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.
Topical Antibiotics to Prevent Post-Operative Surgical Infection.
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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

Measures to Reduce SSI & Involving Systemic Antibiotics

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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


Timing of Prophylaxis & Risk of SSI

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

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

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

M Dryden, UK

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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.

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

Charlotte Cooper¹, Gavin Barlow², Niels Fibæk Bertel³, Tracey Guise⁴, Carolyne Horner⁴, Hilary Humphreys⁵

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

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Clinical Practice: Agent & Application

<table>
<thead>
<tr>
<th>Agent</th>
<th>Percentage</th>
<th>n=108 responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound irrigation or lavage</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Collagen sponges or implants</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Dressings or wound sealants</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Powders or pastes</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

Opinion: Topical Antibiotics to Prevent SSI

- There is a significant body of evidence in favour of use:
  - 13% Disagree/Strongly disagree
  - 31% Neither agree or disagree
  - 56% Agree

- Are cost effective:
  - 22% Disagree/Strongly disagree
  - 33% Neither agree or disagree
  - 46% Agree

- Rarely result in detrimental side effects for the patient:
  - 7% Disagree/Strongly disagree
  - 34% Neither agree or disagree
  - 35% Agree

- Don’t contribute to antibiotic resistance:
  - 12% Disagree/Strongly disagree
  - 31% Neither agree or disagree
  - 81% Agree

- Confer additional benefits to other forms of prophylaxis:
  - 24% Disagree/Strongly disagree
  - 23% Neither agree or disagree
  - 53% Agree

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**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?**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High sustained local concentration</td>
<td>- contact dermatitis</td>
</tr>
<tr>
<td>- No disruption of microbiome</td>
<td>- interference with wound healing</td>
</tr>
<tr>
<td>- Active at the site of entry of infection</td>
<td>- the potential for increased antibiotic resistance</td>
</tr>
<tr>
<td>- No systemic toxicity</td>
<td></td>
</tr>
<tr>
<td>- No <em>C. difficile</em></td>
<td>- cytotoxicity</td>
</tr>
<tr>
<td>- May be particular benefit for high risk e.g. diabetes mellitus, smokers, ischaemic etc.</td>
<td></td>
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</tbody>
</table>

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Short-Term Antibiotic Treatment Has Differing Long-Term Impacts on the Human Throat and Gut Microbiome
Jakobsen 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 \textit{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

- Ophthalmology
- ENT minor surgery
- Dermatology
- Plastic surgery

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Topical Bacitracin to Prevent Sternal Wound Infections After Cardiac Surgery

- 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

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

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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)

GCS & Sternal SSI after Cardiac Surgery

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


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**GCS & Colorectal Surgery**

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

![Graph](Image)

*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


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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

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

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WHO Recommendations 2016

“... antibiotic incisional wound irrigation before closure should not be done”

Conditional Recommendation
Low quality of evidence

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

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
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


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 powder or dissolved in saline
- Levels taken 30 min – 720 min
- Mean concentration in urine was 24.4 at day 1


Safety Quality of Antibiotic Preparation

Site of Preparation of Antibiotic Solutions

Am J Infect Control 2017; 45: 1259-1266

n = 106

Preparation Site

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Conclusions & Final Thoughts

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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Thank you

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<tr>
<th>Date</th>
<th>Title</th>
<th>Speaker</th>
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<tr>
<td>May 3, 2018</td>
<td>FREE WHO Teleclass - Europe</td>
<td>Prof. Didier Pittet, University of Geneva Hospitals</td>
</tr>
<tr>
<td>May 10, 2018</td>
<td>HOW THE CERTIFICATION BOARD OF INFECTION CONTROL (CBIC) WORKS FOR YOU</td>
<td>Ivan W. Gowe, CBIC Director, and Lita Jo Henman, CBIC Past President</td>
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<tr>
<td>May 17, 2018</td>
<td>THE SILENT TSUNAMI OF AZOLE-RESISTANCE IN THE OPPORTUNISTIC FUNGUS ASPERGILLUS FUMIGATUS</td>
<td>Prof. Paul E. Verweij, Radboud University Center of Expertise in Mycology, The Netherlands</td>
</tr>
<tr>
<td>May 23, 2018</td>
<td>TREKKING SAFELY THROUGH THE STORM – MANAGING COMPLEX IPAC ISSUES</td>
<td>Dr. Mark Joffe, Alberta Health Services</td>
</tr>
<tr>
<td>May 29, 2018</td>
<td>SIMULATION AS AN EDUCATION TOOL</td>
<td>Dr. Ghazwan Atabbaa and Diane Kolodka, Rockview Hospital, Calgary</td>
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