A Cost-Benefit Analysis of the ENIGMA Trial

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ABSTRACT

Background: The ENIGMA trial was a prospective, randomized, multicenter study that evaluated the clinical consequences of including N_2O in general anesthesia. Patients who were given a N_2O-free anesthetic when undergoing major surgery for which the expected hospital stay was at least 3 days had lower rates of some postoperative complications. This suggests that, despite a higher consumption of potent inhalational agent, there could be a financial benefit when N_2O is avoided in such settings.

Methods: A retrospective cost analysis of the 2,050 patients recruited to the ENIGMA trial was performed. We measured costs from the perspective of an implementing hospital. Direct health care costs include the costs for maintaining anesthesia, daily medications, hospitalization, and complications. The primary outcome was the net financial savings from avoiding N_2O in major noncardiac surgery. Comparisons between groups were analyzed using Student *t* test and bootstrap methods. Sensitivity analyses were also performed.

Results: Rates of some serious complications were higher in the N_2O group. Total costs in the N_2O group were $16,203 and in the N_2O-free group $13,837, mean difference of $2,366 (95% CI: 841–3,891); $P = 0.002$. All sensitivity analyses retained a significant difference in favor of the N_2O-free group (all $P \leq 0.005$).

Conclusions: Despite N_2O reducing the consumption of more expensive potent inhalational agent, there were marked additional costs associated with its use in adult patients undergoing major surgery because of an increased rate of complications. There is no cogent argument to continue using N_2O on the basis that it is an inexpensive drug.

What We Already Know about This Topic

- The ENIGMA trial showed that N_2O-free anesthesia for patients scheduled for major surgery may reduce postoperative complications. It is unknown if this translates into less hospital costs for treatment.

What This Article Tells Us That Is New

- A retrospective analysis of 2,050 patients of the ENIGMA trial shows that the use of more expensive potent inhalational anesthetics is not associated with higher overall costs. The total costs in the N_2O-oxide group were significantly higher compared with the costs of the N_2O-free group.

NITROUS oxide has traditionally been viewed as an inexpensive drug, especially when the additional benefit of reduced requirement for other more expensive anesthetic agents

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is considered. However, this view does not take into account the cost implications of the side effects of N_2O.

We have previously reported the results of the ENIGMA trial.[1] In this study, patients who were given a N_2O-free anesthetic when undergoing major surgery had lower rates of major complications, as well as less severe postoperative nausea and vomiting (PONV). In addition, the patients in the N_2O-free group were more likely to be discharged from the intensive care unit (ICU) on any given day than those in the N_2O group. These findings suggest that a possible financial benefit of avoiding N_2O in the ENIGMA trial exists despite no statistically significant difference in hospital length of stay between groups. A criticism of the ENIGMA trial has been that it failed to acknowledge the costs saved by the use of N_2O to reduce consumption of more expensive alternatives.[2] The aim of this retrospective analysis therefore was to determine whether there were economically significant differences in the cost of the in-patient stay between the two patient groups in the ENIGMA trial, taking into account the costs of drugs used and adverse clinical outcomes.

Materials and Methods

The ENIGMA trial was a prospective, randomized, multicenter study that analyzed 2,050 patients.[1] Inclusion criteria required patients to be at least 18 yr old, presenting for surgery expected to exceed 2 h and expecting a postoperative stay of at least 3 days. Patients were excluded if they were undergoing cardiac surgery, if one lung ventilation was required, or if the anesthesiologist considered N_2O to be contraindicated. The attending anesthesiologists were advised to administer a gas mixture of 70% N_2O and 30% oxygen in the N_2O group, and 80% oxygen and 20% nitrogen in the N_2O -free group. All other drugs were administered at the discretion of the attending anesthesiologist.

The data collected for the ENIGMA trial included details of the duration of surgery, the time to fitness for discharge from the postanesthetic care unit (PACU), the fractions of inhaled gases, other anesthetic agents used, and prophylactic as well as therapeutic antiemetics. Severe PONV was defined by two or more episodes of expulsion of gastric contents at least 6 h apart or requiring three or more doses of antiemetic medication. Wound infection was defined by purulent discharge with or without positive microbial culture, or pathogenic organisms isolated from an aseptically obtained microbial culture. Pneumonia was defined by radiologic changes in conjunction with a temperature greater than 38°C, a leukocyte count greater than 12,000/ml, or positive sputum culture. The mean ± SD durations of surgery and anesthesia were the same in each group, 3.3 ± 2.0 h and 3.7 ± 2.0 h, respectively. The main findings of the ENIGMA trial are summarized in table 1.

