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Optimising antimicrobial drug use in surgery: an intervention study in a Dutch university hospital

I. C. Gyssens[a], I. E. J. Geerligs[b], J. M. J. Dony[c], J. A. van der Vliet[d], A. van Kampen[e], P. J. van den Broek[f], Y. A. Hekster[b] and J. W. M. van der Meer[a]

[a]Department of General Internal Medicine, University Hospital Nijmegen, and Department of Clinical Microbiology, University Hospital Rotterdam; [c]Departments of Obstetrics and Gynaecology, [d]Surgery, [e]Orthopaedic Surgery, [b]Clinical Pharmacy, and General Internal Medicine, University Hospital Nijmegen; and [f]Department of Infectious Diseases, University Hospital Leiden, The Netherlands

Following a one-month prospective study of antimicrobial drug use in surgical departments, new guidelines were implemented. The review was repeated after two years. In both study periods, one third of patients were prescribed antimicrobial drugs. Prophylactic antibiotic consumption decreased from 0.75 to 0.53 defined daily doses/operation. Compliance with guidelines improved from 32% to 79%. Duration of prophylaxis >24 h decreased from 21% to 8%. Single dose prophylaxis increased from 34% to 80%. Quality of the prophylactic courses improved, as evaluated by experts using established criteria. For prophylaxis, cost savings amounted to 57%. Better quality of therapeutic courses was associated with a cost increase of 15%. Indicators of satisfactory outcome with the new policy were a stable median length of stay (5.5 days in the first review and 5.0 days after intervention) and a reduction in the number of nosocomial infections treated with antimicrobial drugs/100 bed days (1.0 before intervention *vs* 0.77 after intervention).

Introduction

Antimicrobial drugs account for 13–37% of the drug budget in European hospitals (Hekster & Barrett, 1987); 30–60% of the courses are for prophylactic use (Maki & Schuna, 1978; Nickman, Blissenbach & Herrick, 1984). The main reasons for monitoring antimicrobial drug use are to optimise medical care, to limit and reduce the spread of resistant microorganisms and to contain costs. In Europe, the pressure to reduce costs is still increasing in countries with budgeting systems, such as in the Netherlands. In addition to a concern about increasing costs of antimicrobial drugs, many authors have described inappropriate use (Kunin *et al*., 1990; Dunagan *et al*., 1991). Surgical prophylaxis with antimicrobial drugs is long known as an area where

Correspondence to: Inge C. Gyssens, Department of Clinical Microbiology, University Hospital Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Tel: +31(0)10 463 3511; Fax: +31(0)10 463 3875.

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overuse is often found and where it is also the easiest to correct (Smith *et al.*, 1988; Galandiuk *et al.*, 1989). Many antimicrobial drugs intervention strategies are described to optimise quality at lesser cost, including the development of protocols (Marr, Moffet & Kunin, 1988). A number of criteria for optimal therapy and prophylaxis are well established (Kunin, Tupasi & Craig, 1973; Gyssens *et al.*, 1992). A widely accepted regimen of preoperative prophylaxis is 1 g of the first generation cephalosporin cephazolin, given within an optimal period before incision, and repeated if the operation lasts for more than 3 h (Abramowicz, 1989; Classen *et al.*, 1992). We conducted a prospective intervention study in three surgical departments in a large university hospital: to define antimicrobial drug use (prophylaxis and therapy) in terms of quality and costs; and to measure the effect of interventions to improve the quality of antimicrobial drug courses.

Patients and methods

Setting

The University Hospital Nijmegen is a 948-bed teaching hospital with 344 surgical beds, and approximately 1600 operations/month on in-patients. The study took place in the departments of gynaecology and obstetrics (G), surgery (S) and orthopaedic surgery (O). The hospital formulary listed 20 parenteral and 26 oral antibacterial drugs at the start of the study. In the previous year, antimicrobial drugs accounted for 22% of the hospital drug budget of Dfl 14 million (£5.3 million). The Antibiotics Committee had issued a new edition of an antimicrobial drug formulary. In addition, some surgical departments had their own treatment protocols. We refer to both as 'guidelines'. The classification of Cruse & Foord (1980) for surgical procedures was used with adaptations (Abramowicz, 1989). Length of stay was calculated as follows: number of in-hospital days of patients included in the study/number of patients included in the study.

