Global
Antibiotic
Resistance
Partnership

CDDEP
THE CENTER FOR
Disease Dynamics,
Economics & Policy
WASHINGTON DC • NEW DELHI

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Antibiotics – Where have they gone

Micro-organisms win the battle

Microorganisms 5, Healthcare 0

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GARP – February 2010
Pharmaceutical Industry Perspectives
Device Industry Perspectives

Andy Zoepke

Why am I here

Topical antimicrobials

Is there a place for topical antimicrobial agents to help fight infections?

Can topicals assist in helping prevent the spread of antibiotic resistant micro-organisms?

Types of Chronic Wounds

Addressing bacteria can lead to an improvement in as little as 2 weeks

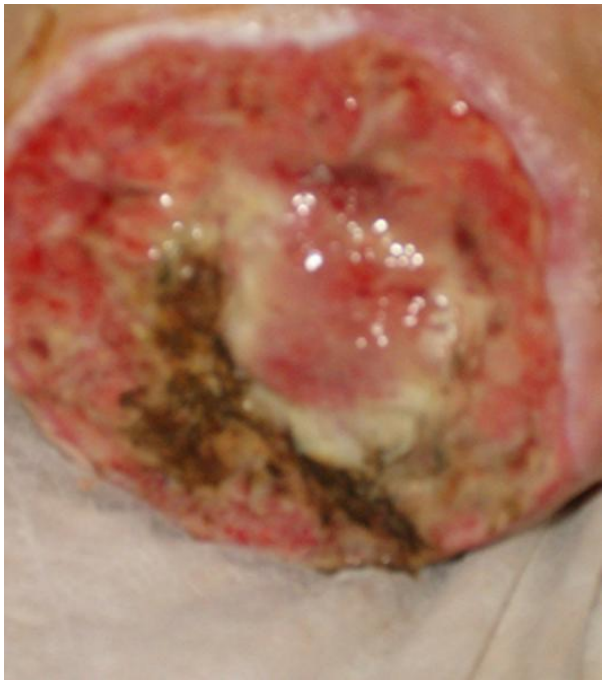
22 yr history of complex leg ulcer with recurring Pseudomonas infection and failed skin grafting

April 2003

May 2003

September 2003

4th April 2005



11th April 2005

15th April 2005

Burn Wounds

"Can you fix a flat?"

