Pharm World Sci (2006) 28:257–264
DOI 10.1007/s11096-006-9035-5

RESEARCH ARTICLE

The impact of an intensive antimicrobial control program in a Taiwanese medical center

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Received: 20 April 2005 / Accepted: 16 May 2006 / Published online: 26 October 2006

Abstract
Objective The study evaluates the short term impacts of an intensive control program for the appropriate us of antimicrobials, and to provide a novel strategy for antimicrobial control in inpatient wards in Taiwan.
Method In September 2002, a dual intensive antimicrobial control program was implemented within a 921-bed medical center in Taiwan. The study sample included all patients admitted to the medical center during the basal period (October–December 2001) and the intervention period (October–December 2002), where at least one type of parenteral antimicrobial was administered. The sample comprised of 5046 patients during the basal period and 5054 patients during the intervention period.
Main outcome measure Analysis of the impact of the intensive antimicrobial control program was undertaken by comparing clinical outcomes, parenteral antimicrobial consumption and bacterial susceptibilities, before and after the establishment of the intensive antimicrobial control program.
Results No statistical differences were found between the basal and intervention periods with regard to either the demographic variables, such as age and gender, or the incidence of nosocomial infections. The clinical outcomes, including length of stay in the medical center, mortality and readmission rates, were also similar for both periods. As compared to the basal period, the consumption of parenteral antimicrobials—in defined daily doses (DDDs) per 100 patient days (PDs)—declined by 13.2% during the intervention period (71.2 vs. 61.8). There were significant increases in the susceptibilities of *Pseudomonas aeruginosa* to both amikacin and ciprofloxacin, and *Serratia* spp. to ciprofloxacin ($P < 0.05$), while all others remained stable.
Conclusion This study reports positive responses to intensive antimicrobial control measures among health professionals within a Taiwanese medical center. Following the implementation of the intensive control program, both prescriptions and consumption levels of parenteral antimicrobials were reduced without compromising the clinical outcomes of patients, while the susceptibility patterns of bacterial organisms mostly remained stable. Long-term control of parenteral antimicrobials under such a program may well produce significant benefits for inpatients through the overall rationalization of antimicrobial usage, leading to potential reductions in both the incidence of adverse effects and the burden of resistant organisms. A method of incorporating this intensive control program into a computerized prescription order system is currently under construction.

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Keywords Antimicrobial control program · Inpatients · Parenteral antimicrobials · Rationalized antimicrobial usage · Susceptibility · Taiwan

Introduction

Given that antimicrobial resistance is clearly a global problem [1, 2]; in response to this threat, the World Health Organization (WHO) developed the first *Global Strategy for Containment of Antimicrobial Resistance* in 2002. Since then, significant progress has been made in some of the advanced countries where national programs have been developed to reduce both antimicrobial abuse [1, 3, 4] and pharmacovigilance [5], and to provide effective education at local levels [6, 7]. Bassetti et al. [8] initiated a successful restriction program for antimicrobial control in a 2500-bed hospital in Italy, reporting a subsequent 8.5% reduction in the use of antibiotics. Saizy-Callaert [9] also suggested that antibiotic prescription controls on inpatients could result in better infection control, and consequent reductions in antimicrobial costs.

The implementation of an antimicrobial control policy within an intensive care unit also led to reductions in antibiotics-selective pressure and the costs linked to antibiotics [10], as well as a selective reduction in nosocomial infections due to antimicrobial-resistant microorganisms such as methicillin-resistant *Staphylococcus aureus* and ceftriaxone-resistant *Enterobacteriaceae*. In a study of a comprehensive antibiotic-control intervention program implemented within a university-affiliated teaching hospital, Ruttimann et al. [11] reported a significant reduction (30–46%) in total antibiotic consumption per patient admissions—expressed as defined daily doses (DDDs)—as well as reductions in both oral and parenteral DDDs.

