U.S. FOOD & DRUG ADMINISTRATION

General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

Classification of Wound Dressings Combined with Drugs

September 20-21, 2016

Sep 20: Clinical Discussion

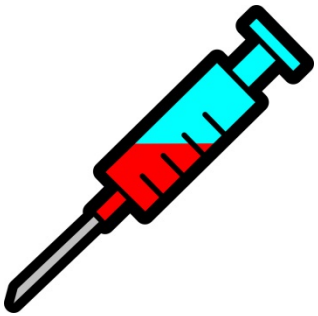
What is a Combination Product?

Melissa Burns
Senior Program Manager
FDA Office of Combination Products

What is a Combination Product?

- A ***"combination product"*** is:
  - A product composed of **two or more different types of medical products** (e.g., drug and device, drug and biological product, device and biological product, or all three together)

- Examples
  - Prefilled Syringes
  - Drug-Eluting Stents
  - First Aid Kits with Devices and Drugs



What is a "Constituent Part"?

- ***Constituent part***: A drug, device, or biological product that is part of a combination product. *See* 21 CFR 4.1.

- Examples

Example	Constituent Parts		
	Drug	Device	Biological Product
Prefilled Vaccine Syringe		Syringe	Vaccine
Drug-Eluting Stent	Drug coating	Stent	
First-Aid Kit	Antibiotic Ointment, Antiseptic, Analgesic, etc	Gauze, Bandages, Tweezers, etc.	

What is “Mode of Action”?

- A combination product has at least two “modes of action” (*See* 21 CFR 3.2(k)), one per constituent part
- Each type of constituent part has its own mode of action:
  - Drug
  - Device
  - Biological Product
- For example, a prefilled vaccine syringe has:
  - a biological product mode of action (vaccine) and
  - a device mode of action (syringe)

Common Types of Combination Products

	"Single-entity"		"Co-packaged"
Description	Chemically or physically combined constituent parts		Constituent parts packaged together
Examples	• Drug-eluting stent • Prefilled syringe • Transdermal patch • Bone void fillers impregnated with drugs		• First-aid or surgical kit • Syringe packaged with vial of drug
Reference	21 CFR 3.2(e)(1)		21 CFR 3.2(e)(2)

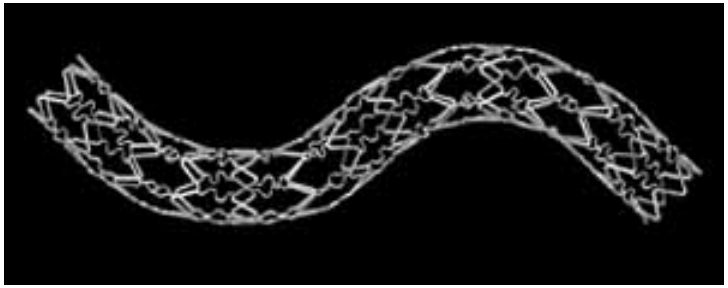
What is NOT a Combination Product?

- A combination product is **NOT:**
  - A product composed of **only two or more of the same type of medical product** (i.e., drug and drug, device and device, or biologic and biologic).
  - A **medical product combined only with a non-medical product** (e.g., drug and food, drug and cosmetic). *See* 21 USC 353(g).
- The following **ARE NOT** combination products:
  - Drugs combined only with each other, such as fixed dose combination drugs
  - Kits of JUST devices, JUST drugs, or JUST biological products
  - Separately distributed general use delivery devices (e.g., syringes) and drugs or biologics with which they can be used

How Does FDA Determine Center Assignment for Combination Products?

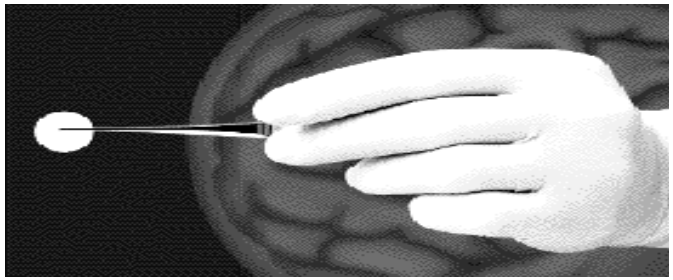
- Combination Products are assigned to a "Lead Center" having primary responsibility for their review
- Lead Center is based upon:
  - The "primary mode of action" (PMOA): Single mode of action of a combination product that provides the greatest contribution to the product's intended effects (21 CFR 3.2)

PMOA Example



Drug Eluting Stent

- PMOA – stent opens artery (device)
- Secondary MOA – drug prevents inflammation and restenosis
- Assigned to CDRH



Drug Eluting Disk

- PMOA – chemotherapy for brain tumor (drug)
- Secondary MOA – local delivery of drug by the device
- Assigned to CDER

Resources/References

- 21 CFR 3 Product Jurisdiction https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=3&showFR=1&subpartNode=21:1.0.1.1.3.1
- Definitions
  - Drug (FD&C Act 201(g), 21 USC 321(g))
  - Device (FD&C Act 201(h), 21 USC 321(h))
  - Biological Product (PHS Act 351(i), 42 USC 262(i))
- OCP Webpage: http://www.fda.gov/CombinationProducts/

Classification of Wound Dressings Combined with Drugs CDRH/FDA Presentations

Charles Durfor

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CDRH Presentation on Wound Dressings with Drugs

Agenda

- Regulatory History – Charles Durfor
- Regulation of Wound Dressings combined with Drugs – Cynthia Chang
- Types of data in 510(k) applications for Wound Dressings combined with Drugs – Cynthia Chang and Brandon Kitchel

CDRH Presentation on Wound Dressings with Drugs

Agenda (cont.)

- Clinical Perspectives on Unclassified Wound Dressings combined with Drugs– Laura Marquart
- Post-market Surveillance data for Wound Dressings combined with Drugs – Karen Nast
- Benefit/Risk considerations for Antimicrobial Drugs in Wound Dressings – Brandon Kitchel

Wound Dressings Combined with Drugs

Definitions-

- Wound dressings combined with a drug may meet the definition of a combination product (21 CFR 3.2)
- Preamendment Device – in commercial distribution before enactment of the Medical Device Amendments (5/28/76)
  - Adhesive Bandages containing Boric Acid
  - Adhesive Bandages containing Mercurochrome
- Procode – Each generic device category is identified by a 3 letter Product code (Procode) and Device Name
  - Procode FRO = Wound Dressing combined with Drug

Wound Dressings with Drugs Progress to Classification

- 9/19/89 – FR Vol. 54, No. 180, p. 38605 - proposed classification of 11 devices including the following Class III Device:

Interactive Wound Dressings – "a device … intended to actively promote the healing of a wound or burn by interacting directly or indirectly with body tissues. The device is intended to serve as a long-term skin substitute or temporary synthetic skin… The device also may be intended to prepared to prepare a wound bed for autograft." Regulated as a Class III Medical Device.

- These products are not the subject of this Panel Meeting

Wound Dressings with Drugs Progress to Classification

- 10/5/99 – F.R. Vol. 64 No. 192 p. 53927 – classification of:
  - Sec. 878.4014 – Non-resorbable gauze/sponge for external use
  - Sec. 878.4018 - Hydrophilic wound dressing
  - Sec. 878.4020 - Occlusive wound dressing
  - Sec. 878.4022 - Hydrogel wound dressing and burn dressing
- The final rules omitted wound dressings with drugs, biologics, or animal sourced materials.
- These Devices are not a subject of this Panel Meeting.

Wound Dressings with Drugs Progress to Classification

10/16/2009 – F.R. Vol. 74 No. 199 p. 53167 – classified:

- CFR 878.4015 - Wound Dressing with Poly(diallyl) dimethyl ammonium chloride) (pDADMAC) Additive

A wound dressing with pDADMAC additive is intended for use as a primary dressing for exuding wounds, first and second degree burns, and surgical wounds, to secure and prevent movement of a primary dressing, and as a wound packing. Class II

- This device group is not a subject of the Panel Meeting.

Summary of the 8/26/05 Meeting of the General and Plastic Surgery Devices Panel

- Topics discussed:
  - Product Descriptions – Number and Composition of Devices
  - Indications for Use
  - Summary of Post Market Experience
  - Risks to Health – AMR, Sensitization, Prescription / OTC Use
  - Adequacy of Special Controls
  - Contents of a Special Controls Guidance (Risks and Controls)
- Note
  - AMR was not identified as a potential risk for mitigation
  - Evidence illustrating the benefit of adding a drug to a Wound Dressing was not the subject of the 2005 Panel Meeting

Summary of the 8/26/05 Meeting of the General and Plastic Surgery Devices Panel

Conclusions

- Panel recommended Class II status
- Wound Dressings combined with Drugs remain unclassified
- Based on changes in wound care, product technologies, indications for use, and risks to health (e.g., AMR) since 2005, FDA believes that this follow-up meeting can provide important information

Next Steps in Wound Dressing Classification

Day 1 - Clinical and Scientific Discussion and Recommendations

Day 2 - Classification Discussion and Recommendations

After the Panel Meeting, FDA will:

1. Determine the appropriate device class (taking into account Panel recommendations and public comments);
2. Publish a proposed rule outlining the classification and request public comment;
3. Review all comments on the proposed rule; and
4. Publish a final rule classifying the FRO Wound Dressings as a Class I, II or III device (and call for PMAs for Class III devices).

Current Regulation of Wound Dressings

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Overview

- Classification of Wound Dressings
- Wound Dressings with Drugs
  - Solid Wound Dressings
  - Gels/Creams/Ointments
  - Liquid Wound Washes
- 510(k) Process Overview
  - Information and Testing

Classification of Wound Dressings

Class I	Class II	Class III
• Typically do not require premarket review • Does not contain drugs, biologics, or animal derived material	• 510(k) premarket review pathway • Substantial equivalence • Special controls	• Premarket approval – safety and effectiveness • Intended for wound treatment • Intended to be a skin substitute • Life-supporting or life-sustaining

Classification Discussion for Day 2

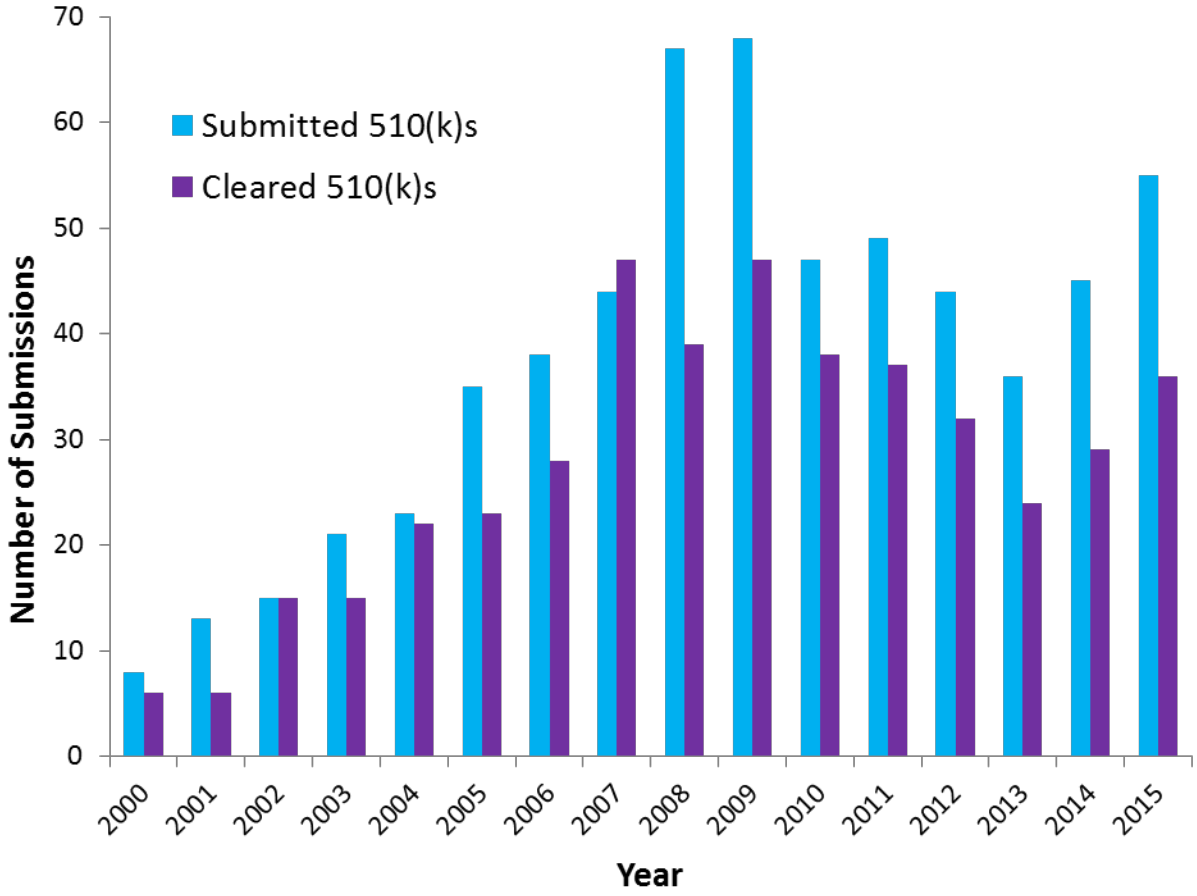
Class I	Class II	Class III
• Typically do not require premarket review • Does not contain drugs, biologics, or animal derived material	• 510(k) premarket review pathway • Substantial equivalence • Special controls	• Premarket approval – safety and effectiveness • Intended for wound treatment • Intended to be a skin substitute • Life-supporting or life-sustaining

Unclassified Wound Dressings Combined with Drugs (FRO)

- **No classification regulation**
- **510(k) pathway**

Wound Dressings with Drugs

- 700+ 510(k) submissions cleared to date
- Focus of classification panel meeting



Wound Dressings with Drug Subcategories

		
Solid Dressings	Gels, Creams, Ointments	Wound Wash Solutions

Solid Wound Dressings: Composition

- Base material
  - Synthetic/naturally derived
  - Biodegradable/non-biodegradable
- Structural strength for physical form
  - Scaffold/matrix
  - Single or multiple layers
- Typically combined with antimicrobials
  - Silver, bismuth, chlorhexidine, polyhexamethylene biguanide (PHMB), and bacitracin.

