



MONASH University

Medicine, Nursing and Health Sciences

Antimicrobials

Antiseptics & Antibiotics

in Wound Care

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Clayton Campus

Inflammation & Infection

- High bacterial counts or prolonged inflammation in chronic wounds can retard healing due to:
 - ↑ Inflammatory cytokines
 - ↑ Protease activity
 - ↓ Growth factor activity
- Can result from underlying inflammatory disease
 - Consider if not responding to first line treatment
 - Consider impact of anti-inflammatory medicines

Infection & Chronic Wounds

- Infection depends on exposure
- Clinical signs require systemic management
 - Empirical therapy initially
 - See Antibiotic Guidelines
 - Identification by bacteriology
 - Identify specific antibiotic sensitivities
- Chronic wounds will be colonised – this does not mean that they are infected
- Chronic wounds do not require antibiotics or antiseptics as a matter of course

Bacterial pathogenesis contributes to the pro-inflammatory cycle in chronic wounds.¹



Pathogenic bacteria in the wound hinders wound healing²

- Excess virulence factors such as **bacterial proteases** produced
- Increased host inflammatory response
- Tissue damage

1. Gibson D, Cullen B, Legerstee R, Harding KG and Schultz G. MMPs made easy. Wounds International. 2009;1(1):1-6. http://www.woundsinternational.com/media/issues/61/files/content_21.pdf
2. Koziel J, Potempa J. Protease-armed bacteria in the skin. Cell Tissue Res. 2012 ; 351(2): 325-37.

Using Antibiotics & Antiseptics in Wound Care

Need to understand:

- Issues with bacterial presence in wounds
- Difference between antiseptics & antibiotics
- Potential risks & benefits of use
- Use of best practice guidelines

Bacterial Burden in Wounds

- Contamination
 - The presence of non-replicating micro organisms within the wound.
- Colonisation
 - The presence of replicating micro organisms that do not cause injury to the host.
- Local Infection
 - The presence of replicating micro organisms that are beginning to cause local tissue damage.
- Infection Spreading & Systemic
 - The presence of replicating micro organisms that are capable of causing injury to the host.

1: The infection continuum

Increasing clinical signs and increasing harm to patient

Increasing clinical signs and increasing risk of infection					
Contamination	Colonisation	Topical infection	Local infection	Regional infection	Sepsis
No overt signs of infection		May be local subtle signs of infection	Usually overt local signs of infection	Usually overt regional signs of infection	Usually overt systemic signs of infection
Wound healing progresses		Wound healing impaired			Patient health impaired
Host/Patient defences prevail					Bacteria prevail



Topical infection



Local infection



Regional infection (cellulitis)

Bacterial Balance

Control mechanisms

- Intact skin is physical barrier
- pH is not conducive to bacterial growth
- Skin secretes fatty acids and antibacterial polypeptides
- Normal flora aide in preventing pathogenic flora from establishing

Bacterial Burden

Contamination - Infection Continuum



Trengove(1996) found that there was significantly greater chance of failure to heal if four or more groups of bacteria were present in the wound

**Host
Resistance**

**Bacterial quantity
and virulence**



Bacterial Balance

Local perfusion

Immunosuppression

Diabetes

Medications

Adhesins

Cell Capsules

Biofilms

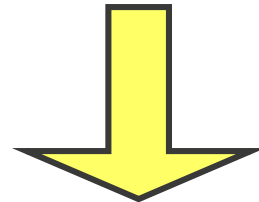
Antibiotic Resistance

Clinical Presentation

Acute Wound
Infection
or
Severe
Chronic Wound
Infection



Advancing erythema
Fever
Warmth
Oedema / swelling
Pain
Purulence



“Classic” Signs & Symptoms

Clinical Presentation

Critically Colonized

-

Bioburden

-

↑ Bacterial Burden

-

Local

Wound Infection

Delayed healing

Change in color of wound bed

Friable granulation tissue

Absent or abnormal granulation tissue

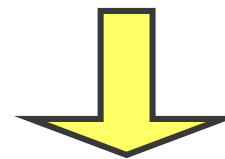
↑ or abnormal odor

↑ serous drainage

↑ pain at wound site

Cutting & Harding (1994)

Gardner, Frantz & Doebbeling (2001)



“Secondary” Signs & Symptoms

- “Traditional” Signs & Symptoms need not be present for local wound infection to be present in chronic wounds.
- Quantitative tissue biopsy demonstrated that “secondary” signs & symptoms occurred more often than “classic” in chronic wound infections.
- No single sign or symptom is 100% sensitive suggesting that none should be considered crucial or necessary to identify a chronic wound infection.
- Increasing pain and wound breakdown considered sufficient.

Gardner SE, Frantz RA, Doebbeling BN (2001) “The validity of the clinical signs and symptoms used to identify localized wound infection” Wound Repair and Regeneration 2001;9(3):178-186

Basic Background of Bacterial Biofilms

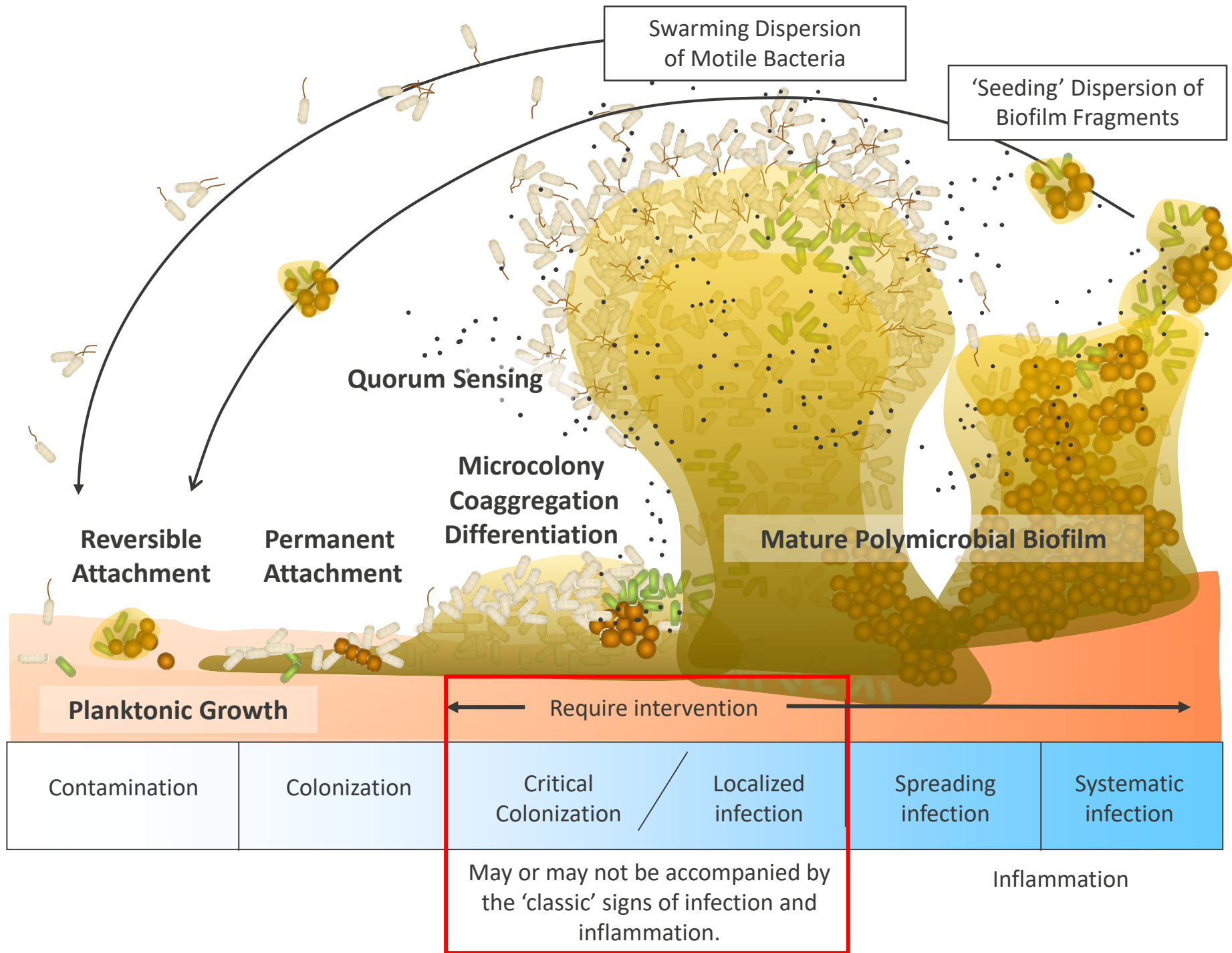
- **Bacterial biofilms** - are a structured community of bacteria cells enclosed in a self-produced matrix that is attached to a living or inert surface
- **Biofilms** - constitute a protected mode of growth that allows survival in a hostile environment – provides defense against phages (bacterial viruses), amoeba (eat bacteria), phagocytosis (inflammatory cells), biocides (natural ROS, synthetic antiseptics), or antibiotics
- **Planktonic bacteria** – are free floating “single” bacteria
- **Sessile bacteria** – tightly attached bacteria
- **Quorum sensing** – communication process by which bacteria ‘sense’ molecules produced by other bacteria in the vicinity – leads to altered gene expression and changes in phenotypic growth patterns

How quickly do biofilms form?

Experimental laboratory studies have shown that planktonic bacteria, eg *Staphylococci*, *Streptococci*, *Pseudomonas* and *Escherichia coli*, typically:

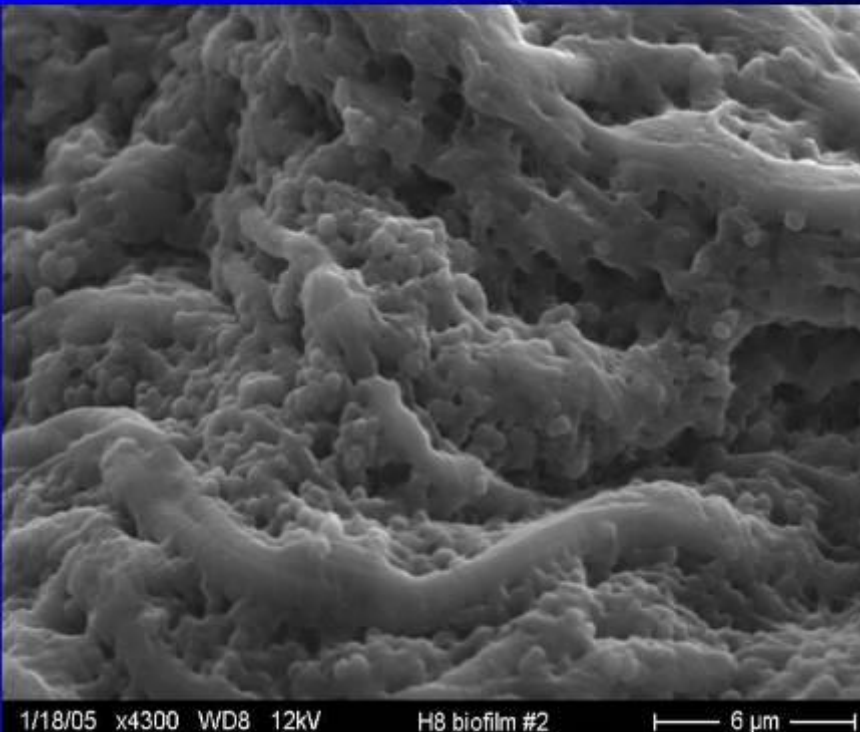
Attach within minutes, form strongly attached microcolonies within 2–4 hours develop initial EPS and become increasingly tolerant to biocides, eg antibiotics, antiseptics and disinfectants, within 6–12 hours

Evolve into fully mature biofilm colonies that are extremely resistant to biocides and shed planktonic bacteria within 2–4 days, depending on the species and growth conditions rapidly recover from mechanical disruption and reform mature biofilm within 24 hours.

