Cost of hospital antimicrobial chemotherapy

A method for global cost calculation

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Introduction

The true cost of health care is what health care consumes of society's resources. Under a traditional medical system, hospital costs (*i.e.* consumption of hospital services such as those provided by the pharmacy and laboratory) are passed on to the patient or third-party payers and generate revenues for the hospital, contributing to the inflationary spiral in health care costs.

In general hospitals in the Netherlands, the current budget system was introduced in 1983 and university hospitals followed in 1984. These budgets are based on a hospital's consumption of resources during the year 1982 for general hospitals and 1983 for university hospitals. In this budget system, it has become of primary importance to contain internal costs since the Government has limited hospital costs in an external budget. In 1988, a function-directed budget system was introduced for general hospitals [1].

A significant portion of a hospital's total operating budget consists of drug purchases. As in the prospective payment system which is used in the United States (*i.e.* reimbursment categorized according to diagnosis-related groups), drug costs for in-patients generate no revenues. Antimicrobial drugs account for the largest proportion of all drugs, ranging from 13 to 37% of these purchases by hospitals in a European study [2]. However, the true cost of antimicrobial therapy for the institution involves considerably more than the purchase cost of the drug employed [3]. The recognition that some drugs, which are very inexpensive to purchase, are expensive to use prompted the development of methods to estimate the global cost of antimicrobial chemotherapy [4-6].

We performed a cost-identification analysis as described by Eisenberg [7], during a review of antimicrobial drugs usage evaluation. We applied a method for global cost calculation which takes into account acquisition costs, administration and preparation costs, and monitoring costs in our hospital [8]. We subsequently constructed a cost-calculation system which quantifies the cost difference for each route and each intravenous system of antimicrobial drug administration. The method permits comparison of the cost of actual and alternative antimicrobial drug policies in the quality-of-use review.

Methods

During a review of antimicrobial drug use evaluation in the 948-bed University Hospital of Nijmegen (the Netherlands), cost parameters were determined for the following components of antimicrobial chemotherapy of in-patients: antimicrobial drug purchase costs, clerical costs, costs to prepare and administer the drugs and costs to monitor the drugs. The various cost components were arranged in a spreadsheet, which permits calculation of the global cost per dose.

Purchase costs

The prices on the official wholesale price-list "Groothandelsprijslijst Courant Brocacef 1990" were chosen to determine the acquisition cost of antimicrobial drugs, instead of the contract prices of the hospital. Contract prices tend to vary between hospitals, reflecting the institution's antibiotic and purchase policy. The true

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Abstract

We will describe the method of cost-identification analysis, which was performed in a Dutch hospital during a review of antimicrobial drugs usage. In the present Dutch hospital budget system, in-patients' drug costs generate no revenues. Efforts to diminish drug costs result in financial benefit for the institution. To maximize cost containment, efforts are to be directed to all cost components. We chose wholesale purchase prices of antimicrobial drugs and national prices for salaries and hospital costs. Global cost comparison shows the most cost effective system of intravenous administration. Push injection is the most economic way to administer intravenous drugs which do not require dilution or prolonged infusion time. For stable solutions, such as metronidazole, ready-to-infuse bags are the most economic system. A global cost calculation is listed for commonly used antimicrobial drugs for in-patients. A cost comparison is given for vancomycin CP and teicoplanin, two antistaphyloccocal drugs, which are probably equieffective. The result of global cost comparison contributes to the decision to include new drugs into the hospital formulary or to replace older ones.

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acquisition costs of antimicrobial drugs in hospitals are, in general, below the wholesale price. However, the invoice prices of drugs include additional 6% taxes.

Clerical costs

Antimicrobial drugs listed in the hospital formulary are kept in stock in the wards. For formulary drugs, clerical costs per dose were determined by the labour time of nurses filling out the patient's medication sheet. In case of nonformulary drugs, extra time was needed to obtain individual receipts from the treating physician.

Costs to prepare and administer drugs

Only the time of nurses was taken into account, since pharmacists were not involved in the preparation of admixtures for injection, and formulary drugs were kept in stock in the wards.

Oral administration, intravenous push (bolus) injection, intravenous piggyback (quick, small-volume infusion) and intermittent intravenous infusion (large volumes up to 500 ml, requiring 30 min or more) were studied for cost comparison. Intramuscular injections were rarely used for antimicrobial drug administration in hospitalized patients.

