



Dr Richard Everts

Infectious Disease Specialist

Microbiologist and General Physician, Nelson

Friday, August 12, 2016

(Room 3)

16:30 - 17:25 WS #50: Topical Antiseptics & Managing Cough in Primary Care

17:35 - 18:30 WS #60: Topical Antiseptics & Managing Cough in Primary Care (Repeated)

Topical Antiseptics in Primary Care



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Infectious Disease Specialist and Microbiologist
Nelson Bays Primary Health
NZ South GP Meeting 12 August 2016

Conflicts of interest

- I got some free samples of Microdacyn

Topical antimicrobial agents

Antibiotics

- e.g. *mupirocin, fusidic acid, neomycin*
- One mechanism
- Kill only bacteria; narrow spectrum
- Resistance and cross-resistance
- Some used systemically
- Higher risk of allergy.

Antiseptics

- e.g. *iodine, alcohol, chlorhexidine*
- Multiple mechanisms
- Broad spectrum
- Rare resistance
- Too toxic to human cells for systemic use
- Occasional allergy.

Topical antibiotics in NZ 2016

Drug name	Trade names	Parenteral form	Spectrum	
Mupirocin	Bactroban	-	GPC	
Fusidic acid	Foban	Fusidic acid	GPC	
Gramicidin	Viaderm KC, Sofradex, Kenacomb	-	GPC	
Clindamycin	ClindaTech, Duac (with benz perox)	Clindamycin	GPC	
Neomycin	Viaderm KC, Pumifucort, Kenacomb, Maxitrol	Gentamicin		GNB
Framycetin	Soframycin, Sofradex	Gentamicin		GNB
Ciprofloxacin	Ciproxen HC	Ciprofloxacin	+/- GPC	GNB
Clioquinol	Locorten-Vioform	-	GPC	GNB
Sulfadiazine	Flamazine (with silver)	Cotrimoxazole	GPC	GNB
Chloramphenicol	Minims Chloramphenicol, Chlorafast, Chlorsig	Chloramphenicol	GPC	GNB
Metronidazole	Rosex, Metronidazole	Metronidazole	Anaerobes	

Mupirocin 2% (Bactroban®)



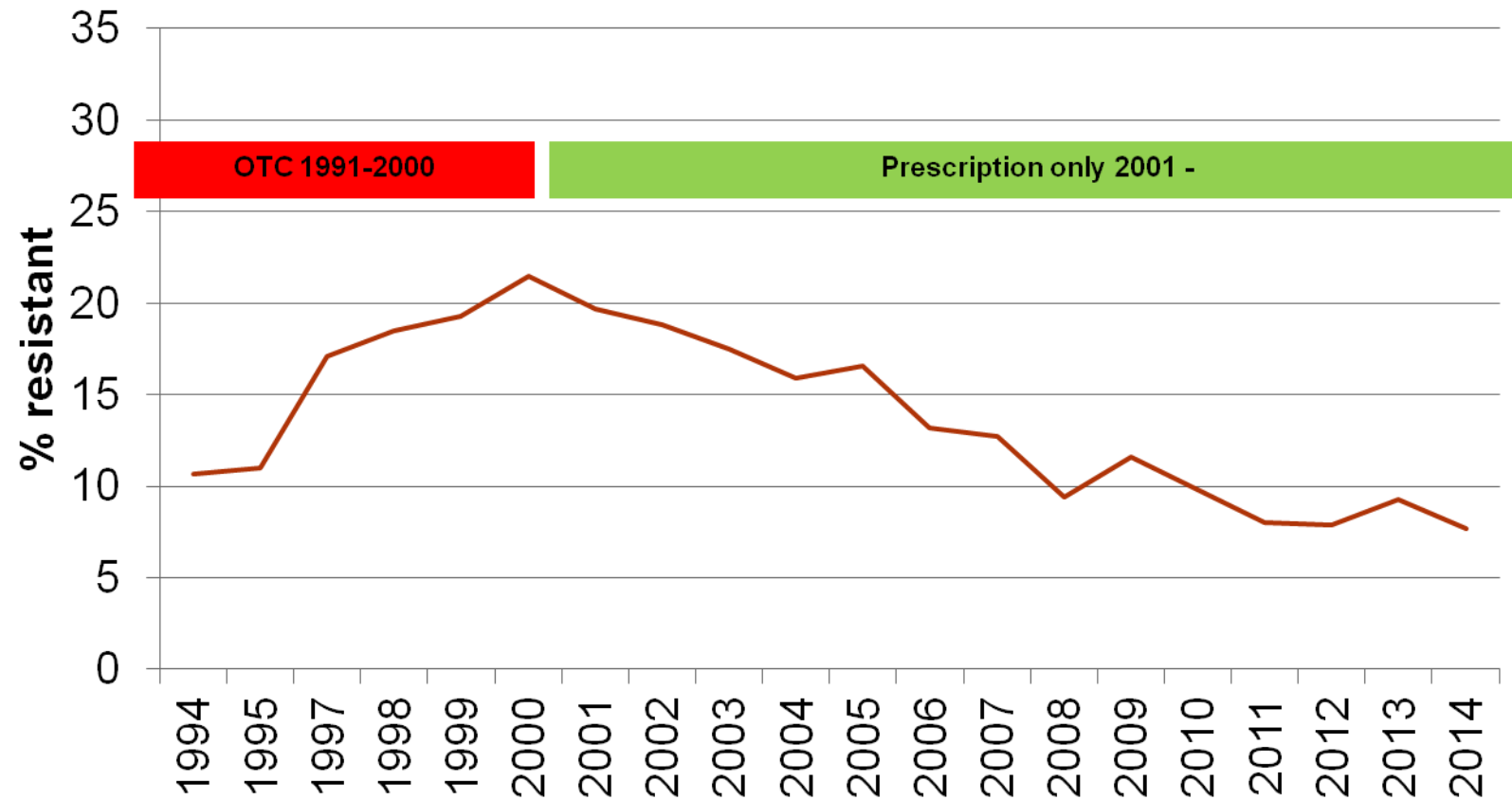
- From *Pseudomonas fluorescens*
- Active for *Staphylococcus aureus*, β -haem strep
- Effective:
 - Impetigo and other minor skin infections
 - Nasal *Staph. aureus* decolonisation
- Resistance – develops easily
 - MRSA outbreak Canadian hospital $\rightarrow$ mupirocin ++ $\rightarrow$ MRSA resistance 2.7% in 1990, 65% in 1993.
 - 2 hospitals in Brazil. One used mupirocin ++ vs one not $\rightarrow$ *S. aureus* mupirocin resistance 61% vs 6%.

