Gentamicin-collagen sponge reduces the risk of sternal wound infections after heart surgery: Meta-analysis

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ABSTRACT

Objectives: Sternal wound infections are serious postoperative complications that increase the length of hospital stay and healthcare costs. The benefit of implantable gentamicin-collagen sponges in reducing sternal wound infections has been questioned in a recent multicenter trial. We aimed to perform a comprehensive meta-analysis of studies assessing the efficacy of implantable gentamicin-collagen sponges in sternal wound infection prevention.

Methods: Multiple databases were screened for studies assessing the efficacy of implantable gentamicin-collagen sponges after heart surgery. The primary end point was sternal wound infection, and secondary end points were the occurrence of deep sternal wound infection, superficial sternal wound infection, mediastinitis, and mortality. Randomized controlled trials and observational studies were analyzed separately. By means of meta-regression, we examined the correlation between sternal wound infection and extent to which the bilateral internal thoracic artery was harvested.

Results: A total of 14 studies (N = 22,135, among them 4 randomized controlled trials [N = 4672]) were included in the analysis. Implantable gentamicin-collagen sponges significantly reduced the risk of sternal wound infection by approximately 40% when compared with control (risk ratio [RR], 0.61; 95% confidence interval [CI], 0.39-0.98; *P* = .04 for randomized controlled trials and RR, 0.61; 95% CI, 0.42-0.89; *P* = .01 for observational studies). A similar, significant benefit was demonstrated for deep sternal wound infection (RR, 0.60; 95% CI, 0.42-0.88; *P* = .008) and superficial sternal wound infection (RR, 0.60; 95% CI, 0.43-0.83; *P* = .002). The overall analysis revealed a reduced risk of mediastinitis (RR, 0.64; 95% CI, 0.45-0.91; *P* = .01). The risk of death was unchanged. A significant positive linear correlation (*P* = .05) was found between the log RR of sternal wound infection and the percentage of patients receiving bilateral internal thoracic artery grafts.

Conclusions: Implantable gentamicin-collagen sponges significantly reduce the risk of sternal wound infection after cardiac surgery, with evidence consistent in randomized and observational-level data. However, the extent of this benefit might be attenuated in patients receiving bilateral internal thoracic artery grafts. (J Thorac Cardiovasc Surg 2015;149:1631-40)

Efficacy of implantable gentamicin-collagen sponge in preventing sternal wound infections.

Central Message

Implantable gentamicin-collagen sponge significantly reduces the risk of sternal wound infection after cardiac surgery by nearly 40% with evidence highly consistent in randomized- and observational-level data. However, the extent of this benefit might be attenuated in patients receiving bilateral internal thoracic artery grafts.

Perspective

Recent randomized study introduced substantial uncertainty regarding the efficacy of implantable gentamicin-collagen sponge in sternal wound infections prophylaxis. Present study confirms and corroborates in a systematic fashion the findings from the previous studies showing statistically significant reduction of sternal wound infections in patients in whom gentamicin sponge was implanted. Lower benefit conferred by the gentamicin sponge in patients receiving bilateral internal thoracic artery grafts should direct the surgeon's attention to these patients in particular because other potentially preventive measures must be undertaken in this population.

See Editorial Commentary page 1641.

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Abbreviations and Acronyms

BITA	= bilateral internal thoracic artery
BMI	= body mass index
CI	= confidence interval
DSWI	= deep sternal wound infection
IGCS	= implantable gentamicin-collagen sponge
logRR	= log risk ratio
RCT	= randomized controlled trial
RR	= risk ratio
SSWI	= superficial sternal wound infection
SWI	= sternal wound infection

Supplemental material is available online.

Routine intravenous antibiotic prophylaxis initiated before cardiothoracic surgery has been consistently shown to reduce the postoperative rates of infections and in turn associated morbidity and mortality.¹ Sternal wound infections (SWIs) are serious postoperative complications increasing both length of hospital stay and healthcare costs. Several early randomized and observational studies demonstrated implantable gentamicin-collagen sponges (IGCSs) to further reduce (by 33%-62%) the infectious complications compared with intravenous (IV) prophylaxis alone when inserted between sternal halves immediately before closure of the mediastinum.²⁻⁵ These implants deliver high concentrations of gentamicin locally within the wound, therefore preventing the systemic adverse effects of such high regimens and at the same time lowering the risk of acquired bacterial resistance to antibiotics.⁶ On the other hand, the recent SWIPE-1⁷ trial questioned those results, showing no extra benefit of IGCS among US patients at high baseline risk, including diabetes, body mass index (BMI) >30 kg/m², or both. The study showed no difference between IGCS and control groups for the outcomes of superficial SWI (SSWI), deep SWI (DSWI), and rehospitalization for wound infection at 90-day follow-up. Driven by the conflicting results and limited number of randomized studies, we aimed to perform an updated and comprehensive meta-analysis of randomized controlled trials (RCTs) with an addition of observational data to further corroborate the obtained results. In addition, for the first time, we try to explore the efficacy of the IGCS in the setting of bilateral internal thoracic artery (BITA) harvest.

