

# Medical Management Of The Haemopoietic Syndrome In Acute Radiation Sickness

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## Introduction

Most radiologically injured casualties can be successfully treated by aggressive resuscitation of the bone marrow. Clinical monitoring, laboratory evaluation, and conventional management of the immunocompromised state are important. Early use of marrow-stimulating cytokines will result in a shortened window of relative immune incompetence. Use of broad-spectrum antibiotics is recommended only during this timeframe. Patients who have multiple injuries complicated by radiation injury will require more aggressive treatment than their non-irradiated counterparts. Combined injury will markedly increase morbidity due to synergism and requires all surgeries to be completed within 36 to 48 hours of irradiation.

## Introduction

The aim of this article is to provide the theory and some practical aspects of the medical management of the haemopoietic syndrome at role 2 and 3 with an insight into management at role 4. The author has drawn upon NATO AMedP 6C (1) and US Medical Management of Radiological Casualties Handbook, 2003 (2).

Modern medical care dramatically improves the survivability of radiation injury. When medical care is not provided,

the median lethal dose of radiation, the LD 50/60 (that which will kill 50% of the exposed persons within a period of 60 days) is estimated to be 3.5 Gy. The two most significant radiosensitive organ systems in the body are the haematopoietic and the gastrointestinal (GI) systems (Figure 1).



Fig 1. The Acute Radiation Syndrome (ARS) is a combination of clinical syndromes occurring in stages during a period of hours to weeks after exposure to radiation, as injury to various tissues and organs is expressed.

The article focuses on the predictable deterministic effects of irradiation of 250-500mGy on the haemopoietic system. The simplest effect is cell death which prevents the cell from reproducing and performing its primary functions. The reader should recognise that the stochastic effects of bone marrow DNA damage leading to cancers have no threshold and may appear many years following exposure. These probability based effects will not be discussed. The target cells of radiation are the haemopoietic stem cells. The latent period is 14-28 days. The lymphocytes are the first to fall in numbers followed by neutrophils and the platelet count. Death is due to the complications of marrow failure which are infection and fatal haemorrhage. The systemic effects of the haemopoietic syndrome are those of bone marrow failure, for example, anaemia, immune dysfunction and haemorrhage. In addition, these factors, together with radiation microvascular damage, result in impaired wound healing. The management of the haematopoietic syndrome will need to take into consideration co-existing physical and NBC insults which when combined have a synergistic effect (Table 1).

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Table 1. A summary of the components of the haemopoietic syndrome and the clinical features.

Cell line	Clinical condition	Clinical features
<b>Mature cells</b>		
Erythrocytes Reticulocytes, red cells	Anaemia	Pallor, lethargy, dyspnoea
Granulocytes Neutrophils, Eosinophils, Basophils	Neutropenia	Fever, malaise, infections of mouth and throat, skin, chest, perianal region and septicaemia
Megakaryocytes Platelets	Thrombocytopenia	Spontaneous bruises, purpura, bleeding gums and venepuncture sites. Major internal haemorrhage.
Pancytopenia Red cells, granulocytes and platelets	Aplastic anaemia	Any of the above

## Blood cell formation (Haemopoiesis)

The bone marrow is the only source of new blood cells in the adult and during normal childhood. The developing cells are situated outside the bone marrow sinuses. Mature cells pass into the sinuses to be released into the general circulation. A common pluripotential stem cell gives rise after a number of cell divisions and differentiation steps to a series of progenitor cells for 3 main marrow cell lines erythroid, granulocytic /monocytic and megakaryocytic. The marrow is also the source of the common lymphoid stem cell (Figure 2)