Costs

Health economic studies use one or more evaluation methods according to the study objectives.[3] A cost-minimization analysis is used when the clinical benefits are found to be equivalent, and the aim is to determine which is the most cost-efficient way of achieving a given objective; cost-effectiveness and cost-utility analyses use natural units such as life-years gained (for the former) or quality adjusted life-years (for the latter) to determine the most efficient way of allocating spending; a cost-benefit analysis uses monetary terms to determine whether a given objective should be pursued to a greater or lesser extent.[3] Cost minimization, cost-effectiveness, and cost-utility analyses base their evaluations on a single measurable benefit. Cost-benefit analysis allows better alternative use of the resources and is a particularly useful framework for structuring decision-making problems.[3] The ENIGMA trial identified several possible outcome benefits of avoiding N_2O, and each of these may affect the cost of hospitalization. We therefore chose to use a cost-benefit analysis in this study.

Table 1. Main Results of the ENIGMA Trial (Modified from Myles *et al.*[1])

Variable	N_2O-free Group (n = 997)	N_2O Group (n = 1,015)	Adjusted Odds Ratio* (95% CI)	*P* Value
Severe nausea or vomiting	104 (10)	229 (23)	0.40 (0.31–0.51)†	<0.001
Wound infection	77 (7.7)	106 (10)	0.72 (0.52–0.98)‡	0.036
Fever	275 (28)	345 (34)	0.73 (0.60–0.90)	0.003
Pneumonia	15 (1.5)	30 (3.0)	0.51 (0.27–0.97)	0.040
Atelectasis	75 (7.5)	127 (13)	0.55 (0.40–0.75)	<0.001
Pneumothorax	1 (0.1)	3 (0.3)	—	—
Myocardial infarction	7 (0.7)	13 (1.3)	0.58 (0.22–1.50)	0.26
Thromboembolism	16 (1.6)	10 (1.0)	1.60 (0.72–3.55)	0.25
Blood transfusion	188 (19)	202 (20)	0.96 (0.75–1.21)	0.71
Stroke	1 (0.1)	1 (0.1)	—	—
Awareness	0 (0.0)	2 (0.2)	—	—
Death within 30 days	3 (0.3)	9 (0.9)	0.33 (0.09–1.22)	0.096

Values are expressed as number with percentage in parentheses.

* Adjusted for age, American Society of Anesthesiologists' physical status score, and duration of anesthesia unless otherwise stated. † Adjusted for postoperative nausea and vomiting risk score (see text) and intraoperative antiemetic drug use. ‡ Adjusted for National Nosocomial Infections Surveillance System score (see text), lowest intraoperative temperature, and smoking status.

Costs were measured from the perspective of an implementing hospital. Direct health-care costs include the costs for maintenance of anesthesia (volatile anesthetics or propofol infusion), hospitalization, and medications. Additional visits to other health-care providers (*i.e.*, family practitioner, medical specialist), professional home care, nonhealth care costs such as paid and unpaid help, and indirect costs of absenteeism of paid and unpaid work were not included.

The direct costs of drugs (including intravenous anesthetics) and antiemetics were obtained from the Alfred Hospital's Pharmacy Department and are based on prices in the year 2010. Intravenous drug costs were rounded up to a complete ampoule. A fixed cost was used for antiemetic prophylaxis as complete details of individual drug data were not collected in the original study. The combined use of dexamethasone and generic ondansetron was assumed for this purpose. The acquisition cost of inhalational anesthetics were obtained from previously published figures.[4]

The costs of N_2O, oxygen, and medical air were obtained from the Alfred Hospital's Engineering Department and were cross-checked with two commercial providers' prices and contemporary reported prices in the literature.[5] Actual recorded inspired and end-expired gas concentrations and duration of anesthesia were used to calculate consumption. We did not collect fresh gas flow data in the ENIGMA trial, and so we assumed a value of 2 l/min for sevoflurane and 1 l/min for both isoflurane and desflurane to reflect common practice in many centers. Subsequent costs of inhalational agents were determined using established formulae.[6]

A literature review was undertaken to determine the costs of complications reported in the ENIGMA trial. A literature search was undertaken using the PubMed database and search terms: "surgical site infection," "pneumonia," "respiratory complications," "intensive care," "postanesthetic care unit" and "recovery room," which were cross-referenced with "postoperative," "costs" and "cost analysis." All searches were limited to adult studies and those published between 1980 and 2010. Non-English language papers were included if results appeared in the translated abstract. Studies deriving costs of complications after cardiothoracic surgery were included in our literature review, despite the exclusion of coronary artery bypass graft surgery from the ENIGMA trial, because the additional costs should be comparable in either case. Studies were excluded if they focused on only part of the postoperative stay (such as ICU stay) or if the focus was on social costs or costs after discharge, which was beyond the scope of the original ENIGMA trial. Studies that incorporated original data from other studies were excluded so as not to double-count cost estimates in our analysis. Studies addressing the cost of PACU and ICU stay were excluded if data were not presented in a "per patient, per day" format and if insufficient data were provided to calculate this cost (see tables 1–5 of Supplemental Digital Content 1, http://links.lww.com/ALN/A752). The median from each group of studies was used as the estimate of cost for complications. For those published studies that incorporated hospital stay in their estimates, we used our attributable cost per day in hospital from the published estimates to more accurately reflect the actual complication costs. All costs are presented in US dollars at September 2010 and were derived from the currency exchange rates at the time of original publication, indexed to inflation from that time.

