TAB 9 **FDA Reviewer's Evaluation of CTFA/SDA Submission (CP7 & C80) Regarding Clinical Benefit:**

- **Healthcare Personnel Handwashes – Steven Osborne, M.D.**
- **Patient Preoperative Skin Preparations -Steven Osborne, M.D.**
- **Surgical Hand Scrubs – Michelle M. Jackson, Ph.D.**

Medical Officer's Review

Docket No. 75N-183H
Product Name: Healthcare Antiseptics
Use: Healthcare Personnel Handwash and Patient Pre-operative Preparation
Type of Document: Citizen Petition (CP) and Comment (C) to Healthcare Antiseptic Rulemaking
Petitioner: Cosmetic, Toiletry, and Fragrance Association
Date Submitted: August 6, 2001 (CP7) and August 27, 2003 (Comment 80)
Date Reviewed: January 20, 2005
Reviewer: Steven Osborne, M.D.

Purpose

The purpose of this review is to determine if data submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in a citizen petition and comment to the healthcare antiseptic rulemaking support their request to revise the proposed effectiveness criteria in the Health-Care Antiseptic Drug Products Monograph. CTFA requested that the log reduction criteria in the 1994 tentative final monograph be lessened for ingredients marketed as healthcare antiseptics. They submitted numerous articles from the medical literature to support their recommendations. This review focuses on healthcare personnel handwashes and patient pre-operative preparations. As noted in the table of contents, the review first provides a brief synopsis of each literature report (page 6 – 27). Tabular summaries of the same studies are provided as attachments.

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Background

The Food and Drug Administration (FDA) published a Tentative Final Monograph (TFM) on Health-Care Antiseptic Drug Products on June 17, 1994. In the TFM, topical antimicrobial products were organized into seven categories based on their use situation. In general two broad use situations were found:

1. in the hospital/healthcare setting
2. in the home

FDA also published guidelines for establishing performance and effectiveness criteria for healthcare antiseptic products. FDA outlined and defined three categories of drug products:

1. *Patient preoperative skin preparation.* A fast-acting, broad spectrum, and persistent antiseptic-containing preparation that substantially reduces the number of microorganisms on intact skin.

2. *Antiseptic handwash or Healthcare Personnel Handwash.* An antiseptic-containing preparation designed for frequent use; it reduces the number of microorganisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying; it is broad-spectrum, fast-acting, and if possible, persistent.

3. S*urgical hand scrub.* An antiseptic-containing preparation that substantially reduces the number of microorganisms on intact skin it is broad-spectrum, fast-acting, and persistent.

In the TFM, FDA classified antiseptics into category I, category II, or category III.
The following list denotes the category definitions and proposed classification of antiseptics:

1. Category I: generally accepted as safe and effective and not misbranded

2. Category II: not generally accepted as safe and effective or misbranded

3. Category III: available data are insufficient to classify as safe and effective, and further testing is required

Table I below illustrates the proposed classifications of the ingredients. Note that a product can have different categorizations depending upon the indication as a skin preparation, handwash, or surgical scrub. Also, safety (S) and effectiveness (E) can differ for a product depending upon the indication.

Table 1. Topical Antimicrobial Ingredients: Summary of Health-Care Antiseptic Active Ingredients

Active Ingredient	Patient preoperative skin preparation	Antiseptic handwash or health-care personnel handwash	Surgical hand scrub
PCMX (chloroxylenol)	IS, IIIE	IIISE	IIISE
Hexachlorophene	II	II	II
Chlorhexidine gluconate	Requires NDA	Requires NDA	Requires NDA
Povidone-iodine 5 to 10%	I	I	I
Benzalkonium chloride	IIIE	IIISE	IIISE
Benzethonium chloride	IIIE	IIISE	IIISE
Triclosan	IIIE	IIISE	IIISE
Alcohol 60-95 percent (ethanol):	I	I	I
Isopropyl alcohol (IPA) 70-91.3 percent	I	IIIE	IIIE
Triclocarban:	IIIE	IIIE	IIIE

Other products and combinations are listed in the TFM but have much lower use in the marketplace and are not targeted by the CTFA data considered in this review.

This classification of products in the TFM affects the potential status of antiseptics already marketed. In particular, the category II and category III products containing PCMX, triclosan, benzalkonium chloride, benzethonium chloride, methylbenzethonium chloride, isopropyl alcohol 70-91.3 percent, triclocarban, and hexachlorophene could face restricted use or removal from the market[1]. If that were to occur, the products involved could be resubmitted as new drug applications with all the required elements of that process.

The CTFA responded to the TFM with a Citizen's Petition (CP7) on August 6, 2001, and again on August 23, 2003 with a Comment to the Docket (C80). The CTFA proposes that the criteria for proving benefit from a healthcare antiseptic product be relaxed by lowering the standard for reduction in bacterial counts. This review addresses CP7 and C80 particularly with regard to patient preoperative skin preparations and health-care personnel handwashes (or antiseptic handwash). Surgical hand scrubs are covered in a separate review. Definitions for abbreviations can be found in the Legend on page 32.

REVIEW

In CP7 and C80 the CTFA outlined their argument regarding the safety, effectiveness, and clinical benefit of currently marketed healthcare antiseptics. The CTFA proposed classifying the benefits of topical antimicrobial products in two categories involving either *Invasive Procedures or Non-Invasive Procedures.* This review follows the CTFA format in order to facilitate correlation with the arguments of CP7 and the C80. Following the review, a summary of clinical benefit will be presented that follows the

[1] If additional data does not support a change in the classification of the ingredient to category I prior to finalizing the monograph, the ingredients will be designated nonmonograph (category II).

TFM categories of patient preoperative skin preparation and antiseptic handwash or healthcare personnel handwash.

The CTFA described Invasive Procedures as those when infection might occur due to the transfer of resident bacteria into wounds, incisions, injection sites, or damaged skin. They described Non-Invasive Procedures as those when infection might occur due to the acquisition of transient bacteria and their transfer to a point of entry into the host, and to oneself due to skin infections from one's own resident skin flora.

The CTFA asserted that the use of topical antimicrobial products provides benefit in the two broad clinical settings of **invasive situations** and **non-invasive situations**. The CTFA states that:

1. *In invasive situations topical antimicrobial products interrupt or minimize the risk of infection due to the transfer of resident bacteria into wounds, incisions, and injection sites or damaged skin.*

In CP7, CTFA stated that the aim of skin disinfection in **invasive procedures** is the quick removal and killing of as many of the skin flora as possible at the site of a planned invasive procedure in order to prevent their translocation into the underlying tissues by a knife blade or a needle. The petitioner states that the organisms that are primarily associated with these types of infections are Gram positive bacteria derived from the patient or from the caregiver. In CP7, **invasive procedures** are divided into seven Clinical Settings Categories:

Seven Clinical Settings (Invasive Procedures):

1. Surgery
2. Catheters, ventilators, and intravenous lines
3. Ophthalmic surgery
4. Skin graft preparation
5. Blood cultures
6. Surgical glove failure
7. Preoperative or post-operative body wash

2. In non-invasive situations topical antimicrobial products interrupt or minimize disease transmission to others and oneself due to the acquisition of transient bacteria and their transfer to a point of entry into the host, and to oneself due to skin infections from one's own resident skin flora.

In CP7, the CTFA stated that the aim of skin disinfection in **non-invasive procedures** is the killing or inhibition of the skin flora to: a) prevent the conveyance of transient bacteria from one person directly or via a fomite to oneself or another person, or b) reduce the resident bacteria and thereby control the risk of pyogenic infection, or c) decrease the numbers of resident bacteria associated with diseases such as atopic dermatitis. The petitioner states that the organisms that are associated with these types of infections include Gram positive and Gram negative bacteria. In CP7, **Non-Invasive Procedures** are divided into six Clinical Setting Categories, six Institutional Setting Categories, and seven Home Setting Categories.

Six Clinical Settings (Non-Invasive Procedures):

1. Reduced nosocomial infection rates
2. Control of methicillin-resistant Staphylococcus aureus
3. Reduction in transfer of bacteria from patient's to caregiver's hands
4. Significant reduction in total bacterial load on caregiver's hands
5. Significant reduction in Staphylococci and other gram positive organisms
6. Significant reduction in gram negative organisms

Six Institutional Settings (Non-Invasive Procedures):

1. School absenteeism reduced
2. Reduction in respiratory infection rate in adult day care centers
3. Reduced symptoms of enteric disease
4. Reduced eye and skin/wound infection rates
5. Healing of scrapes and scratches
6. MRSA eradicated in day care setting

Seven Home Settings (Non-Invasive Procedures):

1 Atopic skin
2 Skin infection risk
3 Adjunct to acne treatment
4. Reduced respiratory illness in mothers
5. Reduced puerperal mastitis rate in nursing mothers
6. Reduced eye infection
7. Reduction of bacteria on contact lens

Assignment of Clinical Benefit Categories:

- This reviewer has assigned the 130 references reviewed into categories having clinical benefit, no clinical benefit, or arguable clinical benefit. The assignment was done in the context of identifying clinical data that could be used to support regulatory decisions regarding efficacy of an antiseptic (e.g. a study correlating specific bacteria log reductions on the skin to a clinical outcome).
- For an article to show clinical benefit, the investigators should have reported a clinical trial in which they randomized patients, blinded the researchers, used a control, adequately powered the study, had good data collection, and achieved statistically significant and clinically significant results.
- If a reference studied an indication not listed in the TFM (such as a dermatological use of a topical antiseptic), then that reference is categorized as not showing clinical benefit, since it is not on point with the TFM categories of patient preoperative skin preparation or antiseptic handwash or healthcare personnel handwash.
- If a reference does not demonstrate the good methodology characteristics of a study showing clinical benefit, then the reference is simply rated as not showing clinical benefit.

- All 130 studies had fatal flaws in methodology, such as nonrandomization, lack of a control, no blinding, poor data collection, or they did not seek a clinical outcome or they did not address a TFM indication.

Citizen Petition 7
Review of Articles Regarding Invasive Procedures

The CTFA states that studies examining clinical endpoints support the benefits of using topical antimicrobial products in invasive procedures. These are summarized below.

Clinical Settings

1. Surgery – The CTFA states that the following clinical studies have shown the benefit of using topical antimicrobial products to control the resident flora on surgeons' hands and at the site of incision in many different types of surgery including: intrathoracic procedures (Hughes et al. 1966; Klovekorn et al. 1985), gynecological surgery (Beaton undated), neurological procedures (Jackson 1972), intraperitonial procedures (Gruer et al. 1984; Brown et al. 1984), vascular surgery (Grinbaum et al. 1995; Denton 1991), and general or elective surgery (Georgiade et al. 1990; Brandberg et al. 1981; Cruse and Foord 1973; Connell and Rousselot 1964; Burkhardt et al. 1986; Berry et al. 1982; Denton 1991; Rubio 1987; Onesko and Wienke 1987).

Hughes et al 1966 is a retrospective report of hospital antisepsis procedures and not an observational trial. The report notes no endocarditis in 86 consecutive patients over 29 months while using topical 3% hexachlorophene, as well as topical and intravenous antibiotics. The author did not report prior procedures and infection experience and did not report any comparison statistics.

Klovekorn et al 1985 is a retrospective report of the authors' ten year experience with using povidone-iodine in patients undergoing open-heart procedures and not an observational trial. The authors noted a 5% and 0.5% incidence of superficial and deeper wound infections in 7566 open-heart surgery patients on whom povidone-iodine was used as a preoperative bath, preoperative solution, and surgical scrub. The authors did not make a comparison with any infection data prior to the ten year period or report any comparison statistics with a control product. The study is confounded by use of alcohol foam.

Beaton undated, no citation, is a retrospective report of the author's clinical experience using Betadine Surgical Scrub (mostly on external genitalia) plus Betadine Solution (intravaginal) in 137 hysterectomy patients. Five percent of the 137 patients developed a temperature over 102°F ($P<0.05$) compared with 11.3% (99 of 880) in a previous group who had only Betadine Surgical Scrub used mostly externally. Some or all of both groups had "prophylactic antibiotics" (prophylactic antibiotics are not defined). The author used the patient's temperature as a surrogate for infection, but did not present specific infection or culture data.

Jackson 1972 is a retrospective report on the use of povidone-iodine in patients undergoing neurosurgical procedures and not an observational trial. In 393 neurosurgical procedures from Jan 1968-March 1971 only one infection (0.254%) was found. The investigator used PI as a surgical scrub and as a patient preoperative prep. He did not make a comparison with any prior infection data, nor did he provide a description of the cleansing methodology. The study did not use a control product.

Gruer et al. 1984 conducted a randomized 3-month study of the effectiveness of two methods of handwashing in 31 patients undergoing continuous ambulatory peritoneal dialysis (CAPD). The 10 patients in group A used non-medicated soap for general handwashing, while group B used Hibiscrub. Prior to CAPD bag exchange, Group A washed with a standard method of Betadine Surgical Scrub, followed by an application of 5 ml of 70% ethanol with a 1% glycerol emollient. Group B applied 5ml of 70% ethanol and 1% glycerol to their hands. Group A cleaned the exit site with PI detergent, while Group B used CHG detergent. Also, Group B sprayed the connector and tubing with 70% ethanol. The mean bacterial counts from the fingers of patients in Group A rose, while the counts fell in Group B ($P<0.001$). However, over the 3-month study there were 7 instances of peritonitis in six Group A patients and 9 instances in six group B patients (no difference). In both groups the incidence of coagulase-negative staph peritonitis was lower than prior to the study. A reduction in bacterial counts did not equate to an improvement in clinical outcome. The study design did not allow for an assessment of the benefit of the individual components of the cleansing regimen. The patient sample size was small.

Brown et al. 1984 is a prospective, randomized, study comparing a spray of 0.5% CHG in 70% isopropanol versus an iodophor scrub (PI) as a Patient Pre-op Preparation in 3 types of surgical procedures in 791 patients. The authors found 29/359 infections (8.1%) in the PI group and 23/378 infections (6.0%) in the CHG group ($P>0.05$). However, for sepsis there were 5/359 in the PI group versus 1/378 in the CHG group ($P<0.05$). The CHG group had foreign material removed from the skin folds and umbilicus. Concomitant antibiotics were not tallied in either group (a potentially significant bias) and there was no standardization for use of antibiotics. Overall infections showed no difference.

Grinbaum et al. 1995 is a case-control study investigating an outbreak of surgical site infections in a vascular surgery unit. Six of nine cases developed infection when PI surgical scrub was replaced by bland soap. In the prior 9 months there were 28 infections in 244 surgery patients ($P=0.002$). The control group had 3 infections (odds ratio 10.0, $P=0.016$). Comparing 14 risk factors in cases versus controls, only scrubbing with soap was significantly ($P<0.0001$) different. Following reinstitution of povidone-iodine, only one SSI developed in the 13 procedures performed in the following 15 days. This study was retrospective. The handscrubbing technique was not described or observed. Also, alcohol with 2% PI was available for handwashing (but not scrubbing), which is a confounder.

Denton 1991 provided an extensive review of CHG data for a book chapter. CHG was synthesized about 1950. Products include various 2%-4% handwashes, patient preoperative preps, and a 0.05% eye irrigant. CHG has a broad spectrum, killing gram positive bacteria and MRSA. CHG kills gram negative bacteria better than triclosan or hexachlorophene. CHG is virucidal against lipid-coated, but not protein-coated, viruses. This article is a review and not a clinical trial of a healthcare antiseptic.

Georgiade et al 1990 assessed the bactericidal and clinical efficacy of a preoperative skin prep procedure with 7.5% PI surgical scrub followed by 10% PI antiseptic solution in an open study of 150 hospitalized patients undergoing elective surgery. None of the 146 evaluable patients developed infections at the incision or suture site, and in 99 patients with bacterial colonization prior to surgery, 84 (85%) had no detectable level of bacteria at the completion of the protocol ($P=0.004$). This study did not use randomization or a control. The finding of no detectable level of bacteria in 47 patients before the skin prep and 84 after could indicate an insensitive assay for bacteria.

Brandberg et al 1981 studied postoperative wound infections in 341 vascular surgery procedures, comparing the effect of a pre-operative whole body disinfection by shower-bath with chlorhexidine soap (Hibiscrub) with a "standard pre-op prep". Post-op infection was noted in 7.7% of the 170 Hibiscrub patients, versus 17.5% in 171 control pts ($P<0.05$). This study was neither randomized nor blinded. The standard pre-op prep was not defined. This study addressed disinfection by a showering, which is not a TFM indication.

Cruse and Foord 1973 conducted a prospective study of 23,649 surgical wounds, excluding oral, rectal, and vaginal operations, burns, and circumcisions. They found 1,124 infections in the 23,649 wounds (4.8%). The rate was 1.8%, 8.9%, and 21.5%, and 38.3% among clean to dirty wounds, respectively. They noted infection rate for not showering, showering with soap, or showering with hexachlorophene was 2.3%, 2.1%, and 1.3%, respectively. From 1967-1971, when green soap and alcohol were used for skin preparation in the operating room, the clean infection rate was 2%. With use of a povidone-iodine scrub on the ward followed by a Hibitane prep in the operating room, the infection rate fell to 1.2%. The investigators concluded that a hexachlorophene detergent shower helps to reduce the wound infection rate. The study was neither blinded nor randomized. Different antiseptic products were used on the same patient. The methodology and data collection were poorly described.

Connell and Rousselot 1964 provided an evaluation of povidone-iodine. They sprayed a 0.5% PI aerosol onto the preoperative site of 150 patients, and then assessed the number of bacteria present. They found a 98% bacterial reduction compared with a 96% bacterial reduction in 50 patients treated with hexachlorophene. They used a 0.75% PI surgical scrub 55 times in a "number of doctors", finding a 98% reduction in bacteria on 50 hands at 4 minutes post-scrub, compared with an 84% reduction in bacteria on 50 hands with hexachlorophene. The investigators swabbed 125 infected wounds or ulcers with a 1% PI antiseptic solution and found that 86% of the wounds exposed to a continuous soak of full strength PI had a bacteria reduction to below 100 organisms per cc. The investigators did not study an outcome other than bacteria reduction. Patients or surgeons' hands were not randomized. The amount of PI antiseptic applied was not stated in any of the 3 experiments.

Burkhardt et al 1986 evaluated the effect of local antibacterial agents on a prosthetic breast capsular contracture in 124 mammoplasty surgery patients in an observational, prospective, randomized, double-blind study. Patients were randomized into a cephalothin, cephalothin + PI, PI alone, dual antibiotic +steroid foam, or a nonmedicated (saline) group. The antibiotic was instilled into the prosthesis or the surgical pocket. The incidence of a Class 3 or 4 contractures for groups 1-5 was 26% (cephalothin), 18%, 18%, 14%, 41% (control) respectively ($P<0.05$ for control, no difference between each of the antibiotic groups). The investigators concluded that irrigation with 5% PI (50% Betadine) was as effective as other techniques. The antiseptic PI was studied in the surgical cavity, with or without cephalothin in the prosthesis. The study does not address any of the TFM indications since PI was not studied as a preoperative skin preparation, surgical scrub, or handwash.

Berry et al. 1982 compared the effectiveness of 10% and 7.5% povidone-iodine in alcohol as a surgical scrub and skin preparation solution, respectively, with chlorhexidine (CHG, Hibitane and Hibiscrub) as a surgical scrub and skin preparation solution in the prophylaxis of postoperative wound infection. The authors conducted this prospective, randomized study in 866 patients undergoing general surgery. The investigators assessed wounds at day 3-4 post-op or at discharge, whichever came sooner. The CHG group had a 9.7% infection rate and the PI group had a 14.8% infection rate ($P=0.03$) at the time of discharge, but there was no difference at 3-4 days postoperatively. The authors concluded that there is no overwhelming evidence for using one compound over the other as an all-purpose preparation and scrub.

This study was not blinded. The authors did not list the amount and type of alcohol in the PI products. The authors did not justify the assessment of wound abnormality only at the 3-4 days time point, but not later. Some patients received antibiotics routinely.

Rubio 1987 studied Septisol Antiseptic Foam (0.23% hexachlorophene in a 46% ethanol base) as a two minute surgical scrub over an eight year period. The study is retrospective, unblinded, and uncontrolled. In 3,480 cases there were 11 postoperative infections. The author describes the 11 patients. There is no evaluation of the bacteria on the hands or forearms of the surgeons. There is no link between the Septisol Antiseptic Foam used and any result reported.

Onesko and Wienke 1987 reported on the influence of Ido-Kare (0.05% complexed iodine soap with skin conditioners) on the reduction of nosocomial infection, especially MRSA. They found a nosocomial attack rate of 10.56% in the 12 month PI period (189/1800), of which 5 cases were MRSA. This was an 80% reduction in MRSA, and a 21.5% reduction in nosocomial infection. The MRSA reduction was statistically significant, but the nosocomial infection reduction was not statistically significant. There was no randomization or control group. The clinical outcome of MRSA cases was not mentioned.

