



Pre and postoperative blood glucose levels and the risk of deep surgical infection

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SUMMARY STATEMENT

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REQUEST

Does controlling pre and/or post operative blood glucose levels affect the risk of deep surgical infection in patients undergoing coronary artery bypass surgery?

REQUESTED BY

Kaye Bellis, Infection Control Consultant, Infection Control,
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METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request

Patients (Subjects): Patients undergoing coronary artery bypass surgery
Intervention: Maintaining appropriate pre and post operative blood glucose levels
Comparisons: No intervention
Outcomes: Deep surgical infection

Search terms

(see Appendix 2 for exact search strategy)

Patient (Subject): coronary artery bypass, cardiac surgical procedures
Intervention: blood glucose, hyperglycaemia, hypoglycaemia
Comparison:
Outcome: surgical wound infection, postoperative complications

Resources Searched

We searched the following databases and internet websites:

The Cochrane Library (CD-ROM) 2003 Issue 2

Medline (OVID)- 1966 to April Week 2, 2003

EBM Reviews- Cochrane DSR, ACP Journal Club, DARE, and CCTR (OVID)- 1st Quarter 2003

CINAHL (OVID)- 1982 to April Week 2, 2003

Current Contents (ISI Web of Knowledge)- to April 10, 2003

PREMEDLINE (OVID)- April 28, 2003

Australasian Medical Index- April 28, 2003

National Guideline Clearinghouse- April 29, 2003

PubMed – National Library of Medicine – accessed April 29, 2003

Refinements, Searching & Reporting Constraints

We included items of evidence that were available to us on May 8th, 2003. We only included articles published in the last 10 years. Critical appraisal was performed on the subset of studies published in English.

RESULTS

From our sources we identified 12 potentially relevant articles. We obtained the full text of these articles to determine their relevance.

After examination of the 12 articles, the following were excluded as follows:

Reason for exclusion	Number
Level IV evidence	1
Surgical wound infection data not reported separately	5
Total	6

6 articles then remained for appraisal. These studies are classified as follows:

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	0
Pseudorandomised controlled trials	0
Controlled trials, cohort or case-control analytic studies	6
Total	6

Based on our refinements, searching and reporting constraints we are reasonably confident these articles represent the most relevant findings published to date.

Brief Summary of Results of Appraisal

Many of the articles identified have significant methodological flaws as is noted in the appraisal tables, and no relevant randomised controlled trials were identified, however there is a clear, consistent message from the articles reviewed.

In diabetic patients, increased postoperative blood glucose control (and therefore, decreased incidence of hyperglycaemia) when undergoing coronary artery bypass operations has been shown to be significantly associated with decreased risk of deep surgical wound infection (Furnary et al 1999, Golden et al 1999, Guvener et al 2002, Latham et al 2001, Zerr et al 1997).

The study by Latham et al (2000) found this same association in patients who had not been diagnosed with diabetes. Therefore, Latham et al 2000 suggest that "screening for diabetes and hyperglycemia in patients having cardiothoracic surgery may be warranted to prevent postoperative and chronic complications of this metabolic abnormality."

The two studies identified that investigated preoperative blood glucose control in patients undergoing coronary artery bypass operations (Guvener et al 2002 and Trick et al 2000) also report significant positive associations between preoperative hyperglycaemia and risk of postoperative infection in diabetic patients. No studies were identified that provided data on preoperative blood glucose control in non-diabetic patients.

Guvener et al (2001) suggest that "In conclusion, blood glucose regulation in preoperative period is as necessary as in postoperative period to reduce postoperative infectious complications in diabetic patients undergoing coronary artery bypass surgery."

