

Marked Differences in Antibiotic Use and Resistance Between University Hospitals in Vilnius, Lithuania, and Huddinge, Sweden

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ABSTRACT

Antibiotic use and antimicrobial resistance was compared between Vilnius and Huddinge University hospitals. Drug use data were expressed in number of defined daily doses/100 bed-days; antimicrobial resistance were given as percentages of resistant isolates. Thirty-five and 48 different antibiotic drugs were used in Vilnius and Huddinge, respectively. The overall consumption of antibiotics was 15 DDD/100 bed-days in Vilnius and 43 DDD/100 bed-days in Huddinge. Benzylpenicillin, ampicillin, and aminoglycosides were the major antibiotics in Vilnius; β -lactamase-resistant penicillins, cephalosporins, and quinolones in Huddinge. In Vilnius, gentamicin made up one-quarter of the use. *Staphylococcus aureus* and Gram-negative isolates from wounds and blood were more resistant to gentamicin in Vilnius. *S. aureus* was more often methicillin resistant in Vilnius than in Huddinge. There was no *S. aureus*-resistant to vancomycin in either hospital. The vancomycin-resistant enterococci made up from 4% to 10% in Vilnius hospital, but they were not detected in Huddinge hospital (0%). The majority of *Streptococcus pneumoniae* isolates were sensitive to benzylpenicillin in both hospitals. The higher resistance of microorganisms to some antibiotics in Vilnius may be explained by heavy use of few antibiotics. Lower level of hygiene procedures, sampling bias, and other methodological issues may also have contributed. Guidelines for antibiotic use and hygienic procedures are now under development in Vilnius.

INTRODUCTION

ANTIMICROBIAL RESISTANCE to antibiotic drugs is a growing problem in primary health care and hospitals in Lithuania as in many other countries. Infections caused by drug-resistant bacteria are associated with increased morbidity, prolonged hospital stays, greater direct and indirect costs, prolonged periods during which individuals are infectious, and greater opportunities for the spread of infection to other individuals.²¹ Because microorganisms know no national boundaries, no single country can solve the problem alone.¹⁷ Thus "The Copenhagen Recommendations" were released after the European Union conference on The Microbial Threat in Copenhagen, 1998. This document addressed the strategies to prevent and control the

emergence and spread of antimicrobial resistant microorganisms in the EU.¹⁸ Several lines of evidence suggest that there is a causal association between the use of antimicrobial agents and the prevalence of drug resistance in microorganisms.^{2,6,7,12} Therefore, the Copenhagen recommendations emphasized the importance of collecting and comparing data on antibiotic use and bacterial resistance to antibiotics from different countries. Such data could help to develop guidelines on rational use of antibiotics.

Routine monitoring of the use of antibiotic drugs and antimicrobial resistance was started in Vilnius University Hospital a few years ago (in 1997) with the aim to prevent the growing increase in antimicrobial resistance and expenditures of treatment. Previous studies on drug use have shown that the use

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of antibiotic drugs varies quantitatively and qualitatively between countries.^{9,10} Previous studies have shown that antibacterial resistance is not a major problem in Sweden.^{5,15,20} Data on antibiotic deliveries from the pharmacy have been collected for several years but have hitherto not been analyzed in relation to resistance data.

The aim of the present study was to compare the antibiotic pressure between Vilnius and Huddinge University Hospital and see if it was related to differences in antibiotic resistance.

MATERIAL AND METHODS

Hospitals

Vilnius University Hospital (VUH) and Huddinge University Hospital (HUH) are about 1,000-bed tertiary care teaching facilities. All departments at VUH (Departments of Internal Medicine, Cardiology, Pulmonology and Allergology, Nephrology, Endocrinology, Neurology, Gastroenterology, Haematology, Rehabilitation, Heart Surgery, Abdominal Surgery, Gynaecology, Urology and Hemodialysis, and three intensive care units) and the corresponding departments at HUH were included. During study year, 21,387 patients were admitted to VUH, and the number of bed-days was 289,142. Corresponding data from HUH was 29,309 patients and 125,820 bed-days.