2. Catheters, ventilators and intravenous lines:

The CTFA states that the following articles demonstrate benefit from the use of topical antimicrobial products:

> **2a. Decrease in catheter related and ventilator associated infections due to the patient's flora** (Levin et al. 1991; Maki et al. 1991; Garland et al. 1995; Beneda and Finney 2000; Tuominen et al. 1981).

Levin et al 1991 evaluated the prevention of hemodialysis-subclavian catheter infections by topical povidone-iodine in a randomized, controlled, but unblinded study of 171 catheters in 129 uninfected patients with acute or chronic renal failure. Both groups had an identical site preparation, but the treated group had daily PI ointment applied to the site while the control group had sterile gauze. Catheter exit site infections were significantly less in the treatment (T) group (5%) than in the control (C) group (18%), $P<0.02$. The incidence of septicemia was significantly less in the T group (2%), than in the C group (17%), $P<0.01$. The beneficial effect of PI ointment was most evident in the S. aureus carriers, with exit site infections 0% in T versus 24% in C, and septicemia 0% in T versus 29% in C, $P<0.05$. The use of the PI ointment at the site of the catheter insertion is a wound treatment and the study does not address a TFM indication.

Maki et al 1991 studied the effectiveness of three antiseptics in disinfecting a patient's central venous and arterial catheter insertion sites. The authors studied 668 catheter sites in patients randomly assigned at the time of catheter insertion to 2% aqueous chlorhexidine (214 pts), 10% povidone-iodine (227 pts) or 70% isopropyl alcohol (227 pts). Research nurses inspected the catheter site daily and also at dressing changes every 48 hours. The designated antiseptic solution was also used for cleansing of the site at the dressing changes every 48 hours. Chlorhexidine yielded the lowest incidence of local infection (2.4 per 100, versus 9.1 for alcohol, and 9.3 for PI, $P=0.02$ for CHG versus alcohol and PI combined). Chlorhexidine yielded an insignificant trend towards the lowest bacteremia (0.5 per 100 vs 2.3 for alcohol and 2.6 for PI, $P=0.18$). The authors concluded that chlorhexidine should be considered as a first line antiseptic for prevention of infection with percutaneously-inserted intravascular catheters of all types. The investigators were not blinded but the microbiologist was blinded. It is not clear that the skin prep technique was standardized. In contrast with the conclusion of the investigators, the use of the test product post-

operatively confounds the results and precludes concluding there is a clinical benefit for preoperative chlorhexidine in preventing catheter infections.

Garland et al 1995 compared the efficacy of 10% PI against 0.5% CHG in 70% IPA, applied prior to catheter placement, for the prevention of catheter colonization in neonates in an observational, prospective, nonrandomized, unblinded study. The setting was a NICU in a tertiary hospital with 45-50 admits/month. During the first 6 months, 38/403 (Betadine) catheters were colonized (9.3%) and 12% grew positive blood cultures. During 2nd 6 months, 20/418 (Hibistat) catheters were colonized (4.7%, P=0.01) and 12% grew positive blood cultures. The investigators concluded that cutaneous antisepsis with Hibistat results in a lower rate of peripheral intravenous catheter colonization than antiseptic cleansing with Betadine. Catheter colonization was less with Hibistat, but positive blood cultures were equal in each group. A clinical outcome was not reported. This study had many methodology weaknesses.

Beneda and Finney 2000 discussed a MRSA decolonization protocol and vancomycin usage in a poster presentation at a conference. This reference provides insufficient information for a review.

Tuominen et al 1981 studied the effect of chlorhexidine in preventing infection from central venous catheterization. This hospital study was observational and randomized. Two groups of patients had a subclavian vein catheterization by standard technique or medial cubital vein catheterization (via cutdown). The investigators did not report how the skin was prepared prior to catheterization. One group of 54 patients (60 catheters) had 0.05% CHG-impregnated gauze applied to the insertion site twice daily, while the other group of 59 pts (64 catheters) had sterile gauze twice daily. The CHG group had 13% + cultures, while the sterile gauze group had 16% + cultures, $P<0.05$. Sepsis developed in 3 from the CHG group and in 1 from the sterile gauze group (no statistic given). CHG was significantly better after a cutdown, but not after a percutaneous CVC procedure. This study provides a mixed result with fewer positive skin cultures in the CHG group, but higher sepsis in CHG group. The use of CHG in this study at the site of the catheter insertion is a wound treatment and not a TFM indication.

2b. Decrease in catheter related and ventilator associated infections due to the caregiver's hands (Gould 2000; Boyce et al. 1990; Brooks et al. 1999; Jones and Newman 2000; Amarante et al. 2000; Fauerbach et al. 2000).

Amarante 2000, Fauerbach 2000, and Jones and Newman 2000 are poster presentations. Gould 2000 is an abstract. All four provide insufficient information to support clinical benefit.

Brooks et al 1999 is an abstract that reports use of a foamed alcohol hand antiseptic, among other interventions, that led to a reduction in ventilator-associated pneumonia (VAP) rate in ICU patients. In addition, VAPs due to MRSA decreased from a prior rate of 92% to zero. This was a retrospective study without a comparator group. In addition, the study was confounded by the introduction of plastic (disposable) laryngoscopes and a change in the ventilator circuit pattern.

Boyce et al 1990 reported a case-control study of a common source outbreak of S. epidermidis infection among 10 patients undergoing cardiac surgery. Ten patients developed a S. epidermidis infection in the sternum, vein graft site, or heart valve and were linked to one infected surgeon (surgeon A). After surgeon A scrubbed his hands with a CHG scrub preparation, the epidemic strain no longer could be cultured from his hands. The statistics quoted that linked surgeon A with the outbreak were not significant.

3. Opthalmic surgery – The CTFA states that pre-operative preparations for the conjunctiva have been shown to decrease the bacterial contaminants in the eye (Isenberg et al. 1985; Isenberg et al. 1997; Apt et al. 1989).

Isenberg et al. 1985 and Isenberg et al. 1997 are articles about care of the eye before and after surgery. The latter article studied 42 eyes in 35 consecutive patients. One or two drops of a broad-spectrum antibiotic or 1.25% to 2.5% of povidone-iodine were instilled in the treated eye(s) at the conclusion of surgery and thrice daily for the first postoperative week. Twenty-eight untreated eyes served as controls. During the first postoperative week, bacterial colonies increased in both treated groups and the control group, but less so in both treated groups ($P<0.02$). The treated groups did not differ from each other until after one week had elapsed. The investigators did not provide a clinical outcome. The authors concluded that povidone-iodine ophthalmic solution is an alternative to postoperative topical antibiotics since it controls conjunctival bacterial colonies, and it is low cost, and available. This study does not address a TFM indication.

Apt et al. 1989 evaluated the effect of preoperative outpatient povidone-iodine (PI) eyedrops on conjunctival bacterial counts in 40 consecutive ophthalmologic surgery patients. The investigators randomized patients into two groups. Regardless of which eye was scheduled for operation on the third day pre-op the patients instilled 2.5% PI eyedrops in one designated eye, and Neosporin ophthalmic eyedrops in the other eye. On the operating table PI was instilled in both eyes, and then conjunctival cultures were taken. Eyes with Neopsporin plus PI were sterile 47.5% of the time, while eyes with PI plus PI were sterile 30% of the time ($P=0.03$). The investigators concluded that 3 days of pre-op antibiotic eyedrops, combined with 5% PI eyedrops on the operating table, reduces conjunctival bacterial counts. They also speculated that this approach should contribute to a decrease in postoperative infections. There was no inactive control, no clinical outcome data, and the number of eyedrops was not specified. This study does not specifically address a TFM indication.

4. Skin graft preparation – The CTFA states that the following study shows that use of topical antimicrobial preparations minimize bacterial infection of the donor skin, potentially leading to a greater supply of skin for grafting (May et al. 1991).

May et al. 1991 showed that the potential for gram positive bacterial contamination in transplantable cadaver skin may be significantly reduced by the addition of CHG to the standard PI and isopropanol cleansing solutions. The investigators prepared skin from 294 cadavers with PI and isopropanol, and from 48 cadavers with 4% CHG (Hibiclens), then cultured defined areas on the skins. They found that 5.6% of the areas prepped with CHG were contaminated, versus 13.7% of areas prepped with PI. Also, the gram positive contamination was 2.2% with CHG versus 12.1% without CHG, an 82% reduction that was highly significantly. This study was not randomized, nor was an inactive control used, nor was a clinical outcome studied. This study does not address a TFM indication.

5. Blood cultures – The CTFA states that use of topical antimicrobial preparations on the skin prior to withdrawing blood has been shown to reduce the number of contaminated blood cultures. This reduces the number of times blood needs to be drawn and prevents the prescription of unnecessary medication to fight non-existent infections (Schifman and Pindur 1993; Tanaka et al. 1988).

Schifman and Pindur 1993 described the effect of skin disinfectants on reducing contaminated blood cultures. The investigators collected 1546 blood cultures after randomly assigning the preparation sites to a standard method (70% isopropyl pad, followed by a 10% PI swab) or "PREP Method" (acetone-isopropyl pad, followed by a PI swab and isopropyl pad). There was a 4.6% contamination with the standard method (N=763) versus a 2.2% contamination with the Prep Method (N=783, P=0.011). The investigators did provide clinical outcome data. The study only assessed the efficacy of a combination of ingredients, thus confounding the evaluation of any single ingredient.

Tanaka et al. 1988 evaluated two rapid-drying hand disinfectants in an ICU setting. Two hundred thirty seven (237) nurses washed with 0.2% CHG in 70% ethanol and 250 nurses washed with 0.2% benzalkonium in 70% ethanol. Both products reduced the bacteria count (P<0.01) but differed insignificantly from each other. The investigators did not randomize subjects, use an inactive control, or assess a clinical outcome.

6. Surgical glove failure – The CTFA states that use of topical antimicrobial preparations reduced the number of skin bacteria released through pinholes of punctured gloves (Furuhashi and Miyamae 1979).

The CTFA notes that it did not include the Furuhashi and Miyamae 1979 article in the references it provided. An abstract is not available in Pub Med. A clinical outcome study is not apparent from the title. ("Effect of pre-operative hand scrubbing and influence of pinholes appearing in surgical rubber gloves during operation". Bull Tokyo Med Dent Univ. 1979; 26: 73-80)

7. Pre-operative or post-operative body wash – The CTFA states that use of topical antimicrobial preparations for washing patients either before or after surgery was shown to significantly reduce the number of bacteria on patients' skin (Stuart Pharmaceuticals 1986c; Garibaldi et al. 1988; Kaiser et al. 1988; Hayek et al. 1987).

Stuart Pharmaceuticals 1986c: This is not a clinical study but rather a summary of the research of others. As such it provides no original information.

Garibaldi et al 1988 performed a randomized evaluation of three preoperative shower and scrub regimens in reducing bacterial counts on the incision site and in preventing intraoperative wound contamination. Five hundred seventy-five surgical patients washed pre-op, then were scrubbed on the operating table with either Hibiclens-CHG; Betadine-Betadine, or medicated soap (Safeguard, triclocarban)-Betadine. The post-shower colony count was lowest for the CHG group (P<0.001). Intraoperative wound cultures grew bacteria in 4% of the CHG-CHG group, 9% in the Betadine-Betadine group, and 15% in the Safeguard-Betadine group (P<0.025 vs Betadine-Betadine, P<0.001 vs Safeguard-Betadine). The investigators concluded the CHG shower and scrub are more effective than the other two test methods in reducing pre-op and intraoperative bacterial counts. A clinical outcome was not studied. This study assesses a pre-operative shower-scrub regimen and, as such, does not address a TFM indication.

Kaiser et al 1988 studied the effectiveness of Hibiclens, Betadine, and lotion soap in diminishing the preoperative staphylococci skin flora of patients. The investigators randomized 25 patients to an evening shower with one of the test products, and 14 patients to an evening and morning shower. A single shower with Hibiclens, Betadine, or lotion soap did not significantly reduce the staphylococci count in either site. Lotion soap did not reduce groin staphylococci and insignificantly increased staphylococci at the subclavian site. Two showers with Hibiclens significantly reduced the staphylococci count in both sites (2.07 reduction in the groin and 1.61 reduction in the subclavian site, P<0.05 for both). Two showers with

Betadine insignificantly lowered the staphylococci count at both sites, while two showers with lotion soap increased the staphylococci counts at both sites. A clinical outcome was not studied. The number of patients studied was very small.

Hayek et al 1987 evaluated the infection rate with the use of a 4% CHG pre-op shower (Hibiscrub) compared with bland soap and placebo. The investigators enrolled 1989 patients (689 Hibiscrub, 626 bland soap, 700 placebo) and followed them for 6 weeks postoperatively. The investigators randomized the wards but not the actual patients. Hibiscrub led to a lower infection rate of 9%, versus 12.8% with bland soap and 11.7% for placebo ($P<0.05$ for CHG versus bland soap). The S. aureus infection rate was 2.6% with Hibiscrub, 5.3% with bland soap, and 4.0% with placebo ($P<0.05$ for CHG versus bland soap). The investigators did not define the placebo, nor did they state whether Hibiscrub was significantly better than bland soap. The investigators did not indicate what preoperative skin preparation was used in the subjects before surgery. This is a potential bias since the preoperative skin prep is the last antiseptic on the skin before surgery. The investigators tested products in a pre-operative shower regimen and, as such, they did not address a TFM indication.

Review of Articles Regarding Non-Invasive Procedures

The CTFA states that studies examining clinical endpoints support the benefits of using topical antimicrobial products in **non-invasive procedures.** These studies are summarized below.

Clinical Settings

1. **Reduced nosocomial infection rates** – The CTFA states that a number of studies showed a significant reduction in infection rates in clinical settings from the use of handwash products: hospital nursery (Frappier-Davignon et al. 1959; Johnson et al. 1976; Cooper and Gibson 1974; Forfar et al. 1968; Murray and Calman 1955); dialysis unit (Malone and Larson 1996); transplant unit (Klausner et al. 1999; Thompson et al. 2000); and intensive care units (Doebbeling et al. 1992; Maki and Hecht 1982; Maki 1989; Onesko and Wienke 1987; Sakata et al. 1989; Conly et al. 1989; Denton 1991; Webster et al. 1994; Webster 1992; Facagal et al. 1999).

Frappier-Davignon et al. 1959 evaluated the influence of nursing technique on the incidence of staphylococcal infection. The investigators studied 4 groups of nurses. The groups either: did not wash before handling a baby, used Phisohex (hexachlorophene), used bland soap, or dipped their hands in Dettol (PCMX). From 16,053 births there were 201 infections (staphylococcal), with an average of 1.25%, and a range 0-4.7% in each of the groups. The investigators found that the use of soap is preferable to Dettol, there is no difference between Dettol and no washing, and the results did not support any particular antiseptic. This study was not randomized, only 13 of 26 participating hospitals provided data, and results came from the second year of the study noting results from the first year of the study. The investigators did not show a statistically significant benefit of a particular handwash.

Johnson et al 1976 studied various modes of skin and umbilical care and the incidence of staphylococcal colonization and infection in the neonate. CP7 states that this article is not available in the references.

Cooper and Gibson 1974 provided a literature review comparing hexachlorophene (HCP) with povidone-iodine in the control and prophylaxis of neonatal and surgical infection. They noted a 1964 "well-controlled" trial that showed 3% HCP effective in reducing staphylococcal infection in newborns when used for 3 weeks, but could not prove a decrease due to HCP alone as other care measures were used concomitantly. Also, they noted a 1972 study which showed no significant difference in post-op wound infections when pre-op iodophor or HCP hand scrubs were used. Due to potential toxicity, they concluded that the use of HCP should be restricted to personnel handwashing and to the temporary bathing of infants over 2500 grams with 2 days of 3% HCP washings followed by rinsing. This is a review article that did not provide useful clinical efficacy data. Temporary bathing of infants is not a TFM indication.

Forfar et al. 1968 provided a 10.5 year retrospective evaluation of the effect of hexachlorophane use on newborns and by staff on the incidence of staphylococcal and gram negative infection in the nursery at two hospitals. In hospital E the introduction of hexachlorophane was associated with a decline in staphylococcal infection from 11.1% in the first period to 2.8% in the second period, along with rise in gram negative infection from 1.4% to 3.8%. In hospital W there was no striking difference in staphylococcal or gram negative infection over both periods. The authors concluded that hexachlorophane might directly stimulate the multiplication of gram negative organisms. This retrospective study has multiple flaws, such as not describing washing volumes or washing techniques with hexachlorophene or providing any specific link between infections and the use of the product. (Note: product name listed as "hexachlorophane")

Murray and Calman 1955 described attempts to reduce the incidence of cross-infection by treatment of the hands of persons attending patients. They tested 1% "hibitane" cream (chlorhexidine diacetate and dihydrochloride) on 3 subjects' fingers. Using an early "glove-juice method" they found that resident bacteria are suppressed more with 0.2g of hibitane than 0.1g, and that controls had much higher bacterial growth at 30 min and 60 min. After placing hibitane emollient cream on the wards they found staphylococcal infections reduced and not clustered, but provided no actual numbers before or after use.

Malone and Larson 1996 identified factors associated with a significant reduction in hospital-wide nosocomial infection rates. They conducted a 3-year retrospective and 10-month follow-up study in a 500 bed hospital. In the retrospective study they noted the baseline infection rate of 3.9% decreased to 2.6% in 1993 ($P<0.001$), which they attributed to implementation of Occupational Safety and Health Administration (OSHA) standards, a DermaMed barrier foam for the hands (to protect against latex allergy), and increased glove use. In the 10-month prospective study on an inpatient dialysis unit the authors found a 5.8% infection rate with an alcohol foam use and 13.4% without the alcohol foam. This study was not randomized, nor was there an inactive control. The authors did not report training in the use of the barrier foam or observation of handwashing technique. The authors did not report the nosocomial infection types in the followup study. The study was confounded by multiple interventions.

Klausner et al. 1999 described an outbreak of S. matophilia among bone marrow transplantation (BMT) recipients and explained the role that mislabeling hand lotion and handwashing soap may have played in the development of the outbreak. In a case-control study the investigators pinpointed that for 1-day during the exposure period the antimicrobial soap dispenser in one case's room actually contained foam moisturizer lotion. The investigators speculated that a nurse cared for this person, washed with mislabeled soap, and then transmitted the bacteria to another person. The authors did not state the type of antimicrobial soap, how many controls were in the groups, or provide any data about the handwashing practice of the suspected nurse-transmitter.

Thompson et al. 2000 is a poster presentation that does not provide sufficient information to support clinical benefit.

Doebbeling et al 1992 evaluated the effects of CHG and isopropanol handwashes on nosocomial infection rates in hospital ICUs. In this nonrandomized, unblinded, 8-month crossover study, staff washed with a 4% CHG solution or 60% isopropanol. They added soap to the alcohol only if their hands were visibly soiled. The investigators employed a handwashing training program and spot-monitored compliance. The investigators found a NI rate of 152/1352 with CHG and 202/1382 in the alcohol-soap group, an insignificant trend favoring CHG, IDR 0.87, 95% CI 0.67-1.15. Mortality was calculated as 47.9 deaths/1000 pt-days with CHG, 50.9 with alcohol-soap (IDR 0.94, 95% CI 0.68-1.3). The staff used twice as much CHG as alcohol, and washed with CHG 48% of the time versus 30% with alcohol in the observations. This study had many methodology flaws.

Maki and Hecht 1982 is an abstract summarizing a crossover comparison of Hibiclens, 7.5% PI ("Betadyne Scrub"), and nongermicidal soap for six weeks each in 38 HCWs. Hibiclens provided superior degerming of the hands, with a significantly lower number of cultured organisms and S. aureus than either PI or bland soap ($P<0.05$). In addition there was a lower rate of nosocomial infections (NI) with Hibiclens compared to bland soap ($P<0.001$), and a lower rate of NI with PI compared to bland soap ($P<0.05$). Hibiclens was tolerated, while PI was poorly tolerated with half of the HCWs developing skin irritation. This study was not randomized or blinded. The investigators did not comment on training or the handwashing technique. They did not comment on the order of use of the three agents, nor mention any "washout" period.

Maki 1989 reviewed the history and status of the various handwashing studies including a summary of six of his own articles. He notes a 10-min scrub was considered mandatory for decades, but 2 studies (Dineen 1969, Galle 1978) showed that a 5-minute scrub is effective "in reducing counts of hand organisms". He notes that a vigorous scrub with a nonmedicated soap for 10-15 seconds will reliably remove gross microbial contamination, such as occurs with changing an infant's diaper. Also, he summarizes data showing that a typical handwashing last only 7-10 seconds. Maki states his opposition to air flow hand dryers, and he asks whether the periodic application of antiseptic-containing evaporative lotions, used without water, should replace some of the conventional handwashing or at least compensate for the suboptimal handwashing currently practiced. Maki does not present new work in this review.

