Research

Open Access

Importance of nondrug costs of intravenous antibiotic therapy

Arthur RH van Zanten[1], Peter M Engelfriet[2], Karin van Dillen[3], Miriam van Veen[3], Mark JC Nuijten[4] and Kees H Polderman[5]

[1]Senior Consultant in Intensive Care, Director of Intensive Care, Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands
[2]Project Manager, Medtap International Inc., Jisp, The Netherlands
[3]Research Nurse, Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands
[4]Managing Director, Medtap International Inc., Jisp, The Netherlands
[5]Senior Consultant in Intensive Care, Department of Intensive Care, VU University Medical Center, Amsterdam, The Netherlands

Correspondence: Arthur RH van Zanten, zantena@zgv.nl

Received: 1 July 2003

Revisions requested: 20 August 2003

Revisions received: 26 August 2003

Accepted: 17 September 2003

Published: 14 October 2003

Critical Care 2003, **7**:R184-R190 (DOI 10.1186/cc2388)

This article is online at http://ccforum.com/content/7/6/R184

Abstract

Introduction Costs are one of the factors determining physicians' choice of medication to treat patients in specific situations. However, usually only the drug acquisition costs are taken into account, whereas other factors such as the use of disposable materials, the drug preparation time and the staff workload are insufficiently taken into consideration. We therefore decided to assess true overall costs of intravenous (IV) antibiotic administration by performing an activity-based costing approach.

Methods A prospective survey on costs and workload by means of a time and motion analysis and activity-based costing was performed in a 605-bed secondary referral centre with 20 intensive care unit beds. The subjects were 50 consecutive patients admitted to our hospital with community-acquired pneumonia or intra-abdominal infections requiring treatment with IV antibiotics. A time and motion analysis of 103 routine acts of preparing and administering IV antibiotics was performed in the intensive care unit and in the Department of Internal Medicine. To measure the entire process an inventory and work flowchart were made using detailed questionnaires completed by members of the nursing staff, the medical staff and the pharmacy staff. In addition, questionnaires were distributed to management and secretarial staff to determine additional overhead costs. The average costs for different methods of IV antibiotic administration were then compared by timing all steps in the process. Four different methods of drug administration were used: administration by volumetric pump, administration by syringe pump, administration by 'unaided' infusion bag, and administration by direct IV injection.

Results The average times required for each of these procedures, including preparation and administration of the drug, were 4:49 ± 2:37, 4:56 ± 2:03, 5:51 ± 3:33 and 9:21 ± 2:16 min (mean minutes:seconds ± standard deviation), respectively. When the costs for expended staff time and materials (not including drug costs) were calculated this resulted in average costs of €5.65, €7.28, €5.36 and €3.83, respectively, for administration of each dose of antibiotics. These costs represent between 11% and 53% of the total daily costs of antibiotic therapy. Compared with the acquisition costs, these indirect costs ranged from 13% to 113%. Not included in this comparison is the time required for insertion of an IV catheter, which was found to be 10:15 ± 6:31 min with an average calculated cost of €9.17.

Conclusions Total costs of IV antibiotic administration are formed not only by the costs of the drugs themselves, but also, to a substantial degree, by the time expended by medical and nursing staff, costs of disposable materials and overhead costs. Physicians making decisions regarding the use of specific medications in intensive care unit patients should take these factors into account. Use of IV antibiotics is associated with considerable workload and additional costs that can exceed the acquisition costs of the medications themselves.

Keywords activity-based costing, antibiotics, costs, drug administration, indirect costs, material costs, personnel costs, workload

HCU = high care unit; ICU = intensive care unit; IV = intravenous.

Introduction

A number of studies have suggested that the overall quality of care, outcome, and patient and family satisfaction in intensive care units (ICUs) may be linked to the workload and staffing levels [1–4]. Budgetary restrictions may play an important role in the organisation of the ICU, and cost reduction is an important issue in intensive care medicine today since ICU costs account for up to 10% of overall hospital expenditure [5,6].

