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Review

Enterobacteriacae resistance to antibiotics and treatment options

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Summary

Bacterial resistance to antibiotics is a problem that arose simultaneously with the beginning of their use and on a global level represents one of the biggest threats to public health. At the beginning of the twenty-first century, the emphasis of the medical and pharmaceutical public is on Gram-negative bacteria, especially enterobacteria, which show resistance to most, and some to all, available antibiotics. Treatment of infections caused by multiresistant bacteria is a big challenge for clinicians. Although bacterial resistance to antibiotics is a global problem, resistance rates vary significantly from country to country, and when it comes to hospital pathogens, from institution to institution. Monitoring antibiotic resistance in one's own environment is one of the first steps in the prevention and control of infections caused by multiresistant bacteria.

Key words: antibiotics resistance, carbapenemase, Enterobacteriaceae, antimicrobial therapy

Introduction

The discovery of antibiotics introduced us into the golden age of medicine. Antibiotics have influenced the development of all branches of medicine and are among the most commonly used drugs, and at the same time they are also among the most "abused" group of drugs. When Alexander Fleming received the Nobel Prize in 1945, he already announced that the mass use of penicillin would lead to the development of bacterial resistance to that antibiotic. Bacterial resistance to antibiotics represents the greatest threat to public health and causes over five million deaths annually [1]. Medical experts warn of a return to the pre-antibiotic era. The massive and irrational use of antibiotics in both human and veterinary medicine has accelerated the selection of resistant strains of bacteria. The selective pressure created by the

use of antibiotics favors resistant clones and is considered the main driver of the emergence and spread of resistance. The discovery and use of new types of antibiotics was accompanied by the emergence of resistance to them. Namely, due to selective pressure, bacteria acquire resistance to antibiotics through various mechanisms. Resistance can be primary (congenital or intrinsic) or acquired. Acquired resistance has greater clinical and epidemiological significance. Once acquired resistance can be passed on to offspring. Resistance genes can be located on the chromosome, in which case they are transferred directly to the offspring (clonal), which is known as vertical transport, while genes located on plasmids, transposons, integrons and bacteriophages are transferred horizontally between bacteria of the same or different species and genera (horizontal transfer genes) [2].

In the last twenty years of the last century, the medical and pharmaceutical profession was focused on fighting the spread of resistant Gram-positive bacteria, primarily methicillin-resistant staphylococci and vancomycin-resistant enterococci. At the beginning of the 21st century, the focus is on Gram-negative bacteria, especially enterobacteriacae, which show resistance to most, and some to all available antibiotics [3]. Of particular concern is the fact that many enterobacteria are resistant to carbapenems, which are used as a last line of defense for the treatment of serious infections.

The Enterobacteriacae family consists of aerobic and facultatively anaerobic gram-negative bacilli. They are widely distributed in the external environment, in food and water, which allows them to spread more easily in the human population. There are 30 genera and more than 120 species and subspecies in this family. Enterobacteria can be strictly pathogenic (*Salmonella, Shigella, Yersinia*) or conditionally pathogenic (*Escherichia coli, Klebsiella pneumonia* and *Proteus mirabilis*) [4]. The main virulence factors of enterobacteriacae are: colonization, invasiveness, endotoxins, enterotoxins, verotoxins, bacteriocins [5]. The common virulence factor of all species is lipopolysaccharide -LPS, which is located on the outer membrane and is responsible for the onset of infection symptoms. The formation of biofilm on various medical devices (catheters - intravascular, urinary) is one of the characteristics of these bacteria. They cause a whole range of diseases, the most important of which are urinary infections, wound infections, digestive tract infections, meningitis, sepsis, skin infections, and are often isolated from abscesses [6]. From the aspect of antimicrobial resistance, the most important bacterium from the Enterobacteriacae group is Klebsiella. Based on virulence, Klebsiella pneumoniae is classified into two phenotypes: hypervirulent K. pneumoniae and "classic" K. pneumoniae. The first type is hypervirulent and is characterized by the ability to cause life-threatening infections such as endophthalmitis, meningitis, liver abscesses, and pneumonia in a previously healthy host. The second "classic" variant behaves as an opportunistic bacterium causing disease in hospitalized patients and behaves like MDR (*Multidrug-resistant*) [7]. *Klebsiella pneumoniae* together with *Enterococcus faecium, Staphylococcus aureus, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp* is classified in the so-called "ESKAPE" group of pathogens, pathogens that "escape" antibiotics by developing resistance [8]. Enterobacteriaceae resistant to carbapenems, and among them *Klebsiella pneumoniae* in particular, have been characterized as one of the greatest threats to public health by the Centers for Disease Control and Prevention (CDC) [9].

