

Assessment and treatment requirements of public hospitals to radiation emergencies

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Abstract

Radiological emergencies present unique challenges to the public health care system and carry the potential for major disruptions to clinical care. This review aims to present, first a brief guide of the main clinical and laboratory diagnostic tools for the assessment of the absorbed dose in cases of radiological emergencies and second, the best treatment options for acute whole body and local radiation syndromes. Clinical and laboratory state-of-the-art biodosimetry tools, therapies for acute radiation syndromes according to the severity of the radiation sickness and isotope-specific preparedness medications as counter-measures for internal contamination are herein proposed as the necessary stockpile of public hospitals against severe radiological accidents.

Key words: radiological incidents, radiation emergencies, biodosimetry, acute radiation syndromes, radiation treatment

Introduction

The public exposure to ionizing radiation poses a tremendous and complex challenge to the health system [1], due to the degree of hospital preparedness, the availability of special resources and the technical skills from the involved personnel required to confront this kind of emergency [2]. Among the requirements to cope with radiation emergencies, public hospitals need high-end diagnostic tools and treatment options. Both these items will be described beneath, according to the data of relevant bibliography and the long occupational experience of the authors.

Radiation Dose Assessment

After either external exposure to radiation or contamination with radionuclides, the radiation dose received by the victims should be assessed for optimal medical treatment, prognostic advice and epidemiological analysis. This is particularly important, because in whole body absorbed doses of more than 1 Gy, dose-dependent deterministic effects, like radiation sickness or hematological syndrome, may appear in the following weeks or months to the victims. On the other hand, in absorbed doses of less than 1 Gy, chronic stochastic effects, like cancer or genetic abnormalities may develop and the potential risk of that perspective needs to be calculated to

establish continuing follow-up of these high-risk individuals [3]. Estimation of absorbed dose may be accomplished mainly by dosimetric readings, physical reconstruction of the exposure conditions, clinical symptoms and signs and specific laboratory measurements.

Radiation biodosimetry is a continually developing field, which focuses on specific clinical and laboratory biological markers, whose values express known relationship to the absorbed dose of ionizing radiation [4]. The field of radiation biodosimetry starts from hospital triage and emergency treatment and extends to mass screening and managing large-scale population exposures to unknown levels of radiation [5, 6]. From the hospital-care point of view, radiation biodosimetry is based on clinical symptoms and laboratory measurements; both will be presented underneath.

Clinical biodosimetry

The most common clinical symptom after exposure to high doses of ionizing radiation is vomiting; the time to onset of vomiting and the severity of the symptoms are related to the dose rate and the total dose received. Generally, the higher the absorbed dose, the faster is the onset of vomiting and the heavier the severity of symptoms [7, 8]. As an example, vomiting onset in less than 4 hours after irradiation corresponds to whole body absorbed dose of more than 2 Gy and it is strongly indicative that acute

hematologic syndrome will develop in about 30% of victims; if however, vomit occurs within one hour, the exposure is expected to be lethal in more than 90% of victims, with an estimated whole body absorbed dose of more than 6 Gy. Though non-specific, because other pathologic or psychogenic causes of vomiting need to be excluded, the time to onset of vomiting remains the most sensitive clinical sign to assess absorbed dose [3].

As regards local organ injury, skin is the most typical example of dose related damage; erythema will appear in local doses of more than 3 Gy; desquamation, blister formation and ulceration will need doses in the range of 10-20 Gy, whilst necrosis will emerge in even higher doses. In all cases of skin damage the time of onset is expected within 2-3 weeks [9].

Laboratory biodosimetry

C-reactive protein and serum amylase were two of the first biochemical serum markers of whole body irradiation [10]. Through the years laboratory biodosimetry has largely expanded into the fields of genomics (changes in genome expression investigated by use of recombinant DNA technologies and bioinformatics) and proteomics (changes in proteomic profiles of cytokines), to estimate the level of individual radiation exposure. In real practice however, the two major laboratory techniques are the lymphocyte depletion kinetics and the cytogenetic biodosimetry.

Lymphocyte depletion kinetics (LDK)

Lymphocytes are the most sensitive blood cells in irradiation and show a rapid and predictable decline after exposure to radiation. The total lymphocyte count should be measured every 6 hours for the first 2 days and then periodically. A fall of more than 50% in the first day suggests a potentially lethal absorbed dose [11]. A similar pattern is also observed in the medium term, showing practically zero lymphocyte count at 6 days after exposure in lethal doses (> 8 Gy) [9].

