ORIGINAL ARTICLE

The effect of an antibiotic policy on the control of vancomycin-resistant enterococci outbreak and on the resistance patterns of bacteria isolated from the blood of patients in a hematology unit

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KEY WORDS

antibiotic resistance, antibiotic policy, bacteremia, vancomycin-resistant enterococci (VRE)

ABSTRACT

INTRODUCTION Antibiotic resistance has become one of the main medical problems worldwide. This is mainly due to an overuse and misuse of antibiotics.

OBJECTIVES The aim of the study was to assess the effect of an antibiotic policy and enhanced infection control on the occurrence of epidemic strains of vancomycin-resistant enterococci (VRE) and resistance patterns of bacteria isolated from the blood of patients hospitalized in two departments of a hematology center in Poland.

PATIENTS AND METHODS Antibiotic use was calculated in daily defined doses (DDD) per 100 patient-days during the two 5-month periods, before and after the introduction of the policy. Infection control measures included a 1-week screening for VRE rectal carriage and contact isolation.

RESULTS Antibiotic consumption decreased from 82.1 to 57.3 DDD per 100 patient-days, mainly because of a decrease in the use of co-trimoxazole, other antimicrobials active against anaerobes, and cephalosporins. A significant change in antibiotic resistance patterns was observed and in vitro efficacy of antibiotics against bacteria isolated from the blood increased remarkably. We managed to eradicate the outbreak of VRE.

CONCLUSIONS The introduction of antibiotic policy and enhanced infection control measures may prove efficacious in VRE control.

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INTRODUCTION Overuse and inappropriate use of antibiotics are the major factors responsible for the emergence and dissemination of resistant microorganisms, mainly in intensive care units and other departments where immunocompromised patients are hospitalized.[1,2] The introduction of an effective antibiotic policy as part of infection control scheme is considered more difficult to achieve in hematology units than in general hospitals. A long and variable list of microorganisms that have to be covered by a formulary, including many opportunistic pathogens causing pneumonia, bacteremia, skin and central nervous system infections, presents a considerable challenge.[3] Although there are not many data on antibiotic consumption in hematology units,[4] the observed occurrence of infectious episodes is very high[5,6] and nosocomial outbreaks have been recorded.[7-9] Vancomycin-resistant enterococci (VRE) are one of the opportunistic alert pathogens which are easily transmitted among immunocompromised patients and which cause difficult to treat, mostly nosocomial infections.[10,11] Currently, VRE account for 10% to 25% of all nosocomial enterococcal isolates in a number of countries, which underlines particular significance of this multidrug-resistant pathogen.[12-14] In Poland, the first nosocomial outbreaks of VRE

occurred in hematology departments in the late 1990s.[15-19] The aim of this study was to investigate the effect of antibiotic policy, introduced at the Institute of Hematology in Warsaw, Poland, on the resistance patterns of pathogens isolated from patients with bloodstream infections, and on the course of the VRE outbreak.

PATIENTS AND METHODS

The setting The Institute of Hematology and Blood Transfusion is a 120-bed tertiary care center with about 5000 admissions per year mainly with diagnoses of acute and chronic leukemia and lymphoma and were receiving induction or consolidation chemotherapy. It consists of two wards (for adult patients with hematological malignancies) and the department of vascular surgery. The two wards have a similar layout, namely two isolation rooms with toilets and a bath, and six rooms of 4 to 8 beds with two dedicated bathrooms.

The VRE outbreak Until September 1999, when isolations of VRE with VanB phenotype started in one of the wards, there were no antibiotic guidelines other than for neutropenic fever. Following the first isolation of VRE, the Infection Control Team (ICT) was set up with an infection control physician, an infection control nurse, and a microbiologist. The main goal of the team was to reinforce the system of infection control and to introduce an antibiotic policy that would involve analyzing antibiotic prescriptions, formulating new recommendations, and educating the medical staff.

