Repurposing of approved products for use against public health threats: Radiological and Nuclear

Ron Manning
CBRN/BARDA
Topics

• ARS Refresher
• Rad/Nuc Product Development Strategy
• Repurposing
• Thermal Burns
• Blood and Blood Products
Acute Radiation Syndrome (ARS)

Hematopoetic System
0.1-1 Gy: Slight decrease blood count
1-3.5 Gy: Mild to severe bone marrow damage, 1 hour- 48 hours
3.5-7.5 Gy: Pancytopenia, 1 hour- 48 hours
7.5-10 Gy: Bone marrow damage, <1 hour- 48 hours
>10 Gy: Severe bone marrow damage, minutes- 48 hours

Neurological
> 10 Gy Neurological damage 1-10 days

GI System
3.5-7.5 Gy: Mild to moderate GI damage, 1 hour- 48 hours
7.5-10 Gy: Moderate to severe GI damage, <1 hour- 48 hours
>10 Gy: Severe GI damage, minutes- 48 hours

Cardiovascular
>10 Gy
Minutes- 48 hours

Cutaneous Radiation Injury
≥ 2 Gy

Gastro-intestinal (GI)
>10 Gy: Severe GI damage, minutes- 48 hours
Delayed Effects of Acute Radiation Exposure (DEARE)

- Cataracts
- Radiation Burns
- Blood Disorders
- Inflammatory Conditions
- Cancers
- Lung Fibrosis
- Potential Genetic Damage to Progeny

Long Term Follow-up of Exposed Individuals
ARS and DEARE timeline: PHEMCE priorities

PHEMCE PRIORITIES

Marrow/Skin/GI  Lung Kidney  Organ dysfunction  Secondary malignancy

Days  Weeks  Months  Years  Decades

IRRADIATION

RAD/NUC Strategy

- Multitude of syndromes arise from acute radiation exposure (blood, GI, skin, lung, cardiac, neurological)
- “First syndromes first”
- Each syndrome requires separate animal model system
- Repurposing existing oncology drugs to treat hematopoietic syndrome (first line Point Of Care drugs)
  - Strategy: procure sufficient cytokines from existing manufacturers and maintain through stock rotation system
  - Generate sufficient data to support EUA and licensure
- Invest in second line (definitive care) drugs to treat hematopoietic syndrome for patients without functional bone marrow
- Stand up infrastructure and develop animal models for other ARS syndromes
- Continue to invest in product improvements (IV to oral) for decorporation agents with an emphasis on pediatric formulations
Repurpose pharmaceuticals already in use for related indications

- Many candidates

- Still need to demonstrate efficacy for ARS

- Pursue Fixed Price Acquisition with cost-reimbursement support of ARS clinical indication

- Stress Life Cycle Management (sustainability) considerations

- Candidate ARS subsyndromes include hematopoietic (neutropenia), skin (burn) and lung (fibrosis, pneumonitis)
• MCMs of this type are needed in emergency medicine as well as in the event of terrorist attacks

• BARDA is funding novel technologies that may revolutionize emergency medicine
  – Spray-dried plasma (Velico)
  – KeraStat burn gel (Keranetics)
  – Autologous cells from adipose tissue (Cytori)
Burn Care: Small Market, Limited Clinical Capacity

• Burn care is a relatively small ("boutique") market
  – 45,000 hospitalizations per year (55% in burn centers)
  – 7,500 cases requiring “skin substitute alternative countermeasures”
  – Estimated 350-450 burn surgeons in North America
  – Opinions on best treatments vary

• Our nation’s burn treatment capacity is limited
  – 125 burn centers nationwide: ~1800 burn beds total
  – Average daily availability: ~400 burn beds (can drop as low as 200)
  – Capacity is decreasing (7 fewer centers than in 2004)

• Burn care is labor and resource intensive
  – Requires specific medical expertise (excision, grafting, etc.)
  – Long hospital stays - 1 day per % total body surface area (%TBSA)
  – Frequent attention: changing dressings, administering fluids and medication, monitoring wounds - 1 nurse per 1 patient
Burn Treatment: Key Findings