The drug and median complication costs derived from our literature search and adjustments for current US dollars provided the following estimates used in our analysis:

1. Bulk gas supplies: N_2O $0.0123 per liter, oxygen and medical air $0.003 per liter
2. Propofol: $1.40 per 200 mg ampoule
3. Thiopental: $12.60 per 500 mg ampoule
4. Inhalational agents (per minimum alveolar concentration hour): sevoflurane $11.40, isoflurane $1.50, desflurane $12.60
5. Prophylactic antiemetic therapy: $4.95
6. PACU stay: $0.81 per min (3 studies)[7–9]
7. PONV (1 or more episodes): $22.56 (7 studies)[10–14]
8. Wound infection: $10,514 (30 studies)[15–45]
9. Pneumonia: $13,439 (9 studies)[16,20–22,27,34,46–48]
10. ICU stay: $2,110 per day (11 studies)[49–59]

We did not include intraoperative opioid consumption in our estimates because there was no measurable difference between groups in our original study.[1] Notional costs for atelectasis, pneumothorax, and fever were not included, nor were those endpoints that were not significantly different between the groups (blood transfusion, pneumothorax, myocardial infarction, thromboembolism, stroke, and anesthetic awareness). Total cost thus included the acquisition costs of anesthetic drugs, calculated costs attributed to differences in complications rates, and hospital and ICU stay. Hospital length of stay included the day of surgery.

In Australian hospitals, the average diagnosis-related group funding for a typical major abdominal surgical procedure representative of surgeries undertaken on ENIGMA trial patients is $12,403 per case. This represents a total estimate of hospital costs per procedure, incorporating both fixed and variable costs. The average costs for an extra day in the hospital vary according to the extent of surgery and the case mix; we used the median value for a selection of diagnosis-related group codings typically used in abdominal surgery, being $750 per day, and a 5-day hospital stay. This is consistent with published cost data for colonic[60] and pancreatic[61] surgery. Thus, the episode cost was assumed to be $8,653 for a 5-day stay, and $750 per day for each day thereafter. The summed costs attributed with each complication were treated separately.

Economic Evaluation

The aim of the economic evaluation was to determine and compare the total costs for patients receiving either N_2O-free or N_2O-containing anesthesia. We calculated cost-benefit according to published recommendations.[3,62,63]

Variable costs were used in this analysis because the fixed costs component did not differ between groups (the groups were well balanced for age, sex, American Society of Anesthesiologists physical status, types of surgery, and surgical duration). The net costs were calculated for the primary clinical effect measures of the trial (*i.e.*, adverse outcomes, ICU, and hospital stay). The primary outcome was the net financial savings or loss from avoiding N_2O during major noncardiac surgery.

Sensitivity Analyses

To estimate the uncertainty surrounding the cost estimates, we undertook a sensitivity analysis by replacing our derived costing data with 0.25-fold and fourfold cost substitutions, being approximately the 10th and 90th percentiles of the cost distribution found in all the retrieved costing studies. This was done separately for major complications and ICU and hospital stay.

We explored the effect of including the nonsignificant intergroup differences for pneumothorax, myocardial infarction, and stroke. We chose not to include awareness because of its low rate (incidence, 0.001%) and because we had no data on long-term stress and treatment costs. We then attributed a notional cost for pneumothorax equal to that of pneumonia and used published data for myocardial infarction ($3,700) and stroke ($13,000).[64]

Statistical Analyses

The primary analysis included all patients randomly assigned to each group and treated accordingly; that is, a per-protocol analysis. We used actual PACU stay, ICU stay, and hospital stay data for all economic calculations. Patients who died in the hospital had their hospital stay cost calculation based on actual inpatient days (not allocated the maximum value) because there are no additional bed-day costs. Baseline characteristics of the two groups were tabulated using appropriate summary statistics. Analysis of the primary outcome of cost-benefit was performed using a Student *t* test, after testing for equality of variance.[62,63] In addition, bootstrap methods using 5,000 replicates were undertaken to estimate *P* values and 95% CI for differences in mean costs between the two groups. The bootstrap technique is a computation-intensive resampling method that makes no assumption regarding the underlying population distribution. All *P* values are two-sided. A *P* value of less than 0.05 was considered statistically significant. We used the Statistical Package for Social Sciences-SPSS (Version 18, SPSS Inc. Chicago, IL) for all analyses.