Antimicrobial drug use review

The first review took place during separate one-month study periods in 1990. Antimicrobial drug use was reviewed in 766 consecutive surgical patients. After a period of intervention, a similar review of 744 consecutive patients was repeated in 1992. The studies were performed by an infectious diseases physician and junior clinical pharmacists, who collected data daily on all patients receiving antimicrobial drugs. Abstracts were made of each course. A course was defined as an episode of clinical or suspected infection or increased risk of infection, in which prescription(s), either consecutively or in combination, were written as treatment or prophylaxis. Clinical information was retrieved from the patients' records. Infections were defined according to the Centers of Disease Control (Garner *et al.*, 1988). Nosocomial infection was defined as active infection that was not present or incubating at the time of admission. Microbiology results were obtained directly from the laboratory. The schedule of systematic antimicrobial drug treatment was copied from the medication chart and from the anaesthesia record.

Antimicrobial drug use was converted into Defined Daily Doses (DDD). The DDD represents the average therapeutic dose for an adult for the standard indication

(Anonymous, 1982). Quantitative use was analysed by calculating the number of courses in the population at risk in the study periods (courses/100 bed days, incidence rate) and by comparing DDD/100 bed days. The DDD/100 bed days has been chosen by the WHO Drug Utilization Research Group as a unit of comparison between hospitals (Bergman *et al.*, 1979). Direct and indirect costs were calculated in Dutch guilders (Dfl1 = £0.38) by a method for global drug cost calculation, which includes costs of drug administration and costs of monitoring (Gyssens *et al.*, 1991).

Qualitative use was analysed in two ways. First, compliance with existing hospital guidelines was checked at the time of the initial review, and compliance with the department's new protocol after the intervention. Second, two independent experts in infectious diseases (termed reviewer 1 and reviewer 2) evaluated quality in the following way: prescriptions were assessed using six categories of antimicrobial use by means of established criteria arranged in a flow chart. The method is based on the original criteria of Kunin *et al.* (1973) and is described previously (Gyssens *et al.*, 1992). In short, prescriptions can be definitely appropriate (category I), unjustified (category V) or the records insufficient for categorization (category VI). The other prescriptions are placed in categories of inappropriate use II, III, and IV. Inappropriate prescriptions can be allocated to several categories at the same time: incorrect dose (IIa), interval (IIb) or route (IIc), duration too long (IIIa) or too short (IIIb). If relevant, the experts cite a better alternative agent for reasons of optimal effectiveness (using microbiological and pharmacodynamic criteria) (category IVa), lower toxicity (IVb), lower cost (IVc) or less broad spectrum (IVd). Global costs of actual and alternative policies (in this study the alternative policy proposed only by reviewer 1) were compared in order to estimate savings due to changes in policy. Reviewer 1 was chosen in this context for both simplicity and because he was the infectious diseases expert of the study centre.

Intervention

After the first review, reports were sent to the heads of each department. The report was accompanied by recommendations for the alternative antibiotic policy of reviewer 1, in accordance with the antimicrobial drug policy. The principal goal was to introduce a universal surgical prophylaxis standard of single-dose cephazolin at incision (with metronidazole if necessary to provide anti-anaerobe activity). The recommendations were adapted to new protocols with the help of a surgical staff member. After approval by the Antibiotics Committee, a presentation was held in the department, aided by the surgical staff member. In most departments, the first dose of antimicrobial prophylaxis was given by the anaesthetist in the operating room. Because anaesthesias were performed by a rotating pool of 40 anaesthetists (staff and residents), the department of anaesthesiology was interviewed by means of a questionnaire. The inquiry showed deficient communication between anaesthetists and surgeons on the subject of administration and timing of antibiotic prophylaxis (Gyssens, Knape & Van der Meer, 1995). The results of the inquiry were reported in an educational setting.

