[1]Laboratory Unit of Microbiological Diagnostics of the Clinical Hospital No. 1 in Lublin
[2]Department of Clinical Biochemistry, Medical University of Lublin

ELŻBIETA PUACZ[1], KINGA LEŚNIEWSKA[2], HELENA DONICA[2]

*The impact of antibiotic therapy on the increase of resistance
to Pseudomonas aeruginosa and Acinetobacter baumannii
carbapenems and a discussion on the results of introducing hospital
antibiotic policy regulations*

Wpływ stosowanej antybiotykoterapii na wzrost oporności na karbapenemy pseudomonas aeruginosa
i acinetobacter baumannii i rezultaty wprowadzenia zasad szpitalnej polityki antybiotykowej

The rapidly increasing microorganic resistance to antibiotics has been a serious problem of public health preservation. Clinical prognosing of antibiotic treatment effectiveness constitutes a complex problem requiring microbiological, epidemiological, pharmacological knowledge and the consideration of the patient's resistance. Many cases of the antibiotic therapy implementation result in failure, which is most often caused by a wrong erratic dosage, inadequate choice of an antibiotic related to the localization of the infection site, inadequate application time, frequent change of an antibiotic [6]. The number of multi-resistant bacteria depends on the specificity of the hospital, the medical procedures executed in it, the population of treated patients, hospitalization time and the antibiotic therapy applied [7].

Non-fermenting bacteria, especially *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* have caused as a serious problem for the hospitalized patients. The increase of resistance to antibiotics among these strains is a therapeutic problem. Uncontrollable application of imipenem and meropenem in infectious illnesses therapy leads to the selection of hospital strains resistant to carbapenems, which are the last chance drugs.

The aim of the study is the analysis of the dependences between the use of carbapenem antibiotics in the Department of General Surgery and the resistance to this group of antibiotics among the isolated strains of the non-fermenting Gram-negative bacteria and the evaluation of the impact of the introduction of the Hospital Antibiotic Policy in the discussed clinic on shaping the resistance to carbepenems among the the non-fermenting Gram-negative bacteria.

MATERIAL AND METHODS

The study material were *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from the samples of the materials taken from patients hospitalized at the General Surgery Department in the Clinical Hospital No. 1 in Lublin in the years of 2004–2007. Bacteria were identified and the drug resistance was described using the tests from miniApi (bioMerieux). Resistance mechanisms were

evaluated according to the recommendations of the State Centre for Drug Resistance.

The data pertaining to the use of carbapenems in the years covered by the study were obtained from the hospital pharmacy. The extent of the use was presented in the form of the defined 24-hour doses (Defined Daily Doses, DDD) [8]. A Defined Daily Dose both for meropenem and imipenem is 2g of the drug for 24 hours [3].

In order to introduce control over antibiotic application in the discussed hospital, in 2007, a program of Hospital Antibiotic Policy was introduced. Basing on the analysis of the hospital flora and its drug resistance, on the basis of state recommendations, the regulations were elaborated for the antibiotic application in the hospital area. The division into different antibiotics was introduced. Carbapenems were included in the category of the restricted drugs issued on the basis of bacteriological results documentation and the acceptance of the department's head.

RESULTS

The analysis of carbapenems use in the years of 2003–2007 points to a significant increase of application of this group in 2003–2006. The use of imipenem in the whole hospital increased, and in the years of 2004 and 2005 the increase was 10-fold as compared to the preceeding year. The indicators of both antibiotics used decreased more than twice in 2007. This is connected with the introduction of a Hospital Antibiotic Policy.