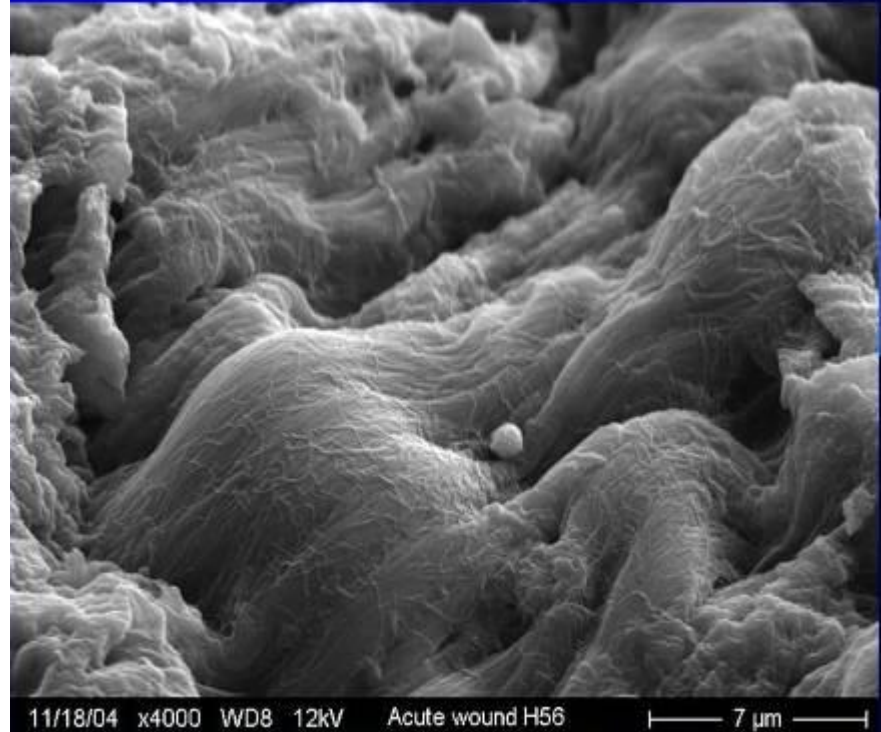


Electron Micrographs Reveal Biofilms on 60% of Chronic Wounds But <10% of Acute Wounds

Biofilm!



Acute Wound



Topical and systematic antibiotics and antibodies unable to penetrate the biofilm which also acts as a microbial reservoir for infection of neighboring tissue

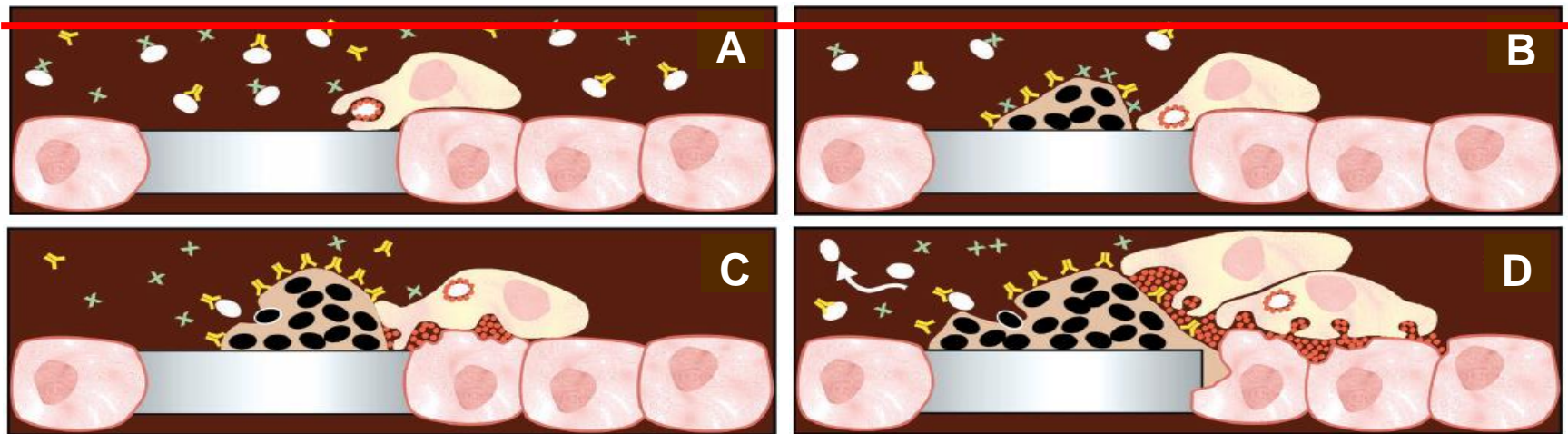
Macrophage
unable to clear
biofilm

Bacterial
secreted
cytotoxins kill
host immune cells

Chronic inflammation,
release of proteases and reactive
oxygen species, result in tissue damage



How Does The Immunological Response to Biofilms Cause Tissue Damage?



 Antibiotic  Antibody  Planktonic cell  Biofilm cell  Phagocyte enzymes

In Panel A, planktonic bacteria can be cleared by antibodies, phagocytosis, and are susceptible to antibiotics. Adherent bacterial cells (Panel B) form biofilms preferentially on inert surfaces or devitalized tissue, and these sessile communities are resistant to antibodies, phagocytosis and antibiotics. Phagocytes (Panel C) are attracted to the biofilms, but phagocytosis is frustrated. Phagocytic cells still release enzymes and ROS. Phagocytic enzymes (Panel D) damage tissue around the biofilm, and planktonic bacteria are released from the biofilm, causing dissemination and acute infection in neighboring tissue.

Costerton, Stewart, Greenberg, Science 284, 1999

Biofilm Based Wound Care

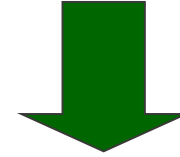
A combination strategy is recommended for managing biofilms:

1. Biofilm removal



**Frequent aggressive
debridement**

**2. Prevention of biofilm
reconstitution**



**Antibiotics
Biocides
Antibacterial agents**

Topical Antibiotics Effectively Kill Planktonic Bacteria in Pig Skin Wounds But Only Reduce Bacteria in Biofilms 2-Logs After 48 Hours

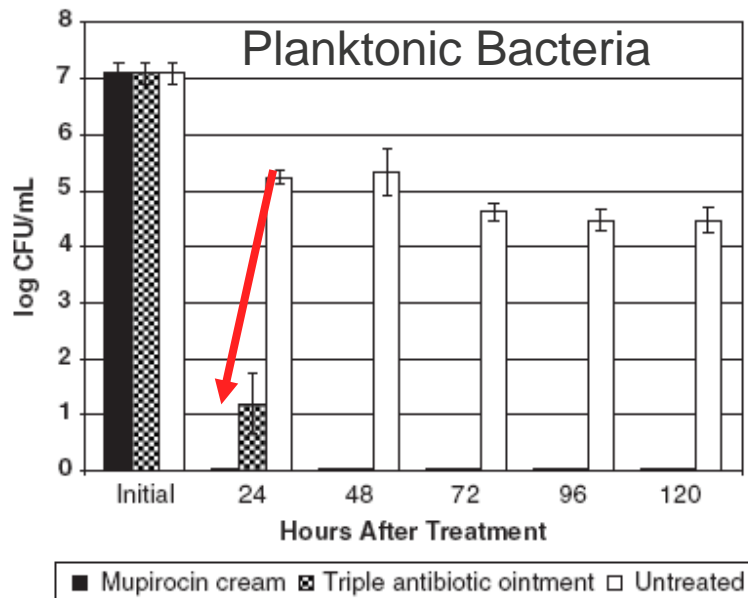


Figure 4. Results of antimicrobial activity on planktonic cells (log CFU/mL).

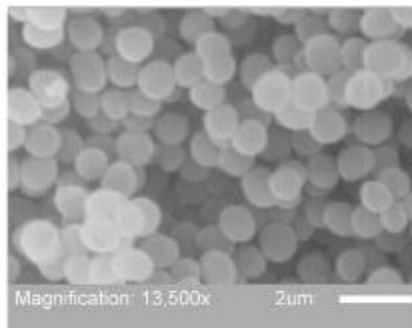


Figure 3. Scanning electron micrograph of bacteria grown on agar plates overnight. We see that there is no presence of an amorphous matrix surrounding the bacteria and we speculate that these are planktonic cells.

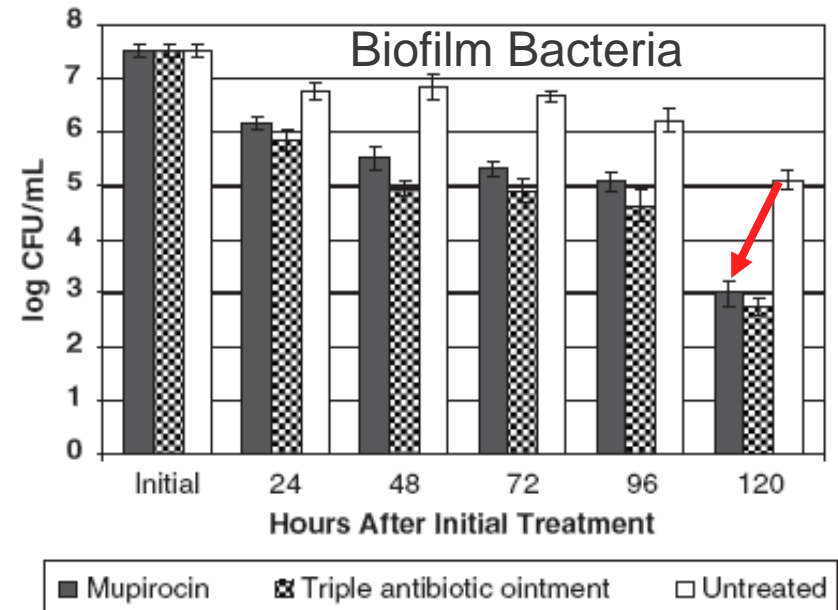


Figure 5. Results of antimicrobial activity on biofilm cells (log CFU/mL).

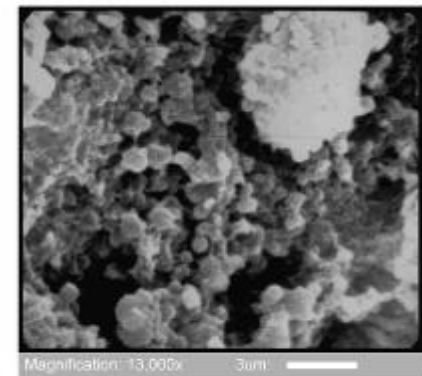


Figure 2. Scanning electron micrograph at $\times 13,000$ magnification of colonies of bacteria surrounded by an amorphous matrix on the surface of the wound bed.