The antibiotic policy Antibiotic use was calculated in daily defined doses (DDD) per 100 patient-days for the two 5-month periods (October 1999 to February 2000 vs. March to August 2000) before and after the introduction of the antibiotic policy. It covered most classes of antibiotics: cephalosporins (cefuroxime, ceftriaxone, ceftazidime), carbapenems, glycopeptides, aminoglycosides, fluoroquinolones, co-trimoxazole, and some other agents belonging to different chemical groups, such as tetracyclines, macrolides, nitrofurans, and penicillins. Because of a particular impact on the spread of VRE, a strong negative effect on the natural flora and the consequent colonization of the digestive tract with multidrug-resistant hospital strains, a separate group of agents active against anaerobic bacteria was monitored.[20] It included penicillins with inhibitors of β-lactamases, metronidazole, and clindamycin. In February 2000, the ICT published the hospital guidelines for antibiotic treatment and prophylaxis that focused on the most common infections in an immunocompromised host e.g., neutropenic fever, bloodstream infection, pneumonia, neutropenic enterocolitis, *C. difficile* diarrhea. They introduced strict indications for prophylaxis in neutropenic patients and described procedures for clinical situations associated with a common overuse of antibiotics, such as fever in a patient suffering from any hematological malignancy without neutropenia. The guidelines included indications and dosing of antibiotics used for the treatment of infections caused by specific pathogens, and recommendations for prescribing each of antibiotics listed in the hospital formulary. An education program for doctors on rational antibiotic therapy followed the distribution of guidelines among the medical staff. The program focused on three major recommendations. First, do not routinely prescribe an antibiotic for a patient with fever and without neutropenia or symptoms of a local infection. Second, restrict the use of co-trimoxazole in prophylaxis. This should be routinely prescribed only for allogenic hematopoietic stem cell transplantation recipients and some patients with acute lymphoblastic leukemia.[21] Third, use a broad diagnostic approach towards neutropenic patients with fever and patients who are not responding to antibiotics.

Infection control measures Following the Hospital Infection Control Practices Advisory Committee guidelines for preventing the spread of vancomycin-resistance,[22] two other measures were included in our infection control scheme beside the rational use of vancomycin.

1 A 1-week screening for VRE rectal carriage among patients on antibiotics hospitalized for more than 7 days (considered as high-risk factor), and on admission if the patient was hospitalized in our hospital before.[23]

2 Contact isolation of patients infected or colonized with VRE involved either placement in separate rooms or cohortation, obligatory alcohol rubbing of hands before and after every contact with patients, disinfection of not dedicated and nondisposable diagnostic tools (stethoscopes, etc.) between usage on every patient, disposable gloves and coats when carrying the VRE-positive patient.

Microbiological and epidemiological data collection and evaluation Records of patients with bacteremia were reviewed for the 5-month periods before and after the introduction of the antibiotic policy. The number of bacteremias was described in absolute values and the number of infections was calculated for 1000 patient-days. Phenotypes of resistance to antibiotics used for treatment of neutropenic fever were noted, including extended-spectrum β-lactamase (ESBL) production by *Enterobacteriacae*, resistance to carbapenems of Gram-negative rods, VRE, and methicillin-resistance of *Staphylococcus aureus* (MRSA). The frequency of new VRE isolates in diagnostic cultures and screening, as well as the change of the frequency of antibiotic-susceptible blood isolates were calculated.

The data were collected using common procedures. Blood cultures were investigated in the automatic system BACTEC 9050 (Becton Dickinson, United States) according to the manufacturer's instructions. The species identification

was obtained with ATB Expression system (bioMerieux, France), according to the manufacturer's protocol. Antimicrobial susceptibility testing was performed using the disc-diffusion method and interpreted according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[24,25] MRSA and VRE resistance phenotypes were detected by the screening methods according to the NCCLS guidelines.[24,25] The VanB phenotype was confirmed in the reference center by the minimum inhibitory concentration for vancomycin and teicoplanin and specific polymerase chain reaction reaction. Finally, the clonal relatedness of the VRE isolates was investigated by pulsed-field gel electrophoresis.

Statistical analysis The consumption of antimicrobials was compared in the two 5-month periods by the U-test for fraction, and changes in antimicrobial resistance during these two periods were analyzed by comparing proportions with the Fisher's exact test.

RESULTS

Antibiotic consumption In the two 5-month periods, before and after the antibiotic policy was introduced, a comparable number of patients were hospitalized (1296 vs. 1421) with a similar number of patient-days (12 303 vs. 12 414) and hematological malignancies diagnosed.

Changes in the antibiotic consumption during these two periods are presented in TABLE 1. Before the scheme was introduced, antibiotic consumption had been 82.1 DDD per 100 patient-days. Agents active against anaerobic bacteria, including amoxicillin-clavulanate, ampicillin-sulbactam, clindamycin, and metronidazole, were the most commonly used. The second (cefuroxime), the third (ceftriaxone, ceftazidime), and the fourth (cefepime) generation cephalosporins were found to be the second most prevalent group. Comparatively high consumption of co-trimoxazole as well as fluoroquinolones was observed, mainly because of the general prophylactic scheme in neutropenic patients.

