US DoD Comprehensive CBRN/trauma treatment program

U.S. Army Institute of Surgical Research

COL Andrew P. Cap, MS, MD, PhD, FACP

Chief, Coagulation and Blood Research Program, USAISR
Program Director, SAMMC Clinical Research Fellowship
Associate Professor of Medicine, Uniformed Services University
Adjunct Associate Professor, University of Texas
Hematology-Oncology Consultant to the Army Surgeon General

Disclaimer:

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The Challenge: Surviving in a CBRN Environment

- "The Cold War called and it wants its medical planning back."

- Recent events: this is real!
  - Nerve agent, chlorine in Syria
  - DPRK scenario? Iran?
  - Terrorism?
  - Others?

- US Military, NATO, civilians, etc. → multiple missions
  - Major combat operations in contaminated environment
  - SOF missions (counter-terrorism, weapon seizure/destruction, secure nuclear fuel cycle facility or chemical plant or biological lab)
  - Homeland defense, react to event

Trauma + CBRN?

- **We are talking about guns + explosives + CBRN → trauma is going to happen. A lot.**

- **Current CBRN doctrine:**
  - **Stove-piped by class of exposure (understandable)**
  - **Focus on decontamination, supportive care**
  - **Completely disconnected from resuscitation, trauma care**

- **Current trauma + CBRN management:**
  - **Up-code triage of any patient with CBRN exposure**

And that's about it…

Trauma + CBRN issues

- **Lethality of trauma + lethality of agent**
- **Delay in care for decontamination:**
  - Patient movement
  - Team division (hot zone vs. clean)
  - Communication breakdown
- **Potential interaction questions:**
  - Plasma, RBCs contain cholinesterase (bioscavenger)?
  - Plasma, platelets, etc. for hemorrhagic fever viruses?
  - Impact of lymphocytes in RBCs, WB in R/N casualties, need for PRT/irradiation?

Recent small exercises:
-- Mountain Path (3SFG)
-- RDCR PreConf

→ results: the BEST pre-hospital teams don't do this well!

So, the plan is…

- **This is really complicated.**
- **There is no plan…**
  - There are many teams, many plans…
  - DoD, BARDA, others working on it…
  - “Some assembly required”
- **For “simplicity” let’s consider just R/N… Ha!**
  - There is nothing simple about this.

Exposure Scenarios

- Scenarios of military exposure to radiation
  - External device
  - Ingesting or inhaling radiological particulates
  - Loose radioactive material deposited on the skin or equipment.
- **High-level external radiation** from an improvised nuclear device or radiation exposure device is most lethal in an acute setting.
- **Ingestion or inhalation** of radioactive material may cause internal dose to the whole body or to a specific organ over a period of time.

The National Council on Radiation Protection Report No. 138

Exposure vs. Contamination

Types of devices by which military could be exposed:

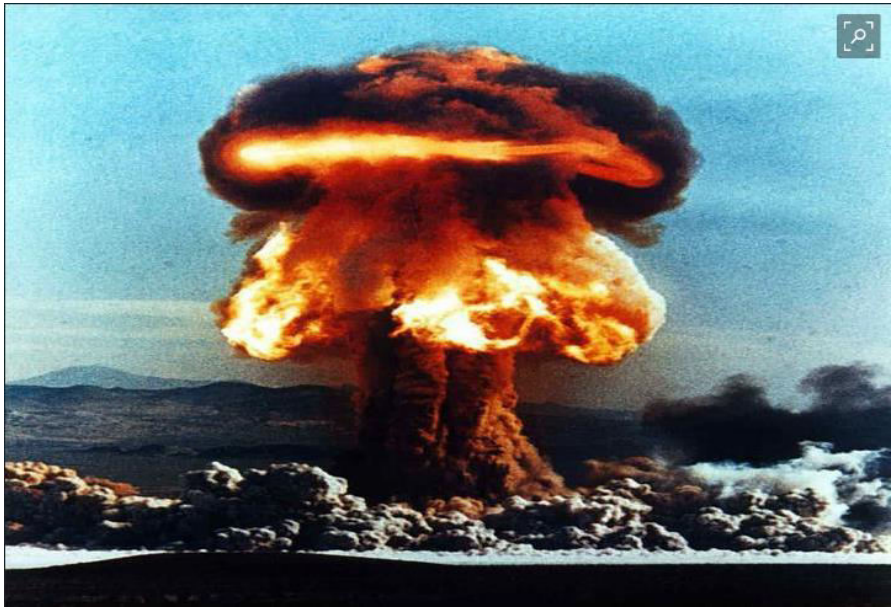
- Radiation exposure device (RED): Radioactive material, in a sealed source or container, intended to expose people in the vicinity of the device to a high-level external dose.
  - Cause exposure, usually not contamination
  - e.g. Hidden source in a train car

Exposure vs. Contamination

- Radiological dispersion device (RDD): Any device that causes intentional dissemination of radioactive material without a nuclear detonation.
  - Inhalation, food/food chain contamination
  - Causes casualty and site contamination, complicates medical evacuation.
  - e.g. Mix of explosives and radioactive material **(dirty bomb)**

Ultimate Bad News

- Nuclear: Nuclear weapon, Improvised nuclear device (IND), attack on nuclear facility
  - high-level external dose, trauma, inhalation of radioactive materials, particulate contamination, and ingestion of radioactive materials in the food chain.



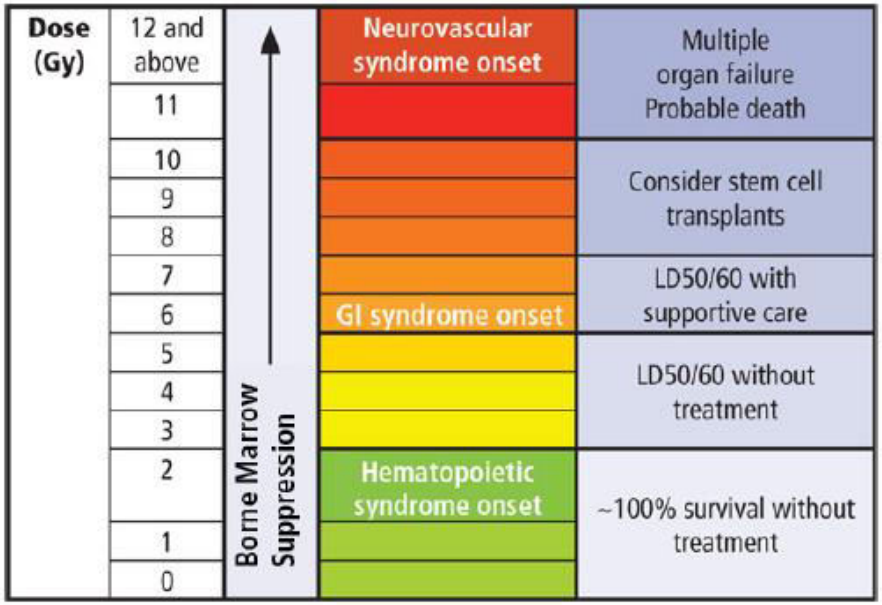
The Challenge: Surviving Radiation Exposure

- **Acute Radiation Syndrome**
  - Occurs after whole body or significant partial body irradiation
    - Typical doses >1Gy
    - Four sub-syndromes: hematopoietic, cutaneous, gastrointestinal, and neurovascular systems

Hematopoietic syndrome (> 2 Gy)

