Medical Management of Radiation Accidents: Management of the Acute Radiation Syndrome

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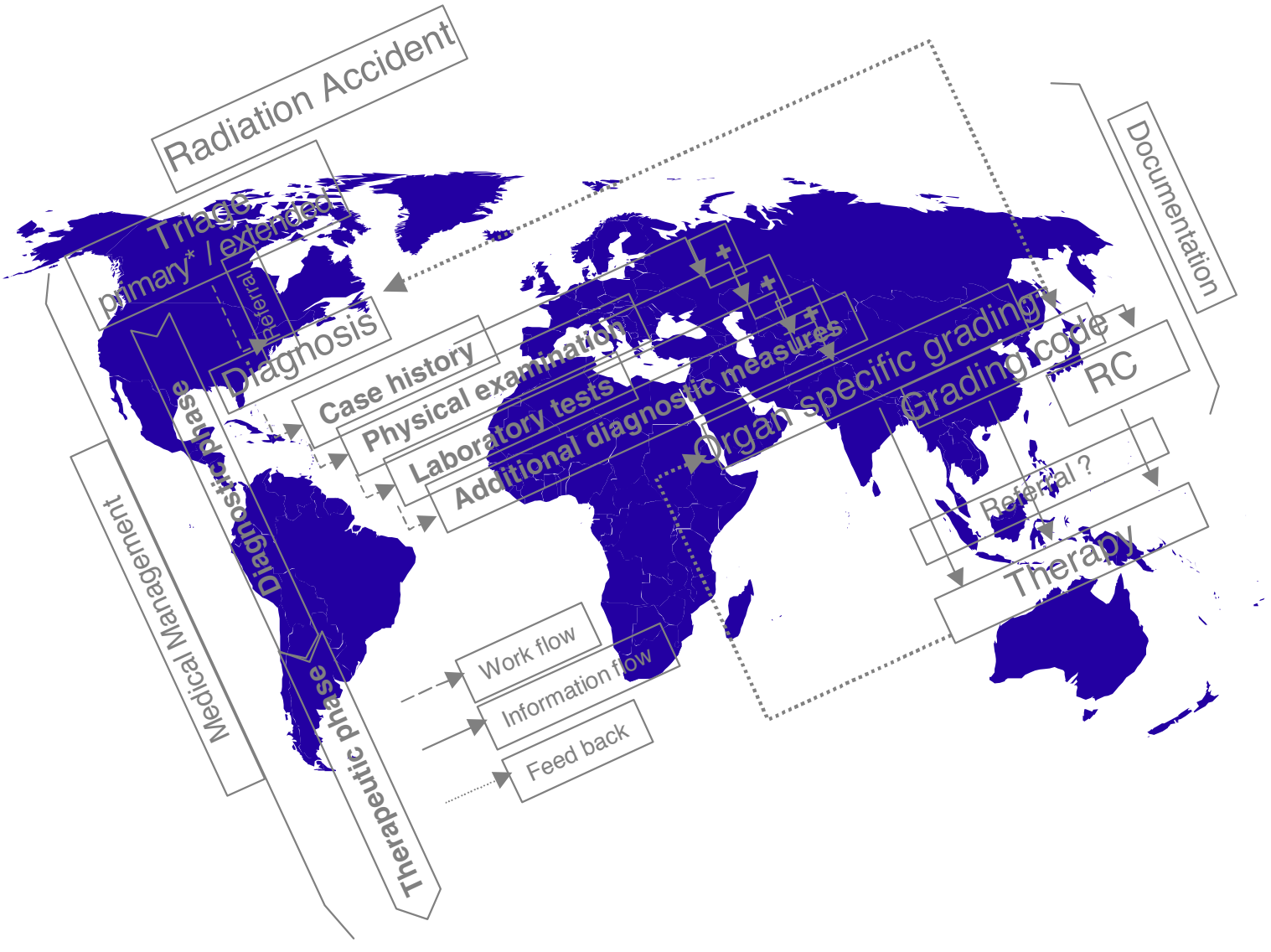
MEDICAL MANAGEMENT OF RADIATION ACCIDENTS

Edited by T M Fliedner, I Friesecke and K Beyrer



MANUAL ON THE ACUTE RADIATION SYNDROME

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MEDICAL MANAGEMENT OF RADIATION ACCIDENTS – MANUAL ON THE ACUTE RADIATION SYNDROME –

This manual is the result of a Concerted Action called **METREPOL** (**Me**dical **Tre**atment **P**rotoc**ol**s for Radiation Accident Victims as a Basis for a Computerised Guidance System), which was supported by the European Commission.

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NOTICE

Every effort has been made by the authors of this manual to ensure that recommendations are in agreement with the standards of practice at the time of publication. However, owing to progress in clinical experience and continuing laboratory studies these recommendations may need to be changed with time. Therefore, we urge that the reader check especially the diagnostic and therapeutic recommendations against the latest developments in clinical (radiation) medicine. In addition, there may be special cases that are beyond the scope of this manual and therefore require individual care and external expert advice.

THE EDITORS

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FOREWORD

In the Nuclear Fission Safety Program (DG XII Science) of the European Atomic Energy Community, the Commission of the European Communities accepted and supported a Concerted Action called “Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerised Guidance System”, in short METREPOL (Contract number FI4PCT970067). The work of the Concerted Action started in December 1997.

One of the main purposes of this interdisciplinary project was to develop a new approach in the medical management of radiation accidents with respect to diagnostic procedures and therapeutic options based on the recognition and evaluation of health impairments after acute radiation exposure. The work of the group is presented in the form of this manual on the acute radiation syndrome.

The acute radiation syndrome (ARS) is very complex, because the interactions and combined effects of damage to different organ systems after radiation exposure are diverse and not yet fully understood. Furthermore, the clinical management of patients suffering from an ARS requires immediate and specialised care. In cases of accidental exposure to ionising radiation, guidance for appropriate diagnostic and therapeutic procedures is therefore required. This manual is compiled to help assess in the shortest time possible the state and possible outcome of radiation accident victims. It specifies what has to be examined and what should be documented, and it provides a scientific basis for deciding the most appropriate therapeutic interventions.

It is hoped that the wide distribution and broad acceptance of this manual on the acute radiation syndrome will make a useful contribution to the management, harmonisation and standardisation of diagnosis and therapy of future radiation accident victims. It is also hoped that an international standard for the scientific evaluation of health impairments of radiation accident victims is promoted, no matter in which country or region a radiation accident occurs and what level of health care is available.

The Co-ordinator is grateful to the participants of this Concerted Action. The development of this manual was possible only with their continuous commitment and input based on special scientific/medical experience. Furthermore, on behalf of the METREPOL team, the Co-ordinator would like to thank the external experts for reviewing this manual and giving their advice and support.

THE EDITORS

EXECUTIVE SUMMARY

The medical management of radiation accident victims, in terms of diagnosis and treatment, is classically centred on the assessment and reconstruction of the radiation dose. In the past, this has been the key information for medical decision-making and patient prognosis. The argument for adopting such an approach is the strong relationship between the radiopathological manifestations and the energy deposited.

However, the physical parameter "dose" is not sufficient to predict the clinical evolution of damage in an individual patient. It is not a reliable prognostic indicator in the development of the acute radiation syndrome (ARS). In operational situations, dose assessment and reconstruction is a lengthy process involving considerable uncertainties. This becomes particularly apparent at low doses owing to the heterogeneity of the exposure and the radiation quality, both of which affect the pathophysiological processes in man. Therefore, dose is of little help in assessing either the complex interplay of irradiation with tissues and organ systems or the extent of biological damage to the whole organism. Nevertheless, it plays a key role in the description of the accident.

In this manual entitled "Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome" a new strategic approach for the diagnosis of the ARS is proposed, the response category (RC) concept. It focuses on the integrative quantification of the impairment of the organism by ionising radiation and does not rely at all on physical or biological estimates of the radiation dose. The aim is to assess the damage to an organ system as a function of time (grading) and to establish a grading code providing a semi-quantitative description for prognostic probabilities of the patient's outcome. The combination of the grading code for the four early responding systems, *i.e.* the haematopoietic, neurovascular, cutaneous and gastrointestinal systems, allows the establishment of a response category (RC). This summarises the health status of a patient at a certain point in time.

Thus a clinical scoring scheme is available; this is dynamic since the clinical manifestations of the ARS evolve over time as a function of the organ damage and the treatment. Therefore, the corresponding RCs also vary as a function of time. On the basis of the specific signs and symptoms that develop within the first hours and/or days post exposure, a patient can be assigned very early to a particular grading code and RC. However, regular and systematic re-evaluation of the clinical symptoms of each organ system is required to identify the dynamic nature of the ARS.

In addition to the RC concept, this manual provides a description of the scientific and pathophysiological background as well as the clinical manifestations of the ARS. Furthermore, the principles for the diagnosis and therapy of ARS patients are given.

GLOSSARY

The glossary describes terms used in the context of this manual.

Abortive rise	A transient increase in the absolute number of cells in any compartment (usually the functional compartment) of a nearly depleted haematopoietic cell renewal system. The abortive rise is followed by final recovery.
Acute exposure	Exposure to penetrating external radiation over a short time period (short term exposure), *i.e.* a few minutes to, at most, a few hours.
Acute radiation syndrome (ARS)	Composite of characteristic signs, symptoms and health impairments after TBI or large volume PBI. These develop owing to damage to early reacting organ systems and appear within a period of 60 days. A prodromal phase can be distinguished from a manifest illness phase.
Chronic exposure	Continuous exposure to radiation over a long period of time (long term exposure), *i.e.* a few days, months or years.
Cutaneous syndrome (CS)	Summarises the characteristic signs and symptoms after TBI or large area exposure of the skin. CS is the "cutaneous manifestation of ARS".
Degree of severity	Describes the severity of symptoms that are relevant for the clinical characterisation of the organ specific manifestation of ARS. For this purpose discrete and continuous quantities are transformed to an ordinal scale from 1 to 4. It is necessary to assess the degree of severity to establish the organ specific grading, the corresponding grading code and the RC.
Early reacting organ systems	Organ systems involved in the development of the ARS, in particular the neurovascular system (N), the haematopoietic system (H), the cutaneous system (C) and the gastrointestinal system (G).
Fatigue syndrome	Self-recognised state of overwhelming, sustained exhaustion and decreased capacity for physical and mental work—not relieved by rest. Typical descriptions are drained, finished off, lethargic, beaten, exhausted, worn out or prostration and drowsiness. Components are physical, cognitive, emotional/affective.
Gastrointestinal syndrome (GIS)	Summarises the characteristic signs and symptoms after TBI or large volume PBI to the gastrointestinal tract. GIS is the "gastrointestinal manifestation of ARS".
Grading	Classification of the radiation induced damage for each of the early reacting organ systems on the basis of characteristic clinical symptoms and their degree of severity.
Grading code	Term for the combination of the organ specific grading, providing a weighted description of the major radiation reactions of each early reacting organ system.
Haematopoietic syndrome (HS)	Summarises the characteristic signs and symptoms after TBI or large volume PBI to the haematopoietic system. HS is the "haematopoietic manifestation of ARS".
Incapacitation	Incapacitation is a physiologically based inability to perform complex and clearly defined movements. It can be characterised by a period of unconsciousness (absolute incapacitation) and/or a period of confusion/ disorientation (relative incapacitation).
Intermittent exposure	Repeated exposure to ionising radiation spread out over a few days, months or years. Also termed protracted exposure.
Late effect phase	In this phase, organ specific radiation induced effects may develop that are not attributable to either the prodromal or the manifest illness phase of ARS.

Manifest illness phase	Covering the time period from the end of the prodromal phase up until day 60; includes development of the complete picture of ARS and/or first signs of recovery.
Neurological deficit	Comprising neurological symptoms such as fainting, dizziness, ataxia and other motor signs, sensory signs or atypical reflexes.
Neurovascular syndrome (NVS)	Summarises the characteristic signs and symptoms after TBI or large volume PBI to the neurovascular system. NVS is the "neurovascular manifestation of ARS". This term was introduced to emphasise the effects of radiation on the central and peripheral nervous system as well as the vasculature of the brain, which is responsible for a wide range of critical effects on higher regulatory structures. The term NVS replaces the term CNS syndrome, which is often used but not considered broad enough to cover the interactions of the different structures involved.
Partial body irradiation (PBI)	Exposure to penetrating external radiation, clearly limited to a large part of the body while the rest remains unexposed.
Prodromal phase	Covering a time period of up to the first week after exposure, crucial for an initial assessment of the extent of damage to the individual on the basis of prodromal symptoms.
Prodromal symptoms	Effects resulting from the damage in early reacting organ systems that can be seen within the prodromal phase; symptoms are primarily nausea, vomiting, diarrhoea, decrease in lymphocyte count, erythema.
Protective environment	Induction of a patient environment free of bacteria or other microbial elements by appropriate methods (lamina flow situation, physical barrier, etc.). Also known as "gnotobiotic state" in experimental settings.
Recovery	Refers to a partial or total regeneration of a tissue. This is brought about in principle via cellular proliferation and is based on repair mechanisms at different levels of biological organisation.
Response category (RC)	Integration of the grading to characterise the effects of ionising radiation on man based on appropriate indicators of effect and repair. The RC has a strategic influence on the medical management of radiation accident patients. It also allows comparisons to be made of intra- and inter-individual data on a national as well as an international level. An initial RC resulting from the prodromal phase can be distinguished from an epicritic RC that summarises retrospectively, at day 60, the clinical course.
Total body irradiation (TBI)	Exposure of the entire body to penetrating external ionising radiation.
Triage	The sorting of patients according to the urgency of their need for care: the most severely injured patients need the most immediate care. Two levels of triage are required. **Primary triage** is the assessment of vital signs and symptoms, common to any emergency situation. In addition, patients with injuries that require immediate surgery should be identified. The **extended triage** is when radiation induced effects should be first identified. This assessment will have implications for further evaluation and treatment. In this context see also prodromal symptoms, grading, RC.

ABBREVIATIONS

$5\text{-}HT_3$	5-hydroxytryptamine
ARDS	Adult respiratory distress syndrome
ARS	Acute radiation syndrome
ATG	Anti-thymocyte globulin
BMSCT	Bone marrow stem cell transplantation
BP	Blood pressure
C	Cutaneous system
CAMPATH 1H	Cambridge pathology 1 humanised (monoclonal panleucocyte antibody)
CCI	Corrected count increment
CNS	Central nervous system
CRP	C-reactive protein
CS	Cutaneous syndrome
CT/CCT	Computed tomography/cranial computed tomography
CTZ	Chemoreceptor trigger zone
EC	European Commission
EEG	Electroencephalogram
ENT	Ear nose throat = otorhinolaryngology
G	Gastrointestinal system
G-CSF	Granulocyte colony stimulating factor
GEMM-CFU	Granulocyte–erythrocyte–monocyte–megakaryocyte colony forming unit
GH	Growth hormone
GIS	Gastrointestinal syndrome
GIT	Gastrointestinal tract
GM-CFU	Granulocyte–macrophage colony forming unit
GM-CSF	Granulocyte–macrophage colony stimulating factor
GvHD	Graft *versus* host disease
Gy	Gray
H	Haematopoietic system
HEPA	High efficiency particulate air (filtration system)
HR	Heart rate
HS	Haematopoietic syndrome
HSC	Haematopoietic stem cells
IAEA	International Atomic Energy Agency
IFN	Interferon
IGF-1	Insulin growth factor 1
IL	Interleukin
ITF	Intestinal trefoil factor
KGF	Keratinocyte growth factor

LTB	Leukotriene B
METREPOL	**Me**dical **Tre**atment **P**rotoc**ol**s for radiation accident victims as a basis for a computerised guidance system
MRI	Magnetic resonance imaging
N	Neurovascular system
NF-κB	Nuclear factor κB
NVS	Neurovascular syndrome
PADS	Patient accompanying documentation sheet
PBI	Partial body irradiation
PBSCT	Peripheral blood stem cell transplantation
PCT	Procalcitonin
PET	Positron emission tomography
PGE	Prostaglandin E
RANTES	Regulated upon activation, normal T-cell expressed and presumably secreted (chemokine secreted by T-cells, platelets, endothelial cells, etc.)
RC	Response category
REMPAN	Radiation Emergency Medical Preparedness and Assistance Network
SCT	Stem cell transplantation
SEARCH	System for Evaluation and Archiving of Radiation accidents based on Case Histories
TBI	Total body irradiation
TCDO	Tetrachlorodecaoxide
TNF	Tumour necrosis factor
TPO	Thrombopoietin (growth factor)
UBC	Umbilical cord blood
WHO	World Health Organisation

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Compendium

CHAPTER 1: INTRODUCTION

1.1 Scope and purpose

A Concerted Action called "Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerised Guidance System", in short METREPOL, was accepted within the framework of the Nuclear Fission Safety Program (DG XII Science) of the European Atomic Energy Community. Within this project an international group of selected experts agreed to define consensus guidelines and protocols for the handling of radiation accident victims based on experimental data as well as on an analysis of data of former radiation accidents. To this end the METREPOL group co-operatively developed this manual, which describes the main aspects of the development of the acute radiation syndrome (ARS) together with options for diagnostic and therapeutic management.

The participants of this Concerted Action are members of the following institutions:

- Radiation Medicine Research Group and WHO–Collaborating Center for Radiation Accident Management at the University of Ulm, Germany (co-ordination).
- Institute of Protection and Nuclear Safety, Fontenay aux Roses, France.
- Research Institute of the University of Oxford at the Churchill Hospital, Oxford, United Kingdom.
- Department of Dermatology of the University of Ulm at the Armed Forces Hospital in Ulm, Germany.
- Institute of Hematology of the Erasmus University, Rotterdam, The Netherlands.

Starting in December 1997, the expert groups identified, on the basis of experience gained from earlier radiation accidents, three common and sometimes problematic features in accident management:

1. Past radiation accidents led to emergencies that required intensive patient care.
2. Medical management of the patients was influenced by the diverse views of the experts involved.
3. Medical staff responsible for the initial patient management were not always specialists in radiation medicine.

The European Commission believed that there is a need to develop standardised and internationally accepted recommendations for the diagnosis and therapy of accidentally overexposed individuals. Therefore, in the first instance, a consensus among experts on the most appropriate diagnostic and therapeutic options was developed. This consensus was based on sound scientific evidence, taking into consideration the state of the art in clinical medicine and research.

A prerequisite for any successful medical intervention is a detailed description and assessment of a patient's health status and the ensuing changes, *i.e.* improvement or deterioration. This is not a static process—on the contrary, it is highly dynamic. To cope with this demand it is important to observe the patient very carefully and regularly and to be alert for any adverse developments through systematic documentation of clinically relevant signs and symptoms. However, since the response to irradiation is not aetiology specific but organ and organ systems specific, assessment of these combined effects is the only reliable way of analysing the clinical course and the probable outcome for the patient. Furthermore, there is a consensus among the METREPOL team that physical dose estimates are not sufficient to guide the medical doctors in their clinical decisions. This reservation is based on the facts that dose estimates are not available immediately after the accident and that they are usually unable to reflect the exact dose rate and dose distribution in a particular individual. Therefore dose estimates are at best indicators of exposure but not indicators of effect or repair. The "philosophy" governing this manual is that medical decisions have to rely on the examination of indicators of effect and repair that describe radiation induced changes at different biological levels, *i.e.* total organism, organ systems, cell systems, cellular and subcellular levels. These indicators are observable signs and symptoms as a function of time after radiation exposure. They will reflect the clinical manifestation of interactions and the severity of the damage to be caused by radiation exposure. Therefore they will be used as the basis for the assessment of the ARS and the development of clinical guidelines.

The manual is designed for use under the following conditions:

- The reference time for the different classification approaches after an acute radiation exposure is fixed to the first 60 days.
- Only lesions and risks from ionising radiation are covered. Chemical, mechanical

and thermal injuries, important as they may be for the clinical course of a patient, are excluded.
- The radiation accident pattern is that of acute exposure with a large volume partial body irradiation (PBI) or total body irradiation (TBI).
- The first medical contact is a medical doctor who may not necessarily have special training in radiation medicine.
- The use of the manual is independent of the number of accident victims.
- The recommendations given in the manual are designed in the first instance for an intact infrastructure, but most are also valid for an impaired infrastructure.
- The manual can be consulted at various times after the radiation accident but preferably should be used as early as possible after exposure.

Clearly, it is not the purpose of this manual to deal with ill defined or intermittent irradiation patterns nor with contamination or incorporation or the combination of any of these. Also, it is not meant to be a textbook on the ARS, but rather a practical manual and a reference for the daily clinical routine in patient management after acute overexposure to ionising radiation. This implies that the physician also has to assess the health status of the patient in the light of other contributing effects. Diagnostic procedures needed for the assessment of the extent of damage that are presented in this manual should be as minimally invasive for the patient as possible but should provide sound information and should be able to validate effectiveness, especially with respect to subsequent treatments.

The task of the METREPOL team was mainly to review existing approaches and knowledge in the field of radiation medicine and radiation research to compile a meaningful information base for developing the present manual. It was recognised that knowledge in this area was incomplete and that further research is needed. However, all members of the team used their professional competence, knowledge and experience in their medical and scientific fields. To ensure international acceptance, external experts were involved for reviewing the work of this Concerted Action.

It is hoped that users of this manual, *i.e.* medical staff involved in the daily care of radiation accident victims, will find this guide useful. The authors are grateful for any comments and suggestions that will help to improve future manuals.

1.2 Structure of the manual

The manual is divided into two parts. The main part deals with the detailed description of the characteristics of ARS; the Compendium gives useful keywords for the medical management of radiation accident victims as well as a preformed documentation template (PADS).

In particular, Chapter 2 outlines the basic tasks and responsibilities that are essential for the successful medical management of radiation accident victims by medical personnel. This chapter focuses on the steps to be taken for diagnosing and assessing the dynamic characteristics of organ specific manifestations of ARS. It shows the importance of a thorough clinical examination to determine therapeutic strategies.

Chapter 3 describes the pathophysiological and clinical background for developing an organ specific grading. A prerequisite for this grading is that it is easy to handle in the daily clinical routine and provides the opportunity to assess very early after a radiation accident the extent of the individual's impairment as a basis for further diagnostic and therapeutic regimes, which may well require the involvement of different medical specialists. To facilitate and provide an overview of the complex mechanisms involved in the response to radiation overexposure, this chapter considers in detail the four most critical organ systems in question, *i.e.* the neurovascular system (N), the haematopoietic system (H), the cutaneous system (C) and the gastrointestinal system (G). A comprehensive description is given of the organ specific radiation induced effects, their pathophysiological mechanisms and the clinical characteristics. Furthermore, each organ specific subchapter provides a description of relevant diagnostic methods and therapeutic options, together with references for further and more detailed reading.

In Chapter 4 the interactions of the characteristic features of the different organ specific impairments are described, leading to a discussion of the response category (RC) concept with respect to its clinical application, as this allows a systematic framework for the medical management of accidentally irradiated persons to be established.

The purpose of Chapter 5 is to summarise the therapeutic principles applicable in the medical management of radiation accident victims. However, therapeutic recommendations are subject to rapid changes owing to ongoing basic and applied research in the field of radiation medicine. Therefore the emphasis is on general principles. Specific therapeutic measures have to be adapted according to the latest clinical research.

CHAPTER 2: MANAGEMENT PRINCIPLES IN THE CARE OF RADIATION ACCIDENT VICTIMS

Within 60 days after exposure to ionising radiation the ARS develops, with typical clinical signs and symptoms as a function of time. The interactions and combined effects of radiation induced damage to different organ systems are diverse and not yet fully understood. Therefore, when accidental exposure to ionising radiation is known or suspected, guidance for immediate diagnostic procedures and specialised care is required to handle the complexity of the ARS.

The following four organ systems are considered to be of critical significance for the development of ARS and should therefore receive special attention in the medical management of radiation accident cases:

- Neurovascular system (N)
- Haematopoietic system (H)
- Cutaneous system (C)
- Gastrointestinal system (G)

Each radiation accident represents an acute emergency and requires a sequence of steps to be taken. Although physicians in charge might be confronted with a situation they have not encountered previously, it is important to assess quickly whether exposure to ionising radiation has occurred and to what extent the patient suffers from radiation related damage. This is necessary to produce the first tentative working diagnosis, and to decide whether or not hospitalisation is required and what type of health care facility and subspecialty consultation will be necessary. In short, four cardinal issues must be considered in the management of a patient after a radiation accident:

- Assessment of the severity of damage
- Decision on the kind of hospitalisation
- Provision of appropriate therapeutic interventions
- Evaluation of the patient's prognosis

A flow chart showing the different phases (triage, diagnosis and therapy) in the management of radiation accident victims is depicted in Figure 1. This will be described briefly in the following section. More detailed information on the organ specific manifestations of ARS and their interactions is provided in subsequent chapters of this manual. Material to support the clinical routine is given in the Compendium.

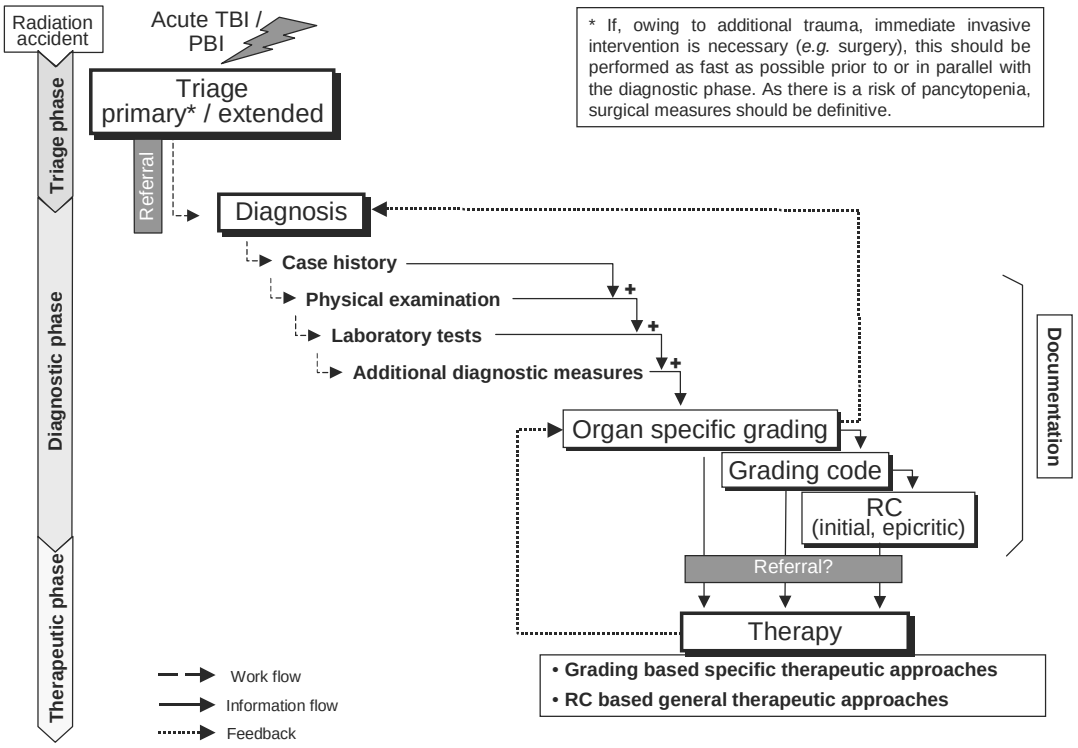

Figure 1. Flow chart for medical management of radiation accidents. Triage, diagnostic and therapeutic phases can be distinguished. These are connected by work flow, information flow and feedback of information.

