Topical Antibiotics to Prevent Post-Operative Surgical Infection. Is the Paradigm Changing?

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Hosted by Paul Webber
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Declaration

The views expressed are of a professional but personal nature & are not necessarily those of the RCSI & Beaumont Hospital, Dublin.

I have recently received research funding from Pfizer & Astellas. I have also provided professional advice or education for Pfizer.

Outline

1. Measures to reduce surgical site infection (SSI) & involving antibiotics
2. Lack of & or poor quality of evidence for topical or local antibiotics
3. Unintended consequences
4. Conclusions

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Measures to Reduce SSI & Involving Systemic Antibiotics

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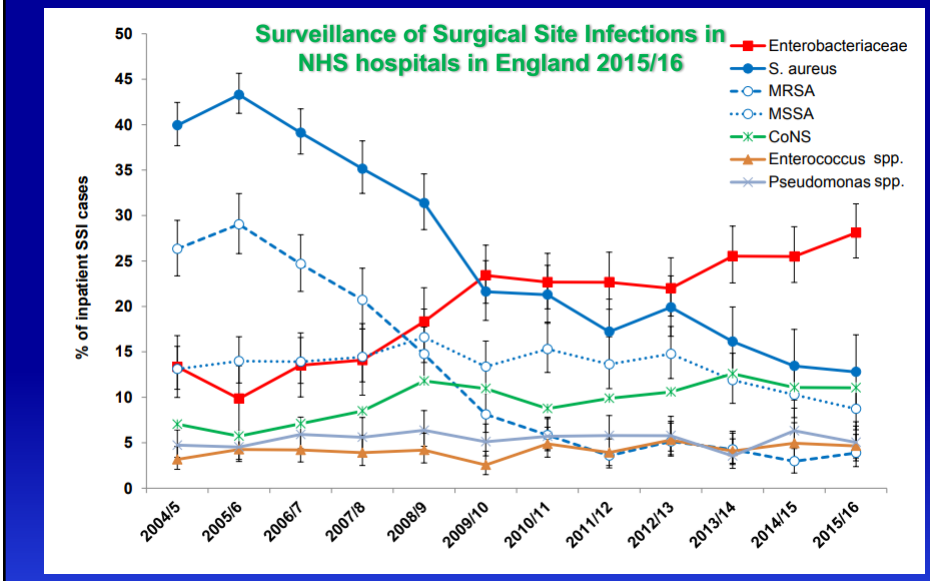

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IV surgical prophylaxis: why do we use it?

- To prevent surgical infection
- Evidence based. Really? What quality of evidence?
- Prior to incision
- Need rapid tissue levels
- Choice of antibiotic depends on likely contaminating microbes
- Single dose currently in vogue

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Timing of Prophylactic Antibiotics & Risk of SSI

- Elective surgery in Salt Lake City
- ~ 3,000 patients, 55% of total eligible
- 100%, for 24h & 80% for ≥ 48h

New Eng J Med 1992; 326: 281-6

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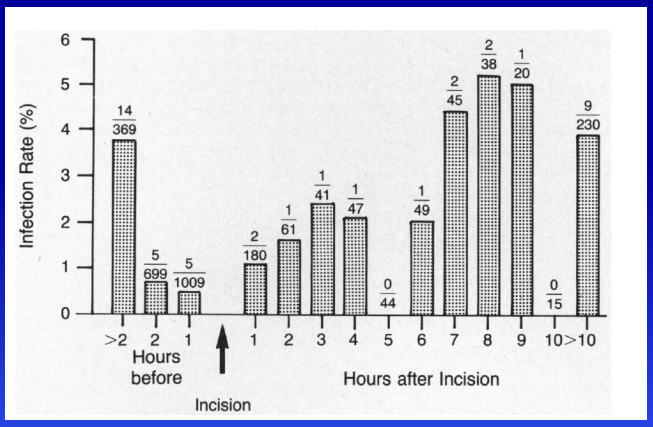
Timing of Prophylaxis & Risk of SSI

- Age, gender, surgeon & postsurgical procedures were not significant



New Eng J Med 1992, 326: 281-6

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A Review of 28 Studies of Antibiotic Prophylaxis & Quality Indicators

Indication, timing, choice & duration

Compliance – 9-80%, but up to 100% after interventions overall
- 19-91%, with indication
- 30-95%, for timing

Interventions – education, MDT, computer-based ordering, etc.