MATERIALS AND METHODS**Data Sources and Search Strategy**

Established methods were used in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

for reporting systematic reviews and meta-analyses in health care interventions.⁸ PubMed, EMBASE, CINAHL, Scopus, the Web of Science, the Cochrane Register of Controlled Clinical Trials (CENTRAL), and Congress proceedings from major cardiothoracic and cardiothoracic societies meetings were screened for randomized and observational studies comparing the efficacy of the IGCS in prophylaxis of SWI after cardiac surgery with placebo or no intervention. Search terms were *gentamicin collagen sponge*, *gentamicin implant*, *gentamicin sponge*, *cardiac surgery*, *heart surgery*, *DSWI*, *SSWI*, and *mediastinitis*. No language, publication date, or publication status restriction was imposed. Both blinded and open-label trials were considered eligible. The most updated or inclusive data for each study were used for abstraction. References of original and review articles were cross-checked.

Selection Criteria and Quality Assessment

Citations were screened at title/abstract level and retrieved as full reports if they fulfilled the inclusion criteria: (1) human studies; (2) RCTs or observational studies with control group; and (3) prespecified outcome of SWI reported. Two independent reviewers (M.K. and W.P.) selected the studies for the inclusion and extracted studies and patient characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with a third reviewer (L.A.). Three authors (M.K., W.P., and M.E.K.) independently assessed the trials' eligibility and risk of bias. The bias risk for randomized studies was assessed using the components recommended by the Cochrane Collaboration, that is, random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.⁹ The quality of observational studies was appraised with the Newcastle–Ottawa Scale, a tool used for assessing the bias (the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure or outcome of interest) in case-control and cohort studies included in a systematic review or meta-analyses.¹⁰

Outcome Measures

The primary end point was the occurrence of SWI after cardiac surgery. Secondary end points were the occurrence of DSWI, SSWI, mediastinitis, and mortality. Definitions for the type, degree, and depth of the infection were applied as per study protocol.

Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Randomized and observational studies were assessed separately. Risk ratios (RRs) and 95% confidence intervals (CIs) were used as summary statistics. Heterogeneity was assessed by the Cochran Q test.¹¹ The statistical inconsistency test was $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-square statistic and df is its degrees of freedom. Thresholds for the interpretation of I^2 for low, moderate, and considerable degree of heterogeneity were values of 25%, 50%, and 75%, respectively.¹² Pooled RRs were calculated using a fixed-effects model for a randomized trials subset in case of low heterogeneity. Pooled RRs from observational studies were calculated using random-effects model with the Mantel–Haenszel method as the most conservative approach. Potential publication bias was examined for the primary end point constructing a “funnel plot” in which the standard error of the log risk ratio (logRR) was plotted against the RR. The asymmetry of the plot was estimated both visually and by a linear regression approach. Random-effects meta-regression analyses accounting for within- and between-study variations were conducted to evaluate linear correlations between the occurrence of any surgical site infection and the percentage of patients in each study receiving BITA and single internal thoracic artery (SITA) grafts, with the sample size as weight.¹³ Finally, we addressed the influence of each study and potential publication bias by testing whether deleting each study in turn would have significantly changed the pooled results of the meta-analysis for the

FIGURE 1. Flow diagram of the review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Total number of patients is reduced by N = 967 because of the exact control group in 2 studies.^{3,5} ICGS, Implantable gentamicin-collagen sponge.

primary end point. Likewise, prespecified sensitivity analyses were also performed after exclusion of studies with high risk of bias, studies available as abstracts only, and studies in which a non–Food and Drug Administration–approved gentamicin sponge was used. To better quantify the contribution of proper, manufacturer-advised sponge placement, the analysis was repeated after exclusion of 4 studies reporting the ICGS to be premoistened in normal saline before implantation. Review Manager 5.1 (The Nordic Cochrane Center, København, Denmark) and Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, NJ) were used for statistical computations. *P* values are reported as 2-sided.

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart, describing the process of publication screening and the reasons for exclusion, is shown in [Figure 1](#). Of 642 potentially relevant reports that were retrieved for scrutiny, 623 were excluded during secondary screening. The remaining 19 underwent thorough assessment based on prespecified eligibility criteria. One study was excluded because 2 different gentamicin sponges (equine and bovine collagen matrix) were compared,¹⁴ and another was excluded because ICGS was given as an addition to intervention for deep sternal wound complications¹⁵ and not as a prophylaxis. Another 2 studies did not report the outcomes of interest.

A total of 14 studies^{2-7,16-23} (N = 22,135; among them 4 RCTs [N = 4672]) were eventually included for data abstraction and entered the analysis. All published studies were retrieved as full texts. Congress proceedings abstracts were available as separate reports. The characteristics of included studies stratified by study design are listed in [Table 1](#).

Among the RCTs, only 1 was multicenter,⁷ 1 was 2-center,³ and 2 were conducted in single institutions.^{2,16} The study by Schimmer and colleagues¹⁶ was the only one to use a placebo-impregnated sponge, therefore attenuating the allocation concealment bias. Eleven observational studies (N = 18,430) entered the analysis.^{4-6,16-23} Study characteristics are listed in [Table 1](#). Three studies were available as abstracts only.²⁰⁻²² Potential sources of bias according to Newcastle–Ottawa Scale are described in [Table E1](#).