EVIDENCE SUMMARIES

<p style="text-align: center;">Evidence Summary Therapy/Intervention</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: 80%;"> <p>Operative blood glucose levels and the risk of deep surgical infection</p> </div>	<p style="text-align: center;">Study 1</p>	<p style="text-align: center;">Study 2</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level III-3 – Prospective Cohort Study with Historical Control</p>	<p>Level III-2 – Nonconcurrent Prospective Cohort Study</p>
<p>DESCRIPTION: Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients (subjects): 2,467 diabetic patients who underwent open heart surgical procedures. Control group, January 1, 1987- September 1, 1991, n=968; study group, September, 1991- November 30,1997 n=1499. Intervention: Study group had blood glucose levels manipulated by means of continuous intravenous insulin (CII). Comparisons: Control group received sliding scale guided subcutaneous injections (SQI) as a method of post-operative glucose regulation. Outcomes: Deep sternal wound infection (DSWI). Inclusion & Exclusion Criteria: not described.</p>	<p>Patients (subjects): 411 adult diabetic patients who underwent coronary artery surgery. Comparisons: Postoperative blood glucose levels. Outcomes: Postoperative infection, including pneumonia, urinary tract infection, wound infection or other infection. Inclusion & Exclusion Criteria: Patients were excluded if they had missing data, infectious complications within 36h of surgery, evidence of positive culture, infiltrate, or use of antibiotics on admission, or death within 36hr of surgery.</p>
<p>VALIDITY: Methodology, rigour, selection</p>	<p>Blinding: Not reported. Similar groups: No significant difference with respect to age, sex, procedure, redo sternotomies, cardiopulmonary bypass time or transfusions. CII group had a significantly higher prevalence of hypertension, renal insufficiency, obesity, steroid usage, and use of grafts in patients undergoing bypass grafting.</p>	<p>Blinding: Data on the main exposure of interest (blood glucose levels) were abstracted from the medical records before data were collected on the main outcome (infectious complications). Similar groups: Not applicable</p>

	<p>SQI group had a higher prevalence of congestive heart failure, prolonged inotropic support, more transfusions and longer postoperative stay.</p>	
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Deep sternal wound infections occurred in 31 of the 2,467 diabetic patients (1.3% overall).</p> <p>CII approach resulted in much tighter glucose control. Mean blood glucose levels on the day of operation through the third postoperative day (POD) were significantly lower in the CII group.</p> <p>CII produced a significant decrease in risk of DSWI (P= 0.005; relative risk 0.34) in comparison to SQI.</p>	<p>5.6% of patients developed sternal wound infections.</p> <p>After adjusting for age, sex, race, co-morbidity, acute severity of illness and length of stay in ICU, patients with higher mean blood glucose levels were at increased risk of developing postoperative infections. Compared with patients in the first (lowest) glucose quartile, the relative odds of infection among patients in quartiles 2, 3 and 4 were 1.17, 1.86, and 1.72 respectively. (p for trend = 0.05)</p> <p>Analysis limited to surgical wound infection also showed a trend towards increased risk of infection with increasing blood glucose levels however the trend was not statistically significant. (Data not reported).</p>
<p>AUTHOR(S) CONCLUSIONS: Limitations, implications for practice and research</p>	<p>"This present study reconfirms... that hyperglycemia in the first 3 PODs is significantly associated with, and is an independent predictor of, DSWI."</p> <p>"When postoperative hyperglycemia was manipulated through an aggressive intravenous insulin infusion aimed at maintaining glucose levels in the 150 to 200mg/dL range, the incidence of DSWI was significantly decreased."</p> <p>"The major weakness of this study is its temporal sequential nature. We recognize that there have been subtle cumulative improvements in all areas of open heart surgical intervention over the last 11 years, which may play a role in both the diminution of mortality and DSWI seen during the course of this study."</p>	<p>"These data suggest that hyperglycemia is an independent predictor of the short term risk of infection. Patients with mean glucose concentrations >200mg/dl within 36 h following surgery were more likely to develop infectious complications than their counterparts who were under better glycemic control. This risk was independent of age, sex, race, underlying comorbidity on admission, and severity of illness assessed during recovery."</p>

