TREATMENT of EXPOSED PATIENTS

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Disclosure Information

Opinions presented are those of the authors. Any “off-label” use of medications is at the discretion of a licensed medical provider.

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This lecture does not constitute official policy of the United States Department of Defense.
Objectives

After this session, attendees should be able to:

• Describe the diagnosis and treatment of the Acute Radiation Syndrome (ARS)
• Understand the differences in diagnosis and treatment following external and internal contamination
• Identify possible late effects and explain appropriate medical follow-up.
Topics

Acute Radiation Syndrome (ARS)
- Definition and diagnosis
- Treatment

External and Internal Contamination
- Definition and diagnosis
- Treatment

Examples, Follow-Up Care, Research Areas
Acute Radiation Syndrome

A combination of clinical signs and symptoms occurring in stages over a period of hours to weeks due to a significant *partial body* or *whole body* exposure of >1 Gy (100 cGy), as injury to various tissues and organs is expressed.
What Happens After WBI?

What is the most fundamental event following irradiation?

CELL DEATH

As dose increases, which cells are most susceptible?

DIVIDING CELLS

Which dividing cells are most radiosensitive?

STEM / PRECURSOR CELLS
## Tolerance Doses (TD<sub>5/5</sub> - TD<sub>50/5</sub>)

<table>
<thead>
<tr>
<th>Tissue/Region</th>
<th>Single Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovary</strong></td>
<td>2 - 6</td>
</tr>
<tr>
<td><strong>Bone marrow</strong></td>
<td>2 - 10</td>
</tr>
<tr>
<td><strong>Eye (lens)</strong></td>
<td>2 - 10</td>
</tr>
<tr>
<td><strong>Testes</strong></td>
<td>2 - 10</td>
</tr>
<tr>
<td><strong>Lymphoid</strong></td>
<td>2 - 20</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>5 - 10</td>
</tr>
<tr>
<td><strong>Mucosa</strong></td>
<td>5 - 20</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>7 - 10</td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
<td>10 - 20</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td>10 - 20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>15 - 20</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>15 - 20</td>
</tr>
<tr>
<td><strong>Spinal cord</strong></td>
<td>15 - 20</td>
</tr>
<tr>
<td><strong>Peripheral nerve</strong></td>
<td>15 - 20</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td>15 - 25</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>18 - 20</td>
</tr>
<tr>
<td><strong>Bone and cartilage</strong></td>
<td>&gt;30</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td>&gt;70</td>
</tr>
</tbody>
</table>

**Microvasculature (endothelial cells) / epithelial cells**

The Human Lethal Dose - LD$_{50/60}$

- **No** medical intervention
- Homogenous & total
- 60 days - expression of effects on hematopoiesis

Note: surviving to 60 days does not ensure long-term survival

**Sources:**
- Japanese atomic bomb
- Accidents (e.g. Chernobyl)
- Therapeutic exposures
# LD_{50/60} Estimates (DS86): Atomic Bomb

<table>
<thead>
<tr>
<th>Source</th>
<th>City</th>
<th># persons (deaths)</th>
<th>Source of sample</th>
<th>LD_{50/60} (Gy)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RERF Survey</td>
<td>Hiroshima</td>
<td>7593 (1095)</td>
<td>Master sample</td>
<td>2.7 -- 3.1</td>
<td>LD_{50/60} based on linear fit, excluding first day deaths</td>
</tr>
<tr>
<td>Special survey</td>
<td>Hiroshima</td>
<td>53 (27)</td>
<td>Female students, Shintoku high school</td>
<td>4.0</td>
<td>Dose estimates based on chromosomal aberrations in survivors</td>
</tr>
<tr>
<td>Hiroshima University survey</td>
<td>Hiroshima</td>
<td>1216 (201)</td>
<td>Persons located 600-1300m from hypocenter</td>
<td>2.44</td>
<td>Survey by RINMB and city authorities</td>
</tr>
<tr>
<td>Oak Ridge-Dikewood Nuclear Def Agy</td>
<td>Nagasaki</td>
<td>97 (79)</td>
<td>Young adult occupants of Chinzei and Shiroyama Schs</td>
<td>2.9</td>
<td>Extension of study for Nuclear Defense Agency</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td></td>
<td><strong>8959 (1402)</strong></td>
<td></td>
<td><strong>3.1</strong></td>
<td></td>
</tr>
</tbody>
</table>
Considerations - $\text{LD}_{50/60}$