After the introduction of the antibiotic policy, the consumption of antimicrobials was reduced by about 30%, from 82.1 to 57.3 DDD per 100 patient-days. A significant decrease in the use of antibiotics was observed, especially for agents active against anaerobic microorganisms. Generally, for the whole group it was found to drop from 16.9 to 4.3 DDD per 100 patient-days (75%). For co-trimoxazole it decreased from 8.0 to 5.9 DDD per 100 patient-days (26%), and for cephalosporins from 16.8 to 13.7 DDD per 100 patient-days (18%). The total consumption of other antibiotics, mainly doxycycline, macrolides, nitrofurantoin, and amoxicillin, decreased by about 66%. However, the use of carbapenems and aminoglycosides increased by about 24% and 11%, respectively. Despite their spectrum, carbapenems were not included in the group of agents active against anaerobic bacteria because of their role in the routine treatment of patients with severe neutropenic fever. The agents whose prescription rates did not change significantly were glycopeptides (vancomycin and teicoplanin).

The VRE outbreak control The outbreak at the Institute of Hematology and Blood Transfusion in Warsaw has been the first such incident in Poland caused by VRE harboring VanB gene. During the outbreak (from July 1999 to April 2000), 20 VRE-positive patients were identified, 6 infected and 14 colonized. The last patients colonized with VRE were identified in April 2000, 2 months after the introduction of the antibiotic policy. The screening of high-risk patients was conducted once a week for a period of 2 months after the last isolation of VRE. All the collected samples were VRE-negative.

Resistance patterns of the bacteria isolated from blood Evaluation of retrospective microbiological data revealed that there were 103 episodes of documented bloodstream infections over the two 5-month periods at the two hematology units. Gram-positive microorganisms caused 61 episodes, Gram-negative 39, and fungi were

TABLE 1 Antibiotic consumption in the hematology unit during the two 5-month periods, before and after the introduction of an antibiotic policy

Antibiotic class	Before[a]	After[a]	Difference (%)	*P*
agents active against anaerobic bacteria[b]	16.9	4.3	–75%	<0.001
aminoglycosides	10.6	11.8	+11%	<0.01
carbapenems (imipenem, meropenem)	2.5	3.1	+24%	<0.01
cephalosporins (cefuroxime, ceftriaxone, ceftazidime)	16.8	13.7	–18%	<0.001
co-trimoxazole	8.0	5.9	–26%	<0.001
fluoroquinolones	10.4	10.2		NS
glycopeptides (vancomycin, teicoplanin)	3.5	3.7		NS
others[c]	13.4	4.6	–66%	<0.001
total	82.1	57.3	–30%	<0.001

a data calculated as number of daily defined doses per 100 patient-days
b amoxicillin with clavulanic acid, ampicillin with sulbactam, clindamycin, metronidazole
c doxycycline, amoxicillin, clarithromycin, nitrofurans
Abbreviations: NS – nonsignificant

TABLE 2 Bloodstream pathogens isolated from patients of the hematology unit during the two 5-month periods, before and after the introduction of an antibiotic policy

Pathogen		Total number of isolates	Before	After
Gram-positive	*Staphylococcus epidermidis*	32	16	16
	Staphylococcus aureus[a]	12	5	7
	MRSA	2	1	1
	Enterococcus spp.[a]	10	6	4
	VRE	1	1	0
	Corynebacterium spp.	6	2	4
	Streptococcus spp.	1	1	0
Gram-negative	*Escherichia coli*[a]	18	6	12
	E. coli ESBL +	5	4	1
	Pseudomonas aeruginosa	5	1	4
	Enterobacter spp.	4	1	3
	Acinetobacter baumannii	4	3	1
	Proteus mirabilis	4	2	2
	Klebsiella pneumoniae[a]	2	1	1
	K. pneumoniae ESBL +	1	1	0
	Morganella morganii	1	0	1
	Burkholderia cepacia	1	0	1
Candida spp.		3	2	1
Total		103	46	57

a all the isolates of a particular species included

Abbreviations: ESBL – extended spectrum β-lactamase, MRSA – methicillin-resistant *Staphylococcus aureus*, VRE – vancomycin-resistant enterococci