- Burn wounds do not require *immediate* specialized intervention
  - Prevention of bacterial infection is the primary goal
  - Anti-microbial covering is sufficient for first few days
  - Definitive treatment can wait until transfer to a medical center
- Systemic complications of large burn wounds (>20% TBSA) are potentially fatal in the first 72 hours
  - Must address fluid resuscitation, airway management, pain management
- A polypharmacy solution will be necessary
- Autografting is the only permanent solution for full-thickness burns
- The scarcity of surgeons and resources restrict *product usability*
  - Mass casualty may require care administration by unconventional practitioners (*Cosmetic surgeons, Physician assistants etc*)
- There is little market incentive to develop new products
  - Limited interest from the private sector for investment

Timeline Post-Detonation

0 - 72 hrs

GOALS

• Administer fluids
• Secure airway
• Manage pain
• Provide early nutrition
• Prevent wound infection

Burn Wound Treatments
1. Anti-microbial barrier burn bandages

Key Complementary Products
A. Oral rehydration therapy sachets
B. Point-of-care airway management
C. Analgesics (oral/intramuscular)
D. Nutritional supplies (oral)

72 hrs - Beyond

GOALS

• Conclusive burn wound care
• Functional recovery
• Provide fluids & nutrition

Burn Wound Treatments
2. Autologous-based treatment products
3. Natural biological products
4. Manufactured biological products
5. Anti-microbial burn dressings

Key Complementary Products
E. Burn care surgical equipment
F. Rehydration fluids (oral/intravenous)
G. Nutritional supplies (oral/nasogastric)
H. Pharmaceuticals (analgesics, sedatives, systemic antibiotics)

Phase I Products
Field Care

Phase II Products
Definitive Care

Definitive Care Burn Product Goals

• Cost competitive
  – Total cost-of-care

• Usable by a wider group of medical professionals
  – CONOPS friendly

• Maximize health care benefit
  – Fewer clinical procedures (e.g., repeat grafting)
  – Shorter hospital stay
  – Reduce need for complementary medical supplies (e.g., analgesics)

• Amenability to stockpile or managed inventory solutions
  – Storage conditions
  – Shelf-life (expiry)

• Acquisition Approaches
  – Surge capacity / warm base
Damage Control Resuscitation (DCR) is a transfusion strategy that addresses massive blood loss following traumatic injury
- Fresh whole blood or plasma, packed red blood cells, and platelets used in a 1:1:1 ratio

Fresh frozen plasma (FFP) is obtained from whole blood
- Shelf life is 1 year at -18°C
- Once thawed FFP should ideally be used within 6 hours
- Thawing can delay treatment for 60 to 90 minutes

Battlefield results

During the battle in Mogadishu, approximately one-third of available FFP stored in bag fractured upon thawing. The U.S. Army Medical Research Materiel Command has reported up to 40 percent of FFP units breaking during shipment from the continental United States (CONUS) to theater. Other reports have indicated between 10 and 30 percent of FFP is lost to breakage during shipping. This has resulted in significant waste, particularly of universal plasma (Type AB), which is available from only four percent of U.S. donors.

“Does transfusion of stored red blood cells cause clinically important adverse effects? A critical question in search of an answer and a plan” (Paul Ness, Transfusion, 2011)

Multiple studies reporting an association between transfusions, and an increase in length of hospitalization, post-operative infections, lung injury, tissue hypoxia, bleeding/thrombosis, and multiple organ failure which may relate to a transfusion-related immunomodulation (TRIM) effect.

Accumulating evidence suggesting that transfusion of “older” blood that has been stored for longer periods of time, may not be as beneficial as transfusion of “fresher” blood in terms of oxygenation and TRIM- and inflammatory-induced complications.

Most recent meta-analysis included 21 studies that evaluated the age of the stored RBCs transfused and had mortality data (Wang et al., Transfusion 2011)
• Address Acute and Delayed effects of radiation exposure

• Develop products for both field use and definitive care

• Pursue repurposing candidates for ARS subsyndromes

• Support improvements in burn and blood products