Onesko and Wienke 1987 reported the influence of a well-accepted, mild, low-iodine, lotion soap on the reduction of nosocomial infection, especially MRSA. The authors selected wards with highest MRSA colonization and infections (10-bed ICU and 40 bed medical division) to change from a nonmedicated liquid natural handsoap to a low-iodine healthcare personnel handwash (Ido-Kare—a 0.05% complexed iodine soap with skin conditioners). Also, they replaced the PI surgical scrub used for isolation cases with Ido-Kare. They found the nosocomial attack rate declined from a previous 13.25% to 10.56% in the 12 month Ido-Kare period (189/1800), of which 5 cases were MRSA. This was an 80% reduction in MRSA, and 21.5% reduction in nosocomial infection. The MRSA reduction was statistically significant, but the nosocomial infection reduction was not statistically significant. The study was not randomized or controlled and the handwashing technique was not documented or observed.

Sakata et al. 1989 reported a cluster of neonates with A. anitratus septicaemia in the NICU and described the effect of control measures to reduce infection. In October 1985 the handwashing procedure changed from an immersion in a basin of 0.02% CHG to a spray of ethanol (ethanol concentration % not

mentioned) with 3% glycerine. Staff were encouraged to wash before entering the unit and before and after handling each infant. Colonized infants were separated from non-colonized infants. Indications for antibiotics were tightened and shorter courses promoted. From Oct 1983-Mar 1986, there were 42 septic infants, of which 19 had A. anitratus. After January 1986 A. anitratus was not found on the hands of staff. Also, there was a decreased number of colonized infants. The percentage decrease was not specified. No sepsis occurred in the nine-month period after Apr 1986. The authors instituted multiple interventions without randomization or control, of which handwashing was just one intervention. They did not specify the ethanol concentration and did not observe handwashing or provide any training documentation.

Conly et al 1989 correlated nosocomial infection rates in an intensive care unit with handwashing practices before and after two educational programs. A nurse observed actual handwashing practices with 4% CHG in June 1978, and then the authors implemented handwashing training in October 1978 via an inservice, posters, and memoranda. Before the educational program the nosocomial infection rate was over 30%, but decreased to 12% after education. A subsequent rise in the infection rate to 30% in 1982 was followed by a reduction to 10% after a 2nd education program. In October 1978 handwashing compliance improved from 73% to 81% with education, slipped to only 26% in December 1982, then improved to 60% after the second training program. The investigators did not show a clear link between handwashing and nosocomial infections. The variable in this study appears to be handwashing technique and not the antiseptic ingredient.

Denton 1991 is reviewed above.

Webster 1992 conducted a seven week study evaluating the effectiveness of 4% CHG and 1% triclosan against MRSA. Staff was "asked to wash" with 1% triclosan (Novaderm) in the ICN, while 4% CHG was used in the SCN. Webster collected data the next 7 weeks. Staff continued daily cord care and a 2nd daily sponging with CHG 0.5% in isopropyl alcohol 60% Handwashing in the ICN with Novaderm was the only change. Webster found 3.4 new cases of MRSA colonization per week in the control period of Jan 1990-Oct 1990. During the 7-week trial ending Oct 1990, only 1 of 46 babies was colonized with MRSA, a 0.14/week rate. Webster found no corresponding reduction in the number of new cases in the SCN. Novaderm was more accepted by staff versus Hibiclens. This study was neither randomized nor placebo-controlled, there was no documentation of handwash training or observation, and there was confounding continued use of CHG for cord care and rapid skin disinfection with Hexol (CHG).

Webster et al 1994 evaluated the effect of reintroducing CHG on the MRSA colonization rate and on the incidence of new cases in the ICN and discussed the outcome of a 12-month triclosan handwash trial. The investigators conducted a prospective, nonrandomized 12-month follow-up study based on a previous 7-week pilot trial of triclosan 1% handwash (see Webster 1992). MRSA colonization of infants fell during the 7-week triclosan pilot, but returned to baseline when CHG was re-introduced (because the pilot trial ended). After the triclosan 1% 12-month trial began there was a progressive reduction in the number of new cases of MRSA colonization each week. Nosocomial infection totaled 36 out of 893 total infections with CHG use; with triclosan the corresponding numbers were 23/1023 (significantly lower, P=0.05). The authors did not provide documentation of handwash training or technique observation, and during the triclosan handwash period infants still received umbilical cord care and rapid disinfection with Hexol (CHG). The study was not randomized, and used a historical control.

Facagal et al 1999 is listed without an article name or a reference. The CTFA did not provide an article for review.

2. Control of Methicillin Resistant Staphylococcus aureus – The CTFA states that studies have shown the benefit of using topical antimicrobial products for hand and body washing to control or eradicate MRSA (Brady et al. 1990; Bartzokas et al. 1984; Webster et al. 1994; Zafar and Butler 1999; Onesko and Wienke 1987; Tyzack 1985; Majury et al. 2000; Mitsuda et al. 1999; Tuffnell et al. 1987).

Brady et al. 1990 evaluated the incidence of MRSA colonization in a thoracic surgery unit and the effect of interventions to control MRSA. From 1983-1985, MRSA grew in 154 patients out of 3915 operations. From March-April 1986, 23 of 84 patients cultured MRSA+. The perineum was colonized in 69.6%, the nose in 43.5%. Interventions started in January 1987 and continued until June 1988. During this period 37 patients were MRSA+ out of 2076 operations ($P<0.001$). The interventions were: reduced cephalothin peri-op to q4h, 20 hrs duration (was 48hrs), and whole body wash pre-and post op with 1% triclosan (rather than soap) with particular attention to the perineum, and isolation of all MRSA + patients. The patients were not randomized, there were multiple interventions confounding the study, and the investigators did not report a clinical outcome of the patients colonized with MRSA.

Bartzokas et al. 1984 reported the method of control of a hospital outbreak of MRSA. The investigators conducted a prospective handwash and whole body wash study after 6 patients developed MRSA infections in one month. All patients (25) and ward staff (40) washed with 2% triclosan for 3 weeks regardless of carrier status, and made thrice daily applications to the nares, axillae, and perineum. The infected patients and staff were clear of MRSA within an average of 22 days. The investigators did not randomize, employ a control, or provide a clinical outcome. The study looked at bathing and handwash procedures and not at handwashing alone as per the TFM.

Webster et al. 1994 is reviewed above.

Zafar and Butler 1999 retrospectively described an MRSA outbreak and the interventions that eliminated the outbreak and prevented a recurrence. One MRSA case occurred in Jan 1990, 3 cases in Feb 1990, at which time multiple interventions were and added along with a CHG handwash. Eight cases occurred in March 1990, then 7 in April 1990, at which time they switched from a CHG handwash to a triclosan handwash on April 12, 1990. Thereafter, 1 case occurred in May, June, and July 1990, and then no further MRSA cases occurred in the next 3.5 years. The investigators concluded that their study demonstrated control of an epidemic of MRSA infection by a simple change of handwashing and bathing soap. They did not use an inactive control, made no mention of handwashing training or observation, did not apply any statistics, and published about nine years after the fact. The study design precludes obtaining efficacy data about a particular product.

Onesko and Wienke 1987 is reviewed above

Tyzack 1985 evaluated a four-prong approach to control an MRSA outbreak. The investigators utilized re-training, an isolation ward, computer documentation of infection statistics, and a uniform disinfection regimen with povidine-iodine (PI) to prevent and manage MRSA. The regimen incorporated handwashing with PI surgical scrub for all HCW and visitors associated with MRSA-colonized patients, a PI bath for MRSA patients, intranasal PI ointment four time daily to all ICU and isolation patients, and PI ointment on all wounds and sores. Subsequently, MRSA infections fell from 74 in the 4 month period prior to the program to 5 in the 4 month period ending Dec 1983. The investigators initiated multiple changes and, as such, did not assess the value of the handwash alone.

Majury et al 2000 is a poster presentation about reducing a MRSA reservoir. This poster does not provide insufficient information to support clinical benefit.

Mitsuda et al 1999 studied the prevalence of MRSA carriage among HCWs to elucidate the transmission of MRSA from HCWs to their families and to newborn infants. The investigators tested 2 persistent MRSA carriers (out of 53 nurses) for a MRSA genotype (electrophoresis, DNA). They cultured the nares of the carrier and the nares of their family members. They found that 65% of the MRSA isolates from newborn infants appeared to be derived from the 2 nurses, who also transmitted MRSA to their children. The investigators did not study a clinical outcome related to a TFM product.

Tuffnell et al 1987 reported the successful control of an outbreak of methicillin-resistant Staphylococcus aureus using isolation and once-daily whole-body washing with triclosan. The investigators studied all cases of colonization at Warrington District General Hospital, UK, from Feb 1983-Sep 1985. Colonized patients were initially treated with mupirocin nasal cream, then with mupirocin nasal cream, 3% hexachlorophene body wash and isolation, then with isolation and a 2% triclosan body wash. The MRSA colonization rate decreased to 32 cases over 9 months with the triclosan body wash compared with 76 cases over the previous 6 months. The investigators concluded that conventional isolation techniques and once-daily whole body washing of affected patients with triclosan successfully controlled the outbreak. The investigators did not randomize this study nor use an inactive control. The nasal ointment and body wash method were not standardized among the recipients (patients or HCWs). The multiple interventions confounded the results. A whole body wash is not a TFM indication.

3. Reduction in transfer of bacteria from patients' to caregiver hands – The CTFA states that a significant decrease in bacteria was seen when topical antimicrobial products were used for routine handwashing (Casewell and Phillips 1977; Mortimer et al. 1962).

Casewell and Phillips 1977 investigated the hands as a route of transmission of Klebsiella in an ICU setting at St. Thomas Hospital, London. They determined that Klebsiella types 21 and 47 survived 20-150 minutes on dry, artificially inoculated hands. Also, they detected 100-1000 Klebsiella organisms on the hands of 28 nurses who simply touched a patient, but thought they had clean hands. The investigators studied four handwash methods, looking for a 98% or 100% reduction in viable Klebsiella:

1. rubbed hands 20 seconds with warm tap water
2. rinse warm tap water 5 seconds, wash non-medicated soap 15 seconds, rinse 5 seconds
3. rinse warm tap water 5 seconds, wash triclosan-medicated soap 15 seconds, rinse 5 seconds
4. rinse warm tap water 5 seconds, wash 4% CHG hand cleanser15 seconds, rinse 5 seconds

They found 4% CHG most effective at achieving a 98-100% reducion of viable bacteria, followed by triclosan soap. Nonmedicated soap and water and warm water rarely reduced viable Klebsiella by 98% or 100%. They documented a reduction in patient colonization from 22.6% to 15.5% after a handwash program in the ICU. This study did not use blinding, nor was a clinical outcome studied. The number of participants was too small to provide meaningful results.

Mortimer et al. 1962 tested the effectiveness of handwashing by nursery personnel in preventing the spread of staphylococci organisms between infants. He conducted a 48-day study designed to assess the transfer of staphylococci by touch, and a 55-day study to assess the transfer of staphylococci by air. The 48-day study showed that 17 of 32 babies ("HW babies") handled after nurses washed their hands with pHisoHex grew staphylococcus (nares and umbilicus), versus 45 of 49 handled after not handwashing at

all. In the 55-day study he found that 12 of 42 HW babies grew staphylococcus versus 28 of 37 non-HW babies. Six of 39 babies not handled by the nurses grew staphylococcus. Mortimer concluded that staphylococcus is transmitted by touch more than by air and that handwashing reduces transmission. This study was not randomized, though a control (no washing) was employed. Mortimer did not provide statistics nor did he document handwash training or observation of handwashing.

4. Significant reduction in total bacterial load on caregivers' hands – The CTFA states that routine use of topical antimicrobial products led to a demonstrated reduction in the bacterial flora of hands (Amortegui and Buffenmyer 1978; Kirita et al. 1993; Stuart Pharmaceuticals 1986; Goldblum et al. 1983).

Amortegui and Buffenmyer 1978 compared the antiseptic effect of two iodophor preparations on hand washing in a well-baby nursery in a crossover, single blind handwash study. The nurses double-washed with Betadine or Prepodyne surgical scrubs upon reporting for duty, after which a total of 1,806 hand cultures were taken: a) from nurse's left hand after washing, b) from baby umbilicus before bathing, c) from nurse's right hand after baby handling. The investigators found both agents effective but with no significant difference in antiseptic effect. Betadine and Prepodyne reduced the percentage of positive cultures of the right hand from 78.4% and 73.2%, respectively, after infant handling and to 22.3% and 26.5%, respectively, of the left hand after initial handwashing. The investigators did not use a bland soap control, so the effectiveness of the 2 active products cannot be assessed. The investigators did not study a change in infection rate.

Kirita et al. 1993 evaluated the efficacy and safety of a quick drying rubbing type handwash composed of PI and ethanol in the disinfection of the transient skin flora on the fingers of 30 medical staff. Staff rubbed 3 ml of solution (50mg available iodine, 83% ethanol) on their hands for 3 minutes several times daily for 4 weeks. The investigators found bacterial reduction rates of 8.9% to 99.8% at various times over the four weeks, with the dispersion possibly due to different hand washing methods among individual subjects. There were reductions of 98% in S. aureus and micrococcus. Staff washed their hands 33 to 287 times during the 4-week study with a mean of 104 washes. Two nurses had transient dry skin. The investigators did not randomize the staff, did not use an inactive control, and did not study a clinical outcome. It is unclear why there was so much variability in the number of handwashes among the staff.

Stuart Pharmaceuticals 1986 is reviewed above.

Goldblum et al. 1983 compared the effectiveness of 4% chlorhexidine gluconate (Hibiclens) and povidone-iodine (Betadine) for skin disinfection in 42 hemodialysis (HD) patients and 24 HD personnel. In this 13 week crossover study, patients and staff scrubbed the volar surface of the forearm for one minute with Betadine thrice weekly for 13 weeks, then with Hibiclens thrice weekly for the next 13 weeks. The investigators found that Hibiclens reduced the total bacterial count and S. aureus count significantly more than Betadine. They found no bacterial resistance to Hibiclens and no chlorhexidine in blood samples over the 13-week period. The investigators did not use an inactive control or study a clinical outcome. The number of patients (25) and personnel considered in the results was substantially lower than the number of participants.

5. Significant reduction in Staphylococci and other Gram positive organisms – S. aureus is a pathogenic strain frequently isolated from the hands and in the nares of carriers. The CTFA states that a

number of studies have shown that the use of topical antimicrobial products reduces the Gram positive flora on various body sites (Voss 1975; Stuart Pharmaceuticals 1986; Gould et al. 2000).

Voss 1975 reported the effects of antibacterial soap on the ecology of aerobic bacterial flora on human skin. Voss did not report any clinical outcome data.

Stuart Pharmaceuticals 1986 is reviewed above

Gould et al. 2000 is an abstract that reported a decrease in nosocomial infections and CVL-related infections after HCWs began to use Prevacare in April 1999. The authors did not report specific data, did not mention any control product or randomization, did not comment on handwashing training or observation, and did not report any statistics.

6. Significant reduction in Gram negative organisms – The CTFA states that routine use of topical antimicrobial products led to a demonstrated reduction in the Gram negative flora on patients' skin and transferal to caregivers' hands. (Eckert et al. 1989; Eckert et al. 1989a; Ehrenkranz et al. 1991; Gilmore et al. 1984; Ayliffe et al. 1975; Stuart 1986; Knittle et al. 1975; Casewell and Phillips 1977; Raimondi et al. 2000).

Eckert et al.1989, 1989a studied 22 patients and 11 nursing assistants in nursing homes to determine if Proteeae and gram negative bacteria can be reduced or removed by soap or alcohol, and to determine if the transfer of these bacteria can be limited. The investigators randomly allocated the patients to the test agent 60% alcohol (Calstat), or soap (Safe-N-Sure lotion soap) and tested them at 2-3 week intervals over 11 weeks. Washing the subject's groin with soap decreased the bacterial pickup on the HCWs gloves ("hands") by a median 1.3 log (range 0.3-4.6), while washing with alcohol decreased pickup by a median 3.6 log (range 0.6-5.1). They found that alcohol treatment of high burden carriers is beneficial, but there is no difference between soap and alcohol in low burden carriers. There was no clinical outcome data, and no testing of whether the bacteria picked up by the HCWs could be transferred to other patients if the HCW removed the gloves and washed their hands. The number of patients studied was small and the variability of log reductions too large to draw conclusions.

Ehrenkranz 1991 is an editorial wherein the author distinguishes a bland soap handwash from an antisepsic. He states that the upper limit of degerming efficacy of bland soap handwash is a reduction of 2-3 logs, citing 4 references. In contrast hand antisepsis is better by 1-2 logs, (a 3-5 log reduction) citing 5 references. He states that staphylococcal contamination of a HCW's hands from bedmaking and urinary catheter bag manipulation might exceed the threshold for complete degerming by soap. For this he cites his article titled "Failure of handwashing to prevent hand transfer of patient bacteria to urethral catheters". He states that gloves give a false sense of security, citing a 20% failure to use gloves with IV insertion in study of 22 hospitals. Ehrenkranz does not address a clinical infection outcome.

Gilmore et al. 1984 evaluated the effect of bathing with triclocarban soap, Betadine surgical scrub, 4% CHG or pHresh, (a low pH skin cleanser) on the skin flora of the perineum of men with spinal cord injury. Investigators selected 20 patients with Pseudomonas on 2 consecutive cultures and randomized them to bathe with one of the four agents. Investigators bathed, rinsed, and dried patients, then took cultures from the perineum and penile shaft. PI decreased pseudomonas on the penile shaft more than CHG ($P<0.01$), but not significantly difrefernt from pHresh or triclocarban. Triclocarban decreased

Klebsiella on perineum more than PI and pHresh ($P<0.05$) but not more than CHG. None of the 4 agents were significantly more effective than the others in reducing total aerobic bacteria. This study provided culture data but no clinical outcome data. The products were tested as baths and not for a TFM indication.

Ayliffe et al. 1975 compared a standard handwash sampling technique with a simple finger-streak sampling method in assessing the relative effectiveness of a number of alternative preparations used for disinfecting a surgeon's hands. In each study they evaluated the removal of organisms from the skin with antiseptics. They studied 70% ethanol, 0.5% chlorhexidine digluconate (CHG) in 95% ethanol with 1% glycerol, Hibiscrub, 0.5% chlorhexidine digluconate, Zalclense, Desderman, and bar soap. They did not randomized the subjects nor blind the investigators or participants. The investigators found alcoholic CHG to be most effective, removing 97.9% and 99.7% of bacteria after one and six applications respectively. Bar soap was the least effective, removing 14.6 % and 30.5% of bacteria after one and six applications respectively. The handwash sampling and finger-streak sampling technique showed a fairly good correlation. The investigators did not study a clinical outcome.

Stuart 1986 is reviewed above

Knittle et al 1975 studied the nature of hand contamination and evaluated its role in the nosocomial transmission of gram-negative bacteria. When nurses used hexachlophene between patient contacts in April 1971, the investigators recovered gram negative bacteria from 80% of the hand cultures. When nurses used PI for handwashing the investigators recovered fewer gram negative organisms. This study did not have randomization, a description or observation of handwashing technique, and no clinical outcome.

Casewell and Phillips 1977 is reviewed above.

Raimondi et al. 2000 is a poster presentation about control of a multi-drug resistant Acinetobacter that does not provide sufficient information to support clinical benefit.

Selwyn 1985 summarized previous evaluations of skin disinfectants in vivo by excision biopsy. He reiterated results from his 1979 study, when he swabbed the abdomen of volunteers for 30 seconds with antiseptics, then excised a standard square of skin, liberated the bacteria by abrasion and agitation, and counted the bacteria. He found that iodine in ethanol reduced bacteria by 96%, followed by PI with an 89% reduction, and CHG in ethanol with 88%. CHG alone reduced bacteria by 82%, while benzalkonium chloride reduced bacteria by 39%. Selwyn does not state the number of volunteers or report a randomization scheme or statistical analysis of the results. He did not study a clinical outcome.

Institutional Settings

7. School absenteeism reduced – The CTFA states that use of hand sanitizer reduced absenteeism among elementary school teachers and students (Hammond et al. 2000; Shinder and Dyer, undated).

The elementary school setting presents multiple uncontrolled confounders that preclude any conclusion about a definitive benefit for a hand sanitizer.

8. Reduction in respiratory infection rate in adult day care centers – The CTFA states that use of a hand sanitizer as a supplement to handwashing was implicated in the significant reduction of respiratory infections in three adult day care centers (Falsey et al. 1999).