isolated from 3 patients. As shown in TABLE 2, coagulase-negative staphylococci were the leading cause of bacteremia (32 cases), followed by *Escherichia coli* (18 cases), *Staphylococcus aureus* (12 cases), *Enterococcus* spp. (10 cases), and *Pseudomonas aeruginosa* (5 cases). After the introduction of the antibiotic policy, no changes in the frequency of Gram-positive bloodstream infections were observed (30 in the first period, 31 in the second, which is 2.43 and 2.49 infections per 1000 patient-days, respectively). The number of documented Gram-negative bloodstream infections increased significantly from 14 to 25 episodes, which is from 1.14 to 2.01 bacteremia per 1000 patient-days. However, the resistance patterns of Gram-negative bacteria were considerably different in the two analyzed periods. Despite an increased frequency of isolation of *Enterobacteriaceae*, mainly *E. coli*, in the second period, fewer of them produced ESBL (5 vs. 1 in the first and the second period, respectively). The number of Gram-negative bacteria susceptible only to carbapenems decreased from 8 isolated in the first period to 4 in the second (that is from 57% to 16% of all isolations within this group). VRE was isolated from the blood of 1 patient in the first period and there were no VRE isolations from infections during the 5 months following the introduction of the antibiotic policy.

As shown in TABLE 3, in bacteria isolated from blood, there was a significant difference in in vitro susceptibility to all β-lactams between those isolated before and after the introduction of the antibiotic policy. Blood cultures positive for *S. epidermidis* and *Corynebacterium* spp. were excluded from the study on antimicrobial susceptibility, mainly because of a high probability of contamination and, in the case of *S. epidermidis*, almost universal resistance to methicillin.

DISCUSSION The control of the VRE outbreak was achieved by a more rational use of certain groups of antimicrobials and by the screening of high-risk patients for VRE colonization, which allowed us to quickly isolate the positive cases. We managed to control the outbreak despite the fact that there was no significant decrease in the prescription rate of glycopeptides. Our results are consistent with those of Lautenbach et al.[26] who showed that this point is not critical for VRE spread. Similarly to Loeb et al.,[27] who identified cephalosporin use as the only independent risk factor for VRE colonization, we observed the signs of outbreak control when the use of cephalosporins was reduced by about 18%. A positive effect of even a transient reduction of cephalosporins along with an increase of piperacillin/tazobactam on VRE outbreak control was also documented by Bradley et al.[28] However, all these data are in opposition to Stiefel et al.,[29] who demonstrated no such effect.

The consumption of antibiotics in the two hematology wards of the Warsaw center decreased significantly after the introduction of the antibiotic policy. This is particularly significant in the case of agents active against anaerobic

TABLE 3 Antimicrobial susceptibility of bacteria isolated from the blood of patients from the hematology unit during the two 5-month periods, before and after the introduction of an antibiotic policy (isolations of *Staphylococcus* spp. and *Corynebacterium* spp. were excluded)

Antibiotic	Before[a]	After[a]	*P*
ceftriaxone	9/26 (35%)	20/36 (55%)	NS
ceftazidime	10/26 (38%)	25/36 (69%)	<0.05
cefepime	10/26 (38%)	25/36 (69%)	<0.05
imipenem	21/26 (81%)	33/36 (92%)	NS
meropenem	21/26 (81%)	33/36 (92%)	NS
piperacillin with tazobactam	13/26 (48%)	31/36 (86%)	<0.01

a data calculated as number of susceptible isolates vs. all the isolates (percentage of susceptible strains in brackets)

Abbreviations: see TABLE 1

bacteria. They are generally considered as less useful in the treatment of infections in neutropenic patients (except for those active against *P. aeruginosa*, such as piperacillin with tazobactam and ticarcillin with clavulanate for neutropenic fever, and metronidazole for *Clostridium difficile* infection). At the same time, they reduce the colonization resistance caused by the patient's natural digestive tract flora, composed mainly of anaerobes. This may increase the probability of replacing the digestive tract flora with multidrug-resistant hospital pathogens. Our study allowed us to conclude that the consumption of antibiotics active against anaerobic bacteria may indeed be no less important than that of cephalosporins and/or vancomycin as a selective pressure for VRE occurrence. This confirms the trend observed for metronidazol and clindamycin by Launtenbach et al.[26] The reduction in antibiotic consumption in our hematology center helped us to identify more bloodstream infections (mostly due to bacteremia of Gram-negative etiology), which is consistent with the previously published data.[30,31] Kauffman et al. and Cruciani et al. observed more infectious episodes (without an impact on mortality rate) when co-trimoxazole or fluoroquinolones prophylaxis was not used. In our study, this observation can be partly explained by the fact that a blood culture is a more sensitive method of microorganisms detection when the patient is not on antibiotic therapy or prophylaxis,[32] which was more frequently the case after the introduction of the policy.

