Why evidence should have biological plausibility: The story of chlorhexidine and its role in skin antisepsis

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History of Antisepsis

Ignaz Philipp Semmelweis (1818-1865)
Joseph Lister, 1st Baron Lister (1827-1912)

• Implemented hand antisepsis;
  i.e. killing of microorganisms on hands
• Distinct from: hand washing

• Implemented wound antisepsis and spraying of phenol in operating rooms
• Precursor of skin antisepsis

History of Skin Antisepsis

• Hand and skin antisepsis already prevalent in early 1900s
• Seminal work by Price during ~1930s to 1950s

Evidence-Based Medicine (EBM)

• Branch of medicine that makes conscientious, explicit and judicious use of current best evidence in making decisions
• Measure: real clinical outcomes after different treatment
• Stages of evaluation:
  (1) Clinical trials: randomized clinical trial (RCT) is best
  (2) Systematic reviews
  (3) Meta-analyses (mathematical calculation)
  (4) Evidence-based clinical practice guidelines

Process of Evidence-Based Medicine

1. Assessed for Eligibility
2. Systematic Review
3. Meta-Analysis (Quantitative Synthesis)
4. Formal Evaluation: Evidence-Based Clinical Practice Guidelines
Skin Antisepsis: Modern Relevance

• Skin antisepsis is now a firmly established method to prevent infections in healthcare.

A few main applications:
(1) Before blood culture collection
   – To prevent blood culture contamination
(2) Before vascular catheter insertion
   – To prevent catheter colonisation and bloodstream infection
(3) Before surgery (surgical ‘skin prep’) 
   – To prevent surgical site infections
• Plus several more applications

Chlorhexidine featured in several prominent clinical studies

The “Keystone Project” in Michigan ICUs →

Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis

At some point we noticed something unusual . . .

• All compared study outcomes from the combination of chlorhexidine plus alcohol (i.e., two active ingredients) versus povidone-iodine alone (i.e., one active ingredient)
• All concluded: “Chlorhexidine is better than povidone-iodine”

Chlorhexidine started to feature in practice recommendations and evidence-based guidelines

Examples:
• A 2007 Clinical and Laboratory Standards Institute (CLSI) guideline on blood cultures
• The 2002 CDC guideline and 2009 draft guideline on intravascular catheters
• The 2010 Australian NHMRC Inf. Cont. Guidelines (for surgical skin preparation)
• A 2011 public call for revision of the UK NICE Guidelines (surgical skin preparation)
• Numerous keynote presentations at conferences

Questions posed:
• What is the factual evidence for (a) chlorhexidine alone, or (b) its combinations, in skin antisepsis?
• How common is the attribution of study outcomes from a combination of antiseptics to chlorhexidine alone?
• Could this phenomenon have skewed evidence-based guidelines unjustly in favor of chlorhexidine?
Why Evidence Should Have Biological Plausibility

**Systematic Review Strategy**

Exhaustive search for primary & secondary literature:
1. Clinical Trials
2. Systematic Reviews

Chlorhexidine versus competitors in:
A. Skin antisepsis for blood cultures
B. Intravascular catheter insertion
C. Surgical skin preparation
   -- Classical skin antisepsis assessed, not antiseptic body
   washing or mucous membrane antisepsis

Criteria for literature assessment:
1. Attribution of study outcomes from ALC+CHG to CHG alone?
2. Factual evidence for CHG
   Non-exhaustive review of tertiary literature

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**Potential Scheme of a Clinical Trial**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Trial Arm A</th>
<th>Active Ingredient 1</th>
<th>Clinical Outcome A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Arm B</td>
<td>Active Ingredient 2</td>
<td>Clinical Outcome A</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
<td>Trial Arm B</td>
<td>Active Ingredient 3</td>
<td>Clinical Outcome B</td>
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</tr>
</tbody>
</table>