Sternal Wound Infection

Randomized controlled trials. Four studies (N = 4672) were included in the analysis of SWI ([Figure 2, A](#)). The ICGS-based intervention was associated with a significant, approximately 40% risk reduction when compared with

TABLE 1. Characteristics of included studies

Study	No. of patients		Procedural characteristics	
	IGCS	Control	Gentamicin sponge	Type of surgery
RCTs				
Bennett-Guerrero and colleagues, 2010 ⁷	727	733	Collatamp (EUSA Pharma, Oxford, England)*	Cardiac surgery via median sternotomy and at high risk for SWI
Eklund and colleagues, 2005 ²	272	270	Collatamp	Elective on-pump CABG via median sternotomy
Friberg and colleagues, 2005 ³	983	967	Collatamp	Cardiac surgery via median sternotomy including surgery on the thoracic aorta
Schimmer and colleagues, 2012 ¹⁶	353	367	GENTA-COLL (RESORBA, Nuremberg, Germany)	Cardiac surgery via median sternotomy including surgery on the thoracic aorta
Observational studies				
Benedetto and Raja, 2014 ¹⁷	329	8315	Collatamp	Cardiac surgery via median sternotomy
Birgand et al and colleagues, 2013 ¹⁸	175	377	Syntacoll	Cardiac surgery via median sternotomy; BITA harvest
Čanádyová and colleagues, 2012 ¹⁹	120	116	Collatamp	Cardiac surgery via median sternotomy including surgery on the thoracic aorta; excluding heart transplantations
Cohen and colleagues, 2010 ²⁰	108	108	Collatamp	Cardiac surgery via median sternotomy
Friberg and colleagues, 2009 ⁵	1359	967†	Collatamp	Cardiac surgery via median sternotomy including surgery on the thoracic aorta
Friberg and Bodin, 2013 ²¹	576	374	Collatamp	Cardiac surgery via median sternotomy including surgery on the thoracic aorta
Madej and colleagues, 2013 ²²	543	505	GENTA-COLL	Elective cardiac surgery via median sternotomy
Popescu and colleagues, 2013 ²³	122	2116	Collatamp	Cardiac surgery via median sternotomy
Raja, 2012 ⁶	97	97	Collatamp	Cardiac surgery via median sternotomy
Schersten, 2007 ⁴	1091	935	Collatamp	Cardiac surgery via median sternotomy

BITA, Bilateral internal thoracic artery; CoNS, coagulase-negative staphylococci; IGCS, implantable gentamicin collagen sponge; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; RCT, randomized controlled trial; SITA, single internal thoracic artery; DSWI, deep sternal wound infection; CABG, Coronary artery bypass grafting. *Available under various names. †Represents the control group from Friberg and colleagues.³

TABLE 1. Continued

Procedural characteristics					
Background antibiotic prophylaxis	IGCS placement and closure technique	BITA (%) SITA (%)	Most commonly isolated bacteria	Primary end points	Follow-up
IV antibiotics	Premoistened in saline; placement along the full length of the sternum	3.2%; 79.4%	<i>Staphylococcus aureus</i> ; CoNS; Enterobacteriaceae	SWI	90th day postoperatively
IV cefuroxime; IV cefuroxime + vancomycin	Retrosternal placement	10%; 96%	CoNS; <i>S aureus</i>	SWI	90th day postoperatively
IV isoxazolyI-penicillin	Placement along the full length of the sternum; also retrosternally at proximal and distal ends; 6-8 sternal wires	0.9%; 71.9%	CoNS; <i>S aureus</i>	SWI	60th day postoperatively
IV cefuroxime	Retrosternal placement; trans-/peristernal, figure of 8, or band cerclages sternal wiring	NR	CoNS; G(–) bacteria; <i>Propionibacterium acnes</i> ; <i>S aureus</i>	DSWI	30th day postoperatively
Observational studies NR	Placement along the full length of the sternum	18.4	NR	DSWI	Perioperative
IV cefamandole; IV vancomycin or gentamicin in MRSA carriers or in case of allergy	Premoistened in saline; placement along the full length of the sternum	92.6	Enterobacteriaceae; CoNS; <i>S aureus</i> ; <i>Pseudomonas aeruginosa</i>	DSWI	60th day postoperatively
IV cefazolin	Premoistened in saline; placement of single layer along the full length of the sternum, also retrosternally at proximal and distal ends; 8-10 sternal wires	NR	<i>S aureus</i> ; CoNS; <i>Escherichia coli</i> ; Enterobacteriaceae; <i>Morganella morganii</i> ; <i>Corynebacterium</i> species	Surgical site infection	90th day postoperatively
Standard of care	NR	NR	NR	SWI	perioperative
IV isoxazolyI-penicillin	Placement along the full length of the sternum; also retrosternally at proximal and distal ends; >7 sternal wires	0.1%; 56%	CoNS; <i>S aureus</i> ; G(–) bacteria; <i>Propionibacterium acnes</i>	SWI	60th day postoperatively
IV cloxacillin; IV clindamycin in case of allergy	Placement along the full length of the sternum; use of 2 sponges was recommended. Average n of sternal wires = 7.8	0.2%; 43.6%	CoNS	SWI	60th day postoperatively
Standard of care	Retrosternal placement	NR	<i>S aureus</i> ; <i>S epidermidis</i>	Freedom from mediastinitis	30th day postoperatively
IV antibiotics	NR	NR	NR	SWI	Perioperative
Standard of care	Retrosternal placement; trans-/peristernal wires	36.4%	NR	SWI	42nd day postoperatively
IV isoxazolyI-penicillin	Placement along the full length of the sternum; >7 sternal wires (at least 2 in the xiphoid region)	NR	CoNS; <i>S aureus</i> ; Enterobacteriaceae; Acinetobacter sp. <i>Propionibacterium acnes</i>	Mediastinitis	Perioperative

