TITLE: Antimicrobial Sutures for Wound Closure after Surgery: A Review of the Clinical Effectiveness, Safety, Guidelines, and Cost-effectiveness

DATE: 16 May 2013

CONTEXT AND POLICY ISSUES

Sutures can be a source of surgical wound contamination due to bacterial adherence and colonization.[1] Sutures impregnated or coated with antimicrobial agents have been developed in an attempt to reduce surgical site infections (SSI).[1] Triclosan, a broad spectrum antiseptic agent, is commonly used to coat surgical sutures.[1] Several triclosan-coated sutures (TCS) are marketed in Canada including Vicryl Plus (triclosan-coated polyglactin 910), Monocryl Plus (triclosan-coated poliglecaprone 25) and PDS Plus (triclosan-coated polydioxanone).[2] There are concerns that triclosan used as a coating agent could lead to bacterial resistance and to side effects due to systemic absorption.[1]

A CADTH Rapid Response dated August 2010[3] concluded that evidence from one randomized controlled trial (RCT) and one evidence-based guideline was insufficient to determine whether or not the rate of surgical site infection was lower with triclosan-coated sutures compared to uncoated sutures. Since 2010, a number of RCTs have been published and this report will provide an update of the clinical effectiveness, safety, guidelines recommendations, and cost-effectiveness for use of antibacterial sutures for preventing surgical site infections (SSI).

RESEARCH QUESTIONS

1. What is the clinical effectiveness of antibacterial sutures for the prevention of surgical site infections?

2. What are the adverse events associated with antimicrobial suture use including the development of drug-resistant bacteria?

3. What are the guidelines for using antimicrobial sutures for wound closure?

4. What is the cost-effectiveness of using antimicrobial sutures for wound closure?

KEY FINDINGS

Randomized controlled trials of triclosan coated sutures compared to uncoated sutures have shown benefits in terms of reduced surgical site infections. No information was available on the adverse events associated with antimicrobial suture use including the development of drug-resistant bacteria, and on guidelines and cost effectiveness of using antimicrobial sutures for wound closure.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between Jan 1, 2010 and Apr 19, 2013.

Selection Criteria and Methods

One reviewer screened citations to identify publications that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria

Population	Adults undergoing surgery Sub-group: colorectal surgery
Intervention	Antimicrobial/ antibacterial sutures
Comparator	No antimicrobial/ antibacterial sutures
Outcomes	Surgical site infections, adverse events/ harms (including bacterial resistance), guideline recommendations, and cost-effectiveness
Study Designs	Q.1 and Q. 2 Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials Q.3 Evidence based clinical practice guidelines Q.4 Economic evaluations

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria. Health technology assessments, meta-analyses, systematic reviews and guidelines were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or more rigorous review or guideline. Randomized controlled trials (RCTs) were excluded if they were described in a systematic review included in this report. Economic evaluations that reported only costs and were not cost-effectiveness or cost-utility analyses were also excluded.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The methods used when conducting the literature search, study selection, quality assessment, data extraction, and summarizing the data were appraised for systematic reviews. For RCTs, this included assessment of allocation concealment, blinding, intention to treat analysis and losses to follow up.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 351 citations. Upon screening titles and abstracts, 334 citations were excluded and 17 potentially relevant articles were retrieved for full-text review. Two additional potentially relevant reports were retrieved from the grey literature. Of the 19 potentially relevant reports 16 were excluded. One systematic review[4] and two RCTs[5,6] met the inclusion criteria. No evidence-based clinical practice guidelines and no economic evaluations were found. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

The details of two cost analyses are provided in Appendix 5.

Summary of Study Characteristics

One systematic review and meta-analysis and two RCTs were retrieved and are described in Tables 1 and 2 in Appendix 2.