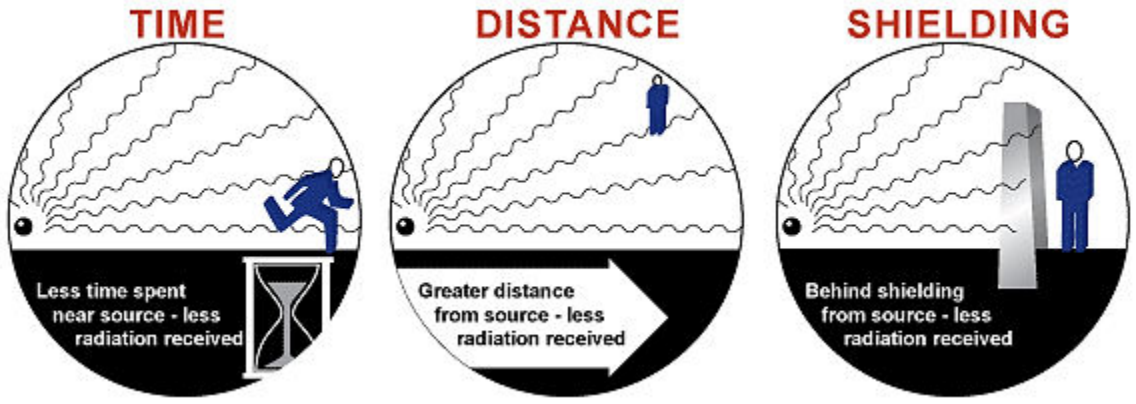
GI syndrome (> 6 Gy)

Neurovascular syndrome (> 12 Gy)



Factors driving lethality

- Acute Radiation Exposure - Several factors determine the lethality of ionizing radiation
  - **Dose rate (Gy/hr):** Doses received over a shorter period of time cause more damage.
  - **Distance from the source:** The dose rate decreases as the square of the distance from the source (inverse square law).
  - **Shielding:** Can reduce exposure, depending upon the type of radiation and the material used.
  - **Available medical therapy**



Dose Rate & Distance

- **Acute Radiation Exposure**
  - Severity/Survival depends on dose rate (Gy/hr) and distance from the source

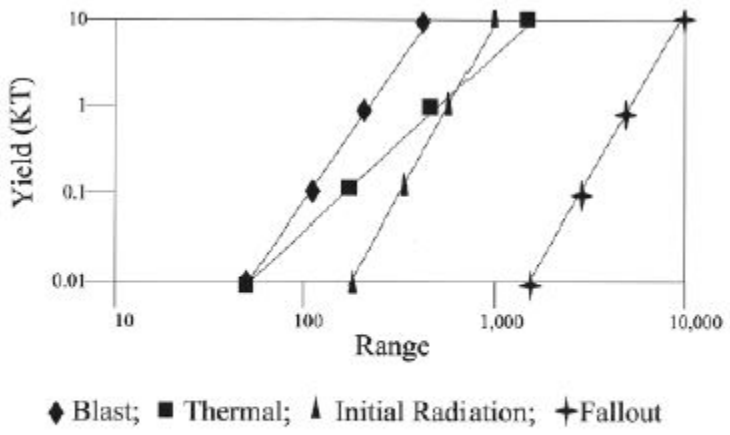


Figure 2. Distance at which 50% fatality occurs versus size of nuclear weapon.

Time (s)	Distance (m) 1	2	5	10	20	50	100
1	1.00E+00	2.50E-01	4.00E-02	1.00E-02	2.50E-03	4.00E-04	1.00E-04
2	2.00E+00	5.00E-01	8.00E-02	2.00E-02	5.00E-03	8.00E-04	2.00E-04
5	5.00E+00	1.25E+00	2.00E-01	5.00E-02	1.25E-02	2.00E-03	5.00E-04
10	1.00E+01	2.50E+00	4.00E-01	1.00E-01	2.50E-02	4.00E-03	1.00E-03
20	2.00E+01	5.00E+00	8.00E-01	2.00E-01	5.00E-02	8.00E-03	2.00E-03
50	5.00E+01	1.25E+01	2.00E+00	5.00E-01	1.25E-01	2.00E-02	5.00E-03
100	1.00E+02	2.50E+01	4.00E+00	1.00E+00	2.50E-01	4.00E-02	1.00E-02
200	2.00E+02	5.00E+01	8.00E+00	2.00E+00	5.00E-01	8.00E-02	2.00E-02
500	5.00E+02	1.25E+02	2.00E+01	5.00E+00	1.25E+00	2.00E-01	5.00E-02
1000	1.00E+03	2.50E+02	4.00E+01	1.00E+01	2.50E+00	4.00E-01	1.00E-01
2000	2.00E+03	5.00E+02	8.00E+01	2.00E+01	5.00E+00	8.00E-01	2.00E-01
5000	5.00E+03	1.25E+03	2.00E+02	5.00E+01	1.25E+01	2.00E+00	5.00E-01

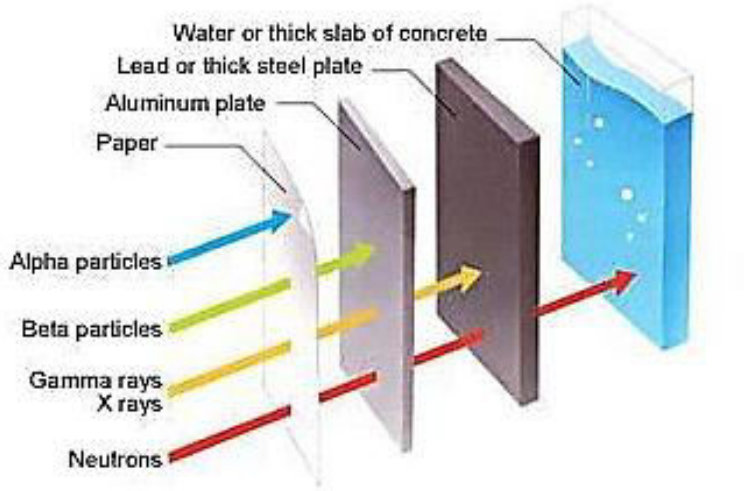
HIGH exposure category
MODERATE - HIGH exposure category
MODERATE exposure category
MODERATE - LOW exposure category
LOW exposure category

Figure F2. Dependence of exposure category on distance and time.