Solid Wound Dressings: Indications

- Intended use
  - Cover/protect wound
  - Absorb exudate
  - Provide/support moist wound environment
- Wound types
  - Traumatic, partial thickness burns, ulcers, surgical wounds
  - Catheter insertion sites, other percutaneous device insertion sites

Gels, Creams, Ointments: Composition

- Amorphous
  - High water content with thickeners
  - Oil-water emulsions
- Typically combined with drugs
  - Antimicrobials/preservatives
  - Plant-derived materials or extracts
- Packaged in tubes or bottles
  - Single or multiple use
  - May or may not be sterilized

Gels, Creams, Ointments: Indications

- Intended use
  - Provide/support moist wound environment
    - Relieve the symptoms of skin irritations, such as dryness, itching, and pain
- Wound types
  - Traumatic, partial thickness burns, ulcers, surgical wounds
  - Skin irritations, various dermatoses
    - Radiation dermatitis
    - Seborrheic dermatitis

Liquid Wound Washes: Composition

- Liquid solutions
  - Water or saline-based
- Often combined with drugs
  - Salts/surfactants
  - Antimicrobials
    - Hypochlorous acid/sodium hypochlorite
    - Silver
    - PHMB
- Packaged in bottles with caps or pump sprays
- May or may not be sterilized

Liquid Wound Washes: Indications

- Intended use
  - Rinse or irrigate a wound
  - To remove foreign material, such as debris, microbes, and wound exudate.
- Wound types
    - Traumatic
    - Partial thickness burns
    - Ulcers
    - Surgical wounds

Ingredients Present in FRO Products

Acesulfame K
Acetamide MEA (monoethanolamine)
Acetic acid
Activated charcoal
African palm oils
Alcohol
Alcohol (ethyl alcohol)
Allantoin
Almond meal
Aloe vera
Aluminum hydroxide
Aluminum magnesium hydroxide stearate
Aluminum oxide
Aluminum pigment
Aluminum sulfate
Ammonium phosphate
Angelica sp.
Aqueous wheat extract
Arachidyl alcohol
Ascorbyl palmitate (Vitamin C ester)
Ascorbyl tetraisopalmitate (Vitamin C ester)

Avocado oil
Bacitracin
Beeswax
Behenyl alcohol (docosanol, Abreva)
Benzalkonium cetyl phosphate
Benzalkonium chloride
Benzocaine
Benzoic acid
Benzyl alcohol
Betaines (various forms)
Bisabolol (chamomile oil)
Bismuth subgallate
Bismuth tribromophenate
Borneol
Butylated Hydroxytoluene (BHT)
Butylene glycol
Butyrospermum parkii
Cadexomer iodine
Calamine
Calcium
Calcium carbonate
Calcium chloride
Calcium oxide
Calcium sulfate
Camella sinensis
Candelilla wax
Capryloyl glycine
Carvacrol
Centella asiatica
Ceramide
Ceteareth-10 phosphate
Cetearyl alcohol (Cetostearyl alcohol)
Ceteth-20
Cetyl alcohol
Cetyl dimethicone copolyol
Cetyl palmitate
Cetylpyridinium chloride
Chlorhexidine
Chlorhexidine gluconate
Chlorine dioxide
Chlorophyllin copper complex sodium
Cholesterol
Chromium chloride
Citric acid
Citris grandis extract
Cloflucarban
Cobalt chloride

Cocoamphodiacetate
Colloidal silica
Combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine
Conjugated linoleic acid
Copper
Copper chloride (cupric chloride)
Crystal violet
Cupuacu butter
Cyclodextrin
Cyclomethicone
DEA Cetyl phosphate
Decanoic acid (capric acid)
Dehydroacetic acid
Dialkyl carbamoyl chloride
Diazolidinyl urea
Dicetyl phosphate
Diisopropyl adipate
Dimethicone
Dipolyhydroxystearate
Dissolved oxygen
DMDM hydantoin
EDTA
Ethanol
Ethoxydiglycol
Ethylene glycol monostearate
Ethylhexyl glycerin
Ethylhexyl palmitate
Eucalyptus oil
Eugenol
Extracts of licorice (deglycyrrhizinated)
Ferric chloride Hexahydrate
Ferric oxide
Fluorosalan
Fruit extract
Fumed silica
Gentian violet
Germaben II
Glycerin (glycerol)
Glyceryl monolaurate
Glyceryl monostearate
Glyceryl stearate
Glycyrrhetinic acid (licorice extract)
Guar gum (Cyaiuopsis letragonolobus)
Gum mastic
Hectorite clay
Hexachlorophene
Hexyl laurate
Hydrochloric acid
Hydrocortisone
Hydrogen peroxide
Hydrogenated castor oil
Hydrogenated lecithin
Hydroquinone
Hydrous lanolin
Hydroxypropyl bispalmitamide MEA (ceramide)
Hydroxypropyl guar
Hypochlorous acid
Iodine
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
Iodoform
Iodophors (Iodine-containing ingredients)
Iron (various forms)
Iron sulfate
Isohexadecane
Isopropyl alcohol
Isopropyl alcohol
Isopropyl myristate
Isopropyl sorbate
Kaolin
Karaya gum
Keratin
Konjac flour
Lactic acid
Lavender
Lecithin
Lemon
L-glutamic acid
Lidocaine
Light mineral oil
Liquid Germall Plus (propylene glycol, diazolidinyl urea, iodopropynyl butylcarbamate)
Lyophilized formulate porcine plasma
Magnesium aluminum silicate
Magnesium oxide
Magnesium stearate
Magnesium sulfate
Malic acid
Maltodextrin
Manganese chloride
Manganese oxide
Mannitol
Meadowsweet extract
Menthol
Methyl salicylate
Methyl triethoxysilane (MTES)
Methylal
Methylbenzethonium chloride
Methylene blue
Mineral oil
Molybdenum chloride
Myristyl myristate
Myrtillus extract
Nonylphenoxypoly (ethyleneoxy) ethanoliodine
Oak extract
Oat glucan
O-cymen-5-ol (Biosol)
Olive oil
Ozone
Palm glycerides
Palmitamide MEA
Palmitic acid
Panthenol FCC (form of vitamin B)
Parabens (various forms)
Paraffin
Pentalyn-H (Pentaerythritol ester of rosin)
Pentylene glycol
Petrolatum
Phenol (greater than 1.5 percent)
Phenol (less than 1.5 percent)
Phenoxyethanol
Phosphoric acid
Phosphorus pentoxide
Piroctone olamine
Poloxamer—iodine complex
Polyaminopropyl biguanide (PAPB)
Polygonum cuspidatum
Polyhexamethylene biguanide
Polyhexamethylene biguanide (PHMB, polyhexanide)
Polymyxin B sulfate
Polyricinoleate
Polyvinyl pyrrolidone-iodine
Potassium ferrate
Potassium iodide
Potassium iron oxyacid salt
Potassium sorbate
Povidone iodine
Povidone USP (Plasdone K 29-32)
Povidone-iodine 5 to 10 percent
Propyl gallate
Propylene glycol
Pyroglutamic acid
Quaternium 15
RADA-16 peptide
Rubidium chloride
Saccharin
Salicylic Acid
Salicylic acid
Sandalwood oil
Sarcosine
Secondary amyltricresols
Shea butter
Silver (various forms)
Silver sulfadiazine
Sodium benzoate
Sodium citrate
Sodium fluoride
Sodium hypochlorite
Sodium lactate
Sodium metabisulfite
Sodium oxychlorosene
Sodium selenite
Sodium sulfate
Sodium tetraborate (Borax)
Solanum lycopersicum (tomato) extract
Sorbic acid
Sorbitan sesquioleate (Arlacel C)
Sorbitol
Soy protein
Squalane
Steareth-10
Stearic acid
Styrax
Sucralfate (sucrose octasulfate, aluminum hydrochloride)
Sucrose
Sucrose laurate
Sulfur dioxide
Tara Gum
Tartaric acid
Tea tree oil
Tea tree oil
Telmesteine
Theobroma Grandiflorum seed butter
Thrombin
Thymol
Titanium dioxide
Titanium oxide
Tonalin FFA 80
Transcinnamaldehyde
Tribromsalan
Triclocarban
Triclosan
Triethanolamine (TEA)
Triglycerol (polyglycerol-3)
Triiodide resin
Triple dye
Trolamine
Tromethamine USP
Undecoylium chloride iodine complex
Vaccinium (blueberry)
Vegetable oil
Vitamin C (ascorbic acid)
Vitamin E (tocopherol)
Vitis vinifera (grape)
White petroleum
Wintergreen fragrance
Wood pulp core
Xanthan gum
Xylitol
Zinc (various forms)
Zirconium oxide

510(k) Process Overview

- Premarket notification process
- Evaluation for substantial equivalence to a predicate device
- Intended use
- Technological characteristics

510(k) Content

Information Provided
Device Description
Draft Labeling
Biocompatibility Testing / Toxicological Risk Analysis
Animal Testing*
Clinical Testing*
Absorption Testing
Shelf Life Testing
Sterility and Bioburden Testing
Antimicrobial / Preservative Effectiveness Testing

*When appropriate

Performance Claims and Supporting Test Methods

Brandon Kitchel

Microbiologist

FDA Center for Devices and Radiological Health

Overview

- Background
  - Performance claims in CDRH
  - General Microbiology Testing Setup
- Minimum Effective Concentration (MEC)
- Performance Claims & Supporting Testing
  1. Preservative Effectiveness
  2. Antimicrobial Effectiveness
  3. Microbial Barrier Effectiveness

Background

- All antimicrobial performance claims cleared in CDRH are limited to an action within the product
- Most performance claims based on *in vitro* testing
- No antimicrobial effectiveness testing standards recognized
  - Sponsors encouraged to submit protocols via our pre-submission process
- Claims should be supported by quantitative testing
  - Colony counting and log reduction analysis

Microbiology Testing Setup

1. Define the Test Article
   - Final product, at end of shelf life
   - Conditioned to emulate factors of clinical use
2. Inoculate the Test Article
   - ≥ 1 x 10^6 Colony forming units (CFUs)
3. Incubate for specified period of time
   - Use-life
   - Test standard

Microbiology Testing Setup

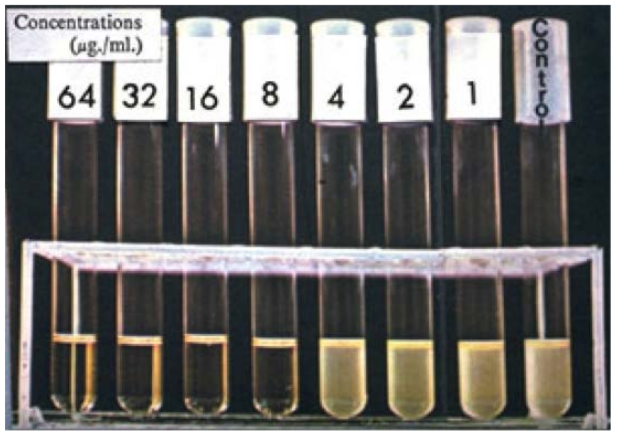
4. Extract surviving test organisms
   - Neutralization buffer
5. Plate surviving microorganisms and count colonies
   - USP<61>
6. Calculate **Log Reduction**

   = $\log_{10}$ (organisms before treatment) – $\log_{10}$ (organisms after treatment)
   - 1 log reduction = 90% reduction
   - 2 log reduction = 99% reduction
   - 3 log reduction = 99.9% reduction
   - 4 log reduction = 99.99% reduction

Minimum Effective Concentration (MEC)

Minimum Effective Concentration (MEC)

- Concentration critical to safety and performance
  - Too much antimicrobial could lead to safety risks
  - Not enough may compromise performance
- MEC Testing
  - Serial dilution of antimicrobial in product
  - Inoculate with test organism
  - Identify lowest concentration that met the acceptance criteria



Performance Claims & Supporting *in vitro* Testing

1. "**Preservative Effectiveness**" - microbial growth within the product while on the shelf
2. "**Antimicrobial Effectiveness**" - microbial growth within the dressing while in use
3. "**Microbial Barrier Effectiveness**" – microbial penetration through the dressing while in use

1) Preservative Effectiveness

Preservative Claims

- Products
  - Wound gels, creams and ointments
  - Wound washes/ irrigation solutions

- Rationale for Antimicrobial
  - To improve the shelf life of a non-sterile product
  - To permit repeated opening after breaking the sterile seal
- Claims
  - "Maintains a low bioburden during shelf storage and after repeated openings of the package"
  - "Inhibits the growth of bacteria such as *S. aureus, P. aeruginosa, E. coli, P. mirabilis, S. marcescens, A. baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and fungi such as *C. albicans* and *A. niger* within the product"

Preservative Testing

- USP<51>
  - Test organisms:
    S. aureus, P. aeruginosa, E. coli, C. albicans, and *A. niger*
  - Test Article: Aged product in final packaging
  - Period of Incubation: 7, 14, and 28 days
  - Control - NA
  - Acceptance criteria
    - Bacteria: ≥2 log reduction (99%)
    - Yeast/Mold: No increase from initial count

2) Antimicrobial Effectiveness

Antimicrobial Claims

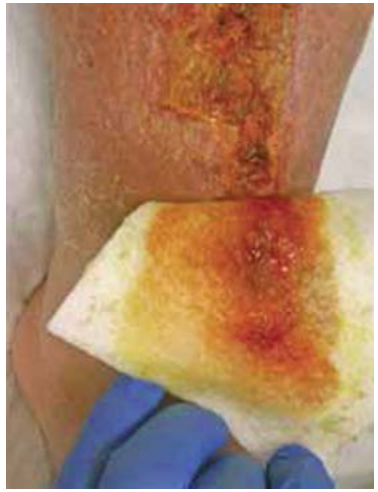
- Products
  - Wound dressings in solid form
- Rationale for Antimicrobial
  - To reduce bacterial colonization of the dress
- Claims
  - "An antimicrobial effect to minimize microbial contamination/ colonization of the dressing"
  - "Kills a broad spectrum of bacteria including MRSA and VRE within the dressing"
  - "Provides sustained antimicrobial activity in the dressing for up to 7 days"

Antimicrobial Testing

- Modified AATCC Test Method 100
  - Test organisms
    - 3 gram-positive bacteria, 3 gram-negative bacteria, 1 yeast and 1 mold
  - Test article: Swatch of finished product (aged)
    - Dressing should be conditioned to emulate clinical use
  - Period of Incubation: Product use-life (e.g., 7 days)
  - Control
    - Material control (subject dressing without antimicrobial)
  - Acceptance Criteria: ≥4 log reduction

