

# WHO Surgical Site Infection Prevention Guidelines

## Web Appendix 9

### Summary of a systematic review on antimicrobial skin sealants

#### 1. Introduction

The endogenous bacteria on a patient's skin is believed to be the main source of pathogens that contribute to surgical site infection (SSI) <sup>1</sup>. The standard of care in preoperative surgical site skin preparation includes scrubbing or applying alcohol-based preparations containing antiseptic agents prior to incision, such as chlorhexidine gluconate or iodine solutions. These agents are considered effective against a wide range of bacteria, fungi and viruses. Additional technologies are being researched and developed to reduce the rate of contamination and subsequent SSI.

Antimicrobial skin sealants are sterile, film-forming cyanoacrylate-based sealants that are commonly used as additional antimicrobial skin preparation after antisepsis and prior to skin incision. These sealants are intended to remain in place and block the migration of flora from surrounding skin into the surgical site by dissolving for several days postoperatively. As an antimicrobial substance, sealants have been shown to reduce bacterial counts on the skin of the operative site. However, their use in surgical site preparation to prevent SSI is still under debate. In a recent review of the literature, Dohmen and colleagues highlighted that antimicrobial sealants decrease skin flora contamination and bacterial growth and cited some studies demonstrating a significant reduction of SSIs following the use of sealants <sup>2</sup>.

Currently available SSI prevention guidelines do not comment on the use of antimicrobial skin sealants and their effect to prevent SSI. The purpose of this systematic review is to evaluate the effect of the use of antimicrobial sealants to prevent SSI.

#### 2. PICO question

In surgical patients, should antimicrobial sealants (in addition to standard surgical site skin preparation) vs. standard surgical site skin preparation be used for the prevention of SSI?

- **Population:** inpatients and outpatients of any age undergoing surgical operations (any type of procedure)
- **Intervention:** antimicrobial sealant in addition to standard surgical site skin preparation
- **Comparator:** standard surgical site skin preparation
- **Outcomes:** SSI, SSI-attributable mortality

#### 3. Methods

The following databases were searched: Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and the WHO Global Health Library. The time limit for the review was between 1 January 1990 and 31 March 2015. Language was

restricted to English, French and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1).

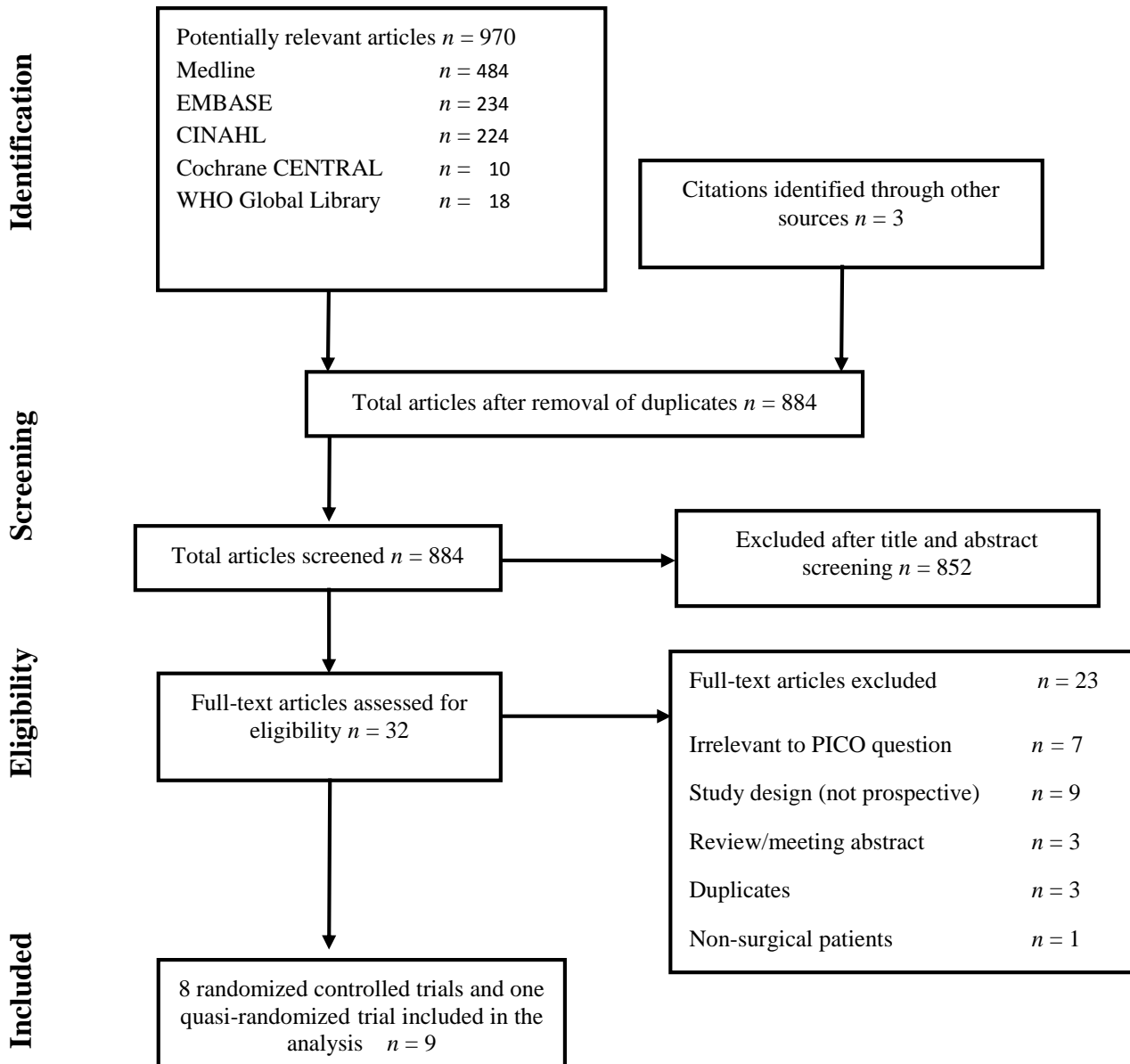
Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained. Two authors independently reviewed the full text articles for eligibility based on inclusion criteria. Duplicate studies were excluded.

