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)

Photo: funkandwagnalls.com Copyright 1999, 2000 Emerging Infectious Diseases 7 (2); 2001

Seminal Work:
Semmelweis IP. Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers. Pest, Wien und Leipzig: C. A. Hartleben's Verlags-Expedition; 1861

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

Joseph Lister, 1st Baron Lister (1827-1912)

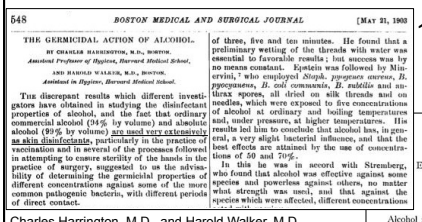
Photo: Wikipedia
http://www.universitystory.gla.ac.uk/image/?id=UGSP00886

Seminal Work:
Lister J. On the Antiseptic Principle in the Practice of Surgery. British Medical Journal 2 (351): 245-260; 1867.

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

History of Skin Antisepsis

1903



648 BOSTON MEDICAL AND SURGICAL JOURNAL [MAY 21, 1903

THE GERMICIDAL ACTION OF ALCOHOL.

BY CHARLES HARRINGTON, M.D., BOSTON.
Assistant Professor of Hygiene, Harvard Medical School,
AND HAROLD WALKER, M.D., BOSTON.
Assistant in Hygiene, Harvard Medical School.

THE discrepant results which different investigators have obtained in studying the disinfectant properties of alcohol, and the fact that ordinary commercial alcohol (94% by volume) and absolute alcohol (99% by volume) are used very extensively as skin disinfectants, particularly in the practice of vaccination and in several of the processes followed in attempting to ensure sterility of the hands in the practice of surgery, suggested to us the advisability of determining the germicidal properties of different concentrations against some of the more common pathogenic bacteria, with different periods of direct contact.

of three, five and ten minutes. He found that a preliminary wetting of the threads with water was essential to favorable results; but success was by no means constant. Epstein was followed by Minervini,[7] who employed *Staph. pyogenes aureus, B. pyocyaneus, B. coli communis, B. subtilis* and anthrax spores, all dried on silk threads and on needles, which were exposed to five concentrations of alcohol at ordinary and boiling temperatures and, under pressure, at higher temperatures. His results led him to conclude that alcohol has, in general, a very slight bacterial influence, and that the best effects are attained by the use of concentrations of 50 and 70%.

In this he was in accord with Sternberg, who found that alcohol was effective against some species and powerless against others, no matter what strength was used, and that against the species which were affected, different concentrations

Charles Harrington, M.D., and Harold Walker, M.D.
The Germicidal Action of Alcohol.
Boston Med Surg J 1903; 148: 548-552. May 21, 1903.

1939

Arch Surg. 1939;38(3):528-542.

ETHYL ALCOHOL AS A GERMICIDE

PHILIP B. PRICE, M.D.
BALTIMORE

Alcohol is probably the most popular of all cutaneous disinfectants. It is generally used in every country, not only in dressing wounds and in preoperative preparation of the surgeon's hands and the field of operation, but for a multitude of minor procedures, such as vaccinations, hypodermic injections and punctures of the skin for blood counts. Reasons for its popularity are obvious: It is relatively cheap and easy to obtain, it is pleasant to use and it "wets" the skin efficiently. An alcohol-soaked pledget can wipe away a certain amount of grease and dirt, and in universal experience its application seems capable of preventing infections from needle punctures and the like.

Laboratory tests, however, as reported in the literature, have on the whole shown alcohol to be but weakly bactericidal, and the prevailing conclusion of present day writers is that whatever efficiency it may have as a cutaneous disinfectant is due mainly to detergent properties.

A study of disinfectants, carried on over a period of several years, has led me to a different point of view. Using original quantitative tests of bactericidal activity, I have found ethyl alcohol, within certain narrow limits of concentration, to be strongly germicidal, both in vitro and on the skin. In addition, certain principles have been discovered which, I believe, govern the proper preparation and effective use of alcohol in surgical procedures.

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

Brief History of Antiseptic Testing

- 1881: Robert Koch published tests with *Bacillus anthracis* and alcohol (did not work well – as we now know spores)
- 1890s: Different authors (e.g. Reinicke 1894, Ahlfeld 1896, Epstein 1897) tested antiseptics for hands and skin
- 1930s to 50s: Price (USA) published seminal papers; precursors to US FDA/ASTM test methods
- 1950s to 70s: Lowbury & Lilly (UK) published seminal work
- 1958: Germany published 1st national set of test methods
- 1970s: US FDA tentative final monographs (TFMs) published
- 1970s to 80s: Various national sets of test requirements in European countries generated
- From 1990s: National European sets unified in EN standards

