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Technology Assessment Unit of
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Efficacy and cost-effectiveness of Collatamp-G for infection prophylaxis in cardiac surgery

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Report prepared for the Technology Assessment Unit (TAU)

of the McGill University Health Centre (MUHC)

by

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Invitation.

This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.

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Abbreviations and Acronyms

AETMIS	L'Agence d'évaluation des technologies et des modes d'intervention en santé
BMI	Body mass index
CABG	Coronary artery bypass grafting
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	US Centers for Disease Control and Prevention
CG	Control group
CoNS	Coagulase-negative staphylococci
CRD	Centre for Reviews and Dissemination
GCS	Gentamicin-loaded collagen sponge
IG	Intervention group
INAHTA	International Network of Agencies for Health Technology Assessment
LOS	Length of stay
MIC	Minimum inhibition concentration
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
RCT	Randomized controlled trials
SSI	Surgical site infection
SWI	Sternal wound infection

Messages

- There is evidence suggesting that a gentamicin-collagen sponge may reduce the risk of sternal wound infection and that it may sufficiently lower hospital costs to offset the costs of its use, when applied to high-risk patients
- However, the evidence is not strong enough to constitute the basis for the redevelopment of permanent policy
- The Department of cardiac surgery should be encouraged to conduct research to identify the risk factors predictive of SWI at the MUHC and to determine the effectiveness of GCS in lowering the incidence of SWI through an RCT.
- Every support should be given to the Department to find the necessary funding for these projects.

Sommaire

Contexte :

Les infections sternales (IF) sont associées à une morbidité importante ainsi qu'à une augmentation des coûts de santé. Certains rapports ont mentionné que les risques d'infections sternales peuvent être réduits par l'insertion dans la plaie d'éponges de collagène imbibées de Gentamicin (ECG) au moment de la chirurgie.

Objectif :

Les objectifs de ce rapport d'évaluation sont : i) de faire une revue systématique de la littérature en regard de l'efficacité des ECG comme moyen de prévention des infections suite à une chirurgie cardiaque, ii) de faire une revue systématique la littérature en regard des facteurs de risques pour les infections sternales suite à une chirurgie cardiaque, iii) d'estimer la fréquence des infections sternales suite à une chirurgie cardiaque au CUSM ainsi que l'influence des facteurs de risques putatifs, et iv) de déterminer le coût-efficacité et l'impact budgétaire des ECG dans le contexte du CUSM.

Méthodologie :

Une revue systématique de la littérature fut faite à partir de bases de données en ligne et de sites Internet dédiés à l'évaluation des technologies. La qualité des études identifiées fut évaluée à l'aide de grilles standards. Enfin, une méta-analyse fut utilisée pour combiner les taux de risques mentionnés dans les études retenues.

Résultats :

Deux études randomisées ainsi que deux études de cas sur l'efficacité des ECG furent identifiées. Enfin, trois études furent aussi identifiées sur les facteurs de risque en regard des infections sternales.

Efficacité :

Toutes les études ont rapporté une réduction des risques d'infections sternales suite à l'utilisation des ECG avec une diminution moyenne absolue variant entre 1,15% et 5,30%. Cependant, une seule étude randomisée était de grande qualité et soulignait que l'effet bénéfique de cette technologie était essentiellement lié à la prévention des infections superficielles. Enfin, deux études ont mentionné des cas de chirurgies additionnelles dues à des saignements ou à une instabilité sternale suite à l'utilisation des ECG.

Facteurs de risques :

Les facteurs de risques pour les infections sternales profondes comprennent l'obésité, le diabète sucré, les maladies pulmonaires obstructives chroniques (MPOC) et la cigarette. Ces facteurs semblent responsables d'un risque deux fois plus grand d'une infection sternale. Au CUSM, le risque d'une infection sternale se traduisant par une réadmission était de 4,5% (1,2% pour les infections sternales superficielles, 1,4% pour les infections sternales profondes et 1,9% pour les infections du médiastin). Les patients diabétiques montraient le niveau de risque le plus élevé. Enfin, environ 19% des patients ayant subi une chirurgie cardiaque au CUSM étaient diabétiques, une condition associée à un risque 7 fois plus élevé pour développer une infection sternale.

Impact budgétaire :

Le coût brut pour utiliser les ECG chez les 928 patients cardiaques serait de 716 470 $ par année. Par contre, si les bénéfices escomptés sur la santé étaient aussi importants qu'on l'estime, l'impact budgétaire net serait environ que de 225 460 $ par année. De même, le coût brut pour l'utilisation des ECG chez les patients à haut risque, seulement, seraient de 506 954 $ par année et dans le contexte de l'hypothèse précédente, l'impact budgétaire net serait de 15 944 $ par année.

Coût-efficacité :

En prenant en considération les bénéfices escomptés sur la santé découlant de l'utilisation des ECG, le rapport coût-efficacité serait de 15 031 $ par infection sternale évitée si on l'utilisait

chez tous les patients, et de 2 657 $ pour une utilisation chez les patients à haut risque, seulement.

Conclusion :

Les évidences disponibles nous suggèrent que les ECG pourraient réduire l'incidence des infections sternales et plus particulièrement, les infections sternales superficielles. Les évaluations préliminaires nous indiquent que si les ECG étaient utilisées chez tous les patients cardiaques au CUSM, les coûts brut et net seraient respectivement de 716 470 $ et 225 460 $ par année. Cependant, ces évidences ne sont pas suffisantes pour supporter une politique d'utilisation sur une base permanente.

Recommandations :

- Quoique prometteur, les évidences des bénéfices attendus de l'usage des ECG ne supportent pas leur utilisation sur une base continue.
- Cependant, l'indice de bénéfices éventuels et la possibilité qu'ils puissent réduire les coûts d'opération de façon à compenser pleinement les coûts d'utilisation des ECG nous suggèrent fortement de mettre l'accent sur l'obtention de nouvelles évidences.
- Le département de chirurgie cardiaque devrait être encouragé à mettre en place un programme de recherche visant deux objectifs : 1) déterminer les facteurs de risque précurseurs à une infection sternale au CUSM ainsi que leur fréquence, et 2) déterminer l'efficacité clinique des ECG à réduire les incidences des infections sternales à partir d'une étude randomisée.
- Le département de chirurgie devrait recevoir le support nécessaire pour trouver les fonds lui permettant de réaliser ces projets.