Falsey et al. 1999 evaluated the effect of a 4-month handwashing intervention in reducing respiratory illness in senior day-care centers. The investigators gave staff in three adult day-care centers a fanny pack with virucidal alcohol foam with instructions to wash their hands and supplement with alcohol foam after each patient care event and if they coughed or sneezed in their hands. The staff used the alcohol foam for two months and used their standard procedure for two months. The investigators compared the 4-month infection rate with a 3-year historical control. The study was not randomized or controlled. Handwashing compliance was not assessed. Rates of infection in the adults in the day care centers were not significantly different in the 2-month test period versus the 2-month standard procedure. The investigators found no apparent added benefit of virucidal foam.

9. Reduced symptoms of enteric disease – The CTFA states that hand rinses significantly reduced these symptoms in family day care homes (Butz et al. 1990).

Butz et al. 1990 is covered in another review of healthcare antiseptics by an interdisciplinary scientist in the Division of Over-the-Counter Drugs.

10. Reduced eye and skin/wound infection rates – The CTFA states that use of a topical antimicrobial product significantly reduced infection rates in a long-term care facility (Hoffmann et al. 1999). Eckert and Falsey (above) address this topic. Hoffman et al. 1999 is an abstract with insufficient information to support clinical benefit.

11. Healing of scrapes and scratches – The CTFA states that bathing with topical antimicrobial products and use of those products to clean cuts, scratches and abrasions led to a significantly improvement in wound healing and a lower frequency of infection (Dubow and Winter 1967; MacKenzie 1970; Somerville et al. 1970).

Dubow and Winter 1967 compared the effects of an antibacterial soap containing hexachlorophene and trichlorocabanilide (Dial soap) and a placebo soap upon the occurrence of infections from superficial cuts, scratches, and abrasions. The investigators conducted a double blind, controlled, study of 320 males from ages 8-16 years old housed in a juvenile detention home. All subjects were required to bathe daily with the soap assigned to the dorm. The test soap and placebo soap were each assigned to half the dorms. When a subject sustained a cut, scratch or abrasion, he was required to report to a nurse who washed the wound. The nurse assessed the wound severity as mild, moderate or severe, and documented healing. No other medication was used. The investigators assessed overall healing to be better in the test soap group with 158 total assessed as having good, average or poor healing. The placebo group had 225 total assessed as having good, average, or poor healing ($P<0.001$). This study was not randomized, the placebo group had substantially more subjects, potentially skewing results, and the assignment of wound severity is a clinical judgment, requiring standardization of assessment, which was not discussed by the authors. Additional washing of the wound by the subjects was not precluded or prohibited by the protocol. In addition, this study does not address a TFM indication.

The MacKenzie and Somerville articles do not address a TFM indication.

12. MRSA eradicated in a day care setting – The CTFA states that an antimicrobial regimen including the daily use of a topical antimicrobial product was reported to have cleared up an MRSA infection in one child and two other infected contacts within three months (Shahin et al. 1999).

Shahin et al 1999 involves only 3 subjects, which is insufficient to establish clinical benefit.

Home Settings

13. Atopic skin – The CTFA states that use of topical antimicrobial preparations improved the overall health of the skin as measured by a decrease in areas affected by atopic dermatitis and significantly fewer bacterial numbers on the skin (Breneman et al. 1998; Akiyama et al. 1997; Sugimoto et al. 1997). These three articles involve the topical application of antimicrobials to abnormal skin and do not address a TFM indication.

14. Skin infection risk – The CTFA states that a mathematical model showed that the use of antibacterial soap would result in a considerable reduction in the risk of infection (Rose and Haas 1999). Also, the CTFA states that use of topical antimicrobial preparations reduced the recurrence of infective skin lesions (Leigh and Joy 1993).

Rose and Haas 1999 developed a mathematical model regarding the risk of infection but did not study a clinical outcome. Gibson, Rose, Haas, Gerba, and Rusin 2002 expanded on the mathematical model using Shigella as an example, but again do not study a clinical outcome. The Gibson et al 2002 article is reviewed under the CTFA C80 submission below.

Leigh and Joy 1993 compared the use of mupirocin nasal ointment and a chlorhexidine/neomycin combination cream in eradicating staphylococcal nasal carriage. Mupirocin is a prescription product. The combination of chlorhexidine with neomycin in a cream used topically in the nose does not address a TFM indication.

15. Adjunct to acne treatment – The CTFA states that use of topical antimicrobial preparations decreased inflammation and improved skin condition when used as an adjunct treatment in acne patients (Brown 1977; Franz et al. 1978; Jampani et al. 2000a; Jampani et al. 2000b).

Brown 1977 studied topical povidone-iodine foam (Betadine Skin Cleanser Foam) in the treatment of 36 young adults with acne vulgaris. Subjects used concomitant therapy with another topical product, an oral contraceptive, ultraviolet light, or oral tetracycline. The investigators assessed 19 of the 32 subjects completing the six month study to have "benefited considerably", while 8 derived "some benefit" and 5 showed no improvement. This study did not employ an inactive control. The methodology was confounded by multiple interventions and the population was small. The investigators did not have a validated scale or acne pustule count method for their assessment. This study does not address a TFM indication.

Franz et al. 1978 studied three groups of young adult subjects with mild to moderate acne in a double-blind, randomized protocol for eight weeks, treating them with topical acne creams containing vehicle (Group A, active control, contained alcohol and sulfur), 0.1% triclosan Group B, or 0.1% triclosan plus

0.75% propylene phenoxetol (Group C). The investigators counted lesions, the degree of inflammation, and also included the subject's assessment of their condition. Fifty five of 72 subjects completed the treatment, with 19 in Group A, 22 in Group B, and 14 in Group C. Dropouts were primarily due to transfer of personnel. The investigators found 96 non-inflamed and 79 inflamed lesions in Group A; 78 non-inflamed and 56 inflamed lesions in Group B, and 79 non-inflamed and 57 inflamed lesions in Group C ($P<0.05$ for B&C versus A, no difference between B&C). Subjects rated the Group C product better than Group B, which was better than Group A. This randomized, controlled trial had a substantial number of dropouts and lasted only 8 weeks. Of note, this study does not address a TFM indication.

Jampani et al. 2000a is a poster presentation discussing a transepidermal delivery of topical antimicrobials and moisturizers. There is insufficient information to support clinical benefit. Jampani et al. 2000b is a poster presentation reporting use of a hand gel in reducing the number of acne lesions in 14 subjects after 12 weeks use. The authors did not identify the hand gel. There is insufficient information to support clinical benefit and these posters do not study the TFM indications under consideration.

16. Reduced respiratory illnesses in mothers – The CTFA states that hand disinfecting treatments significantly reduced respiratory illnesses in mothers caring for sick children (Hendley and Gwaltney 1988).

Hendley and Gwaltney 1988 reviewed the literature regarding the mechanisms of transmission of rhinovirus infections, and then summarized a study of 231 families they conducted from 1979-1982. They instructed mothers to dip their fingers in an iodine or placebo solution periodically (about every 3-4 hours for up to two weeks) after noticing symptoms of an acute respiratory illness in a family member. In the iodine group from 1979-1982, 4 of 57 mothers exposed to a respiratory illness became ill, while 16 of 79 in the placebo group became ill ($P=0.047$). When a rhinovirus was actually cultured, 0 of 11 mothers became ill in the iodine group, while 5 of 16 in the placebo group became ill ($P=0.1$). This study was randomized but compliance was gauged solely by observing a brown discoloration on the fingers. Subjects could also use soap and other household products. Other confounders were present such as the time delay in exposure of the mother versus when the patient first developed symptoms. Of note, when rhinovirus was actually cultured there was no difference between infections in the iodine and placebo group.

17. Reduced puerperal mastitis rate in nursing mothers – The CTFA states that use of a hand disinfectant significantly reduced the incidence of puerperal mastitis in cows (Peters and Flick Fillies 1991). There is considerable precedence for this in the dairy literature which repeatedly shows the importance of topical antimicrobial products in preventing the transfer of Staphylococci during the milking process (Boddie et al. 1990; Boddie et al. 1997; Hicks et al. 1981; Pankey et al. 1983; Kovars 1985; Sheldrake and Hoare 1981; Sheldrake and Hoare 1983; National Mastitis Council Research Committee 2000).

Since this review concerns human clinical benefit, and not dairy literature, the 9 references in this group are not reviewed.

18. Reduced eye infection – The CTFA states that use of an antibacterial hand soap correlated with fewer staphylococcal infections of the eye (Samalonis 1999).

Samalonis 1999 is an abstract or report by Lisa Salmalonis, a correspondent, who interviewed Warren Cross, MD for Eyeworld, a newsmagazine. Cross studied 427 patients with eye infections and noted that 89% used a nondeodorant facial soap. He looked at cases without a control group and did not provide a statistical analysis. He recommended that a deodorant soap be used before and after ocular surgery. The specific ingredient in a deodorant soap is not mentioned. This report does not address the TFM issues under consideration in this review.

18. Reduction of bacteria on contact lens – The CTFA states that it is prudent to keep a contact lens as free of bacteria as possible, not only by sterilization of the lens, but by decreasing the risk of bacterial transfer from the hands to the lens (Ly et al. 1997).

Ly et al. 1997 does not study a clinical outcome and does not study a TFM indication.

19. Nosocomial infections: overview

The CTFA notes in 1978 Britt et al. estimated that over 2 million nosocomial infections occur each year, accounting for 29 million days of acute hospital care (Britt et al. 1978).

Britt et al. 1978 discusses nosocomial infections, but this is not an article about the clinical benefit of a healthcare antiseptic.

20. Additional Topic:
In CP7 the CTFA also presented a monograph on chlorhexidine, published in 1986 that included 24 brief publications including 2 editorials and 22 abstracts or short papers. This reviewer found that none of the 24 publications proved clinical benefit.

Comment 80
On August 27, 2003 (C80) the CTFA reiterated their arguments from CP7 and updated some references they believe support their position. In each category the statements are those of the CTFA.

Invasive Procedures

1. Blood Cultures: The CTFA states that the use of topical antimicrobial preparations on the skin prior to withdrawing blood has been shown to reduce the number of contaminated blood cultures. This reduces the number of times blood needs to be drawn and prevents the prescription of unnecessary medication to fight non-existent infections. Additional studies are related to this benefit (Calfee and Farr 2002, Olmsted et al. 2002).

Calfee and Farr 2002 performed a randomized, investigator-blinded, crossover study of 12,692 percutaneously-drawn blood cultures from a hospital emergency room and wards. They compared the effectiveness of four antiseptics, 10% PI, 70% IPA, tincture of iodine, or PI with 70% ethanol (Persist), in the prevention of contamination of the blood cultures over successive 12 week study periods interspersed with a 2 week washout. A total of 333 (2.62%) of the 12,692 blood cultures were contaminated during the study period compared to 3.21% of 12,859 during the previous 12 month period (RR 0.82, 95% CI=0.71-0.94, P=0.006). The individual contamination rates, PI=2.93%, 70% IPA=2.50%, tincture of iodine=2.58%, Persist=2.46%, were insignificantly different. The investigators concluded than IPA might

be the optimal antiseptic due to low cost and tolerability, but they did not link contamination rates with a clinical outcome. They did not describe the method of data collection from the earlier 12 month comparison period. This study did not address clinical outcomes or a specific TFM indication.

Olmsted et al. 2002 found that tincture of iodine reduced the overall contamination rate of blood cultures to 2% compared to a 4% contamination rate when 10% PI was used. As in the Calfee and Farr study, Olmsted's article does not link contamination with a clinical outcome. Also, the article does not address a TFM indication.

2. Catheters and Intravenous Lines– The CTFA states that contamination of these invasive prostheses comes from both the patient and from the hands of the caregiver and that additional examples of benefit from the use of topical antimicrobial products have been shown (Chaiyakunapruk et al. 2002, Kinoshita et al. 2002).

Chaiyakunapruk et al. 2002 performed a meta-analysis of eight randomized trials comparing chlorhexidine gluconate (CHG) with povidone-iodine (PI) in preventing catheter-related bloodstream infection. One of the trials is the Maki et al. 1991 study reviewed above, two are abstracts, one is a paper presentation, and the remaining four are published studies. A total of 4,143 catheters were involved. The various studies used different formulations of CHG and slightly different definitions of bloodstream infection. All studies used 10% PI for the control group. Five of the studies clearly described the procedure for care of the catheter site. Four of the studies specified that antibiotic ointments were not used. Only one study blinded investigators to the antiseptic used. Patient eligibility criteria were clearly described in five of the studies. Several of the studies defined catheter-related bloodstream infection differently, and none reported strategies to distinguish bacteremia from blood culture contamination. However, all required isolating the same organism from the catheter and the bloodstream. The risk for catheter colonization and catheter-related bloodstream infection were significantly lower in the CHG group than in the PI group. The infection rate was about 1% with CHG and 2% with PI, with an overall summary risk ratio for catheter-related bloodstream infection of 0.49 (95% CI, 0.28 to 0.88) with CHG versus PI. While this article is helpful in summarizing the available data, it does not provide conclusive information. The many differences in methodology between the studies make suspect any firm conclusion about the benefit of CHG over PI.

The CTFA did not supply the Kinoshita et al. 2002 article and this reviewer did not find the article in PubMed.

Regarding **Non-invasive Procedures**, The CTFA states:

3. Reduced Infection Rates – The CTFA states that three studies showed significant reduction in infection rates in a clinical settings from the use of alcohol hand sanitizers (Fendler et al. 2002; Hilburn et al. 2003), and in a non-clinical setting from the use of 1.2% triclocarban (Luby et al. 2002).

Fendler et al 2002 conducted a 34-month, nonrandomized, unblinded study in an extended care facility, from July 1997-May 2000. The investigators studied an alcohol gel hand sanitizer (Purell Instant Hand Sanitizer) in caregivers on 2$^{nd\ and}$ 3rd floors (subacute care), while the first floor was a control (chronic care). All 3 floors had antimicrobial soap (Micrell Antimicrobial Lotion Soap). The Purell group was instructed to use the antimicrobial soap after every fifth use of the Purell. The investigators found that the units using the Purell had a 30.4% lower infection rate. The infections were mostly UTIs, respiratory tract,

and wound infections. The actual number of times caregivers washed hands, while caring for patients, was not compared between the units. The concomitant use of Micrell in the Purell group is a confounder. The medical problems in the study populations differed (subacute vs. chronic). The absence of randomization and blinding complicates any interpretation.

Hilburn et al. 2003 is an extension of the Fendler et al 2002 article reviewed above, and presents similar methodology flaws. The investigators studied the Purell Instant Hand Sanitizer in a hospital over 10 months. They found a 36.1% decrease in nosocomial infections over a 10-month period when Purell was used by the HCWs on the orthopedic surgical unit and overflow surgery unit. Surgical site infections (SSIs) increased slightly, but insignificantly. A lower number of UTIs accounted for eighty percent of the reduction in nosocomial infections. The lack of improvement in SSIs, but the marked improvement in UTIs, is of unclear significance. The authors did not comment on Foley catheter care technique. The study did not observe handwashing, and did not employ a control, such as plain soap.

Luby et al. 2002 evaluated the effect of using an antibacterial soap on the incidence of impetigo in low-income households in Karachi, Pakistan. In a randomized and blinded study the investigators provided 162 households with a regular supply of 1.2% triclocarban soap (Safeguard) or identical placebo soap (81 in each group). Participants were instructed to continue their regular routine of bathing and hand washing, but to substitute their usual soap with the study soap. The investigators enrolled 79 nearby households as controls, which washed or did not wash per their custom. Behavior with regard to handwashing was not assessed in the data collection. Households with triclocarban soap had a 23% lower incidence of impetigo compared to placebo soap, (P=0.28, not statistically significant), and a 47% lower incidence than standard practice households (P= 0.02). The placebo group had a 24% lower incidence of impetigo than standard households, which was not significantly different. The investigators noted that a 70% increase in sample size would have been needed to provide stronger statistics. The overall incidence of impetigo was lower in the study than what they had anticipated from a pilot trial. This study provided a clinical outcome. The study was randomized, blinded, used a placebo, plus had a separate control group. However, since the active soap was not better than the placebo soap, the lower incidence of impetigo with the triclocarban soap compared with standard practices might have been due to a difference in behavior rather than due to the active soap.

4. Mathematical Modeling – Two mathematical models were published providing quantitative assessment of risk reduction from hand washing with antibacterial soaps (Gibson et al. 2002, Marie et al. 2002).

Gibson et al. 2002 provides a mathematical model to assess the probability of becoming infected based upon known characteristics of the infectious agent and the means of transmission. This article is not a clinical study of a healthcare antiseptic.

Marie et al 2002 employs similar mathematical techniques to assess salmonella risk from raw chicken. As with the Gibson et al article above, this article is not a clinical study of a healthcare antiseptic.

The CTFA presents four additional handwash studies in Comment 80 noting that these studies are published since CP7:

Trick et al 2003 studied the effects of using plain soap and water and either a 62% alcohol gel or a 1% benzethonium chloride wipe on the transient flora on the hands of 66 surgical intensive care unit nurses.

The investigators defined a transient organism as all organisms other than methicillin-resistant coagulase-negative (MRCN) staphylococci. They found that hands cleansed with alcohol-based hand gel were significantly less likely to be contaminated with MRCN staphylococci, Candida species, or any transient organism compared with the use of plain soap and water. The investigators did not study a clinical outcome.

Sickbert-Bennet et al 2002 is a poster presentation comparing the effects of 13 handwash products in 10-second washes. The investigators did not report the number of subjects nor list all 13 products; however, as an example, they found that 4% CHG reduced Serratia by 3.77 log, bland soap by 1.64 log, and 62% ethanol by 0.67 log. The investigators did not assess a clinical outcome.

Weber et al 2003 studied the effectiveness of CHG, ethanol, chlorine-containing wipes, and soap and water in removing Bacillus atrophaeus spores as a surrogate of Bacillus anthracis. The investigators did not study a clinical outcome.

Voss and Goroncy-Bermes 2000 is an abstract of a study comparing a CHG handwash, an alcohol disinfectant and bland soap in removing S. aureus from the hands. The investigators did not study a clinical outcome.

The CTFA also presented new data on Surgical Scrub Preparations, Surrogate Organisms, and Neutralization. These topics are covered in other reviews of healthcare antiseptics by interdisciplinary scientists in the Division of Over-the-Counter Drugs.

Summary

The CTFA submitted literature regarding healthcare antiseptics to support their request that FDA revise the performance and effectiveness guidelines in the Health-Care Antiseptic Drug Products Monograph. The CTFA outlined an argument about the benefit and efficacy of healthcare antiseptics in the clinical arena and also in other settings, including extended care facilities, schools, and the home. The majority of the literature articles cited develops conclusions that cannot be supported by the data due to design flaws in the studies. Examples of the design flaws are failure to randomize or blind, failure to use an inactive control, failure to document proper training, failure to observe and document handwashing or preoperative site preparation technique, inadequate statistical power, and in some cases in the failure to analyze results for statistical significance. Studies that evaluated the antibacterial performance of a healthcare antiseptic(s), without a correlation with a clinical outcome, might provide interesting information about the antiseptic(s) but do not provide a a direct correlation between a specific reduction in bacteria on the skin with a reduction in infection rates. Studies that evaluated the performance of a healthcare antiseptic for indications other than those proposed in the TFM, are not helpful in assessing efficacy of ingredients for indications proposed in the monograph.

Conclusions:

The literature articles and abstracts that CTFA proffered as support for its request that FDA revise the performance and effectiveness guidelines in the Health-Care Antiseptic Drug Products Monograph are, in fact, not supportive of the request. From 130 articles and abstracts evaluated, none can clearly support a change in the efficacy criteria for the antiseptic(s) indications studied, principally because of methodology flaws or non-clinical endpoints.

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Concurrence

LEGEND

- ACF=acute care facility
- AGNB=aerobic gram negative bacteria
- APIC=27th Annual Educational Conference & International Meeting June 2000
- Betadine=10% povidone-iodine formulation
- CHG=chlorhexidine gluconate, often 2% or 4%
- CVC=central venous catheter
- CVL=central venous line
- Dettol=PCMX=parachlorometaxylenol
- ECF=extended care facility
- HCW=health care worker
- Hexol= 0.5% CHG+60% isopropanol
- Hibiclens=4% chlorhexidine gluconate formulation
- Hibiscrub=4% CHG in 70% isopropyl alcohol
- ICN/ICU/SCN=intensive care nursery/intensive care unit/special care nursery
- IPA=isopropyl alcohol
- MRSA=methicillin-resistant Staphylococcus aureus
- N/A=not applicable
- NI = nosocomial infection(s), usually defined as NI if infection occurs more than 72 hrs after admission
- NIC=no inactive control (ie no formulation alone, no excipient alone, not compared to water alone)
- NICU=neonatal intensive care nursery
- NR=not randomized
- pHisoHex=3% hexachlorophene formulation
- PI=povidone-iodine, often 7.5%
- PPP=Patient Preoperative Preparation
- SS= surgical scrub
- SSI=surgical site infection
- UTI=urinary tract infection
- VAP=ventilator-assisted pneumonia

Healthcare Review Articles

1. Aly et al 1998
Aly R et al. Clinical efficacy of a chlorous acid in preoperative skin antiseptic. Am J Infect Control 1998; 26: 406-12

2. Alyiffe et al 1975
Alyiffe GA et al. Comparison of two methods of assessing the removal of total organisms and pathogens from the skin. J Hyg Camb 1975; 75: 259-274.