Wound Care

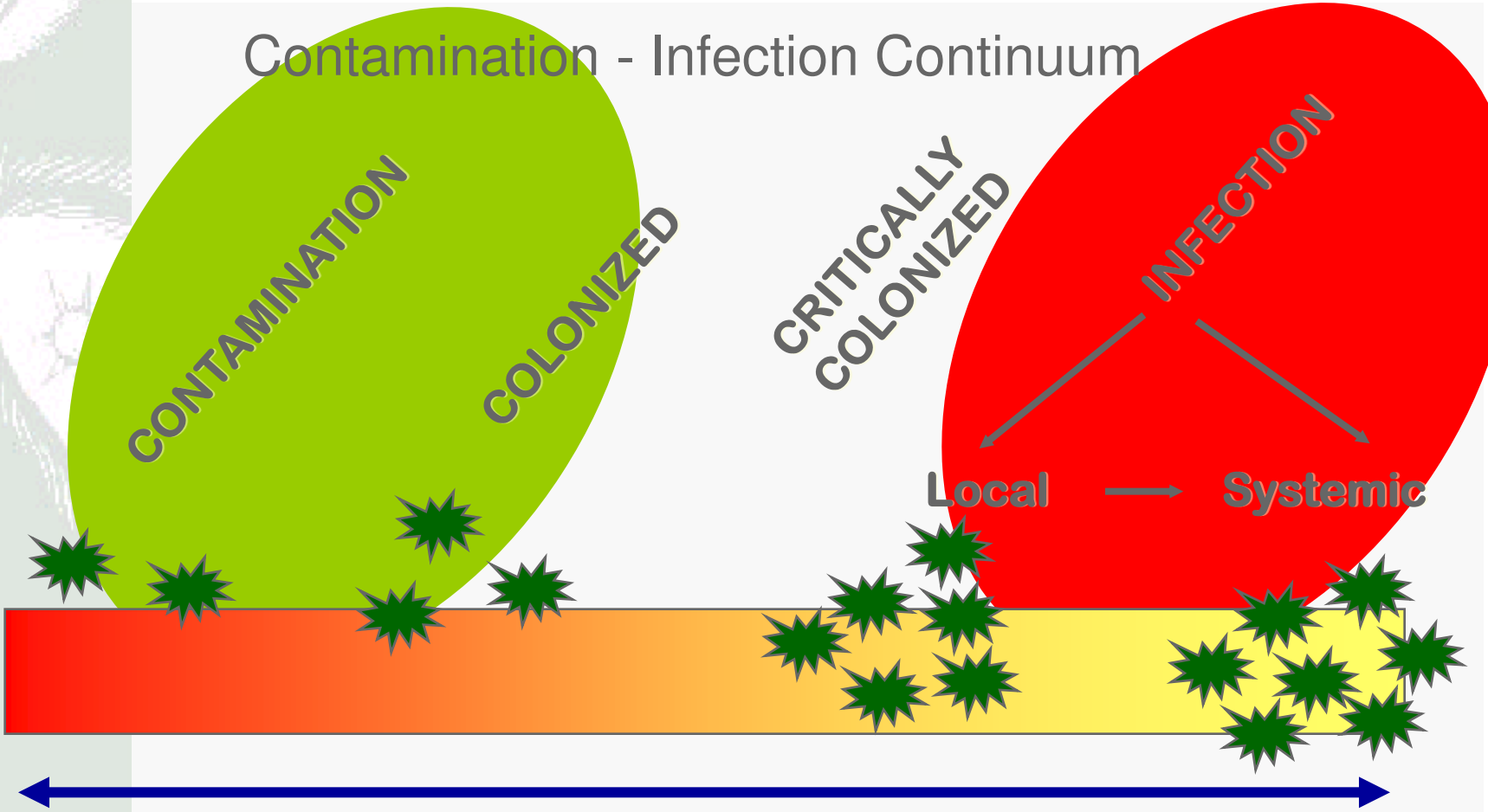
- Bottom of the HCP's food chain
- Surgeons?
- Nurses, PnP's
- Patients move
- Swabs are taken to determine presence of bacteria, sensitivity
- Quantitative investigations – expensive & time consuming, not available
- Antibiotics often prescribed
- Mupuricin/Flagyl often used
- No follow up

Key Assessment Challenge

- When is the Wound Infected?