Two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool <sup>3</sup> to assess the risk of bias of randomized controlled studies (Appendix 3). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager v5.3 <sup>4</sup> as appropriate (Appendix 4). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software, <http://grade.pro.org/>) <sup>5</sup> was used to assess the quality of the body of retrieved evidence (Appendix 5).

#### 4. Study selection

Flow chart of the study selection process



## 5. Summary of the findings and quality of the evidence

Eight randomized clinical trials (RCTs)<sup>6-13</sup> and one prospective, quasi-randomized trial<sup>14</sup> with SSI outcome were identified. They evaluated antimicrobial sealants compared to standard surgical site preparation with antiseptics for the prevention of SSI. All 9 studies compared a cyanoacrylate-based sealant to standard antiseptic preparation without sealant.

One study<sup>8</sup> included children and adults, while the remaining 8 included adult patients only. Both elective and emergency procedures were included; the types of surgery were cardiac, vascular, colorectal, hernia repair, scoliosis correction and trauma. In each study, the intervention and control groups received the same surgical site skin preparation with the addition of antimicrobial sealant in the intervention groups. The type and concentration of skin preparation varied. Some studies used chlorhexidine gluconate, while others used povidone iodine, all in an alcohol-based solution.

The effects of the intervention on the prevention of SSI varied among studies. One study<sup>10</sup> reported that antimicrobial sealants may have some benefit compared to standard skin preparation. Five studies<sup>9,11-14</sup> showed some effect of antimicrobial sealants, but the effect estimate was not statistically different compared to the standard skin preparation. Two studies<sup>7,8</sup> found that antimicrobial sealants may cause harm, but this effect was not statistically significant.

Meta-analysis of the 8 RCTs and the quasi-randomized trial showed that there was no overall difference between antimicrobial sealants and standard surgical skin preparation in reducing the incidence of SSI (odds ratio [OR]: 0.69; 95% confidence interval [CI]: 0.38-1.25) (Appendix 4). In a sensitivity analysis comparing the overall effect of the included studies with or without the quasi-randomized trial, there was no difference in the results if the trial was included or not ( $P=0.658$ ). The overall quality of evidence of the identified studies for this systematic review was very low due to a serious risk of bias and very serious imprecision (Appendix 5).

In conclusion, the retrieved evidence can be summarized as follows: very low quality evidence showed that the preoperative use of antimicrobial sealants has neither benefit nor harm in reducing SSI rates when compared to standard surgical site skin preparation.