2.1 Triage

In this phase patients are clustered according to the urgency of their need for care; the most severely injured patients need the most immediate care. Two phases can be distinguished, as depicted in Figure 2. Primary triage means the assessment of vital signs and symptoms as known from any other emergency. Injured patients who require immediate surgery (*e.g.* to prevent life-threatening bleeding from mechanical injury) should be given special attention. They need to receive immediate care to ensure survival. The primary triage will most likely take place at the site of the accident under the responsibility of either a medical doctor or well trained first-aid or ambulance personnel.

In the subsequent extended triage phase a patient with suspected radiation exposure of unknown severity will be taken to a medical service capable of identifying radiation induced effects. This assessment will have implications for further evaluation and treatment. It should be done quickly after exposure. A brief case history must be taken, either from the patient himself or from a person who is aware of the circumstances of the accidental radiation exposure. Furthermore, a basic physical examination should lead to an organ system oriented inventory of the health impairments. Depending on the availability of resources, extended triage will probably take place at the primary care institution under the responsibility of the medical doctor in charge.

Blood samples should be taken at the earliest possible stage after irradiation to establish baseline values. Blood counts, leukocyte concentrate samples, blood grouping, histocompatibility tests, chromosomal analyses and a "clinical chemistry" profile are of critical significance.

It should again be pointed out that this manual focuses on the ARS and does not deal with radioactive contamination or with incorporation of radionuclides. If this occurs then measures should be initiated to perform decontamination, such as removing clothing and attempting to wash if possible (hair, arms, legs, etc.) or administer certain chemicals to reduce the radioactive burden.

2.2 Diagnostic strategies

After the triage phase the true diagnostic phase commences and the first and foremost medical task is to assess in detail the extent of radiation induced damage to the patient. Table 1 contains a list of those clinical signs and symptoms seen frequently after accidental irradiation. These characteristics are not just specific for radiation exposure; patients may present with ordinary complaints and symptoms that should be interpreted in the context of radiation medicine.

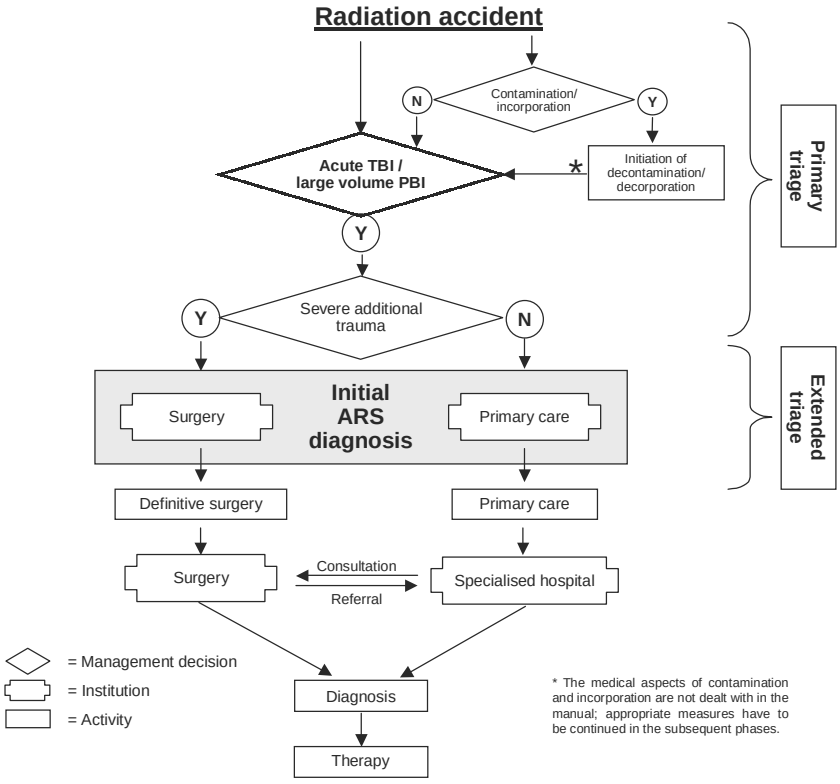

Figure 2. Major management decisions to be made in the triage phase (Y = yes; N = no).

Table 1. Symptoms of special relevance in assessing the extent of radiation induced damage (in alphabetical order)

Abdominal cramps/pain	Erythema	Nausea
Anorexia	Fatigue syndrome	Neurological deficits
Blistering	Fever	Onycholysis
Blood loss	Granulocyte changes	Sensation/itching
Cognitive deficits	Hair loss	Swelling and oedema
Desquamation	Headache	Thrombocyte changes
Diarrhoea (characterised by frequency, consistency, mucosal loss and bleeding)	Hypotension	Ulcer/necrosis
	Infection	Vomiting
	Lymphocyte changes	

From experience of previous radiation accidents, it is obvious that, as in any other emergency situation, systematic acquisition of clinical information is needed, which should be based on the following:

- Case history, including evaluation of the conditions of exposure
- Physical examinations
- Laboratory tests
- Additional diagnostic measures including imaging studies

Case history and conditions of exposure

The first step in the diagnostic phase is to obtain a detailed case history. This should include the patient's demographic data, information on age and gender, a detailed past medical history (including prior hospitalisation), past and current medications, allergies, alcohol and tobacco use, drug habits and social and occupational history as well as family history.

The record of current illness/symptoms should document the major complaints and focus on the early reacting organ systems such as the neurovascular system, the haematopoietic system, the skin and the gastrointestinal system. Emphasis should be placed on characteristic prodromal signs and symptoms such as vomiting, diarrhoea and erythema. A decrease in the lymphocyte count or an initial granulocytosis also belongs to this group of prodromal signs, but these can only be detected by laboratory tests (see below).

Thermal, mechanical and non-radiation related injuries should be recorded, particularly as these injuries may aggravate a patient's prognosis. Surgical interventions, if required, may only be possible within the first days after the accident. These interventions have to follow specific rules owing to the possible onset of pancytopenia, leading to an increased risk of bleeding and infection. Patients who initially present in shock, coma or with ataxia have a particularly poor prognosis.

To assess the patient's radiation related complaints, it is of special importance to collect information on the accident and on the patient's personal exposure conditions. This should include the beginning and the end of the exposure period (if known), the location of the patient in relation to the radiation source, and the quality of external radiation (or contamination and incorporation). This information should be supported by a witness statement, if available. In addition, a sketch of the accident scene would be useful.

Physical examination

The physical examination follows common rules and should carefully assess the entire body from head to toe as well as vital signs, including blood pressure, pulse, respiratory rate and body temperature.

Special emphasis should be given to inspecting the whole of the skin and the mucous membranes. It is important to describe conspicuous findings such as local erythema, blisters, epilation, etc. in great detail and as a function of time. Findings should be documented by coloured photographs, if possible. The eyes should be examined fully, including inspection of the conjunctivae, for haemorrhage and/or erythema. Neck examination should include lymph node status as well as size and tenderness of the salivary glands. Cardiac and pulmonary examination should be conducted, as in all patients. Abdominal examination should document the quality and frequency of bowel sounds, abdominal tenderness, abdominal masses and the presence/absence of diarrhoea and/or melaena. Liver size, spleen size and tenderness should be documented. Extremities should be examined for the presence of oedema and evidence of bleeding. A complete neurological examination is essential in evaluating the patient, including an assessment of the patient's communication and co-ordination capabilities, which can be obtained while doing the physical examination.

Laboratory tests

Another source of information on the extent of damage to the individual is from laboratory tests. The analysis of peripheral blood samples is of primary importance. The absolute numbers of peripheral cell counts should be depicted not only in tabular form but also graphically. To obtain the best interpretation, these measurements have to be repeated on a regular basis. The frequency will depend on the severity of the patient's health impairment.

These examinations have to be followed subsequently by other diagnostic methods such as quantitative and qualitative assessment of bone marrow smears to detect typical radiation induced changes such as giant cells, binucleated cells, karyomeres or cytoplasmatic and chromosomal bridges. Additional methods should be used to assess the extent of the radiation induced damage at the level of molecular or cellular changes; these should include quantitative clonogenic progenitor cell assays, lymphocyte subpopulation analysis and lymphocyte proliferation tests for assessing the haematopoietic stem cells or changes in the immune status, respectively.

In cases where stem cell transplantation may be needed it is important to start quickly to search for a compatible stem cell or bone marrow donor, and to perform the necessary histocompatibility tests.

To prepare for effective antimicrobial therapy it is useful to obtain an inventory of the intestinal (and skin) microbial flora and its sensitivity to antibiotics. Most infections in neutropenic or pancytopenic patients are due to their endogenous flora. These infections result in an increased risk of mortality. However, it can be difficult to detect infections in these patients, and laboratory tests should include the assessment of interleukin-8 (IL-8), procalcitonin (PCT) and C-reactive protein (CRP) and microbiological colonisation tests from blood cultures, other body fluids or the skin as required.

Laboratory tests should also include an assessment of electrolyte and fluid loss. In addition, functional tests of liver, kidney, metabolism and the endocrine system (including the thyroid gland) should be performed. Exposure to single radiation doses is likely to affect the reproductive system. Therefore, semen analysis should be undertaken for radiation accident victims. Blood levels of luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone and prolactin should also be measured.

Additional diagnostic measures (including imaging studies)

Additional information can be obtained from imaging studies, which can be used either to evaluate the patient's present state or to establish reference information for follow-up examinations.

Diagnostic X-ray facilities are usually available even in small hospitals. These can provide useful information:

- chest radiograph (status of the lung, early detection of ARDS, etc.)
- abdominal radiograph (in case of suspected ileus)

If available, CT scans or MRI sequences are useful for specific indications such as assessing the extent of oedema, inflammatory reactions, necrosis/atrophy or the depth of ulcers. Furthermore, MRI might be helpful in detecting gut fistulas. Endoscopy is rarely indicated in severely injured patients after radiation exposure, since the risk of perforation in pre-injured structures is high, and therefore this technique cannot be recommended.

Ultrasound examination can be useful in providing a routine assessment of the organs in the abdominal cavity.

Special emphasis should be placed on skin ultrasound using 7.5 MHz and higher for the detection of skin thickness and density as well as the depth of ulcers. In addition, thermography, capillary microscopy, profilometry, bone scintigraphy and histology might be useful.

Furthermore, an electroencephalogram (EEG) is a valuable tool for the assessment of changes in the electrical activity of the brain, as slowing of the EEG waves is an indicator for high dose exposure.

Electrocardiography (ECG) is part of every diagnostic routine inventory and provides basic information on the cardiovascular system.

Physical and biological dosimetry is useful for evaluating clinical symptoms from an epicritical point of view. However, physical dosimetry of accidental TBI usually requires the retrospective reconstruction of the accident. Experience gained with previous accidents shows that such a retrospective analysis can be performed technically but takes days, weeks or even months. For the medical team it is important to have information on the quality of radiation (X-rays, γ-rays, β-rays, neutrons,diarrhoea, etc.), the probable dose rate and pattern of exposure, the dose distribution or other qualitative specifications of exposure. For biological dosimetry, it is important to obtain relevant material for examination (*e.g.* blood samples for chromosomal analysis) as soon as possible after the accident. However, the results obtained, for instance on the incidence and type of chromosomal aberrations, will not be available until several days after exposure. Therefore, they are helpful for the general assessment of the clinical course and the probability of late effects but will not be of much help in the initial clinical management of a patient.

Table 2. Overall prognostic aspects of the ARS on the basis of the organ specific grading

Organ system	Grading and severity of damage			
	1: mild damage	2: moderate damage	3: severe damage	4: serious/fatal damage
N	Recovery certain	Recovery with possible deficit	Recovery with severe deficit	Recovery most unlikely
H	Autologous recovery certain	Autologous recovery likely	Autologous recovery possible	Autologous recovery most unlikely
C	Recovery certain	Recovery without deficit likely	Recovery with deficit likely	Recovery most unlikely or with serious deficit
G	Recovery certain	Recovery with possible deficit	Recovery may be possible	Recovery most unlikely

Purpose of the diagnostic phase

The ARS develops following damage to the organism and its organ systems caused by ionising radiation. The effects are complex and result in a broad spectrum of clinical signs and symptoms. To cope with this complexity a standardised clinical classification scheme should describe objectively the different stages of radiation induced damage. To this end the RC concept was developed (see also Chapters 3 and 4). Apart from the basic medical skills required to take a case history (observation, interrogation, inspection) and to carry out a physical examination, only routine laboratory techniques are needed to gain the information necessary to establish the RC.

The basic idea behind this concept is to unravel the complexity of the ARS. The first step is to divide the ARS into more easily assessable elements, *i.e.* those clinical signs and symptoms that characterise the extent of damage to the four early reacting organ systems under concern. Capital letters are used for reference to these organ systems: N (neurovascular system), H (haematopoietic system), C (cutaneous system) and G (gastrointestinal system). The second step is to consider the single elements of ARS again in the light of the response of the individual.

After exposure to ionising radiation the early reacting organ systems express different clinically observable signs and symptoms. They are used as indicators of effect. To this end, semi-quantitative criteria are used to describe these symptoms. Each symptom is assessed by rating it with a degree of severity between 1 and 4. 1 is defined as mild damage and 4 as very severe damage. A zero is used when there are no observable symptoms in a particular system. Combining the characteristic clinical symptoms in the course of the ARS and the degree of severity allows an assessment of the damage to an organ system as a function of time. This procedure is termed grading. The highest degree of severity determines the organ specific grading ("maximum approach"). After this grading is established, the corresponding grading code can be determined. This code is a weighted description of the major radiation induced clinical problem areas in an individual and therefore provides an indication of the patient's likely prognosis (see Table 2).

For radiation accident management, this grading code is then translated into an RC, which allows comparison to be made intra- and inter-individually and also facilitates national and international communication and interdisciplinary consultation. It also determines the general therapeutic principles and the corresponding institutional requirements for the patient concerned.

The basic steps and terminology for implementing the RC concept are depicted in Figure 3. The example in Figure 3 shows a grading code of N2 H3 C1 G2. This indicates a severe impairment of the haematopoietic system (H3), moderate lesions of the neurovascular and gastrointestinal system (G2, N2) and hardly any symptoms in the cutaneous system (C1). The haematopoietic system has the highest grading, *i.e.* the worst prognosis, thus it has the greatest influence on the patient's management. An overall RC equal to three on day 2 (xd $\Rightarrow$ 2d) would be assigned to this individual.

A complete review of all relevant symptoms (see Compendium) should be repeated every 6 h for the first 48 h and every 12 h until the end of the first week (prodromal phase) depending on the patient's health condition. Very severely injured patients of course need more attention and closer supervision than those with mild impairments. This procedure allows changes in and development of symptoms to be documented and appropriate action taken. However, the frequency outlined above is only a rule of thumb to ensure that all decisive clinical features are recorded.

Thus an initial RC can be established very easily. In cases of severe injury this is best done within 24–48 h. In cases of only mild or moderate impairment it can usually be established during the first week after exposure when symptoms develop.

Beyond the first week, a new phase commences, the ARS manifestation phase. Here therapeutic interventions have to and definitely will show effects

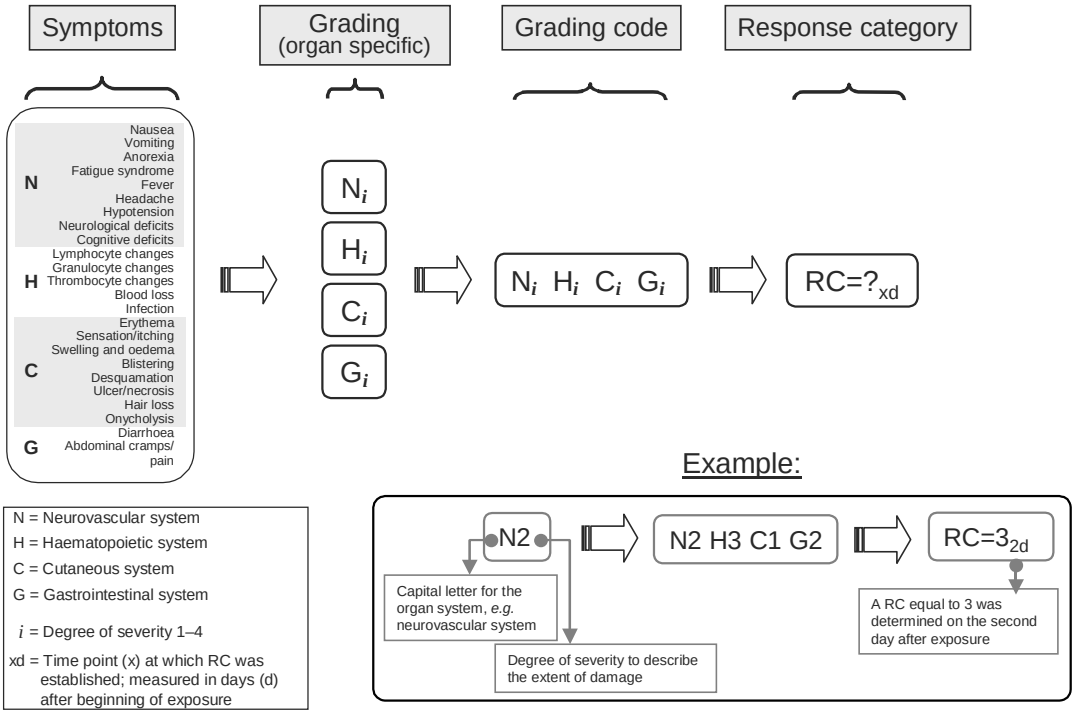

Figure 3. Terminology of the RC concept: from the organ specific grading to the grading code and the corresponding RC at different times during ARS.

influencing the organ specific grading. At this stage the detailed grading code is of particular interest as it summarises the clinical problem areas, hinting at the most critical organ systems and the corresponding arsenal of diagnostic and therapeutic measures to be adopted.

Owing to the diversity of medical procedures, the amount of information relevant and critical for the management of the patient increases until day 60. With every additional piece of information the degree of certainty of the assessment of the patient's state increases. Therefore, on day 60 it should be possible to evaluate retrospectively the clinical picture in the form of an epicritic RC summarising the severity of damage, the course and the outcome of the patient. The criteria for establishing the epicritic RC are described in the clinical characterisation of the four critical organ systems (see Chapter 3, which outlines the typical patterns of the clinical manifestation of the different organ specific gradings during the acute phase). It is possible to make a proper assignment of the epicritic grading code and RC by comparing the patient's course retrospectively with these descriptions. However, as the individual patient may not follow these model courses exactly, adjustments may be required. This epicritic RC, in comparison with the initial RC, can be used to evaluate the management in general and the therapeutic strategies in particular, and build up the basis for follow-up examinations of radiation accident victims.

During the acute phase a pattern of change for the most important indicators of effect (such as vomiting, lymphocyte and granulocyte values, erythema and diarrhoea, etc.) evolves and will allow the stepwise implementation of further diagnostic and/or therapeutic measures. Owing to this dynamic situation, close observation of the patient's state is necessary. This may result in the reclassification of the patient and thus in a reconsideration of the therapeutic strategies, depending not only on the pathophysiological damage patterns but also on the therapeutic effects. This is of particular importance, as during the first hours and days after exposure decisions have to be made that undoubtedly have an impact on whether the patient will survive and whether a *restitutio ad integrum* can be expected.

Daily examinations according to the tables listed in the Addendum/Compendium ensure that the symptoms of the organ specific manifestations are assessed and documented thoroughly and systematically. In documenting the clinical findings at least the date and time of the examination, the patient-specific code number, the date of exposure and the physician (see also Compendium and PADS) should be noted.

An example of a simplified documentation spreadsheet including fictitious data is shown in Figure 4.

In spite of this systematic approach there will always remain a degree of uncertainty as to the outcome of a radiation accident victim. This is because:

- Depending on the extent of damage, symptoms either develop at different times after exposure or will not show up at all.

- Assessment of some of the symptoms is more reliable (*e.g.* results of laboratory tests) than others (*e.g.* symptoms characterised by subjective perceptions).

However, the RC concept has been designed and should be used in such a way that a patient will be assigned to a higher RC rather than to a lower RC. This policy ensures that a patient will initially receive more rather than less medical attention.

In summary, with a minimum of routine procedures the RC concept allows the assessment of the extent and development of the ARS. The RC concept is intended to act as a clinical scoring scheme for the medical management of radiation accident patients. It is based on the description of the organ specific manifestation of the ARS, the pathophysiological response mechanisms involved and the clinical characteristics of the most affected organs and organ systems. The intention of this classification is not only to guide the physician in the clinical management of the patient and to provide prognostic criteria but also to provide a framework for comparisons of doses, morbidity, mortality and treatment outcomes on an international basis for persons exposed to ionising radiation. Important prerequisites to achieve such an internationally accepted system are valid and reproducible information, common terminology, clearly defined signs and symptoms relevant for the description of organ specific manifestations of the ARS, and prospective documentation of relevant parameters on a regular and systematic basis.

2.3 Therapeutic options

Therapeutic measures should be adapted to the patient's general health and in particular to the extent of damage to different organs and organ systems as a result of the radiation exposure. In accordance with the characteristic clinical signs and symptoms and the corresponding grading, grading code and RCs, the following different treatments can be suggested (see Chapter 5 for more details):

- Supportive care
  - Antiemetic therapy
  - Analgesic therapy
  - Brain oedema therapy
  - Adapted nutrition (including electrolyte and fluid replacement)
  - Antibiotic treatment (including antifungal and antiviral therapy)
  - Skin treatment
  - Further approaches (psychological interventions, physiotherapy, etc.)

Patient ID	999		Begin of exposure	01.01.2000 10:00		Examiner	N.N.	
Date of examination	01.01.00 11:00	01.01.00 17:00	⇒					
N	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	
Symptom A	2	2						
⇩ Symptom Z	1	1						
Maximum	**2**	**2**						
Grading N	**2**	**2**						
H	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	
Symptom A	2	3						
⇩ Symptom Z	1	2						
Maximum	**2**	**3**						
Grading H	**2**	**3**						
C	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	
Symptom A	2	2						
⇩ Symptom Z	1	1						
Maximum	**2**	**2**						
Grading C	**2**	**2**						
G	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	
Symptom A	1	2						
⇩ Symptom Z	1	1						
Maximum	**1**	**1**						
Grading G	**1**	**2**						
Grading code	N2 H2 C2 G1	N2 H3 C2 G2	N_ H_ C_ G_	N_ H_ C_ G_	N_ H_ C_ G_	N_ H_ C_ G_	N_ H_ C_ G_	
RC =	**2**	**3**						
Days after Expos.	0,04	0,29						

Figure 4. Spreadsheet used for documentation of clinical signs and symptoms after a radiation accident. The prodromal symptom with the highest degree of severity determines the initial RC. A repeated complete system review provides information that may change the initial RC as a function of time (see example given for the first hours). Arrows indicate that this sheet is to be extended according to the Addendum/Compendium.

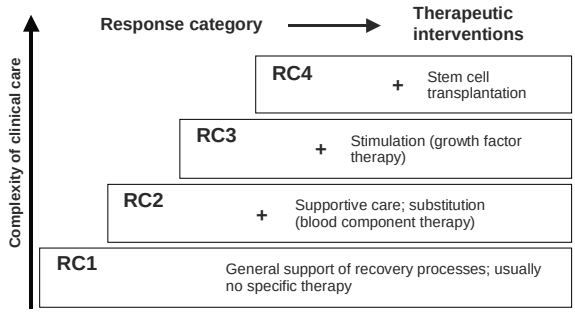

Figure 5. Different levels in the complexity of clinical care depending on the RC. See also Figure 15.

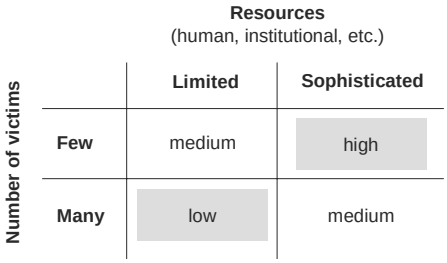

Figure 6. Chances of survival depending on the number of victims in a radiation accident and the available resources.

- Substitution (blood component therapy)
  Erythrocyte concentrates
  Thrombocyte concentrates
  Granulocyte concentrates
- Stimulation (growth factor therapy)
- Stem cell transplantation (SCT)
- Surgery

Figure 5 gives an overview of the principles of different levels of therapeutic interventions depending on the RC classification.

Despite the systematic approach and maximum effort invested by the medical team, it has to be accepted that there may be adverse developments that are beyond the medical and managerial skills of the personnel involved. Because of this *force majeure*, 100% survival of the patients cannot be expected. For example, where there are a few victims and very sophisticated resources then a high survival rate can be expected. However, in a major accident involving many people where resources are limited the chances of survival may well be low (see Figure 6).

2.4 Responsibilities of the medical team

Following triage, patients will be transported to the most appropriate hospital for the first basic assessment and care. “Appropriate” in this context means

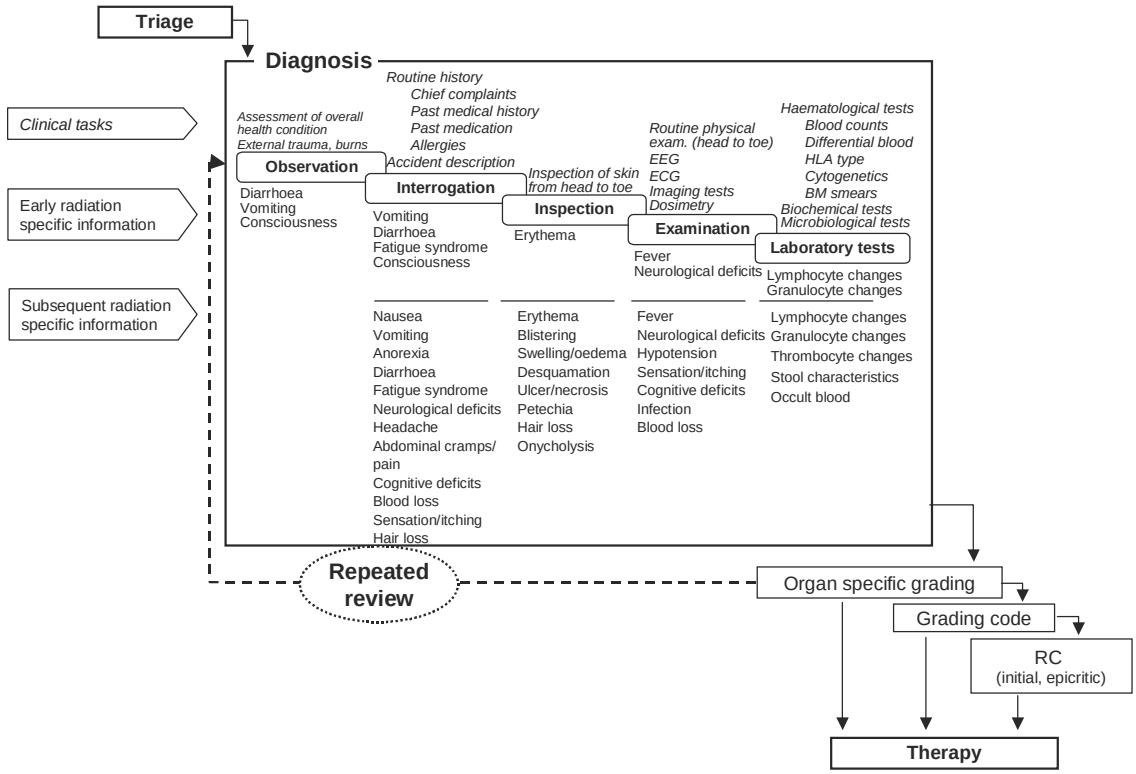

Figure 7. Schematic representation of the early tasks for the medical team in the diagnostic phase of the assessment of characteristic signs and symptoms of ARS. Some symptoms are listed several times as they can be verified in different ways.

finding a compromise between the nearest and the best equipped (human and technological resources) hospital capable of handling such patients.