Antibiotics are among the most frequently used drugs in intensive care patients, and thus account for a substantial proportion of drug expenditure in ICUs [7]. When performing pharmacoeconomic evaluations of ICU expenditure, it is customary to consider only the direct price of purchasing these medications. To assess the total costs of intravenous (IV) drug therapy in the ICU setting, however, it is necessary to take into account the effect on the workload of nurses and medical staff as well as other health care workers, and to evaluate other costs associated with preparation, administration and monitoring of IV antibiotic therapy. Gaining insight into all the factors that contribute to the actual total overall costs of drug therapy may help increase awareness into what actually drives the costs of hospital services, and to identify opportunities for cost savings.

To assess the costs associated with drug preparation and administration we performed an observational time and motion study in two ICUs in our hospital. For comparison, we also performed this analysis in a general internal medicine ward. The basis of a time and motion study is the measurement, through direct observation by the investigators and the research nurses involved in the study, of staff members performing specific tasks in a process that is subdivided into various components [8]. Indirect costs related to drug therapy, such as costs incurred in assessment of safety and efficacy, were not considered in this study.

Materials and methods

This time and motion analysis was conducted from December 2000 until June 2001 in Gelderse Vallei Hospital, a 605-bed secondary referral centre in The Netherlands.

Activity-based costing is a method originally developed for business administration that is increasingly being used in the health care environment and in hospital administration. Its goal is to determine the actual costs that need to be incurred to deliver a product or service, and to assess and quantify the various components making up the total cost [9,10]. We used activity-based costing to calculate the actual costs of treating patients with IV antibiotic therapy. The costs were subdivided into four components: the acquisition costs of drugs; the costs of the disposable materials used; the costs related to the use of medical and nursing staff, calculated by multiplying the time expended by individual staff members to perform specific tasks by the costs of employing these staff members (wages, fringe benefits and taxes); and the allocation of indirect costs such as overheads, use of storage space and the electricity used.

Questionnaires were initially given to hospital staff, and interviews were conducted to assess and record the entire process related to the administration of IV antibiotics. This preliminary analysis was performed in order to develop appropriate data transcription forms, to obtain data on salaries and material costs, and to identify additional factors contributing to total costs. The questionnaires, in combination with existing protocols, were then used to compile an extensive list of all the separate actions that were required for the preparation and administration of each of the medications studied, and for each of the methods of drug administration used in our hospital.

Fifty consecutive patients requiring treatment with IV antibiotics who were admitted to the ICU ($n=22$), to the high care unit (HCU) ($n=24$) or to the internal medicine ward ($n=4$) with community-acquired pneumonia or intra-abdominal infections were included in the study. No specific exclusion criteria were used as this study aimed at the process of, and not at the indications or efficacy of, IV antibiotic administration. Informed consent was obtained from the patient or relatives according to the hospital's ethical guidelines and the declaration of Helsinki.

A total of 103 routine acts of preparing and administering IV antibiotics were observed and timed by stopwatch by two research nurses familiar with IV antibiotic preparation and administration while observing 76 single (ICU) nurses performing the 103 procedures of preparation and administration of the antibiotics. The preparation and administration of IV antibiotics in our hospital is performed by nurses. No satellite pharmacy is available on wards and there are no IV additive services by the Department of Pharmacy.

Four pharmacists and two technicians were involved in the study. Preparation and administration of antibiotics were measured separately. The time intervals as well as the materials used were recorded on data transcription forms. The medications studied were six of the most widely used IV antibiotics: amoxicillin/clavulanic acid, piperacillin/tazobactam, cefotaxim, metronidazole, gentamicin and erythromycin. Four different methods of administration were studied: infusion by syringe pump, infusion by volumetric pump, infusion by direct IV injection (bolus injection, IV push injection), and simple piggyback infusion (medication added to infusion bag of an ordinary drip). Actions associated with the insertion and removal of a peripheral IV catheter were studied separately because most patients in the ICU already have venous access.

Cost assessment

The data recorded on the data transcription forms were used as the basis for the assessment of costs of preparation and of administration. Average total costs for each of the different methods of drug administration were calculated by considering the following cost components.

Wages

Yearly salaries for relevant staff members were converted to hourly wages by dividing the yearly income by the number of 'workable hours'. These hourly wages were then used to convert time measurements into costs per procedure.