Results

Of the original 2,012 patients in the ENIGMA trial, 12 died within 30 days of surgery (three in the N_2O-free group and nine in the N_2O group); in-hospital deaths limit hospital stay and so reduce costs for these patients.

As previously reported,[1] there were 122 patients in the N_2O-free group (12%) and 140 patients in the N_2O group (14%) were admitted to the ICU immediately postoperatively ($P = 0.30$). The median (interquartile range) duration of hospital stay was 7.0 (4.0–10.9) days in the N_2O-free group and 7.1 (4.0–11.8) days in the N_2O group. However, the rate of hospital discharge did not differ between groups (hazard ratio = 1.09; 95% CI, 1.00–1.19; $P = 0.06$). The median duration of ICU stay was 1 day in both groups, but patients in the N_2O-free group were more likely to be discharged on any given day (hazard ratio = 1.35; 95% CI, 1.05–1.73; $P = 0.02$). Rates of severe PONV, pneumonia, and wound infection were higher in the N_2O group.

Table 2. Demographic and Perioperative Characteristics (Modified from Myles *et al.*[1])

Characteristic	N_2O-free Group (n = 997)	N_2O Group (n = 1,015)
Age, mean ± SD, yr	56 ± 17	55 ± 16
Male sex, No. (%)	533 (54)	520 (51)
Duration of surgery, hours	3.3 ± 2.0	3.3 ± 2.0
Duration of anesthesia, hours	3.7 ± 2.0	3.7 ± 2.0
ASA physical status		
1	209 (21)	206 (20)
2	548 (55)	557 (55)
3	230 (23)	241 (24)
4	10 (1)	11 (1)
Type of surgery, No. (%)		
General	472 (47)	448 (44)
Colorectal	157 (16)	142 (14)
Neurosurgery	144 (14)	151 (15)
Urology	127 (13)	130 (13)
Orthopedic	86 (8.6)	105 (10)
Gynecology	74 (7.4)	73 (7.2)
Ear, nose, throat, or maxillofacial	40 (4.0)	50 (4.9)
Vascular	40 (4.0)	45 (4.4)
Plastics	14 (1.4)	12 (1.2)
Any abdominal	577 (58)	563 (56)
Propofol infusion	191 (19)	132 (13)
Prophylactic antiemetic	342 (34)	356 (35)

ASA = American Society of Anesthesiologists.

Table 2 shows the distribution of perioperative characteristics in both groups; additional details can be found elsewhere.[1] Baseline characteristics were comparable in each group. Types of anesthetic techniques and use of prophylactic antiemetic therapy were also comparable.

Total variable costs per patient in the N_2O group were $16,203 and in the N_2O-free group $13,837, a mean difference of $2,366 (95% CI: 841–3,891); $P = 0.002$ (table 3). The parameters most affecting the cost differential between groups are extra bed-days and wound infection. All sensitivity analyses retained a significant difference in favor of the N_2O-free group (all $P \leq 0.005$) (table 4). The bootstrap technique estimations were comparable, with a mean difference of $2,366 (95% CI: 844–3,935); $P = 0.003$.

Table 3. Estimated Costs, Rounded to Whole US Dollars, Mean ± SD

	N_2O-free Group (n = 997)	N_2O Group (n = 1,015)	*P* Value
Anesthetic drugs*	27 ± 22	26 ± 22	0.16
Bed days†	12,793 ± 11,547	14,685 ± 18,718	0.005
Complications‡	1,017 ± 3,496	1,500 ± 4,210	0.006
Total costs	13,837 ± 13,256	16,203 ± 20,842	0.002

* Includes bulk gas supplies, intravenous induction drug, inhalational anesthetic drug (if used), additional propofol for maintenance of anesthesia (if used). † Includes postanesthesia care unit stay, hospital bed, and intensive care stay. ‡ One or more of: severe postoperative nausea and vomiting, wound infection, or pneumonia.

Discussion

This cost-benefit analysis provides an estimate of the financial burden from the use of N_2O in major surgery. The analysis is from the hospital perspective and is limited to the dollar value of complications that occurred during the first 30 postoperative days, within the boundaries of the original study. Consequently, this analysis addresses neither complications occurring after the original admission nor societal repercussions from lost productivity in the community. It is expected that these theoretic additional costs, if included, would increase the difference between the two study groups as observed in previous reports.[11] Furthermore, we did not attempt to place a monetary value on the pain and suffering associated with PONV or other complications.

This analysis has wide applicability. The pragmatic design of the ENIGMA trial allowed the treating anesthesiologists from 19 different institutions to provide their usual anesthetic care for the patient and procedure, apart from the N_2O/oxygen and oxygen/nitrogen variables. Consequently, data in the ENIGMA trial reflect a breadth of anesthetic practice that can be generalized and reliably applied in our cost analysis.