Several focused studies have examined the prevalence of antimicrobial resistance in Taiwan [12–14]; and indeed, between 1995 and 1998, a number of regulations and recommendations aimed at enforcing antimicrobial controls were introduced by the Bureau of National Health Insurance (BNHI) through the implementation of the universal national health insurance (NHI) system. Taiwan's NHI system, under which drug costs and other expenditure are reimbursed, is run by the Department of Health at the Executive Yuan. Between 2000 and 2001, a reduction in the use of antimicrobials for upper respiratory infections in ambulatory patients was recommended [15], and in order to enforce these recommendations, evidence of bacterial involvement was required before the costs for such antimicrobial usage were reimbursed [16]. Further restrictions have also been placed upon the use of prophylactic antibiotics for surgery.

Several prior studies in Taiwan have focused on both antimicrobial utilization and resistance, reporting for example, the resistance rates of clinical isolates obtained from eight medical centers [14], and the antimicrobial susceptibilities within a new regional hospital in southern Taiwan [17]. The former study also showed that the use of antimicrobials by inpatients in Taiwan was greater than that found in other studies in other countries [14].

The medical center involved in the current study has adopted several multidisciplinary programs since 2000, and indeed, implemented an intensive antimicrobial control program for parenteral antimicrobials in 2002, in an effort to enforce the appropriate use of antimicrobials for inpatients, and to further reduce antimicrobial resistance. Analysis of the short-term impacts of this intensive antimicrobial control program was undertaken by comparing clinical outcomes, parenteral antimicrobial consumption and bacterial susceptibilities, between the two study periods.

Method

An antimicrobial utilization team was formed within the study medical center in an effort to promote the rational use of antimicrobials. The team comprised of a subcommittee from the infection control committee, and included two infectious disease physicians, an infection control professional, a clinical pharmacist and other medical specialists. The intensive control program—which was developed by the team, and included dual controls on both surgical prophylaxis and the prescription process (see Fig. 1)—was implemented within a 921-bed medical center in northern Taiwan in September 2002.

The recommendations of this intensive program included (i) no continuous use of antimicrobial therapies for more than 14 days; and (ii) a limitation, to three prescription days, on post-surgery prophylactics, with a new prescription order being required if there was any continuing need for antimicrobial usage. In accordance with the program guidelines, regular education campaigns were also undertaken, while the approval of an infectious disease consultant, or support from microbiological data (with appropriate susceptibility testing for isolates), was required for all prophylactic antibiotic usage in surgical settings, as well as for prescriptions for second-line and third-line parenteral antimicrobials.