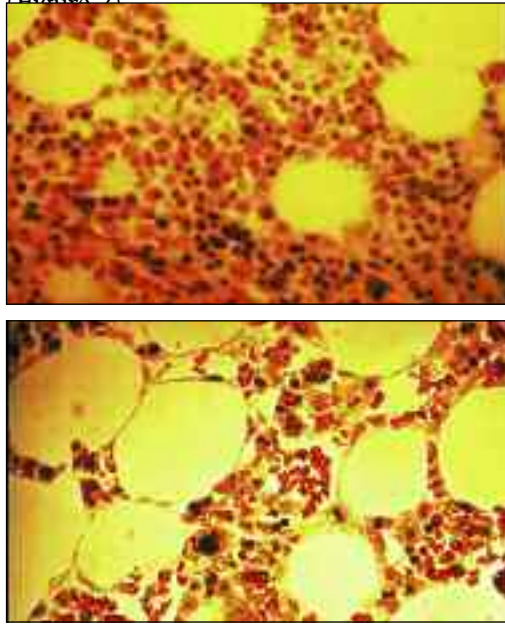


Fig 2. Bone marrow before and after irradiation. Radiation results in the loss of all 3 cell lines resulting in aplastic anaemia. The bone marrow trephine biopsy shows marrow hypoplasia with loss of haemopoietic tissue. Survival follows regeneration of the marrow from unaffected islets of cells

**Red cells.** The erythropoietic system is responsible for the production of mature erythrocytes (red cells). This system rapidly regenerates following radiation. Anaemia may lead to symptoms of lethargy and shortness of breath. Although anaemia may be evident in the later stages of the haemopoietic syndrome, it should not be considered a survivability limiting factor.

**White cells.** The function of the myeloid line is mainly to produce mature circulating granulocytes. The neutrophils are the most important cell type in this cell line because of their role in combating infection. The production of the mature neutrophil normally requires 3-7 days before distribution to venous splenic and bone marrow pools. All pools will be depleted soon after exposure to radiation, therefore evidence of damage to myelopoiesis occurs within 2-4 days. Recovery lags behind erythropoiesis and is accompanied by rapid increases in the numbers of differentiating

and dividing cells in the marrow.

**Platelets.** Platelets are produced by megakaryocytes in the bone marrow. Both platelets and megakaryocytes are relatively radiosensitive. The production period ranges from 4-10 days followed by a platelets lifespan of 8-9 days. Thrombocytopenia is reached 3-4 weeks after middle-range doses. Regeneration normally lags behind both erythropoiesis and myelopoiesis. Regeneration may be accompanied by a rebound phenomenon with supernormal levels of platelets.

**Lymphocytes.** Lymphocytes are the most radiosensitive aspect of the haemopoietic system. Shortly after exposure to ionizing radiation, mature lymphocytes show early necrosis and lymph nodes demonstrate nuclear debris within hours of irradiation. Lymphocytes disappear from the peripheral circulation in a dose-related fashion. The lymphopenia will begin within hours and proceed to its nadir within 48 to 72 hours. The fall in circulating lymphocytes can be used as a crude biodosimetry tool to estimate the effective radiation dose received.

The total bone marrow cellular mass is normally in an equilibrium state between cell formation, proliferation, maturation, and death. The haemopoietic system maintains a continuously high cell turnover rate and has a large reserve capacity. Figure 3 illustrates the sequence of cell line recovery following an exposure of 3 Gy.

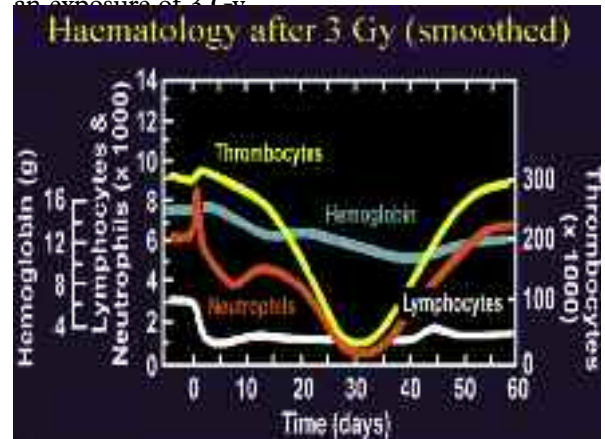


Fig 3. The higher the radiation dose, the more the marrow is affected. The risk period for opportunistic infections peaks after 3 weeks.