However, some studies have major limitations. Many trials were small and there was a variation in the definition of SSI across studies. Within the analysis, there was also a lack of consistency in the effects of the intervention on the prevention of SSI. Of note, most studies were funded by the manufacturers of commercial sealants. A serious risk of bias was detected, mainly due to unclear blinding, incomplete outcome data and selective outcome reporting.

## 6. Other factors considered in the review

The systematic review team identified the following other factors to be considered.

### *Potential harms*

As antimicrobial sealants remain on the skin for a longer period than standard surgical site preparation, potential harms to further consider include adverse effects on the skin. Only one study reported skin irritation in one patient in the intervention group. It was noted that this may have been from the investigational device and did not require additional treatment<sup>11</sup>. No other studies included in this analysis reported adverse reactions. However, previous studies have indicated that cyanoacrylate-based sealants may cause adverse events in paediatric patients, including cutaneous reactions<sup>11,15</sup>.

### *Resource use*

Costs of antimicrobial sealants are a major resource concern, particularly in low- and middle-income countries. SSIs are associated with added morbidity, prolonged hospitalization by approximately 2 weeks and an increase in average health care costs of up to US\$ 26 000 per patient<sup>16</sup>. Therefore, an intervention that is shown to consistently reduce SSI can reduce the cost of treating these infections. However, Lipp and colleagues found that no studies included in a meta-analysis reported the cost of cyanoacrylate sealants as a preoperative preparation of the surgical site and no benefit was shown in preventing SSI<sup>17</sup>.

### *Feasibility and equity*

In addition to economic concerns related to cyanoacrylate sealant costs for preoperative use, the availability of these commercial products may be an added barrier in low- and middle-income countries. Furthermore, training in the proper technique for use would need to be available for surgical staff.

## 7. Key uncertainties and future research priorities

Several studies were excluded as they reported only bacterial colonization and not SSI as the primary outcome. Further studies are needed to identify evidence associated with important outcomes, including SSI rates (rather than microbial data), length of stay and cost-effectiveness.

Most of the included studies investigated the use of cyanoacrylate-based sealant in contaminated procedures and the use of these agents may be more or less effective in other procedures. Importantly, the protocol for standard surgical site preparation with antiseptics varied across studies, thus making it difficult to discern the actual effect of the sealant alone. Trials including a more diverse surgical patient population are needed. For example, more evidence is needed with paediatric surgical patients. Therefore, large, high quality RCTs reporting SSI as a primary outcome are required in the future to further investigate this issue.

## APPENDICES

### Appendix 1: Search terms

#### Medline (through PubMed)

((("tissue adhesives"[Mesh] OR "fibrin tissue adhesive"[Mesh] OR "acrylates"[Mesh] OR "tissue adhesives" [TIAB] OR "tissue adhesive" [TIAB] OR (sealant\*[TIAB] AND (microbial\*[TIAB] OR fibrin [TIAB] OR antimicrobial\* [TIAB] OR skin [TIAB])) OR Dermabond [TIAB] OR Integuseal [TIAB] OR acrylate\* OR cyanoacrylate\* OR octylcyanoacrylate\* OR butylcyanoacrylate\* OR bucrylate\* OR enbucrilate\* OR (sealing [TIAB] AND skin [TIAB]))) AND (("surgical wound infection"[Mesh] OR surgical site infection\* [TIAB] OR "SSI" OR "SSIs" OR surgical wound infection\* [TIAB] OR surgical infection\*[TIAB] OR post-operative wound infection\* [TIAB] OR postoperative wound infection\* [TIAB] OR wound infection\*[TIAB]))

#### EMBASE

'fibrin tissue adhesive'/exp OR 'fibrin tissue adhesive' OR 'acrylates'/exp OR 'acrylates' OR 'tissue adhesives'/exp OR 'tissue adhesives' OR 'tissue adhesive'/exp OR 'tissue adhesive' OR (sealant\* AND (microbial\* OR 'fibrin'/exp OR fibrin OR antimicrobial\* OR 'skin'/exp OR skin)) OR 'dermabond'/exp OR dermabond OR 'integuseal'/exp OR integuseal OR acrylate\* OR cyanoacrylate\* OR octylcyanoacrylate\* OR butylcyanoacrylate\* OR bucrylate\* OR enbucrilate\* OR (sealing AND ('skin'/exp OR skin)) AND ('surgical wound infection'/exp OR 'surgical wound infection' OR surgical AND site AND infection\* OR 'ssi' OR 'ssis' OR surgical AND ('wound'/exp OR wound) AND infection\* OR surgical AND infection\* OR 'post operative' AND ('wound'/exp OR wound) AND infection\* OR postoperative AND ('wound'/exp OR wound) AND infection\* OR 'wound'/exp OR wound) AND infection\* AND [embase]/lim AND [1990-2015]/py