Sources:

- Japanese atomic bomb
  - Additional injuries from the bomb
  - Typhoon (typhoid fever)
  - Disturbed environment
  - Poor nutrition
  - Under-representation of middle-aged men
  - Dosimetry (also accidents)
- Therapeutic exposures
  - Poor health + malignancy
- Other factors
  - Age, gender, medical care (supportive)
Best Estimates - $\text{LD}_{50/60}$

- Acute TBI, no medical support = 2.5-3.5 Gy
- Acute TBI + supportive care = 4.5 Gy
- Acute TBI + supportive care + CSFs = 6-8 Gy
- Acute TBI + BMT = 8-10 Gy
Whole Body Irradiation (WBI)

Radiation Exposure

Prodromal phase

Latent period

Manifest illness

Recovery or death

Time

time of onset
severity
duration
dose
dose rate
quality
Prodromal Phase

Gastrointestinal
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Intestinal cramps
- Salivation
- Fluid loss
- Dehydration
- Weight loss

Neuromuscular
- Easy fatigability
- Apathy or listlessness
- Sweating
- Fever
- Headache
- Hypotension
Prodromal Phase

Gastrointestinal
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Intestinal cramps
- Salivation
- Fluid loss
- Dehydration
- Weight loss

Neuromuscular
- Easy fatigability
- Apathy or listlessness
- Sweating
- Fever
- Headache
- Hypotension

50% lethal dose
Prodromal Phase

Gastrointestinal

- Anorexia
- Nausea
- Vomiting
- Immediate diarrhea
- Intestinal cramps
- Salivation
- Fluid loss
- Dehydration
- Weight loss

Neuromuscular

- Easy fatigability
- Apathy or listlessness
- Sweating
- Fever
- Headache
- Hypotension

**Supralethal dose**
## Prodromal Phase

<table>
<thead>
<tr>
<th>Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Onset</td>
</tr>
<tr>
<td>0 - 1 Gy</td>
</tr>
<tr>
<td>1 - 2 Gy</td>
</tr>
<tr>
<td>2 - 6 Gy</td>
</tr>
<tr>
<td>6 - 8 Gy</td>
</tr>
<tr>
<td>10 - 30 Gy</td>
</tr>
<tr>
<td>&gt;30 Gy</td>
</tr>
</tbody>
</table>

Adapted from Burnham and Franco: Crit Care Clin, 2005.
# Prodromal Phase

<table>
<thead>
<tr>
<th>Radiation Dose (Gy)</th>
<th>Nausea, vomiting</th>
<th>Time of onset</th>
<th>Duration</th>
<th>Lymphocyte count</th>
<th>CNS function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1 Gy</td>
<td>None</td>
<td></td>
<td></td>
<td>Minimally affected</td>
<td>No impairment</td>
</tr>
<tr>
<td>1- 2 Gy</td>
<td>5 - 50%</td>
<td>3 - 6 hr</td>
<td>&lt;24 hr</td>
<td>Minimally decreased</td>
<td>No impairment</td>
</tr>
<tr>
<td>2- 6 Gy</td>
<td>50 - 100%</td>
<td>2 - 4 hr</td>
<td>&lt;24 hr</td>
<td>&lt;1000 at 24 hr</td>
<td>Impairment for 6 - 20 hr</td>
</tr>
<tr>
<td>6 - 8 Gy</td>
<td>75 - 100%</td>
<td>1 - 2 hr</td>
<td>&lt;48 hr</td>
<td>&lt;500 at 24 hr</td>
<td>Impairment for &gt;24 hr</td>
</tr>
<tr>
<td>10 - 30 Gy</td>
<td>90 - 100%</td>
<td>&lt;1 hr</td>
<td>&lt;48 hr</td>
<td>Decreases in hrs</td>
<td>Rapid incapacitation</td>
</tr>
<tr>
<td>&gt;30 Gy</td>
<td>100%</td>
<td>Minutes</td>
<td>N/A</td>
<td>Decreases in hrs</td>
<td>Rapid incapacitation</td>
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Adapted from Burnham and Franco: Crit Care Clin, 2005.
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</table>

Adapted from Burnham and Franco: Crit Care Clin, 2005.
Onset of Vomiting

Radiation Dose vs Time to Onset of Vomiting
Anno et al. (1989) + Goans et al. (2001)