Executive Summary

Background:

Sternal wound infections (SWI) are associated with serious morbidity and increased healthcare costs. There have been reports that the risk of SWI can be reduced by insertion of a Gentamicin-loaded collagen sponge (GCS) in the wound at the time of surgery.

Objective:

The aims of this technology assessment report are: i) to systematically review the literature on the efficacy of GCS in preventing infections following cardiac surgery, ii) to review the literature on risk factors for SWI after cardiac surgery, iii) to estimate the frequency of SWI following cardiac surgery at the MUHC and to estimate the influence of putative risk factors and iv) to determine cost-effectiveness and budget impact of GCS in the MUHC setting.

Methods:

A systematic literature search was performed using major online databases of the medical literature and health technology assessment (HTA) reports. Study quality was assessed using standard scales. Meta-analysis was used to combine risk ratios across studies.

Results:

Literature Review: Two randomized controlled trials and two cohort studies of the efficacy of GCS were identified, together with four studies on risk factors for SWI

Efficacy and safety of GCS: All studies reported a reduction in risk of SWI following use of GCS, with an average reduction in absolute risk ranging from 1.15% to 5.30%. Based on a meta-analysis, use of GCS was associated with a lower risk of all types of SWI (Superficial SWI: Relative Risk (RR)=0.44, Deep SWI: RR=0.62, Mediastinitis: RR=0.79), though only the association with superficial wounds was statistically significant. Only 1 RCT was of a high quality and it found that the beneficial effect was primarily for preventing superficial wound infections.

It also found that early reoperation due to bleeding was more common in the GCS group (4.0% vs. 2.3%, p=0.03). No other side effect or complication was reported regarding GCS use.

Risk factors for SWI: Risk factors for deep SWI include obesity, diabetes mellitus, COPD, and smoking. All appear to increase SWI risk more than two fold.

Sternal Wound Infections at the MUHC: During 2008-2009 there were 42 sternal wound infections in 935 cardiac procedures [4.5% (Superficial SWI 1.2%, deep SWI 1.4% and mediastinitis 1.9%)]. Four of these patients died (9.5%). Diabetes patients were at the greatest risk of SWI. Approximately 19% of cardiac surgery patients at the MUHC had diabetes, which was associated with a 7-fold increase in risk of SWI. Routine use of GCS for all cases might reduce SWI from 42 to 27 cases per year. Restriction of GCS to high risk cases might reduce SWI from 42 to 36 cases per year.

Budget impact The *gross* cost of using GCS for all 928 cardiac patients would be $716,470. If the health benefit was as substantial as assumed, the estimated *net* budget impact would be approximately $225,460. The *gross* cost of using GCS in high-risk cases only would be $506,954 and, with the same assumptions, the *net* budget impact approximately $15,944.

Cost-effectiveness With the same assumptions concerning health benefits, use of GCS for all patients would result in a cost-effectiveness (C/E) ratio of, $15,031 per SWI prevented, and use of GCS for high-risk patients only, a C/E ratio of $2,657.33 per SWI prevented.

Conclusions:

The available evidence suggests that GCS may well reduce the incidence of SWI, particularly of superficial infections. Initial estimates indicate that GCS might be used for all cardiac patients at the MUHC at a gross cost of $716,470 and if the health benefits are fully realised, a net cost of approximately $225,460 per annum. However, the available evidence is not sufficiently substantial for the development of a permanent ongoing policy.

Recommendations:

- Though promising, evidence of the benefit of GCS is insufficiently strong to justify a recommendation that it should be used on a permanent ongoing basis.

- However, the evidence of possible benefit and the likelihood that it may lower hospital costs enough to largely offset the costs of its use strongly suggests that an effort to procure better evidence would be justified.
- The Department of cardiac surgery should be encouraged to conduct research with two objectives: 1) To determine the risk factors predictive of SWI at the MUHC and their frequency, and 2) To determine the effectiveness of GCS in lowering the incidence of SWI through an RCT.
- Every support should be given to the Department to find the necessary funding for these projects.

Introduction

Sternal wound infection:

Despite diligent efforts, post-operative infectious complications in cardiac surgery have not been completely eradicated. Deep sternal wound infections (SWI), including mediastinitis, are a particularly serious concern as they are associated with life-threatening complications causing tremendous physical and emotional burden, and prolonging patients' length of hospital stay.[2]

The estimated incidence of deep SWI is 0.2-2.3%.[2] A recent review[2] indicated that the average number of days of hospitalization for cardiac surgical patients without infectious complications ranged from 6-14 days, whereas hospitalization could extend to 26-40 days on average for patients who develop a sternal wound infection.[1] Serious, persistent SWI could eventually lead to death.

Sternal wound infection can be of three types: i) superficial: involving only the skin and subcutaneous tissues, ii) deep: involving deep soft tissues (e.g. fascial or muscle layers) frequently associated with osteomyelitis and sternal instability., iii) mediastinitis: with evidence of deep mediastinal infection.[1] Detailed classification criteria for cardiac surgery wound infections are given in Appendix 1.