3. Amortegui 1978
Amortegui AJ and Buffenmyer C. Comparison of the antiseptic effect of two iodophor preparations on hand washing in a well-baby nursery. JOGN Nursing 1978; 35-38.

4. Apt et al 1989
Apt L et al. Outpatient topical use of povidone-iodine in preparing the eye for surgery. Ophthalmology 1989; 96: 289-92.

5. Arata et al 1993
Arata T et al. Evaluation of povidone-iodine alcoholic solution for operative site disinfection. Postgrad Med J 1993; 69: S93-S96.

6. Bartzokas et al 1982.

Bartozokas CA et al. Control and eradication of methicillin-resistant Staphylococcus aureus on a surgical unit. NEJM 1984; 311: 1422-5.

7. Beaton undated
Beaton JH. Clincal experience with Betadine solution in gynecology. No Journal Reference, undated, p61-2, Michigan State Univ.

8. Berry et al 1982
Berry AR et al. A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of postoperative wound infection. J Hosp Infect 1982; 3: 55-63.

9. Boyce et al 1990
Boyce JM et al. A common source outbreak of Staphylococcus epidermidis among patients undergoing cardiac surgery. J Infect Dis 1990; 161: 494-9.

10. Boyce JM and Pittet D 2002
Boyce JM, Pittet D. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep. 2002;51:1-45, quiz CE1-4.

11. Brady et al 1990
Brady LM et al. Successful control of endemic MRSA in a cardiothoracic surgical unit. Med J Australia 1990; 152: 240-5.

12. Brandberg et al 1981
Brandberg A and Andersson I. Preoperative wound infections in vascular surgery: effect of pre-operative whole body disinfection by shower-bath with chlorhexidine soap. Chapter 13. Skin Microbiology, Relevance to Clinical Infection. Maibach HI and Aly R(eds.) Spring-Verlag, New York. 1981, 93-97.

13. Brandberg and Andersson 1981
Brandberg A and Andersson I. Preoperative whole body disinfection by shower bath with chlorhexidine soap: effect on transmission of bacteria from skin flora. Chapter 12. Skin Microbiology, Relevance to Clinical Infection. Maibach HI and Aly R(eds.) Spring-Verlag, New York. 1981, 93-97.

14. Britt et al 1978
Britt MR, Schieupner CJ, Matsumiya S. Severity of underlying disease as a predictor of nosocomial infection. JAMA 1978; 239: 1047-51.

14. Brown et al 1984
Brown TR et al. A clinical evaluation of chlorhexidine gluconate spray as compared with iodophor scrub for preoperative skin preparation. Surgery, Gynecology, and Obstetrics 1984;158: 363-6.

15. Brown 1977
Brown EJ. A Povidone-iodine skin cleanser foam in the management of acne vulgaris. The British J Clin Practice 1977; 31: 218-9.

16. Burkhardt et al 1985
Burkhardt et al. Capsular contracture: A prospective study of the effect of local antibacterial agents. Plastic and Reconstructive Surgery 1986; 919-30.

17. Butz AM et al 1990
Butz AM et al. Occurrence of infectious symptoms in children in day care homes. Am J Infect Control 1990; 18: 347-53

18. Calfee and Farr 2002
Calfee DP and Farr BM. Comparison of four antiseptic preparations for skin in the prevention of contamination of percutaneously drawn blood cultures: a randomized trial. J Clin Micro 2002; 40: 1660-5.

19. Casewell and Phillips 1977
Casewell and Phillips. Hands as route of transmission for Klebsiella species. Br Med J 1977; 2: 1315-7.

20. Chaiyakunapruk et al 2002
Chaiyakunapruk N et al. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: A meta-analysis. Ann Int Med 2002; 136: 792-801.

21. Conly JM et al 1989
Conly JM et al. Handwashing practices in an intensive care unit: The effects of an educational program and its relationship to infection rates. Am J Infect Control 1989; 17: 330-9.

22. Connell and Rousselot 1964
Connell JF and Rousselot LM. Povidone-Iodine: extensive surgical evaluation of a new antiseptic agent. Am J Surgery 1964; 849-55.

23. Cooper JW and Gibson TC 1974
Cooper, JW and Gibson TC. Hexachlorophene versus. povidone-iodine in the control and prophylaxis of neonatal and surgical infection. Hosp. Form. Management 1974; 12-17.

24. Cruse and Foord 1973
Cruse PJE and Foord R. A five-year prospective study of 23,649 surgical wounds. Arch Surg 1973; 107: 206-10.

25. Denton, GW 1991
Denton GW. Chlorhexidine (Chapter 16). In: Block SS, ed. Disinfection, sterilization, and preservation. 4th ed. Philadelphia, PA: Lea and Febiger, 1991.

26. Doebbeling BN et al 1992
Doebbeling BN et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. NEJM 1992; 327: 89-93.

27. Dubow and Winter 1967
Dubow E and Winter L. Effect of an antibacterial soap in the management of scratches, cuts, and abrasions. Curr Ther res 1967; 9: 631-3.

28. Eckert DG et al 1989
Eckert DG et al. Proteeae groin skin carriage among nursing home residents—resistance to antiseptics. Infect Control Hosp Epidemiol 1989;10: 155-160.

29. Eckert et al 1989
Eckert DG et al. Indications for alcohol or bland soap in removal of aerobic gram-negative skin bacteria: assessment by a novel method. Infect Control Hosp Epidemiol 1989; 10: 306-311.

30. Ehrenkranz NJ 1992
Ehrenkranz NJ. Bland soap handwash or hand antisepsis? The pressing need for clarity. Infect Control Hosp Epidemiol 1992; 13: 299-301.

31. Falsey et al 1999
Falsey AR, Criddle MM, Kolassa JE, McCann RM, Brower CA, Hall WJ. Evaluation of a Handwashing Intervention to Reduce Respiratory Illness Rates in Senior Day-Care Centers. Infect Control and Hosp Epidemiol 1999; 20: 200-2.

32. Faoagali et al 1995
Faoagali J et al. Comparison of the immediate, residual, and cumulative antibacterial effects of Novaderm R, Novascrub R, Betadine Surgical Scrub, Hibiclens, and liquid soap. Am J Infect Control 1995; 23: 337-343.

33. Fendler et al 2002
Fendler EJ et al. The impact of alcohol hand sanitizer use on infection rates in an extended care facility. Am J Infect Control 2002; 30: 226-33.

34. Field EA and Martin MV 1986
Field EA and Martin MV. Disinfection of dental surgeon's hands with detergent preparations of triclosan and chlorhexidine. J Dent 1986; 14: 7-10.

35. Forfar JO et al 1968
Forfar JO et al. Effect of hexachlorophene on incidence of staphylococcal and gram-negative infection in the newborn. Lancet 1968; 177-180.

36. Franz et al 1978
Franz E et al. The effectiveness of topical antibacterials in acne. A double-blind clinical study. J Int Med Res 1978; 6: 72-7.

37. Frappier-Davignon L et al 1959
Frappier-Davignon L et al. Staphylococcal infection in hospital nurseries: influence of three different nursing techniques. Canadian Medical Assn Journal 1959; 81: 531-6.

38. Garibaldi et al 1988
Garibaldi RA et al. The impact of preoperative skin disinfection on preventing intraoperative wound contamination. Infect Control Hosp Epidemiol 1988; 9: 109-13.

39. Garland et al 1995
Garland JS et al. Comparison of 10% povidone-iodine and 0.5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: a prospective trial. Pediatr Infect Dis J 1995; 14: 510-6.

40. Georgiade et 1990
Georgiade GS et al. The effect of povidone-iodine solutions used as surgical preparations on the bacterial flora of the skin. Advances in Therapy 1990; 7: 1-8.

41. Gibson LL et al 2002
Gibson LL et al. Quantitative assessment of risk reduction from hand washing with antibacterial soaps. J Applied Micro (Symposium Supplement) 2002; 92: 136S-43.

42. Gilmore DS et al 1984.
Gilmore DS et al. Effect of antiseptic agents on skin flora of the perineum of men with spinal cord injury. Infect Control 1984; 5: 431-4.

43. Goldblum et al 1983
Goldblum SE et al. Comparison of 4% chlorhexidine gluconate in a detergent base (Hibiclens) and povidone-iodine (Betadine) for the skin preparation of hemodialysis patients and personnel. Am J Kidney Dis 1983; 2: 548-52.

44. Grinbaum et al 1995
Grinbaum RS et al. An outbreak of handscrubbing-related surgical site infection in vascular surgical procedures. Infect Control Hosp Epidemiol 1995; 16: 198-202.

45. Gruer et al. 1984
Gruer LD et al. Disinfection of hands and tubing of CAPD patients. J Hosp Infect 1984; 5: 305-12.

46. Hayek et al
Hayek et al. A placebo-controlled trial of the effect of two preoperative baths or showers with chlorhexidine detergent on postoperative wound infection rates. J Hosp Infect 1987; 10: 165-72.

47. Hendley and Gwaltney 1988
Hendley JO and Gwaltney JM. Mechanisms of transmission of rhinovirus infections. Epidemiol Reviews 1988; 10: 242-58.

48. Hibbard et al 2002
Hibbard JS et al. A clinical study comparing the skin antisepsis and safety of ChloraPrep, 70% Isopropyl alcohol, and 2% aqueous chlorhexidine. J Infusion Nurs 2002; 25: 245-9.

49. Hilburn MT et al 2003
Hilburn MT et al. Use of alcohol hand sanitizer as an infection control strategy in an acute care facility. Am J Infect Control 2003; 31: 109-16.

50. Hughes 1966
Hughes RK. A method of improved antisepsis for open-heart surgery. Ann Thorac Surg 1966; 2: 230-6.

51. Isenberg et al 1997
Isenberg SJ et al. Efficacy of topical povidone-iodine during the first week after ophthalmic surgery. Am J Ophthalmol 1997; 124: 31-5.

52. Jackson 1972
Jackson FE. The utilization of povidone-iodine in the prevention of neurosurgical infections. In: Polk HC Jr, Ehrenkranz NJ , eds. Therapeutic Advances and new Clinical Implications: Medical and Surgical Antisepsis with Betadine Microbicides. Yonkers , NY: Purdue Frederick, 79-86;1972.

53. Jones RD et al 2000
Jones RD et al. Triclosan: A review of effectiveness and safety in health care settings. Am J Infect Control 2000; 184-96.

54. Kaiser et al 1988.
Kaiser AB et al. Influence of preoperative showers on staphylococcal skin colonization: A comparative trial of antiseptic skin cleansers. Ann Thoracic Surg 1988; 45: 35-8.

55. Kirita T et al 1993
Kirita T et al. Efficacy and safety of a quick drying rubbing type povidone-iodine alcoholic disinfectant solution. Postgrad Med J 1993; 69: S27-S32.

56. Klausner JD et al 1999
Klausner JD et al. Outbreak of Stenotrophomonas maltophilia bacteremia among patients undergoing bone marrow transplantation: association with faulty replacement of handwashing soap. Infect Control Hosp Epidemiol 1999; 20:756-8.

57. Klovekorn et al 1985
Klovekorn WP et al. Ten years experience with povidone-iodine in heart surgery. J Hosp Infect 1985; 6: 117-21.

58. Knittle MA 1975
Knittle MA et al. Role of hand contamination of personnel in the epidemiology of gram-negative nosocomial infections. J Pediatr 1975; 86: 433-7.

59. Levin et al 1991
Levin A et al. Prevention of hemodialysis subclavian vein catheter infections by topical povidone-iodine. Kidney International 1991; 40: 934-8.

60. Leyden et al 1991
Leyden JJ et al. Computerized image analysis of full-hand touch plates: a method for quantification of surface bacteria on hands and the effect of antimicrobial agents. J Hosp Infect 1991; 18: 13-22.

61. Leyden et al 1996
Leyden JJ et al. A new method for in vivo evaluation of antimicrobial agents by translocation of complex dense populations of cutaneous bacteria. Skin Pharmacology 1996; 6: 60-8.

62. Luby S et al 2002
Luby S et al. The effect of antibacterial soap on impetigo incidence, Karachi, Pakistan. Am J Trop Med Hyg 2002; 67: 430-5.

63. Maki DG 1989
Maki DG. The use of antiseptics for handwashing by medical personnel. J Chemotherapy 1989; 1: 3-11.

64. Maki et al 1991
Maki DG et al. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. Lancet 1991; 338: 339-43.

65. Malone N and Larson E 1996
Malone N and Larson E. Factors associated with a significant reduction in hospital-wide infection rates. Am J Infect Control 1996; 182: 180-5.

66. May SR et al 1991
May SR et al. Reduced bacteria on transplantable allograft skin after preparation with chlorhexidine gluconate, povidone-iodine, and isopropanol. J Burn Care and Rehabilitation 1991; 12: 224-228.

67. Mitsuda T et al 1999
Mitsuda T et al. The influence of methicillin-resistant Staphlococcus aureus (MRSA) carriers in a nursery and transmission of MRSA to their households. J Hosp Inf 1999; 42: 45-51.

68. Mortimer EA et al 1962.
Mortimer EA et al. Transmission of staphylococci between newborns. Am J Dis Children 1962; 104: 289-295.

69. Murray J and Calman RM 1955.
Murray J and Calman RM. Control of cross-infection by means of an antiseptic hand cream. Br Med J 1955; 81-83.

70. Onesko KM and Wienke EC 1987
Onesko KM and Wienke EC. The analysis of the impact of a mild, low-iodine, lotion soap on the reduction of nosocomial methicillin-resistant Staphylococcus aureus: a new opportunity for surveillance by objectives. Inf Control 1987; 8: 284-288.

71. Rubio 1987
Rubio PA. Septisol antiseptic foam: a sensible alternative to the conventional surgical scrub. Int Surg 1987; 72: 243-6.

72. Sakata H et al 1989
Sakata H et al. Acinetobacter calcoaceticus biovar anitratus septicaemia in a neonatal intensive care unit: epidemiology and control. J Hosp Infect 1989; 14: 15-22.

73. Schifman and Pindur 1993
Schifman RB and Pindur A. The effect of skin disinfection materials on reducing blood culture contamination. Am J Clin Pathol 1993; 99: 5536-8.

74. Selwyn 1985
Selwyn S. Evaluating skin disinfectants in vivo by excision biopsy and other methods. J Hosp Infect 1985; 6: 37-43.

75. Tanaka et al 1988
Tanaka K et al. Evaluation of rapid drying hand disinfectant preparations in the intensive care unit. Crit Care Med 1988; 16: 540-2.

76. Trick WE et al 2003
Trick WE et al. Impact of ring wearing on hand contamination and comparison of hand hygiene agents in a hospital. Clin Infect Dis 2003; 36: 1383-90.

77. Tuffnell DJ et al 1987
Tuffnell DJ et al. Methicillin resistant staphylococcus aureus; the role of antisepsis in the control of an outbreak. J Hosp Infect 1987; 10: 255-9.

78. Tuominen et al 1981
Tuominen M et al. The effect of local antiseptic, chlorhexidine, in preventing infection from central venous catheterization. A clinical study. Ann Clin Res 1981; 13: 425-8.

79. Tyzack R. 1985.
Tyzack R. The management of methicillin-resistant Staphlococcus aureus in a major hospital. J Hosp Infect 1985; 6: 195-199.

80. Vorherr et al 1988
Vorherr H et al. Comparative effectiveness of chlorhexidine, povidone-iodine, and hexachlorophene on the bacteria of the perineum and groin of pregnant women. Am J Infect Control 1988; 16: 178-81.

81. Weber D 2003
Weber D et al. Efficacy of selected hand hygiene agents used to remove Bacillus atrophaeus (a surrogate of Bacillus anthracis) from contaminated hands. JAMA 2003; 289: 1274-77.

82. Webster J 1992
Webster J. Handwashing in a neonatal intensive care nursery: product acceptability and effectiveness of chlorhexidine gluconate 4% and triclosan 1%. J Hosp Infect 1992; 21: 137-41.

83. Webster J et al 1994
Webster J et al. Elimination of methicillin-resistant Staphylococcus aureus from a neonatal intensive care unit after hand washing with triclosan. J Pediatr Child Health 1994; 30: 59-64.

84. Zafar et al 1995
Zafar AB et al. Use of 0.3% triclosan (Bacti-Stat) to eradicate an outbreak of methicillin-resistant Staphylococcus aureus in a neonatal nursery. Am J Infect Control 1995; 23: 200-8.

Selected Abstracts:

85. **Maki and Hecht 1982**
Maki GG and Hecht JA. Comparative study of handwashing with CHG, PI and nongermicidal soap for prevention of nosocomial infection. Clin Research 1982; 30: 303A. (Note: also published in Proceeding of 22nd ICAAC Oct 1981

86. Cross 1989
Cross WD. Decreasing the incidence of external ocular eye disease. Eyeworld 1999; 4: 52-53. Reported by Lisa Salmonis, correspondent. (international news magazine for ophthalmology)

Clinical Benefit of Patient Preoperative Preparations*

Clinical Benefit Summary of 39 Patient Preoperative Articles and Abstracts: 0 YES, 0 MAYBE, 39 NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
1. Connell and Rousselot	Evaluate new antiseptic, povidone-iodine	Prospective hospital study of degerming effect of PI	0.5% PI aerosol spray 0.75% PI surgical scrub 1.0% PI solution compared with hexachlorophene	150 surgery pts 25 doctors 195 wounds or burns	PI spray and scrub and solution reduced predominant bacteria about 86%-98%, while hexachlorophene reduced bacteria about 84%-95% (no P values)	NR no P values no control group for the PI solution did not state amount of PI used in any of the studies	NO
2. Hughes et al 1966	To report the antisepsis procedures followed for open-heart surgery	Retrospective report of antisepsis procedures at hospital, not a study (article)	3% hexachlorophene (pHisoHex) + topical bacitracin/polymixin B, + IV antibiotics	86 patients over 29 months	No endocarditis in 86 consecutive pts over 29 months	Retrospective, report of hospital procedures, not a study, changes in protocol from prior timeframe not stated	NO
3. Jackson 1972	Report the use of PI in neurosurgical operations and the incidence of infection	Retrospective; hospital data summary PI used as surgical scrub & Pt Pre-op Prep (article)	PI (Betadine Surgical Scrub and Betadine Solution	393 patients	In 393 neurosurgical procedures from Jan 1968-March 1971 only one infection (0.254%); no prior comparison, no P values	NR, NIC, retrospective, no P values, not a clinical trial	NO
4. Seeberg & Bergman 1979	Evaluate Hibiscrub in pre-op patients	Prospectivel, lab study, 3 washes (abstract)	Hibiscrub(CHG)	28 pre-op patients	After 3 washes operation site had 0-1 cfu/plate, groin<100 cfu/plate in 90%	NR, NIC, No clinical outcome data	NO
5. Brandberg et al 1981	Evaluate effect of Preop Hibiscrub shower on post op wound infections	Prospectivel, groin incisions, no pre-op prophy antibiotics (article)	Hibiscrub(CHG) vs "standard pre-op prep"	341 vascular surgery pts (171+ 170)	Post-op infection 13/170(7.7%) in Hibiscrub group, vs 30/171 (17.5%) in control group (P<0.05)	NR, not blinded, standard pre-op prep not defined	NO