Epidemiol Prev 2015; 39: Suppl 1, 27-32

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Measures to Reduce SSI
&
Involving Topical Antibiotics

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Definition

"Antibiotic agents applied directly to the surgical site intra-operatively or post-operatively *via* powders, sponges, irrigation solutions, sealents or dressings"

Antiseptic agents excluded

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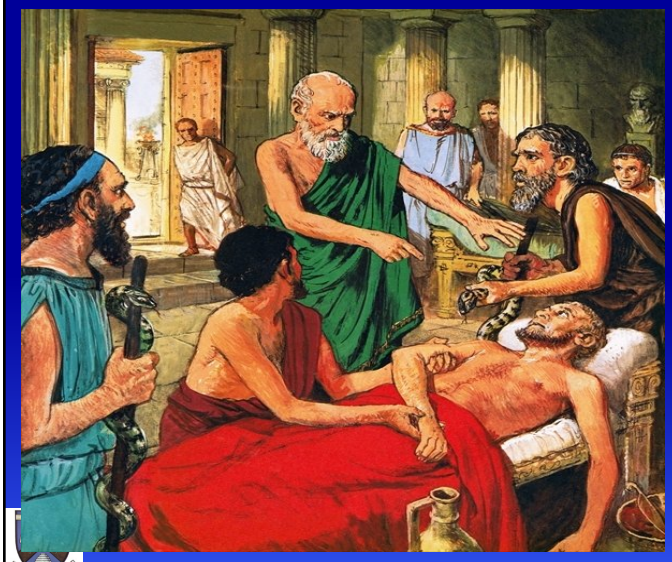
Topical Antibiotic Use



- Orthopaedic
- General surgery
- Plastics
- ENT
- Ophthalmology
- Dermatology
- Interventional cardiology
- Emergency department
- General practitioners

- Widely used
- Geographical & specialty variation in use

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J Antimicrob Chemother 2011; **66**: 693–701
doi:10.1093/jac/dkr009 Advance Access publication 3 February 2011

Journal of Antimicrobial Chemotherapy

The role of topical antibiotics used as prophylaxis in surgical site infection prevention

S. M. McHugh[1,2]*, C. J. Collins[3], M. A. Corrigan[1,2], A. D. K. Hill[1,2] and H. Humphreys[3,4]

The selective use of topical antibiotics as surgical prophylaxis is justified for specific procedures, such as joint arthroplasty, cataract surgery and, possibly, breast augmentation.

"Selective" might include obese patients

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BSAC BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

EWMA EUROPEAN WOUND MANAGEMENT ASSOCIATION

MIBTP Midlands Integrative Biosciences Training Partnership

The use of topical antibiotics to prevent surgical site infection; a survey of practice and opinion

Charlotte Cooper[1], Gavin Barlow[2], Niels Fibæk Bertel[3], Tracey Guise[4], Carolyne Horner[4], Hilary Humphreys[5]

[1]School of Biosciences, University of Birmingham, UK [2] Hull and East Yorkshire NHS Trust, Hull, UK [3]European Wound Management Association, Frederiksberg, Denmark [4]British Society of Antimicrobial Chemotherapy, Birmingham, UK [5]Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin, Ireland