General Surgery Department was shown to have used the greatest quantity of carbapenems, reaching 38.5% of the total antibiotic usage in the hospital. In this department, the most commonly applied antibiotic was meropenem and the greatest increase pertains to the year 2005 (250 DDD). A significant difference in the application of imipenem and meropenen is visible in 2003 and 2004, in the later years both antibiotics were applied at a comparative level.
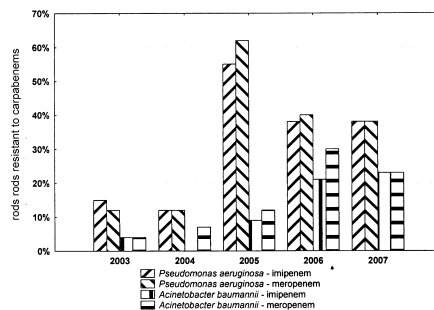

Fig. 1. Resistance to carbapenems of *P. aeruginosa and A. baumannii* at the General Surgery
Department as for the use of meropenem in the years of 2003–2007

At the General Surgery Department (Fig. 1) the resistance to imipenem and meropenem among *Pseudomonas aeruginosa* increased gradually between 2003–2006. The resistance to both antibiotics among *Acinetobacter Baumannie* was gradually increasing from 2003 to 2005, with a radical increase from 11% to 31% in the period of 2005–2006. In 2007, after the introduction of the regulations of Hospital Antibiotic Policy, a significant decrease of resistance to carbapenem antibiotics was noted in two types of microorganisms.
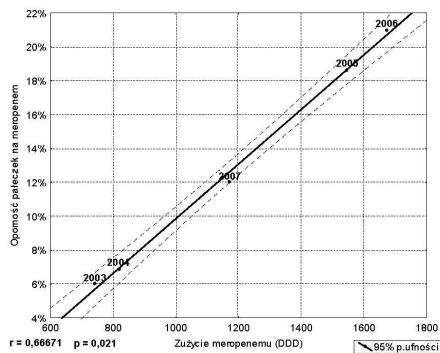
Fig. 2. Correlation between resistance of non-fermenting bacteria and meropenem

A statistical analysis pointed to an additional dependence pertaining to Gram-negative bacteria strains from carbapenem antibiotics and their application in the therapy in the whole hospital. A correlation between the resistance of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* to meropen and the actual usage of this antibiotic was observed (Fig. 2). Correlation coefficient, r = 0.66 and the substantiality coefficient p = 0.02. A positive correlation was found between the resistance to imipenen of the studied strains and the actual usage of imipenen (Fig. 3). In this case, the coefficient was r = 0.62, and the substantiality coefficient was p = 0.02. A strong positive linear correlation means in practice that the increase of usage of both meropenem and imipenem caused the increase of resistance to this particular group of antibiotics among the *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains.
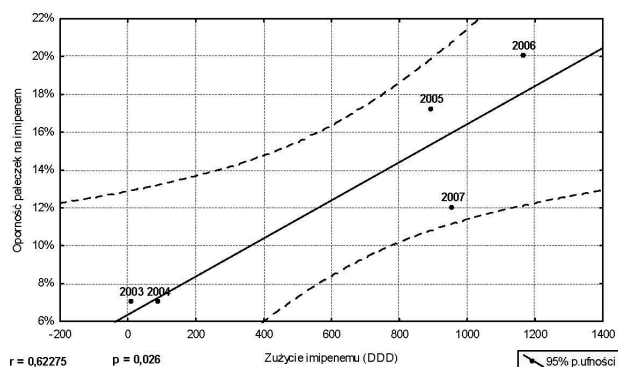

Fig. 3. Correlation between resistance of the non-fermentingbacteria and imipenem
in the years of 2003–2007

