

## THE IMPORTANCE OF OLD ANTIBIOTICS IN OVERCOMING RESISTANCE TO ANTIBIOTICS

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Antibiotics are medications used to prevent or cure infections caused by bacteria. Discovery and introduction of antibiotics into medical practice brought about revolutionary changes in therapy and eradication of infectious diseases. There is a rise of interest for usage of old antibiotics. These drugs could be invaluable in the treatment of certain infections and, in order for them to remain effective, it is necessary to conduct certain measures which would prove their worth. The aim of antibiotic therapy is to deliver the antibiotic to the place of infection and to retain it in the place of infection for a long period of time. Most of all, it is of utmost importance to educate about this all medical personnel in health care system, especially physicians. The fact that the availability of these drugs remains low in comparison to the efforts made in attempt of discovering new antibiotics, imposes the need for national regulatory agencies to get involved in regulating the usage of these drugs.

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### Introduction

Antibiotics are medications used to prevent or cure infections caused by bacteria. Discovery and introduction of antibiotics into medical practice brought about revolutionary changes in therapy and eradication of infectious diseases. It is believed that the "antibiotic era" has begun at the beginning of the twentieth century, but the evidence suggests that antibiotics have been used since ancient times. It is clear that antibiotics had been used in forms com-

pletely different from contemporary industrially produced ones. Nevertheless, this does not diminish the fact that certain herbal medicines which have antibiotic properties were known to ancient Greeks and Romans and that they constituted an important part of their medical practices (1).

Uncontrolled and excessive antibiotic use quickly led to the emergence of antibiotic resistant strains of bacteria. Results of many studies have shown that it is of utmost urgency that the use of antibiotics must be put under control. Unless certain changes are made, it is estimated that by the year 2050, 50.000.000 deaths will be caused by bacterial infections annually, a number surpassing the number of deaths caused by cancer (2).

Data suggests that 80% of antibiotics are used out of hospitals, while 20% fall into the category of intrahospital treatment. 20%-50% of prescribed antibiotics are not used rationally. All of these circumstances led to the emergence of multiresistant bacterial strains, and some strains of bacteria, such as *Enterococcus faecium*, are resistant to all known types of antibiotics (3). The research has also shown that resistant strains of bacteria frequently occur in intensive care units, proving that even rational antibiotic use leads to emergence of resistant bacteria.

Due to the global problem of bacterial resistance, data is being collected in Europe and certain strains of bacteria of great epidemiological importance, such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE), III generation cephalosporin and carbapenem resistant *Enterobacteriaceae* (*Escherichia Coli*, *Klebsiela*

pneumoniae), carbapenem resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and penicillin resistant *Streptococcus pneumoniae*, are being monitored (4).

Acknowledgment that the Earth's population might become powerless even when it comes to the most banal infections, raised alarm among member countries of the UN at the annual gathering of General Assembly in New York in 2016 and it was decided that certain measures are to be introduced in order to reduce the risk of infections caused by multiresistant strains of bacteria (5):

1. Acceleration of development of new antimicrobial drugs
2. Acceleration of development of new vaccines
3. Acceleration of development of reliable diagnostic tests which would enable the reduction of antibiotic use
4. Monitor and collect data about antibiotic use, as well as about antibiotic resistant bacteria
5. Impose closer monitoring of antibiotic use
6. Establish national strategies which would allow for a more rational prescription of antibiotics
7. Attempt to re-introduce old ("forgotten") antibiotics

Since the introduction of new antibiotics is fairly slow and expensive, and the occurrence of resistant bacteria increased, the idea about making the old antibiotics available and used again is becoming an important topic. Unfortunately, many of these antibiotics are unavailable in most countries (the EU, the US, Australia), reasons being varied and complex.

It is not easy to explain the definition "old" and "forgotten". These are antibiotics once used, but, for various reasons (in connection to their properties or unprofitability) removed from the pharmacies or were never used in clinical practice. However, there are findings pointing that these antibiotics could be administered at the present moment or in the future and that their usefulness is beyond doubt.

