardiac) Disorders]

Artery malformation (see SOC 1500: Fetal Disorders)

Atherosclerosis [see SOC 1040: Vascular (Extracardiac) Disorders]

Atrial septal defect (see SOC 1500: Fetal Disorders)

Cardiac aneurysm

Synonyms: *Aneurysm of the heart; Ventricular aneurysm*

Preamble

Aneurysm is a general term for a localized widening of the arterial lumen or a distension of an artery or of the wall of the heart. Only aneurysm of the heart wall is considered here.

Definition

Cardiac aneurysm is a localized distension of part of the ventricular wall, more often the left ventricular wall, which has become thin as a result, most commonly, of transmural infarction.

Basic requirements for use of the term

Confirmation by appropriate imaging techniques, such as ultrasound, contrast or radionuclide cardiography, CT scan or magnetic resonance imaging. Calcified aneurysms may also be diagnosed by X-ray examination.

Reference 6

Cardiomyopathy

Preamble

Cardiomyopathy is the term used for heart-muscle disease of unknown etiology. Heart-muscle disease due to toxic agents, nutritional deficiencies, granulomata, connective tissue disorders, etc. are termed *specific heart muscle diseases*. Cardiomyopathy may be of the dilated (so-called 'congestive'), hypertrophic, or restrictive type. Hypertrophic cardiomyopathy is in most cases a hereditary condition. Previous myocarditis may lead to dilated cardiomyopathy, and alcohol may worsen it. As an adverse drug reaction, heart muscle disease is almost exclusively of the dilated type and is a well-known complication of anthracycline in the treatment of cancer.

Definition

Cardiomyopathy is a pathological condition of the heart muscle, of unknown etiology, with either degenerative changes or inappropriate hypertrophy of cardiac muscle cells.

Basic requirements for use of the term

The condition can be suspected on clinical grounds, in cases of unexplained heart failure with cardiomegaly and gallop rhythm. Echocardiography, or ventriculography with contrast media, or nuclear magnetic resonance is required to make a diagnosis, by demonstrating either a dilated, poorly contracting ventricle in the dilated type (after exclusion of atherosclerotic or rheumatic heart disease) or inappropriate cardiac hypertrophy involving the septum more often than the free wall (hypertrophic type). In the restriction type, echo-Doppler techniques demonstrate impeded ventricular filling.

Reference 6

Coronary artery disorder

Preamble

Coronary artery disorder (also called *coronary artery disease*) is a group term for a number of conditions, which may include any form of ischaemic heart disease.

Definition

Coronary artery disorder (coronary artery disease) signifies any disease of the coronary arteries, but is frequently used to indicate arteriosclerosis or coronary artery spasm leading to ischaemic heart disease.

Basic requirements for use of the term

The term *coronary artery disorder* is undesirable in adverse-drug-reaction reporting; a specific diagnosis should be established.

Reference 6

Endocarditis

Preamble

Endocarditis is, with rare exceptions, a bacterial infection, in more than 80% of cases due to gram-positive streptococci or staphylococci. It may also, rarely, be a fungal infection, usually in intravenous drug abusers or in patients with prosthetic valves. It is therefore generally termed *infective endocarditis*. Immunological and drug-related causes have also been described.

It is characterized by the presence of vegetations on the surface of the valves or in the endocardium itself. Apart from direct infection, rheumatic fever is the commonest cause of endocarditis.

Definition

Endocarditis is an inflammatory process affecting the endocardium, and particularly the heart valves. Infective endocarditis indicates a direct infection of the heart by a pathogen.

Basic requirements for use of the term

Infective endocarditis may be suspected on clinical grounds in the presence of fever of unknown origin and the appearance of a new heart murmur or unexplained heart failure. To establish the diagnosis, echocardiographic demonstration of vegetations or a positive blood culture is necessary.

Reference 6

Fibrosis endomyocardial

Synonyms: *Fibrosis endocardial; Fibrosis myocardial*

Preamble

Although *fibrosis endocardial* and *fibrosis myocardial* are listed as preferred terms, the conditions they represent cannot be clinically differentiated; the term *endomyocardial fibrosis* is preferable, therefore, and should be used instead of either term.

The specific entity called *endomyocardial fibrosis* is a cardiomyopathy (i.e., of unknown etiology) which occurs commonly in tropical Africa and

sporadically elsewhere, and shows extensive endocardial, subendocardial, and myocardial fibrosis with overlying thrombosis. Apart from this specific entity, fibrosis of the cardiac tissues will usually represent the histological result of ischaemic heart disease or of an inflammatory process. Abnormality of the blood eosinophils with hypereosinophilia is present in cases in temperate climates. Myocardial fibrosis without extensive fibrosis can occur in coronary heart disease.

Definition

Endomyocardial fibrosis is a state of proliferative fibrotic change affecting the endocardium and myocardium, predominantly at the apex of one or both of the ventricles.

Basic requirements for use of the term

Demonstration by an imaging technique (particularly echocardiography or angiography) of proliferative fibrotic changes, predominantly at the apex of a ventricle, often involving papillary muscles and chordae, thus resulting in atrioventricular valve regurgitation.

Reference 6

Haemopericardium

Synonyms: *Haematopericardium; Haemorrhagic pericarditis*

Preamble

Haemopericardium may present in either acute or chronic form. It may be the first sign of acute pericarditis. It may be associated with bleeding disorders, anti-coagulant therapy, full-thickness anterior myocardial infarction, tuberculosis, neoplastic disease or trauma. As an adverse drug reaction it occurs relatively commonly in drug-induced systemic lupus erythematosus; it may also occur as an immunological reaction to a drug. The fluid consists mainly of blood.

Definition

Haemopericardium is the accumulation of blood or of fluid containing blood in the pericardial cavity.

Basic requirements for use of the term

Demonstration of blood in the pericardial cavity by echocardiography or pericardiocentesis.

Reference 6

Mitral insufficiency

Synonyms: *Mitral regurgitation, Mitral incompetence*

Preamble

Mitral insufficiency results from improper closing of the mitral valve leaflets. The main causes are rheumatic heart disease, mitral valve prolapse, coronary artery disease or congenital mitral abnormality.

Definition

Mitral insufficiency is failure of the mitral valve to close properly during systole, resulting in regurgitation of blood into the left atrium.

Basic requirements for use of the term

Demonstration of regurgitation of blood from the left ventricle into the left atrium, by Doppler techniques or left ventricular angiography.

Reference 6

Myocardial infarction

Preamble

Myocardial infarction represents in most cases the most severe stage of ischaemic heart disease resulting from coronary atherosclerosis. It may, however, also occur as a consequence of embolization or severe spasm of a coronary artery.

Variants of the term are:

Acute myocardial infarction. Necrosis of a portion of the heart muscle as a result of inadequate coronary blood supply. Synonyms: *acute cardiac infarction; coronary heart attack; coronary occlusion; coronary thrombosis.*

Transmural myocardial infarction. Infarction in which myocardial necrosis involves the full thickness of the ventricular wall.

Subendocardial myocardial infarction. Infarction in which the necrosis involves the subendocardial layer of the myocardium, without extending to the epicardium. Synonym: *nontransmural myocardial infarction,* corresponding often to *non-Q-wave infarction.*

Silent myocardial infarction. Myocardial infarction that has occurred with little or no pain and with no other symptoms but is detected by ECG or at autopsy. Synonym: *asymptomatic myocardial infarction.*

Definition

Myocardial infarction is myocardial necrosis resulting from inadequate blood supply.

Basic requirements for use of the term

Typical time-course of any two of the following:

1. Characteristic course of cardiac pain.
2. CK-MB (Creatine-Kinase Muscle-Brain type) elevations.
3. Specific ECG changes.

Reference 6

Myocardial ischaemia

Preamble

Myocardial ischaemia can be induced by a variety of abnormalities such as coronary artery sclerosis, coronary artery spasm, coronary artery thrombosis, myocardial hypertrophy and hypertension. It may be precipitated by tachycardia. Myocardial ischaemia may be present without anginal symptoms ('silent ischaemia').

The term designates a pathophysiological entity. In adverse-drug-reaction reporting, clinical terms, such as *angina pectoris* or *proven myocardial infarction*, are to be preferred.

Definition

Myocardial ischaemia is an inadequate coronary blood supply resulting in oxygen deprivation of the myocardium.

Basic requirements for use of the term

An accurate diagnosis should be established. For adverse-drug-reaction reporting the cause of the ischaemia should be established by appropriate investigations, such as radionuclide imaging with thallium or coronary angiography.

Reference 6

Myocardial rupture (post infarct)

Preamble

Rupture of the myocardial free wall is usually fatal and therefore diagnosis will usually be post mortem. Rupture of the ventricular septum is not uniformly fatal but causes severe heart failure.

Definition

Myocardial rupture is rupture of the cardiac wall after myocardial infarction. The term *myocardial rupture* is sometimes used to denote post infarct necrosis of the interventricular septum or papillary muscles.

Basic requirements for use of the term

Demonstration at autopsy or heart surgery of a ruptured myocardial wall *or* demonstration by an imaging technique or haemodynamic examination of a new ventricular septal defect. For example, in the case of post-myocardial-infarct interventricular septal rupture, Doppler echocardiography or angiocardiography can demonstrate a left-to-right shunt.

Reference 6

Myocarditis

Preamble

The term *myocarditis* denotes an inflammatory disease of the heart muscle. The myocardium shows an inflammatory infiltrate, with adjacent myocytes showing necrosis or degeneration. Fibrosis may or may not be present. The condition occurs mainly as an incidental part of a generalized infection, but immunological, chemical, and drug-related causes have been well documented.

Definition

Myocarditis is involvement of the heart in an inflammatory process affecting the myocardium.

Basic requirements for use of the term

The diagnosis of myocarditis is highly likely when acute global myocardial dysfunction occurs in association with an infectious disease. It may or may not be accompanied by overt heart failure. The diagnosis is made by echocardiography.

The diagnosis of myocarditis can be made with absolute certainty only by histological examination (myocardial biopsy or autopsy).

Reference 6

Pericardial effusion

Synonyms: *Hydropericardium*; *Hydrops pericardii*; *Dropsy of the pericardium*

Preamble

Pericardial effusion may present in either acute or chronic form. It may be the first sign of acute pericarditis. It may also occur in heart failure and cardiomyopathy of various types, and in myxoedema.

As an adverse drug reaction it occurs relatively commonly in drug-induced systemic lupus erythematosus; it may also occur as an immunological

reaction to a drug. The fluid may be serous, serofibrinous, serosanguineous or chylous.

Definition

Pericardial effusion is the accumulation of fluid in excess of normal in the pericardial cavity.

Basic requirements for use of the term

Demonstration of fluid in the pericardial cavity by echocardiography.

Reference 6

Pericarditis

Preamble

Pericarditis may have many causes. It is frequently idiopathic. The most common known causes are viral or bacterial infection, immunological disease and uraemia. As an adverse drug reaction, pericarditis is relatively common in drug-induced systemic lupus erythematosus; it appears to be induced by certain other drugs as the result of an immunological reaction.

The most common type of acute pericarditis, occurring typically in late adolescence or early adulthood, is idiopathic. Pericarditis is common in rheumatic fever.

Definition

Pericarditis is an inflammation of the pericardial sac, with or without effusion.

Basic requirements for use of the term

The condition can be diagnosed at auscultation from a typical friction rub. The diagnosis should be confirmed by either echocardiographic signs or typical electrocardiographic changes (generalized S -T segment elevation).

Reference 6

Pulmonic stenosis congenital (see SOC 1500: Fetal Disorders)

Thrombosis coronary

Preamble

Coronary artery thrombosis is one form of coronary artery disease. Most transmural infarcts occur distal to a totally occluded coronary artery. In

adverse-drug-reaction reporting the term *coronary thrombosis* should not be used unless thrombosis has been demonstrated.

Coronary artery occlusion is frequently caused by thrombosis on top of a coronary atheroma. The terms *coronary occlusion* and *coronary thrombosis* are also used, inaccurately, as synonyms of myocardial infarction.

Definition

Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or myocardial infarction.

Basic requirements for use of the term

Angiographic demonstration of coronary artery occlusion. Coronary thrombosis cannot be diagnosed with certainty *in vivo* except by angioscopy. Autopsy findings should be reported.

Reference 6

Heart Rate and Rhythm Disorders (SOC 1030)

Arrhythmia

Preamble

Several varieties of arrhythmia are considered, both as it is understood by clinicians and in the narrower sense implied by its use as a high-level term of the WHO Adverse Reaction Terminology.

1. Arrhythmia is a clinical sign, not a disease. It is frequently associated with debilitating conditions such as palpitations, dyspnoea, angina pectoris, syncope, cardiac failure and cardiac shock.
2. Identification of the specific rhythm disorders requires analysis of the clinical conditions in which they occur, and examination of the electrocardiogram (ECG) (ECG findings should be included or the record attached).
3. The significance of an arrhythmia depends on the underlying heart disease or predisposing condition (e.g., electrolyte, metabolic or respiratory disorders, digitalis intoxication).
4. The occurrence of cardiac arrhythmia worsens the prognosis in cases of cardiac failure (ejection fraction of the left ventricle < 35 per cent), ischaemic heart disease, cardiomyopathy, or another type of arrhythmia.
5. All arrhythmias can be caused by antiarrhythmic and other drugs.

Definition

Arrhythmia is any disorder of the formation or conduction of the cardiac impulse. Arrhythmia may be primary, due to electrophysiological disorder, or secondary, caused by haemodynamic or other abnormalities. The spectrum of arrhythmia ranges from bradyarrhythmia to tachyarrhythmia. Tachycardias may be divided into narrow- and wide-QRS-complex tachycardias.

Basic requirements for use of the term

Single or combined occurrence of the following ECG disturbances (a 24-hour ECG is not a basic requirement):

1. (a) Bradycardia (< 60 beats/min.)
   Tachycardia (> 100 beats/min.)
   (b) Regular bradycardiac or tachycardiac rhythm.
   Irregular rhythm.
   (c) Narrow QRS-complex (< 0.12 sec) tachyarrhythmias:
   supraventricular extrasystoles or tachycardia.

Wide QRS-complex (> 0.12 sec) ventricular or supraventricular extrasystoles or tachycardia.

2. (a) Atrial fibrillation or flutter: characteristic findings by electrocardiogram or totally irregular heart-rate with pulse deficit.

   (b) Paroxysmal tachycardia (supraventricular, ventricular or unspecified): a history of recurrent episodes of rapid heart-rate, with both abrupt onset and abrupt termination.