If bacteria in biofilms are difficult to kill with topical or systemic antibiotics, antimicrobials, or antiseptics, how can we treat biofilms?

Remove biofilms by effective debridement techniques then prevent the re-formation of biofilms by applying effective dressings, antibiotics, antimicrobials, or antiseptics

Prevention of Biofilm Formation by Silver-Containing Dressings

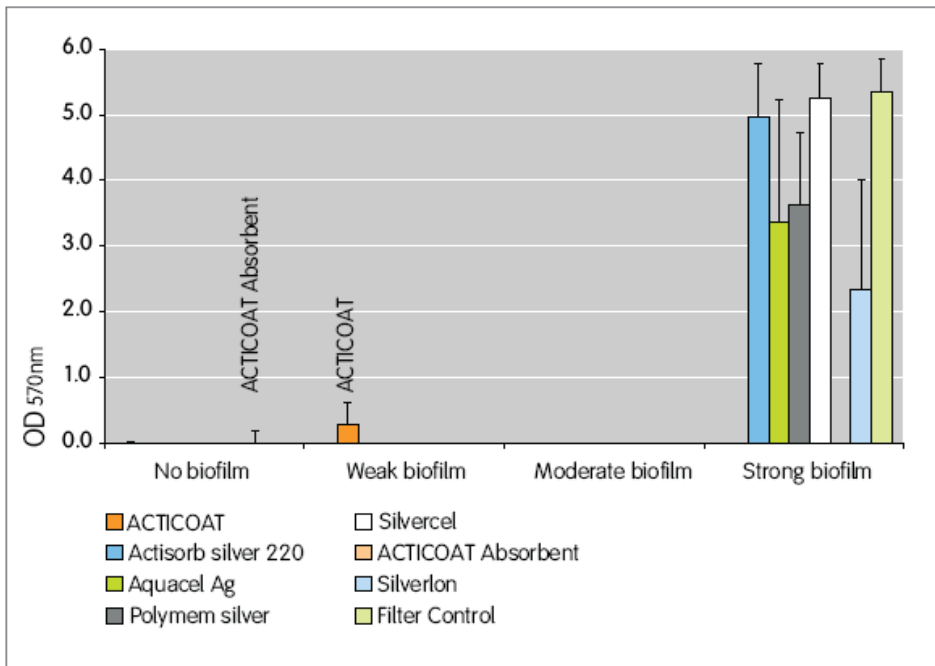


Figure 1. Bacterial mix DFU-1 (*S. aureus* NCTC 10788, *P. aeruginosa* NCIMB 8626, *St. pyogenes* NCIMB 13285) biofilm formation after 48 hours incubation with various silver-based antimicrobial dressings

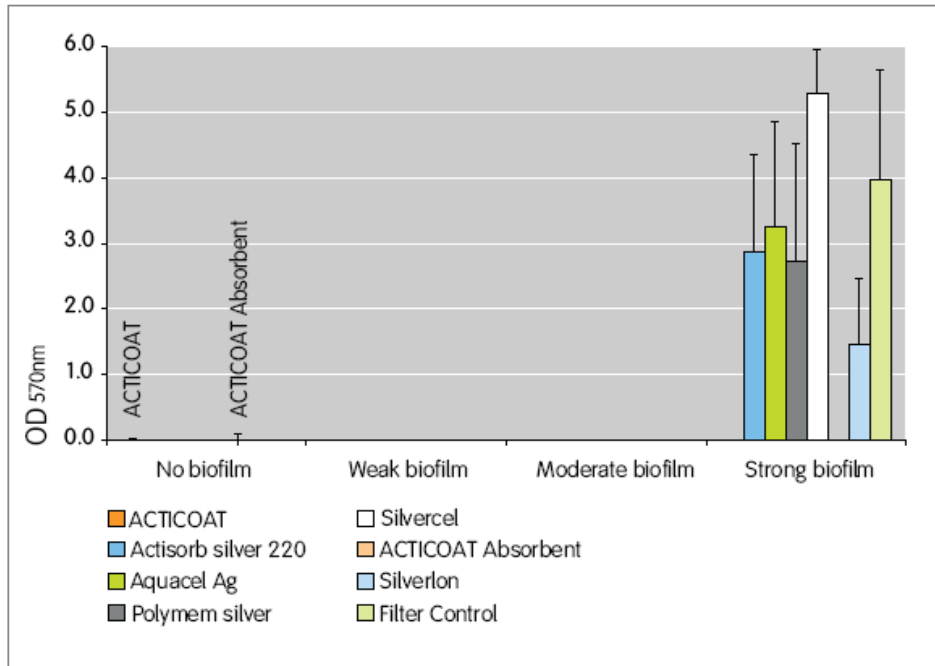


Figure 2. Bacterial mix PU-1 (*S. aureus* NCTC 10788, *P. aeruginosa* NCIMB 8626, *S. epidermidis* NCIMB 8853) biofilm formation after 48 hours incubation with various silver-based antimicrobial dressings

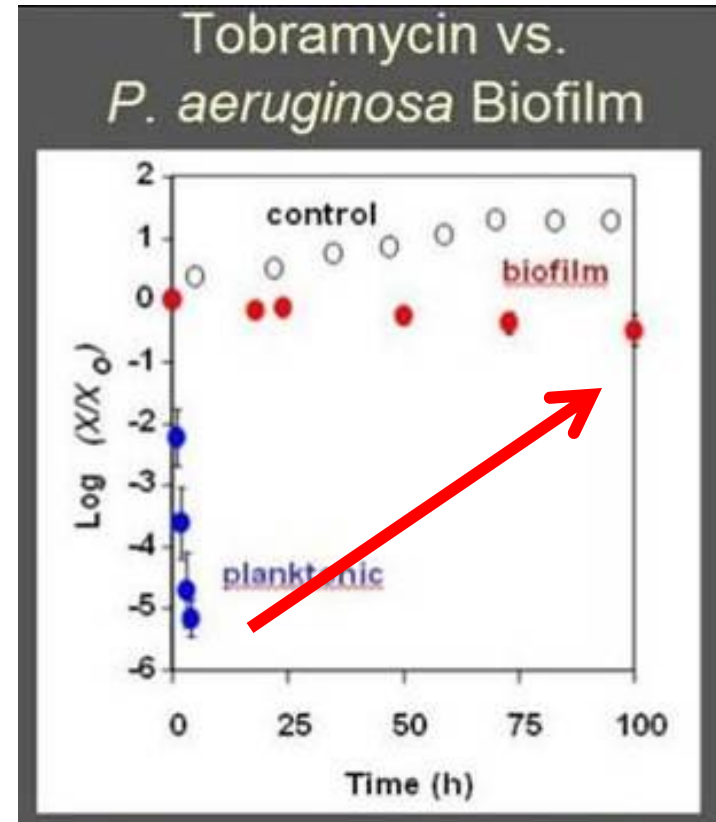
Biocides verses Biofilms

Bacteria are Hard to Kill in Biofilms



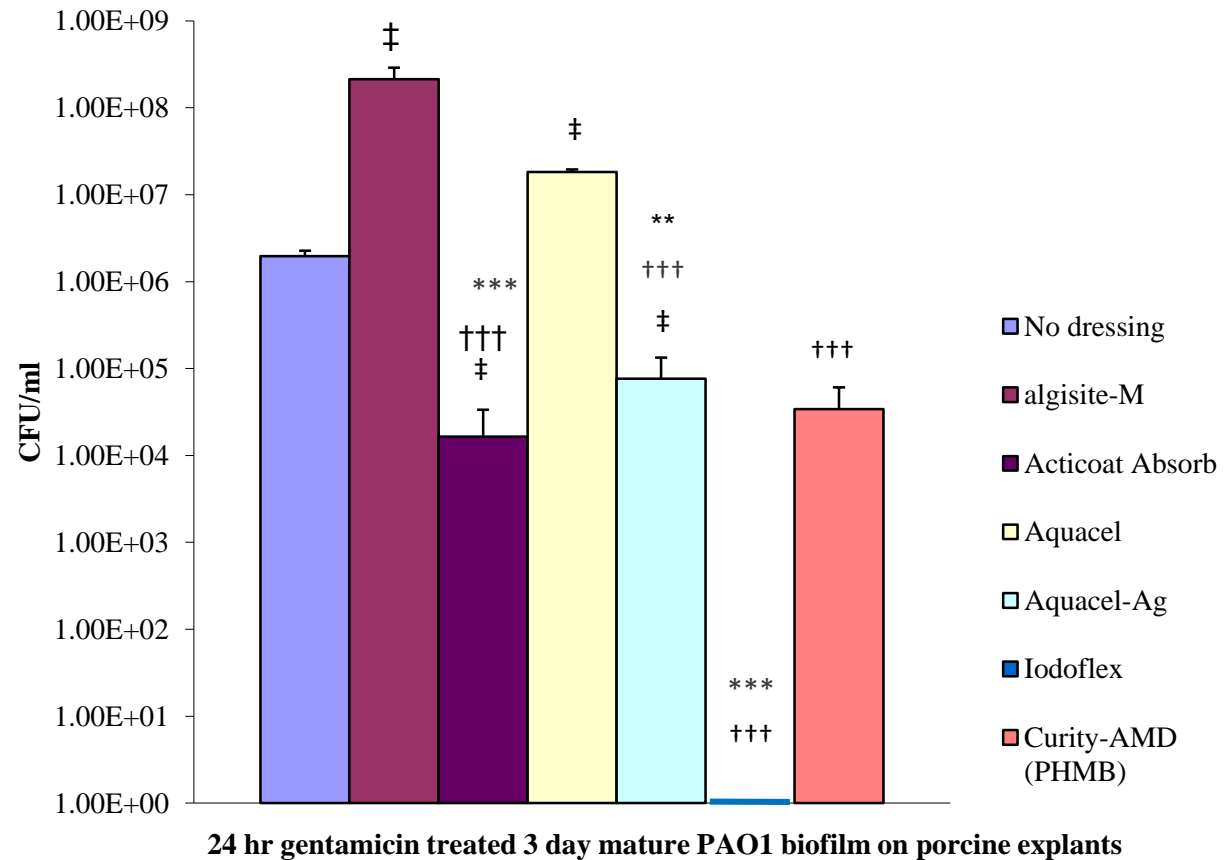
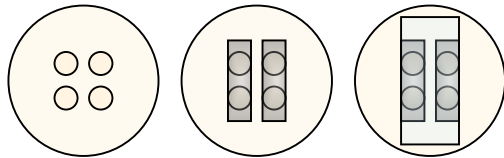
After 60 minutes of exposure to dilute bleach (Dakin's solution), many bacteria in this biofilm were dying (green cells), but many cells in the interior of the biofilm were still alive (orange cells)

Costerton, Sci Am, 2001



Tobramycin rapidly kills planktonic *Pseudomonas aeruginosa* (●) very effectively, but is not effective against biofilm *Pseudomonas* (●).

