A Hospitalwide Intervention Program to Optimize the Quality of Antibiotic Use: Impact on Prescribing Practice, Antibiotic Consumption, Cost Savings, and Bacterial Resistance

Carlos Bantar,1 Beatriz Sartori,2 Eduardo Vesco,3 Claudia Heft,2 Mariano Saúl,2 Francisco Salamone,4 and María Eugenia Oliva1

1Committee for Prevention and Control of Nosocomial Infection and Departments of 2Pharmacy, 3Internal Medicine, and 4Microbiology, Hospital San Martín, Paraná, Entre Ríos, Argentina

Several findings from Argentina provide compelling evidence of the need for more rational use of antimicrobial agents. Thus, a multidisciplinary antimicrobial treatment committee for the development of a hospital-wide intervention program was formed to optimize the quality of antibiotic use in hospitals. Four successive steps were developed during 6-month periods: baseline data collection, introduction of a prescription form, education, and prescribing control. Sustained reduction of drug consumption was shown during the study ($R^2 = 0.6885; P < 0.01$). Total cost savings was US$913,236. To estimate the consumption of cefepime and aminopenicillin-sulbactam in relation to that of the third-generation cephalosporins, 2 indices were calculated: Icfp and Iams, respectively. Decreasing resistance to ceftriaxone by Proteus mirabilis and Enterobacter cloacae proved to be associated with increasing Icfp. Decreasing rates of methicillin-resistant Staphylococcus aureus were related to increasing Iams. The present study indicates that a systematic program performed by a multidisciplinary team is a cost-effective strategy for optimizing antibiotic prescribing.

Appropriate antibiotic use is one of the main goals of the medical community [1]. Overuse of antimicrobial agents has been described worldwide in both community [2, 3] and hospital [4, 5] settings. In addition to the effect on patients [6, 7], antibiotic misuse can provoke the emergence of bacterial resistance [4, 8] and increase health care costs [9]. It is evident that optimizing antibiotic use is a challenge that deserves to be undertaken.

It has been observed that the infectious diseases physician plays a crucial role in controlling antibiotic use in the hospital [10], as does a multidisciplinary team approach, with the active involvement of clinical microbiologists and pharmacists [8, 9, 11–13]. Bantar et al. [14] published alarming rates of bacterial resistance in a surveillance study involving 27 Argentinean health care centers, and Bantar and others have noted high rates of nosocomial infection, surgical prophylaxis errors leading to unnecessary cost increases in the hospital [15], and confirmation of misuse of antibiotics in the same hospital [5]. These findings provide compelling evidence of the need for more-rational use of antimicrobial agents in Argentina. To our knowledge, a systematic strategy for control of antibiotic use in our country has not been published. Thus, we designed a multidisciplinary antimicrobial treatment team for de-
veloping a hospital-wide intervention program to optimize antibiotic use in our hospital. Here, we report the impact of this program on prescribing practice, antibiotic use, cost savings, and bacterial resistance.

METHODS

Setting. The Hospital San Martín is a 250-bed public teaching hospital for adult patients in Paraná, a city in Argentina of ~350,000 inhabitants. It has a 10-bed intensive care unit (ICU) and several surgical wards (including orthopedic, abdominal, thoracic, gynecological, and neurological units) and lacks facilities for solid-organ or bone marrow transplantation and cardiac surgery.

