USE OF AMOXICILLIN-CLAVULANATE AND RESISTANCE IN *ESCHERICHIA COLI* OVER A 4-YEAR PERIOD

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ABSTRACT

OBJECTIVE: To reduce the use of amoxicillin-clavulanate after high-resistance rates in *Escherichia coli* were detected.

DESIGN: Intervention study; the interventions were introduced successively over a 4-year period while closely monitoring the resistance patterns.

SETTING: A 260-bed acute-care hospital in Switzerland.

INTERVENTIONS: Introduction of therapeutic guidelines for specific departments or indications, which proposed alternative antibiotics to amoxicillin-clavulanate. The perioperative prophylactic use of amoxicillin-clavulanate was eliminated completely.

RESULTS: The absolute amount of amoxicillin-clavulanate consumed decreased by 23%, from 24.8 g per 100 patient days in 1992 to 18.5 g per 100 patient days in 1995. The number of courses, a parameter that takes the prophylactic use into account, decreased by 62% from 2.3 per 100 patient days in 1992 to 0.9 per 100 patient days in 1995. The percentage of sensitive strains increased from 54.9% (n=512) in 1992 and 54.0% (n=506) in 1993 to 72.1% (n=546) in 1994 and 83.1% (n=668) in 1995. No major changes were detected for other antimicrobials, such as cotrimoxazole, tetracycline, or cefuroxime, used in this 4-year period.

CONCLUSIONS: A decrease in the use of amoxicillin-clavulanate was followed by an increase in susceptibility of *E coli* to it. It was not possible to prove a causative relationship. Only a temporal association was discovered. The reduction of the use of amoxicillin-clavulanate was achieved through the implementation of treatment guidelines, facilitated through a close collaboration among the clinical pharmacists, the infection control practitioner, the microbiology laboratory, and the physicians in charge of the respective departments (*Infect Control Hosp Epidemiol* 1998;19:653-656).

Several articles have been published that show a connection between the use of antimicrobials and the development of resistance. In 1979, Buckwold and Ronald[1] discussed this issue and proposed improved medical education, the adaptation of a policy restricting the use of specific antimicrobial agents, the introduction of guidelines, and a close collaboration among hospital infection and pharmacy committees and the clinical microbiology laboratories. Hollmann[2] analyzed data on antimicrobial consumption and resistance patterns in 1980 and discovered a correlation. In 1983, Daschner et al[3] stated that the restriction of the use of antimicrobials often leads to a decrease in resistance rates. In 1983, McGowan[4] compiled a review of studies performed from 1950 to 1980, which showed a relation between antibiotic use and resistance. In 1987, he assumed that epidemiological criteria for a causal relationship between antibiotic use and resistance of hospital organisms was supported by new data despite confounding variables inherent in the studies.[5] In 1994, McGowan stated that the temporal association between resistance and use already asked for the development of appropriate measures such as education of prescribers, the implementation of restrictions, and intensive control programs.[6] Several authors published data that compared specific antimicrobials with specific species of bacteria. Ma et al reported a substantial decrease in cephalosporin resistance in gram-negative bacilli after a marked decrease in prescribing of these drugs.[7] Data on antibiotic purchases and bacterial susceptibilities in 18 hospitals in the United States revealed a statistically significant correlation between increasing ceftazidime use and increasing *Enterobacter cloacae* resistance.[8] Richard et al reported the results of a case-control study and found that treatment with fluoroquinolones was an independent risk factor for nosocomial infections caused by fluoroquinolone-resistant gram-negative bacilli.[9]

Sanders and Sanders[10] published a review of resistance to β-lactam antibiotics in gram-negative rods. There are several possible factors determining resistance to amoxicillin-clavulanate in *Escherichia coli*. One is TEM-1 β-lactamase hyperproduction.[11-13] Another mechanism of resistance may be an altered permeability of the outer cell membrane.[14] Others described mutations in the genes encoding for TEM-1 β-lactamases.[15-17] Published data on the rate of resistance to amoxicillin-clavulanate in *E coli* vary considerably. In France, isolates from urine in 1993 showed 25% of strains were resistant, and 15% were intermediate.[11] On the other hand, a survey of isolates from six intensive-care units in Switzerland in 1994 showed 93% of strains were sensitive.[18] Kastanakis et al from Crete reported that 18%

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of strains in urine and 30% of strains from other sources were resistant,[19] whereas Kouppari et al[20] reported less than 2% of strains isolated from neonates in the Children's Hospital in Athens were resistant.

