“Radiation Emergency Medicine at REAC/TS”

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865-576-1005 (24/7 number)
The Department of Energy’s National Nuclear Security Administration is prepared to respond immediately to any type of radiological accident or incident anywhere in the world with these seven emergency response assets.

Aerial Measuring System
AMS detects, measures, and tracks radioactive material at an emergency site to determine contamination levels.

Atmospheric Release Advisory Capability
ARAC develops predictive plots generated by sophisticated computer models.

Accident Response Group
ARG is deployed to manage or support the successful resolution of a U.S. nuclear weapons accident anywhere in the world.

Federal Radiological Monitoring and Assessment Center
FRMAC coordinates federal radiological monitoring and assessment activities with those of state and local agencies.

Radiological Assistance Program
RAP is usually the first NNSA responder for assessing an emergency situation and deciding what further steps should be taken to minimize the hazards of a radiological emergency.

Radiation Emergency Assistance Center/Training Site
REAC/TS provides treatment and medical consultation for injuries resulting from radiation exposure and contamination, as well as serves as a training facility.

Nuclear Emergency Support Team
NEST provides the nation’s specialized technical expertise to the federal response in resolving nuclear/radiological terrorist incidents.
REAC/TS Medical Experience in Radiation Accident Response (1976-4/2008)

Calls for Assistance  2416

Patients seen at REAC/TS  222
The new REAC/TS Automated Cytogenetic Workstation has automated slide handling and scanning. Computer karyotyping (identification/arranging) of the chromosomes and identification of aberrations, unlike the old system where the cytogeneticist had to score by hand.
Objectives

- Describe the signs and symptoms, diagnostic procedures and clinical phases of the acute radiation syndrome (ARS).
- Discuss the pathology of the various components of the acute radiation syndrome.
- Describe the current medical capabilities and role for supportive and other medical care (drugs/procedures) in the initial management of ARS patients.
Acute Radiation Syndrome

- ARS is an acute illness, which follows a generally predictable course over a period of time ranging from a few hours to several weeks after high-level exposure to ionizing radiation, effecting initially and primarily (in the lower doses) the marrow compartment.

- ARS is characterized by the dose dependent development of groups of signs and symptoms which are manifestations of the reactions of various body organ systems (BM, GI, CNS, Pulmonary, SKIN) to large volume or essentially whole body irradiation.
Comparison of Lymphocyte Counts with Values Predicted by Andrews’ Model

Time to Emesis (Function of Whole Body Radiation Dose)
The coefficients $\alpha$ and $\beta$ with estimates of SE for dicentric calibration curves

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>$\alpha \pm \text{SE}(\text{Gy}^{-1})$</th>
<th>$\beta \pm \text{SE}(\text{Gy}^{-2})$</th>
<th>$\alpha/\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60Co gamma rays</td>
<td>0.059 $\pm$ 0.0136</td>
<td>0.029 $\pm$ 0.0046</td>
<td>2.03</td>
</tr>
<tr>
<td>250-kVp x rays</td>
<td>0.098 $\pm$ 0.0209</td>
<td>0.044 $\pm$ 0.0093</td>
<td>2.23</td>
</tr>
<tr>
<td>Fission neutrons</td>
<td>0.667 $\pm$ 0.003</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
# AFRRI Recommendations for Chromosome Biodosimetry