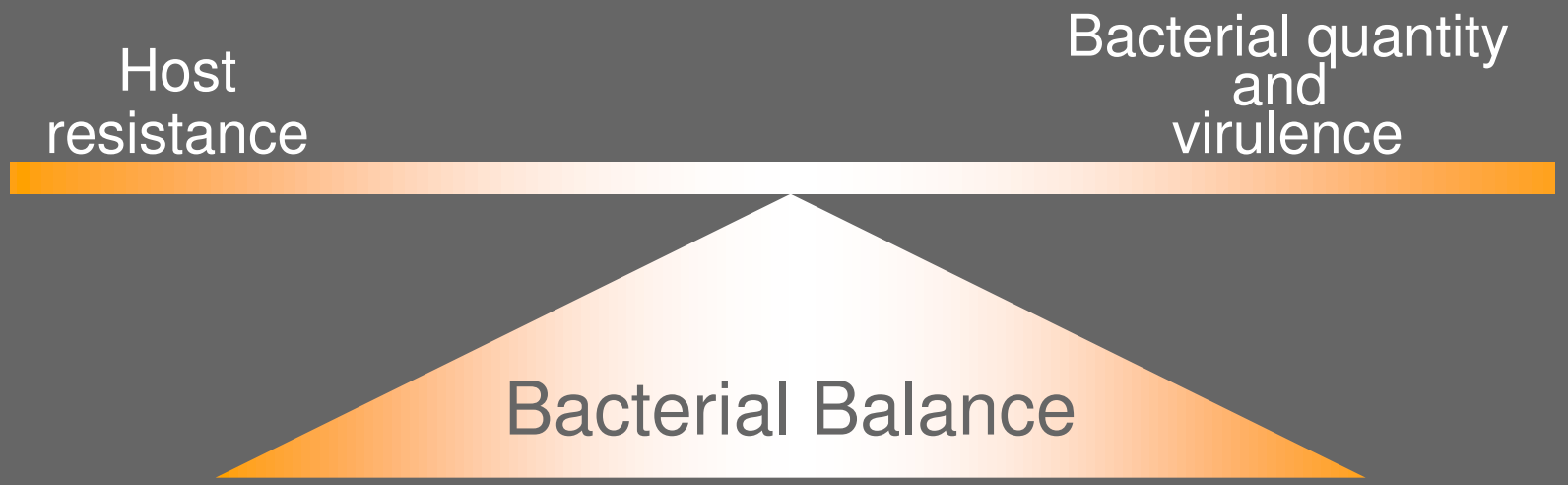
- Need to know the point of when to intervene
  - With a topical antimicrobial?
    - With a systemic antibiotic?

Understanding the Bacterial Burden in Wounds



CRITICALLY COLONIZED – evolving concept in wound care

Scales of Wound Infection



Local perfusion
Immunosuppression
Diabetes
Medications

Adhesins
Cell capsules
Biofilms
Antibiotic resistance

Sibbald et al (2000) Dow (2001)

Topicals


Hydrogen
Peroxide


BETADINE
solution
Broad-Spectrum
Topical Antiseptic
Microbicide for
Degerming Skin and
Mucous Membranes

Omiderm
Smith&Nephew
Flamazine
INADINE
9.5cm x 9.5cm
Johnson&Johnson
WOUND MANAGEMENT
Bactroban
topical
Iruxol mono
HIBITANE
Antiseptic Cream
SILWER NITRAAT AANWE

Why am I here?


HERMAN®
by Jim Unger
8-24
© LaughingStock International Inc./dist. by United Media, 2005
"Today's topic is 'public awareness.'"

