Editorial

Devil is in the detail—how to critically analyze studies designed to assess effectiveness of topical antibiotics in preventing sternal wound infections?

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Sternal wound infections (SWIs), however rare, pose as important predictor of mortality and reduced long-term life expectancy after heart surgery and in particular coronary artery bypass grafting (CABG) (*Figure 1*) (1).

Use of topical antibiotics aside intravenous prophylaxis has been of growing interest among cardiothoracic surgeons with many facilities applying it routinely. Among them vancomycin and gentamycin have been used extensively. However, there is a continuously heated discussion whether this procedure has scientific justification. Numerous studies have been published so far however differing in methodology and topical agent employed which poses difficulties in comparison of their sometimes conflicting results. Several meta-analyses have been published in attempt to pool the above studies in search for definite conclusions (2,3). Based on the available evidence, an expert consensus was issued on behalf of American Association for Thoracic Surgery (AATS) stating that "topical antibiotics should be applied to the cut edges of the sternum on opening and before closing all cardiac surgical procedures involving a sternotomy." (4). This recommendation for the first time was given class I—which stands for "procedure/treatment should be performed". Since then other studies were made available that unexpectedly pointed to zero benefit with topical antibiotics; when analysed in detail, however, they present certain methodological flaws which make interpretation of their biased results cumbersome.

Pervaiz *et al.* in the recent issue of *Journal of Surgery and Surgical Research* reports on a randomized trial of 276 patients scheduled for elective CABG and divided into two equal groups; one receiving 0.2 vancomycin saline solution 'sprinkled' over a sternal wound, while the other group received a spray of normal saline (5). The incidence of DSWI in the vancomycin group versus normal saline group was found to be 4 (2.9%) *vs.* 6 (4.3%); however, this was not statistically significant (P=0.07). While we acknowledge and commend any scientific effort in the field of SWI prevention, the study by Pervaiz *et al.* is severely biased and must be interpreted with caution, in particular because it was the first RCT of topically used vancomycin in cardiac surgery to ever get published.

Firstly, the study is obviously underpowered for DSWI; with literature reported incidence ranging between 2–3%, adequately powered study (1:1 randomization ratio; 80% power, alpha 0.05) should enroll at least 1,500 subjects to detect the difference; authors report P value for comparison of 0.07; we are not aware of any appropriate statistical test of 4/138 *vs.* 6/138 returning the P of 0.07. In fact, risk ratio for the above numbers is 0.67 (0.19–2.31) with level of significance P=0.52 which puts the statistical testing behind

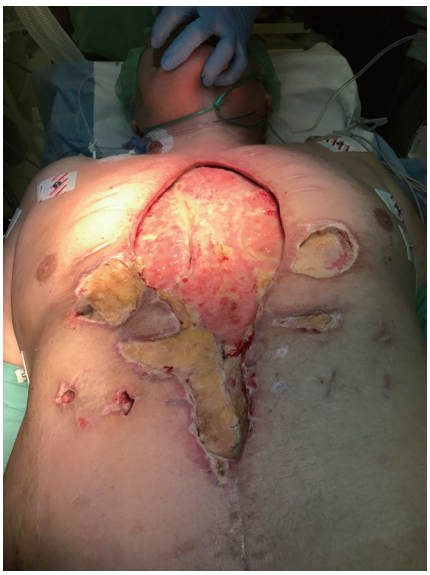

Figure 1 Complicated deep sternal wound infection.