REMM RADIATION EMERGENCY MEDICAL MANAGEMENT

Shielding is Good

- Shielding - sources of radiation can be shielded with solid or liquid material, which absorbs the energy of the radiation
  - Can reduce exposure, depending upon the type of radiation and the material used

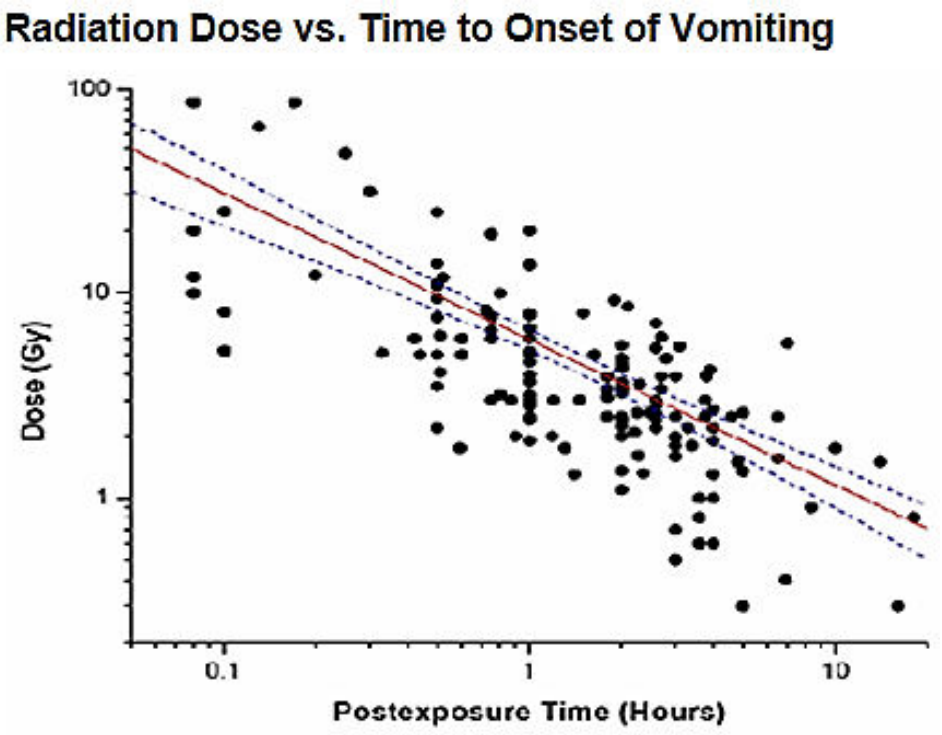


Dosimetry: What happened?

- Dosimetry: Measurement of absorbed dose delivered by ionizing radiation
  - Measured in grays (Gy) – energy absorbed/kg
- Physical dosimetry – direct measurement with dosimeter
  - Not practical for accidental/wartime exposure
- **Clinical dosimetry-** estimate based on clinical information
  - ***Time to onset of emesis*** (most practical)
- **Biodosimetry**
  - ***Lymphocyte depletion*** kinetics (2nd most practical)
  - Chromosomal aberrations – frequency of chromosomal aberrations in lymphocytes correlates with radiation dose
    - Requires 24Hr post exposure sample
    - Takes 3+ days for result

Rule of Thumb: Barf is Bad

- **Time to onset of vomiting**



Estimation of External Radiation Dose Related to Onset of Vomiting*		
Vomiting Post Incident	Estimated Dose	Degree of ARS
Less than 10 minutes	> 8 Gy	Lethal
10-30 minutes	6-8 Gy	Very Severe
Less than 1 hour	4-6 Gy	Severe
1-2 hours	2-4 Gy	Moderate
More than 2 hours after	Less than 2 Gy	Mild

* For acute external exposures only. Gray (Gy) is the SI unit of measurement for radiation absorbed dose.

CBC abnormalities: not good

- **Lymphocyte Depletion Kinetics**

Estimating dose from a single Absolute Lymphocyte count (ALC).
SERIAL MEASUREMENTS MORE ACCURATE and are strongly recommended
Using AFRRI BAT tool on REMM is also more accurate.

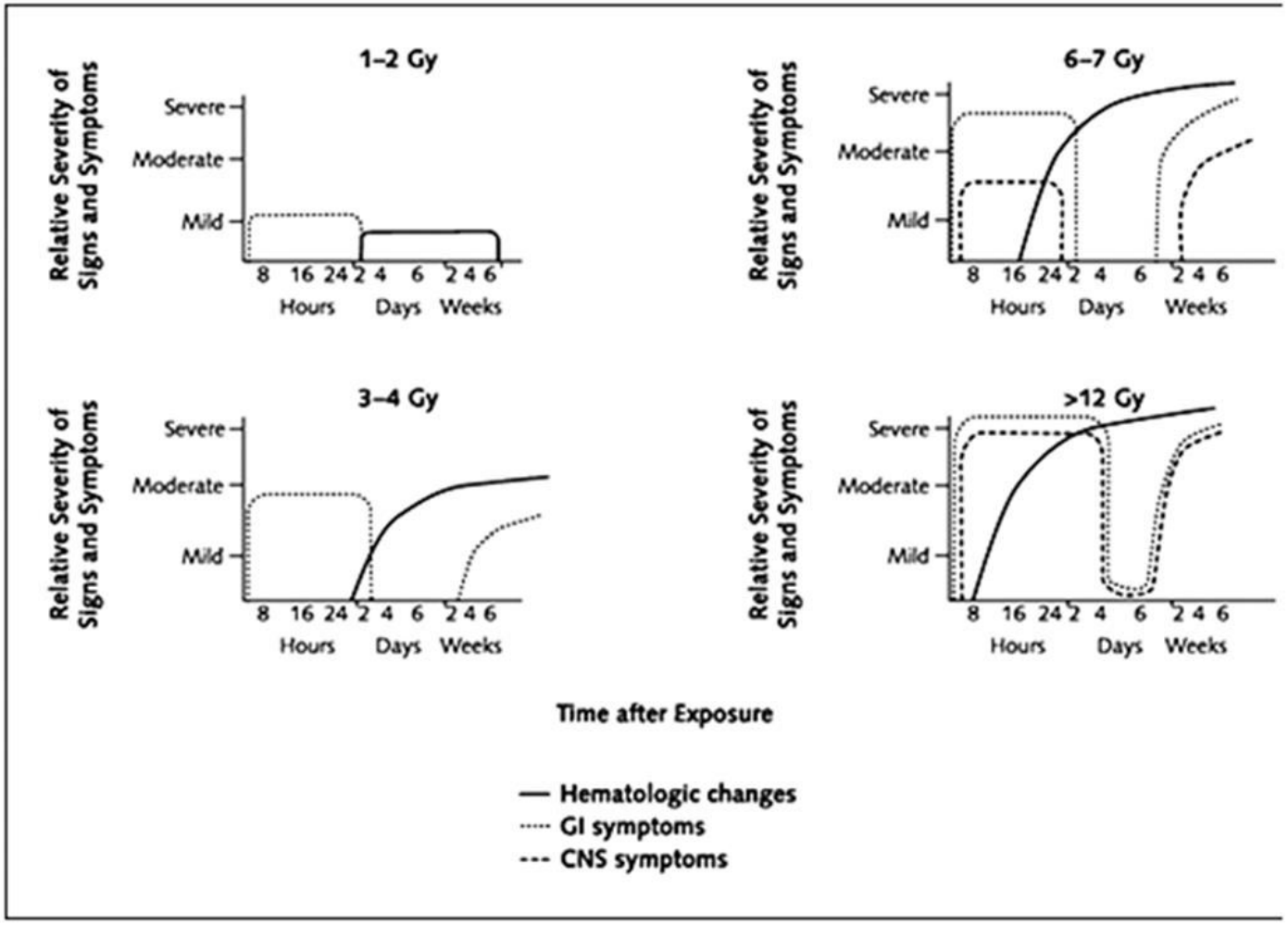
Instructions: 1) Determine the ALC for that patient, 2) read down by the number of hours after the incident and 3) read across for estimate of whole body dose.
(Table adapted by Scarce Resources Group from AFRRI dose calculator on REMM (www.remm.nlm.gov)