#### CINAHL

'fibrin tissue adhesive'/exp OR 'fibrin tissue adhesive' OR 'acrylates'/exp OR 'acrylates' OR 'tissue adhesives'/exp OR 'tissue adhesives' OR 'tissue adhesive'/exp OR 'tissue adhesive' OR (sealant\* AND (microbial\* OR 'fibrin'/exp OR fibrin OR antimicrobial\* OR 'skin'/exp OR skin)) OR 'dermabond'/exp OR dermabond OR 'integuseal'/exp OR integuseal OR acrylate\* OR cyanoacrylate\* OR octylcyanoacrylate\* OR butylcyanoacrylate\* OR bucrylate\* OR enbucrilate\* OR (sealing AND ('skin'/exp OR skin)) AND ('surgical wound infection'/exp OR 'surgical wound infection' OR surgical AND site AND infection\* OR 'ssi' OR 'ssis' OR surgical AND ('wound'/exp OR wound) AND infection\* OR surgical AND infection\* OR 'post operative' AND ('wound'/exp OR wound) AND infection\* OR postoperative AND ('wound'/exp OR wound) AND infection\* OR 'wound'/exp OR wound) AND infection\*

#### Cochrane CENTRAL

(wound infection or surgical wound infection) AND skin antisepsis

#### WHO Global Health Library

(ssi) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections) OR (postoperative wound infection) AND ("skin preparation" OR "skin preparations" OR sealant)

ti: title; ab: abstract

## Appendix 2: Evidence table

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Daeschlein, 2014 <sup>11</sup>	<p>Prospective, blinded RCT</p> <p>Germany</p> <p>Population: 128 adults (male and female) receiving trauma surgery</p> <p>Exclusion criteria: infected wounds, AIDS, HBV/HCV, known drug users</p>	<p>To measure the number of bacteria at the base of the wound, along the wound margin, and on the wound sutures in patients undergoing surgery with and without the use of a cyanoacrylate-based adhesive sealant.</p>	<p>Modified CDC definition, observed by the attending surgeon; not primary study measure.</p> <p>Follow-up: 3 months postoperatively.</p>	Trauma surgery	<p>After assessing eligibility, patients were randomized by opening a sealed envelope, which contained pre-set computer generation number sequence.</p> <p>Skin antisepsis was performed using a 70% propanol-based product for 1-3 minutes. The control group was covered with a sterile drape prior to incision. The intervention group received an application of cyanoacrylate sealant (InteguSeal®) after antisepsis, but before draping.</p> <p>Follow-up: 3 months. Three intraoperative swabs were taken from each surgical site and incubated for colony-forming unit data.</p>	<p>Group 1: no sealant</p> <p>Group 2: cyanoacrylate sealant</p>	<p>SSI:</p> <p>Group 1: 0/66</p> <p>Group 2: 0/62</p> <p>OR: NA</p> <p>CI: NA</p> <p>This study was financed through the routine research grant of the Institute for Hygiene and Environmental Medicine.</p> <p>The authors have no competing interests to report.</p>



Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Doorly, 2015 <sup>8</sup>	<p>Prospective, randomized trial</p> <p>Single institution, multicentre; USA</p> <p>Population: patients undergoing clean-contaminated colorectal procedures</p> <p>Exclusion: less than 18 years, pregnancy, history of hypersensitivity to cyanoacrylate-formaldehyde-acetone, emergent surgery, laparotomy within 60 days (or planned), sepsis, neutropenia, previous abdominal wound infection, serum creatinine &gt; 3mg/dL, chemotherapy/radiation within 30 days, steroid use, HIV</p>	To assess the role of a skin antimicrobial sealant for reducing the rate of superficial and deep wound SSI in a blended case mix of open and laparoscopic clean-contaminated procedures.	CDC criteria	Clean-contaminated colorectal procedures	<p>Consenting patients were blinded to allocation; randomization occurred via sealed envelopes containing either “InteguSeal®” or “Control”.</p> <p>Enrolled patients received the same mechanical bowel preparation and prophylactic antibiotics. Abdomen was prepped with hair removal by clippers and ChlorPrep® (chlorhexidine gluconate 2%, isopropyl alcohol 70%; CareFusion, San Diego, CA, USA) prior to sealant application (in the intervention group). SCIP and a standardized enhanced recovery protocol implemented for all.</p> <p>Follow-up at 4 weeks.</p>	<p>I: cyanoacrylate sealant</p> <p>C: no sealant</p> <p>The sealant was provided by the InteguSeal® manufacturer.</p>	<p>SSI:</p> <p>I: 7/50</p> <p>C: 5/50</p> <p><i>P</i>=0.545</p>