The department of epidemiology and disinfection (in total, 18 persons; 1 doctor, head of the department, 1 epidemiologist, 4 nurses, and 12 other technical personnel) was responsible for infection control in VUH. Its activity was mainly limited to disinfection, sterilization, and infection control in the operating theater. The hospital infection reporting rate and surveillance were very poor.

The infection control team in HUH consisted of 1 senior doctor (also responsible for two other smaller hospitals), 2 infection control nurses, and a laboratory unit. Their main workload consisted of teaching, development of guidelines and policies, and outbreak management all over the hospital. They also performed limited surveillance of resistance and periodically registration of infections in certain clinics. There is an infection control committee, which meets twice yearly with about 15 representatives for crucial clinics, operation theaters, sterilization unit, and building and construction led by the chief medical officer.

Drug consumption

Data on the use of antibiotics during 1997 were obtained from the hospital pharmacies and analyzed using ATC (Anatomical-Therapeutic-Chemical classification)/DDD (Defined Daily Dose) methodology.¹ Use of antibiotics was expressed as the number of DDDs per 100 bed-days.¹¹ In the VUH, drugs bought by the patients themselves and drug donations received could not be included (about 20% of all antibiotics used; personal communication from V. Vasiliauskas, head of hospital pharmacy).

Susceptibility testing

Data on microbial susceptibility to antibiotic agents among clinical isolates was obtained from the bacteriological labora-

tories of both hospitals. The disc diffusion method was used to test susceptibility of isolates. The bacteriological laboratory of HUH used oxoid discs on ISA-medium and species-related breakpoints.¹⁹ The disc diffusion tests in the VUH bacteriological laboratory were performed using Mueller-Hinton agar and the Becton Dickinson Microbiology system (BBL Sensi-Disc Antimicrobial Susceptibility Test Discs) according to NCCLS.¹⁴ The susceptibility results were evaluated as Sensitive, Intermediate (VUH)/Indeterminate (HUH) or Resistant. Testing for resistance of isolates from urine, sputum, wounds, and blood to certain antibiotic agents were performed as shown in Table 1. The percentage of resistant isolates was calculated as number of resistant isolates/number of tested isolates (not all isolates of a certain species were tested against all relevant antibiotics in both hospitals).

TABLE 1. PATTERNS OF RESISTANCE TESTING TO CERTAIN ANTIBIOTICS FOR BACTERIA ISOLATED FROM URINE, SPUTUM, WOUNDS, AND BLOOD

<i>Isolates</i>	<i>Antibacterial agents</i>
Urine	
{ <i>Escherichia coli</i> <i>Klebsiella</i> spp. <i>Pseudomonas aeruginosa</i> <i>Proteus mirabilis</i> <i>Enterococcus</i> spp.	{ Ampicillin Nitrofurantoin Norfloxacin Trimethoprim
Sputum	
{ <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Klebsiella</i> spp.	{ Benzylpenicillin Ampicillin Tetracycline Ampicillin Cefuroxime Gentamicin Ciprofloxacin
Wounds	
{ <i>Staphylococcus aureus</i> <i>Enterococcus</i> spp. Group A streptococci	{ Ampicillin Methicillin Erythromycin Clindamycin Vancomycin
{ <i>Escherichia coli</i> <i>Klebsiella</i> spp. <i>Pseudomonas aeruginosa</i> <i>Proteus mirabilis</i>	{ Cefuroxime Gentamicin Ciprofloxacin Ceftazidime
Blood	
{ <i>Staphylococcus aureus</i> Coagulase-negative staphylococci <i>Enterococcus</i> spp.	{ Methicillin Erythromycin Clindamycin Vancomycin Fusidic acid Rifampicin
{ <i>Escherichia coli</i> <i>Klebsiella</i> spp.	{ Cefuroxime Ceftazidime Cefotaxime Gentamicin Ciprofloxacin

TABLE 2. RANKING OF TOP 10 ANTIBIOTIC DRUGS IN VUH AND HUH AS PERCENTAGES OF TOTAL ANNUAL USE IN DEFINED DAILY DOSES (DDDs)