Costs for disposable material

The average numbers of items used for each procedure were multiplied by unit prices to arrive at average total costs for disposable material for each procedure.

Other costs

Estimates were made to determine the impact of other costs on total costs by considering the categories 'monitoring activities', 'infusion pumps', 'administrative costs', 'storage, distribution and inventory', and 'waste disposal'.

A number of potential additional costs were disregarded because they were assumed not to be directly related to the IV administration route and for various other reasons, including the following:

- Overhead costs associated with storage, distribution and inventory. As already stated, these costs were considered insignificant compared with the other costs involved, and were assumed to be the same for different types of medication, and for both oral or IV medications.
- The processing of a prescription for IV antibiotics. This procedure is the same for all types of prescriptions.
- Time spent by the head of the hospital pharmacy on quality assurance, providing advice regarding antibiotic therapy, developing protocols, and so on. These costs were considered unavoidable in any type of therapy, and were considered central to the task of the pharmacy.
- Costs for disposal of waste. IV administration of antibiotics obviously generates 'extra' waste, such as empty syringes, IV tubing, gauzes and needles, and so on. Although this waste is collected and disposed of as part of a general system of waste disposal in the hospital, some of the costs associated with the maintenance of this system should probably be allocated to IV antibiotics administration. We decided not to allocate these costs because they could not be exactly calculated, and therefore allocation would involve a more or less random estimate. The additional costs incurred for waste disposal are unlikely to significantly affect the overall differences in costs; in addition, disposal costs are higher for IV medications, so any differences observed in the present study are probably underestimated.
- Costs associated with complications related to access to the blood stream. The risks of IV access, especially through central venous catheters, are well recognised and represent an important issue for physicians working in the ICU. The most important of these is infection, which can lead to significant morbidity, mortality and extra costs [11–15]. Another significant potential problem is needle stick injury. However, the magnitude of the costs due to such hazards, and what proportion of these costs should be attributed to IV antibiotics therapy, would again involve a more or less random estimate. Moreover, our study was not designed to address this issue. Therefore, these costs were also not taken into account.

Statistics

Calculations and statistical analysis were performed using Excel and SSPS9 software for Windows. All data are expressed as the mean ± standard deviation. Student's unpaired *t* test was used for comparisons between the different modes of antibiotic preparation and antibiotic administration. Costs were calculated and compared both including and excluding the costs of the antibiotics themselves. Costs associated with the insertion and removal of central and/or peripheral intravascular devices were analysed separately. Statistical significance was accepted for $P < 0.05$.

Results

Thirty-four male patients (mean age, 72 years; range, 35–86 years) and 16 female patients (mean age, 55 years; range, 31–87 years) were included in the study. A total of 103 procedures for IV antibiotic administration were observed in these patients. Community-acquired pneumonia was diagnosed in 35 patients (70%) and intra-abdominal infections diagnosed in 15 patients (30%). Overall, 45 procedures (44%) were observed in the ICU, 46 procedures (45%) in the HCU and 12 procedures (12%) in the general internal ward. The data were initially analysed separately; when no significant differences were found between the ICU, the HCU and the internal medicine ward, the data were pooled.

Table 1 presents the times required for each of the subcategories of procedures, the expenditure on hourly wages (depending on location and category of staff involved), the costs for disposable material and the resulting total costs per procedure. The figures depict the total time expended on preparation and administration of the study medications, averaged over the different medications, the different wards and the different reasons for starting antibiotic therapy. No medication costs are included.

Results are based on the following yearly average wages: ICU nurse, €36,211.66; HCU nurse, €31,093.02; ward nurse, €29,895.04; pharmacist, €92,189.99; pharmacy technician, €31,528.65; ward assistant, €21,454.73; and consulting physician, €108,907.25.