The systematic review and meta-analysis[4] included 17 RCTs. TCS were compared to uncoated sutures. The primary end-point of interest was the incidence of surgical site infection as defined by the US Centers for Disease Control and Prevention (CDC). Sub-group analyses were conducted for age groups (children and adults), level of contamination (clean, clean-contaminated, and contaminated/dirty), type of surgery, duration of follow-up, study quality, and publication status (abstract and full article).[4]

The trials retrieved in the systematic review were published between 2005 and 2012.[4] Four of the included trials were published as abstracts. Five were multi-centred RCTs, 11 were single-centred RCTs, and this information was unavailable for two RCTs. Ten RCTs were double-blinded, two were single-blinded, three had an open-label study design, and the type of blinding was unknown for two RCTs. Sample sizes ranged from 52 to 510 patients for a total of 3720 patients [1726 patients randomized to TCS (including Vicryl Plus, Monocryl Plus, and PDS Plus) and 1994 patients randomized to uncoated sutures]. Length of follow-up ranged from 30 days to 24 months. One RCT did not report the duration of follow-up. Fifteen RCTs were conducted in adults whereas two RCTs were conducted in children. The types of surgeries included abdominal (7 RCTs), breast (3 RCTs) and cardiac (3 RCTs) surgeries. The majority of surgeries were considered clean surgeries (9 RCTs) whereas 6 RCTs included clean-contaminated surgeries and two RCTs included contaminated/dirty surgeries.[4]

Two additional RCTs were published in 2013 and were not included in the systematic review and meta-analysis by Wang et al. Nakamura et al.[6] compared TCS (Vicryl Plus) to uncoated sutures (Vicryl) in patients undergoing elective colorectal surgery. This RCT enrolled 410

consecutive patients and patients were followed weekly for 30 days. The primary end-point was the incidence of surgical site infection as defined by the CDC. A secondary end-point consisted of calculating the extra cost of caring for a patient with an infected wound (see Appendix 5).[6]

Thimour-Bergström and colleagues[5] conducted a double-blind, single-centre RCT in 374 patients who needed leg-wound closure following open vein harvesting for coronary artery bypass (CABG) surgery. Patients were randomized to receive TCS (Vicryl Plus for subcutaneous suture and Monocryl Plus for intracutaneous suture) or matching uncoated sutures from the same manufacturer. Follow-up included a clinic visit at 30 days and a telephone interview at 60 days. The primary end-point was the incidence of surgical site infection in the vein-harvesting leg within 60 days after surgery as defined by the Centre for Disease Control.[5]

Summary of Critical Appraisal

Study strengths and limitations are presented in Appendix 3.

The systematic review and meta-analysis by Wang et al.[4] was well designed and conducted. A comprehensive search was done of all major bibliographic databases and included hand-searching reference lists and consulting trial registries. However, no other attempts were made to search the grey literature. Publication date and language of publication were unrestricted. The inclusion criteria were limited to RCTs of TCSs. Randomisation, allocation concealment, blinding, loss to follow-up, and reporting of data were considered using Cochrane's Risk of Bias Tool. There was a category for 'other biases', but these potential sources of bias were undefined. Statistical heterogeneity was assessed using both Chi-squared based Q test and the I^2 statistic. Results were presented in a forest plot and appropriate sub-group analyses were conducted although there was no mention as to whether or not patients received concomitant antibiotic prophylaxis. Furthermore, other infection control interventions (for example pre-operative skin cleansing, surgical hair removal) which may have affected the results were not reported. Publication bias was also assessed in a funnel plot and it showed no evidence of bias. Impact of funding sources (industry vs. non-industry funding) on the results was not considered. The investigators qualified three of the included RCTs as being of high quality (low risk of bias). The risk of bias was unclear in 8 RCTs because of a lack of information on the methods of randomization and allocation concealment. The risk of bias was deemed high in six RCTs due to the lack of blinding of investigators, patients or both (performance and detection biases), or due to selective reporting (reporting bias).[4]

Nakamura et al.[6] did not specify inclusion and exclusion criteria a priori, but rather used consecutive surgical patients. The presence of surgical site infection was ascertained using CDC definitions. Surgeons were not blinded to type of sutures used, however the physicians assessing the conditions of the wounds were blinded. It is stated that randomization was done according to the 'envelop method' but no other information was provided as to allocation concealment. Baseline patient characteristics were balanced. There were no losses to follow-up.