ICHE 1996; 17(12): 811-3

ICHE 1996; 17(12): 813-6

Mupirocin resistance in NZ

Community + Hospital *Staphylococcus aureus*



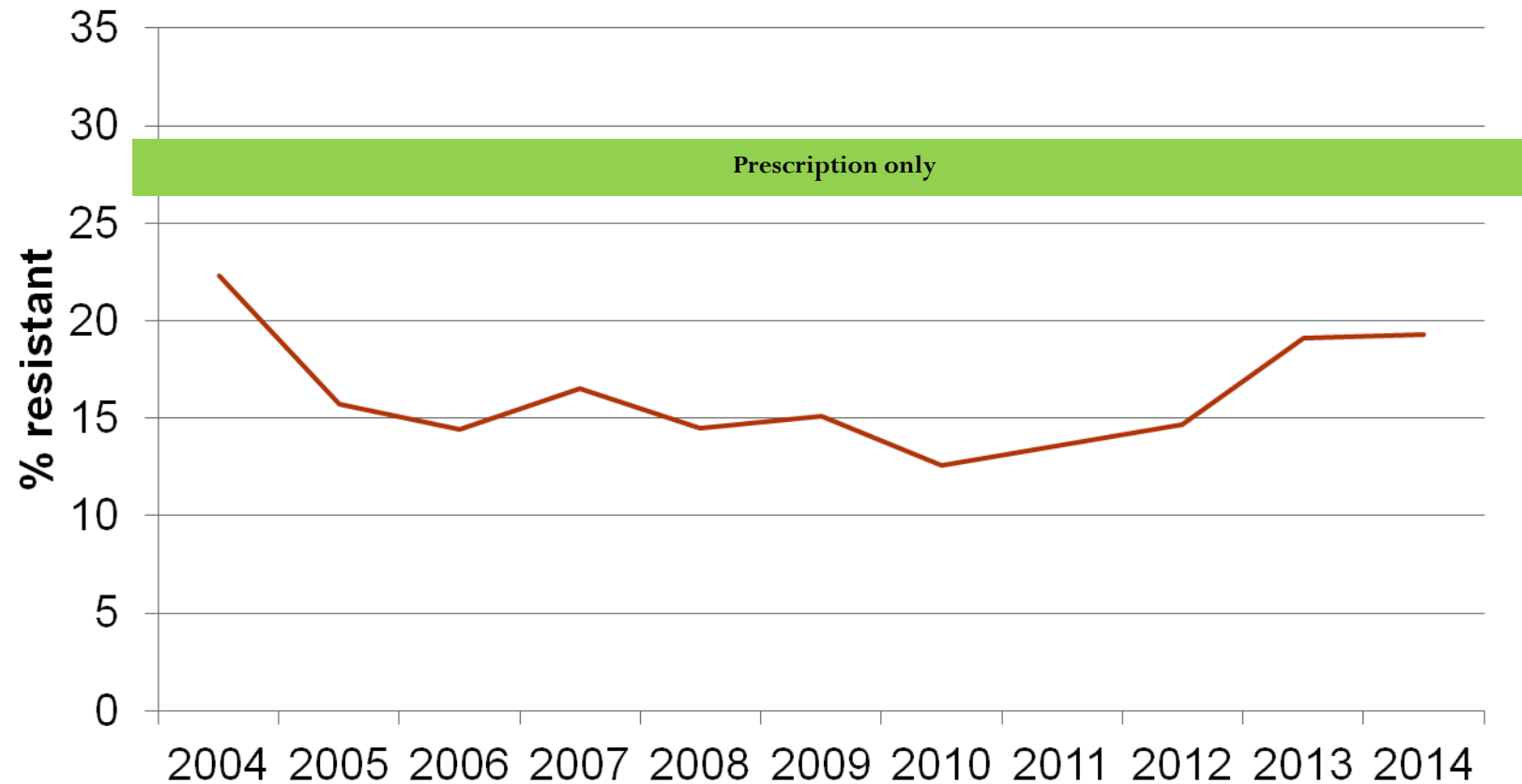
Fusidic acid (Foban®)



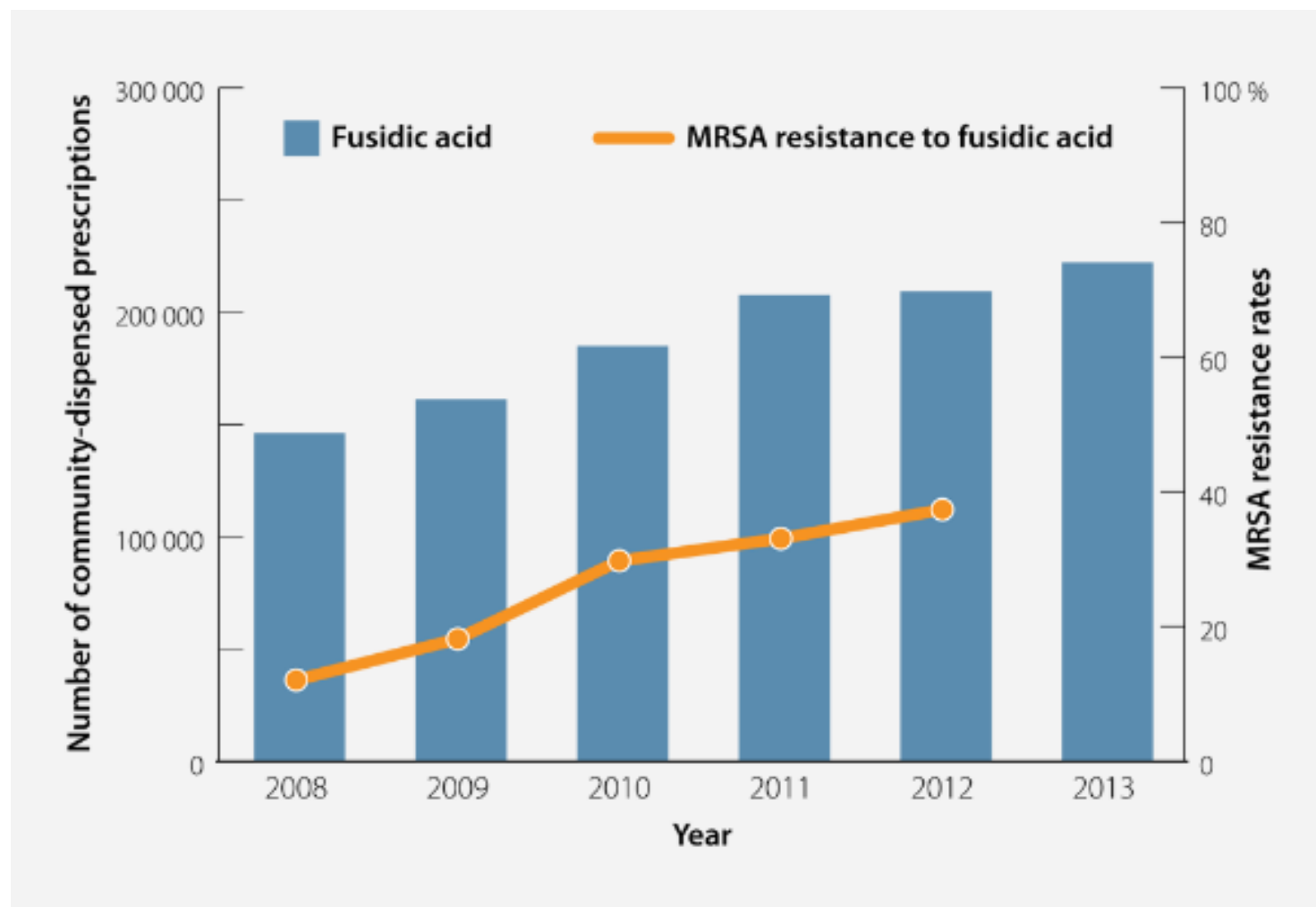
- From *Fusidium coccineum*
- Active for *Staphylococcus aureus*, streptococci
- Effective:
 - Impetigo and other minor skin infections
 - Orally (+ rifampicin) for MRSA infections
- Resistance
 - Commonly develops during course of treatment.