Implementation of the protocols was assisted by the department of clinical pharmacy. Junior pharmacists organized briefings for nurses, and the prophylaxis guidelines were displayed in the wards and operating rooms. Operating room drug stocks were reorganized. In departments S and O, pharmacy technicians discussed protocol violations with prescribers and nurses on their twice weekly visits to the wards, as a long term surveillance exercise.

Statistical analysis

Generally, chi-squared tests were applied to establish systematic differences. The Wilcoxon test was used for the comparison of lengths of hospital stay. Fisher's exact test was used to compare durations of prophylaxis. Agreement between the experts was assessed by κ coefficients.

Results

Quantitative use

Table I shows the characteristics of the study populations in the first and second study periods. The numbers of patients hospitalized and operations performed in the study periods, and the proportions of patients given antimicrobial drugs were similar in both reviews. The median length of hospital stay in the two study periods was not statistically different in departments G and S. In department O, the median length of stay decreased significantly ($P = 0.005$). Mean patient age was 40.9 (range 2–88) and 43.4 (range 0–94) before and after the intervention, respectively. The proportion of parenteral antibiotic DDDs increased from 62% to 80%. Quantitative data were analysed in detail according to prophylaxis and therapy.

Prophylaxis. Thirty-nine prophylactic courses/100 operations were performed after intervention, compared with 34 courses/100 operations in the first review. However, the use of prophylactic antimicrobial drugs expressed in DDD/operation decreased. After the intervention, only 16% of total use (in DDDs) was for prophylactic use, compared with 31% in the first review. Before intervention, a variety of antimicrobial drugs were used for prophylaxis in regimens lasting 24 h (Figure 1).

When the medication order on the anaesthesia record mentioned "24 h", some nurses in the wards did not take into account the antibiotic dose given by the anaesthetist in the operating room. This practice resulted in an extra dose in 10% (department O) and in 50% (department S) of the prescriptions for 24 h of prophylactic antibiotics. After the intervention, fewer regimens were used in favour of a single dose of cephazolin (plus metronidazole).

Therapy. Therapeutic courses/100 bed days decreased from 2.1 to 1.8. Abdominal (37%) and pelvic (40%) infections were the most frequent type of infections treated with antibiotics in both reviews. Urinary tract infections accounted for 23% and 24% of infections in the two study periods. The number of nosocomial infections treated with antimicrobial drugs/100 bed days was 1.0 before intervention and 0.77 after intervention. There was an increase of DDD/therapeutic course from 8.8 to 17.1. The main reason for the increase was that the new protocols advised treatment of severe infections, such as osteomyelitis, with larger dosages and for longer periods.

The major changes in the therapeutic antimicrobial drugs prescribed are presented in Table II. After the intervention, narrow spectrum penicillins (penicillin G, flucloxacillin) were used more often in directed therapy. Penicillin use increased four-fold and prescription of iv cephalosporins increased by half. However, some changes occurred unexpectedly; for example, amoxycillin-clavulanate had been introduced in the new protocol of department G for the treatment of post-partum

Table I. Demographics of three surgical departments and antimicrobial drug use (two separate one-month reviews)

	Before intervention				After intervention			
Department	G[a]	S[b]	O[c]	Total	G	S	O	Total
number of patients	331	286	149	766	282	302	160	744
Number of operations	150	258	134	542	144	245	133	522
clean	104	112	73	289	94	115	84	293
clean/prosthesis	—	46	51	97	—	46	43	89
contaminated	46	47	—	93	50	52	—	102
dirty	—	53	10	63	—	32	6	38
Median length of stay, days (range)	2.5 (1–42)	7.5 (1–232)	9 (1–92)[d]	5.5 (1–232)	2.5 (1–52)	7 (1–172)	6 (1–60)[d]	5 (1–172)
Bed days	1586	2292	1199	5077	1284	2373	1085	4742
Total number of antibiotic courses	82	129	79	290	68	149	71	288
Prophylactic antibiotic courses	52	78	55	185	53	96	53	202
Therapeutic antibiotic courses	30	51	24	105	15	53	18	86
Total consumption, DDD[e]	352	655	320	1327	340	835	574	1749
Prophylactic DDD/operation	0.91	0.65	0.76	0.75	0.78	0.45	0.41	0.53
Therapeutic DDD/100 bed days	13.6	20.9	18.2	18.1	17.7	30.6	47.9	31.0

[a]Gynaecology and obstetrics; [b]Surgery; [c]Orthopaedic surgery; [d]$P = 0.005$, Wilcoxon test; [e]Defined Daily Dose.