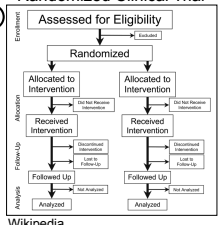
Note: Listing is not comprehensive

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

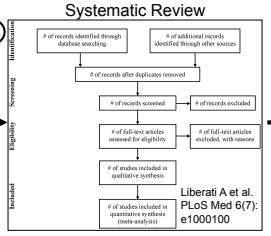
Process of Evidence-Based Medicine

Randomized Clinical Trial



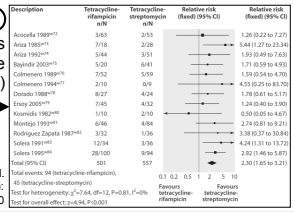
Wikipedia

Systematic Review



Liberati A et al. PLoS Med 6(7): e1000100

Meta-Analysis (Quantitative Synthesis)



Liberati A et al. PLoS Med 6(7): e1000100

4 Formal Evaluation: Evidence-Based Clinical Practice Guidelines

Skin Antisepsis: Modern Relevance

- Skin antisepsis is now a firmly established measure 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

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Antimicrobial Spectrum and Activity of Skin Antiseptics

Larson EL. Guideline, topical antimicrobial agents. AJIC 1988; 16: 253-66
Mangram AJ et al. ICHE 1999; 20: 250-78 ('CDC surgical guideline')

Agent	Mechanism of Action	Gram-Positive Bacteria	Gram-Negative Bacteria	Mtb	Fungi	Virus	Rapidity of Action	Residual Activity	Toxicity	Uses
Alcohol	Denature proteins	E	E	G	G	G	Most rapid	None	Drying, volatile	SP, SS
Chlorhexidine	Disrupt cell membrane	E	G	P	F	G	Intermediate	E	Ototoxicity, keratitis	SP, SS
Iodine/Iodophors	Oxidation/substitution by free iodine	E	G	G	G	G	Intermediate	Minimal	Absorption from skin with possible toxicity, skin irritation	SP, SS

E, excellent; G, good; F, fair; P, poor; SP, skin prep.; SS, surgical scrubs

- Alcohols are generally the most rapid-acting & most effective skin antiseptics (best activity at ~70-90%)
- Combination of alcohol plus chlorhexidine (CHG) or iodine (PVI) provides advantages: added effects, persistency
- Alcohol is unsuitable for mucous membrane antisepsis

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Chlorhexidine featured in several prominent clinical studies

The "Keystone Project" in Michigan ICUs -->

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 28, 2006 VOL. 355 NO. 26

N Engl J Med 2006;355:2725-32.

An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU

Peter Pronovost, M.D., Ph.D., Dale Needham, M.D., Ph.D., Sean Berenholtz, M.D., David Sinopoli, M.P.H., M.B.A., Haitao Chu, M.D., Ph.D., Sara Cosgrove, M.D., Bryan Sexton, Ph.D., Robert Hyzy, M.D., Robert Welsh, M.D., Gary Roth, M.D., Joseph Bander, M.D., John Kepros, M.D., and Christine Goeschel, R.N., M.P.A.

ORIGINAL ARTICLE

N Engl J Med 2010;362:18-26.

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

Rabih O. Darouiche, M.D., Matthew J. Wall, Jr., M.D., Kamal M.F. Itani, M.D., Mary F. Otterson, M.D., Alexandra L. Webb, M.D., Matthew M. Carrick, M.D., Harold J. Miller, M.D., Samir S. Awad, M.D., Cynthia T. Crosby, B.S., Michael C. Mosier, Ph.D., Atef AlSharif, M.D., and David H. Berger, M.D.

JANUARY 7, 2010 VOL. 362 NO. 1

N Engl J Med 2010;362:9-17.

Preventing Surgical-Site Infections in Nasal Carriers of *Staphylococcus aureus*

Lonneke G.M. Bode, M.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Heiman F.L. Wertheim, M.D., Ph.D., Diana Bogaers, I.C.P., Christina M.J.E. Vandenbroucke-Grauls, M.D., Ph.D., Robert Roosendaal, Ph.D., Annet Troelstra, M.D., Ph.D., Adrienne T.A. Box, B.A.Sc., Andreas Voss, M.D., Ph.D., Ingeborg van der Tweel, Ph.D., Alex van Belkum, Ph.D., Henri A. Verbrugh, M.D., Ph.D., and Margreet C. Vos, M.D., Ph.D.

Note:
Bode et al. 2010 not on skin antisepsis in a strict sense

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At some point we noticed something unusual . . .