   (c) Ectopic beats (all types): the finding of one or more heartbeats that occur at intervals different from the regular intervals of beats of the underlying rhythm.

Additional comments

Arrhythmias as adverse drug reactions (pro-arrhythmic effects of anti-arrhythmic drugs) are characterized by:

1. Exacerbation of an underlying or presenting arrhythmic disorder (e.g., ventricular premature beats, or increase in rate and duration of ventricular tachyarrhythmia (VT)).
2. The occurrence of arrhythmia for the first time in a patient (e.g., polymorphic or monomorphic VT, ventricular fibrillation).
3. The occurrence of a bradyarrhythmia (e.g., symptomatic bradycardia, conduction abnormalities).

Reference 1

Arrhythmia ventricular

The non-specific term *arrhythmia ventricular* should not be used for reporting an adverse drug reaction. Instead, terms that describe the specific arrhythmias should be used.

Reference 11

AV block

Preamble

Atrioventricular (AV) block is one form of heart block, either permanent or transient, due to anatomical or functional impairment. When AV block is reported as an adverse drug reaction the specific term should be used when possible.

Definition

Atrioventricular block is a disturbance of impulse conduction between the atria and the ventricles. The conduction disturbance is classified as: *first-*

degree block, in which conduction time is prolonged but all impulses are conducted; *second-degree block, type I*, characterized by a progressive lengthening of the conduction time until an impulse is not conducted; *second-degree block, type II*, in which there is occasional or repetitive sudden block of conduction of an impulse without prior measurable lengthening of conduction time; and *third-degree (complete) block*, in which no impulses are conducted.

Basic requirements for use of the term

Electrocardiogram showing delayed conduction (first-degree block) or non-conduction (second- or third-degree block) or P waves.

Reference 11

Cardiac arrest

Preamble

The term *cardiac arrest* is frequently misused in reporting adverse drug reactions in cases of sudden death. It should not be used for events not known to be primarily of cardiac origin.

Definition

Cardiac arrest is cessation of cardiac function.

Basic requirements for use of the term

Evidence of cessation of cardiac function.

Reference 11

Cardiac failure (see SOC 1010: Cardiovascular Disorders, General)

Fibrillation atrial

Preamble

A report of atrial fibrillation as an adverse drug reaction should indicate whether the arrhythmia is of recent onset and whether the patient had had it before.

Definition

Atrial fibrillation is an arrhythmia characterized by totally disorganized atrial depolarizations without effective atrial contraction.

Basic requirements for use of the term

Electrocardiographic findings compatible with the definition. Electrical activity of the atrium may be detected electrocardiographically as small, irregular baseline undulations (F-waves) of variable amplitude. In general, the ventricular rate is 'irregularly irregular' (absolute arrhythmia).

Reference 11

Fibrillation ventricular

Preamble

Ventricular fibrillation occurs most frequently in patients with ischaemic heart disease but it may also be induced by antiarrhythmic drugs. It is a severe derangement of cardiac rhythm and usually ends fatally within 3-5 min if untreated.

Definition

Ventricular fibrillation is an arrhythmia characterized by totally disorganized ventricular depolarizations without effective ventricular contraction.

Basic requirements for use of the term

Electrocardiographic findings compatible with the definition. Electrical activity of the ventricle may be detected electrocardiographically as irregular baseline undulations of variable amplitude.

Reference 11

Palpitation

Definition

Palpitation is unpleasant awareness of forceful, rapid or irregular beating of the heart.

Basic requirements for use of the term

As defined.

Reference 11

Torsade de pointes

Preamble

Torsade de pointes, which literally means 'twisting of the points', refers to an unusual form of ventricular tachycardia characterized by undulations

of the QRS complexes in relation to the electrocardiographic baseline, producing a polymorphic arrhythmia. This arrhythmia begins with a ventricular premature beat in the setting of abnormal ventricular repolarization characterized by prolongation of the QT interval. It may be self-limiting or progress to ventricular fibrillation. Prominent among the causes of acquired long-QT-interval syndromes are drugs that prolong repolarization. They include antiarrhythmic drugs with classes I and III activities and some psychotropic drugs. Other important causes include electrolyte imbalances — especially hypokalaemia and hypomagnesaemia —, central nervous system lesions, myocarditis and myocardial ischaemia, and marked bradycardia.

Definition

Torsade de pointes is an atypical rapid ventricular tachycardia associated with periodic rise and fall of configuration and amplitude of the QRS on the electrocardiograph.

Basic requirements for use of the term

Demonstration of the characteristic electrocardiographic findings.

Reference 11

Vascular (Extracardiac) Disorders (SOC 1040)

Arteriosclerosis

Preamble

Arteriosclerosis is a general term used for thickening and loss of elasticity of the arterial wall. Atherosclerosis is the most important form of arteriosclerosis. *Arteriosclerosis* and *atherosclerosis* are frequently, but incorrectly, used as synonyms. Although pathological distinctions may be made between arteriosclerosis and atherosclerosis, none of the clinically available methods used to demonstrate arterial narrowing, such as ultrasound, magnetic resonance imaging or arteriography, can demonstrate that they are separate conditions.

Definition

Arteriosclerosis is a group of diseases characterized by thickening and loss of elasticity of the arterial wall. It comprises three distinct forms: atherosclerosis, Mönckeberg's medial sclerosis and arteriolosclerosis.

Basic requirements for use of the term

A specific diagnosis should be established whenever possible. This usually requires demonstration of arterial narrowing by means of ultrasound, magnetic resonance imaging, arteriography or other techniques.

Reference 6

Atherosclerosis

Preamble

Atherosclerosis and atheroma are the most important forms of arteriosclerosis. Atherosclerosis is a multifactorial process of proliferative changes in the intima of arteries, including the focal accumulation of lipids, blood platelets, fibrous tissue and calcium deposits, and proliferation of smooth-muscle cells; this process is usually associated with changes in the media. The main risk factors for atherosclerosis are hypertension, hyperlipidaemia and smoking.

Sometimes, only the sequelae of atheroma are apparent, such as angina pectoris, myocardial infarction, aneurysm or intermittent claudication.

Definition

Atherosclerosis is the common form of arteriosclerosis. Yellow plaques (atheromas) containing fibrin, cholesterol, lipid material, lipophages and

other substances are formed in the intima and inner media of large and medium-sized arteries.

Basic requirements for use of the term

A specific diagnosis should be established whenever possible. This usually requires demonstration of arterial narrowing by means of ultrasound, magnetic resonance imaging, arteriography or other techniques.

Reference 6

Cerebral haemorrhage

Preamble

About 20% of strokes are due to cerebral haemorrhage; the rest are due to ischaemic cerebral infarction. Cerebral haemorrhage is frequently difficult to distinguish from cerebral infarction. The clinical symptoms depend on the site of the infarction. When infarction and haemorrhage cannot be distinguished, the term *stroke* should be used.

Definition

Cerebral haemorrhage is haemorrhage into the cerebrum.

Basic requirement for use of the term

Demonstration of haemorrhage by an appropriate method such as computer tomography (CT) or magnetic resonance imaging (MRI) or histopathology.

Reference 11

Cerebral infarction

Preamble

About 80% of strokes are due to ischaemic cerebral infarction. Cerebral infraction (or ischaemic stroke) may result from either embolic or thrombotic occlusion of an artery. Stroke symptoms may be absent. When present they generally evolve over a variable time course. When infarction and haemorrhage cannot be distinguished, the term *stroke* should be used.

Definition

Cerebral infarction is the death of brain tissue from vascular obstruction or occlusion.

Basic requirement for use of the term

Demonstration of infarction by an appropriate method such as computer tomography (CT) or magnetic resonance imaging (MRI) or histopathology.

Reference 11

Cerebrovascular disorder

The use of the term *cerebrovascular disorder* should be avoided in reporting adverse drug reactions. As far as possible a precise description of the condition should be given.

Reference 11

Deep vein thrombosis

(see SOC 1230: Platelet, Bleeding and Clotting Disorders)

Haemorrhage intracranial

The use of the term *haemorrhage intracranial* should be avoided in reporting adverse drug reactions. Specific terms such as *extradural, subdural*, or *subarachnoid haemorrhage* should be used instead. Intracranial haemorrhage involving the cerebrum should be reported as cerebral haemorrhage.

Reference 11

Intestinal ischaemia

(see SOC 0600: Gastro- Intestinal System Disorders)

Pulmonary embolism

(see SOC 1230: Platelet, Bleeding and Clotting Disorders)

Renal vasculitis

(see SOC 1300: Urinary System Disorders)

Thrombophlebitis

(see SOC 1230: Platelet, Bleeding and Clotting Disorders)

Thrombosis and Embolism

(see SOC 1230: Platelet, Bleeding and Clotting Disorders)

Vasculitis

(see SOC 0300: Collagen Disorders)

Respiratory System Disorders (SOC 1100)

Introduction

Many respiratory-medicine terms have overlapping meanings and, although their use is sometimes unavoidable, they need to be used with great care. For example, *chronic obstructive lung disease*, *chronic obstructive airways disease* and *chronic obstructive pulmonary disease*, although they provide variations of emphasis, are often used interchangeably to describe almost any form of long-standing pulmonary or airways obstruction. There is no need to use these non-specific terms when individual patients can be better described as having asthma, bronchitis or emphysema, but difficulty arises in patients with a mixed picture, perhaps of end-stage disease, when asthma, bronchitis and emphysema co-exist. To establish that a patient has one or more of these conditions there must for asthma be evidence of spontaneous or drug-induced reversibility and of recurrent episodes in the pattern of the illness, for emphysema a clear fall in total and specific lung transfer factors (LTCO and KCO respectively), and for bronchitis evidence of sputum production and an illness that is basically inflammatory in nature and characterized by exacerbations and remissions.

Similarly, such terms as *bronchospasm* and *acute bronchial obstruction* need to be used with as much precision as possible. *Bronchospasm* is a poor term for episodes in which the bronchial tree is obstructed by oedema, secretions and exudates; it should be restricted to conditions in which nothing other than constriction of the bronchial muscles is present. Drugs sometimes cause single episodes of bronchospasm but these should not be labelled *asthma*.

Some terms (such as *respiratory disorder*, *pulmonary infiltration* and *chest x-ray abnormal*) are so unsatisfactory and non-specific that their use in reporting adverse drug reactions is highly undesirable. No attempt has been made to define such terms; when reporters use them a follow-up should invariably take place to obtain further precision, so that the individual report can be better characterized and computerized.

Terms

Acute respiratory distress syndrome (ARDS)

Preamble

Acute respiratory distress syndrome (ARDS) is the preferred term to designate the syndrome previously referred to as the adult respiratory distress syndrome. It may occur in patients of any age. ARDS occurs in association with a wide variety of causes, including sepsis, aspiration of gastric contents, primary pneumonia and multiple trauma. It is character-

ized by primary alveolo-capillary membrane injury and secondary pulmonary surfactant dysfunction. ARDS should be distinguished from the infantile respiratory distress syndrome (IRDS), which occurs only in premature neonates and is the result of pulmonary surfactant deficiency.

Definition

Acute respiratory distress syndrome is a syndrome of acute diffuse pulmonary inflammation and oedema, of diverse etiology, accompanied by respiratory insufficiency and severe arterial hypoxaemia.

Basic requirements for use of the term

The diagnosis is established when the following criteria are met:

1. Acute onset
2. Partial pressure (in mmHg) of oxygen in arterial blood (PaO_2) over fractional content of oxygen in expired air (F_1O_2) (which can vary from 0 to 1) must not exceed 200 mmHg (regardless of level of positive end-expiratory pressure)
3. Bilateral infiltrates seen on chest radiograph
4. Absence of left atrial hypertension (if pulmonary-artery wedge pressure is measured it should not exceed 18 mmHg)

Reference 7a

Special remarks

Administration of some drugs may rarely result in ARDS. IRDS may occur as an adverse drug reaction if a drug administered during pregnancy results in premature labour. Sometimes ARDS and cardiogenic pulmonary oedema can co-exist.

Reference 7a

Apnoea

Preamble

Apnoea is the absence of breath and should be distinguished from dyspnoea and hypopnoea. There are at least two forms: central, due to neurological disease, and peripheral, due to obstruction of the airways. See also *respiratory arrest*.

Definition

Apnoea is cessation of airflow at the nose and mouth, for at least 10 seconds.

Basic requirements for use of the term

Demonstration according to the definition.

Reference 7a

Asphyxia

Preamble

In clinical practice the term *asphyxia* is usually employed to denote acute obstruction of airflow. Physiologically, however, asphyxia is defined in relation to the effect of acute hypoxia on cells.

Definition

Asphyxia is impairment of tissue oxygenation, due to reduced oxygen intake to the lung with normal blood perfusion, leading to immediate or imminent cell death.

Basic requirements for use of the term

The only rigorous definition is that referring to cell death. The clinical circumstances that will lead to such a state, such as acute obstruction of the airways, must be present.

Reference 7a

Asthma

Preamble

The word *asthma* was formerly used in the terms *bronchial asthma* and *cardiac asthma*. Nowadays it should be reserved for bronchial asthma, and the term *cardiac asthma* should be replaced by the appropriate specific term, e.g., *left ventricular failure*.

Definition

Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli[16].

[16] NHLB1 / WHO Workshop report: Global Strategy for Asthma Management and Prevention. National Heart, Lung, and Blood Institute (Bethesda, USA), Publication Number 95-3659, January 1995

Basic requirements for use of the term

Recurrent episodes of breathlessness, wheezing, chest tightness and cough, not of cardiac origin. The diagnosis is supported if lung-function tests demonstrate variable airways-obstruction, especially if the obstruction is partly or completely reversed by appropriate therapy.

Reference 7a

Bradypnoea

Preamble

Bradypnoea is relative; some healthy athletes have slow respiratory rates. In other people, respiratory depression may be associated with an abnormally slow breathing pattern.

Definition

Bradypnoea is a slow respiratory rate.

Basic requirements for use of the term

According to the definition.

Reference 7a

Bronchoconstriction

Preamble

The term *bronchoconstriction* should be reserved for spasm or contraction of the bronchial smooth muscle. Bronchoconstriction is one form of bronchial obstruction, which is obstruction of the distal airways from any cause. The less precise term *bronchospasm* should be abandoned.

Definition

Bronchoconstriction is airflow limitation due to contraction of bronchial smooth muscle.