		Absolute Lymphocyte Count (ALC) Value × 10 to the ninth (single value)												
		1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
		Estimate of whole body dose from radiation exposure ☐ Below 2 Gy ▢ 2-6 Gy ■ Above 6 Gy												
Hours after exposure	24	0	0	1.8	2.5	3.3	4.2	5.2	6.3	7.7	9.3	>10	>10	>10
	48	0	0	0	1.5	2.0	2.5	3.1	3.8	4.6	5.6	6.9	8.7	>10
	72	0	0	0	0	0.9	1.8	2.2	2.7	3.2	3.9	4.8	6.1	8.2
	96	0	0	0	0	0	0	1.7	2.1	2.5	3.1	3.8	4.8	6.5

ARS Phases: GI sx lead; early CNS sx suggest lethal exposure

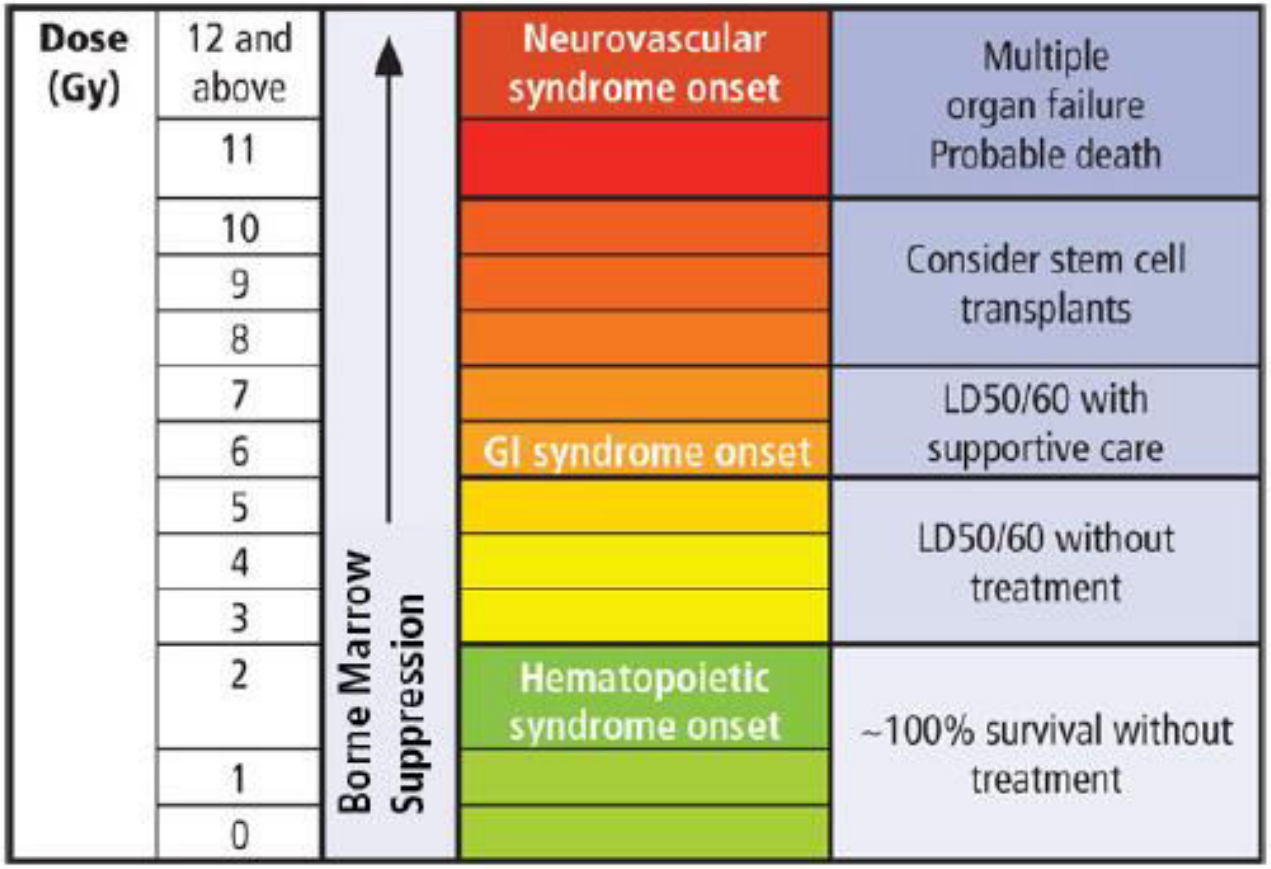
- **Phases of ARS**

a) Prodromal phase: 0–2 days after exposure.
b) Latent phase: 2–20 days after exposure.
c) Manifest illness: 21–60 days after exposure.



Hematopoietic Syndrome

- **Bone Marrow Failure**
  - Loss of immune system, platelets, RBCs



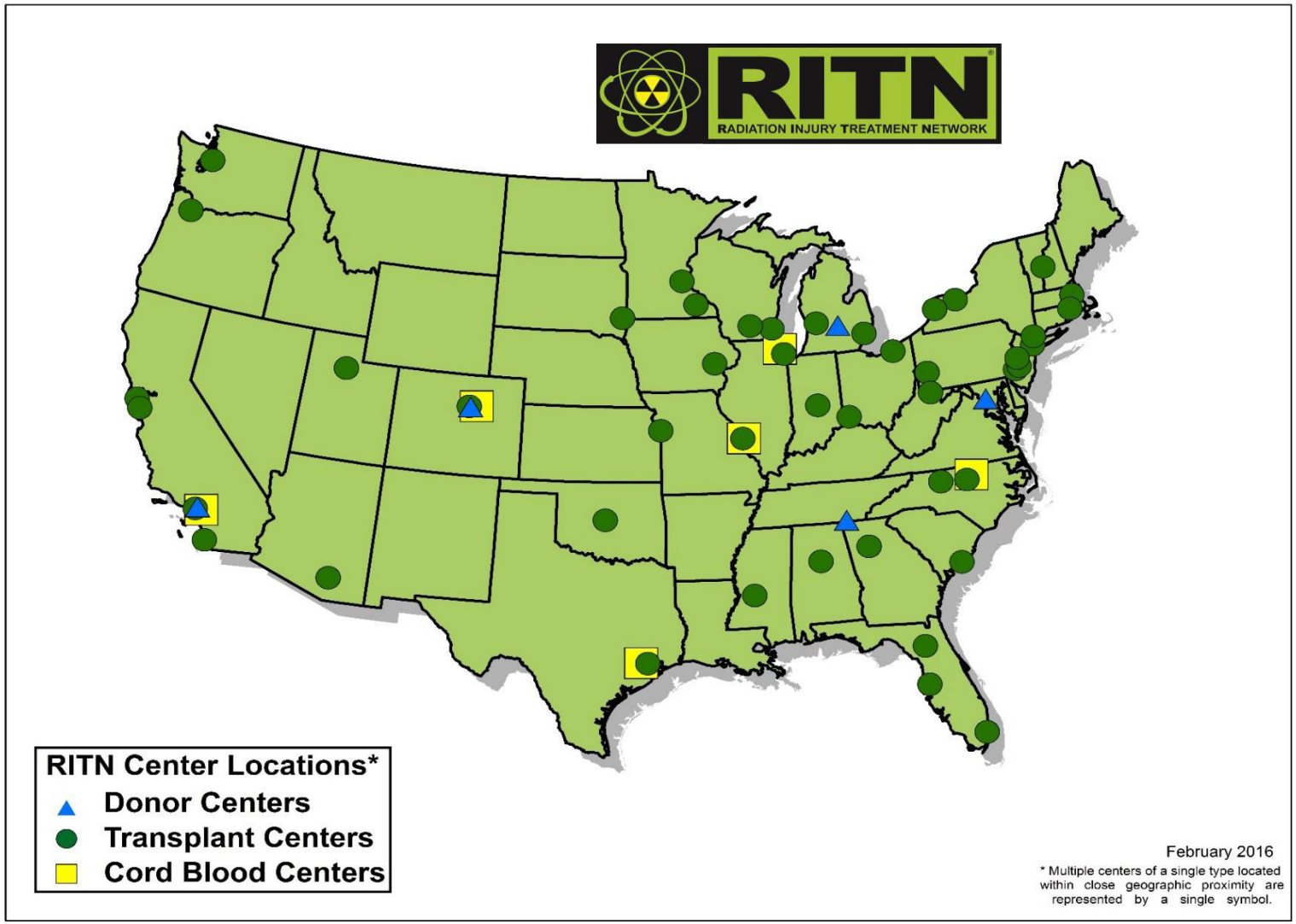
Turns out we've paid for a plan… ONR-funded civilian network