* See Legend Page 9

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
6. Brandberg & Andersson 1981	Evaluate transmission of bacteria from skin flora after Hibiscrub Pre-op shower	Prospective , lab study (article)	Hibiscrub (CHG) vs wash with bland soap	16 volunteers	Soap shower spreads contamination with aerobic bacteria by most loci of skin;, Hibiscrub reduced aerobic bacteria for one week	NR, No clinical outcome data No P values	NO
7. Seeberg et al 1981	Evaluate Hibiscrub in reducing bacterial counts	Prospective, lab study, 3 washes (abstract)	Hibiscrub(CHG)	5 volunteers	After 3 washes no S. aureus in groin or axilla, some on lip	NR, NIC, No clinical outcome data	NO
8. Tuominen et al 1981	Evaluate effect of CHG in preventing infection from CVC	Prospective, randomized Setting hospital Cultured insertion sites and catheter tips	0.05% CHG-impregnated gauze vs sterile gauze at insertion site	54 patients (60 catheters)=CHG 59 pts (64 catheters)=sterile gauze	CHG group 13% + cultures Sterile gauze group 16% + cultures, P<0.05 Sepsis in 3 from CHG, 1 from sterile gauze (no statistic given) CHG better after cutdown, but not after percutaneous CVC procedure	Positive skin cultures less with CHG--impregnated gauze, but sepsis higher in CHG group=mixed result	NO
9. Berry et al 1982	Evaluate PI solution and scrub vs CHG solution and scrub in preventing post-op infections	Prospective, randomized Setting: hospital, May 1978-Feb 1980 Observed surgical wounds at day 3-4 (article)	10% PI in alcohol plus 7.5% PI in alcohol as solution and scrub versus Hibitane plus Hibiscrub	413 patients PI regimen 453 patients CHG regimen	PI group 14.8% infection at discharge (before Day 3-4) vs. 9.7% in CHG group (P=0.03). At Day 3-4 there was no difference.	Partially blinded Amount of alcohol in PI regimen not stated Day 3-4 assessment not justified (wound infections occur later).	NO
10. Brown et al 1984	Evaluate CHG spray vs iodophor scrub for Patient Pre-op Prep in 3 types of surgical procedures	Prospective, randomized Setting: hospital , Dec 1979-Nov 1980 (article)	0.5% CHG in 70% IPA vs PI 6 min scrub	737 evaluable of 791 total pts (laparotomy, C-section, mastectomy)	29/359 infections PI (8.1%) 23/378 infections CHG (6.0%, P>0.05%=not significant; however, sepsis 5/359 PI vs 1/378 CHG(P<0.05)	CHG group had foreign material removed from skin folds&umbilicus, Concomitant antibiotics not tallied Overall infections no difference	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
11. Selwyn 1985	Describe an in vivo evaluation of skin disinfection	Review article, mostly summarizes prior results describes skin biopsy method. Swabbed abdomen, took skin biopsy, abraded skin, counted bacteria (article)	Iodine in ethanol PI CHG in ethanol 60% isopropyl 70% ethanol CHG benzalkonium	unknown	Iodine in ethanol most effective, reduces 96% of control count of bacteria, PI next @89%	This is a review article, not a current study NR, NIC, no P values, No clinical outcome	NO
12. Klovekorn et al 1985	Describe 10 years experience using PI in pts undergoing open-heart operations	Retrospective: 10 year summary Setting: German Heart Center (article)	1:1000 PI preoperative bath, 10% PI solution, PI scrub	7566 open-heart surgery patients	5% incidence of superficial wound infections, 0.5% incidence of severe, deeper infections; "...antiseptic measures significantly reduced postoperative wound problems"	Retrospective. no actual data on incidence of infections pre-1974, no description of previous antiseptic regimne for comparison	NO
13. Burkhardt et al 1986 **Interesting study**	Study effect of local antibacterial agents on capsular contracture in mammoplasty surgery	prospective, randomized, double-blind Setting: surgery + outpt followup for up to 40 months (article)	1. cephalothin 2. cephalothin + PI 3. PI 4. Dual Antibiotic +steroid foam 5. Unmedicated	124 patients with augmentation mammoplasty	Incidence of Class 3 or 4 contracture: 26% (cephalothin), 18%, 18%, 14%, 41% (control) respectively ($P<0.05$ for control, no difference between each of the abx groups)	Interesting study but no OTC antibiotics, all are typical prescriptions and for parenteral use	NO
14. Hayek et al 1987	Evaluate infection rate with use of 4% CHG pre-op shower . (Hibiscrub)	Prospective , placebo-controlled; wards randomized & crossed over every 2 months for 2 years. 6 week patient followup Setting: 2 surgical wards (article)	4% CHG (Hibiscrub) or bland bar soap or placebo (vehicle of Hibiscrub) used as a pre-op bath or shower	1989 patients: (689 Hibiscrub, 626 bland soap, 700 "placebo")	4% CHG pre-op led to lower infection rate=9%, vs 12.8% bland soap, vs 11.7% placebo ($P<0.05$ for CHG & bland soap); S. aureus infection rate 2.6% w/CHG, 5.3% w/bland soap, 4.0% w/placebo ($P<0.05$ for CHG & bland soap)	Wards randomized, but not patients. Placebo changed after 5 months (had antimicrobial effect) Bland soap also significantly better than placebo Patient Pre-op Prep not accounted for!! Big bias.	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
15. Kaiser et al 1988	Evaluate efficacy of shower with antiseptic in removing staph from skin of patients	Prospective, block randomized Hospital setting (article)	1. Hibiclens (CHG) 2. Betadine cleanser (PI) 3. Lotion soap	25 pts took 1 shower (8,9,8 in group 1,2,3) 14 pts took 2 showers (5,5,4 in group 1,2,3)	CHG best reductions of staph: 1.61 log at subclavian site and 2.07 log at inguinal site with 2 showers ($P<0.05$) No extra benefit bathing twice with PI; lotion soap increased staph bacteria counts.	No clinical outcome correlated with the staph bacteria reductions.	NO
16. Vorherr et al 1988	Compare antimicrobial efficacy of Hibiclens vs PI vs 3% hexachlorophene against groin & perineum bacteria	Prospective, randomized into 3 groups, each woman had one test product & served as own control (other side of groin) (article)	1. Hibiclens, 2. 10% PI (Betadine), 3. 3% hexachloro (pHisoHex)	150 pregnant women	Log reductions of bacteria sig greater for Hibiclens and PI (about 4.0, 3.5 both $P<0.001$) vs hexachlophene (about 2.0) in groin & perineum; but no sig difference between Hibiclens & PI in groin	NIC, no clinical outcome, length of swab time not mentioned Missing data on 3-7 pts in each group	NO
17. Garibaldi et al 1988	Evaluate 3 pre-op shower/scrub regimens in reducing wound bacterial counts	Prospective, randomized, blinded study over 19 months at hospital (article)	4% CHG 7.5% PI 1% triclocarban soap	575 surgical patients	Showering twice with 4% CHG post-op yielded about 2.1-2.44 log reduction of bacteria	No clinical outcome—postop infections not tallied An active control was used (Safeguard soap)	NO
18. Tanaka et al 1988	Evaluation of rapid drying hand disinfectants in ICU Nurses washed hands with 2 products	Prospective, lab study, hospital setting (article)	1. 0.2% CHG in 70% ethanol 2. 0.2% benzalkonium chloride in 70% ethanol	237 nurse product 1, 250 nurses product 2	No difference between Product 1 and 2 but both reduced number of bacterial colonies recovered from hands ($P<0.01$)	NR, NIC, No clinical outcome	NO
19. Apt et al 1989	Evaluate effect of preoperative outpatient PI eyedrops in ophthalmologic surgery	Prospective, randomized; 3 days pre-op one eye PI, other Neosporin; on operating table both eyes got PI (article)	2.5% PI+PI vs Neosporin +PI	40 consecutive patients	Neosporin + PI=47.5% sterile; PI+PI=30%, $P=0.03$ Both eyes significantly lower bacteria counts than before any drops	NIC, bacteriologic data presented, but no clinical outcome, no blinding, #of pre-op drops not specified, the result was not surprising (abx drops reduce bacteria counts)	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
20. Boyce et al 1990	Evaluate common source outbreak of S. epi infections among cardiac surgery patients	Case-control, culture data collection (article)	N/A	10 cases (patients), 67 controls; 8 surgical personnel cultured	Epidemic S. epi strain found in valve pts more than CABG pts (P=0.03). Surgeon A carried S. epi strain same as in patients. Surgeon A used bland soap & recently used mineral oil before gloving hands.	not a clinical trial, NR	NO
21. Georgiade et al 1990	Assess efficacy of pt pre-op 7.5% PI scrub followed by 10% PI solution	Prospective , hospital setting, culture data & wound infection data (article)	7.5% PI scrub followed by 10% PI solution	150 patients, (129 breast surgery, 7% abdomen)	In 99 pts with pre-op bacterial contamination, 84 had no detectable bacteria after protocol. None of 146 evaluables developed wound infection.	Not randomized, no control group	NO
22. Maki et al 1991	Assess efficacy of antiseptics in preventing catheter-associated infection	Clinical trial, prospective randomized, hospital SICU setting (article)	10% PI 70% alcohol 2% CHG Apply pre-catheter, then every 48hrs	668 catheters	CHG lowest incidence of local infection (2.4 per 100, P=0.02), vs 9.1 for alcohol, 9.3 for PI); CHG lowest bacteremia (0.5 vs 2.3 and 2.6, P=0.04)	NIC, no standardization of technique of prepping skin, unknown number of different physicians placing catheters, re-treatment every 48 hours is confounding	NO
23. May et al 1991	Demonstrate reduced Gram + contamination of cadaver skin by adding CHG to standard PI & isopropanol	**See HW table** (article)	See HW table	See HW table	See HW table	See HW table	NO
24. Levin et al 1991 **Good Study**	Report decrease in CVC--associated infections with use of PI ointment	Clinical trial, Prospective randomized, setting: hospital (article)	PI ointment versus sterile gauze	125 pts 171 catheters	Septicemia 2% with PI vs 17% with sterile gauze(P<0.01) Catheter exit site infection 5% with PI vs 18% (P<0.02)	Control was not a vehicle (such as Vaseline); not blinded to physicians; does not study a TFM indication	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
25. Arata et al 1993	Evaluate four PI-alcohol solution for operative site disinfection	lab study prospective, all four solutions applied to each subject (article)	1. PI+ethanol 2. PI+IPA 3. polaxamer-iodine+IPA 4. PI-aqueous	15 volunteers	PI-ethanol most effective with 2.02 log reduction from baseline, Isodine the worst with reduction 1.17 log	NR, NIC, no P values, no clinical outcome data	NO
26. Schifman and Pindur 1993	Describe effect of skin disinfectants on reducing contaminated blood cultures	Prospective, randomized Setting 325 bed hospital (article)	70% isopropyl pad+10% PI swab (standard method) vs PREP Method (acetone-isopropyl+PI+isopropyl pad)	1546 blood culture specimens	4.6% contamination with standard method vs 2.2% with Prep Method (P=0.011)	NIC; minimal difference in method between standard & Prep method, no clinical outcome	NO
27. Garland et al 1995	Compare efficacy of 10% PI with 0.5% CHG in 70% IPA for prevention of catheter colonization in neonates	Prospective nonrandomized Setting: NICU, 45-50 admits/month (article)	10% PI (Betadine) versus 0.5% CHG in 70% IPA (Hibistat)	254 infants; 1104 total eligible catheters, of which 826 catheters cultured	During ist 6 months (Betadine) 38/403 catheters colonized (9.3%), 12% positive blood cult. During 2nd 6 months (Hibistat) 20/418 catheters colonized (4.7%, P=0.01), 12% positive blood cult.	NR, NIC, catheter colonization less with Hibistat, but positive blood cultures same in each group, not clear that colonization reflects a clinical outcome Why only 826/1104 catheters in study?	NO
28. Leyden JJ et al 1996	Desribe microbiology of human axilla & its relationship to odor	Prospective, lab study. Tranlocated bacteria from axilla & perineum to forearm, then treated with antiseptics (article)	1% PCMX 7.5% PI 1% triclosan hexachlorophene 70% ethanol 0.5% CHG w/isopropanol	52 adults	Micrococcal aerobic diptheroids primarily responsible for axillary odor; CHG w/isopropanol suppressed bacteria the most after 24 hrs (P<0.0001)	No clinical outcome	NO
29. Aly et al 1998	Report clinical efficacy of chlorous acid preoperative skin antiseptic	Prospective, Latin-square randomization (article)	1. Chlorous acid 2. 4% CHG (Hibiclens) 3. vehicle	85 volunteers, 61 abdominal sites, 107 inguinal sites	Log reductions for 1,2,3 @10min= 2.74, 2.13, 1.09 (P<0.05 vs vehicle) @6 hrs=3.34, 2.95, 2.22 (P<0.05 vs vehicle) CHG and chlorous acid no difference	No clinical outcome	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
30. Brooks et al 1999	Evaluate MRSA Infection Control Measures on incidence of Ventilator-associated pneumonia (VAP)	**See HW table** (abstract)	See HW table	See HW table	See HW table	See HW table	NO
31. Gould 2000	Evaluate nosocomial infection & HCW skin care	**See HW table** (abstract)	See HW table	See HW table	See HW table	See HW table	NO
32. Calfee & Farr 2002	Compare efficacy of 4 antiseptics in preventing blood culture contamination	Prospective, randomized (article)	10% PI 70% isopropanol tincture of iodine PI w/70% ethanol	12,692 patients-blood cultures	2.62% contaminated out of 12,692, vs 3.21% of 12,859 prior year, RR=0.82, 95% CI=0.71-0.94 No significant difference in the four antiseptics, but suggestion alcohol-antiseptics were more effective	No statistical difference in four antiseptics. No clinical outcome of patients	NO
33. Chaiyakunapruk et al 2002	Evaluate efficacy of skin disinfection with CHG vs PI solution in preventing catheter-related bacteremia	Meta-analysis from literature 1966-2001 (article)	CHG PI	4143 various catheters (CVC and other types) – all in hospitalized pts	8 studies from 1966-2001 met criteria. Summary risk ratio for bacteremia=0.49 (95% CI=0.28-0.88) when CHG used instead of PI. With CVC, CHG reduced risk by 49%	NR, NIC, different formulations of CHG used, sometimes different definitions of bloodstream infection	NO
34. Hibbard et al 2002	Assess the immediate and persistent antimicrobial efficacy and safety of ChloraPrep compared with 70% isopropanol or CHG	Prospective, randomized, parallel-group, open-label trial (lab techs were blind) (article)	ChloraPrep (CHG+isopropanol) CHG 70% isopropanol	106 subjects	ChloraPrep provided more persistent antimicrobial action on abdominal sites than isopropanol (P=0.03) or CHG (P=0.28) at 24 hours. CloraPrep not irritating to skin	NIC, no clinical outcome, just microbial counts.	NO

The Following are Poster Presentations or incomplete references from CP 7 and were not found in PubMed

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
35. Amarante et al 2000	Compare CVC fungal infections with use of PI or CHG. Evaluate impact of frequency of catheter changing.	Prospective, 3 groups: PI+7 day systematic changes, CHG+7day changes in catheters, CHG w/no systematic changes **Poster presentation**	PI CHG	Grp I,II, III= 731,534,1859 "catheters" Patients not listed	Fungal infection 0% in Groups I&II, 0.32% in Grp III (P<0.007) Author concluded: CHG care with less frequent catheter changes increases fungal infections	NR, NIC; no description of patients, study location, concomitant medications, timeframe, staff training, or clinical significance of fungal data; (fungal infections normally seen in pts on prolonged, broad spectrum antibiotics making pt comparisons critical in any conclusions)	NO
36. Beaton "undated", post 1975 Article provided, but undated & no citation	To report on a clinical experience with Betadine solution in gynecology surgery	Retrospective **Undated article in unknown forum**	Betadine Surgical Scrub (BSS)+ & Solution Vs BSS alone	1017 hysterectomy pts—137 w/Solution, 880 without="Control group"	7 of 137 (5%) w/Betadine Solution had Temp>102F, vs 99 of 880 (11.3%) in control group, P<0.05)	not found in published literature retrospective some or all had parenteral abx as well as scrub with BSS, thus role of pre-op Betadine Solution is unclear	NO
37. Beneda & Finney 2000	To determine the effects on infection rate of a decolonization protocol in patients with known MRSA	Observational Case-control **Poster presentation**	Study group: triple abx+ topical mupirocin to nares &any tube site, + CHG bath & mouth rinse daily Control group meds: not listed	29 pts w/MRSA=study group 20 pts w?MRSA=control group	Vancomycin use 10.1% in study group vs 46.1% in control group 0 bacteremia & 0 pneumonia in study group vs 2 & 8 cases in control group	NR, NIC, multiple interventions, no mention of what treatment, if any, the control group received, no P values	NO
38. Fauerbach et al 2000	Evaluate management of CVC & implement strategy to reduce infection	Observational Setting: hospital **Poster presentation**	Hibistat site prep	Unknown # of patients or catheters	15 of 19 units showed mean decrease of 2.64 infections/1000 days of catheter use	NR, NIC, multiple interventions, not a controlled trial	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
39. Mulberry et al 1994	Unknown	Article not found, no 1994 Mulberry articles CP7 reference "Mulberry et al 1994"	unknown	unknown	unknown	not found in published literature	NO

LEGEND

- ACF=acute care facility
- AGNB=aerobic gram negative bacteria
- APIC=27th Annual Educational Conference & International Meeting June 2000
- Betadine=10% povidone-iodine formulation
- CHG=chlorhexidine gluconate, often 2% or 4%
- CVC=central venous catheter
- CVL=central venous line
- Dettol=PCMX=parachlorometaxylenol
- ECF=extended care facility
- HCW=health care worker
- Hexol= 0.5% CHG+60% isopropanol
- Hibiclens=4% chlorhexidine gluconate formulation
- Hibiscrub=4% CHG in 70% isopropyl alcohol
- ICN/ICU/SCN=intensive care nursery/intensive care unit/special care nursery
- IPA=isopropyl alcohol
- MRSA=methicillin-resistant Staphylococcus aureus
- N/A=not applicable
- NI = nosocomial infection(s), usually defined as NI if infection occurs more than 72 hrs after admission
- NIC=no inactive control (ie no formulation alone, no excipient alone, not compared to water alone)
- NICU=neonatal intensive care nursery
- NR=not randomized
- pHisoHex=3% hexachlorophene formulation
- PI=povidone-iodine, often 7.5%
- PPP=Patient Preoperative Preparation
- SS= surgical scrub
- SSI=surgical site infection
- UTI=urinary tract infection
- VAP=ventilator-assisted pneumonia

Clinical Benefit of Healthcare Handwashes (Abstracts and Articles)*

24 CHG Publications from a 1986 Monograph on CHG—presented in chronological order
Clinical Benefit Summary of 24 CHG Publications: 0 YES, 0 MAYBE, 24 NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
1. Garibaldi 1986	Overview of problem & control of NI	Editorial 1986	CHG	N/A	N/A	No clinical outcome data, only editorial	NO
2. Larson 1986	Handwash agents for control of NI	Editorial 1986	CHG	N/A	N/A	No clinical outcome data, only editorial	NO
3. No author listed	Show invitro test data (MIC values)	Lab data, background (abstract)	CHG	N/A	MIC<50 ppm for most gram neg bacteria, <10 ppm for most gram positive. Hibiclens 40,000 ppm CHG, far above effective bactericidal levels	No clinical outcome data, no stats	NO
4. Rosenberg et al. 1976	Evaluate bacterial reductions of 3 CHG preps & Evaluate tolerance vs pHisoHex & pHisoDerm (cleanser)	Prospective, lab study (abstract)	3 CHG preps + hexachloro	30-36 subjects	Hibiclens effective 3.9 log reduction, substantive, & better-tolerated than pHisoHex & pHisoDerm	No clinical outcome data, NIC, no stats	NO
5. Aly & Maibach 1976	Evaluate long term effect of Hibiclens –6 months washes	Prospective, randomized (16/11); daily washes (abstract)	Hibiclens vs Ivory soap	37 male subjects	Average aerobic bacteria lower for Hibiclens over 6 months in axilla & groin (P<0.01 for both, but not for fingerweb (P=0.28;, though gram neg higher in axilla/groin with Hibiclens	11 subjects not evaluated, no clinical outcome data	NO
6. O'Reilly 1977	Evaluate tolerance of Hibiclens in BM transplant pts	Prospective, 10 daily washes, 94 months daily immersion (abstract)	Hibiclens	13 children	After 10 pre-op washes and "94 months" daily immersion only 10 single bacterial cultures found on skin decontaminated w/Hibiclens; no absorption; infection only GI	NR, NIC, confounded by systemic antibiotics, no stats	NO
7. Maki et al. 1979	Evaluate immediate & prolonged antibacterial efficacy of HW agents	Prospective 4 week crossover, added "frequent applications" of 52% ethanol foam (abstract)	Hibiclens, 0.75% iodophor, bland soap	10 nurses	Hibiclens lowered cfu 1.4 log (P<0.05), soap & PI ineffective; after 1 week use Hibiclens lowest cfu (P<0.05); gram neg recovered (re-growth) slowest with Hibiclens (P<0.001)	No clinical outcome data Analysis confounded by "frequent applications" of 52% ethanol foam	NO
8. Vorherr et al 1980	Evaluate bacterial effectiveness and tolerability of Hibiclens in pregnant women & pre-op pts	Observational, washed groin and perineum (abstract)	Hibiclens	101 +49 women	Groin, perineum, vaginal bacterial counts reduced 99.97-99.99%	NR, NIC, no clinical outcome	NO

