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Problem of Antimicrobial Resistance of Fecal Aerobic Gram-Negative Bacilli in the Elderly

TIINA LEISTEVUO,[1,2]* PÄIVI TOIVONEN,[3] MONICA ÖSTERBLAD,[1] MAUD KUISTILA,[1]†
ANJA KAHRA,[4] AAPO LEHTONEN,[2] AND PENTTI HUOVINEN[1]

Department of Medicine and Geriatrics[2] and Department of Pharmacy,[4] Turku City Hospital, Department of Statistics, Turku University,[3] and Antimicrobial Research Laboratory, National Public Health Institute,[1] FIN-20521 Turku, Finland

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In this study, we assessed the magnitude of risk (odds ratio [OR]) of patients being colonized with fecal aerobic gram-negative bacilli in two geriatric hospitals compared with the community, and we associated the use of antimicrobial agents with bacterial resistance. One fecal sample was collected from each of 341 patients, aged 60 years or older, during the hospital stay or when visiting the outpatient service. Samples were collected in 1988 and 1993 to 1994. The aerobic gram-negative bacilli from all samples were examined for resistance to seven antimicrobials by a replica plating method. The long-term-hospitalized patients had a significantly higher risk of being colonized with bacilli resistant to ampicillin (OR, 14.3; 95% confidence interval [95% CI], 6.0 to 34.1), cefuroxime (OR, 7.5; 95% CI, 2.7 to 20.8), trimethoprim (ORs, 22.3; 95% CI, 8.6 to 57.8), and tetracycline (OR, 5.2; 95% CI, 2.4 to 10.9) than the outpatients. The respective ORs among the short-term-hospitalized patients compared with the outpatients were 4.0 (95% CI, 1.9 to 8.4), 7.5 (95% CI, 2.7 to 20.8), 5.5 (95% CI, 2 to 14), and 2.0 (95% CI, 1 to 4). In 1993 to 1994 compared with 1988, in both hospitals there was a significantly increased risk of colonization by bacilli resistant to ampicillin (OR, 3.1; 95% CI, 1.9 to 5.1), cefuroxime (OR, 3.8; 95% CI, 2.1 to 6.7), and tetracycline (OR, 1.6; 95% CI, 1.0 to 2.5). However, the total use of antimicrobial agents increased only among the patients of the short-term-care hospital.

Today antimicrobial resistance is one of the major problems confronting clinicians in their work (4). The increasing prevalence of resistance to most antimicrobials complicates the use of antimicrobial agents and the control of infectious diseases (2, 21). Invasive medical interventions and the prolonged survival of many patients with chronic debilitating disease amplify the problem (32). Some hospital strains of invasive gram-negative enteric bacteria and enterococci are no longer susceptible to any available drug (14). Therefore, all data on how antimicrobial resistance develops in a hospital environment are essential for successful treatment practice in the future.

We studied fecal aerobic gram-negative bacilli because most hospital-acquired infections usually are caused by aerobic gram-negative bacilli originating from the fecal flora (6, 31). One example of this kind of infection is urinary tract infection, the most common type of infection in the elderly. Several studies have shown that antimicrobial agents and hospitalization have an impact on the aerobic fecal flora (16, 17, 22, 24, 27). However, there have been few studies comparing the effects of these two factors on antimicrobial resistance in the fecal flora of the elderly (35). This is alarming considering the changing demographics of the society (7).

In this study, we estimated the magnitude of risk (odds ratio [OR]) of patients being colonized with fecal aerobic gram-negative bacilli in long-term- and short-term-care geriatric hospitals compared with patients in the community, and we associated the use of antimicrobials with the antimicrobial resistance of fecal aerobic gram-negative bacilli.

* Corresponding author. Mailing address: Antimicrobial Research Laboratory, National Public Health Institute, P.O. Box 57, FIN-20521 Turku, Finland. Phone: 358-21-2519 255. Fax: 358-21-2519 254. Electronic mail address: tiilei@utu.fi.

† Deceased.