Resistance

There are two types of resistance: primary (congenital or intrinsic) and secondary (acquired). Primary resistance is a naturally inherited property of the absence of a target site for an antibiotic in a microorganism. An example of natural resistance is the resistance of mycoplasmas to β-lactam antibiotics because

these bacteria do not possess a cell wall, which makes them naturally resistant to β-lactam antibiotics. Secondary resistance occurs when a bacterium that was naturally sensitive to a certain antibiotic due to selective pressure becomes resistant to it.

Among β-lactam antibiotics, carbapenems have the widest spectrum of action, they are effective against both Gram-positive and Gram-negative bacteria [10]. At the base of their structure is a beta lactam ring. It differs from penicillin in that it has an unsaturated bond between C2 and C3 and a carbon atom that replaces sulfur at the C1 position of the thiazolidine ring. Like other β-lactam antibiotics, carbapenems cannot easily diffuse through the cell membrane. In order to reach the periplasmic space where peptidoglycan synthesis takes place, they use outer membrane proteins known as porin channels. In the periplasmic space, they bind to penicillin-binding proteins and thus prevent the synthesis of peptidoglycan, which ultimately leads to the bursting of the bacterial cell due to an increase in osmotic pressure [11]. The first carbapenem that was introduced into clinical practice in 1985 is imipenem. It is a semi-synthetic derivative of thienamycin and is deactivated by renal dehydropeptidase (DHP-I), which is why the DHP-I inhibitor cilastatin was added to it. After imipenem, other carbapenems meropenem, doripenem, ertapenem, which are resistant to DHP-I, were developed. Like other β-lactam antibiotics, they are eliminated through the kidneys, which is why dose correction is necessary in patients with impaired kidney function.

As carbapenems are used as the last therapeutic option for the treatment of infections caused by multidrug-resistant bacteria, the increasing prevalence of carbapenem-resistant enterobacteria is a problem of global proportions. The mechanisms of resistance to carbapenems correspond to the mechanisms of resistance to other β-lactam antibiotics and can be mediated enzymatically (production of β-lactamases-carbapenemases) or by some of the non-enzymatic processes (reduction in production or replacement of the outer membrane, efflux pumps, production of low-quality penicillin-binding proteins). Because of the above, the terms "carbapenem-resistant *Enterobacteriaceae*" (CRE), "carbapenem-non-susceptible *Enterobacteriaceae*" (CNSE) and "carbapenemase-producing enterobacteria" are often used in the literature ("Carbapenem-producing *Enterobacteriaceae*", CPE). It is important to distinguish between these terms because the first two refer to reduced sensitivity to carbapenems without taking into account the mechanism of resistance, while CPE refers exclusively to enterobacteria that produce carbapenemases [12].

The efflux pump as one of the mechanisms of resistance to carbapenems in enterobacteria is significant only in combination with some of the other mechanisms of resistance (reduced permeability or enzymatic degradation). The best known and best studied so far is the three-component efflux pump AcrAB-TolC in *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter spp*. [13].

The permeability of the cell membrane of enterobacteria is mainly regulated by the 35 kDa and 36 kDa porins, which are encoded by the omp35-like and omp36-like genes. Porins are protein channels of the outer membrane that are responsible for the transport of both nutrients and the extraction of metabolites from the bacterial cell, and also affect the entry of antibiotics into the cell. Due to the selective pressure caused by the use of antibiotics, bacteria develop different defense mechanisms. Considering the above, this type of resistance is also unfavorable for the bacterial cell itself, because it compromises the intake of nutrients. As a result of exposure to subtherapeutic doses of antibiotics, the permeability of the cell membrane is reduced, which is a consequence of the loss or reduced expression of porins that arise due to various genetic mutations. Reduced

membrane permeability can rarely lead to resistance on its own and is mostly in combination with some other mechanism [14].