<p>OUR COMMENTS: Opportunity for bias, weakness and strength</p>	<p>Potential for bias: Including only patients identified as diabetic at time of admission may introduce bias by excluding patients with undiagnosed diabetes.</p> <p>Weakness/es: The weakness of the temporal sequential methodology identified by the authors above is considerable. Improvement in coronary artery bypass surgery techniques over the 11 years of the study would be expected to result in decreased mortality and incidence of DSWI in patients in the later, study group, as was seen.</p> <p>Strength/s: Prospective study design is a strength.</p>	<p>Potential for bias: All results for this study were obtained from medical records introducing the possibility of information bias. Variation in level of glucose control (which was not randomised) introduces opportunities for bias. Patients with longer ICU stays displayed better glycemic control, this may bias the results towards the null hypothesis.</p> <p>Weakness/es: No data on preoperative glycemic control.</p> <p>Strength/s: Data on the main exposure of interest (blood glucose levels) were abstracted from the medical records before data were collected on the main outcome (infectious complications)</p>
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<p style="text-align: center;">Evidence Summary Therapy/Intervention</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p>Operative blood glucose levels and the risk of deep surgical infection</p> </div>	<p style="text-align: center;">Study 3</p>	<p style="text-align: center;">Study 4</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level III-2 – Retrospective Cohort Study</p>	<p>Level III-2 – Case-Control Study</p>
<p>DESCRIPTION: Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients (subjects): 400 patients who underwent coronary artery bypass surgery in a five year period and who had type II diabetes mellitus. Comparisons: Pre and postoperative blood glucose levels. Outcomes: Deep sternal wound infection (DSWI), superficial sternal wound infection (SSWI) and donor site infections (DSI), urinary tract infection (UTI) and lung infection. Inclusion & Exclusion Criteria: not described.</p>	<p>Patients (subjects): 74 patients who developed surgical-site infections (SSI) after cardiothoracic surgery and 970 uninfected cardiothoracic surgery patient controls. Comparisons: Pre and postoperative blood glucose levels. Outcomes: Surgical site infection. Inclusion & Exclusion Criteria: not described.</p>
<p>VALIDITY: Methodology, rigour, selection</p>	<p>Blood glucose levels were manipulated by means of a continuous insulin infusion (CII). Blinding: Not reported. Similar groups: Not applicable.</p>	<p>Selection of 44 of the 74 patients with postoperative SSI is not described. Preoperative blood glucose levels were available for 61 cases and 915 controls. Postoperative blood glucose levels were available for 72 cases and 902 controls. Blinding: Not well described. Similar groups: Several demographic and operative characteristics were “similar”. Statistical analysis not provided.</p>

<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>20 patients (5%) were diagnosed with a postoperative infection. SSWI in 3 cases, DSI in 4 cases and DSWI in 5 cases. UTI and lung infection occurred in 8 cases.</p> <p>High preoperative mean glucose levels were the main risk factor for the development of postoperative infection (p=0.012, and p=0.028 for 1 and 2 days before operation respectively.)</p> <p>In patients with DSWI, mean levels of blood glucose were significantly higher on the 2nd day post operation than in those without DSWI (p=0.012). Mean levels were also higher on the first and third days postoperatively, however the association was not statistically significant.</p> <p>Data other than mean and p values not provided.</p>	<p>Of the 74 patients who developed infections, there were 30 cases of mediastinitis and 24 chest wound infections.</p> <p>After multivariate adjustment, postoperative hyperglycemia increased the risk of SSI in both patients with known diabetes (OR 1.86, 95%CI 1.04, 3.34, p=0.03) and patients without a known history of diabetes (OR 2.14, 95%CI 1.05, 4.40, p=0.04).</p> <p>Compared with postoperative glucose levels less than 200mg/dl, the OR of SSIs were 2.54, 2.97 and 3.32 among patients with blood glucose levels of 200-249, 250 to 299 and 300 mg/dl or greater, respectively.</p>
<p>AUTHOR(S) CONCLUSIONS: Limitations, implications for practice and research</p>	<p>“In conclusion, blood glucose regulation in preoperative period is as necessary as in postoperative period to reduce postoperative infectious complications in diabetic patients undergoing coronary artery bypass surgery.”</p>	<p>“Hyperglycemia during the immediate postoperative period was an independent risk factor for developing infection among those patients with and without a history of diabetes, and the risk of infection correlated with the degree of glucose elevation.”</p> <p>“... we found that a number of patients were referred for cardiothoracic procedures with evidence of diabetes but without previously having the diagnosis made or intervention begun. These patients had an increased risk of developing SSIs at a rate that was comparable to those with known diabetes.”</p>