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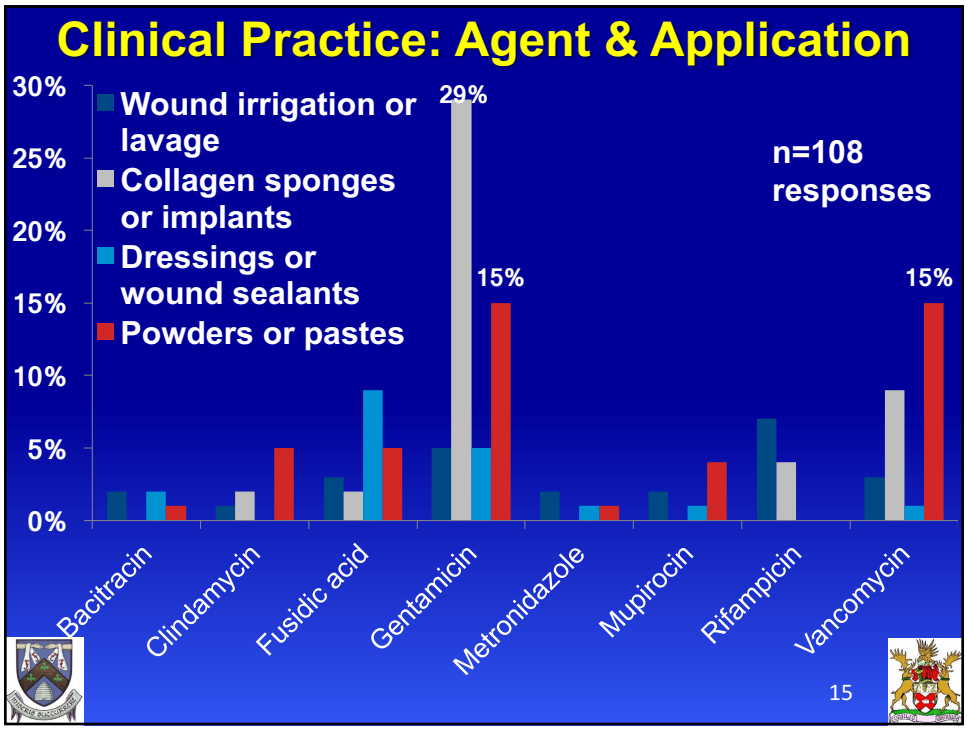
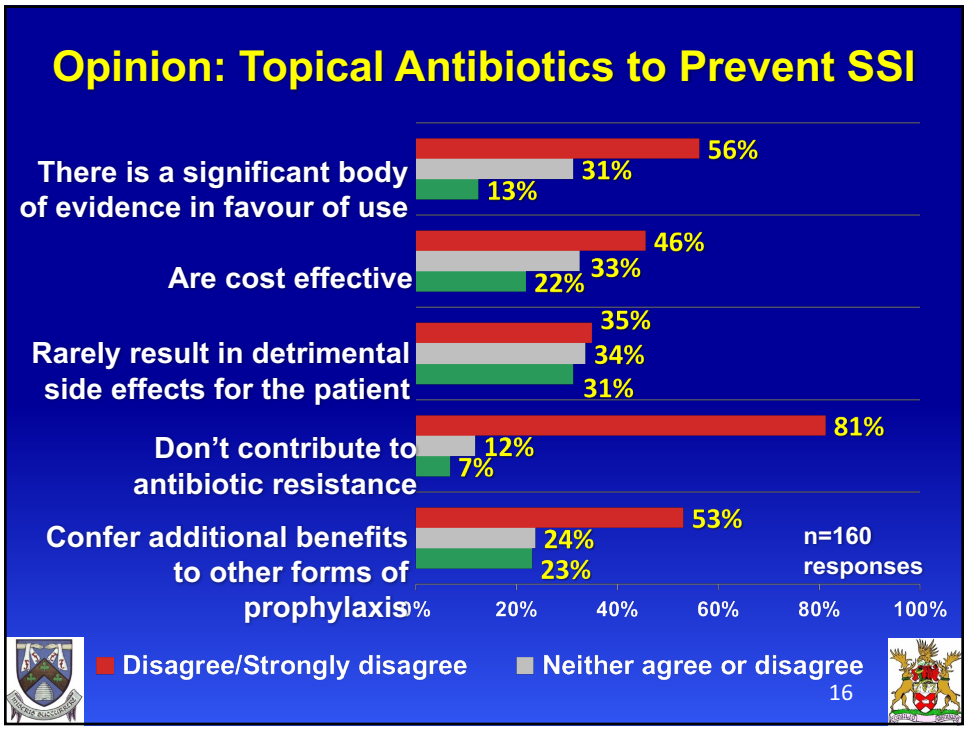

Clinical Practice: Agent & Application
30%
25%
20%
15%
10%
5%
0%
Wound irrigation or lavage
Collagen sponges or implants
Dressings or wound sealants
Powders or pastes
29%
15%
15%
n=108 responses
Bacitracin
Clindamycin
Fusidic acid
Gentamicin
Metronidazole
Mupirocin
Rifampicin
Vancomycin
15


Opinion: Topical Antibiotics to Prevent SSI
There is a significant body of evidence in favour of use
56%
31%
13%
Are cost effective
46%
33%
22%
Rarely result in detrimental side effects for the patient
35%
34%
31%
Don't contribute to antibiotic resistance
81%
12%
7%
Confer additional benefits to other forms of prophylaxis
53%
24%
23%
n=160 responses
0%
20%
40%
60%
80%
100%
Disagree/Strongly disagree
Neither agree or disagree
16

British Society of Antimicrobial Chemotherapy (BSAC) Literature Review

June 2010 to June 2017 focussing on orthopaedic (21), cardiac surgery (11) & abdominal studies (7)

"Conflicting results within & between studies depending on the type of surgical site infection (SSI); total, deep, superficial & organ space. Studies are largely underpowered, not controlled and with little standardisation meaning results can only be treated as trends rather than confirmed effects"

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Topical antibiotics: why not?