<table>
<thead>
<tr>
<th>Dose Range (Gy)</th>
<th>Proposed Validated Dosimetry Method</th>
<th>Prodromal Effects</th>
<th>Manifest Symptoms</th>
<th>Survival Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 - 1</td>
<td>Dicentric/PCC</td>
<td>none to mild (1-48 h)</td>
<td>none to slight decrease in blood count</td>
<td>almost certain</td>
</tr>
<tr>
<td>1.0-3.5</td>
<td>Lymphocyte depletion kinetics/dicentrics/PCC</td>
<td>mild to moderate (1-48 h)</td>
<td>mild to severe bone marrow damage</td>
<td>0-10% death</td>
</tr>
<tr>
<td>3.5-7.5</td>
<td>Lymphocyte depletion kinetics/PCC</td>
<td>severe (1-48 h)</td>
<td>pancytopenia, mild to moderate GI damage</td>
<td>10-100% death within 2-6 weeks</td>
</tr>
<tr>
<td>7.5-10.0</td>
<td>Lymphocyte depletion kinetics/PCC</td>
<td>severe (&lt;1 h -48 h)</td>
<td>combined BM and GI damage</td>
<td>90-100% death within 1-3 weeks</td>
</tr>
<tr>
<td>&gt; 10.0</td>
<td>PCC</td>
<td>severe (minutes to &lt;48 h)</td>
<td>GI, neurological, cardiovascular damage</td>
<td>100% death (within 2-12 days)</td>
</tr>
<tr>
<td></td>
<td>Day 0 (4:00 p.m.)</td>
<td>Day 1 (7:00 a.m.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worker A</td>
<td>176</td>
<td>2143</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worker B</td>
<td>421</td>
<td>2454</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worker C</td>
<td>104</td>
<td>1094</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prodromal Signs and Symptoms of High Level Radiation Exposure

- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Fever
- Conjunctivitis
- Skin erythema
When Patient is Medically Stable, Further Triage Is By Estimation of Radiation Dose Through Multi-Parameter Techniques

- Obtain patient history, especially the time to onset and severity of nausea and vomiting following the time of radiation exposure.
- Obtain CBC as early and as frequently as possible after exposure for monitoring the rate of decline in absolute lymphocyte count and possibly the neutrophil / lymphocyte ratio.
- Obtain a blood sample for quantifying chromosome dicentric aberrations (the Gold Standard), or possibly micronuclei, in the peripheral blood lymphocytes—and, for determination of serum amylase.
Low-dose Deterministic Effects

- \(< 10\) cGy, whole body: no detectable difference in exposed vs. non-exposed patients
- \(\sim 20\) cGy, whole body: detectable increase in chromosome aberrations. No clinical signs or symptoms
- \(\sim 12\) cGy, whole body: sperm count decreases to minimum about day 45
- \(\sim 75-100\) cGy, whole body: detectable bone marrow depression
Acute Radiation Syndromes

Subclinical ........ 0 - 100 cGy

Hematopoietic......100 - 800 cGy

Gastrointestinal......800 - 3000 cGy

CV/CNS...............> 3000 cGy
Bone Marrow Depression

G.I. Death

Dose (Gy)

0  2  4  6  8  10  12

LD$_{50/60}$ (no treatment)

LD$_{50/60}$ (with antibiotics and nursing)

Stem Cell Transplant

Phases of the Acute Radiation Syndrome

- Prodromal period.
- Latent period.
- Period of manifest illness.
- Period of recovery or death.
Haematopoietic syndrome

Normal bone marrow cells
Survival potential

Bone marrow damaged by radiation injury
Hematological response to 1-3 Gy, whole body exposure to ionizing radiation
Neutrophil Counts after Chernobyl

White Blood Cells in Patients Exposed to Radiation During the Chernobyl Accident

Vorobiev, Stem Cell; 15 (suppl2): 269-274

Leukocytes/mm³

Time Postirradiation (days)
Systemic Effects of Hematopoietic Syndrome

- Stem cell depletion
- Neutropenia and often pancytopenia
- Increased infectious complications - sepsis
- Hemorrhage
- Anemia
- Impaired wound healing
Effects of Gastrointestinal Syndrome

- Malabsorption
- Ileus - vomiting; GI distention
  - fluid and electrolyte shifts
  - dehydration
  - acute renal failure
  - cardiovascular collapse
- GI bleeding
- Sepsis
Gastrointestinal (GI) syndrome (8-30 Gy)

Pathophysiology of the GI Syndrome

- Depletion of the epithelial cells lining lumen of gastrointestinal tract
- Intestinal bacteria gain free access to body
- Haemorrhage through denuded areas
- Loss of absorptive capacity
Cardiovascular / CNS Syndrome