Basic requirements for use of the term

The diagnosis of bronchoconstriction must be demonstrated by an improvement in airflow in response to bronchodilators. To take account of natural variability in airflow, the usual standard is an improvement of not less than 12%, and of not less than 200 ml, in the forced expiratory volume in one second (FEV_1).

Additional comments

The terms *aggravated bronchoconstriction*, *aggravated bronchospasm* and *paradoxical bronchoconstriction* are frequently used when treatment of lung diseases with inhalation aerosols is associated with unexpected bronchoconstriction in certain individuals. This can occur after any inhalation therapy as an adverse drug reaction, possibly unrelated to a specific active ingredient but caused by the inhalation procedure itself or by irritation due to the aerosol (including the inactive vehicle). In clinical studies it can be defined as a decrease of FEV_1, of not less than 12% and 200 ml, which occurs within 10 minutes after inhalation and may last for about half an hour[17].

Reference 7a

Chronic obstructive pulmonary disease

Preamble

Chronic obstructive pulmonary disease (COPD) is a term of convenience used to describe any longstanding obstruction of the airways until a more specific diagnosis becomes available. Mixed pictures of bronchitis, emphysema, and asthma are frequently described as chronic obstructive pulmonary disease, but these conditions should be differentiated and reported separately whenever possible. It is rarely caused by drugs.

Definition

Chronic obstructive pulmonary disease incorporates at least three disorders: emphysema, peripheral (inflammatory) airway disease, and chronic bronchitis. A patient may have one or all three conditions, but the dominant clinical feature is always impairment, or limitation, of expiratory airflow.

Basic requirements for use of the term

Demonstration by lung function test of significant airflow-limitation that is of long-standing and largely irreversible despite appropriate therapy.

Reference 7a

Dyspnoea

Preamble

Dyspnoea, uncomfortable breathing, should be distinguished from apnoea and respiratory distress.

[17] Cocchetto, D.M. et al.: Paradoxical bronchospasm after use of inhalation aerosols: A review of the literature, Journal of Asthma, 28(1), 49-53 (1991).

Definition

Dyspnoea is awareness of unnatural breathing.

Basic requirements for use of the term

Dyspnoea is a symptom. Patients complain of 'shortness of breath', 'breathlessness', 'tightness', inability to take a deep breath, 'suffocating', 'cannot get enough air', or pain on breathing.

Reference 7a

Hypercapnia

Preamble

When ventilatory failure occurs because of either reduced respiratory drive or a too high ventilatory workload, in respiratory-muscle failure, there is retention, and a consequent increased arterial-blood level, of carbon dioxide ($PaCO_2$). This may occur also, transiently, in states of metabolic acidosis, when there is excess production of CO_2.

Definition

Hypercapnia is excess of CO_2 in the arterial blood significantly above 40 mmHg.

Basic requirements for use of the term

According to the definition.

Reference 7a

Hypertension pulmonary

(see SOC 1010: Cardiovascular Disorders, General)

Hypoventilation

Preamble

Isolated hypoventilation is an uncommon event and usually occurs as a result of central-nervous-system depression or respiratory-muscle failure. It is almost invariably accompanied by hypoxaemia. Hypoventilation most purely is a reduction of alveolar ventilation, leading to hypercapnia and often hypoxaemia. Alveolar ventilation may be reduced owing to central mechanisms, respiratory muscle fatigue, increases in dead space, or ventilation/perfusion mismatching.

Definition

Hypoventilation is the development of hypercapnia due to inadequate alveolar ventilation.

Basic requirements for use of the term

Arterial PCO_2 should be more than 6 kPa (45 mmHg).

Reference 7a

Hypoxia

Preamble

Arterial hypoxaemia may lead to tissue hypoxia. Hypoxaemia is most commonly caused by ventilation/perfusion mismatch, shunt or hypoventilation. Less common precipitating causes include reduction of inspired partial pressure of oxygen and limitation of diffusion.

Definition

Hypoxia is a reduction below physiological levels of oxygen supply to tissue despite adequate perfusion of the tissue by blood.

Basic requirements for use of the term

Demonstration of significant arterial hypoxaemia.

Reference 7a

Interstitial lung disease

Preamble

Interstitial lung disease (excess inflammatory cells or abnormal material in the interstitium of the lung) should be distinguished from alveolitis and interstitial pulmonary oedema. Interstitial lung diseases can arise from many causes, are often reversible, but may proceed to diffuse pulmonary fibrosis.

Definition

Interstitial lung disease is a diagnostic term used to denote those disorders characterized by excess inflammatory cells or abnormal material in the interstitium of the lung.

Basic requirements for use of the term

The diagnosis is made by the presence of reticular or nodular shadows on a chest radiograph or sometimes by the combined presence of reduced lung volumes and diminished transfer of carbon monoxide.

Additional comments

Various drugs sometimes cause interstitial lung disease/pulmonary fibrosis. Among them are anticancer drugs (e.g., bleomycin, cyclophosphamide), cardiovascular drugs (e.g., amiodarone, hydralazine), anti-inflammatory drugs (e.g., gold, phenylbutazone), and antibiotics (e.g., nitrofurantoin, sulphonamides).

Reference 7a

Pneumonitis

Preamble

Pneumonitis is a term used for pulmonary inflammation of non-infectious origin resulting in diffuse alveolar damage (alveolitis), which may or may not be followed by fibrosis. It may present acutely or as slowly progressive fibrosis. When the predominant feature is an eosinophilic reaction the preferred term *allergic eosinophilic pneumonitis* is used.

Definition

Pneumonitis is a pulmonary inflammation of non-infectious origin.

Basic requirements for use of the term

An infectious etiology should be excluded and a careful history of recent drug treatment obtained. The diagnosis is confirmed by radiographic or histological evidence of alveolar damage or progressive fibrosis. In eosinophilic pneumonitis the diagnosis is confirmed by histological findings of tissue or peripheral-blood eosinophilia or eosinophilic infiltrates in the lungs.

Additional comments

Drugs that cause pneumonitis include cytotoxic and immunosuppressive drugs and amiodarone, nitrofurantoin and oxygen. Eosinophilic pneumonitis is associated with a range of drugs including sulphonamides, penicillins, tetracycline, sulphasalazine, nitrofurantoin and gold salts.

Reference 7a

Pulmonary fibrosis

Preamble

Several interstitial and inflammatory lung diseases can proceed to pulmonary fibrosis.

Definition

Pulmonary fibrosis is a pathological condition characterized by the diffuse presence of excess scar tissue/fibrotic change in the lung.

Basic requirements for use of the term

The term should be used only when fibrotic change can be demonstrated by biopsy or high resolution imaging.

Reference 7a

Pulmonary oedema

Preamble

Pulmonary oedema is part of the pathology of many diseases; it is important, whenever possible, to define and report its cause.

Definition

Pulmonary oedema is the extravasation of fluid from the pulmonary capillaries into the interstitial or alveolar spaces of the lung.

Basic requirements for use of the term

In some circumstances the diagnosis can be established on clinical grounds alone, such as by the presence of rales of recent origin or the appearance of frank oedema fluid at the mouth. In other circumstances radiographic proof is necessary. In the chest X-ray, interstitial pulmonary oedema is characterized by the appearance of septal and perilobular lines (Kerley lines), peribronchial cuffing, subpleural fluid, perihilar haze and diffuse clouding. Alveolar oedema appears as patchy loss of translucency either around the hili or in the lower zones.

Reference 7a

Respiratory arrest

Preamble

Respiratory arrest can result from failure of central ventilatory drive, acute obstruction to airflow, a massive increase in airways resistance, or a profound reduction of lung compliance. It is an acute medical emergency.

Definition

Respiratory arrest is cessation of ventilation and therefore of gas-flow at the mouth.

Basic requirements for use of the term

Clinically, respiratory arrest is manifested by apnoea; in experimental circumstances this may be confirmed by measurements of gas-flow at the mouth.

Reference 7a

Respiratory depression

Preamble

Respiratory depression occurs when the activity of the respiratory centres is suppressed, usually either by intracranial pathology or by drugs.

Definition

Respiratory depression is present when there is an inappropriate rise in arterial carbon dioxide partial pressure ($PaCO_2$) secondary to depression of the respiratory centres.

Basic requirements for use of the term

In the case of severe respiratory depression, a manifest increase in $PaCO_2$; more subtle depression can be demonstrated by an impaired ventilatory response to increases in $PaCO_2$.

Reference 7a

Respiratory paralysis

Preamble

The respiratory muscles consist of the diaphragm, the intercostal-accessory and the abdominal muscles. Paralysis can occur with neuromuscular disorders and with the administration of drugs causing neuromuscular blockade. It is a life-threatening condition.

Definition

Respiratory paralysis is the failure of all respiratory muscles to contract, with consequent complete absence of ventilatory function.

Basic requirements for use of the term

There should be demonstrable failure of movement of air into and out of the lungs; measurements of oesophageal and transdiaphragmatic pressures confirm that this failure is caused by paralysis of the respiratory muscles.

Reference 7a

Red Blood Cell Disorders (SOC 1210)

Anaemia

Preamble

In anaemia the concentration of haemoglobin and volume of packed red blood cells (haematocrit) are less than normal. The normal range of haemoglobin concentration varies with age, sex and altitude; the lower limits are 120g/l in females and 130g/l in males.

In validating case reports, established local values should be used.

Anaemia can have many causes. It may be genetic or acquired, and the result of diminished production or increased destruction of red cells. Its most common form is hypochromic microcytic anaemia due to iron deficiency from diminished intake of iron, increased demand or chronic blood loss. Vitamin B_{12} and folate deficiency anaemias are characterized by macrocytosis and megaloblastosis. Anaemia due to increased destruction of red cells is termed *haemolytic anaemia* (see *Anaemia haemolytic*).

Definition

Anaemia is a decrease of the haemoglobin concentration below the normal limits for sex, age and altitude.

Basic requirements for use of the term

Blood-test findings satisfying the definition.

Reference 13

Bone marrow suppression / depression

(see SOC 1220: White Cell and RES Disorders)

Anaemia haemolytic

Preamble

Haemolytic anaemia is anaemia characterized by increased reticulocyte values ($> 100 \times 10^9$/l). Additional features can be increased unconjugated serum bilirubin, and decreased (or absent) serum haptoglobin.

The causes of accelerated destruction of red cells in haemolytic anaemia can be grouped as:

- abnormalities of the red-blood-cell interior (e.g., enzyme defects, haemoglobinopathies)

- abnormalities of the red-blood-cell membrane (e.g., hereditary spherocytosis, paroxysmal nocturnal haemoglobinuria, spur cell anaemia)
- extrinsic factors [e.g., splenomegaly, antibodies (allo-antibodies and auto-antibodies), microangiopathic haemolysis, infections, toxins].

Drug-induced immune haemolysis can be due to drug binding to the cell membrane, immune complex formation, or the induction of auto-antibodies.

Definition

Haemolytic anaemia is anaemia with signs of premature destruction of red blood cells and compensatory erythroid hyperplasia.

Basic requirements for use of the term

Blood-test findings satisfying the definition.

Reference 13

Anaemia microcytic hypochromic

Preamble

Microcytic hypochromic anaemia results from deficiency of one or more of the three components of haemoglobin: iron, heme and globin. The deficiency is generally associated with reduced size of red cells. Iron deficiency anaemia is in principle microcytic and hypochromic. Iron deficiency is by far the most frequent origin of microcytic hypochromic anaemia, as a result of poor supply — e.g., malabsorption or impaired transportation; blood loss — e.g., in the gastrointestinal tract; or increased requirements — e.g., from menstruation, childbirth or lactation. Chronic disease (infection, inflammation, neoplasms and trauma) frequently leads to a milder form of the condition. Other causes include thalassaemia minor and lead poisoning. Non-iron deficiency anaemias are often normochromic (mean corpuscular haemoglobin concentration > 30g/dl). The condition is sometimes reported as either *anaemia microcytic* or *anaemia hypochromic*.

Definition

Microcytic hypochromic anaemia is defined by low haemoglobin levels (see *Anaemia*), a mean corpuscular volume of $< 80\mu^3$ in adults, or $< 75\mu^3$ in children of under one year, and a mean corpuscular haemoglobin concentration of < 30g/dl; or by a typical blood smear, characterized by microcytes, poikilocytes and hypochromic cells.

Basic requirements for use of the term

A blood smear showing hypochromia and microcytosis.

A serum ferritin level of < 15 mcg/l is diagnostic of iron deficiency anaemia and differentiates iron deficiency from the less common etiologies of disturbed haemoglobin formation. Ferritin levels can be within normal range in patients with iron deficiency and chronic disorders. Transferrin saturation is then the preferred test (saturation < 10% on an empty stomach).

Reference 13

Anaemia aplastic

Preamble

Aplastic anaemia is a very rare, critical condition manifested by a decrease of all the cellular elements of the blood (pancytopenia) and bone-marrow hypocellularity in the absence of infiltration. In validating reports it is useful to check for signs and symptoms of anaemia: pallor, fatigue and weakness, loss of appetite, headache, dyspnoea, and palpitation at rest or on exertion; of leukocytopenia: intercurrent infections, especially of the mucous membrane (stomatitis, gingivitis, necrotizing angina) and the skin; and of thrombocytopenia: petechiae, ecchymoses, bleeding and melaena.

A proportion of cases of aplastic anaemia are secondary to drug use; a complete drug history is essential, therefore. As viral hepatitis may also be a cause of aplastic anaemia, it is important to document a history of jaundice.

Aplastic anaemia is considered severe if two of the following three criteria are fulfilled:

- polymorphonuclear (PMN) count $< 0.5 \times 10^9$/l
- reticulocytes < 1 % (corrected for haematocrit) (or 20×10^9 /l)
- platelets $< 20 \times 10^9$ /l,

and if bone-marrow biopsy shows severe hypocellularity, or moderate hypocellularity with < 30% of residual cells haematopoietic.

See also *Pancytopenia.*

Definition

Aplastic anaemia is a decrease of all the cellular elements of the blood (pancytopenia), with, in addition, bone-marrow trephine biopsy showing histological evidence of decreased cellularity, absence of infiltration and absence of significant fibrosis.

Basic requirements for use of the term

The presence of pancytopenia and the bone-marrow changes as defined above.