*see legend page 12

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9. Maki & Hecht 1981	Evaluate effectiveness of 3 HW agents in preventing NI	Prospective, crossover every 6 weeks (abstract)	Hibiclens, Betadine, bland soap	38 ICU HCWs	Hibiclens fewest bacteria on hands (P<0.05) and fewest NI (20, P<0.001)) vs Betadine (27, P<0.05), bland soap (33). Hibiclens better tolerated.	Clinical outcome data, but no mention of training, wash time, observation of washing; or infection type. Washes not randomized (but crossover)	NO
10. Aly 1981	Evaluate bacterial contamination of stock CHG	Lab study (abstract)	CHG (Hibiclens)	N/A	Hibiclens little/no risk of bacterial contamination	NIC (could have used water bottle as control), No clinical outcome data	NO
11. Spiers et al 1981	Evaluate bacterial isolates in cancer pts S/P chemotherapy and after topical /GI antiseptic/abx	Observational, GI decontamination + skin disinfection (abstract)	Hibiclens + 3 GI abx	18 cancer pts	No pseudomonas isolated, topical skin & vaginal flora reduced by 50% after 2 weeks, no more at 4 weeks; 4 infections	NR, NIC, no clear relationship of Hibiclens to infection rate, no stats	NO
12.Taplin 1981	Describe results of CHG study in Costa Rica (FDA approval study for CHG, pre-1981)	Prospective, randomized, double-blind; sprayed 5x weekly for 6 weeks (abstract)	Hibiclens solution?	304 children	16 CHG skin infections vs 91 in control group (P<0.001); Staph or strep cultures 58% w/CHG, 80% w/control—down from 88% pre,Rx	Describes old study; not a new study—the Costa Rica study with CHG & skin infection has clinical benefit, while Taplin's rehash of this study does not add anything.	NO
13. Oneill et al 1982	Evaluate whether chlorhexidine absorbed by neonatal skin in ist 3 days of life	Prospective, pilot study, randomized, 3 day study (abstract)	Hibiclens, 1:10 dilution vs bland soap	51 neonates	CHG in stool of 23 neonates, attributed to skin contamination; not found in blood; no selective colonization; no side effects over 12 months	No clinical outcome, unclear whether washing had any benefit,	NO
14. Goldblum et al 1983	Compare antimicrobial efficacy of Hibiclens vs PI as skin disinfectant at vascular access site in dialysis pts.	Prospective, randomized, 26 week crossover (abstract)	Hibiclens, vs PI	46 dialysis pts + 24 HCWs	Hibiclens reduced skin colony counts sig more than PI @2 & 4 hrs in pts (P<0.01) & at 2 hrs in HCWs (P<0.05). Glove juice cultures not significantly different	NIC, no clinical outcome, length of swab time not mentioned	NO
15. Vorherr et al 1984	Compare antimicrobial efficacy of Hibiclens vs PI against vaginal bacteria	Prospective, randomized, swabbed vagina 1 min, took sample 5 min later (abstract)	Hibiclens, 10% PI	150 women	Log reductions of bacteria sig higher for Hibiclens vs PI (3.47 vs 3.10, P<0.01); CHG possibly in blood 2 women	NIC, no clinical outcome	NO
16. O'Brien et al 1984	Evaluate chlorhexidine absorption in ist 3 days of life, evaluate effect on bacteria; followup to #22	Prospective, randomized, 3 day study (abstract)	Hibiclens vs castile soap	100 neonates	CHG not found in bloodstream; no side effects over 12 months; recovery rates for S. aureus lower in umbilicus (day 3) and nares (day 14) with Hibiclens	No clinical outcome, unclear whether washing had any benefit	NO
17. Mycock 1985	Evaluate S. aureus (MRSA) MIC values	Lab study MICs (abstract)	CHG, PI, hypochlorite	N/A	High MIC for PI & hypochlorite (>1000 ppm), CHG MIC <1.0 ppm)	No clinical outcome data,	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
18. Kolstad et al 1985	Evaluate Hibiclens in removing spores	Observational, lab study, randomized (abstract)	Hibiclens vs liquid detergent	15 volunteers	Hibiclens removed 97.7% of spores, insignificantly different from detergent	No clinical outcome data, no stats	NO
19. La Rocca et al pre-1986	Evaluate antibacterial efficacy of 3 HW agents	Prospective, randomized, lab study (abstract)	Hibiclens, PCMX, bland soap	47 volunteers	Hibiclens most effective, 3-5 log reduction ($P<0.05$); PCMX more effective than soap after multiple washes	No clinical outcome data	NO
20. Vorherr et al pre 1986	Compare antimicrobial efficacy of Hibiclens vs PI vs 3% hexachlorophene against groin & perineum bacteria	Prospective, randomized (abstract)	Hibiclens, 10% PI (Betadine), 3% hexachloro (pHisoHex)	150 pregnant women	Log reductions of bacteria sig greater for Hibiclens and PI (about 4.0, 3.5 both $P<0.001$) vs hexachlophene (about 2.0) in groin & perineum; but no sig difference between Hibiclens & PI in groin	NIC, no clinical outcome, length of swab time not mentioned	NO
21. "FDA Summary re: Hibiclens" pre-1986	Evaluate 15 & 30 sec CHG handwashes, compare with bland soap	Observational, lab study (abstract)	CHG, bland soap	36 volunteers	Hibiclens effective 15 sec handwash, more effective than soap on day 3 & Day 5, $P<0.01$	No clinical outcome data, soap still effective	NO
22. Larson et al. 1986	Evaluate tolerance and effectiveness of Hibiclens	Prospective, lab study, randomized (abstract)	Water, soap, Hibiclens, & 2 PI preps	53 women	Hibiclens 3.58 cfu post wash vs 4.3 prewash ($P<0.05$), other preps no change; gram neg bacteria equal among all groups (important?)	No clinical outcome data	NO
23. Saatman et al 1986	Evaluate effects of Hibiclens & CHG on healing of incisions in guinea pigs	Prospective, controlled, sacrificed pigs @ days 3, 6, 9, 14, or 21 days (abstract)	Hibiclens, control base, saline	Guinea pigs, number of pigs not mentioned	4% CHG delayed healing of abrasions but not sutured incisions; @21 days no difference between test & control	NR? Application to humans? No apparent clinical benefit to guinea pigs, no stats	NO
24. "From FDA Summary Basis of Approval for Hibiclens".pre-1986	Describes studies using Hibiclens as pt pre-op prep (FDA approval study? Year?)	Observational, lab study (abstract)	Hibiclens	50 subjects ?6 studies	Reductions in bacterial flora of 1.8-5.7 log (ie up to 99.99%) in either abdomen, umbilicus, perineum or groin; persistence@240 minutes	Describes old studies; not a new study No clinical outcome data	NO

Ot Other Handwash Abstracts of Various Products
(#25-#37 below)
Clinical Benefit Summary of 13 Abstracts 0 YES, 0 MAYBE, 13 NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
25. Maki & Hecht 1981 and 1982 (published twice)	Compare effectiveness of 3 HW agents in preventing nosocomial infection	Clinical trial; ?sequential use of 3 agents; cultured hands periodically (abstract)	CHG, PI, bland soap	38 HCWs	CHG=superior de-germing of hands compared w/ PI & bland soap, measured CFUs ($p<0.05$) and NI (20, 27, 33; $p<0.001$ for CHG, $p<0.05$ for PI) CHG tolerated, PI poorly tolerated	NR, no description of when or how each agent used except used 3 agents six weeks each. No data on training or technique. NI rate with CHG not compared to PI	NO
26. Cross 1999	Evaluate role of deodorant-antibacterial soap in reducing recurrent eye infections	Observational study (abstract)	Deodorant soap w/without antibacterial	427 consecutive pts w/ext eye infection	89% of 427 cases used nondeodorant facial soap;	Retrospective, NR, no control group (only looked at cases)	NO
27. Brooks et al 1999	Evaluate MRSA Infection Control Measures on incidence of Ventilator-associated pneumonia (VAP)	Prospective (in part) & retrospective (in part) (abstract)	"Foamed alcohol" hand antiseptic	SICU pts	VAP rate decreased from 13.2 to 0.8; MRSA VAPs decreased from 92% to 0%	NR, NIC, type & % alcohol unclear, multiple interventions, (circuit changes and plastic laryngoscopes), no P values	NO
28. Abdul & Butler 1999	Evaluate MRSA Infection Control	Prospective (in part)& retrospective (in part) (abstract)	Triclosan 0.3%	infants	22 w/MRSA: infections continued for 3 months post triclosan, then none for 8 yrs	Written 9 yrs after fact NR, NIC; multiple interventions No handwash training/observation, no P values	NO
29. Jones et al 1999-2000	Evaluate antimicrobial hand gel; impact on NI* (MRSA, VAP, CVL)	Observational, compared current trial infection rates with historical (abstract)	Alcohol gel	?80 HCWs, 256 bed hospital	MRSA, VAP, CVL infections decreased (?47% reduction MRSA, 76% VAP, 65% CVL) ($p=0.05$, $p<0.001$, $p<0.005$)	Did not specify the type of alcohol gel. NR; used posters, flyers, but no formal handwash training or observation (Uncertain # of HCWs and % reduction MRSA)	NO
30. Majury et al 1999+	Assess value of eradicating MRSA	Clinical Trial; treated pts w/MRSA (abstract)	Mupirocin +4% CHG bath; +oral antibiotics	135 Pts with MRSA	88% eradication in 2 days, 48% in 2 weeks; no resistance to mupirocin or rifampin; eradication reduces reservoir MRSA	NR, NIC, no clinical outcome--, no P values (year of study unclear)	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
31. Cross 1999	Evaluate preoperative use of antibacterial & deodorant soaps on	Survey study (abstract)	Deodorant-antibacterial soap vs nondeodorant-antibacterial soap	427 pts with eye infection	S. epi & S. aureus eye infections occurred in 52% of nondeodorant/antibacterial soap users, and 30% occurred in deodorant/antibacterial soap users.	NR, not a clinical study but a survey of pts regarding soap use. No P values	NO
32. Gould 2000	Evaluate nosocomial infection & HCW skin care	Clinical trial (abstract)	Prevacare April 1999	NICU/PICU pts & staff	"Dramatic" decrease in CVL-related infections compare w/1998; Decrease in NNIS rate for infections	NR, Uncontrolled, NIC Number of pts not reported; No actual data reported, no handwash training/observation, no P values	NO
33. Fendler et al 2000	Effect of lotion/gel on effectiveness of 2% CHG	Observational; log reductions (abstract)	2% CHG; some alcohol	Some humans	Hand lotion & alcohol gel did not reduce effectiveness of CHG	No clinical outcome data, no P values	NO
34. Voss & Goroncy-Bermes 2000	Compare antiseptic efficacy in removing S. aureus from hands	Prospective, lab study (abstract)	CHG Alcohol hand disinfectant Bland soap		Log reductions: alcohol 1.93 CHG 0.48 Bland soap 0.36	No clinical outcome data	NO
35. Jampani et al 2000	Report use of a hand gel in reducing number of facial lesion	Observational (Poster)	"Hand Gel" (not otherwise described	14 subjects	The "hand gel" reduced the number of acne lesions and pseudofolliculitis barbae lesions after 12 weeks	NR, NIC, no P values, "hand gel" not defined, doesn't state is gel used on hands or on face or both	NO
36. Sickbert-Bennett et al 2002	Compare effectiveness of 13 HW products in 10 sec wash	Lab trial; log reductions after Serratia wash off (abstract)	13 products, CHG, ethanol etc	Did not report # of subjects	CHG reduced Serratia by 3.77 log; Bland soap 1.64 log 62% ethanol 0.67 log Provided confidence interval stats	NR, names of all 13 products not reported, did not say how many HCWs or subjects tested, no clinical outcome data	NO
37. Fischler et al 2003	Compare TFM wash method using Serratia & E. coli	Experimental; measured cfu after 1 & 10 washes; used neutralization (abstract)	Dial Complete (triclosan) & Hibiclens	Human hands	E. coli shown to have >4 log reduction with triclosan & CHG	NR, no clinical outcome, no P values	NO

Literature Handwash Articles of Various Products
(#38-#86 below)
Clinical Benefit Summary of 49 Articles 0 YES, 0 MAYBE, 49 NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
38. Murray & Calman 1955	Describe attempts to reduce cross-infection by treating staff hands	Initial lab study followed by 18 month prospective; Hospital nursery;	1% hibitane cream	3 staff, 3 subjects in lab study; unknown # in 18 month	Resident bacteria suppressed more w/ 0.2g than w/ 0.1g Hibitane. Staph infections fewer and less serious in 18 month study, no numbers provided.	NR, NIC, pt outcome not tallied, no statistics	NO
39. Frappier-Davignon et al 1959	Evaluate 4 wash methods in reducing staph skin infections	Prospective, not randomized, 26 hospital nurseries in Quebec 1954-1956	1. No wash vs 2. pHisoHex 3. plain soap 4. Dettol (PCMX)	16,053 newborns	Total 201 staph infections (1.25% average); soap beats Dettol= no wash; if infant does not leave nursery=not washing increases infection (gave idea that less handling is important)	NR only 13 of 26 nurseries gave good data=50% of data lost gave data from 2nd year of study but not first; no P values	NO
40. Mortimer et al 1962	Evaluate effectiveness of handwashing in reducing transmission of staph to newborns	Prospective, not randomized, hospital nursery, 48 day study A (handling) and 55 day study B (airborne)	.pHisoHex	81 babies (49 HW group, 32 no HW)	Study A: 17 of 32 HW babies staph + vs 45 of 49 non-HW babies staph+ Study B: 12 of 42 HW babies staph+ vs 28 of 37 non-HW babies staph+ vs 6 of 39 airborne babies: Conclusion: staph transmitted by touch more than by air; HW reduces transmission	NR Did not document staff HW training or actual HW compliance No P values Hexachlorophene now prescription only. No safety comments.	NO
41. Forfar et al 1968	Evaluate effect of hexachlorophane use on G neg and staph infections	Retrospective 10.5 yrs; 2 hospital nurseries (E+W); ist phase 1954-1960.5; 2nd phase 1960.5-1964	hexachlorophane	14,909/14,395 births @ hosp E/W	Hospital E: staph reduced from 11.1% incidence to 2.8% from 1st-2nd phase; Gram neg infections increased from 1.4%-3.8% Hospital W: no striking difference in staph or gram neg over 2 periods	NR, NIC, retrospective, no documentation of training or washing; *hexachlophane* likely meant to be hexachlorophene No P values	NO
42. Cooper & Gibson 1974	Review literature re: control/prophylaxis neonatal & surgical infections	Review article	Hexachlorophene vs PI	various	A 1964 study: 3% hexa effective in infants if used for 3 weeks; potential neurotoxicity w/hexa (3% absorbed); a 1972 study: 2.4% wound infection for pre-op PI &hexachlorophene=same	Hexachlorophene now Rx Not much info re: PI	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
43. Knittle et al. 1975	Evaluate role of hand contamination in nosocomial transmission of G-bacteria	Prospective, not randomized, Int. Care Nursery setting	pHisoHex (3% hexachlorophene) ; PI	13 nurses+ 9 nurses	86.1% hand cultures Jan-Mar 1971 yielded G neg bact (hexachloro used); after PI introduced only 50% of hand cultures grew G neg bacteria	NR*, NIC** No control group of nurses Study did not actually address nosocomial transmission	NO
44. Casewell & Phillips 1977	Investigate routes of transmission of Klebsiella in ICU Setting:	Prospective, microbiology study Setting: ICU	1. water 2. bland soap 3. triclosan 4. 4% CHG	28 staff	Pre-wash 17% of handwashings yielded Klebs. Post-wash 98% reduction in 19 of 23 experiments with CHG; 2/4 bland soap, 10/13 triclosan, none with water. No Klebs in air sample. Patient colonization reduced from 22.6% to 15.5%.	NR, no clinical outcome data, no P values (Note: this study showed 100-1000 klebsiella can be transferred by touch alone—not a deficiency)	NO
45. Brown 1977	Evaluate Betadine skin cleanser foam in management of acne	Prospective, outpatient, not randomized, no comparison product	Betadine skin foam cleanser	36 subjects	32 subjects completed study, 19 benefited considerably, 8 derived some benefit, 5 had no improvement	NR, NIC, did not study a TFM indication for an antiseptic	NO
46. Amortegui 1978	Compare Betadine & Prepodyne in reducing bacterial cultures on nurses' hands and infants' umbilicus	Observational, crossover, single blind to nurses	Betadine vs Prepodyne	4-6 nurses? Plus some babies?	Both reduced culture + from 78.4%/73.2% after infant handling to 22.3%/26.5% after handwashing. No significant difference between products. S. epi most common bact.	NR, NIC, no clinical outcome data, # of nurses and babies involved not stated (? repeat cultures on same people?)	NO
47. Franz et al 1978	Evaluate effectiveness of antibacterial in treatment of acne	Prospective, randomized	Two triclosan products	72 subjects	17 of 72 subjects dropped out 2 triclosan preps equally effective	Did not study a clinical indication from TFM (acne treatment is a dermatological indication)	NO
48. Bartzokas et al 1982	Report method of control of MRSA outbreak in a 800 bed hospital	prospective handwash, body wash study	2% triclosan hand & body wash	25 pts, 40 staff	14 pts (of 25) and 3 staff (of 40) initially MRSA+ All pts & staff had 2 weeks daily shower + thrice daily handwash. Infected pts & staff clear of MRSA in 22 days avg.	NR, NIC, no clinical outcome, Frequency of bathing, handwashing not documented, no bacterial counts (just culture + or neg).	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
49. Gilmore et al 1984	Evaluate effect of antiseptics on skin flora in perineum and penis of men w/spinal cord injury	Prospective, randomized, Setting:: apparently hospital ; bathing done by investigators	Triclocarban soap, PI (Betadine surgical scrub), Hibiclens , pHresh (	21 pts with spinal cord injury w/ condom catheter	Log reductions: no sig dif among all 4 agents, P>0.05). For Klebsiella: triclocarban better than PI, pHresh(P<0.05) on perineum; for Pseudomonas, PI better than CHG (P<0.01) on penis	None more effective than control (pHresh) in total bacteria removal. No documentation of training with bathing. No clinical outcome	NO
50. Reverdy et al 1984	Evaluate effects of nine soaps or antiseptics on bacterial flora of hands	Prospective, lab study	2 Bland soap, 2 CHG PI, 2 alcohol water	10 volunteers	Greatest reduction=70% Isopropanol=1.7 log after one wash (P<0.05), followed by ethanol 70%; soaps <0.5 log	No clinical outcome Article untranslated from French	NO
51. Tyzack 1985	Evaluate a multi-faceted approach to control MRSA	Observational, Hospital (?) wards	PI surgical scrub, PI baths for MRSA pts, PI ointment to nares & wounds	Total # of pts or HCWs not mentioned	74 MRSA infections or colonizations in 4 months prior to intervention, reduced to 5 MRSA for 4 month period ending Dec 1983; Overall infection rate & wound infection rates reduced from 8%/3.5% to 5%/1.5% (no P value)	NR, NIC, no P values No documentation of training or compliance Total # of pts or HCWs not reported	NO
52. Field & Martin 1986	Evaluate disinfection of dental surgeon's hands with CHG vs triclosan	Prospective, lab study, "randomized", surface sampling of hands for bacteria before & after dental work	4% CHG (Hibiscrub) vs 2% triclosan (Zalcleanse)	21 dental students, # of dental pts worked on is not mentioned	16 triclosan group: pre-treatment wash=cfu +31% (worsened), post-treatment cfu -18% (improved) 5 CHG group: pre-treatment wash=cfu -76% (improved), post-treatment cfu -83% (improved)	"Randomized" but ended up with 16 in one group, 5 in another; NIC, no P values comparing CHG & triclosan; no clinical outcome	NO
53. Larson et al 1986	Evaluate efficacy of alcohol hand rinses under frequent use conditions	Prospective, block randomized, lab study, 15 washes/day for 5 days	1. Bland soap 2. 60% IPA+0.5% CHG 3. 4%CHG+4% IPA 4. 70% IPA 5. 60% IPA	50 volunteers	After Day 1 all except bland soap (P=0.18) had 2 log or greater reductions in bacteria (P<0.001). After Day 5 all except bland soap had significant reductions from baseline (P=.002 or lower), but the 4 active agents were not significantly different from each other	"Pseudo-randomized" -- forced 10 into each of 5 categories No clinical outcome data	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
54. Larson & Laughon 1987	Compare antimicrobial efficacy of 4 CHG formulations	Prospective, lab study, block randomized; 15 washes/day for 5 days	1& 2. 2% or 4% CHG detergent 3. 4% CHG foam 4. Bland soap	50 volunteers	All CHG products (but not soap) with significant reductions in bacteria on Days 1 & 5 ($P<0.05$ for all) , but no differences between CHG groups. Log reductions for CHG 0.62-1.64 (Day 1) and 1.80 - 2.36 (Day 5)	"Pseudo-randomized" -- forced 10 into each of 5 categories No clinical outcome data	NO
55. Onesko & Wienke 1987	Report influence of mild, low-iodine, lotion soap on reduction of NI, especially MRSA.	Part retrospective (year 1), part prospective, year 2 500 bed hospital	Nonmedicated liquid natural handsoap +/- PI scrub vs low-iodine HW (Ido-Kare)	# of HCWs and # of total pts not mentioned	Year 1 NI rate 13.25% (243/1833 pts, includes 25 MRSA+) Year 2 NI rate 10.56% (189/1800, includes 5 MRSA), decrease not significant, but MRSA decrease sig, P=0.005)	NR no documentation of handwashing training or compliance, NI rate insignificantly different in Yr 1 and 2, clinical outcome of MRSA cases not mentioned	NO
56. Tuffnell et al. 1987	Evaluate measures for control of MRSA in hospitalized pts	Part prospective, not randomized, compared pt cleansing with nasal antiseptic + body wash at UK hospital from Feb 1983-Sep 1985.	Triclosan body wash +mupirocin nasal Vs. Hexachlorophene +mupirocin	All 130 pt + 20 staff cases of MRSA colonization	32 cases w/triclosan; 5+38+76 w/ hexachlorophene (MRSA caused morbidity in 62 pts)	NR, NIC, Multiple techniques introduced (Isolation ward Jul 84, changed wash after fact)	NO
57. Maki 1989	Review literature on use of antiseptics by HCWs	Review article/ Various Settings	10% PI, 4% CHG, bland soap	various	5 min surgical scrub OK (vs 10 min); most studies show hygienic handwash reduces bacteria more than bland soap; 10-15 second scrub with bland soap removes gross contamination	Review article	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
58. Eckert et al 1989	Determine if Proteeae &G neg bacteria can be reduced/removed by antiseptics	Prospective, 1st study rubbed groin; 2nd study bathed	1st study= 4% CHG +60%, isopropanol; 2nd study=CHG, or 0.75% PI or bland soap, all plus cefazolin parenteral	11 Proteeae carriers ist experiment, 10 Proteeae carriers in 2nd experiment.	Ist experiment: CHG 0.2 log decrease@ 8 hrs (P>0.05=insig), isopropanol decrease 2.2 log@30 min(P=0.015), but back to **baseline@4** & 8 hrs (all Proteeae) 2nd experiment: no significant difference in AGNB @14 hrs with either CHG, PI, slight decrease 0.12 log , P=0.03, w/soap baths (all plus cefazolin)	NR, no clinical outcome data, insignificant decrease in total gram negative bacteria in groin with CHG or PI (both plus cefazolin); only sig decrease was with soap+cefazolin (and stats look unusual, decrease 0.12 log & P=0.03?)	NO
59. Eckert DG et al 1989	Determine if Proteeae & other gram negative bacteria can be reduced/removed by soap or alcohol	Prospective, touched groin for 15 sec after scrubbing with soap or alcohol, counted bacteria on finger	60% alcohol (Calstat) or liquid soap (Safe-N-Sure)	10 nursing home subjects, plus 6 nurses	Soap scrub reduced bacteria pickup by HCW after 15 sec touching by 1.3 log; while alcohol reduced by 3.6 log. With heavy bacteria burden alcohol decreased bacteria much more than soap, but not with lower burden	No clinical outcome data	NO
60. Sakata et al. 1989	Report Acinetobacter sepsis and describe control measures	Retrospective NICU Setting:	"soap/H2O + 0.02% CHG immersion; changed to ethanol/glycerin e spray in Oct 1985	536 infants admitted from Oct 1983-Dec 1986	52 of 72 infants colonized & 14 septic with A. anitratus before control measures; decreased infant colonization, none septic, no isolates from HCW	NR, NIC, %infant colonization post-control measures not reported; multiple interventions; the %ethanol not reported; handwashing not observed or trained	NO
61. Conly et al 1989	Correlate NI rate with HW practices before/after 2 HW educational programs	Retrospective , single blind re: HW observations MICU Setting:	4% CHG	73+77 pts in 1978 48+47 pts in 1982	Before ist education, NI rate >30% (24 inf/73pts), 12% after ist, 12% after 2nd education (P=0.02); HW compliance improved to 60% from about 25% after 2nd program 1982.	NR, NIC, published 11 yrs after ist study, 6 yrs after 2nd study (? data integrity after 11 yrs), multiple factors to control besides HW. No clear relation between wash & infections	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Pop-ulation (Subjects)	Results	Deficiencies	Clinical Benefit
62. Brady et al 1990	Evaluate incidence of MRSA colonization and effect of interventions	Part Retrospective, part prospective, 2 surgical wards, 37 beds	1% triclosan soap; pts also received cephalothin IV 20hrs, instead of 48hrs	154 retrospective; 84 pts prospective, plus,	1983-5=154 MRSA+ out of 3915 operations Culture survey Mar-Apr 1986: 23 of 84 pts cultured MRSA+. Perineum colonized in 69.6%, nose 43.5%--then intervention started Jan 1987-Jun 88: 37 MRSA+ out of 2076 operations (chi sq P<0.001)	NR, NIC, no documentation of HW training or observation; intervention triclosan soap, shorter course cephalothin, plus isolation ; No clinical outcome data	NO
63. Butz et al 1990	Evaluate effectiveness of intervention program in decreasing incidence of infectious disease symptoms in day care	Prospective, randomized to intervention or control, Family day care Setting:	Alcohol hand rinse (plus vinyl gloves, disposable diapers, handwash education)	24 day care centers	Diarrhea & vomiting reduced in intervention group vs control group (P<0.05); respiratory symptoms no difference (P=0.35)	Did not document provider adherence to 4 interventions of program, ?contribution of alcohol hand rinse over simple handwashing; no difference in respiratory symptoms; is viral vs bacterial transmission a factor?	NO (clinical outcome, but 4 interventions confound)
64. Denton 1991	Review article; summarize CHG data for book chapter	Review of literature	CHG, various concentrations	various	Synthesized 1950, 4% HW, .05% eye irrigant, spectrum: kills gram + & MRSA, better gram neg kill than triclosan or hexachloro; virucidal w/lipid coat (not protein coat viruses)	Not a study, per se No clinical outcome	NO
65. May et al 1991	Demonstrate reduced Gram + contamination of cadaver skin by adding CHG to standard PI & isopropanol	Prospective, two cohort, not randomized	Betadine scrub+Betadine soln (BS)+ 70% isoropyl (Iso) vs 4% CHG +BS+Iso	294 skin donors (regimen 1) + 48 skin donors (regimen 2)	5.6% of areas prepped with CHG contaminated with any bacteria, vs 13.7% w/ PI (P=0.002). Gram + contamination 2.2% with CHG vs 12.1% without CHG=82% reduction (P=0.001).	NR, NIC, no clinical outcome, no log reductions, just total colonies & type of bacteria isolated.	NO
66. Leyden et al 1991	Describe method to quantify bacteria on hands & evaluate antiseptics	Prospective, lab study, 30 sec handwash & 3 min scrub	Bland soap 4% CHG 7.5% PI 1% triclosan 1% PCMX 70% isopropanol	60 subjects	Demonstrated computer-assisted image analysis of touch plates; Seemingly unrelated experiment showed CHG & isopropanol provide best bacterial reduction after 30 sec wash (92.6 –98.7% reduction), P<0.001	NR, no clinical outcome	NO