MATERIALS AND METHODS

Description of sample populations. We studied the fecal carriage of resistant aerobic gram-negative bacilli in a total of 341 patients in 1988 and in 1993 to 1994. The study population consisted of short-term- and long-term-hospitalized patients as well as outpatients. All 341 patients were 60 years old or older. The patients in five wards of the short-term-care hospital (160 beds) were studied in 1988 and 1993, and the patients in five wards of the long-term-care hospital (206 beds) were studied in 1988 and 1994. The outpatients were studied in 1993.

Patients in the short-term-care hospital. Fecal samples were collected from patients in two hospitals of the Department of Medicine and Geriatrics in Turku, Finland. The short-term-care hospital consists of internal medicine and surgical wards which are in a separate part of the building. The short-term-care patients were all from the internal medicine wards. At four of the wards the patients were similar with regard to their illness, while at a fifth ward more neurological patients were placed. To our knowledge patient characteristics have remained similar during these years, and there have been no radical changes in the policy of care. In addition, as far as we know, there were no outbreaks of infection in the hospitals during the study periods. Exclusion criteria of the hospitalized patients were (i) hospitalization for less than 7 days and (ii) antimicrobial treatment for a community-acquired infection either before hospitalization or within the first 6 days in the hospital.

Thirty-four short-term-hospitalized patients in 1988 and 43 such patients in 1993 who had not received any antimicrobial therapy within 3 months before sampling were included in the study population (Table 1). Twenty-six short-term-hospitalized patients in 1988 and 27 such patients in 1993 were treated during their stay in hospital, and all of them had received antimicrobial therapy within three weeks before sampling.

Patients in the long-term-care hospital. The long-term-care hospital is a separate building near the short-term-care hospital. The long-term-care hospital consists of five long-term-care wards and one rehabilitation ward. Because the patients at the rehabilitation ward were not typical long-term-care patients, we did not include them in the study. Forty-two long-term-hospitalized patients in 1988 and 39 such patients in 1994 who had not received any antimicrobial treatment within 3 months before sampling were included in the study population (Table 1). Thirty-eight long-term-hospitalized patients in 1988 and 31 such patients in 1994 were treated during their stay in hospital, and all of them had received antimicrobial therapy within three weeks before sampling. Exclusion criteria were the same as those for the short-term-hospitalized patients.

Outpatients. We studied 61 outpatients in 1993 (Table 1). The patients were from the outpatients' geriatric internal medicine service of the same short-term-care hospital. Exclusion criteria were (i) antimicrobial therapy and (ii) hospitalization during the 3-month period preceding the sampling. This was checked from the case records by the physician. All outpatients lived at their own home.

TABLE 1. Patient (n = 341) characteristics

Facility	Mean age (years)	Range (years)	Standard deviation	Mean hospitalization time (months)	Range (months)	Standard deviation
1988 long-term care						
Antimicrobial use	83.26	68–94	7.16	28.00	1–80	22.85
No antimicrobial use	83.90	63–98	7.23	32.45	2–91	23.71
1994 long-term care						
Antimicrobial use	82.97	68–92	6.05	20.50	1–130	27.40
No antimicrobial use	82.31	62–95	7.82	23.40	1–137	31.84
1988 short-term care						
Antimicrobial use	82.65	67–98	8.11	2.90	0.5–12	2.66
No antimicrobial use	82.97	66–101	6.88	5.00	0.25–22	5.09
1993 short-term care						
Antimicrobial use	80.22	61–92	7.47	1.40	0.25–120	1.07
No antimicrobial use	75.56	61–95	8.60	0.80	0.25–146	0.86
1993 outpatients (no antimicrobial use)	70.05	60–87	7.28			

Data collection and methods. Fecal samples were taken from the hospitalized patients from the rectum or by swabbing a fresh stool with a sterile Dacron swab. The outpatients brought their fresh stool samples when visiting the outpatient service. Samples were transported within 2 h to the laboratory for bacterial culture. Four serial 10-fold dilutions of each fecal sample were made in physiological saline and cultured onto MacConkey plates (Oxoid Ltd., Basingstoke, England) by using a sterile cotton swab. The MacConkey medium selects for growth of fecal aerobic gram-negative bacilli. The plates were incubated aerobically overnight at 35°C. A plate with 100 to 1,000 colonies was used for replica plating.