Antimicrobial Testing

- Simulated Use Testing
  - Purpose: Emulate clinical conditions of use as part of performance testing in order to add degree of clinical relevance to *in vitro* results
  - Includes conditioning product with simulated wound fluid (SWF) for a specified period of use
    - Potential interfering factors such as temperature, pH, soiling and protein deposition
    - Maximizes amount of antimicrobial leaching away



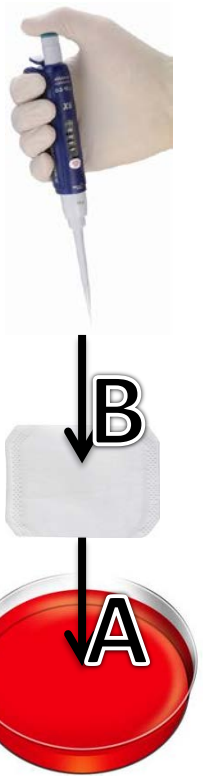
3) Microbial Barrier Effectiveness

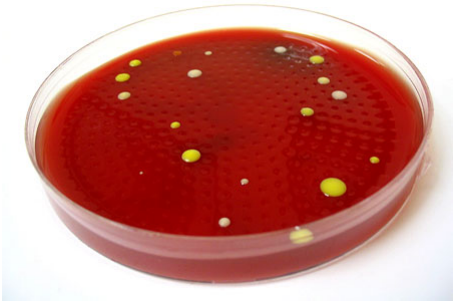
Microbial Barrier Claims

- Products
  - Wound dressings in solid form (primary or secondary)
- Rationale for Antimicrobial
  - To provide a barrier against microbial entry into a wound
    - Physical barriers (e.g., Polyurethane backing)
    - Antimicrobial barriers
- Claims
  - “Covers and protects the wound”
  - “A barrier to penetration of microbes to the wound, which may reduce the risk of infection”
  - “To enhance the microbial barrier function and minimize growth of microbes in the wound dressing”

Microbial Barrier Testing

- Performance Testing Setup
  a. Place sterile conditioned dressing on agar plate
  b. Inoculate top of dressing with $1x10^6$ CFU test organism
  c. After specified time, remove dressing and incubate the plate to look for growth





Microbial Barrier Testing

- Test organisms
  - 2 Gram-positive and 2 Gram-negative bacteria including motile species
- Test article: Conditioned final dressing (or swatch)
- Period of Incubation: Use-life
- Controls: Positive control and material control
- Acceptance Criteria: No growth

Clinical Perspectives on Unclassified Wound Dressings

Laura Marquart

Medical Officer

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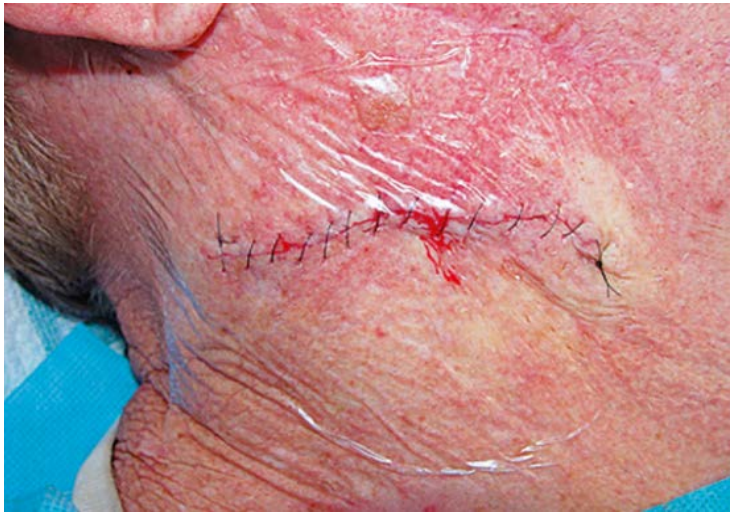
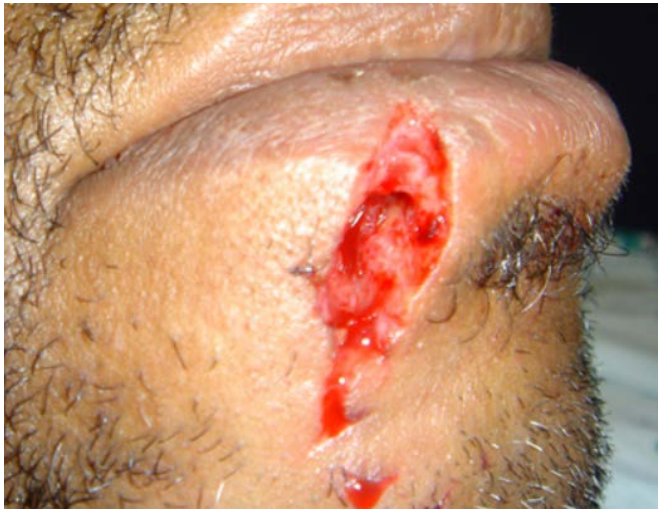
Overview

- Types of Wounds
- Guidelines and Clinical Studies
- Indications for Use

Acute Wounds



Surgery of the Skin: Procedural Dermatology 2nd Ed



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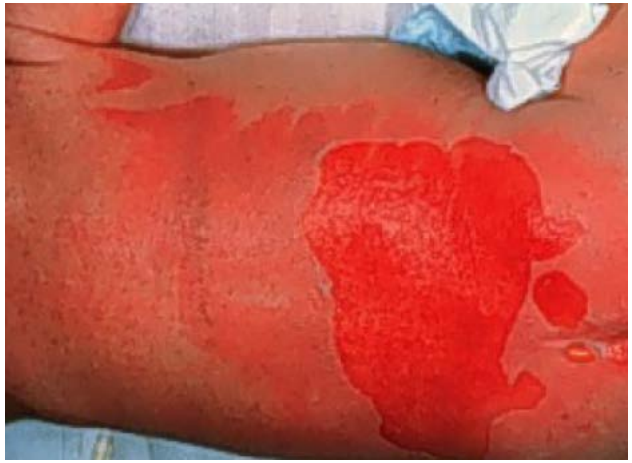

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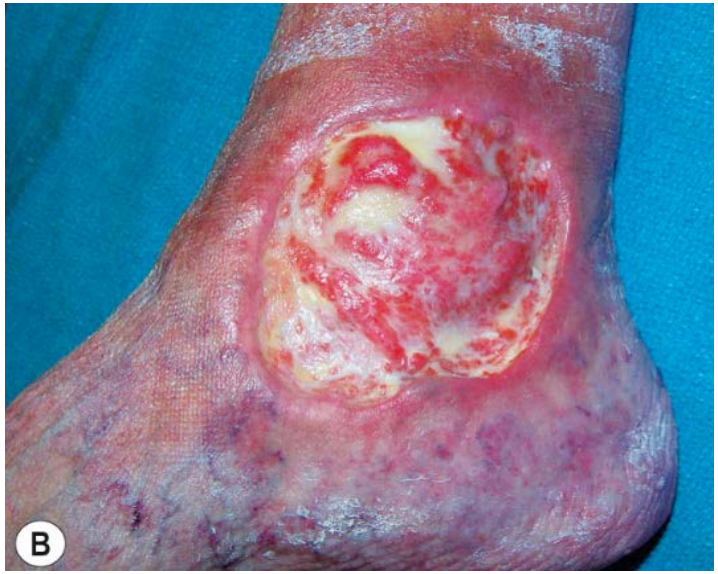
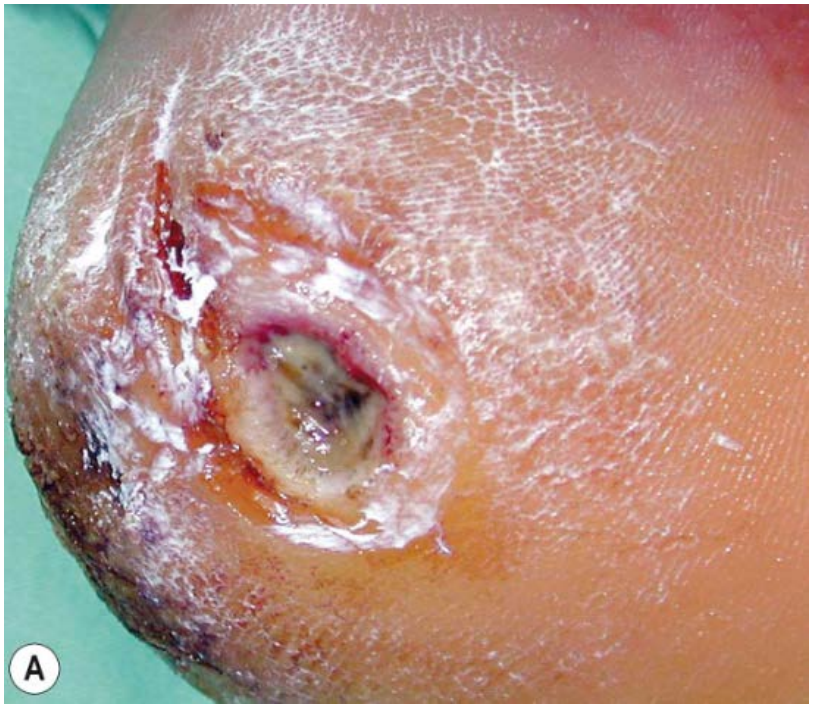
Chronic Wounds





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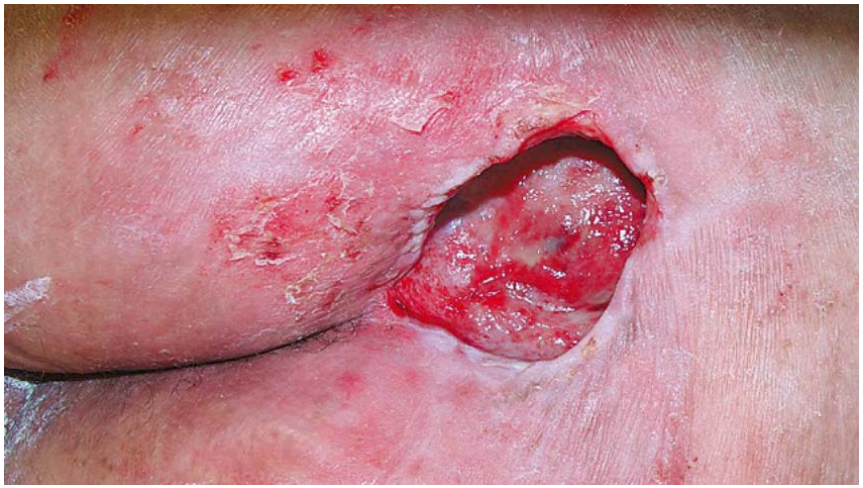

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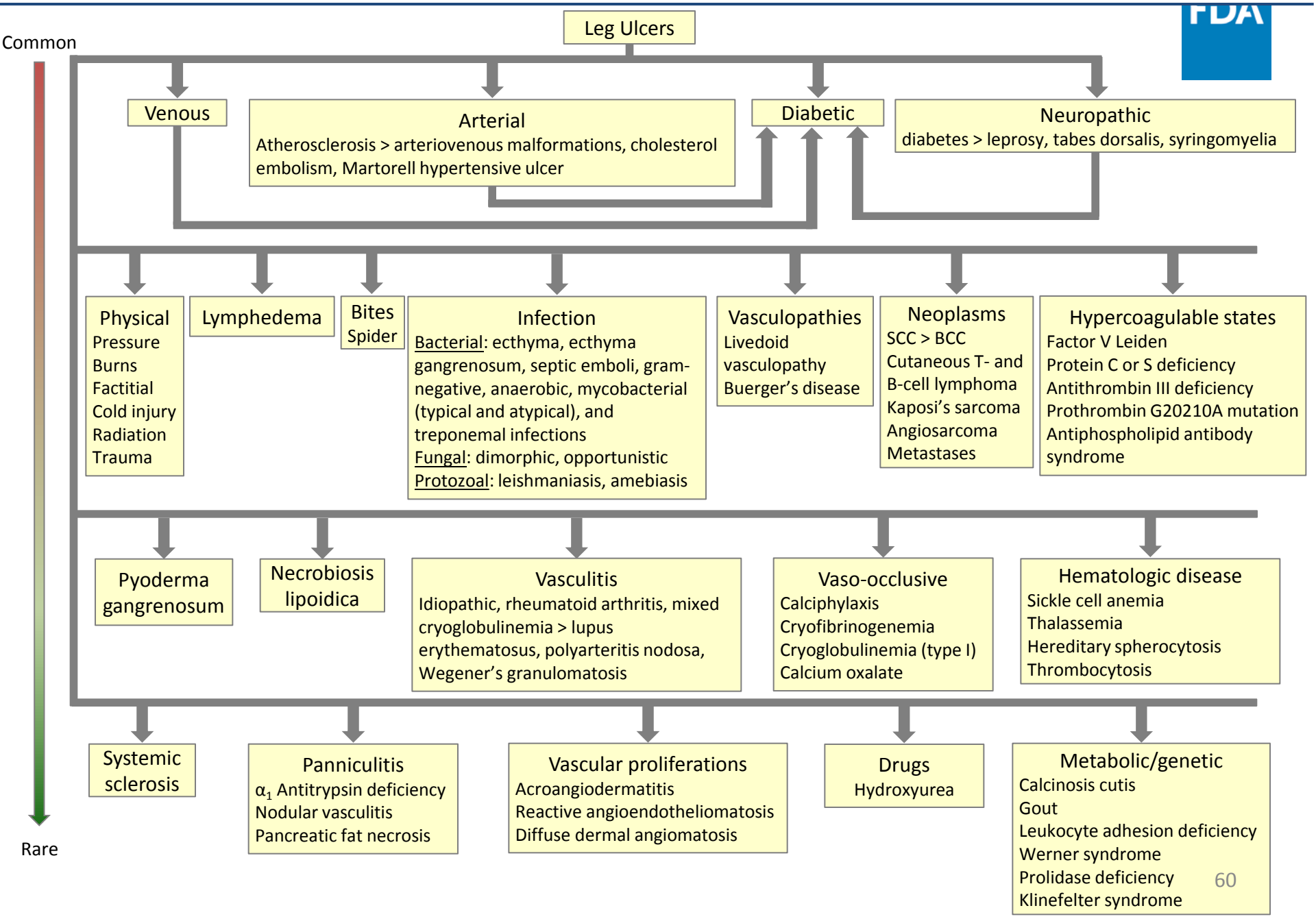
Causes of Leg Ulcers