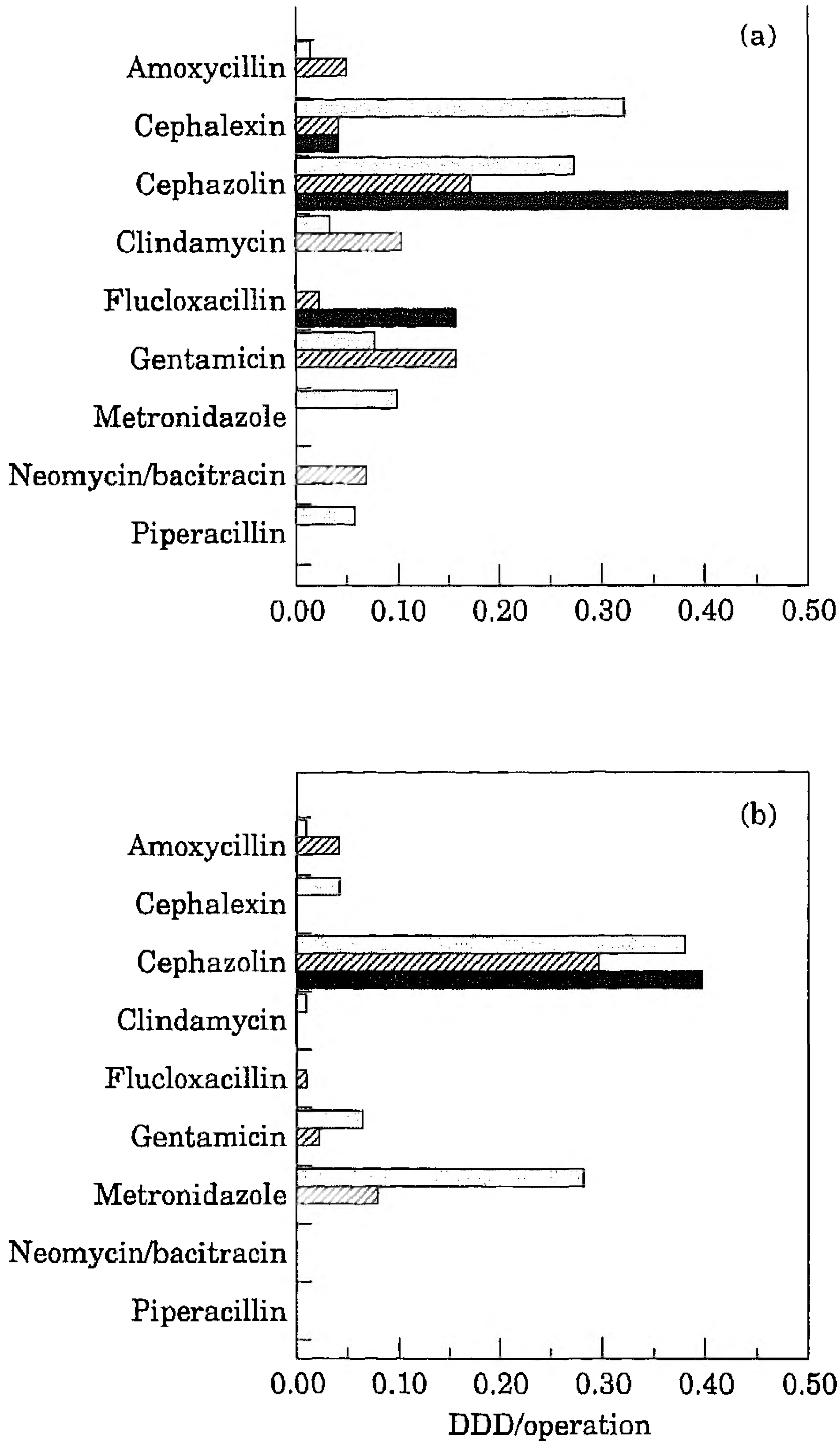

Figure 1. Use of antimicrobial drugs for surgical prophylaxis before (a) and after (b) an intervention in departments of Gynaecology and obstetrics ▩, Surgery ▨ and Orthopaedic surgery ■.

endometritis only. In the second review, amoxycillin-clavulanate use had increased from 0 to 6.9 DDD/100 bed days and represented 39% of the departments' total therapeutic use.

Costs

Total (global) costs amounted to Dfl 37,448 (£14,131) before the intervention and to Dfl 33,289 (£12,562) in the second review, resulting in total cost savings of 11%. Projected annual savings amounted to Dfl 49,800 (£18,792).

Table II. Use of antimicrobial drugs for therapy (DDD/100 bed days) by three surgical departments. See **Table I** for legend

	Before intervention				After intervention			
Department	G	S	O	total (%)	G	S	O	total (%)
Penicillins	2.8	6.6	1.4	4.2 (23)	8.0	13.5	39.4	18.0 (58)
Cephalosporins	1.6	2.3	8.3	3.5 (19)	2.3	7.4	3.8	5.2 (17)
Gentamicin	0.4	3.0	—	1.5 (8)	—	2.1	—	1.1 (3)
Clindamycin	—	1.7	2.3	1.3 (7)	—	—	0.9	0.2 (1)
Doxycycline	4.0	—	0.3	1.3 (7)	1.6	—	—	0.4 (1)
Metronidazole	4.0	2.4	—	2.4 (13)	3.5	3.0	—	2.5 (8)
Co-trimoxazole	—	2.9	1.9	1.8 (10)	1.2	2.7	1.4	2.0 (6)
Ciprofloxacin	—	—	—	—	—	0.6	0.2	0.3 (1)
Miscellaneous	0.8	2.3	3.8	2.2 (12)	1.1	1.3	2.2	1.4 (5)
Total	13.6	21.2	18.2	18.1 (100)	17.7	30.6	47.9	31.0 (100)

Prophylaxis. The cost of prophylactic antibiotics was Dfl 13,376 (36% of the total antibiotic budget) in the first review and Dfl 5,725 (17%) after intervention. Figure 2 presents the total distribution of costs of prophylaxis by antimicrobial drug group before and after the intervention. Before the intervention, piperacillin, which