control (RR, 0.61; 95% CI, 0.39-0.98; $P = .04$; $I^2 = 71\%$); corresponding event rates were 5.27% (123/2335) versus 8.13% (190/2337) for IGCS and the control group, respectively.

Observational studies. Ten observational studies entered the analysis with $N = 18,430$ patients (Figure 2, A). SWIs occurred in 152 of 4520 IGCS-treated patients and 470 of 13,910 controls. Prophylaxis with IGCS was associated with a 39% reduced risk of SWI compared with the control group (RR, 0.61; 95% CI, 0.42-0.89; $P = .01$; $I^2 = 64\%$).

Overall. Pooled together, randomized and observational studies demonstrated the gentamicin-collagen sponge to be associated with a significant 38% reduced risk of SWI (RR, 0.62; 95% CI, 0.47-0.81; $P < .001$; $I^2 = 63\%$) (Figure 2, A). Analysis of differences between RCTs and observational studies showed no signs of inconsistency: test for subgroup differences: chi-square = 0.00; $P = .99$; $I^2 = 0\%$. Regression of logRR against the percentage of patients receiving BITA grafts demonstrated a significant positive correlation ($P_{\text{slope}} = .05$) between the risk of SWI and the extent to which BITA harvest was performed (Figure 2, B). Analysis regressing the percentage of single ITA against logRR revealed a borderline significant negative correlation ($P_{\text{slope}} = .06$) (Figure 2, C).

Deep Sternal Wound Infection

Randomized controlled trials. Data on DSWI were available from 4 RCTs; gentamicin sponge prophylaxis reduced the risk of DSWI by 40% compared with the control group (RR, 0.60; 95% CI, 0.42-0.88; $P = .008$; $I^2 = 19\%$); the corresponding event rates were 43 of 2335 IGCS-treated patients (1.84%) and 71 of 2337 controls (3.04%) (Figure 3, A).

Observational studies. Four observational studies reported on the incidence of DSWI with $N = 11,716$ patients. A nonsignificant risk reduction was observed with IGCS when compared with the control group (RR, 0.60; 95% CI, 0.32-1.13; $P = .12$; $I^2 = 56\%$) (Figure 3, A).

Overall. In the overall analysis, gentamicin sponge prophylaxis demonstrated a 38% risk reduction compared with the control group (RR, 0.62; 95% CI, 0.44-0.87; $P = .006$; $I^2 = 34\%$) (Figure 3, A). Analysis of differences between RCTs and observational studies showed no signs of inconsistency: test for subgroup differences: chi-square = 0.00; $P = .96$; $I^2 = 0\%$. Regression of logRR against the percentage of patients receiving BITA grafts demonstrated a significant positive correlation ($P_{\text{slope}} = .05$) between the risk of DSWI and the extent to which BITA harvest was performed (Figure 3, B). Analysis regressing the percentage of single ITA against logRR revealed a significant negative correlation ($P_{\text{slope}} = .05$) (Figure 3, C).

Superficial Sternal Wound Infection

Randomized controlled trials. Four RCTs ($N = 4672$ patients) reported SSWI incidence (80/2335 [3.43%] vs 119/2337 [5.09%]; RR, 0.65; 95% CI, 0.34-1.25; $P = .20$; $I^2 = 76\%$) (Figure 4, A).

Observational studies. In 5 observational studies ($N = 3922$ patients), data on the incidence of SSWI were available; a significant 45% risk reduction was observed with IGCS when compared with the control group (RR, 0.55; 95% CI, 0.36-0.86; $P = .008$; $I^2 = 66\%$); event rates were 129 of 2260 (5.71%) and 185 of 1662 (11.13%), respectively (Figure 4, A).

Overall. Pooled together (9 studies), gentamicin sponge prophylaxis demonstrated a significant, 40% risk reduction compared with the control group (RR, 0.60; 95% CI, 0.43-0.83; $P = .002$; $I^2 = 66\%$) (Figure 4, A). No signs of inconsistency were found for the comparison between observational and randomized studies; test for subgroup differences: chi-square = 0.15; $P = .70$; $I^2 = 0\%$. No correlations between the risk of SSWI and the extent to which both BITA and SITA harvest was performed were found by meta-regressions (Figure 4, B and C, respectively).