Wound Management

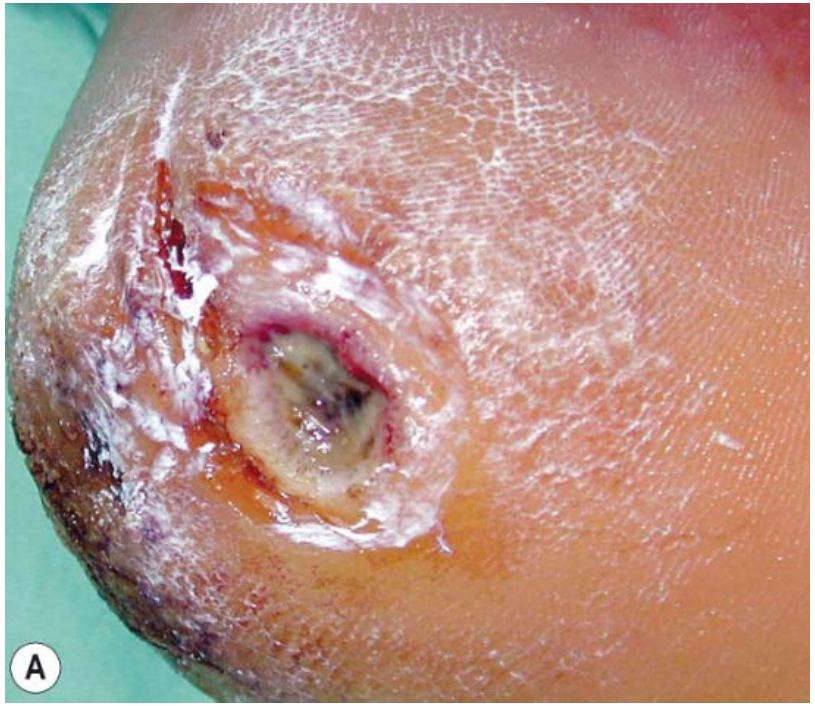
- Control bleeding
- A clean wound- Wound Wash
- Debridement
- Wound dressings- Dressings/Gel/Creams
- Off loading
- Antimicrobials (topical and systemic)- Gel/Creams

Clinical Practice Guidelines

Type of wound	Source of Recommendation	Antimicrobial Dressings Recommended
Diabetic foot ulcer	IDSA (2012)	No
	IWGDF (2015) and Lipsky et al., (2016)	No
	International Consensus on the Diabetic Foot (2007)	No
Venous leg ulcer	Society for Vascular Surgery and American Venous Forum (2014)	No
	Australian Wound Management Association and New Zealand Wound Care Society (2011)	No
	Scottish Intercollegiate Guidelines Network (2010)	No
	Expert Working Group, Harding et al., (2015)	Maybe
	Canadian Association of Wound Care (2006)	Maybe
Pressure ulcer	Canadian Association of Wound Care (2006)	Maybe
	National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance (2014)	Maybe
	UK's NICE (2014). Clinical Guideline – Pressure ulcers: prevention and management	Maybe
Wound (general)	UK's NICE Advice (2015)	No
	Canadian Association of Wound Care (2006)	Maybe
	American Society of Plastic Surgeons: Clinical Practice Guideline – Chronic Wounds of Lower Extremity (2007)	No
	The Wound Healing Society: Chronic Wound Care Guidelines (2006)	Maybe
Burn	American Burn Association: Practice Guidelines (2001)	No
Catheter Insertion Sites	CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections (2011)	Yes

Diabetic Foot Ulcer

- Insufficient evidence to recommend one specific dressing type
- Antimicrobial dressings are not recommended



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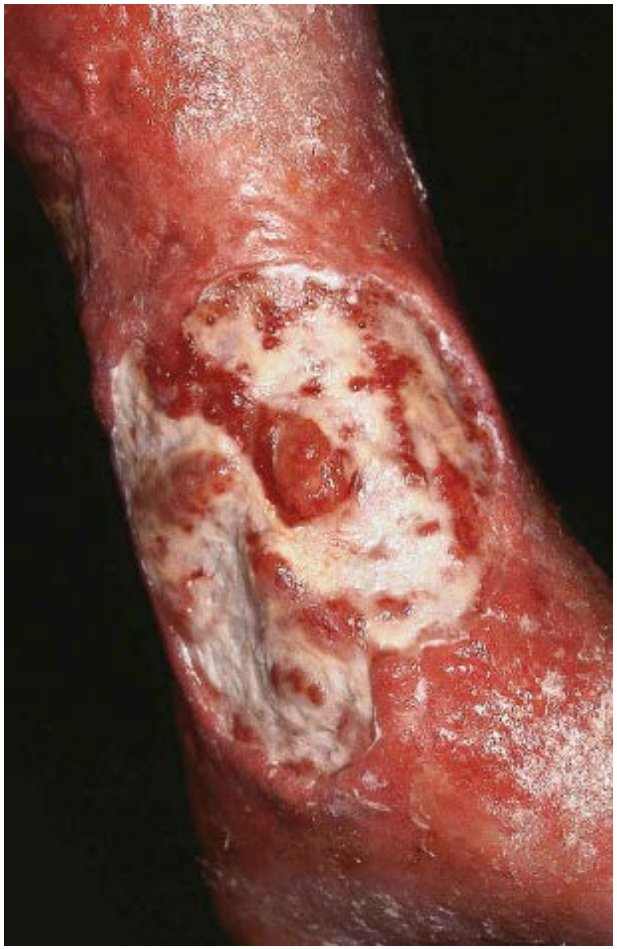
Venous Leg Ulcer

- 3 guidelines do not recommend the use of antimicrobial dressings
- 2 guidelines indicate there may be situations where antimicrobial dressings should be used



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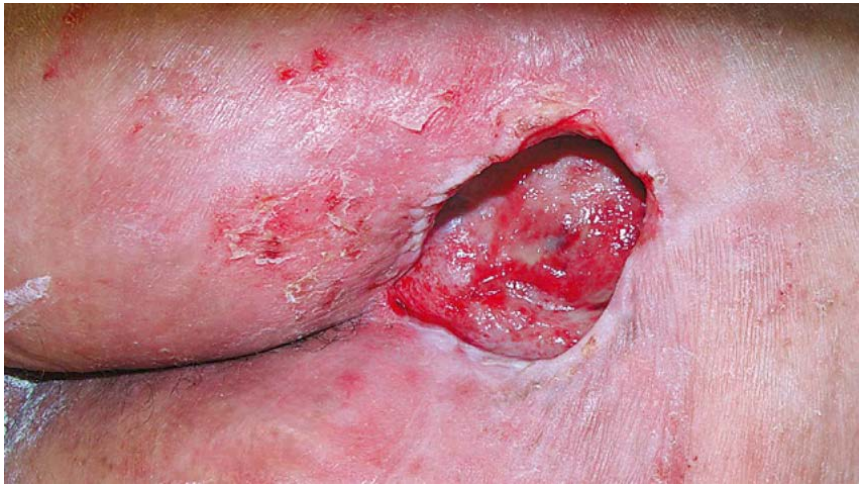
Pressure Ulcer

- There may be situations where antimicrobial dressings should be used



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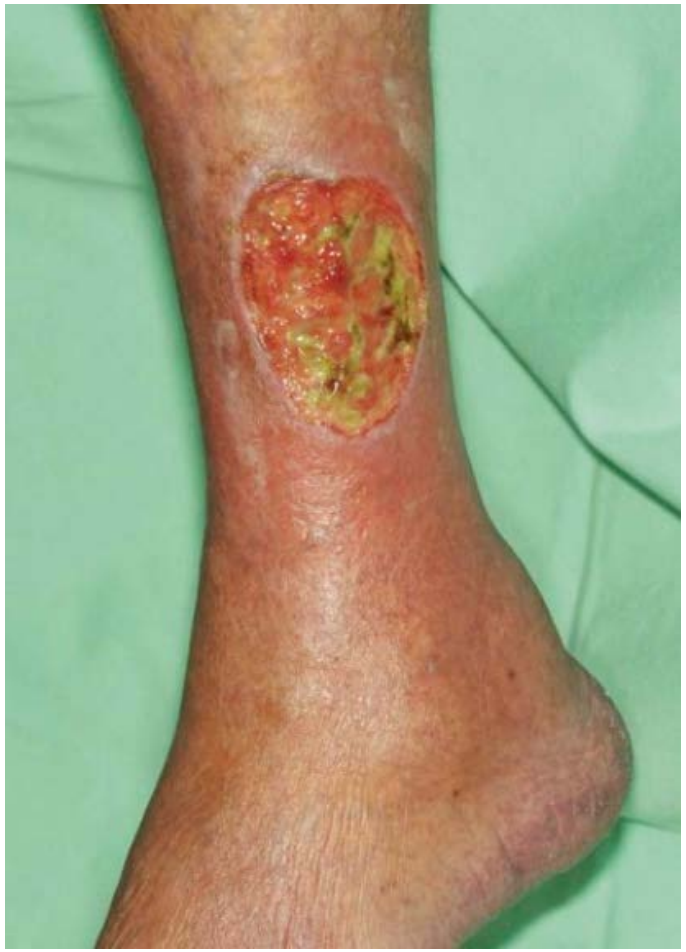
Wound (General)

- 2 guidelines do not recommend the routine use of antimicrobial dressings
- 2 guidelines indicate there may be situations where antimicrobial dressings should be used



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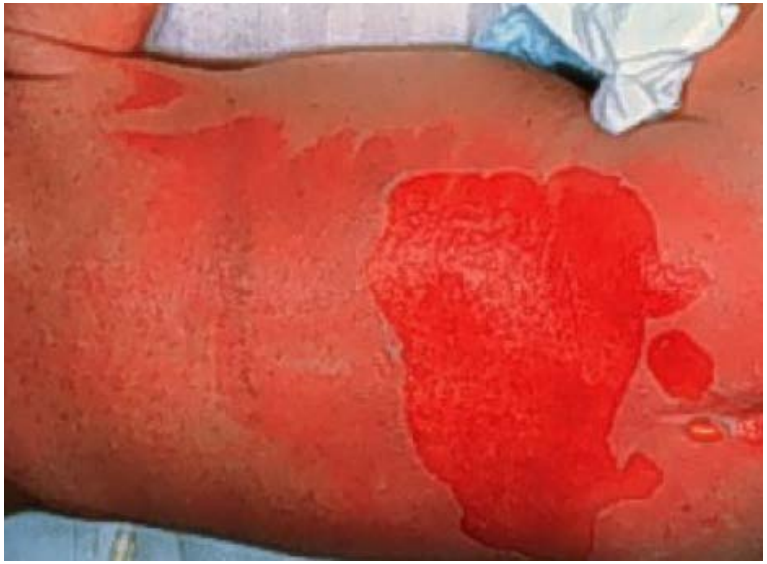
Burns

- Antimicrobial dressings are not recommended



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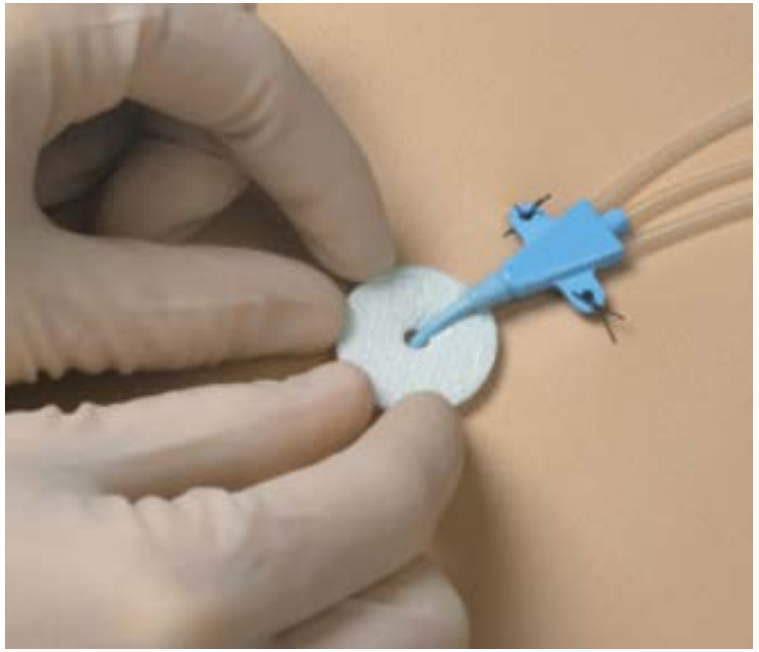
Catheter Insertion Sites

- Antimicrobial dressing recommended in specific situations



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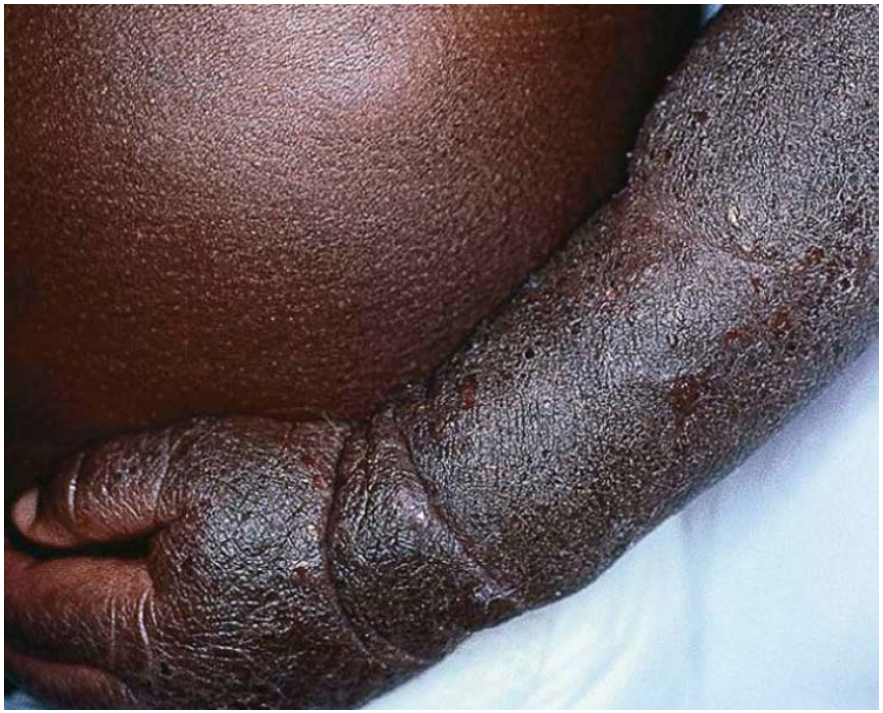
Atopic Dermatitis