**Blood Culture Studies**

<table>
<thead>
<tr>
<th>Blood cultures: Primary studies and meta-analyses</th>
<th>Reference</th>
<th>Study design</th>
<th>Outcome</th>
<th>Attribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary studies</td>
<td>A. CHG 0.5% + ALC (%)</td>
<td>RCT</td>
<td>PNI</td>
<td>Incorrect</td>
</tr>
<tr>
<td>Clinical meta-analyses</td>
<td>B. PA 1%</td>
<td>RCT</td>
<td>Insignificant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. IT</td>
<td>RCT</td>
<td>Insignificant</td>
<td></td>
</tr>
<tr>
<td>Criteria for Assessment</td>
<td>A. CHG 0.5% + ALC</td>
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<td>RCT</td>
<td>Insignificant</td>
<td></td>
</tr>
<tr>
<td>Articles concluding:</td>
<td>Outcome A is caused by Ingredient 1*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ingredient 1 is superior to Ingredient 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The evidence supports Ingredient 1*</td>
<td></td>
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</tr>
</tbody>
</table>

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**Blood culture meta-analyses**

Chlorhexidine plus Alcohol versus Povidone-Iodine alone

Chlorhexidine plus Alcohol versus Iodine Tincture plus Alcohol

Chlorhexidine plus Alcohol versus PVI plus Alcohol

- Washer et al. 2010: CHG+ALC vs. PVI+ALC (RR: 1.61; 95% CI: 0.98-2.64)
### Blood Culture Summary

1. No evidence that CHG alone is effective
2. Excellent evidence for CHG+ALC vs. aqueous PVI
3. CHG+ALC vs. IT+ALC vs. PVI+ALC unresolved
4. Caldeira et al. 2011 Syst. Rev.: ALC alone may be sufficient

### Blood Culture Tertiary Sources

- Phlebotomy textbook
  - Echoing CLSI statements
- ClinMicroNet E-Mail Discussion Group
  - Multiple contributions discussing "chlorhexidine"

### Catheter Studies (part 1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
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<tbody>
<tr>
<td>Nais et al. 1991</td>
<td>RCT</td>
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<td>Shizukura et al. 1995</td>
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</tr>
<tr>
<td>Garlick et al. 1996</td>
<td>Seq. study</td>
<td>A</td>
<td>Not applicable</td>
</tr>
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<td>McEwen et al. 1998</td>
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### Catheter Studies (part 2)

<table>
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<tr>
<th>Reference</th>
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<tr>
<td>Kelly et al. 2008</td>
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</tr>
<tr>
<td>Bandyopadhyay et al. 2005</td>
<td>Seq. study</td>
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<td>Monnet et al. 2007</td>
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### Catheter meta-analyses

#### (1) Chlorhexidine alone (aq.) versus Povidone-Iodine alone (aq.)

<table>
<thead>
<tr>
<th>Study of Handgrip</th>
<th>CHG</th>
<th>Total</th>
<th>Weight</th>
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<tr>
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### Catheter meta-analyses

#### (2) Chlorhexidine + ALC versus Povidone-Iodine alone (aq.)

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Catheter Summary

(1) Excellent evidence for CHG+ALC vs. aqueous PVI
(2) CHG aq. performs well vs. PVI aq.; but no statistical significance for CR-BSI (consistent with earlier meta-analyses)
(3) CHG+ALC vs. PVI+ALC unresolved
(4) Clearly better evidence supporting use of CHG+ALC than CHG aq.

Surgical Studies

(1) Berry et al. 1982: RCT
   - CHG 5% + ALC (1%)
   - CHG 5% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference

(2) Brown et al. 1994: RCT
   - CHG 5% + ALC (1%)
   - CHG 5% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference

(3) Ostrander et al. 1995: RCT
   - CHG 5% + PVI (1%)
   - CHG 5% + ALC (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference

(4) Veiga et al. 1998: RCT
   - CHG 5% + ALC (1%)
   - CHG 5% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
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   - CHG 5% + ALC vs. CHG 5% + PVI: no difference

(5) Veiga et al. 1999: RCT
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   - CHG 5% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference

(6) Cheng et al. 1999: RCT
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   - CHG 5% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
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(7) Plotch et al. 2000: RCT
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(8) Plotch et al. 2000: RCT
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   - CHG 6% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 6% + ALC vs. CHG 6% + PVI: no difference
   - CHG 6% + ALC vs. CHG 6% + PVI: no difference
   - CHG 6% + ALC vs. CHG 6% + PVI: no difference