One blood culture study

Blood Culture Contamination Rates after Skin Antisepsis with Chlorhexidine Gluconate versus Povidone-Iodine in a Pediatric Emergency Department

Infect Control Hosp Epidemiol 2010; 31:171-176

Lauren Marlowe, MD; Rakesh D. Mistry, MD, MS; Susan Coffin, MD, MPH; Kateri H. Leckerman, MS; Karin L. McGowan, PhD; Dingwei Dai, PhD; Louis M. Bell, MD; Theoklis Zaoutis, MD, MSCE

Two Systematic Reviews concerning surgical skin preparation

Systematic Review and Cost Analysis Comparing Use of Chlorhexidine with Use of Iodine for Preoperative Skin Antisepsis to Prevent Surgical Site Infection

Infect Control Hosp Epidemiol 2010; 31(12):1219-1229

Ingi Lee, MD, MSCE; Rajender K. Agarwal, MD, MPH; Bruce Y. Lee, MD, MBA; Neil O. Fishman, MD; Craig A. Umscheid, MD, MSCE

Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine *versus* povidone–iodine in clean-contaminated surgery

British Journal of Surgery 2010; **97**: 1614–1620

A. Noorani[1], N. Rabey[3], S. R. Walsh[1] and R. J. Davies[2]

- 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"

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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

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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?

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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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OPEN ACCESS Freely available online PLOS ONE

The Forgotten Role of Alcohol: A Systematic Review and Meta-Analysis of the Clinical Efficacy and Perceived Role of Chlorhexidine in Skin Antisepsis

PLoS ONE 7(9): e44277; 2012.
doi:10.1371/journal.pone.0044277

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Abstract

Background: Skin antisepsis is a simple and effective measure to prevent infections. The efficacy of chlorhexidine is actively discussed in the literature on skin antisepsis. However, study outcomes due to chlorhexidine-alcohol combinations are often attributed to chlorhexidine alone. Thus, we sought to review the efficacy of chlorhexidine for skin antisepsis and the extent of a possible misinterpretation of evidence.

Methods: We performed a systematic literature review of clinical trials and systematic reviews investigating chlorhexidine compounds for blood culture collection, vascular catheter insertion and surgical skin preparation. We searched PubMed, CINAHL, the Cochrane Library, the Agency for Healthcare Research and Quality website, several clinical trials registries and a manufacturer website. We extracted data on study design, antiseptic composition, and the following outcomes: blood culture contamination, catheter colonisation, catheter-related bloodstream infection and surgical site infection. We conducted meta-analyses of the clinical efficacy of chlorhexidine compounds and reviewed the appropriateness of the authors' attribution.

Results: In all three application areas and for all outcomes, we found good evidence favouring chlorhexidine-alcohol over aqueous competitors, but not over competitors combined with alcohols. For blood cultures and surgery, we found no evidence supporting chlorhexidine alone. For catheters, we found evidence in support of chlorhexidine alone for preventing catheter colonisation, but not for preventing bloodstream infection. A range of 29 to 43% of articles attributed outcomes solely to chlorhexidine when the combination with alcohol was in fact used. Articles with ambiguous attribution were common (8–35%). Unsubstantiated recommendations for chlorhexidine alone instead of chlorhexidine-alcohol were identified in several practice recommendations and evidence-based guidelines.

Conclusions: Perceived efficacy of chlorhexidine is often in fact based on evidence for the efficacy of the chlorhexidine-alcohol combination. The role of alcohol has frequently been overlooked in evidence assessments. This has broader implications for knowledge translation as well as potential implications for patient safety.

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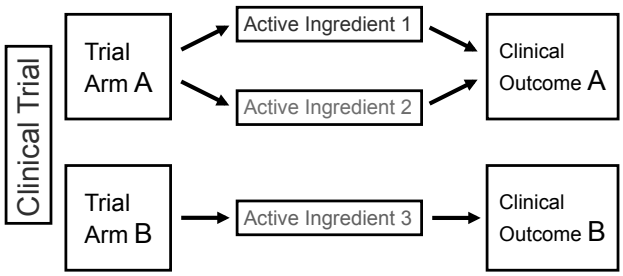
Potential Scheme of a Clinical Trial



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Criterion for Assessment

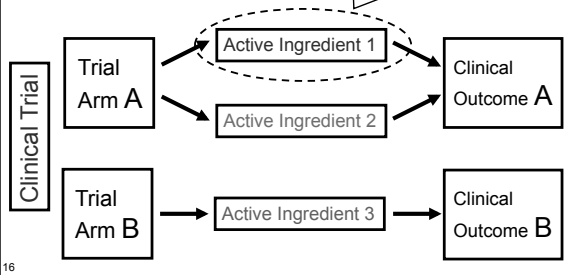
Attribution of study outcomes from CHG+ALC to CHG alone

Articles concluding:

"Outcome A is caused by Ingredient 1"

"Ingredient 1 is superior to Ingredient 3"

"The evidence supports Ingredient 1"



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Blood Culture Studies

Blood cultures: Primary studies and meta-analyses.