Most intravenously administered antimicrobial drugs had to be reconstituted with sterile water from powder vials as in the case of cephalosporins and penicillins. Some manufacturers provide dilution fluid as is the case for teicoplanin. Ampoules contain a high concentration of antibiotic solution like gentamicin marketed as Garamycine®. Reconstituted vials were either injected with the help of a 20 ml syringe (push) into the tubing, or were injected in a piggyback or into a large-volume infusion bag for intermittent infusion when dilution was required, *e.g.* clindamycin marketed as Dalacin®.

The direct costs associated with antimicrobial drug administration were broken down into personnel time and supplies. A questionnaire was given to the senior nurses of two wards. They were asked to collect several (minimum three) time measurements from their staff for all the components of oral and intravenous antimicrobial drugs administration. The nurses noted the time required with the help of a wristwatch. Subsequently, the senior nurses were interviewed. Surveillance time of the intravenous intermittent infusions was estimated for duration of infusions (30, 60, 120 and 240 min). Both measurements and experience data were used to deduce mean administration time. Personnel time was multiplied by the average hourly wage for nurses to determine personnel costs.

System supply costs were also obtained from a

Table 1
Costs of antimicrobial drugs (NLG)

Generic name	Brand	Dosing schedule (mg)	Route‡	Wholesale cost/dose	Administration cost/dose	Monitoring cost/dose	Global cost/dose	Global cost/day	Wholesale global cost (%)
Benzyl-penicillin	Natrium Pen G	1 MU/6 h	*i.v. push*	*1.30*	*5.80*	*0*	*7*	*28*	*18*
			i.v. infusion	1.30	8.80	0	10	40	13
Cefazolin	Kefzol	operating room 1 × 1000	*i.v. push*	*15.02*	*1.90*	*0*	*17*	*17*	*89*
			i.v. infusion	15.02	5.80	0	21	21	72
		1,000/8 h	*i.v. push*	*15.02*	*5.80*	*0*	*21*	*62*	*72*
			i.v. infusion	15.02	8,80	0	24	71	63
Ceftazidime	Fortum	1,000/8 h	*i.v. push*	*48.60*	*7.00*	*0*	*56*	*167*	*87*
			i.v. infusion	48.60	10.00	0	59	176	83
Cefuroxime	Zinacef	750/8 h	*i.v. push*	*14.19*	*5.80*	*0*	*20*	*60*	*71*
			i.v. infusion	14.19	8.80	0	23	69	62
Clindamycin	Dalacin C	300/6 h	i.v. infusion	12.10	9.40	0	22	86	56
		600/8 h	i.v. infusion	24.20	10.60	0	35	104	70
Gentamicin	Garamycin	120/12 h, < 72 h	*i.v. infusion*	*19.80*	*7.70*	*0*	*28*	*55*	*72*
		120/12 h*	i.v. infusion	19.80	7.70	6.30	34	68	59
Metroni-dazole	Flagyl	2 × 250/8 h	oral	1.20	0.60	0	2	5	67
	generic product	operating room 1 × 500	*i.v. infusion*	*4.00*	*1.80*	*0*	*6*	*6*	*69*
		500/8 h	i.v. infusion	4.00	3.60	0	8	23	53
Piperacillin	Pipcil	operating room 1 × 4,000	i.v. infusion	46.55	5.80	0	52	52	89
Cipro-floxacin	Ciproxin†	500/12 h	oral	6.22	0.90	0	7	14	87
		200/12 h	i.v. infusion	69.51	3.90	0	73	147	95

*> 72 h or renal function impairment.
†Nonformulary drug.
‡ i.v.: intravenous.

wholesale price-list. Similarly, contract prices of supplies are usually lower since large quantities are purchased. An additional 18.5% taxes are added in the invoice. Costs of personnel time and supplies were arranged in a separate spreadsheet to allow calculation of the administration costs per dose for each system of administration.