METHODS

Setting

The present study was conducted at a 260-bed acute-care hospital in Schaffhausen, Switzerland. The data from the four major departments (surgery, internal medicine, obstetrics-gynecology, and the interdisciplinary intensive-care unit) have been analyzed, amounting to approximately 65,000 to 70,000 patient days per year.

Antibiotic Consumption

The hospital pharmacy's annual analysis of the amount of antimicrobials delivered to all of the departments in the hospital has been calculated in two different ways:

1. In gram of substance; this parameter showed the total amount of the drugs used in the hospital.

2. In number of courses; this parameter indicated how many times the decision to use amoxicillin-clavulanate was made. This was of particular interest because the interventions taken concerned the prophylactic use of the drug, as well as the dosages. The following assumptions have been made: (1) the quantities of prophylactic courses were known from a survey of all surgical patients in 1993 and from the number of hysterectomies and cesarean sections performed in the hospital; (2) for therapeutic use, an average duration of treatment of 7 days has been assumed for the ward and 3 days for the intensive-care unit (according to the average length of stay in that unit).

Surveillance of Resistance

Data from routine resistance testing in the microbiology laboratory were analyzed using a computer program (ResiMed, written by M. L. Mueller and C. Conrad[21]). The system eliminated duplicate specimens if the isolates came from the same patient in the same material and with the same resistance pattern. The fact that isolates from multiple sites from the same patient are included in the analysis did not have any influence on the results.

Routine resistance testing was performed by the disc diffusion method[22] using culture media from Bio-Life (Milan, Italy) and antibiotic discs from Becton-Dickinson–Europe (Meylan, France).

Control of the Resistance Testing

Between November 1994 and February 1995, 30 consecutive isolates determined by routine testing to be intermediately sensitive to amoxicillin-clavulanate were collected. Their susceptibility was tested again using materials from different manufacturers. For the disc diffusion method,[22] antibiotic discs from Becton-Dickinson, as well as from Sanofi (Sanofi Diagnostics Pasteur, Marnes La Coquette, France) were used. To determine the minimum inhibitory concentrations, E-Test-strips (AB Biodisk, Solna, Sweden) were used. Both methods were performed on culture media from Bio-Life, as well as from Sanofi. The interpretation of the results was made according to the guidelines of the National Committee for Clinical Laboratory Standards.[22]

Interventions

To influence the use of amoxicillin-clavulanate, the following interventions were undertaken:

- In the guidelines for the prophylactic and therapeutic use of antimicrobials in the department of gynecology and obstetrics, implemented at the beginning of 1993, the use of amoxicillin-clavulanate was abandoned completely. For prophylaxis, amoxicillin was substituted alone, because these patients usually come directly from home and are not expected to carry nosocomial pathogens. For treatment, cefuroxime was introduced instead.
- In the guidelines for treatment of urinary tract infections, introduced in all departments in October 1994, cefuroxime replaced amoxicillin-clavulanate for the indications "pyelonephritis" and "urosepsis."
- In the guidelines for perioperative antimicrobial prophylaxis in the department of surgery, introduced at the beginning of 1995, amoxicillin-clavulanate was replaced by cefoxitin.
- For the treatment of infections caused by *Staphylococcus aureus* and for soft-tissue infections, it was proposed that flucloxacillin be used whenever possible.
- Furthermore, it was advised that amoxicillin-clavulanate be used in a very restricted manner in the intensive-care unit.

All of these changes were made in close interdisciplinary collaboration among the physicians, the clinical pharmacist, and the infection control practitioner and on the basis of comprehensive surveillance data. The implementations consisted of oral presentations of the new guidelines, information for all prescribing physicians, and the introduction of the guidelines in the handbooks of the departments. Beginning in 1993, all physicians new at the hospital were trained by the infection control practitioner and the clinical pharmacist about the local situation concerning resistance problems and guidelines for use. Additionally, a consultation service running during working hours and daily ward rounds of the infection control practitioner and the clinical pharmacist were implemented.