Program design. An antimicrobial treatment committee (ATC), which comprised an infectious diseases physician (M.E.O.), a clinical microbiologist with experience in pharmacokinetics and pharmacodynamics (C.B.), a laboratory microbiologist (F.S.), 2 pharmacists (B.S. and C.H.), an internal medicine specialist (E.V.), and a computerized system analyst (M.S.), was convened in 1999 to design a sequential intervention program to optimize antibiotic use within the hospital. By early 1999 (before the study), specific computerized systems for data recording and analysis were implemented in the departments of pharmacy, microbiology, and prevention and control of nosocomial infection. Thereafter, 4 successive intervention steps were developed during 6-month periods, as follows: period 1 (the last 6 months of 1999; baseline), introduction of an optional antibiotic order form and collection of baseline data (i.e., data on bacterial resistance, antibiotic use, prescribing practice, and nosocomial infection and crude mortality rates); period 2 (the first 6 months of 2000; initial intervention period), feedback activities, according to the baseline findings, and transformation of the optional antibiotic order form into an obligatory requirement for procuring the drug from the pharmacy; period 3 (the last 6 months of 2000; education phase), like period 2, but with the addition of policy activity for every antibiotic prescription (except for surgical prophylaxis, which was already standardized) and bedside discussion among the infectious diseases physicians, the clinical microbiologist, and the attending physicians; and period 4 (the first 6 months of 2001; active control period), like period 3 but included modification of prescription, if necessary, by the ATC.

There were no restrictions on antibiotic-prescribing habits. However, during the education phase, physicians were informed about the increased risk for the selection of bacterial resistance associated with the overuse of the third-generation cephalosporins and carbapenems, as well as the potential benefits of their replacement (when appropriate) with aminopenicillin-sulbactam or with the available fourth-generation cephalosporin, cefepime. To evaluate the impact of the antimicrobial-control program, no specific actions to control and prevent nosocomial infections (beyond the standard precautions that were being undertaken before starting the study) were introduced by the pertinent committee during the 24 months of the study.

Strategy and data collection. Use of antibiotics was recorded as total number of grams of the drug on a homemade computerized system (SOUFARMA) [5] and then converted into defined daily doses (DDDs) per 1000 patient-days, in accordance with the World Health Organization recommendation [6]. Only the expenditure for drugs that are administered intravenously was analyzed. Data regarding antibiotic use associated with surgical prophylaxis were excluded. To estimate the rates of use of cefepime and aminopenicillin-sulbactam in relation to that for the third-generation cephalosporins, 2 indices were calculated: Icfp and Iams. Icfp was calculated as consumption of cefepime/consumption of ceftriaxone and cefazidime \( \times 100 \). Iams was calculated as consumption of aminopenicillin-sulbactam/consumption of ceftriaxone plus cefazidime \( \times 100 \). Consumption was measured in DDDs per 1000 patient-days.

Bacterial resistance rates were recorded and analyzed using a homemade computerized system (SIR) described elsewhere [14] that was developed by one of the authors (C.B.). The antibiotic order form required the physician to state the certainty of infection diagnosis, as well as the most relevant epidemiological data. The infectious diseases physician filled out a unique form with the same data as the antimicrobial order form and additional data, such as any interruption or modification of treatment suggested by the ATC. Criteria used to define the need for antimicrobial therapy were adopted from the current edition of Principles and Practices of Infectious Diseases [17]. Therapy was considered appropriate if it was included in any of the primary or alternative regimens suggested in The Sanford Guide to Antimicrobial Therapy [18]. Data were finally recorded and analyzed using Epi Info software, version 6.0 (Centers for Disease Control and Prevention).

Density of nosocomial infection was estimated as described elsewhere [15]. Data on the number of patient admissions and discharges, number of patient-days, and crude mortality were kindly supplied by S. Hayy from the Department of Statistics (Hospital San Martín).

Bacterial resistance and antibiotic use. To evaluate the impact of changes in antibiotic use on bacterial resistance, we selected certain worrisome multidrug-resistant species detected in the baseline period for analysis, such as third-generation cephalosporin-resistant Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Proteus mirabilis; imipenem-resistant Pseudomonas aeruginosa; and methicillin-resistant Staphylococcus aureus (MRSA). In addition, 2 phenotypes were selected to assess the impact of the increase of Iams and Icfp indices, aminopenicillin-sulbactam-resistant E. coli and cele-
pime-resistant *P. aeruginosa*. To date, vancomycin-resistant enterococci (VRE) has never been isolated in our hospital; thus, this organism was not included in the analysis. Variations in the resistance phenotype above, which were estimated as a 6-month prevalence rate from each period, were compared with those for every antibiotic showing any sustained trend over the study period by linear regression analysis.