- Topical moisturizers
- Prescription emollient devices (PEDs)



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Type of wound	Source of Recommendation	Antimicrobial Dressings Recommended
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Clinical Literature Review

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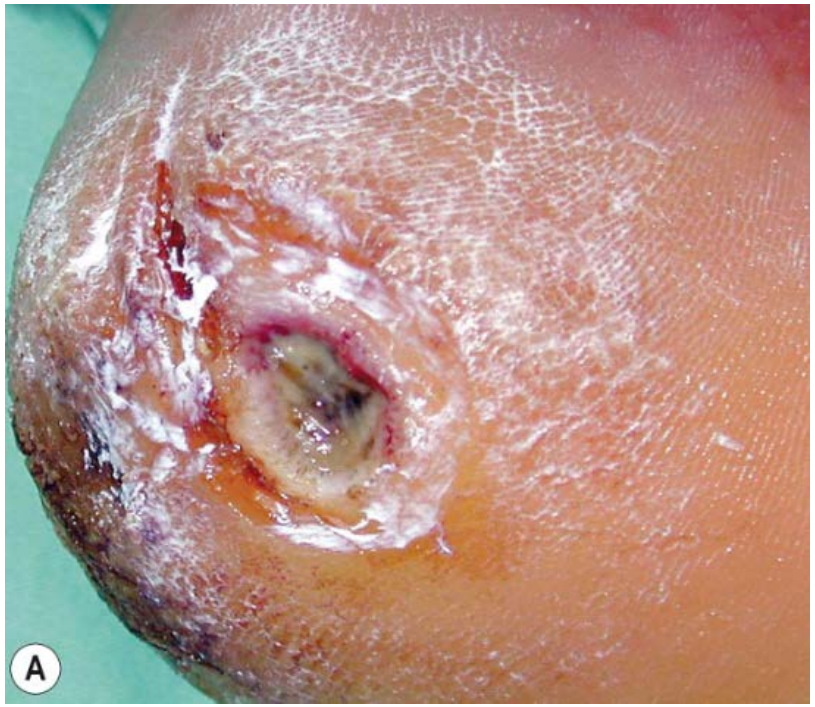
Venous leg ulcer	O'Meara et al, 2014	Maybe
Pressure ulcer	Norman et al, 2016	Maybe
Wound (general)	Lo et al, 2008	Maybe
Burn	Wasiak et al, 2013	No
Catheter Insertion Sites	Ullmann et al, 2016	Yes*

Diabetic Foot Ulcer

- No topical disinfectants or antiseptics demonstrated superior outcomes in ulcer healing or resolution or prevention of infection compared to non- antiseptic dressings.



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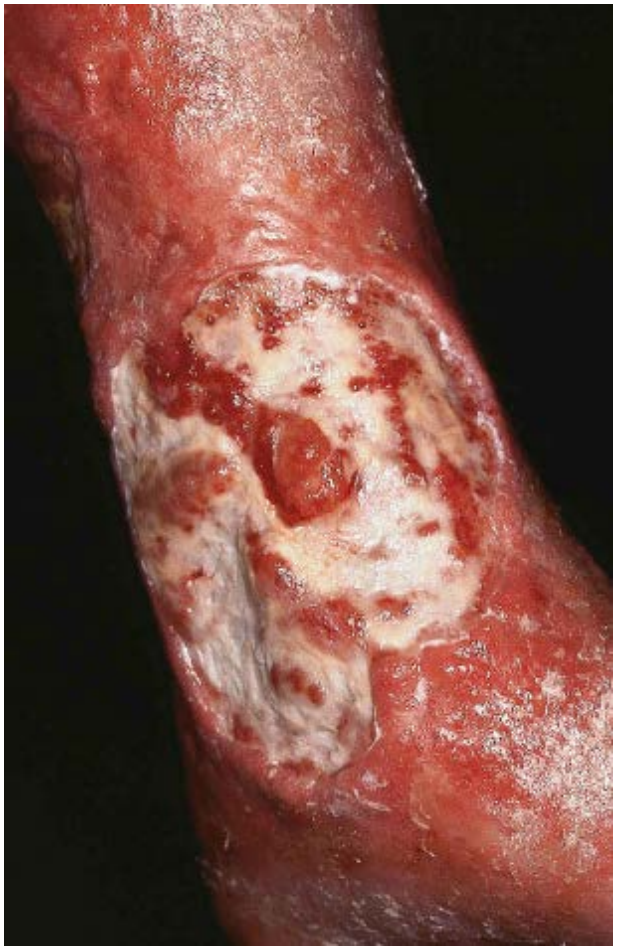
Venous Leg Ulcer

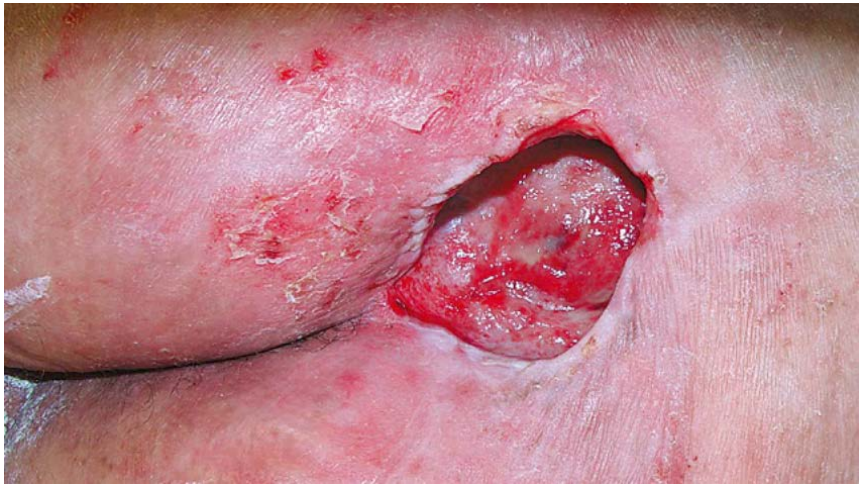
- Some evidence supports the use of cadexomer iodine but it is associated with more frequent adverse effects than standard of care.
- Current evidence does not support the routine use of honey- or silver-based preparations.



Dermatology 3rd Ed

Pressure Ulcer

- Limited data
- No conclusions could be drawn on the effects of antimicrobials on pressure ulcers



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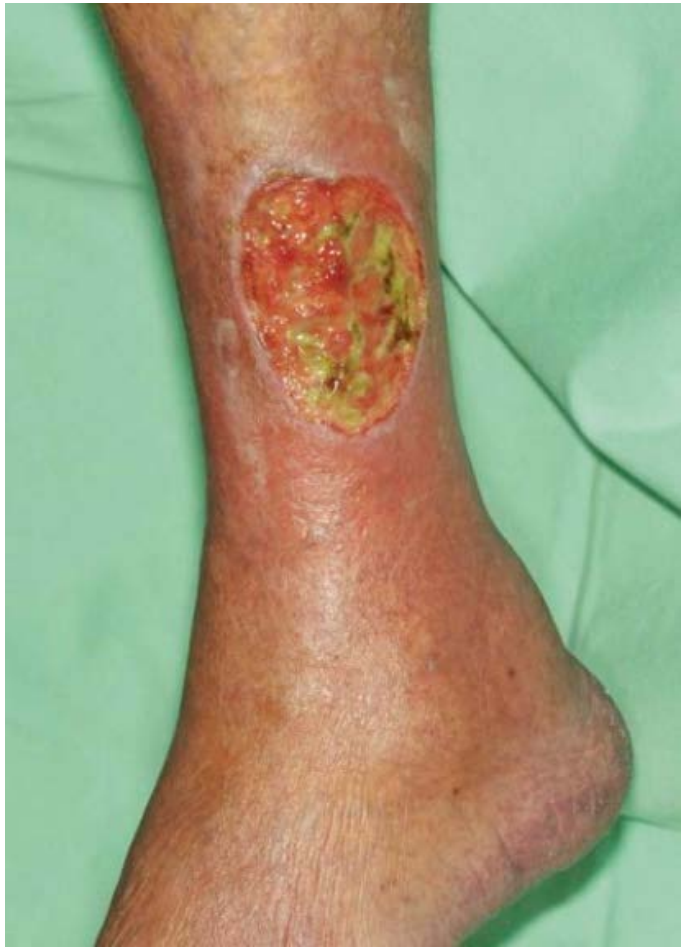
Wound (General)

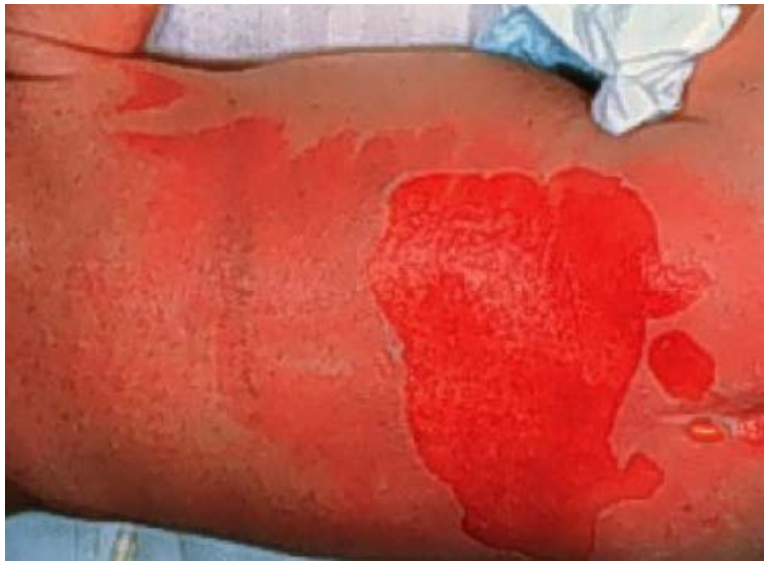
- Data on silver-releasing dressings suggested positive wound healing effects however confounding factors like antimicrobial use limits conclusions that can be drawn



Dermatology 3rd Ed

Burns

- The available evidence is limited and, in general, does not demonstrate that antimicrobials (including topical and systemic) prophylaxis reduces the risk of burn wound infection, invasive infections, or mortality associated with infection.



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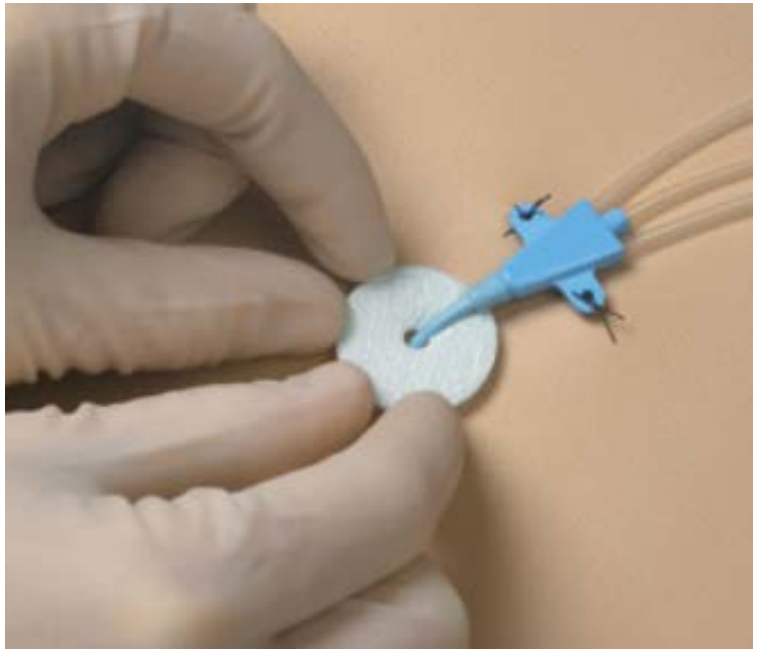
Catheter Insertion Sites

- Depends on the specific indication and population
- Risks of skin irritation and contact dermatitis



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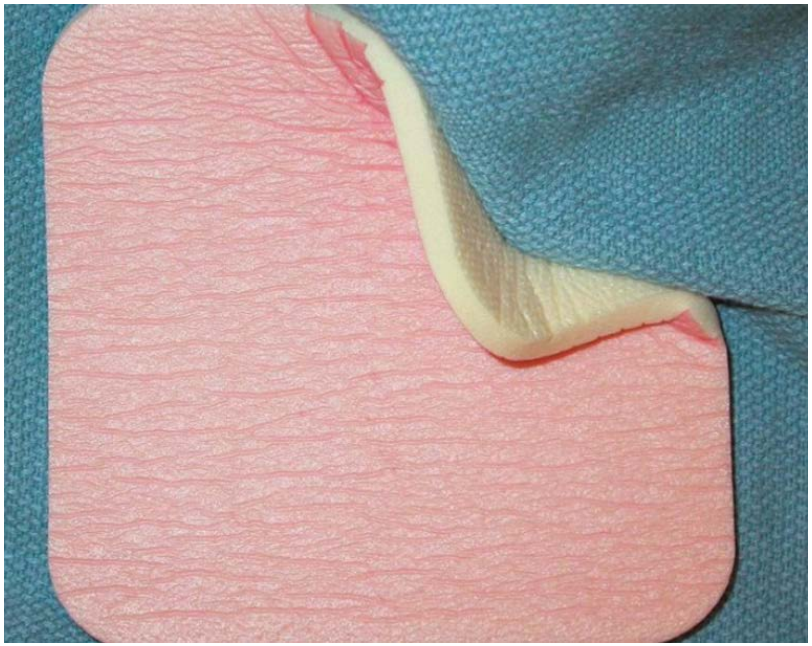
Catheter Insertion Sites	Ullmann et al, 2016	Yes*