- Vomiting and diarrhea within minutes
- Confusion and disorientation
- Severe hypotension
- Cerebral edema
- Convulsions - coma
- Hyperpyrexia
- Fatal within 24 to 48 hours
Influence of Clinical Support and Cytokine Therapy on Survival ($LD_{50/30}$) of Irradiated Canines

- Non Support
- Clinical Support
- Cytokine Therapy

Percent Mortality vs Dose (cGy)

- $LD_{50/30}$
- 260
- 338
- 510

Key:
- rhG-CSF
- rcSCF
- rcG-CSF
- rcSCF + rcG-CSF
Medical Management of the ARS

- Primary goal of hematopoietic support is reduction in both depth and duration of leukopenia.
- Prevention and management of infection is mainstay of therapy.
- Quantitative relationship between degree of neutropenia and increased risk of infectious complications.
- Absolute neutrophil count (ANC) < 100/mm³ is greatest risk factor.
Colony Stimulating Factors

- G-CSF - Neupogen™
- Pegylated G-CSF - Peg-filgrastim, Neulasta™
- Granulocyte-Macrophage (GM-CSF) - Leukine™, sargramostim
- Use G-CSF or GM-CSF as soon as diagnosis of serious radiation injury is made
- ~PBSC or cord blood transplant if > 8 Gy, or
- ~BMT > 9 Gy
Absolute Neutrophil Count (ANC) for Canines Exposed to 350 cGy Cobalt

Canine Serum

G-CSF 10µg/kg BID d1-23 or
G-CSF 10µg/kg QD d1-23
G-CSF 5 µg/kg QD d1-23
G-CSF 5µg/kg QD d10-23 or
d9-23

Severe Neutropenia
Initiation and Duration of Cytokine Administration

- Benchmark absolute lymphocyte count less than 500/mm$^3$ threshold for beginning cytokine therapy in first 2 days
- Continue cytokine administration with daily injections to reach ANC of 1000/mm$^3$
- This regimen provides an optimum opportunity for neutrophil recovery
Cytokine Dosage

- **G-CSF Filgrastim (Neupogen<sup>R</sup>)**
  - 2.5-5.0 µg/kg/day (100-200 µg/m²/day)

- **GM-CSF Sagramostim (Leukine<sup>R</sup>)**
  - 5.0-10.0 µg/kg/day (200-400 µg/m²/day)
  - Begin therapy as early as practical for maximum effect
Infection Management of the ARS

- Antibiotic prophylaxis
- Barrier/isolation
- Gut decontamination
- Antiviral agents
- Antifungal agents
- Pneumocystis prophylaxis
- Early cytokine therapy
- Close wounds
- Avoid invasive procedures
Isolation Issues

- Treat ARS patients with estimated WB > 2 Gy in isolated rooms.
- Warn nursing personnel of the need for rigorous environmental control including:
  - Laminar flow isolation
  - Strict hand washing before and after patient care
  - Surgical scrubs for staff
  - Gowns, caps, gloves, masks for staff
  - Double bagging of all disposables
Prevention of Infection in Immunocompromised Patients

- Suppression of micro-organisms
- Physiological interventions
  - Maintenance of gastric acidity
  - Avoidance of antacids and H₂ blockers
  - Use of sucralfate for stress ulcer prophylaxis when indicated to reduce gastric colonization and pneumonia
- Early oral enteral nutrition (when feasible)
- Adequate personal hygiene
  - Povidone-iodine (Betadine) or chlorhexidine for skin disinfection, shampoo
  - Oral hygiene (brushing and flossing)
Antibiotics

- Antibiotic prophylaxis (Gram negative, HSV, fungal)
  - Fluoroquinolone
  - Acyclovir
  - Diflucan
  - Infectious Disease Society of America (IDSA) guidelines are helpful
- Address underlying foci for neutropenic fever
  - Integument and GI injury
  - Anaerobic coverage if indicated
Neutropenic Fever