**Statistical analysis.** Rates were analyzed by comparison of proportions with the \( \chi^2 \) or Fisher’s exact tests using the Epi Info statistical package. Trends over time and correlation among variables were assessed by simple linear regression analysis, performed using Statistix software for Windows, version 2.0 (Analytical Software). \( P \leq .05 \) was regarded as statistically significant. All values are in US dollars.

## RESULTS

**Antibiotic use and cost savings.** Variations in intravenous antibiotic consumption during the different periods are shown in table 1. The numbers of patient-days for periods 1, 2, 3, and 4 were 37,556, 38,086, 39,954, and 38,905, respectively. A significant global decrease in the use of antibiotics was observed between period 1 (baseline period) and period 2 (initial intervention period). Simple linear regression analysis showed that this trend continued during the remaining periods (adjusted \( R^2 = 0.6885 \); \( P = .01 \)).

Linear regression analysis revealed a sustained increase in the Icfp and Iams indices throughout the study (adjusted \( R^2 = 0.88 \) [\( P = .04 \)] and 0.81 [\( P = .06 \)], respectively). The evolution of both indices along the 4 periods is shown in figure 1. Cost savings from period 1 (baseline) to period 2, from period 2 to period 3, and from period 3 to period 4 were $261,955, $57,245, and $12,881, respectively. The cumulative total savings during the 18 months of intervention was $913,236.

**Prescribing practice.** In all, 450 and 349 successive unique antimicrobial order forms (corresponding to 1 patient each) were analyzed during periods 1 and 4, respectively. Antibiotics to be given orally were also included in this analysis. Because the ATC members might modify a considerable number of antimicrobial orders during period 4, prescription rates during this period were divided between the prescribing intention and definitive treatment (after correction by the ATC members).

### Table 1. Variations in use of intravenous antibiotics after implementation of successive intervention steps for optimizing the quality of antimicrobial prescription in the hospital.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Consumption, divided daily doses per 1000 patient-days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1: baseline</td>
</tr>
<tr>
<td>Amikacin</td>
<td>40.18</td>
</tr>
<tr>
<td>AMP-SUL</td>
<td>24.75</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>13.54</td>
</tr>
<tr>
<td>Cefepime</td>
<td>3.86</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>29.46</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>62.85</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>9.48</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>80.68</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>16.02</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7.87</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>42.75</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>51.13</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>19.78</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>28.53</td>
</tr>
<tr>
<td>Total</td>
<td>430.89</td>
</tr>
</tbody>
</table>

**NOTE.** AMP-SUL, aminopenicillin-sulbactam; NS, not significant.

* See the section “Program design” in Methods for detailed definitions.
* Determined by \( \chi^2 \) test.
* Significant decrease was observed between period 1 and period 2 (\( P < .05 \)).
* Significant increase was observed between period 2 and period 3 (\( P < .05 \)).
Data are shown in table 2. An alarmingly high rate of carbapenem prescription (44%) was noted at baseline. In addition, an appreciable use of ceftriaxone (17%) was observed. On the other hand, cefepime and aminopenicillin-sulbactam were seldom ordered. After the education phase, a dramatic decrease was observed in the prescribing intention of carbapenem and ceftriaxone, as shown in period 4. On the other hand, prescription rates for cefepime and aminopenicillin-sulbactam and the respective indices, Icfp and Iams, increased in this period. All of these trends were reinforced by the active intervention of the ATC members at the time of definitive treatment (table 2).