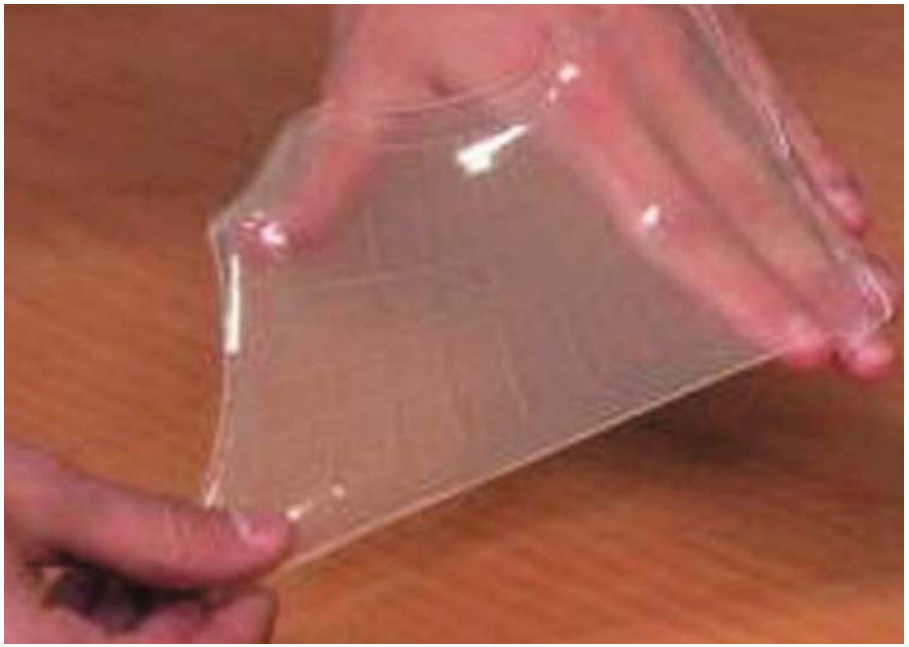
RCT Literature Review Conclusions

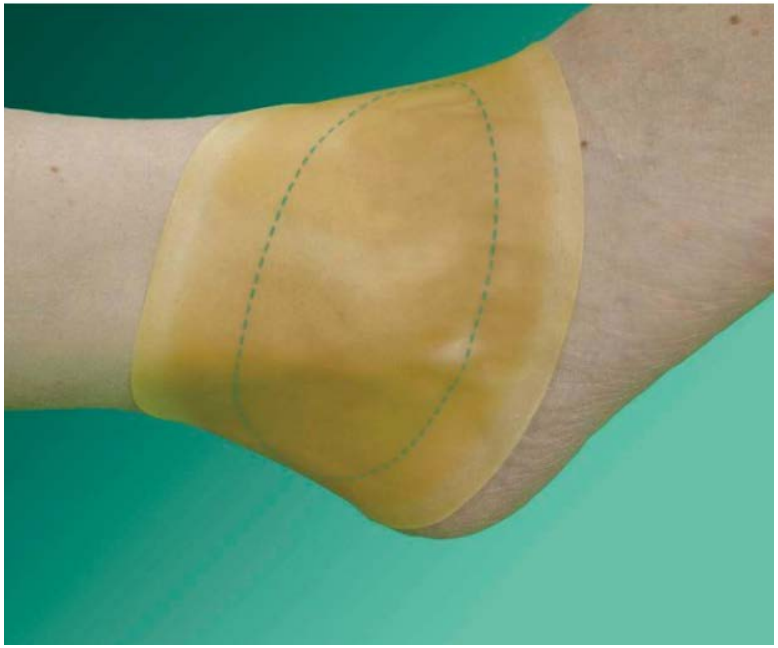
- There is a lack of appropriate trials supporting the use of antimicrobial dressings versus non-antimicrobial dressings
- For diabetic ulcers, venous ulcers, surgical wounds, and burns, there is not evidence to support that antimicrobial dressings versus non-antimicrobial dressings provide a meaningful difference in preventing wound infections.

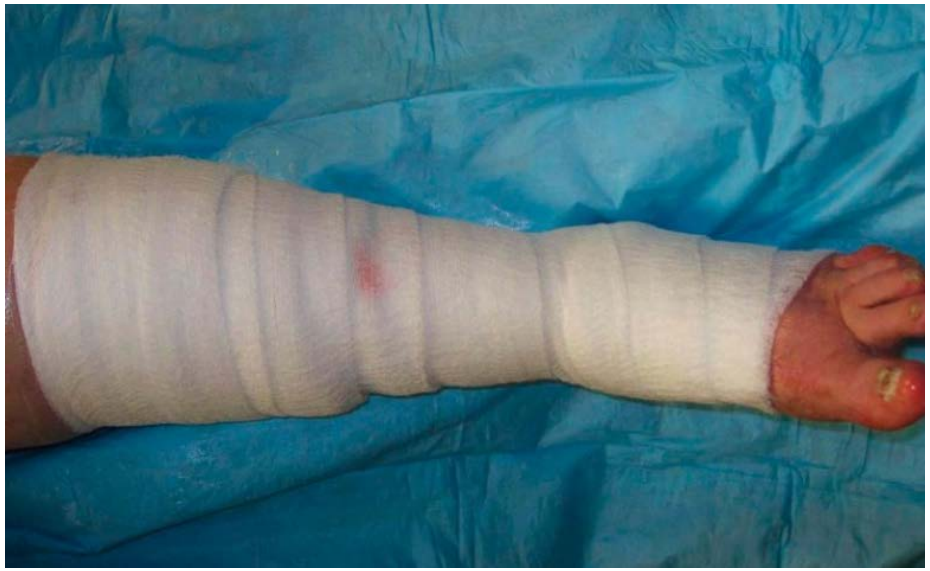
Antimicrobial Dressings Safety

- Delayed Wound Healing with Silver and Povidone-Iodine
- Toxic Reactions with Silver, CHG, PHMB, Povidone-Iodine
- Irritant and Allergic Reactions with CHG, Neomycin, Bacitracin, Hypochlorous Acid
- Antimicrobial Resistance









Dermatology 3rd Ed

Indications for Use Statement

- Identifies the condition and patient population
- Typically indicated for Prescription Use
  - Over-the-counter use limited to minor types of wounds
- Cleared for use on infected or colonized wound
  - To cover, absorb exudate, create a moist wound environment, rinse debris
  - Not cleared for use as a treatment for infection

Clinical Studies for Devices

- Clinical studies are typically requested by the FDA when:
  - Bench and animal testing are not sufficient to support the claims
  - New technology where the technology differs from the cleared product
  - New indications for use for a product of the same type

Representative Indication for Use for a Wound Wash

- Brand X Wound Wash is intended for professional use for **cleansing and removal of foreign material** including micro-organisms and debris from wounds such as **stage I-IV pressure ulcers, diabetic foot ulcers, post-surgical wounds, first and second degree burns, grafted and donor sites**

Representative Indication for Use for an Antimicrobial Dressing

- Brand X Dressing is indicated for use on partial and full thickness wounds **up to 7 days**.
- This includes: **first and second degree burns, as a protective covering for grafts, surgical sites, venous ulcers, pressure ulcers, diabetic ulcers**

Representative Indication for Use for an Antimicrobial Dressing

- Under the supervision of a healthcare professional Brand X Dressings are intended for up to **7 day use** for wounds such as **vascular access or peripheral IV sites, orthopedic external pin sites, wound drain sites, surgical wounds (donor and graft sites, incisions), and partial to full thickness dermal ulcers (stage I-IV pressure sores, venous stasis ulcers, arterial ulcers, diabetic ulcers).**

- Brand X Dressing is indicated for the management of infected wounds, as the silver in the dressing provides an **antimicrobial barrier** that may be helpful in managing these wounds. In addition, the **moist wound healing environment** and **control of wound bacteria** within the Brand X Dressing may help reduce the risk of wound infection and support the body's healing process.

- Brand X Dressing may be used for the **management of painful wounds**. Brand X Dressing's non-adherent wound contact layer reduces pain during dressing changes and evaporation of moisture in the dressing may soothe the wound

Representative Indication for Use for a Catheter/Port Site Dressing

- Brand X Dressing is intended for use as a hydrophilic wound dressing that is used to **absorb exudate** and to **cover a wound** caused by the use of vascular and non-vascular percutaneous medical devices such as **Vascular Devices, IV Catheters, Central Venous Lines, Arterial Catheters, Dialysis Catheters, Peripherally Inserted Coronary Catheters, Mid-Line Catheters, Non-vascular percutaneous devices, Drains, Chest Tubes, Externally Placed Orthopedic Pins, Epidural Catheters**.
- It is also intended to **reduce local infections, catheter related blood stream infections (CRBSI), and skin colonization** of microorganisms commonly related to CRBSI, in patients with central venous or arterial catheters.

Representative Indication for Use for a Cream Managing Symptoms of Skin Disease

- Under the supervision of a healthcare professional, Brand X Wound Dressing is indicated to **manage and relieve the burning, itching and pain e**xperienced with various types of dermatoses, including **radiation dermatitis, atopic dermatitis and allergic contact dermatitis.**
- Brand X Wound Dressing may be used to **relieve the pain of first and second degree burns**. Brand X Wound Dressing helps to relieve dry waxy skin by maintaining a **moist wound & skin environment**, which is beneficial to the healing process.

Medical Device Report Analysis

Karen Nast

Nurse Consultant/MDR Analyst

FDA Center for Devices and Radiological Health

Limitations of MDR Data

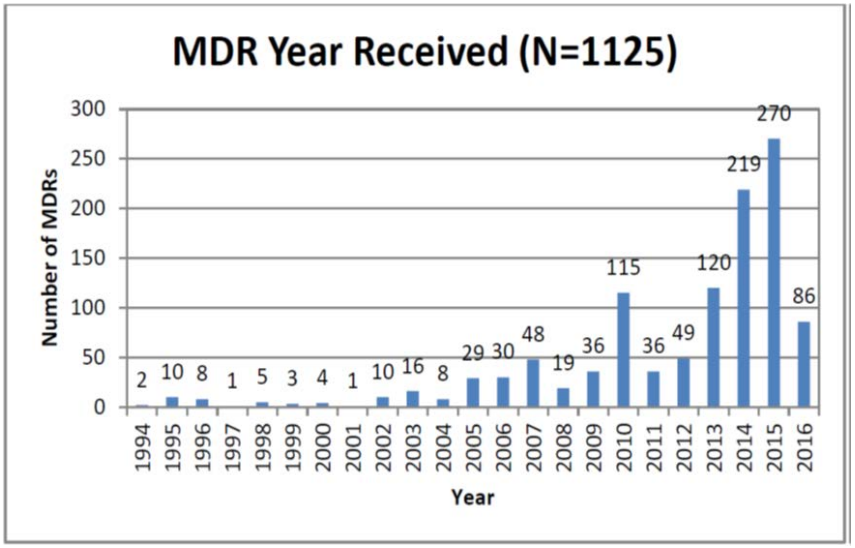
- Under-reporting
  - Users unfamiliar with reporting or fear of unintended consequences if they report
  - Confusion about HIPAA privacy and reporting
  - Malfunction or injury may not be clinically apparent
- Data Quality
- Limitations of MDR Regulation: Certain device malfunctions may not meet MDR reporting requirements
  - Therefore, lack of MDRs ≠ lack of problems
- Inability to Establish Causality
  - Cannot determine link/causality between the use/malfunction of the device and the negative clinical adverse event or outcome in that report

Methods

- FDA Medical Device Adverse Event Database
- MDR Search Inclusion Criterion
  - The search was conducted on July 28, 2016 using the parameter of device product code FRO- (Dressing, Wound, Drug), with no date restrictions.
- Search Results: 1,125 relevant MDRs

MDR Results

The figure below shows the number of reports received each year



- 1,010 reports submitted by the Manufacturer/Distributer
- 78 reports submitted by voluntary reporters
- 37 reports submitted by User Facilities
- 623 reports from the US
- 502 reports from Outside the US

MDR Event Types

- 17 Deaths, 725 Serious Injuries, 383 Malfunctions
- Seventeen death reports were received in the past 22 years
  - Five of the deaths, the manufacturer deemed as not likely related to the device.
  - Twelve of the deaths, the manufacturer could not determine if the death was related to the reported device.
  - When provided in the MDRs, the patients' cause of death was reported as: Septic shock (n=3), Sepsis (n=2), Infection (n=1), Fentanyl intoxication (n=1), Severe pulmonary arterial hypertension (n=1), and Cardiac decompensation (n=1)

Patient Problems

- Each report was individually reviewed for patient problems. The table below shows the top 10 patient problems.

Patient Problem	Count
Erythema	159
Infection	100
Blister(s)	86
Allergic Reaction (including anaphylaxis)	82
Skin tear/Skin Breakdown/Tissue Damage	76
Discharge/Drainage	71
Rash	50
Skin Irritation	47
Burn/Chemical Burn/Burning sensation	50
Dermatitis/Cellulitis	37

Note: It is not always clear if the reported patient problem is a result of the device or was already present. Also, one report may contain multiple patient problems.

Device Problems

- Each report was individually reviewed for device problems. The table below shows the top 5 device problems.

Device Problem	Count
Packaging Issue	114
Foreign Material Present	104
Difficult to Remove Dressing	84
Improper Use	35
Poor Adhesion	22

Note: One report may contain multiple device problems.

Conclusions

- In the past 22 years, 1,125 MDRs have been received for product code FRO
- The most commonly reported patient problems are erythema, infection, and blisters.
- The most commonly reported device problems are packaging issues, foreign materials, and difficulty removing the product.
- The 17 reported deaths could not be conclusively linked to the use of the device.