Acute Radiation Syndrome Treatment Guidelines

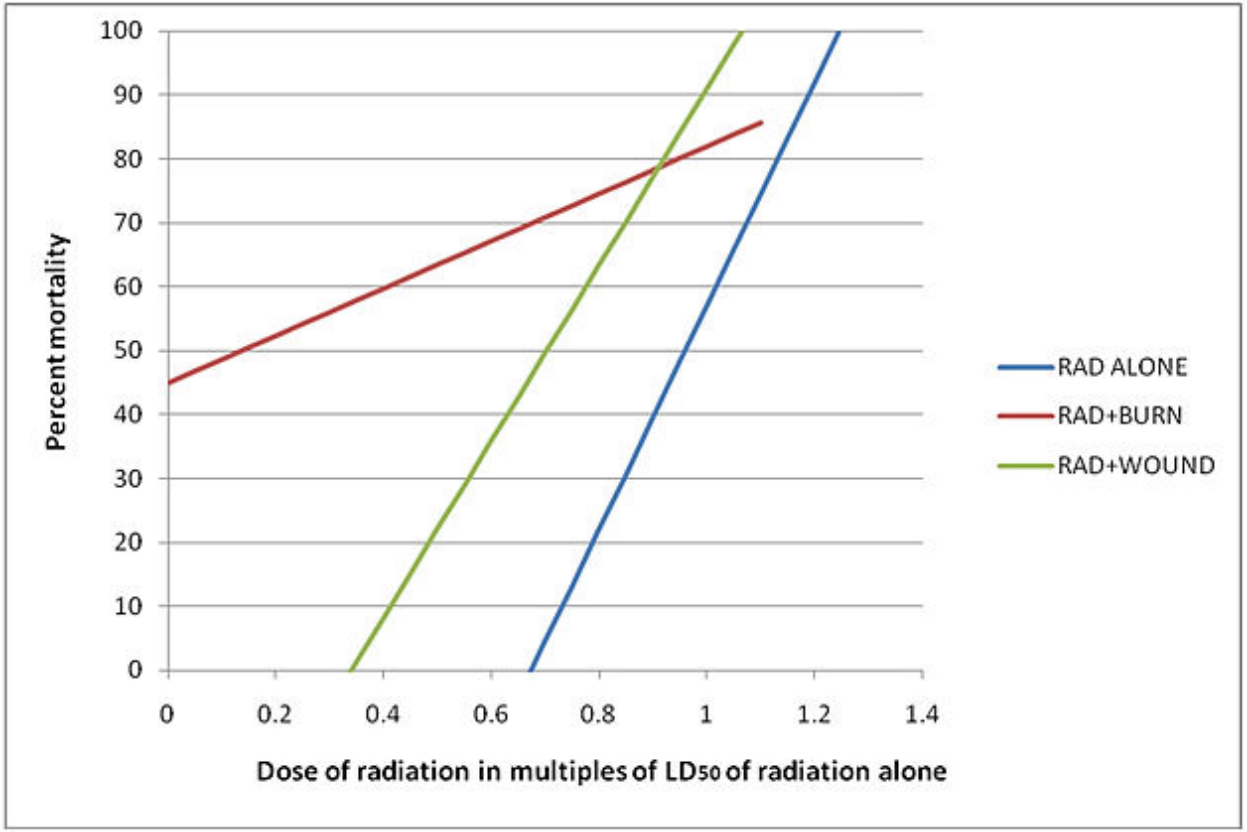
March 2016

Please forward comments or suggestions to RITN@nmdp.org

No DoD hospitals in the network yet!



Clinical Presentation of Radiation



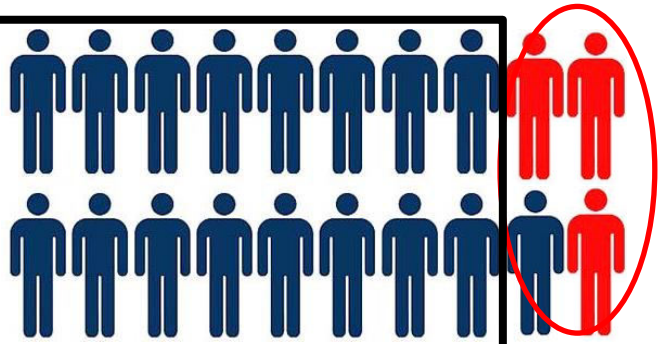
Combined injury increases mortality above radiation alone. Relationship between dose of radiation (rad) and probability of death for radiation alone and combined injuries (i.e., with burn or wound) based on a meta-analysis of animal data. Note that the studies utilized a burn with >40% mortality alone while trauma alone had no mortality.

Turns out that trauma + RAD is a problem RITN will not address!

Casualty Profile

So… the "elsewhere" is where exactly?