The trial by Thimour-Bergström et al.[5] had adequate allocation concealment and blinding. The presence of surgical site infection was ascertained using CDC definitions. Baseline patient characteristics were balanced. The major limitation of this trial was the fact that the analysis was not ITT, but was based on the number of patient treated. In the intervention group, three patients were lost to follow-up including one patient who died and two patients who could not be

reached. In the control group, two patients were lost to follow-up including one patient who died and one who declined follow-up. These five patients were not included in the analysis.[5]

Summary of Findings

Details of the results of the systematic review and RCTs are available in Appendix 4.

The 17 RCTs identified by Wang et al.[4] were meta-analysed and a pooled relative risk (RR) of 0.70 (95% confidence interval [CI]: 0.57 to 0.85) was obtained (I^2=29%). Hence the use of TCS resulted in a statistically significant reduction in the rate of surgical site infections. Results remain statistically significant for all sub-groups except for children (2 RCTs), breast surgery patients (3 RCTs), cardiac surgery patients (3 RCTs), and contaminated/ dirty surgeries (2 RCTs). Results were also not statistically significant when the risk of bias was unclear (8 RCTs) or high (6 RCTs).[4]

In Nakamura et al.,[6] it is reported that 4.3% of patients (9/206) had a wound infection with TCS compared to 9.3% of patients (19/204) in the control group (P=0.047). The relative risk and associated confidence interval were not reported.[6]

Thimour-Bergström et al.,[5] found that the RR for SSI as defined by CDC was 0.63 (95% CI: 0.39 to 1.00), P=0.0497, indicating a lower risk of SSI in the TCS group. The findings were not statistically significant for culture proven SSI.[5]

Adverse events associated with the use of antimicrobial suture (including the development of drug-resistant bacteria) were not an outcome of interest in any of the evidence reviewed, although there were two deaths in Thimour-Bergström et al. (one each in the treated and control group).[5]

Limitations

The results of the systematic review and meta-analysis[4] must be interpreted in light of the following: Not all included RCTs clearly defined what constituted an SSI. Moreover, some RCTs did not have SSI as a primary outcome. The RCTs were conducted in various surgical procedures which would limit the generalizability of the findings. Some sub-group analyses (for example the sub-group of dirty surgeries where the sample size was 87 from 2 RCTs) may not have had enough patients to show a statistically meaningful effect. Patient-related factors which are known to be risk factors for SSI (such as diabetes, smoking and large BMI) were not considered. Other strategies used for the prevention of SSIs (for example antibiotic prophylaxis, hair removal and other skin preparations) were not considered as well. Finally, the impact of industry funding on the results were not evaluated.

Results from the two RCTs not included in the systematic review and meta-analysis were statistically significant with the P value less than 0.05.[5,6] In one RCT,[5] the confidence interval for the result was wide which may suggest uncertainty as the true value may be lie anywhere within the interval. The other RCT did not provide a confidence interval. Furthermore, in one RCT,[5] the analysis excluded five patients of which 2 patients died with no explanations as to cause of death.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence of benefits of antimicrobial sutures relied on one systematic review and meta-analysis of 17 RCTs in 3720 patients who underwent a variety of surgeries. It was shown that, overall, triclosan-coated sutures reduced the rate of surgical site infections by 30%. Two additional recent randomized controlled trials found similar results. However in sub-group analyses, the rates of SSI were not statistically significantly different in breast and cardiac surgeries. Further research must address the benefits of antimicrobial sutures in specific patient populations in independently-run trials. Unanswered questions remain on the harms and potential for the development of bacterial resistance and on the cost effectiveness of antimicrobial sutures.