ACTICOAT-ABSORB and IODOFLEX Reduce Levels of Mature Pseudomonas Biofilms Grown on Porcine Skin Explants



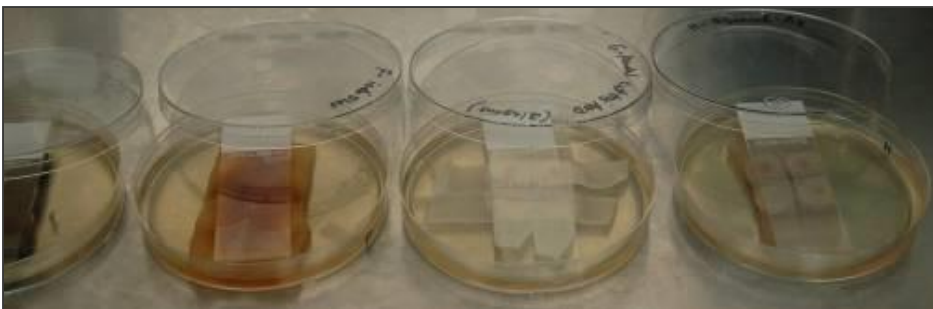
*** Indicates a $p < 0.001$ difference between each dressing and no dressing

** Indicates a $p < 0.01$ difference between each dressing and no dressing

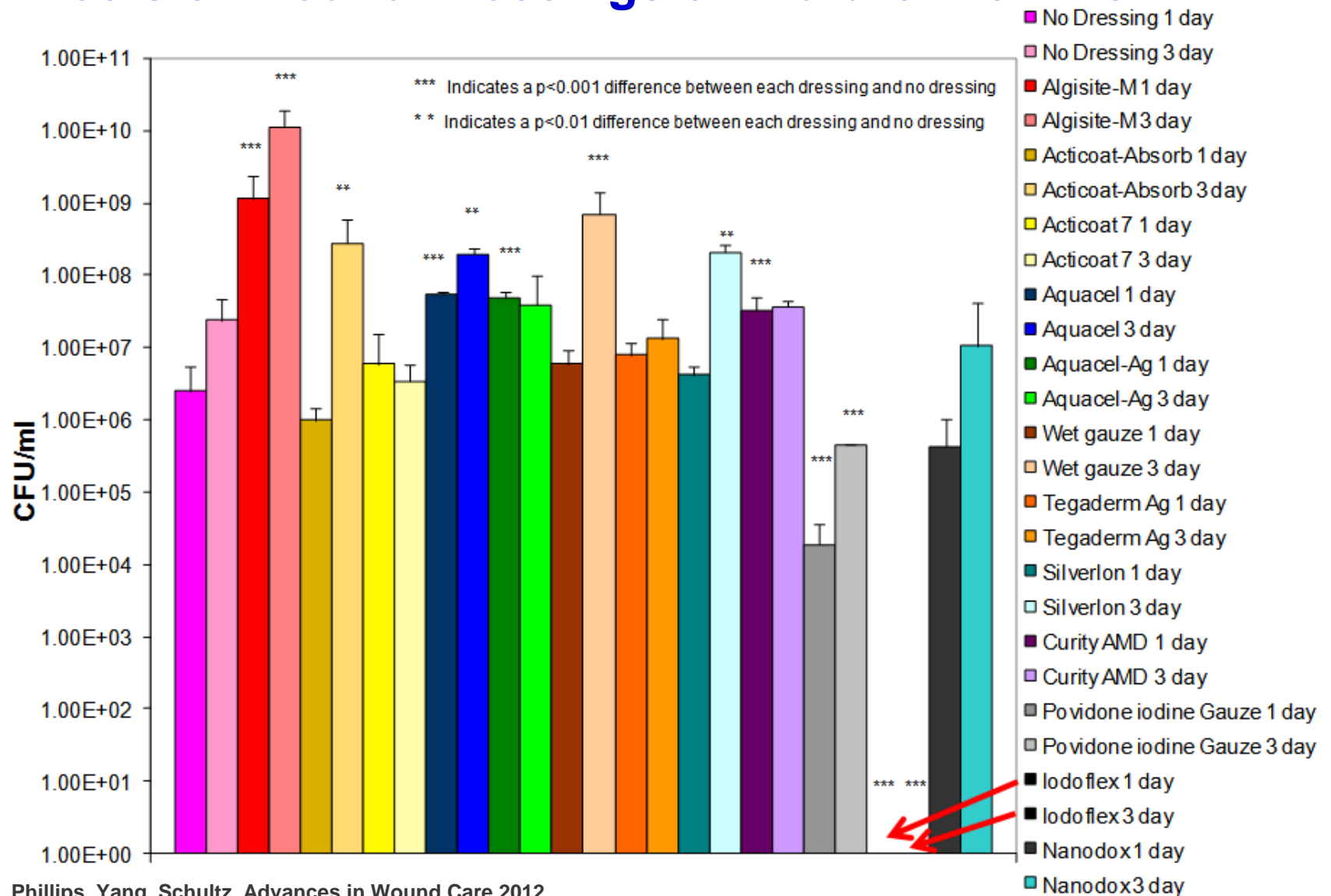
††† Indicates a $p < 0.001$ difference between each dressing and Algisite

‡ Indicates a $p < 0.001$ difference between counterpart dressing types:

Algisite vs Acticoat Absorb; Aquacel vs Aquacel-Ag



Effects of Wound Dressings on Mature Biofilms

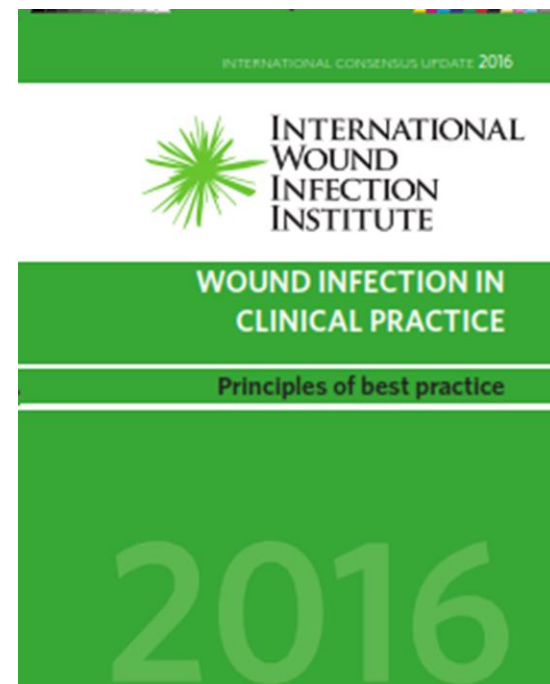


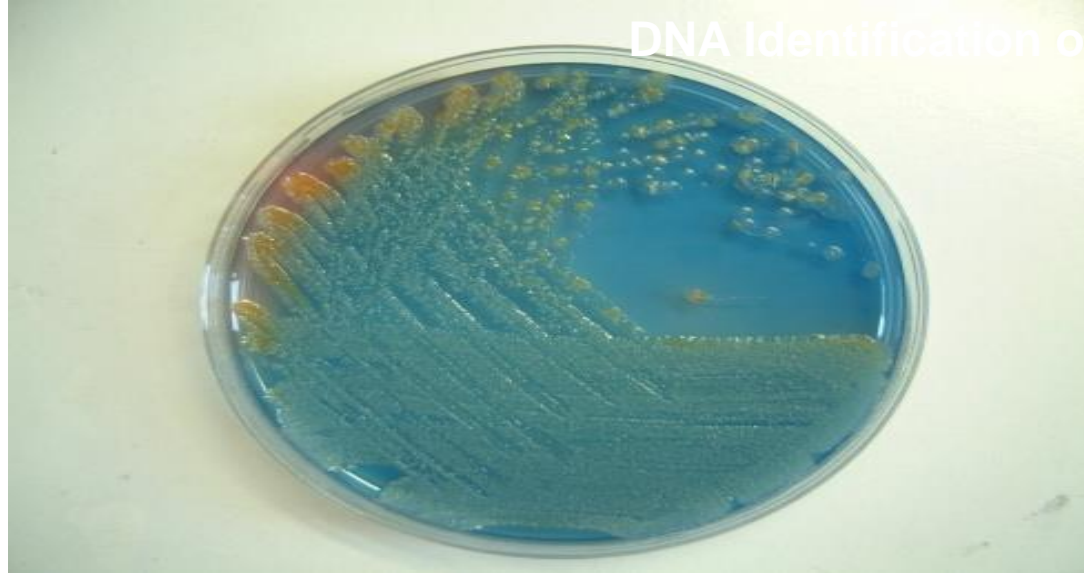
- ▶ The latest clinical information on wound infection
- ▶ Access the Institute's many experts on wound infection
- ▶ Free Membership

Resources:

- The role of biofilms in wound infection
- Evidence wound matrix
- Wound infection curriculum
- Consensus documents
- Links

www.woundinfection-institute.com





- Traditional microbiology plate growth assays only identify a small number of bacterial species
- DNA amplification and sequencing techniques can identify all bacterial species in a wound sample
- Optimal topical formulations of antibiotics can be prepared for each patient

James *et al* (2008)- Biofilms in Chronic Wounds ***Wound Repair and Regeneration*** 16: 37-44
Davies CE *et al* (2004) Use of 16S ribosomal DNA PCR and denaturing gradient gel electrophoresis for analysis of the microfloras of healing and nonhealing chronic venous leg ulcers. ***J Clin Microbiol.***;42:3549-57.

Identification of Different Bacterial Genuses in a Biopsy of a Chronic Pressure Ulcer

A total of 36 different bacterial genres were identified by nucleic acid sequences.

The % represents the percentage of the total sequences analyzed within the sample
7 of the top 8 (70%) Are Anaerobes

Genus	Seq	%	Gram	Aerotolerance	Shape
<i>Staphylococcus</i> spp.	10874	29.72	+	Facultative anaerobe	Cocci
<i>Peptoniphilus</i> spp.	2555	6.98	+	Anaerobic	Cocci
<i>Rhodopseudomonas</i> spp.	2541	6.94	-	Facultative anaerobe	Rod
<i>Enterococcus</i> spp.	2341	6.40	+	Facultative anaerobe	Cocci
<i>Veillonella</i> spp.	1978	5.41	-	Anaerobic	Cocci
<i>Clostridium</i> spp.	1975	5.40	+	Anaerobic	Rod
<i>Fingoldia magna</i>	1953	5.34	+	Anaerobic	Cocci
<i>Haemophilus</i> spp.	1701	4.65	-	Facultative anaerobe	Rod
<i>Acinetobacter</i> spp.	1301	3.56	-	Aerobic	Rod
<i>Morganella</i> spp.	1240	3.39	-	Facultative anaerobe	Rod
<i>Serratia</i> spp.	1125	3.07	-	Facultative anaerobe	Rod
<i>Proteus</i> spp.	1072	2.93	-	Facultative anaerobe	Rod
<i>Dialister</i> spp.	1029	2.81	-	Anaerobic	Rod
<i>Streptococcus</i> spp.	751	2.05	+	Facultative anaerobe	Cocci
<i>Stenotrophomonas</i> spp.	669	1.83	+	Aerobe	Rod
<i>Peptococcus niger</i>	588	1.61	+	Anaerobic	Cocci
UWB	342	0.93	unk	Unk	Unk
<i>Klebsiella</i> spp.	326	0.89	-	Facultative anaerobe	Rod
<i>Actinomyces</i> spp.	307	0.84	+	Facultative anaerobe	Rod
<i>Gordonia</i> spp.	302	0.83	+	Aerobic	Rod
<i>Delftia</i> spp.	251	0.69	-	Aerobic	Rod
<i>Gemella</i> spp.	168	0.46	+	Anaerobic	Cocci
<i>Corynebacterium</i> spp.	157	0.43	+	Facultative anaerobe	Rod
UWB	143	0.39	unk	Unk	Unk
UWB	107	0.29	unk	Unk	Unk
<i>Salmonella enterica</i>	102	0.28	-	Facultative anaerobe	Rod
<i>Fusobacterium</i> spp.	99	0.27	-	Anaerobic	Rod
<i>Varibaculum cambriense</i>	54	0.15	+	Anaerobic	Rod
<i>Enterobacter</i> spp.	52	0.14	-	Facultative anaerobe	Rod
<i>Bacillus</i> spp.	51	0.14	+	aerobic	Rod
<i>Eikenella</i> spp.	42	0.11	-	facultative anaerobe	Rod
<i>Anaerococcus</i> spp.	42	0.11	+	anaerobic	Cocci
<i>Hydrogenophaga</i> spp.	40	0.11	-	aerobic	Rod
<i>Alcaligenes faecalis</i>	36	0.10	-	aerobic	Rod
<i>E coli</i>	32	0.09	-	facultative anaerobe	Rod
<i>Sphingomonas</i> spp.	26	0.07	-	aerobic	Rod
<i>Acidovorax</i> spp.	26	0.07	-	aerobic	Rod
<i>Prevotella</i> spp.	22	0.06	-	anaerobic	Rod
UWB	20	0.05	unk	unk	Unk
<i>Eubacterium</i> spp.	20	0.05	+	anaerobic	Rod
<i>Bacteroides</i> spp.	20	0.05	-	anaerobic	Rod
UWB	17	0.05	unk	unk	Unk
UWB	16	0.04	unk	unk	Unk
<i>Selenomonadaceae</i> spp.	16	0.04	-	anaerobic	Rod
<i>Brevibacterium</i> spp.	14	0.04	+	aerobic	Rod
<i>Riemerella</i> spp.	13	0.04	-	aerobic	Rod
UWB	11	0.03	unk	unk	Unk
<i>Bradyrhizobium</i> spp.	11	0.03	-	aerobic	Rod
<i>Pantoea agglomerans</i>	10	0.03	-	facultative anaerobe	Rod