The use of data from previous studies to determine the costs of wound infection and postoperative pneumonia improves the general applicability of this study. Various methods were used in these previous studies, providing cost estimates for the relevant postoperative complications. These methods ranged from prospective direct microcosting techniques to retrospective charge-to-cost conversion based analysis. These methods have their own benefits and limitations, which have been discussed widely, including in the original articles. No discrimination was made in the inclusion of these results based on the methods used in the original studies. However, a sensitivity analysis was undertaken to address any potential limitations.

All of the studies that contributed to the cost estimation of complication used hospital length of stay as a component in their calculation of costs. Hospital stay was the primary endpoint of the ENIGMA trial, and although stay was longer in the group who received N_2O, this finding was not found to be statistically significant ($P = 0.06$). We chose to use the point estimates for length of stay and complication rates for each group, as recommended for cost-effectiveness studies.[65,66] Because there are overlapping factors that contribute to the costs generated by the management of postoperative complications in addition to length of stay, we chose to exclude hospital stay in the cost calculations for both wound infection and pneumonia. However, those complications not incorporating the cost of hospital stay in their individual cost estimates (PONV, PACU, and ICU stay) were included.

The ENIGMA trial found that, in addition to severe PONV, wound infection, and pneumonia, the incidence of atelectasis or any pulmonary complication was also higher in the patients who received N_2O. Atelectasis was not included in the analysis because there were no precedent studies identified in our literature review that estimated any cost consequences of postoperative atelectasis. We thus assumed there was no cost (unless pneumonia ensued). We ignored the cost of processed electroencephalographic monitoring, including disposable sensors, because of variations in this practice

Table 4. Sensitivity Analyses of the Cost Comparisons, Mean ± SD

	N_2O-free Group (n = 997)	N_2O Group (n = 1,015)	*P* Value
Total estimated variable costs (US dollars)	13,837 ± 13,256	16,203 ± 20,842	0.002
Assuming cost estimates of the following as 1/4 that used in the main analysis			
Wound infection	13,228 ± 12,421	15,379 ± 19,902	0.004
Pneumonia	13,686 ± 12,734	15,915 ± 20,136	0.003
Bed-days	4,242 ± 5,301	5,187 ± 7,487	0.001
Assuming cost estimates of the following as fourfold higher than that used in the main analysis			
Wound infection	16,273 ± 18,712	19,500 ± 26,536	0.002
Pneumonia	14,444 ± 16,127	17,356 ± 24,631	0.002
Bed-days	52,218 ± 47,604	60,269 ± 76,765	0.005
Cost estimates if including non-statistically significant complications: pneumothorax, myocardial infarction, and stroke	13,890 ± 13,595	16,303 ± 21038	0.002

around the world. We also ignored infrastructure costs needed to supply N_2O (bulk gas supplies, piping, anesthetic machine). The cost of processed electroencephalographic monitoring and infrastructure costs are biased against the avoidance of N_2O, and so if these costs are altered they would add further cost to the N_2O group and will not alter our conclusions.

The estimated costs were drawn from studies undertaken in the United States, Canada, Europe, Australia, New Zealand, and Southeast Asia, providing a representative sample of different clinical practices. However, this sample was skewed toward practice in the developed world and is therefore limited in its representation of developing countries. This finding is the result of a lack of health economic studies about postoperative complications conducted in developing countries and identified by our literature review. Use of previous studies to derive cost estimates has limitations. Despite providing a pooled estimate from a variety of health care settings, it may not truly represent the study setting of the original ENIGMA trial, and the magnitude of the complication cost may differ across groups. It does, however, provide data that are more readily generalizable.[66]

An adverse effect of N_2O on severe PONV is the most robust finding of the ENIGMA trial. Several studies[68–71] have reported that avoiding PONV is a high priority for our patients. Gan *et al.*[68] found that patients were willing to pay approximately $100 for an effective antiemetic that would avoid PONV, a finding consistent with that of other studies.[69,71] Using a cost-benefit rationale, it would seem reasonable to spend up to these values in prophylactic strategies to avoid PONV. Because N_2O is a well-established contributor to PONV risk and a small contributor to the cost of anesthesia, avoidance of N_2O would seem to be a cost-effective strategy in this context.

The concept of a financial burden proportional to PACU length of stay has been disputed previously. Dexter and Tinker[72] found that the major determinant of PACU costs was the distribution of admissions throughout the day because the costs are primarily the result of wages (98%), which remain constant despite faster recovery, avoidance of PONV, or early discharge. However, the model used by Dexter and Tinker does not consider the cumulative effect of fixed PACU resources if the PACU closes. This is significant from a practical point of view and is an additional financial burden because the cost of operating room time is greater than that of a PACU bed. In addition, the rate of postoperative adverse events proportionally increases the nursing resources needed in PACU.[73] Therefore, the speed to suitability for PACU discharge, including the absence of PONV, is a relevant factor in considering PACU costs.