Gentamicin-loaded collagen sponge (GCS):

Routinely, antibiotic prophylaxis for cardiac surgery is delivered intravenously or by mouth.[3] However, due to the persistent risk of SWI and the growing risk of multiresistant organisms, additional or alternative options of antibiotic prophylaxis are increasingly being considered.[4]

The use of a gentamicin-loaded collagen sponge (GCS) for prevention and treatment of surgical site infection dates back to the 1980's.[5;6] As an add-on prophylactic agent to prevent SWI, a piece of GCS can be cut to the desired shape or length and placed behind or between the sternal halves before the surgeon closes up the wound. When applied locally and directly to the wound, the concentration of gentamicin in the sternal fluid is relatively high at 300mg/L compared to the serum level of 2mg/L at 36 hours post-operatively.[1;3] The high gentamicin concentration in wound exudates is maintained for 2-3 days at a level that exceeds the minimum inhibition concentration (MIC) for most microbial organisms without the danger of

systemic toxicity.[3] The collagen portion of the sponge is reabsorbed by the body completely within one to seven weeks.[7]

In cardiac surgery, GCS has been shown to be effective as an *adjuvant treatment* for sternal wound infections[3] and graft wound infections[8] including Szilagyi type 3 prosthetic infections.[9] However, these positive conclusions were only based on results of small sample size case series and cohort studies.[3;8;9]

Objectives

i. To determine the efficacy of GCS with respect to infection and mortality risk in cardiac surgery, when used in addition to routine intravenous antibiotic prophylaxis.
ii. To identify the risk factors for post-operative infection in cardiac surgery in order to define sub-groups of patients most likely to benefit from the use of GCS.
iii. To determine the risk of SWI at the MUHC and the risk of SWI associated with standard risk factors in the sample from the MUHC.
iv. To determine the cost, cost-effectiveness and budget impact of GCS.

Methods

Systematic Review:

A systematic literature search was performed using the Ovid MEDLINE and EMBASE databases. Six major online publishers (INAHTA, NICE, AETMIS, Cochrane, CADTH, and CRD) of health technology assessment (HTA) reports were also searched for existing reports. Keywords used in the search were: “gentamicin”, “collagen sponge”, “mediastinitis”, “risk factor OR risk group OR high risk”, and “sternal wound infection.” Additionally, searches of citations on SWI risk factors were limited to recent review articles published since 2000. Furthermore, in order to identify articles on SWI risk in the MUHC, “McGill University” was added as a search keyword.

The search covered all articles and reports published in all languages up to November, 2009. Clinical research studies using either an RCT or observational design were included. Data on number of patients, antibiotic dose, number of pieces of GCS, length of follow-up, were abstracted from the selected citations. Study quality was assessed using the Jadad scale[10] for

randomized controlled trials (RCTs) or the Newcastle-Ottawa Scale[10] for case-control and cohort studies.

Random effects meta-analysis was used to pool risk ratios across the 2 RCTs.[11] We chose not to include the observational studies in the meta-analysis due to possible biases associated with their study designs.

Data collection at the MUHC:

In order to estimate the risk of SWI at the MUHC and the associated increase in length of stay, we extracted information from charts maintained by Christine Page of the Cardiac Surgery department. Admission and discharge dates from ICU and cardiac surgery ward, were extracted for all patients who developed SWI at the first admission or were readmitted with an SWI, and an equal number of randomly selected control patients who did not develop SWI, during the 2008-2009 fiscal year in the MUHC. Controls were operated within 1 week of the cases. We also extracted information on whether the patient had one of four risk factors for SWI: diabetes, obesity, chronic obstructive pulmonary disease (COPD), smoking. This study design is referred to as a nested case-control design. It allows us to obtain unbiased estimates of the prevalence of risk factors as well, as the risk ratio for SWI associated with each risk factor. This analysis should be regarded as descriptive as we made no attempt to ensure that the sample size was sufficiently large to obtain a high precision.

Results of Systematic Review

A flowchart summarizing the systematic search of current literature can be found in Figure 1. No previous HTA report regarding the efficacy and cost-effectiveness of GCS had been published at the time of this report.

The literature search returned 102 citations, out of which two citations of original RCTs were relevant and retained.[1;12] Both RCTs were carried out in Europe and were funded by the manufacturer of Collatamp-G, Schering-Plough Inc. In addition, two non-randomized studies[13;14] using historical 'non-exposed' groups were also retained. Both studies compared a historical cohort of patients in whom GCS was not used, to a prospectively followed cohort of patients for

whom GCS was routinely used in addition to the standard intravenous antibiotic prophylaxis at their institutions.[13;14]

Further, six more peer-reviewed citations[4;7;13;15-18] published by the authors of the two RCTs provided additional data from these studies and were retained for completeness of discussion. Four studies that addressed the objective of establishing the criteria for high-risk patients were identified.[19-21] Two studies reporting on risk factors for sternal wound infection at the MUHC were identified.

Patient characteristics in included studies

Characteristics of the included studies are summarized in Table 1. Together, the two RCTs[1;12] reported data on 1,237 control and 1,255 GCS intervention group patients. In both RCTs, the average age of patients was around 65 years old, and the proportion of female patients was less than 30%. Patients enrolled in the RCTs underwent a cardiac procedure that involved median sternotomy, and were not allergic to gentamicin. Pregnant or breastfeeding women were excluded from both trials.

The observational studies were both hospital-based cohort studies.[13;14] In both cases, the hospital had adopted the use of GCS recently as a mandatory measure to prevent surgical infection following cardiac surgery, thereby forming the 'exposed' group. The 'non-exposed' groups were historic cohorts observed at the same institutions prior to routine use of GCS. Together, the two cohort studies reported data on 1,902 'non-exposed' patients and 2,450 patients who received GCS. The average age was 68 years, and less than 30% of patients were female. All patients who underwent cardiac surgery via median sternotomy were included, except for pregnant women and breastfeeding mothers.

Impact of GCS on post-operative infection risk and risk ratio

Both RCTs reported lower overall infection risks in the GCS group, as well as at all depths of infection (superficial, deep and mediastinitis). Incidence of infections was recorded up to two[1] or three months[12] after surgery (Table 2). The differences reported by Eklund et al.[12] were not statistically significant (overall SWI risk Controls=5.9% vs. GCS=4.0%, p=0.20). This was due to the low risk of SWI in the control group, as well as the smaller sample size. Friberg et al.[1]

reported an overall 50% lower infection risk in the GCS group (Controls=9.0% vs. GCS=4.3%, p<0.001). The high SWI risk of 9.0% in the control group was in fact higher than the 4% risk expected at the time of planning the RCT. From personal correspondence with the first author we know that the higher SWI risk was due to the follow-up being extended beyond the end of the first admission. In this control group, the risk of SWI prior to discharge was only 17/967 (1.7%). This RCT also found that the magnitude of benefit was statistically significant for superficial infections (Controls=5.7% vs. GCS=1.9%, p<0.001), though not for deep infections or for mediastinitis.[1] The pooled risk ratios (RR) (GCS vs. Control) for different types of SWI based on the RCTs are given in Table 3. The pooled RR suggested benefit for all types of SWI, but was statistically significant only for superficial SWI.