Time from exposure to onset of vomiting:
3.00 hours

Estimated dose at time of exposure:
2.7 gray (Gy)

95% LCL-UCL (Gy)
2.2 - 3.2

Patient: exposed, mat
Whole Body Irradiation (WBI)

Radiation Exposure → Prodromal phase → Latent period → Manifest illness → Recovery or death

Time
## Latent Phase of Acute Radiation Syndrome (ARS)

<table>
<thead>
<tr>
<th>Degree of ARS and approximate dose of acute WBE (Gy)</th>
<th>Mild (1–2 Gy)</th>
<th>Moderate (2–4 Gy)</th>
<th>Severe (4–6 Gy)</th>
<th>Very Severe (6–8 Gy)</th>
<th>Lethal (&gt;8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency period (d)</td>
<td>21–35</td>
<td>18–28</td>
<td>8–18</td>
<td>7 or less</td>
<td>None</td>
</tr>
<tr>
<td>Lymphocytes (G/L) (days 3–6)</td>
<td>0.8–1.5</td>
<td>0.5–0.8</td>
<td>0.3–0.5</td>
<td>0.1–0.3</td>
<td>0.0–0.1</td>
</tr>
<tr>
<td>Granulocytes (G/L)</td>
<td>&gt;2.0</td>
<td>1.5–2.0</td>
<td>1.0–1.5</td>
<td>≤ 0.5</td>
<td>≤ 0.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>None</td>
<td>None</td>
<td>Rare</td>
<td>Appears on days 6–9</td>
<td>Appears on days 4–5</td>
</tr>
<tr>
<td>Epilation</td>
<td>None</td>
<td>Moderate, beginning on day 15 or later</td>
<td>Moderate or complete on days 11–21</td>
<td>Complete earlier than day 11</td>
<td>Complete earlier than day 10</td>
</tr>
<tr>
<td>Medical response</td>
<td>Hospitalization not necessary</td>
<td>Hospitalization recommended</td>
<td>Hospitalization necessary</td>
<td>Hospitalization urgently necessary</td>
<td>Symptomatic treatment only</td>
</tr>
</tbody>
</table>

Adapted from IAEA: Diagnosis and treatment of radiation injuries; 1998.
Whole Body Irradiation (WBI)

Radiation Exposure → Prodromal phase → Latent period → Manifest illness → Recovery or death

Time
Acute Radiation Syndromes (ARS)

- Hematopoietic
- Gastrointestinal
- Multiple organ failure
- Cardiovascular/CNS
Hematopoietic Syndrome

Critical cells: Hematopoietic precursor cells
Dose: 1-5 Gy
Humans: peak mortality at 30 days, to 60 days
LD_{50/60}: 2.5 - 3.5 Gy
Symptoms: Prodromal phase: nausea, vomiting, anorexia, malaise, possible diarrhea (onset 3-16 hours)
Human 4.5 Gy

Andrews et al., 1967.
LYMPHOCYTE KINETICS

![Graph showing the relationship between dose (Gy) and lymphocyte rate constant (day⁻¹).]

Goans et al., 2005.
Human 4.5 Gy

1 week = granulocytopenia

Andrews et al., 1967.
Human 4.5 Gy

2 weeks = thrombocytopenia

Andrews et al., 1967.
Hematopoietic Syndrome

Symptoms:
ARS: chills, fatigue, petechial hemorrhages in skin, ulceration of mouth, epilation (2 weeks >3 Gy) bone marrow atrophy, infections, fever, bleeding, anemia

Death: infection important cause

Chernobyl: 134 personnel >1 Gy; 37 - severe bone marrow failure; 28 died in first 4 months
GI Syndrome

Critical cells: Epithelial lining of the g.i. tract
GI Syndrome

0 Gy

10 Gy

14 Gy

Courtesy Hauer-Jensen.
GI Syndrome

**Critical cells:** Epithelial lining of the g.i. tract

**Dose:** $\geq 6 \text{ Gy}$

**Symptoms:**
- Prodromal phase: nausea and vomiting, prolonged (watery) diarrhea (onset 1-4 hours)
- Latent phase: malaise, weakness
- ARS: severe vomiting, diarrhea (bloody) + fever, shock, death
## CV/CNS Syndrome

**Dose:** >20 Gy  
**Symptoms:** severe nausea and vomiting, disorientation, loss of coordination, respiratory distress, diarrhea, convulsive seizures, coma  
**Cause of death:** ?
CV/CNS Syndrome