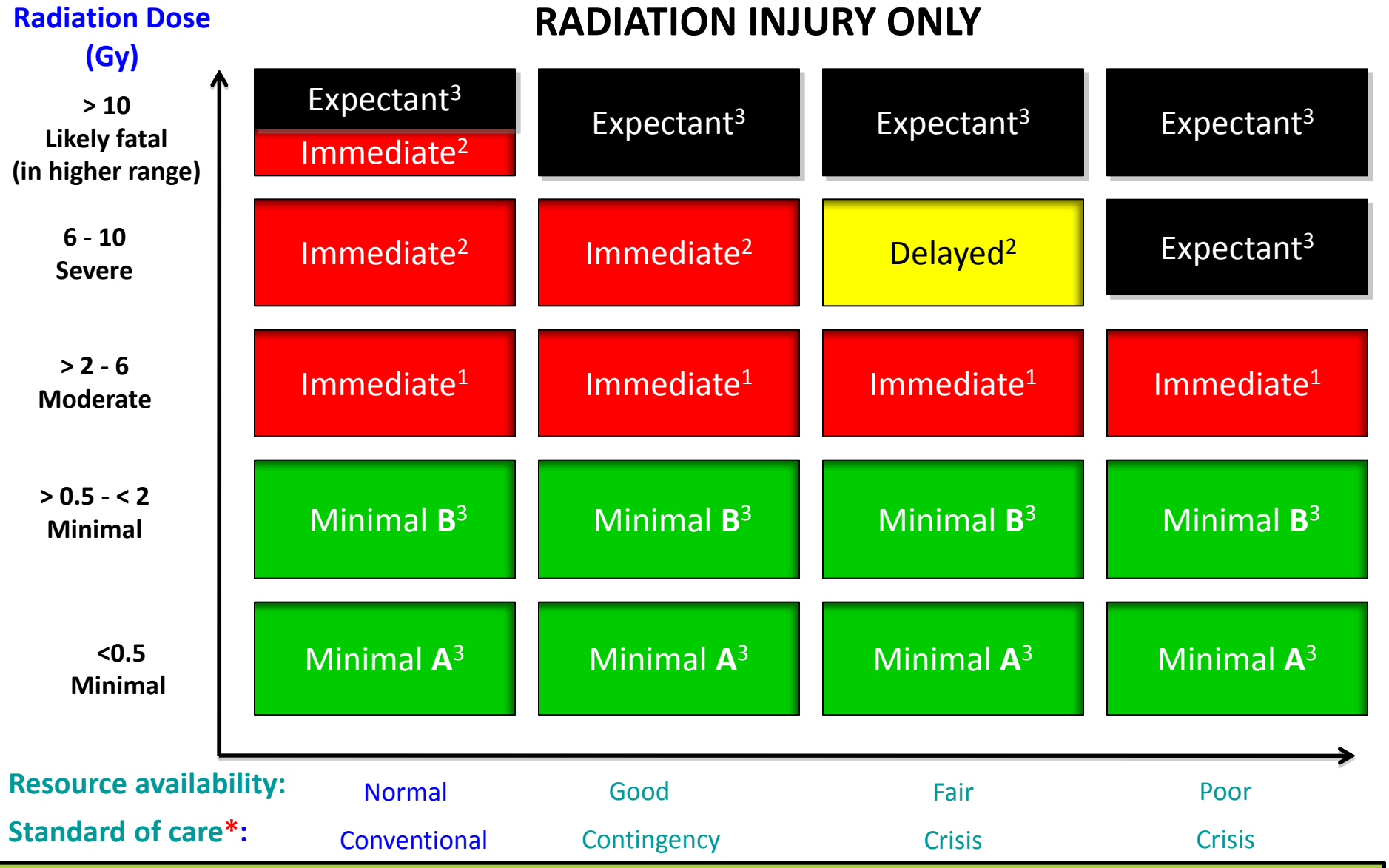
85% of casualties will have trauma or combined injuries and receive treatment elsewhere



15% will have "radiation only" injuries and be sent to RITN centers for definitive medical care

Casualty Estimates adapted from: Knebel AR, Coleman CN, Cliffer KD; et al. Allocation of scarce resources after a nuclear detonation: setting the context. Disaster Med Public Health Prep. 2011;5 (Suppl 1):S20-S31

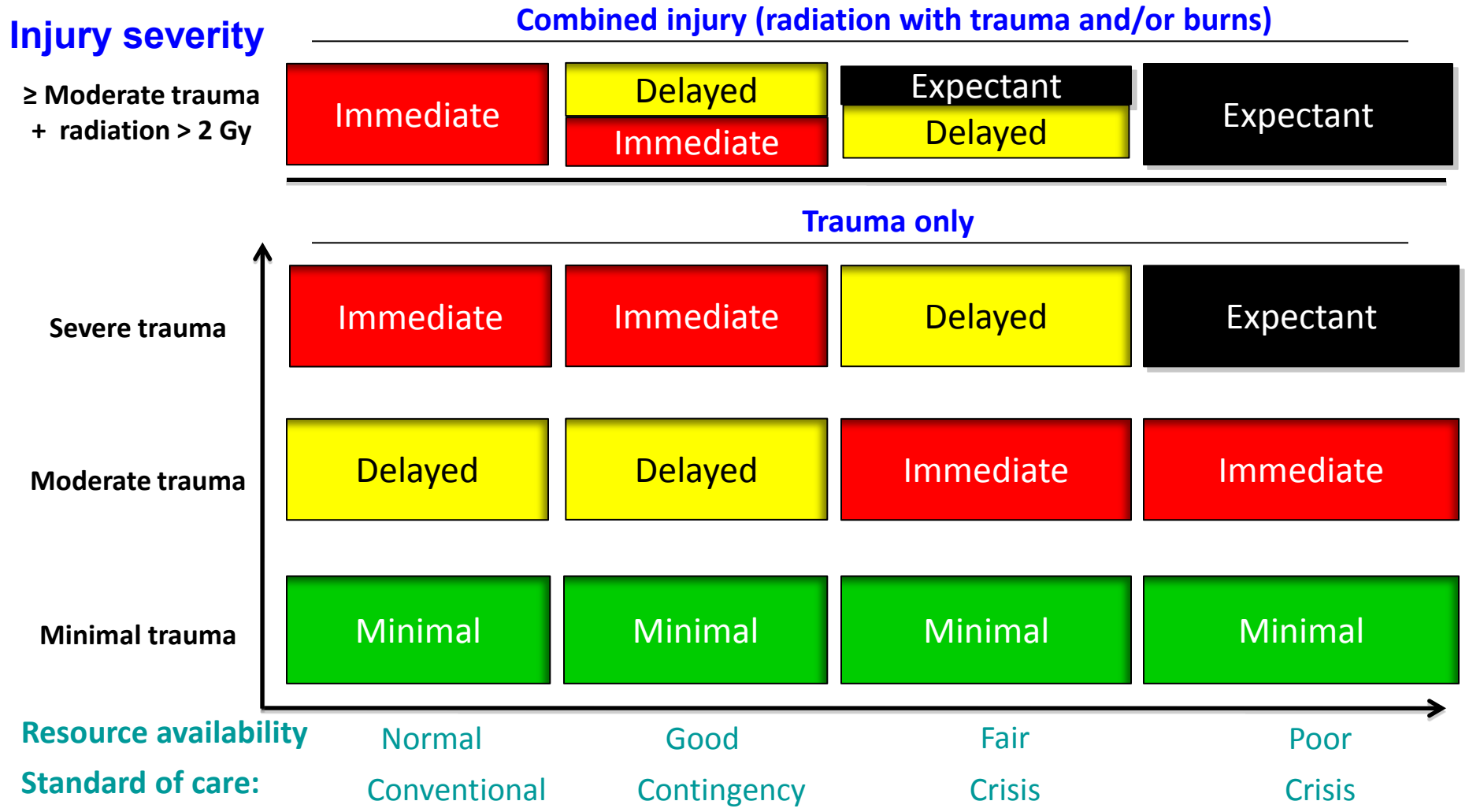
RADIATION INJURY ONLY



NOTES: Triage for victims with radiation injury only affected by resource availability. Most victims transported to RITN centers are expected to have minimal or no traumatic or burn injuries, and thus fit into the "Radiation Injury Only" group. Triage separates victims into those who should receive Immediate care, those Delayed after the Immediate cohort, those who require Minimal intervention and those who should receive Expectant (*i.e.* palliative only) management. Under crisis standards, those who received >6 Gy irradiation are triaged to Delayed or Expectant. Radiation doses are whole body or to a significant portion of the whole body. Legend for standard of care and myeloid cytokine treatment is included in the next slide. From the DHHS Scarce Resources Project.

TRAUMA and COMBINED INJURY

BURN >15% BSA worsens triage category 1 level



NOTES: Triage for victims with trauma or burn alone, in combination or with radiation injury. Most victims transported to RITN centers are expected to have minimal or no traumatic or burn injuries, and thus be triaged according to "Radiation Injury Only" (slide 14). Triage separates victims into those who should receive Immediate care, those Delayed after the Immediate cohort, those who require Minimal intervention and those who should receive Expectant (*i.e.* palliative only) management. Under crisis standards, those with severe injuries are deprioritized to Delayed or Expectant because of their worse prognosis and their greater need for resources. Radiation dose >2Gy indicates whole body or to a significant portion of the whole body. Legend and definitions of trauma categories are on the next slide. From the DHHS Scarce Resources Project.