	Reference	Study design	Antiseptics	Outcomes	Attribution		
1	Mimoz et al. 1999	RCT	A: CHG 0.5% + ALC (?%) B: PVI aq. 10%	Favouring CHG + ALC	Incorrect	✗	☹
2	Trautner et al. 2002	RCT	A: CHG 2% + IPA 70% B: IPA 70% seq. IT	Insignificant	Correct	✓	☺
3	Barenfanger et al. 2004	Seq. design	A: CHG 2% + IPA 70% B: IT (composition?)	Insignificant	Incorrect	✗	☹
4	Madeo et al. 2008	Retrosp.	A: CHG 2% + IPA 70% B: Unknown	Favouring CHG + ALC	Correct	✓	☺
5	McLellan et al. 2008	Seq. design	A: CHG 2% + IPA 70% B: IPA 70%	Insignificant	Correct	✓	☺
6	Stonecypher 2008	Alt. months	A: CHG 2% + IPA 70% B: PVI aq. 10%	Favouring CHG + ALC	Incorrect	✗	☹
7	Suwanpimolkul et al. 2008	RCT	A: CHG 0.5% + ETH 70% B: PVI aq. 10%	Favouring CHG + ALC	Correct	✓	☺
8	Tepus et al. 2008	Retrosp.	A: CHG 2% + IPA 70% B: IPA 70% seq. IT	Favouring CHG + ALC	Intermediate	~	😐
9	Marlowe et al. 2010	Retrosp.	A: CHG 3.15% + IPA 70% B: PVI aq. 10%	Favouring CHG + ALC	Incorrect	✗	☹
10	Washer et al. 2010	RCT	A: CHG 2% + IPA 70% B: IPA 70% seq. PVI 10% C: IPA 70% seq. IT	Insignificant	Correct	✓	☺
11	Malani et al. 2007	Syst. Rev.	2 CHG trials	No clear evidence	Correct	✓	☺
12	Caldeira et al. 2011	Syst. Rev.	3 CHG trials	Complex	Correct	✓	☺

RCT, randomized clinical trial; Seq., sequential; Alt., alternative; CHG, chlorhexidine; ALC, alcohol; ETH, ethanol; IPA, isopropanol; IT, iodine tincture

Attribution Results:
Correct 7 (58%), intermediate 1 (8%), incorrect 4 (33%)

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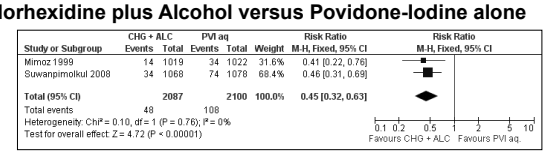
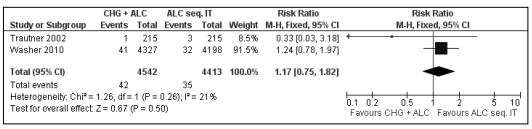
Blood culture meta-analyses

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)

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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

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Blood Culture Tertiary Sources

2007
CLINICAL AND LABORATORY STANDARDS INSTITUTE®
M47-A
ISBN 1-56238-641-7
Volume 27 Number 17
ISSN 0273-3099
Principles and Procedures for Blood Cultures; Approved Guideline

- "... chlorhexidine gluconate [without reference to alcohols] ... is the recommended skin disinfectant for older infants, children, and adults."

Phlebotomy textbook

- Echoing CLSI statements

ClinMicroNet E-Mail Discussion Group

- Multiple contributions discussing "chlorhexidine"

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Catheter Studies (part 1)

Vascular catheters: Primary studies and systematic reviews.

	Reference	Study design	Antiseptics	Outcomes	Attribution	
1	Maki et al. 1991	RCT	A: CHG aq. 2% B: PVI aq. 10% C: IPA 70%	Favouring CHG aq (col.)	Not applicable	N.A.
2	Sheehan et al. 1993	RCT	A: CHG aq. 2% B: PVI aq. 10%	Favouring CHG aq (col.)	Not applicable	N.A.
3	Garland et al. 1995	Seq. study	A: CHG 2% + IPA 70% B: PVI aq. 10%	Favouring CHG alc (col.)	Incorrect	✗ ☹
4	Meffre et al. 1996	RCT	A: CHG 0.5% + ALC (?%) B: PVI aq. 10%	Favouring CHG alc (col.)	Correct	✓ ☺
5	Mimoz et al. 1996	RCT	A: CHG triple comb. B: PVI aq. 10%	Favouring CHG triple (col.)	Correct	✓ ☺
6	Legras et al. 1997	RCT	A: CHG 0.5% + ALC (?%) B: PVI aq. 10%	Insignificant	Intermediate	~ 😐
7	Cobbett & LeBlanc 2000	RCT	A: CHG 0.5% + IPA 70% B: ALC seq. PVI aq. C: PVI aq. seq. ALC	Insignificant	Correct	✓ ☺
8	Humar et al. 2000	RCT	A: CHG 0.5% + ALC (?%) B: PVI aq. 10%	Insignificant	Intermediate	~ 😐
9	Maki et al. 2001	RCT	A: CHG 1% + ALC 75% B: PVI aq. 10%	Favouring CHG alc.	Intermediate	~ 😐
10	Langgartner et al. 2004	RCT	A: CHG 0.5% + IPA 70% B: PVI aq. 10% C: Seq. A & B	Seq. significant (col.)	Correct	✓ ☺
11	Astle & Jensen 2005	RCT	A: CHG 0.5% + IPA 70% B: ExSept	Insignificant	Incorrect	✗ ☹