accounted for 7% of the antibiotic consumption of department G, accounted for 34% of costs. In department S, clindamycin, which accounted for 16% of total use, accounted for 48% of costs. Potential savings in prophylaxis, calculated by the experts after the first review, were estimated at 83%. The savings realized in the second review amounted to 57%. Prophylactic cost/operation was halved, from Dfl 2.2 to Dfl 1.1. Savings were mainly realized by replacing piperacillin (Dfl 44.9/single dose) and the regimen of gentamicin with clindamycin (Dfl 107.6/24 h course) by cephazolin (Dfl 6.3/single dose) with or without metronidazole (Dfl 6.1/single dose).

Therapy. After the intervention, overall costs of therapy increased by 15%. This increase was mainly due to higher dosage and longer duration of treatment. The drugs of the new protocol were often cheaper; after intervention, the cost/therapeutic DDD had decreased from Dfl 26.1 to Dfl 18.7. Part of the costs were still due to inappropriate prescriptions.

Qualitative aspects

Prophylaxis. After intervention, there was a higher overall compliance with the new protocols than with the old guidelines ($P < 0.0001$) (Table III). The difference was significant in each of the three departments. Parameters of quality for prophylaxis improved; the use of a prophylactic course for >24 h decreased significantly in department S but not in departments G or O. Single dose prophylaxis increased significantly in each of the three departments. The intervention also improved the timing of the first dose of antibiotic (administration within 1 h before surgical incision) in departments S and O, as reported previously (Gyssens *et al.*, 1996).