Fusidic acid resistance in NZ

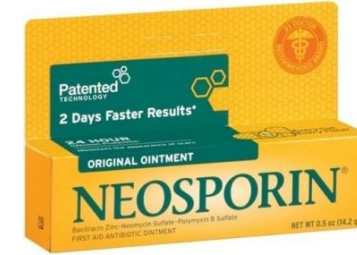
Community + Hospital *Staphylococcus aureus*



Fusidic acid resistance in NZ



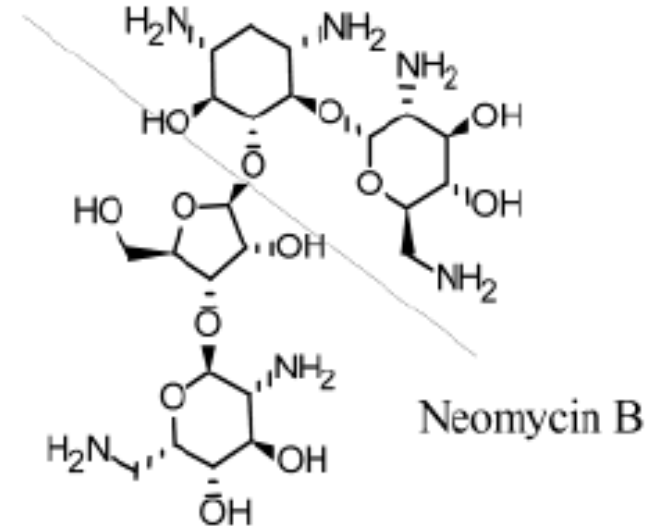
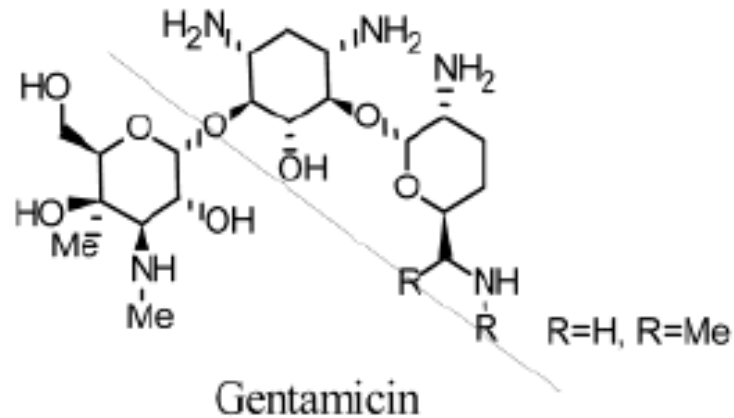
Neomycin



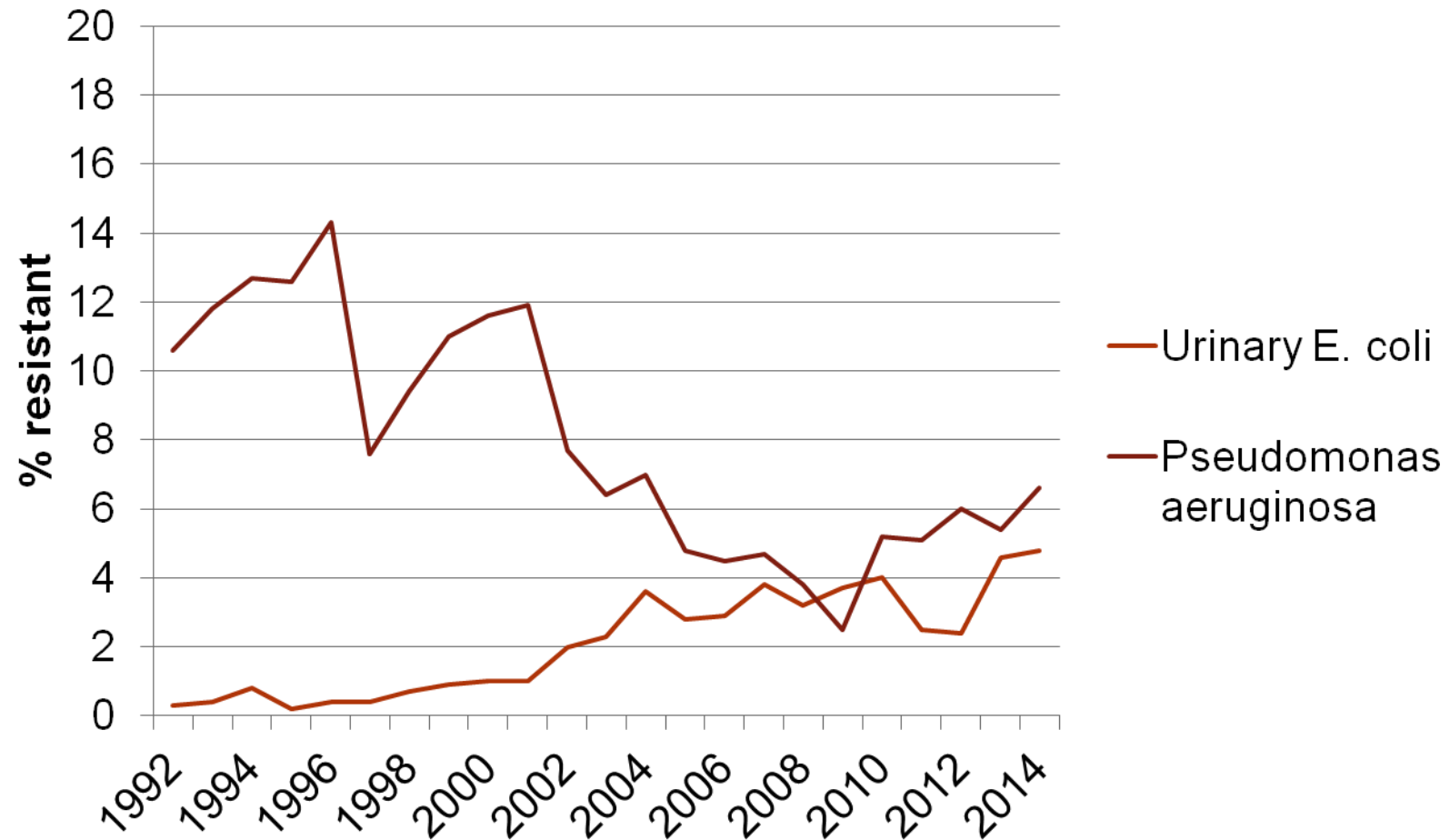
- From *Streptomyces fradiae*
- Active for gram-negative bacilli >> GPC
- Effective:
 - Non-absorbed oral drug – used for liver failure
 - In combination topical preparations:
 - (Neosporin[®]/Triple AB[®]/Mycitracin[®] = neomycin + bacitracin + polymyxin B – no longer available in NZ)
 - Viaderm KC = neomycin + gramacidin + nystatin + triamcinolone
 - Pumifucort = neomycin + natamycin + hydrocortisone
 - Kenacomb ear drops = neomycin + gramacidin + nystatin + triamcinolone
 - Maxitrol eye drops = neomycin + polymyxin B + dexameth.