The most dominant mechanism of resistance of enterobacteria to carbapenems is the production of carbapenemases. Carbapenemases can be classified by structure or by functional characteristics. One of the most frequently cited classification schemes that divides enzymes according to functional characteristics was proposed by Bush in 1988. [15] which was extended in collaboration with Jacoby and Medeiros in 1995 [16]. The last revision of their classification was made in 2010. in which avibactam was added as an inhibitor and β-lactamases were divided into three main groups and 16 subgroups [17]. The first classification based on structural characteristics was proposed by Ambler in 1980 according to which carbanemases were divided into four groups A, B, C, D. Groups A, C, D are the so-called serine carbapenemases because they contain the amino acid serine in the active site. Group B carbapenemases is also called metallo-β-lactamases (MBL), which hydrolytic activity requires the presence of one or two zinc ions [18]. Functional classification is more precise, takes into account their functional characteristics and is based on the hydrolytic profile of their substrates. However, due to simplicity, the Ambler classification is used much more. According to the functional classification, carbapenemases are classified into three functional groups, i.e. three Ambler classes A, B, D.

Class A carbapenemases belong to the 2f functional group. The most important representatives of this group are GES (*Guiana extended-spectrum*), KPC (*Klebsiella pneumoniae carbapenemase*), SME (*Serratia marcescens enzymes*), NMC (*Non-metallo-carbapenemase-A*), and IMI (*Imipenem-resistant*). Resistance to carbapenems caused by these enzymes can be of plasmid or genetic origin. Enzymes from this group hydrolyze all penicillins, cephalosporins, aztreonam and carbapenems. Carbapenemases KPC are currently the most clinically significant carbapenemases of class A. It was first identified in an isolate of K. pneumoniae in 1996 in the USA [19], and then spread to the entire territory of the United States of America, South America, Israel, China, Greece and many other European countries [20]. So far, 24 variants of this enzyme have been described, the most significant being KPC-2 and KPC-3 [21]. KPC-type β-lactamases are not inhibited by clavulonic acid and tazobactam, however, they are well inhibited by newer β-lactamase inhibitors such as avibactam, relebactam, and vaborbactam [22, 23]. KPC enzymes represent the most dominant carbapenemases in Europe [24] and are endemic in Italy and Greece [25]. Mortality in infections caused by KPC-producing strains is over 50% [26].

Class B carbapenemases, metallo β-lactamases (MBL) according to Ambler belong to functional group 3 according to K. Bush. Their hydrolytic activity is conditioned by zinc ions, which is why they are insensitive to classic β-lactamase inhibitors, but they are inhibited by ethylenediamine-tetraacetic acid (EDTA) and dipicolic acid [27]. Class B carbapenemases are divided into three subclasses with a large number of enzymes, but the most important MBLs are VIM (*Verona integron-encoded metallo- β-lactamase*), IMP (*active on imipenem*), NDM (*New Delhi metallo- β-lactamase*). VIM is the most widespread MBL, described for the first time in 1997 in Verona in an isolate of P. aeruginosa [28]. VIM occurs in Southern Europe, Southeast Asia, sporadically in Africa and some European countries. When it comes to neighboring countries, it was detected in Croatia [29] Hungary [30] and Serbia [31, 32]. NDM ("New Delhi metallo-β-lactamase") was first described in Sweden in 2008 in a K. pneumoniae isolate from a patient previously treated in India [33]. Initially, the occurrence of NDM was confined to the Indian subcontinent, however, Belgium, China, Japan, France, Austria, Germany, Norway, Hong Kong, Sweden, the Netherlands,

Australia, and Canada also serve as secondary reservoirs of blaNDM genes [33]. Namely, this enzyme was detected in an isolate from a patient from Bosnia and Herzegovina who was treated in Croatia, without any anamnestic information about his stay in India [34]. The blaNDM gene has been described in many species of enterobacteria, but the most significant presence is in isolates of K. pneumoniae and E. coli [33].