Old antibiotics with narrow spectrum of action which were withdrawn from the pharmacies or never used in praxis could potentially prove to be useful in treatment of certain infections which would reduce the usage of broad spectrum antibiotics whose frequent prescription results in emergence of multiresistant bacteria (6). Moreover, old antibiotics could be used in treatment of infections caused by multiresistant bacteria, such as sepsis, endocarditis and meningitis.

Usefulness and effectiveness of old antibiotics could be summed up as following (7):

1. Old antibiotics could be useful because of their special microbiological criteria (antimicrobial spectrum; special mechanisms of action)
2. According to special pharmacological criteria
3. According to clinical criteria
4. Based on the fact that they are the only efficient antibiotics in relation to the cause of infection
5. Based on the fact that a certain antibiotic has no replacement

6. Based on the fact the certain antibiotic is the only efficient antibiotic in a certain group of antibiotics.

### Overview of selected antibiotics

Penicillin G is used parenterally in the form of sodium and potassium salts. In addition to penicillin G, procaine benzylpenicillin and bezanthine benzylpenicillin are used. Despite the fact that many bacteria have become penicillin G resistant, it is important to stress that *Streptococcus pyogenes* remains susceptible to this drug. Therefore, this old antibiotic is important when it comes to the treatment of infections caused by this bacterium, such as sepsis, endocarditis and meningitis (8). This is the drug of choice in treatment of syphilis. Due to these facts, penicillin G should be available for treatment of streptococcal infections and syphilis. The main reason behind the deficit of this drug is of economic nature (a cheap antibiotic). This drug is available in the Serbian pharmacies.

Temocillin is a derivative of ticarcillin. Despite its unique properties it was never widely used. It is a narrow spectrum of action drug and it is stable in relation to beta lactases. What makes this antibiotic unique is that resistant strains of bacteria have never emerged. It is active against *Burkholderia cepaciae* and the specific and unique indication for this antibiotic is an infection caused by this bacterium. This type of infection occurs frequently and can be serious in patients with cystic fibrosis (9).

The main causes of infrequent use of this antibiotic are low prices and the lack of knowledge among physicians about the usefulness of this narrow spectrum of action antibiotic. This drug is not available in the Serbian pharmacies.

Izoxazole penicillins are halfsynthetic penicillins resistant to beta lactamase which is synthesised by *Staphylococcus*. The basic and extremely important indications for the use of these antibiotics (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) are infections caused by *Staphylococcus aureus* susceptible to methicillin, such as dermal infections, cellulitis, infected burns, postoperative abscesses. They could be used in treatment of serious cases of pneumonia, meningitis, endocarditis and septic arthritis. If *Staphylococcus aureus* is proven to be the cause of osteomyelitis, these antibiotics are the drugs of choice (10). The reason behind the deficiency of these antibiotics in the pharmacies is their low price.

Cefoxitin is a cephalosporin of II generation which is administered intravenously and which penetrates through the surgical patient's peritoneum very well. *Streptococcus* and *Staphylococcus* (apart from MRSA) are very susceptible to this drug. A special characteristic of cefoxitin is its excellent action against *Mycobacterium abscessus*, fast growing nontubercular bacteria which cause infections of soft tissues, medial nervous system, eye and bacteriemia. Fifty percent of *Mycobacterium fortuitum* are susceptible to cefoxitin. Therefore, this drug is used to treat infections caused by this bacterium (dermal infections, osteomyelitis, and joint and cornea infections).

These infections are common in immunocompromised patients what makes this antibiotic necessary and valued in the treatment of immunocompromised patients and infections caused by atypical mycobacteria (11). This drug is available in the Serbian pharmacies.