Bacterial colonies on the selected plate were counted. The best of each pair of MacConkey plates (i.e., clearly isolated colonies) was replicated by using a velvet replica plating method (15, 23) onto a series of antibiotic-containing Iso-Sensitest agar plates (Oxoid). These plates contained different antimicrobial agents (concentrations in μg/ml) as follows: ampicillin (32), cefuroxime (16), ceftazidime (16), trimethoprim (8), sulfamethoxazole (512), tetracycline (4), or ciprofloxacin (1). One plate without any antibiotic was used as a control. After aerobic incubation overnight at 35°C, colonies on the antibiotic plates and on the control plate were counted. Colonies of ambiguous appearance were Gram stained and disregarded if they proved not to be fecal aerobic gram-negative bacilli. If 1% or more of the original colonies grew on the antimicrobial plate the sample was regarded as resistant.

Antimicrobial use by the study patients. Because individual use of certain antimicrobial agents has an impact on individual levels of bacterial resistance, the use of antimicrobials by the study patients was recorded. Data on the use of antimicrobial agents by the treated patients within the 3-month period before the sampling were collected separately by the physician. The use of antimicrobial agents was determined as defined daily doses (DDD) (13) per patient.

Antimicrobials (e.g., methenamine salts) not mentioned in this study were excluded because they are not used for treating infections caused by aerobic gram-negative bacilli or have only a minimal effect on aerobic gram-negative bacilli and the appearance of resistance in these bacteria in the gut. Moreover, several of the agents not mentioned were not used in these hospitals.

Data analysis. The comparisons of proportions of colonized patients in the two types of hospitals and at three different time points, 1988, 1993, and 1994, were statistically analyzed using logistic models (1). ORs and 95% confidence intervals (95% CI) for them were calculated to quantify the differences. P values less than 0.05 were interpreted as being statistically significant. Statistical calculations were performed with the SAS statistical program package (28).

Ethical approval. This study was approved by the ethics committee of the Turku City Health Service, Turku, Finland.

RESULTS

Use of antimicrobial agents by the study patients. (i) The long-term-care hospital. The antimicrobially treated study patients (n = 38) had received a total of 3.9 DDD per patient of different antimicrobial agents within the 3 months before sampling in 1988. In 1994, the corresponding amount was 10.5 DDD per patient (n = 31). The use of trimethoprim and trimethoprim-sulfonamides combined increased from 3.1 to 8.0 DDD per patient, and the use of amoxicillin increased from 0.2 to 0.7 DDD per patient. The use of cephalosporins doubled from 0.6 to 1.2 DDD per patient, and the use of ciprofloxacin increased from 0 to 0.6 DDD per patient.

(ii) The short-term-care hospital. The treated patients (n = 26) had received a total of 9.7 DDD of different antimicrobial agents per patient during the 3 months before sampling in 1988, and the corresponding amount in 1993 (n = 27) was 13.6 DDD per patient. The use of trimethoprim and trimethoprim-sulfonamides decreased from 3.0 to 2.0 DDD per patient. The use of amoxicillin decreased from 5.0 to 0.9 DDD per patient. The use of cephalosporins increased from 1.1 to 1.9 DDD per patient.