Cytogenetic biodosimetry (CB)

Cytogenetic biodosimetry refers to a range of sophisticated laboratory techniques to quantify ionizing radiation doses absorbed by exposed individuals [12]. The most important cytogenetic biodosimetry tools are:

a. Dicentric chromosome assay (DCA); it is based on the principle that radiation causes DNA double strand breaks, thus producing an accurately dose-dependent number of dicentric chromosomes in peripheral blood lymphocytes. DCA is the optimal biodosimetry technique when blood samples are collected in less than 2 months after irradiation [13], it is standardized by ISO at all reference biodosimetry laboratories [14] and is alone recommended as the reference technique by the IAEA [15]. DCA requires significant technical expertise and is time consuming, requiring at least 3-5 days after sampling, thus making non-applicable dosimetric requirements on an emergency basis, but is very sensitive and specific even at doses as low as 0.05 Gy [16].

b. Cytokinesis-block micronucleus (CBMN) assay is another accurate laboratory biodosimetry tool, being easily automated, simpler and technically less demanding than DCA. It is sensitive to absorbed doses above 0.3 Gy, an adequate value to discriminate victims of radiological emergencies from individuals requiring continuous surveillance [15, 17].

c. Fluorescence in situ hybridization (FISH) assay; it retrospectively identifies radiation-induced chromosomal translocations, which unlike DCA and CBMN, can persist

decades after the exposure. Though of limited availability and accuracy, as well as of higher cost, the FISH technique is superior to the previous assays in samples older than one year [18, 19].

d. Less common laboratory biodosimetry assays are the premature chromosome condensation and the electron paramagnetic resonance assays, with the second used in dry specimens, e.g. teeth, bones and fingernail clippings. Furthermore, it has been applied in longitudinal studies of severe radiological exposures from accidents or atomic bomb survivors [3].

In addition to clinical and laboratory biodosimetry tools, absorbed dose of internal radiological contamination may be assessed by surveying activities with specific radiation counting devices and probes from the whole body and specific organs, as well as from urine, faeces, pulmonary and gastric lavage washings, nasal swabs and wound dressings. Whole body counters are much more sensitive to detect internal and residual external contamination compared to portable detectors. And yet, various online algorithms for absorbed dose estimation based on clinical and biological data are available from the Radiation Event Medical Management website [20].

Depending on the availability of the equipment, the type of the assay applied, the number of patients to be measured and logistics, laboratory dosimetric results may require several days till weeks to be available [21]. Since biodosimetry resources are crucial for the mitigation of radiological incidents, standardized and reproducible assays among laboratories are essential for accurate biodose assessment. Many countries have established biodosimetry laboratories which apply standardized techniques as an integral part of their national radiation protection strategy. Albeit DCA is intrinsically time-consuming and available only in selected certified centers worldwide, there is currently an urgent need for revising existing biodose laboratory tools, by shortening the analysis time (e.g. with computer-aided microscopy), by interconnecting with similar laboratories through the web and by improved documentation and reporting [22]. A broader applied, user-friendly software tool to assist in the comprehensive evaluation and interpretation of clinical, dosimetric and therapeutic data of radiation victims has been developed by the U.S. Armed Forces Radiobiology Research Institute and is called Biodosimetry Assessment Tool (BAT) [23]. Nonetheless, although the utility of approaches using only clinical and routine laboratory findings to stratify victims into risk groups during large radiological incidents is still unclear [24, 25], time to onset of vomiting and the absolute lymphocyte count are universally considered the most practical clinico-laboratory combination to rapidly estimate the absorbed dose during the first days after exposure [7].

Treatment requirements

Treatment of Acute Radiation Syndromes

Acute radiation sickness (ARSI) is defined a serious illness occurring after irradiation of the entire body with high doses in a short time. Typically, the first symptoms of ARSI are non-specific, including nausea, vomiting and diarrhea. The first symptoms start within hours to days after irradiation and last for hours up to several days; the victim may then feel healthy for some time (latent period), till he/she will become sick again with more severe symptoms, even seizures and coma. The third stage may last for hours up to months [26]. ARSI is manifested with various clinical syndromes called acute radiation syndromes (ARS); their severity is dose related,

as follows [27]: Haemopoietic syndrome, in doses more than 2-6 Gy, gastrointestinal syndrome, in doses more than 6-8 Gy and neurological syndrome, in doses more than 12-15 Gy. The clinical pattern of each syndrome is divided into three phases: a prodromal phase, occurring during the first few hours after exposure, a latent phase that shortens with increasing total dose and dose rate, and a manifest clinical phase that will result either in recovery or death [28]. Depending on whole body absorbed dose victims can be stratified into those who:

- a. Will not need further medical intervention;
- b. Could benefit from supportive treatment;
- c. Require aggressive treatment;
- d. Cannot be saved.