By adding up costs for each type of procedure the following total costs per procedure were obtained: €3.91 for volumetric pump administration, €3.23 for syringe pump administration, €11.69 for direct IV administration, €5.40 for piggy

Table 1

Total costs of intravenous antibiotic administration using different methods of administration

Procedure	Time required (standard deviation) (min:s)	Hourly wages (€)	Time costs (€)	Materials costs (€)	Total costs (€)
Volumetric pump	5:04 (2:29)	21.90	01.85	02.06	03.91
Syringe pump	4:56 (2:03)	21.58	01.78	01.45	03.23
Bolus injection	9:21 (2:16)	74.09	11.59	00.10	11.69
Piggyback infusion	5:51 (3:33)	19.75	01.93	03.47	05.40
Insertion of intravenous catheter	10:15 (6:31)	23.51	04.02	04.30	08.32
Removal of intravenous catheter	02:22 (0:36)	19.41	00.74	01.00	01.74

Data presented are the time expenditure required for each of the procedures considered, the appropriate hourly wage rates (depending on the ward and the type of staff involved), the costs for disposable material and the resulting total costs per procedure. The values quoted refer to the total time for preparation followed by administration of the medication, averaged over medications, wards and indications studied. No medication costs are included.

back infusion, €8.32 for the insertion of an IV catheter and €1.74 for the removal of an IV catheter. No observations using central venous catheters were made. Again, it should be emphasised that these costs do not include the costs of the drugs themselves. Direct IV administration is time consuming due to fact that the antibiotic has to be infused slowly, and costs are high because only certified nurses or physicians are allowed to perform such procedures.

Although it was not possible to precisely determine costs incurred by other categories of activities–such as storage space, time spent by other personnel (e.g. pharmacy technicians), unallocated time, depreciation of medical equipment (e.g. infusion pumps) and overheads–it was estimated that these other costs were minor compared with personnel costs and material costs. Monitoring for IV antibiotics therapy in general does not take up much time and is usually performed between other nursing activities. Procedures that pertain to the maintenance of an IV access port cannot be considered due to antibiotics therapy in ICUs, as all patients will require an IV access site for various other purposes. The same applies to dealing with the complications that are caused by central venous catheters. On general wards, however, an IV catheter may be inserted with the specific goal of administering antibiotics. Costs due to monitoring and complications in such cases could therefore, in principle, be allocated to the administration of IV antibiotics.

Costs associated with the monitoring of drug levels through assessment of serum levels of gentamicin were estimated based on the materials used and the staffing time costs for the blood sampling, the measurement of drug levels, the time used for kinetic modelling using MW/Pharm software (Mediware, Zuid-Hoorn, The Netherlands) and the time for recommending the optimal dosing strategy. Calculated in this way, the costs for therapeutic drug monitoring were €36.00 per dose based on a once-daily gentamicin dosage. These costs would decrease proportionately if longer dosing intervals were used.

The equipment used to administer IV drugs is quite expensive and requires maintenance. Gelderse Vallei Hospital uses Braun Infusomat® fmS volumetric pumps and Braun Perfusor® fm syringe pumps (Braun Medical AG, Melsungen, Germany). The depreciation period is set at 10 years (10% per year). If maintenance costs are disregarded, the cost is less than €0.34 per administration procedure.

The pharmacy of the hospital processes about 170,000 prescriptions per year, with one prescription requiring about 3–5 min of work by a pharmacy assistant. The number of administrations per prescription should divide this time. In general, one prescription will lead to at least 10 administrations (two per day for 5 days), so costs of less than €0.17 can be allocated to the pharmacy cost item.

Average times required for preparation and administration of antibiotics showed an ascending order from the ICU to the HCU to the internal medicine ward. A subanalysis of cases where the same drug was administered according to the same method on different wards revealed a number of nonsignificant trends toward smaller time expenditure in the ICU. For example, a difference between average times required for administration of erythromycin via a volumetric pump in the ICU and in the HCU was noted (8:21 ± 2:38 min versus 9:7 ± 2:21 min, $P = 0.38$). For cefotaxim administration via syringe pump these values are 4:2 ± 2:3 min versus 4:53 ± 0:36 min, respectively ($P = 0.13$). However, our study was not designed to detect differences between various units.