Scott Dowd, et al. BioMed Central Microbiology, 8:43, 2008.

Distribution of Aerotolerance of Bacterial Populations in Chronic Wounds

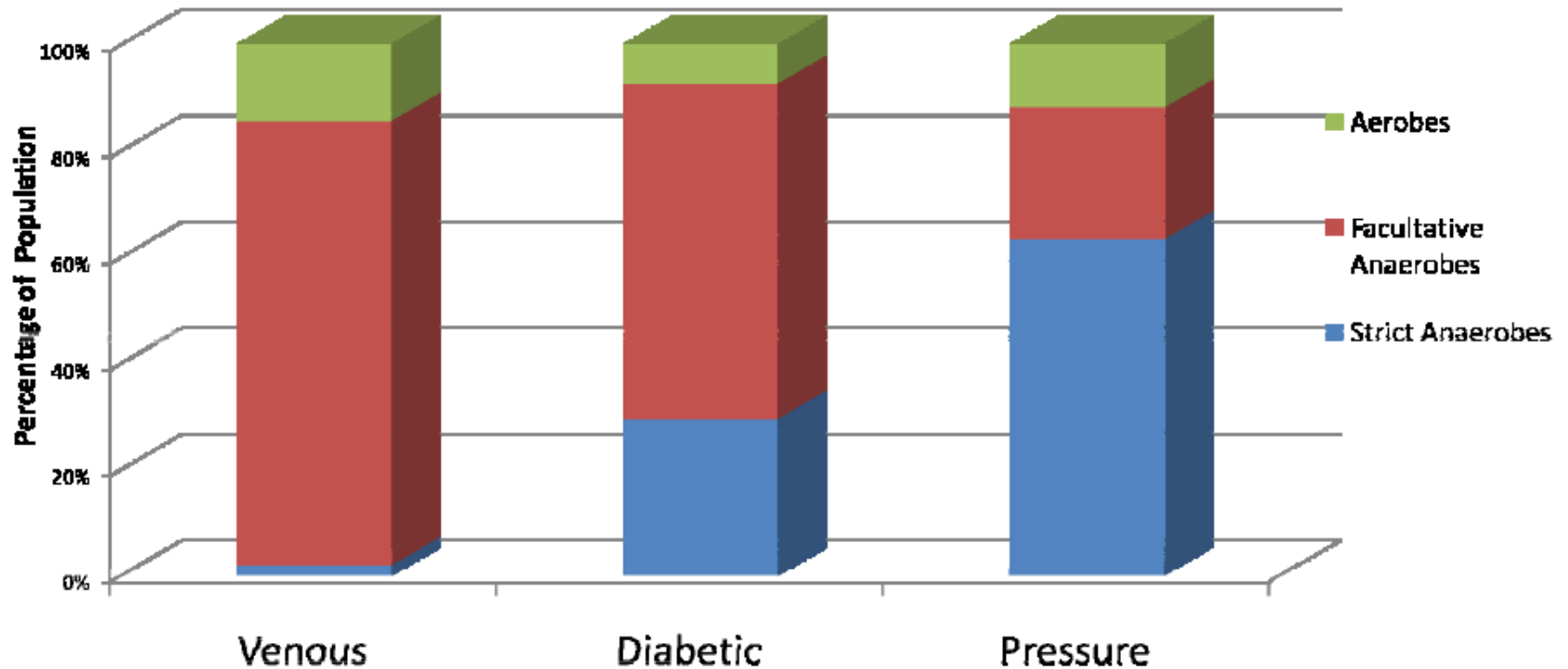


Figure 1

Distribution of Bacterial Populations in Chronic Wounds in Relation to Aerotolerance. Diabetic, venous, or pressure ulcer types were analyzed separately using pyrosequencing and the resulting populations grouped into 3 categories based upon their suggested aerotolerance. This figure graphically illustrates the relative distribution of these functional categories among the wound types.

THE USE OF ANTISEPTICS

Acute injuries will often be contaminated by the surroundings where the injury occurred eg. Dirt, gravel, grass, clothing or other foreign material. The risk of infection developing in these wounds is high due to the inflammatory nature of the wound as the tissue commences the healing process.

ANTISEPTICS

The thorough decontaminating of the wound with a good surfactant product will help to remove most of the foreign material and reduce the risk of infection. It is also appropriate to apply a topical antiseptic Before dressing the wound such as Povidone Iodine This is usually left in place for 3-5 minutes and then washed off with clean water.

Use of Antiseptics

- Antibiotics show selectivity only for certain micro-organisms
- antiseptics are completely non-selective
→ damage ALL cells on contact

Need to carefully evaluate the use of all chemical agents used in wound management

Topical Management

■ Silver

- Ionic Ag⁺
- Nanocrystalline silver has demonstrated anti-inflammatory and wound healing properties
- Iodine
- Sustained release dressings may be effective against biofilms^{5–7}

■ Honey

- Lowers infection⁸
- Promotes debridement⁹
- May be effective against biofilms

■ PHMB

- Wound cleansing
- Gauze dressing

SILVER CONTAINING DRESSINGS

Centuries of proven antimicrobial activity and Silver Has been used for many years in particular in the treatment of burns as a Silver Sulphadiazine Cream. This cream has also been applied to some wounds. The difficulty is the a cream is formulated to be applied to intact skin. When applied to a wound it encourages the development of muscilagenous slough.

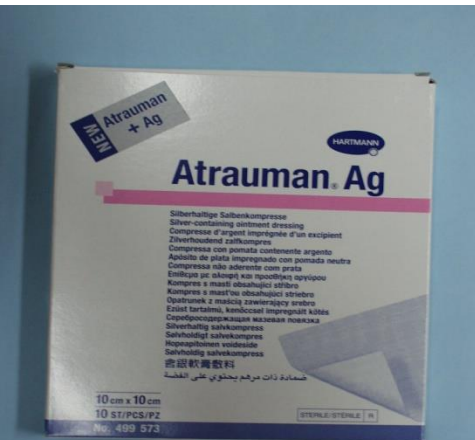
NEW SILVER IMPREGNATED DRESSINGS

Topical application of silver products in the early management of necrotic burns to reduce the risk of infection is indicated.

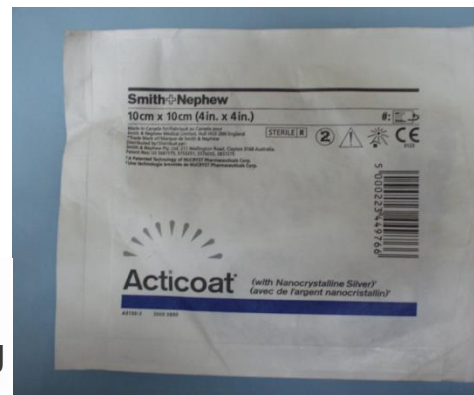
In recent year a range of dressings that contain or combine Silver into their structure have been released. They include

- ❖ High Density Polyethylene dressings [Acticoat]
- ❖ Foam Dressing [Acticoat Moisture Control, Mepilex Ag], Allevyn Ag
- ❖ Alginate Dressing [Acticoat Absorbent]
- ❖ Hydroactive Dressing [Biatain Ag]
- ❖ Hydrofibre Dressing [Aquacel Ag]
- ❖ Tulle Dressing [AtraumanAg]

New Silver Dressings



BIATAIN Ag



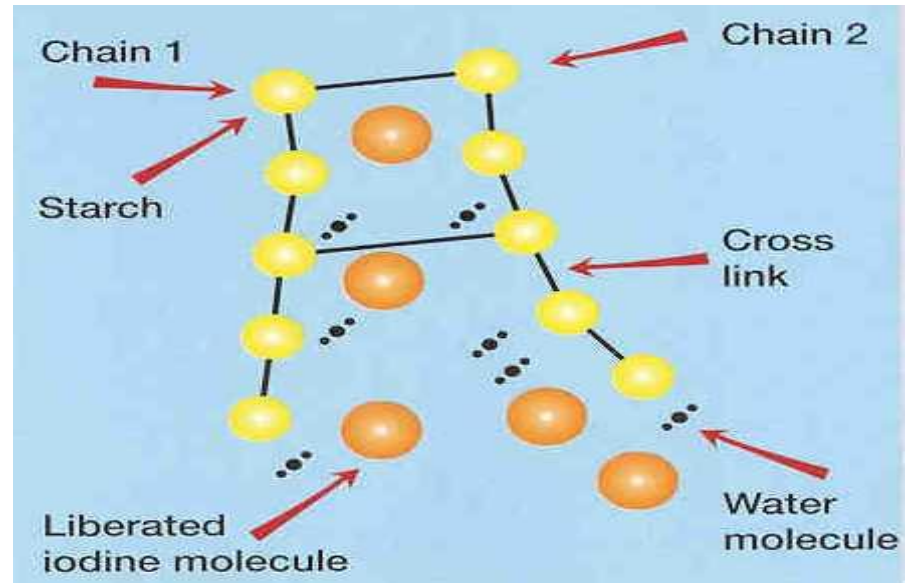
Common Antiseptics Iodine

- Iodine in its various forms has been used as a topical antiseptic since 1840.
- The newer forms of iodophores have been
- Used since the 1950's. Most of these new forms
- Combine Iodine in a complex with a polymer
- eg. Povidone, Cadexomer these slowly release the iodine.
- Iodine is active against bacteria, mycobacteria, fungi, protozoas and viruses. There is no evidence of resistance to Iodine.