After an international consensus meeting in 2005, a biodose clinical grading system has been established, as a unified basis for individualized medical management of victims from radiological accidents, based on clinical data from 70 such accidents, including 800 victims. That system is called METREPOL (Medical Treatment Protocols for Radiation Accident Victims) and assesses acute neurovascular (N), hematologic (H), cutaneous (C) and gastrointestinal (G) damage for early prognosis of multi-organ failure. The severity grade for each index ranges from 0 (no damage) to 4 (irreversible damage). The final scoring is expressed in alphanumeric form e.g. N2H3C4G0 [29].

Dosimetric considerations

When speaking of partial-body, fractionated or chronic irradiation, outcome prediction is challenging due to difficulties in partial-body dosimetric calculations, variations of damage among organs and activation of the body's repairing mechanisms which mitigate the initial radiobiological impact. Due to the complex nature of radiation injury no single therapy or medication will provide benefit against all aspects of it; combined and specialized supportive therapies will probably be required in more patients than initially expected to gain significant prognostic improvements [30].

Experience from severe past radiological incidents indicates that supportive care alone can increase survival probability [28]. More specifically, the LD50 values in victims with no or minimal medical treatment have been estimated to 4.5 Gy in low rate irradiation and 3.29 Gy in high rate; when best supportive medical treatment is applied, respective values get almost double, to 7.81 and 6.13 Gy, respectively. However, longitudinal survival rates are much less impressive; the twelve-month survival rate from acute whole body irradiation with more than 6 Gy approximates zero, due to a systemic syndrome affecting the internal organs and mostly the cardiovascular system, called radiation-induced multi-organ dysfunction (RiMOD) [3].

Treatment of high absorbed whole body doses

Patients having received doses lower than 2 Gy, are generally not expected to manifest ARS and may be provided home-care instructions and close outpatient follow-up. In doses higher than 2 Gy, after initial triage, decontamination and diagnosis of ARS, treatment modalities include [11]:

- a. Symptomatic relief, i.e. analgesia, antipyretics for fever and common anti-emetics for nausea and vomiting; however in doses higher than 3 Gy most patients will require serotonin receptor antagonists.
- b. Fluid administration, to maintain fluid balance and

well-cooked, low-residue enteral feeding, free as possible from infection sources, to preserve calorie balance and gut function.

c. Acute radiation exposure definitely compromises the immune system of radiological victims and polymicrobial septic infections tend to accompany radiation injuries [31]; thus antibiotics should be prophylactically administered when the neutrophil count is lower than 500 cells per microliter, conjugated with prophylactic or therapeutic anti-viral treatment.

d. Blood product transfusions will be required in radiological victims suffering non-irreversible myeloablation. Blood may be transfused either as whole, or as blood products (red cells and platelets).

e. Granulocyte-colony stimulating factors (G-CSFs) have the potential to accelerate bone marrow recovery after whole body irradiation [32] and act as radio-mitigators when combined with additional supportive care and blood product transfusions. G-CSFs have been successfully applied in radiation victims of the Goiânia, San Salvador, Soreq and Nesvizh accidents [33-36]. Despite many extensive reviews in recent bibliography, only two of these growth factors, Neupogen® and Neulasta® have been approved till now by U.S. FDA for treatment of ARS [3].

f. Stem cell transplants, including umbilical cord blood and bone marrow transplants, may be required in victims of large-scale radiological incidents who will suffer irreversible myeloablation. Till 2005, only 31 patients worldwide have undergone allogenic haemopoietic stem cell transfusion (HSCT) after severe radiological accidents [37] and no more thereafter. Although bone marrow transplantation (BMT) is the only alternative when spontaneous marrow recovery is not possible [38], the medical data gathered from the accidents at Chernobyl and Soreq in Israel [39, 35] strongly suggest that due to age and histocompatibility constraints, BMT should be considered only for victims having received uniformly distributed whole body doses of 8 till 12 Gy, with no serious cutaneous or conventional injuries and with no severe internal contamination.