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Dromzee, 2012 <sup>9</sup>	<p>Prospective randomized trial</p> <p>June 2010 – June 2011; paediatric orthopaedic unit, France</p> <p>Population: children and adolescents undergoing scoliosis correction</p> <p>Exclusion criteria: previous spinal surgery and surgery indicated for anterior or combined procedures.</p>	To explore the use of an antimicrobial sealant applied before the surgical incision to reduce SSI in patients with scoliosis.	Not specified	Spine	<p>Randomization by random number table; impossible to blind surgical attendants.</p> <p>All patients showered with povidone-iodine the day before and the morning of surgery. Skin was cleaned and prepared in the operating room with 2 consecutive applications of one-step alcohol povidone-iodine 5% solution. Patients were draped either after skin preparation (control) or after the sealant dried (intervention).</p>	<p>Group 1: drape only after skin preparation (n=28)</p> <p>Group 2: drape after sterile, film-forming cyanoacrylate liquid application (InteguSeal®; n=28)</p>	<p>SSI</p> <p>Group 1: 1/28</p> <p>Group 2: 5/28</p> <p><i>P</i>=0.096</p> <p>“No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.”</p>

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Falk-Brynhildsen, 2014 <sup>4</sup>	<p>RCT</p> <p>May 2010-October 2011; Sweden</p> <p>Population: patients scheduled for elective CABG, with the saphenous vein used for at least two CABG with or without another concomitant cardiac procedure.</p> <p>Exclusion: emergency operation, previous cardiac surgery, long-term corticosteroid treatment and/or antibiotic treatment within 14 days preoperatively skin disease, infection, or preoperative use of an intra-aortic balloon pump.</p>	To compare the use of microbial skin sealant vs. bare skin at the saphenous vein harvesting site in patients undergoing CABG with regard to bacterial growth on the skin and in the surgical wound, including the postoperative wound infection rate.	<p>Primary endpoint was bacterial growth on the wound-adjacent skin or from the subcutaneous wound tissue. Secondary endpoint – SSI: defined as wound complications requiring physician-prescribed antibiotic treatment (telephone call via dedicated nurse)</p> <p>Follow-up: 2 months</p>	Coronary artery bypass graft with saphenous vein harvesting site	Patients were randomized via computer-generated block randomization by an external statistician allocated to two groups: bare skin (control) or microbial skin sealant (intervention). After preoperative disinfection with chlorhexidine 0.5% in ethanol 70%, or nurse-applied microbial skin sealant (InteguSeal®) on the saphenous vein harvest site (in intervention group) prior to incision.	<p>Sealant group: cyanoacrylate sealant</p> <p>Control: no sealant</p>	<p>SSI: I: 7/61 C: 14/64 P=0.120</p> <p>Kimberly Clark Health Care supported the investigators by providing InteguSeal® to be studied in an elective cardiac surgery population. Kimberly Clark provided no financial support to any author.</p>