Pros

- High sustained local concentration
- No disruption of microbiome
- Active at the site of entry of infection
- No systemic toxicity
- No *C.difficile*
- May be particular benefit for high risk e.g. diabetes mellitus, smokers, ischaemic etc.

Cons

- contact dermatitis
- interference with wound healing
- the potential for increased antibiotic resistance
- cytotoxicity

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Short-Term Antibiotic Treatment Has Differing Long-Term Impacts on the Human Throat and Gut Microbiome
Jakobsson HE et al., , March 24, 2010

Systemic antibiotic use is like napalm – it destroys all with long-term consequences. It is ecological vandalism.

Four years after treatment high levels of the macrolide resistance gene *erm*(B) were found, indicating that antibiotic resistance, once selected for, can persist for longer periods of time than previously recognized.

This highlights the importance of a restrictive antibiotic usage in order to prevent subsequent treatment failure and potential spread of antibiotic resistance.

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Some Studies on Topical or Local Antibiotics

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Chloramphenicol

BMJ RESEARCH

Does single application of topical chloramphenicol to high risk sutured wounds reduce incidence of wound infection after minor surgery? Prospective randomised placebo controlled double blind trial

Clare F Heal, senior lecturer,[1] Petra G Buettner, senior lecturer,[2] Robert Cruickshank, general practitioner,[3] David Graham, general practitioner,[4] Sheldon Browning, general practitioner,[4] Jayne Pendergast, practice nurse,[5] Herwig Drobetz, staff orthopaedic surgeon,[6] Robert Glaer, medical student,[1] Carl Lisec, surgical registrar[6]

ABSTRACT

Objective To determine the effectiveness of a single application of topical chloramphenicol ointment in preventing wound infection after minor dermatological surgery.

Design Prospective randomised placebo controlled double blind multicentre trial.

Setting Primary care in a regional centre in Queensland, Australia.

Participants 972 minor surgery patients.

Interventions A single topical dose of chloramphenicol (n=488) or paraffin ointment (n=484; placebo).

Main outcome measure Incidence of infection.

Results The incidence of infection in the chloramphenicol group (6.6%; 95% confidence interval 4.9 to 8.8) was significantly lower than that in the control group (11.0%; 7.9 to 15.1) (P=0.010). The absolute reduction in infection rate was 4.4%, the relative reduction was 40%, and the relative risk of wound infection in the control group was 1.7 (95% confidence interval 1.1 to 2.5) times higher than in the intervention group. The number needed to treat was 22.8.

Conclusion 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.

Trial registration Current Controlled Trials ISRCTN73273053.

infection. Despite this, it is regularly used in areas outside its main indication. Before our study, several of the investigating general practitioners had applied it to sutured wounds as prophylaxis against wound infection. A survey of UK plastic surgeons reported that 60% used chloramphenicol eye ointment in their practice, mainly as prophylaxis against infection.[4] The ointment has been used as an adhesive for replacement of the nail bed.[5] A comprehensive Medline search found only one other study relating to the use of topical chloramphenicol ointment on wounds; this study investigated the application of chloramphenicol ointment to wounds after hip replacement.[6] The incidence of wound infection in the intervention group was reduced (4% v 8%), but the sample size was small and the results were not statistically significant.

Topical ocular chloramphenicol is widely used in the United Kingdom and Australia for the treatment of conjunctivitis, but is very rarely prescribed for this indication in the United States.[7] Some controversy previously existed about the link between aplastic anaemia and topical ocular chloramphenicol, on the basis of a small number of single case reports,[7] but two international case-control studies provided no support for this association. Although the association between ocular chloramphenicol and aplastic anaemia cannot be excluded, the risk is less than one in a million per treatment course.[8] No incidences of aplastic anaemia after dermatological application have been reported, despite widespread use.