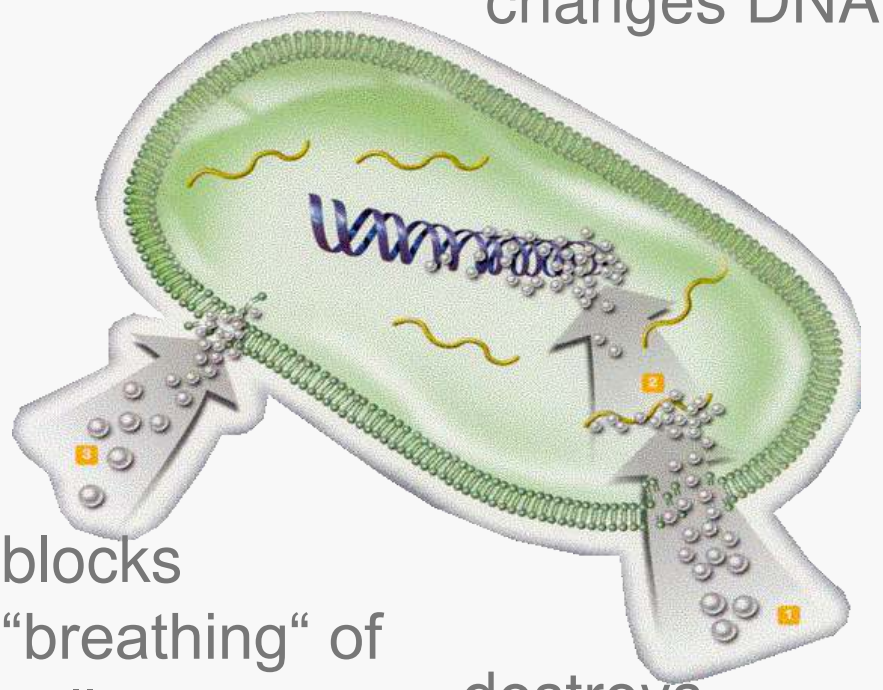
SILVER - BACKGROUND

- Powerful antimicrobial and bactericidal actions[1]
- 1884 (Crede)-1% $AgNO_3$ - ophthalmic rinse
- 1887 (von Behring)- 0.025% $AgNO_3$- typhoid bacillus / 0.01% $AgNO_3$ – anthrax bacillus
- Used beaten silver foil and placed it on wounds to fight infection

- 1920 – Colloidal Silver – wounds, (anti-inflammatory effects were recorded)
- 1964 (Moyer, Monafo & Burke) - 0.5% $AgNO_3$ for burns
- 1968 (Fox) - Silver sulfadiazine – P. aeruginosa & others
- 1997 (Burrell) - Nanocrystalline silver

Silver ions (Ag+) - Mechanism of Action

- Broad spectrum antimicrobial agent -yeasts, molds & bacteria, including MRSA and VRE
- Does not induce resistance (???) if used at adequate levels
- Low Mammalian cell toxicity
- Possible Anti-inflammatory properties
  - Decrease surface inflammation (other heavy metals - gold)
  - Decrease MMP and TNFα activity (linked to decr Zn activity)



Minimum Inhibitory Concentrations (MIC)

Pathogens	MIC
Staphylococcus aureus	12.5 ppm
Staphylococcus epidermidis	10.0 ppm
Escherichia coli	7.5 ppm
Klebsiella pneumoniae	5.0 ppm
Pseudomonas aeruginosa	7.5 ppm

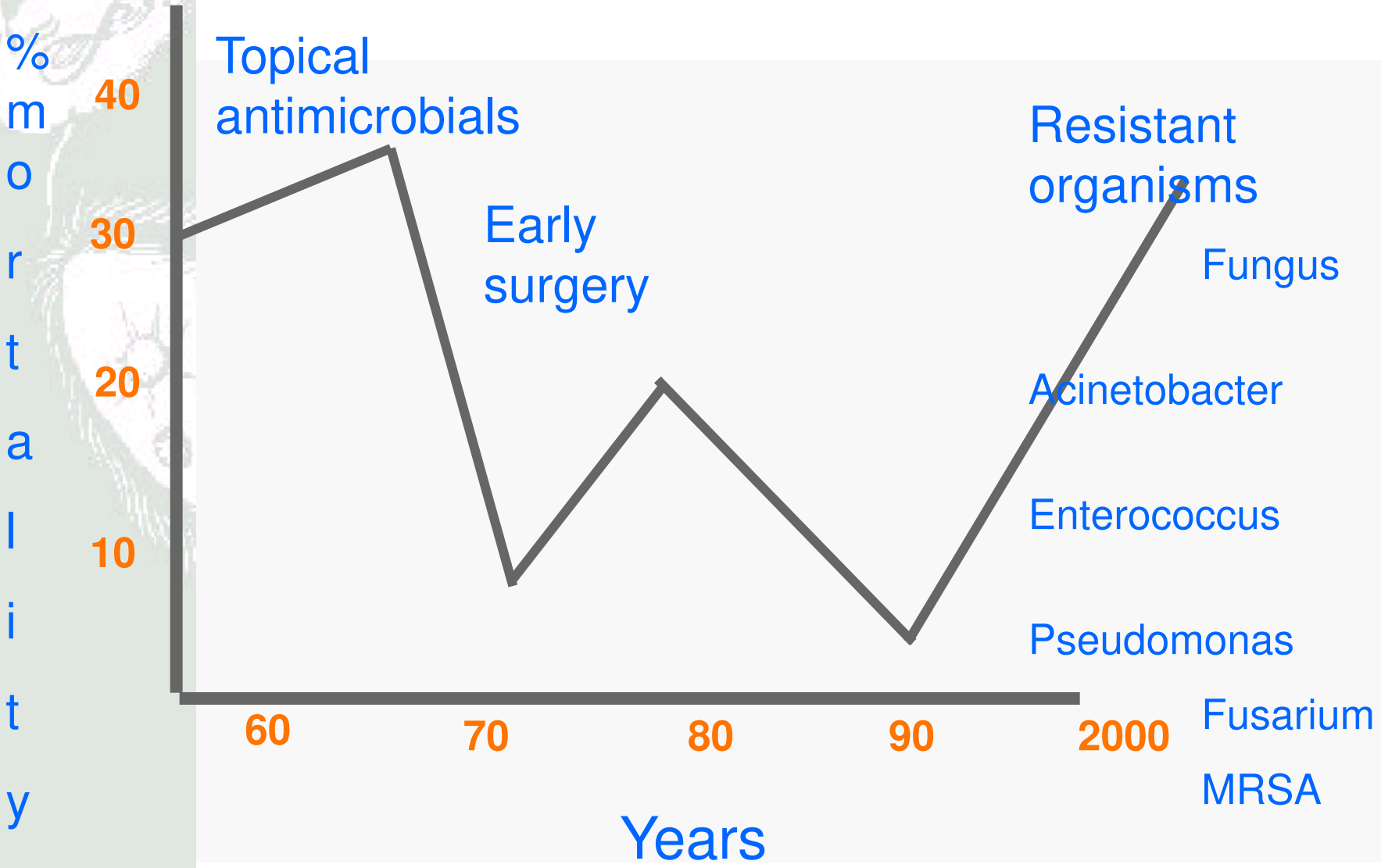
[19]Yin HQ et al (1999)