Representatives of class D carbapenemases are also called oxacillinases (OXA-48) and according to the functional classification belong to subclass 2d. OXA-48 is a carbapenemase that is most often detected in isolates of enterobacteria, dominantly in *K. pneumoniae*, but also described in *E. coli* and *E. cloacae*. OXA-48 was described for the first time in an isolate of *K. pneumoniae* in 2003 in Turkey [35] and after that there is a significant expansion and detection of this enzyme in numerous European countries [36]. Many variants of this enzyme have been described, differing only in a few amino acids, which are designated as OXA-48-like enzymes.

Treatment of infections caused by enterobacteriacae resistant to carbapenems

Treatment of infections caused by multidrug-resistant bacteria is a major challenge for clinicians. The optimal treatment method for infections caused by carbapenem-resistant bacteria has not yet been established. As for meropenem, it is reasonable to use it if the minimum inhibitory concentration (MIC) for carbapenems is < 8 mg/l, because in this way a good therapeutic response is achieved. One of the interesting combinations of antibiotics is treatment with a combination of two synergistic carbapenems (ertapenem plus meropenem, imipenem or doripenem). The explanation for this combination is the fact that ertapenem binds with high affinity to the active site of carbapenemase and thus prevents the hydrolysis of meropenem and enables its bactericidal activity [37–39].

A list of antibiotics that act on carbapenemase-producing bacteria is shown in Table 1.

Aztreonam is a monobactam antibiotic that is effective against bacteria producing carbapenemases of classes B and D. Since bacteria of this group often produce ESBLs that hydrolyze aztreonam, this has limited its use as monotherapy. Aztreonam is not active against bacteria that produce group A carbapenemases, including the most widespread KPC carbapenemase, which further limits its role in the therapy of infections caused by CRE [40]. However, the combination of aztreonam with ceftazidime/avibactam is a promising treatment option, which we will discuss below.

Polymyxins

This group of antibiotics became available in 1950, but their use in humans (except for rare exceptions) was abandoned primarily due to pronounced nephrotoxicity and the availability of less toxic antibiotics. It is believed that due to the non-use of these drugs, the selective pressure was reduced, which explains the sensitivity of many bacterial pathogens to these antibiotics. Due to the emergence of resistance to most antibiotics, and especially to carbapenems, at the beginning of this century, polymyxins began to be used again in the treatment of severe infections. However, due to pronounced nephrotoxicity and inferiority compared to new drugs, they are currently not recommended for the treatment of infections caused by CRE. An exception is the application of colistin as an alternative therapy in CRE cystitis [41].

Table 1. Spectrum of Activity anti-CRE therapeutics

Agent	Therapeutic Class	Activity against Class A	Activity against Class B	Activity against Class D	Notes
Aztreonam	Monobactam	–	+	+	Not recommended. CRE often have co-occurring ESBL enzymes which render aztreonam ineffective.
Colistin, Polymyxin B	Polymyxin	+/–	+/–	+/–	Limited efficacy, significant toxicities, alternative therapy in CRE cystitis
Fosfomycin	Phosphoenolpyruvate analogue	+	+	+	Primarily used for urinary tract infections.
Tigecycline	Tetracycline	+/–	+/–	+/–	Approved for cIAI , ABSSSI osteomyelitis and for respiratory infections if optimally dosed
Ceftazidime-avibactam	β-lactam-β-lactamase inhibitor	+	–	+	Approved for cUTI, cIAI (with metronidazole), HAP/VAP. Can be used with aztreonam for treatment of NDM-producing infections.
Meropenem-vaborbactam	β-lactam-β-lactamase inhibitor	+	–	–	Approved for cUTI, cIAI, HAP/VAP.
Imipenem-relebactam	β-lactam-β-lactamase inhibitor	+	–	–	Approved for cUTI, cIAI by FDA. Approved for HAP/VAP, BSSSI, resistant GN infections by EMA.
Plazomicin	Aminoglycoside	+	+	+	Approved for cUTI by FDA. Not approved by EMA.
Cefiderocol	Cephalosporin	+	+	+	Approved for cUTI and HAP/VAP by FDA. Approved for resistant GN infections by EMA.

