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# How to treat infections caused by multidrug-resistant bacteria?

## Jak leczyć zakażenia wywołane przez bakterie wielolekooporne?

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### Abstract

Multidrug resistance of bacteria is a rising problem in treatment, especially of seriously ill patients hospitalised in the departments of intensive therapy. Mechanisms of antibiotic resistance are enzymatic inactivation, defects of permeability, antibiotic outflow from bacterial cells, protection, change and overproduction of antibiotic target site, binding up antibiotics and circumvention of inhibited process. Resistance to antibiotics is a consequence of genetic mutations which occur in bacterial populations. Articles describing the effectiveness of antibiotics *in vitro* on isolates, in case reports and *in vivo* in randomised and retrospective studies are presented in the present paper. The attached Recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) show guides for monotherapy and on combination of antibiotics in case of infections with confirmed bacterial resistance.

Keywords: resistance to antibiotics, antibiotics, multidrug resistance, β-lactamases

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## Introduction

Infections caused by antibiotic-resistant bacteria are a growing clinical problem occurring in patients treated in hospitals, especially in intensive care units (ICUs). Bacterial resistance is the lack of response to treatment with antibiotics commonly recommended for specific pathogens. A characteristic feature of bacteria is their natural resistance to certain groups of antibiotics, which means that they are already inherently unsuitable for administration in infections with a confirmed specific aetiology. An example is the resistance to ampicillin found in bacteria of the *Enterobacteriaceae* family, including *Klebsiella and Enterobacter spp.* [1]. In the case of *Escherichia coli,* at least 40% of the bacteria are affected by this resistance [1].

The second type of resistance is acquired resistance. It can affect one antibiotic or several. The abbreviation XDR (extensively drug resistance) refers to resistance to a broad group of drugs, which occurs when bacteria are non-susceptible (resistant or intermediate-susceptible) to at least one antibiotic, of all but two groups of antibiotics, active against a particular type [2].

Multidrug resistance (MDR) is bacterial resistance to antibiotics from three groups. Bacterial resistance to all antibiotics is referred to as PDR (pandrug resistance). Widely used antibiotics contribute to the selection

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of resistance because it is under their influence that bacterial strains that are not susceptible to their effects develop [2].

## Mechanisms of bacterial resistance to antibiotics

At least eight mechanisms of bacterial resistance to antibiotics have been described. All arise from genetic changes occurring in the genetic material of the bacteria. One mechanism is point mutations of nucleotide base pairs (microevolutionary changes) [3]. Genetic changes of this type affect the substrate specificity of bacterial enzymes or the binding sites of bacteria to antibiotics, which in turn alters their sensitivity to antibiotics.

Genetic mutations referred to as macroevolutionary mutations involve more than point changes in nucleotide pairs. The rearrangement of nucleotide pairs includes their reversal, doubling, the introduction of new ones or their deletion, as well as the translation of DNA fragments from one position in the bacterial chromosome or plasmid to another location in the genome [3]. The high plasticity of the bacterial genome is made possible by systems and elements possessed not only by bacteria but by all living organisms that, by moving DNA fragments or rearranging them, seek to survive in altered environmental conditions such as the presence of an antibiotic in the bacterial environment. These systems include integrons, transposons and insertion sequences [4, 5].

The most frequent occurrence of antibiotic resistance is in healthcare-associated infections (HAIs). HAI is diagnosed when the infection becomes apparent from day 3 after hospital admission (i.e. after 48 hours) or as early as day 1–2 after hospital admission, but when the following criteria are met: there are features of surgical site infection revealed up to 30 days after surgery or up to 90 days after surgery during which an implant was placed, the patient was discharged from the healthcare facility within the last 48 hours, and if a vascular catheter was implanted or an endotracheal/tracheotomy tube was inserted [6]. *Clostridioides difficile* HAIs are also diagnosed in patients discharged within the last 28 days from a hospital or long-term care unit [6].