Silver Salt Solubility…or the problem with Silver

Silver Form		Water Conc at 24 h	Dressing
Initial	Solution	ppm	
Ag^{o} nanocrystal	Ag^{+} Ag^{o}/Ag^{+} clusters	70 - 100	
Ag metal	Ag^{+}	5	
Ag halide	Ag^{+}	<1	
AgCMC	Ag^{+}	1	
Ag/Ca PO_4	Ag^{+}	30	
Ag carbon	Ag^{+}	<1	
Ag/Pt metal	Ag^{+}	<1	
Ag zeolite	Ag^{+}	<1	
Ag/SD	Ag^{+}	3025	
$AgNO_3$	Ag^{+}	3176	

Burn wound infection

Eradication difficult



Resistance Patterns

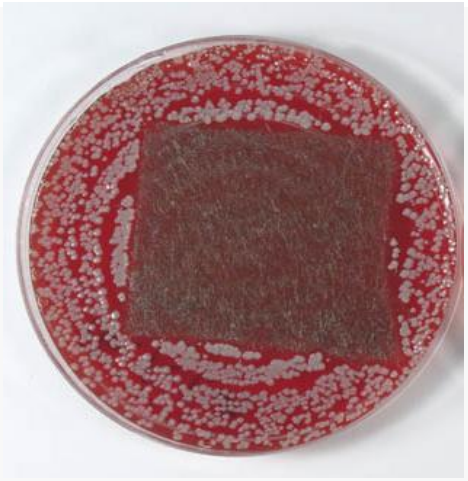
Year	93	94	95	96	97	98	99	00	01	02
Povidone Iodine										
%	2	3	7	20	19	25	37	52	46	48
Silver Sulphadiazine										
%	4	5	6	5	6	4	6	23	20	44
Mupirocin										
% MRSA	16	11	9	19	22	25	18	15	16	13
Other's	9	5	6	14	21	22	17	15	16	0