- Cultures covering all possible foci of infection should be performed.
- In patients who experience first fever, traditionally the FQ is stopped and therapy directed at gram-negative bacteria (in particular, Pseudomonas aeruginosa) as infections of this type may be rapidly lethal.
- Anti-pseudomonal coverage serves as the foundation and additional coverage is then added to address other foci of infection such as mucosal or integument injury.
- Empiric therapy of patients with febrile neutropenia with or without a focus of infection should be guided by the current infectious disease recommendations.
- Any foci of infection that develops during the neutropenic period will require a full course of therapy.
Case Study: Wood River Junction, RI, USA; U-235 Recovery Plant
July 24, 1964

- Criticality excursion; patient stunned; ran from the building; immediate vomiting.
- Immediate diarrhea; c/o abdominal cramps, HA, thirst; profuse perspiration;
- BP160/80; P100; R20; T 38C
- Transient difficulty in speaking; 4h post admission BP 85/40; P110, T 38.9 C
- X-ray 16h post admission showed hilar congestion
Clinical Timeline: Wood River Junction
U-235 Recovery Plant July 24, 1964

- Left hand and forearm edematous; conjunctivitis and periorbital edema on the left.
- Clinical deterioration on the 2nd day; BP maintained with difficulty; no urinary output.
- Six hours prior to dearth, patient very disoriented.
- Patient died 49 h after the event of multi-organ failure (MOF).
Karas, JS et al., NEJM 272:755-761, (April 15, 1965)
Pulmonary injury currently seems to be the major limiting organ for medical remediation.

30 years later, 2 workers at the TOKAMURA ACCIDENT died 3-6 months later from a criticality accident of MOF, primarily pulmonary injury.
<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Date</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA’s daughter</td>
<td>5.7 Gy</td>
<td>23 OCT</td>
<td>(died) 23 OCT (27 mCi internal Cs137-enough to be lethal)</td>
</tr>
<tr>
<td>DF</td>
<td>7 Gy</td>
<td></td>
<td>(lived) Possibly spent more time outside (fractionated)</td>
</tr>
<tr>
<td>MA</td>
<td>10 MBq (270 μCi)</td>
<td></td>
<td>intake, 4.3 Gy external (cytogenetics)</td>
</tr>
<tr>
<td>IS</td>
<td>4.5 Gy</td>
<td>27 OCT</td>
<td>(died) 27 OCT Probable very acute dose.</td>
</tr>
<tr>
<td>AS</td>
<td>5.3 Gy</td>
<td>28 OCT</td>
<td>(died) 28 OCT Probable very acute dose.</td>
</tr>
<tr>
<td>LF2</td>
<td>1 Gbq (27 mCi)</td>
<td></td>
<td>intake, 6 Gy external (died) 23 OCT</td>
</tr>
<tr>
<td>GS</td>
<td>100 MBq (2.7 mCi)</td>
<td></td>
<td>intake, 3 Gy , burn on shoulder</td>
</tr>
<tr>
<td>Dr. PM</td>
<td>1.3 Gy</td>
<td></td>
<td>negligible intake (left source in bag)</td>
</tr>
</tbody>
</table>
## Results of Initial Cytogenetic Dosimetric Estimates (External Exposure)

<table>
<thead>
<tr>
<th>Range [Rem]</th>
<th>No. of Persons</th>
<th>Relative Frequency [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 50</td>
<td>43</td>
<td>61.43</td>
</tr>
<tr>
<td>50 - 100</td>
<td>8</td>
<td>11.43</td>
</tr>
<tr>
<td>100 - 200</td>
<td>6</td>
<td>8.57</td>
</tr>
<tr>
<td>200 - 300</td>
<td>5</td>
<td>7.14</td>
</tr>
<tr>
<td>300 - 400</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>400 - 500</td>
<td>3</td>
<td>4.29</td>
</tr>
<tr>
<td>500 - 600</td>
<td>3</td>
<td>4.29</td>
</tr>
<tr>
<td>600 - 700</td>
<td>2</td>
<td>2.58</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100.00</td>
</tr>
</tbody>
</table>
# Goiania Data