When do we use it?

- Sloughy wounds with exudate
- “Smelly” wounds
- Recalcitrant wounds
- Diabetic wounds
- Cavities and superficial wounds
- Powder for very wet wounds
- Paste/flex for less exudate

Cadexomer Iodine



Honey positives

- High osmolarity
 - reduce oedema and maceration
 - unsuitable environment for bacterial growth
- low pH
 - inhibit cell growth
- Produces enzymes
 - may promote slough separation
- May reduce odour
- Inexpensive??
- Easily obtained
- Easy to apply
- May reduce pain
- Anti-inflammatory??

Honey negatives

- Infection not biggest problem in chronic wounds
- Doesn't address underlying causes
 - vascular problems
 - pressure, shear, etc
 - diabetes
- Anti-bacterial activity can vary by up to 100-fold from one batch to next
- Pain in some patients
- Hydrogen peroxide not recommended in wound care
 - Feeble antiseptic and may cause oxygen emboli
- May contain bacteria or spores if unsterilised
 - Inactive if heat sterilised

For more on honey, Dr Peter Molam's website is:

www.honey.bio.waikato.ac.nz

New Antiseptics

Prontosan® range is a ready to use solution containing Polyhexanide and Betaine for cleansing and moistening of wounds

Polyhexanide is a preservative that prevents bacterial growth ensuring the solution can be used for up to 8 weeks; and is proven non toxic with no skin irritation and can be used long term

Betaine is a surface active solution that penetrates difficult coatings and removes debris, bacteria powerfully yet gently

New Antiseptics

Flaminal

Flaminal is available as two hydrogels with a high alginate content which are promoted for the reduction of bacterial growth in wounds

Flaminal® hydrogels are based upon gelled alginate and not on other polymers

Flaminal® hydrogels use the enzymes glucose oxidase and lactoperoxidase to control the bioburden in a similar way to honey.

New Antiseptics

Flaminal

The lactoperoxidase binds specifically to receptors in the bacterial cell wall. Here it releases the captured oxygen radicals, which then penetrate the bacterial cell walls and help to destroy it.

Lactoperoxidase has no affinity for human cell membranes. There are no receptors with which it can bind. No harm is caused to the granulating cells that work to heal the wound.

No bacterial resistance to Flaminal ® has been reported

Flaminal

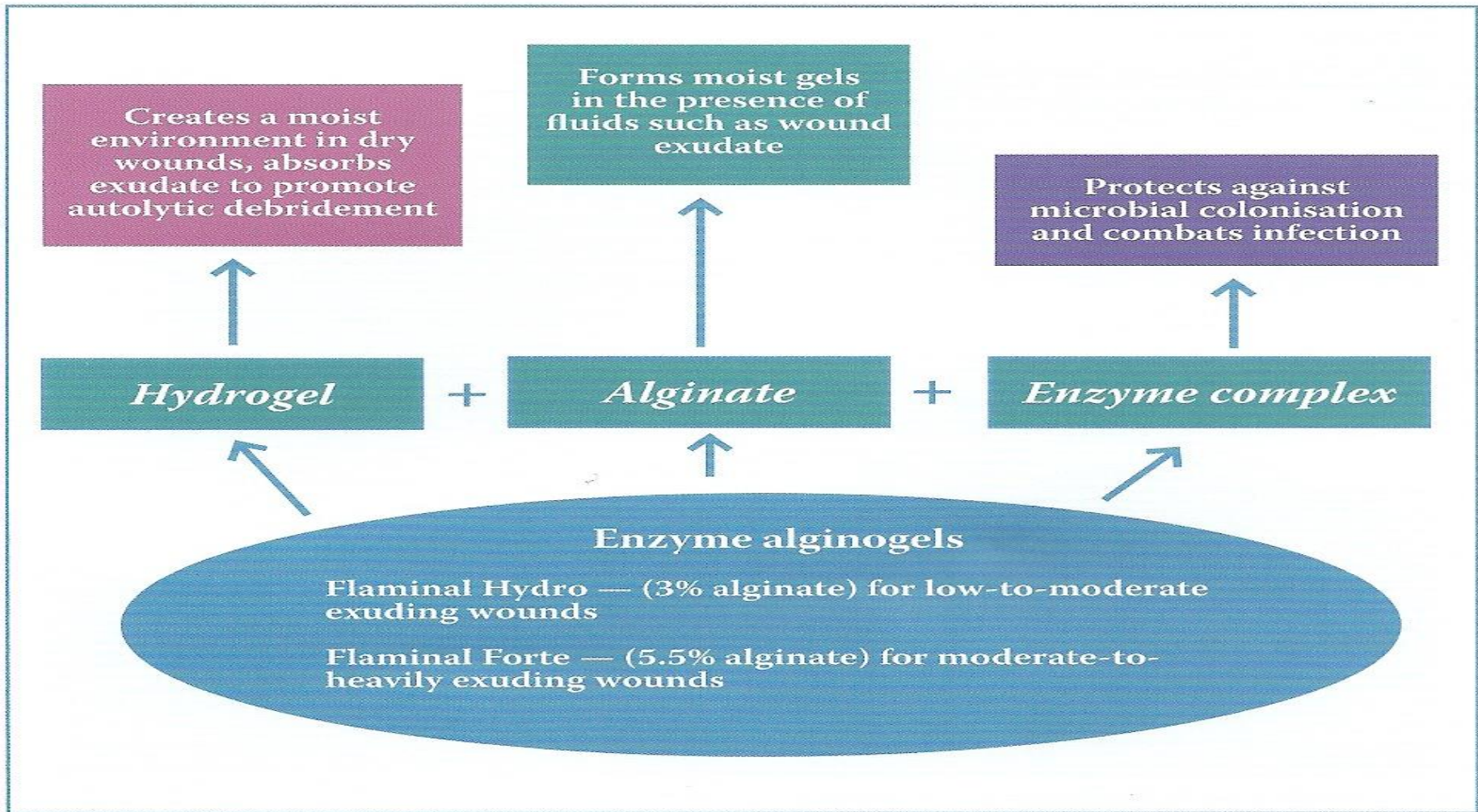


Figure 1: The components and mechanism of action of Flaminal (White, 2006).

Dialkylcarbamoylchloride coated Fibre

Selective binding of microorganisms

- Only bind pathogenic microorganisms

Instant action

- Binds bacteria and fungus within 15-30 seconds

High binding capacity

- Continues to bind, does not become saturated.

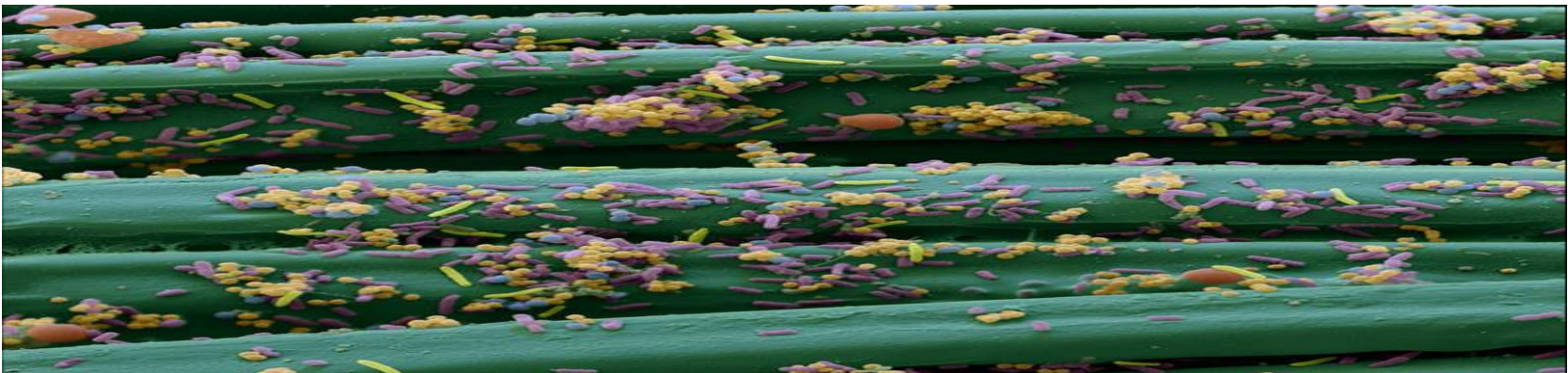
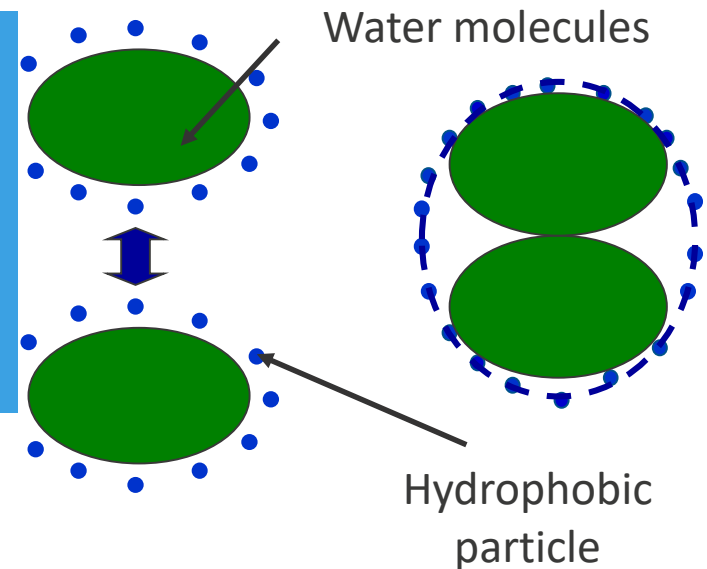
Natural process

- No risk of resistance
- No known side effects
- No negative environmental effects
- Fibre coated with dialkylcarbamoylchloride (commonly known as DACC)

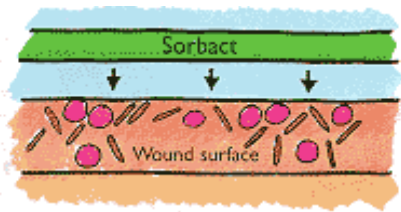
The Sorbact®-

Bacteria and fungus bind to surfaces via hydrophobic interaction.

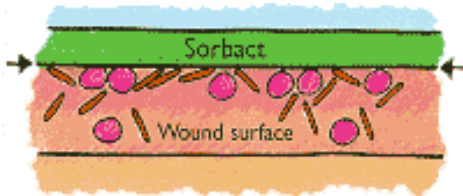
When two hydrophobic particles come in direct contact they bind together with the binding force of the surrounding water molecules = Hydrophobic interaction



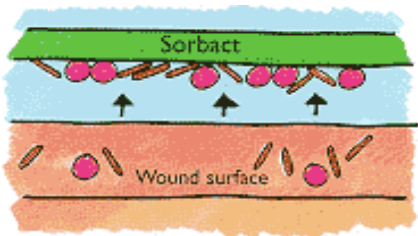
Sorbact uses the same binding process that bacteria and fungus use to bind to surfaces, hydrophobic interaction.



Sorbact applied **directly** on the wound surface.



Pathogenic microorganisms **bind** to the Sorbact surface and become **inactivated**.