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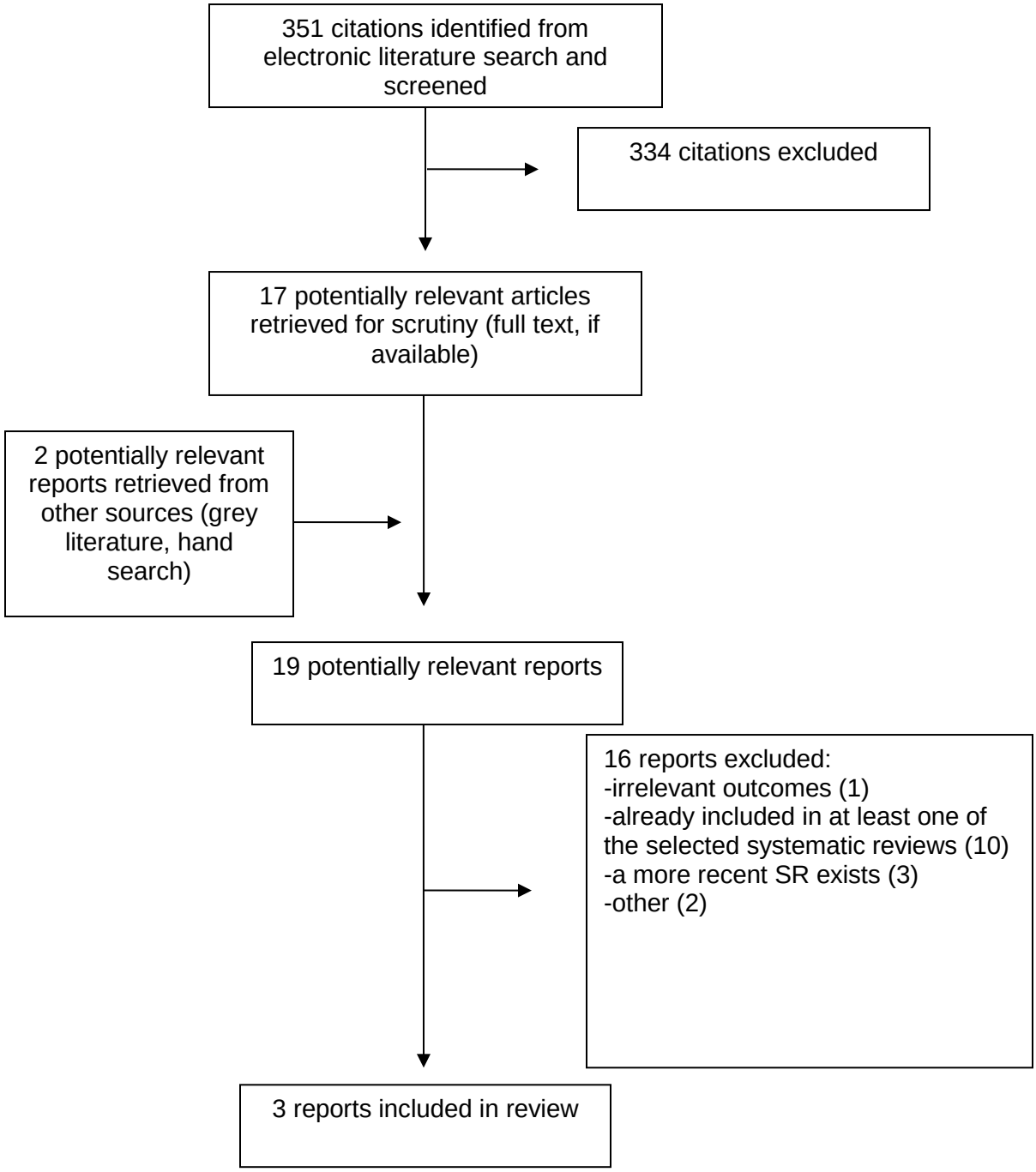
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

Table 1: Characteristics of Included Systematic Review

Author, year, funding source	Key inclusion criteria, N studies	Interventions	Outcomes
Wang et al., 2013[4] Funded by Grants for Key Clinical Centres of Institutes and Science Fund of Ministry of Health of China	RCTs (cut-off June 2012); no language or date of publication restrictions 17 RCTs (3720 patients)	TCS vs. uncoated sutures	Incidence of SSI Sub-group analyses: • Age • Classification of wound contamination • Surgery type • F/U period ≤ 1month and > 1 month • Quality of the RCTs • Publication status