Table 2 presents the workload, the staff costs, the material costs, the medication costs and the total costs for the six different antibiotics studied. A marked difference in costs of erythromycin administration compared with the other antibiotics

Table 2

Daily costs of six antibiotics intravenously administered by syringe pump

Antibiotic	Dose (mg)	Dosages (*n*)	Drug costs (€) (A)	Average time (min:s)	Staff costs (€) (B)	Material costs (€) (C)	Administration costs (€) (B + C)	Total daily costs (€) (A + B + C)
Amoxicillin/clavulanic acid	1000/200	3	07.35	12:21	03.99	04.35	08.34	15.69
Cefotaxim	1000	4	49.40	18:48	06.08	05.80	11.88	61.28
Erythromycin	1000	4	54.44	36:44	11.88	05.80	17.68	72.12
Gentamicin	320	1	20.34	03:39	01.18	01.45	02.63	22.97*
Metronidazole	500	3	12.24	05:24	01.74	04.35	06.09	18.33
Piperacillin/tazobactam	2250	3	43.14	16:31	05.40	04.35	09.75	52.89

Data presented are the medication costs, the time expenditure required, the staff wage and the disposable material costs for each of the antibiotics per day administrated via syringe pump. The figures quoted refer to the total time for preparation and administration of each medication per day, averaged over wards and indications studied. Costs are based on list prices provided by Dutch health care authorities [17].
*If therapeutic drug monitoring costs for gentamicin based on 24-hourly intervals would be included, the total costs would be €58.97 per day.

is primarily due to the relative insolubility of erythromycin powder, requiring significantly longer preparation times. The short preparation time for metronidazole is due to the fact that it is delivered as a 0.5% solution contained in a 100 ml bottle ready for infusion. This is the only drug in the study that is prepared by the hospital pharmacy.

Discussion

The results of the present study demonstrate that administration of antibiotics is associated with significant hidden costs, which in some cases even exceed the costs of the antibiotics themselves. This is due mainly to the fact that medical staff and, especially, nursing staff spend a considerable amount of time preparing and administering the medications chosen for the study. Although the scope of the study was limited to antibiotics, our results probably also apply to other types of medication.

In the ICU setting, patients in ICUs with a high workload are significantly more likely to die than patients in ICUs with a lower workload, even after adjustment for severity of illness [2,3]. Other studies have demonstrated that the time required for weaning off the ventilator in patients with severe chronic obstructive pulmonary disease is dependent on the availability and time of (qualified) nurses [4]. In addition, the degree of satisfaction with the ICU care of patients and their families appears to be related to staffing levels and to workload [1]. All these factors underscore the importance of controlling the workload as well as the costs associated with the administration of antibiotics, as well as other types of medications. Decreasing this type of workload will allow health care workers to spend more time on other aspects of patient care, which would probably improve outcome and overall care of ICU patients and their families.

The present results demonstrate that the workload required for drug preparation and administration should be taken into account when performing an overall cost assessment. This also applies to costs incurred from usage of disposable materials; in fact, the workload and costs for disposable materials were important cost drivers in our study, accounting for 13–53% of the overall costs for treatment with IV antibiotics and for 13–113% of the total acquisition costs of medication. Moreover, our study probably overestimates the contribution of acquisition costs to overall costs because list prices were used to determine acquisition costs. In The Netherlands (as in most other European countries) hospitals often negotiate price reductions varying from 20% to 70% of listed prices for IV antibiotics. We did not take this into account because of the variable nature of these discounts; however, the impact on the overall prices is probably substantial. In addition, differences in costs have probably been underestimated because additional costs incurred by central line infections and waste disposal were not taken into account for the reasons outlined in Materials and methods.

When performing pharmacoeconomic evaluations of IV antibiotics administration it is thus important to include costs associated with preparation and with administration, as these can be the major cost drivers. This is exemplified by a study by Kreter [16], who demonstrated that acquisition costs of imipenem-cilastatin monotherapy were considerably higher compared with clindamycin/aminoglycoside combination therapy for treatment of serious lower respiratory infections, intra-abdominal infections, gynaecologic infections and urinary tract infections. When costs at that moment related to preparation, to administration and to monitoring of both regimens were also taken into account, however, the overall costs of the two antibiotic regimes were not significantly different [16].