Anesthesiologists now work within an environment of limited resources and increasingly must justify the costs of our clinical decisions. This cost-benefit analysis found that despite the very low acquisition cost of N_2O, there are marked additional costs associated with its use. There is no cogent argument to continue using N_2O on the basis that it is an inexpensive drug.

References

1. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E, ENIGMA Trial Group: Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. Anesthesiology 2007; 107:221–31
2. Sharma D: Nitrous oxide: Time to laugh it off? Not quite. Anesthesiology 2008; 108:541–2
3. Drummond MF, Jefferson D: Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party BMJ 1996; 313:275–83
4. Weinberg L, Story D, Nam J, McNicol L: Pharmacoeconomics of volatile inhalational anaesthetic agents: An 11-year retrospective analysis. Anaesth Intensive Care 2010; 38:849–54
5. Dalgleish D, Fletcher M: Oxygen wastage. Anaesthesia 2007; 62:1188
6. Dion P: The cost of anaesthetic vapours. Can J Anaesth 1992; 39:633–4
7. Ballantyne JC, Chang Y: The impact of choice of muscle relaxant on postoperative recovery time: A retrospective study. Anesth Analg 1997; 85:476–82
8. Chan VW, Peng PW, Kaszas Z, Middleton WJ, Muni R, Anastakis DG, Graham BA: A comparative study of general anesthesia, intravenous regional anesthesia, and axillary block for outpatient hand surgery: Clinical outcome and cost analysis. Anesth Analg 2001; 93:1181–4
9. Kain ZN, Gaal DJ, Kain TS, Jaeger DD, Rimar S: A first-pass cost analysis of propofol *versus* barbiturates for children undergoing magnetic resonance imaging. Anesth Analg 1994; 79:1102–06
10. Carroll NV, Miederhoff PA, Cox FM, Hirsch JD: Costs incurred by outpatient surgical centers in managing postoperative nausea and vomiting. J Clin Anesth 1994; 6:364–9
11. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, Gan TJ: Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol or placebo. Anesthesiology 2000; 92:958–67
12. Pueyo FJ, Olaondo L, Sanchez-Ledesma MJ, Ortega A, Carrascosa F: Cost-effectiveness of three combinations of antiemetics in the prevention of postoperative nausea and vomiting. Br J Anaesth 2003; 91:589–92
13. Watcha MF, Smith I: Cost-effectiveness analysis of antiemetic therapy for ambulatory surgery. J Clin Anesth 1994; 6:370–7 [letter]
14. Zarate E, Watcha MF, White PF, Klein KW, Sa Rego M, Stewart DG: A comparison of the costs and efficacy of ondansetron versus dolasetron for antiemetic prophylaxis. Anesth Analg 2000; 90:1352–8
15. Alfonso JL, Pereperez SB, Canoves JM, Martinez MM, Martinez IM, Martin-Moreno JM: Are we really seeing the total costs of surgical site infections? A Spanish study. Wound Repair Regen 2007; 15:474–81
16. Brown PP, Kugelmass AD, Cohen DJ, Reynolds MR, Culler SD, Dee AD, Simon AW: The frequency and cost of complications associated with coronary artery bypass grafting surgery: Results from the United States Medicare program. Ann Thorac Surg 2008; 85:1980–6
17. Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P: Adverse impact of surgical site infections in English hospitals. J Hosp Infect 2005; 60:93–103
18. Coello R, Glenister H, Fereres J, Bartlett C, Leigh D, Sedgwick J, Cooke EM: The cost of infection in surgical patients: A case-control study. J Hosp Infect 1993; 25:239–50
19. Coskun D, Aytac J, Aydinli A, Bayer A: Mortality rate, length of stay and extra cost of sternal surgical site infections

following coronary artery bypass grafting in a private medical centre in Turkey. J Hosp Infect 2005; 60:176–9

20. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr: Hospital costs associated with surgical complications: A report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg 2004; 199: 531–7
21. Haley RW, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JE Jr: Extra charges and prolongation of stay attributable to nosocomial infections: A prospective interhospital comparison. Am J Med 1981; 70:51–8
22. Hall RE, Ash AS, Ghali WA, Moskowitz MA: Hospital cost of complications associated with coronary artery bypass graft surgery. Am J Cardiol 1997; 79:1680–2
23. Herwaldt LA, Cullen JJ, Scholz D, French P, Zimmerman MB, Pfaller MA, Wenzel RP, Perl TM: A prospective study of outcomes, healthcare resource utilization, and costs associated with postoperative nosocomial infections. Infect Control Hosp Epidemiol 2006; 27:1291–8
24. Hollenbeak CS, Murphy D, Dunagan WC, Fraser VJ: Nonrandom selection and the attributable cost of surgical-site infections. Infect Control Hosp Epidemiol 2002; 23:177–82
25. Jenney AW, Harrington GA, Russo PL, Spelman DW: Cost of surgical site infections following coronary artery bypass surgery. ANZ J Surg 2001; 71:662–4
26. Kasatpibal N, Thongpiyapoom S, Narong MN, Suwalak N, Jamulitrat S: Extra charge and extra length of postoperative stay attributable to surgical site infection in six selected operations. J Med Assoc Thai 2005; 88:1083–91
27. Khan NA, Quan H, Bugar JM, Lemaire JB, Brant R, Ghali WA: Association of postoperative complications with hospital costs and length of stay in a tertiary care center. J Gen Intern Med 2006; 21:177–80
28. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ: The impact of surgical-site infections in the 1990s: Attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol 1999; 20:725–30
29. de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB: Surgical site infection: Incidence and impact on hospital utilization and treatment costs. Am J Infect Control 2009; 37:387–97
30. Mahmoud NN, Turpin RS, Yang G, Saunders WB: Impact of surgical site infections on length of stay and costs in selected colorectal procedures. Surg Infect 2009; 10:539–44
31. McGarry SA, Engemann JJ, Schmader K, Sexton DJ, Kaye KS: Surgical-site infection due to Staphylococcus aureus among elderly patients: Mortality, duration of hospitalization, and cost. Infect Control Hosp Epidemiol 2004; 25:461–7
32. Mugford M, Kingston J, Chalmers I: Reducing the incidence of infection after caesarean section: Implications of prophylaxis with antibiotics for hospital resources. BMJ 1989; 299: 1003–6
33. Olsen MA, Chu-Ongsakul S, Brandt KE, Dietz JR, Mayfield J, Fraser VJ: Hospital-associated costs due to surgical site infection after breast surgery. Arch Surg 2008; 143:53–60; discussion 61
34. Penel N, Lefebvre JL, Cazin JL, Clisant S, Neu JC, Dervaux B, Yazdanpanah Y: Additional direct medical costs associated with nosocomial infections after head and neck cancer surgery: A hospital-perspective analysis. Int J Oral Maxillofac Surg 2008; 37:135–9
35. Plowman R, Graves N, Griffin MA, Roberts JA, Swan AV, Cookson B, Taylor L: The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. J Hosp Infect 2001; 47:198–209
36. Pollard TC, Newman JE, Barlow NJ, Price JD, Willett KM: Deep wound infection after proximal femoral fracture: Consequences and costs. J Hosp Infect 2006; 63:133–9
37. Rubinstein E, Green M, Modan M, Amit P, Bernstein L, Rubinstein A: The effects of nosocomial infections on the length and costs of hospital stay. J Antimicrob Chemother 1982; 9:93–100
38. Schäfer U: Cost analysis in nosocomial infections. A 1-year study in the Surgical Department of Riesa District Hospital. Zentralbl Chir 1987; 112:1552–60
39. Sheng WH, Chie WC, Chen YC, Hung CC, Wang JT, Chang SC: Impact of nosocomial infections on medical costs, hospital stay, and outcome in hospitalized patients. J Formos Med Assoc 2005; 104:318–26
40. Upton A, Smith P, Roberts S: Excess cost associated with Staphylococcus aureus poststernotomy mediastinitis. N Z Med J 2005; 118:1–4
41. Urban J: Cost analysis of surgical site infections. Surg Infect 2006; 7:S19–22
42. Vegas AA, Jodra VM, García ML: Nosocomial infection in surgery wards: A controlled study of increased duration of hospital stays and direct cost of hospitalization. Eur J Epidemiol 1993; 9:504–10
43. Weber WP, Zwahlen M, Reck S, Feder-Mengus C, Misteli H, Rosenthal R, Brandenberger D, Oertli D, Widmer AF, Marti WR: Economic burden of surgical site infections at a European university hospital. Infect Control Hosp Epidemiol 2008; 29:623–9
44. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ: The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: Adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol 2002; 23:183–9
45. Zoutman D, McDonald S, Vethanayagan D: Total and attributable costs of surgical-wound infections at a Canadian tertiary-care center. Infect Control Hosp Epidemiol 1998; 19: 254–9
46. Dietrich ES, Demmler M, Schulgen G, Fekec K, Mast O, Pelz K, Daschner FD: Nosocomial pneumonia: A cost-of-illness analysis. Infection 2002; 30:61–7
47. Muscedere JG, Martin CM, Heyland DK: The impact of ventilator-associated pneumonia on the Canadian health care system. J Crit Care 2008; 23:5–10
48. Thompson DA, Makary MA, Dorman T, Pronovost PJ: Clinical and economic outcomes of hospital acquired pneumonia in intra-abdominal surgery patients. Ann Surg 2006; 243: 547–52
49. Edbrooke DL, Stevens VG, Hibbert CL, Mann AJ, Wilson AJ: A new method of accurately identifying costs of individual patients in intensive care: The initial results. Intensive Care Med 1997; 23:645–50
50. McLaughlin AM, Hardt J, Canavan JB, Donnelly MB: Determining the economic cost of ICU treatment: A prospective ''micro-costing'' study. Intensive Care Med 2009; 35: 2135–40
51. Moerer O, Plock E, Mgbor U, Schmid A, Schneider H, Bernd Wischnewsky M, Burchardi H: A German national prevalence study on the cost of intensive care: An evaluation from 51 intensive care units. Crit Care 2007; 11:R69
52. Moran JL, Peisach AR, Solomon PJ, Martin J: Cost calculation and prediction in adult intensive care: A ground-up utilization study. Anaesth Intensive Care 2004; 32:787–97
53. Norris C, Jacobs P, Rapoport J, Hamilton S: ICU and non-ICU cost per day. Can J Anaesth 1995; 42:192–6
54. Noseworthy TW, Konopad E, Shustack A, Johnston R, Grace M: Cost accounting of adult intensive care: Methods and human and capital inputs. Crit Care Med 1996; 24:1168–72
55. Parno JR, Teres D, Lemeshow S, Brown RB Hospital charges and long-term survival of ICU versus non-ICU patients. Crit Care Med 1982; 10:569–75
56. Rechner IJ, Lipman J: The costs of caring for patients in a