Agreement (excepting category VI) between the two experts assessing quality of prophylaxis before and after intervention was very high in both reviews ($\kappa = 0.80$). Therefore, only the assessment of one expert, reviewer 1, is discussed here and is

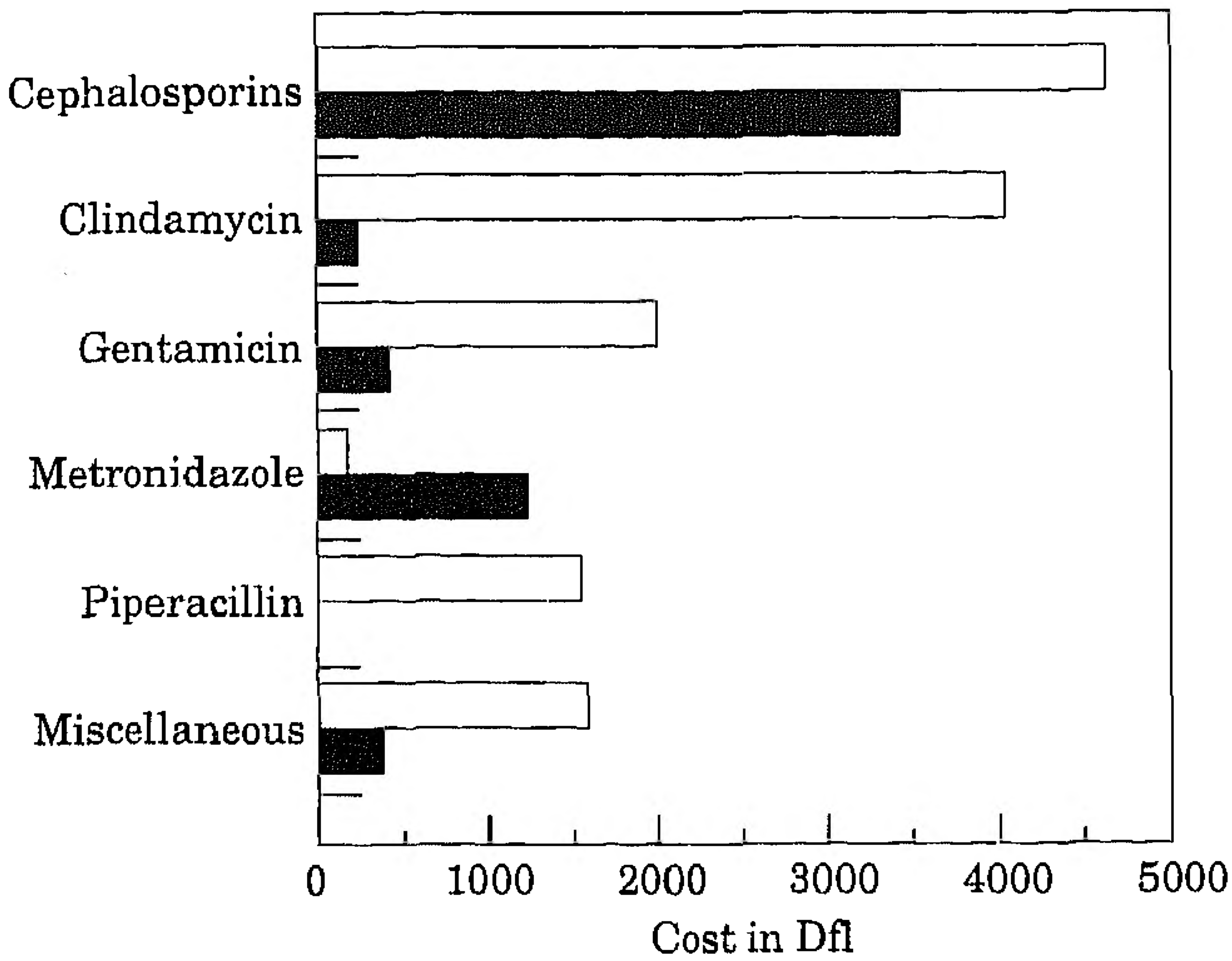

Figure 2. Costs in Dfl (Dfl 1 = £0.38) of antimicrobial drugs for surgical prophylaxis before □ and after ■ an intervention.