Mediastinitis

Randomized controlled trials. Three RCTs ($N = 3212$ patients) were available for inclusion in the analysis of mediastinitis; event rates were 18 of 1608 (1.12%) versus 33 of 1604 (2.06%) (RR, 0.50; 95% CI, 0.19-1.33; $P = .16$; $I^2 = 51\%$) (Figure E1).

Observational studies. Six observational studies ($N = 7096$ patients) contributed to the analysis of mediastinitis; a significant 33% risk reduction was observed with IGCS when compared with the control group (RR, 0.67; 95% CI, 0.45-0.99; $P = .04$; $I^2 = 6\%$); event rates were 46 of 3841 (1.20%) and 67 of 3255 (2.06%), respectively (Figure E1).

Overall. In total, 9 studies were included; gentamicin sponge prophylaxis demonstrated a significant, 36% risk reduction compared with the control group (RR, 0.64; 95% CI, 0.45-0.91; $P = .01$; $I^2 = 16\%$) (Figure E1). Observational studies were found statistically consistent with RCTs; test for subgroup differences (chi-square = 0.29; $P = .59$; $I^2 = 0\%$).

Mortality

Six studies contributed to the analysis of mortality; no differences between the IGCS-based prophylaxis and the control group were found in both randomized (RR, 0.87; 95% CI, 0.55-1.38; $P = .55$; $I^2 = 0\%$) and observational studies (RR, 0.97; 95% CI, 0.33-2.84; $P = .96$; $I^2 = 0\%$), with findings consistent between these 2 subgroups (chi-square = 0.05; $P = .83$; $I^2 = 0\%$) (Figure E2).

FIGURE 2. A, Summary analysis of primary end point SWI. RRs and 95% CIs. Size of *squares* is proportional to the statistical weight of each trial. *Diamonds* represent RR point estimates; *horizontal lines* represent CIs for given point estimate; positioning of both *diamonds* and *squares* (along with CIs) beyond the *vertical line* (unit value) suggests significant outcome. Meta-regression analysis of the logRR of primary end point on the percentage of patients receiving BITA (B) and SITA (C) grafts. Size of *circles* corresponds to the number of patients in each study. *BITA*, Bilateral internal thoracic artery; *CI*, confidence interval; *df*, degrees of freedom; *IGCS*, implantable gentamicin-collagen sponge; *M-H*, Mantel-Haenszel; *SITA*, single internal thoracic artery.

Sensitivity Analyses

Sensitivity analyses performed by removing each of the studies one at a time and repeating the calculations did not alter the direction or magnitude of the effect (Figure E3). The estimates did not change after exclusion of studies with a high risk of bias, studies available as

abstract only, and studies in which other than Food and Drug Administration-approved Collatamp (EUSA Pharma, Oxford, England) was used. The results also remained consistent when we excluded studies in which gentamicin sponge was premoistened quickly in saline before implantation.

FIGURE 3. A, Summary analysis of DSWI. RRs and 95% CIs. Size of *squares* is proportional to the statistical weight of each trial. *Diamonds* represent RR point estimates; *horizontal lines* represent CIs for given point estimate; positioning of both *diamonds* and *squares* (along with CIs) beyond the *vertical line* (unit value) suggests significant outcome. Meta-regression analysis of the logRR of DSWI on the percentage of patients receiving BITA (B) and SITA (C) grafts. Size of *circles* corresponds to the number of patients in each study. *BITA*, Bilateral internal thoracic artery; *CI*, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel; *SITA*, single internal thoracic artery.

Study or Subgroup	Gentamycin sponge		Control		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Randomized controlled trials (RCTs)							
B-Guerrero G et al. 2010	48	727	45	733	16.4%	1.08 [0.73, 1.59]	
Eklund AM et al. 2005	6	272	8	270	6.8%	0.74 [0.26, 2.12]	
Friberg O et al. 2005	19	983	55	967	14.1%	0.34 [0.20, 0.57]	
Schimmer C et al. 2012	7	353	11	367	7.8%	0.66 [0.26, 1.69]	
Subtotal (95% CI)	2335		2337		45.0%	0.65 [0.34, 1.25]	
Total events	80		119				
Heterogeneity: Tau ² = 0.32; Chi ² = 12.28, df = 3 (P = 0.006); I ² = 76%							
Test for overall effect: Z = 1.29 (P = 0.20)							
1.1.2 Observational studies							
Canadyova J et al. 2012	60	120	86	116	19.7%	0.67 [0.55, 0.83]	
Cohen G et al. 2010	0	106	10	108	1.3%	0.05 [0.00, 0.80]	
Friberg O et al. 2009	30	1359	55	967	15.5%	0.39 [0.25, 0.60]	
Friberg O et al. 2013	37	576	28	374	14.8%	0.86 [0.53, 1.38]	
Raja SG et al. 2012	2	97	6	97	3.6%	0.33 [0.07, 1.61]	
Subtotal (95% CI)	2260		1662		55.0%	0.55 [0.36, 0.86]	
Total events	129		185				
Heterogeneity: Tau ² = 0.13; Chi ² = 11.68, df = 4 (P = 0.02); I ² = 66%							
Test for overall effect: Z = 2.65 (P = 0.008)							
Total (95% CI)							
Total events	4595		3399		100.0%	0.60 [0.43, 0.83]	
Heterogeneity: Tau ² = 0.13; Chi ² = 23.84, df = 8 (P = 0.002); I ² = 66%							
Test for overall effect: Z = 3.09 (P = 0.002)							
Test for subgroup differences: Chi ² = 0.15, df = 1 (P = 0.70), I ² = 0%							