ARS Prevention/Mitigation

STEMRAD360$^{\gamma}$

Personal Protection with Mobility

Highly complex design based on knowledge of radiation's effects and body composition

Optimal hip and shoulder distribution for support, comfort and mobility

Effective even against the most lethal radioisotopes such as Cs-137

8 different sizes to accommodate a heterogeneous population

Compatible with firefighting and other PPE worn by disaster response professionals

Positioned on the body's center of gravity, the 360 Gamma offers protection while maintaining full mobility

Ergonomically designed for optimal support and maximal comfort

100% fire-resistant, 100% durable

Specialized features such as reflector strips and ballistic resistance

"While whole body shielding is inherently heavy, partial body shielding is lighter in weight and selectively shields tissues of increased radiosensitivity (i.e. bone marrow) with substantial amounts of shielding material to protect hematopoietic functions; therefore, potentially preventing the acute health effects of exposure to gamma radiation". Occupational Radiation Protection in Severe Accident Management, 2015

ARS management

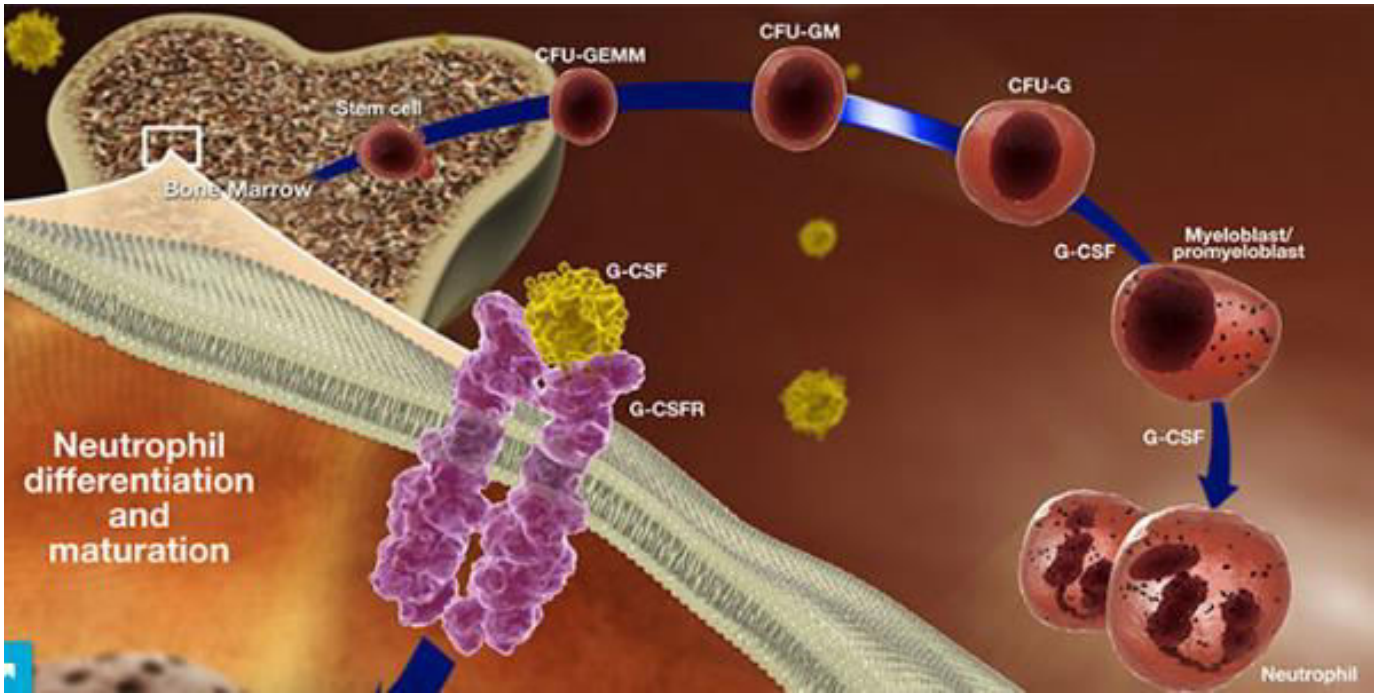
ARS Management: similar to leukemia therapy

- ARS Management: utilizes same approach as for cancer patients on myelosuppressive therapy
  - Hospitalization, if necessary
  - Prophylactic antibiotics and myeloid cytokines
  - Central venous access
  - Management of emesis, gastrointestinal toxicity and nutrition
  - Reverse isolation and dietary restrictions
  - Irradiated and leukocyte-depleted transfusions
  - Consider stem cell support only* in those without recovery at 21 days (if no/minimal combined injury)

* Informed by dismal historical experience of allogeneic transplantation for ARS…

Cytokines as supportive care

- Myeloid Cytokines – stimulate production of granulocytes (immune cells)



Myeloid cytokines

- In pivotal animal studies[1] of TBI, overall survival is improved if G-CSF or PEG-G-CSF is initiated **within 24 hours** after radiation exposure and continued until resolution of neutropenia
- In animal studies[2] with even 5% partial body shielding, G-CSF can be initiated 1, 3 or 5 days after irradiation with similar improvement in duration of neutropenia
- While G-CSF biosimilars and GM-CSF have not been approved for this indication, existing data suggests similar effects to Neupogen
- Transfer to RITN centers is not expected for multiple days to weeks after exposure and many victims will have received no or inconsistent cytokines prior to transfer
- At RITN centers, use of myeloid cytokines should follow standard approaches with the goal of shortening neutropenia and preventing neutropenia-associated complications

NOTES: 1 Schuening FG, et al., Effect of recombinant human granulocyte colony-stimulating factor on hematopoiesis of normal dogs and on hematopoietic recovery after otherwise lethal total body irradiation. Blood. 1989 Sep;74(4):1308-13.
2 MacVittie TJ, et al., The Effect of Radiation Dose and Variation in Neupogen® Initiation Schedule on the Mitigation of Myelosuppression during the Concomitant GI-ARS and H-ARS in a Nonhuman Primate Model of High-dose Exposure with Marrow Sparing. Health Phys. 2015 Nov;109(5):427-39.