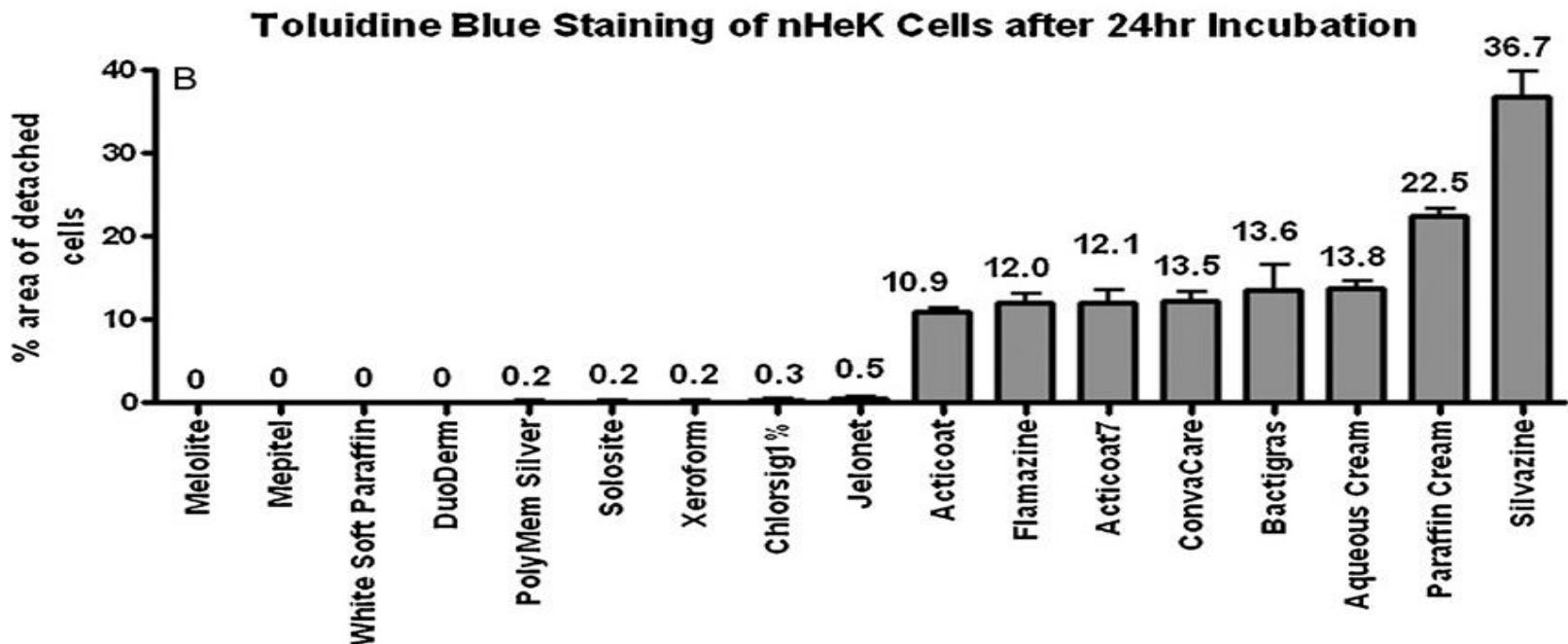
The bound microorganisms are **removed** when the dressing is changed.

Antiseptics with Limited Place in Therapy

- Many antiseptic cytotoxic effects outweigh antibacterial effects including:
 - Toxicity to fibroblasts
 - Occlude microcirculation
 - Retard collagen deposition
 - Oxygen embolus risk (peroxides)
 - Cause localised oedema, hypernatraemia, hyperthermia, burns (hypochlorites)
- Some are feeble antiseptics
- Includes: Hypochlorites, peroxides, phenolics, mercurochrome, pot permanganate

Tissue Toxicity

The most cytotoxic products included those which contained silver or Chlorhexidine & Paraffin Cream™ a moisturizer which contains the preservative Chlorocresol.



Margit Kempf *, Roy M. Kimble, Leila Cuttle Cytotoxicity testing of burn wound dressings, ointments and creams: A method using polycarbonate cell culture inserts on a cell culture system burns 37 (20 1 1) 9 9 4 – 1 0 0 0

Recommendations

CONTAMINATION

COLONIZED

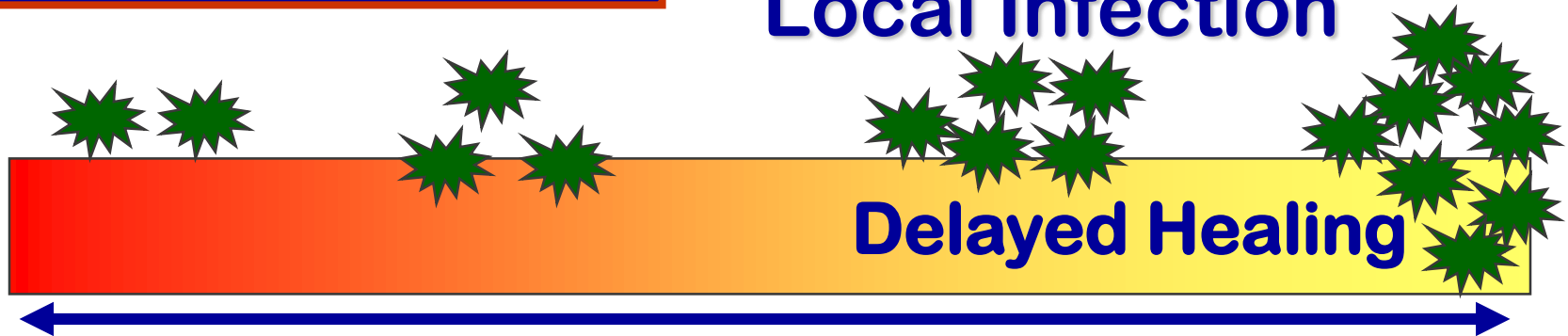


- Exudate management
- Routine wound cleansing

Recommendations

Local Infection

Local Infection

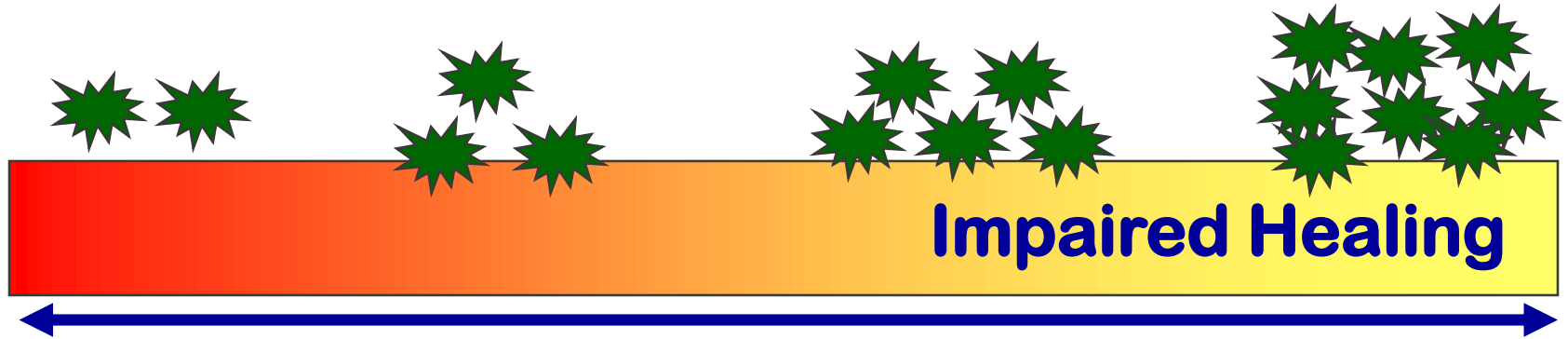


- Thorough cleansing
- Debridement
- Consider topical antimicrobials
 - Silver
 - Slow release cadexomer iodine
- Exudate management



Recommendations

Infection



Courtesy AAWC



- Thorough cleansing
- Debridement

• Systemic antibiotics

- Consider topical antimicrobials
 - Silver
 - Slow release cadexomer iodine
- Exudate management

Indications for Systemic Antibiotics

- Clinical indications
 - Local heat
 - Pyrexia
 - Erythema
 - Increased pain
 - Increased exudate
 - Frank pus
 - Lab tests – WCC, ESR, CRP, etc
- Confirmed/identified by
 - Microscopy
 - Culture
 - Serology

Antibiotic Facts

- Chemical compounds that either kill or inhibit growth of bacteria
(i.e. bactericidal or bacteriostatic)
 - Not viruses or fungi (There are specific antiviral and anti fungal drugs)
- Show selectivity only for certain bacteria
 - Spectrum of action varies from compound to compound
(This may be either Narrow or broad)

ANTIBIOTICS: MODES OF ACTIONS

- 1. Inhibition of cell wall synthesis**
eg. penicillins, cephalosporins, vancomycin, bacitracin, novobiocin
- 2. Inhibition of cell membrane function**
egs, polypeptides (polymyxin, colistin), tyrothricin, polyenes (amphotericin, nystatin), itra-, keto-, fluconazole, terbinafine, amorolfine
- 3. Inhibition of nucleic acid synthesis**
eg actinomycin, mitomycin, colicin, quinolones, griseofulvin, ethambutol, rifamides, isoniazid.
- 4. Inhibition by competitive inhibition**
egs, sulfonamides, para-aminosalicylate, dapsone, 5-flucytosine, nitrofurantoin
- 5. Inhibition of protein synthesis**
egs, chloramphenicol, tetracyclines, macrolides, lincosamides, aminoglycosides, linezolid.

Principles of Antibiotic Use

(From: Australian Antibiotic Guidelines)

- General
 - Used only where benefits scientifically demonstrable
 - Use narrowest spectrum agent to cover likely pathogen(s)
 - Single drugs used unless proven that combination therapy required
 - Dose high enough to ensure efficacy & minimise risk of resistance without toxicity
- Therapy
 - Therapy based on culture (directed therapy) or known common pathogens & their resistance patterns (empirical therapy)
 - Duration as short as possible (not >7days unless proof that extended therapy needed)
- Prophylaxis
 - Choice based on known or likely target pathogens
 - Duration as short as possible

Topical Wound Management

Antibacterials may be used topically with care

They include:

➤ Antibiotics

➤ Antiseptics

Topical Antibiotics

Topical antibiotics should only be used in infected wounds under very specific circumstances by experienced clinicians

Topical metronidazole gel might be used for the treatment of malodour in fungating wounds

Silver Sulphadiazine in burns and in wounds

Mupiricin a specific topical antibiotic with no similar Compounds used systemically or orally

Topical Antibiotics

Chloramphenicol ophthalmic ointment is widely used by plastic surgeons as topical surgical prophylaxis post-operatively.

Application of a single dose of topical chloramphenicol to high risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate that is statistically but not clinically significant.

A theoretical but as yet not conclusively proved risk of chloramphenicol induced idiosyncratic aplastic anaemia exists with topical ophthalmic therapy, UK in the past 10 years, 11 reports (all non-fatal) of suspected topical chloramphenicol induced blood dyscrasia have been reported

BMJ 2009;338:a2812

Topical Antibiotics

- Don't penetrate tissue
- Decompose in contact with tissue
- Diluted by exudate and decomposition
- Inhibition of contraction
- Delay re-epithelialisation
- Can cause sensitization
- Induce Resistance
- Mostly formulated to be applied to skin (or elsewhere) and act locally, not for exposed tissue

The overall evidence on the efficacy of topical antimicrobials in the management of wounds is confusing.