presented in Table III. There were significant differences in quality before and after the intervention in departments G ($P < 0.0001$), S ($P < 0.0001$) and O ($P = 0.004$).

Table IV shows most frequent type of errors (evaluation categories II–V) by prophylactic drug before intervention. Oral cephalexin prophylaxis started post-operatively and continued for five days was considered unjustified (category V). Oral prophylaxis with neomycin/bacitracin was followed by iv gentamicin plus clindamycin at induction of anaesthesia in 15 of 28 courses. The oral prescriptions were judged unnecessary (category V). Moreover, the review revealed some erroneous practices. In department S, nurses administered neomycin/bacitracin to all patients undergoing a bowel purging procedure, including those patients due to have anorectal operations (category V). Most oral prophylaxis (use of oral plus iv regimens or postoperative) was abandoned after the intervention. Prophylaxis with piperacillin was considered to be too

Table III. Quality parameters of antimicrobial drug prophylaxis in three surgical departments. See **Table I** for legend

Department	Before intervention G	S	O	total	After intervention G	S	O	total
Number of prophylactic courses[d]	52	78	55	185	53	96	53	202
According to guidelines (%)	15	32	47	32[a]	66	90	74	79[a]
Duration >24 h (%)	27	23[b]	11	21	15	3[b]	9	8
Single dose (%)	58	21	31	34[c]	77	78	85	80[c]
Evaluation by reviewer 1								
Prophylactic prescriptions[d]	91	113	61	265	110	141	52	303
Definitely appropriate (cat I) (%)	1	10	43	15	59	73	73	68
Unjustified (cat V) (%)	63	22	36	39	21	4	10	11
Inappropriate (cat II–III–IV) (%)	36	64	21	44	18	22	15	20
Unevaluable (cat VI) (%)	0	4	0	2	2	1	2	1

[a,c]$P < 0.0001$, χ^2 test; [b]$P < 0.0001$, Fisher's exact test.
[d]See "Patients and methods" for definitions of courses and prescriptions.

Table IV. Quality evaluation of 265 prophylactic antibiotic prescriptions in three surgical departments before intervention

Prophylactic antibiotic	Number of prescriptions	Total (Dfl)	Most frequent type of error[a]	Number (%) of unjustified prescriptions (category V)	Cost avoidance Dfl (%)
Cephalexin	17	364	V	15 (88)	307 (84)
Cephazolin	88	3401	V, IIIa	35 (40)	1028 (30)
Cefuroxime	9	203	V	3 (33)	58 (29)
Clindamycin	26	4247	IVc, IIIa	3 (12)	496 (12)
Gentamicin	33	1757	IVa,b,c, IIIa	7 (21)	196 (11)
Metronidazole	9	265	V, IIIa	4 (44)	152 (57)
Neomycin/bacitracin	28	610	V, IIb, IVa	15 (54)	331 (54)
Piperacillin	31	1392	IVc,d	14 (45)	628 (45)
Miscellaneous	24	1138	V	8 (33)	519 (46)
Total	265	13377		104 (39)	3715 (28)

[a]Category IIb, incorrect dosage frequency; category IIIa, too long; category IVa, alternative agent more effective; category IVb, alternative agent less toxic; category IVc, alternative agent less expensive; category IVd, alternative agent less broad spectrum; category V, unjustified.

broad and expensive (category IV c, d). Overall, 39% of prophylactic prescriptions were judged unjustified. Their cost represented 28% of total cost of prophylactic antibiotics (Table IV) and 66% of the predicted cost savings with the alternative policy proposed by reviewer 1.