(9) Saia et al. 2010: RCT
   - CHG 5% + ALC (1%)
   - CHG 5% + PVI (1%)
   - Comparison: CHG + ALC
     - Evidence Category: IA
   - CHG 5% + ALC vs. CHG 5% + PVI: no difference
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(10) Saia et al. 2010: RCT
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     - Comparison: CHG + ALC
       - Evidence Category: IA
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     - CHG 5% + ALC vs. CHG 5% + PVI: no difference

Surgery Summary

(1) No evidence for CHG alone (superf. skin)
   (CHG alone commonly fails US FDA/ASTM regulatory requirements)
(2) Excellent evidence for CHG+ALC vs. aqueous PVI
(3) CHG+ALC vs. PVI+ALC remains unresolved
Interim Conclusions

(1) Excellent evidence for CHG+ALC over PVI aq. in blood cultures, catheters and surgery
(2) CHG+ALC vs. PVI+ALC inconclusive
(3) No evidence for CHG alone for blood cultures and surgery (superf. skin)
(4) Moderate evidence that CHG aq. works for catheters (but less evidence than for CHG+ALC)
(5) Perceived efficacy of CHG is often based on evidence for efficacy of CHG+ALC combination

Significance of the Findings

(1) CHG misattribution is scientifically incorrect
(2) The phenomenon has sizeable proportions
(3) Unsubstantiated recommendations in clinical practice recommendations and evidence-based guidelines
(4) Potentially mistaken a priori rejection of alternative or competitor antiseptics
(5) Potential implications for patient safety

--> Broader implications for evidence-based medicine

(1) Scientific Relevance

To recapitulate:

<table>
<thead>
<tr>
<th>Trial Arm</th>
<th>Active Ingredient 1</th>
<th>Active Ingredient 2</th>
<th>Clinical Outcome A</th>
</tr>
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</table>

• In the above scheme, it is NOT possible to conclude which active ingredient caused Clinical Outcome A

Nevertheless:

• This occurred in ~1/3 to 1/2 of the EBM literature on skin antisepsis, and affected all levels of evidence assessment:
  (1) Original clinical trials
  (2) Systematic reviews and meta-analyses
  (3) Clinical practice recommendations
  (4) Evidence-based guidelines

(2) Proportions and Impact Size

• Sizeable proportions:
  – Affects (1) blood cultures, (2) vascular devices, (3) surgery
  – Rates of incorr. attrib. btw. 29% and 43% (plus ambiguous)
  – Surgery more incorrect (43%) than correct (36%) attribution

• Significant impact on how CHG is viewed in Infection Control community

• Less than 30% of evaluated articles did both:
  – Correctly listed active ingredients of trialed antiseptics, and
  – Correctly attributed outcomes to actual antiseptics tested

(3) Impact on Clinical Guidelines

• Skewing of syst. reviews, practice recommendations and evidence-based guidelines in favor of CHG
  – Including US CLSI, CDC, Australian NHMRC, UK NICE

• New 2011 CDC vascular catheter guideline received correction during the public comment phase

• Multiple recommendations at conferences, professional websites, etc.

• See also earlier slides

(4) Impact on Alternative Antiseptics

• Common rejection of alternative antiseptics on the basis that they do not contain CHG

• Perception of efficacy pegged to CHG, not to alcohol

• Works by negative implication:
  “It does not contain CHG, therefore it is not supported by evidence”

• Multiple examples of such published articles
Why Evidence Should Have Biological Plausibility

(5) Patient Safety Aspects

- Caregivers may take recommendations to use “chlorhexidine” literally and use aqueous CHG
- Blood cultures: no direct threat to patients (but indirect impact from contaminated BCs)
- Catheters: CHG aq. has some protective effect
- However, Surgery:
  - No evidence that CHG alone is effective
  - Significant differences in SSI rates btw. antiseptics
- Caregivers may be unaware of ALC and use ALC-containing antiseptics on mucous membranes
  --> Potential impact on patient safety

Possible Origins of the Chlorhexidine Misattribution

Unclear; matter of speculation

(1) Alcohol may be viewed as a carrier substance or solvent for chlorhexidine
- Common view: “chlorhexidine in alcohol”
(2) Alcohol may not be universally viewed as an effective antiseptic
- E.g. CLSI Guideline on Blood Cultures: “cleansing” agent
(3) Word “chlorhexidine” may be used for CHG+ALC combination
- This would be medically/scientifically incorrect

Principles of Antiseptic Testing

(1) Suspension tests
- Tests in reagent tube format; qualitative or quantitative
- Shown is qualitative suspension test

(2) Tests under practical conditions
- E.g. on real hands, skin, etc.