Figure 4 presents the use of meropenem and imipenem and the actual shaping of the resistance to these drugs among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains in the years of 2003–2007 in the studied department.
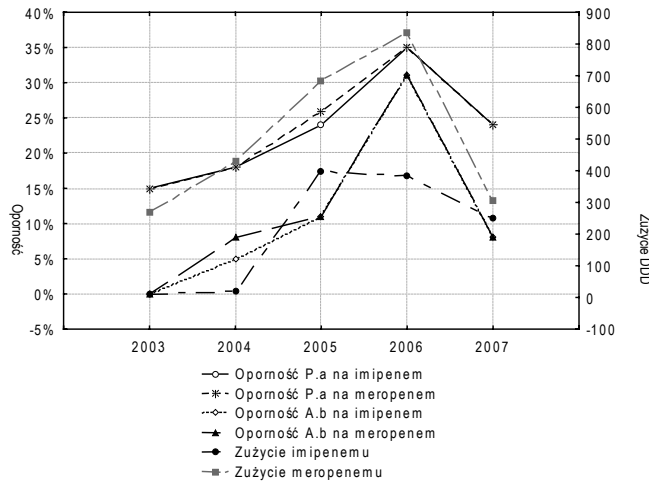
Fig. 4. Resistance of non-fermenting strains and the use of meropenem and imipenem
at the General Surgery Department in the years of 2003−2007

According to the presented positive correlation between the usage of meropenem and imipenem
and the resistance to these drugs among *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
strains, the resistance among the non-fermenting bacteria was rising until 2006 and went down in
2007 as a result of the controlled ordination of antibiotics (Table 1). The use of imipenem in the
studied years was twice as small than as of meropenem. And the non-fermenting bacteria show the
differences in resistance against these antibiotics equaling 1% a year of the greatest value of resistant
strains.

Table 1. The number of resistant non-fermenting strains in the years of 2003−2007
at the surgery department

Year	Antibiotic	Number of *P. aeruginosa* strains	Resistant strains of *P. aeruginosa*		Number of *A. baumannii* strains	Resistant strains of *A. baumannii*	
2003	imipenem	47	7	15%	10	0	0%
	meropenem	47	7	15%	10	0	0%
2004	imipenem	40	7	18%	39	2	5%
	meropenem	40	7	18%	39	3	8%
2005	imipenem	34	8	24%	18	2	11%
	meropenem	34	9	26%	18	2	11%
2006	imipenem	40	14	35%	42	13	31%
	meropenem	40	14	35%	42	13	31%
2007	imipenem	37	9	24%	37	3	8%
	meropenem	37	9	24%	37	3	8%

DISCUSSION

The bacteria of *Pseudomonas spp.* and *Acinetobacter spp.* strains are an important and frequent reason for hospital infections, mainly in patients from a high risk group [4]. In the studies by Gospodarek et al. [1] conducted in the years of 1999–2005, the increase of the usage of carbapenems (imipenem) was shown to increase from 805 DDD in 1999 to 1841, 25 DDD in 2005. The increase of used DDD triggered the increase in the isolation of *Pseudomonas aeruginosa* strains resistant to imipenem from 4.1% in 1999 to 37.8% in 2005. Similarly, the results of three years of study (1997–2000) of Lepper et al. [5] showed that the periods of the intensive application of imipenem are similar to the periods of resistance increase of *Pseudomonas aeruginosa* to imipenem. A positive correlation of r = 0.63 was found pertaining to the usage of imipenem and the resistance of *Pseudomonas aeruginosa* to this antibiotic.

The confirmation of the correlation between the usage of the antibiotic and the problem of resistance appeared in the studies of Patzer et al. [10]. Patzer clearly presents a five-fold increase of carbapenems in the years of 1993–2003 and the correlation connected with the fact that appearance of *Pseudomonas aeruginosa* strains resistant only to imipenem and of multi resistant strains, resistant to imipenem [10].

In order to lower the rate of resistance increase, in accordance with the recommendations of the World Health Organization and the European Union, the Minister of Health initiated in 2004 a National Program of Antibiotics Protection. The far reaching aim of the scheme is the elimination of the antibiotic overuse in medicine and extra-medical areas, prohibiting drug resistance in Poland and the implementation of the programs in this sphere according to the directives of the European Council [11].

The analysis presented in this study confirms the increase of the isolated numbers of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* and the fast increase of resistance due to the uncontrolled application of antibiotic therapy. It also points to the fact that the introduction of the basic principles of the Hospital Antibiotic Policy is effective in the improvement of the target therapy, the restriction of the growth of resistance of microorganisms to antibiotics.