Neomycin

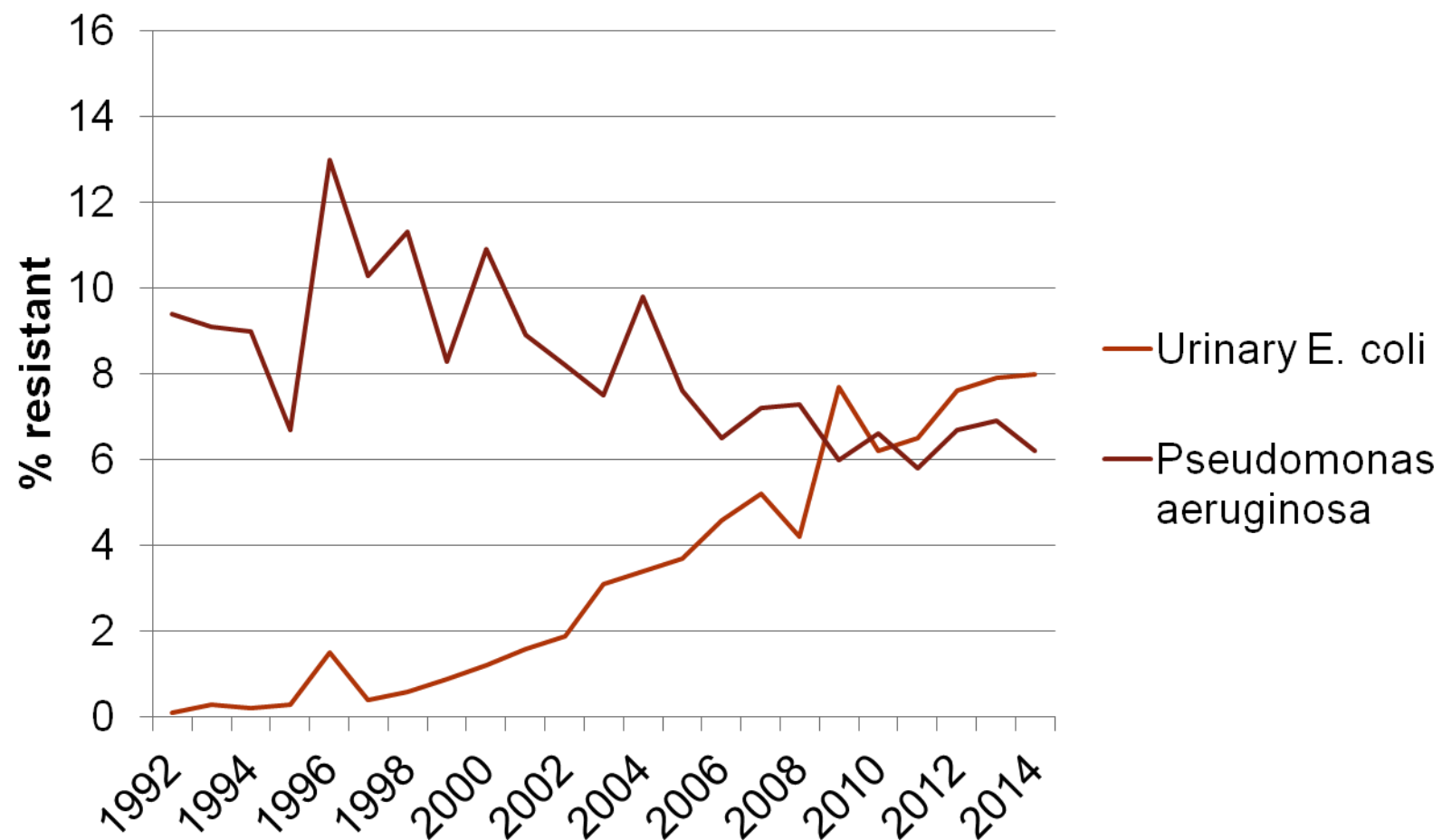
- Allergic contact dermatitis - 7.2 to 13.1%
- Cross-resistance with gentamicin, tobramycin



Gentamicin resistance in NZ

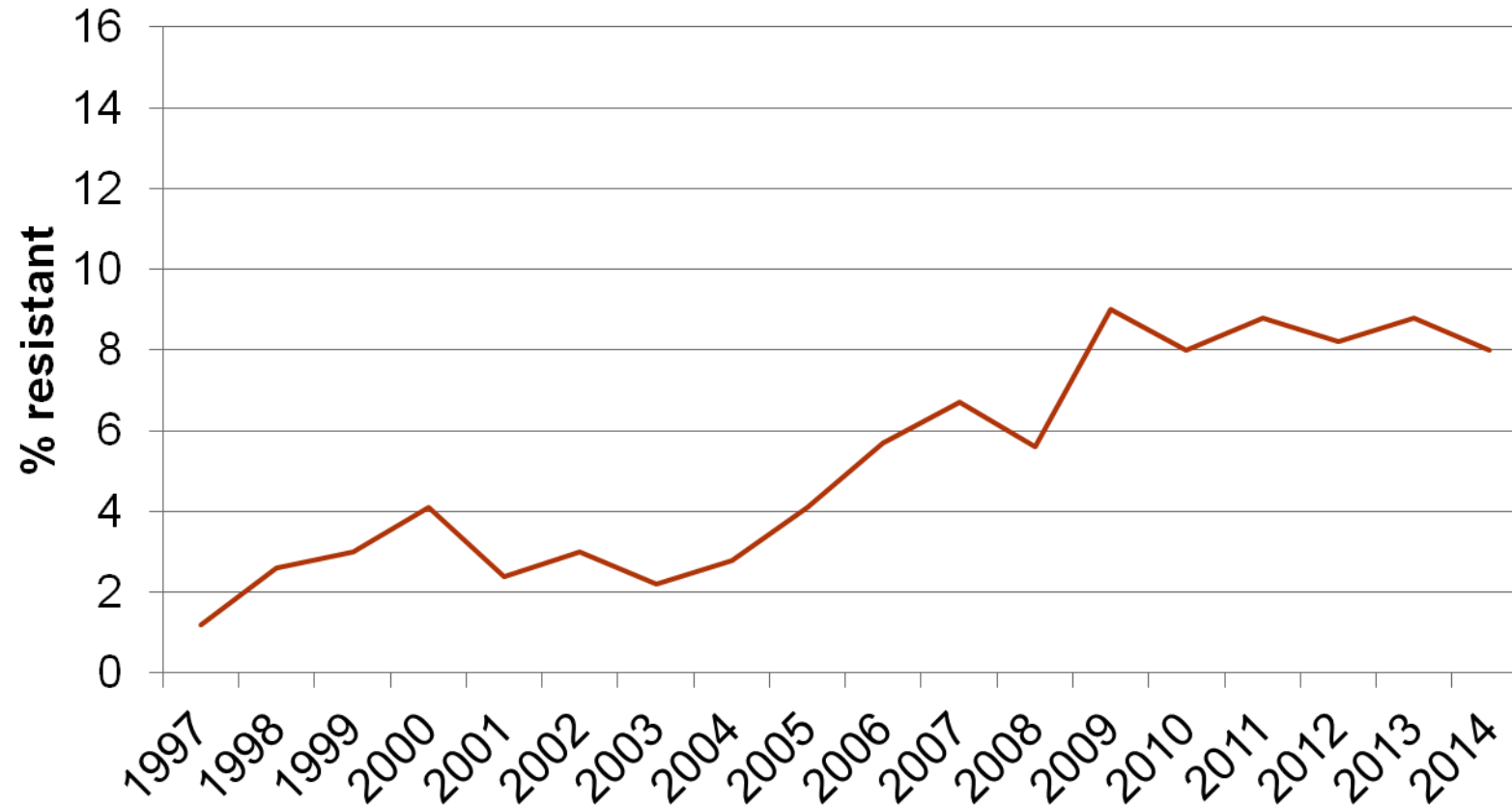


Ciprofloxacin resistance in NZ



Clindamycin resistance in NZ

Staphylococcus aureus



Topical antibiotics

Effective, but....