g. Cutaneous radiation injury (CRI) is the injury caused by significant irradiation of the skin. It may result either alone, or combined with the systemic symptoms of ARS or conventional injuries, such as thermal burns or blast trauma. The clinical symptoms vary and the onset is usually delayed. Treatment of CRI is notoriously challenging, involving specialized assessment of plastic surgeons and radiation oncologists as well as lifelong follow-up in severe cases due to the very long healing time of deep lesions. More specifically, CRI treatment is largely symptomatic, requiring general supportive measures against dehydration, hypothermia, infections and nutritional deficiency. In the acute phase of skin irradiation, continuous washing with cool water may reduce initial inflammation, followed by antihistamine, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or even opioids in severe cases with intense pain, to achieve adequate analgesia. Infection is a major complication often conjugated with compromised hematopoietic system and requires careful application of antiseptics and antimicrobials. Skin necrosis requires autologous cutaneous grafts whenever possible, although in extended or combined injuries this may be inapplicable [3].

In case of a severe radiological incident requiring tertiary hospital management, both non-contaminated and decontaminated patients are triaged for estimation of the severity of radiological deterministic effects, either of ARS or subclinical radiological effects:

- a. Patients with subclinical deterministic radiological effects have typically received a dose of less than 2 Sv, are all in ambulatory state and without clinical symptoms, or they present

mild signs of radiation sickness. They usually need no Intensive Care Unit (ICU); rather they are admitted in the general ward of the Hospital, wherein they undergo radiobiological estimation of stochastic and chronic effects and future health risks and they are also enrolled in long-term health follow-up protocols.

b. Patients with mild or moderate ARS (1st - 2nd degree) are ambulatory and they are admitted in either the general ward of the Hospital, or in general ICU, wherein they receive broad-spectrum antibiotics, blood or blood components transfusion and possibly, anti-neutropenic agents, e.g. colony stimulating factors.

c. Patients with severe ARS (3rd - 4th degree) are urgently admitted in specialized ICU, or by case in a Burn Care Unit (BCU), wherein apart from previous therapies, they receive total parenteral nutrition, growth factor therapy, and typically require stem-cell allogenic transplantation (Table 1).

Table 1

ARS therapies according to severity of the syndrome

THERAPY	ACUTE RADIATION SYNDROME THERAPIES			
	1st degree	2nd degree	3rd degree	4th degree
Ambulatory – General ward admission	√			
General Intensive Care Unit		√		
Broad-spectrum antibiotics		√	√	√
Blood components transfusion		√	√	√
Colony Stimulating Factor (CSF)*		√	√	√
Specialized Intensive Care Unit			√	√
Total Parenteral Nutrition			√	√
Plasmapheresis			√	√
Growth Factor Therapy			√	√
Cytokines therapy (Interleukin-3)			√	√
Stem-cell allogenic transplantation				√

* Anti-neutropenic agents (e.g. Filgrastim)

Internal contamination medications

Internal contamination refers to internal dispersion and incorporation of radionuclides by the human tissues and organs via inhalation, ingestion or any other route of biological absorption depending on their chemical and biodistribution properties [40]. Their depletion from the body varies largely and is measured by the effective half-life of each radionuclide, ranging from a few days (e.g. one week for radio-iodine) to many decades (e.g. 50 years for plutonium). Although it is unusual for internally absorbed doses to provoke ARS, the ongoing irradiation of tissues and organs increases the risk for stochastic effects, mostly of malignancies [21]. The key point for maximum effectiveness of internal contamination countermeasures is therapy commencement with radionuclide-

specific medications, called radiological antidotes, as early as possible. Antidotes administration should be based on chemical and metabolic behavior of each radionuclide, the route of exposure and absorption, availability of resources and individual patient status [41]. The main categories of radiological antidotes clinically approved for human use are the following:

Potassium iodide

Potassium iodide it is an effective blocking agent against radioiodine uptake from the thyroid gland after a radiological emergency releasing radioactive iodine (e.g. a nuclear plant accident). Normal thyroid accumulates avidly about 30% of the radioiodine and blocking of the gland should start not longer than 4 hours after exposure [42, 43]. The recommended dose is a 130 mg received orally for adults, half that dose for children 3-18 years, one quarter for infants 1 month to 3 years and one eighth for new-born infants. Potassium iodine stockpiling for immediate post-exposure mass prophylaxis is a prudent public health measure, albeit the presence of this agent in large quantities carries a potential risk for unintentional or deliberate misuse [44].