Antiseptic Testing Standards

(1) US Standards
- Methods described in FDA TFM 1994
- Corresponding methods published by ASTM
- Examples: Suspension test: ASTM E2783
  Test on skin: ASTM E1173
(2) European Standards
- National protocols partly unified in EN standards
- Examples: Suspension test: EN 13727
  Test on skin: national tests

What are the Benefits and Limitations of Microbiological Testing vs. Clinical Trials?

(1) Microbiological Testing
- Does NOT measure real clinical endpoints
- Is a surrogate marker; clinical outcomes may differ
- However, in antiseptic history, results predict outcomes reasonably well (minor inconsistencies)
- No risk for patients from real infections
- Testing can be very detailed; many compounds can be tested under different conditions
- Manufacturers can “tweak” and optimize antiseptic composition according to test results

(2) Clinical Trials
- Provide information on real clinical outcomes
- Can be analyzed in syst. reviews & meta-analyses
- Strongest evidence to support clinical decisions (!)
- Limited by numbers of agents to be compared
- Each test requires 100s (1000s?) of real patients
- Risk from real infections; e.g. SSIs can be serious
- Open question: is it ethical to go into a trial with ~10:1 microbiological difference btw. antiseptics?
  (Applies to some published trials)
Why Evidence Should Have Biological Plausibility

Microbiological Performance of Antiseptics

• Alcohols signif. better (immed.) than either CHG aq. or PVI aq. (~ Factor 10)
• CHG+IPA = IPA alone (in immediate activity)
• CHG adds persistency to alcohol


Skin Antiseptics in Combination

Microbial data on skin indicate:
• PVI + ALC has additive/synergistic activity
• CHG + ALC has greater persistency

Biological & Functional Requirements

Blood Culture Collection
Antisepsis performed
~2 Minutes

Surgical Skin Preparation
Hours

Vascular Catheter Insertion and Maintenance

Days (-weeks)

Implications for Evidence-Based Medicine

Attribution problem affected systematic reviews and strict evidence-based guidelines

--> What are the reasons and further implications?

(1) Subjective views by authors
- May have assumed ALC is a solvent

(2) Biological plausibility
- This is a requirement for epidemiological research ("Bradford-Hill Criteria")
- No current requirement in EBM (Cochrane Handbook etc.)

Famous Bradford-Hill Criteria:
Set of criteria to prove causality in epidemiological research

Biological Plausibility in Epidemiological Research

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In other words:
The cause-and-effect relationship should be biologically plausible. It must not violate the known laws of science and biology. (From: German S, commentary on Sciencebloggs)
Why Evidence Should Have Biological Plausibility

Relevant Implications for Patient Care

- Sometimes it is useful to "look behind the scenes" of what exactly published evidence is based upon
- Alcohol is a powerful antiseptic, and the CHG+ALC or PVI+ALC combinations have added benefits
- Chlorhexidine – on its own – may not be the actual antiseptic supported by evidence
- Be aware, if or if not an antiseptic contains alcohol – it is then contraindicated for mucous membranes
- The jury is still out whether CHG+ALC or PVI+ALC is better for some applications

Conclusions

- A significant medical literature error has occurred in the area of skin antisepsis
- A likely reason is that published non-EBM information was not looked at or not taken into account
- Authors did not check whether new conclusions were consistent with principles of biol. plausibility
- From this instance, it is clear that biol. plausibility should be taken into account in EBM assessments
- However, it is unclear exactly how a plausibility check can be incorporated as a formal EBM requirement

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Declaration

- No conflicts of interest