## Medical Management

The medical management of radiation and/or combined injuries can be divided into three stages: triage, emergency care, and definitive care. Clinical management will depend on the number of casualties, available medical facilities, and resources. Recommendations for the treatment of a few casualties may not apply to the treatment of mass casualties because of limited resources.

## Triage and Emergency Care

Effective triage relies on accurate analysis of early signs and symptoms, substantiated by biological parameters associated with

radiation exposure. Treatment plans must be determined after assessment of both radiation and other injuries.

Emergency care of the radiological casualty is based on treatment for any injuries other than radiation. This includes standard emergency procedures, as radiation injury does not induce immediately life-threatening conditions. Emergency care for these casualties includes antiemetics and maintenance of fluids and electrolytes.

Infection due to neutropenia will typically not be a problem until a week after exposure. However, invasive monitoring provides a nidus for infection which in the presence of neutropenia may present a life threatening risk. The use of central lines and urinary catheters should be kept to a minimum. Prophylactic antibiotics are not routinely required. The present recommendations are that treatment with antibiotics is only required in irradiated patients when there are specific signs of infection. In combined injuries, antibiotics should be administered as normal.

Estimation of the degree of radiation damage and exposure is difficult. Sequential diagnosis and reassessment is mandatory throughout the patient's clinical course. Prodromal symptoms begin within hours of exposure. They are characterized by gastrointestinal and neurovascular signs and symptoms, which can include nausea, vomiting, diarrhea, fatigue, weakness, fever and headache. The prodromal gastrointestinal symptoms generally do not last longer than 24 to 48 hours after exposure, but a vague weakness can persist for an undetermined length of time. The time of onset, severity, and duration of these signs are dose dependent and dose-rate dependent and should be used in conjunction with early biological parameters, such as lymphocyte and granulocyte levels, to determine the presence and severity of the acute radiation syndrome.

## Clinical Monitoring and Laboratory Testing

The rate and degree of decrease in blood cells are dose dependent. An initial baseline sample should be obtained as early as possible after irradiation. A useful rule of thumb is that if the lymphocytes have decreased by 50% and are less than  $1 \times 10^9/l$  within 24 to 48 hours, then the patient has received at least a moderate dose of radiation (see Figure 4).

In combined injuries, lymphocytes may be an unreliable indicator. Patients with severe burns and/or trauma to more than one system often develop lymphopenia. Associated injuries (trauma/burn) should be assessed by standard procedures, but signs and symptoms of tissue injuries can mimic and obscure those caused by acute radiation effects

Laboratory testing is primarily focused on protecting the patient and determining biological dosimetry. Table 2 lists recommended clinical laboratory studies (1) and the medical treatment level where they should be performed. It is important that peripheral blood specimens be drawn as early as possible and transported to the nearest laboratory with this capability for the establishment of a baseline complete blood count because of the rapid early decline of lymphocytes. Whenever possible, laboratory testing should include chromosomal aberration analysis. This sample, however, should not be drawn until 24 hours have elapsed to enable damaged lymphocytes to redistribute in equilibrium between peripheral circulation and tissue so that the sample obtained is representative of the whole- or partial-body exposure. If possible, clothing should be stored for later dosimetry evaluation. Physical dosimetry should be managed as described in STANAG 2474 (Table 2).