Allergies ++ Resistance and cross resistance ++

Topical antiseptics

Chemical	Trade names	Spectrum		
Ethanol		GPC	GNB	V ⁺ /- norovirus, F
Hydrogen peroxide (and BP)	Crystaderm	GPC	GNB	V, F, spores
Povidone iodine	Betadine	GPC	GNB	V, F, +/- spores
Chlorhexidine	Savlon (Ch + cetrimide)	GPC*	Most GNB	+/- V, +/- F * recent C-R SA
Sodium hypochlorite	(Bleach)	GPC	GNB	V, F, spores
Super-oxidising solutions	Microdacyn	GPC	GNB	V, F, spores
Triclosan	Triclosan	GPC	< GNB	+/- F
Acetic acid	(Vinegar)		GNB	
Benzalkonium	Bepanthen	GPC	Most GNB	+/- V, +/- F
Chloroxylenol	PCMX, Dettol	GPC	Most GNR	Not Pseudo, +/- V
Honey	(raw, in dressings)	GPC	GNB	F
Manuka oil		GPC	-	+/- F
Silver	(in dressings)	GPC	GNB	+/- F

Ethanol 60-90%



- Kills everything
 - Not great for norovirus, does not kill spores
 - No risk resistance
- Effective:
 - Hand sanitiser
 - Pre-procedure skin prep
- Toxicity
 - Drying of skin
 - Not for broken skin.

Method	↓ bacteria to...
Wash ordinary soap - 15 seconds - 4 minutes	1 in 10 1 in 10,000
Wash chlorhexidine soap	1 in 1,300
Alcohol-based sanitiser	1 in 6,300-630,000

Iodine



- The most studied antiseptic
- Kills all bacteria, no resistance after > 100 years
- Long effect (12-14 hours)
- Effective:
 - Pre-op skin scrub, acute injuries, *Staph. aureus* decolonisation, chronic ulcers and wounds
- Toxicity
 - Allergy – low (0.73%)
 - Staining skin, clothes, sheets
 - Hypothyroidism in very low birth-weight infants
 - ?? Adverse effect on wound healing.

1960s-90s

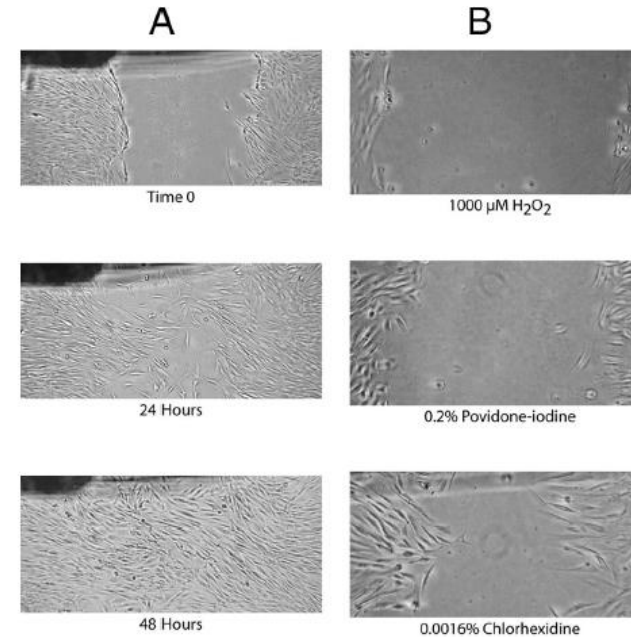
Topical antiseptics reduce wound infection

				Saline: $\uparrow 3.4 \times 10^4$
Roberts	J Hand Surg Brit 1985	Hand or finger laceration	152/170	Pov-iodine: 4.6% Control: 5.3%
Morgan	Brit J Clin Pract 1979 and Lancet 1978	Lacerations	166/154	Pov-iodine: 6% Control: 14.3%
Langford	Ann Pharmacoth 1997	Children, trauma	177 total	Cetrimide, bacitracin, polymyxin B: 1.6% Control: 12.5%
Naunton-Morgan	Injury 1980	Hands	91/105	Pov-iodine: 6.6% Control: 19%
Naunton-Morgan	Injury 1980	Non-hand locations	150/179	Pov-iodine: 4.7% Control: 12.8%
Gravett	Ann Emerg Med 1987	Acute lacerations in ED	201/194	Pov-iodine: 5.5% Control: 15.5%
Bickerstaff	J Royal Coll Surg Edin 1984	Lacerations – hands	108/127	Pov-iodine: 6.5% Control: 10.2%
Bickerstaff	J Royal Coll Surg Edin 1984	Lacerations – non-hand locations	245/300	Pov-iodine: 5.3% Control: 7.7%
Gosnold	Practitioner 1979	Lacerations in ED	120/122	Pov-iodine: 2.5% Control: 9.8%
Dire	Ann Emerg Med 1990	Acute sutured wounds in ED	531 total	Pov-iodine: 4.3% 'Pleurolon': 5.6% Saline: 6.9%
Maddox	J Am Acad Derm 1985	Minor skin trauma		Bacitracin+Polysporin+neomycin: 15% Placebo: 47%
Dire, Coppola	Acad Emerg Med 1995	Lacerations in ED	465 total	Poly B+neom+bacitr: 4.5% Bacitracin: 5.5% Silver sulfadiazine: 12.1% Petrolatum: 17.6%
Caro, Reynolds	Brit J Clin Pract 1967	Superficial wounds	432 total	Neomycin+bacitracin+polymyxin B: 9.1% Control: 11.4%
Lindsey	J Trauma 1982	Suture repair in ED	260 total	Penicillin soln: 10% Control: 31%



2000-2010

Topical antiseptics damage fibroblasts, keratinocytes, lymphocytes *in-vitro*



‘Don’t put in your wound
what you wouldn’t put in your eye!’

In-vitro toxicity of antiseptics

- Higher conc → worse *in-vitro* cytotoxicity
 - PI and NaClO low conc kill bacteria without fibroblast toxicity Lineaweaver 1985, Hidalgo 2002.
- Not all antiseptics are equally toxic *in-vitro*
 - Silver, SOS best, chlorhexidine OK, PI worst Le Duc 2007
 - H₂O₂ and PI worse than silver and chlorhex Thomas 2009
 - Best antibacterial to toxicity ratio is chlorhexidine, then PI, then benzalkonium, then triclosan, and silver worst Muller 2008.
- Does it matter *in-vivo*?
 - 27 RCTs of PI versus a comparator in chronic ulcers and wounds showed no delay in wound healing Vermeulen 2010.

Microdacyn®

- Topical antiseptic, in NZ since 2015.
- Rapid and potent microbicide (bacteria - $> 5 \log_{10}$ in 30 sec, viruses, fungi, spores).
- Mechanism:
 - Hypo-osmolar
 - Reactive oxygen species (super-oxidised solution)
 - Hypochlorous acid (HOCl), sodium hypochlorite (NaClO)
- No resistance.
- Breaks down biofilms and kills bacteria within biofilms.