cUTI = complicated urinary tract infection; cIAI = complicated intraabdominal infection; HAP/VAP = hospital acquired pneumonia/ventilator-associated pneumonia; GN = gram negative; ABSSSI = acute bacterial skin and skin structure infection; CABP = community acquired bacterial pneumonia; FDA = United States Food and Drug Administration; EMA = European Medicines Agency

Fosfomycin

Fosfomycin is an "old" antibiotic, cheap, safe, with few side effects, which has recently been increasingly used to treat infections caused by multiresistant bacteria. According to various studies, the resistance of enterobacteria that produce carbapenemases to fosfomycin is between 7.6% [42] and 41.2% [43]. It has been traditionally used as an oral formulation for lower urinary tract infections. It is used intravenously to treat infections caused by

resistant pathogens. Due to poor penetration into the renal parenchyma, it is not used in the treatment of infections of the upper urinary tract [44]. So far, there are not enough studies to indicate its effectiveness in treating infections caused by multi-resistant bacteria, mainly because it is used in combination with other antibiotics so that its effectiveness could not be assessed.

One of the therapeutic options is tigecycline, a tetracycline antibiotic, which is effective against many gram-negative and gram-positive pathogens. Its activity is independent of the presence or type of carbapenemase. It achieves rapid distribution in tissues, which leads to limited concentration in urine and serum, which is why they are not recommended for infections of the urinary tract and bloodstream. Tigecycline is an alternative therapy for intra-abdominal infections, skin and soft tissue infections, osteomyelitis and for respiratory infections if it is optimally dosed [41].

Plazomicin is a new semi-synthetic aminoglycoside. It has a broad spectrum of activity against enterobacteria, including those with ESBL enzymes, KPC, VIM, IMP and OXA-48. It shows variable activity according to the group of NDM carbapenemases. It was approved by the FDA in 2018 for the treatment of complicated urinary tract infections including pyelonephritis. As with other aminoglycosides, nephrotoxicity and ototoxicity are unwanted effects [44].

Cefiderocol is a new siderophoric cephalosporin. It shows activity against various pathogens that produce KPC, NDM, VIM, IMP, OXA-48. Cefiderocol is FDA approved for the treatment of complicated urinary tract infections. In clinical trials of the use of cefiderocol in the treatment of infections outside the urinary tract, increased mortality was shown in the group of patients who received cefiderocol. Because of the above, the drug is currently only indicated for urinary tract infections (45).

β-lactam/ β-lactamase combinations

New β-lactam/β-lactamase combinations currently approved for use are ceftazidime-avibactam, meropenem-vaborbactam and imipenem-cilstatin-relebactam.

Ceftazidime-avibactam is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for complicated urinary tract infections and for complicated intra-abdominal infections in 2015. After a series of studies, the indications were extended to include community-acquired pneumonia as well as ventilator-associated pneumonia. Even if the majority of causative agents (around 99.8%) are still sensitive to ceftazidime-avibactam, cases of resistance have been reported, especially in carriers of the KPC enzyme (44). Since ceftazidime-avibactam has no activity against MBL, it is recommended to be given in combination with aztreonam for infections caused by MBL-producing bacteria [46].

Meropenem-vaborbactam is the combination of the carbapenem antibiotic meropenem with a new β-lactamase inhibitor. It was approved in 2017 by the FDA for the treatment of complicated urinary tract infections in adults, and the indications were expanded in 2018 by the EME for the treatment of pyelonephritis, complicated intra-abdominal infections, hospital-acquired pneumonia including ventilator-associated pneumonia, as well as bacteremias occurring in connection with any of these infection. In the European Union, meropenem-varborbactam is indicated for the treatment of infections caused by aerobic gram-negative organisms in adults. It shows activity against carbapenemases of groups A and C, while it has no effect on pathogens that produce carbapenemases of classes B and D [47].