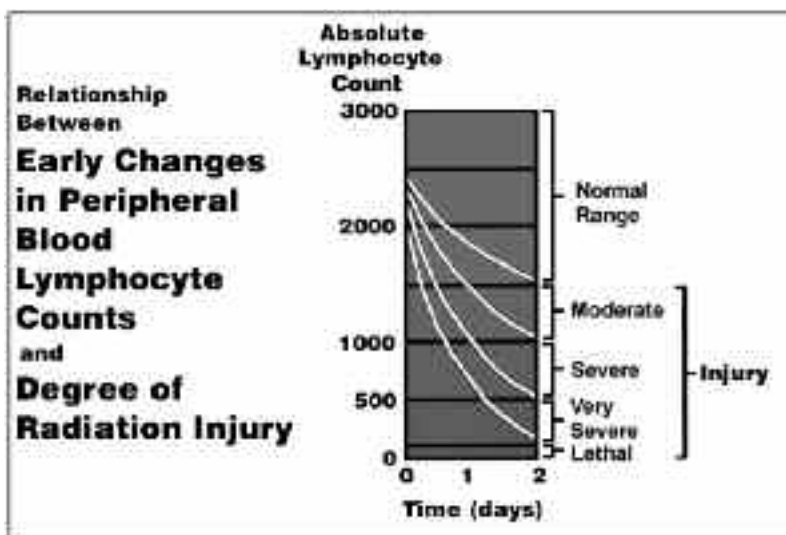


Fig 4. Lymphocyte nomogram. The curves roughly correspond to dose levels of 3.0, 4.5, 5.5, and 7 grays.

## Definitive medical care

Following a radiation incident, injured persons should be resuscitated and stabilized before transportation to treatment centres for further management. Patients who have received significant radiation injury should be referred to treatment centres that can evaluate and treat bone-marrow failure. While bone-marrow transplant is unlikely to be necessary, transplant teams generally have the most experience in resuscitation of the marrow. Patients with severe combined injury will have the best chance of survival at major medical centres. It should be noted that surgery must be completed by 36-48 hr or deferred until the effects of radiation on tissue healing and haemopoiesis have recovered. Mild haemopoietic syndrome patients can be treated at district general hospitals and as outpatients with advice and

consultation from radiation medicine experts. Mild to moderate combined injury casualties should be evacuated to hospitals with a broad range of medical and surgical specialties.

### Management of Neutropenia and Infection

Sepsis and its sequelae are the major causes of death in severely irradiated patients. The prevention and management of infection are the mainstays of therapy. There is a quantitative relationship between the degree of neutropenia and the increased risk of infectious complications. Antibiotic prophylaxis should only be considered in afebrile patients who are at the highest risk for infection.

Although the degree of neutropenia (absolute neutrophil count less than  $0.1 \times 10^9/l$  for more than 7 days) is the greatest risk factor for developing infection, other factors influence the treatment choice and outcome. Such factors include duration of neutropenia, bactericidal functionality of surviving neutrophils, alteration of physical defense barriers, the patient's endogenous microflora, and organisms endemic to the hospital and community. As the duration of neutropenia increases, the risk of secondary infections such as invasive mycoses also increases. For these reasons, adjuvant therapies such as cytokines will prove invaluable in the treatment of the severely irradiated person.

Table 2. Medical assay of the radiological patient.

Location /test	Decontamination point	Medical treatment unit (NATO role 2)	Hospital (NATO role 3)	Tertiary care (NATO role 4)
Nasal swabs for inhalation of contaminants	+		+	
External contamination	+		+	
Urine and stool sample for internal contamination	Baseline sample	24-h sample	+	
Complete blood count/platelets (4ml EDTA)	If practical	Baseline sample And daily	Daily x 2 wk	Daily x 2 wk
Absolute lymphocyte count (same sample as above)		Every 4-12 h	Every 4-12 h x 3 d	
Human leukocyte antigen subtyping (20 ml EDTA or Lithium heparin)		+	Draw sample before lymphocyte count falls	Draw sample before lymphocyte count falls
Cytomegalovirus *			+	+
Human syncytial cell virus antibodies				+
Human immunodeficiency virus (clotted sample)			+	+
Vesiculovirus				+
Haemoglobin agglutinin			+	+
Lymphocyte cytogenetics** (4 x 8ml Lithium heparin)		Draw sample and send to lab	Draw sample before lymphocyte count falls	+

\* Not available at UK role 3 facilities, will be performed at receiving role 4 hospitals.

\*\* The sample should be received as soon as possible after collection, therefore time collection with flight/courier schedules. Mix the samples well and keep cool but not frozen during transit. Packages for transit should be marked "DO NOT X-RAY" together with the usual biological sample markings.