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Iyer, 2011 <sup>5</sup>	Prospective RCT 2008; New Zealand  Population: patients undergoing CABG	To report the effect of pretreatment with an n-butyl cyanoacrylate-based microbial skin sealant in a population undergoing cardiac surgery and discuss its potential use in decreasing infections in other kinds of surgical procedures.	Southampton score divides wounds into 5 grades: 0=normal healing; 1= normal with bruising or erythema; 2=erythema with other signs of inflammation; 3=haemorrhagic discharge; 4=purulent discharge; 5=deep or severe infection with or without tissue breakdown.	CABG	Hair removal was performed using an electric clipper the day before surgery. Patients washed with soap on the morning of surgery and the skin was disinfected with an alcohol-based povidone-iodine solution and left to dry for 3 minutes before a one-layer application of antimicrobial sealant, which was applied on the intervention leg on a random basis. No sham application was applied on the other leg. Wounds were examined daily during postoperative stay. In the case of infection, swabs were taken; if no infection was present, a culture swab was applied to a segment of the incision before discharge.  Findings were recorded and 1-2 blinded assessors followed up at 4 weeks.	Group 1: Cyanoacrylate-based sealant (InteguSeal®)  Group 2: No sealant	SSI Group 1: 1/47 Group 2: 12/47  <i>P</i> =0.0011  “Authors have nothing to disclose with regard to commercial support.”

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Towfigh, 2008 <sup>10</sup>	<p>Prospective randomized multicentre trial</p> <p>Six teaching hospitals; USA</p> <p>Population: adult patients undergoing open inguinal hernia repair</p> <p>Exclusion criteria: sensitivity to cyanoacrylate, existence of infection or use of antibiotics, chemotherapy, diabetes with HbA &gt; 7 within 90 days, pregnant, nursing, participation in other studies</p>	<p>To compare the safety and effectiveness of antimicrobial sealant in reducing the incidence of surgical incision bacterial contamination relative to surgical skin preparation alone.</p>	Not specified	Hernia repair	<p>Patients were randomized using a 1:1 allocation; each site was supplied with sealed envelopes and the schedule was blocked within the centre to ensure an even distribution. It was not possible to blind the surgeon to the assigned study group.</p> <p>All patients underwent intraoperative microbial wound sampling at 2 stages during the operation; colony-forming units were quantified.</p> <p>Follow-up at 2 and 4 weeks postoperatively for signs of infection.</p>	<p>Group 1: cyanoacrylate sealant</p> <p>Group 2: control</p>	<p>SSI</p> <p>Group 1: 0/68</p> <p>Group 2: 3/80</p> <p>OR: 0.45</p> <p>95% CI: 0.238-0.88</p> <p>P=0.02</p> <p>Funding given for InteguSeal® applicator, standardized microbial sampling supplies and facility reimbursement of study-related costs.</p>

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Vierhout, 2014 <sup>6</sup>	<p>Discontinued RCT</p> <p>The Netherlands</p> <p>Population: patients undergoing vascular reconstruction</p> <p>Exclusion: thrombectomies through inguinal incision, patients under 18 years and those with a previous groin incision or vascular reconstruction done cranially to the site of incision.</p>	To investigate whether the use of cyanoacrylate skin sealant at the site of surgery could reduce the incidence of SSI in the groin after vascular procedures.	Southampton wound assessment scale greater than grade III, erythema plus inflammation and clear or sero-sanguinous discharge (G3) or pus (G4).	Vascular reconstruction	<p>Randomization was completed in a 1:1 ratio by the drawing of a sealed envelope in the operating room 30 minutes before surgery by the surgeon.</p> <p>All patients received cefazolin (2 g intravenous) before incision. Hair removal by clipper done before disinfection with chlorhexidine (0.5% in 70% isopropyl alcohol) and draped with sterile disposable drapes. Intervention group patients received application of cyanoacrylate-based sealant (InteguSeal®) prior to draping and after skin preparation.</p>	<p>Group 1: control</p> <p>Group 2: cyanoacrylate sealant</p>	<p>SSI:</p> <p>Group 1: 2/22</p> <p>Group 2: 1/25</p> <p><i>P</i> = NS</p>

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Von Eckardstein, 2011 <sup>7</sup>	<p>Randomized, controlled, parallel-group, multi-centre, open-label clinical trial</p> <p>April 2006 to February 2009; 5 centres in Asia, Europe, Latin America and the USA</p> <p>Population: adult patients undergoing CABG</p> <p>Exclusion criteria: complex procedures, sensitivity to cyanoacrylate, isopropyl alcohol or iodine; abnormal skin condition; antimicrobial-impregnated incise drapes; chemotherapy, immunosuppressive therapy; steroid or</p>	<p>To determine if the use of this skin sealant before CABG could reduce surgical wound contamination by skin microflora and decrease post-procedure infections</p>	CDC criteria	Cardiac	<p>Randomization in a 1:1 ratio using a computer-generated randomization schedule balanced by randomly permuted blocks; allocations were concealed in a sealed envelope.</p> <p>Surgical site was prepared with either povidone-iodine or iodine 0.7% in isopropyl alcohol. In the experimental group, sealant was applied after drying.</p> <p>Microbial samples were tested for the total bacterial burden and all patients were monitored 30 days postoperatively for SSI.</p>	<p>Group 1: cyanoacrylate sealant (InteguSeal®)</p> <p>Group 2: control</p>	<p>SSI:</p> <p>Group 1: 9/146</p> <p>Group 2: 14/147</p> <p>Risk reduction: 35.3%</p> <p>This clinical study was initiated and funded by the Kimberly Clark Corporation.</p>