RCTs=randomized controlled trials, SSI=surgical site infection, TCS=triclosan-coated sutures

Table 2: Characteristics of Included Randomized Controlled Trials

Author, year, funding source, country	Study design	Population	Interventions
Nakamura et al., 2013[6] Funding not reported Japan	Open-label (although assessment of wound was blinded), SC	*Description* Elective colorectal surgery *Inclusion/ exclusion criteria* None (consecutive patients)	*Intervention* polyglactin 910 coated with triclosan (Vicryl Plus®) suture n=206 *Comparator* polyglactin 910 (Vicryl) suture n=204 All patients received antibiotic prophylaxis (a cephalosporin) 30 minutes prior to incision and then every 3 hours for 48 hours.
Thimour-Bergström et al.,2013[5] Funded by Västra Götaland Healthcare Region and Ethicon Inc. Sweden	DB, SC	*Description* Leg-wound closure following open vein harvesting in CABG *Inclusion criteria* Patients with CABG, CABG with aortic valve replacement or mitral valve repair or replacement with the use of a saphenous vein graft *Exclusion criteria* On-going sepsis or septicemia, on-going bacterial infections or antibiotic treatment, severe disease that may influence wound healing, emergency surgery	*Intervention* polyglactin 910 coated with triclosan (Vicryl Plus®) for the SQ suture and polyglecaprone 25 coated with triclosan (Monocryl Plus®) for the intracutaneous suture n=184 analysed (193 allocated to treatment group) *Comparator* identical sutures without triclosan n=190 analysed (199 allocated to control group) All patients received antibiotic prophylaxis (cloxacillin or clindamycin) 30 minutes prior to incision and then 2 hours after first dose, 6 hours and 24 hours thereafter.

CABG=coronary artery bypass grafting, DB=double-blind, RCT=randomized controlled trial, SC=single centre, SQ=subcutaneous

APPENDIX 3: Critical Appraisal of Clinical Studies

Author, year	Strengths	Limitations
Systematic reviews		
Wang et al., 2013[4]	• In general well designed and conducted • Appropriate sub-group analyses	• Limited search of the grey literature • No mention as to whether or not patients received concomitant antibiotic prophylaxis or if other infection control interventions were used • No mention as to baseline characteristics and whether or not these were balanced
Randomized controlled trials		
Nakamura et al., 2013[6]	• SSI ascertained using CDC definition • Blinded assessment of wound • No patients lost to follow-up • Baseline patient characteristics were balanced	• Allocation concealment unclear • Randomization of consecutive patients • Inclusion/ exclusion criteria not stated • Open-label
Thimour-Bergström et al., 2013[5]	• Randomization sequence used sealed envelopes & opened by nurse not involved in study • Randomization was done in blocks of 25 patients. Randomization was stratified for diabetes • Sutures looked identical • Wounds were inspected by nurse blinded to group allocation • SSI ascertained using CDC definition • Wound classification done before randomization code broken • Baseline patient characteristics were balanced	• Analysis not ITT

CDC=Centre for Disease Control, ITT=intention to treat

APPENDIX 4: Summary of Results of Clinical Studies

Table 1: Surgical Site Infections Reported in Clinical Studies

Author	Treated group, n/N	Control group, n/N	Relative Risk (95% CI)
Systematic reviews			
Wang[4]	149/ 1726	227/ 1994	0.70 (0.57, 0.85), I^2 =29%
Randomized controlled trials			
Nakamura[6]	9/ 206 (4.3%)	19/ 204 (9.3%)	NR, P=0.047
Thimour-Bergström[5]	23/ 184 (13%)	38/ 190 (20%)	0.63 (0.39, 1.0), P=0.0497

CDC=Centre for Disease Control, CI=confidence interval, NR=not reported

Table 2: Surgical Site infections by Sub-groups in Wang et al.[4]