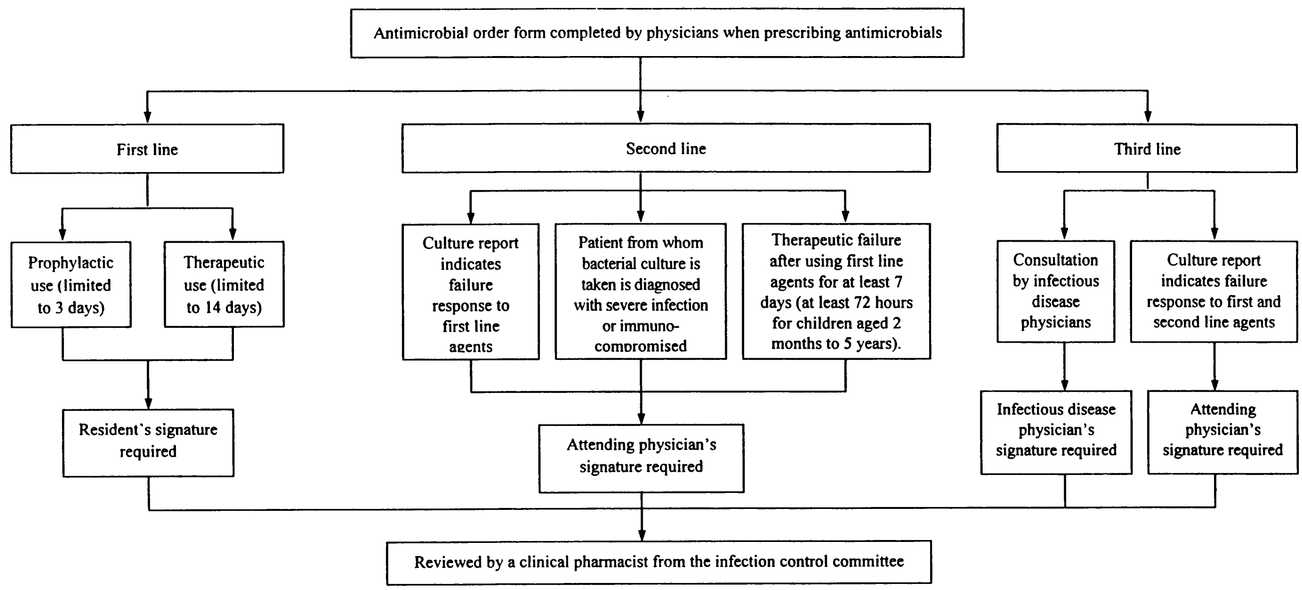

Fig. 1 The intensive control program. The program, which was developed by the antimicrobial utilization team for parenteral antimicrobials, includes dual controls on the surgical prophylaxis and prescription process in a 921-bed medical center in northern Taiwan

In order to effectively evaluate the impact of the intensive program, this study was coordinated by a clinical pharmacist who had entered the graduate training program within a university clinical pharmacy research group between 2002 and 2004, and who was also a member of the infection control team. The inclusion criteria for the study sample were patients admitted to the study medical center between October and December 2001 (the basal period) or between October and December 2002 (the intervention period) where at least one parenteral antimicrobial was administered during their period of hospitalization.

The study sample comprised of 5046 patients for the basal period and 5054 patients for the intervention period, with their related medical information and medical diagnoses being recorded retrospectively, as described in earlier studies [2, 18, 19]. The general characteristics of the patients, the incidence of nosocomial infections, antibiotic-selective pressure (the number of days and dosage of antibiotic treatment per 100 days of hospitalization), ICU stay records, and the presence of resistant microorganisms, were each recorded separately for the purpose of further normalizing antimicrobial usage within the ICU [20].

Major medical diagnoses of the study populations were catalogued using the ICD-9-CM [21]. The number of hospitalization days, mortality rates, re-hospitalization rates, drug utilization, and the types of prescriptions were also monitored. Parenteral antibiotics usage is usually expressed under the international measure, 'defined daily dose' (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults. In order to carry out a comparison with earlier antimicrobial studies, drug consumption in the current study was expressed as DDDs/100 patient days (PDs), calculated as [22]:

$$[\text{No. of Antibiotics used (vials)} \times \text{Antibiotic Strength (g/vial)} \times 100]/(\text{DDD(g)} \times \text{No. of patient-days}),$$

where the number of DDDs was calculated from the prescribed antimicrobial dosage per patient admission, available from the database [23].

Parenteral antibiotic usage was further described by the type of antibiotic chosen (first-, second- or third-line), with the susceptibilities of the bacteria isolated from nosocomial infection cases also being analyzed within this population. The unpaired Student *t*-test was used to compare differences between the pre- and post-program implementation periods, while the Chi-square test was used for comparison of the categorical variables, in order to evaluate changes in the proportion of any particular antibiotics within a group. The Student *t*-test was used for the continuous variables. Two-sided tests were used for all analyses, which were performed using SPSS 11.5. A *P* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics and clinical outcomes

Hospital activity, in terms of the number of admissions, consultations and bed-days, remained stable during both the basal and intervention periods, with the patients in each of the two periods being comparable with respect to case numbers, age, gender distribution, principle diagnoses, proportion receiving intensive care and nosocomial infections. There were no statistical differences in clinical outcomes, which included the length of stay in the medical center, mortality rates and re-hospitalization rates (see Table 1).

Parenteral antimicrobial usage and prescription analysis

With the patient population number remaining unchanged, there was a reduction of 4.2% (583 cases) in parenteral antibiotic-prescribed cases during the intervention period. The total reduction in parenteral antibiotic usage (DDD/100 PDs) was 13.2%, with intervention resulting in a 3.9% reduction in the average number of parenteral antibiotics prescriptions per patient day. Analysis of parenteral antibiotic usage for each of the first-, second- and third-line types is provided in Table 2.