Our observations of high costs incurred by bolus injection administration of antibiotics are in contrast with the widely held view that this is the cheapest method of administration.

Several factors can account for this observation. Most antibiotics used in our study had to be administered slowly, implying a longer time period required for complete administration coupled with higher staff costs. On the contrary, during piggy back infusion we did not count the total duration but only those moments that could be related to the process of preparation, of administration and of monitoring of the infusion.

In addition, as explained earlier, a number of additional costs were not taken into account in the present study because it was not possible to obtain exact measurements. These included costs for waste disposal and costs associated with catheter-related complications or other problems. Although not measured in this study, these costs are probably considerable [11–15]. Therapeutic drug monitoring for a single measurement of gentamicin levels was previously estimated by other workers to be approximately €25 [18] and was found to be €36 in our study. The difference is explained by cost increases over time and by the fact that we included the time used for obtaining the blood sample and for the kinetic modelling. If costs related to aminoglycoside-induced nephrotoxicity are taken into account the amount would be considerably higher [18]. The calculations in our study thus almost certainly substantially underestimate the contribution of nonacquisition costs to the overall costs of antibiotic therapy. Further studies will be required to adequately assess the importance of yet other potential cost factors, which might even include costs due to medical errors and other complications of IV therapy.

The present study evaluated only monotherapy antibiotic regimens. However, ICU patients often develop complex infections that are difficult to treat, and they often require combinations of different IV antibiotic formulations. It seems probable that such regimens will require disproportionately more time for preparation and for administration, thereby significantly increasing the workload and costs. Moreover, such treatments may require insertion of a central venous catheter, increasing costs even further. As already discussed, significant additional costs (up to €20,000) may be incurred if the patient develops a central line infection [11–13].

In the present study it proved difficult to accurately determine what overhead costs were directly related to IV antibiotic therapy. In addition, the design of the study did not allow an accurate evaluation of sources of variation. Nevertheless, the results indicate that these costs varied according to the department, to the category of staff involved (differential wage rates) and to the type of medication administered (due to differences in preparation time). These variables, however, are not independent; we observed a trend toward longer preparation and administration time in general wards, but lower nursing staff wages compared with ICU nurses in part compensated the costs for this.

Strategies to reduce total costs of IV antibiotics may include the use of single daily dose regimens, the reduction of treatment duration, the use of drugs with low toxicity so that monitoring of drug levels is not necessary and the use of quickly dissolvable drug powders and/or ready-to-use-vials or syringes. Furthermore, rational antibiotic therapy policies that take these aspects into account can help promote a beneficial economic impact without adverse effects on outcome [19]. It should be noted that, at present, there is an increasing tendency to switch from the IV route to the oral route for administration of antibiotics at an early stage of therapy [20]. This strategy may help reduce costs. However, this requires that the patient is capable of oral intake, that the antibiotic is suitable for oral use and has a high bioavailability, and that the patients' intestinal function is intact. Especially in intensive care patients there is insufficient evidence that such a strategy is safe and effective.

A limitation of the present study is that the calculations are based on the Dutch situation, using Dutch wages and Dutch medication prices. These costs are unlikely to be completely different in other European countries, however, and our observation that nondrug costs are important cost drivers in IV antibiotic use in the ICU almost certainly also apply to other countries.

In conclusion, we observed that the indirect costs of IV antibiotic administration such as the workload and the use of disposable materials are considerable. Our findings are probably also applicable to medications other than antibiotics. In our opinion this type of cost should be taken into account when determining the overall expenditure for specific therapies, and physicians should become more aware of such 'hidden' costs. Significant cost savings could potentially be realised by taking these factors into account when choosing a specific medical therapy, and by developing alternative methods of preparation and administration that require less work and less use of disposable materials. Apart from the financial aspect such reductions in time and workload may help improve outcome and patient satisfaction in the ICU, especially in situations of high workload and limited resources.

Competing interests

None declared.

Acknowledgements

The authors wish to thank EB Milbrandt, Vanderbilt University school of Medicine, Nashville, Tennessee, USA and YG van der Meer, PharmD, Gelderse Vallei Hospital, Ede, The Netherlands for their critical appraisal of our manuscript. They also wish to thank all the nurses performing the preparations and administration. This study was supported by a grant from Merck & Co, USA.