RESULTS

Use of Amoxicillin-Clavulanate

The total amount of amoxicillin-clavulanate used decreased over the period of 4 years by 23%, from 24.8 g per 100 patient days in 1992 to 18.5 g per 100 patient days in 1995. The number of courses over the same period dropped by almost 62%, from 2.3 per 100 patient days in 1992 to 0.9 per 100 patient days in 1995. Detailed data are shown in Table 1.

Development of Resistance

There was a continuous increase in the susceptibility of *E coli* to amoxicillin-clavulanate since 1994. In 1992,

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TABLE 1
CONSUMPTION OF AMOXICILLIN-CLAVULANATE BY SERVICE AND YEAR

	Use per 100 Patient Days									
	Surgery		Internal Medicine		Obstetrics-Gynecology		Intensive-Care Unit		Total	
Year	Grams	Courses	Grams	Courses	Grams	Courses	Grams	Courses	Grams	Courses
1992	22.0	2.4	23.3	1.4	23.7	3.6	98.8	6.8	24.8	2.3
1993	22.5	2.2	27.9	1.3	2.3	0.2	70.1	4.0	22.5	1.5
1994	19.9	2.0	21.5	1.0	1.1	0.1	53.3	3.0	18.2	1.3
1995	17.3	0.8	24.2	1.1	2.7	0.2	52.7	3.3	18.5	0.9
1995 vs 1992	−21.4%	−65.5%	+3.8%	−24.3%	−88.6%	−95.2%	−46.6%	−51.3%	−23.0%	−61.8%

TABLE 2
RESISTANCE IN *ESCHERICHIA COLI* TO AMOXICILLIN-CLAVULANATE BY SERVICE AND YEAR

	Percentage of Strains Categorized as (R)esistant, (I)ntermediate, and (S)ensitive														
	Surgery			Internal Medicine			Obstetrics-Gynecology			Intensive-Care Unit			Total		
Year	R	I	S	R	I	S	R	I	S	R	I	S	R	I	S
1992	32.4	23.4	44.2	14.7	30.7	54.6	6.8	39.0	54.2	34.9	30.2	34.9	17.2	27.9	54.9
1993	23.0	21.2	55.8	16.7	31.0	52.3	14.5	36.1	49.4	29.3	27.6	43.1	16.8	29.2	54.0
1994	24.7	25.3	50.0	2.9	21.4	75.7	0	17.0	83.0	36.2	24.6	39.1	9.2	18.7	72.1
1995	5.1	11.3	83.6	7.9	13.0	79.1	7.7	13.9	78.4	6.3	12.5	81.3	5.7	11.2	83.1

54.9% of the 512 strains isolated were sensitive, and in 1993, 54% of 506 strains were sensitive. But this percentage increased in 1994 to 72.1% (n=546), and in 1995 to 83.1% (n=668). Surprisingly, in 1992 a high percentage of intermediate strains were isolated, 27.9%, which decreased to 11.2% in 1995. In 1992, 17.2% of strains were resistant, and this figure decreased to 5.7% in 1995. The detailed data are summarized in Table 2.

Use and Resistance of Other Antimicrobials

Three other antimicrobials used over the 4-year period from 1992 to 1995 were evaluated: cotrimoxazole, tetracycline, and cefuroxime. No major changes in susceptibility could be detected. The susceptibility of *E coli* remained stable to cotrimoxazole and tetracycline with 80.7% to 87.6% and 68.3% to 75.7%, respectively, and even increased to cefuroxime from 87.4% to 96.8%. The amount of the drug used varied for cotrimoxazole, doubled for tetracycline, and increased 10-fold for cefuroxime (Table 3).

The use of broad-spectrum antimicrobials increased from 1992 to 1995, but no changes were detected in the resistance pattern of *E coli.* Because these substances were not in use during the entire 4-year period, the data are not shown in detail.