HUH	DDDs	DDD (%)	VUH	DDDs	DDD (%)
Cefuroxime	6,280	11.6	Gentamicin	11,628	25.9
Ciprofloxacin	6,034	11.1	Benzylpenicillin	8,520	19.0
Cloxacillin	3,496	6.5	Ampicillin	8,240	18.3
Phenoxymethylpenicillin	3,297	6.1	Kanamycin	3,594	8.0
Amoxicillin	3,106	5.7	Ampicillin + oxacillin	3,570	7.9
Metronidazole	2,875	5.3	Ciprofloxacin	1,832	4.1
Doxycycline	2,762	5.1	Nitrofurantoin	1,512	3.4
Dicloxacillin	2,749	5.1	Cefuroxime	1,231	2.7
Norfloxacin	2,459	4.5	Cefamandole	956	2.1
Sulfamethoxazole + trimethoprim	2,213	4.1	Metronidazole	413	0.9

All *Staphylococcus aureus* found resistant to oxa-/methicillin were reported as methicillin-resistant *S. aureus* (MRSA) in this study, regardless of whether they were true *mecA* gene-positive MRSA or *mecA*-negative borderline resistant *S. aureus* (BORSA, which was true for most isolates at HUH). Because it is difficult to distinguish clinically significant isolates from contaminant strains of coagulase-negative staphylococci, we tried to reduce this problem by only including the resistance of this pathogen in blood isolates.

RESULTS

The use of antibiotic drugs

In total, 35 and 48 different systemic antibiotic drugs (ATC code J01, G04) were used in VUH and HUH, respectively. Antibiotic drugs from all ATC groups were available in both hospitals. The overall consumption of antibiotic drugs in VUH was 15 DDD/100 bed-days and almost three times higher in HUH (43 DDD/100 bed-days) (Fig. 1).

The top 10 antibiotic drugs used in each hospital are compared in Table 2. Three drugs—gentamicin, benzylpenicillin,

and ampicillin—made up more than 63% of all DDDs in VUH, whereas in HUH, the DDDs of all the top 10 drugs made up 65%. Although penicillins were the most often used antibiotics in both hospitals (46% and 35% of total DDDs in VUH and HUH, respectively), the profile of penicillin consumption was quite different. Benzylpenicillin and ampicillin predominated in VUH, β -lactamase-resistant penicillins (J01CF) in HUH (Table 3).

Resistance of microorganisms

Escherichia coli, *Klebsiella* species (spp.), *Pseudomonas aeruginosa*, and *Proteus mirabilis* isolated from wounds (Table 4) or blood (Table 5) were considerably more often resistant to gentamicin in VUH than in HUH. Only few isolates of Gram negative rods from wound infections in each hospital were resistant to cefuroxime, whereas ciprofloxacin resistance was higher in VUH. *Klebsiella* spp. isolated from blood was usually multidrug resistant in VUH. In HUH, only 5% of *Klebsiella* isolates were resistant to cefuroxime, cefotaxime, or ciprofloxacin, but all were sensitive to gentamicin. The resistance of trimethoprim and ampicillin among the most common pathogens causing urinary tract infections was higher in VUH than in HUH (Table 6).

TABLE 3. COMPARISON OF PENICILLIN CONSUMPTION IN VUH AND HUH

ATC code	Antibiotic	DDD (mg)	VUH DDD/100 bed-days	HUH DDD/100 bed-days
J01C A01	Ampicillin	2,000	2.85	0.55
J01C A02	Pivampicillin	1,050		0.03
J01C A03	Carbenicillin	12,000	0.05	
J01C A04	Amoxicillin	1,000	0.02	2.47
J01C A08	Pivmecillinam	600		0.4
J01C A12	Piperacillin	14,000		0.15
J01C E01	Benzylpenicillin	3,600	2.95	1.72
J01C E02	Phenoxymethylpenicillin	2,000		2.62
J01C F01	Dicloxacillin	2,000		2.18
J01C F02	Cloxacillin	2,000		2.78
J01C F04	Oxacillin	2,000	0.04	
J01C F05	Flucloxacillin	2,000		1.75
J01C R02	Amoxicillin + enzyme inhibitor	1,000	0.01	0.17
J01C R05	Piperacillin + enzyme inhibitor	14,000		0.11
J01C R50	Ampicillin + oxacillin	2,000	1.23	