On or prior to admission, the doctor in charge should familiarise himself with the problems and brief the entire staff. This doctor will most likely be trained in internal medicine with basic knowledge in all other medical specialities. He has to fulfil several tasks and should delegate some to his staff.

The scope of the main activities will comprise the following:

- Medical care, including diagnosis and treatment
- Co-ordination of care, including involvement of other subspecialties
- Custody of the patient (*e.g.* restriction of blood sampling to the absolutely essential)
- Dealing with family and relatives
- Contact person for own staff
- Documentation of patient's course, findings and interventions
- Informing appropriate national and/or international organisations
- Communication with mass media

It should be stressed that the co-ordination of care and the selection of consultants is of critical significance, since physicians of different specialties are likely to be required for each patient. A haematologist should evaluate all patients in whom exposure is suspected. It is essential to obtain a bone marrow aspirate to perform cytological analysis. Depending on the presence of symptoms and their degree, a dermatologist, neurologist or gastroenterologist may also be essential. In some cases it is useful to involve other consultants such as ophthalmologists, dentists and ENT specialists, not necessarily to detect acute radiation induced effects but to assess a patient's status for further follow-up examinations and to outline the basis for early detection of the development of late effects. The same approach is valid for investigations of the cardiovascular, respiratory and endocrine systems. Furthermore, it is necessary to have well trained nursing staff, as close monitoring is essential for the care of all hospitalised patients and in particular those in intensive care. In addition, social workers or psychologists (psychiatrists) may be important when dealing with the psychological impact of the exposure on the patients and their families.

When confronted by all these tasks and responsibilities the doctor in charge usually depends on systematic and easy to follow guidance so as not to omit important medical procedures in the very early but decisive phases of ARS. The Compendium to this manual provides practical support; however, it is strongly recommended that the detailed information provided in the main text of this manual is referred to.

In Figure 1, a general flow chart was given for the medical management of a radiation accident, whereas Figure 7 illustrates the different procedures of the diagnostic phase.

CHAPTER 3: ORGAN SPECIFIC MANIFESTATIONS OF THE ACUTE RADIATION SYNDROME

In this chapter the pathophysiological basis and the organ specific clinical manifestations of the ARS are described in detail. In each organ specific chapter, diagnostic methods, therapeutic options and relevant references are provided.

As pointed out in the Introduction, this manual is restricted to the health impairments after an acute TBI or large volume PBI. Since the most severe effects manifest themselves and show first signs of recovery within the first 60 days, this period of time received the highest priority in assessing the acute phase after radiation accidents. In addition, based on experience with cases of radiation overexposure, this manual deals only with the neurovascular system, the haematopoietic system, the cutaneous system and the gastrointestinal system as they represent the most critical organs and organ systems for the survival of patients. The respiratory system was considered not to be of primary importance for the initial clinical assessment of a patient. However, this does not mean that the effects of radiation on the respiratory system are of no importance. It is well known from radiation accident cases that respiratory distress including pulmonary oedema and adult respiratory distress syndrome (ARDS) may occur after high doses and that later in the clinical course bacterial and viral pneumonia should be avoided by taking appropriate measures.

To aid the reader in the following chapters, organ specific syndromes are named for instance as neurovascular syndrome or gastrointestinal syndrome, but it has to be stated clearly that these are only short terms indicating that one is confronted with the organ specific, *i.e.* the neurovascular or gastrointestinal, manifestations of the ARS.

Reference criteria for establishing the organ specific grading are provided in the Addendum.

3.1 Neurovascular syndrome

Historically, the central nervous system (CNS) was considered to be a radioresistant tissue owing to the limited potential of cell renewal. However, experimental studies have shown that, owing to complex interactions between cellular and subcellular components, the higher regulatory control mechanisms of the nervous system are functionally radioresponsive. The radiation induced effects can be divided into different phases with specific signs and symptoms resulting either from effects related to vascular injury or ensuing changes via release of mediators or from effects on the parenchymal components of the brain. Therefore, after an acute radiation exposure at moderate or high dose a neurovascular manifestation of ARS may occur, called the neurovascular syndrome (NVS) [1].

The onset and duration of the different phases of NVS depend on the characteristics of the radiation exposure (quality, dose, dose rate and localisation). Symptoms such as nausea, vomiting and anorexia characterise the prodromal phase [2]. Although these clinical symptoms are expressed by the gastrointestinal system, the control site is located in the brain. In this phase, functional abnormalities in the EEG can be seen, even after low doses [3].

From observations in accident and/or radiotherapy patients, after high dose exposure the severity of radiation induced effects increases gradually, giving rise to a so called fatigue syndrome. Owing to vascular changes, the development of additional symptoms such as hypotension and dizziness becomes clinically relevant. An increase in the severity of the fatigue syndrome indicates a worsening of NVS. Clinically important symptoms in this phase are fever, headache and neurological deficits such as dizziness, fainting, ataxia and other motor/sensory signs. With increasing severity of NVS, survivors have a high risk of developing late effects, resulting mainly in impaired cognitive function or neurological deficits.

The acute emetic response can be observed in all phases of NVS, the severity decreasing with dose. After high doses (>10 Gy) the vomiting response is suppressed and a generalised CNS depression develops characterised by sedation or incapacitation [4].

Vomiting and fatigue may have a somatic origin and must be considered characteristic of the initial (prodromal) phase of ARS. They are essential for the triage of irradiated persons. However, it is important to note that these symptoms may be of psychosomatic origin [5]. The initial clinical grading of NVS is based on these symptoms and constitutes a basis for prognosis. In fact, the onset, duration and number of vomiting episodes are important for an early clinical assessment of the severity of ARS. The signs and symptoms of neurovascular damage and their time of onset are listed in Table 3. These symptoms form the basis for classifying the severity of NVS in the initial phase of ARS.

Accidental irradiation of the brain is relatively rare. Therefore our understanding of neurovascular signs and symptoms that occur during the initial phase after accidental exposure is derived from data from animal studies as well as from clinical observations made in patients who have received therapeutic radiation for primary CNS tumours or intracerebral metastasis, or

Table 3. NVS symptoms within the first weeks after exposure and their latent period

Symptoms	Time of onset
Nausea	immediate–hours
Anorexia	immediate–hours
Vomiting	immediate–hours
Fatigue syndrome	immediate–hours
Fever	hours–days
Hypotension	hours–days
Headache	hours–days
Neurological deficits	hours–weeks
Cognitive deficits	hours–weeks

in children with acute lymphatic leukaemia (ALL). On this basis, clinical effects on the brain are defined as acute, subacute, early delayed and late.

3.1.1 Pathophysiology

As a characteristic symptom of the prodromal phase, vomiting is very important for triage after accidental irradiation. In addition to impairing gastric emptying [6], irradiation has a direct effect on CNS function. The CNS contains two distinct areas of the medulla oblongata that are involved in the development of the emetic response: the vomiting centre and the chemoreceptor trigger zone (CTZ). The CTZ is located in the area postrema in the floor of the fourth ventricle, where it is accessible to noxious stimuli from both blood and cerebrospinal fluid. Stimulation of the CTZ results in activation of the vomiting centre, which has no autonomous capability to induce vomiting. The neurochemical control mechanism of vomiting is not well understood. The CTZ is known to contain receptors for serotonin, dopamine, acetylcholine, histamine (H1 and H2) and opiates. The vomiting centre is located in the lateral reticular formation adjacent to structures involved in the coordination of vomiting: the respiratory, vasomotor and salivary centres, and the cranial nerves VIII and X. This centre receives input from the peripheral nervous system (pharyngeal and gastrointestinal afferents), the vestibular system, the CTZ and the limbic cortex. The final common pathway that mediates all emesis is through efferent output to the diaphragm, gastrointestinal tract and abdominal musculature [7].

Research has shown that the epigastric region is the most sensitive area in terms of radiation induced emesis and that vagotomy limits the immediate and delayed onset vomiting response. Ablation of the area postrema also blocks radiation induced vomiting. It is thought that radiation induces the release of neuroactive agents and/or agents from cells in the upper gastrointestinal mucosa, leading to a discordant afferent discharge of the vagus nerve to both the vomiting centre and the area postrema [7]. Work on the effects of dopamine antagonists has shown that with increased dose the anti-emetic effects are due to antagonism of 5-hydroxytryptamine ($5\text{-}HT_3$) receptors. Drug development has therefore focused on compounds that selectively block the $5\text{-}HT_3$ receptor [8].

Irradiation may cause both cerebrovascular disorders and nervous tissue injury. The symptoms are dose related and are most likely linked to cerebral oedema with an increase in intracranial pressure. Irradiation of the brain increases the permeability of the blood–brain barrier, allowing excess water into the extracellular space (vasogenic oedema) and an ion imbalance is responsible for tissue swelling (cytotoxic oedema). Furthermore, the clinical manifestations of radiation effects on the brain are expressed differently depending on the area irradiated, the dose and the patient's neurological status prior to irradiation. Whatever the injury, the brain will rapidly develop oedema. Along with early oedema, acute inflammatory reactions occur. This has additional consequences for the development of brain injury, although these manifestations are not supported by early well defined morphological evidence of tissue lesions, which may be localised and transient. Lesions that become evident much later than 60 days after exposure qualify as late effects owing to a second phase of inflammation and/or the progressive ischaemia.

The main features of the acute period are [9]:

- Impairment of the capillary circulation
- Damage to the blood–brain barrier
- Pericapillary and interstitial oedema and acute inflammation
- Hypertrophy of perivascular astrocytes
- Petechial haemorrhages
- Meningitis and choroid plexitis

At low dose levels, these changes may be localised or transient, and/or they may be repaired; at high dose radiation, they may be more widespread, severe and persistent. The cellular composition of the perivascular and interstitial inflammatory infiltrate may change from a predominance of polymorphonuclear cells (granulocytes) to a predominance of mononuclear cells (lymphoid and plasma cells) as a function of time after irradiation. There may be some connective tissue proliferation in the meninges and choroid plexus and in the walls of the arterioles and large vessels. Damage to the blood vessels and capillaries is commonly seen in the brain during the NVS but lesions of larger blood vessels are generally expressed later. These changes include haemorrhage, capillary endothelial vacuolisation and vasculitis [10]. Degeneration of vessel walls, occlusion of the lumen

by thrombosis and fibrosis may occur after high radiation doses. The astrocytic basal lamina is fused with the basement membrane of the endothelial cells and the barrier function is thus probably shared by the astrocytes. Thus radiation damage of the blood–brain barrier may be associated with a delayed necrosis of the CNS [11]. Whether the acute and delayed breakdown in the blood–brain barrier function is alone responsible for tissue necrosis is not known. Nevertheless the damage to the vascular system is believed to contribute to local cellular damage and to be the primary factor in the delayed necrosis of the brain. Neurones of the cerebrum also show some morphological changes after irradiation.

Radiation induced functional abnormalities of the brain have been observed in experimental animal models at the synaptic level and in integrated brain structures. Electrophysiological measurements have been used to illustrate the changes in brain function after exposure to ionising radiation [12]. Radiation exposure significantly modifies dopaminergic neurones, which are present in high concentrations in the caudate nucleus. In this region dopamine acts for the most part as an inhibitory neurotransmitter. Thus alterations of this inhibitory input to the caudate nucleus following radiation exposure could lead to corresponding changes in motor activity. Similarly, concentrations of other neurotransmitters, such as acetylcholine and 5-HT_3, undergo significant changes. Low irradiation doses of up to 5 Gy increase levels of these amines [10], whereas higher doses decrease levels [13]. In parallel, acetylcholinesterase activity is decreased within 2 h of whole body irradiation at 10 Gy [14]. Electrophysiological studies using intracellular electrodes showed that irradiation of 6 Gy produces significant changes in monosynaptic excitatory and post-synaptic potentials [15]. Lower doses also resulted in an arousal response, implicating the reticular activating system. These functional changes, however, were not correlated with structural changes [16]. The precise mechanism of radiation effects on synapses is unknown.

Many changes in spontaneous activity (as shown by changes in the EEG) as well as altered electrical activity (evoked potentials) may be observed after exposure at doses much lower than the lethal range for whole body irradiation. Desynchronisation in the neocortex with slight activation of the reticular system and hyperactivity in the archicortex has been reported following low dose irradiation (4–6 Gy) to the head of rabbits [17]. However, higher gamma exposure of about 9 Gy slightly moderates neocortical activity and reticular excitability. This biphasic action of γ-irradiation was also demonstrated with the electrographic arousal reactions induced by electrical stimulation of the midbrain reticular system, or posteroventral hypothalamus. In rodents, significant decreases in both low and high frequencies of EEG recordings were observed within 12 h following a 7 Gy whole body X-irradiation [18]. An increase in amplitude and a mild decrease in frequency of EEG occurs in the prepyriform cortex after X-ray TBI [19, 20]; these abnormalities were observed during the first few days following 2.5 Gy exposure, and up to 35 days for higher doses (5 Gy). After single whole body X-ray radiation (0.15–5 Gy), the threshold of electroshock seizures in rats is dose-dependently reduced within weeks or months following irradiation [21, 22].

These data suggest that whole body irradiation could produce a state of brain excitability. In rabbits, slow waves and spikes were observed using electrophysiological recordings of the hippocampus after 4–4.5 Gy TBI [23, 24]. These abnormalities were associated with marked disturbances in the activity of hippocampal neurones [25] and an abnormal sleep pattern, which occurred 60 min after irradiation in this species [26]. Spontaneous spike activity has been reported for doses as low as 1 Gy in the first few hours following irradiation. In rat hippocampus, spontaneous discharges of pacemaker-like neurones are induced by X- and γ-ray doses lower than 0.08 Gy [27]. This indicates that the hippocampus appears to be a very radiation responsive brain structure, and that the cortex is more radiation resistant than the hypothalamus, brain stem or cerebellum.

Animal studies have demonstrated parallel changes in neurotransmission and behaviour after exposure to radiation. One area of the brain that is specifically affected following irradiation is the caudate nucleus of the basal ganglia, an area involved in motor coordination.

With regard to behavioural disturbances, studies using quantitative methods for assessing cognitive functions are not available, but there is evidence of significant cognitive decline after cranial irradiation. Memory and attention deficits are most frequent after high dose irradiation. Neuropsychological tests such as information processing speed, recent memory and learning performance, sustained vigilance, attention and concentration, problem-solving capacity and executive functions have shown diminished performance in irradiated patients. The onset of cognitive decline is apparent immediately after irradiation. The prognosis concerning improvement in the patient's cognitive status seems to be related to age.

The preceding paragraphs clearly show that the CNS exhibits a functional radiosensitivity with a wide range of expression. However, the pathophysiological consequences of the intercellular or interorgan communications of such neuronal disturbances require further elucidation.

3.1.2 Clinical characterisation

The clinical grading corresponding to the damage to the NVS and the prognostic probabilities are shown in Table 4.

Table 4. Overall prognostic aspects of the NVS on the basis of the clinical grading

Grading	Extent of impairment	Prognosis
N1	Mild damage	Recovery certain
N2	Moderate damage	Recovery with possible deficit
N3	Severe damage	Recovery with severe deficit
N4	Fatal damage	Recovery impossible

Since most of the selected symptoms may occur or recur at different times in the development of the NVS, different phases can be subdivided as described in Figure 8.

The development of clinical signs and symptoms after exposure to ionising radiation is outlined below in more detail for each of the different grades of the neurovascular manifestation of ARS, *i.e.* N1 to N4. Also included are aspects of clinical patient management such as diagnostic and therapeutic options.

Grading N1

Symptoms of the prodromal phase such as nausea, anorexia and vomiting may appear within 24 h of exposure; the severity will usually not exceed degree 1. These symptoms indicate mild damage to the neurovascular system. Complete disappearance of the symptoms is certain within 48 h of exposure. However, in a second phase starting 2 or 3 days after exposure, symptoms of mild fatigue syndrome may occur and persist for several weeks. Usually there is no headache, fever, hypotension, neurological deficit or impairment of cognitive functions.

Outpatient treatment will be sufficient. Administration of 5-HT_3 receptor antagonists for coping with nausea and vomiting may be indicated. Otherwise no specific medication is necessary.

Data from animal studies indicate modifications of brain electrical activity (EEG), which will most likely also occur in humans, with a few paroxysmal bursts and modifications of the evoked potentials. To date, no data are available that would enable other diagnostic methods such as MRI or positron emission tomography (PET) to be used in the assessment of these mild symptoms in the very early stages of NVS.

Grading N2

Within the first hours after exposure there may be moderate nausea and anorexia accompanied by only a few episodes of vomiting. Symptoms are unlikely to exceed degree 2 and may persist for a period of about 2 days. After a symptom free interval, similar symptoms may recur 3–6 weeks after exposure. Additionally, degree 1–2 fatigue symptoms may appear and continue for several weeks. Furthermore, exposed persons suffer from headaches and drowsiness for about 24 h. Besides these prodromal symptoms there are no visible signs of neurological deficits. There will usually be fever, hypotension or impaired cognitive functions in this group.

Hospitalisation of these patients for clinical monitoring is necessary. Administration of 5-HT_3 receptor antagonists for coping with nausea and vomiting is highly recommended. Furthermore, glucocorticoids may reduce the severity of the prodromal signs—but contraindications and/or interference with clinical signs and symptoms or therapeutic approaches of other organ systems should be checked first.

Brain electrical activity (EEG) displays an increase in paroxysmal spike and wave discharges, and disappearance of biorhythm.

Grading N3

Exposed persons present severe nausea, anorexia and vomiting (degree 2–3) within the first hours after exposure for a period of about 2 days. Symptoms usually recur after a symptom free interval at the end of the first week post exposure and persist for about 2 weeks. Electrolyte imbalance will probably occur as a result of the episodes of prolonged and severe vomiting. It should be kept in mind that these symptoms

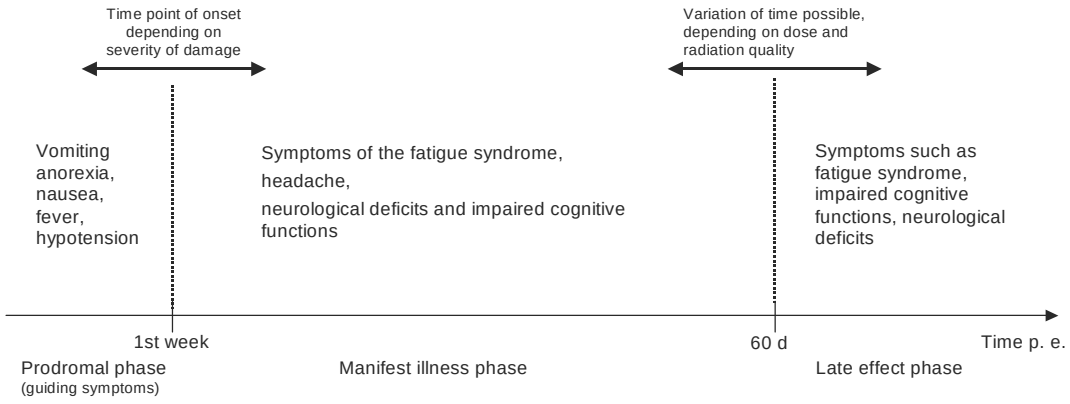

Figure 8. Different phases in the development of the NVS as a function of time (p.e.= post exposure).

Table 5. NVS: diagnostic methods

Method	Relevance for the NVS
EEG	Non-invasive method for the assessment of changes in brain electrical activity. Brain electrical activity displays an increase in paroxysmal spikes, wave discharges and disappearance of biorhythm. These brain electrical modifications are roughly linked to the dose: slowing of brain electrical activity is a sign of high dose. The duration of the recording must be at least 1 h.
Ophthalmoscopy	Non-invasive method for the detection of brain oedema. Papilloedema is a sign of increased intracranial pressure.
Laboratory	Routine screening for the early assessment of electrolyte loss or imbalance as well as fluid loss. Important for the exclusion of other reasons for CNS perturbations (such as infectious diseases).
Cranial CT	Method for the assessment of swelling and oedema of the brain. In the late effect phase of ARS, atrophy and calcification can be detected if there is suspicion of structural cerebral lesions.
MRI	Method for the assessment of swelling and oedema of the brain. In the late effect phase of ARS, if there is suspicion of structural cerebral lesions it may be possible to detect white matter changes and dystrophic cerebral calcification.

may be accelerated by diarrhoea related to gut damage, or severe skin lesions with the development of blisters, which therefore complicate the patient's general status. In addition to prodromal symptoms within the first hours, patients suffer from headaches and severe symptoms of fatigue syndrome (degree 3), particularly dizziness for 24 h. Hypotension and fever will probably occur.

Owing to these severe symptoms, patients need to be hospitalised. Without therapeutic interventions, severe dehydration and circulatory collapse may lead to coma and death around the second week after exposure. Therefore, medical treatment should include sufficient fluid and electrolyte replacement, analgesics and i.v. glucocorticoids. Intensive therapy will probably lead to recovery but with severe deficit mainly expressed as impaired cognitive function.

Brain dysfunction can be characterised by a slowing of the brain electrical activity and a decrease in paradoxical sleep (REM sleep). Clinical signs of intracranial pressure due to oedema can be detected by ophthalmoscopy.

Grading N4

Transient or permanent incapacitation occurs with severe vomiting and nausea, severe headaches and drowsiness almost immediately after exposure to ionising radiation. Vomiting (degree 4) appears, accompanied by degree 3–4 nausea and anorexia. Furthermore, patients suffer from headache and fever, the severity of which can be degree 1–4. These symptoms usually decline after 3 days. Additionally, patients will develop symptoms of fatigue (degree 3–4) that can persist for several weeks.

Moreover, owing to accelerated gut and/or skin related fluid and electrolyte losses, patients will develop severe dehydration and electrolyte imbalance within several hours of exposure, which will clearly contribute to hypotension. Before the end of the first week, life-threatening neurological signs will appear.

Recovery is most unlikely and mainly primary symptoms continue intermittently until the patient's death. Only sufficient fluid and electrolyte replacement, analgesic medication and the application of i.v. glucocorticoids and/or mannitol infusions to reduce oedema will increase the patient's chance of survival, provided there are no other serious complications in other organ systems.

Ophthalmoscopy can be used to diagnose intracerebral oedema.

3.1.3 Diagnostic methods

In addition to information obtained by observation, interrogation and detailed physical examination, Table 5 lists the diagnostic methods that may be relevant for the verification of the organ specific grading, and also as a starting point for further control and follow-up examinations. The best time for an examination depends on the characteristics of the symptom and the method selected.

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3.2 Haematopoietic syndrome

The cellular components of blood are essential for functions such as O_2/CO_2 exchange. In addition, blood transports nutrients, metabolites and other active agents (*e.g.* hormones). These components are important in preserving organ perfusion and acid–base integrity, in the prevention of bleeding through the generation of clotting proteins, and in maintaining immunity by specific and non-specific cellular defence mechanisms such as phagocytosis and development of antibodies. Disturbances in haematopoiesis owing to acute penetrating large volume PBI or TBI in almost all cases lead to clinical symptoms that can be gathered under the term haematopoietic syndrome (HS) [1, 2]. There may be concomitant disturbances of the neurovascular and gastrointestinal systems. These abnormalities are described in the organ specific sections 3.1 and 3.4 as well as in Chapter 4.

HS occurs following radiation induced damage of the haematopoietic tissue in the bone marrow. It is mainly based on the hypoplasia or aplasia of the bone marrow, which may involve multiple haematopoietic cell lineages, responsible for the typical clinical signs and symptoms of HS in a patient. Generally, after radiation overexposure of the whole or nearly the whole body, erythropoiesis as well as granulopoiesis, thrombopoiesis and lymphopoiesis are affected. Although it is plausible that impairment of haematopoiesis increases with radiation dose, there is no apparent threshold limit responsible for uniform effects in similar cell lineages in different patients. Nevertheless, the dose–effect concept is of little

consequence for clinically based grading of prognosis and therapy of individuals exposed to radiation. The physician must rely on characteristic signs and symptoms related to organ damage to evaluate and treat acute radiation overexposure. Inherent in this clinical approach is the concept that damage to the stem cell compartment in the bone marrow is dose dependent. However, bone marrow failure may be ameliorated by autologous regeneration of the haematopoietic system or by stem cell transplantation [1, 2].

As mentioned previously, radiation induced cytopenia is strongly related to dose. This phenomenon is best explained by the sensitivity of rapidly dividing cells in the bone marrow where production is of the order of 10^{11} cells per day. An elaborate hierarchical structure assures that, to maintain homeostasis, the cells in the blood are continuously replaced by newly formed cells from the bone marrow in accordance with their peripheral blood transit times. Therefore, different response patterns of blood cell lineages form the basis for assessing the extent of damage to the bone marrow. The peripheral blood markers—granulocyte, lymphocyte and thrombocyte blood concentration—which are considered to be of particular importance within the first few days after exposure, can be obtained easily and regularly from the peripheral blood in an emergency situation. The response patterns can be described by changes in the peripheral cell concentration as a function of time after the exposure. Differences in the resulting response curves are mainly caused by the duration and pattern of the descending part of the curve (reflecting peripheral survival time and consumption), the duration of the nadir (reflecting the magnitude of stem cell damage), the ascending portion of the curve (reflecting reconstitution from residual stem cells), and the lowest level of absolute cell count within the first 60 days after exposure.

During this early phase, clinical complications of exposure arise primarily from the extent of disturbance of the cell lineages involved: granulocytopenia results in an increased risk of infection while thrombocytopenia enhances the risk of bleeding. Besides reduced immune competence, lymphocytopenia is one of the earliest and most reliable indicators of radiation exposure. Therapeutic decisions must take into account the extent of damage to the haematopoietic system [3, 4].