Types and amounts of antimicrobials used

Table 3 provides information on the frequency of usage of the various types of parenteral antimicrobials during each of the study periods. The use of both types of first-generation cephalosporins and penicillins accounted for more than 25% of overall antibiotic usage during each period. Aminoglycosides were the second most frequently used antimicrobials, at a rate of between 17.5% and 19.2%. Following intervention, a comparison of usage in DDD/100 PDs revealed a declining consumption trend for first-, second-, third- and fourth-generation cephalosporins (– 9, – 32.4, – 26.7 and – 80%, respectively).

In addition, consumption of glycopeptides and tetracyclines declined by more than 30%. There were, however, three types of antibiotics which revealed increased consumption; these were the macrolides (100%; erythromycin), penicillins (19.2%), and quinolones (13.3%).

Table 1 Characteristics of the study population and outcome measures, before and after establishment of the intervention program[a]

Characteristics	Basal period (n = 5046)		Intervention period (n = 5054)		P-value[b]
	No.	%	No.	%	
Age (mean years ± SD)	44.9 ± 21.9		45.1 ± 22.4		0.53
Gender					
Male	2233	44.3	2822	55.8	0.93
Female	2813	55.7	2232	44.2	
Principal diagnosis (ICD-9-CM)					
Complications of pregnancy, childbirth and the puerperium (630–677)	949	18.8	982	19.4	
Diseases of the circulatory system (390–459)	739	14.6	706	14.0	
Diseases of the genitourinary system (580–629)	641	12.7	671	13.3	
Diseases of the digestive system (520–579)	532	10.5	566	11.2	
Injury and poisoning (800–999)	514	10.2	473	9.4	
Neoplasms (140–239)	424	8.4	383	7.6	
Diseases of the respiratory system (460–519)	346	6.9	423	8.4	
Infectious and parasitic diseases (001–139)	66	1.3	57	1.1	
Others	835	16.5	793	15.7	
Length of stay in hospital (days)	6.2 ± 7.0		6.3 ± 7.4		0.47
Intensive care received during hospitalization	465	9.2	497	9.8	0.29
Re-hospitalization rates (within 30 days)	528	10.5	491	9.7	0.21
Nosocomial infections[c]	203	2.7	218	2.8	0.63
Mortality rates	81	1.6	80	1.6	0.93

[a] Unless otherwise indicated, the data refer to the number and percentage of patients

[b] There were no significant differences in P-values between the basal and intervention periods

[c] Populations comprised of patients discharge from the hospital within each of the study periods

Table 2 Antimicrobial utilization and prescriptions, before and after establishment of the intervention program

Antimicrobial utilization	Basal period (53,663 PDs)	Intervention period (53,291 PDs)	Percentage change
First-line	47.0	41.6	– 12.2
Total No. of prescriptions (% share)	10,855 (78.4)	10,398 (78.4)	– 457 (0.0)
Ampicillin	1.0	0.9	– 10.0
Benzathine PCN	0.1	0.1	–
Clindamycin	0.9	0.8	– 11.1
Cefazolin	22.3	20.3	– 9.0
Erythromycin	0.1	0.2	+100
Gentamicin	12.4	9.8	– 21.0
Oxacillin	6.9	6.3	– 8.7
Penicillin G	3.2	2.9	– 9.4
Streptomycin	0.1	0.1	–
Second-line	16.2	14.5	– 10.5
Total No. of prescriptions (% share)	1648 (11.9)	1696 (12.8)	+48 (+0.9)
Amikacin	1.2	0.6	– 50.0
Amoxicillin/clavulanate	4.8	5.9	+22.9
Cefuroxime	1.3	0.8	– 38.5
Cefmetazole	5.8	4.0	– 31.0
Isepamicin	–	0.3	–
Minocycline	0.7	0.3	– 57.1
Netilmicin	0.03	–	–
Ofloxacin	0.9	0.9	0
Piperacillin	1.3	1.4	+7.7
Ticarcillin/clavulanate	0.2	0.2	–
Third-line	8.0	5.8	– 27.5
Total No. of prescriptions (% share)	1341 (9.7)	1167 (8.8)	– 174 (– 0.9%)
Aztreonam	0.1	0.1	–
Ceftazidime	1.0	0.7	– 30.0
Ceftizoxime	0.7	0.6	– 14.3
Ceftriaxone	0.6	0.5	– 16.7
Ciprofloxacin	0.5	0.7	+40.0
Cefepime	1.0	0.2	– 80.0
Flomoxef	0.6	0.4	– 33.3
Meropenem	0.2	0.3	+50.0
Imipenem/cilastatin	0.5	0.2	– 60.0
Teicoplanin	0.7	0.5	– 28.6
Piperacillin/tazobactam	0.6	0.7	+16.7
Vancomycin	1.3	0.9	– 30.8
Total consumption	71.2	61.8	– 9.4
Total No. of prescriptions	13,844	13,261	– 4.2
Total prescriptions/patient day	0.258	0.248	– 3.9