Additional comments

If trephine biopsy has not been performed or a bone marrow aspiration only has been undertaken, any diagnosis of aplastic anaemia should be regarded as presumed and unconfirmed only. In these circumstances, it is better to report the bicytopenia or pancytopenia, as observed

Reference 13

Pancytopenia (see SOC 1220: White Cell and RES Disorders)

White Blood Cell and RES (Reticulo-Endothelial System) Disorders (SOC 1220)

Agranulocytosis

Preamble

Agranulocytosis can occur as a reaction to a great variety of toxic agents, including drugs. lt results from impaired production of cells.

Agranulocytosis is life-threatening owing to increased susceptibility to infection. lt is a rare condition with an overall annual incidence of the order of less than 1:100,000 of the general population.

Severe neutropenia can arise as an expected result of the use of cytostatic drugs or radiation. All unexpected and drug-related cases must be very carefully evaluated.

If there are no relevant clinical symptoms or signs of infection, then *severe neutropenia* is the preferred term when the white blood cell count reaches the levels defined below.

Definition

Agranulocytosis is a disorder in which severe neutropenia ($< 0.5 \times 10^9$/l of circulating granulocytes) is associated with the sudden onset of signs and symptoms of bacterial infection, such as fever, malaise and prostration, and typical presentation with oropharyngeal or anorectal lesions.

The term *agranulocytosis* is also used as a synonym for *severe neutropenia*.

Basic requirements for use of the term

Severe neutropenia must be demonstrated, i.e., $< 0.5 \times 10^9$/l.

The traditional definition of agranulocytosis includes the demonstration of infection in accordance with the definition given above.

If possible, full blood counts and repeated white blood cell counts should be reported.

Reference 3

Bone marrow suppression / Bone marrow depression

Preamble

Bone marrow suppression or *bone marrow depression* is a descriptive term used for reversible cytopenia. The term should not be used for reporting purposes, as it is an all-embracing term with a range of meanings in different countries. The term is at present generally used to describe the dose-dependent, predictable effects of cytostatic agents or energy-rich

irradiation. lt is also used to describe the unexpected and rare effects of a wide range of drugs. When it is used in the latter sense it is important that additional information be obtained to establish a more precise diagnosis.

Definition

Bone marrow suppression or bone marrow depression is reversible cytopenia due to haemopoietic failure.

Basic requirements for use of the term

Demonstration of deficiency of the formed blood elements due to inadequate activity of the bone marrow.

Reference 3

Granulocytopenia

Definition

Granulocytopenia is a decrease in the granulocyte count to less than 1.5 x 10^9/l as indicated by an automated counter, not distinguishing eosinophilic and basophilic cells from neutrophilic granulocytes.

Basic requirements for use of the term

See definition.

Reference pre 2

Leukopenia

Definition

Leukopenia is a decrease to $< 3.0 \times 10^9$/l in the white blood cells.

Basic requirements for use of the term

According to the definition.

Reference pre 2

Neutropenia

Definition

Neutropenia is a decrease to less than 1.5 x 10^9/l of segmented polymorphonuclear and band cells. Neutropenia is considered as "severe" below 0.5 x 10^9/l.

The terms *leukopenia* and *granulocytopenia* should be used only if there is no further information about the distribution of the white blood cells.

Basic requirements for use of the term

See definition

Reference pre 2

Pancytopenia

Preamble

Pancytopenia refers to reduction to less than normal in the numbers of blood cells of all three lineages (in bicytopenia, of two lineages) white blood cells, red blood cells and platelets.

It occurs in association with many conditions, such as aplastic anaemia, myelodysplastic syndromes, myelofibrosis, hairy cell leukaemia, bone marrow infection or infiltration by tumour cells, or splenomegaly. Once one of these diagnoses is made, the specific term for the condition should be used.

The term *pancytopenia (*or *bicytopenia*) should be used only if there is no reliable information on bone-marrow cellularity. When there is such information, and bone-marrow trephine biopsy shows histological evidence of hypocellularity, absence of infiltration and absence of significant fibrosis, the diagnosis of aplastic anaemia is definite and the term *aplastic anaemia* should be used. When bone-marrow aspiration shows only hypocellularity and absence of infiltration, aplastic anaemia is probable, and the condition should be reported as such, together with supporting haematological data.

When, in the presence of pancytopenia (or bicytopenia), bone-marrow trephine biopsy shows normocellularity, absence of infiltration, and absence of significant fibrosis, additional clinical and laboratory investigations or follow-up examinations are required.

Definition

Pancytopenia is a decrease of all the cellular elements of the blood — red and white cells and platelets. The diagnostic criteria for pancytopenia are: severe anaemia (haemoglobin level < 100 g/l), neutropenia (PMN count $< 1.5 \times 10^9$/l), and thrombocytopenia (platelet count $< 100 \times 10^9$/l). Bicytopenia is defined by the presence of two of those criteria.

See also *Anaemia aplastic*.

Basic requirements for use of the term

According to the definition.

Reference 13

Platelet, Bleeding and Clotting Disorders (SOC 1230)

Bone marrow suppression / depression

(see SOC 1220: White Cell and RES Disorders)

Cerebral haemorrhage

[see SOC 1040: Vascular (Extracardiac) Disorders]

Coagulation disorders

Preamble

Coagulation disorders is a very broad term, unsuitable for reporting purposes, as it includes a variety of conditions and is used differently in different European languages. When the term is used for reporting suspected adverse drug reactions, every attempt must be made to obtain additional information and establish an exact diagnosis.

When validating reports special attention should be paid to the following:

1. Any evidence of an underlying systemic disorder that may be accompanied by defective haemostasis, such as liver disease, systemic lupus erythematosus, uraemia or malignancy.
2. Family history of bleeding or thromboembolic syndrome.
3. Drug ingestion and history of drug therapy, including concomitant and non-prescription medication.

Unless a precise diagnosis can be established in accordance with the following definition, laboratory values out of the normal range should be reported as such; the normal values for the laboratory concerned should be given.

Definition

Coagulation disorders are a group of conditions with abnormal haemostasis and bleeding or with a thromboembolic syndrome.

Basic requirements for use of the term

A. Clinical evidence: One of the following signs:

- petechiae
- ecchymoses
- mucosal bleeding
- haemarthrosis
- haematoma

or a history of abnormal bleeding or bruising occurring either spontaneously or after injury, dental extraction, etc.

B. Laboratory evidence: Any result out of the normal range of one of the following laboratory tests:

- bleeding time
- platelet count
- prothrombin time
- partial thromboplastin time
- thrombin clotting time
- fibrinogen concentration
- inhibitors of coagulation
- any other specific test

Reference 3

Gastrointestinal haemorrhage
(see SOC 0600: Gastro- Intestinal System Disorders)

Haematemesis (see SOC 0600: Gastro-Intestinal System Disorders)

Haemorrhage intracranial
[see SOC 1040: Vascular (Extracardiac) Disorders]

Melaena (see SOC 0600: Gastro-Intestinal System Disorders)

Pancytopenia (see SOC 1220: White Cell and RES Disorders)

Thrombophlebitis

Preamble

The terms *thrombosis* and *deep venous thrombosis* have been defined separately.

The clinical significance of thrombophlebitis is different from that of deep venous thrombosis. The term *thrombophlebitis* is used in some European countries to describe a group of conditions, which include deep venous thrombosis. Thrombophlebitis and superficial thrombophlebitis should be distinguished from deep venous thrombosis when validating reports.

The terms *thrombophlebitis* and *phlebitis* should not be used to describe superficial thrombophlebitis, which is not in itself a critical clinical condition.

Definition

Thrombophlebitis is inflammation of a vein, associated with a thrombus.

Basic requirements for use of the term

Demonstration of:

1. Inflammation of a vein.
2. An associated thrombus.

Reference 3

Thrombocytopenia

Definition

Thrombocytopenia is defined as a platelet count of less than 100×10^9/l. In the absence of bleeding, thrombocytopenia should be confirmed and pseudo-thrombocytopenia should be excluded by using another anti-coagulant for sampling or by demonstrating decreased platelet numbers on a blood smear made directly from the patient.

Basic requirements for use of the term

According to the definition.

Reference Pre 2

Thrombosis, Embolism, Thromboembolism

Preamble

Thrombosis and embolism are conditions that may occur in different parts and organs of the body and thus present very different signs and symptoms. It is difficult, therefore, to propose a single set of basic requirements that would suffice to validate case-reports of thrombosis and embolism as suspected adverse drug reactions. For this reason, the terms *thrombosis* and *embolism* are defined in only a general sense, and three more specific terms — *deep venous thrombosis, pulmonary embolism* and *arterial occlusion disease* — are treated in more detail.

As a rule, and independently of the part of the body or organ affected, special attention should be paid to:

1. Pre-existing and predisposing conditions, such as smoking, hyperlipo-proteinaemia, diabetes mellitus, hypertension, pre-existing valvular heart disease, hypercoagulability (e.g., antithrombin III deficiency, lack of fibrinolysis activators).
2. History of thromboembolic accidents.
3. History of drug therapy — in particular, oral contraceptives and other hormonal drugs.

Definitions

- Thrombosis: the formation of a thrombus in a blood vessel or the heart.
- Embolism: sudden partial or complete occlusion of a blood vessel by an embolus carried in the bloodstream.
- Thromboembolism: sudden partial or complete occlusion of a blood vessel by an embolus, with subsequent thrombosis.

Arterial occlusion disease

Clinical signs of arterial occlusion disease include intermittent claudication and trophic disturbances of the skin, such as ulceration. The peripheral pulse is weak or absent.

Basic requirements for use of the term

Clinical signs and Doppler ultrasound measurement.

Note:

Arterial occlusive (occlusion) disease is a non-specific term that should not be used to describe an adverse drug reaction. Instead, the specific condition should be described.

References 1, 11

Thrombosis venous deep

Clinical signs of deep venous thrombosis include oedema, swelling of the affected extremity, and painful tension. Diagnosis is confirmed by phlebography, fibrinogen uptake test, Duplex-scan, Doppler-ultrasound measurement, and impedance plethysmography.

Basic requirements for use of the term

Clinical signs and one of the following:

- Duplex-scan.
- Doppler ultrasound measurement.
- Fibrinogen uptake test

OR

Clinical signs and phlebography

Reference 1

Embolism pulmonary

Clinical signs of pulmonary embolism include tachycardia and dyspnoea, shock and, if pulmonary infarction occurs, cough and haemoptysis. The typical clinical picture includes sudden dyspnoea in the presence of established deep venous thrombosis.

Basic requirements for use of the term

Clinical signs and one of the following:

- Pulmonary angiography
- Proved deep venous thrombosis
- Inhalation scintigraphy
- Perfusion scintigraphy

OR

Clinical signs and two of the following:

- ECG.
- X-ray of the chest
- Blood-gas analysis

Reference 1

Thrombosis coronary

(see SOC 1020: Myocardial, Endocardial, Pericardial and Valve Disorders)

Urinary System Disorders (SOC 1300)

Introduction

The kidneys provide the final common pathway for excretion of most drugs and their metabolites, and are therefore subjected to high concentrations of potentially toxic substances. Consequently, many groups of drugs can cause renal damage and their effects are increased in the presence of pre-existing renal disease. The main effects of drugs on the kidney are:

- pre-renal effects (e.g., water or electrolyte loss, increased catabolism, vascular occlusion or altered renal haemodynamics)
- obstructive uropathy (due to tubular blockage, ureteric fibrosis or calculi)
- allergic or immunological damage (resulting in vasculitis, interstitial nephritis or glomerulonephritis)
- direct nephrotoxicity (giving rise to acute tubular or interstitial damage, or renal papillary necrosis)

Drugs can also have adverse effects on the bladder or urothelium, such as retention of urine, haemorrhagic cystitis or carcinoma of the urinary tract.

In many cases the clinical features of drug-induced renal damage are similar to those of spontaneous renal diseases, and drugs can also exacerbate pre-existing renal failure or insufficiency (often called ''acute or chronic renal failure'').

The terms considered here refer to adverse drug reactions that predominantly affect the kidney and are potentially severe (e.g., acute tubular necrosis or glomerulonephritis), or that affect the kidney in a major way as part of a systemic disorder (e.g., vasculitis). The terms used may be based on an anatomical description (e.g., *carcinoma of the bladder*), a histological process (e.g., *acute interstitial nephritis*), a functional problem (e.g., *urinary retention*), or a collection of symptoms and signs (e.g., *nephrotic syndrome*).

A recommended new term, *glomerular vasomotor disorder*, is included; the rationale for its introduction is given in the preamble to this term and in the recommendation at the end of the part ''Urinary Tract Disorders''.

It is important to be as precise as possible when describing drug effects on the kidney and urinary tract. Terms such as *tubulo-interstitial disorder* should be avoided and replaced by *tubular disorder* when the major effect is on the renal tubules and by *interstitial disorder* when the major effect is on the renal interstitium. Similarly, the term *toxic nephropathy* should be discouraged; whenever possible the cause of the renal damage should be indicated (e.g., *analgesic nephropathy*, or *penicillamine-induced membranous glomerulonephritis*).

Laboratory findings

The most commonly used tests and their results to indicate abnormal renal function are:

- Serum urea increased
- Serum creatinine increased
- Creatinine clearance decreased
- Glomerular filtration rate decreased

A given serum creatinine or creatinine clearance value does not indicate the same level of renal function in every patient; values vary with age, sex and body weight. Creatinine clearance provides an approximate measure of the glomerular filtration rate and is best determined by the Cockcroft and Gault formula[18]:

> Creatinine clearance (ml/min) = Weight (kg) x (140 – age) / K x serum creatinine (μmol/l)

Factor K is equal to 0.814 if the serum creatinine level is expressed in μmol/l; for women, the result has to be multiplied by 0.85.

Certain conditions increase creatinine production (e.g., severe febrile illness or rhabdomyolysis) and some drugs can reduce renal tubular creatinine secretion (e.g., probenecid, cimetidine). In these cases abnormal values do not indicate a fall in glomerular filtration rate. If serum creatinine is increased but less than 150 μmol/l, the term *renal function test abnormal* is used. If serum creatinine is greater than 150 μmol/l, or if creatinine clearance is less than 50 ml/min, the term *renal failure* should be used. More precise methods of measuring glomerular filtration rate include ^{51}Cr-EDTA clearance or iothalamate clearance.

Terms

Glomerular vasomotor disorder

Synonym: *Renal vascular disorder*

Preamble

Glomerular vasomotor disorder is a recommended new term for a group of conditions in which acute renal failure results from acute haemodynamic renal changes which impair the normal mechanism of preserving glomerular filtration. This results in a fall in glomerular filtration rate, which may be particularly severe in patients who are dehydrated, arteriosclerotic or elderly, or who already have impaired renal function.