- Ophthalmology
- ENT minor surgery
- Dermatology
- Plastic surgery

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Topical Bacitracin to Prevent Sternal Wound Infections After Cardiac Surgery

Annals of Thoracic Surgery; 2017; 104: 1496-1500

- 9 year experience of peri-operative sternal wound bacitracin
- 0% deep infection rate *versus* expected rate of 0.29%
- 4 superficial infections
- Well tolerated. No serious adverse effects
- Readily available & inexpensive therapy

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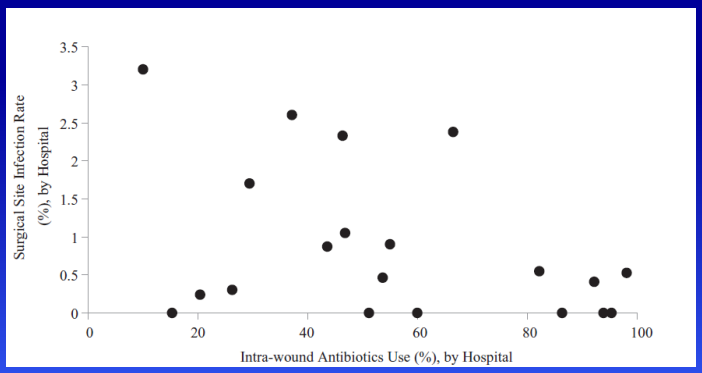
Intra-Wound Antibiotics (IWA), Infection & Spinal Fusion Surgery

- 9,823 patients in 20 Washington State Hospitals, 55% receiving IWA
- 111 (1.1%) with SSI; 0.8% (IWA)* *vs* 1.5% (no IWA)
- After adjustment, no difference



Surg Infect 2016; 17: 177-186

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Local Gentamicin to Wound for Abdominoperineal Resection

- 582 articles from search (1988-2012) but only 8 suitable
  - 4 RCTS
  - 3 consecutive studies
  - 1 cohort (no controls)
- Sponges (3), beads (4), injection (1)
- Substantial heterogeneity in studies
- Evidence does not support perineal application of gentamicin

World J Surg 2015; 39: 2786-2794

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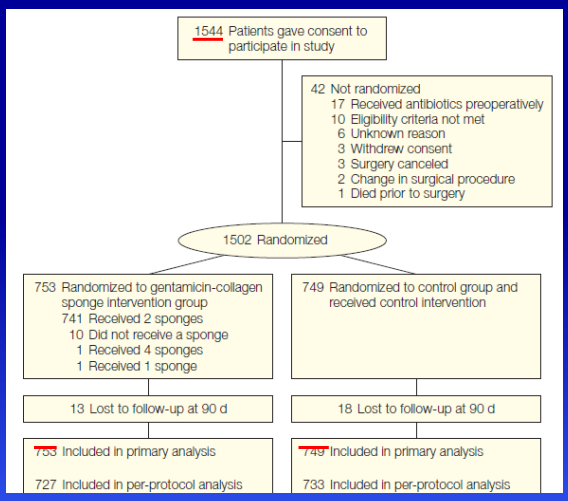
Gentamicin Collagen Sponges (GCS), Sternal SSI after Cardiac Surgery

Phase 3, single blind, RCT of 1502 patients at high risk (DM or BMI> 30)



JAMA 2010; 304: 755-762

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GCS & Sternal SSI after Cardiac Surgery

Per Protocol Analysis	GCS (727)	Control (749)
Any SSI	8.4%	8.6%
Surgically treated SSI	3.2%	4.9%
Superficial SSI	6.6%	6.1%
Deep SSI	1.8%	2.5%
Re- hospitalisation for SSI	3.0%	3.3%
Post-operative length of stay	6.0 d	6.0 d

JAMA 2010; 304: 755-762

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GCS & Colorectal Surgery

- 2 sponges (260 gentamicin) to patients in 39 US sites
- From 674 enrolled, 602 randomised (GCS 300, control 302)
- Adjusted SSI of 29% in GCS group & 21% in control (p=0.03)
- GCS patients more likely to visit ED or surgeon's office (19.7% *v* 11%, p = 0.004)
- 15 gentamicin resistant isolates, 13 in GCS group

N Engl J Med 2010; 363: 1038-49

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GCS & Colorectal Surgery

- Initial effect but not sustained due to a lack of sustained antibiotic levels

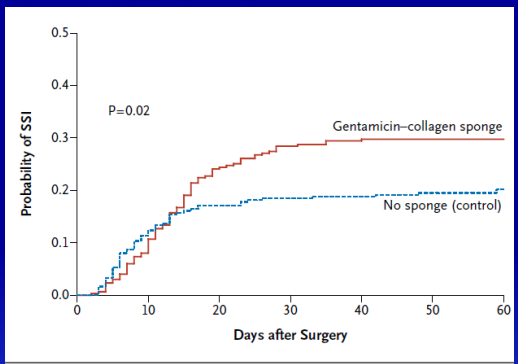

Figure 2. Kaplan–Meier Estimates of the Number of Days from Surgery to Surgical-Site Infection (SSI) within the 60-Day Postoperative Period, According to Study Group.