References

1. Heyland DK, Rocker GM, Dodek PM, Kutsogiannis DJ, Konopad E, Cook DJ, Peters S, Tranmer JE, O'Callaghan CJ: **Family satisfaction with care in the intensive care unit: results of a multiple center study.** *Crit Care Med* 2002, **30:**1413-1418.
2. Tarnow-Mordi WO, Hau C, Warden A, Shearer AJ: **Hospital mortality in relation to staff workload: a 4-year study in an adult intensive-care unit.** *Lancet* 2000, **356:**185-189.

3. Tucker J, UK Neonatal Staffing Study Group: **Patient volume, staffing, and workload in relation to risk-adjusted outcomes in a random stratified sample of UK neonatal intensive care units: a prospective evaluation.** *Lancet* 2002, **359:**99-107.
4. Thorens JB, Kaelin RM, Jolliet P, Chevrolet JC: **Influence of the quality of nursing on the duration of weaning from mechanical ventilation in patients with chronic obstructive pulmonary disease.** *Crit Care Med* 1995, **23:**1807-1815.
5. Norris C, Jacobs P, Rapaport J, Hamilton S: **ICU and non-ICU cost per day.** *Can J Anaesth* 1995, **42:**192-196.
6. Chalfin DB, Cohen IL, Lambrinos J: **The economics and cost-effectiveness of intensive care medicine.** *Intensive Care Med* 1995, **21:**525-537.
7. Marschner JP, Thurmann P, Harder S, Rietbrock N: **Drug utilization review on a surgical intensive care unit.** *Int J Clin Pharmacol Ther* 1994, **32:**447-451.
8. Niebel BW: *Motion and Time Study*. Homewood, IL: Irwin; 1976.
9. Canby JB: **Applying activity-based costing to healthcare settings.** *Healthc Financ Manage* 1995, **49:**54-56.
10. Gabram SG, Mendola RA, Rozenfeld J, Gamelli RL: **Why activity-based costing works.** *Physician Exec* 1997, **23:**31-37.
11. Pittet D, Tarara D, Wenzel RP: **Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality.** *JAMA* 1984, **271:**1598-1601.
12. Martin MA, Pfaller MA, Wenzel RP:**Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay.** *Ann Intern Med* 1989, **110:**9-16.
13. Polderman KH, Girbes ARJ: **Central venous catheter use part 2: infectious complications [review].** *Intensive Care Med* 2002, **28:**18-28.
14. Polderman KH, Girbes ARJ: **Central venous catheter use. Part 1: mechanical complications [review].** *Intensive Care Med* 2002, **28:**1-17.
15. Pearson ML, Hospital Infection Control Practices Advisory Committee: **Guideline for prevention of intravascular device-related infections. Part I. Intravascular device-related infections: an overview.** *Am J Infect Control* 1996, **24:**262-277.
16. Kreter B: **Cost-analysis of imipenem-cilastatin monotherapy compared with clindamycin + aminoglycoside combination therapy for treatment of serious lower respiratory, intra-abdominal, gynaecologic, and urinary tract infections.** *Clin Ther* 1992, **14:**110-121.
17. Gribnau FWJ, Van Luijn JCF: *Het Farmacotherapeutisch Kompas 2002*. Naarden: Synavant, College voor Zorgvoorzieningen; 2002.
18. Hitt CM, Klepser ME, Nightingale CH, Quintiliani R, Nicolau DP: **Pharmacoeconomic impact of once-daily aminoglycoside administration.** *Pharmacotherapy* 1997, **17:**810-814.
19. Blanc P, Von Elm BE, Geissler A, Granier I, Boussuges A, Durand Gasselin J: **Economic impact of a rational use of antibiotics in intensive care.** *Intensive Care Med* 1999, **25:**1407-1412.
20. Sevinc F, Prins JM, Koopmans RP, Langendijk PN, Bossuyt PM, Dankert J, Speelman P: **Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital.** *J Antimicrob Chemother* 1999, **43:**601-606.