One cohort study[14] reported a reduction in mediastinitis incidence close to 60% (from 1.9% to 0.75%, p=0.017). The other cohort study[13] also reported a significant decrease in SWI risk, both superficial and deep. It should be noted that this study used the RCT control group mentioned above that had a relatively high SWI risk of 9.0%.[1] These results must be interpreted with caution. The control cohort may have been treated at an earlier date, when post-operative infections were more frequent.

Table 4 summarizes the distribution and types of microbial cultures found in the wound infections.

Effectiveness in high risk patients:

In subgroups of patients who were diabetic, or whose BMI was greater than 25, the RCT by Friberg et al.[1] found that the magnitude of the beneficial impact of GCS was greater and statistically significant at all depths of infection (2.01% vs. 6.7% for superficial SWI (p<0.001), and 2.44% vs. 4.37% for deep SWI (p<0.047)).

Impact on length of hospital stay, cost and mortality

The two RCTs[1;12] at first concluded that there was no significant difference in the post-operative days of hospital stay or days spent in the intensive care unit (Table 2).[1;12] However, a later publication by Friberg et al.[22] concluded that there was a significantly lower cost of treatment of the GCS group due to reduced hospital related costs. Using data from their RCT[1] they

estimated the average cost of a deep SWI to be roughly €14,500 (median €3,790, range €257-€161,269). This included costs incurred from surgical revision, CT-scan, days in the ICU and in the ward, and outpatient visits. They showed that the use of GCS lowered costs of care, especially in high-risk patients who were diabetic or had BMI>25.[1] From our personal communication with the first author we know that the number SWI related hospitalization days in the GCS group were substantially lower (661 in the GCS group vs. 1020 days in the control group). There was no significant difference in mortality risk.[1;12;13]

Complications

One RCT reported that early reoperation due to bleeding was more common in the GCS group (4.0% vs. 2.3%, p=0.03)[1] No other side effect or complication was reported regarding GCS use.

Risk factors for SWI

Four studies of risk factors for SWI in cardiac surgery were identified (Table 5). Cardiac patients who were also diabetic were 2.4 times more likely to develop an infection (95% CI=1.6-3.4).[20] Obesity,[13;19;20] smoking,[19;20] chronic obstructive pulmonary disease (COPD),[13] and hypertension,[21] were other significant risk factors of SWI.

The use of internal mammary artery graft (single or double) also increases the risk of SWI.[13] On the other hand, the use of seven or more sternal fixation wires [to promote sternal stability] significantly reduced deep SWI (p=0.002) including mediastitnitis (p=0.0006) but not superficial SWI (p=0.58).[23]

In summary, in these four studies, three risk factors are identified by at least two authors: diabetes (RR = 2.4, 2.1), obesity (RR = 6.49, 1.6), and smoking (RR = 3.27, 2.7). For purposes of risk prediction we will conservatively assume that presence of any of these factors, will double the risk of SWI.

Sternal Wound Infection at the MUHC

During the 2008-2009 fiscal year, 935 cardiac procedures (involving 928 patients) were done through median sternotomy at the MUHC. The total number of sternal wound infections identified at the first admission or resulting in a readmission was 42 (or approximately 4.5%) (Table 6). Specifically, 1.9% suffered mediastinitis, 1.2% suffered deep SWI and 1.4% suffered superficial SWI. Four patients who suffered SWI (1 deep, 3 superficial) died. All four patients were terminally ill and likely to have died due to complications other than the SWI. Thus, the estimated mortality rate among patients with SWI was 9.5%.

The relationship between infection and length of stay is explored in Table 7. There appears to be a progressive increase in both intensive care unit (ICU) and surgical ward use with increasing levels of SWI. Patients with deep wound infection or mediastinitis experience on average three more days in the ICU and 23 more days in the surgical ward, than patients who have no SWI.

Risk factors for SWI at the MUHC

Table 8 summarizes the information on the risk factor distribution among patients with and without SWI in our sample of 42 SWI patients and 42 controls. The only risk factor with a significant association with SWI was diabetes, which was associated with a 7 fold increase in risk. The prevalence of diabetes was estimated at 19% in all patients. This was supported by a previous study carried out at the MUHC.[24]

In addition, a case-control study published in 2003 by Dr. Sandra Dial identified autotransfusion of more than 6 hours as a major risk factor of mediastinitis even after adjustment for obesity and frequency of re-exploration.[25] Obesity defined by BMI≥30 ($p=0.002$) and greater number of preoperative antibiotics used ($p=0.02$) were two other confirmed risk factors in their sample but not diabetes. On average, patients who had mediastinitis presented 2 more risk factors than control patients. (In Dial et al's study, 4 out of the 11 mediastinitis patients died, whereas there was no mortality in the control group).

Cost, Budget impact and Cost-effectiveness

Assumptions.

- Two pieces of GCS, at a unit cost of CAD$200.00, will be used for each patient. Total unit cost of GCS: CAD$400.00 per patient. (Theramed Canada)
- Annual volume of cardiac surgery at the MUHC: 928 patients (2008-2009 MUHC data)
- Patients at high risk for SWI: 20% or 186 patients annually. (Dr. de Varennes)
- Cost of stay in the ICU: $1,217.97/day (Nicolas Robert)
- Cost of stay in the surgical ward: $417.47/day (Nicolas Robert)
- Overall risk of SWI at MUHC is: Superficial 1.4%, Deep 1.2%, Mediastinitis (no reoperation) 0.5%, Mediastinitis (reoperation) 1.4% (Table 6).
- Risk of SWI in high risk patients is double the overall risk of SWI
- Decrease in risk of SWI with use of GCS is: superficial SWI=0.44, deep SWI=0.62, mediastinitis 0.79. Based on meta-analysis (Table 3)
- Length of hospital stay given by estimates in Table 7.