Favours gentamycin sponge

Favours control

A

C

FIGURE 4. A, Summary analysis of SSWI. RRs and 95% CIs. Size of *squares* is proportional to the statistical weight of each trial. *Diamonds* represent RR point estimates; *horizontal lines* represent CIs for given point estimate; positioning of both *diamonds* and *squares* (along with CIs) beyond the *vertical line* (unit value) suggests significant outcome. Meta-regression analysis of the logRR of SSWI on the percentage of patients receiving BITA (B) and SITA (C) grafts. Size of *circles* corresponds to the number of patients in each study. *BITA*, Bilateral internal thoracic artery; *CI*, confidence interval; *df*, degrees of freedom; *M-H*, Mantel–Haenszel; *SITA*, single internal thoracic artery.

DISCUSSION

The incidence of SWI after heart surgery varies from 0.9% to 20.0% across the available literature.²⁴ In the present meta-analysis, it accounted for 3.82% in IGCS-treated patients and 3.98% in controls. The present report highlights the potential role of gentamicin sponge implantation as an SWI prophylaxis during cardiac surgery. Unlike previous reports,^{25,26} this is the first meta-analysis to also include observational studies. The main findings of the present meta-analysis are as follows: (1) IGCS is universally associated with an approximately 40% SWI risk reduction, with results consistent between randomized and observational data; (2) in the overall analyses, this reduction is sustained for separate single end points: DSWI, SSWI, and mediastinitis; (3) mortality was not influenced by IGCS; and (4) the benefit provided by the gentamicin sponge might be attenuated when BITA is harvested.

SWIPE-1 questioned for the first time the long-established efficacy of gentamicin sponge implantation for SWI prophylaxis.⁷ In a large 48-center study, the authors demonstrated no reduction of SWI with gentamicin-impregnated collagen sponges in patients undergoing cardiac surgery, thus showing results contradictory to those from previous randomized and observational data. The authors explained the between-study discrepancies by the potential of onsite monitoring and source data verification with central adjudication of outcomes by an independent blinded committee and the multicenter design, and therefore higher ethnic and regional variability, in turn

associated with diverse bacterial pathogens distribution (6.3% of methicillin-resistant *Staphylococcus aureus* in the SWIPE-1 vs 0.0% in study by Friberg and colleagues^{3,27}). The latter may be of lesser importance in light of increasing methicillin resistance across coagulase-negative staphylococci strains and the majority of the pathogens generally susceptible to gentamicin. Concern remains regarding the high percentage of Gram-negative G(–) strains in the US trial obtained from microbial swabs compared with the remaining studies (63% vs 0%-13%). This poses the question of when exactly the surgical site infection occurred because G(–) flora should not be present in the air of the operating room and do not generally reside on the skin of the chest as do G(+) pathogens, and in particular coagulase-negative staphylococci. Therefore, it was argued^{26,28} that infections occurred postoperatively rather than in the perioperative period and to a lesser extent were dependent on the gentamicin prophylaxis. In a counter publication, Friberg and Bodin²¹ listed the flaws of the SWIPE-1 design, with a failure to follow manufacturer-advised sponge implantation protocol as their strongest argument. The differences in outcomes in the 2 studies were attributed to a longer exposure of gentamicin sponge to saline solution soon before implantation, thus resulting in different concentrations of gentamicin sulphate in the collagen-based matrix. The importance of this phenomenon was further corroborated by Lovering and Sunderland,²⁹ who found in an in vitro study a mean loss of 6.7% of gentamicin concentration after 2 seconds of exposure to saline,

increasing to 40.5% at 1 minute. Collagen sponge without gentamicin was further speculated to act as a culture medium and supported by the highest benefit of IGCS compared with placebo sponge in the study by Schimmer and colleagues.¹⁶ Quick deployment of the sponge with or without conditional short-dipping in the water solution, just to enable easier handling, therefore seems to play an essential role in the SWI prophylaxis; however, to date no single randomized study has addressed this concern.

The majority of the studies published so far have shown that the use of IGCS may significantly reduce the incidence of infectious complications after cardiac surgery. The current article is the first to demonstrate the consistent infection risk reduction in both a randomized and observational subset of patients; this is of particular importance because randomized trials tend to enroll highly selected groups of patients, thus compromising real-world scenario analyses. With the exception of SWIPE-1, which enrolled high-risk patients undergoing cardiac surgery (diabetes, BMI >30 kg/m², or both), all RCTs were conducted in a mostly elective setting with the percentage of diabetic persons ranging from 18.3% to 32.4% and average BMI ranging from 26 to 28 kg/m². Our analysis demonstrated, apart from substantial reductions in DSWI and SSWI, a 33% significant (RR, 0.67; 95% CI, 0.49-0.92; $P = .01$) mediastinitis risk reduction with IGCS.