Relationship between long-term versus short-term hospitalization and colonization with resistant fecal aerobic gram-negative bacilli. (i) Ampicillin. When we compared the hospitalized patients in 1993 to 1994 with the outpatients in 1993, we found that the hospitalized patients had an almost seven times (OR, 6.9; 95% CI, 3.5 to 13.5) greater risk of being colonized with ampicillin-resistant fecal aerobic gram-negative bacilli. However, when only the long-term-hospitalized patients were compared with the outpatients, the long-term-hospitalized patients had a 14 times greater risk of being colonized with ampicillin-resistant bacilli (Table 2). In addition, when the hospitalized patients from 1988 were compared with patients hospitalized in 1993 to 1994, the latter group had a three times (OR, 3.1; 95% CI, 1.9 to 5.1) greater risk of being colonized. When the long-term patients were compared with the short-term-hospitalized patients, the risk of being colonized with ampicillin-resistant fecal aerobic gram-negative bacilli was almost two times higher (OR, 1.8; 95% CI, 1.1 to 2.9) among the former; i.e., an increased hospitalization time almost doubled the risk.

(ii) Cefuroxime. When we compared the patients hospitalized in 1993 to 1994 with the outpatients in 1993, we found that both the long-term- and the short-term-hospitalized patients had an increased risk of being colonized with cefuroxime-resistant fecal aerobic gram-negative bacilli (Table 2). In addition, both the long-term- and the short-term-hospitalized patients had an increased risk of being colonized with resistant bacilli (OR, 3.8; 95% CI, 2.1 to 6.7) and those who had received antimicrobials had almost a two times (OR, 1.8; 95% CI, 1.0 to 3.2) greater risk than those who had not received antimicrobials.

TABLE 2. Relationship between short-term versus long-term hospitalization and colonization with resistant fecal aerobic gram-negative bacilli[a]

Antimicrobial agent	Short-term-hospitalized patients (n = 70)		Long-term-hospitalized patients (n = 70)	
	OR (95% CI)	P value	OR (95% CI)	P value
Ampicillin	4.0 (1.9 to 8.4)	0.0002	14.3 (6.0 to 34.1)	0.0001
Cefuroxime	7.5 (2.7 to 20.8)	0.0001	7.5 (2.7 to 20.8)	0.0001
Ceftazidime	7.5 (0.9 to 63.7)	0.057	3.6 (0.4 to 33.4)	0.254
Trimethoprim	5.5 (2 to 14)	0.0003	22.3 (8.6 to 57.8)	0.0001
Sulfamethoxazole	1.1 (0.5 to 2.2)	0.830	1.5 (0.8 to 3.0)	0.233
Tetracycline	2.0 (1 to 4)	0.064	5.2 (2.4 to 10.9)	0.0001
Ciprofloxacin	6.7 (0.8 to 55.2)	0.080		

[a] OR and 95% CI were calculated by using logistic models to quantify the differences. The study year for outpatients and short-term-hospitalized patients was 1993, the study year for long-term-hospitalized patients was 1994, and the study year for the reference group of outpatients (n = 61) was 1993.

(iii) Ceftazidime. The short-term- or the long-term-care patients had no statistically significant greater risk of being colonized with ceftazidime-resistant fecal aerobic gram-negative bacilli than the outpatients (Table 2). When the short-term-hospitalized patients were compared with the long-term patients, there was no statistically significant difference, regardless of whether the patients were treated with antimicrobials, and regardless of how long they had been hospitalized or if they had been hospitalized in 1988 or 1993 to 1994.

(iv) Trimethoprim. When the long-term-hospitalized patients were compared with the outpatients, the hospitalized patients had an over 22 times higher risk of being colonized with resistant bacilli (Table 2). The respective OR among the short-term-hospitalized patients was 5.5 compared with the outpatients. The long-term-hospitalized patients had an almost three times (OR, 2.7; 95% CI, 1.6 to 4.4) greater risk of being colonized with trimethoprim-resistant fecal aerobic gram-negative bacilli than the short-term-hospitalized patients. In addition, the risk of being colonized with trimethoprim-resistant fecal bacilli was increased by almost two times among the long-term-care patients (OR, 1.8; 95% CI, 1.1 to 2.8) in 1994 compared with such patients in 1988.

(v) Sulfamethoxazole. There was statistically no significant difference in the risk of being colonized with sulfonamide-resistant bacilli among the hospitalized patients compared with the outpatients.