[18] Cockcroft, D. W. and Gault, M. H. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

Drugs that produce this effect include non-steroidal anti-inflammatory drugs (NSAIDs) and cyclosporin, which induce glomerular afferent arteriole vasoconstriction, and ACE inhibitors and angiotensin-Il blockers, which, by their action on angiotensin-II, cause vasodilatation of the efferent glomerular arteriole. Combinations of drugs with these two mechanisms (e.g., NSAIDs and ACE-inhibitors) are particularly dangerous and renal function may not recover, even after withdrawing the drug.

Definition

Renal vascular disorder is a form of acute renal failure caused by changes in haemodynamics of the renal vasculature. This may be vasoconstriction of the glomerular afferent arteriole or vasodilation of the glomerular efferent arteriole.

Basic requirements for use of the term

1. Abnormal renal function or renal failure
2. Recent administration of the drug concerned, or an episode of hypovolaemia or hypotension in a patient already taking one or both of the drugs

Reference 8

Glomerulonephritis (acute and chronic)

Preamble

Many drugs are associated with the occurrence of glomerulonephritis. Most forms of glomerulonephritis are mediated by immunological mechanisms. Two syndromes can he differentiated: acute nephritic syndrome, with haematuria, red cell casts, decreased renal function and proteinuria; and nephrotic syndrome (oedema, heavy proteinuria), often with minimum loss of renal function. The term *glomerulonephritis* is also applied to a number of glomerular lesions that are not, strictly speaking, inflammatory processes. In such cases the term *glomerulonephropathy* is considered preferable

The term *glomerulonephritis, rapidly progressive,* describes a condition characterized by specific histological changes (crescentic glomerulonephritis).

Definition

Glomerulonephritis is a condition characterized by inflammatory, sclerosing or other pathological changes in the glomeruli; it may be acute, chronic or rapidly progressive.

Basic requirements for use of the term

The definitive diagnosis is made by renal biopsy. For a diagnosis based on clinical assessment the following signs are important indicators: haematuria, proteinuria, reduced glomerular filtration rate (increased serum creatinine or decreased creatinine clearance) and hypertension. It is a matter of medical judgement whether one or more of these findings justify the diagnosis.

Reference 8

Nephritis interstitial (acute and chronic)

Preamble

Interstitial nephritis is inflammation of the kidneys due to different pathogenic factors, involving mainly the renal interstitium. There may also be tubular damage, and the terms *tubulo-interstitial nephritis acute* and *tubulo-interstitial nephritis chronic* are commonly used. Analgesic nephropathy is a specific entity and is defined separately.

Definitions

Nephritis interstitial, acute. Acute interstitial nephritis is an acute inflammatory disease involving the renal interstitium, characterized by inflammatory cell infiltrates (mainly lymphocytes and mononuclear cells), interstitial oedema and, in some cases, pathological changes in the tubules.

Nephritis interstitial, chronic. Chronic interstitial nephritis is a chronic inflammatory renal disease, usually insidious in onset, characterized by inflammatory cell infiltrates and tubulo-interstitial scarring (fibrosis), leading to progressive chronic renal failure.

Basic requirements for use of the terms

Nephritis interstitial, acute. The definitive diagnosis can only be made by renal biopsy. It is essential to demonstrate abnormal renal function, or abnormal urinalysis (proteinuria, haematuria and leukocyturia). The presence of eosinophiluria supports the diagnosis.

Also, one or more of the following associated features should be present: abnormal tubular function, fever, arthralgia, skin rash, or eosinophilia.

Nephritis interstitial, chronic. The definitive diagnosis can only be made by renal biopsy. The clinical diagnosis is based mainly on abnormal renal function, ultrasound examination (in advanced stages, small kidneys with irregular outlines), and urinalysis (proteinuria, haematuria and leukocyturia).

Reference 8

Nephropathy analgesic

Preamble

Analgesic nephropathy is the commonest form of chronic drug-induced renal damage, and in some countries accounts for more than 20% of patients on renal replacement therapy. It is caused by long-term use of analgesics, particularly by combinations of paracetamol (a tubular toxin) and non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid, which reduces renal medullary blood flow by inhibition of prostaglandin synthetase. Renal failure usually develops slowly and symptoms may be absent for many years, but many patients have recurrent urinary tract infections and haematuria, while a few pass renal papillae or fragments of papillae in the urine. Renal papillary necrosis is always present but can be demonstrated, by intravenous urography, in only about 20% of cases. Renal imaging typically shows small kidneys with irregular outlines. Renal biopsy shows chronic interstitial fibrosis. There is an increased incidence of transitional cell carcinoma of the urothelium.

Definition

Analgesic nephropathy is a form of drug-induced chronic renal damage, characterized by renal papillary necrosis and chronic interstitial fibrosis.

Basic requirements for use of the term

1. History of long-term and heavy consumption of non-narcotic analgesics (in most cases, combinations)
2. Abnormal renal function
3. Demonstration of renal papillary necrosis, whenever possible

Other features include recurrent urinary tract infections, small irregular kidneys, tubular impairment and haematuria.

Reference 8

Nephropathy toxic

The term *nephropathy* refers strictly to any kidney disease, but it is usually applied to non-inflammatory diseases, which may be divided into glomerular, tubular, interstitial, and vascular disease. As the term *nephropathy toxic* is highly non-specific with regard to both toxic agent and kidney reaction, its use is to be discouraged.

The term used should specify if possible both the toxic agent and the reaction of the kidney — e.g., *glomerulonephritis membranous due to penicillinamine*, or at least the toxic agent — e.g., *nephropathy analgesic*.

Reference 8

Nephrotic syndrome

Preamble

Nephrotic syndrome is a consequence of a variety of disease processes, such as immunological disorders, toxic injuries, metabolic abnormalities and vascular disorders, leading to changes in the glomerular capillary wall and thus to excessive glomerular leakage of plasma proteins into the urine. Common causes of nephrotic syndrome include minimal change disease, idiopathic membranous glomerulonephritis, and diabetic glomerulosclerosis, but it may be caused also by drugs.

Definition

Nephrotic syndrome is a condition characterized by severe proteinuria, hypoalbuminaemia, oedema, and frequently hypercholesterolaemia.

Basic requirements for use of the term

Protein excretion rate > 3 g/day, hypoalbuminaemia (< 30 g/l) and oedema.

Reference 8

Renal failure

Synonym: *Renal insufficiency*

- Renal failure, acute, subacute and chronic
- Renal failure, aggravated
- Oliguria
- Anuria

Preamble

Drugs can cause renal failure, which may be acute (developing within hours or days), subacute (within weeks), or chronic (within months or years); they may also exacerbate pre-existing renal failure. Renal failure is usually recognized by the finding of a rising serum creatinine and serum urea concentration, associated with reduced creatinine clearance.

The presenting symptoms of drug-induced renal failure are the same as those of renal failure due to other causes. Whenever possible in reporting a suspected adverse drug reaction, the pre-existing level of renal function should be included in addition to the actual change in function.

Renal biopsy or ultrasound examination is recommended to determine the precise nature of renal damage and the likely outcome.

Definition

Renal failure is a reduction or suppression of the excretory function of the kidney, characterized by a decrease in creatinine clearance.

The term *renal failure, aggravated* should be limited to cases with pre-existing renal failure in which the already high level of serum creatinine has increased further by more than 50%, or creatinine clearance has decreased further by at least 50%.

The term *oliguria* means the passing of less than 400 ml of urine a day, and *anuria* the finding of no urine in the bladder by ultrasound examination or by catheterization.

Basic requirements for use of the term

Demonstration of increase in serum creatinine above 150 μmol/l, or reduction in creatinine clearance below 50 ml/min per 1.73 m^2 of body surface. Age, sex, weight and whether the patient is pregnant should be considered in determining abnormality of levels of serum creatinine or creatinine clearance.

Reference 8

Renal failure (intrinsic) acute

Synonyms: *Renal tubular necrosis acute; Renal tubular necrosis; Nephrosis lower nephron*

Preamble

Acute (intrinsic) renal failure is induced by renal ischaemia or nephrotoxins and frequently by a combination of both. The extent of tubular injury is strongly related not only to the concentration of the toxin and duration of exposure but also to the multiple predisposing host-factors that govern susceptibility and resistance (e.g., age, dehydration, pre-existing renal failure). The most frequently implicated nephrotoxic drugs are antibiotics, contrast media, and chemotherapeutic and immunosuppressive agents.

Definition

Acute (intrinsic) renal failure is a decrease in glomerular filtration rate resulting from renal hypoperfusion or a nephrotoxin, not immediately reversed upon discontinuation of the insult (dechallenge) and associated with some tubular cell damage.

Basic requirements for use of the term

1. Presence of a clinical syndrome compatible with an abrupt loss of renal blood flow (e.g., shock, hypovolaemia, severe heart failure), or history of actual exposure to a nephrotoxin
2. Acute decrease in renal excretory function

Reference 8

Renal tubular disorder

Preamble

Renal tubular disorders alone as a major manifestation of renal disease are rare. Renal tubular function is impaired in most cases of renal disease. In children renal tubular disorders occur mainly as genetic disorders. In adults they may represent a late appearance of genetic disease or acquired defects, inducing damage due to drugs. Some cases are symptom-free; others present with complications such as renal tubular acidosis. In some patients a single specific transport system may be affected; in others the disorders may be more complex.

The term *renal tubular disorder* should not be used to designate acute tubular necrosis.

Definition

Renal tubular disorder is an anomaly of tubular transport of various substances — for example, water, amino acids, sugars, and phosphate, bicarbonate, or hydrogen ions, or other electrolytes.

Basic requirements for use of the term

Documented abnormal renal excretion of the relevant substance or a related indicator. For a definitive diagnosis, renal function tests should be within the normal range.

Reference 8

Renal vasculitis

Synonym: *Renal allergic (hypersensitivity) vasculitis*

Preamble

The term *renal vasculitis* refers to a group of conditions that include acute allergic vasculitis, microangiopathy, thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, Henoch-Schönlein disease, and Wegener's granulomatosis; they are characterized by inflammation or necrosis of small blood vessels, including arterioles and glomerular capillaries. Vasculitis is mediated by immunological or direct toxic mechanisms, and drugs are implicated in some cases. The disorder may occur as a primary glomerular disease, but it is usually associated with systemic vasculitis, in which case such features as purpura, thrombocytopenia, skin vasculitis or fever may be present. It is often asymptomatic initially, but sometimes presents as rapidly progressive glomerulonephritis.

The preferred term is *renal vasculitis*: the term *angiitis* is to be discouraged.

Definition

Renal vasculitis is a condition characterized by focal and segmental necrosis of glomerular capillaries, inducing proliferation of glomerular epithelium, fibrin deposition and crescent formation.

Basic requirements for use of the term

Renal biopsy is necessary for the definitive diagnosis; it should, however, be performed only if it is medically acceptable to do so, as some patients have a severe bleeding tendency.

Clinical requirements are: abnormal renal function and urinalysis showing numerous red cells, white cells and red cell casts. Proteinuria is usually also present. Other features include purpura, epistaxis or gastrointestinal bleeding. The blood film may show thrombocytopenia or a microangiopathic picture. It is a matter of medical judgement whether one or more of these findings justify the diagnosis.

Reference 8

Vasculitis (see SOC 0300: Collagen Disorders)

Urinary retention

Preamble

Urinary retention may be due to partial or total impairment of bladder emptying. It may be acute or chronic.

Drugs may cause urinary retention or exacerbate a pre-existing retention caused by organic or mechanical obstruction or malfunction of the innervation of the bladder.

Definition

Urinary retention is the presence of urine in the bladder as a consequence of inability to empty the bladder.

Basic requirements for use of the term

Demonstration by ultrasound examination or catheterization of residual urine in the bladder after micturition.

Reference 8

Recommendation to include a new term

It is recommended that a new term, *glomerular vasomotor disorder*, be included in the MedDRA classification to cover drug effects on the renal vasculature.

Introduction

In considering the effects on the kidney of drugs, toxins and other insults, it is recognized that not all 'drug effects' fit comfortably into the existing MedDRA classification. Most adverse drug reactions can be attributed to direct tubular damage (usually called acute tubular necrosis), or to damage mediated through immunological mechanisms (e.g., glomerulonephritis), or to inflammatory changes (e.g., acute interstitial nephritis). It has recently been realized, however, that there is a group of drugs whose chief action and side-effects are on the intrarenal vasculature — i.e., a haemodynamic effect. The main drugs that produce such effects are:

1. Angiotensin converting enzyme (ACE) inhibitors
2. Angiotensin-II receptor antagonists
3. Non-steroidal anti-inflammatory drugs (NSAIDs)
4. Cyclosporin and tacrolimus

ACE inhibitors and angiotensin-II receptor antagonists are used in the management of hypertension, and ACE inhibitors also have a major role in the management of cardiac failure. Both groups of drugs, as part of their recognized action, block the vasoconstrictive effect of angiotensin-II on the efferent arteriole of the renal glomerulus. This effect may protect the kidney in some conditions, such as diabetes mellitus, but in others (e.g., pre-existing renal failure, bilateral renal artery stenosis, hypovolaemia or relative renal ischaemia) the kidney becomes critically dependent on the vasoconstriction of the efferent arteriole to maintain glomerular filtration. The administration of an ACE inhibitor or angiotensin-II receptor antagonist will cause a fall in glomerular capillary pressure and thus a fall in glomerular filtration, leading potentially to renal failure. This form of renal impairment or renal failure is thus haemodynamically mediated.

Non-steroidal anti-inflammatory drugs also have major effects on renal blood flow. By inhibiting prostaglandin synthetase they counteract the vasodilating effect of prostaglandins on renal blood vessels, particularly the renal medullary arterioles and the glomerular afferent arteriole. This results in both renal medullary ischaemia and reduction in glomerular blood flow. While prostaglandins probably play a major role in healthy individuals who are well hydrated, in patients with dehydration, arteriosclerosis or pre-existing renal insufficiency the kidney may become dependent on prostaglandin activity to maintain glomerular perfusion. In such circumstances NSAIDs may cause acute renal failure.

Cyclosporin and tacrolimus have a number of effects on the kidney, including vasoconstriction of the afferent glomerular arteriole. This action contributes to the nephrotoxicity of the drug. In some cases structural changes occur in the arteriolar wall, with occlusion of the arteriole by thrombus formation, leading to severe renal impairment.