Dose: >20 Gy

Symptoms: severe nausea and vomiting
disorientation
loss of coordination
respiratory distress
diarrhea
convulsive seizures
coma

Cause of death: increased brain fluid content
due to small vessel leakage
Cutaneous Syndrome

- **Erythema** (skin reddening) occurs hours to days depending on dose
- Duration of 1-2 days
- Body location
- Target cells reside in epidermis, dermis, hair follicles, subcutaneous tissues

- Symptoms: pruritus, blisters, hair loss, moist desquamation, ulceration
- **Epilation**: 10-20 days after >3-4 Gy
Cutaneous Syndrome

- Acute erythema can occur 1-2 days after 2-6 Gy
- Erythema and epilation can occur 2-3 weeks after 5 - 10 Gy
- Desquamation can occur 2-3 weeks after 15 - 20 Gy
- Re-epithelialization takes place after 6 - 8 weeks

Courtesy W. McBride/Boreham.
Combined Injury

Biomedical consequences of radiation exposure are exacerbated by trauma and/or disease, including burns and wounds.

- Radiation: $LD_{50/30} = 963$
- Radiation + burn: 820
- Radiation + wound: 761

Modified from Pellmar & Ledney, 2005.
Dosimetry (State of the Science)

PHYSICAL DOSIMETRY

DOSE RECONSTRUCTION
Biophysics

BIOLOGICAL DOSIMETRY

OTHER BIOINDICATORS
Cytology, protein changes, novel biomarkers EPR

CYTOGENETICS
Dicentrics

CLINICAL DOSIMETRY

SYMPTOMS
Type Time of onset

PERIPHERAL BLOOD
Lymphocyte depletion
Topics

Acute Radiation Syndrome (ARS)
- Definition and diagnosis
- Treatment

External and Internal Contamination
- Definition and diagnosis
- Treatment

Examples, Follow-Up Care and Research
ARS - When Treatment is Too Late

Hiroshima
ARS Victim
(~Day 20)

Causes of death: Infection and bleeding

Photo: DOE, National Archives
First Action for Responders/ Receivers – the ABCs

- **Universal Precautions**: Protect yourself with scrubs, mask, gloves
- **Standard medical emergency procedures**
  - Airway/ Breathing/ Circulation
- **Decontaminate AFTER stabilized**
- **Radiation injury NOT acutely life threatening**
ARS Treatment

- Supportive care
- Specific therapy
Supportive Care

- Clean environment
- IV fluids, antiemetics, anti-diarrheals
- Pain medication
More on Supportive Care

• **Antiemetics**
  – Kytril™ (granisetron) and Zofran™ (odansetron). Need should abate within 48 hours

• **Antidiarrheals**
  – e.g. Imodium™ (loperamidine)

• Replace **fluids**, **electrolytes**, **blood products**, and **platelets**
ARS Treatment Specific Therapy

- Antimicrobials for neutropenic fever
  - Anti-bacterial, anti-viral, anti-fungal
- Granulocyte Colony Stimulating Factor
Antibiotics - Initial Management

Fever (temperature ≥38.3°C) + Neutropenia (<500 neutrophils/mm³)

- Low risk
  - Oral: Ciprofloxacin + Amoxicillin-clavulanate (adults only)
  - iv: Vancomycin not needed

- High risk
  - iv: Vancomycin needed

Monotherapy:
- Cefepime, Ceftazidime, or Carbapenem

Two Drugs:
- Aminoglycoside +
  - Antipseudomonal penicillin, Cefepime, Ceftazidime, or Carbapenem ± aminoglycoside

Vancomycin +
- Cefepime, Ceftazidime, or carbapenem

Reassess after 3–5 days

Justification for Use of Colony Stimulating Factors (CSF) in Radiation-Induced Neutropenia

1. Oncology data with chemotherapy
   - Enhanced neutrophil recovery by 3-6 days
2. Pre-clinical animal data
   - Enhanced neutrophil recovery of radiation induced neutropenia
   - Enhanced survival with early initiation

Benefit of Supportive Care and G-CSF

Canines Co60

LD 50/30 = 260 cGy
LD 50/30 = 338 cGy
LD 50/30 = 488 cGy

FDA-Approved CSFs

Only 3 approved in USA for reducing neutropenia. None currently approved for radiation-induced neutropenia.