Microdacyn[®] comparative trials

Condition	Design	Comparator	N=	Outcome for Microdacyn group	Stats	Ref
DFS	Non-R	Pov-iodine	218	Faster healing ↓ infection	< 0.001	Dalla Paola 2006
Post-op DFS	Non-R	Pov-iodine	33	Faster healing, ↓ antibiotics	< 0.01	Goretti 2007
Chronic wounds	RCT	Pov-iodine	40	↓ symptoms/signs of infection, ↓ days hospital	?	Ricci 2007
DFS	RCT	Pov-iodine	45	Faster healing, ↓ odour	?	Martinez-De Jesus 2007
Diab ulcers	RCT	Saline	100	Faster healing, ↓ bacteria	0.05	Suri 2008
Chronic wounds	Non-R	Pov-iodine	30	Faster healing	0.0045	Abhyanker 2009
Post-op DFS	RCT	Pov-iodine	40	Faster healing, ↓ antibiotic, ↓ re-operation	< 0.01	Piaggese 2010
Sternotomy wounds	RCT	Pov-iodine	190	↓ infection	0.033	Mohd 2010
Various wounds	Non-R	Pov-iodine	200	Faster healing, ↓ inflammation	?	Kapur 2011
Post-op wounds	RCT	Pov-iodine	100	Faster healing, ↓ infection	< 0.0005	Pandey 2011
Mild DFS	RCT	Levofloxacin	67	Faster healing	NS	Landsman 2011
Infected traumatic wounds	RCT	Pov-iodine	60	Fewer symptoms and signs of infection	< 0.004	Mekkawy 2014
DFS	RCT	Pov-iodine	60	Faster healing	0.024	Prabhaker 2016

Microdacyn®

- Free active chlorine sub-toxic
- Little to no measurable cytotoxicity in *in-vitro* fibroblast cytotoxicity study or in a skin graft model.

Int JWound J 2007; 4(3):241

Brit J Derm 2007

- No toxicity in any trial performed so far.
- Non-staining and non-volatile.
- Relatively cheap.
- Not poisonous if ingested.



No effect on fibroblast migration

- HOCl solution = 218 ppm (M = 20 ppm)

Wounds 2014; 26(12): 342-50

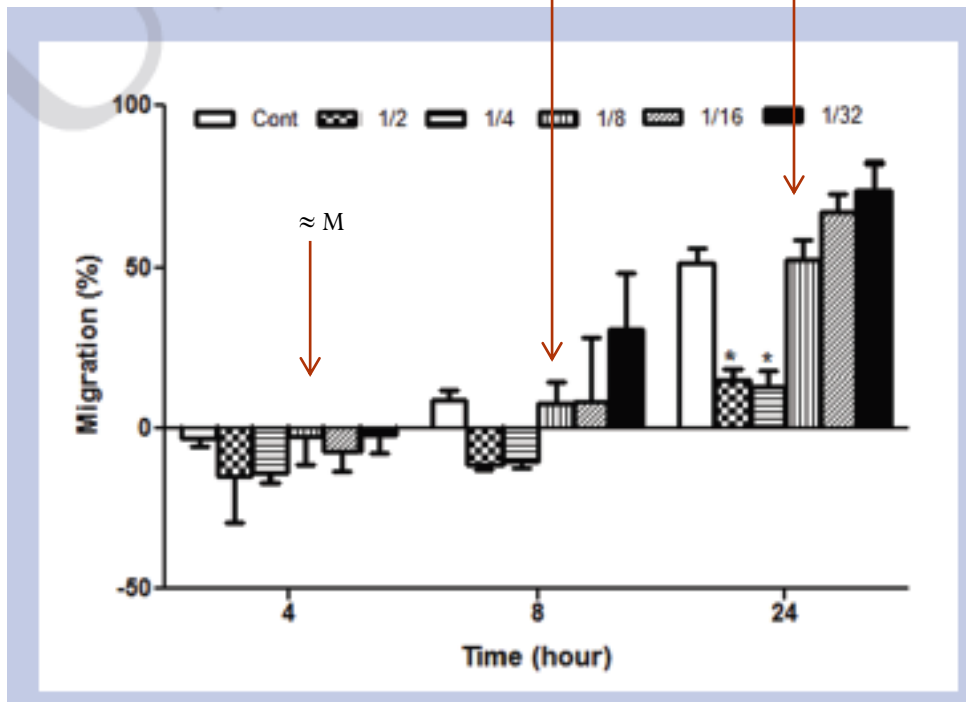
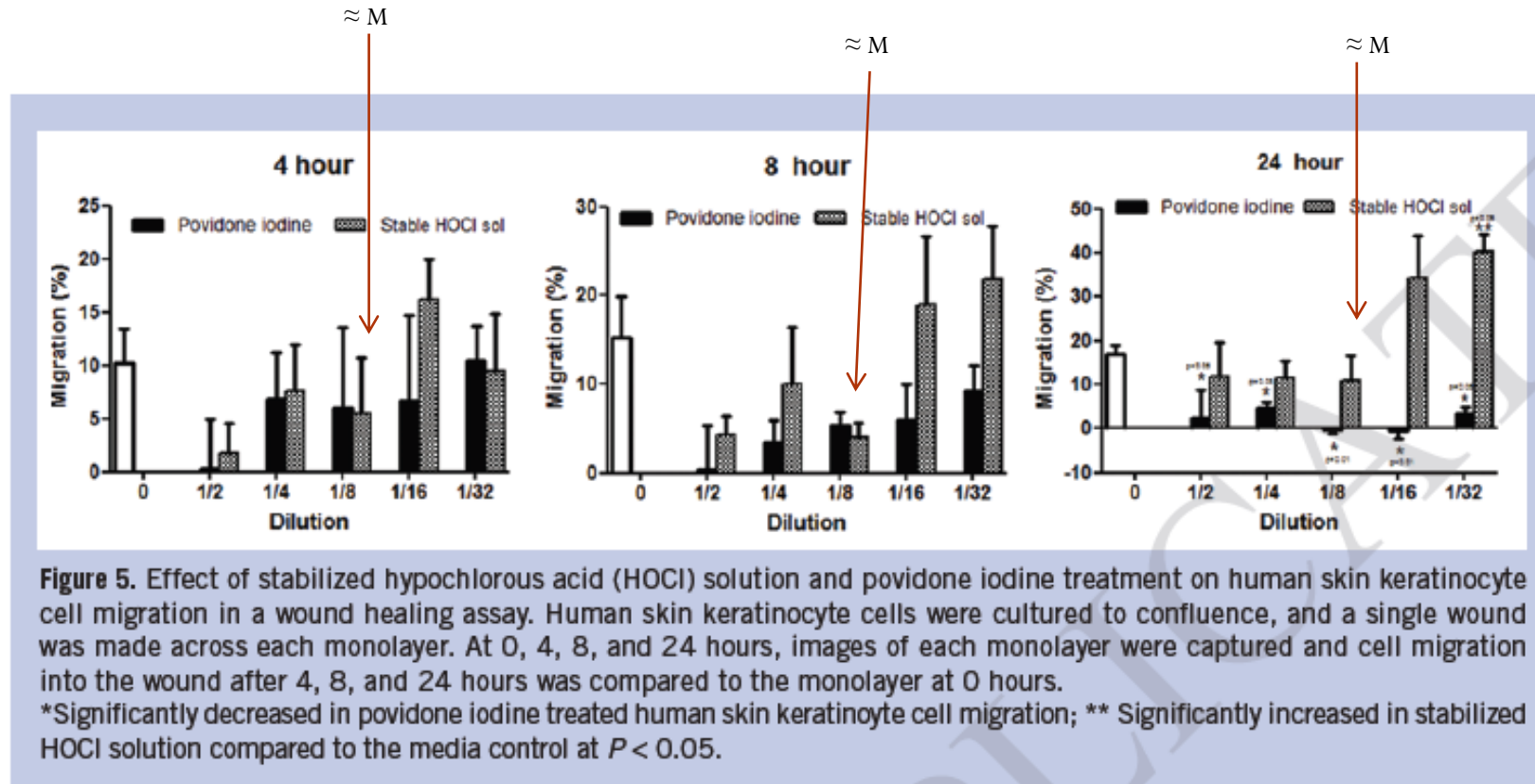


Figure 3. Effect of stabilized hypochlorous acid (HOCl) solution treatment on skin fibroblast cell migration in a wounding healing assay. Skin fibroblast cells were cultured to confluence, and a single wound was made across each monolayer. At 0, 4, 8, and 24 hours, images of each monolayer were captured and cell migration into the wound after 4, 8, and 24 hours was compared to the monolayer at 0 hours.