Costs of hospitalization following cardiac surgery

Costs of SWI.

The additional cost per patient resulting from a SWI is estimated to be: Superficial $4,175, Deep $12,490, Mediastinitis (no reoperation) $12,038, Mediastinitis (reoperation) $18,614.

Budget impact. (Table 9)

The estimated costs resulting from SWI in a cohort of 928 patients = $491,010

The *net* budget impact of use of GCS in all patients = $225,460

The net budget impact of restricting use of GCS to high risk patients = $15,944

Cost Effectiveness. (Table 9)

- Use of GCS for all patients could be expected to prevent 15 cases of SWI at a net cost of $225,460 or $15,031 per SWI prevented.
- Use of GCS for high-risk patients only would be expected to prevent 6 cases of SWI at a net cost of $15,944 or $2,657 per SWI prevented

Conclusion

The available evidence suggests that the use of GCS will probably reduce the incidence of SWI, including mediastinitis, across all patients. However, the evidence from the largest randomized controlled trial at present[1] suggests that benefit is greatest among patients with superficial SWI. Thus, the beneficial impact of GCS depends on the baseline risk of SWI, and the proportion of this risk due to superficial SWI.

From the available data at the MUHC, the risk of SWI is lower than the figure reported in Friberg et al.[1] (4.5% at the MUHC compared to 9% in the Friberg et al.'s control group) and only a minority of patients have a superficial SWI (31% at the MUHC compared to 63% in the study by Friberg et al.). These factors influence the results of our cost analysis and explain in part why we found there was a net cost of using GCS unlike in the cost-effectiveness analysis by Friberg et al.[22] Our cost-analysis suggests that the MUHC may benefit from a lower net cost when GCS is applied only to patients at high risk of a sternal wound infection, such as patients with diabetes.

It must be stressed that our estimates are mostly based on tenuous evidence. Thus, the risk factors for SWI are poorly defined and sometimes conflicting; the estimate that 20% of patients at the MUHC are at increased risk for SWI is based on an *ad hoc* judgement of one individual, the head of cardiac surgery. The estimate that high risk individuals are on average at twice the risk of SWI is uncertain and is probably an underestimate.

***For these reasons these estimates should be used to indicate possible outcomes but they are insufficiently precise to define ongoing policy*.** It therefore remains to be seen whether these outcomes will be realized at the MUHC. To arrive at more certain conclusions would require: a retrospective chart review to systematically document the risk of SWI, the prevalence of risk factors of SWI, the percentage of high risk patients and the risk profile of these patients at the MUHC. In addition, final decisions involving the commitment of considerable sums of money over the years requires better evidence of the benefit of GCS than is available in the two RCTs[1;12] and two cohort studies so far identified.[13;14]

It should also be noted that we only considered the additional cost of hospitalization due to SWI in our analyses. Accounting for other costs such as antibiotic use and re-operation

costs would further lower the estimated net budget impact of this technology. Similarly, if the risk of SWI in the high risk group of patients turned out to be greater than twice the average risk, this too, would lower the estimated net budget impact.

Recommendations

- The committee concludes that the evidence of benefit of GCS is insufficiently strong to justify a recommendation that it should be used, either for all cases or for high-risk cases on a permanent ongoing basis.
- However, the evidence of its possible benefit and the likelihood that it may sufficiently lower hospital costs to offset the costs of its use, strongly suggests that an effort to procure better evidence would be justified.
- The Department of cardiac surgery should be encouraged to conduct research with two objectives: 1) to determine the risk factors predictive of SWI at the MUHC and their frequency; 2) to determine the effectiveness of GCS in lowering the incidence of SWI through an RCT. Every support should be given to the Department to find the necessary funding for these projects.

Table 1: Summary of characteristics of included studies

First author, Year; Country(s); [Jadad score]	Study design; Follow-up period	Target population	Control Group n=; Age, mean/median (range, SD); % Female; Treatment	Intervention Group n=; Age, mean/median (range, SD); % Female; Treatment	Funding source
Friberg, 2005;[1] Sweden; [5, Adequate]	Multi-centre, double-blinded, randomized clinical trial; 2 months	All patients undergoing cardiac surgery through median sternotomy with no known allergy to gentamicin, were not pregnant or breastfeeding	n=967; Age 68(20-87); Female 24.0% Routine IV prophylaxis: 2g cloxacillin or 1g dicloxallin once or twice during surgery, continued every 8 hours for 24-48 hours post-operatively	n=983; Age 68(25-87); Female 23.4% Routine IV prophylaxis & *2* 10x10x0.5cm collagen sponges each contained 130mg gentamicin placed *between sternal halves*	Research Committee of Örebro County Council (provided funding); Schering-Plough Corporation (provided funding and free Collatamp-G)
Eklund, 2005;[12] Finland; [2, Adequate]	Single-centre, double-blinded, randomized controlled trial; 3 months	All patients underwent elective CABG surgery through a median sternotomy	n=270; Age 64.7(9.3); Female 29.0% Routine IV prophylaxis: 2 doses of 1.5g cefuroxime in 6 hours; patients stayed >3 days in the hospital prior to surgery also received 500mg vancomycin on 2 occasions	n=272; Age 64.4(9.3); Female 24.0% Routine IV prophylaxis & *1* 10x10x0.5cm collagen sponge containing 130mg gentamicin placed *behind sternum*	Helsinki University Central Hospital; Schering-Plough Corporation
Schersten, 2007;[14] Sweden; [7]*	Prospective cohort with historic controls; NR	All patients accepted for cardiac surgery; CG recruited in 2005, IG recruited in 2006	n=935; Age NR; % Female NR; Routine IV prophylaxis: isoxazolyn-penicillin, 2g x 4 during first 24 post-operative hours	n=1091; Age NR; % Female NR; Routine IV prophylaxis & *1* 10x10x0.5cm collagen sponge containing 130mg gentamicin placed *between sternal halves*	(Internal funding; hospital protocol revision)
Friberg, 2009;[13] Sweden; [7]*	Propsective cohort with historic controls; 2 months	All cardiac surgery patients operated through median sternotomy excluding pregnant and breastfeeding women	n=967; Age 68(20-87); Female 24.0% Routine IV prophylaxis: 2g cloxacillin or 1g dicloxallin once or twice during surgery, continued every 8 hours for 24-48 hours post-operatively	n=1359; Age 68(19-85); Female 27.0% Routine IV prophylaxis & *2* 5x20x0.5cm collagen sponges each contained 130mg gentamicin placed *between sterna wounds*	N/A