Monitoring costs

When an antimicrobial drug has a narrow therapy versus toxicity range, additional laboratory tests are required to monitor drug concentrations in blood and organ function. For the calculation of the monitoring costs of aminoglycosides, we assumed that no extra laboratory tests were required during the first 72 h of treatment from patients with normal renal function and no haemodynamic instability [9]. However, patients presenting unstable circulation due to Gram-negative septicaemia, patients with burns, or patients who had impaired renal function required two extra measurements of creatinine and one set of aminoglycoside serum concentrations (peak and trough) a week for monitoring. If treatment continued beyond 72 h, even in patients with normal renal function, similar extra laboratory tests were needed.

Since the real costs of laboratory tests are unknown on a national level, laboratory cost calculations were based on cost approximation by the 'Spaander points' system (national guidelines). This system takes into account total laboratory operating costs (laboratory staff wages, supplies, equipment, energy *etc.*). Each laboratory test is given a number of 'Spaander points' which reflects the relative contribution of the test to workload and its consumption of supplies. The total annual production by a laboratory is expressed in an amount of 'Spaander points.' Dividing the total production by the total operating costs results in a cost per 'Spaander point,' which varies per laboratory. However, to allow cost comparison of laboratory tests on a national level, the average national cost per 'Spaander point,' based on national guidelines was used for calculations [10].

Results

Purchase costs

The acquisition costs (wholesale price) per dose for commonly used antimicrobial drugs are listed in Table 1 (column 5).

Clerical costs

A nurse's clerical time per dose was considered a question of seconds for formulary drugs, and was not taken into account. However, nonformulary drugs took more time, *i.e.* an average of 0.5 min per dose.

Costs to prepare and administer drugs

The results of the nurse's average time needed to reconstitute, prepare and administer formulary drugs are shown in Table 2. Oral doses (tablets or capsules) required 1 min. Total time for intravenous push injections ranged from 4.5 min to 8.5 min, depending on the complexity of reconstitution. Reconstitution times varied from 1.5 to 4 min. To ease the calculations, we allocated the antimicrobial drugs to two groups: normal reconstitution (mean 2 min) and difficult reconstitution (mean 4 min).

The average time required for injection into tubing (push) was 4.5 min. Suspending an infusion bag and connecting it to the patient's intravenous device (intravenous infusion tubing or heparin-lock catheter), averaged 2 min. All antimicrobial drug infusions were regulated with the help of a rollerclamp. Total infusion times were according to the package insert. For surveillance of the infusion, 1 min extra time

Table 2
Nurse's time needed for reconstitution, preparation and administration of one dose of an antimicrobial drug

Route of administration	Nurse's time (min)			Total time (min/dose)
	reconstitution	administration	surveillance*	
Oral	0	1	0	1
Intravenous push	0	4.5	0	4.5
	2 (normal)	4.5	0	6.5
	4 (difficult)	4.5	0	8.5
Intravenous infusion	0	2	1 (15)	3
			2 (30)	4
			4 (60)	6
	2 (normal)	2	1 (15)	5
			2 (30)	6
			4 (60)	8
			10 (240)	14
	4 (difficult)	2	1 (15)	7
			2 (30)	8
			4 (60)	10

*Infusion time in parentheses; 1 min surveillance time per 15 min infusion time up to 60 min, then 1 min surveillance time per 30 min infusion time.

Table 3
Costs of intravenous supplies per dose (NLG)

Supplies	Method of administration			
	push injection	infusion/piggyback	infusion/intermittent	infusion/bag
Syringe 5 ml	0.32	0.32	0.32	–
Syringe 20 ml	0.69	–	–	–
Needles	0.32	0.32	0.32	–
Gauze, disinfectant	0.07	0.06	0.06	0.10
Aqua distillata	0.50*/–	0.50*/–	–	–
Infusion bag (50-500 ml)	–	2.90	2.90	–
Y site	–	1.70	1.70	1.70
Total	1.90*/1.40	5.80*/5.30	5.30	1.80

*Reconstitution fluid needed.

Table 4
Costs to prepare and administer teicoplanin and vancomycin CP

Generic name	Route	Dosing schedule (mg)	Time (min)	Time* cost (NLG)	Supplies cost (NLG)	Administration cost/dose (NLG)
Teicoplanin	intravenous push	400/24 h	13.50	8.10	1.40	9.50
Vancomycin CP	intravenous infusion	1,000/12 h	11.00	6.60	5.80	12.40

*The cost of a nurse's minute is NLG 0.60.

was needed for 15 min infusion time, up to a total of 4 min for 1-h infusion time. Intravenous antimicrobials which took 2 h infusion time (vancomycin CP 1 g) and 4-6 h infusion time (amphotericin B) scored 2 min/h extra.