Authors (Publication)	Objective (Purpose)	Study Design (Endpoints)/ Setting:	Active Ingredient (Dosage)	Population (Subjects)	Results	Deficiencies	Clinical Benefit
67. Ehrenkranz & Alfonso 1991	Compare efficacy of bland soap handwash & IPA rinse in preventing hand transfer of bacteria to urethral catheters	Prospective, crossover of hands, touch bacterial source, then wash, touch catheter & recover bacteria	Bland soap Vs 70% IPA	59 pts with catheters 6 HCWs (12 hands)	Soap HW failed to prevent transfer of bacteria in 11/12 experiments, while IPA failed in 2/12 (P<0.01)	No clinical outcome	NO
68. Doebbling et al. 1992 **Flaws but Fair Study**	Evaluate effects of CHG & isopropanol HW on NI rates in ICU	Prospective, 4 mo. Pilot, then 8 mo. "crossover" ICU Setting:	4% CHG vs 60% isopropanol with optional bland soap (if hands visibly contaminated)	1894 pt admits; 932 CHG + 962 isoprop	Compliance better with CHG, twice as much CHG used. 96 pt infected w/CHG use, 116 w/isopropanol use (IDR 0.87, CI=0.67-1.15). Mortality insig difference, 47.9/1000days CHG vs 50.9/1000 days w/isopropanol	NR, not blinded, crossover involved different pts, thus staff crossed over but not pts, mortality insig different, not clear if CHG infections statistically fewer, soap use by isopropanol-soap group not recorded	NO
69. Ehrenkranz 1992	Evaluate literature re: bland soap HW or hand antisepsis	Literature review & opinion	N/A	Various pts--from references	Bland soap reduces bacteria 2-3 log, antisepsis better by 1-2 log more; recommends precise terms "bland soap handwash" vs "hand antisepsis"	Editorial, not a study	NO
70. Webster 1992	Evaluate acceptability & effectiveness of 4% CHG against MRSA vs 1% triclosan.	Retrospective 10 month control followed by prospective for 7 weeks; Neonatal ICN and neonatal SCN	4% CHG (Hibiclens) vs 1% triclosan (Novaderm); Same CHG cord care & Hexol skin care in both units)	46 babies in 7 weeks observational study; 109 midwives + nurses	In ICN (Novaderm) 1 of 46 babies MRSA+ vs 3.4 babies/week in control group (P<0.0001) In SCN (CHG) insignificant downward trend. Novaderm 60.7% adverse effect on hands, while CHG=95.3% AEs	NR, NIC, no documentation of handwash training or observation, confounding of MRSA in babies by continued use of CHG for cord care & rapid skin disinfection with Hexol.	NO (stats impressive on MRSA reduction, but NR & confounders)
71. Kirita et al 1993	Evaluate efficacy & safety of quick hand rub PI-alcohol disinfectant	Prospective 4 weeks; not randomized; Hospital wards	PI-ethanol mix quick rub	30 staff (28 MD, 2 nurses	Staff washed 33-287 times in 4 weeks, mean 104. All 30 had S. epi at onset. Bacterial colonies reduced 87% with initial wash, 91.5% after wash at 4 weeks.	NR, NIC, only 3ml handwash (not 5ml), no standard HW frequency—varied 33 to 287 washes, no clinical outcome data, no P values	NO

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72. Webster et al 1994	To report the effect of reintroducing CHG HW on incidence of MRSA, and to report results of a 12 month triclosan trial	Prospective, Neonatal ICN neonatal SCN	4% CHG (Hibiclens) vs 1% triclosan (Novaderm)	893 babies with 12 months CHG; 1023 babies with 12 months triclosan	See Webster et al 1992 for 7 week triclosan results vs prior CHG. Triclosan re-placed in ICN & SCN, next 7 months "progressive reduction" in MRSA to zero Total NIs 36/893 babies w/CHG, sig lower (P=0.05) with triclosan 23/1023 babies.	NR, NIC, no documentation of handwash training or observation, confounding of MRSA in babies by continued use of CHG for cord care & rapid skin disinfection with Hexol, Uses historical CHG "control", not a concurrent trial.	NO
73. Zafar et al 1995	Describe MRSA outbreak and interventions that eliminated recurrence	Retrospective Setting:: 57 bed neonatal nursery@350 bed hospital	0.3% triclosan soap (Bacti-Stat)	Actual # of newborns at risk not reported	Before multiple interventions 1MRSA Jan 1990, 3 cases Feb 1990, then multiple interventions and added CHG, 8 cases March+ 7 in April, switched CHG to triclosan April 12, 1990, 1 each in May, June , July, none next 3.5 yrs.	NR, NIC, retrospective, not a clinical trial, n P values, no documentation of actual training or observation of handwashing, unclear whether change to triclosan related to elimination or MRSA or not	NO
74. Grinbaum et al 1995	To investigate outbreak of surgical site infections in a vascular surgery unit	Case-control study, 1000 bed hospital (article)	Bland soap for scrubbing vs 70% alcohol with 2% PI for patient pre-op & hand cleansing	9 cases with surgery; 18 controls	6 of 9 cases developed infection when PI was replaced by bland soap; prior 9 months 28 infections in 244 surgery (P=0.002). Control group had 3 infections (odds ratio 10.0, P=0.016). Evaluated 14 risk factors in cases vs controls, only scrubbing with soap was significant (P<0.0001)	Not prospective 70% alcohol with 2% PI available for hand cleansing (not scrubbing)=confounder No handwash technique instruction or observation	NO
75. Malone & Larson 1996	Identify factors associated with significant reduction in hospital nosocomial infection rates	3 yr retrospective 500 bed hospital, plus 10 month prospective study in 23 bed dialysis unit	barrier hand foam= DermaMed	23 dialysis beds, # of beds filled & frequency not mentioned	3yr retrospective study: infection rate 3.9% baseline, decreased to 2.6% in 1993 (P<0.001), attributed to 1992 OSHA, maybe somewhat to lower patient-days. 10 month study: 4 months barrier foam inf rate 5.8%, 6 months no foam infection rate 13.4% (P<0.006) Glove use increased about 55% from 1991-1993 (maybe reduces infection)	NR, NIC, # of pts in dialysis not mentioned, multiple factors involved with reduced infection rate (OSHA, gloves, barrier foam), no mention of HW technique or observation (did survey only)	NO (stats impressive but can't attribute to any one factor)

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76. Klausner et al. 1999	Describe Stenotrophomonas maltophilia outbreak in bone marrow transplant (BMT) recipients & handwash role	Case-control ICU setting	"antimicrobial soap"	3 BMTcases & 2 control groups (?6 controls)	One HCW worked with all cases, but no controls; during outbreak an antimicrobial foam dispenser in one case's room mistakenly contained moisturizing lotion	Antimicrobial soap undefined; # of controls unclear; no data on handwashing; no P values for infection risks	NO
77. Mitsuda et al 1999	Study prevalence of MRSA carriage among HCWs; eval transmission of MRSA from HCWs to newborn infants & nurse's families.	Prospective Setting:: Municipal Maternity Facility, 800 births/yr	PI nasal cream	53 nurses MRSA carriers & their families, plus newborns	7 of 53 nurses MRSA+, 2 of the 7 were persistent carriers; all 7 treated mid 1993 with PI nasal cream. Infant MRSA rate 0-25% 1991-93. After MRSA eradicated from nurses, infant MRSA + rate 15% 1994, then <5% 1995-1997 2 of 3 children MRSA+ from persistent nurse A, 1 from nurse B=same strain within families	No P values Wildly varying MRSA rates 0%-25%, even 15% year after nurse carriers eradicated. No comments on handwashing or isolation. Helps to understand MRSA prevalence but no clinical outcome data.	NO
78. Falsey et al 1999	Evaluate effect of education combined with virucidal alcohol foam on respiratory infections in adult Daycare Center	4 month prospective, Setting: 3 Adult Daycare Centers (2 months foam, 2 months without)	Virucidal alcohol foam (Alcare Plus), plus soap	210 adults, 60-135 staff	"In intervention year" pt Infection rate fell to 5.7/100 person-months (P<0.001) vs 10.4-14.5/100 in previous 3 yrs (historical data). Staff infection rate insignificantly different. During alcohol foam period no difference in infection in pt or staff	NR, NIC, handwash method undefined, cultured viral infections, but unknown infection equal or greater; alcohol foam use didn't decrease infection in pt or staff, but education program might have helped.	NO
79. Jones et al l 2000	Review of triclosan safety & effectiveness	Review article	Various triclosan preps	References various studies	1% triclosan offers ideal balance of antimicrobial effectiveness and tolerance in health care setting; acknowledges concern for use outside health care setting	Review article, not a clinical study, no new information	NO
80. Luby et al. 2002 **Flaw on study power, but Good Study**	Evaluate if 1.2% triclocarban soap reduces impetigo incidence	Clinical trial, randomized, controlled, ?blinded=not sure Primary outcome=incidence density of impetigo	1.2% triclocarban soap vs bland bar soap	241 households in Karachi, Pakistan in 2000	Impetigo 23-30% lower with triclocarban than with bland soap=insignificant (P>0.05), 47% lower than standard (P=0.02), bland soap 24% lower than standard=insignificant (P>0.05)	Dry summer, overall impetigo lower by 40%, design effect 1.69, 70% increase in sample size needed; triclocarban better than standard but not placebo	NO

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81. Gibson et al 2002 *Elegant math model, but not a study of effectiveness of HW products*	Evaluate risk reduction w/different soap formulations after diaper changing	Literature review & developed math model re:microbial quantitative risk assessment approach	Bland soap vs 4% CHG vs 1.5% triclosan soap	24 volunteers	Used Bartzokas 1987 Serratia reductions of 2.56, 2.61, 2.91 log reductions for bland/CHG/triclosan; extrapolated to Shigella=prob of symptomatic infection 15/100-90/100 with triclosan=best	Not a study per se, just description of math model for predicting likelihood of infection, No clinical outcome	NO
82. MMWR 2002	Advise guidelines for hand hygiene in healthcare settings	Review article and guidelines	Various products	Various studies	Alcohol hand gel should be considered in most healthcare setting:s.	Not a study per se	NO (reinforces hand hygiene, but not a clinical trial)
83. Fendler et al 2002	Evaluate impact of alcohol hand sanitizer on infection rate in ECF	Prospective 34 month study, ECF Setting:; 2 floors w/alcohol+soap, 1 floor w/soap alone	Micrell Antimicrobial soap +/- alcohol gel	275 beds, avg pt days about 5000/month all pts in study	Infection rate 30% lower in alcohol hand sanitizer units over 34 months ($P<0.05$)	NR, not blinded, "alcohol gel hand sanitizer" not defined; Ist floor (soap) pts long term chronic pts=different population from subacute $2^{nd}/3^{rd}$ floor pts; no documentation of training or observation of washing hands	NO
84. Hilburn et al 2003	Evaluate alcohol hand sanitizer for infection control in ACF	Prospective 6month baseline infection data, 6-10 months intervention; Ortho wing 498 bed hospital	0.3% PCMX soap vs Purell alcohol gel hand sanitizer	total pt days about 800 PCMX, 950 Purell (actual #pts not mentioned)	Most infections UTI & SSI; Baseline infection rate 8.2%, intervention period rate 5.3% (P not mentioned)	NR, NIC, no observations of method of or compliance with HW; 2 bad months with PCMX throw off results, no stats presented despite ANOVA intention, unclear length of study	NO
85. Trick et al 2003	Compare effects of antiseptics on transient flora of caregiver's hands	Prospective Surgical ICU	Bland soap 62% alcohol gel 1% benzethonium Cl wipe	66 surgical nurses	Alcohol gel removed more transient organisms than bland soap	No clinical outcome	NO

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86. Weber et al 2003	Compare ability of selected hand antiseptics to remove Bacillus anthracis surrogate from hands	Prospective	Bland soap 2% CHG 61% ethanol gel Chlorine hand wipes		2% CHG= 1.5-2.0 log reduction Chlorine wipes=1.3-2.2 log reduction 61% ethanol =lowest reduction (but not allowed to dry)	No clinical outcome	NO

LEGEND

- ACF=acute care facility
- AGNB=aerobic gram negative bacteria
- APIC=27th Annual Educational Conference & International Meeting June 2000
- Betadine=10% povidone-iodine formulation
- CHG=chlorhexidine gluconate, often 2% or 4%
- CVC=central venous catheter
- CVL=central venous line
- Dettol=PCMX=parachlorometaxylenol
- ECF=extended care facility
- HCW=health care worker
- Hexol= 0.5% CHG+60% isopropanol
- Hibiclens=4% chlorhexidine gluconate formulation
- Hibiscrub=4% CHG in 70% isopropyl alcohol
- ICN/ICU/SCN=intensive care nursery/intensive care unit/special care nursery
- IPA=isopropyl alcohol
- MRSA=methicillin-resistant Staphylococcus aureus
- N/A=not applicable
- NI = nosocomial infection(s), usually defined as NI if infection occurs more than 72 hrs after admission
- NIC=no inactive control (ie no formulation alone, no excipient alone, not compared to water alone)
- NICU=neonatal intensive care nursery
- NR=not randomized
- pHisoHex=3% hexachlorophene formulation
- PI=povidone-iodine, often 7.5%
- PPP=Patient Preoperative Preparation
- SS= surgical scrub
- SSI=surgical site infection
- UTI=urinary tract infection