The characteristics of the control intervention by ATC members in the last period were also examined. A significant increase was found in the rate of microbiologically based prescribing intention in comparison with that of the baseline period (62.8% vs. 27%, respectively; P < .0001). In all, 87 (24.9%) of 349 prescriptions were modified, and 13 order forms (3.7%) were withdrawn by the ATC. Therapy was reduced, in terms of either dose or duration, in 11.5% of cases. Furthermore, 86.1% of the corrections involved less-expensive therapy, and 47% used a drug with a narrower antimicrobial spectrum. Among the 87 order forms that were modified by the ATC, 5, 43, and 39 corresponded to mild, moderate, and severe infections, respectively. The presumed or documented sources of the infection corresponding to these orders were lower respiratory tract (44.2%), abdomen (12.6%), catheter (12.6%), skin and soft tissue (9.2%), urinary tract (8.0%), CNS (6.9%), bone (3.4%), and other sources (3.1%).

Nosocomial infection, crude mortality rates, and hospital and ICU stay. The nosocomial infection rates were 8.0, 8.5, and 8.9 cases per 1000 patient-days for periods 1, 2, 3, and 4, respectively. The corresponding rates of crude mortality were 9.4, 7.3, 6.6, and 7.4 deaths per 1000 patient-days. The mean lengths of hospital stay (± SD) for infected patients decreased significantly (P = .04) between period 1 and period 4, as follows: 474 ± 40.4, 286.8 ± 28.1, 259.9 ± 24.6, and 255 ± 23.3 days. The mean durations of total stay in the ICU (± SD) were 261.7 ± 52.8, 228.5 ± 47.3, 233.2 ± 43.1, and 218.8 ± 40.5 days. Decreasing antibiotic use correlated with duration of both hospital and ICU stay (R² = .99 [P < .004] and R² = .86 [P = .047], respectively), whereas a trend was observed for crude mortality (R² = .82 [P = .06]).

Correlation between bacterial resistance and antibiotic use. Data on bacterial resistance and antibiotic use are summarized in table 3. No correlation was found between variations in antibiotic use and resistance to third-generation cephalosporins by E. coli or K. pneumoniae, whereas decreasing rates of this kind of resistance for P. mirabilis and E. cloacae proved to be associated with the increase in the Icfp index over time. Likewise, decreasing rates of MRSA were related to an increasing Iams index, as well as to a sustained reduction in vancomycin use. No correlation was shown between bacterial resistance variations and the consumption of any one antibiotic included in the formulas for the above indices. The frequency of imipenem-resistant P. aeruginosa strains decreased to 0% in the last period. This finding was strongly associated with a reduction in carbapenem consumption over time. No changes

Table 2. Variation in the frequency of prescription of different antibiotics during a systematic intervention program.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Frequency of prescription, %b</th>
<th>Period 4: active control (n = 349)</th>
<th>P for period 1 vs. definitive treatmentc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prescribing intention</td>
<td>Definitive treatment</td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>44 (n = 450)</td>
<td>2.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>17</td>
<td>8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>8</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Cefepime</td>
<td>0.5</td>
<td>7.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AMP-SUL</td>
<td>6</td>
<td>38</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Iams</td>
<td>24</td>
<td>52</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Icfp</td>
<td>2</td>
<td>52</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

NOTE. AMP-SUL, aminopenicillin-sulbactam; NS, not specific.

a Icfp was calculated as frequency of prescription of cefepime/ceftriaxone and cefazidime × 100. Iams was calculated as frequency of prescription of AMP-SUL/ceftriaxone plus cefazidime × 100.

b See the section "Program design" in Methods for detailed definitions of periods.

c Determined by χ² test.

P < .05 vs. baseline.
were observed in the resistance rates to aminopenicillin-sulbactam and cefepime by E. coli and P. aeruginosa, respectively.