HAIs mainly affect acutely ill patients who require prolonged hospital stays and often advanced, invasive treatments. The most common HAIs include hospital-acquired pneumonia (HAP), ventilatory-associated pneumonia (VAP), surgical wound infections, vascular bed infections associated with central or peripheral vascular access insertion or due to an ongoing infection elsewhere, e.g. urinary tract infection (UTI), pneumonia, gastrointestinal infection, surgical site infection, skin and subcutaneous tissue infection, bone infection or meningitis. Sometimes the primary cause of vascular bed infection cannot be detected.

The contribution of individual bacteria to HAIs varies from continent to continent, country to country and may even be different in different medical facilities in the same country or city. Recognition of the microbiological situation in the hospital or ward is a very important element in determining appropriate antibiotic therapy. Until 10–20 years ago, HAIs were caused mainly by Gram-positive bacteria, especially staphylococci. Today, it is estimated that Gram-positive bacteria cause 41% of HAIs, of which 25% are the cause of HAP [2]. Increasingly, Gram-negative bacteria are the cause of HAIs [2].

The eight mechanisms of bacterial resistance mentioned are enzymatic inactivation of antibiotics (mainly affecting β-lactams and aminoglycosides), removal of antibiotics from the bacterial cell (tetracyclines, macrolides), reduced permeability of the bacterial cell to the antibiotic (mainly glycopeptides), alteration of the target site of action (polymyxins, streptogramins, glycopeptides, quinolones, macrolides, rifampicin, β-lactams, aminoglycosides), protection of the target site (tetracyclines), overproduction of the target site (sulphonamides), binding of the antibiotic (glycopeptides) and bypassing the process inhibited by the antibiotic (rarely sulphonamides and trimethoprim) [3].

## β-lactamases and their breakdown

One of the largest groups of antibiotics is the β-lactams. These include penicillins, cephalosporins, carbapenems and monobactams. Bacterial resistance to the use of β-lactam antibiotics is manifested by the production of β-lactamases, i.e. enzymes that hydrolyse β-lactam antibiotics, the production of so-called PBP (penicillin-binding protein) proteins with low affinity for antibiotics, reduced permeability of cell membranes to antibiotics, and the shedding of antibiotics from the bacterial cell. Therefore, the effectiveness of the antibacterial response is determined by the parameters that characterise the efficiency of the aforementioned mechanisms, i.e. the rate of hydrolysis, the degree of affinity for the antibiotic, the amount of β-lactamase produced by the bacterial cell, the susceptibility of the PBP to bind to the antibiotic and the rate of ejection of the antibiotic from the bacterial cell. Depending on the type of bacteria, the mechanisms described are subject to modification and have varying degrees of potentiation of the antibacterial resistance effect. It is also possible for different resistance mechanisms directed against β-lactam antibiotics to accumulate in a single patient.

Production of β-lactamases occurs in both Gram-negative and Gram-positive bacteria, but much less frequently in the latter group. In Gram-negative bacteria, β-lactamases are secreted into the cell, making each bacterial cell responsible for defending itself against the antibiotic. In Gram-positive bacteria such as *Staphylococcus aureus*,

the enzymes are secreted outside the bacterial cell, so the more bacteria, the more enzymes and the less chance of the antibiotic reaching the bacterial cell. This is the so-called 'inoculum effect', i.e. inhibition of the therapeutic effect of the antibiotic when there is a sufficiently large accumulation of bacteria.

There are currently two classifications of β-lactamases. The first and historically older is the 1995 Ambler classification. [7]. The second, from 2009, is the Bush-Jacoby classification [8]. Both classifications and the relationship between them are shown in Table 1. The Ambler classification distinguishes four classes of β-lactamases [7, 8]. The division is based on the structure of the active site that cleaves amide β-lactam bonds [7]. Class A, C and D are β-lactamases that hydrolyse the β-lactam ring with serines. Class B are enzymes belonging to metallo-β-lactamases (MBLs) that break amide bonds with zinc ($Zn^{2+}$) [7].