(vi) Tetracycline. The long-term-care patients had an over five times higher risk of being colonized with tetracycline-resistant fecal aerobic gram-negative bacilli than the outpatients (Table 2). The respective OR among the short-term-hospitalized patients was lower. In addition, among all hospitalized patients the risk of being colonized with tetracycline-resistant fecal aerobic gram-negative bacilli was almost two times greater than that of the outpatients (OR, 1.6; 95% CI, 1.0 to 2.5), and the respective figure among the long-term-care patients compared with the short-term-care patients was almost three times greater (OR, 2.6; 95% CI, 1.4 to 5.1).

(vii) Ciprofloxacin. For short-term-hospitalized patients the risk of being colonized with resistant fecal aerobic gram-negative bacilli was over 11 times (OR, 11.6; 95% CI, 1.4 to 92.8) higher than for long-term-hospitalized patients. None of the long-term patients had resistance to ciprofloxacin in 1994. There was no significantly increased risk of being colonized with ciprofloxacin-resistant bacilli among the hospitalized patients in 1993 to 1994 compared with 1988.

DISCUSSION

Compared with the outpatients, the long-term-care patients were at a significantly higher risk of being colonized with fecal aerobic gram-negative bacilli resistant to ampicillin (OR, 14.3), trimethoprim (OR, 22.3), and tetracycline (OR, 5.2). The respective ORs among the short-term-hospitalized patients for being colonized with ampicillin-, trimethoprim-, or tetracycline-resistant bacilli compared with the outpatients were 4.0, 5.5, and 2.0, respectively. Surprisingly, the risk of being colonized with cefuroxime-resistant bacilli was equal in the short-term- and the long-term-care hospital (OR, 7.5) compared with the community. The risk of being colonized with resistant bacilli increased in both hospitals between the study years 1988 and 1993 to 1994; the OR for acquiring resistance to ampicillin, cefuroxime, or tetracycline was 3.1, 3.8, or 1.6, respectively.

In the late 1960s and early 1970s a number of studies on the frequency of antimicrobial resistance in fecal flora were performed (9, 10, 27, 30, 34). However, these studies cannot be directly compared with our study because of methodological and quantitative differences. Surprisingly, very few comprehensive surveys are available from the 1980s and 1990s, and few of these deal solely with bacterial resistance among the elderly (3, 18, 19, 26, 29, 35). Among these studies, there is one in which replica plating was used (19). This study by Levy et al. is still difficult to compare with ours because of the different breakpoints used, but in general the study of Levy et al. found high frequencies of antimicrobial resistance in the fecal flora of ambulatory and hospitalized patients, whether or not they were taking antimicrobials.

It is interesting that there was no increased risk of acquiring sulfamethoxazole resistance associated with hospitalization. The hospitalized patients on antimicrobial therapy were at a higher risk of being colonized than the outpatients, but the difference was not statistically significant. The reason for the difference not being significant may be related to an already high baseline level of resistance. This general high baseline level may be caused by the extensive use of this agent; in Finland sulfatrimethoprim agents are at present the most commonly used drugs for treating infections in elderly people (unpublished data).

The ciprofloxacin resistance pattern was also aberrant because the very low frequency of resistance skewed the results. The risk of acquiring ciprofloxacin-resistant bacilli was over 11 times higher (OR, 11.6) for the short-term-hospitalized patients than for the long-term-hospitalized patients. But the 95% CI was very wide (1.4 to 92.8), reflecting the fact that only a few (8 short-term-hospitalized patients) of the patients studied in the 1993 to 1994 period (n = 201) had bacterial resistance to ciprofloxacin. Thus, these results cannot be given too much weight.