1. Granulocyte-colony stimulating factor, G-CSF, or filgrastim (Neupogen®)

2. Pegylated granulocyte-colony stimulating factor, PEG-G-CSF, or pegfilgrastim (Neulasta®)

3. Granulocyte-macrophage-colony stimulating factor, GM-CSF, or sargramostim (Leukine®)

G-CSF is part of the US Strategic National Stockpile
Granulocyte Colony Stimulating Factor (G-CSF)

- ASCO GUIDELINES* - Includes management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of G-CSF or pegylated G-CSF
## CSF Therapy for ARS

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Adults</th>
<th>Pediatrics</th>
<th>Pregnancy</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF or Filgrastim <em>(Neupogen®)</em></td>
<td>5 µg/kg per day SQ injection started as early as possible**</td>
<td>5 µg/kg per day SQ injection started as early as possible**</td>
<td>Category C</td>
<td>Sickle cell disease, significant CAD, ARDS. Adverse reaction: bone pain Consider discontinuation if pulmonary infiltrates develop at neutrophil recovery **continued until ANC &gt;1,000</td>
</tr>
<tr>
<td>Pegylated G-CSF or Pegfilgrastim <em>(Neulasta®)</em></td>
<td>6 mg SQ x 1 dose</td>
<td>For adolescents &gt;45 kg: Give 6 mg SQ x 1 dose</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td>GM-CSF or Sargramostim <em>(Leukine®)</em></td>
<td>250 µg/m² SQ per day started as early as possible**</td>
<td>250 µg/m² SQ per day started as early as possible**</td>
<td>Category C</td>
<td></td>
</tr>
</tbody>
</table>

**Combined Injuries Syndrome**

Ref: AFRRI

<table>
<thead>
<tr>
<th>Model</th>
<th>Injury</th>
<th>Lethality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>20% Burn</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>100 cGy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>73%</td>
</tr>
<tr>
<td>Pig</td>
<td>10-15% Burn</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>400 cGy</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>31-35% Burn</td>
<td>50%</td>
</tr>
<tr>
<td>Rat</td>
<td>250 cGy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>95%</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>1.5% Burn</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>250 cGy</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>38%</td>
</tr>
</tbody>
</table>

Ref: AFRRI
# Combined Injury Patient Triage is Based on Traditional Triage Methods

<table>
<thead>
<tr>
<th>Physical injury without irradiation</th>
<th>Expected changes in triage categories after whole-body irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninjured</td>
<td>Ambulatory monitoring</td>
</tr>
<tr>
<td></td>
<td>Ambulatory monitoring, routine care and delayed hospitalization</td>
</tr>
<tr>
<td>Minimal</td>
<td>Immediate</td>
</tr>
<tr>
<td>Delayed</td>
<td>Immediate</td>
</tr>
<tr>
<td>Immediate</td>
<td>Expectant</td>
</tr>
</tbody>
</table>

## ARS Treatment
### Moderate-Dose Exposure*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Estimated Radiation Dose (Gy)</th>
<th>Treatment Summary</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic syndrome (only)</td>
<td>1 - 4</td>
<td>Fluids, antimicrobials, may require cytokines</td>
<td>Excellent, continue therapy for 3-4 weeks</td>
</tr>
<tr>
<td>Hematopoietic (and GI?) syndromes</td>
<td>4 - 7</td>
<td>Early cytokine Tx, fluids, GI nutrition, antimicrobials, avoid infection</td>
<td>Good with aggressive Tx, will require at least 4-5 weeks’ inpatient care</td>
</tr>
</tbody>
</table>

*Radiation injury only, no complicating trauma or chemical/biological weapons

Modified from AFRRI
## ARS Treatment

### Moderate-Dose Exposure*

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<tr>
<th>Syndrome</th>
<th>Estimated Radiation Dose (Gy)</th>
<th>Treatment Summary</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hematopoietic with GI syndrome</td>
<td>7 - 10</td>
<td>Fluids, symptomatic Tx, cytokines, antimicrobials. Stem cell transplant?</td>
<td>Some survival with aggressive Tx; will require weeks of inpatient Tx with barrier protection</td>
</tr>
<tr>
<td>Hematopoietic GI and Cerebrovascular syndromes</td>
<td>10 - 30</td>
<td>Aggressive treatment versus palliative care</td>
<td>Near 100% mortality</td>
</tr>
</tbody>
</table>

*Radiation injury only, no complicating trauma or chemical/biological weapons

Modified from AFRRI