*Study quality assessed by the Newcastle-Ottawa Quality Assessment Scale; total score=9.

Abbreviations: n=Sample size; SD=Standard deviation; IV=Intravenous; CABG=Coronary artery bypass grafting; CG=Control group; IG=Intervention group; NR=Not reported, N/A=Not applicable.

Table 2: Summary of clinical outcomes reported in included studies

First author, Year; Country(s); Total n=; Follow-up period	Sternal wound infection		Length of hospital stay, days (SD)		Mortality n= (%)	
	Control	Intervention	Control	Intervention	Control	Intervention
Friberg, 2005;[1] Sweden; n CG=967, IG=983; 2 months	All n=87 (9.0%) *Superficial SWI n=55 (5.68%)* *Deep SWI n=17 (1.75%)* *Mediastinitis n=15 (1.55%)*	All n=42 (4.3%) *Superficial n=19 (1.93%)* *Deep SWI n=10 (1.01%)* *Mediastinitis n=13 (1.32%)*	7.1;* Median=6	6.7;* Median=6	n=17 (1.8%)	n=19 (1.9%)
Eklund, 2005;[12] Finland; n CG=270, IG=272; 3 months	All n=16 (5.9%) *Superficial SWI n=8 (2.96%)* *Deep SWI n=2 (0.74%)* *Sternum osteitis n=1 (0.37%)* *Mediastinitis n=5 (1.85%)*	All n=11 (4.0%) *Superficial SWI n=6 (2.21%)* *Deep SWI n=2 (0.74%)* *Mediastinitis n=3 (1.10%)*	ICU: 1.7 (1.7)	ICU: 1.8 (1.8)	n=1 (0.4%)	n=3 (1.1%)
Schersten, 2007;[14] Sweden; n CG=935, IG=1091; NR	Mediastinitis n=18 (1.9%)	Mediastinitis n=8 (0.75%)	NR	NR	NR	NR
Friberg, 2009;[13] Sweden; n CG=967, IG=1359; 2 months	All n=87 (9.0%) *Superficial SWI n=55 (5.68%)* *Deep SWI n=17 (1.75%)* *Mediastinitis n=15 (1.55%)*	All n=50 (3.7%) *Superficial n=30 (2.20%)* *Deep SWI n=6 (0.44%)* *Mediastinitis n=14 (1.03%)*	NR	NR	n=17 (1.8%)	n=24 (1.8%)

*Total LOS (days): Control=1020, GCS=661. (Personal communication with author)

Abbreviations: n=Sample size; SD=Standard deviation; CG=Control group; IG=Intervention group; SWI=Sternal wound infection; ICU-Intensive care unit; NR=Not reported.

Table 3: The risk ratio associated with GCS compared to controls (Meta-analysis of Friberg et al. & Eklund et al.)

Outcome	**Overall risk ratio from meta-analysis* [95% Confidence Interval]**
Mediastinitis	0.79 [0.41; 1.52]
Deep SWI	0.62 [0.30; 1.28]
Superficial SWI	0.44 [0.21; 0.90]
Any SWI	0.51 [0.37; 0.70]

* Risk ratio less than 1 indicates lower risk of outcome in the intervention (GCS) group than in the control group.

Table 4: Type of pathogens cultured in confirmed cases of sternal wound infection

First author, Year; Country(s); Follow-up period	Pathogens cultured	
	Control group	**Intervention group**
Friberg, 2005;[1] Sweden; 2 months	*CoNS* n=35 *S. aureus* n=21 *Gram-negative* n=4 *P. acnes* n=6 Multiple agents n=6 Negative or missing n=15	*CoNS* n=11 *S. aureus* n=8 *Gram-negative* n=1 *P. acnes* n=7 Multiple agents n=2 Negative or missing n=11
Eklund, 2005;[12] Finland; 3 months	*S. epidermidis* n=6 *S. aureus* n=1 Negative n=4	*S. epidermidis* n=6 *S. aureus* n=2 *Multiple agents* n=2 Negative n=6
Schersten, 2007;[14] Sweden; NR	*CoNS* 33% *S. aureus* 50% *Entercocci* 7% *P. acnes* 10%	*CoNS* 25% *S. aureus* 50% *Enterococci* 12.5% *Acinetobacter sp.* 12.5%
Friberg, 2009;[1] Sweden; 2 months	*CoNS* n=35 *S. aureus* n=21 *Gram-negative* n=4 *P. acnes* n=6 Multiple agents n=6 Negative or missing n=15	*CoNS* n=24 *S. aureus* n=5 *Gram-negative* n=2 *P. acnes* n=3 Multiple agents n=8 Negative or missing n=8

Abbreviations: n=Sample size; CoNS=Coagulase-negative staphylococcus; NR=Not reported.