Most use is based on laboratory studies and not on clinical research.

Some of the research use animal models and there is debate as to how relevant these studies are to chronic wounds.

What is the greatest risk to the world today Climate Change ?






What is the greatest risk to the world today

No

**it is Antibiotic
Resistance**



In its recent annual report on global risks, the World Economic Forum concluded that “arguably the greatest risk . . . to human Health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. Antibiotic resistance and the collapse of the antibiotic research and- development pipeline Continue to worsen despite our ongoing efforts on all these fronts.

n engl j med 368;4 nejm.300 org january 24, 2013

Antimicrobial resistance kills

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death.

As an example, the death rate for patients with serious infections caused by common bacteria treated in hospitals can be about twice that of patients with infections caused by the same non-resistant bacteria. MRSA (methicillin-resistant *Staphylococcus aureus*, in the community and in hospitals) are estimated to be 64% more likely to die than people with a non-resistant form of the infection.

Present situation Resistance in bacteria

WHO's 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill.

Lack of New Antibiotics

In 2017, antibiotic development continues to stagnate. Two systemic antibacterial agents have been approved for use in humans by the U.S. FDA from 2008 through the current year. Compare that to sixteen that were approved from 1983-1987. In particular, we have had no new classes of antibiotics to treat Gram-negative bacilli for more than 40 years – amazingly, the fluoroquinolones were the last new class of antibiotics to treat Gram-negative bacilli. Meanwhile, antibiotic resistance continues to spread like wildfire, particularly among the Gram-negative bacilli. It was reported in the last few weeks of the death in the US of a woman with untreatable gram neg infection resistant to all classes of antibiotics.

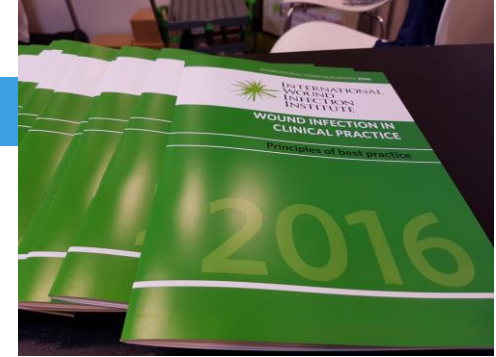


Lack of New Antibiotics

MONASH University

Antibiotic class; example	Year of discovery	Year of introduction	Year resistance observed	Mechanism of action	Activity or target species
Sulfadruugs; prontosil	1932	1936	1942	Inhibition of dihydropteroate synthetase	Gram-positive bacteria
β -lactams; penicillin	1928	1938	1945	Inhibition of cell wall biosynthesis	Broad-spectrum activity
Aminoglycosides; streptomycin	1943	1946	1946	Binding of 30S ribosomal subunit	Broad-spectrum activity
Chloramphenicols; chloramphenicol	1946	1948	1950	Binding of 50S ribosomal subunit	Broad-spectrum activity
Macrolides; erythromycin	1948	1951	1955	Binding of 50S ribosomal subunit	Broad-spectrum activity
Tetracyclines; chlortetracycline	1944	1952	1950	Binding of 30S ribosomal subunit	Broad-spectrum activity
Rifamycins; rifampicin	1957	1958	1962	Binding of RNA polymerase β -subunit	Gram-positive bacteria
Glycopeptides; vancomycin	1953	1958	1960	Inhibition of cell wall biosynthesis	Gram-positive bacteria
Quinolones; ciprofloxacin	1961	1968	1968	Inhibition of DNA synthesis	Broad-spectrum activity
Streptogramins; streptogramin B	1963	1998	1964	Binding of 50S ribosomal subunit	Gram-positive bacteria
Oxazolidinones; linezolid	1955	2000	2001	Binding of 50S ribosomal subunit	Gram-positive bacteria
Lipopeptides; daptomycin	1986	2003	1987	Depolarization of cell membrane	Gram-positive bacteria
Fidaxomicin (targeting <i>Clostridium difficile</i>)	1948	2011	1977	Inhibition of RNA polymerase	Gram-positive bacteria
Diarylquinolines; bedaquiline	1997	2012	2006	Inhibition of F_1F_o -ATPase	Narrow-spectrum activity (<i>Mycobacterium tuberculosis</i>)

Future Development



- Antibiotic sparing therapies
- Antimicrobial peptides (AMP's) such as talactoferrin or pexiganan
- Bacteriophage therapy (long time use in Eastern Europe and Russia)
- Targeted monoclonal antibiotics
- Antibody-antibiotic conjugates
- Nanoparticles to deliver targeted therapy
- Photodynamic therapy
- Drugs to interrupt quorum sensing

Antibiotic Stewardship

- The CDC estimates that half of antibiotic use is unnecessary. Stewardship programs should be developed and used to optimize the use of antibiotics. Although this is currently happening, the CDC calls for acceleration in the implementation of these efforts.
- Until recently, there has been a steady pipeline of antibiotics entering the marketplace. Unfortunately, at this point, new drugs may be a decade away.
- The report includes descriptions of bacteria that cause human infections, as well as the antibiotics that are used to treat the infections. It does not include viral infections such as HIV and influenza or parasitic infections such as malaria.

Antibiotic Resistance Threats in the United States, 2013. CDC. Published online September 16, 2013.

Wound Specific Diabetes and Infection

Infection of foot ulcers is a common, often severe and costly complication in diabetes. Many factors linked to the host, mainly immune defects, neuropathy and arteriopathy, as well as bacteria-related factors, interact in a complex way and account for the susceptibility of diabetic individuals to foot infections, the severity of such infections and difficulty to treat them.

Wound Specific Diabetes and Infection

Due to the frequent infections or recurrences, the diabetic patients have more exposure to antibacterial agents. Immunocompromised state and frequent antibiotic use are associated with antibiotic resistance of the causative agents of the infections in these patients, such as methicillin-resistant *Staphylococcus aureus* , *Streptococcus pneumoniae* , Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* , bacteria in diabetic foot infections, and involvement of different opportunistic and rare pathogens or multidrug-resistant strains in the infections.

Wound Specific Diabetes and Infection

A study was aimed to know the bacteriological and resistance profile of isolates obtained from diabetic patients

In all, 38 of 125 diabetic patients (30.4%) had bacterial infection *Escherichia coli* among gram-negative bacteria and *Staphylococcus aureus* among gram-positive bacteria were the predominant pathogens. Methicillin resistance was found in 50%.

Resistant bacterial infections in diabetic patients are common.

N Am J Med Sci v4(11) 2012 Nov Bacteriological and Resistance Profile in Isolates from Diabetic Patients

Can You Make a Difference Yes we can

Ulcer healing time and antibiotic treatment before and after the introduction of the Registry of Ulcer Treatment: an improvement project in a national quality registry in Sweden. Rut F Öien, Henrik W Forssell <http://bmjopen.bmj.com/> on April 28, 2015

This study investigated changes in ulcer healing time and antibiotic treatment in Sweden following the introduction of the Registry of Ulcer Treatment (RUT), a national quality registry, in 2009.

According to the adjusted registry in December 2012, patients' median age was 80 years (mean 77.5 years, range 11–103 years). The median healing time for all ulcers, adjusted for ulcer size, was 146 days (21 weeks) in 2009 and 63 days (9 weeks) in 2012 ($p=0.001$). Considering all years between 2009 and 2012, antibiotic treatment for patients with hard-to-heal ulcers was reduced from 71% before registration to 29% after registration of ulcer healing ($p=0.001$).

Conclusions: Healing time and antibiotic treatment decreased significantly during 3 years after launch of RUT

Prudent Use to ↓ Resistance

- Use antibiotics only when necessary
- Select agent with narrow spectrum
- Reserve broad spectrum agents for more resistant bacteria
- Continue for an “appropriate” duration
- Avoid chronic prophylaxis if possible
- Policy (guidelines, formulary, restrictions)
- Monitor trends in microbial sensitivity
- Pharmacokinetic/Pharmacodynamic Optimisation
- Cycling of antibiotics

Long-term strategies to reduce the burden of antibiotic resistance

- Establish a central database of national antimicrobial use
- Restrict agricultural use of antibiotic classes used in human medicine
- Prevent nosocomial infections using a systematic implementation plan
- Strong advocacy and implementation of antimicrobial stewardship
- Improve microbiological diagnostics, including rapid testing
- Reduce legislative barriers to drug development
- Facilitate public–private partnerships to help bring new drugs to market

Ten top tips to reduce Antibiotic Resistance

1. Develop new treatments almost 20 years, no new classes of antibiotics have been discovered
2. Provide education to prescribers and consumers on the benefits of judicious use of antimicrobial agents in wound care
3. Develop faster methods of identifying wound infection New and rapid methods are required to accurately identify infection
4. Use conservation programmes to address inappropriate use of antimicrobials
5. Develop and follow policy Controlling antibiotic resistance requires a multi-pronged approach

Sussman G Ten top tips: reducing antibiotic resistance Wounds International
2014 | Vol 5 Issue 4 |4-8

Ten top tips to reduce Antibiotic Resistance

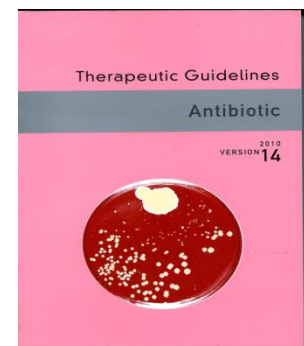
6. Ensure facility cleaning and waste storage recommendations regarding cleaning of facilities where patient care is provided
7. Adopt management strategies for infected wounds All wound care must be performed using a high standard of infection control and prevention principles
8. Use risk assessment and management Managing risk must be a global response to the issue of antibiotic resistance
9. Employ wound cleansing
10. Improve population health and healthcare systems One of the most important methods of reducing antibiotic use and thereby resistance is by improving the general health of the population to reduce their need for hospitalisation

Sussman G Ten top tips: reducing antibiotic resistance Wounds International
2014 | Vol 5 Issue 4 |4-8

Use Therapeutic Guidelines: Antibiotic when prescribing antimicrobials

- Local guidelines should take into account recommendations in Therapeutic Guidelines: Antibiotic and also reflect local antimicrobial susceptibilities
- Consult the best available evidence and specialist clinicians for guidance on the management of infections not covered by guidelines
- Ensure guidelines are readily accessible wherever antimicrobials are prescribed

AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE



Systematic Approach for Use of Antimicrobials

Confirm the presence of infection



Identification of the pathogen



Selection of therapy



Monitor therapeutic response

THE ANTIBIOTIC CREED

(Antibiotic Guidelines 14th edition 2010)

M I N D M E

Microbiology guides therapy whenever possible

Indications should be evidence-based

Narrowest spectrum required

Dosage appropriate to site & type of infection

Minimise duration of therapy

Ensure monotherapy in most situations

Conclusion

Despite the use of many other antimicrobials in a wide range of situations evidence supporting their efficacy in the treatment of wound infection is more limited. Clinicians will use newer products however it is important that further good clinical research to be undertaken and published to validate their use in wound management

Conclusion

Infection will continue to be a problem with wounds
Complicating the issue is the increased resistance
to Antibiotics and the lack of development of new
Antibiotics. Antiseptics play an important role in
Reducing bioburden and as an antimicrobial barrier.
It is essential to understand when they are
appropriate and how best and how long to use them.