Penicillinases belong to group A according to Ambler (table 1). This is a very heterogeneous group. It includes classical β-lactamases such as TEM1 and SHV1 (sulfhydryl variable) [8]. TEM1 is a β-lactamase encoded on plasmids of Gram-negative bacteria, which include *Enterobacteriaceae,* as well as *Pseudomonas aeruginosa, Haemophilus influenzae* and *Neisseria gonorrhoeae.* The enzyme hydrolyses penicillins and narrow-spectrum first-generation cephalosporins but does not degrade second-, third- and fourth-generation cephalosporins or carbapenems and monobactams [8].

Quite soon after the appearance of classical β-lactamases, mutations in the genes encoding them led to the development of extended substrate-spectrum β-lactamases, abbreviated as ESBLs and directed against β-lactam antibiotics, apart from cefamycins and carbapenems. They should not be confused with the classical β-lactamases of the so-called broad substrate spectrum, which include the already mentioned TEM-1 and SHV1 enzymes (group 2b according to Bush–Jacoby, table 1). Currently, more than 200 ESBL enzymes with an origin derived from the β-lactamase TEM are known [9]. They degrade monobactams and most cephalosporins (10–12). The emergence of ESBL(+) bacteria has limited their susceptibility to only carbapenems, which are the recommended antibiotics for treating infections caused by these bacteria.

AmpC-type β-lactamases or AmpC chromosomal cephalosporinases (class C according to Ambler and class 1 according to Bush-Jacoby, table 1) induce resistance to many β-lactam antibiotics and are produced by bacteria belonging to the *Enterobacterales* and by some of the Gram-negative non-fermenting bacilli [8, 13]. A characteristic feature of this group of enzymes is their lack of sensitivity to β-lactamase inhibitors such as clavulanic acid [13]. There are 3 mechanisms for this type of resistance, but the main one is increased AmpC production secondary to antibiotic-induced expression of the chromosomal AmpC gene [14]. This is particularly true for bacteria such as *Klebsiella aerogenes, Enterobacter cloacae and Citrobacter freundii* [13–15]. Strong inducers of the ampC gene are aminopenicillins, narrow-spectrum cephalosporins and cefamycins [15]. After administration of cefoxitin (an antibiotic from the cefamycin group), a significant, up to six hundredfold, transient increase in enzyme production was shown for bacteria of the genus *Enterobacter, Serratia, Morganella, Citrobacter,* Providencia and *Pseudomonas* [13]. After discontinuation of the antibiotic, the concentration of the induced enzyme returns to low levels, but there is also a risk of a sustained increase in the production of AmpC-type β-lactamases [14, 15]. Third-generation cephalosporins, especially ceftriaxone, cefotaxime and ceftazidime, irrespective of the initial preserved susceptibility of the bacteria, when used to treat infections can inhibit the mutated group of bacteria and induce antibiotic resistance and consequently higher mortality, as has been demonstrated in bacteraemia [15, 16]. For bacteria of the genus *Enterobacter* isolated from blood, it is prudent to avoid treatment with a third-generation cephalosporin, regardless of *in vitro* sensitivity [15, 16].

Group D according to Ambler includes oxacillinases (table 1). The name and acronym OXA are derived from oxacillin, which hydrolyses very efficiently [17]. OXAs play an important role in high-level resistance in *Pseudomonas* aeruginosa bacteria, and some of them were even originally detected and described in infections caused by this bacterium [17]. OXA-group enzymes have been the reason for the resistance of *Pseudomonas aeruginosa* strains to ceftazidime, which is among the drugs of choice for the treatment of infections caused by this bacterium [17]. OXA-type β-lactamases that hydrolyse carbapenems are also found in class D (table 1). The presence of carbapenemases in the oxacillinase group is a natural feature of evolutionary changes occurring within the class. Resistance based on OXA-type carbapenemases affects, among others, bacteria of the genus *Acinetobacter* [17, 18]. OXA-48 and type OXA-48 oxacillinases are of increasing clinical importance in infections caused by *Enterobacterales* [18]. They are characterised by high phenotypic variability and the enzyme activity as carbapenemases includes penicillins, first-generation cephalosporins and carbapenems, with a low degree of hydrolysis of the latter [18].