Therapy. Overall agreement between the two reviewers was much lower for therapy, both before ($\kappa = 0.37$) and after ($\kappa = 0.30$) intervention. New protocols were based on the alternative policy of reviewer 1. Considering the overall evaluation of 224 and 169 therapeutic prescriptions of the three departments, before and after intervention by reviewer 1, respectively, the proportion of prescriptions that were considered definitely appropriate (category I) increased from 70 (31%) to 80 (47%). Prescriptions unjustified for therapy (category V) decreased from 35 (16%) to 14 (8%). Inappropriate prescriptions accounted for 100 (45%) and 61 (36%), respectively ($P = 0.007$).

Discussion

From the initial review we concluded that antimicrobial drug use in the surgical departments could be improved both in terms of quality and costs. In our hospital, major misuse such as prophylaxis >48 h or a combination of more than three antibiotics (Kunin *et al.*, 1973) was seldom encountered. Non-compliant physicians were rare.

The intervention succeeded in implementing a widely accepted regimen of single dose antibiotic (cephazolin ± metronidazole) for surgical prophylaxis. This type of intervention has been successful in departments of gynaecology and obstetrics (Smith *et al.*, 1988; Everitt *et al.*, 1990). The contribution of parenteral clindamycin to costs is considerable (Kunin, 1985), and its replacement by metronidazole is known to be cost-containing (Fletcher *et al.*, 1990). We implemented the regimen in several surgical specialties for all procedures where prophylaxis was deemed appropriate. The intervention included the education of anaesthetists, nurses and surgeons. The preparation and acceptance of the new guidelines took several months. At implementation, however, the effect was sometimes immediate, for example, by changing the operating room drug stock. The regimen replaced a variety of broad spectrum antimicrobial drugs, previously chosen on the basis of personal preferences and possibly the result of promotional efforts by pharmaceutical companies. Prophylaxis with cephazolin was generally cheaper, even in combination with metronidazole (Gyssens *et al.*, 1991). Cost-containment was also obtained by shortening the duration of prophylaxis. Compliance with guidelines improved, as did the result of the evaluation by the experts. Both reviewers largely agreed upon the improvement of quality of prophylaxis.

Improvement in the quality of therapeutic antibiotic prescribing was less striking, and was achieved at higher cost. There was limited agreement between the two experts concerning the quality of surgical therapy. Reviewer 2 judged less therapeutic prescriptions appropriate and more prescriptions unjustified, both before and after the intervention. However, his assessment also changed significantly after the intervention (data not shown). Correction of undertreatment of severe infections increased costs.

Reviews of this type are time consuming. However, the in-depth analysis detected many logistic problems, solutions to which seemed crucial for the successful implementation of adequate prophylaxis. Organizational aspects were of major importance, as others described recently in the UK (Dobrzanski *et al.*, 1991). The in-depth analysis also detected problems with specific antibiotics. We used DDDs as a unit of measurement to allow international comparison of the utilization data. However, the main problem with DDDs in hospitalized patients is that the Prescribed Daily Dose (PDD) for certain antibiotics can be quite different from the DDD depending on the indication. When DDDs are used as a unit of measurement for single dose antibiotic surgical prophylaxis low usage figures result. For prophylaxis, the DDD/100 bed days underestimates the population exposed, whereas for severe infections the number of patients treated with the antibiotic is overestimated. The latter may partly explain why in all surgical departments, due to previous underuse, therapeutic antibiotic use defined in DDDs increased, and yet the same proportion of patients were treated. The overall proportion of patients receiving prophylaxis increased slightly, but more of these prescriptions were judged appropriate. There was no systematic registration of wound infections during the study periods, and therefore we cannot fully assess the relative efficacies of prophylaxis regimens.

We conclude that this intervention resulted in an optimisation of the quality of prophylactic and therapeutic antimicrobial regimens in surgical departments at a lower cost. Indicators of satisfactory outcome with the new policy were a stable median length of hospital stay and a reduction in the number of nosocomial infections treated with antimicrobial drugs/100 bed days.

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