The calculated cost of a nurse's minute was NLG 0.60 in 1990, based upon factual nursing costs of this hospital.

The supplies and associated cost (disinfection) needed for all procedures are listed in Table 3. As an illustrative example, the comparison between the costs to prepare and administer teicoplanin and vancomycin CP is shown in Table 4. For teicoplanin and vancomycin CP, the exact measurements for preparation and administration time are used. Reconstitution of a single vial required 3 min for both drugs. Since teicoplanin was manufactured in vials of 200 mg, for the reconstitution of teicoplanin 400 mg, 6 min were needed. For injection of teicoplanin, 7.5 min were needed, due to the production of foam when nurses automatically shaked the vial during the reconstitution process.

Table 5
Costs of laboratory tests for antimicrobial drug monitoring (NLG)

Test	'Spaander points'*	Cost
Leukocytes	2	2.72
Creatinine	5	6.80
Potassium	5	6.80
Aspartate amino-transferase	8	10.88
Serum concentration		
Gentamicin	20	37.40
Vancomycin	35	65.45

*'Spaander points' of the chemistry laboratory NLG 1.36; 'Spaander points' of the bacteriology laboratory NLG 1.87.

Monitoring costs

Laboratory costs are listed in Table 5. Monitoring aminoglycosides, such as gentamicin, raised the weekly treatment costs by NLG 88.40. This amount was due to serum creatinine measurement, NLG 6.80, twice a week + one aminoglycoside serum peak and trough concentration, NLG 74.80. In a dosing schedule of gentamicin twice daily the additional monitoring cost/dose was NLG 6.30. Similar monitoring of vancomycin CP amounted to NLG 144 a week. When audiometry was performed, as advised in case of prolonged administration by the package insert, the weekly costs were NLG 174 or NLG 12.40 per dose (twice daily dosing). The package insert of teicoplanin advises to monitor renal and auditory function in patients with renal function impairment or prolonged administration, without measurement of serum concentrations. These costs amounted to NLG 44 per week or NLG 6 per dose. Serum (trough) concentrations were only considered meaningful for monitoring efficacy. The cost of a serum concentration of teicoplanin was NLG 65.45. Laboratory costs per dose for vancomycin and teicoplanin are listed in Table 6.

Table 6
Cost comparison of vancomycin CP and teicoplanin (NLG)

Generic name	Brand	Dosing schedule (mg)	Route†	Wholesale cost/dose	Administration cost/dose	Monitoring cost/dose	Global cost/dose	Global cost/week
Teicoplanin	Targocid	400/24 h*	i.v. push	250.02	9.50	0	259	2,072*
		400/24 h	i.v. push	250.02	9.50	6.00	265	1,855
Vancomycin	Vancocin CP	1,000/12 h	i.v. infusion	119.06	12.40	0	131	1,834
		1,000/12 h	i.v. infusion	119.06	12.40	12.40	143	2,007

*First week; including 1 loading dose prolonged administration
†i.v.: intravenous.

Global costs

The resulting global costs of common antimicrobial drugs are listed in Table 1. The most economic systems of intravenous administration are printed in italics (a complete list can be obtained from the authors upon request). As an illustrative example, global cost comparison between a formulary antimicrobial drug (vancomycin CP) and a newly marketed antimicrobial drug with similar efficacy (teicoplanin) is shown in Table 6. For teicoplanin, at least one loading dose is needed to rapidly achieve steady-state concentrations [11]. For the first week of treatment with teicoplanin, the costs per week are the result of eight doses.

Discussion

In a cost-identification analysis of hospital antimicrobial drug therapy, the computer spreadsheet technique permits quick calculation if values of the cost components change, such as purchase prices or nurse's wages.

Sinces purchase contracts differ between hospitals due to competitive bidding or quantity of drug purchased, wholesale prices were preferred to allow objective comparison between drugs on a national level. The contract acquisition price of an antimicrobial drug which is commonly used in an institution can be as low as 25% of its official wholesale price. However, this situation is rather exceptional, and it exists only for a few older drugs. The acquisition cost of most antimicrobial drugs is about 10% lower than the official price after taxes.