Chloramphenicol was the first broad spectrum antibiotic to have been discovered. The advantage of this antibiotic lies exactly in its broad spectrum of action and the possibility of treating the infections caused by multiresistant bacteria (*Enterococcus*, *Rickettsia*, *Streptotrophomonas maltophilia*). The great importance and advantage of this drug is its ability to penetrate into the brain and eye tissues (12).

This antibiotic was withdrawn because it caused the depression of bone marrow. However, its low price means it is still being used in developing countries. If introduced back into the markets of developed countries, it could be used to treat infections in elderly patients, as well as in brain infections when treatment with other types of antibiotics fails. Chloramphenicol is especially important because of its ability to penetrate the brain and eye tissues. This drug is not registered in Serbia.

Quinupristin/dalfopristin is an antibiotic from the group of streptogramins. This antibiotic has excellent action against gram-positive bacteria. *Enterococcus faecium*, which is resistant to vancomycin, is especially susceptible to this drug. This constitutes the main reason behind its use in treatment against infections caused by this bacterium. Its use is also indicated in treatment of infections caused by *Enterococcus faecium* which are resistant to ampicillin and which are connected to the implantation of intravascular catheter (13). Despite its usefulness, this antibiotic is not widely used and it's rarely available in many countries.

Spectinomycin is structurally similar to streptomycin, but it is not an aminoglycoside. Today, it is used solely in the treatment of gonorrhea in the case of anorectal disease or gonococcus infections in patients allergic to beta-lactam antibiotics. Never the less, it is important to have this antibiotic available in the market due to the rise of gonococcus bacteria resistant to most antibiotics (14).

Teicoplanin is a glycopeptide antibiotic similar to vancomycin. It is effective exclusively against gram-positive bacteria, including MRSA resistant staphylococci. Teicoplanin is the antibiotic of choice in the treatment of infections caused by *Enterococcus gallinarum* and *Enterococcus casseliflavus* which are vancomycin resistant and which are not affected by any other antibiotic.

The advantage of teicoplanin in comparison to vancomycin lies in the possibility of one-day parenteral application, as well as in nonhospitalized patients, in addition to having less unwanted effects than vancomycin (15).

Tobramycin is an aminoglycoside antibiotic. The main advantage of this drug in comparison to other aminoglycosides is its effectiveness against *Pseudomonas aeruginosa*. Moreover, significant benefit of tobramycin is the possibility of administration by inhalation in patients with cystic fibrosis (16). It could also be applied intrarectally when the indications are appropriate. The use of tobramycin could

reduce the prescription of wide spectrum antibiotics such as carbapenems and colistin. This drug is available in the Serbian pharmacies.

Colistin is a polypeptide antibiotic which is used in the form of colistin sulfonate and colistin methanesulfonate (prodrug). This drug is active against gram negative multiresistant bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumani* and *Klebsiella pneumoniae*.

Colistin was withdrawn from the market due to dosage-dependent nephrotoxicity which passed with when the treatment with this antibiotic ceased. It was reintroduced to the market and it represents irreplaceable and valued antibiotic for treatment of infections caused by multiresistant gram negative bacteria (17). This drug is available in the Serbian pharmacies.

Colistin and quinupristin/dalfopristin are the antibiotics without alternatives. Colistin is the last drug of choice in the treatment of infections caused by gram negative bacteria, and quinupristin/dalfopristin is used to treat infections caused by *Enterococcus faecium* which are resistant to vancomycin, daptomycin and amoxicillin.

Fosfomycin is an antibiotic with a specific mechanism of action. This drug is effective against gram positive (*Staphylococcus aureus*, including MRSA strains and *Enterococci*) and gram negative (*Salmonella*, *Shigella*, *Proteus mirabilis*, *Enterobacteriaceae*, *Serratia* strains and *Citrobacter*) bacteria. Fosfomycin was abandoned, then reintroduced, and today, it represents a valued antibiotic in the treatment of acute cystitis in women without complications. Intravenously applied fosfomycin is used in the treatment of sepsis, serious cases of pneumonia, otomyelitis, infections of medial nervous system, but only in cases when proven-efficacy antibiotics have no effect (18).