By assessing the typical changes in the cell lineage responses and the clinical signs and symptoms related to complications, an approach can be developed to establish a haematological grading system that may determine prognosis.

3.2.1 Pathophysiology

For a better understanding of the pathophysiological mechanisms following radiation overexposure it is necessary to give a short overview of the physiological functioning of the haematopoietic tissue in the bone marrow. The haematopoietic system is particularly sensitive to radiation and thus is very likely to be impaired after an accidental exposure to ionising radiation.

The impact of acute radiation exposure on the physiology of normal haematopoiesis is well characterised from both *in vitro* experiments and *in vivo* investigations after exposure of humans and animals [5–8]. All blood cell lineages are derived from pluripotent stem cells localised in the bone marrow distributed in the skeleton. To current knowledge, the capacity of stem cells for self-renewal is still believed to be unlimited. Each of these stem cells has the potential to produce lineage-committed progenitor cells. Mature and maturing cells from the myeloid cell lineage (erythrocytes, leukocytes, thrombocytes) and from the lymphoid cell lineage (T and B lymphocytes) are released into the peripheral blood after passage through the blood–marrow barrier consisting of endothelium, macrophages and support elements. For all haematopoietic cell lineages, the compartment transit times, the mean and ranges of the quantities of mature cells in the peripheral blood and the mean lifetimes are well defined.

Normal human erythrocytes have a life span of the order of 120 days. Therefore, even after a complete blockade of all erythropoietic development, the decline of erythrocytes per litre of blood amounts to only 1:120 per day. Thus, after 30 days, the blood erythrocyte concentration declines to about 70% of normal values. Therefore, under a normal clinical course of TBI, anaemia is usually not a significant clinical problem and red blood cell concentrate transfusions should not be necessary, although in some radiation accidents, such as Lockport, Oak Ridge or Vinca [1], there was evidence of red cell (or haematocrit) diminution at day 30 after exposure. An exception might occur under specific circumstances, for example: in addition to a temporary blockade of erythrocyte production due to nutritional deficiency of radiation induced apoptosis; blood loss as a consequence of a severe trauma and/or thrombocytopenia; or accelerated haemolysis as a consequence of damage to circulating red cells (haemolytic crises after severe burns).

These phenomena are in contrast to reports of findings in experimental animals (mice, rats, dogs, etc.) where there is evidence of anaemia after midlethal whole body radiation exposure, because their red cell life span is much shorter than that of humans [1].

The status of degeneration and regeneration of erythropoiesis can be assessed by monitoring reticulocytes over time. Reticulocyte life span in the blood is of the order of 1–3 days. Therefore, reticulocyte counting in radiation accident victims (such as in Lockport 1960 or in Oak Ridge 1958) reveals a

pattern of change that is very similar to that observed for circulating granulocyte concentration curves [1].

Unfortunately, for most of the accident cases involving humans, reticulocyte counts have not been monitored regularly owing to the difficulties in standardising the methods involved. This has changed owing to the development of a flow cytometric method of counting that can be automated. Thus the routine reticulocyte count will become more important as a clinical tool for patient management. Data from experimental animals have already demonstrated that reticulocyte monitoring is a simple and reliable quantitative marker of haematopoietic reconstitution and response to therapy [9].

Even if the factors responsible for the differentiation of stem cells into granulopoietic precursors are not completely known, the kinetics of granulocytopoiesis are reasonably well understood. Granulopoietic cells are derived from the stem cell compartment, which undergoes differentiation into mature granulocytes of the peripheral blood [10]. The transit time for cells from the myeloblast to the first non-dividing cell in man is about 6 days. The transit time through the maturing pool, that is from the metamyelocyte to the granulocyte, is 3–4 days. The total transit time from the stem cell to the mature granulocyte in the marrow is 9–10 days. Granulocytes disappear from the blood in a random fashion with a half-life of 6.6 h [11]. The elimination of granulocytes is a random process and terminates by senescence after 30 h through the process of apoptosis (*i.e.* programmed cell death) [12].

Thrombocytes are produced by the megakaryocytes, which in turn differentiate to form megakaryocytic progenitor cells. The total transit time from the appearance of the most immature megakaryocyte in the marrow to the release of platelets in the peripheral blood is 8–10 days. The platelet life span in the peripheral blood in humans is 8–10 days [13]. Platelets are removed from the circulation by a random process.

The lymphocyte-producing organs constitute a unique system characterised by lymphocyte migration streams [14, 15]. Using modern surface markers, it has been possible to distinguish many classes of lymphocytes, each having unique migration and life span patterns and sensitivity to ionising radiation, the CD4+ subpopulation being more resistant than the CD8+ population and activated T-cells more resistant than resting ones [16–18]. The nature of radiation death of T-lymphocytes is apoptotic rather than mitotic. The haematology laboratory may evaluate lymphocytes in routinely prepared peripheral blood smears as large, medium size or small in size. However, functional analysis of lymphocytes and/or assessment of immune state requires the use of flow cytometry to quantify lymphocytes based upon surface markers [19–21].

After TBI or large volume PBI, reductions in lymphocyte concentration in the peripheral blood are considered to be the most sensitive indicator of effect within the first hours. Indeed, a radiation exposure resulting in a severe or even lethal haematopoietic syndrome is characterised by a marked initial lymphocyte depression so that in such cases the lymphocyte number drops to values below 0.5×10^9/l within 6 h. Such observations have suggested that lymphocytes are particularly radiosensitive. However, exposure of lymphocytes to doses up to 12 Gy *in vitro* followed by phytohaemagglutinin stimulation results in DNA synthesis and subsequent cell division, like any other mammalian cell capable of division [22]. Thus it is evident that the high sensitivity of the blood lymphocyte concentration to radiation may be related to migration from the circulation to the tissues. Alternatively, radiation may induce apoptosis in lymphocytes, a process that is completed in 16–24 h [23, 24]. In contrast to granulocytes, lymphocytes recirculate as first shown by Gowans [15]. Accordingly, lymphocytes produced in lymph nodes are released into the efferent lymphatic vessels (for instance the thoracic duct), from which they enter the circulation. Peripheral blood lymphocytes may re-enter lymph nodes via precapillary venules (afferent lymphatic vessels). It appears that the process of transit from blood to the lymphatic tissue and back to the blood is sensitive to radiation. Furthermore, it is well known that the capillary bed is highly sensitive to radiation [25]. Therefore, radiation modifies the recirculation properties of lymphocytes, resulting in a prompt decline of lymphocytes (particularly of T-cells).

In the context of recirculation, it is of interest to note that in the development of thrombocytopenia with platelet counts approaching 50×10^9/l one of the earliest pathological findings was the accumulation of red cells in the lymph node sinuses and the appearance of many red cells in the thoracic duct re-entering the blood circulation (which causes a reduced life span of erythrocytes). After platelet transfusion there is an almost instantaneous halt of erythrocytes entering the lymphatic vessels [26]. This phenomenon gives weight to the dynamics of cellular migration through the lymphatic circulation being intimately associated with the blood circulation.

Radiation induced damage to haematopoiesis is clinically manifested by diminished defence mechanisms and by an increased tendency for bleeding. Granulocytopenia and thrombocytopenia predispose to infection and bleeding, respectively.

The normal function of the haematopoietic system depends on the functionality (self-renewal and cell renewal) of the pluripotent stem cell. Therefore it is essential to assess very early after radiation exposure the extent of damage to the bone marrow and its residual repair capacity. The important question is

Table 6. Overall prognostic aspects of the HS on the basis of the clinical grading (critical phase = duration with constant cell counts below the normal range, resulting in high or low risk groups for developing clinical symptoms such as bleeding and infectious diseases owing to differences in the absolute cell counts)

Grading	Extent of impairment	Prognosis
H1	Mild damage	Autologous recovery certain without critical phase
H2	Moderate damage	Autologous recovery certain with low risk critical phase
H3	Severe damage	Autologous recovery certain with high risk critical phase
H4	Fatal damage	Autologous recovery most unlikely

whether or not the impairment to the haematopoietic system will show endogenous regeneration. Thus it is necessary to determine the number and quality of haematopoietic stem and progenitor cells in the bone marrow as well as in the circulating blood [27, 28]. This can be done in a more classical way by assessing colony-forming units in culture (GM-CFU, GEMM-CFU, etc.) or by determining very early haematopoietic cells characterised by surface markers (for instance the CD34+ population). Quantitative assessment of stem and progenitor cells in the blood allows "stem cell traffic" to be evaluated as a function of time after radiation [29]. This is owing to the fact that there is now ample evidence that normal homeostasis of blood cell production and removal in the organism is generated by a continual stream of migrating stem cells through the circulation to sites of haematopoiesis in the bone marrow. Thus the level of stem and progenitor cells in the circulation is an indicator of normal or abnormal stem cell trafficking. The heterogeneity of radiation exposure should be considered when evaluating stem cells in the bone marrow. In maximally exposed bone marrow sites hardly any stem or progenitor cells can be found, whereas in less severely exposed sites significant numbers of stem and progenitor cells can be seen. Examination of quantity and/or quality of stem and progenitor cells in blood and bone marrow will guide decision making, particularly regarding the need for stem cell transplantation as a "causative" therapy of the HS.

However, it should be kept in mind that this haematopoietic grading system is based only on the peripheral cell response patterns and that the outcome after acute radiation overexposure is also dependent on the combination of syndromes in other organ systems as well as the general condition of the patient.

3.2.2 Clinical characterisation

To make early predictions of the clinical course and outcome of a patient after radiation exposure, it is necessary to differentiate between reversible and irreversible damage to the stem cell compartment of the bone marrow. This is possible by the pathophysiological interpretation of typical haematopoietic response patterns of peripheral blood cell lineages (see also Figure 11).

The clinical grading summarises the extent of the damage to the individual and the corresponding prognosis. The interpretation of the grading of HS is outlined in Table 6.

Without or prior to any treatment, four different grades of the HS can be distinguished based on the extent of damage to haematopoiesis as well as on the prognosis for autologous recovery of the system. The different phases in the development of the HS are described in Figure 9.

The basic procedure is to assess the different cell lineage response patterns as a function of time after a radiation accident. To this end the peripheral blood

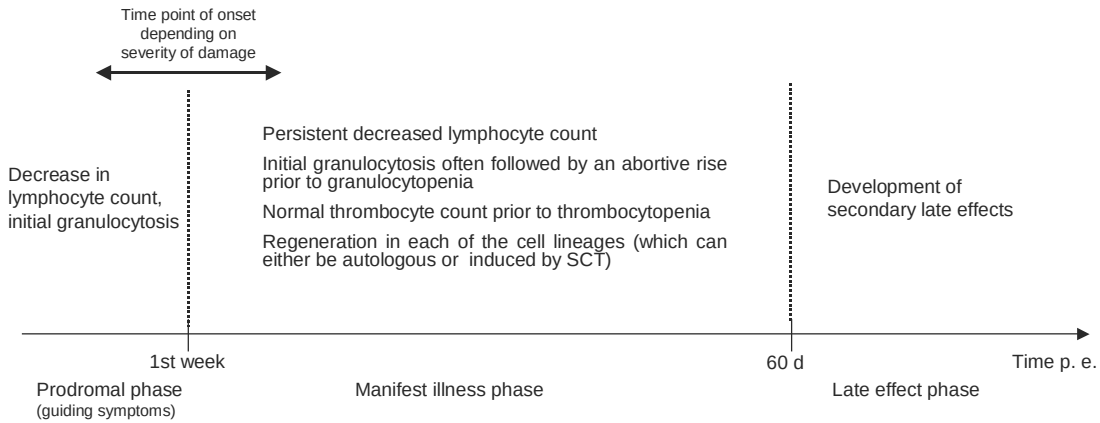

Figure 9. Different phases in the development of the HS as a function of time (p.e. = post exposure).

Table 7. Phases of response patterns of different peripheral cell lines

Phases of the curve patterns	Segment number	Special relevance for
Degeneration phase		
Initial changes (within 24–48 h)	1	Granulocytes, lymphocytes
Shoulder	2	Thrombocytes
First phase of degeneration	3	Granulocytes, thrombocytes, lymphocytes
Abortive rise	4	Granulocytes
Second phase of degeneration	5	Granulocytes
Nadir phase		
Level, beginning and duration	6	Granulocytes, thrombocytes, lymphocytes
Regeneration phase		
Beginning of regeneration	7	Granulocytes, thrombocytes, lymphocytes

cell counts of the lymphocytes, granulocytes and platelets in first 60 days after the exposure have to be examined. Owing to the long half-life of the erythrocytes (about 120 days) and the lack of reliable data on reticulocytes, the erythropoietic cell lineage is not used for this classification.

In describing the four different grades the following phases of the cell line curves as a function of time (onset and duration) are of importance (Table 7; Figure 10).

Each attempt to describe an event as complex as the haematological effects after radiation overexposure has its shortcomings. Therefore, all time points for duration or onset of observations should be taken as gross reference points that reflect the inter- and intra-individual variation of patients. They are by no means definitive owing to individual variations; some cases might not even fit this pattern. The time points given for specific observed phenomena are expressed in days after the actual exposure.

The description of the characteristics for each single cell line response pattern after exposure to ionising radiation is outlined below in more detail for each of the different grades of the haematological manifestation of ARS, *i.e.* H1 to H4. Aspects of the clinical management of the patient are also included, such as the diagnostic and therapeutic options.

Grading H1

Clinical symptoms such as bleeding or infectious diseases will not usually be seen. If there are any symptoms, they should not exceed degree 1. The measurable cell counts might be at or around the lower border of the normal range.

This response pattern of the cell lineage curves can be explained as follows. Owing to the low exposure dose, only the most sensitive cells were damaged, most likely without complete cell loss or cell death in the affected compartment. The stem cell damage is not reflected by major changes in the number of blood cells and the capacity of the haematopoietic system to expand production is sufficient to maintain peripheral blood cell numbers.

The resulting pattern can be described as follows:

- Lymphocytes: cell counts remain between the normal range of (1.5–3.5) $\times$ 10^9/l (degree 1); single cell counts as low as 1.0 $\times$ 10^9/l are accepted.

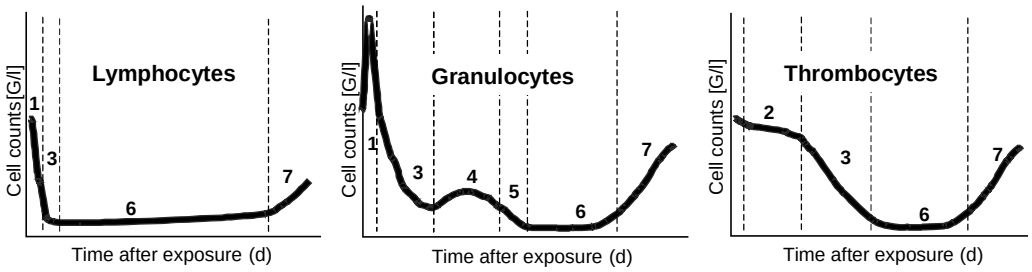

Figure 10. Crucial segments for the assessment of different cell line response patterns (see Table 7 for segment numbers). The curves are for illustrative purposes only.

- Granulocytes: from the very beginning the cell counts will remain within the normal range of (4–9) $\times 10^9$/l (degree 1); owing to the postulated exposure to ionising radiation, single drops in the granulocyte cell count below the lower range of the normal border are accepted for this grading. However, the cell count never drops below the clinically critical threshold of 1×10^9/l.
- Platelets: normally the cell counts remain within the normal range of (150–350) $\times 10^9$/l (degree 1). However, it is accepted that for single declines below the lower border down to 100×10^9/l there is no increased risk of clinical bleeding or poor prognosis. Between days 25–35 there will be a tendency towards a discrete drop of cell counts close to the lower border of the normal range.

Since there is no increased risk of infection or bleeding due to granulocytopenia or thrombocytopenia, no specific haematological therapy is necessary. Only mild impairment of the haematopoietic system can be seen and autologous recovery is certain without any critical phase.

Grading H2

H2 patients suffer from only moderate impairment of the haematopoietic system. The cell lineage curve will show a descending pattern with measurable cell counts clearly below the lower border of the normal range. Without any concomitant injuries such as open wounds or skin burns, patients will not usually complain about any symptoms. However, owing to the apparent cytopenia, there is a risk of developing an infection or bleeding, especially in patients with concomitant injuries. Symptoms will probably not exceed degree 1–2 for bleeding and degree 2 for infection.

Compared with H1, less sensitive haematopoietic cells will be damaged and the quantitative damage is more pronounced.

The resulting pattern can be described as follows:

- Lymphocytes: cell counts decline from a normal level within the first 2 days after exposure and remain between 0.5×10^9/l and 1.5×10^9/l (degree 2).
- Granulocytes: granulocytosis appears within the first few days as a result of release of already mature granulocytes both from the bone marrow into the circulation and from the marginal pool of intravessel granulocytes. Between days 5 and 10 an abortive rise (explained by the injured stem cell theory) begins, leading to cell counts close to the lower border of the normal range. After this abortive rise (duration about 8–12 days), cell counts decline slowly, reaching levels below 1×10^9/l around day 20 (nadir, degree 2). This low cell count prevails for about 10 days. There are usually signs of increasing cell counts after days 30–35. The pattern of recovery varies: it may be slow or rapid leading to an overshoot.
- Platelets: cell counts remain above the lower border of normal range (150×10^9/l) down to 100×10^9/l until days 10–12. After this shoulder the cell count declines and reaches the nadir at about day 22 at a level of 50×10^9/l. The cell count remains at this level for about 5–10 days (nadir, degree 2). First signs of regeneration appear between days 30 and 32. The pattern of recovery varies: it may be slow or rapid leading to an overshoot but most likely shows an undulating pattern.

Treatment of these patients should be by blood component therapy if indicated by bleeding, or appropriate antibiotic agents to cope with bacterial infections (in the case of manifest infections after bacterial typing).

Autologous recovery is certain; patients are at low risk of developing infectious diseases or bleeding.

Grading H3

The H3 haematopoietic cell lineage response pattern is very similar to that of H2 with respect to the descending part, the nadir and the ascending part of the curve. But the impairment to the haematopoietic system is more severe, there being a shorter period of time before the cell counts begin to decline, a subsequent longer duration of the nadir and delay before recovery starts. Endogenous recovery is still certain if the pancytopenic period can be bridged by supportive therapy. Patients are at a higher risk of developing severe bleeding or infectious diseases compared with those of H2 owing to the longer duration of low cell counts. Symptoms will possibly reach degree 3–4 for bleeding and degree 3–4 for infection.

The resulting pattern can be described as follows:

- Lymphocytes: cell counts drop almost linearly within the first 48 h after exposure and remain between 0.25×10^9/l and 1.0×10^9/l (degree 3).
- Granulocytes: initial granulocytosis can be observed within days 1–3 with a subsequent decrease until day 5. An abortive rise can also be seen starting at around day 5, keeping the cell count at an average of 1×10^9/l for about 5–8 days. Hereafter, the cell counts drop to levels below 0.5×10^9/l around days 10–15. This low level is maintained for about 20 days (nadir, degree 3). Signs of increasing cell counts become obvious around days 30–35. The pattern of recovery varies: it may be slow or rapid leading to an overshoot.
- Platelets: cell counts remain above the lower border of the normal range (150×10^9/l) down to 100×10^9/l until days 5–10. The nadir is reached at about day 16–18 at a level of $(0–50) \times 10^9$/l. The nadir lasts for about 12–15 days (nadir, degree 3). The recovery pattern varies from slow to overshooting and mostly shows an undulating pattern but does not begin before days 35–40.

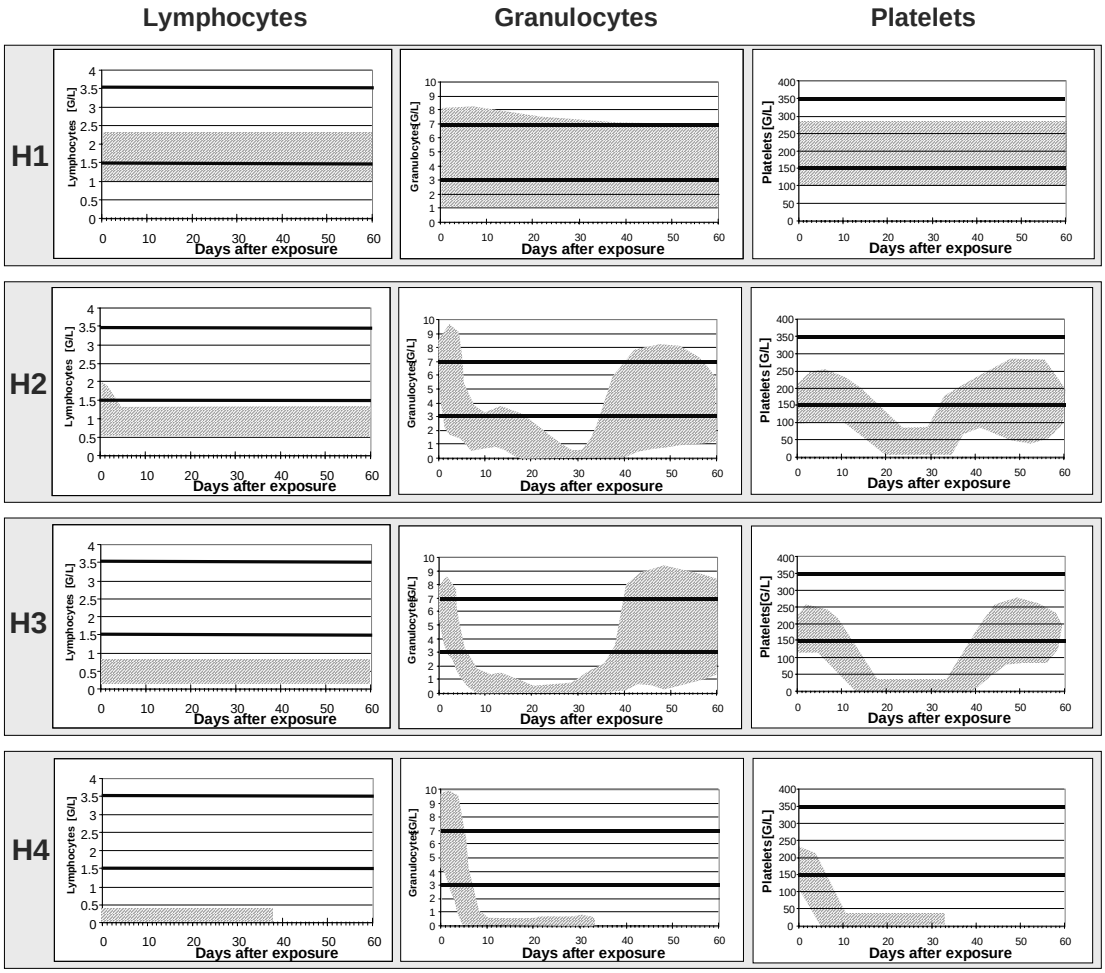

Figure 11. Schematic illustration of different cell line response patterns as a function of time for H1–H4.

Appropriate treatment options are the same as those in H2, *i.e.* selective blood cell transfusions and antibiotic drugs, including those aimed at gastrointestinal decontamination. Additionally, to influence positively the duration and extent of the nadir, cytokines/growth factors should be administered as early as possible (see Chapter 5).

Autologous recovery is possible. However, patients are at high risk of developing infectious diseases or haemorrhage, either of which may be fatal.

Grading H4

In this category, damage to the haematopoietic system is fatal without appropriate treatment. Cell counts decline very rapidly (see below) to the status "not measurable" or slightly above zero. The stem cell compartment and precursor cell compartments in the bone marrow are severely reduced. Patients are at a very high risk of developing bleeding and infectious diseases, and degree 4 symptoms will most likely occur.

The possibility that a patient will die within the first few days after acute radiation exposure and before stem cell transplantation is very high and increases if there are other severe organ and/or organ system impairments in combination with the HS.

The resulting pattern can be described as follows:

- Lymphocytes: cell counts decline almost linearly within the first 24 h after exposure and remain between 0.1×10^9/l and 0.25×10^9/l (degree 4). The level remains this low for several weeks.
- Granulocytes: initial granulocytosis can be observed within 48 h, somewhat earlier than in H2 or H3. Then the cell counts decrease rapidly, reaching values of $(0–0.5) \times 10^9$/l at days 5–7, this level persisting for several weeks (nadir, degree 4) if the patient survives and is appropriately treated in a protective environment.
- Platelets: the cell count declines nearly linearly. The nadir is reached at about day 10. This low level remains for several weeks (nadir, degree 4).

Most patients in this category do not survive the first 2 weeks owing to severe impairment not only of the haematopoietic system but also of other relevant organ systems. If only supportive therapy is administered a discrete increase in the cell count might be observed at about days 30 to 40. However, without SCT this will not result in a sustained recovery. The only treatment that rescues patients is a stem cell transplantation, supplemented by all other non-invasive or

Table 8. HS: diagnostic methods

Method	Relevance for the haematopoietic syndrome
Blood cell counts	Routine screening of at least lymphocytes, granulocytes and platelets to perform the grading. It is necessary to obtain laboratory results on a regular basis.
Reticulocyte count	Reliable quantitative marker to monitor haematopoietic reconstitution and the efficacy of therapy. Facilities for automated reticulocyte counting are available and are increasingly used in the clinical routine.
Blood smears	Regular blood smears are used to analyse and determine the composition of leukocytes as a basis for establishing the concentration of granulocytes and lymphocytes. Blood leukocyte concentrate smears allow one to determine the pattern of mitotically connected abnormalities in granulocytes and lymphocytes to assess the type and extent of injury to the underlying cell systems.
HLA typing	To be prepared for SCT, it is important to take a blood sample for human leukocyte antigen typing within 24 h of exposure.
Cytogenetic tests	The results of these tests can be used as indicators of effect and repair. The blood samples for these tests should be taken as early as possible after the exposure and should be kept in a refrigerator for future reference and for further evaluation by consulted experts. In general—but less relevant for the acute phase—the following methods are appropriate for the assessment of genotoxic changes: ▪ assessment of the spontaneous frequency of micronuclei in mononuclear lymphocytes. ▪ detection of different forms of chromosomal aberrations such as dicentrics, rings, fragments, etc. ▪ verification of DNA single- or double-strand breaks with the comet assay, if routinely used. ▪ sequential analysis of the N-ras gene and the p53-ras gene in haematopoietic progenitors or peripheral blood cells.
Stem cell tests	If the facilities are available, it is useful to start by measuring peripheral blood CD34+ cells and analysing CFU-GM proliferation assays, which in general produce a fluctuating curve, of which the absolute numbers give a quantitative measure of the frequency of stem cell damage.
Lymphocyte and macrophage tests	The current status of the immune system can be assessed by enumeration of lymphocyte subpopulations and performing lymphocyte proliferation tests. Phagocytosis tests are also used to obtain information on the capacity of the immune system.
Bone marrow examinations	If possible, bone marrow biopsies should be performed early after exposure (24 h) and at weekly intervals (from the most exposed as well as the least exposed sites) to determine the pattern of degeneration and the onset of haematopoietic regeneration. It is helpful also to obtain bone marrow biopsy to determine, from histological sections, the overall cellularity, structural changes and the onset and pattern of regeneration. Quantitative clonogenic progenitor assays may measure the extent of the radiation damage to the haematopoietic system and the capacity of endogenous self-renewal can be calculated. Such an examination requires the preparation of bone marrow particle smears and not just smears of a drop of bone marrow blood.

less invasive therapeutic options such as supportive care, substitution (blood component therapy) and stimulation (growth factor therapy).

