

General and Plastic Devices Advisory Panel Meeting

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David J Barillo, MD, FACS, FCCM

Disaster Response / Critical Care Consultants, LLC
Mount Pleasant South Carolina



Disclosures

- Consultant to Argentum Medical, LLC
- Co-principal Investigator on BARDA Contract # HSSO100201300019C developing silver-based burn dressings for radiation, mustard gas and other mass casualty use



Background

- 25+ years of experience as burn surgeon & chronic wound surgeon
- Board Certification in General Surgery, Plastic & Reconstructive Surgery and Surgical Critical Care
- Retired Colonel, USAR with 5 tours / 12 years at US Army Burn Center
- Former Professor of Surgery / Chief of Wound Center, U of Florida
- Former Associate Professor of Surgery / Chief of Plastic Surgery MUSC
- Involved in development of Southern Region and National Burn Disaster Plans
- Research in use of silver products for wound healing and burn care



Concern: Effect of regulatory changes on burn care

- The United States has barely sufficient resources to manage the day-to-day care of burn patients
- There are 123 burn centers, approximately 1700 burn beds and approximately 350 experienced burn surgeons in the US. Recruitment of nurses and physicians into the specialty is very difficult
- The Federal Government recognizes that there is insufficient surge capacity to manage a WMD or burn mass casualty incident in the US
- Burn care is tremendously resource-intensive and difficult to provide. Multiple dressing techniques and materials are often necessary. Several of the antimicrobials in daily use date back to the 1960's.
- Many of the newer dressings come from small businesses that cannot afford the regulatory burden of device reclassification / PMA application or post-marketing studies



Silver: A naturally-occurring element

- Silver ion is normally present in humans from natural ingestion
(blood levels of <2.3 ug/L, urine excretion 2 ug/day)
- Silver has been used for jewelry, currency and food handling for > 5000 years
(mentioned in the First Book of the Old Testament)
- Alexander the Great used silver vessels to keep water pure (335 BC)
- Ambrose Pare (1590) used silver clips in surgery.
- Crede in 1880 first applied silver nitrate to eyes of newborns to prevent ophthalmia neonatorum – in US *required by law for most of the 20th century*
- Halstead (Johns Hopkins, 1889) used silver foil to prevent surgical infection
- A mainstay of burn treatment since the 1960's

REF: Marx et al - Burns 2014; 40s: 9-18
Barillo et al - Burns 2014; 40s: 3-8



Microbial Resistance to Silver is Extremely Uncommon

- Silver ion has 4 antimicrobial mechanisms of action and all 4 need to be overcome to induce resistance – difficult to do even intentionally in the lab
- There are 3 known silver-resistance genes but the presence of these genes does not protect bacteria against high levels of silver ion
- Warriner: “silver does not induce bacterial resistance if used at adequate concentrations”
- Chopra: fewer than 20 cases of silver resistance found in a 32-year literature review—some were intentionally induced and 1 *Pseudomonas* strain found in a silver mine
- No clinical problems in 60+ years of burn experience with silver nitrate and silver sulfadiazene

REF: Marx- Burns 2014; 40s: 9-18

Chopra- J Antimicrobial Chemotherapy 2007;59:587-90

Warriner- Adv Skin Wound Care 2005; 18 (suppl): 2-12



Silver Dressings = Less Antibiotic Use

- Appropriate use of topical silver dressings provides high antimicrobial effect at site of infection (wound)
- High and sustained levels of silver ion at the wound PREVENT the development of microbial resistance
- **With Silver-Nylon Dressings, silver ion is not absorbed into systemic circulation or found in solid organs, even after long-term use:**
This effect has been demonstrated in at least three species (minipig, rat, hairless guinea pig); in three depths of burn injury (superficial partial thickness, deep partial thickness, full thickness); and in 2 different mechanisms of injury (thermal burns and chemical burns)
- **Silver based dressings allow local control of wound infection rather than using oral / intravenous systemic antibiotics**

REF: Barillo et al - J Burn Care Res 2013;34 (2 suppl): S125

Barillo et al -*The Toxicologist*, Supplement to *Toxicological Sciences*, 2016;
Abstract # 2111.



Microbial Resistance is a Valid Concern

- For those of us in intensive-care unit practice, this is a daily problem
- Responsible stewardship of systemic antibiotics is advocated by many medical societies
- Topical antibiotics, however, are not the problem



Animal Use of Antibiotics As Growth-Promoting Agents

- In 2011, 13.6 million kilograms of antimicrobials were sold for use in food-producing animals, **representing ~ 80% of all antibiotics sold in the United States** (US FDA Data)
- Khachatourians: ‘About 90% of the antibiotics used in agriculture are given as growth-promoting & prophylactic agents rather than to treat infection’
- Union of Concerned Scientists : ‘Nontherapeutic livestock use accounts for 70% of total antimicrobial use. When all agricultural uses are considered, this share could be as high as 84%.’

REF: US FDA 2013 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, 2015 & US FDA, CDER, Office of Surveillance and Epidemiology Drug Use Review April 5, 2012

Khachatourians – CMAJ 1998;159 (9):1129-1136

Union of Concerned Scientists: Hogging it!: Estimates of Antimicrobial Abuse in Livestock, April 2004



#213

Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. All written comments should be identified with the Docket No. FDA-2011-D-0889.

For further information regarding this document, contact William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9084. E-mail: william.flynn@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm> or <http://www.regulations.gov>.



Summary

- Antimicrobial resistance is a major concern for all of us
- Silver ion, with several millennia of human experience, is not causing antimicrobial resistance
- Topical wound therapies allow targeted therapy at the site of infection and decrease the use of systemic antibiotics
- It makes no sense to further hinder the difficult work of burn care providers by unnecessary over-regulation of products that we already know are working
- Reclassification of *Wound Dressings Combined with Drugs* will likely put small medical device companies out of business and further restrict the limited therapeutic options available to practicing clinicians
- Further regulation? Lets reconsider the 80% of antibiotics sold in the US that now are used in agriculture rather than to treat human disease