TABLE 4. RESISTANCE OF ISOLATES FROM WOUNDS IN VUH AND HUH, RESPECTIVELY, IN 1997

Isolates	Antibiotic agent	VUH		HUH	
		Total number of isolates	Resistance (%)	Total number of isolates	Resistance (%)
<i>S. aureus</i>	Methicillin	88	11	1067	1
	Gentamicin	127	21	78	6
	Clindamycin	51	35	85	9
	Ciprofloxacin	52	33	37	27
<i>Enterococcus</i> spp.	Ampicillin	58	29	473	22.2
	Ciprofloxacin	12	58	99	52
	Vancomycin	44	4	473	0
<i>E. coli</i>	Gentamicin	83	27	152	1
	Cefuroxime	21	5	152	5
	Ciprofloxacin	75	24	152	9
<i>Klebsiella</i> spp.	Cefuroxime	9	11	74	7
	Gentamicin	64	64	73	1
	Ciprofloxacin	50	30	76	3
<i>P. aeruginosa</i>	Gentamicin	42	67	100	1
	Ciprofloxacin	42	45	110	11
<i>Proteus mirabilis</i>	Gentamicin	46	37	54	0
	Ciprofloxacin	47	15	55	9

All *S. aureus* isolates were sensitive to vancomycin. *S. aureus* isolates from blood were more resistant to all tested antibiotic drugs, including methicillin, in VUH, whereas resistance of coagulase-negative staphylococci was quite similar in both hospitals. No isolate of vancomycin-resistant enterococci was found in HUH,

whereas 4–10% of isolates were resistant in VUH, depending on the sample investigated (10 isolates in total; 6 *Enterococcus faecalis*, 1 *E. faecium*, 3 *Enterococcus* spp.). There was no isolate of *Streptococcus pneumoniae* resistant to penicillin in HUH, and only 2 resistant isolates were found in VUH (Table 7).

TABLE 5. RESISTANCE OF ISOLATES FROM BLOOD IN VUH AND HUH, RESPECTIVELY, IN 1997

Isolates	Antibiotic agent	VUH		HUH	
		Total number of isolates	Resistance (%)	Total number of isolates	Resistance (%)
<i>S. aureus</i>	Methicillin	17	29	112	3
	Gentamicin	16	25	111	0
	Erythromycin	18	39	112	3
	Clindamycin	14	29	109	2
	Ciprofloxacin	13	31	111	5
	Fusidic acid	15	0	112	4
	Vancomycin	11	0	112	0
Coagulase-negative staphylococci	Methicillin	67	51	59	39
	Gentamicin	66	53	59	25
	Erythromycin	68	69	59	39
	Clindamycin	54	44	57	14
	Ciprofloxacin	52	33	59	32
	Fusidic acid	59	25	59	22
	Vancomycin	43	0	59	0
<i>Enterococcus</i> spp.	Ampicillin	24	25	68	43
	Ciprofloxacin	23	87	54	54
	Vancomycin	23	10	68	0
<i>E. coli</i>	Gentamicin	10	0	126	1
	Cefotaxime	10	0	126	0
	Ciprofloxacin	7	0	126	5
<i>Klebsiella</i> spp.	Cefuroxime	7	57	43	5
	Cefotaxime	27	74	42	5
	Ceftazidime	28	68	43	2
	Gentamicin	28	100	43	0
	Ciprofloxacin	25	44	43	5

TABLE 6. RESISTANCE OF ISOLATES FROM URINE IN VUH AND HUH, RESPECTIVELY, 1997

Isolates	Antibiotic agent	VUH		HUH	
		Total number of isolates	Resistance (%)	Total number of isolates	Resistance (%)
<i>Enterococcus</i> spp.	Ampicillin	149	24	663	14
	Nitrofurantoin	135	36	658	1
	Vancomycin	130	5	663	0
<i>E. coli</i>	Ampicillin	477	44	1644	24
	Nitrofurantoin	450	6	1643	3
	Trimethoprim	439	87	1643	16
	Norfloxacin	97	8	1643	3
<i>Klebsiella</i> spp.	Trimethoprim	80	95	391	18
	Norfloxacin	29	17	390	5
<i>P. aeruginosa</i>	Norfloxacin	5	60	63	16
<i>Proteus mirabilis</i>	Ampicillin	54	72	121	15
	Nitrofurantoin	48	63	121	98
	Trimethoprim	46	98	121	14
	Norfloxacin	13	8	121	2