Thus, the drugs listed above can cause significant renal impairment or acute renal failure as a result of effects on the glomerular arterioles. Combinations of drugs (e.g., NSAIDs plus ACE inhibitors) are even more likely to produce renal failure than the individual drugs alone, and nephrologists have increasingly recognized this danger. In some cases, renal function does not recover even if the drug or drugs are withdrawn.

The drugs described produce renal impairment or renal failure owing to haemodynamic changes in the renal vasculature. The 'vasomotor' effects of drugs cannot easily be fitted into the current MedDRA classification. For this reason there appears to be a strong case for including these 'drug effects' in the general category 'Renal vascular disorder', with a new subcategory 'Glomerular vasomotor (or vascular) disorder'. The term *vasomotor* probably expresses more accurately the haemodynamic effects of these drugs.

Recommendation

It is recommended that the following term be added to the MedDRA classification:

Preferred term: ***Glomerular vasomotor disorder***
(Alternative *Glomerular vascular disorder*)

High-level term: ***Renal vascular disorder***

Fetal Disorders (SOC 1500)

Aortic coarctation

Preamble

Aortic coarctation is one of the most common cardiovascular malformations; it may be associated with patent ductus arteriosus and intracardiac defects — in particular, ventricular septal defects. Such combinations may lead to infantile cardiac failure. Aortic valve anomalies, especially bicuspid aortic valve, are common.

Coarctation of the abdominal aorta is a rare lesion; in most cases it is acquired.

Definition

Aortic coarctation is a localized narrowing of the descending aorta distal to the isthmus and close to the ductus arteriosus or ligament, with or without a narrowing of the isthmus or horizontal aortic arch.

Basic requirements for use of the term

The diagnosis of coarctation of the aorta is highly likely when the arterial pulse in the lower extremity is absent, delayed or weak in a child or young adult, and when the systolic blood pressure is higher in the upper than in the lower extremities. To establish the diagnosis, however, it is necessary to demonstrate narrowing of the descending aorta by an imaging technique: angiography, magnetic resonance or echocardiography.

Reference 6

Aortic stenosis

Preamble

Congenital types of aortic stenosis include valvular, subvalvular (discrete or tunnel type), and supravalvular stenosis. Acquired aortic stenosis can occur as a result of rheumatic endocarditis or fibrotic or calcific degeneration. Bicuspid aortic valve is an important risk factor for development of aortic valve stenosis in middle age. Aortic stenosis alone is always congenital. Rheumatic fever causes mainly aortic regurgitation with some stenosis.

Definition

Aortic stenosis is a narrowing of the ventricular outflow tract leading to the aorta.

Basic requirements for use of the term

Demonstration of the narrowed site, by an imaging technique, or of a significant pressure gradient (> 20 mm Hg) between the left ventricle and the aorta, by either catheterization or Doppler techniques.

Reference 6

Artery malformation

Preamble

In reporting adverse drug reactions, *artery malformation* should be a group term rather than a preferred term, because it covers a number of entities. Malformation can occur in the large central arteries: e.g., vascular rings, aortic arch abnormalities, interruption of the aortic arch. Artery malformation may also be observed in small arteries: e.g., anomalies of coronary arteries (abnormally connected to the pulmonary artery or abnormally distributed). Congenital stenosis of peripheral arteries is uncommon, but it is seen most often in the pulmonary arteries (see *Pulmonic stenosis*).

Arterial aneurysms are most often acquired lesions. Occasionally they may be the result of congenital lesions of the arterial wall.

Arteriovenous fistulas, strictly speaking, are malformations of both arteries and veins. They can be congenital (e.g., pulmonary arteriovenous fistula, coronary fistulas).

Definition

Artery malformation is an anatomical abnormality of an artery, present at birth and resulting from faulty embryological development.

Basic requirements for use of the term

Demonstration by an imaging procedure of an arterial abnormality that appears to be congenital. Arteriography is the method of choice, although magnetic resonance and echocardiography with Doppler techniques may be diagnostic when the great arteries are involved.

Reference 6

Atrial septal defect

Preamble

Atrial septal defect is one of the three most common congenital heart defects. It is most often located within the fossa ovalis, and is due to partial or complete absence of the 'flap valve' of the foramen ovale; this is called 'secundum' atrial septal defect. The defect may also be in the inlet of the

atria near the superior vena cava ('sinus venosus type'). The so-called 'primum type' is part of a more complex anomaly, namely atrioventricular canal defect. An atrial septal defect is often associated with other heart malformations.

Patent foramen ovale is not a congenital malformation but represents rather a normal condition of the fetus, newborn and infant, which may persist into adult life.

Definition

Atrial septal defect is an abnormality in which the atrial septum is incomplete, allowing communication between the left and right atria.

Basic requirements for use of the term

The condition may be suspected from clinical appearances, electrocardiographic findings, or chest X-ray, but imaging techniques or haemodynamic measurements are required to confirm the diagnosis.

Reference 6

Heart malformation

Synonyms: *Congenital heart defect; Congenital heart disease*

Preamble

Heart malformation is a group term. Heart malformations occur in about 7/1000 live births. Etiological factors include heredity, chromosomal abnormalities, metabolic disorders, and the effects of teratogens. Teratogens are either physical, biological (e.g., viral infection) or chemical. Chemical teratogens include such substances as alcohol and drugs. Thus a congenital heart defect may occur as an adverse drug reaction if the drug or its metabolite affects organogenesis. Heart malformations as a result of a single etiological factor are uncommon. In most cases the etiology is multifactorial, attributable to a combination of hereditary predisposition and environmental factors.

Substances taken before or early in pregnancy can affect organogenesis; therefore, a careful drug history should be taken, covering the period preceding pregnancy as well as the first trimester of pregnancy. Only very few drugs have been found indisputably to increase the risk of heart malfunction in the fetus.

Definition

A heart malformation is an anatomical abnormality of the heart, present at birth and resulting from faulty embryological development.

Basic requirements for use of the term

Cardiac malformation may be suspected from clinical features (e.g., cardiac history, cardiac murmur), X-ray appearances, etc. but the diagnosis can be established only by cardiac imaging (echocardiogram, angiocardiography and cardiac catheterization, magnetic resonance) or a demonstration of altered haemodynamics (cardiac catheterization, dye-dilution, or Doppler techniques).

Reference 6

Pulmonic stenosis congenital

Synonym: *Congenital pulmonary stenosis*

Preamble

Congenital pulmonic stenosis is one of the most common cardiovascular abnormalities. It may occur as an isolated defect or accompany other intracardiac malformations, notably the tetralogy of Fallot. The most common site is the pulmonary valve (commissural fusion). Pulmonic stenosis may also be subvalvular (infundibular), as in the tetralogy of Fallot, or, rarely, supravalvular; or there may be a narrowing of one or several branches of the pulmonary artery.

Definition

Pulmonic stenosis is a narrowing of the right ventricular outflow tract of the great vessels supplying the lungs.

Basic requirements for use of the term

The condition may be suspected from clinical appearances, ECG and chest X-ray, but to establish the diagnosis the narrowed site must be demonstrated by an imaging technique, *or* a significant pressure gradient (e.g., 20-30 mm Hg) must be demonstrated between the right ventricle and the pulmonary artery by either catheterization or Doppler techniques.

Reference 6

Body as a Whole — General Disorders (SOC 1810)

Abdominal pain

(see SOC 0600: Gastro-Intestinal System Disorders)

Aggravation / Exacerbation

Preamble

The adjective *aggravated*, or *exacerbated*, not in itself an adverse-reaction term, is used to qualify a term signifying a condition considered to be an adverse reaction, as in *arthralgia aggravated, bilirubinaemia aggravated,* or *psoriasis aggravated.* It signifies the worsening of a disease for which a drug was used or of a concomitant disease.

The use of *aggravated* (or *exacerbated*) is especially difficult in relation to diseases that run a fluctuating course. In such cases the baseline is the pattern or expected pattern of the disease over time. The relevant time period depends on the course of the disease, which may fluctuate by hours or daily (circadian), or by seasons or years.

Definition

Aggravated refers to deterioration of a disease or condition, in terms of severity or frequency or in any other respect.

Basic requirements for use of the term

Findings in accordance with the definition.

Reference 13

Anaphylactic reaction

Preamble

The administration of a drug or other substance is sometimes followed rapidly by an acute systemic adverse reaction, simultaneously involving several organ systems. Characteristic symptoms of such a reaction are:

- Skin: itching, erythema, urticaria, angioedema
- Respiratory system: laryngeal oedema or spasm, bronchospasm
- Cardiovascular system: hypotension, shock
- Gastrointestinal system: abdominal cramps, diarrhoea
- Neuropsychological symptoms: anxiety, agitation, loss of consciousness.

This type of reaction may result from either immunological (anaphylactic) or non-immunological (anaphylactoid) mechanisms, resulting in the liberation of histamine and other mediators. Well-known causes of anaphylactic reactions are ß-lactam antibiotics, anti-venoms and solutions of hyposensitization (desensitization); those of anaphylactoid reactions are minor analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and radio-contrast media. Clinically the two types of reaction are indistinguishable; for the reporting of adverse reactions, therefore, *anaphylactic reaction* is the preferable term to use.

When it is the cardiovascular system that is predominantly involved in an anaphylactic reaction, shock may occur, manifested typically by tachycardia or bradycardia, pulselessness, hypotension, psychological signs of adrenergic stimulation (such as anxiety), and signs of cerebral ischaemia (loss of consciousness). Anaphylactic shock is associated with systemic vasodilation. Although often more than one organ/system is involved, shock may occasionally occur as the sole manifestation of an anaphylactic reaction. When a reaction affects predominantly the respiratory system, life-threatening laryngeal oedema or refractory bronchospasm may occur (with or without shock).

Anaphylactic reaction may occur after parenteral as well as enteral administration; with the latter the reaction may be delayed or less severe. The shorter the reaction time, the more severe the reaction is.

For adequate assessment of a case, exact information is needed about all exposures to drugs and other agents during the 24 hours preceding the reaction. Also, information about previous reactions may be pertinent.

Definition

Anaphylactic reaction is an acute hypersensitivity/allergic reaction of the immediate type, characterized by one or more of the following symptoms:

Skin: itching, erythema, urticaria, angioedema

Respiratory system: laryngeal oedema or spasm, bronchospasm

Cardiovascular system: hypotension.

In addition, the following symptoms may occur:

Gastrointestinal system: abdominal cramps, diarrhoea

Neuropsychological: anxiety, agitation, loss of consciousness

Basic requirements for use of the term

According to the definition.

Reference 13

Anaphylactic shock

Preamble

See Preamble to *Anaphylactic reaction*.

Definition

Anaphylactic shock is the most acute and severe form of hypersensitivity reaction, dominated by cardiological and respiratory symptoms (arterial hypotension, laryngeal oedema or bronchospasm).

Basic requirements for use of the term

The occurrence soon after exposure to a drug or other substance of clinical signs of shock, such as hypotension, tachycardia or bradycardia, pulselessness or loss of consciousness, together with one or both of the following groups of symptoms:

Skin: itching, erythema, urticaria, angioedema

Respiratory system: laryngeal oedema or spasm, bronchospasm.

Reference 13

Anaphylactoid reaction

Preamble

See Preamble to A*naphylactic reaction*.

Definition

Anaphylactoid reaction is an acute hypersensitivity reaction, which shows the symptoms of an anaphylactic reaction as specified above. It is not, however, an immunological reaction: no specific IgE antibodies can be found.

Basic requirements for use of the term

According to the definition.

Reference 13

Asthenia

Preamble

Asthenia is an unsatisfactory term for reporting adverse drug reactions. If the symptom mentioned by the patient is one of those contained in the

definition (below) it should be reported as such. Symptoms may be due to the disease or to the drug.

Definition

Asthenia is a collective term embodying complaints of fatigue, tiredness, lassitude, lack of energy, or generalized weakness.

Basic requirements for use of the term

According to the definition.

Reference 13

Cardiomyopathy

(see SOC 1020: Myocardial, Endocardial, Pericardial and Valve Disorders)

Hypovolaemia

Hypovolaemia is an unsatisfactory term for reporting adverse drug reactions. A more specific term should be used, according to the signs and symptoms, e.g., *hypotension, diarrhoea, vasodilation.*

Reference 13

Lupus erythematosus (see SOC 0300: Collagen Disorders)

Malaise

Preamble

Malaise is a common prodromal symptom of infections, but may be due to drugs or to the diseases for which they have been given.

Definition

Malaise is a general feeling of being unwell.

Basic requirements for use of the term

According to the definition.

Reference 13

Myocarditis

(see SOC 1020: Myocardial, Endocardial, Pericardial and Valve Disorders)

Rigors / Shivering

Preamble

Rigors are common in bacterial, rickettsial, and protozoal diseases and influenza (but not other viral diseases). Rigors are also common with drug-induced fevers.

Chills are a sensation of cold occurring in most fevers. Shivering is a readily observable generalized tremor. Chills, shivering and rigors are part of the response of the nervous system to the thermoregulatory 'set point' calling for more heat.

In some countries *rigor* is used for stiffness, as in *rigor mortis*. This usage should be differentiated from that of *rigors* as defined here.

Definition

The term *rigor* signifies a profound chill, with piloerection (goose flesh), teeth-chattering and severe shivering.

Basic requirements for use of the term

According to the definition.

Reference 13

Syncope

(see SOC 1010: Cardiovascular Disorders, General)

Withdrawal syndrome / Rebound effect

Preamble

Withdrawal syndrome occurs in substance-dependent persons with cessation or withdrawal of such psychoactive substances as alcohol, tobacco, amphetamines, cocaine, opioids, hypnotics, or anxiolytics. *Withdrawal,* as in *withdrawal syndrome*, should be differentiated from *withdrawal* in the sense of discontinuing a treatment drug. Withdrawal syndrome can be observed in non-dependent subjects taking long-term treatment.

The included term *rebound effect* refers to the recrudescence of a disease after the withdrawal of a treatment drug — e.g., propranolol in coronary artery disease.

Definitions

Withdrawal syndrome is a substance-specific effect of cessation of, or rapid reduction in, substance use that has been heavy and prolonged. The

substance-specific syndrome is one of clinically significant physiological or psychological distress or impairment in social, occupational or other important areas of functioning.

Rebound effect is recrudescence or overshooting of the symptoms of a disease after a treatment drug has been withdrawn.

Basic requirements for use of the terms

In accordance with the definitions of the terms.