Clarifying Questions from Panel

Benefit/Risk Considerations for Antimicrobial Agents in Wound Dressings

Brandon Kitchel

Microbiologist

FDA Center for Devices and Radiological Health

Overview

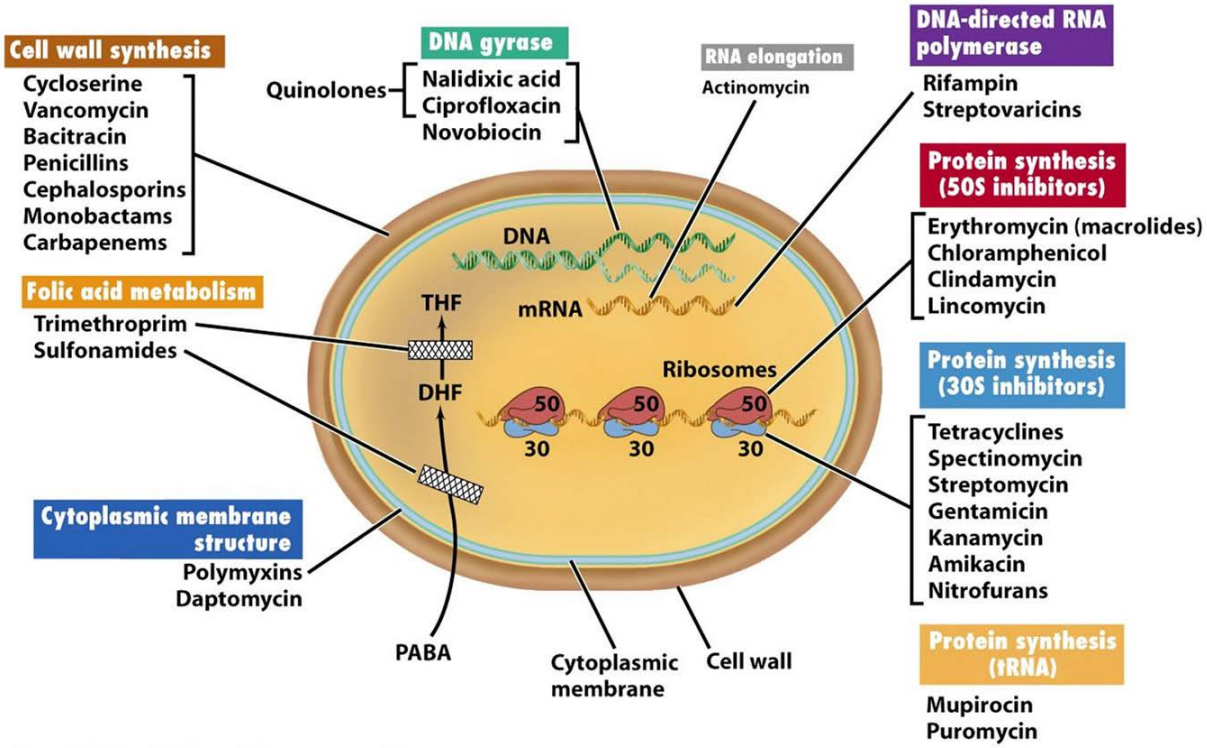
1. Background on antimicrobial usage and resistance
2. Antimicrobials utilized in wound dressings
    a. Historical usage
    b. Mechanism of activity
    c. Resistance
3. Benefit/Risk Considerations
    a. Individual Patient
    b. Societal

Background – Antimicrobials

- Implemented on multiple levels to curb clinical infections and transmission of pathogens
  - **Antibiotics (**and their synthetic counterparts**)**
  - **Antiseptics**
  - **Disinfectants**

Background – Antimicrobials

- **Systemic antibacterial drugs**: natural or synthetic substances which inhibit or destroy selective bacteria
  - Numerous classes developed to attack specific bacterial targets



Background – Antimicrobials

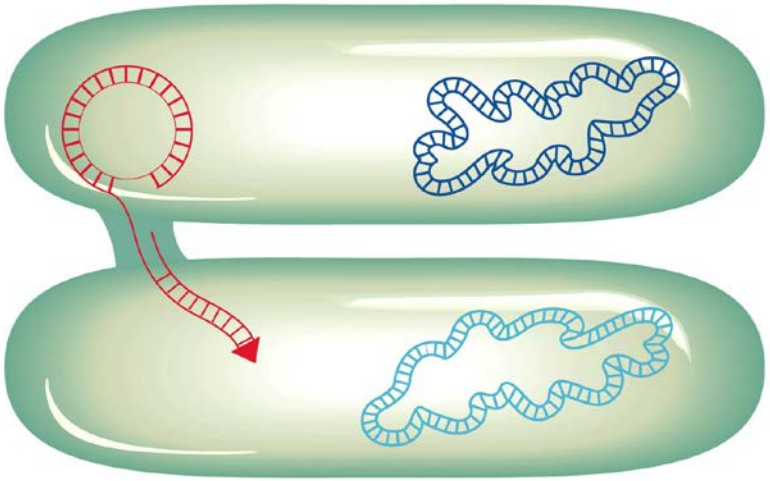
- **Antiseptics:** applied on living tissue
- **Disinfectants**: used on inanimate objects or surfaces
  - Broad spectrum
  - Examples: Benzalkonium chloride, chlorhexidine, alcohol, hydrogen peroxide
  - Proper usage considered most appropriate first line of defense and can minimize reliance on antibiotics

Background – Antimicrobial Resistance

- Effective for a limited segment of the microbial world
  - Naturally resistant
  - Acquired resistance

a) Random genetic mutation

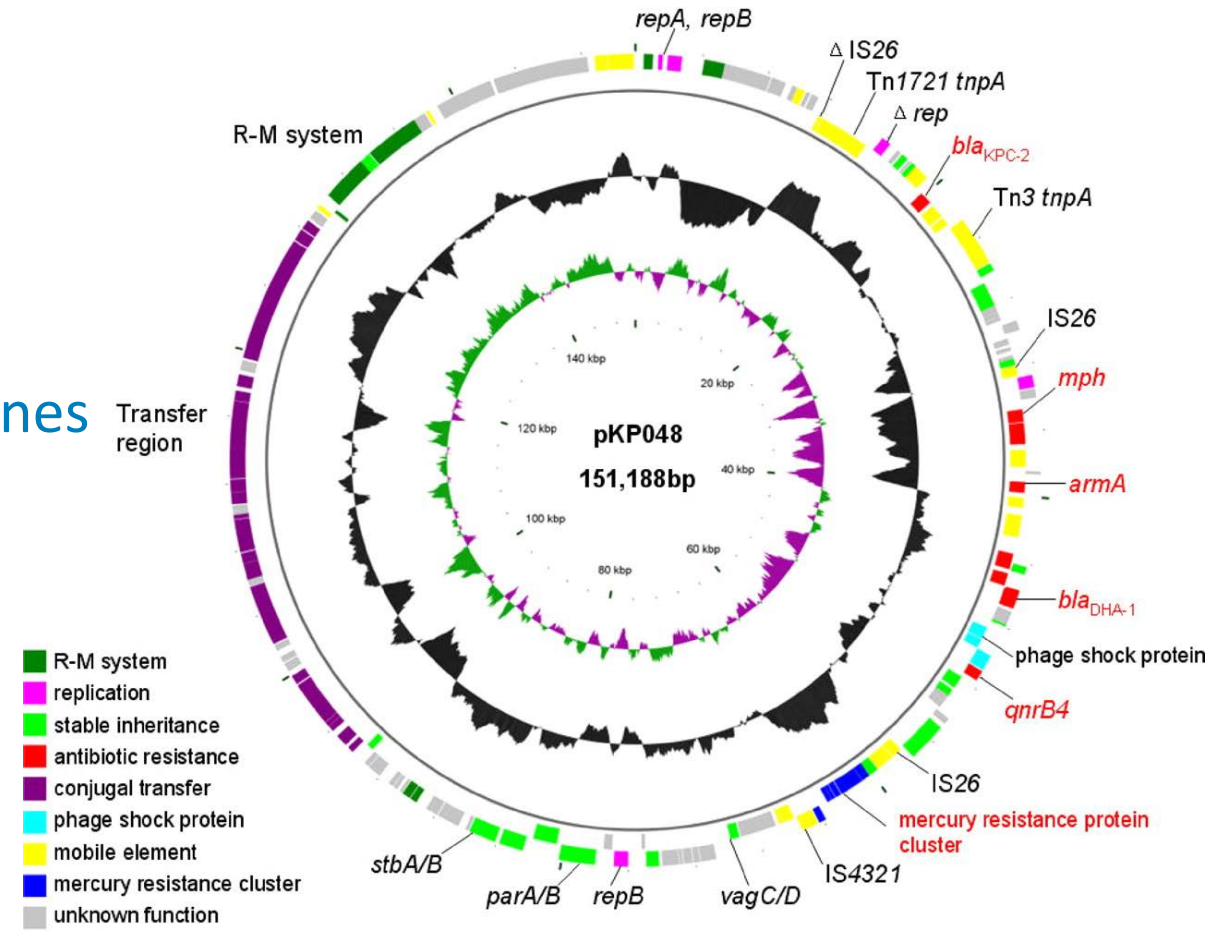
b) Acquisition of a resistance gene



Background – Antimicrobial Resistance

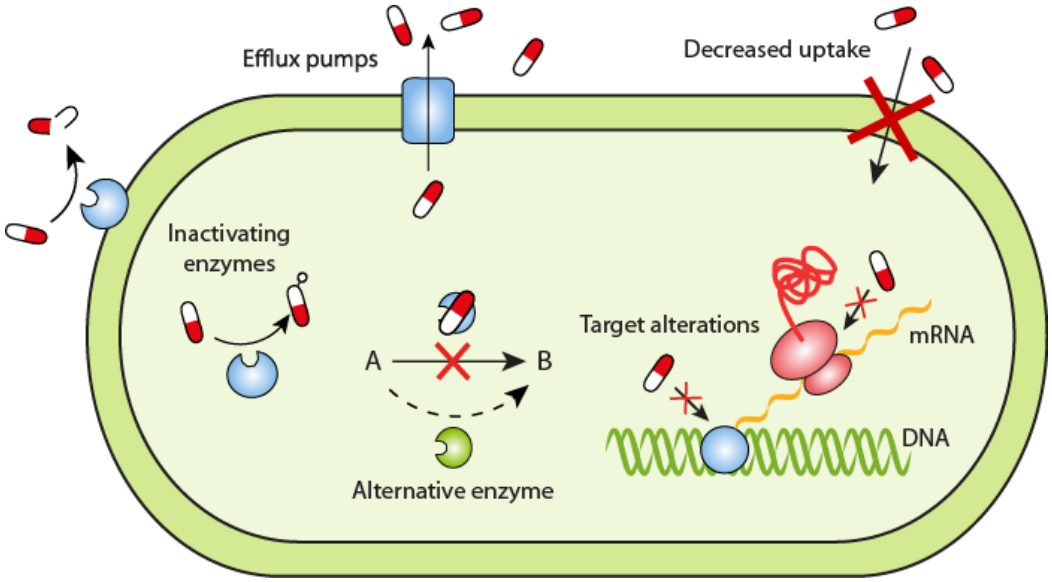
Plasmids

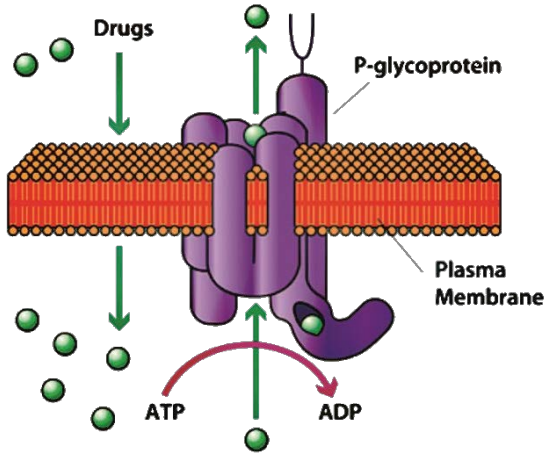
- Horizontal transfer of resistance
- Multiple resistance genes



Background – Antimicrobial Resistance

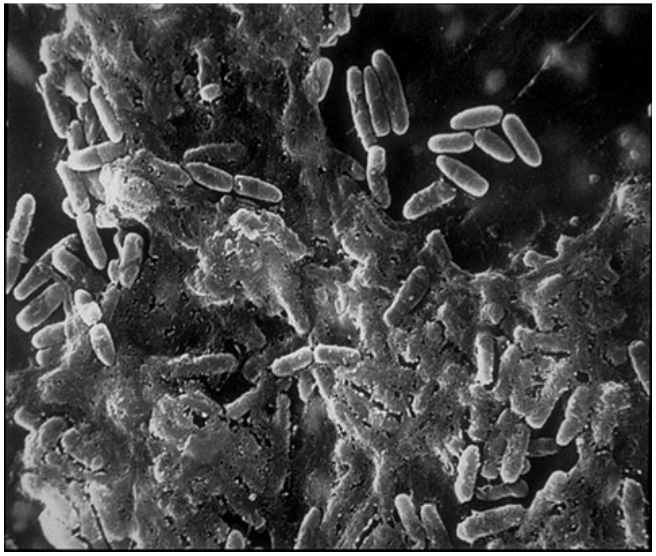
- Selection of bacteria with a vast array of resistance mechanisms
  - Hydrolytic enzymes, Efflux pumps, Decreased cell permeability…

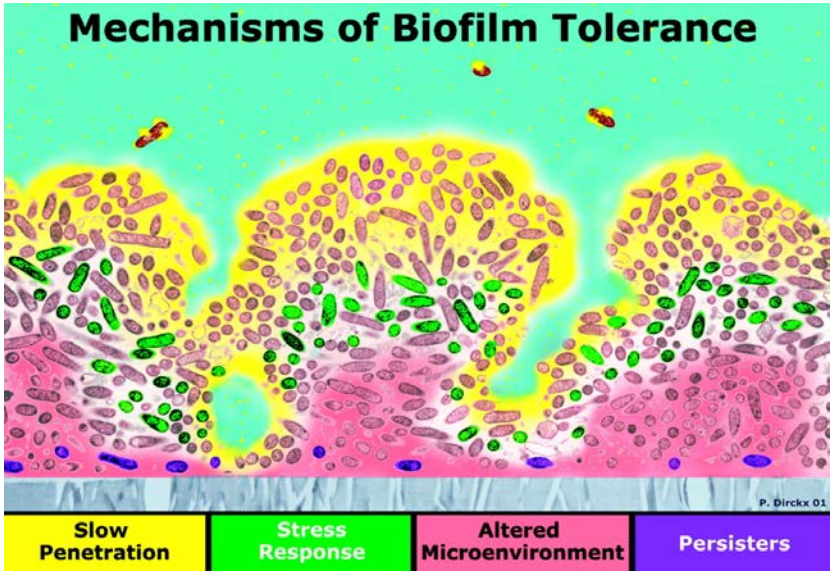




Background – Antimicrobial Resistance

- Biofilms
  - Provides added level of resistance
    - Reduced penetration of antimicrobial
    - Shared resistance mechanisms





Background - Antimicrobial Resistance

Impact

- Abundance of drug-resistant organisms
- >2 million people infected with drug-resistant bacteria, and ≥23,000 die as a direct result each year in U.S.
- Serious public health concern
- Need for improved antimicrobial stewardship