- Collagen sponge may be a mechanical barrier to rapid & effective closure of wound

N Engl J Med 2010; 363: 1038-49

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NICE - SSI Prevention & Treatment, 2017

Pre-operative

e.g. antibiotic prophylaxis

Intra-operative

Do not use wound irrigation to reduce the risk of SSI

Do not use intra-cavity lavage to reduce the risk of SSI

Do not use intra-operative skin re-disinfection or topical cefotaxime in abdominal surgery to reduce the risk of SSI

Post-operative

Do not use topical antimicrobial agents for surgical wounds that are healing by primary intention to reduce the risk of SSI

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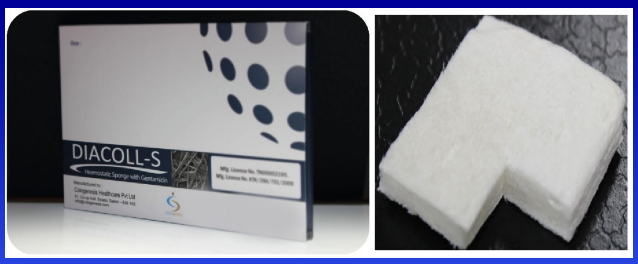
Preventing SSI in Acute Care Hospitals, 2014 SHEA, IDSA, AHA & APIC

Gentamicin collagen sponges (GCS)

- Colorectal surgery, SSI higher with GCS
- Cardio-thoracic, mixed evidence
- GCS not approved by FDA in USA



Infect Control Hosp Epid 2014; 35: 566-588

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WHO Recommendations 2016

"…. antibiotic incisional wound irrigation before closure should not be done"

Conditional Recommendation

Low quality of evidence

Lancet Infect Dis 2016; 16: e288-303

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Unintended Consequences

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Impact of Topical Vancomycin in Spinal Surgery

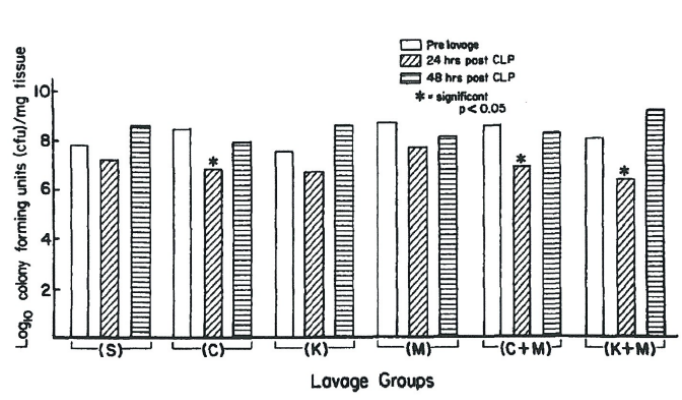
- Retrospective review of 981 patients receiving 1-2 gr vancomycin, 2011-13
- 6.7% SSI – 5.2% had + ve cultures; 44/51 (86%) Gram + ve, & 31 (61%) Gram negative

  Historical controls had Gram-ves in 21% (p=0.0001)
- Use of topical vancomycin for prophylaxis shifts causes to Gram negative

Spine 2014: 39: 530-555 33

Impact of Topical Antibiotics on Flora

- Animal studies on rats & impact of antibiotics on flora, i.e. cephazolin, kanamycin, metronidazole & combinations
- Saline lavage does not alter anaerobic flora
- Antibiotics had transitory impact on flora, re-colonisation at 4h



World J Surg 1990; 14: 176-183 34

Antibiotics & Intra-Abdominal Adhesions

Group 1	16 rats + saline
Group 2	8 rats + cefazolin
Group 3	8 rats + tetracycline