We did not take into account pharmacy handling costs. Pharmacy distribution costs vary with the logistic organization of drug distribution within the hospital. Steenhoek combined pharmacy and nurse handling costs in his cost comparison of antibiotic therapies [1].

The present cost calculation points out the most economic way and system to administer intravenous antimicrobial drugs. Different cost components seem relatively important for different drugs. The administration costs of benzylpenicillin 1 MU intravenously represent 83 to 88% of the global cost per dose and intravenous push injection is 30% less expensive than intravenous piggyback infusion (Table 1). When the predominant cost element is the acquisition cost of the drug (vancomycin CP, teicoplanin), the proportional savings by changes in the system of administration (intravenous push or intermittent infusion) and dosing schedule seem negligible (Table 6). However, administration costs of intravenous piggyback infusions (generally NLG 8.80) are almost always larger than those of intravenous push injection (generally NLG 5.80), as shown for benzylpenicillin and cefazolin in Table 1. The infusion bag (50 to 500 ml) accounts for most of the cost difference between both systems. Thus, push injection invariably saves a fixed amount of money per dose of drug which does not require dilution or prolonged infusion.

Although in some Dutch hospitals nurses are not authorized to perform injections into intravenous tubing or intravenous catheters, the reports of the committee on responsibility of nurses in general hospitals advise the same code of authorization for the medical acts of intravenous infusion and intravenous injection [12 13]. Moreover, push injection has increased security since rapidly occurring side-effects are noted earlier. Thus, both for safety reasons and from a cost-containment point of view, intravenous push injection (3-5 min) is preferable to short-term (<15 min) piggyback infusion. Intermittent infusion (large volumes, requiring more than 30 min) should be reserved for drugs that require dilution or a prolonged infusion time, such as vancomycin or amphotericin B.

For stable solutions, ready-to-infuse bags are the most economic system for intermittent administration (metronidazole) (Table 1). Teicoplanin has the advantage over vancomycin CP that it can be administered by push injection. However, by inadvertence, the production of foam during reconstitution can add several minutes to the subsequent injection and savings are less than one would expect (Table 5).

Another strategy of antimicrobial drug administration which can save time of nurses and supplies is illustrated in surgical prophylaxis. All anaesthesiologists in our hospital preferred to administer cefazolin by push injection [Gyssens IC, unpublished observations]. On the other hand, nurses in surgical wards almost invariably administered cefazolin in piggyback. The cost of one dose of cefazolin for peri-operative prophylaxis given by the anaesthesiologist in the operating theatre is NLG 17. The same dose administered preoperatively on the ward by a nurse amounts to NLG 21. Both calculations are shown in Table 1.

The cost of aminoglycosides rises by NLG 6.30 per dose (twice daily dosing) after 72 h when monitoring becomes a necessity. Aminoglycosides are much less expensive when used in empiric therapy for synergy and broadening of the spectrum during the first days before culture results become known. Monitoring costs can be avoided by replacing empirically given aminoglycosides by less toxic antimicrobial drugs in subsequent documented therapy.

From Table 1 it is clear that single-dose prophylaxis with a combination of antimicrobial drugs is not always more expensive than prophylaxis with one drug. For example, peri-operative prophylaxis with one dose of piperacillin (NLG 52) is more than twice as expensive as the combination of cefazolin with metronidazole (NLG 23).

The global cost per day (Table 1) or per week (Table 6) should be considered for cost comparison between drugs, since the daily cost of antimicrobial therapy can be largely influenced by differences in dosing schedules and monitoring.

We did not include complication costs in our calculation system. To our knowledge, there are no European data on the subject. Figures from the United States are irrelevant for the European situation as they are largely influenced by litigation costs. Still, we feel that for antimicrobial drugs with established renal and otovestibular toxicity, such as the aminoglycosides, a certain amount of money has to be added to obtain the true global cost of these drugs. This is a reason to try and replace toxic antimicrobial drugs from the formulary by less toxic, equieffective ones. Global cost considerations should guide decisions to introduce new drugs for the hospital formulary rather than purchase costs of antimicrobial drugs.

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