Minor effect on keratinocyte migration

- HOCl solution = 218 ppm (M = 20 ppm)

Wounds 2014; 26(12): 342-50



Using topical antiseptic agents in primary care

Prevention

1. Hand hygiene
2. Acute traumatic wounds
3. Burns
4. Minor surgical procedures

'Treatment'

1. Impetigo
2. Infected eczema
3. Recurrent boils
4. Hidradenitis suppurativa
5. Goopy chronic ulcers

Hand hygiene

- Alcohol 70% is current standard.
- Need moisturiser, not chlorhexidine.
- Benefits for patient, staff.
- WHO 5-moments
 1. Before contact
 2. After contact
 3. Before aseptic procedure
 4. If hands contaminated (soap/water)
 5. After handling patient environment.
- Placement – hospital, primary care.
- (+ travel.)

My recommendation

Any brand with >70%
alcohol + moisturiser



Acute traumatic wounds

- Infections after trauma cost ACC \$6.3m/year.
- 2% to 17.5% get infected.
- Risk factors - host general factors (e.g. diabetes), wound location (e.g. legs, hands), wound type (e.g. crush injury), contamination, delay >24 hrs.
- Cleansing and debridement reduces infection
 - Tap water = saline; pressurized cleaning no advantage
- Topical antiseptics reduce infection by 10-70%
- Dressings (moisture) benefit wounds.
- Systemic antibiotics if very high risk.

Acute traumatic wounds

- Topical antiseptics reduce infection by 10-70%
 - 11+ animal studies; 13+ human trials, mostly pov-iodine or 'Triple AB'.
- No Microdacyn or Savlon clinical trial yet
- H₂O₂
 - Effervescence cleaning action is theory, not studied
 - Studies - no ↓ bacterial wound count; no clinical trial
 - Mod-highly cytotoxic *in-vitro* but ? Relevant
 - Improves outcomes in chronic ulcers
- Don't contaminate the bottle.

My recommendation

1. Microdacyn
2. Savlon (chlorhex+ cetrimide)
3. Pov-iodine or H₂O₂
4. Dilute bleach - cheap

Minor burns

- Clean and debride; dressings (but which?)
- Topical antiseptics/antibiotics
 - Honey - 2 good RCTs show healing faster than standard; 6 poor RCTs show = to SSD (Cochrane 2015)
 - Silver dressings or gel – kills bacteria but only 1 of 14 RCTs shows benefit on healing.
 - Silver sulfadiazine - #1 used but no trials, ?↓healing.
 - Dilute bleach –↓ bacteria, low toxicity, no trials.
 - Pov-iodine, chlorhexidine, Triple AB – no trials.
 - Microdacyn – great in 1 non-randomised trial.

UpToDate 2016

My recommendation

1. Honey
2. Microdacyn
3. Dilute bleach - cheap

Minor dermatologic procedures

- Overall 1.3 to 1.5% infection risk
- Skin prep and dressing probably important
- Topical antibiotics or antiseptics
 - Meta-analysis of > 4000 patients, 4 RCTs (Bacitracin, chloramphenicol, mupirocin, or gentamicin ointment)
 - Pooled odds of infection 0.71
 - Authors' conclusion: not indicated due to low risk

J Derm Treatment 2015; 26(2): 151-8

My recommendation

1. No topical antiseptic or antibiotic
2. If high-risk consider Microdacyn, H₂O₂, Savlon
(chlorhex+ cetrimide)
3. (Avoid mupirocin and chloramphenicol)

Impetigo (minor)

- Meta-analysis of 68 RCTs, 5578 patients
 - mupirocin, fusidic acid effective
 - Placebo – 0 to 42% cure in 7 days

Cochrane 2012

- H₂O₂ 72% cure (vs FA 82%, NS)

Acta Dermato-Venerologica 1994; 74(4): 460-2

- Povidone-iodine 67.5% cure

J Pediatr ID 2006; 1: 219-23

- No studies of Microdacyn, NaClO, chlorhexidine.

My recommendation

1. H₂O₂
2. Mupirocin or fusidic acid (but anticipate resistance)
3. Try Microdacyn or dilute bleach?

Infected eczema

Canad. Med. Ass. J.
Mar. 14, 1964, vol. 90

CURRENT DRUG THERAPY: DRUGS FOR "ECZEMA" OF CHILDREN 693

CURRENT DRUG THERAPY

*This series of articles has been arranged by an editorial subcommittee of the
C.M.A. Committee on Pharmacy.*

Drugs for Eczema of Children

ARTHUR R. BIRT, M.D.,* Winnipeg, Man.

Condy's crystals



Potassium permanganate is the simplest agent for use in the control of secondary infection in eczema. Through oxidation it controls bacteria and it also dries denuded areas. Potassium permanganate solution should be made freshly for each bath, using one drachm of crystals to every six gallons of water (1: 6,000). It should not be used in a good bathtub. If it is used in a tub that does not have any abrasions on its surface, the brown stains can be removed with an ordinary household bleach.

Infected eczema

- Benzalkonium + triclosan baths – no effect, irritation in cases
- Dilute bleach (NaClO) baths – effective for submerged skin

Pediatrics 2009; 123: e808-14

Ped Dermatol 2003; 30(3): 308-15

- Microdacyn-like products – effective

Cutis 2012; 90: 97-102

Allergy 1997; 52: 1012-6

My recommendation

1. Dilute bleach baths
2. Microdacyn

Add 1/4 to 1/2 cup bleach to bath or 3 teaspoons bleach to a 10 L bucket of water. Then soak or wipe over skin for 5 to 10 min, rinse in fresh water, apply emollients etc...

Recurrent boils

- Often due to eczema, occasionally psoriasis
 - Treat underlying eczema, psoriasis
 - Bleach baths or Microdacyn
 - PRN oral antibiotics, I&D, ?? topical AS (e.g. H₂O₂)
 - Low success with decolonisation.
- Invasive, virulent *Staph. aureus* strain
 - Rarely immune-compromise, IVDU, Munchausens
 - Usually clears spontaneously (months, years) – may be sped up by good hygiene (cover active lesions), wash and no share clothing and towels, surface cleaning, antiseptic bodywash
 - PRN oral AB, I&D, ?topical AS
 - Formal decolonisation – nasal mupirocin or pov-iodine, body wash with chlorhexidine or triclosan or dilute bleach), rifampicin, surface cleaning, fabric items.

Hydradenitis suppurativa

- Stop smoking, lose weight, avoid trauma/friction, dairy-free diet, low glycaemic diet, anti-androgens, TNF-alpha inhib (infliximab, adalimumab, etanercept), metformin, zinc.....
- Topical antiseptics and antibiotics?
 - Topical clindamycin 1% works (one RCT, n=27)
 - Triclosan, chlorhexidine, others sometimes recommended but not studied.