RCT, randomized clinical trial; Seq., sequential; Alt., alternative; CHG, chlorhexidine; PVI, povidone-iodine; ALC, alcohol; ETH, ethanol; IPA, isopropanol

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Catheter Studies (part 2)

Vascular catheters: Primary studies and systematic reviews. (Continued).

	Reference	Study design	Antiseptics	Outcomes	Attribution	
12	Kelly et al. 2005	RCT	A: CHG 2% + IPA 70% B: PVI aq. 10%	Favouring CHG alc.	Incorrect	✗ ☹
13	Balamongkhon et al. 2007	Seq. study	A: CHG 2% + ETH 70% B: PVI aq. 10%	Insignificant	Intermediate	~ 😐
14	Mimoz et al. 2007	RCT	A: CHG triple comb. B: PVI 5% + ETH 70%	Favouring CHG triple (col.)	Intermediate	~ 😐
15	Small et al. 2008	RCT	A: CHG 2% + IPA 70% B: IPA 70%	Favouring CHG alc. (col.)	Correct	✓ ☺
16	Vallés et al. 2008	RCT	A: CHG 2% + ALC (?%) B: CHG 2% aq. C: PVI aq. 10%	Favouring CHG alc. (aq. insig.)	Correct	✓ ☺
17	Garland et al. 2009	RCT	A: CHG 0.5% + ALC (?%) B: PVI aq. 10%	Insignificant	Incorrect	✗ ☹
18	Ishizuka et al. 2009	Alt. month design	A: CHG aq. 0.05% B: PVI aq. 10%	Insignificant	Not applicable	N.A.
19	Chaiyakunapruk et al. 2002	Syst. Rev.	8 CHG trials	Complex; CHG alc. signif.	Incorrect	✗ ☹
20	Rickard and Ray-Barruel 2009	Syst. Rev.	5 CHG trials	Complex; CHG alc. signif. (col.)	Intermediate	~ 😐

RCT, randomized clinical trial; Seq., sequential; Alt., alternative; CHG, chlorhexidine; PVI, povidone-iodine; ALC, alcohol; ETH, ethanol; IPA, isopropanol

Attribution Results (excl. 3 N.A.):
Correct 6 (35%), intermediate 6 (35%), incorrect 5 (29%)

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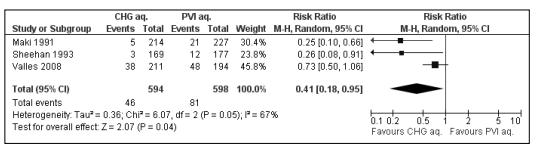
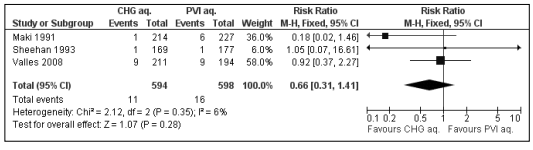
Catheter meta-analyses

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

(a) Catheter colonization



(b) Catheter-related bloodstream infection



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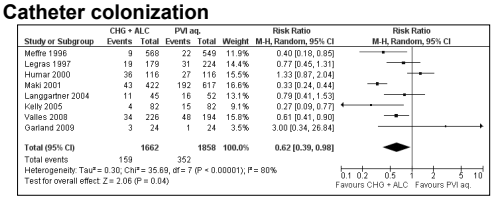
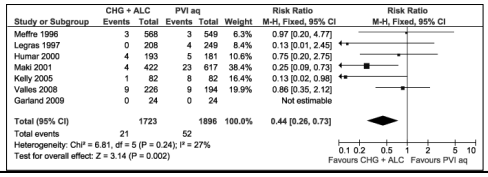
Catheter meta-analyses

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

(a) Catheter colonization



(b) Catheter-related bloodstream infection



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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.

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Catheter Tertiary Sources

The Keystone Project

ESTABLISHED IN 1812 DECEMBER 28, 2006 VOL. 355 NO. 26
Pronovost P et al. N Engl J Med 2006;355:2725-32.
An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU

- Intervention of five evidence-based procedures: ". . . cleaning the skin with chlorhexidine . . ." (ALC not mentioned)
- However, participating hospitals use CHG+ALC combination

CDC 2002 Catheter Guideline Plus Draft for 2011 Guideline

Morbidity and Mortality Weekly Report
Recommendations and Reports August 9, 2002 / Vol. 51 / No. RR-10
Guidelines for the Prevention of Intravascular Catheter-Related Infections

- Use "a 2% chlorhexidine preparation for skin antisepsis" (ALC as 2ndary alternative). Evidence Category IA.