Validation of the Routine Resistance Testing

Control assays of intermediate strains from the routing testing yielded homogeneous results. For the agar disc diffusion tests, the diameters measured lay between 11 and 21 mm and their averages between 14.5 and 16.6 mm, depending on the materials used. Determination of the minimum inhibitory concentration by E-test resulted in values from 4 to 16 µg/mL, with averages between 10.3 and 11.8 µg/mL. The different test media yielded the same results.

TABLE 3
CONSUMPTION AND RESISTANCE PATTERNS OF OTHER ANTIMICROBIALS FROM 1992 TO 1995 (ALL DEPARTMENTS)

	Use in Grams per 100 Patient Days (% Sensitive)			
Antibiotic	1992	1993	1994	1995
Cotrimoxazole	4.8 (86.1)	10.5 (87.6)	5.4 (80.7)	3.3 (84.1)
Tetracycline	0.0 (71.4)	0.1 (68.3)	0.1 (69.5)	0.1 (75.7)
Cefuroxime	0.4 (87.4)	0.8 (94.6)	0.9 (95.4)	3.7 (96.8)

Cross-Resistance

E coli strains with decreased susceptibility to amoxicillin-clavulanate also had decreased susceptibility to first-generation cephalosporins, cotrimoxazole, and tetracycline, and, to a lesser extent, to second- and third-generation cephalosporins (Table 4). There were only a few strains intermediately sensitive or resistant to tobramycin, imipenem, or piperacillin-tazobactam.

DISCUSSION

In the present study, a decrease in the use of amoxicillin-clavulanate was followed by an increase in suscepti-

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TABLE 4
CROSS-RESISTANCE IN *ESCHERICHIA COLI* IN 1992 AND IN 1995, ISOLATES OF ALL DEPARTMENTS

	1992			1995		
Resistant to:	**AMC-Sensitive**	**AMC-Intermediate**	**AMC-Resistant**	**AMC-Sensitive**	**AMC-Intermediate**	**AMC-Resistant**
Ceph-1	61.2%	97.9%	95.3%	20.7%	85.3%	79.0%
Ceph-2	0%	3.4%	24.7%	1.2%	8.0%	21.1%
Ceph-3	0%	0%	4.7%	0.2%	0%	2.6%
Tetracycline	18.3%	41.2%	56.4%	18.1%	54.6%	52.7%
Cotrimoxazole	2.9%	21.0%	27.1%	10.9%	38.6%	44.7%

Abbreviations: AMC, amoxicillin-clavulanate; ceph-1, first-generation cephalosporin; ceph-2, second-generation cephalosporin; ceph-3, third-generation cephalosporin.

bility of *E coli* to it. The reduction in amoxicillin-clavulanate use was achieved mainly through the introduction of treatment guidelines into daily clinical practice, in which alternative antibiotics were suggested whenever possible.

It is not possible to show a causative relationship between these two parameters, but there was a clear temporal association between antibiotic-use restriction and resistance patterns.

During the study period, a dramatic increase in the use of cefuroxime occurred. Thus far, this has not had any adverse effect on resistance rates. However, use and susceptibility must be monitored closely in the future, because follow-up monitoring of the present study was short, with only 4 years' worth of data.

The high percentage of intermediate strains in *E coli* raised doubts as to the appropriateness of the routine testing. However, control tests performed with materials from different manufacturers yielded the same results and thus confirmed the data.

The mechanism of resistance was not proven, but analysis of the pattern of cross-resistance could imply that the cause of resistance may be overproduction of TEM-1 β-lactamases, as described in the introduction.

An important aspect of the present study was that all actions were taken in close collaboration with the clinical pharmacists, the infection control practitioner, the microbiology laboratory, and the physicians in charge of the respective departments. This interdisciplinary approach facilitated the implementation of the necessary measures. Ongoing surveillance of the development of resistance, as well as the use of antibiotics in a specific setting, are an important procedural basis from which to detect any adverse events as soon as possible and to take appropriate measures. This procedure will allow control over, and will restrict the use of, antibiotics, as well as the development of resistance.

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