Table 5: Risk factors for deep sternal wound infection or mediastinitis: Summary results from multivariate logistic regression models

First author, Year; Country(s)	Study design; n=	Target population	Odds Ratio (95% Confidence interval)
Abboud, 2004;[19] Brazil	Matched case-control; n Case=39, n Control=78	All mediastinitis cases identified during 1995-2001 with control patients matched by age and date of surgery.	Obesity: 6.49 (2.24-18.78) Post-op ICU stay >2 days: 4.50 (1.57-12.90) Post-op Infection at another site: 8.86 (1.86-42.27) Smoking: 3.27 (1.04-10.20)
Cayci, 2008;[20] USA	Retrospective cohort; n=7,978	All patient undergone cardiac surgery via median sternotomy.	BMI>30: 1.6 (1.1-2.4) Diabetes mellitus: 2.4 (1.6-3.4) Smoking history in last 1 year: 2.7 (1.9-4.9) Smoking history in last 2 weeks: 2.6 (1.9-4.5)
Omran, 2007;[21]* Iran	Retrospective cohort; n=9,201	All patient undergone cardiac surgery via median sternotomy 2002-2006.	Hypertension: 10.76 (3.30-35.13) Re-exploration for bleeding: 13.415 (4.521–39.802) Female sex: 2.71 (1.45-5.07)
Friberg, 2009;[13] Sweden	Prospective cohort; n Exposted=1,359, n Unexposed=967	Unexposeds recruited in 2000-02 RCT, Exposed recruited 2007-08	BMI: 1.11 (1.06-1.15) Age: 0.97 (0.96-0.99) COPD: 1.93 (1.05-3.57) Diabetes mellitus: 2.16 (1.43-3.27) IMA** – single: 1.50 (0.97-2.34) IMA** – double: 6.04 (1.45-25.12)

*Including superficial sternal wound infection.
**Using none as reference.

Abbreviations: n=Sample size; ICU=Intensive care unit; IMA=Internal mammary artery.

Table 6: Distribution of types of sternal wound infection among cardiac surgery patients at the MUHC during 2008-09*

Infections by surgical site	n (%)
Superficial sternal wound infection	13 (1.4%)
Deep sternal wound infection	11 (1.2%)
Mediastinitis (no re-operation)	5 (0.5%)
Mediastinitis (required re-operation)	13 (1.4%)
TOTAL	**42 (4.5%)**

* Total cardiac procedures n=935 (in 928 patients)

Table 7: Length of stay in intensive care unit and coronary care unit at the MUHC among patients with and without sternal wound infection*

	Number of patients	Median (95% CI) ICU stay (day)	Median (95% CI) Ward stay (day)
No infectious complication	42	1 (1,1)	5 (5,6)
Superficial SWI	13	1 (1,5)	15 (9.6,24.6)
Deep SWI	11	2 (1,3.3)	32 (22.4,39.6)
Mediastinitis (no re-op)	5	3 (1,10)	28 (11,65)
Mediastinitis (re-operation)	13	6 (4,9.8)	35 (28.2,104.9)

*Among cardiac surgery patients at the MUHC during the 2008-2009 fiscal year

Table 8: Prevalence of risk factors for sternal wound infection at the MUHC and their association with risk of SWI

Patient Group	Prevalence			
	Diabetes	Obesity	COPD	Smokers
Control (n=42)	19%	7%	7%	31%
SWI (n=42)	62%	9.5%	2%	41%
Risk ratio (95% C. I.)	6.9 (2.6, 18.6)	1.4 (0.3, 6.5)	0.3 (0.03, 3.2)	1.5 (0.6, 3.7)

Table 9: Cost-effectiveness of GCS

Patient group	Expected number of SWI cases per 928 patients	Cost per patient ($)		Budget Impact	Net Budget Impact
		Additional hospitalization due to SWI	GCS		
Scenario					
No GCS	42	$529	0	$491,010	--
GCS for all patients	27	$372	400	$716,470	$225,460
GCS for high risk patients only	36	$466	80	$506,954	$15,944