DISCUSSION

Although both hospitals are similar in their activities, the number of DDDs per 100 bed-days was almost three times higher in HUH than in VUH 1997. There are several possible explanations for this. Although not specifically studied, we believe that a higher proportion of inpatients at HUH received prophylaxis either for surgery or in relation to bone marrow or organ transplantation (in a recent point prevalence study, one-quarter of all hospitalized patients on antibiotics in HUH; J.S., unpublished data) than in VUH. Furthermore, the mean stay at VUH was three times longer than that in HUH (13.5 days and 4.4 days, respectively) due to the different health care systems. The weak connection between outpatient and inpatient care in Lithuania forces physicians to keep patients in hospital until full recovery. Surgery patients could enter the hospital long before an operation and stay there until sutures were taken out without any treatment. This suggests that the intensity of treatment may partly explain the different level of use of antibiotic

drugs. Finally, it was not possible to include antibiotic donations received because of lack of a centralized registration system. Although the prescribed daily doses may vary considerably in relation to DDD among hospitalized patients and outpatients,¹⁶ and also between countries, these methodological flaws altogether cannot explain the large difference in the antibiotic pressure that we found.

Surprisingly, the relation between antibiotic pressure and resistance was inverted; although antibiotic use was almost three times higher in HUH, resistance was more prevalent among most species in VUH. For example, both Gram-negative and Gram-positive isolates were considerably more resistant to gentamicin in VUH than those in HUH. These data corroborate the aminoglycoside data from 12 different countries published 10 years ago where a clear correlation between bacterial resistance inside and outside the hospital to the total amount of aminoglycosides, particularly gentamicin, use in hospitals was found.⁸ This suggests a direct link between the high prevalence of resistance and continuous selective pressure of a single antibiotic.

TABLE 7. THE COMPARISON OF THE RESISTANCE OF ISOLATES FROM SPUTUM IN VUH AND HUH, RESPECTIVELY, 1997

Isolates	Antibiotic agent	VUH		HUH	
		Total number of isolates	Resistance (%)	Total number of isolates	Resistance (%)
<i>S. aureus</i>	Methicillin	31	6	38	13
	Gentamicin	42	10	12	17
	Tetracycline	18	44	7	29
	Ciprofloxacin	19	26	6	50
<i>Streptococcus pneumoniae</i>	Penicillin	239	1	103	0
<i>Haemophilus influenzae</i>	Ampicillin	163	9	142	0 ^a
<i>Klebsiella</i> spp.	Cefuroxime	21	5	17	18
	Gentamicin	89	15	18	0
	Ciprofloxacin	84	5	18	0

^aIn HUH only strains not producing β -lactamase were tested.

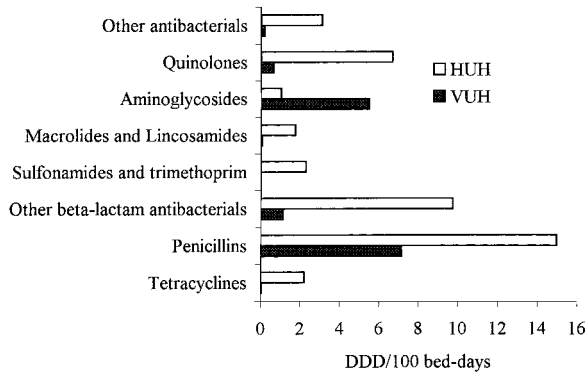


FIG. 1. The use of different groups of antibiotics in VUH and HUH.