More adhesions after 2/52 in groups 2 & 3 compared to group 1

Mesothelial thickening & extensive collagen deposition, especially in Group 3

Am J Surg 1989; 158: 435-437

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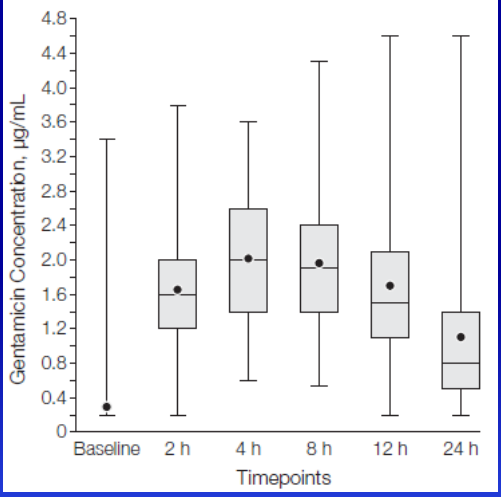
GCS, Sternal SSI after Cardiac Surgery Impact of Gentamicin

- Levels taken 2h before & 2,4,8,12 & 24h after closure of wound
- No difference in adverse events



JAMA 2010; 304: 755-762

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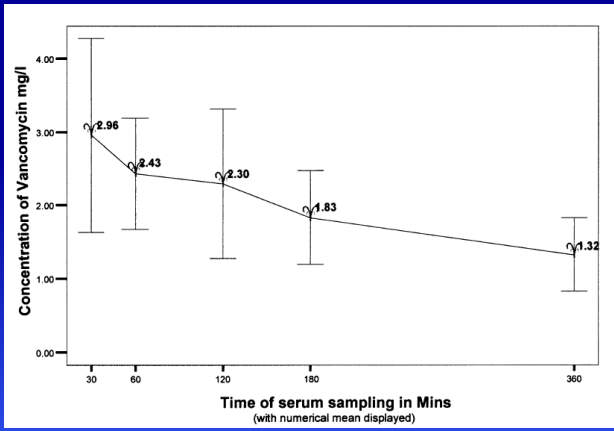
Vancomycin Levels & Sternotomy Wounds

- 500 mg vancomycin power or dissolved in saline
- Levels taken 30 min – 720 min
- Mean concentration in urine was 24.4 at day 1



Eur J Cardio-Thoracic Surg 2003; 23:765-770

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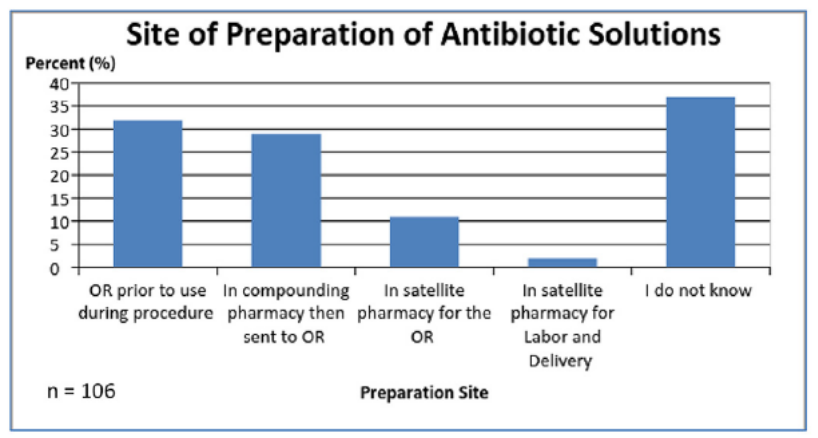
Safety Quality of Antibiotic Preparation



Am J Infect Control 2017; 45: 1259-1266

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Conclusions & Final Thoughts

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1. Almost all of the studies showing a benefit for topical antibiotics are flawed
2. RCTs suggest no impact & or even possibly increased SSI
3. Risks include increased resistance, altered flora & adhesions
4. Benefits include less reliance on systemic antibiotics & possibly reduced infection rates
5. Potential advantages for selected patients after specific procedures

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Topical Antibiotics to Prevent Post-Operative Surgical Infection.
Dr. Hilary Humphreys, Royal College of Surgeons in Ireland
A Webber Training Teleclass

www.webbertraining.com/schedulep1.php	
May 3, 2018	*(FREE … WHO Teleclass - Europe)* **SPECIAL LECTURE FOR 5 MAY** Speaker: **Prof. Didier Pittet**, University of Geneva Hospitals
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