Cytokines in the deployed setting

- G-CSF in Animal Studies
  - **Survival is improved if initiated within 24 hours*** and continued until resolution of neutropenia
  - With even 5% partial body shielding, G-CSF can be initiated 1, 3 or 5 days after irradiation with similar improvement in duration of neutropenia

**** In other words, G-CSF should be on the packing list for certain missions/ environments… and you should have the phone number of a hematologist☺***

Transfusions

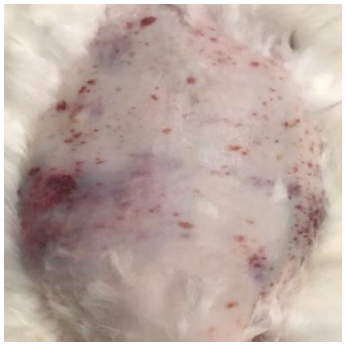
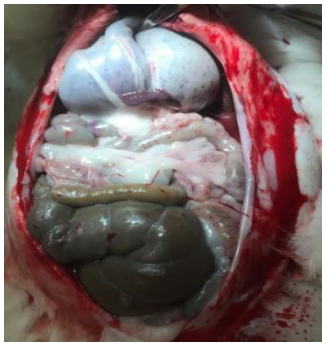
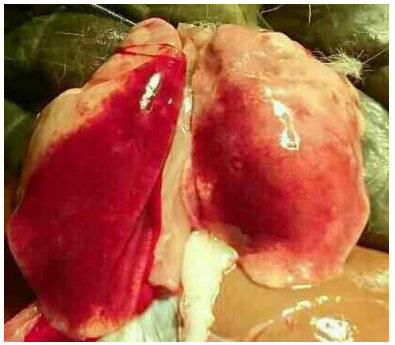
- Unless the casualty is known to have received < 1Gy irradiation, **all transfused blood products should be irradiated and leukoreduced**

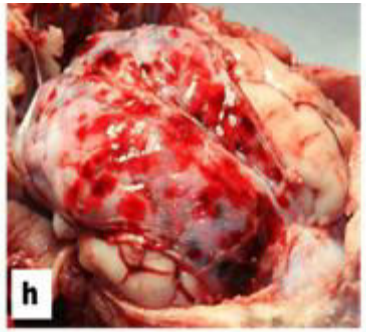
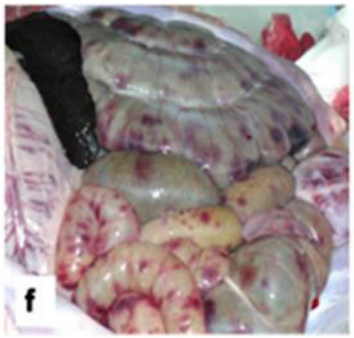
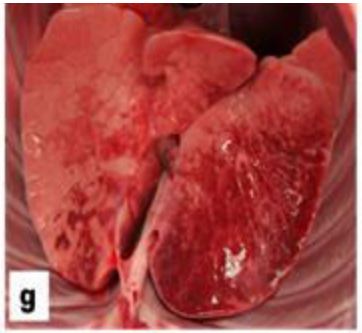
- Assuming adequate resource availability, standard thresholds for transfusions should be utilized

This will be a challenge in the deployed setting!

Coagulopathy Initiative

- Gross pathology of irradiated rabbits and G. Minipigs are similar.

	Skin Petechia	Intestines	Lungs
• Rabbit			

	Brain	Intestines	Lungs
• Minipi			

Prophylactic antibiotics

- Use standard approaches during neutropenia*:
  - Anti-HSV (*e.g.* acyclovir)
  - Anti-bacterial (*e.g.* levofloxacin)
  - Anti-fungal (*e.g.* fluconazole)
- After resolution of neutropenia in victims who received higher doses (>4 Gy), consider:
  - Anti-VZV (*e.g.* acyclovir)
  - Anti-PCP (*e.g.* bactrim)
  - Monitoring for CMV reactivation

@ D10 escalate abx
-- add imipenem for 14 days?

NOTES: *See ASCO, IDSA and NCCN treatment guidelines for fever and neutropenia.

Stem cell support

Role of Hematopoietic Stem Cell (HSC) Support

- Potentially of benefit for patients with a range of exposure inducing **hematopoietic and GI syndrome of ARS**
  - 2Gy – 8Gy
  - Coexisting trauma/burn reduces survivability
  - **Medevac within 5-7 days of exposure**
  - 1-3Gy or less than full body exposure: may recover with G-CSF and other supportive measures

Limitations of HSC Support

- **Delay (sepsis/bleeding), mismatch cells (GVHD, graft failure)**
  - Non-availability of allogeneic HSCs
    - No Unrelated Donors that are an HLA match
    - May not be available for 2-3 months
  - May not be safe
    - Donor's Cells React Against Patient
      - GVHD
  - May not be effective
    - No patient has ever survived long term using allogeneic HSC support
    - Limited Data

Making HSC Support Possible

- **Pre-Collection of Stem Cells for high risk population?**
  - Availability
    - Cells are **pre-collected and frozen** until needed
    - **Immediately available** once patient reaches transplant facility
  - Safety
    - **Autologous** (patient's own) stem cells have not been shown to cause GVHD
  - Efficacy
    - Has never been attempted in ARS
    - Animal models demonstrate efficacy
    - Common procedure in treatment of multiple myeloma, lymphoma

Not as easy as it sounds…

- **Challenges inherent to a Pre-Collection Strategy**
  - Must identify a population at high risk prior to exposing event
  - Risk To Patient (donor)
    - Very small but real risk of injury to patient (bone pain, “flu-like symptoms,” splenic rupture – may not feel great for a week most likely outcome)
  - Resource Intense and Costly
    - 5-7 days of commitment for each patient
    - $10,000 - $20,000 per patient
    - Facility capacity

Long Term Issues

Stem Cells

- Cells are stored for at least 10 years at SAMMC.
  - Stored cells have shown viability at the 10 year mark.
- *Stem Cells are typically discarded after 10 years.*
  - *If the soldier wishes to keep the cells they have to coordinate the transportation and storage to another facility?*
  - *If the soldier remains on active duty the cells will continue to be stored?*
  - *Donate stem cells to research?*

Other Medical Support Issues

- Other banking? (sperm)
- Practicality – how many per week, cost, storage issues, TTD testing, etc.
- Other issues: Command approval, TDY, FACT accreditation, etc

There are other options…

- **If HSC collection is a bridge too far, could provide:**
  - HLA typing
    - Accelerate identification of donors for allogeneic transplantation in the event of an exposure
  - Cytokine support (G-CSF)
    - Should be prepared to do this from POI, through evacuation to CONUS
- ***Tiered levels of support?***
  - Highest risk offered HSC collection → next, HLA typing → cytokines for all in high risk environment…

Historical Experience

- **Human Experience – Focus on Hematologic ARS**
  - 1986 – Chernobyl Power Plant Explosion
    - 134 workers developed ARS, 28 deaths
    - 13 patients had cell transplant (13 BMT, 6 fetal liver) - 10% survival
  - 1987 - Goiania, Brazil - Scrap metal recyclers steal abandoned cancer radiation device, open device, and release Cesium
    - 249 people contaminated, 8 with ARS
      - 50% survival with cytokine (GM-CSF) alone

Historical Experience

- Clinical Case Study Review - 58 most severe (>5Gy) radiation exposures reported internationally
  - 29 had BMT, 29 did not
  - All patients died

- 1999 – Tokai-Mura Japan – Accident at uranium processing facility
  - 2 victims received radiation of 8.5 Gy and 4.5 Gy and treated with SCT
    - Graft successful in both (HLA mismatched CB, matched PB)
    - Died at 82 and 210 days of multi-organ failure

Need management plan from POI → Definitive Care

Need a comprehensive management plan: JTS CPG

-- recognize injury (immediate call to SAMMC BMT)

-- triage

-- decon

-- field tx (G-CSF, other injuries, transfusion issues and tGVHD (need LR/irr blood), lab samples to help with biodosimetry)

-- en route care

-- transport to dedicated centers – specialized transport?

-- multi-D management (Trauma, Burn, Heme-Onc, Blood Bank, ID, GI, etc.)

Implementation Steps?

There is a lot to do.

Chem & Bio exposure scenarios present additional challenges.

We need to get busy.

Questions?

ASBP
Armed Services Blood Program