Reference 13

APPENDICES

1. Meetings and Publications

This Appendix lists all the meetings held under the project *Definitions and basic requirements for the use of terms for reporting adverse drug reactions*, including two international "consensus meetings" organized by Roussel-Uclaf, Paris, under CIOMS auspices, and referenced below as *pre 1* and *pre 2*.

First Consensus Meeting (June 1989) *Reference pre 1*

Publication: Standardization of definitions and criteria of causality assessment of adverse drug reactions. Drug-induced liver disorders: report of an international consensus meeting. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 1990; 28(8): 317-322.

Second Consensus Meeting (April 1990) *Reference pre 2*

Publication: Standardization of definitions and criteria of causality assessment of adverse drug reactions. Drug-induced cytopenia. *International Journal of Clinical Pharmacology, Therapy and Toxicology,* 1991; 29(2): 75-81.

Meeting 1 (January 1991) *Reference 1*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions. *Pharmacoepidemiology and Drug Safety*, 1992; 1: 39-45.

Meeting 2 (November 1991) *Reference 2*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (II). *Pharmacoepidemiology and Drug Safety*, 1992; 1: 133-137.

Meeting 3 (April 1992) *Reference 3*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (III). *Pharmacoepidemiology and Drug Safety*, 1992; 1:191-196.

Meeting 4 (November 1992) *Reference 4*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (IV). *Pharmacoepidemiology and Drug Safety*, 1993; 2:149-153.

Meeting 5 (April 1993) *Reference 5*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (V). *Pharmacoepidemiology and Drug Safety*, 1993; 2:189-193.

Meeting 6 (May 1993) *Reference 6*

Publication: Definitions of Adverse Drug Reactions and Minimum Requirements for Their Use — Cardiovascular Disease Terms. *Pharmacoepidemiology and Drug Safety*, 1993; 2: 591-602.

Meeting 7a (June 1995) *Reference 7a*

Meeting 7b (October 1995) *Reference 7b*

Publication (7a and 7b): Harmonizing the Use of Adverse Drug Reaction Terms. Definitions of terms and minimum requirements for their use: Respiratory Disorders and Skin Disorders. *Pharmacoepidemiology and Drug Safety,* 1997; 6:115-127.

Meeting 8 (June 1996) *Reference 8*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (VIII): Renal and Urinary System Disorders. *Pharmacoepidemiology and Drug Safety,* 1997; 6: 203-211.

Meeting 9 (November 1996) *Reference 9*

Publication: Definitions of Terms for Reporting Adverse Drug Reactions (IX): Nervous System and Psychiatric Disorders. *Pharmacoepidemiology and Drug Safety*, 1998; 7: 39-49.

Meeting 10 (April 1997) *Reference 10*

Publication: Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (X): Gastrointestinal System Disorders. *Pharmacoepidemiology and Drug Safety,* 1998; 7: 281-287.

Meeting 11 (November 1997) *Reference 11*

Publication: Definitions and Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (XI): Cardiovascular System Disorders. *Pharmacoepidemiology and Drug Safety,* 1998; 7: 351-357.

Meeting 12 (September 1998) *Reference 12*

Publication: Definitions and Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (XII): Collagen Disorders and Musculo-Skeletal Disorders. *Pharmacoepidemiology and Drug Safety*, 1999; 8: 141-145.

Meeting 13 (October 1998) *Reference 13*

Publication: Definitions and Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (XIII): Clinical Pathology and General Disorders. *Pharmacoepidemiology and Drug Safety*, 1999; 8: 217-224.

2. Participants of meetings 1 – 14

In parentheses, reference numbers of the meetings attended

ACHENBACH, C. (5,6)
Medizinisch-Pharmazeutische Studiengesellschaft e.V.,
Postfach 24 01 43,
Dreizehnmorgenweg 44,
D – 5300 Bonn 2,
Germany

AELLIG, W. (3 – 14)
Clinical Safety and Epidemiology,
Novartis Pharma AG,
CH – 4002 Basel,
Switzerland

ANTY, R. (6)
Medical Research Department,
ICI Pharmaceuticals ZENECA,
Mereside, Alderly Park,
Macclesfield, Cheshire SK10 4TG,
United Kingdom

ATSMA, W. J. (6)
Product Surveillance Department,
Organon International BV,
P.O.Box 20,
NL – 5340 BY Oss,
The Netherlands

BADER, J.-P. (10)
OVP,
33 ave Wagram,
F – 75000 Paris,
France

BANKOWSKI, Z. (1 – 9,11-14),
Council for International Organizations of Medical Sciences,
c/o World Health Organization,
CH – 1211 Geneva 27,
Switzerland

BASS, R. (10)
Human Unit,
European Agency for the Evaluation of Medical Products,
7 Westferry Circus,
Canary Wharf,
London E14 4HB,
United Kingdom

BAUMBAUER, E. (7a, 8,10)
Research and Development,
Verband Forschender Arzneimittelhersteller e.V.
Johanna-Kinkel-Str. 2-4,
D – 53143 Bonn,
Germany

BAUMELOU, E. (3)
Hôpital Foch,
Suresnes,
France

BEERMANN, B. (6)
Section of Information and Pharmacovigilance,
The Medical Products Agency,
S – 75103 Uppsala,
Sweden

BEGAUD, B. (1)
Commission nationale de Pharmacovigilance,
DPHM, Ministère de la Santé,
1 Place Fontenoy,
F – 75007 Paris,
France

BEGLINGER, CH. (10)
Division of Gastroenterology,
University Hospital,
CH – 4031 Basel,
Switzerland

BENICHOU, C. (3)
Département central de Pharmacovigilance,
Roussel Uclaf,
35 blvd des Invalides,
F – 75007 Paris,
France

BERNEKER, G.-C. (1)
F. Hoffmann-La Roche & Co Ltd,
Grenzacherstrasse 124,
CH – 4002 Basel,
Switzerland

BERTELSMANN, A.-K. (7b)
Pharmacovigilance,
European Agency for the Evaluation
of Medical Products,
7 Westferry Circus,
Canary Wharf,
London E14 4HB,
United Kingdom

BERTOLOTE, J. M. (9)
Division of Mental Health and
Prevention of Substance Abuse,
World Health Organization,
CH – 1211 Geneva 27,
Switzerland

BIRIELL, C. (2)
WHO Collaborating Centre for
International Drug Monitoring,
P.O. Box 26,
S – 75 103 Uppsala,
Sweden

du BOIS, R. M. (1)
National Heart and Lung Institute,
Department of Thoracic Medicine,
Emanuel Kaye Building,
Manresa Road,
London SW3 6LR,
United Kingdom

BOUSQUET, J. (7a)
Service des Maladies Respiratoires.
Hôpital Arnaud de Villeneuve,
371 Avenue de Doyen Gaston Giraud,
F – 34295 Montpellier, Cedex 5
France

BRUNNER, H. (1,6)
Département de Médecine interne,
CHUV,
Rue Bugnon,
CH – 1011 Lausanne,
Switzerland

BRUPPACHER, R. (25,7-11,14)
Alleeweg 8,
CH – 4310 Rheinfelden,
Switzerland

BRUPPACHER-GELLIER, M. (5)
Alleeweg 8,
CH – 4310 Rheinfelden,
Switzerland

CAMUS, P. (7a)
Service de Pneumologie et de
Réanimation respiratoire,
CHU-Dijon,
B.P. 1543
F – 21034 Dijon,
France

CAPPUS, H. (2)
INTERPHARMA,
Generalsekretariat,
c/o Sandoz Pharma AG,
Postfach
CH – 4002 Basel
Switzerland

CARLHANT-KOWALSKI, D. (10)
Service de Pharmacologie
fondamentale et clinique,
Centre de Pharmacovigilance et
d'Information sur le Médicament,
C.H.U. Morvan 5, avenue Foch,
F – 29609 Brest Cedex,
France

CASSANO, G. B. (9)
Instituto di Psichiatria,
Università di Pisa,
Ospedale S. Chiara,
Via Roma 67,
I – 56126 Pisa,
Italy

CASTOT, A. (7b)
Pharmacovigilance Unit,
Agence du Médicament,
Direction de l'Evaluation,
143-147 blvd Anatole France
F – 93285 Saint-Denis,
France

CHAMBERLAIN, D. (6)
Department of Cardiology,
Royal Sussex County Hospital,
Eastern Road,
Brighton, East Sussex BN2 5BE,
United Kingdom

CHAMBERS, W. (5)
Division of Anti-infective Drug Products,
Office of Drug Evaluation,
Centre for Drug Evaluation and Research,
Food and Drug Administration,
5600 Fishers Lane,
Rockville,
Maryland 20857,
USA

CHANTRAINE, A. (12)
Hôpital cantonal universitaire,
Beau-Séjour,
CH – 1211 Geneva 14,
Switzerland

CONE, M. (7)
International Federation of Pharmaceutical Manufacturers Associations (IFPMA),
30 rue de St Jean,
CH – 1211 Geneva 18,
Switzerland

COVE-SMITH, R. (8)
South Cleveland Hospital,
Marton Road,
Middlesborough,
Cleveland TS4 3BW,
United Kingdom

CRUSIUS, I. (9 – 13)
Boehringer Ingelheim GmbH,
Corporate Drug Safety
D – 53216 Ingelheim am Rhein,
Germany

DELINI-STULA, A. (9)
F. Hoffmann-La Roche Ltd.
Hohlgasse 31,
CH – 4102 Binningen,
Switzerland

DENNISON, D. (7a)
Royal Brompton Hospital,
Sydney Street
London SW3 6NP,
England

DIEKMANN, U. (4, 7a)
Corporate Drug Safety,
Boehringer Ingelheim GmbH,
D – 55216 Ingelheim-am-Rhein,
Germany

DUBERTRET, L. (7b)
Hôpital Saint-Louis,
Avenue Claude VelleJaux
F – 75475 Paris Cedex 10,
France

DUNNE, J. F. (2 – 6)
Division of Drug Management and Policies,
World Health Organization,
CH – 1211 Geneva 27,
Switzerland

ECKERT, S. (3)
Bayer AG,
Pharma Research,
P.O. Box 101709,
D – 5600 Wuppertal 1
Germany

EDWARDS, I. R. (3 – 7)
WHO Collaborating Centre for International Drug Monitoring,
Box 26,
S – 75103 Uppsala,
Sweden

FALCI, M. (4)
Boehringer Ingelheim GmbH,
B. Medizin,
Corporate Drug Safety,
Postfach 200,
D – 6507 Ingelheim am Rhein,
Germany

FENICHEL, R. (11)
Division of Cardiorenal Drug Products,
Center for Drug Evaluation & Research,
Food and Drug Administration,
Rockville, MD 20857,
USA

FERRERO, F. (9)
Département de Psychiatrie,
Clinique des Psychiatrie II,
Bd St-Georges 16 -18,
CH – 1205 Geneva,
Switzerland

FRACCHIA, G. N. (5,6)
Directorate General for Science, Research and Development,
Joint Research Centre,
Commission of the European Communities,
Rue de la Loi 200,
B – 1049 Brussels,
Belgium

FRAUNFELDER, F. T. (5)
National Registry of Drug-induced Ocular Side Effects,
Casey Eye Institute,
Oregon Health Sciences University,
3375 S.W. Terwilliger Blvd,
Portland, Oregon 97201-4197,
USA

FRIEDLI, B. (6)
Paediatric Cardiology,
Hôpital cantonal universitaire de Genève,
Clinique de Pédiatrie,
CH – 1211 Geneva 14,
Switzerland

FRY, L. (7b)
Department of Dermatology,
St. Mary's Hospital,
London,
United Kingdom

GALLAGHER, J. (1 – 14)
Council for International Organizations of Medical Sciences,
c/o World Health Organization,
CH – 1211 Geneva 27,
Switzerland

GALLO-TORRES, H. (10)
Division of Gastrointestinal Drug Products,
Food and Drug Administration,
Center for Drug Evaluation and Research,
Rockville,MD 20857,
USA

GELLERT, J. (10)
Bayer AG,
Pharma Research Centre,
Drug Safety International,
D – 42096 Wuppertal,
Germany

GOODWIN, J. (6)
Royal Postgraduate Medical School,
Hammersmith Hospital,
Du Cane Road,
London W12 ONN,
United Kingdom

GRATWOHL, A. (14)
Unable to attend but provided consultation
Department of Internal Medicine 1
Division of Hematology,
Kantonsspital Basel,
Universitätskliniken,
CH – 4031 Basel,
Switzerland

GROSS, W. (12)
Zentrum Innere Medizin der Medizinischen Universität Lübeck,
Ratzeburger Allee
D – 23538 Lübeck,
Germany

GYR, K. (2)
Medizinische Klinik,
Kantonsspital Liestal
Rheinstrasse 26,
CH – 4410 Liestal,
Switzerland

HACHEN, H. J. (3)
International College of Angiology,
Case postale 249,
CH – 1211 Geneva 24,
Switzerland

HARAMBURU, F (4)
Centre Régional de
Pharmacovigilance,
Hôpital Pellegrin-Carreire,
Zone Nord-Bâtiment 1A,
F – 33076 Bordeaux Cedex,
France

HARMS, C. (7b)
Clinique et Policlinique de
Dermatologie et de Vénéréologie,
Hôpital cantonal universitaire,
CH – 1211 Geneva 4,
Switzerland

HEIMPEL, H. (3)
Universität Ulm
Medizinische Klinik
und Poliklinik,
Postfach 3880,
D – 7900 Ulm,
Germany

HEUER, H. (7a)
Corporate Drug Safety,
Boehringer Ingelheim GmbH
D – 55216 Ingelheim-am-Rhein,
Germany

HIEMSTRA, S. (4,5)
Pharmaceutical Research Associates
GmbH
Besselstrasse 2-4,
D – 6800 Mannheim 81,
Germany

HOIGNE, R. (1)
CHDM, Zieglerspital,
CH – 3007 Bern,
Switzerland

HULLA, F. (10)
Bayer AG,
Pharma Research Centre,
Drug Safety International,
D – 42096 Wuppertal,
Germany

HUTT, H. J. (2)
Dr. K. Thomae GmbH,
Abteilung Medizin,
Arzneimittelsicherheit,
D – 7950 Biberach 1,
Germany

IDANPAAN-HEIKKILA, J. E.
(8,9,11,14)
Division of Drug Management and
Policies,
World Health Organization,
CH – 1211 Geneva 27,
Switzerland