DISCUSSION

Several strategies for regulating antimicrobial prescribing practices have been proposed, such as formulary replacement or restriction [19], introduction of order forms [20], health care provider education, feedback activities [21], and required approval from an infectious diseases physician for drug prescription [22]. Although most of these interventions have been assessed separately, data from prospective studies evaluating the impact of the different strategies applied systematically over time in the same hospital setting remain scarce. In addition, results of a coordinated approach by a multidisciplinary team composed of infectious diseases physicians, microbiologists, and pharmacists have rarely been reported [13]. We have shown a significant reduction in antibiotic use when feedback activities were performed and when we made the optional antibiotic order form obligatory for getting the drug from pharmacy (i.e., period 2, the initial intervention period). Our findings are opposed to those of Gyssens et al. [20], who reported a 25% increase in antibiotic use after this kind of intervention at a 948-bed university hospital in The Netherlands. This is not surprising, because we noted a number of unjustified prescriptions during the baseline phase. A further decrease in drug consumption was reached during the last 2 intervention periods (education and active control phases). This fact might be attributable to the combination of both kinds of interventions.

Because of the alarming prevalence of bacterial resistance found in the baseline period, our education strategy emphasized 3 major issues: making an effort to document the infection microbiologically before starting antimicrobial therapy, avoiding use of certain antibiotics known to be associated with emergence of bacterial resistance [23, 24], and increasing the use of antimicrobials thought to reduce the frequency of multidrug-resistant organisms [25]. Our results challenge the connection between heavy or inappropriate antibiotic use and bacterial resistance. One of the antibiotics we wanted to use instead of third-generation cephalosporins (when appropriate) was aminopenicillin-sulbactam, a drug active against anaerobic organisms. Although several authors have suggested that use of antibiotics with antianaerobic activity is a strong predictor for VRE acquisition, most studies referred to clindamycin [26] and metronidazole [27], rather than aminopenicillin-sulbactam, or found that use of third-generation cephalosporins and vancomycin was an additional VRE predictor [27, 28]. During our study, use of clindamycin, ceftazidime, and vancomycin decreased, whereas use of metronidazole remained stable. However, because we did not detect VRE during any part of the study period, we cannot assert that this situation had an impact on selection of VRE.

We are unable to assert that the sole substitution of third-generation cephalosporins by aminopenicillin-sulbactam or ce-
fepime results in cost containment. Nevertheless, an indirect contribution to the cost savings by the association between this switch and the sustained reduction of resistance rates over time can be inferred. For instance, third-generation cephalosporin resistance in P. mirabilis and E. cloacae was inversely associated with the increase in the Icfp (also lams for E. cloacae), whereas no correlation was observed with the single components of the index formula. These findings differ from those of Friedrich et al. [29], who found a correlation between use of single antibiotics and changes in the susceptibility patterns of some gram-negative aerobes by using data analysis comparable to that of our study (i.e., simple linear regression).

To our knowledge, the present article is the first report to evaluate a ratio representing the relative consumption between ≥2 antibiotics against variations in resistance rates over time. Thus, our results suggest that, for certain antibiotics, demonstration of the relationship between drug use and a specific phenotype of resistance may require the assessment of a ratio relating to the opposite trends in consumption of different antimicrobial agents. In fact, neither the sole decreasing use of ceftriaxone nor the sole increasing consumption of cefepime or aminopenicillin-sulbactam proved to be related to any variation in resistance rates over time.

Of interest, rates of MRSA were inversely associated with increasing lams, but not with the single drugs included in this index formula. This finding is in agreement with that of Landman et al. [22], who described a reduction in the number of patients infected with MRSA after a dramatic increase in use of ampicillin-sulbactam in parallel with a reduction in third-generation cephalosporin use. We hypothesize that the known in vivo and in vitro inhibitory effect of aminopenicillin-sulbactam over that of the cephalosporins against several MRSA strains might be a suitable explanation for this phenomenon [30, 31].

In summary, the results of the present study support the notion that a systematic program executed by a multidisciplinary team is a cost-effective strategy for optimizing antibiotic use in a hospital and has an evident impact on prescribing practice, antibiotic use, cost savings, and bacterial resistance. Furthermore, this impact may be noted even where there are high rates of bacterial resistance and irrespective of any additional precautions for controlling nosocomial infection.

Acknowledgment

We deeply thank Mary Forrest for her valuable technical assistance in revising the manuscript.

References

22. Landman D, Chockalingam M, Quale JM. Reduction in the incidence