Problems in testing antimicrobial efficacy

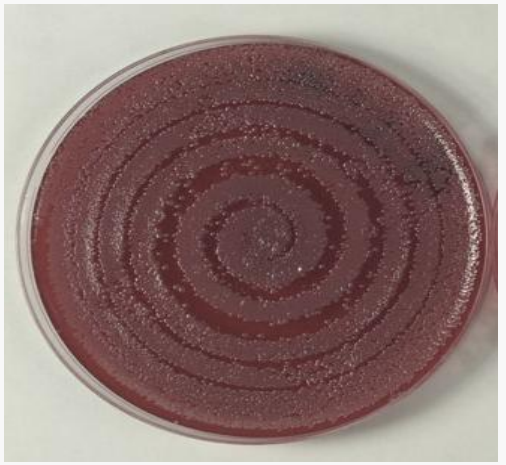
- Topical antimicrobials not registered
- Do not require testing to enter a market
- Robust clinical data is rare
- Most data presented is not published,
  - Case studies series
  - Case Studies

Test 1: Zone of inhibition vs. MRSA (JoWC July 06)

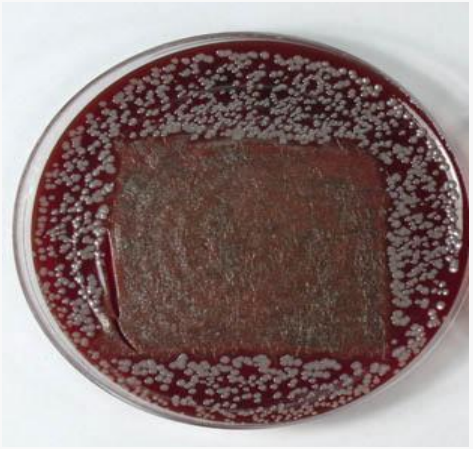
ACTICOAT Absorbent at 1hr



Hydrofiber at 1hr



ACTICOAT Absorbent at 24hrs



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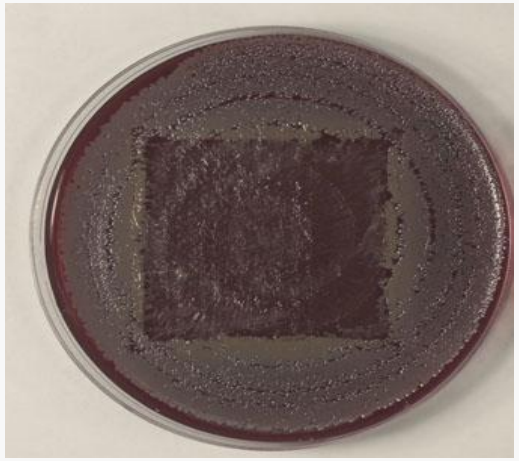
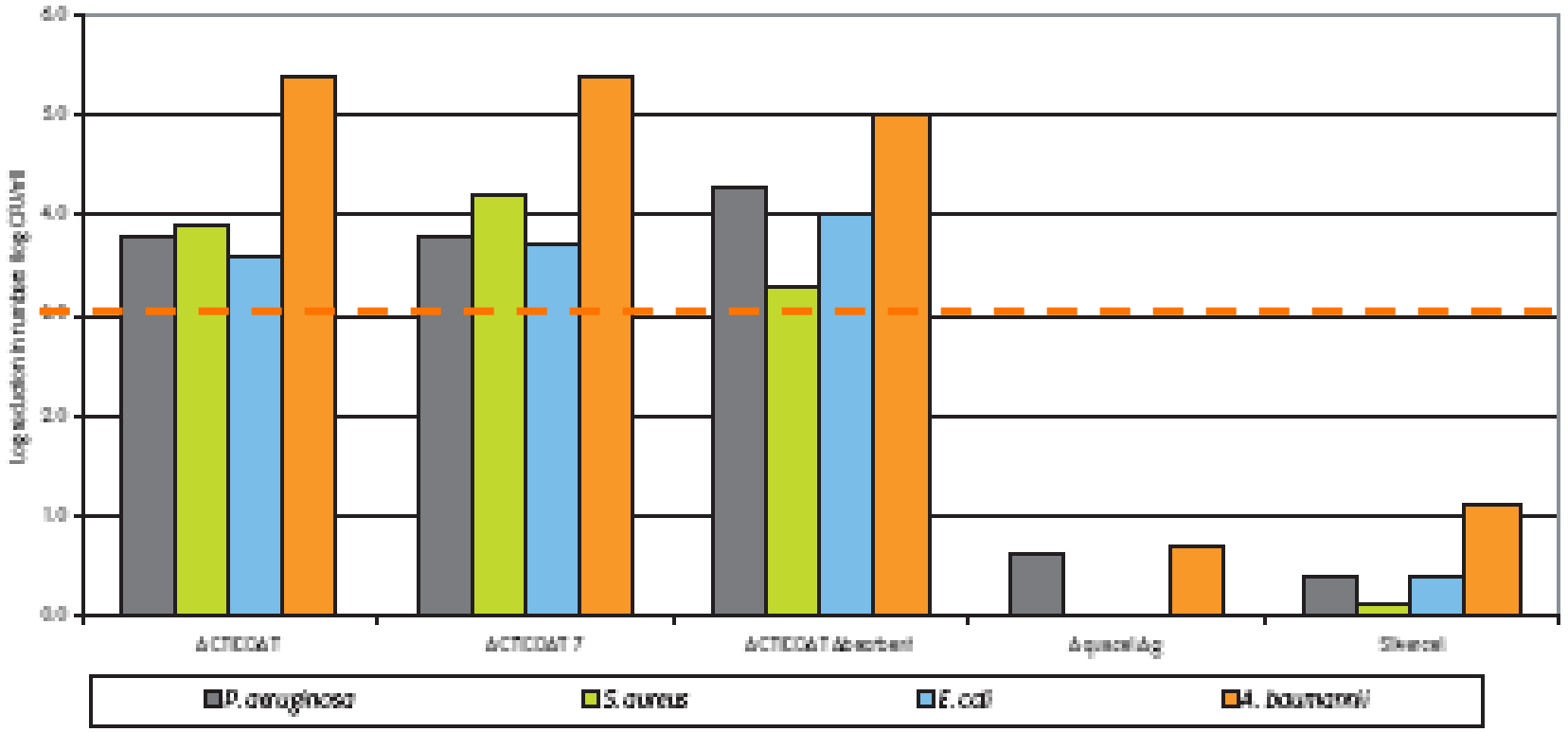


Bactericidal effect – Log Reduction Assays



More Ag^+ = More Efficacy

"The kill rate is directly proportional to Ag^+ concentration, typically acting at multiple targets. The higher the silver-ion concentration, the higher the antimicrobial efficacy"