Autologous regeneration of haematopoiesis is most unlikely. If signs of regeneration can be seen, they are not likely to occur until after several months. Without treatment, this state certainly will lead to the patient's death and even despite maximum therapeutic measures there is a high mortality risk. In practice, this condition should be considered as essentially irreversible damage.

Response curves as a function of time

For the assessment of the extent of damage to the haematopoietic system it is quite helpful to visualise the laboratory values in the form of graphs. The haematological response to radiation exposure is summarised in Figure 11.

The scientific basis for the graphs in Figure 11, which determine the different grades in the development of the HS, can be understood using biomathematical models. It is possible to reproduce the physiological and pathophysiological processes of haematopoiesis that take place in different compartments. Thus it is possible to investigate indirectly the stem cell pool and to make reliable predictions of the extent of irradiation induced damage to these cells. The advantage of such an approach is that it can provide critical information on the patient's probable outcome within a short time after exposure and that only peripheral cell counts are required for the simulation process. The results can be used to estimate the remaining capacity of the stem cell pool required to restore the peripheral cell counts after accidental TBI. Simulation runs show that only a very small percentage of remaining cells in the stem cell

pool is required to ensure recovery of the haematopoietic system. However, below a certain threshold (as is the case in H4) autologous recovery is very unlikely owing to the fact that no pluripotent stem cells are left for repopulation processes. In this case, stem cell transplantation becomes essential for a patient's survival. This is in accordance with the fact that autologous regeneration of haematopoiesis requires intact and repaired pluripotent stem cells in a sufficient number. Results of *in vitro* and *in vivo* studies suggest that stem cells are heterogeneous with respect to their sensitivity to ionising radiation [30] and that clonal repopulation after exposure is determined, in part, by a fraction of undamaged stem cells [31] or accessory cells. Studies in animals indicate that the radiation survival curve for stem cells is curvilinear (rather than single exponential), supporting the notion that radioresistant stem cells may persist in a functional state even after exposure to high doses [32].

Biomathematical models for the different cell lineages have been developed and show corresponding results [28, 33–39]. These results support the validity of the above haematological approach from a pathophysiological viewpoint.

3.2.3 Diagnostic methods

In addition to information obtained from the patient's history and a detailed physical examination, the diagnostic methods listed in Table 8 are relevant for the verification of the diagnosis and the organ specific grading. These methods should also be taken into account as a starting point for further control and follow-up examinations. The best time to undertake an examination depends on the characteristics of the symptom and the method selected.

From the haematological viewpoint it is essential to decide on a day to day basis whether a patient belongs to one or another grading or whether he has to be "reclassified". Therefore routine laboratory diagnosis of haematological parameters should be performed on a daily basis and even more frequently in the first few days. Additionally, it seems to be very helpful to visualise the daily cell counts in graphical form using absolute values.

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3.3 Cutaneous syndrome

The skin is a complex tissue and the cutaneous syndrome (CS) refers to a number of pathologies that may become manifest after exposure of the skin to ionising radiation. Signs and symptoms of the CS appear within hours of exposure; however, the development of lesions can take days to years [1–3]. The latent period for the manifestation of a specific pathology is dependent on the characteristics of the target cells responsible for the development of that lesion and the dose of radiation delivered to those target cells. The intensity and duration of the lesions are also dose dependent. Since the depth dose distribution of a radiation source is dependent on the radiation quality, the development of a specific lesion, its intensity and its duration will also vary with

radiation quality. The CS may appear as an isolated lesion or as a number of lesions occurring simultaneously or over different time scales. In dealing with the cutaneous tissues the concept of dose is meaningless unless it is associated with a reference depth dose distribution to indicate the level of injury to specific target cells [4]. This document is prepared purely on the basis of the clinical appearance of the CS; therefore the prognosis quoted for each grading (C1–4) has to be formulated cautiously as the ultimate outcome will depend on the extent of the injury to the entire organism and the general condition of the patient. Within the first 7 days after exposure acute lesions only develop after extremely high doses (>100 Gy local acute exposure) to cutaneous tissue. This includes lesions such as erythema, oedema, blistering and desquamation. Early dusky mauve erythema might herald the development of acute necrosis. However, similar lesions may develop at a later time after much lower doses. The clinical manifestation and time course of the CS are shown in Table 9.

Table 9. Clinical appearance and time course of CS symptoms. As they may cause the development of characteristic late effects, symptoms of this phase are listed in the lower part of the table

Symptom	Time of onset
Erythema	hours–30 days–10 weeks
Loss of sensation/itching	hours–30 days
Blistering	5 days–3 weeks
Swelling and oedema	5 days–8 weeks
Desquamation	5 days–8 weeks
Ulcer/necrosis	5 days–>12 weeks
Hair loss	2–8 weeks
Onycholysis	2–8 weeks
Hyperpigmentation or depigmentation	>12 weeks
Atrophy	>12 weeks
Onychodystrophy	>12 weeks
Keratosis	>12 weeks
Fibrosis	>12 weeks
Telangiectasia	>12 weeks

3.3.1 Pathophysiology

Although this manual is mainly concerned with the ARS, the pathophysiology of some later occurring lesions will also be explained. The appearance of a cutaneous lesion can be indicative of the target tissue involved in the exposure. Erythema and moist desquamation are arguably the most documented phase of radiation induced damage to the skin. The target cell population, damage to which causes denudation of the epidermis, is the basal cells of the epidermis, including those cells situated within the canal of hair follicles. The reddening or erythema of the skin represents dilatation of the superficial blood vessels and is indicative of an inflammatory reaction [1].

Following irradiation with single doses of X-rays, for exposures just above or just below the threshold for the development of moist desquamation (15–25 Gy), cells are lost from the basal layer of the epidermis at a constant rate. In two strains of pig, the English Large White pig and the Yorkshire pig, this has been shown to be at ~2.6%/d and ~4%/d, respectively [5]. This is consistent with the appearance of moist desquamation after either 32–38 days or 17–21 days in the two strains of pig, respectively. The time scale of response in humans is over a time scale comparable with the Large White pig.

Repopulation of the epidermis following irradiation with doses at the approximate threshold for moist desquamation is predominantly by the proliferation of surviving clonogenic basal cells from within the irradiated area. Cell colonies can easily be recognised in histological sections at 21 days after single doses of 15 Gy and 20 Gy in the Large White pig, earlier in the Yorkshire pig. This is prior to the peak clinical appearance of the skin reaction [5]. The labelling index of cells in these colonies after the injection of ^{3}H-thymidine was between 30% and 40%. A high proportion of regenerating colonies has been found to be associated with the canal of hair follicles [6]. The timing of the occurrence of moist desquamation is thus defined by the total turnover time of the epidermal structure exposed and is not influenced by the magnitude of the radiation dose.

Earlier denudation of the epithelium, *i.e.* shorter than the normal turnover time, occurs when basal cells and more specifically post-mitotic suprabasal cells are killed directly by irradiation, as can occur after very high dose exposures. High dose, localised irradiation of the epidermis, without comparable effects on deeper dermal layers, occurs as a result of exposure to low energy β-emitters. In this situation the primary energy absorption will be in the viable layers of the epidermis above the basal layer. Exposure of the skin to β-emitting isotopes such as ^{147}Pm or ^{60}Co results in highly non-uniform irradiation with respect to the variation in doses with depth in tissue. There may be an ~80% reduction in dose across the epidermis. Cells in the post-mitotic, but viable, upper layer of the epidermis will receive a significantly higher dose than stem cells in the basal layer and within the shaft of hair follicles [1]. Histological investigations in pig skin after ^{147}Pm exposure have shown that the very early but very transient epithelial response is related to the interphase death of suprabasal cells; this

initiates an inflammatory reaction with the subsequent disruption of all cell layers in the epidermis [7, 8].

A late phase of discoloration in moderately exposed areas is characterised by skin with a dusky or mauve appearance after 8–16 weeks [9, 10]. The ischaemic appearance of the skin was confirmed by measurements of reduced blood flow as well as by the presence of severe oedema [11–13]. The occlusion of blood vessels at the base of the dermis, the deep dermal plexus at the junction with the fatty layer, by the proliferation of endothelial cells or as a result of thrombus formation, is thought to be a major factor in the pathogenesis of this late phase of damage [14]. This late phase of erythema may fade or the skin may develop an ischaemic necrosis of the dermis and subcutaneous fatty tissue.

An early dusky mauve appearance may develop after extremely high doses to the skin (>100 Gy due to the high β-ray component associated with some accidents). This may be indicative of development of an acute necrotic reaction, *i.e.* death of dermal cells at interphase. If denudation of the epidermis persists, secondary damage to the dermis will occur as a result of fluid loss, infection and trauma even in the absence of severe radiation induced damage to the dermis. Such events are not unique to radiation induced epithelial denudation. Secondary ulceration of the dermis can only heal by site contraction and scar tissue formation. Since normal dermal structures cannot be reconstructed, radiation induced damage to the dermis, whether it is a consequence of high dose acute necrosis or delayed ischaemic necrosis, can only heal to leave a fibrotic scar [15, 16]. The rate of healing will depend on the surface area of the original skin site involved and the depth of the necrosis. The depth of necrosis depends to a large extent on the radiation dose and radiation quality. Additional factors, such as infection, may exacerbate the extent of the lesion [17]. This kind of dermal and subcutaneous tissue injury is non-specific and resembles the lesions induced by heat, chemicals or surgical excision, which may equally lead to a fibrotic scar.

Table 10. Overall prognostic aspects of the acute CS on the basis of the clinical grading

Grading	Extent of impairment	Prognosis
C1	Mild damage	Recovery certain
C2	Moderate damage	Recovery without deficit likely
C3	Severe damage	Recovery with deficit likely
C4	Critical/fatal damage	Recovery impossible or with serious deficit

3.3.2 Clinical characterisation

The clinical grading summarises the extent of the damage to the individual and the corresponding prognosis. The CS grading is interpreted in Table 10.

Since most of the selected symptoms may occur or recur at different time points in the development of the CS, different phases can be identified, as described in Figure 12.

Grading C1

C1 may start with a brief transient erythema and itching during the prodromal period (degree 1 symptoms). This usually subsides within 36 h of exposure. A second wave of erythema, the true erythema, appears around 5 days after exposure and may last a few weeks. The latent period and duration of the true erythema are variable and the severity will not exceed degree 1. At a later time (20–30 days) skin may appear very dry owing to the loss of sweat and sebaceous glands and may be associated with a dry, scaly desquamation (degree 1). Dry desquamation may also be a consequence of an inflammatory response, leading to transient epidermal hypertrophy in the late

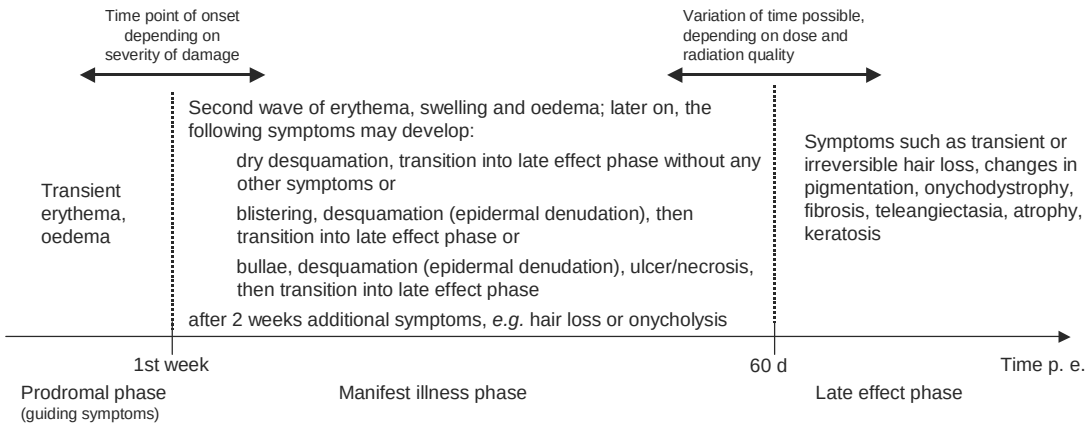

Figure 12. Different phases in the development of the CS as a function of time (p.e. = post exposure).

effect phase of the CS. Recovery is certain and the lesions may disappear completely within a few weeks and these early lesions will not cause clinical late effects.

Outpatient treatment is usually sufficient with refreshing and anti-inflammatory aqueous lotion/powder, topical anti-inflammatory and anti-proliferative non-atrophic glucocorticoids (suppression of cytokine expression) as well as systemic antihistamines. Fat based ointments should not be used as they may act as an occlusive barrier.

If erythema occurs with a non-uniform distribution, ultrasound should be performed (daily in the acute phase and weekly in the manifest illness phase) to determine changes in the thickness and density of the skin. Furthermore, thermography can be used to detect the development of hyperthermic or hypothermic skin areas in addition to the clinical identification of erythema. The findings can be used as a reference for the individual's regular follow-up. A burning itching sensation can occur in this stage, which generally does not cause any additional problems but may require specific treatment such as the administration of antihistamines with non-sedative properties.

Grading C2

C2 can be described as moderate damage to cutaneous tissue. Erythema (in the prodromal phase as well as in the manifest illness phase) can be seen in isolated patches of <10 cm^2 that do not add up to more than 10% of the body surface (degree 2). This may be associated with mild swelling (degree 1–2) and blistering (degree 2) 5–10 days after exposure. Rupture of these blisters causes desquamation (degree 2). Blisters, which occur later after exposure (around day 30), can result in moist desquamation (degree 2). However, moist desquamation can also appear without prior blistering as a consequence of depletion of the epidermal stem cells. Transient hair loss or thinning of the hair diameter may develop at around 14 days after exposure. Recovery without deficit is possible.

Outpatient treatment with topical anti-inflammatory and antiproliferative non-atrophic glucocorticoids, linoleic acid creams and systemic antihistamine, puncture of blisters and non-adherent dressings is usually required. Blisters should not be treated with drying agents such as powders. Prevention of infection (preferentially according to the antibiogram) is important to prevent progression to grading C3.

In C2, 20 MHz sonography should be used on a regular basis (daily in the acute phase, weekly in the manifest illness phase) for determining changes in the skin thickness and density. Furthermore, thermography (once weekly) can be used for the early detection of hyperthermic or hypothermic skin areas. These findings can be used as a reference for regular patient follow-up.

Grading C3

The severity of symptoms is more pronounced than in C2, resulting from damage to cutaneous tissue in isolated or confluent patches, which may add up to 10–40% of the body surface (erythema degree 3). In the manifest illness phase this is associated with severe swelling (degree 2–3) caused by increased vascular permeability and loss of fluids to the extravascular tissues. Blisters may develop about 5 days after exposure (degree 2–3). Rupture of blisters may reveal dermal loss, the depth of which may vary (desquamation degree 2–3, or development of ulcer/necrosis degree 1–2). With delayed healing this may progress even deeper. If moist desquamation heals slowly this may progress to secondary ulceration due to further loss of dermal tissue (ulcer/necrosis degree 3). Given appropriate clinical support, recovery is possible but nonetheless the patient will experience deficits in the late effect phase such as alopecia, tissue contraction, fibrosis, pigment changes and increased vulnerability to trauma. Healed lesions are often susceptible to reopening.

Inpatient treatment is required with aspiration of fluids from blisters, debridement of necrotic tissues, topical application of bacteriostatic agents, anti-inflammatory agents and essential fatty acids (EFAs) together with the use of non-adherent dressings. Systemic anti-inflammatory and antiproliferative glucocorticoids should be used to reduce oedema. An effective analgesia is relevant in C3 (and C4) according to established standards (see Chapter 5).

If necessary, systemic antibacterial and virostatic medication should be applied. Deep ulcerative lesions should be excised and the wound bed should be covered with a good quality, full thickness skin graft.

Sonography with 7.5 MHz or higher resolution and thermography are the methods of choice. In addition to 7.5 MHz sonography, Doppler ultrasound can be used to identify damage to larger vessels (arteries and veins). In cases where ulcers occur, sonography should be used to determine the depth of the lesion. MRI can be quite useful in detecting the damage in deeper tissue, *e.g.* involvement of the musculature.

Grading C4

In C4 there is critical damage to cutaneous and subcutaneous tissues in isolated or confluent patches that may add up to more than 40% of the body surface, with the involvement of underlying tissues (erythema degree 4 in the prodromal phase). In the manifest illness phase this results from a combination of severe damage to epidermal, dermal and subcutaneous tissue, underlying muscles and perhaps bony structures. Usually there is no symptom-free interval. This category is associated with severe swelling (degree 3–4) caused

by an increase in vascular permeability and loss of fluids to the extravascular space. Bullae develop within a few days after exposure (degree 4). Rupture of blisters (desquamation degree 3) will result in severe electrolyte loss. Acute necrosis (degree 3–4) as well as onycholysis will develop, among other symptoms, as a result of interphase death 10–14 days post irradiation. This is different to the degree 1–4 ischaemic necrosis that usually develops in the late effect phase of the CS. These severe skin lesions contribute significantly to multiple organ failure.

Recovery is almost impossible but highly dependent on the pattern and severity of damage. Specialised medical treatment is required. Even in the case of survival, severe deficits such as alopecia, fibrosis, pigment changes, increased vulnerability to trauma, thermal and pressure changes, subcutaneous sclerosis and keratosis will be inevitable. The damage may be so severe that amputation of extremities needs to be considered.

Specific attention must at this point be given to additional implications to the CS from other organ systems. Granulocytopenia may increase the risk of concomitant infections, but owing to an impaired immune function the clinical symptoms may be overlooked. Thrombocytopenia may result in haemorrhagic bullae and larger haemorrhages of the body surface. In deciding whether or not to undertake surgery, these effects should be taken into account.

Inpatient treatment (usually intensive care) will include aspiration of fluids from the bullae, debridement of necrotic tissues, topical application of bacteriostatic agents, anti-inflammatory agents using non-adherent dressings, systemic antihistamines, anti-inflammatory glucocorticoids, analgesics to relieve

Table 11. CS: diagnostic methods

Method	Relevance for the CS
Colour photography	Relevant for the documentation of changes in CS symptoms as a function of time. Should be performed in addition to a detailed description of the observed sign. Calibration is mandatory in each event when photographs are taken (*e.g.* white piece of paper).
Ultrasound (7.5–20 MHz B-scan sonography)	Frequently used, reproducible and non-invasive method for the evaluation of skin thickness, skin density, ulcer depth and the involvement of subcutaneous tissues [18–20]. 7.5 MHz sonography is a procedure for evaluation of dermis, subcutaneous fat tissue, muscle fascia and musculature. Furthermore, the depth of radiation fibrosis and ulcers can be determined by 7.5 MHz sonography [18–21]. The 20 MHz scanner with an axial resolution of about 80 μm and a lateral resolution of 200 μm is suitable for investigating epidermis, dermis and subcutaneous fat tissue up to a depth of about 10 mm. The depth of cutaneous radiation ulcers can be determined by sonography before and during therapy.
Thermography	Useful method for the quantification of the skin temperature and heat loss of the body [22]. The skin surface temperature and the heat emitted from the body surface are connected with the cutaneous vascular system and are indirect parameters for the vascularisation of the skin. Techniques such as infrared thermography, microwave thermography and liquid crystal contact thermography are available. There is a significantly lower local skin surface temperature in patients with necrosis. A significant higher skin temperature was observed in patients with inflammation [21, 22].
Capillary microscopy	Non-invasive method for the qualitative and quantitative evaluation of the capillaries of the stratum papillare of the dermis [23]. The capillaries of the nail fold of fingers or feet are dilated in patients in the manifest stage of CS. The capillaries are smaller and rare in patients in the chronic stage of CS [23]. Additionally, subungual splinter haemorrhages may be visible in distal parts of the nail bed in these stages [9, 24].
Profilometry	Most common method to quantify the skin topography in two and three dimensions [21]. Analysis of the vertical and horizontal distribution of the furrows gives information on the skin surface.
MRI	Non-invasive approach for the examination of the signal intensity of dermis, subcutaneous fat tissue, muscle and bone [17, 21]. Morphological changes can be discovered. The increase in the magnetic resonance signal intensity is the result of fluid in the tissue, which may be present through inflammation, oedema or necrosis. A reduced tissue fluid content leads to a decrease in signal intensity [17, 21]. With nuclear magnetic resonance imaging the extent of skin ulcers in radiation exposed patients can be evaluated. A disadvantage of this method, as currently used, is its lack of ability to discriminate between necrosis and inflammation.
Histology	Invasive method for the determination of skin changes related to CS. The histology of the manifestation stage/subacute stage of CS demonstrates dilated blood vessels, oedema and multiple infiltrations mainly consisting of neutrophils and eosinophils. The histology of the chronic stage/late stage of CS is characterised by epidermal atrophy or hypertrophy, fibrosis of the dermis, rare lymphohistiocytic infiltrations, dilated blood and lymphatic vessels in the upper dermis, hypopigmentation and hyperpigmentation and a loss of hair follicles [17, 21, 24].

pain and therapy to reduce oedema. Necrectomy and full thickness skin grafts may be necessary for deep necrosis, and amputation in the case of distal extremity injuries.

In addition to sonography with 7.5 MHz or higher resolution and thermography, MRI is essential for determining the extent of necrotic tissue as soon as possible, as this is important to know prior to initiation of surgery. It will influence the indication for either necrectomy or amputation. The MRI findings might lead to the decision not to amputate but to apply corticosteroids. The effects of this therapeutic approach should be documented.

However, since there is little chance of recovery, the strategy should be directed towards treatments that are minimally distressing for the patient, with particular emphasis on pain management.

3.3.3 Diagnostic methods

In addition to information obtained by observation, interrogation and inspection, Table 11 lists diagnostic methods that may be relevant for the verification of the organ specific grading. These methods should also be considered as a starting point for further control and follow-up examinations. The best time for an examination depends on the characteristics of the symptoms and the method selected.

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3.4 Gastrointestinal syndrome

The gastrointestinal (GI) system is a complex one that performs many integrated functions such as absorption of fluid and electrolytes, breakdown and absorption of nutrients and excretion of normal and toxic metabolites. The epithelial cell lining, which is present throughout the whole gastrointestinal tract (GIT), undergoes constant renewal and so requires a rapid cell turnover and is thus dependent on the functionality of a pluripotent stem cell population localised in the crypts of Lieberkuhn. It is this intrinsic property that is considered a key factor in the radiosensitivity of this tissue [1–3]. Recently the relevance of these findings to the human situation has been extensively reviewed and discussed [4, 5].

Symptoms related to the GIT observed following exposure to ionising radiation may be divided into the prodromal and the manifest illness phases [6]. The prodromal signs, nausea, vomiting, anorexia and diarrhoea, may occur within hours after exposure, the latency and severity of which depend on the dose received. Both nausea and vomiting may occur after low dose exposure and are not life threatening [6, 7]. It is not clear whether nausea and vomiting stem from effects on the periphery and subsequent stimulation of higher centres or whether these signs are entirely a response of the CNS (see section 3.1). However, if these occur during the first few hours after exposure the role of the central/peripheral nervous system is probably predominant. This is also true for the early onset of diarrhoea. Here diarrhoea can be considered as a prodromal sign, indicating very severe damage and is usually associated with fatal doses [8].

Clinical symptoms of the manifest illness phase of gastrointestinal syndrome (GIS) are mainly abdominal cramps and diarrhoea (Table 12) but can also include nausea and vomiting. At this stage, at least 1–2 weeks after total body exposure, the occurrence of profuse and/or bloody diarrhoea is linked to the denudation of the GI mucosa as well as to thrombocytopenia due to the impairment of the haematopoietic system (see section 3.2). This results in increased loss of fluid and electrolytes and possible entry and action of enteric (pathogenic and non-pathogenic) bacteria. In this case the GIS is manifest and associated with a major loss of the stem cell population in the crypts and subsequent lack of ability to repopulate and to maintain the epithelial barrier. This is concomitant with significant faecal fluid and electrolyte losses and appearance of cells/sheets of GI mucosa in the faeces. However, it must be stated that at doses where the GIS is manifest, the concurrent haematological deficits (granulocytopenia, thrombocytopenia) also aggravate the situation owing to a reduced ability to counteract infections and bleeding. The intestine *per se* also participates in defensive responses since it is constantly exposed to a broad spectrum of antigens. However, following irradiation, the immune capacity of the intestine represented in part by T-cell populations in Peyer's patches, and the responses to antigenic challenge [9, 10] are significantly reduced, compromising the intestinal function further.

This section concentrates on GI manifestations, in particular diarrhoea, which may develop within hours (prodromal phase) and for up to 3 weeks after exposure (manifest illness phase). Early evaluation is important and the following classifications assume that the patient receives medical care within the first 24 h after exposure [8, 11–14].

3.4.1 Pathophysiology

The GIT consists of several different parts, comprising the oesophagus, stomach, small intestine, colon and rectum. All parts of the GIT are lined by an epithelial cell layer consisting of many different cell types each with specialised functions. This epithelial cell lining is normally replaced by desquamation and, like the haematopoietic system, is dependent upon pluripotent stem cells. It is this characteristic that underlies the sensitivity of the GIT to ionising radiation [1, 3]. In the small intestine the stem cells occupy a particular position in the crypts of Lieberkuhn. In the large intestine the stem cells seem to be dispersed throughout the lower third of the crypts [3]. Stem cells have been shown to be most radiation responsive but cells of the surrounding environment (myofibroblasts, intra-epithelial lymphocytes, nerves, etc.) are also of particular importance, especially with regard to late effects such as fibrosis, obstruction and impaired motility following exposure [15, 16].

The small intestine (duodenum, jejunum, ileum) is particularly sensitive to ionising radiation because cell renewal is faster than that in the stomach and in the colon/rectum. GIS is defined as occurring when most of the small intestine is implicated [1]. Following exposure of mice, a significant increase in the number of apoptotic cells in the crypts has been observed within hours, even after low doses (0.01 Gy) [3]. With increasing dose of radiation the stem cells cannot produce enough cells to repopulate the villi, which results in blunting and diminution in villus height. This leads to impaired functional capacity of the villi and thus decreased nutrient absorption. Furthermore, the intestinal barrier may be compromised owing to insufficient production of intestinal cells together with functional changes in epithelial cells,

Table 12. Clinical symptoms associated with the GIS

Symptom	Time of onset
Diarrhoea (prodromal phase)	hours–days
Diarrhoea (manifest illness phase)	days–weeks
Abdominal cramps	hours–weeks

allowing entry and action of enteric bacteria and/or other pathogens. Thus an irradiated person is more susceptible to infection by endogenous and exogenous micro-organisms of which the most fatal and most commonly occurring are those implicating gram-negative species such as *Pseudomonas aeruginosa*. It is clear that intestinal cell proliferation and differentiation as well as granulocyte production are important determinant factors for the establishment of the manifest illness phase of the GIS characterised by persistent, intractable and bloody diarrhoea.