Both the long-term- and the short-term-hospitalized patients were at an increased risk (OR, 7.5) of being colonized with cefuroxime-resistant bacilli compared with the outpatients. The risk of being colonized with cefuroxime-resistant bacilli increased almost four times between 1988 and 1993 to 1994 among the hospitalized patients. At the same time the risk of being colonized with ampicillin-resistant bacilli was 14 times higher among the long-term patients than the outpatients, and there was a threefold increase in risk between the study years. These results can be associated with the consumption of antimicrobials in the hospitals. The most popular antibiotics used in the short-term-care hospital were cephalosporins (data not shown). The intake of these (mainly narrow- and extended-spectrum cephalosporins) increased markedly from 1987 to 1993. The consumption of cephalosporins was clearly

lower in the long-term-care hospital, expressed as total antimicrobial consumption per bed; here the patients consumed only one-sixth of the amount of antimicrobials consumed by the patients in the short-term-care hospital. Also, the individual use of cephalosporins was higher among the short-term-hospitalized patients than the long-term-hospitalized patients. Still, all hospitalized patients had an equal risk of being colonized with cefuroxime-resistant fecal aerobic gram-negative bacilli.

It is known that extended-spectrum cephalosporins can have a major suppressive effect on a patient's endogenous microbial flora (5). It has also been shown that the increased use of certain cephalosporins is a predisposing factor for the emergence and spread of resistant bacteria (8). The narrow-spectrum cephalosporins, when used for long periods as in our study hospitals, can select for resistance in both urinary pathogens and fecal floras (25, 33). The profound impact of certain cephalosporins on the flora of the lower gastrointestinal tract is not surprising since a substantial proportion of these drugs is excreted via the biliary tract (5, 12).

Previous studies have shown that hospitalization has an impact on the aerobic fecal flora (16, 17, 24, 27). The analysis from these studies indicates that at the time of admission to hospital, *Escherichia coli* constituted the predominant fecal aerotolerant flora but was gradually replaced by *Klebsiella*, *Enterobacter*, and *Proteus* species. Although we did not identify our bacteria to the species level, this kind of phenomenon might be partly responsible for the increased cephalosporin and ampicillin resistance in our study. The use of aminoglycosides and ampicillin can make the selective role of cephalosporins difficult to establish (36). However, in the hospitals of the present study, the use of aminoglycosides and ampicillin was marginal; thus, the observed increase in the risk of being colonized with cephalosporin-resistant bacilli might in fact be directly related to the increased use of cephalosporins, along with the other factors mentioned above.

The treatment practice in the Turku area sometimes leads to a transfer of geriatric patients from the University Hospital to the short-term-care hospital of this study. If further hospital treatment is needed the elderly are in most cases transferred from the short-term hospital to the long-term hospital of this study. Thus, the transfer of short-term-care geriatric patients along with possible resistant strains to the long-term-care hospital may mix the strains in these two study hospitals. This may mean that when people interact in different environments, like multiple hospitals, resistant bacteria also interact (20). As a consequence of the prolonged hospitalization, or frequent readmissions, there is ample time for horizontal spread of bacteria, e.g., via the hands of nurses (34).

As an example of this, our study showed that patients hospitalized for longer times were at higher risk of being colonized with trimethoprim-resistant fecal aerobic gram-negative bacilli than the short-term care patients (OR, 2.7). The use of trimethoprim-sulfonamides in general decreased in both hospitals (data not shown), but the individual use was higher among long-term patients; trimethoprim-sulfonamides are often used for long periods in the treatment of urinary tract infections. Resistant bacteria that emerge in the treated patients can then spread horizontally. Thus, the importance of proper hygienic measures in long-term units cannot be stressed enough (11).

In conclusion, the risk of being colonized with resistant fecal aerobic gram-negative bacilli increased in both hospitals during the study years, but long-term hospitalization posed a greater risk than short-term hospitalization. We suggest that more surveys in geriatric-care facilities should be made, because a high frequency of antimicrobial resistance in the fecal flora of geriatric patients can potentially lead to an increase in treatment failures when inappropriate antimicrobial treatment is applied. There is a special call for screening for emerging resistance when hospitalization times are prolonged; such screening should be done both on the individual patient level and on a horizontal level in the ward. In addition, the effects of bacterial resistance carried by the elderly should be studied not only in geriatric facilities but also in acute-care settings, where the consumption of antimicrobials can be high.

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