<p>OUR COMMENTS: Opportunity for bias, weakness and strength</p>	<p>Potential for bias: Retrospective medical chart review introduces opportunities for information bias. Weakness/es: Small number of cases, particularly in analysis of DSWI only. Not all statistical data reported.</p>	<p>Potential for bias: Difficult to determine from the information provided. Weakness/es: Description of methodology of case-control aspect of this paper is unclear. Addition of 44 cardiothoracic patients with surgical site infections who were not initially included in the study is particularly worrying and the process by which they were identified, included or excluded is not well described. Information is not provided in regard to blinding, significance of differences between cases and controls, or distribution of SSI between sites in the initial 30 and additional 44 infected patients. Strength/s: Number of cases investigated was larger than in many other studies in this area.</p>
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<p style="text-align: center;">Evidence Summary Therapy/Intervention</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: 80%;"> <p>Operative blood glucose levels and the risk of deep surgical infection</p> </div>	<p style="text-align: center;">Study 5</p>	<p style="text-align: center;">Study 6</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level III-2 – Case-Control Study</p>	<p>Level III-3 – Comparative Study With Historical Control</p>
<p>DESCRIPTION: Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients (subjects): 30 cases, patients with deep sternal site infection (DSSI) after coronary artery bypass graft surgery (CABG), and 90 randomly selected controls who had undergone CABG surgery but did not acquire DSSI.</p> <p>Comparisons: Preoperative: blood glucose level, BMI, diagnosis, duration of hospitalisation, left ventricular ejection fraction, steroid receipt, tobacco use and urgency of procedure. Intraoperative: associated procedures, day of the week of surgery, duration of hypothermia, National Nosocomial Infections Surveillance (NNIS) surgical risk index, operating room number and personnel, perfusion, pump and aortic crossclamp times, antimicrobial agent administered, time and duration of administration, source and number of grafts, pacemaker placement, type of skin closure. Postoperative: Antimicrobial use, blood glucose level, duration of chest tube placement, duration of prophylactic antimicrobial receipt, number of red blood cell units transfused, severity of illness, volume of chest tube output.</p>	<p>Patients (subjects): 1,585 diabetic patients who underwent open heart operations. Intervention: Implementation of diabetic protocol designed to standardise the titration of intravenous insulin to maintain mean blood glucose levels lower than 200mg/dl during open heart operations. Comparisons: 990 diabetic patients who had open heart operations before implementation of a diabetic protocol and 595 diabetic patients who had open heart operations after implementation of the diabetic protocol. Outcomes: Deep sternal wound infection (DSWI). Inclusion & Exclusion Criteria: not described.</p>

	<p>Outcomes: Deep sternal site infection (DSSI). Inclusion & Exclusion Criteria: not described.</p>	
<p>VALIDITY: Methodology, rigour, selection</p>	<p>Blinding: Not reported. Similar groups: Case and controls were similar for age, ASA classification, sex, hospitalization before operation, duration of preoperative stay, NNIS surgical risk index, repeat CABG, type of graft (except as below), number of grafts, placement of temporary pacemaker, duration of chest tube, operating room, incision time, obesity, surgeon, duration of operation, pump or clamp time, hypothermia, volume from the cell salvage system, Therapeutic Intervention Scoring System (TISS) score, and volume of chest tube output.</p>	<p>Blinding: Not described. Similar groups: Age, sex, weight, smoking, renal failure, peripheral vascular disease, diabetes type, procedure, redo operation, pump time, ventilator >48h, inotropic agents >48h and mortality were not significantly different between the before and after protocol implementation.</p> <p>After protocol implementation, patients were more likely to have a history of hypertension and renal insufficiency, less likely to have a history of congestive heart failure, and had a higher mean BMI.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Deep sternal site infections occurred in 30 of 1796 (1.7%) patients who underwent CABG procedures.</p> <p>In univariate analysis, cases were significantly ($p<0.05$) more likely to have had bilateral internal thoracic artery harvest, staples used for skin closure, diabetes mellitus, glucose level of 200 mg/dl or more before the operation (OR 5.0 (95%CI 1.0, 26) $p=0.02$). Cases also had higher postoperative blood glucose levels ($p=0.04$) and pulmonary artery diastolic pressure ($p=0.01$) (OR and 95% CI not provided for these variables).</p> <p>In multivariate analysis, diabetes mellitus with a preoperative glucose level of 200mg/dl or more was an independent risk factor for DSSI (OR 10.2(95% CI 2.4,43) $p=0.008$). Diabetes mellitus with a preoperative glucose level less than 200mg/dl was not associated with DSSI (OR 1.4(95% CI 0.4,4.8) $p=6$).</p>	<p>33 patients suffered deep wound infections (2.1%), 27 sternal, and 8 at the donor site.</p> <p>Implementation of the diabetic protocol resulted in a decrease in mean blood glucose levels on the first postoperative day (POD) ($p<0.005$), second POD ($p<0.002$) and over 48 hours ($p<0.003$).</p> <p>By the third year after implementation, deep sternal wound infection had fallen from 2.8% pre-implementation to 0.74%.</p> <p>Elevated blood glucose (>200mg/dl) at 48 hours was found to be significantly associated with an increased risk of deep wound infection ($p<0.002$). Blood glucose >200mg/dl on the first and second POD were also significant at $p<0.05$.</p>