Carbapenemases are a group of enzymes that cause widespread and even extreme antibiotic resistance. From an epidemiological point of view, a currently very important enzyme is the KPC or carbapenemase produced by *Klebsiella pneumoniae*. It belongs to class A serine carbapenemases (table 1). KPC-type resistance is also present among other Gram-negative bacteria, such as, for example, *Escherichia coli*, *Citrobacter spp., Enterobacter spp., Serratia spp.* and *Pseudomonas aeruginosa* [19].

**Table 1.** Classifications of resistance associated with β-lactamase production according to Ambler and as modified by Bush-Jacoby [3, 7, 8].

| Class by Ambler | Enzyme, resistance range | Substrate |
|---|---|---|
| Class A — serine | penicillinase: | |
| | broad substrate spectrum | penicillins and narrow-spectrum cephalosporins |
| | extended substrate spectrum (ESBL) | as in broad substrate spectrum + oxyimino-β-lactams[#] |
| | carbapenemases | as in ESBL + cefamycins and carbapenems |
| Class B — Metallo-β-lactamases ($Zn^{2+}$) | carbapenemases | as in ESBL + cefamycins and carbapenems |
| Class C -serine | cephalosprinases | as in ESBL + cefamycins |
| Class D- serine | oxacillinase: | |
| | broad substrate spectrum | penicillins and certain narrow-spectrum cephalosporins |
| | ESBL | as in broad spectrum + oxyimino-β-lactams[#] |
| | carbapenemases | as in ESBL + cefamycins and carbapenems |
| **Breakdown by Bush-Jacoby** | **Substrate, enzyme, resistance range** | **Class by Ambler** |
| 1 | cephalosporins | C |
| 1e | cephalosporins | C |
| 2a | penicillins | A |
| 2b | broad substrate spectrum (penicillins, first--generation cephalosporins) | A |
| 2be | ESBL (cephalosporins, monobactams) | A |
| 2br | penicillins, resistance to β-lactamase inhibitors: clavulanic acid, sulbactam, tazobactam | A |
| 2ber | ESBL (cephalosporins, monobactams), resistance to β-lactamase inhibitors: clavulanic acid, sulbactam, tazobactam | A |
| 2c | carbenicillin | A |
| 2ce | carbenicillin, cefepime | A |
| 2d | cloxacillin | D or A |
| 2de | ESBL (cephalosporins) | D |
| 2df | carbapenems | D |
| 2e | ESBL (cephalosporins) | A |
| 2f | carbapenems | A |
| 3a** | MBLs (carbapenems) | B (B1)* |
| | | B (B3)* |
| 3b** | MBLs (carbapenems) | B (B2)* |

[#]oxyimino-β-lactams include 3rd and 4th generation cephalosporins and aztreonam, the only available monobactam, MBLs — Metallo-β-lactamases, * subclasses of MBLs — division by structure, ** subgroups of MBLs — division by function.

For clinicians, this resistance poses a major problem and therapeutic challenge, as it is often impossible to find an antibiotic that has a sensitivity to KPC-producing strains.

Class B according to Ambler (table 1) includes carbapenemases referred to as metallo-β-lactamases (MBLs), which are mediated by $Zn^{2+}$ rupture β-lactam rings. Bacteria that produce MBLs are resistant to tazobactam, clavulanic acid and sulbactam. MBL-type resistance means that the bacteria are insensitive to all β-lactams except monobactams. Among MBLs, several types of enzymes can be distinguished, but bacterial resistance is particularly high due to the metallo-β-lactamase-1 (NDM-1) currently in the

focus of New Delhi [20]. Bacteria producing this enzyme are now widespread throughout the world. NDM-1 is most commonly found in *Klebsiella pneumoniae* and *Escherichia coli*, but also in *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella oxytoca, Morganella morganii, Providencia spp.* and *Proteus spp*. [20].