## Prevention of Infection

Initial care of medical casualties with moderate and severe radiation exposure should probably include early institution of measures to reduce pathogen acquisition, with emphasis on low-microbial-content food, acceptable water supplies, frequent hand washing (or wearing of gloves), and air filtration. Prophylactic use of selective gut decontamination with antibiotics that suppress aerobes but preserve ordinarily commensal anaerobes may be recommended. These measures help control the alimentary canal source (mouth, esophagus, and intestines) of post-injury infections. Maintenance of gastric acidity (avoidance of antacids and H<sub>2</sub> blockers) may prevent bacteria from colonizing and invading the gastric mucosa and may reduce the frequency of nosocomial pneumonia due to aspiration of these organisms. The use of sucralfate or prostaglandin analogues may prevent gastric hemorrhage without decreasing gastric activity. When possible, an early oral immuno-incompetent diet is preferred to intravenous feeding to maintain the integrity of the gut. A tunnelled central venous catheter can be considered to allow frequent venous access, but meticulous attention to proper care is necessary to reduce disastrous catheter-associated infections.

## Management of Infection

Several principles have been stated that are generally applicable to the febrile neutropenic patient. Empiric antimicrobial regimen are highly effective for initial management of febrile, neutropenic episodes. The chosen regimen should take into account the spectrum of infecting organisms and antimicrobial susceptibility patterns belonging to the host institutions. Life-threatening, gram-negative bacterial infections are universal among neutropenic patients, but the prevalence of life-threatening, gram-positive bacterial infections varies greatly among institutions. The primary consideration should be given to locating the nidus of infection and, if possible, eliminating it. Central venous and indwelling catheters must be considered liabilities in these immunocompromised patients.

Adjuvant therapies for infection include immunoglobulins, cytokines and granulocyte transfusions. Immune globulins have not been shown to be beneficial for radiation casualties on a general basis. Granulocyte transfusion (GTX) of G-CSF-stimulated PMNs could prove effective therapy for severely neutropenic patients with sepsis who have failed to respond to appropriate antibiotic therapy.

## Cytokines

Cytokines are low molecular weight proteins involved in the inflammatory, immunologic and haematopoietic responses. They interact with high-affinity cell surface receptors. Haematopoietic growth factors (GFs), such as G-CSF (filgrastim) and GM-CSF (sargramostim), are potent stimulators of haematopoiesis. G-CSF and GM-CSF have a well proven track record in the support of bone marrow failure. The cytokines stimulate the production of colony forming units, decrease maturation time and increase the function of both neutrophils and macrophages. Cytokines reduce the period of neutropenia and the need for antibiotics leading to decreased hospital stay. Recommended doses are given in Table 3. Note that G-CSF and GM-CSF have not been approved by the FDA for radiation-injuries per se, but merely for the treatment of acute myelosuppression (Table 3).

*Table 3. Cytokine recommendations for patients who are expected to experience severe levels of febrile neutropenia*

G-CSF (filgrastim) 2.5–5.0 mg/kg/d (100–200 mg/m <sup>2</sup> /d)
GM-CSF (sargramostim) 5.0–10.0 mg/kg/d (200–400 mg/m <sup>2</sup> /day)
Recommended administration is once daily subcutaneously or intravenously.

G-CSF and GM-CSF are currently in widespread clinical use for the treatment of acute neutropenic conditions and, in turn, the management of infections following radiochemotherapy of cancer patients. Both agents have high therapeutic ratios, minimal, tolerable side-effects, and can be administered and monitored with relative ease. The predominant side-effect noted with G-CSF is medullary bone pain, which may be observed shortly after initiation of treatment. G-CSF may also exacerbate pre-existing inflammatory conditions. The most noted side-effects with administration of GM-CSF are fever, nausea, fatigue, headache, bone pain, and myalgia.