In the stomach, cell renewal appears to be suppressed and the healing of minor lesions (gastric biopsies) is slowed after a single TBI dose of 7 Gy [17]. However, even after low doses (1.5 Gy) several immediate symptoms have been observed, which include decreased gastric motility, emptying and fluid output [18]. Furthermore, there is evidence of hyperaemia and dilatation of blood vessels. It has been noted that nausea after gastric irradiation is more severe than that following exposure of other segments of GIT. In the acute phase, gastritis may be seen and dyspepsia experienced [11]. In addition, it has been shown that mucus secretion (neutral and acidic glycoprotein) is increased immediately after exposure but then is significantly reduced [19].

The colon and rectum are also radiation sensitive and diarrhoea may result from small intestinal dysfunction, colorectal dysfunction or both. The colon has a significant adaptive capacity to absorb a massive ileocaecal flow (around 6 l per day) [20] even in cases of small intestinal disease. However, if the volume arriving in the colon is too great then this reserve capacity may be surpassed, leading to diarrhoea. In addition to mucosal changes, altered patterns of GIT motility [16] after irradiation may influence nutrient, fluid and electrolyte absorption and are also responsible for the abdominal cramping and associated pain. These are mainly acute effects occurring before substantial loss of the mucosa and are presumably owing to release of several mediators (such as acetylcholine, serotonin, motilin, histamine) that regulate gastrointestinal motility. It is possible that neural mechanisms, either peripheral or central, are implicated. Indeed, elevated circulating and tissue levels of some neurotransmitters and gastrointestinal regulatory peptides have been observed following irradiation [21, 22].

Other agents such as inflammatory mediators [23] are also likely to be implicated following exposure, resulting from a cascade of events, initiated most probably by free radical production and maintained by release of other molecules such as metabolites of arachidonic acid (PGE_2, LTB_4), pro-inflammatory cytokines (IL-1β, TNFα) or chemokines (IL-8, RANTES). Bile acids have also been proposed as being implicated in radiation induced diarrhoea. Bile acid malabsorption and changes in bile acid profiles, either short or long term, have been demonstrated both in experimental animals [24] and in patients who have undergone radiotherapy [25]. A consequence of radiation exposure may be increased concentrations of aggressive agents such as bile acids reaching an already compromised intestinal epithelium particularly in the colon. Other luminal factors apart from bile acids include endogenous non-pathogenic bacteria, which in a normal healthy person do not present a clinical problem. However, following total body exposure, where severe agranulocytosis is manifest (or immunological defence mechanisms are impaired) and intestinal barrier function is compromised, this may serve as a port of entry for bacteria and associated toxins. It has been shown that GI decontamination is beneficial in reducing anaerobic bacteria in cases of TBI [26]. Thus, sepsis and endotoxaemia may be associated with the GIS. In irradiated mice the nature of bacteria that translocate systemically was shown to correlate not only with the nature of intestinal microflora but also with the type of irradiation [27].

Table 13. Overall prognostic aspects of the GIS on the basis of the clinical grading

Grading	Extent of impairment	Prognosis
G1	Mild	Recovery certain
G2	Mild–moderate damage	Recovery with possible deficit
G3	Severe damage	Recovery may be possible
G4	Serious/fatal damage	Recovery most unlikely

3.4.2 Clinical characterisation

The clinical grading summarises the extent of the damage to the individual and the corresponding prognosis. The interpretation of the grading of GIS is outlined in Table 13.

Since the selected symptoms may occur or recur at different times in the development of the GIS, different phases can be subdivided, as described in Figure 13.

The development of clinical signs and symptoms after exposure to ionising radiation is outlined in the following in more detail for each of the different grades of the gastrointestinal manifestation of the ARS, *i.e.* G1 to G4. Also included are aspects of clinical patient management such as diagnostic and therapeutic options.

In principle, treatment of the GIS is directed at replacing the intestinal barrier as well as concomitant therapy targeted at micro-organisms. However, knowledge of the factors that regulate GI epithelial and support tissue growth is far less advanced than, for example, in the haematopoietic system. In general,

for the acute and subacute phases treatment is directed against neurohormonal mediators, and loperamide, which has both antimotility and antisecretory activity, seems to be the drug of choice. Other treatments include use of elemental diets with particular reference to glutamine, cholestyramine to chelate bile acids, probiotics and sucralfate. These latter approaches are used to protect the mucosa and prevent entry of either endogenous and/or exogenous agents.

Several growth factors that appear to promote the restoration of the epithelium and/or the surrounding tissue are currently being investigated. These include IL-11, keratinocyte growth factor (KGF), growth hormone (GH), insulin growth factor-1 (IGF-1) and intestinal trefoil factor (ITF). IL-11 has anti-inflammatory actions (reduction of TNFα, IFNγ, suppression of NF-κB) and has been shown, like KGF, to be useful in reducing graft *versus* host disease (GvHD) following irradiation with a particularly beneficial effect on GI mucosa. However, employment of such growth factors for GIS treatment may be promising but much work remains to be carried out to show clear therapeutic benefit in cases of accidental exposure.

Grading G1

In this category only very mild GI manifestations are observed, limited to one or two episodes of altered stool consistency and frequency (both degree 1) with associated abdominal pain. Loss of intestinal mucosa is not expected. In such cases the patient may express only prodromal (within 24 h), self-limiting symptoms, which may be related to stress.

Outpatient ambulatory treatment, if necessary, may be short-term loperamide. Clinical observation is sufficient for diagnosis of these mild symptoms.

Grading G2

Diarrhoea with changes in frequency (degree 1), consistency (degree 1–2), mucosal loss (degree 1, if at all) and bleeding (degree 1, if at all) together with abdominal cramps (degree 1) can be seen. These symptoms may be due to release of mediators that stimulate increased intestinal motility and so result in decreased GI transit time. They are self-limiting and disappear with no long-term effects, and may be linked to stress factors. In this case the patient may express uniquely the prodromal syndrome with no further manifestations after 24 h. Damage to the intestinal epithelium is relatively minor with a low percentage of stem cell death. Although recovery is certain, it is unknown whether this may lead to later effects due to impaired repair efficacy as well as damage to supportive tissue.

Usually outpatient ambulatory treatment is sufficient with an agent such as loperamide, which has both antimotility and antisecretory actions. Furthermore, use of analgesics or anti-inflammatory agents may be indicated to treat pain. Clinical observation is usually sufficient for diagnosis of these mild–moderate symptoms.

Grading G3

Symptoms are more pronounced compared with G1 or G2 and will most likely occur in several episodes over several days and weeks. Diarrhoea with changes in frequency (degree 1–3), consistency (degree 3), loss of mucosa (degree 2–3) and bleeding (degree 2–3) together with abdominal cramps (degree 2–3) can be seen. However, it is probable that recovery will be incomplete with recurring GI problems such as episodes of diarrhoea, stricture formation and thickening of the gut wall. Diarrhoea that occurs after 20–30 days may be caused by infectious agents resulting from a reduced immune capacity linked primarily to the haematopoietic syndrome as well as from the reduced functional immune capacity of the GIT.

Patients should be hospitalised with fluid and electrolyte replacement therapy in addition to antibacterial/antifungal agents, anti-inflammatory drugs and analgesics. Recovery may or may not be possible owing to the long-term effects of manifestation of

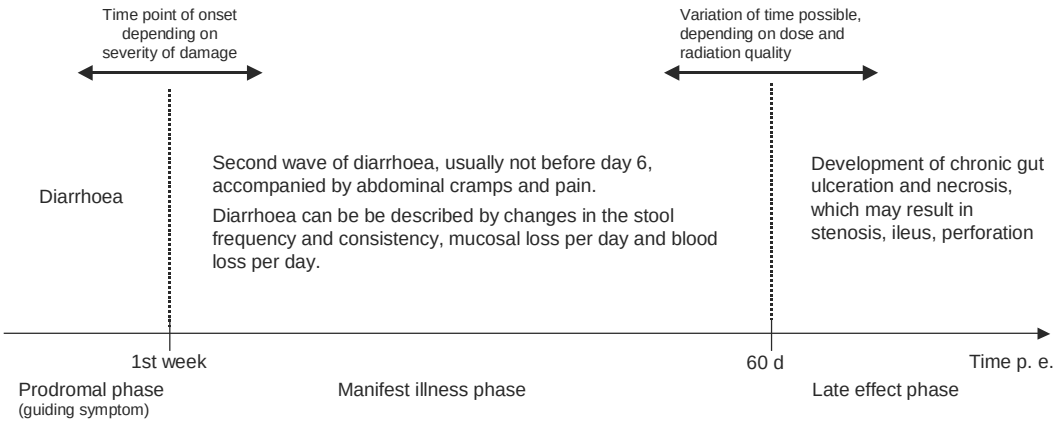

Figure 13. Different phases in the development of the GIS as a function of time (p.e. = post exposure).

mixed pathologies (gastrointestinal, haematopoietic, pulmonary). However, GI function is likely to be significantly impaired for patients who survive. Use of growth factors will greatly ameliorate the prognosis of the patient. Unfortunately to date no such treatments are available, although there are several possible candidates (IL-11, KGF, trefoil peptides).

For diagnosis, regular clinical observation is essential. Furthermore, GI functional tests, laboratory examinations and ultrasound might be helpful in assessing the patient's status. Since there will probably be late effects, ultrasound or MRI might be useful in detecting gut wall thickening and fistula formation.

Grading G4

In these cases onset of diarrhoea is rapid and may be explosive (degree 3–4 in frequency). This is presumably owing to altered regulatory components of GI motility and secretory processes since this occurs before any substantial loss of the intestinal mucosa, but it is still considered to be a primary reaction. In the manifest illness phase, which is related to a substantial loss of mucosa, episodes of diarrhoea (frequency degree 3–4, consistency degree 4, mucosal loss degree 3–4, bleeding degree 3–4) from days 4–8 onwards are accompanied by degree 3–4 abdominal cramps. This results in severe fluid and electrolyte losses as a consequence of balance shift from plasma to the intestinal lumen owing to the severely compromised intestinal mucosa. These changes in whole-body compartmentalisation of fluid and electrolytes may lead to hypovolaemic shock and death. It should be recalled that vomiting also leads to such losses and therefore aggravates the patient's status. The stem cell compartment is lost and cell production is severely limited and thus unable to replace the epithelium adequately. This influences the fluid loss and is also responsible for the entry of enteric bacteria or other pathogens, which might then lead to toxaemia and septicaemia. Recovery from these clinical signs and symptoms is most unlikely.

To date only symptomatic treatment exists for these severe manifestations, including fluid and electrolyte replacement, appropriate systemic antibacterial/antifungal therapy (non-absorbable agents according to current standard guidelines) and analgesics. Inpatients should be maintained in the most sterile environment possible. Recovery is most unlikely.

Regular clinical observation is essential in the diagnosis of G4. Furthermore, functional tests of the GIT, laboratory examinations, endoscopy and ultrasound/MRI might be helpful in assessing the patient's status. However, the use of endoscopy with or without biopsy in the very acute phase will rarely be necessary and could be dangerous for the patient. Radiographic examination may be useful for identification of intestinal obstruction or oedema.

3.4.3 Diagnostic methods

In addition to information obtained from the patient's history and a detailed physical examination, Table 14 lists diagnostic methods that may be relevant for the verification of the diagnosis and the organ specific grading. These methods should also be considered as a starting point for further control and follow-up examinations at appropriate times. The best time point for an examination depends on the characteristics of the symptom and the method selected.

Table 14. GIS: diagnostic methods

Method	Relevance for the GIS
Ultrasound	Suitable to assess the wall thickness and to detect fistula formation. Ultrasound is of minimal value in the acute phase of GIS owing to prominent symptoms, but is more suitable for detection of late effects. The application of this method may be compromised if the abdominal skin is badly damaged.
Abdominal radiography	Single radiographs of the abdomen may be useful to detect obstruction, bowel thickness or oedema.
Functional tests of the gastrointestinal tract	Assessment of gastrointestinal dysfunction can be achieved with standard tests such as intestinal permeability (sucrose/lactulose ratio for the proximal intestine; lactulose/mannitol ratio for the distal intestine), intestinal transit time and bile acid and/or vitamin B12 absorption (for terminal ileal function). Measurement of plasma total homocysteine levels may also be a useful adjunct to assessment of true vitamin B12 deficiency. However, all of these tests may pose a problem in terms of equipment, qualified personnel and rapidity of response. A more simple approach to give an indication of bile acid malabsorption is the measurement of total faecal bile acids using a relatively easy and current enzymatic method.
Laboratory	Routine screening is important to verify early fluid and electrolyte loss. Analysis of stool specimens for microbiological composition and for electrolytes, (occult) blood and pus are indicated.
MRI	Assessment of wall thickness and fistula formation especially in the late effect phase.
Proctoscopy/endoscopy	Assessment of lumen and mucosal surface. However, endoscopy is rarely indicated in severely injured patients after radiation exposure, since the risk of perforation in pre-injured structures is high.

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CHAPTER 4: INTEGRATION OF THE ORGAN SPECIFIC ASSESSMENTS

This chapter provides an overview of a pathophysiologically based interpretation of the biological responses of the individual to radiation exposure. The background is given for the complex reactions and interactions between organ systems that determine a patient's health status. Subsequently, the RC concept and its role in the medical management of radiation accident victims is discussed.

4.1 Interaction of biological responses to irradiation

This section provides the background for the integration of the biological responses as a function of time, whereas a "system-by-system" approach was used in Chapter 3. It is recognised that the most critical organ systems are the neurovascular system (N), the haematopoietic system (H), the cutaneous system (C) and the gastrointestinal system (G). Each of these systems responds to ionising radiation in an organ specific way, which is determined largely by the amount of cell death and/or impairment of cell function.

Some organ systems follow a hierarchical structure of self-renewal wherein development of mature functional cells from stem cells takes place physiologically to maintain tissue homeostasis. In steady state situations, cell loss is compensated by appropriate cell production and differentiation in the stem and progenitor cell as well as the proliferation cell compartments. Typical systems with a hierarchical organisation are the haematopoietic system, the epithelium of the skin and the GIT. A disturbance in homeostasis resulting from exposure to TBI or large volume PBI often leads to a reduction in the quality and quantity of cells in the stem cell compartment. Consequently, this results in a transient or irreversible failure of the system. The latency period for this response (within certain limits of dose) is organ specific and not dose dependent. However, dose correlates with the number of residual stem cells capable of repairing damage in the compartment. The principles governing an accelerated stem cell response, required for balancing a shortage in supply of end cells, are poorly defined.

In parenchymal tissues, which consist of functional as well as supportive cells (such as liver, kidney, lung and CNS), the variation in latency between exposure and tissue injury prior to the clinical manifestation of an impairment is dose dependent. The capacity of these cells to divide and differentiate decreases with increasing dose, but even in the absence of cell division the functional activity of the tissue is initially preserved. However, as cells attempt to proliferate, an accumulated number of cells are lost owing to mitotic death. This cell loss cannot be compensated for by an increased stem cell commitment. Replacement with functional cells is impaired, resulting in loss of organ function. Mechanisms for repopulation usually cannot be found in these tissues and a dose dependent shortening of the latency period is evident.

Organ systems often present a combination of both tissue organisation types mentioned above. This results in mixed damage patterns after radiation exposure. Therefore, in a clinical situation the physician is faced not with isolated organ damage but with a sick person. The health of such a person is determined by the interaction of biological responses to ionising radiation in each of the organ systems. Selected examples are described below.

From a pathophysiological viewpoint the gastrointestinal manifestation of ARS is the result of combined effects of denudation of the intestinal epithelial lining and haematopoietic failure. Owing to destruction of the cellular barrier, intestinal denudation leads to a severe disturbance of fluid and nutritional balance. Furthermore, bacteria and bacterial toxins of the intestinal flora may have direct access to the underlying tissues. At the same time the clinical condition is aggravated by impaired haematopoiesis. Granulocytopenia and thrombocytopenia lead to impaired immune defence mechanisms and bleeding, respectively. When the fluid balance is maintained and the consequences of infection and bleeding are controlled, spontaneous regeneration of intestinal epithelium may occur up to TBI doses that would otherwise be lethal (in mammals up to 20–30 Gy) [1]. Thus, the crucial problem for the gastrointestinal manifestation of ARS is not only the recovery of the gastrointestinal epithelium but also haematopoietic reconstitution either through enhancement of stem cell proliferation and differentiation by appropriate endogenous and/or exogenous stimuli or by stem cell transplantation.

Another example of organ interdependence is the combination of thermal skin burns with the effects of whole body radiation exposure. It is well known from experimental studies that mortality from radiation exposure increases significantly if there are thermal burns in addition to radiation induced effects [2]. In the Chernobyl accident, for example, the morbidity and mortality of several of the victims treated in Moscow was heavily influenced by damage to the skin as well as by damage to the haematopoietic system [3].

In this context, it is of interest to recall the information available on the relationship between radiation dose and shortening of life span after whole body irradiation of different mammalian species. This basic knowledge has been reviewed extensively [4–8]. An example of the results of these studies is presented in Figure 14 [1]. The general relationship between dose and effect is schematically depicted using a log–log scale. Animals studied have included conventional and germ-free mice, rats, guinea pigs, hamsters, monkeys, pigs, goats and burros. In Figure 14, the large central curve (A1–3) represents the pattern of response of most species. The short line above the plateau (B) represents the survival time of species such as monkeys and germ-free mice. Line B is also likely to be valid for man. The broken lines (C) represent approximate extremes of variation in survival times in different species associated with effects of radiation on the CNS.

The three components of this curve consist of an initial dose dependent portion with survival times decreasing from weeks to days after dose in the range up to 1000 R (A1). This is followed by a plateau indicating a constant mean survival time of about 3.5 days, extending over the dose range of approximately 1000–10000 R (A2). In some species discussed below, this plateau occurs at around 6 days (B). The third component of the curve is again dose dependent, with survival times changing from days to hours as the dose increases above 10000 R (A3 and C).

Individual survival times are remarkably similar in the central portion of the plateau. At either end of the plateau, in the dose ranges where the survival times are more dose dependent, the variation in survival times increases.

The reproducibility of the symptomatology and the mean survival times at a given dose have led to the association of each of the three components (A1–3) of this curve with a particular syndrome. Thus, the first dose dependent portion of the curve (A1) has been identified with bone marrow syndrome. The plateau (A2) has been associated with gastrointestinal syndrome, and the second dose dependent segment (A3) with CNS syndrome.

Owing to the apparent correlation of the mean survival times with the various syndromes, it has become customary to equate a particular syndrome with a mean survival time. This practice is convenient, but it must be stressed that it is artificial because the mean survival time represents only one of the several signs and symptoms that compose the various syndromes. However, the use of the mean survival time in this

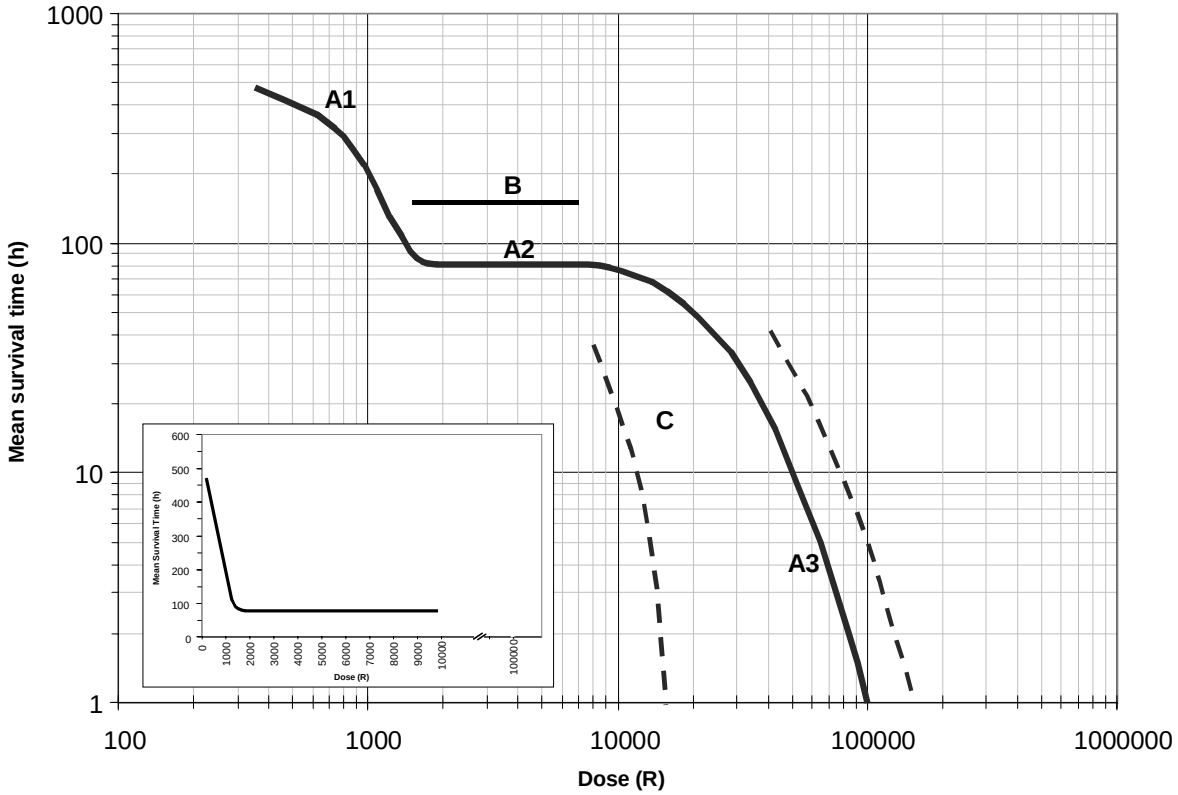

Figure 14. Mean survival time as a function of dose (log–log scale; inset graph, linear scale) for various mammalian species (homogeneous TBI). Curve A describes the general pattern for most species such as mouse, rat, dog, pig and goats. Curve B represents the plateau for species such as germ-free mice, monkeys, and possibly man. At the time of publication in 1965 exposures were measured in Roentgen (100 R =1 Gy). Survival times (in hours) were assessed without therapy.

manner causes little difficulty or misunderstanding except in the transition zone between two syndromes. In these dose regions a syndrome must be defined in terms of all of the various signs and symptoms constituting the syndrome, rather than mean survival time alone. Characteristic pathophysiological mechanisms are responsible for this pattern and indicate the increasing complexity of the response of the individual as a consequence of total body exposure to ionising radiation.

Very high exposure doses (see Figure 14, A3 and C) result in a failure of the regulatory mechanisms of the individual. Neurovascular failure accompanied by interphase cell death can be seen not only in cell systems with renewal but also in resting cell systems such as neurons of the CNS. Thus, all functions become progressively "paralysed" and death will occur in markedly shorter time intervals owing to multiple organ failure.

Intermediate exposure doses (see Figure 14, A2 and B) result in a plateau in survival times of approximately 3.5 days or 6 days, respectively. This is determined by the cell turnover kinetics of the gastrointestinal tract. Owing to the radiation damage to the stem cell compartments of the intestine, the denudation of villi is complete within 3.5 days in certain species (*e.g.* conventional mice) and within about 6–7 days in germ-free mice, large animal species and man. As a consequence, the barrier function of the "internal surface" is broken or absent, resulting in severe perturbation of the fluid balance and the invasion of potentially pathogenic intestinal microorganisms. This denudation process occurs at a time of severe granulocytopenia and thrombocytopenia. Therefore the developing syndrome (often called "gastrointestinal syndrome") has to be seen in its complexity with gastrointestinal, haematological and neurovascular components, resulting in severe, often bloody diarrhoea and serious infectious complications (if no treatment is administered).

Experience gained in radiation accidents (Los Alamos, Sor-Van, Tokai Mura) [9–11] and from the results of animal experiments supports the notion of multiple organ failure resulting in death if no appropriate treatment is administered early after exposure. In the Sor-Van and Tokai Mura accidents, early death was prevented by vigorous and extensive treatment (protective environment, fluid balance, blood component therapy, etc.). However, this may lead to the development of additional clinical complications originating from other organ systems such as the respiratory and urogenital systems. Therefore, one has to be prepared for the clinical condition of the patient to deteriorate owing to these developments.

After lower exposure doses the complexity of responses of mammalian species decreases (Figure 14, A1). Although all organs are exposed and respond in an organ specific way, the extent of damage depends on the radiation sensitivity of the "critical cells" (for instance, stem cells).

In dose ranges between 0.5 Gy and 10 Gy clinical signs and symptoms are governed predominantly by the responses of the haematopoietic renewal system. The key observation is the variation in the onset of the nadir of granulocyte and platelet concentrations in the peripheral blood. After a dose of 0.5 Gy in mammals (mice, monkeys and man) the time of onset is between about 15 days and 30 days. After 10 Gy this variation is between 4 days and 10 days. These nadirs are associated with an increase in susceptibility to infection due to granulocytopenia or bleeding due to thrombocytopenia. Hence, without treatment, at these dose levels individuals may die from the consequences of pancytopenia, the latency of which is a function of the exposure dose.

In summary, the complexity of signs and symptoms after homogeneous total body exposure is related to the exposure dose. Furthermore, it depends on the radiation sensitivity of the different organ systems in terms of cellular as well as functional sensitivity. However, this cannot be described as a linear dose–effect function; to understand the biological responses and the underlying pathophysiological mechanisms requires a profound knowledge of the radiation responses of the critical organ systems and their interplay.

4.2 The RC concept in the clinical setting

As stated earlier, only clinical signs and symptoms associated with radiation are reflected in the RC concept. Other injuries that lead to similar symptoms, such as thermal skin burns, which to a certain extent can be misinterpreted as radiation induced skin lesions, are not considered.

For the clinician responsible for the medical handling of a radiation accident victim, it is of crucial importance to assess as soon as possible the type and extent of the radiation damage inflicted on the patient. Usually, the grading code is sufficiently differentiated to allow the medical specialists and consultants (in intensive care, haematology, gastroenterology, dermatology, neurology, etc.) to recognise their specific challenges, to co-operate fully in patient care and to avoid "overtreatment" or conflicting prescriptions.

This early assessment of the grading, grading code and RC is of importance for two reasons. First, the pathophysiologically based description of the extent of injury must clarify whether it is certain, likely or unlikely that the patient will survive and recover spontaneously, and how the chance of survival can be increased. This will form the basis for selecting the hospital that is best equipped to perform the diagnostic and therapeutic measures necessary for the patient. According to the RC concept this can be done within the triage phase after the accident, taking into account

the prodromal symptoms. When symptoms become more pronounced within 24–48 h this initial assessment becomes more reliable. A valid diagnosis of the radiation induced impairments can be established up until the end of the prodromal phase (*i.e.* within the first week after exposure).