Another important finding of the current meta-analysis is a positive linear correlation between the logRR of SWI and the percentage of patients receiving a BITA graft, indicating the lesser benefit provided by the IGCS in this population. These findings are in line with previous reports demonstrating BITA to be an independent risk predictor for DSWI^{30,31}; however, indicating for the first time that in case of patients' elevated baseline risk (diabetes, high BMI, chronic obstructive pulmonary disease, renal dysfunction) and BITA harvest, IGCS alone might not prevent infectious complications to an extent provided when SITA is used. Another potentially preventive measure must be taken in such patients, such as meticulous pinpoint hemostasis, rigid sternum fixation, avoidance of excessive use of bone wax, strict aseptic technique, and, above all, skeletonization of the internal thoracic arteries should be strongly preferred rather than pedicled harvest.³² We found no linear correlation between risk of SSWI alone and BITA harvesting; this finding might reflect the high potential of locally applied gentamicin to infiltrate the sternal fascia and subcutaneous tissue, unhindered by compromised blood circulation in the sternal region because of bilateral loss of the internal thoracic artery.

Gentamicin-collagen implants have been extensively tested outside the cardiothoracic surgery field and shown to decrease wound infections in other groups of patients undergoing surgical procedures, including open and

endoscopic abdominal, vascular, and breast surgery. Reports are available on IGCS applied during surgical repair of pilonidal sinus, perianal abscess, inguinal hernia, and treatment of *hidradenitis suppurativa*.^{E1-E19} In addition to gentamicin, other topical antibiotics have been tested in SWI prophylaxis with promising results, among them vancomycin and bacitracin. In a recent study by Lazar and colleagues,³³ patients undergoing cardiac surgery and treated with topical vancomycin applied as a slurry to the cut edges of the sternum were less likely to develop SSWI and DSWI (0% vs 1.6%, $P < .0001$ and 0% vs 0.7%, $P = .005$, respectively) compared with a matched control group. Another study found a 6-fold reduction in the risk of mediastinitis after cardiac surgery in patients in whom bacitracin ointment was applied to the sternotomy incision after closure.³⁴ As for the cost-effectiveness, Speir and colleagues³⁵ report \$62,773 of additive costs for patients developing SWI after coronary artery bypass grafting. In our institution, the average estimated cost increases approximately 5-fold from baseline, accounting for hospital stay, antibiotics, vacuum-assisted closure, and definitive surgical treatment. The introduction of IGCS in our department (Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital, Bydgoszcz, Poland) (Figure E4) allowed for an approximately 5-fold reduction in the incidence of SWIs only when implanted in high-risk patients (0.6% SWI rate in 2012 [55% IGCS use] vs 2.53% SWI rate in 2005 [0% IGCS use]). Although the detailed pharmacoeconomic analysis is the subject of an ongoing investigation, its preliminary results demonstrate that one SWI quarterly would outweigh the cost of IGCSs implanted in all patients undergoing operation in this period.

Study Limitations

Several limitations to our meta-analysis should be acknowledged. First, the present analysis shares the limitations of the original studies included; therefore, the results were analyzed on the trial level and not on the patient level. Without individual patient data, we could not adjust for baseline risk factors and clinical characteristics. The criteria for patients' inclusion were broad across the studies, more closely reflecting current clinical practice, enrolling both high-risk and elective surgery cases. Potentially heterogeneous definitions of superficial wound infection might pose another limitation. Because of the substantial paucity of randomized data, observational data, both prospective and retrospective, also were included. As a consequence, the majority of the studies were retrospective in nature and thus are always subject to potential biases, that is, selection bias, with the surgeon implanting the gentamicin sponge in patients in whom the benefit with such prophylaxis was more probable (eg, obese or diabetic patients). On the other hand, observational studies were analyzed separately and using a random effect model; this

approach ensures that any heterogeneity among the studies arising from differences in design, surgeon preferences, and patients' baseline clinical characteristics is identified. We noted no signs of inconsistency for the comparison between observational and randomized studies with the number of tests for subgroup differences. Despite these limitations, the consistency in magnitude and direction of the estimates and overall effect of IGCSs and the stability of the results in sensitivity analyses make the overall estimates justified and support the robustness of the conclusions.

CONCLUSIONS

IGCSs significantly reduce the risk of SWI after cardiac surgery, with evidence consistent in randomized and observational-level data. However, the extent of this benefit might be attenuated in patients receiving BITA grafts.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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FIGURE E1. Summary analysis of mediastinitis. RRs and 95% CIs. Size of *squares* is proportional to the statistical weight of each trial. *Diamonds* represent RR point estimates; *horizontal lines* represent CIs for given point estimate; positioning of both *diamonds* and *squares* (along with CIs) beyond the vertical line (unit value) suggests significant outcome. *CI*, Confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel.