Multiple websites, review articles, talks at conferences

- Evidence supports "chlorhexidine" (mostly no mention of ALC)

CDC 2011 Final Guideline

Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011

- >0.5% chlorhexidine preparation with alcohol
- However, CDC Toolkit continues "chlorhexidine" (no mention of ALC)

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Surgical Studies

Surgery: Primary studies and systematic reviews.

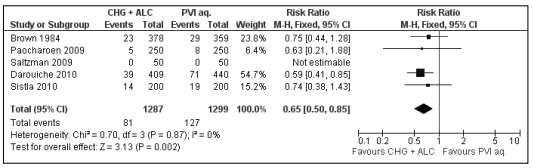
	Reference	Study design	Antiseptics	Outcomes	Attribution
1	Berry et al. 1982	RCT	A: CHG 0.5% + ALC (?%) B: PVI 10% + ALC (?%)	Favouring CHG + ALC	Incorrect
2	Brown et al. 1984	RCT	A: CHG 0.5% + IPA 70% B: PVI aq. (?%)	Insignificant	Incorrect
3	Ostrander et al. 2005	RCT	A: CHG 2% + IPA 70% B: IPOV + IPA 74% C: Chloroxylenol 3%	Insignificant	Intermediate
4	Veiga et al. 2008	RCT	A: CHG 0.5% + ALC (?%) B: PVI 10% + ALC (?%)	Insignificant	Incorrect
5	Cheng et al. 2009	RCT	A: CHG 2% + IPA 70% B: PVI 10% + IPA 23%	Insignificant	Intermediate
6	Paocharoen et al. 2009	RCT	A: CHG 4% + IPA 70% B: PVI aq. (?%)	Insignificant	Incorrect
7	Saltzman et al. 2009	RCT	A: CHG 2% + IPA 70% B: IPOV + IPA 74% C: PVI aq. scrub & paint	Insignificant	Correct
8	Swenson et al. 2009	Seq. study	A: CHG 2% + IPA 70% B: PVI aq. seq. IPA 70% C: IPOV + IPA 74%	Favouring IOD + ALC	Correct
9	Darouiche et al. 2010	RCT	A: CHG 4% + IPA 70% B: PVI aq. scrub & paint	Favouring CHG + ALC	Correct
10	Sistla et al. 2010	RCT	A: CHG 2.5% + ETH 70% B: PVI aq. 10%	Insignificant	Correct
11	Levin et al. 2011	Retrosp. study	A: CHG aq. 2% seq. IPA B: PVI aq. seq. PVI + ETH	Favouring CHG aq. seq. IPA	Correct
12	Edwards et al. 2004	Syst. Rev.	1 CHG trial	Inconclusive	Intermediate
13	Lee et al. 2010	Syst. Rev.	9 CHG trials (5 CHG + ALC vs. PVI aq.)	Favouring any CHG	Incorrect
14	Noorani et al. 2010	Syst. Rev.	6 CHG trials (3 CHG + ALC vs. PVI aq.)	Favouring any CHG	Incorrect

RCT, randomized clinical trial; Seq., sequential; CHG, chlorhexidine; PVI, povidone-iodine; ALC, alcohol; ETH, ethanol; IPA, isopropanol; IPOV, iodine povacrylex; IOD, iodine compounds

27 **Attribution: Correct 5 (36%), intermediate 3 (21%), incorrect 6 (43%)**

Surgery meta-analyses

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



(2) Chlorhexidine + ALC versus Iodine + ALC

No meta-analysis done:

Berry et al. 1982: ALC % in both trial arms unknown
Ostrander et al. 2005: Small trial, only 1 SSI, only in CHG+ALC
Veiga et al. 2008: ALC % in both trial arms unknown
Cheng et al. 2009: ALC % in PVI arm far below active % range
Swenson et al. 2009: No RCT
Levin et al. 2011: No RCT; ALC % in CHG arm >> PVI arm
--> All inconclusive, heterogeneous, and/or design limitations

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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

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Surgery Tertiary Sources

Current Concepts Review
Prevention of Perioperative Infection
J Bone Joint Surg Am. 2007;89:1605-18
By Nicholas Fletcher, MD, D'Mitri Sofianos, BS, Marschall Brantley Berkes, BS, and William T. Obremskey, MD, MPH

- "Chlorhexidine gluconate is superior to povidone-iodine for preoperative antisepsis."