Second, the determination of the extent of injury to the most important organ systems is the basis for planning and initiating a specific treatment as soon as is feasible. For instance, if it is reasonably clear that the haematopoietic system is severely affected but not irreversibly damaged (H3) then the selection of appropriate recombinant growth factors (cytokines) is of foremost importance. In the case of irreversibly damaged haematopoiesis (H4) the search for a suitable stem cell donor should be initiated. If it is evident that the patient will most likely develop severe lesions of the skin and/or the gastrointestinal tract, then every effort should be made to establish a fluid balance (sufficient electrolyte substitution etc.) and to treat the patient in a protective environment (laminar flow, sterile rooms, sterilised food, appropriate antibiotics, gastrointestinal bacterial decontamination, etc.).

The physical examination and the recording of prodromal signs and symptoms as well as the most essential laboratory examinations (especially blood cell counts) should be repeated serially, at least every 6 h during the first 2 days. Later, the intervals can be extended up to 12 h. Every 24 h a complete physical examination according to the organ specific relevant signs and symptoms should be carried out. Further investigation intervals are dependent on the RC; the higher the RC the stricter the monitoring (see Compendium).

From the organ specific point of view the following can be concluded.

It should be possible to establish with high probability whether a patient's clinical course is compatible with the assignment to N1–4 within 48 h. Initially, symptoms such as vomiting, anorexia, nausea, fever and hypotension may be expressed in such a way that it might be difficult to differentiate between grades 1 and 2, or grades 3 and 4. However, a rough indication can be given. The direction of the primary grading can be confirmed with a higher likelihood by the end of the prodromal phase.

The assignment of grade H1–4 depends largely on the determination of blood cell counts as a function of time after accidental radiation exposure. It is of paramount importance to note the precise time of the blood sample taken and it is very helpful to prepare a graph with the absolute counts as a function of time. The lymphocyte count and the neutrophil granulocyte count are decisive. The decline of lymphocytes is pathognomonic for the extent of damage to the individual. For example, if the decline of lymphocytes to values of less than 0.5×10^9/l is apparent within 6–12 h after exposure, severe damage to the haematopoietic system (H4) must be suspected. This grading is justified if, in addition, there is a concurrent granulocytosis within 48 h. A higher degree of confidence in the grading is possible within the first week after exposure if between days 4 and 6 there is a progressive decline of neutrophils to less than 0.5×10^9/l owing to complete blockage of cell proliferation in the bone marrow and to the emptying of the myelopoiesis in the bone marrow and peripheral blood. In addition, if this pattern is associated with a progressive decline of thrombocytes then the initial assignment to H4 is verified. In other words, the H grading can be established with a high probability within 6–12 h, mainly based on the lymphocyte count. The extent of damage becomes more evident as the hours go by and a definite grading can be established within the first week post exposure.

As far as the grading for the gastrointestinal tract is concerned, it is important to monitor carefully the type and frequency of diarrhoea, and the composition of stools (mucosal cell loss, traces of blood, etc.) as well as general signs and symptoms referring to the gastrointestinal system (abdominal cramps, pain). During the first week, it may be difficult or impossible to establish a grading with certainty because the denudation process of the gastrointestinal mucosa does not reach the level of clinical manifestation before days 6–7. At that time significant diarrhoea may begin, resulting in a more or less severe gastrointestinal syndrome. The early bouts of diarrhoea within the first days are associated with neurovascular changes and are usually altered in frequency and consistency ("loose stools"), a transient phenomenon. However, if the N or the H grading indicates a severe or very severe impairment (grade 3 or 4 within 48 h) then marked gastrointestinal tract symptoms may be expected beyond the first week and this needs to be prepared for accordingly.

For the cutaneous system, it is important to enquire about the type of ionising radiation involved in the exposure of the patient. If one is dealing with strongly penetrating γ-irradiation (^{137}Cs, ^{60}Co, etc.) then the skin is less involved than after exposure to neutrons, X-rays or β-rays. Therefore, the initial grading within the first week after the accident is to some extent dependent on the radiation quality. An important early sign is erythema, initially presenting like ordinary sunburn, which may progress to swelling and oedema. If this develops within hours or days, a significant exposure to γ-rays, neutrons or β-rays can be assumed. The pattern of erythema (isolated patches, or uniform areas covering a significant or extensive percentage of the body surface) is helpful to assess the uniformity or non-uniformity of radiation exposure. In the prodromal phase (first week) the appearance of any significant skin reaction (erythema progressing to swelling, oedema, blistering, desquamation, etc.) must

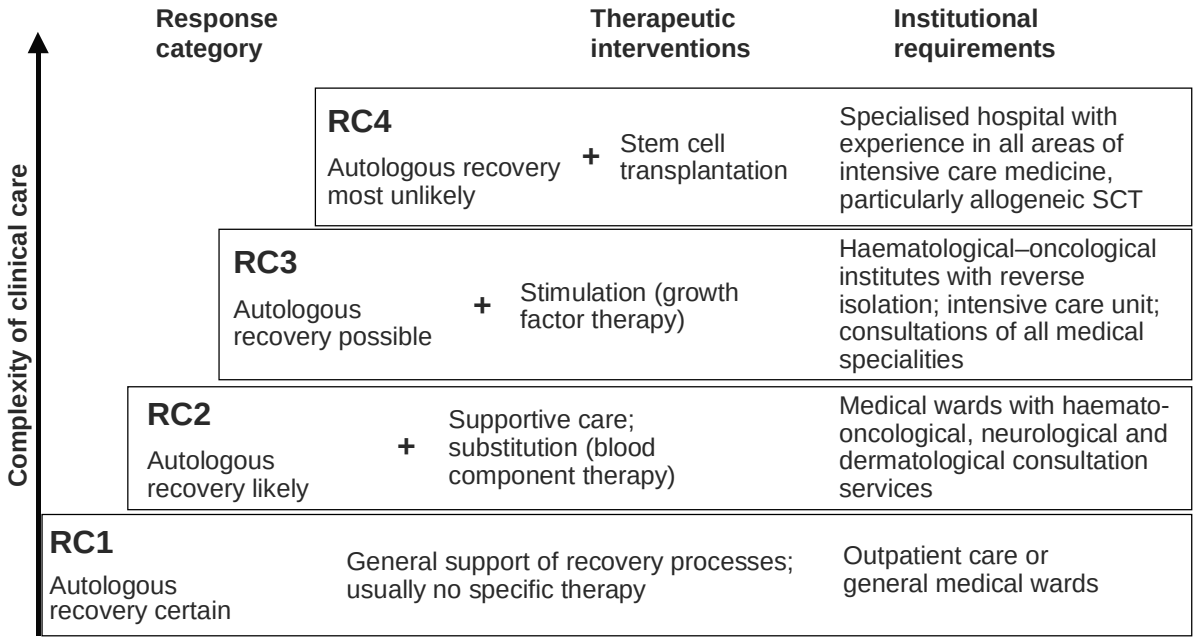

Figure 15. Consequences for patient management in relation to the extent of damage and different RCs.

be taken as a serious symptom of the severity. In combination with a grade N3 or N4 and a grade H3 or H4 it signals a severe course of events requiring medical treatment with all medical specialities "on call".

In the clinical setting, the signs and symptoms of the neurovascular and haematopoietic systems will most likely be of over-riding significance. Usually, their grading will correspond to each other. The higher the grade given in N within the first hours or few days after exposure, the higher will be the grade for H.

The N and H gradings, supplemented by the grading of G and C, will be the basis for assigning a patient to an initial RC. Depending on the severity of the involvement of the four organ systems, the course of ARS can be predicted reasonably well. Thus, the initial RC with its organ specific grading performed during the first week after exposure allows the emergency medical team to select the appropriate clinical services and to set into motion the therapeutic options.

If a patient is assigned to RC 4, a hospital setting should be selected with competence in all medical specialities, but in particular intensive care medicine, stem cell transplantation services, and gastroenterological and dermatological expertise. Patients assigned to RC 3 should be admitted to medical services experienced in handling patients with transient haematopoietic failure (such as seen after treatment for solid tumours or leukaemia). Patients assigned to RC 2 can usually be treated in medical wards but all consultation services should be available. However, patients assigned to RC 2 or RC 3 involving grossly heterogeneous radiation exposure with predominant skin involvement can be handled in dermatological departments when consultants from other fields (haematology, gastroenterology, etc.) are available. Assignment to RC 1 usually means treatment on an outpatient basis with regular follow-up (initially every other day, later twice a week or even once a week for 60 days). In some cases short-term hospitalisation may also be required. The core of the RC concept and its significance for the clinical management of radiation accident victims is summarised in Figure 15.

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CHAPTER 5: GENERAL THERAPEUTIC PRINCIPLES

The aim of this chapter is to summarise therapeutic steps or measures that may be required for patient management during the acute phase, *i.e.* the first 60 days after exposure to ionising radiation. However, these recommendations are subject to rapid changes due to ongoing basic and applied research as well as clinical experience in the field of (radiation) medicine. Therefore, only principles relevant to the medical management of the patient are described here, which by necessity should be adapted to the patient's general health status and in particular to the extent of radiation induced damage to different organs and organ systems.

In accordance with the corresponding RCs, which can be assessed reliably by the organ specific grading approach (see Chapter 2), the following different treatments will be described in more detail:

- Supportive care
- Substitution (blood component therapy)
- Stimulation (growth factor therapy)
- Stem cell transplantation (SCT)
- Surgery

It may be accepted as the rule that the higher the RC the more intense the therapeutic approach must be.

Most likely no therapy will be necessary for patients assigned to **RC 1**. In this RC the impairment of the individual after acute exposure to ionising radiation is only mild and usually will not cause manifest clinical symptoms. However, patients may complain about prodromal symptoms within the first week after exposure, which can be influenced by supportive care adapted to the severity of the symptoms (*e.g.* anti-emetic drugs). Outpatient treatment and repeated follow-up examinations are sufficient for RC1 patients, but hospitalisation in a general medical ward might be required for the first few days after exposure.

For patients assigned to **RC 2** where the damage to the individual is moderate, at least supportive care measures will be needed, especially prophylaxis and treatment of impairments associated with pancytopenia such as infectious diseases. When dealing with manifest clinical symptoms, substitution and stimulation should also be taken into account.

If there are no clinical complications and if the patient agrees to close observation, outpatient treatment might be sufficient, but most likely hospitalisation is necessary in medical wards with haematology/oncology services, and competent neurological and dermatological consultation services.

RC 3 patients are severely injured by radiation exposure and will definitely develop characteristic clinical signs and symptoms as a function of time after exposure. Furthermore, it is very likely that the patient's state will be aggravated by a combination of effects resulting from damage to different organ systems. To improve the patient's course, early application of high quality supportive care, substitution and cytokine stimulation therapy are necessary. From the institutional side, intensive care medicine is required in internal–haematological–oncological services equipped with state-of-the-art isolation systems (such as high efficiency particulate air (HEPA) filtration) and consultation services of all appropriate medical specialities.

In **RC 4** only the combination of high quality supportive, transfusion and growth factor therapy with early application of SCT will increase the probability of saving a patient's life. Most importantly, in this RC group an interdisciplinary therapeutic approach is essential, taking into account the development of complications in the patient's clinical course such as a high risk of development of pulmonary oedema and of renal failure soon after exposure. In the later stages of ARS when haematological recovery has begun, multiple organ failure will lead to severe therapeutic problems. Therefore a specialised hospital is required with experience in all areas of intensive care medicine and particularly in SCT techniques to treat various forms of haematopoietic failure and severe skin damage.

The general principles of these treatments are briefly described below.

5.1 Supportive therapy

Different drug applications as well as other non-invasive measures are included in the term supportive therapy. In particular this includes anti-emetic and analgesic therapy, brain oedema therapy, nutrition, antibiotic approaches, special skin treatments and further measures to improve the patient's state and to bridge the time needed for an impaired organ system to recover and regain control.

All medical interventions have to be seen in the context of their indication and contraindication as well as their possible influence on other drug applications owing to the complex and interacting symptoms.

Anti-emetic therapy

Different groups of anti-emetic drugs can be distinguished. Antihistamines (*e.g.* dimenhydrinate) have only low anti-emetic effectiveness, while 5-HT_3 receptor antagonists (*e.g.* ondansetron, tropisetron, granisetron) and dopamine-D2-antagonists (*e.g.* metroclopramide hydrochloride, alizapride) show high anti-emetic effectiveness.

In the therapy of nausea and vomiting, depending on the degree of severity, antihistamines are either given as monotherapy or are combined with dopamine-D2-antagonists and, if this is not sufficient, with glucocorticoids. Very severe complaints can be treated with 5-HT_3 receptor antagonists alone or again in combination with glucocorticoids. However, the benefits of the use of glucocorticoids must be weighed against risk (*e.g.* impairing immune and other functions) [1].

From anti-emetic therapy regimes in haemato-oncological patients it is also known that increased anti-emetic effects can be obtained by additional application of butyrophenone (*e.g.* haloperidol), phenothiazine (*e.g.* levomepromazine) and benzodiazepines (*e.g.* diazepam, lorazepam). However, as sedation is the main side effect of neuroleptics, the application of these drugs is problematic in the case of a radiation accident as they might cover initial neurological symptoms when given in the first days after radiation exposure [2].

Analgesic therapy

Analgesic therapy for radiation accident victims is modified according to WHO schemes for cancer patients [3–5]. Three levels can be distinguished.

Level I comprises non-steroidal anti-inflammatory drugs such as ibuprofen, meloxicam, diclofenac and paracetamol. The mechanism of action is the inhibition of prostaglandin synthesis, selective inhibition of the cyclo-oxygenase-2 (COX-2) enzyme, spinal and peripheral analgesia and partial spasmolytic effect. Excretion is via hepatic and renal elimination. Relevant side effects are ulcer development, decrease in body temperature, and toxicity to the liver and kidney.

In this group acetylsalicylic acid (Aspirin) is usually mentioned, but owing to its inhibitory action on thrombocyte aggregation, application of this agent is not recommended in radiation accident victims with an increased risk of bleeding due to thrombocytopenia.

Level II covers low effect opiates such as codeine phosphate and tramadol with an effectiveness below 1 (1 = morphine) while level III consists of high effect opiates (effectiveness >1) such as morphine, buprenorphine and pethidine.

The mechanism of effect of these drugs is their morphine receptor μ-antagonism. Excretion is via hepatic metabolism. Side effects, which are dose related, are constipation, nausea, vomiting, hypotension, myosis, urticaria, sedation, tremor, retention of urine, hallucination and apnoea. However, apnoea is inhibited by pain, therefore overdosage of opiates is not usually a problem. Nevertheless, the antidote for overdosage or clinically manifest apnoea is naloxone i.v., given in intervals of 3–5 min or more (in case of stable breathing). Furthermore, it should be mentioned that owing to the side effects of opiates it might be necessary to combine them with anti-emetic and/or purgative drugs

When level III opiates are not sufficient for pain treatment, it is possible to combine them with corticosteroids (dexamethasone) and neuroleptics (*e.g.* promethazine, haloperidol, levomepromazine).

Brain oedema therapy

After TBI or large volume PBI the development of headache as well as other neurological symptomatology such as disorientation, loss of consciousness, etc. is most likely caused by brain oedema leading to increased intracranial pressure. According to common therapeutic recommendations, corticosteroids (dexamethasone) should be applied as first line medication. Low dose schemes with application of 20–40 mg dexamethasone initially, followed by daily doses of about 2–4 mg can be distinguished from high dose schemes with the initial application of 1 mg/kg body weight dexamethasone (equivalent to about 40–100 mg) followed by slow dose reduction. In addition, mannitol 20% and diuretic drugs such as furosemide (40 mg) can be applied intravenously. Furthermore, artificial ventilation might be required in very severe cases as well as neurosurgical intervention [6].

Adapted nutrition (including electrolyte and fluid replacement)

In the case of mild nausea without vomiting and only mild or moderate anorexia, diet adaptation with small portions given several times per day and/or hypercaloric food is usually sufficient. However, depending on the patient's general state, parenteral nutrition might be necessary. In addition to oral or enteral nutrition, peripheral i.v. application of prefabricated complete solutions can guarantee an adequate protein supply. Total parenteral nutrition is only possible via central i.v. application of prefabricated complete solutions or individual nutrition schemes with single components. However, it is necessary to adapt the parenteral nutrition individually to the patient. Sex related calculation of the optimal body mass is the basis for assessing the relation of protein, fat and carbohydrates, which should be 20%:30%:50%, respectively. Close laboratory

monitoring is required to check the quality of parenteral nutrition. In patients with normal serum creatinine, protein supply can be checked by the assessment of urea, which should be <100 mg/dl. In case of liver failure, ammonia assessment is necessary. Carbohydrate supply can be monitored by blood glucose level, which should not be higher than 200 mg/dl. Relevant to fat supply are serum triglyceride levels, which should not exceed 300 mg/dl.

Parenteral nutrition also includes adequate substitution of vitamins and trace elements. For this, prefabricated additives are available. Furthermore, steps should be taken to protect the gut mucosa and to prevent entry of either endogenous and/or exogenous agents. Mainly these involve elementary diets with particular reference to glutamine, cholestyramine to chelate bile acids, probiotics and sucralfate.

In addition, electrolyte substitution and fluid replacement is essential in the medical management of radiation accident victims and must be initiated as soon as possible for all patients, especially in RC 3 and RC 4. Electrolyte substitution must correlate with electrolyte losses, which are highly influenced by diarrhoea, vomiting, blisters, oedema, etc. Therefore, close laboratory monitoring is needed to adapt the administration of electrolytes [7–10].

Antibiotic treatment (including antifungal and antiviral therapy)

In patients overexposed to ionising radiation, immune incompetence occurs as a consequence of effects on the immune system as well as of granulocytopenia, which is usually transient, but in severe cases is long-lasting. Infections that are decisive for the patient's prognosis may occur in the respiratory tract, the mucous membranes, the skin (especially in ulcerations and wounds) or in any internal organ. Such infections may enhance the risk of bleeding once thrombocytopenia develops.

From haemato-oncological neutropenic patients it is known that the development of infectious complications is the main reason for a high mortality. The risk is dependent on the extent and the duration of the nadir phase. Furthermore, about 80% of infections in these patients are due to their endogenous microbial flora present at the time of first admission to the hospital (potential pathogenic organisms) and hospital borne microbial organisms.

Since the early detection of infections is a real problem in immune compromised patients, diagnostic and therapeutic interventions should be done in specialised institutions. Furthermore, it should be taken into account that clinical signs of infections are often hidden by the application of drugs (analgesics etc.) needed to relieve other ARS symptoms. Therefore it is essential to monitor closely clinical signs and symptoms (such as local signs, fever) that indicate the beginning of an infection or a manifest infection. For laboratory tests the assessment of IL-8, PCT, CRP, etc. as well as microbiological colonisation tests (*e.g.* blood cultures, other body fluids, skin, stools, etc.) is recommended after prior consultation with the microbiologists (see also Chapter 2) [11–14].

In patients with a combined haematopoietic and gastrointestinal syndrome it is important to start diagnostic tests and therapy as early as possible and to cover the whole spectrum of potential pathogenic germs. In febrile patients not responding to antibiotic therapy, a fungal infection must be suspected, which may require systemic antifungal therapy. Furthermore, every patient suspected to have undergone a life threatening exposure should immediately—that is, before the gastrointestinal epithelium loses its integrity—undergo gastrointestinal decontamination based on common practices.

Prophylactic administration of antibiotics apart from gastrointestinal decontamination is not recommended because the bacteria eventually responsible for the manifestation of an infection have not been established. In preference, a microbial "inventory" is recommended at regular intervals together with antibiotic sensitivity testing. In this case the medical team is well prepared to act quickly and effectively if there is evidence of the manifestation of an infection. If a microbiological specification is not available, either therapy with broad spectrum penicillin in combination with a cephalosporin of the third generation or monotherapy with one of the latest carbapenem antibiotics might be indicated [15].

The creation of a "protective environment" for a patient, and his subsequent maintenance and care in a sterile environment, has been described and its effect studied after therapeutic TBI as a conditioning regime prior to allogeneic bone marrow transplantation in patients with haematological malignancies [16]. If at all possible, patients should be isolated protectively in rooms equipped with HEPA filtration systems. Aseptic techniques should be used during contact with the patient throughout the treatment phase. Intestinal bacterial decontamination can be performed by application of oral metronidazole and ciprofloxacin. In addition, oral or parental fluconazole for the prevention of candida infection is beneficial. In case of suspected or documented herpes simplex virus infections, acyclovir treatment is indicated. Furthermore, monitoring for replicative cytomegalovirus infections should be performed regularly. Based on a positive assay, ganciclovir or foscavir can be recommended for treatment. It is advisable to follow established guidelines [15] for oral and parenteral nutrition and the treatment of suspected or documented bacterial or fungal infections.

In cases where SCT is required, patients should undergo microbial decontamination of the skin and the intestinal tract by appropriate washings and by

Table 15. Conservative skin treatment relevant at different times after exposure

Stage	Treatment
Prodromal stage (first week after exposure)	Basic therapy with linoleic creams or lotio alba, non-atrophogenic steroids, antihistamines
Manifestation/subacute stage (days 8–60 after exposure)	Topical/systemic steroids, tetrachlorodecaoxide, thrombocytic growth factors, hydrocolloid dressings, antibiotic prophylaxis, analgesics
Chronic stage and late stage (beyond day 60 after exposure)	Basic therapy with linoleic acid, topical/systemic retinoids, interferon gamma, systemic/topical application of superoxide dismutase, systemic application of pentoxifylline and alpha-tocopherol tetrachlorodecaoxide, thrombocytic growth factors, hydrocolloid dressings, semi-synthetic dressings (Integra), analgesics

administration of non-resorbable antibiotics with the goal of establishing a protective environment. Commonly used antibiotics for that purpose are fluoroquinolones (*e.g.* ciprofloxacin, levofloxacin) or a combination of an aminoglycoside (neomycin), polymyxin B and nystatin. However, in the special situation of radiation accident victims, it is most likely that the absorption of antibiotics will depend on the extent of mucosal damage. Therefore precautions such as assessment of antibiotic serum levels must be undertaken to detect organ specific side effects such as renal and hepatic damage. There are four reasons for establishing a protective environment as described above. First, the immunocompromised patient should under all circumstances be protected from nosocomial infections. Second, if the mucous membranes are "open" to bacterial invasion following denudation and through reduced blood granulocyte defence potential, the enteric microbial flora may well contain potential pathogens. Third, it has been shown both in extensive experimental studies [17] and in clinical observations [16, 18] that there is evidence for a significant reduction in graft *versus* host disease (GvHD) in patients given allogeneic stem cell transplantation if they are kept in a protective environment during this therapy. Fourth, it has been shown that bleeding during thrombocytopenia occurs less frequently in patients not having bacterial infections.

Skin treatment

Treatment has to focus on the particular stage of CS and the avoidance of additional risk to the patients [19, 20]. The conservative therapeutic regime is summarised in Table 15.

The prodromal and manifestation stages are characterised by inflammatory processes. Anti-inflammatory creams, *e.g.* linoleic acid cream, should be used as the basic treatment. Additionally, non-atrophogenic local steroids should be used to reduce the inflammation. Systemic steroids (0.5–1.0 mg/kg prednisolone equivalent) should be applied in patients with extensive affected skin areas after contra-indications have been checked to reduce dermal and muscular vasculitis. If the patients suffer from pain, analgesics should be given. Treatment with loratadine, a non-sedative and mast cell stabilising antihistamine, provides marked relief of a burning itch. Additional therapeutic modalities reported to be of value in the manifestation stage are antibiotics for bacterial infections and, if there are no contraindications, heparinisation [19–23].

Xerosis is one of the symptoms of the chronic stage of CS. Basic therapy with a specific ointment containing linoleic acid may reduce the severity of initial transdermal fluid losses. Teleangiectasias, which cause discomfort owing to a burning itch and heat sensation, may disappear after argon laser therapy [19–21, 23].

Tretinoin cream 0.005%, applied once daily, can lead to clearance of focal and patchy radiation keratoses. In more extensive lesions, oral application of retinoids is recommended [19–21, 23].

Radiation fibrosis is characterised by an increase in production of collagen fibres by affected fibroblasts. If left untreated, persistent cutaneous fibrosis may give rise to ulcerations. Various approaches have been undertaken to antagonise this chronic inflammatory process, including systemic and topical application of superoxide dismutase, systemic application of pentoxifylline and alpha-tocopherol and proteinase inhibitors [24–27].

Interferon gamma inhibits collagen production by human dermal fibroblasts [28]. Interferon gamma should be scheduled on a low dose regimen, (2–3) × 100 μg/week s.c. for 6 months, then once per week for another 6 months. A decrease in skin thickness could be observed 6 months after initiation of therapy [28].

Cutaneous radiation ulcers should be treated with topical dressings of tetrachlorodecaoxide (TCDO), which can induce considerable granulation and re-epithelisation of ulcers. Additionally, hydrocolloid dressings or topical thrombocytic growth factors can be used [19, 20]. A recent interesting alternative is a wound dressing composed of semi-permeable fibres. A systematic evaluation of this new approach is pending. Integra, another semi-synthetic skin equivalent, has been used effectively to cover large surgically removed areas of radionecrotic skin [29].

Table 16. Threshold values below which platelet substitution is indicated

Individual medical situation	Threshold values
Uncomplicated patient, no bleeding, close monitoring possible	10×10^9/l
Increased risk of bleeding, manifest bleeding, close monitoring not possible	20×10^9/l
Additional trauma, surgery, mass transfusions, cerebral injury, intracerebral oedema	50×10^9/l

Further approaches

There are other treatments that might also help improve the patient's state after exposure to ionising radiation, especially as in some cases no specific medication is currently available.

Depending on the patient's general status and recovery patterns, physical exercises, occupational therapy, etc. are suitable, for example to shorten the duration of a fatigue syndrome.

Psychological and educational intervention, as well as occupational therapy and physiotherapy, can support the therapy of decreased or impaired cognitive functions, the extent of which should be assessed by neuropsychological tests.

Drug therapy might be indicated for the following clinical symptoms.

Since seizures are possible in the course of neurovascular manifestation of the ARS, occasional or permanent oral medication or i.v. anticonvulsive drugs may be indicated. In the acute phase, symptoms are caused mainly by increased intracranial pressure (oedema), but therapeutic approaches also have to cope with the clinical manifestation of seizures. In this case in addition to observation and interrogation a detailed neurological examination (reflexes, motor and sensor signs, etc.) is required as well as imaging studies (CT, MRI, EEG, etc.) to assess the extent of cerebral involvement.

Hypotension should be treated according to the underlying cause (*e.g.* cardial, neurogenic, hypovolaemic, endocrine, drug related). Initially, the application of sympathomimetics might be helpful following common rules.