Imipenem-relebactam is the newest combination in this class of drugs. It was approved for use by the FDA in 2019. It shows activity against class A carbapenemases but not against MBL and little or no activity against

OXA-48-like enzymes. According to data from the SMART study of surveillance of enterobacteriaceae isolates collected in Europe, it was shown that the addition of relebactam restored susceptibility to imipenem in 67% of isolates carrying the KPC genes, but that all isolates carrying the MBL and OXA-48 genes remained nonsusceptible [48].

The Infectious Diseases Association of America (IDSA) has issued recommendations for the treatment of infections caused by enterobacteria produce extended-spectrum β-lactamases, carbapenem-resistant enterobacteria, and the treatment of infections caused by resistant strains of Pseudomonas aeruginosa. Even if there are differences in the epidemiology of resistance and the availability of antibiotics (some are not available in our country) these recommendations can still be applied in our environment with certain corrections. The recommendations are designed as a series of clinical questions, that is, possible clinical scenarios. Here we will briefly outline the recommended protocol for the treatment of infections caused by carbapenem-resistant enterobacteria [45]. The treatment protocol is different in relation to the fact whether the bacteria produces carbapenemase or the information on carbapenemase production is unavailable or the resistance is a consequence of one of the non-enzymatic processes.

According to these recommendations, the therapy of choice for uncomplicated urinary tract infections caused by CRE would be: nitrofurantoin, trimethoprim/sulfamethoxazole, levofloxacin. If there is resistance to these antibiotics, alternative therapy is fosfomycin (only for infections caused by E. Coli), colistin, ceftazidime-avibactam, meropenem, vaborbactam, imipenem-cilstatin-relebactam, cefiderocol.

For complicated urinary infections and pyelonephritis, it is recommended to use trimethoprim/sulfamethoxazole, ciprofloxacin and levofloxacin if the causative agent is sensitive. In case of resistance to these drugs, the alternative is ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilstatin-relebactam, cefiderocol.

Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilstatin-relebactam are the drugs of choice for infections outside the urinary tract if carbapenemase tests are missing or negative. Alternative therapy for these infections is cefiderocol or tigecycline for infections outside the bloodstream and urinary tract.

The treatment protocol depends on the type of carbapenemase. Namely, for organisms producing KPC, it is recommended to use meropenem-vaborbactam, ceftazidime-avibactam or imipenem-cilastatin-relebactam. Cefiderocol is an alternative therapy for the treatment of infections caused by KPC-producing bacteria and is reserved for metallo-β-lactamase-producing pathogens, as metallo-β-lactamase-producing strains are resistant to the previously mentioned β-lactams. If Enterobacteriacae isolates produce NDM (or any other metallo-β-lactamase), ceftazidime-avibactam plus aztreonam or cefiderocol as monotherapy is preferred. Ceftazidime-avibactam as monotherapy is not effective for the treatment of metallo-β-lactamase-producing strains. If an OXA-48-like enzyme is identified, ceftazidime-avibactam is preferred. An alternative option is cefiderocol, although clinical data on its use in this case are limited. For isolates that produce OXA-48, if the infection is outside the urinary tract or bloodstream, tigecycline can be used [45].

These guidelines refer to the treatment of specific pathogens. Empiric therapy depends on the severity of the disease, the likely source of infection, previous bacterial isolates in the particular patient, or previous antibiotic therapy. Emiric therapy depends on the local epidemiology and resistance.

Irrational use of antibiotics is one of the main reasons for bacterial resistance. In order to optimize the use of antibiotics, the WHO (World Health Organization) created the AWaRe antibiotic classification in 2017 (updated every

two years), according to which antibiotics are divided into three groups: Access, Watch and Reserve. The "Access" group includes antibiotics with a narrow spectrum of action, mostly with fewer side effects, with a lower potential for antimicrobial resistance. It is recommended that antibiotics from this group are used for empirical treatment of the most common infections. Antibiotics from the "Watch" group have a greater potential for the selection of antimicrobial resistance. Their consumption should be carefully monitored to avoid excessive use. The "Reserved" group includes antibiotics that should be used as the last resort for the treatment of confirmed or suspected infections caused by pathogens resistant to other antibiotics.

According to this classification, reserve antibiotics are: ceftazidime-avibactam, fosfomycin, linezolid, colistin and polymyxin B, meropenem-vaborbactam, plazomicin, cefiderocol [49].