IMBS, J.-L. (6)
Commission nationale de la
Pharmacovigilance,
DPHM Ministère de la Santé,
1 place Fontenoy,
F – 75007 Paris,
France

IPPEN, H. (7b)
Springstrasse 67,
D – 37077 Göttingen,
Germany

JENKINS, J. (7a)
Pulmonary Drugs Division,
Food and Drug
Administration,
5400 Fishers Lane,
Rockville, MD 20857,
USA

JOHNSON, J. (6)
Center for Drug Evaluation and
Research,
Food and Drug Administration,
Parklawn Bldg, Room 15B-31,
5600 Fishers Lane,
Rockville, Maryland 20857,
USA

JUNG, D. (12)
Knoll AG,
Rathausplatz 10-12
D – 67059 Ludwigshafen,
Germany

KAPPENBERGER, L. (11)
Division de Cardiologie,
CHUV,
CH – 1011 Lausanne,
Switzerland

KASSEL, G. (12)
Byk Gulden GmbH
Byk-Gulden-Strasse 2
D – 78467 Konstanz,
Germany

KEISU, M. (3)
Division of Drug Epidemiology Information,
Medical Products Agency,
P.O.Box 26,
75103 Uppsala,
Sweden

KERR, L. (4)
International Drug Regulatory Affairs and Safety,
Hoffmann-La Roche & Co., Ltd.,
CH – 4002 Basel,
Switzerland

KLÜGLICH, M. (12)
Drug Surveillance Frankfurt,
Hoechst Marion Roussel Deutschland,
D – 65926 Frankfurt-am-Main,
Germany

KÖNIG, H.-J. (4)
Neurochirurgische Klinik der Westfalia,
Wilhelms-Universität,
Albert-Schweitzer-Str. 33,
D – 4400 Münster,
Germany

KREFT-JAIS, C. (14)
Pharmacovigilance Unit,
Agence du Médicament,
Direction de l'Evaluation,
143 147 blvd Anatole France
F – 93285 Saint-Denis,
France

KREMER, G. (3,4, 7 – 14)
Boehringer Ingelheim GmbH
Corporate Drug Safety
D – 53216 Ingelheim am Rhein,
Germany

KREUTZ, G. (1 – 13)
Bundesinstitut für Arzneimittel und Medizinprodukte,
Seestrasse 10-11
D – 13353 Berlin,
Germany

KRUPP, P. (2)
Pharmacovigilance Group,
Clinical Research Building 386/810,
Sandoz Pharma Ltd.,
4002 Basel,
Switzerland

KUBE, R. (2)
Dr. K. Thomae GmbH,
Abteilung Medizin,
Arzneimittelsicherheit,
D – 7950 Biberach 1,
Germany

KUNZE, K. (9)
Neurologische Universitätsklinik
Martini-Strasse 52,
D – 2000 Hamburg 20,
Germany

LAGIER, G. (5)
Pharmacologie,
Hôpital Fernand Widal,
200, rue du FG Saint Denis,
F – 75475 Paris Cedex 10,
France

LAMACHE, E. (10)
European Agency for the Evaluation of Medical Products,
7 Westferry Circus,
Canary Wharf,
London E14 4HB,
United Kingdom

LAURELL, G. (14)
Department of Otolaryngology,
Karolinska Hospital,
S – 17176 Stockholm ,
Sweden

LEPAKHIN, V. (12)
Office of the Director-General,
World Health Organization,
1211 Geneva 27,
Switzerland

LESKI, M. (8)
Département de Médecine,
Division de Nephrologie,
Hôpital cantonal universitaire,
1211 Geneva 14,
Switzerland

LEVIN, R. (4)
Centre for Drug Evaluation and Research,
Food and Drug Administration,
Room 10-B-45,
5600 Fishers Lane,
Rockville,
Maryland 20857,
USA

LUDIN, H.P. (4)
Department of Neurology,
Cantonal Hospital,
CH – 9000 St. Gallen,
Switzerland

LÜDERITZ, B. (1,6)
Department of Medicine and Cardiology,
University of Bonn,
Sigmund-Freud-Strasse 25,
D – 1000 Berlin 33,
Germany

LUFT, S. (4)
Hoechst AG,
Postfach 80 03 20,
D – 6230 Frankfurt am Main 80,
Germany

LUMPKIN, M. M. (2)
Center for Drug Evaluation and Research,
Office of Drug Evaluation II HFD-500,
Food and Drug Administration,
Rockville,
MD 20857,
USA

MANN, R. D. (1 – 7, 10-14)
Drug Safety Research Unit,
Bursledon Hall,
Southampton S03 8BA,
England

MARSH, J. (13)
Unable to attend but provided consultation
Department of Haematology,
St. George's Hospital,
Blackshaw Road,
London SW17 0QT
England

MEYBOOM, R. H. B. (1)
Netherlands Centre for Monitoring of Adverse Reactions to Drugs,
P.O. Box 5406,
NL – 2280 HK Rijswijk,
Netherlands

MEYER, Ph. (1)
Commission of the European Communities,
Internal Market and Industrial Affairs,
Rue de la Loi 200,
B – 1049 Brussels,
Belgium

MEYER, U. (1)
Gruppe AMG-Belange/GCP,
Boehringer Ingelheim,
Bingerstrasse 173,
D – 6507 Ingelheim/Rhein,
Germany

MOCKENHAUPT, M. (7b)
Dokumentationszentrum schwerer Hautreaktionen,
Universitäts-Hautklinik,
Hauptstrasse 7
D – 791044 Freiburg,
Germany

MOORE, N. (2, 7a)
Hôpital de Bois-Guillaume,
Centre de Pharmacovigilance,
147 Avenue du Maréchal Juin,
B.P. 100,
F – 76233 Bois-Guillaume Cedex,
France

NAZARIO, J. (3)
Centre for Biologics Evaluation and Research,
Food and Drug Administration,
Bethesda, MD 20892,
USA

NORDET, P. (6,11)
Cardiovascular Diseases,
World Health Organization,
CH – 1211 Geneva 27,
Switzerland

OLSSON, R. (2)
Department of Internal Medicine,
Sahlgrenska Hospital,
S – 41345 Göteborg,
Sweden

OPIE, L. H. (6)
Committee on Cardiovascular Drugs,
Heart Research Unit,
University of Cape Town Medical School,
7925 Observatory,
Cape Town,
South Africa

OSTER, M. (8)
Hoechst AG,
D – 62926 Frankfurt,
Germany

PAOLETTI, R. (6)
Institute of Pharmacology,
University of Milan,
via Balzaretti 9,
I – 20133 Milan,
Italy

PAPALUCA, M. (4)
Ministry of Health,
Pharmaceutical Department,
Via della Civiltà,
I – 00144 Rome,
Italy

PAPP, J. G. (6)
Department of Cardiopharmacology,
University of Szeged,
P.O. Box 115,
6701 Szeged,
Hungary

PERRENOUD, J.-J. (6)
Chemin Beau-Soleil 20,
CH – 1206 Geneva,
Switzerland

PERRUCHOUD, A. P. (7a)
Abteilung Pneumologie,
Universitätsklinik Basel,
Petersgraben 4,
CH – 4031 Basel,
Switzerland

PFEIFFER, M. (2,5,7 – 11)
Bayer AG,
Pharma Research Centre,
P.O. Box 101709,
D – 42096 Wuppertal,
Germany

PIERREDON, M. A. (6)
Rhône-Poulenc Rorer, Inc.,
20 ave Raymond Aron,
F – 92165 Antony,
France

PIETREK, M. (5,6)
Drug Safety,
F. Hoffmann-La Roche Ltd.,
CH – 4002 Basel,
Switzerland

PRICHARD, B. N. C. (11)
Department of Clinical Pharmacology,
University College Hospital,
Gower Street,
London WC1E 6JJ,
United Kingdom

RAKOSKI, J. (7b)
Dermatologische Klinik u. Poliklinik der Technischen Universität München,
Biederstein Strasse 29
D – 80802 München,
Germany

RANKET, L. (2)
Medical Department A-2152,
Rigshospitalet,
DK – 2100 Copenhagen,
Denmark

RASTOGI, S. C. (3)
Division of Biostatistics and Epidemiology,
Centre for Biologics Evaluation and Research,
Food and Drug Administration,
Bethesda, MD 20892,
USA

REITER, Ch. (2, 7a, 10)
Bayer AG,
Pharma Research Centre,
Drug Safety International,
D – 42096 Wuppertal,

Germany
RHODES, J. M. (10)
The University of Liverpool,
Gastroenterology Research Group,
University Clinical Department of Medicine,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA,
United Kingdom

ROCCO, F. (8)
Department of Medicine,
University of Milan,
Division of Urology,
Ospedale San Gerardo,
Via Donizetti, 106,
I – 20052 Monza,
Italy

ROCHAT, T. (7a)
Hôpital cantonal et universitaire de Genève,
Centre Anti-TBC,
CH – 1205 Geneva,
Switzerland

ROUJEAU, J.-C. (7b)
Hôpital Henri Mondor,
Service de Dermatologie,
51 ave du Maréchal de Lattre de Tassigny,
F – 94010 Creteil Cedex,
France

ROYER, R.-J. (3)
Commission Nationale de Pharmacovigilance,
DPHM, Ministère de la Santé,
1 place Fontenoy,
F – 75007 Paris,
France

RUSSWURM, R. (7b)
Hoechst AG,
D – 65926 Frankfurt am Main,
Germany

RUTISHAUSER, W. (6)
Centre de Cardiologie,
Hôpital cantonal universitaire,
Rue Micheli-du-Crest,
CH – 1205 Geneva,
Switzerland

SANDER, J. W. A. S. (9)
World Federation
of Neurology,
Epilepsy Research Group,
National Hospital for Neurology and
Neurosurgery,
Institute of Neurology,
33 Queen Square,
London WC1N 3 BG,
United Kingdom

SCHATTENKIRCHNER, M. (4)
Rheuma-Einheit der Medizinischen
Poliklinik der Universität
München,
Ludwig-Maximilians-Universität,
Pettenkoferstrasse 8a,
D – 8000 München,
Germany

SCHOU, J. S. (4 – 9)
Department of Pharmacology,
University of Copenhagen,
Panum Instituttet,
Blegdamsvej 3,
DK – 2200 Copenhagen N,
Denmark

SCHRANK, J. (7b,8,10)
INTERPHARMA,
Petersgraben 35,
P.O. Box,
CH – 4003 Basel,
Switzerland

SCHUMANN, W. (1,4,8,12)
Drug Safety,
Schering AG,
D – 13342 Berlin,
Germany

SPIEGL, W. (8,9,14)
F. Hoffmann-La Roche Ltd.,
CH – 4070 Basel,
Switzerland

SPINELLI, F. (8)
Pharma Division,
PH 3.521, K-490.2.38,
Ciba-Geigy AG.
CH – 4002 Basel,
Switzerland

SPRENGER, K. (1,8)
Bayer AG,
Pharma Research Centre,
P.O. Box 101709
D – 42096 Wuppertal,
Germany

STEINBACH, T. (10,12)
Schwarz Pharma AG,
Alfred-Nobel Strasse 10,
D – 40789 Monheim,
Germany

STERN, R. S. (7b)
Department of Dermatology,
Harvard Medical School,
330 Brookline Avenue,
Boston, MA 02215
USA

STERRY, W. (7b)
Universitätsklinikum Charité,
Medizinsche Fakultät der
Humboldt-Universität zu
Berlin,
Dermatologische Universitätsklinik
und Poliklinik,
Schumannstrasse 20/21
D – 01007 Berlin,
Germany

STOLLER, R. (7a,12-14)
Pharmacovigilance Centre,
Office Intercantonal de Contrôle de
Médicaments,
CH – 3000 Bern 9,
Switzerland

STREBEL, L. (2 – 4,11)
Office Intercantonal de Contrôle de
Médicaments,
CH – 3000 Bern 9,
Switzerland

STROHMEYER, G. (2)
c/o Heinrich-Heine-Universität,
Ltr. d. Abt. für
Gastroenterologie,
MNR-Klinik,
Moorenstrasse 5,
D – 4000 Düsseldorf 1,
Germany

TANCREDE, D. (9)
Direction internationale de la Pharmacovigilance,
Sanofi Pharma S.A.,
82 ave Raspail,
F – 94255 Gentilly Cedex,
France

TEN HAM, M. (1,2, 4,5,7,8,11,12)
Drug Safety,
World Health Organization,
1211 Geneva 27,
Switzerland

TRENQUE, T. (8,9)
Agence du Médicament,
Direction de lÉvaluation,
143 -147 Bd Anatole France,
F – 93285 Saint-Denis Cedex,
France

TRIANTAS, E. (3)
Division of Gastrointestinal and Coagulation Drug Products,
Food and Drug Administration,
Rockville, MD 20857,
USA

TROLIN, I. (7b)
Post Licensing, Safety and Efficacy,
Medical Products Agency,
PO Box 26
S – 751 03 Uppsala,
Sweden

TRÜBESTEIN, G. (1,6,11)
Spessart-Klinik Bad Orb,
Würzburger Strasse 7/11,
D – 63619 Bad Orb,
Germany

VENULET, J. (1 – 14)
Council for International Organizations of Medical Sciences,
c/o World Health Organization,
CH – 1211 Geneva 27,
Switzerland

VILARDELL, F. (2,10)
Former President, World Organization of Gastroenterology,
Juan Sebastian Bach 11,
E – 08021 Barcelona,
Spain

WEIDMANN, E. (2,8)
Drug Safety Department,
Hoechst AG,
D – 65926 Frankfurt am Main,
Germany

WEISS, J.-M. (7b,8)
F. Hoffmann-La Roche & Co. Ltd.,
Grenzacherstrasse 124,
CH – 4002 Basel,
Switzerland

WILKIN, J. (7b)
Division of Dermatologic and Ophthalmologic Drug Products,
Food and Drug Administration,
Rockville, MD 20857,
USA

WOOD, K. L. (8,9)
MedDRA Project,
Medicines Control Agency,
Room 1027,
Market Towers,
1 Nine Elms Lane,
London SW8 5NQ,
United Kingdom

WOOD, S. (2,6)
Pharmacovigilance Unit,
Medicines Control Agency,
Market Towers,
1 Nine Elms Lane,
London SW8 5NQ,
United Kingdom

WROBLEWSKI, H. (3)
Bayer AG,
Pharma Forschungszentrum,
Arzneimittelsicherheit,
D – 5600 Wuppertal 1,
Germany

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