<p>AUTHOR(S) CONCLUSIONS: Limitations, implications for practice and research</p>	<p>“Our data suggest that diabetes mellitus is a risk factor [for DSSI] only when the preoperative blood glucose level is 200mg/dl or higher.”</p>	<p>“We hypothesize that elevated BG [blood glucose] levels after cardiac operations in diabetic patients are associated with a higher incidence of infectious complications.”</p> <p>“We suggest that protocols for maintaining BG [blood glucose] less than 200mg/dL in the immediate postoperative period may be a factor in reducing the incidence of deep wound infection in diabetic patients.”</p>
<p>OUR COMMENTS: Opportunity for bias, weakness and strength</p>	<p>Weakness/es: Full data and analysis of pre and postoperative glucose levels and relationship to DSSI incidence not provided.</p> <p>Strength/s: Good matching of cases and controls. Thorough analysis for confounding criteria. Controls randomly selected from CABG patients without DSSI</p>	<p>Potential for bias: Use of chart review for data collection is open to information bias. Temporal sequential nature of comparison groups also gives opportunities for bias. It would be expected that over the seven years of the study improvements in surgical techniques might have made a significant impact on postoperative infection rates, contributing to the effect reported in this paper.</p> <p>Weakness/es: Data on preoperative blood glucose levels not provided.</p> <p>Strength/s: Number of cases investigated was larger than in many other studies in this area.</p>

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Trick WE, Scheckler WE, Tokars JI, Jones KC, Reppen ML, Smith EM & Jarvis WR (2000). Modifiable risk factors associated with deep sternal site infection after coronary artery bypass grafting. *Journal of Thoracic & Cardiovascular Surgery*. 119: 108-114.

Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V & Starr A (1997). Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Annals of Thoracic Surgery*. 63: 356-361.

ARTICLES NOT CRITICALLY APPRAISED

Level IV Evidence

Sajja LR, Kulshresth P & Yarlagadda RB (2000). Continuous intravenous insulin infusion reduces infections in diabetics after CABG. *Annals of Thoracic Surgery*, 69: 667-668.

Surgical wound infection data not reported separately

Gol MK, Karahan M, Ulus AT, Erdil N, Iscan Z, Karabiber N, Tasdemir O & Bayazit K (1998). Bloodstream, respiratory, and deep surgical wound infections after open heart surgery. *Journal of Cardiac Surgery*. 13: 252-259.

Hill SE, van Wermeskerken GK, Lardenoye JW, Phillips-Bute B, Smith PK, Reves JG & Newman MF (2000). Intraoperative physiologic variables and outcome in cardiac surgery: Part I. In-hospital mortality. *Annals of Thoracic Surgery*. 69: 1070-1075.

Pomposelli JJ, Baxter JK, 3rd, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA & Bistrian BR (1998). Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *Journal of parenteral and enteral nutrition*. 22: 77-81.

Rady MY, Ryan T & Starr NJ (2001). Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. *Critical Care Medicine* 29

Zindrou D, Taylor KM & Bagger JP (2001). Admission plasma glucose: an independent risk factor in nondiabetic women after coronary artery bypass grafting. *Diabetes Care*. 24: 1634-1639.

APPENDIX 1

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Levels Of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

Level I Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials.

Level II Evidence obtained from at least one randomised controlled trial.

- Level III
- 1 Evidence obtained from pseudo-randomised controlled trials (alternate allocation or some other method).
 - 2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case control studies or interrupted time series with a control group.
 - 3 Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.

Level IV Evidence obtained from case series, either post-test or pretest/post-test.

APPENDIX 2

Search strategy

	Search terms for MEDLINE
1	Exp Coronary artery bypass/
2	Exp Cardiopulmonary bypass/
3	Exp Cardiac surgical procedures/
4	Exp Thoracic surgery/
5	Exp Coronary disease/su
6	Exp Sternum/su
7	Cabg.tw
8	Or/1-7
9	Exp Blood glucose/
10	Exp Hypoglycemia/
11	Exp Hyperglycemia/
12	Exp Diabetes mellitus/
13	Exp Hemoglobin a, glycoslyated/
14	Glucose.tw
15	Or/9-14
16	Exp Preoperative care/
17	Exp Postoperative care/
18	Exp Postoperative period/
19	Exp Intraoperative care/
20	Exp Intraoperative period/
21	Or/14-18
22	Exp Surgical wound infection/
23	Exp Opportunistic infections/
24	Exp Infection Control/
25	Exp Postoperative complications/
26	Or/20-23
27	8 and 14 and 20 and 24
28	(8 and 20 and 24) not 27 (limit to human and english language and yr=1993-2003)
29	(8 and 14 and 24) not (27 or 28) (limit to human and english language and yr=1993-2003)

Similar terms, translated so as to be appropriate, were implemented in the other databases.