The last three are not available in our country. Based on this classification, the WHO published the book "The WHO AwaRe (Access, Watch, Reserve)" in 2022 with the aim of providing simple guidelines for the optimal empiric treatment of bacterial infections in children and adults.

The book includes individual chapters for 34 common infections in children and adults with recommendations on therapy. This book is not a formal WHO guideline, although the choice of antibiotic used for a particular infection represents formal recommendations. In addition, it provides information on dosage and length of treatment for certain infections [50]. The recommendations in this book and in general any instructions on the choice of antibiotic therapy must be adapted to local resistance. The lack of representative data from underdeveloped countries significantly limits the generalization of empirical guidelines.

In our country, there are no adequate data on the prevalence of resistance to carbapenems and types of carbapenemases among enterobacteria. All data known so far are based on research that did not include all types of carbapenemases, Colleagues from the University Clinical Center Sarajevo (during 2017 and 2018), proved the production of OXA-48 in K. pneumoniae isolates, while all isolates were negative for other carbapenemases [51]. A subsequent study by the same group of authors proved resistance (by phenotypic methods) of Klebsiella pneumoniae to carbapenems in 188/944 (20%) isolates [52]. Sokolović and colleagues examined the consumption of antibiotics and the presence of multiresistant strains in the regional hospital Doboj (Republic of Srpska) during 2021. According to this research, the resistance of Klebsiella spp to meropenem is 8.8%, and 2.2% to imipenem. E. Coli isolates show resistance to meropenem in 1.3% and to imipenem in 0.4% [53].

For Europe, WHO has established compatible networks for monitoring antibiotic consumption and bacterial resistance to antibiotics for countries that are not members of the European Union, the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR). Bosnia and Herzegovina has been a member of this network since 2015. According to their report, in Bosnia and Herzegovina in 2021 37.1% of Klebsiella pneumoniae isolates were resistant to carbapenems compared to 2017 when that percentage was 10.9%. E. Coli resistance to carbapenems was without significant dynamics from 2017-2021 amounting to about 0.5% in 2021. According to the same source, 62.7% of Klebsiella pneumonia isolates in Serbia are resistant to carbapenems. In Croatia, there is a significant increase in resistance compared to the previous year, and in 2021, 32.9% of Klebsiella pneumonia isolates were resistant to carbapenems [54].

Conclusion

Bacterial resistance to antibiotics on a global scale represents one of the greatest threats to

public health. Irrational use of antibiotics is one of the main drivers of bacterial resistance. In response to this growing problem, the Centers for Disease Control and the World Health Organization advocate the implementation of programs to control antibiotic consumption. In our country, there is no national program for monitoring antibiotic resistance and consumption. Therapy is based on specific clinical guidelines. There is not even a single list of reserve antibiotics, but it is made in each institution separately. Considering the limited therapeutic possibilities in the treatment of infections caused by multiresistant bacteria, the rational use of antibiotics, the introduction and application of programs to control the consumption of antibiotics are still imperative.

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Otpornost enterobakterija na antibiotike i opcije liječenja

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Otpornost bakterija na antibiotike je problem koji se javio istovremeno sa početkom njihove primjene i na globalnom nivou predstavlja jednu od najvećih prijetnji za javno zdravlje. Početkom dvadeset prvog vijeka akcenat medicinske i farmaceutske javnosti je na Gram negativnim bakterijama, naročito enterobakterijama koje pokazuju rezistenciju na većinu, a neke i na sve dostupne antibiotike. Liječenje infekcija uzrokovanih multirezistentnim bakterijama veliki je izazov za kliničare. Iako je otpornost bakterija na antibiotike globalni problem, ipak se stope otpornosti značajno razlikuju od zemlje do zemlje, a kad se radi o bolničkim patogenima onda i od ustanove do ustanove. Praćenje otpornosti na antibiotike u vlastitoj sredini predstavlja jedan od prvih koraka u prevenciji i kontroli infekcija uzrokovanih multirezistentnim bakterijama.

Ključne riječi: otpornost na antibiotike, karbapenemaze, enterobakterije, antimikrobna terapija