the above RCT in doubt. Secondly, authors claimed to "have performed a single center study yet had limited data on details about administration of systemic perioperative antibiotics". The above information is crucial and failure to understand the synergy between iv. and topical prophylaxis is to be condemned. Further, no mention is made as to the mortality and morbidity in these groups of patients, the need for sternal reconstruction, hospital length of stay, readmissions, and whether these outcomes differed amongst the groups. Thirdly, surgical technique is described superficially: authors provide no details on the use of bone wax to the cut edges of the sternum for hemostasis. This is now as class III recommendation since bone wax retards sternal healing and promotes infections. Additionally, internal thoracic arteries (ITAs) were harvested as pedicle in all patients and bilateral ITAs were used at the discretion of the individual surgeon. While benefit of total arterial revascularization is not to be questioned, the use of bilateral ITA harvested as pedicle poses a serious threat to sternal wound healing regardless of topical agents employed. Indeed, total depravation of sternal vasculature has long been showed to cause sternal dehiscence independently of diabetic status, body mass index, and other known SWI predictors (3,6). Again, failure to report the percentage of bilateral ITAs, and incidence of SWIs across patients in whom bilateral ITAs were used is unacceptable in a RCT. The authors talk about "cost effective" data but this data is not listed anywhere; no mention is made as to how this data was derived. Furthermore, we are not told whether the additional costs for the extended hospitalization for patients with a SWI were also included in the analysis which would have favored the vancomycin group. The incidence of SWI in the control group (4.3%) is high and unacceptable. With the adoption of the Society of Thoracic Surgeons guidelines for glycaemic control and the AATS guidelines for the prevention of SWIs, which includes the use of topical antibiotics as a Class I recommendation, the incidence of SWI in the current STS database in now 0.5% for CABG surgery (4). The authors themselves admit that they were not compliant with the guidelines throughout this study, hence patients in this study were subjected to practices which actually promoted SWI what limits any conclusions that can be made. Last and by all means most important, administration of vancomycin was controversial, to say at least—pouring saline solution of drug over the wound makes it impossible to estimate what is the effective concentration of vancomycin that reaches wound tissue. In fact, delivery of vancomycin as a solution and not as a paste is not indicative of the value of "topical vancomycin" which is indicated to be used as a paste/slurry and not a solution. As described elsewhere, the principle behind the use of topical antibiotics is keeping the antibiotic concentration locally as high as possible beyond the serum concentration levels achievable with iv. administration (3,7). SWIPE-1 trial questioned for the first time the long-established efficacy of gentamicin sponge implantation for SWI prophylaxis showing no differences between implantable gentamycin sponge and control groups for the outcomes of superficial and deep SWIs and rehospitalization for wound infection at 90-day follow-up (8). SWIs were present in 63 of 753 patients randomized to the gentamicin-collagen sponge group (8.4%) compared with 65 of 749 in the control group (8.7%). It was later argued by Friberg *et al.* (9) these negative findings resulted from a failure to follow manufacturer-advised sponge implantation protocol. Indeed, gentamicin sponge was exposed to saline solution for much longer than advised 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 (10) 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 min, therefore the active drug was washed out of the implant. Collagen sponge without gentamicin was further speculated to act as a culture medium and supported by the highest benefit of

gentamycin- as compared with placebo sponge in the study by Schimmer and colleagues (11) with nearly 4% DSWIs incidence rates in the placebo arm.

Another largest study to date, performed by Lander *et al.* demonstrated that vancomycin paste did not reduce the incidence of DSWI after CABG surgery (12). Again as described elsewhere in detail (2,13) the study had couple of methodological flaws: of which most important were non-reporting of SSWIs; exclusion of patients with infective endocarditis and receiving heart transplant, given their likelihood to gain most benefit from vancomycin paste and, most importantly, the fact that the use of vancomycin paste over 12 years period of the study peaked from 25% (from the 2003 to 2010 time period) of patients in the first 7 years to 53% of patients (from the 2010 to 2014 time period) while rate of DSWI dropped from 1.29% to 0.29%, which shows that with more frequent vancomycin use the incidence of SWI decreased significantly (13), and apparently factors other than vancomycin must have been responsible for the neutral results of the study.

The aforementioned examples show that extra caution must be used while interpreting studies concerning use of topical antibiotics since easily overlooked details may often be a source of bias when it comes to interpretation of the results. The statement made by the authors of AATS consensus (4) was backed by results of studies with gentamicin based sponges showing substantial benefit (14). Similarly, vancomycin paste has been proved to be of advocacy in prophylaxis of SWI among others by Vander Salm *et al.* (15) who found significantly reduced incidence of SWIs from 3.6% to 0.5% with vancomycin and Lazar *et al.* who in a retrospective, nonrandomized, single-centre study involving over 3,000 patients demonstrated that the use of topical vancomycin applied to both edges of the sternum along with systemic perioperative antibiotics and strict glycaemic control resulted in complete reduction of both superficial and deep SWI (16).

To conclude, the use of topical antibiotics by no means exhausts the subject of perioperative prophylaxis in the context of CABG. The main role of intravenous prophylaxis and strict intraoperative glycaemic control is unopposed, however, so far, reasonably designed studies have shown that topical use of antibiotics comprises an important addition to perioperative antibiotic regimen.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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