SCOAP Surgical Care Initiative

SCOAP Surgical Checklist Initiative "A System for Safer Surgery"

- Checklist Item: "Confirm that skin prep is with chlorhexidine unless contraindicated"

Australian NHMRC National Guideline 2010

- "Chlorhexidine" (without reference to alcohol) should be preferably used for skin preparation

Several other websites

- Evidence supports "chlorhexidine" (mostly no mention of ALC)

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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

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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

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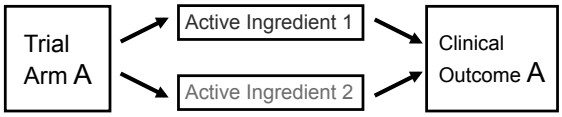
(1) Scientific Relevance

To recapitulate:



- 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

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(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

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(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

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(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

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(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

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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

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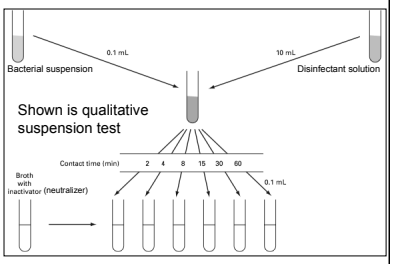
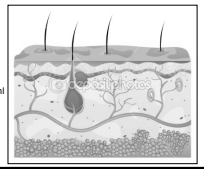
Principles of Antiseptic Testing

(1) Suspension tests
  - Tests in reagent tube format; qualitative or quantitative



Source: Reybrouck G. Evaluation of the antibacterial and antifungal activity of disinfectants. Chapter 7.2. In: Fraise AP, Lambert PA, Maillard JY (eds.). Russell, Hugo & Ayliffe's Principles and Practice of Disinfection, Preservation & Sterilization, 4th ed., Oxford, UK: Blackwell Publishing; 2004

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



Source: http://depositphotos.com/4583685/stock-photo-Skin-cells.html

Note: description of principles simplified

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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

Abbreviations: FDA, Food and Drug Administration; TFM, Tentative Final Monograph; ASTM, American Society for Testing and Materials

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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

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

(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)

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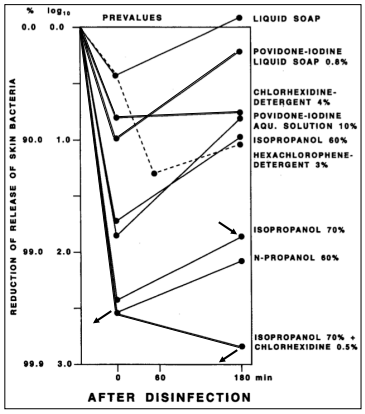
Why Evidence Should Have Biological Plausibility

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

Source: Rotter ML. Hand washing and hand disinfection. In: Mayhall CG, ed. Hospital epidemiology and infection control. Philadelphia: Lippincott Williams and Wilkins; 2004.

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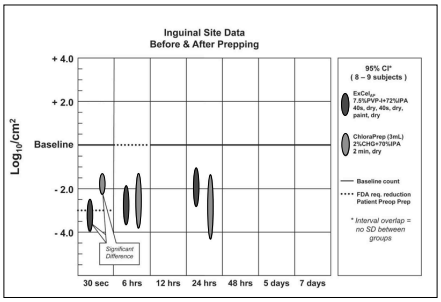
Skin Antiseptics in Combination



Art G.
J Assoc Vasc Access 2007; 12: 156-63

Comparison of PVP-I + ALC versus CHG + ALC Immediate vs. persistent

Microbial data on skin indicate:

- PVI + ALC has additive/synergistic activity
- CHG + ALC has greater persistency

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Biological & Functional Requirements

Blood Culture Collection

↓

~2 Minutes

Surgical Skin Preparation

↓

Hours

Antisepsis performed ↓

- Relative importance of CHG increases with requirements for persistency
- Consistent with outcomes from clin. trials & meta-analyses

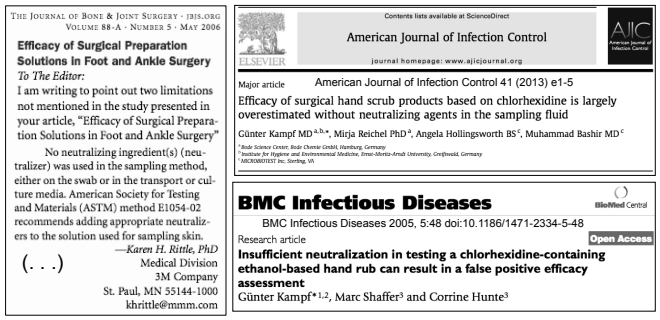
Vascular Catheter Insertion and Maintenance

↓ ↓ ↓ ↓ ↓

Days (-weeks)

45

Microbiological Efficacy of CHG, too, is sometimes overestimated



THE JOURNAL OF BONE & JOINT SURGERY · JBJS.ORG
VOLUME 88-A · NUMBER 5 · MAY 2006

Efficacy of Surgical Preparation Solutions in Foot and Ankle Surgery

To The Editor:

I am writing to point out two limitations not mentioned in the study presented in your article, "Efficacy of Surgical Preparation Solutions in Foot and Ankle Surgery"

No neutralizing ingredient(s) (neutralizer) was used in the sampling method, either on the swab or in the transport or culture media. American Society for Testing and Materials (ASTM) method E1054-02 recommends adding appropriate neutralizers to the solution used for sampling skin.