Table 3 Consumption and frequency of various types of parenteral antimicrobials used in the basal and intervention periods

	Basal period		Intervention period	
	DDD/100 PDs	%	DDD/100 PDs	%
First-generation cephalosporins	22.3	31.32	20.3	32.9
Second-generation cephalosporins	7.1	9.97	4.8	7.78
Third-generation cephalosporins	3.0	4.21	2.2	3.57
Fourth-generation cephalosporins	1.0	1.41	0.2	0.32
Aminoglycosides	13.7	19.24	10.8	17.5
Glycopeptides	2.0	2.81	1.4	2.27
Lincosamides	0.9	1.27	0.8	1.30
Macrolides	0.1	0.14	0.2	0.32
Penicillins	18.1	25.42	18.4	29.82
Carbapenems	0.7	0.98	0.5	0.81
Monobactams	0.1	0.14	0.1	0.16
Quinolones	1.5	2.11	1.7	2.76
Tetracyclines	0.7	0.98	0.3	0.49
Totals	71.2	100.00	61.7	100.00

Antimicrobial susceptibilities

Although susceptibility for most nosocomial isolates declined, this was not statistically significant. There were reductions, in excess of 10%, in antibiotic susceptibilities to gram-positive bacterial pathogens, including *S. aureus* (to oxacillin, clindamycin and gentamicin), *Coagulase (–) staph.* (to penicillin G, oxacillin, clindamycin and gentamicin) and *Enterococcus* spp. (to penicillin G, ampicillin, gentamicin and vancomycin). It is worth noting, however, that the susceptibility of *Enterococcus* spp. to teicoplanin fell by 94.1%. There were also reductions, of more than 25%, in antibiotic susceptibilities to gram-negative pathogens, including *Escherichia coli* (to cefuroxime, aztreonam and ciprofloxacin), *Klebsiella penumoniae* (to amikacin), *Proteus mirabilis* (to amoxicillin/clavulanate), *and Enterobacter* spp. (to ciprofloxacin).

There was a slight increase (5.9%) in the resistance rate of *Enterococcus* spp. to teicoplanin, along with increased resistance (11.1%) to vancomycin. There were significant increases ($P < 0.05$) in the susceptibility of two pathogens, *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Serratia* spp. to certain antimicrobials; the susceptibility of *P. aeruginosa* to amikacin increased significantly from 82.1% to 100.0%, with a similar significant increase, from 53.8% to 79.4%, in susceptibility to ciprofloxacin, and there was a significant increase, from 18.2% to 71.4%, in the susceptibility of *Serratia* spp. to ciprofloxacin.

Discussion

A variety of attempts have been made to rationalize hospital antibiotic policies over recent years [24–26], with several studies having focused specifically on antimicrobial usage and the susceptibility of isolates from inpatients in different settings [8–11, 18]. In this study, we have set out to demonstrate an effective intervention program for antimicrobials within a 921-bed medical center in Taiwan, including dual controls on surgical prophylaxis and a restrictive prescription process; approval was required in our post-intervention period before any use of hospital formulary restricted group of antibiotics would be allowed.

In our comparison with earlier studies, we can demonstrate a greater reduction (13.2%) in parenteral antibiotic usage than the reduction achieved in the study of an Italian general hospital [8], and smaller DDD reductions than those of a restricted program on usage in ambulatory upper respiratory patients [1], and a long-term comprehensive intervention study in a university-affiliated teaching hospital [11].