Antimicrobials in Wound Dressings

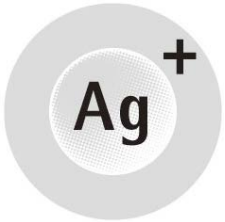
- Types of antimicrobials
- Historical usage
- Mechanism of activity
- Observed resistance

Types of Antimicrobials in Wound Dressings

1. Metal based antimicrobials (e.g., silver, bismuth)
2. Quaternary ammonium compounds (e.g., benzalkonium chloride)
3. Oxidizing agents (e.g., hydrogen peroxide, hypochlorous acid/sodium hypochlorite)
4. Biguanides (e.g., Chlorhexidine, PHMB)

1. Metal Based Antimicrobials

- Examples
  - Silver
  - Bismuth



- Historical Usage
  - One of the oldest antimicrobials
  - Silver coated devices (e.g., endotracheal tubes)
  - Silver embedded PPE (e.g., surgical masks)
  - Water disinfectant on NASA space shuttles

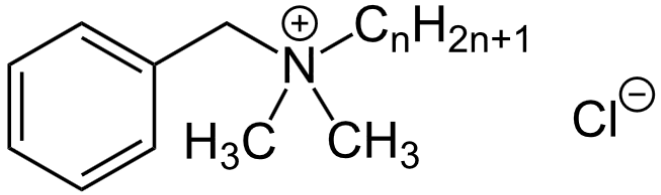
1. Metal Based Antimicrobials

- Mechanisms
  - Silver cations (Ag+) cause damage by binding to thiol groups in cell membrane and deactivating enzymes
  - Ag+ ions interact with nucleic acids

- Known Resistance
  - Retention of Ag+ in negatively charged cell wall
  - Plasmid-mediated efflux pumps

2. Quaternary ammonium compounds (QACs)

- Example
  - Benzalkonium chloride



n = 8, 10, 12, 14, 16, 18

- Historical Usage
  - Widely used as antiseptics and disinfectants
  - Hospitals - Sanitation of noncritical surfaces
  - Appropriate for disinfecting patient contacting medical equipment such as blood pressure cuffs

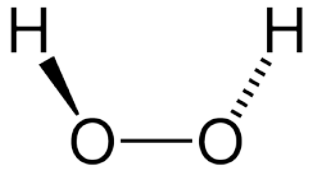
2. Quaternary ammonium compounds (QACs)

- Mechanism
  - Cationic surfactant binds to cell membrane, causing loss of membrane integrity and cellular disruption

- Known Resistance
  - QAC uptake prevention
  - Plasmid-mediated efflux pumps

3. Oxidizing agents

- Examples
  - Hydrogen peroxide (H_20_2),
  - Hypochlorous acid/sodium hypochlorite



- Historical Usage
  - 3% H_20_2 commonly used as wound antiseptic
  - Teeth whitening and hair bleaching
  - Chlorine-releasing agents are widely used for hard-surface disinfection (i.e. household bleach)

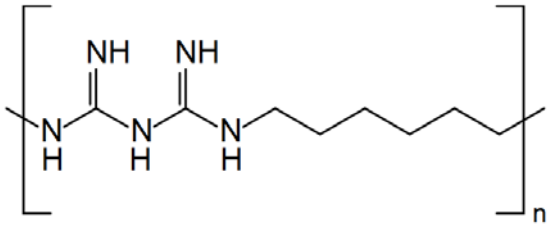
3. Oxidizing agents

- Mechanisms
  - Production of free radicals (•OH) attack essential cell components
  - Chlorine reacts with amino groups (NH_2^-) and sulphydryl groups (SH), inactivating essential bacterial enzymes, crosslinking proteins, disrupts lipid bi-layers, and interferes with DNA base pairing

- Known Resistance
  - Catalase or other peroxidases can increase tolerance

4. Biguanides

- Examples
  - Chlorhexidine (CHX),
  - Polyhexamethylene biguanide (PHMB)



- Historical Usage
  - 1970, CHX first introduced in the U.S.
  - CHX used as coating for various medical devices
  - CHX baths are common infection control practice
  - PHMB used as a disinfectant and antiseptic (contact lens cleaning)

4. Biguanides

- Mechanisms
  - Cationic interaction with membrane phospholipids, affects membrane fluidity and conformation
  - Polymer strands able to disrupt bacterial cell membrane
  - Lethal DNA damage

- Known Resistance (select species)
  - Mucoidal strains – mucoexopolysaccaride “slime” plays protective role (reduced diffusion)
  - Plasmid-mediated efflux pumps

Antimicrobials in Wound Dressings

- Conclusions
  - Antimicrobial agents cleared in wound dressings have historically been used as both disinfectants and antiseptics
    - Attack multiple bacterial targets
    - Broad spectrum
  - Known resistance mechanisms exist in select organisms
  - Prevalence of resistance is unknown without surveillance studies

Benefit / Risk Considerations

Benefit / Risk Considerations

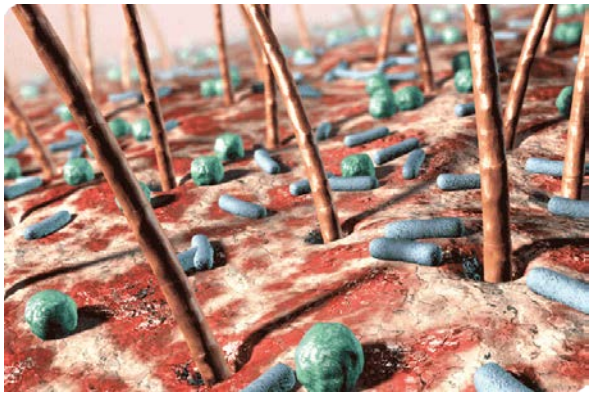
- Potential Benefit - Individual Patient
  - Preservatives in gels, creams, ointments, and washes may ensure the safety of these products by hindering growth of potential contaminating organisms
  - Barrier properties of dressings may help protect wounds from introduction of opportunistic microbial pathogens
  - Antimicrobials in wound dressings may help to reduce bacterial growth within the dressing, which may become a nidus for infection if the dressing is infrequently changed or has prolonged use

Benefit / Risk Considerations

- Potential Risk - Individual Patient
  - Biocompatibility issues (e.g., sensitization, irritation, cytotoxicity), allergic reactions, or delayed wound healing
    - Observed toxic reactions (Silver, CHX, PHMB), irritation and allergic reactions (CHX, Hypochlorous acid)
    - Noted that silver-based dressings may delay re-epithelialization, leading to longer healing time
    - FDA issued a public health notice about the potential hypersensitivity reactions to CHX-impregnated devices (1998)

Benefit / Risk Considerations

- Potential Risk - Individual Patient
  - Conditioning of the host flora
    - Killing off commensal organisms and
    - Increasing susceptibility to opportunistic species
  - Selection for co-resistance to systemic antimicrobials

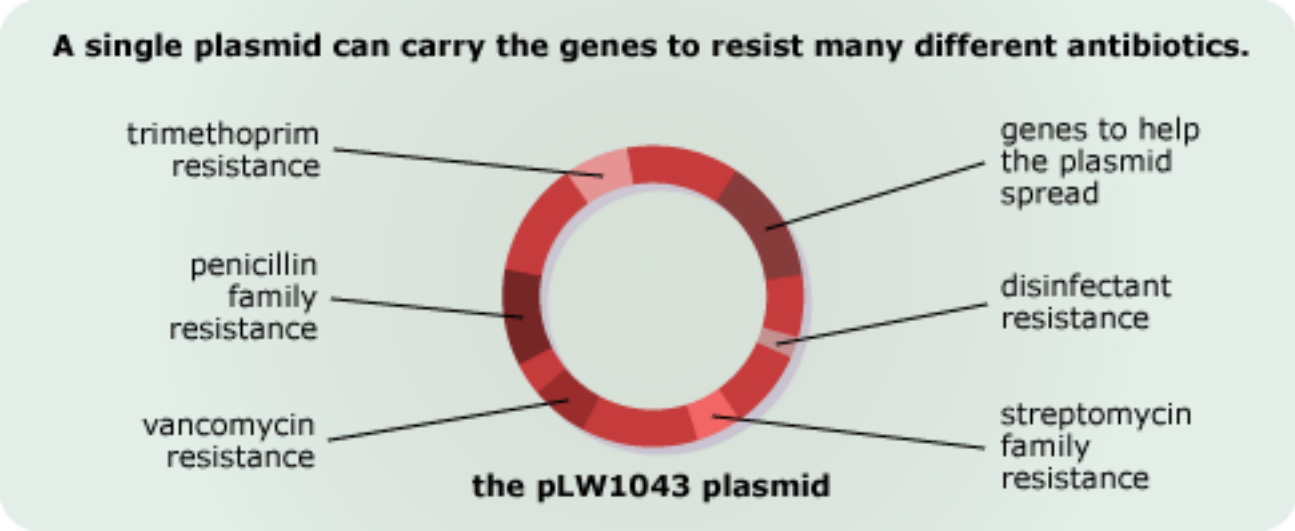


Benefit / Risk Considerations

- Potential Benefit – Society
  - Antimicrobials used in wound dressings overlap with currently utilized hospital antiseptics and disinfectants, and may be considered part of the “first line of defense” that can help minimize reliance on systemic antimicrobials (e.g., antibiotics)

Benefit / Risk Considerations

- Potential Risk – Society
  - Antimicrobial resistance
  - Selection for resistant strains of microbes that contain co-resistance to classes of antibiotics.



Antimicrobial Stewardship

- September 18, 2014 - White House issued an executive order recommending antimicrobial stewardship measures to reduce the emergence and spread of antimicrobial-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections
  - 20-50% of prescribed antibiotics may be unnecessary or inappropriate

- HHS has been engaged in efforts to promote antimicrobial stewardship practices and curb the spread of antimicrobial resistance

U.S. FOOD & DRUG ADMINISTRATION

PANEL QUESTIONS - DAY 1

Scope of the Panel Questions

These questions pertain to wound dressings combined with drugs, which FDA has grouped under product code "FRO." These products include solid wound dressings, gels, creams, ointments, and liquid wound washes. Excluded from this discussion are Class III dressings intended to improve the time or ability for wound healing compared to the normal physiologic response, where human clinical data have been provided to show superiority in wound healing response.

Question 1

Level of Evidence

Products under product code FRO that are the subject of this panel meeting include: 1) solid wound dressings combined with drugs which are intended to provide or support a moist wound environment, absorb wound exudate, and protect against external contamination, 2) wound gels, creams or ointments combined with a drug which are intended to provide or support a moist wound environment, and 3) wound wash solutions combined with a drug which are intended to rinse or irrigate a wound to remove foreign material, such as debris and wound exudate. Clinical data have not generally been required to support clearance of the wound dressings in product code FRO.

These dressings may be combined with different categories of antimicrobials, e.g., 1) metals such as silver and bismuth, 2) biguanides such as polyhexamethylene biguanide (PHMB) and chlorhexidine, 3) quaternary ammonium compounds such as benzalkonium chloride, or 4) oxidizing agents such as hydrogen peroxide and hypochlorous acid/sodium hypochlorite, that are claimed to:

- improve the shelf life of non-sterile products;
- permit the repeated opening of a container after the sterile seal is broken;
- prevent bacterial colonization of a dressing; and
- provide a barrier against microbial entry into a wound.

Question 1a

Level of Evidence

Is there adequate scientific evidence to demonstrate safety and effectiveness of FRO products for these different uses?

i. Are there data from adequate well-controlled trials?
ii. If not, what type of scientific evidence exists?

Question 1b

Level of Evidence

If there is adequate scientific evidence to support the use of FRO products for these different uses, on what endpoints are they based?

Question 1c

Level of Evidence

If not, on what endpoints should they be based? For example, for clinical studies, what endpoints are appropriate (e.g., partial or complete wound healing; amputation rate; patient-reported outcome measures; local or systemic toxicity)?

Question 1d

Level of Evidence

What are the associated risks (such as resistance, systemic absorption and local toxicity) in some or all of these scenarios?

Question 1e

Level of Evidence

Please advise FDA on the additional factors to consider when products contain more than one antimicrobial.

Question 1f

Level of Evidence

In what situations might pre-clinical *in vitro* or *in vivo* (animal) studies be sufficient to predict the clinical safety and/or effectiveness of a product?

Question 2

Wound Management

Please comment on how your selection of a wound dressing would differ for the following clinical settings :

a. Healing vs. non healing wounds
b. Infected vs. non infected wounds
c. Acute vs. chronic wounds
d. Burn wounds (excluding injuries that require a skin graft)
e. Other clinically relevant distinctions?

Question 3

The Benefit/Risk (Individual and Societal)

Please comment on the following questions in the context of infected and non-infected acute, chronic, and burn wounds (excluding burns requiring skin grafts):

Is reduction of the colony count on the dressing predictive of clinical benefit to the patient? If yes:

a. What is this clinical benefit?
b. What is the evidentiary basis?
c. How does one balance this with the risks to the patient and society?

Question 4

The Benefit/Risk (Individual and Societal)

Dressings with lidocaine and corticosteroids are examples used to highlight the risks of systemic absorption, local toxicity, and the potential for impaired wound healing. Please discuss what clinical evidence should be available to assess patient benefit and the associated risks. These dressings are used on partial and full-thickness wounds, including diabetic ulcers, venous stasis, pressure, and ischemic ulcers, surgical and traumatic wounds, superficial burns, donor sites, abrasions and lacerations.

Question 5

Claims and Level of Evidence

For each of the claims cited below, please discuss:

a. Does it represent a clinically meaningful benefit to the patient?
b. If so, what type of data should be provided to support the claim?
c. Does it matter which types of wound dressing (e.g., solid versus gel/cream/ointment versus wound wash/irrigation solution)?

Claims
Maintains a moist wound environment
Covers and protects the wound
Provides a barrier to penetration of microbes to the wound, which may reduce the risk of infection
To enhance the microbial barrier function and minimize growth of microbes in the wound dressing
An antimicrobial effect to minimize microbial contamination/colonization of the dressing
Intended for use up to “x” number of days
A non-adherent layer reduces pain during dressing changes
Maintains low bioburden during shelf storage and after repeated openings of the package
Relieves the symptoms of skin irritations, such as itching and burning
Irrigation loosens and removes debris, exudate, and infectious materials from wound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