(. . .)

—*Karen H. Rittle, PhD*
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St. Paul, MN 55144-1000
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Contents lists available at ScienceDirect
American Journal of Infection Control
journal homepage: www.ajicjournal.org

Major article American Journal of Infection Control 41 (2013) e1-5

Efficacy of surgical hand scrub products based on chlorhexidine is largely overestimated without neutralizing agents in the sampling fluid

Günter Kampf MD[a,b,*], Mirja Reichel PhD[a], Angela Hollingsworth BS[c], Muhammad Bashir MD[c]

[a] Bode Science Center, Bode Chemie GmbH, Hamburg, Germany
[b] Institute for Hygiene and Environmental Medicine, Ernst-Moritz-Arndt University, Greifswald, Germany
[c] MICROMYCETE Inc, Sterling, VA

BMC Infectious Diseases

BMC Infectious Diseases 2005, 5:48 doi:10.1186/1471-2334-5-48

Research article

Insufficient neutralization in testing a chlorhexidine-containing ethanol-based hand rub can result in a false positive efficacy assessment

Günter Kampf*[1,2], Marc Shaffer[3] and Corrine Hunte[3]

- Some antiseptics (esp. CHG) continue to act after sampling
- Neutralizer agents mandated by various testing standards
- Some studies (incl. clin. trials) published data w/out neutralizers

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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.)

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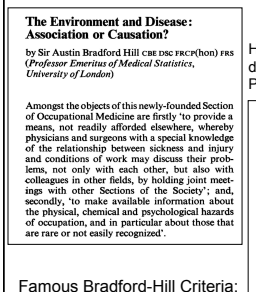
Biological Plausibility in Epidemiological Research



The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS (*Professor Emeritus of Medical Statistics, University of London*)

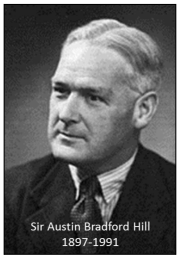
Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

Hill AB (1965) The environment and disease: association or causation? Proc R Soc Med 58: 295–300

(6) *Plausibility:* It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

'. . . no biological knowledge to support (or to refute) Pott's observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other "absurd" associations, that "it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected". And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.'



Sir Austin Bradford Hill
1897-1991

http://multiple-sclerosis-research.blogspot.sg/2011/04/ccsvi-time-for-sir-bradford-hills.html

Famous Bradford-Hill Criteria:

Set of criteria to prove causality in epidemiological research

In other words: The cause-and-effect relationship should be biologically plausible. It must not violate the known laws of science and biology. (From: Gorman S, commentary on ScienceBlogs).

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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

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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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Help with systematic review process, meta-analyses, principles of EBM

- E.S.Y. Chan (Singapore)

Insight into conceptual aspects of hand and skin antisepsis

- A.F. Widmer (Basel, CH); M.L. Rotter (Vienna, AT)

Information on antiseptic testing & regulation in Europe

- A.F. Widmer, M. Dangel (Basel, CH); M.L. Rotter (Vienna, AT); G. Kampf (Bode, Hamburg, DE); M. Braun (Schuelke, Norderstedt, DE)

Information on antiseptic testing & regulation in USA

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Assistance with historical literature

- G. Kampf (Bode, Hamburg, DE); D. Macinga (Gojo, USA)

Other assistance (literature searching, statistics, etc.)

- T.N. Petney (Karlsruhe, DE); D.T. Bautista, P.B.Y. Fong (Singapore)

Declaration

- No conflicts of interest

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12 February *(British Teleclass)* COMMISSIONING INFECTION PREVENTION AND CONTROL SERVICES IN THE NEW NHS
Speaker: Debbie King, NHS Solihull Clinical Commissioning Group, UK

13 February *(South Pacific Teleclass)* HOSPITAL DESIGN AND INFECTION PREVENTION AND CONTROL
Speaker: Dr Massimo Giola, Bay of Plenty District Health Board, New Zealand

28 February THE CLINICAL AND BUSINESS CASE FOR INVESTING IN IMPROVED ENVIRONMENTAL HYGIENE
Speaker: Mark Heller, Unisource Worldwide

06 March *(WHO Teleclass)* PATIENT PARTICIPATION IN HAND HYGIENE PROMOTION AND IMPROVEMENT
Speaker: Prof. Yves Longtin, University of Laval, Canada

07 March RATIONALE AND CONCEPTS IN DENTAL INFECTION CONTROL

www.webbertraining.com/schedulep1.php