FIGURE E2. Summary analysis of mortality. RRs and 95% CIs. Size of *squares* is proportional to the statistical weight of each trial. *Diamonds* represent RR point estimates; *horizontal lines* represent CIs for given point estimate; positioning of both *diamonds* and *squares* (along with CIs) beyond the vertical line (unit value) suggests significant outcome. *CI*, Confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel.

FIGURE E3. Sensitivity analysis for the primary end point conducted by deleting each single study at time and repeating the calculations. Analysis indicates no single study influenced the overall effect. *CI*, Confidence interval; *IGCS*, implantable gentamicin-collagen sponge.

FIGURE E4. Yearly numbers of patients developing SWIs at the Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital in Bydgoszcz plotted against the total number of surgeries and number of surgeries with IGCS implantation. *IGCS*, Implantable gentamicin-collagen sponge; *SWI*, sternal wound infection.

TABLE E1. Newcastle–Ottawa scale of bias risk for observational studies

Study	Adequacy of selection				Outcomes assessment		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Comparability	Assessment of outcomes	Follow-up period long enough for outcome to occur	Adequacy of follow-up period among cohorts
Benedetto and Raja 2014 ¹⁷	**	**	***	*	***	*	*
Birgand and colleagues 2013 ¹⁸	***	***	***	**	***	***	***
Čanádyová and colleagues 2012 ¹⁹	***	***	***	*	***	***	***
Cohen and colleagues 2010 ²⁰	*	*	**	*	**	*	*
Friberg and colleagues 2009 ⁵	***	***	***	**	***	***	***
Friberg and colleagues 2013 ²¹	***	***	***	**	***	***	***
Madej and colleagues 2013 ²²	***	***	**	**	***	***	***
Popescu and colleagues 2013 ²³	**	**	*	*	***	*	**
Raja 2012 ⁶	***	***	***	**	***	**	**
Schersten, 2007 ⁴	*	*	**	*	***	*	*

Asterisks are the star rating as per the Newcastle–Ottawa Scale; ** and *** indicate highest ratings for these categories.

PRISMA checklist

Section/topic	No.	Checklist item	Reported on page no.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable, background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data-collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (eg, RR, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5-7
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	7-8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8, Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and CIs, ideally with a forest plot.	8-11, Figures 2-4, Appendix
Synthesis of results	21	Present results of each meta-analysis done, including CIs and measures of consistency.	8-11, Figures 2-4, Appendix

(Continued)

Continued

Section/topic	No.	Checklist item	Reported on page no.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-11, Figures 2-4, Appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	12-13
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	11-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097. For more information, visit: www.prisma-statement.org. CI, Confidence interval; NA, not available; RR, risk ratio.

Full electronic search in MEDLINE database

Search	Query	Items found
1	Gentamycin OR Gentamicin AND sponge	158
2	Gentamycin OR Gentamicin AND sponge AND cardiac	13
3	Gentamycin OR Gentamicin AND sponge AND cardiovascular	1
4	Gentamycin OR Gentamicin AND sponge AND cardiothoracic	1
5	Gentamycin OR Gentamicin AND sponge AND heart	4
6	Gentamycin OR Gentamicin AND sponge AND thoracic	9
7	Gentamycin OR Gentamicin AND sponge AND bypass	4
8	Gentamycin OR Gentamicin AND sponge AND by-pass	0
9	Gentamycin OR Gentamicin AND sponge AND CABG	1
10	Gentamycin OR Gentamicin AND sponge AND stern*	12
11	Gentamycin OR Gentamicin AND sponge AND mediastin*	3
12	Gentamycin OR Gentamicin AND implant*	742
13	Gentamycin OR Gentamicin AND implant* AND cardiac	63
14	Gentamycin OR Gentamicin AND implant* AND cardiovascular	42
15	Gentamycin OR Gentamicin AND implant* AND cardiothoracic	6
16	Gentamycin OR Gentamicin AND implant* AND heart	48
17	Gentamycin OR Gentamicin AND implant* AND thoracic	19
18	Gentamycin OR Gentamicin AND implant* AND bypass	12
19	Gentamycin OR Gentamicin AND implant* AND bypass	0
20	Gentamycin OR Gentamicin AND implant* AND CABG	2
21	Gentamycin OR Gentamicin AND implant* AND stern*	16
22	Gentamycin OR Gentamicin AND implant* AND mediastin*	6
23	Gentamycin OR Gentamicin AND topical	894
24	Gentamycin OR Gentamicin AND topical AND cardiac	14
25	Gentamycin OR Gentamicin AND topical AND cardiovascular	13
26	Gentamycin OR Gentamicin AND topical AND cardiothoracic	2
27	Gentamycin OR Gentamicin AND topical AND heart	9
28	Gentamycin OR Gentamicin AND topical AND thoracic	8
29	Gentamycin OR Gentamicin AND topical AND bypass	0
30	Gentamycin OR Gentamicin AND topical AND bypass	0
31	Gentamycin OR Gentamicin AND topical AND CABG	0
32	Gentamycin OR Gentamicin AND topical AND stern*	8
33	Gentamycin OR Gentamicin AND topical AND mediastin*	6

CABG, Coronary artery bypass grafting.