Figure 1: Flowchart summarizing literature review

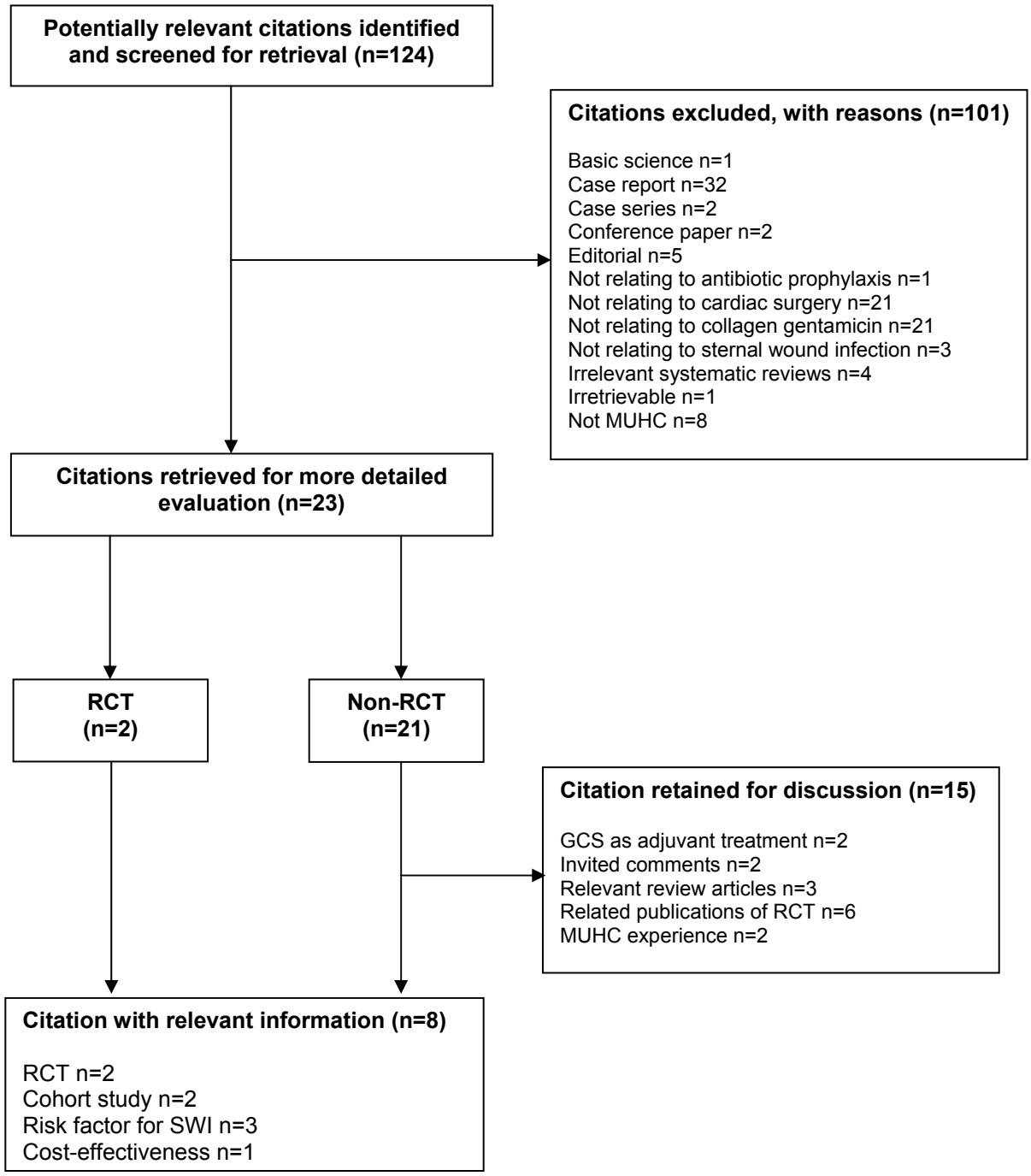
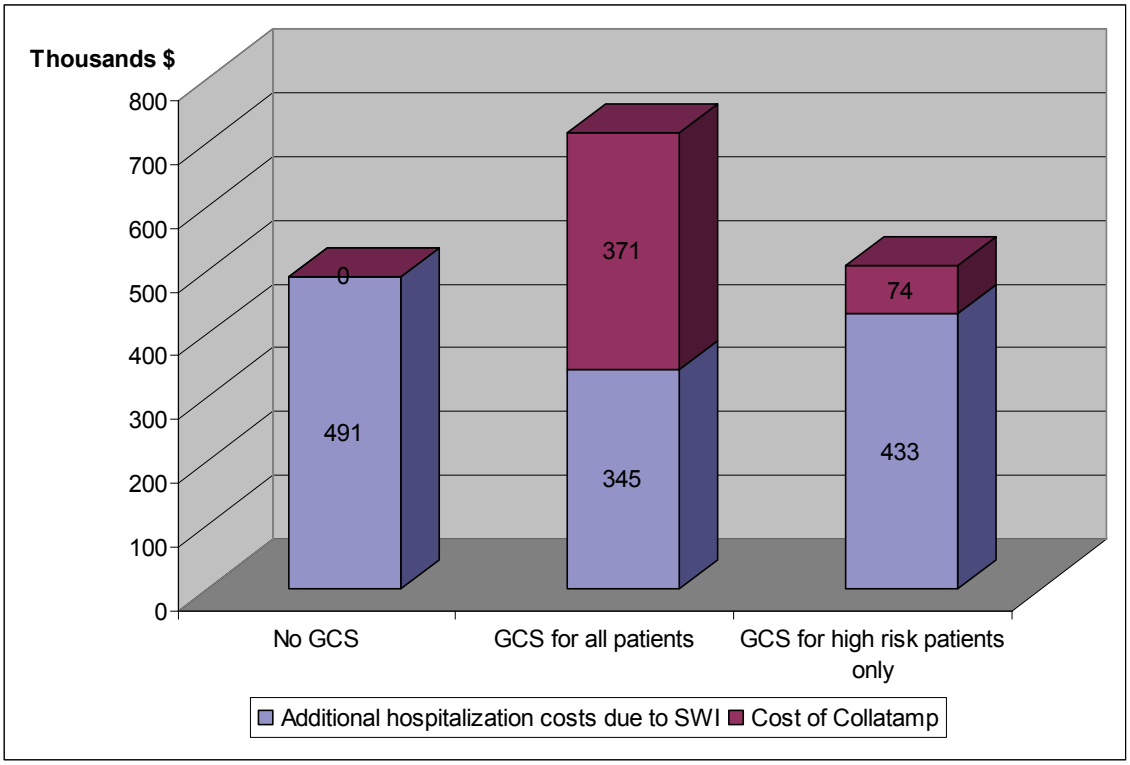


Figure 2: Illustration of budget impact



Appendix 1: Classification of sternal wound infection [USA Centers for Disease Control and Prevention]

Operative category: Cardiac

Category description: "Open chest procedures on the valves or septum of heart; does not include coronary artery bypass graft, surgery on vessels, heart transplantation, or pacemaker implantation."

Classification of infectious complications:

Category	Description
Superficial	A **superficial incisional SSI (Primary or secondary)** must meet one of the following criteria: Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following: a. purulent drainage from the superficial incision. b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision. c. at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, and is culture-positive or not cultured. A culture-negative finding does not meet this criterion. d. diagnosis of superficial incisional SSI by the surgeon or attending physician.
Deep	A **deep incisional SSI (Primary or secondary)** must meet one of the following criteria: Infection occurs within 30 days after the operative procedure if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g. fascial or muscle layers) of the incision and patient has at least one of the following: a. purulent drainage from the deep incision but not from the organ/space component of the surgical site. b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following signs or symptoms of infection: pain or tenderness. A culture-negative finding does not meet this criterion. c. an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination. d. diagnosis of deep incisional SSI by the surgeon or attending physician.
Organ/space	***MED-Mediastinitis,*** must meet at least one of the following criteria: (1) patient has organisms cultured from the mediastinal tissue or fluid obtained during a surgical operation or needle aspiration. (2) patient has evidence of mediastinitis seen during a surgery or in histopathological examination. (3) patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°C), chest pain, or sternal instability; and at least one of the following: a. purulent discharge from the mediastinal area, b. organisms cultured from blood, or from the discharge from the mediastinal area, c. mediastinal widening on x-ray.

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