Schierholz et al (1998)

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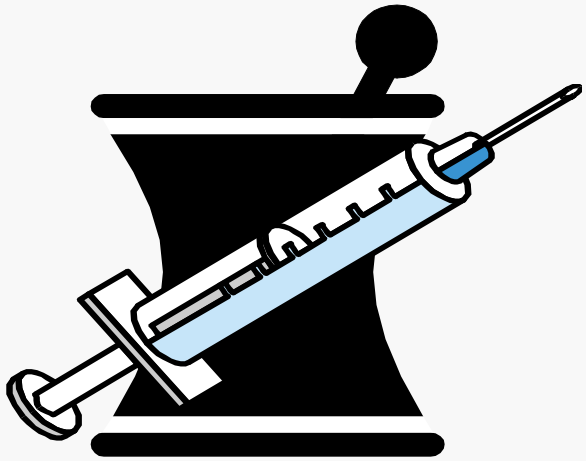
Standardisation of tests to critically evaluate antimicrobial efficacy of topical antimicrobial dressings

Prevention of resistance in the new millennium

- Handwashing/infection control

Antimicrobial use in wound care

- Avoid systemic antimicrobial exposure if possible
- Shorter antibiotic duration
- Hit them hard, Hit them Fast
- **Potent antimicrobial (cidal vs static)**



When does intervention makes a real difference

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HERMAN®

by Jim Unger

"Clamp!"

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Thank You