Sub-group	N studies	Treated group n/N	Control group n/N	Relative Risk (95% CI)
Age				
• Adult	15	144/ 1582	219/ 1907	**0.71 (0.58, 0.87)** I^2 =25%
• Children	2	5/ 144	8/ 87	0.64 (0.04, 10.1) I^2 =66%
Contamination				
• Clean	9	80/ 820	117/ 977	**0.73 (0.56, 0.95)** I^2 =26%
• Clean-contaminated	6	53/ 566	79/ 580	**0.69 (0.50, 0.96)** I^2 =10%
• Contaminated/dirty	2	8/ 42	12/ 45	1.10 (0.14, 8.43) I^2 =71%
Type of Surgery				
• Abdominal	7	53/ 695	85/ 867	**0.69 (0.50, 0.97)** I^2 =34%
• Breast	3	12/ 138	19/ 130	0.59 (0.30, 1.14) I^2 =0%
• Cardiac	3	31/ 380	52/ 553	0.75 (0.49, 1.14) I^2 =42%
Follow-up				
• 1 month	9	115/ 1117	156/ 1285	**0.79 (0.63, 0.99)** I^2 =25%
• >1 month	6	24/ 453	45/ 548	**0.56 (0.35, 0.92)** I^2 =40%
Risk of bias				
• Low	3	32/ 346	51/ 331	**0.60 (0.39, 0.90)** I^2 =0%
• Unclear	8	56/ 715	104/ 1034	0.57 (0.32, 1.00) I^2 =56%
• High	6	61/ 665	72/ 629	0.85 (0.62, 1.18) I^2 =0%
Publication status				
• Full article	13	122/ 1460	181/ 1717	**0.72 (0.58, 0.90)** I^2 =34%
• Abstract	4	27/ 266	46/ 277	**0.61 (0.39, 0.94)** I^2 =20%

CI=confidence interval
Statistically significant results in bold

APPENDIX 5: Cost Analyses

Two cost analyses of potential interest are described below.

Summary of Study Characteristics

Nakamura and colleagues[6] reported the extra costs of treating a wound infection based on the number of SSI obtained in the RCT in the same publication. In the RCT, 206 patients received TCS and 204 patients received uncoated sutures for wound closure in elective colorectal surgery. A total of 28 patients had an SSI. The medical fee table for fiscal years 2008 and 2010 in Japan was used to obtain the medical costs generated during the additional treatment period required for wound management. These were converted to US dollars using an exchange rate of ¥1=US$0.0125. Patients with wound infections were treated either as outpatients or inpatients. The follow-up of patients was 30 days in the RCT, and in the cost analysis, the time horizon was not specified nor did they specify the time frame for the 'additional treatment period required for wound management'.[6]

A cost comparison performed by an American team[7] was based on an RCT published in 2008. In this RCT, 61 patients underwent a total of 84 shunt procedures. Shunt infection rates were 4.3% in the group who received TCS and 21.0% in the group who received untreated sutures. Through a retrospective chart review of hospital billing records, an analysis was performed of all charges associated with the initial admission for shunt surgery and readmissions for infections and subsequent shunt replacement for a period of 6 months post-procedure. Admissions or prolonged admissions due to causes other than an SSI, a predefined formula was applied to calculate the total admission charge due to shunt surgery. The number of days of infection was determined for each patient by chart review. Additional charges due to shunt infection were also calculated.[7]

Summary of Findings

In Nakamura and colleagues,[6] the median additional cost of wound infection management (both inpatient and outpatient settings) was US$2 310 per patient (range 0 to US$15 600). When the actual total costs were calculated, the cost of treating an infection in nine TCS patients was US$18 370 compared to US$60 814 for the 19 patients in the control group, which saved US$42 444 in wound care management. Considering that TCS cost US$10.80 more than uncoated sutures, the actual total savings were US$40 219 for the study period.

Stone et al.[7] calculated the mean cost of a shunt placement to be US$16 527± US$9 854. An additional mean cost of US$88 132 ± US$67 618 was incurred when a patient developed an SSI (included the hospital care for the infection and the cost of replacing the shunt). The most expensive items related to treating an SSI and replacing the shunt were the hospital stay, the OR time, general anesthesia, imaging, antibiotics, ER visit, IV fluids, CSF cultures and laboratory tests.