## Resistance associated with penicillin-binding proteins

Penicillin-binding proteins (PBPs) and the resistance associated with them occur in both Gram-negative and Gram-positive bacteria. PBP proteins are responsible for the synthesis of the bacterial cell wall, or rather its basic component, i.e. peptidoglycan. Through the binding of β-lactams to bacteria, abnormalities in the structure of the cell wall occur, resulting in the breakdown of the bacterial cell [21]. Resistance to β-lactams associated with PBP proteins involves, among other things, the modification of already existing PBP proteins or the synthesis of new ones. These modifications occur as a result of the formation of mutations in the genes responsible for PBP production or the acquisition of already mutated fragments from other organisms and their replacement with homologous sections of their own genes [21, 22].

Resistance of Staphylococcus aureus to methicillin, i.e. the presence of MRSA, is caused by the presence of a PBP with low affinity for β-lactams (PBP2a version). Clinically, this manifests as resistance to oxacillin and cephalosporins [3]. The genetic sequences of the staphylococcal cassette chromosome mec (SCCmec), determine 5 types of MRSA strains [23]. Types I to III are the MRSA strains responsible for nosocomial infections, while types IV and V include strains with less severe resistance. They cause out-of-hospital infections and their susceptibility to non-β-lactam antibiotics is significantly higher [3].

## Other mechanisms of resistance

Other mechanisms of resistance to β-lactam antibiotics include impaired passage of the antibiotic into the bacterial cell as a consequence of reduced or total absence of porin channels in the outer membrane of the bacterial cell and pumping of the antibiotic out of the bacterial cell via pump-pore systems [21]. The above mechanisms of resistance to β-lactam antibiotics are most typical of Gram-negative bacteria.

Resistance of enterococci to glycopeptide antibiotics (vancomycin, teicoplanin) is the result of a modification of the structure of the bacterial cell wall involving a change in the structure of peptidoglycan [24, 25]. Several classes of glycopeptide resistance can be distinguished. Among these are the classes phenotypically defined as VanA, VanB, VanC, VanD and VanE, which are encoded by the vanA, vanB, vanC, vanD and vanE genes, respectively, and which are characterised by varying degrees of resistance to glycopeptides [26–28]. The high resistance to vancomycin and teicoplanin (VanA class) present in *Enterococcus faecium* and *Enterococcus faecalis* strains can be transferred to other Gram-positive bacteria, including *Streptococcus pyogenes*, *Streptococcus sanguis* or *Listeria monocytogenes* [26]. Resistance of *Enterococcus faecium* and *Enterococcus faecalis* in the VanB class, on the other hand, is characterised by a lack of sensitivity to vancomycin with retained sensitivity to teicoplanin. Resistance encoded by vanB genes can be transferred to other enterococci [27].

## Antibiotics for the treatment of multidrug-resistant bacteria

Due to the increasing incidence of MDR bacteria, special attention is now being paid to new antibiotics and older-generation but rarely used antibiotics. The antibiotics used to treat bacteria with MDR and their most important characteristics are listed below. Unfortunately, bacterial resistance is also emerging against these antibiotics.

**Linezolid** — synthetic antibacterial drug, oxazolidinone class, inhibits bacterial proteins of Gram-positive bacteria including MRSA, VISA, (*Staphylococcus aureus* with reduced sensitivity to vancomycin, vancomycin-intermediate *Staphylococcus aureus*), VRE (vancomycin-resistant *Enterococcus*), PRSP (penicillin-resistant *Streptococcus pneumoniae)* [29]. Antibiotic administration is associated with the risk of numerous side effects, e.g. bone marrow suppression and anaemia, especially with > 28 days' use and thrombocytopaenia already with administration beyond 10–14 days. A dangerous side effect is lactic acidosis [29].