Prussian blue

Prussian blue (potassium ferric hexacyano-ferrate); it is a decorporation agent that binds the radionuclides of cesium and thallium, increases their excretion through the feces and prevents their reabsorption from the gut into the blood [45]. The proposed optimum dose in case of, e.g. contamination with Cs-137 is 3 gram per day, administered in fractionated doses at regular intervals. Therapy with this antidote may last for long periods of time, even months, in severe cases, like the case of the accident in Goiânia, Brazil, where 46 individuals in total received orally this medication in various doses and timing [33]. Importantly, the effective half-life of Cs-137 was reduced on average to one third, thus rendering this agent an excellent radiological antidote for Cs-137, even when administered several days after contamination. Nonetheless, stockpiling of this agent before a radiological event in hospitals remains again challenging [33].

Decorporation chelating agents;

Decorporation chelating agents; they eliminate specific radionuclides from blood circulation and body tissues by increasing the biochemical turnover and excretion by the kidneys. Chelating agents are more effective when applied soon after exposure and before incorporation of radionuclides by bone, liver and other target organs [46]. Diethylene-triamine-penta-acetic acid (DTPA) complexes with calcium or zinc have been successfully used in the treatment of internal contamination with soluble salts of various radioactive heavy metals [21, 41, 47]. Considerations regarding the commonest radioactive heavy metals requiring antidotes:

a. Uranium; industrial grade or depleted uranium is weakly radioactive and the chemical toxicity of soluble uranium salts in kidneys is of greater concern compared to its radioactivity [48]. Calcium or zinc DTPA chelates are not effective in the treatment of uranium toxicity, unless administered the very first hours. A rather better option is sodium bicarbonate treatment, which produces a less nephrotoxic complex that is also more readily excreted [49].

b. Americium; after absorption it is deposited mainly in bone and liver, intimidating bone marrow suppression and hepatic failure [50]. DTPA chelates increase urinary excretion of americium by 50 times; calcium chelate is considered more

efficient in the first hours, but zinc chelate is better tolerated.

c. Cobalt; it is an essential metal of most human tissues, mainly concentrated in the liver. DTPA chelates are of limited effectiveness; penicillamine is rather preferred in cases of significant absorption of radioactive cobalt, though urinary excretion is expected to be increased by only one third [51].

d. Polonium; the extremely dangerous isotope polonium-210 is one of the few radionuclides able to cause symptoms of lethal ARS within a week after ingestion; death comes as a result of multi-organic failure after oral ingestion of only 1 microgram of polonium-210, which is regarded as lethal dose, whilst ARS will appear sooner when higher doses are intaken [52-54]. Sulfhydryl-chelates, like DMSA (succimer; dimercaptosuccinic acid) may help in polonium poisoning by increasing renal excretion of polonium, though not undoubtedly [21].

Concerning medications for internal contamination, radiological antidotes may be enough for contamination with low levels of absorbed dose, but alone they are not adequate treatment against high level exposure. Potassium iodide and Prussian blue are included in WHO's list of essential medicines required in a basic health system [55]; decorporation chelates though, are not. In any case, sufficient amounts of antidotes should be immediately available in mass-casualties situations [56]. Thus, radiological preparedness of a hospital requires stockpiling of adequate quantities and types of such medications; several consensus guidelines for radiological antidotes stockpiling have been proposed [57]. These should be added in the preparedness list for hospital medications against radiological accidents (Table 2).

Conclusion

The complex medical nature of radiological emergencies poses unique challenges to the public health care system and carries the potential for major disruptions to clinical care.

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Table 2

Main preparedness medications list against radiological accidents

Radionuclide	Antidote	Main Reference	Efficacy
I-131	KI	[58]	+++
Cs-137	Prussian blue	[9]	+++
Am-241	Ca/Zn-DTPA	[50]	++
U-235/238	NaHCO3	[48]	+
Co-60	penicillamine	[51]	+
Po-210	DMSA	[52]	+

Comprehensive preparedness requirements of public hospitals as described in this study are essential features for proper national and global radiological response. Various aspects of advanced radiological preparedness, including clinical and laboratory biodosimetry, along with treatment of acute radiation syndromes, external irradiation or internal contamination are herein also presented, along with concrete clinical proposals. These aspects imply a novel preparedness doctrine regarding more sophisticated radiological response planning in the public health sector. Ultimately, by further refining the currently available clinical and laboratory diagnostic tools and by providing specific therapeutic protocols and isotope-specific medications, the health management of radiological incidents and emergencies in public hospitals is expected to be further promoted.

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