An objective assessment of the effect of antibiotic consumption on the susceptibility of hospital pathogens is difficult because the spread of these strains depends on many other factors.[33,34] In our study, a decreased antibiotic use was followed by a less common occurrence of *Enterobacteriaceae* producing ESBL and Gram-negative rods sensitive only to carbapenems after the introduction of the policy, as similarly observed by Rice et al.[35]

The rate of bloodstream infections caused by Gram-positive bacteria, mainly coagulase-negative staphylococci, did not change significantly in the course of the study. This is not an unexpected finding because the main risk factor for these infections is the frequent use of central venous catheter. Before the introduction of the antibiotic policy, we identified a very high resistance to the third and fourth generation of cephalosporins and to piperacillin with tazobactam. Afterwards, the sensitivity increased by about 30%. The consumption of antibiotics was expressed as the number of DDD per 100 patient-days because this quantification shows the density of exposure to antibiotics, which is more useful when trying to identify a relationship between antibiotic use and resistance patterns than just a crude amount expressed as grams or dose units.[34] The data concerning the rate of bloodstream infections were expressed as a number per 1000 patient-days, as recommended by the Centers for Disease Control and Prevention National Nosocomial Infections Surveillance system. However, hematology units can differ more in terms of the severity of malignancies than in the number of patients. Consequently, the observed frequency of patients at risk of infection (and antibiotic prophylaxis or therapy) can vary greatly. For that reason, it would be preferable to express the frequency of infections as number per 1000 patient-days with neutropenia, as suggested by Carlisle et al.[6] and Engelhart et al.,[36] or as a frequency of infections in a single chemotherapy cycle, as in a study by Jugo et al.[37] Because such information was not available at the time of data collection, we could not use any of the above possibilities in our study.

In conclusion, we were able to reduce the consumption of antibiotics in the hematology center, mainly by identifying situations in which antibiotics were overused. In the following period, we managed to control the VRE outbreak, and we observed a significant change in susceptibility patterns of bacteria isolated from the blood. The conversion was towards lower frequency of multidrug-resistant isolates and particularly towards fewer dangerous phenotypes of resistance.

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ARTYKUŁ ORYGINALNY

Wpływ polityki antybiotykowej na ognisko epidemiczne enterokoków opornych na wankomycynę i lekooporność drobnoustrojów izolowanych z krwi pacjentów na oddziale hematologicznym

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antybiotykooporność, bakteriemia, polityka antybiotykowa, wankomycynooporne enterokoki (VRE)

STRESZCZENIE

WPROWADZENIE Oporność drobnoustrojów na antybiotyki stała się jednym z najpoważniejszych problemów medycznych na świecie. Przyczyną jest głównie nadużywanie i niewłaściwe stosowanie tych leków.

CELE Zbadanie wpływu polityki antybiotykowej i restrykcyjnego programu kontroli zakażeń na występowanie epidemicznych szczepów wankomycynoopornych enterokoków (*vancomycin-resistant enterococci* – VRE) i lekooporność drobnoustrojów izolowanych z krwi hospitalizowanych pacjentów w dwóch oddziałach centrum hematologicznego w Polsce.

PACJENCI I METODY Zużycie antybiotyków określano w definiowanej dawce dobowej (DDD) na 100 pacjentodni, w dwóch okresach 5-miesięcznych, przed i po wdrożeniu polityki antybiotykowej. Kontrola zakażeń obejmowała cotygodniowe badanie nosicielstwa VRE w odbycie i izolację kontaktową.

WYNIKI Zużycie antybiotyków spadło z 82,1 do 57,3 DDD, głównie z powodu zmniejszenia zużycia kotrimoksazolu, antybiotyków działających na beztlenowce oraz cefalosporyn. Zaobserwowano znaczące zmiany we wzorach lekooporności drobnoustrojów izolowanych z krwi i wzrost ich wrażliwości *in vitro*. Uzyskano eradykację ogniska epidemicznego VRE.

WNIOSKI Wdrożenie polityki antybiotykowej oraz programu kontroli zakażeń może być skuteczne w kontroli VRE.

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