My recommendation

1. Try topical antiseptics – Microdacyn, H₂O₂, Savlon, dilute bleach (cheap), triclosan bodywash

Chronic 'goopy' ulcers



Infected



Heavily colonised = goopy



Chronic 'goopy' ulcers

- Nurses are often the experts
- Fix underlying cause (pressure, arterial disease, venous stasis)
- Debride necrotic/devitalised material/eschar
- Remove slough/goop (toxins, WC, bacteria)?
- Dressings (none better than any other)
- Topical antibacterial/antiseptic agents:
 - ↓ bacteria on surface
 - ↓ bacteria deep in tissue
 - ↓ signs of infection
 - Probably improve healing.

Topical anti-bacterial agents for venous ulcer healing

- Cochrane Database Syst Rev 2014
 - 45 RCTs, 53 comparisons, 4486 patients
 - Poor design - small, high risk of bias, different baseline status, different duration of treatment....
 - Overall – difficult to know if effective or not!
- Results:
 - Cadexomer iodine (12 RCT) – 4 RCT show likelihood of complete healing at 4 to 12 weeks improved by RR 2.17 compared with standard care
 - H₂O₂ (4 RCT) – ↓ ulcer size compared with usual care
 - No evidence of benefit for povidone iodine (7 RCT), silver (12 RCT), chlorhexidine, mupirocin or honey (2 RCT) Note: Cochrane review of honey 2015 – may help burns and post-op wounds

Advantages of cadexomer iodine

- Well studied, effective.
- Broad spectrum (gram-pos, gram-neg bacteria).
- No resistance after > 100 years of use.
- Long effect; convenient for nurses.
- Less allergy than chlorhexidine and antibiotics.

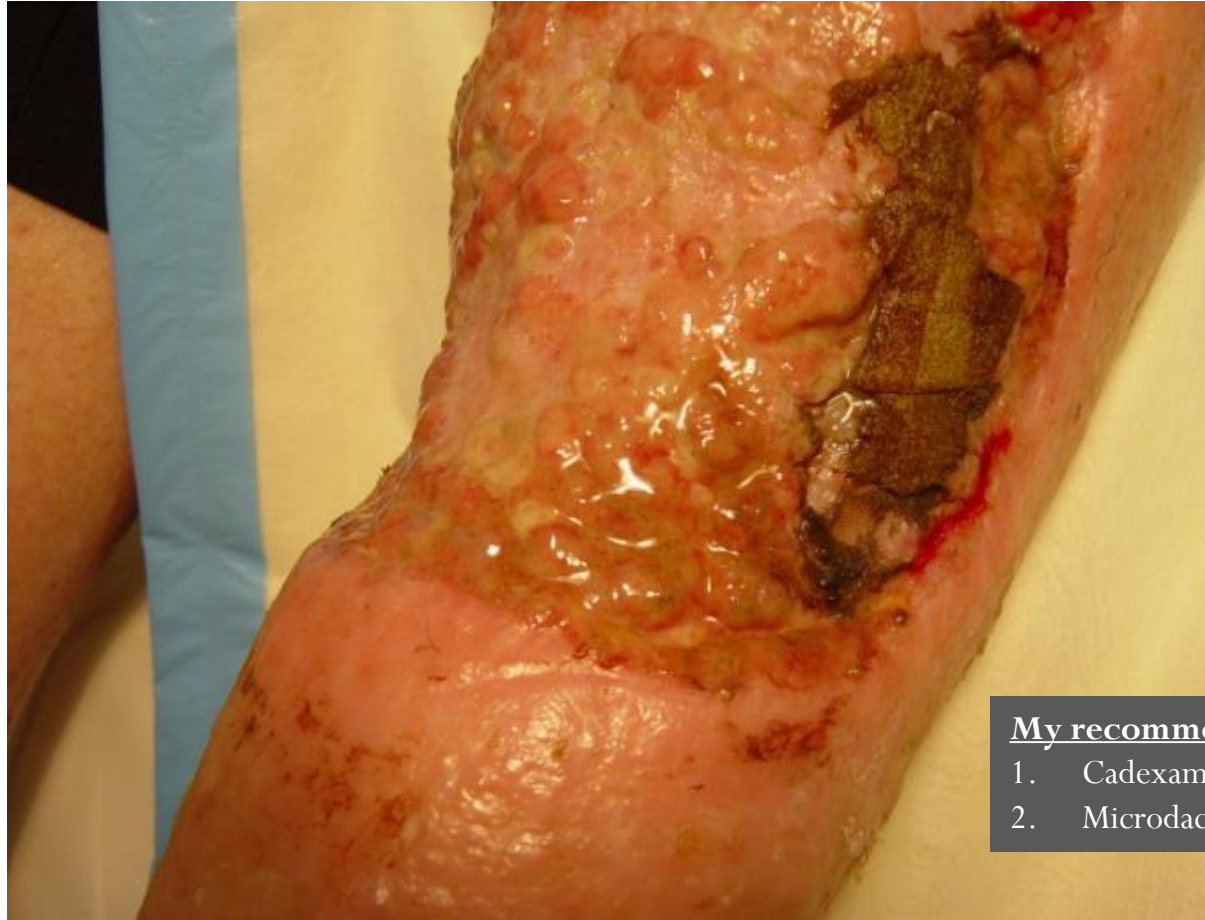
Lachapelle et al. Clin Pract 2013; 10(5): 579-92.

Vermeulen et al. Benefit and harm of iodine in wound care: a systemic review. J Hosp Infection 2010; 76: 191-99.

Microdacyn[®] comparative trials

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Chronic 'goopy' ulcers



My recommendation

1. Cadexamer iodine
2. Microdacyn

Take home points

- Antiseptics preferred over antibiotics
 - Broader spectrum
 - Less resistance
 - Less allergic reactions
- Microdacyn is probably the best
- Bleach baths are safe, effective and cheap
 - Add 1/4 to 1/2 cup bleach to bath or 3 teaspoons bleach to a 10 L bucket of water. Then soak or wipe over skin for 5 to 10 min, rinse in fresh water, apply emollients etc...
- Don't contaminate the bottle.



Thank you
Richard.everts@nbph.org.nz

Major surgical procedures



- Stop smoking, control diabetes.
- Treat distant infection first.
- Nasal *Staph. aureus* decolonisation (50% ↓ infection) – pov-iodine better than mupirocin.
- Chlorhexidine bodywash (7 RCT - no ↓ infection).
- Pre-op skin prep - 70%⁺ ethanol + either chlorhex (0.5% = 2%) or pov-iodine (Cochrane 2013).
- Antibiotic prophylaxis (>50% ↓ infection).
- Intra-op antiseptic – ↓ infection, but out-of-vogue
- Triclosan-coated sutures (13 RCT – 26% ↓ infection).

Major surgical procedures



2 days before the operation				1 day before the operation				Operation day	
									
Apply 4 times a day to skin at the operation site				Apply 4 times a day to skin at the operation site				Apply once or 2 times before the operation to skin at the operation site	

2 days before the operation		1 day before the operation		Operation day	
					
100 mg tab with breakfast	100 mg tab with dinner	100 mg tab with breakfast	100 mg tab with dinner	100 mg tab between 6 and 8 am with water	

	Standard care	Std + doxycycline	Std + Microdacyn
No. wounds	35	35	36
No. samples	130	122	124
Any growth	53 (41%)	33 (27%)	27 (22%)
Moderate or heavy growth	20 (15%)	10 (8%)	4 (3%)