Therapeutic intervention with cytokines is warranted following external radiation exposures sufficient to elicit transient or progressive neutropenias (and/or thrombocytopenias). For acute doses of 2 grays or greater, G-CSF/GM-CSF administration may be recommended on the basis of hematological parameters. A benchmark absolute neutrophil count (ANC) of less than  $0.5 \times 10^9/l$  may be considered a threshold for beginning cytokine therapy in the first 2 days. Cytokine administration should continue, with daily consecutive injections, to reach the desired effect of an ANC of  $1.0 \times 10^9/l$  after the ANC nadir.

### Transfusion support

Blood components should be leucocyte depleted to reduce the risk of cell associated viruses such as cytomegalovirus. All blood products should receive 15 to 20 grays of radiation before infusion to prevent graft-versus-host disease. Packed red cells may be used to maintain haemoglobin above 8 gm/dl. The use of erythropoietin (Epo) after radiation injury is not currently recommended even though it is likely to be safe. Transfusion of platelets remains the primary therapy to maintain adequate platelet counts. As general supportive measures, one should avoid the use of aspirin and nonsteroidal anti-inflammatory drugs. The requirement for platelet support depends on the patient's condition. In irradiated patients without other major medical problems (infection, gastrointestinal problems, or trauma), the platelets should be maintained at greater than  $20 \times 10^9/l$ . If surgery is needed, the platelet count should be greater than  $75 \times 10^9/l$ .

### Bone-Marrow Transplant

Increasing doses of radiation lead to more protracted pancytopenia and increasing risk of death from infection and/or hemorrhage. Bone-marrow or peripheral stem cell transplant may be beneficial in those patients whose dose estimate approaches the LD50/60 for humans receiving clinical support, or 6 Gy free in air for whole-body uniform exposure. Note that accidental human exposures are unlikely to be whole-body uniform exposures. Part of the marrow will receive a lower dose and, therefore, be able to recover.

Stem cell support may be autologous, for example, the patient has predeposited their own stem cells or allogeneic, meaning that the cells are donated from another person. An appropriate tissue match is most likely to be found in a sibling donor. The major complications following autologous bone-marrow transplantation (ABMT) are those related to marrow failure similar to that following severe radiation exposure. In addition, there may be delayed engraftment or incomplete reconstitution, and potential "other organ" damage. Experience with BMT in patients with whole body doses of >12Gy has shown that even if the bone marrow is successfully reconstituted then death follows from other radiation complications (5).

Allogeneic bone-marrow transplant (allo-BMT) also presents the risk of graft-versus-host disease and graft rejection (Table 4).

The timing of marrow grafting is crucial and presents a dilemma. Experimental data suggest that the marrow should be infused within the first 3 to 5 days of radiation

Table 4. Patients being considered for allogeneic bone-marrow transplant must meet the following conditions.

- A fully matched sibling donor is available.
- The patient has an absolute lymphocytopenia
- The radiation dose is unknown but is likely to be between 6 and 20 grays.
- Irradiation is not ongoing from an internal source.
- There are no other injuries or diseases that preclude survival or preclude transplantation (e.g., severe burns).

exposure. This coincides with the peak period of immunosuppression, and graft rejection, therefore, will be less likely. Waiting for a week or longer after the radiation exposure would require some form of conditioning or immunosuppressive treatment to prepare the patient for a marrow graft. Such treatment may be less tolerated by the patient who is a radiation accident victim.

### Conclusions

The management of the haematopoietic syndrome is a key element in the medical care of the acute radiation syndrome. The optimal management must be started within a time line of hours and days rather than weeks. The short time lines require rapid decontamination and triage of radiological and conventional injury. Radiological triage requires, in turn, access to the laboratory or advanced point of care testing for lymphocyte monitoring. Surgery should be completed within 2 days. The optimal management for the moderately irradiated patient may require access to cytokines within 2-3 days to reduce the impact of neutropenia. The situational context will dictate whether this is delivered forward of role 4 facilities. Allogeneic stem cell support is best performed within 3-5 days of exposure in order to reduce the need for additional conditioning with chemotherapy. Most patients have a reasonable chance of surviving a radiation dose of 8 grays without transplant, if supported in an appropriate medical facility with fluids, blood components, antibiotics and cytokines.

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