Methicillin-resistant *S. aureus* (MRSA or BORSA) were mostly isolated from wounds and blood in VUH and from sputum among patients with cystic fibrosis in HUH. Several important risk factors for colonization and infection with MRSA have been identified, including age, nasal colonization, indwelling devices, nasogastric tubes, prolonged hospital stay, and previous antibiotic therapy.³ Coagulase-negative staphylococci were slightly more resistant to all antibiotic drugs in VUH. Other data have also shown that over 50% of coagulase-negative staphylococci are methicillin resistant.^{4,13} These coagulase-negative staphylococci are often resistant to erythromycin, aminoglycosides, and clindamycin as well. *Enterococci*, a common cause of nosocomial infection, are intrinsically resistant to most antibiotics and readily acquire additional resistance. Although vancomycin has been used relatively seldom in VUH (only 84 DDDs), vancomycin-resistant enterococci made up from 4% to 10% of isolates, depending on the sample investigated.

Gram-negative pathogens (*P. aeruginosa*, *Klebsiella* spp., and *P. mirabilis*) which are frequent pathogens in nosocomial infections, were more resistant in VUH. Although cefuroxime and ciprofloxacin were the most often used agents in HUH, the resistance to these agents was similar in both hospitals or even greater in VUH. This suggests that not only the use of an antibiotic agent gives rise to the quantity of resistance. Inappropriate antibiotic use, such as unnecessary therapy, poor drug choice, misguided prophylactics, or inadequate dosing, may enhance the selection of resistant strains. There are also some indications that the antimicrobial resistance is more influenced by the consumption of antibiotics in the outpatient care than in hospitals.^{15,16} The possibility of buying antibacterial drugs without a prescription in Lithuania may also contribute to misuse of these drugs.

The role of potentially different infection control practices was not investigated in this study. Our clinical impression is that they probably are less appropriate in VUH than in HUH. This together with longer hospital stay, which increases the risk for colonization of resistant hospital clones from other patients and the environment, probably contributes to the higher resistance figures in VUH.

The bacteriological laboratories of both hospitals used disc diffusion methods to study susceptibility to the antibiotic

agents. There are some differences in breakpoints between the methods that might have contributed to some of the differences we found. The significance of this, along with other factors that we believe were of greater importance, such as impact of duration of hospital stay, routines for performing culture, etc., merit further study.

Although antibiotic agents of all groups were available in both hospitals, many more different drugs were used in HUH and their use was more evenly distributed (Fig. 1). Penicillins were the most often used antibiotics in both hospitals, but the profile of penicillins was quite different. In VUH, older and cheaper penicillins with extended spectrum (ampicillin and its combination with oxacillin) predominated, whereas newer β -lactamase resistant anti-staphylococcal penicillins were mostly used in HUH. The lower cost and insufficient knowledge on newer penicillins may have been the main criteria for antibiotic choice in VUH. Gentamicin was the number one antibiotic in VUH. It is widely used because of its broad antimicrobial spectrum of activity, low cost, and convenient once-daily administration. Another reason for the persistent use of gentamicin and other aminoglycosides may relate to the perception that they are an essential component of therapy for life-threatening infections. Unfortunately, the possible toxicity of gentamicin usually is not taken into consideration and the serum concentration of gentamicin is not routinely measured. Particularly big amounts of quinolones (especially pefloxacin) were donated in VUH during the study period. Thus, the real utilization figure of quinolones should be considerably higher. At HUH, recommendations have been developed by a drug committee in agreement with the resistance pattern routinely monitored in the bacteriological laboratory for many years. The recommendations have furthermore been divided between outpatient care and from hospitalized patients due to differences in etiology and resistance. This "antibiotic use and surveillance program" is one of the most important ways to combat a local problem with global consequences.

This study has several limitations: (1) it is retrospective, (2) it was not possible to include all antibiotics used in VUH, (3) there are some differences in susceptibility tests and their interpretation, (4) the antibiotic use and antimicrobial resistance data are not related to patient and disease, and (5) differences in indications for performing cultures and time between admission and culture are largely unknown. Still, we believe that our major findings are true and that our study has pointed at some problems and directions for future investigation.

We conclude that resistance was a much greater problem in VUH than in HUH, despite the fact that antibiotic pressure was far less. This shows that a high antibiotic pressure in a single hospital *per se* does not necessarily promote resistance. Other factors that must be considered and are subject to further study include the total antibiotic pressure in the community, adherence to guidelines for doses and duration of antibiotic treatment, and spread of resistant clones and other issues related to good infection control practices.

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