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results
Waldow, 2012 <sup>14</sup>	<p>Single-centre quasi-randomized prospective trial</p> <p>October 2010-April 2011; Germany</p> <p>Population: 998 consecutive adult patients undergoing elective cardiac surgical procedures with median sternotomy</p>	<p>To evaluate the prophylactic effect of a cyanoacrylate-based antimicrobial skin sealant on the incidence of postoperative mediastinitis or any other form of chest skin incision SSI after elective cardiac surgery.</p>	CDC criteria	Elective cardiac	<p>Hair removal by hair clipping and the application of an antiseptic alcohol-based (chlorhexidine-free) solution on the skin surface prior to incision. All measures were performed according to written internal hygienic and perioperative standards valid in the institution.</p> <p>Group assigned to receive a cyanoacrylate-based antimicrobial skin sealant (InteguSeal®) as a drape accessory.</p> <p>All patients were prospectively subdivided into two registries by alternating administration of the antimicrobial sealant every second day of surgery regardless of the operation schedule.</p> <p>SSI follow-up: 30 days</p>	<p>Group 1: cyanoacrylate-based sealant included with standard pre-operative disinfection</p> <p>Group 2: standard preoperative preparation</p>	<p>Group 1: 53/488</p> <p>Group 2: 57/495</p> <p><i>P</i> = NS</p> <p>The work was supported by Kimberly-Clark Health Care, which provided investigators with the original InteguSeal® product to be studied in an elective cardiac surgery population. Kimberly-Clark did not provide any financial support to any author of this publication.</p>

SSI: surgical site infection; CDC: Centers for Disease Control and Prevention; HIV: human immunodeficiency virus; I: intervention; C: control; AIDS: acquired immunodeficiency syndrome; HBV/HCV: hepatitis B virus/hepatitis C virus; NA: not applicable; RCT: randomized controlled trial; CABG: coronary artery bypass graft; OR: odds ratio; CI: confidence interval; SCIP: surgical care improvement project; NS: not significant.



### Appendix 3: Risk of bias assessment of the included studies

RCT, author, year	Sequence generation	Allocation concealment	Participants and personnel blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Daeschlein, 2014 <sup>11</sup>	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR
Doorly, 2015 <sup>8</sup>	LOW	LOW	UNCLEAR	LOW	UNCLEAR	UNCLEAR	HIGH*
Dromzee, 2012 <sup>9</sup>	LOW	LOW	LOW	UNCLEAR	LOW	HIGH	UNCLEAR*
Falk-Brynhildsen, 2014 <sup>4</sup>	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR	HIGH*
Iyer, 2011 <sup>5</sup>	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Towfigh, 2008 <sup>10</sup>	LOW	LOW	LOW	LOW	UNCLEAR	LOW	UNCLEAR*
Vierhout, 2014 <sup>6</sup>	LOW	LOW	HIGH	LOW	UNCLEAR	UNCLEAR	LOW
Von Eckardstein, 2011 <sup>7</sup>	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH*
Waldow, 2014 <sup>14**</sup>	HIGH <sup>1</sup>	HIGH	UNCLEAR	UNCLEAR	LOW	LOW	HIGH*