Table 2: Cesium-137 Effective Half-life During and After Treatment with Insoluble Prussian blue  
(In Days, by Age, and Dose of Insoluble Prussian blue)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (Years)</th>
<th>Insoluble Prussian blue dose (grams/day)</th>
<th>No. of Pts.</th>
<th>During Insoluble Prussian blue Treatment - $^{137}$Cs $T_{1/2}$</th>
<th>Off Insoluble Prussian blue Treatment - $^{137}$Cs $T_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>&gt; 18</td>
<td>10</td>
<td>5</td>
<td>26 ± 6 days</td>
<td>80 ± 15 days (all 21 adult patients)</td>
</tr>
<tr>
<td>Adults</td>
<td>&gt; 18</td>
<td>6</td>
<td>10</td>
<td>25 ± 15 days</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>&gt; 18</td>
<td>3</td>
<td>6</td>
<td>25 ± 9 days</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>12 - 14</td>
<td>&lt; 10</td>
<td>5</td>
<td>30 ± 12 days</td>
<td>62 ± 14 days</td>
</tr>
<tr>
<td>Children</td>
<td>4 - 9</td>
<td>&lt; 3</td>
<td>7</td>
<td>24 ± 3 days</td>
<td>42 ± 4 days</td>
</tr>
</tbody>
</table>
Summary of Treatment Modes (Goiania)

Supportive Care, GMSF, and PB (An Example That Internal Contamination Can Cause Death and Medical Countermeasures May Rarely Be Needed.)
**REAC/TS DTPA and PB IND Programs**

- Maintain Registries of DTPA and PB use in US
- Provide a stock of pharmaceuticals at REAC/TS and with co-investigators for treatment of internal contamination:
  - Ca- and Zn-DTPA
  - Prussian Blue (Radiogardase®)

Through a network of physician co-investigators, special drugs are readily available in the event of radiation emergencies including nuclear terrorism.
Methods for Assessing Intakes

- **Whole Body or Lung Counting**
  - Feasible for nuclides that emit penetrating x or gamma rays
  - Useful also for nuclides emitting energetic beta particles - can be detected by their bremsstrahlung radiation

- **Bioassay**
  - 24 hr urine collections - most widely used
  - 24 hr feces collections
  - Excised material from wounds

- **Cytogenetic Biodosimetry**
Am-241 Inhalation, Example Case

- Two workers were transferring $^{241}\text{Am}$ from a shipping barrel to a disposal container.

- The workers were wearing respiratory protection.

- But, a supervisor, also present, was not wearing respiratory protection.
Am-241 Example (continued)

- On exit, all three workers were noted to be contaminated – and room air samples were positive for alpha.

- Lung count bioassay was advised and performed the next day - all 3 patients were positive.

- 24 hr urine and fecal bioassay collections were advised and begun.
Day 1 Bioassay results

- **Patient #1 (supervisor, male):**
  - Lung content: 400 Bq
  - Urine: 1 Bq per day

- **Patient #2 (female):**
  - Lung content: 200 Bq
  - Urine: 0.12 Bq per day

- **Patient #3 (male):**
  - Lung content: 50 Bq
  - Urine: 0.06 Bq per day
Initial Intake and Effective Dose Estimates

- **Patient #1**: 1.8 kBq, 210 mSv
- **Patient #2**: 0.63 kBq, 73 mSv
- **Patient #3**: 0.15 kBq, 17 mSv (Stop DTPA?).

- Chelation begun on day 2 with Ca-DTPA for the males and Zn-DTPA for the female, and continued daily with Zn-DTPA for 5-6 days.
Bioassay Results - Day 6

- **Patient #1 (supervisor, male):**
  - Lung content: 270 Bq
  - Urine: 22 Bq per day

- **Patient #2 (female):**
  - Lung content: 100 Bq
  - Urine: 1.9 Bq per day

- **Patient #3 (male):**
  - Lung content: 21 Bq
  - Urine: 0.4 Bq per day
Averted Doses

- **Patient #1:**
  - w/o DTPA: 210 mSv
  - w/ DTPA: 49 mSv

- **Patient #2:**
  - w/o DTPA: 73 mSv
  - w/ DTPA: 38 mSv

- **Patient #3:**
  - w/o DTPA: 17 mSv
  - w/ DTPA: 10 mSv