tertiary referral Australian intensive care unit. Anaesth Intensive Care 2005; 33:177–82

57. Ridley S, Biggam M, Stone P: Cost of intensive therapy: A description of methodology and initial results. Anaesthesia 1991; 46:523–30
58. Slatyer MA, James OF, Moore PG, Leeder SR: Costs, severity of illness and outcome in intensive care. Anaesth Intensive Care 1986; 14:381–9
59. Girotti MJ, Brown SJ: Reducing the costs of ICU admission in Canada without diagnosis-related or case-mix groupings. Can Anaesth Soc J 1986; 33:765–72
60. Stephen AE, Berger DL: Shortened length of stay and hospital cost reduction with implementation of an accelerated clinical care pathway after elective colon resection. Surgery 2003; 133:277–82
61. Lemmens L, van Zelm R, Vanhaecht K, Kerkkamp H: Systematic review: Indicators to evaluate effectiveness of clinical pathways for gastrointestinal surgery. J Eval Clin Pract 2008; 14:880–7
62. Briggs A, Gray A: The distribution of health care costs and their statistical analysis for economic evaluation. J Health Serv Res Policy 1998; 3:233–45
63. Barber JA, Thompson SG: Analysis of cost data in randomized trials: An application of the non-parametric bootstrap. Stat Med 2000; 19:3219–36
64. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N: A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess 2007; 11:1–160
65. Poulsen KB, Bremmelgaard A, Srensen AI, Raahave D, Petersen JV: Estimated costs of postoperative wound infections A case-control study of marginal hospital and social security costs. Epidemiol Infect 1994; 113:283–95
66. Perencevich EN, Sands KE, Cosgrove SE, Guadagnoli E, Meara E, Platt R: Health and economic impact of surgical site infections diagnosed after hospital discharge. Emerg Infect Dis 2003; 9:196–203
67. McPeek B: Inference, generalizability, and a major change in anesthetic practice. ANESTHESIOLOGY 1987; 66:723–4
68. Gan TJ, Sloan F, Dear Gde L, El-Moalem HE, Lubarsky DA: How much are patients willing to pay to avoid postoperative nausea and vomiting? Anesth Analg 2001; 92:393–400
69. Kerger H, Turan A, Kredel M, Stuckert U, Alsip N, Gan TJ, Apfel CC: Patients' willingness to pay for anti-emetic treatment. Acta Anaesthesiol Scand 2007; 51:38–43
70. Macario A, Weinger M, Carney S, Kim A: Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg 1999; 89:652–8
71. van den Bosch JE, Bonsel GJ, Moons KG, Kalkman CJ: Effect of postoperative experiences on willingness to pay to avoid postoperative pain, nausea, and vomiting. ANESTHESIOLOGY 2006; 104:1033–9
72. Dexter F, Tinker JH: Analysis of strategies to decrease postanesthesia care unit costs. ANESTHESIOLOGY 1995; 82:94–101
73. Cohen MM, O'Brien-Pallas LL, Copplestone C, Wall R, Porter J, Rose DK: Nursing workload associated with adverse events in the postanesthesia care unit. ANESTHESIOLOGY 1999; 91: 1882–90