CONCLUSIONS

1. The proportional increase of the frequency of isolation of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* bacteria strains to the increase of usage of imipenem and meropenem was confirmed.

2. The restriction of carbapenems use as a result of the introduction of the Hospital Antibiotic Policy caused the decrease of the number of isolated strains of non-fermenting bacteria to this group of antibiotics.

REFERENCES

1. G o s p o d a r e k E., G i e r l o t k a K., D e p t u ł ą A., M i c h a l s k a A.: Oporność pałeczek Gram – ujemnych na imipenem a zużycie tego leku w latach 1999–2005. Med. Dośw. Mikrobiol., 59, 231, 2007.
2. H r y n i e w i c z W.: Narodowy program ochrony antybiotyków w Polsce na lata 2006/2010. http://www.mz.gov.pl/wwwfiles/ma_struktura/docs/zal_ochr_antybiotyk_26032007.pdf

3. http://www.whocc.no/atcddd/indexdatabase/index.php?query=J01DH
4. H u g h e s W. T. et al.: Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin. Infect. Dis., 34, 730, 2002.
5. L e p p e r P. M., G r u s a E., R e i c h l H. et al.: Consuption of imipenem correlates whit β – lactam resistance in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother., 46, 2920, 2002.
6. Ł o p a c i u k U., S e m c z u k K., D z i e r ż a n o w s k a D.: Zapobieganie bakteryjnej oporności. Nowa Klinika, 9(3–4), 360, 2002.
7. Ł o p a c i u k U., B u c i o r K., P i n k a s J.: Zakażenia Gram (-) – schematy terapeutyczne. Zakażenia, 1, 29, 2006.
8. O z o r o w s k i T.: Diagnostyka mikrobiologiczna w systemie szpitalnej polityki antybiotykowej. Aktualności BioMérieux, 21, 22, 2002.
9. P a t z e r J. A., T e l e m a n M. A., D e s h p a n d e L. M. et al.: *Pseudomonas aeruginosa* strains harbouring an unusual blaVIM – 4 gene cassette isolated from hospitalized children in Poland (1998–2001). Antimicrob. Chemother., 53, 451, 2004.
10. P a t z e r J. A.: Występowanie opornych na imipenem pałeczek *Pseudomonas aeruginosa* u hospitalizowanych dzieci. Wykrycie metalo-β-laktamazy VIM-4, Warszawa 2004.
11. Stanowisko Rządu RP wobec Report from the commission to the council on the basis of member states' reports on the implementation of the council recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine.

SUMMARY

In recent times, antibiotic resistance of microorganisms has become a serious problem. Many Polish hospitals lack any regulations of hospital antibiotic policy, which often results in irrational implementation of antibiotic therapy, the increase of infections caused by multi-resistant strains, high therapy costs and the dissatisfaction of the patient. In the present study, the analysis of the correlations between the use of carbapenem antibiotics among the isolated strains of the non-fermenting Gram-negative bacteria and the effectiveness of the application of the basic principles of the regulations of Hospital Antibiotic Policy in restricting the increase of resistance is discussed.

STRESZCZENIE

W ostatnim czasie oporność antybiotykowa wśród drobnoustrojów stała się poważnym problemem terapii zakażeń. W wielu polskich szpitalach nie są wprowadzane zasady Szpitalnej Polityki Antybiotykowej, co skutkuje nieracjonalną antybiotykoterapią, narastaniem zakażeń wywołanych szczepami wieloopornymi, wzrostem kosztów terapii i brakiem satysfakcji pacjenta. W pracy przedstawiono analizę zależności między zużyciem antybiotyków z grupy karbapenemów w Oddziale Chirurgii Ogólnej a opornością na tę grupę antybiotyków wśród wyizolowanych szczepów pałeczek Gram-ujemnych niefermentujących i skuteczność zastosowania podstawowych zasad Szpitalnej Polityki Antybiotykowej w hamowaniu narastania oporności.