This study has found reductions in the number of prescriptions for first- and third-line antibiotics, although we do find a slight increase in the number of prescriptions for second-line antibiotics. The reduced consumption of both second- and third-line antimicrobials (restricted antibiotics) accounted for 76.8% of the total reduction in parenteral antimicrobial usage. The change in restricted antibiotic usage was very similar to the 78.5% reported by Ruttiman et al. [11], despite their definition of restricted antibiotics being different to the definition used in the current study, since their study included only drugs with high risk of resistance and/or high costs.

Given the pressure of the intervention program, the natural response for prescribers would be to choose cefazolin (a common choice for surgical prophylaxis and empirical therapy) [5]; however, following the implementation of the intervention program, we also find a reduction of 9.0% (DDD/100 PDs) in the usage of this particular drug. Nevertheless, the absolute consumption of cefazolin was 20.3–22.3, which was still ten times higher than that reported in Italy [27].

Consumption analysis by ATC classifications indicates an increase in both macrolide and penicillin usage following the implementation of the intervention program (Table 3). First-generation cephalosporins, penicillins and aminoglycosides, and second-generation cephalosporins, were prevalent in each of the two study periods, a pattern which was similar to the findings on ambulatory respiratory infectious patients between 1999 and 2001 [1], particularly with regard to penicillins, first-generation cephalosporins and macrolides. This may, therefore, indicate that in Taiwan, a similar pattern of prescribing behavior exists for all patients, whether that be for upper respiratory infections or other diseases [1]. Increased usage of ciprofloxacin (by 40%) and meropenem (by 50%) may be attributable to the prescription preferences of physicians or to the trend towards increased resistance rates of pathogens to ciprofloxacin. Furthermore, the usage of two glycopeptide antibiotics was similar to, or less than, the DDD/100 PDs found in the Bassetti et al. [27] study in Italy. More conservative use, and close monitoring, of glycopeptide antibiotics should be adopted within this medical center.

P. aeruginosa is primarily a nosocomial pathogen and also the most common gram-negative bacillus leading to hospital-acquired pneumonia. However, we find that, not only did the susceptibility of *P. aeruginosa* to ciprofloxacin recover during the intervention period, but also that the susceptibilities of *P. aeruginosa* to ampicillin and *Serratia spp*. to ciprofloxacin in current nosocomial infection isolates, had increased to the 1995–1996 data levels reported by Chang et al. [14] on eight medical centers in Taiwan. Furthermore, there was a reduction, of about 10%, in the resistance rates to ampicillin and imipenem/cilastatin. The resistance rates for ceftazidime/ciprofloxacin-resistant *P. aeruginosa*, and for vancomycin-resistant *Enterococci*, remained the same as the data reported on the total isolates collected in 2001 by the Infection Control Committee at Shin Kong Wu Ho-Su Memorial Hospital [28], and were also similar to the data reported in the Hsueh study [13].

As compared to the findings on other countries, the resistance to ciprofloxacin in the current study was quite modest (20.6%). This is nevertheless better than the 23.0% rate reported for Spain, the 26.8% reported for Latin America and the finding of a 31.9% rate in Italy, although worse than the 16.1% rate reported for Turkey, and the 10.0% rate in the United Kingdom, as summarized in an earlier study [29].

The findings from this intervention control program may provide guidance for other hospitals or health systems, in Taiwan or elsewhere, to reduce the overuse of antimicrobials and the resultant problems of resistance. However, one limitation of this study is that it was a short-term study, and therefore lacks information on the severity of patient's diseases, as well as the consumption of oral antibiotics.

It is anticipated that restrictions on parenteral antimicrobial usage for inpatients would help to provide a solution to current resistance problems, as long as the use of oral antibiotics remains stable. If this type of antimicrobial control program is adopted continuously, and attempts are made to incorporate this intensive control program into a computerized prescription order system, these effects may persist within this medical center, or there may even be some overall improvement to the current drug resistance problems.

Conclusion

The described intensive control program lead to reduced use of parenteral antimicrobials without clinical consequences. The program will be part of a future computerized prescription ordering system.

Acknowledgements We wish to thank K.Y. Hsu, Director of the Department of Pharmacy, Taipei Medical University and H.C. Chiu, Vice-president of Shin Kong Wu Ho-Su Memorial Hospital, for their critical review of this paper. We also wish to acknowledge the support provided by pharmacists and members of the Infection Control Committee, which is greatly appreciated.

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