The main pharmacokinetic advantage of fosfomycin is the possibility of one time oral application of this drug in patients with acute cystitis since long lasting high concentrations of this drug are achieved. In addition, intravenously applied fosfomycin achieves high concentrations in brain tissues, but it is rarely used in the treatment of meningitis.

Fusidic acid is chemically categorized as an antibiotic similar to steroids. It is active against gram positive bacteria such as *Staphylococcus aureus*, including MRSA strains. It is used in the treatment of staphylococcal infections, but it is not the antibiotic of choice (19). This drug is available in the Serbian pharmacies.

Nitrofurantoin is a drug from the group of nitrofurans, used in the treatment of cystitis and in the prophylaxis of urinary infections. It is effective against many gram positive and gram negative bacteria (*Enterococcus*, *Staphylococcus aureus*, *epidermidis* and *saprophyticus*) (20).

Certain old antibiotics are gaining importance because of their special mechanism of actions which enable both the application of the antibiotic itself and the possibility of combining antibiotics with purpose of achieving synergistic action.

## Conclusion

There is a rise of interest for usage of old antibiotics. These drugs could be invaluable in the treatment of certain infections and, in order for them to remain effective, it is necessary to conduct certain measures which would prove their worth. The aim of antibiotic therapy is to deliver the antibiotic to the place of infection and to retain it in the place of infection for a long period of time.

Most of all, it is of utmost importance to educate all medical personnel in health care system, especially physicians. The fact that the availability of these drugs remains low in comparison to the efforts

made in attempt of discovering new antibiotics, imposes the need for national regulatory agencies to get involved in regulating the usage of these drugs.

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Revijalni rad

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doi:10.5633/amm.2019.0412**ULOGA STARIH ANTIBIOTIKA U PREVAZILAŽENJU REZISTENCIJE NA ANTIBIOTIKE***Zorica Jović<sup>1</sup>, Lidija Ristić<sup>2,3</sup>, Dane Krtinić<sup>1,4</sup>, Gorana Nedin-Ranković<sup>1</sup>, Ana Cvetanović<sup>4,5</sup>, Dušan Simić<sup>6</sup>*<sup>1</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za farmakologiju sa toksikologijom, Niš, Srbija<sup>2</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za internu medicinu, Niš, Srbija<sup>3</sup>Klinika za plućne bolesti, Klinički centar Niš, Niš, Srbija<sup>4</sup>Klinika za onkologiju, Klinički centar Niš, Niš, Srbija<sup>5</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za onkologiju, Niš, Srbija<sup>6</sup>Dom zdravlja Niš, Služba za zdravstvenu zaštitu žena, Niš, Srbija*Kontakt:* Dane Krtinić

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Antibiotici su lekovi koji se koriste za sprečavanje ili lečenje infekcija uzrokovanih bakterijama. Otkrivanje i uvođenje antibiotika u medicinsku praksu dovelo je do revolucionarnih promena u terapiji i iskorenjivanju infektivnih bolesti. Trenutno postoji povećanje interesa za korišćenje starih antibiotika. Ovi lekovi mogu biti neprocenjivi u lečenju određenih infekcija i, kako bi oni ostali efikasni, neophodno je sprovesti određene mere koje bi mogle dokazati njihovu vrednost. Cilj antibiotske terapije je da se isporuči antibiotik do mesta infekcije i da se zadrži na mestu infekcije u dužem vremenskom periodu. Pre svega, izuzetno je važno edukovati, na ovu temu, sve zdravstveno osoblje u sistemu zdravstvene zaštite, posebno lekare. Činjenica da je dostupnost ovih lekova i dalje niska, u odnosu na napore u pokušaju otkrivanja novih antibiotika, nameće potrebu da se nacionalne regulatorne agencije uključe u regulisanje korišćenja ovih lekova.

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