In the case of abdominal cramps, analgesic treatment can be enhanced by application of antispasmodics [30, 31]. In general, for treatment of the acute and subacute phase of the GIS, treatment is directed against neurohormonal mediators. Loperamide, which has both antimotility and antisecretory activity, seems to be the drug of choice.

5.2 Substitution (blood component therapy)

It is well known that there may be signs of GvHD following the use of blood or blood product transfusions in an immune compromised host, owing to contamination with immunoreactive leukocytes. Thus, leukocyte depletion is recommended for blood products (purified red cells and isolated platelets). This can be done by filtration, which leads to depletion of leukocytes down to 0.1–0.01%. The other possibility is irradiation of the cell transfusion to impair the replication potentials of the lymphocytes. In this case, radiation doses of about 20–30 Gy are recommended [32, 33].

It should be mentioned in this context that filtration of thrombocyte concentrates leads to a loss of platelets (5–15%) in the filtration system. In the case of erythrocytes, irradiation reduces the period of possible application owing to potassium loss and development of free radicals.

Thrombocyte concentrates

Recommendations for thrombocyte substitution are mainly based on threshold values of the peripheral platelets as given in Table 16 [34, 35].

Different thrombocyte concentrates are available that differ mainly in the number of thrombocytes per unit [34]. The number of thrombocytes necessary for a desired increment can be calculated as follows:

$$\text{no. thrombocytes} = \frac{\text{desired increment } (\times 10^9/\text{l}) \times \text{blood volume (l)}}{0.7}$$

The aim of therapy with thrombocyte concentrates is to achieve at least a stable value of the peripheral cell count of about 20×10^9/l. The effectiveness of the thrombocyte substitution should be reconsidered regularly by calculating the corrected count increment (CCI), taking into account the thrombocyte values prior to and shortly (5–60 min) after the transfusion as well as the body surface (BS):

$$\text{CCI} = \frac{[\text{thrombocytes post} - \text{thrombocytes prior to transfusion } (\times 10^9/\text{l})] \times \text{BS } (\text{m}^2)}{\text{number of transfused thrombocytes } (\times 10^{11})}$$

The assessment of the CCI is also important for the early detection of the refractory status due to immunological and non-immunological factors [36, 37].

Granulocyte concentrates

Regarding the risk of infections as a consequence of granulocytopenia, the transfusion of separated granulocytes is usually neither indicated nor efficient. The major countermeasure is the use of an induced protective environment and specific antibiotic treatment as mentioned above. Only in cases of septic ulceration (skin, mucous membranes, lung) might a short and intensive course of granulocyte transfusions be useful.

Another dilemma is the high risk of transfusion related cytomegalovirus (CMV) infection, which will have deleterious effects on patient health status.

Erythrocyte concentrates

Owing to the long half-life of erythrocytes, anaemia primarily due to ionising radiation is not very likely to occur, but should be taken into account as a secondary effect in the case of additional injuries or severe bleeding. For example, in patients assigned to RC 3 or RC 4 a phase of anaemia can occur beyond days 24–30, but this does not usually develop to the extent that red cell substitution is required. However, if blood loss has occurred for other reasons, *e.g.* physical injury or severe and uncontrollable thrombopenic bleeding, it should be readily reversed by transfusions, since the risk of thrombopenic bleeding is higher in severe anaemia. It is important to point out the risk of overtransfusion, which would unnecessarily elevate red blood cell concentrations and haematocrit levels and have a negative influence on the proliferation and regeneration of the erythropoietic cell system.

Following the rules of intensive care medicine, transfusion of erythrocytes will become necessary if the haemoglobin decreases below a critical value, which will differ according to the state of the patient. In patients with known coronary heart disease or in clinical situations where there is a high risk of decreased intracerebral perfusion, the indication for erythrocyte transfusion is a threshold Hb value of <10 g/dl. Without any additional risk factors or other clinical indications, transfusion is recommended when Hb values are below 8 g/dl.

5.3 Stimulation (growth factor therapy)

The emergence of recombinant haematopoietic growth factors in the first half of the 1980s has opened up new ways of treatment of radiation damage to the haematopoietic system. Briefly, blood cell production is controlled by specific stromal elements, including membrane bound cytokines and more systemic-acting growth factors, several of which are known to stimulate stem cells, whereas others are strictly lineage specific. Among the approximately 30 haematopoietic growth factors identified to date, only a few have been registered for human use and/or found to be effective if administered after radiation exposure without undue adverse effects. The effective growth factors include granulocyte colony stimulating factor (G-CSF) and granulocyte–macrophage colony stimulating factor (GM-CSF), which have a highly overlapping pharmacological spectrum in stimulating neutrophilic granulocyte reconstitution [38, 39], and the recently discovered growth factor thrombopoietin (TPO), which is the major regulator of platelet production [40, 41]. The therapeutic efficacy of these growth factors declines rapidly as a function of time after irradiation [42–44] as well as with increasing radiation dose. In fact optimal efficacy can be expected to be in the midlethal dose range [45]. An unexpected observation indicates that TPO also appears to be capable of accelerating the reconstitution of immature haematopoietic cells, which results in the production of progenitor cells that may respond to the CSFs [46–49]. However, although the CSFs have been widely used clinically [50–53], so far thrombopoietin has only been tested in experimental animal models and is currently undergoing clinical trials. TPO is capable of stimulating platelet reconstitution, it potentiates the action of CSFs and it accelerates immature CD34+ cell reconstitution. In a non-human primate model the early administration of TPO after irradiation has been shown to promote survival and *in vivo* expansion of immature haematopoietic cells as well as preventing the occurrence of thrombopenic events [43, 44, 46–48]. These findings indicate that in case of a radiation accident TPO should be administered within a few hours after exposure, and at the latest within 24 h to be of optimal efficacy. The logistical consequence is that growth factor therapy should be instigated in each patient suspected of having received a high dose exposure. Based on experimental results, currently the best possible growth factor treatment would appear to be a combination of TPO/G-CSF (5 µg/kg TPO i.v., single administration as soon as possible after exposure; 10 µg G-CSF s.c. for 14 consecutive days after exposure). However, clear clinical data for the application of this regimen for the special situation of radiation accident victims are not yet available. GM-CSF is reported to cause capillary leakage and may therefore be problematic. In rare cases G-CSF treatment may result in long-standing isolated thrombocytopenia [42, 54–56]. The response to growth factor therapy should be apparent as an increase in peripheral blood cell count within 10 days to 2 weeks after the initiation of treatment. More prolonged treatment is probably useless, although isolated long-standing thrombocytopenia may respond favourably to a short course of TPO [45]. Growth factor therapy is still rapidly developing and further improvements may be achieved in the future with other or novel growth factors [57].

In addition to haematopoietic cytokines, several growth factors appear to promote the restoration of the gastrointestinal epithelium and/or the surrounding tissue. IL-11 and KGF are among several factors that are currently being investigated. IL-11 has anti-inflammatory effects associated with a reduction in TNFα and IFNγ levels and suppression of NF-κB, and similarly to KGF, IL-11 has been shown to be useful in reducing GvHD. However, although growth factor therapy for the GIS might be promising, much work remains to be carried out to show clear therapeutic benefit in radiation accident victims.

5.4 Stem cell transplantation therapy

If the prognosis from the RC scheme indicates a high probability of irreversible bone marrow failure, SCT should be considered and instituted, using available protocols in specialised SCT centres [58–60]. In those cases, SCT is the only way to save the patient's life by repopulating the damaged bone marrow.

Haematopoietic stem cells (HSCs) to date can be derived from:

1. Bone marrow (usually available immediately)
2. Peripheral blood (available only after mobilisation)
3. Umbilical cord blood

The procedure of autologous as well as allogeneic SCT is presently used most frequently for the treatment of malignancies in which myeloablative measures are employed to stop the tumour growth. In radiation accident victims, autologous SCT is very unlikely, unless *ex vivo* stem cell expansion protocols become operational. Allogeneic stem cells should preferably be obtained from a human leukocyte antigen (HLA) identical sibling or a family donor (parents/children); if negative, an HLA-matched unrelated donor should be searched for through national and international bone marrow/stem cell registries. It may take up to several weeks to search for unrelated donors.

The target dose of CD34+ bone marrow stem cells for engraftment of an HLA-matched allogeneic bone marrow transplantation (BMT) in the recipient is 3×10^6 CD34+/kg body weight.

More recently it has become clear that peripheral blood is a potent source of pluripotent HSCs. They can be mobilised by cytokine pretreatment before harvesting by leukocytapheresis. Blood stem cells, if given in sufficient numbers, are more effective than bone marrow stem cells with respect to earlier haematopoietic recovery [61, 62]. The major advantage of peripheral blood stem cell transplantation (PBSCT) is the higher number of cells obtained and thereby the better engraftment of the transplanted cells. However, the issue of possible long-term risks for the donor after stimulation with cytokines has not been resolved and the therapeutic delay due to the mobilisation phase of 4–5 days [63] is a clear disadvantage. This may be resolved by alternative "mobilisation" protocols and pharmaceuticals. PBSCs can be collected from the peripheral blood by continuous flow centrifugation (leukocyte apheresis or leukapheresis). Stem cell mobilisation in man can be induced effectively by the administration of growth factors (G-CSF). The CD34 number for a successful engraftment can be given for the autologous PBSCT with a target dose of $(2–4) \times 10^6$ CD34/kg body weight (minimal dose 1×10^6 CD34/kg). For HLA-matched allogeneic blood stem cell transplantation the target dose is $(3–4) \times 10^6$ CD34/kg (minimal 2×10^6 CD34/kg) [62]. Owing to the inhomogeneous nature of accidental radiation exposure, as a general rule the degree of immunosuppression is insufficient for acceptance of an allogeneic stem cell graft. Hence, without additional immunosuppression, most radiation accident patients who might benefit from an allogeneic SCT will eventually reject the graft. Additional immunosupression by infusion of antibodies cytotoxic for T-lymphocytes is recommended, using either monoclonal antibodies such as CAMPATH 1H or ATG. These agents may also have adverse effects and therefore their use should be balanced against the general condition of the patient.

Another potent source of HSCs is placental blood—called umbilical cord blood (UCB)—which can restore the function of the bone marrow in both related and unrelated recipients. UCB should be considered as a source of stem cells in cases where bone marrow and peripheral blood stem cells are unavailable. For patients for whom no suitable voluntary related or unrelated donor is available, the advantages of this source are:

- Relatively easy procurement
- Absence of risk to the donor
- Low likelihood of transmitting clinically important infections
- Low risk of severe GvHD
- Rapid availability of placental blood to transplantation centres

UCB cells were first used for transplantation in 1988, when the blood was drained from the umbilical cord and used for restoration of haematopoiesis in an appropriately conditioned child with Fanconi's anaemia [64]. The procedure of collecting stem cells from the umbilical cord, to store them temporarily, and to establish a cord blood stem cell bank (of cryopreserved cells) has been described in detail [65, 66]. Target doses are usually given in total nucleated cells (TNC) per kg body weight. The target dose for a

successful engraftment is 0.3×10^8 TNC/kg (minimal 0.1×10^8 TNC/kg). It may, however, be difficult to achieve this dose in adult patients. The outcome of placental blood transplants from unrelated donors, which was evaluated among 562 recipients between August 1992 and January 1998, shows that the cumulative rate of engraftment was 81% by day 42 for neutrophils (median day 28) and 85% by day 180 for platelets (median day 90). The speed of myeloid engraftment was associated primarily with the leukocyte content of the graft [67]. In addition, the report of 138 cord blood transplantations listed in the Eurocord Registry up to April 1998 gives numbers of cord blood cells that range from 9.7×10^6 to 552×10^6 per kg body weight and rates of engraftment for all subgroups of patients analysed of about 80–90% [68]. Thus, this approach has been useful not only in children but also in adults. More recently, one of the patients of the Tokai Mura radiation accident in 1999 received a UCB transplant that resulted in at least a temporary engraftment (establishment of mixed chimerism) [69].

Latest developments in SCT also indicate that non-ablative allogeneic SCT ("minimal SCT") is also an option in the treatment of patients with an impaired haematopoietic system and significant co-morbidity. The considerable advantage of mini-allotransplantation is that the transplant-conditioning regimen is a conventionally dosed treatment regimen and therefore less toxic by far. The final goal in these patients is not necessarily establishing 100% donor chimerism but rather some kind of (mixed) donor chimerism that bridges the time period of severe cytopenia until endogenous (autochthonous) reconstitution takes over [70, 71].

5.5 Surgery

If conservative therapy of radiation ulcers or radiation fibrosis as mentioned above (see section 5.1 on supportive care) is not successful, or skin damage is too extensive, surgical treatment should be performed. This includes the excision of ulcers or fibrotic tissue, primary wound closure and split or full thickness skin grafts or vascularised flaps [72, 73]. Basal and squamous cell carcinomas occurring after exposure to ionising radiation should be excised [74].

Furthermore, surgical interventions according to common rules should be considered for the treatment of ileus, gut fistulas, or—if at all possible—brain oedema.

5.6 References

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Footnote to opposing Table

HR, heart rate; BP, blood pressure; Ø, not defined.

[a] Fatigue: self-recognised state of overwhelming, sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest. Typical descriptions are drained, finished off, lethargic, beaten, exhausted or worn out, prostration, drowsiness. Components are physical, cognitive, emotional/affective.

[b] Neurological deficits: reflex status including reflexes of the eye, ophthalmoscopy (oedema of papilla), fainting, dizziness, ataxia and other motor signs, sensory signs.

[c] Reference value: $(1.5–4) \times 10^9$/l.

[d] Reference value: $(4–9) \times 10^9$/l.

[e] Reference value: $(140–400) \times 10^9$/l.

[f] With respect to assessing the CS, the extent of the skin area affected is decisive and should be documented for all skin changes.

[g] Only for penetrating irradiation.

ADDENDUM

List of the degrees of severity of organ specific symptoms

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
N				
Nausea	mild	tolerable	intense	excruciating
Vomiting	occasional, 1/d	intermittent, 2–5/d	persistent, 6–10/d	refractory >10/d or parenteral nutrition
Anorexia	able to eat, reasonable intake	significantly decreased intake but able to eat	no significant intake	parenteral nutrition
Fatigue syndrome[a]	able to work or perform normal activity	interferes with work or normal activity	needs some assistance for self-care	prevents daily activity
Fever	<38 °C	38–40 °C	>40 °C for less than 24 h	>40 °C for more than 24 h or accompanied by hypotension
Headache	minimal	tolerable	intense	excruciating
Hypotension	HR>100/BP>100/70	BP<100/70	BP<90/60; transient	BP<80/?; persistent
Neurological deficits[b]	barely detectable neurological deficit; able to perform normal activity	easily detectable neurological deficit, no significant interference with normal activity	prominent neurological deficit, significant interference with normal activity	life threatening neurological signs, loss of consciousness
Cognitive deficits	minor loss of memory, reasoning and/or judgement	moderate loss of memory, reasoning and/or judgement	major intellectual impairment since accident	complete memory loss and/or incapable of rational thought
H				
Lymphocyte changes[c]	$\geq 1.5 \times 10^9$/l	$<1.5–1 \times 10^9$/l	$<1–0.5 \times 10^9$/l	$<0.5 \times 10^9$/l
Granulocyte changes[d]	$\geq 2 \times 10^9$/l	$<2–1 \times 10^9$/l	$0.5–1 \times 10^9$/l	$<0.5 \times 10^9$/l or initial granulocytosis
Thrombocyte changes[e]	$\geq 100 \times 10^9$/l	$<100–50 \times 10^9$/l	$<50–20 \times 10^9$/l	$<20 \times 10^9$/l
Infection	local; no antibiotic therapy required	local; only local antibiotic therapy required	systemic; p.o. antibiotic treatment sufficient	sepsis; i.v. antibiotics necessary
Blood loss	petechiae; easy bruising; normal Hb	mild blood loss with <10% decrease in Hb	gross blood loss with 10–20% decrease in Hb	spontaneous bleeding or blood loss with >20% decrease in Hb
C				
Erythema[f]	minimal and transient	moderate; isolated patches <10 cm^2; not more than 10% of body surface (BS)	marked; isolated patches or confluent; 10–40% of BS	severe[g]; isolated patches or confluent; >40% of BS; erythroderma
Sensation/itching	pruritus	slight and intermittent pain	moderate and persistent pain	severe and persistent pain
Swelling/oedema	present; asymptomatic	symptomatic; tension	secondary dysfunction	total dysfunction
Blistering	rare, with sterile fluid	rare, with haemorrhage	bullae with sterile fluid	bullae with haemorrhage
Desquamation	absent	patchy dry	patchy moist	confluent moist
Ulcer/necrosis	epidermal only	dermal	subcutaneous	muscle/bone involvement
Hair loss	thinning, not striking	patchy, visible	complete and most likely reversible	complete and most likely irreversible
Onycholysis	absent	partial	Ø	complete
G				
Diarrhoea				
Frequency	2–3 stools/d	4–6 stools/d	7–9 stools/d	≥10 stools/d; refractory diarrhoea
Consistency	bulky	loose	sloppy	watery
Mucosal loss/d	intermittent	intermittent with large amount	persistent	persistent with large amount
Bleeding/d	occult	intermittent	persistent	gross haemorrhage
Abdominal cramps/pain	minimal	tolerable	intense	excruciating

Documentation sheet for signs and symptoms as a function of time

Use the following template to document ARS symptoms as a function of time according to the "Checklist" of ARS specific clinical symptoms of the four early reacting organ systems. Copy as required!

Patient ID:	Beginning of exposure:	Examiner:

Date and time of examination								
N	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity
Nausea								
Vomiting								
Anorexia								
Fatigue syndrome								
Fever								
Headache								
Hypotension								
Neurological deficits								
Cognitive deficits								
Maximum								
Grading N								
H	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity
Lymphocyte changes								
Granulocyte changes								
Thrombocyte changes								
Infection								
Blood loss								
Maximum								
Grading H								
C	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity
Erythema								
Sensation/itching								
Swelling/oedema								
Blistering								
Desquamation								
Ulcer/necrosis								
Hair loss								
Onycholysis								
Maximum								
Grading C								
G	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity	Degree of severity
Frequency (stool)								
Consistency (stool)								
Mucosal loss/d (stool)								
Bleeding/d (stool)								
Abdominal cramps/pain								
Maximum								
Grading G								
Grading code	N_H_C_G_	N_H_C_G_	N_H_C_G_	N_H_C_G_	N_H_C_G_	N_H_C_G_	N_H_C_G_	N_H_C_G_
RC =								
Days after exposure								

ANNEXES

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III. The SEARCH database

One way to help people suffering from overexposure to ionising radiation is to make use of existing knowledge and experience from former radiation accidents. For this purpose, in the early 1990s the Radiation Medicine Research Group at the University of Ulm, which participates as a WHO Collaborating Centre for Radiation Accident Management within REMPAN (see Annex IVb), in co-operation with different partners started to develop and build a powerful acquisition, storage and retrieval system comprising accident data as well as medical data after radiation overexposure. This System for Evaluation and Archiving of Radiation accidents based on Case Histories, in short SEARCH, provides a database for research on different radiation syndromes, which was also used in the development of this manual on the acute radiation syndrome within the METREPOL project. In general, this knowledge can be used to confirm known pathophysiological concepts and to develop new ones to understand the effects of ionising radiation on man and to elaborate new concepts and strategies for diagnosis and treatment of health impairments after acute, chronic or ill defined radiation exposure. In parallel, SEARCH provides a basis for continuous capacity building and a training facility in the field of radiation accident preparedness.

As of June 2000, SEARCH contained 855 case histories from 70 accidents in 14 different countries from the years 1945–1997. Included were follow-ups of 154 acute exposure case histories and 80 chronic exposure case histories.

Standardised questionnaires were used to collect data, which were transferred into the SEARCH relational database, implemented in Oracle™ on a Unix platform. After using appropriate database management technologies for quality control and data security, more than 900 different items per case history of patient and accident information are usually available for exploitation and scientific evaluation.

To improve our preparedness in the medical management of patients exposed to ionising radiation it is necessary to expand continuously our knowledge of radiation accidents. The SEARCH approach successfully provides an information system to collect, archive and evaluate systematically data both on the particular nature of radiation accidents and on the clinical course of people exposed to different radiation patterns. Moreover, such an approach allows comparisons to be made between different accident patterns and individual case histories. Therefore, the scientific community is encouraged to participate in SEARCH and to support the database by providing relevant material to make it a dynamic and non-profit-making knowledge base for health effects following radiation accidents.

Owing to property rights and data protection issues arising from the international use of the data, access to SEARCH requires the signing of a co-operation agreement. For further information please contact the Radiation Medicine Research Group at the University of Ulm or see www.faw.uni-ulm.de/radmed (research project 1).

IV. International management structures

Since the early days of military and civil use of nuclear energy, radiation accidents of greater or lesser extent have been reported that have involved only a few persons or in the worst case scenario have confronted the world with a mass catastrophe. Unfortunately, despite a growing awareness of the risks and growing safety standards, radiation accidents will continue to occur. In particular with major accidents it is highly unlikely that the consequences of radiation overexposure can be dealt with on a national level alone. Particularly in Europe, owing to the relatively high density of the population, the large number of nuclear facilities and the fact that radioactivity does not stop at country borders, radiation accidents will present particularly serious problems in the field of medical emergency management.

Several international organisations will be involved in the case of a radiation accident, as all have adopted two conventions as the basis for their co-operative work: The Early Notification Convention (1986) and The Convention on Assistance in the Case of Nuclear Accident or Nuclear Emergency (1986). The interpretation and collaborative responsibilities of each signature agency have been drafted by the Inter-Agency Committee on Response of Nuclear Accidents (IACRNA).

Participating international organisations in IACRNA are:

- International Atomic Energy Agency (IAEA)
- World Health Organisation (WHO)
- World Meteorological Organisation (WMO)
- United Nations Office of Co-ordination of Humanitarian Affairs (OCHA)
- Food and Agriculture Organisation (FAO)
- Commission of the European Communities (CEC)
- Nuclear Energy Agency of the Organisation of Economical Co-operation and Development (NEA/OECD)

Other international organisations contribute to activities related to the management of radiation emergency situations, such as the International Committee on Radiological Protection (ICRP), the International Federation of the Red Cross and the Red Crescent Societies.

Radiation accidents in recent years have shown that the IAEA and WHO are the first organisations to be informed about accident situations, particularly where people are involved. Usually the IAEA is notified of an accident by the country in which the accident occurs or an affected neighbouring country, and is provided with relevant information on the current situation. Other international organisations, particularly WHO, will immediately obtain this information through the IAEA. Therefore, both the IAEA and WHO, with respect to their mandates and structures, direct and co-ordinate specialised help if requested.

As it is beyond the scope of this manual to describe the interaction and responsibilities of all national and international partners of the radiation emergency response system, only the roles of the IAEA and WHO in the field of radiation accident management are presented in more detail.

a. International Atomic Energy Agency (IAEA)

Global co-operation in the nuclear field was instigated after the formation of the United Nations (UN) system in 1945. In 1954, the General Assembly adopted a resolution that set in motion the establishment of the IAEA. As a specialised agency within the UN system the IAEA came into being in 1957. Since that time the UN and the IAEA have built up an extensive network of global co-operation in the nuclear field with respect to international security, economic and social development and the environment. Apart from an intensive formal framework with specialised agencies within the UN organisation, informal working contacts have been set up with shared interests and knowledge in the fields of radiation as well as co-operation through established interagency forums. Furthermore, co-operation activities and relationships have been set up with non-UN organisations and non-governmental organisations.

Today, the IAEA serves as the world's central intergovernmental forum for scientific and technical co-operation in the nuclear field as well as the international inspectorate for the application of nuclear safeguards and verification measures covering civilian nuclear programmes. Furthermore, on the national as well as the international level the IAEA plays a central role in the development of strategies and standards in the establishment of radiation emergency preparedness and assistance.

If requested for advice or assistance, the IAEA carries out an initial assessment of requirements, which may lead to the mobilisation of the IAEA Emergency Response Network (ERNET) as well as appropriate other partner organisations. ERNET includes agency medical field teams, whose membership of ERNET will be cleared by WHO in advance. The IAEA has the following prime responsibilities to:

- Receive official notification of the accident from the accident state
- Establish primary functional links with the accident and affected states
- Act as the focal organisation for response
- Trigger actions under the Conventions

- Establish functional links with international convention partners
- Co-ordinate international assistance, on request of the member state
- Establish standards of safety for protection of health and environment (from ionising radiation) and promote the application of these standards

For further and more detailed information on the activities of the IAEA in the radiation emergency response see www.iaea.org

b. World Health Organisation (WHO)

According to its 1946 constitution, WHO is the directing and co-ordinating authority on international health. Consequently, environment and health play a leading role in the working activities of WHO, which also covers the problem of unexpected overexposure to ionising radiation. Therefore, more than 20 years ago WHO established a network of international collaborating centres called REMPAN (Radiation Emergency Medical Preparedness and Assistance Network), each of which is based in national institutions. The overall objective of WHO and the REMPAN centres related to radiation accident emergency response is to be prepared to provide advice and help to cope with immediate problems and difficulties of the acute phase after a radiation accident, such as risk assessment, diagnosis and treatment. Assistance is offered in the assessment of long-term impact and advice on relocation, food control and decontamination as well as in the mitigation of the impact on mental health. In addition, assistance in organising follow-up examinations and rehabilitation measures for radiation accident victims and advice on longer-term protective actions is provided.

To date, 16 different centres all around the world are accepted within REMPAN (Argentina, Armenia, Brazil, China, Germany, United Kingdom, Finland, France, India, Japan, Russia, USA). Furthermore, REMPAN works closely with relevant institutions in Chile, Paraguay, Peru and Uruguay. In each country, competent contact persons in the field of radiation emergencies provide the basis for the whole network, which is therefore able to cover all aspects of radiation emergency medical preparedness and response activities.

To carry out the obligations under the conventions of Early Notification and Assistance in Case of Nuclear Accident or Nuclear Emergency, REMPAN was established to:

- Enhance medical preparedness in case of radiation accidents within the WHO member states
- Provide medical advice and assistance to alleviate health consequences to individuals and populations involved in radiation accidents
- Provide public health advice to member states aimed at preventing or reducing long-term effects from low and prolonged exposure of populations living in areas with high levels of radioactive contamination
- Assist in follow-up studies of persons exposed to radiation

To meet these objectives, REMPAN

- Maintains regular communication between network members
- Disseminates immediately official notification of a radiation accident from the IAEA to network members
- Identifies, in collaboration with the IAEA, members to deal with the medical treatment of radiation accident victims
- Collects information on patient treatment and makes this available to network members
- Develops and maintains updated patient treatment protocols
- Maintains via the WHO headquarters close liaison with network members before, during and after accidents and maintains a record of information that can be shared by network members
- Holds meetings to discuss future directions and activities of the network as well as workshops for physicians to discuss the best available treatment of patients
- Maintains a database of information on experience gained on patient injuries and treatments, as well as their success or failure

For further information on the activities of WHO and WHO–REMPAN see www.who.org