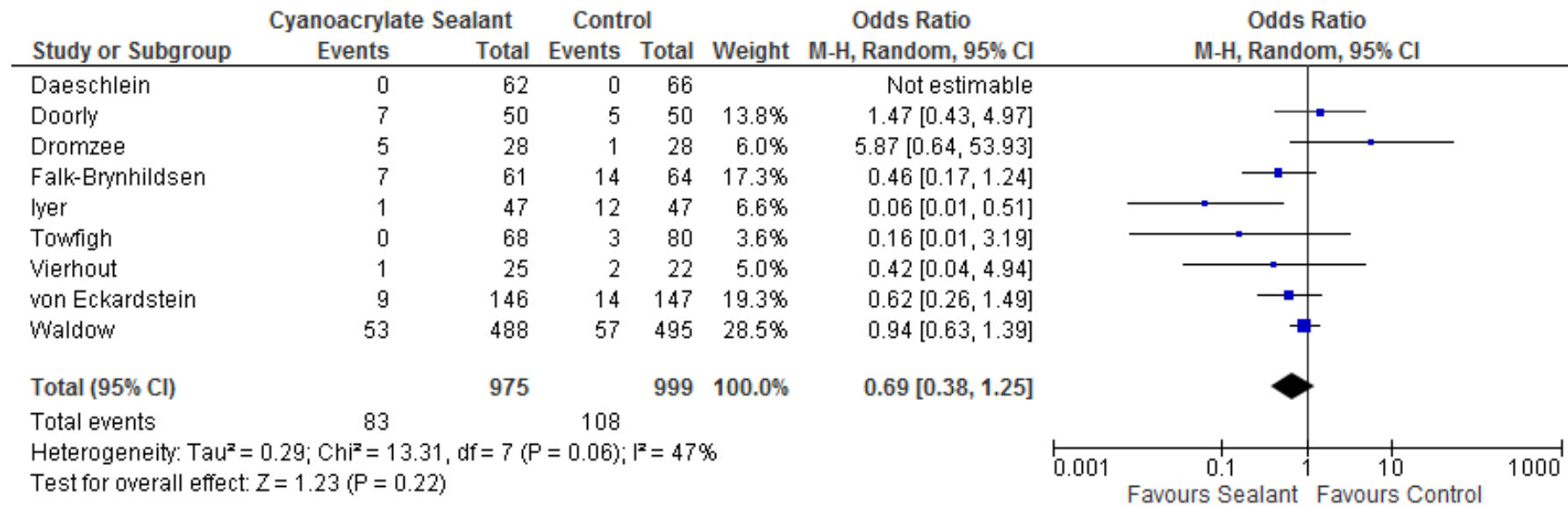
\* Manufacturer of intervention provided product or funding for study.

\*\*Quasi-randomized prospective trial.

RCT: randomized controlled trial.

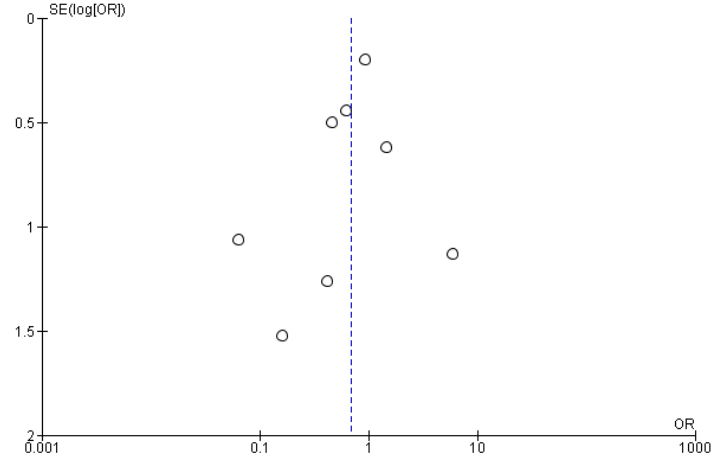
## Appendix 4: Comparison

### Comparison 1: Microbial cyanoacrylate sealant vs. standard surgical site preparation



M.H: Mantel-Haenszel (test) ; CI : confidence interval

**Funnel plot 1: Sealant vs. standard skin preparation**



## Appendix 5. GRADE Table

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Microbial sealant	Standard surgical site preparation	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
9	RCTs *	serious <sup>1</sup>	not serious	not serious	very serious <sub>2</sub>	none	83/975 (8.5%)	108/999 (10.8%)	OR: 0.69 (0.38-1.25)	31 fewer per 1000 (from 23 more to 64 fewer)	⊕○○○ VERY LOW

\*includes one quasi-randomized trial

1. Risk of performance bias, detection bias, attrition bias and reporting bias
2. Optimal information size not met and CI includes both appreciable benefit and harm

RCT: randomized controlled trial; OR: odds ratio; CI: confidence interval

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