**Teicoplanin** — inhibits bacterial cell wall synthesis, a similar mechanism to vancomycin, but differences are in activity. Variability in minimum inhibitory concentration (MIC) for methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS). High MIC and no activity against *Staphylococcus haemolyticus*. Compared to vancomycin, lower MIC for *Enterococcus spp., Streptococcus pneumoniae, Streptococcus gallolyticus* and green streptococci [30].

**Oritavancin, dalbavancin**, and novel glycopeptides inhibit bacterial cell wall synthesis, while oritavancin also depolarises the bacterial cell wall. They act on Gram-positive bacteria including MRSA, VISA and nonVanA enterococci (vancomycin-resistant, but not type A) [30].

**Phosphomycin** — synthetic antimicrobial drug, an epoxy derivative of phosphonic acid. It blocks the activity of phosphoenolpyruvate transferase, which catalyses the formation of N-acetylmuramic acid from N-acetylglucosamine and phosphoenolpyruvate. N-acetylmuramic acid is required

for peptidoglycan synthesis. Detected in the 1960s. It has a broad spectrum. In a low single oral dose used in ZUM, intravenously in high doses in infections caused by Gram-positive bacteria (*Staphylococcus aureus*, including MRSA) and Gram-negative bacteria with MDR including *Klebsiella pneumoniae* KPC with ceftazidime/avibactam resistance. No cross-resistance with other antibiotics, synergistic effect with other antibiotic groups e.g. β-lactams. Should be used in combination with other antibiotics [31].

**Tigecycline** — a glycylcycline antibiotic, a drug of the tetracycline group. Inhibits protein synthesis in bacterial cells by binding to the 30S subunit of the ribosome. Acts on aerobic and anaerobic, Gram-negative and Gram-positive bacteria including MDR, MRSA, VRE, most MDR bacteria in the *Enterobacteriaceae* family (except *Proteus spp.*) and *Acinetobacter spp.*, does not affect *Pseudomonas spp.* [32, 33].

**Plazomycin** — a new-generation aminoglycoside, inhibits protein synthesis by binding to the bacterial 30S subunit of the ribosome. Broad spectrum activity against aerobic Gram-negative bacteria, including *Enterobacteriaceae* producing β-lactamases with an extended substrate spectrum and resistance to carbapenems, as well as bacteria producing aminoglycoside-modifying enzymes [34]. It shows activity against non-fermenting bacilli and MRSA. No significant nephrotoxicity or ototoxicity was observed in early phase studies. Due to limited safety data in adult complicated UTIs in the absence of alternative treatment options, intravenous 15 mg/kg/day (every 24 h) for 4–7 days is used [34].

**Daptomycin** — a group of lipopeptides, active against Gram-positive bacteria [35]. For the treatment of complicated skin and soft tissue infections and infected endoprostheses, and CNS (central nervous system) infections. Used in right-sided IE (infective endocarditis) and to treat bacteraemia [35]. Acts on methicillin-sensitive *Staphylococcus aureus* (MSSA), MRSA, MRCNS, and enterococci including VRE and *Cutibacterium acnes*. Can be used when there is a high MIC for vancomycin (> 2 mg/L) or when serious adverse reactions present during vancomycin use and when β-lactam or vancomycin cannot be used. Do not use in pneumonia as the surfactant inactivates the antibiotic [35].

**Ertapenem** — a drug from the carbapenem group, active against *Enterobacterales*, inactive against *Pseudomonas aeruginosa* and *Acinetobacter spp.* Use is limited to treatment of infections caused by bacteria resistant to other antibiotics. No activity against carbapenemase-producing bacteria, ampicillin-resistant enterococci, MRSA, MRCNS, *Enterococcus faecium, Stenotrophomonas* and *Burkholderia* bacilli [36, 37].

**Meropenem/vaborabactam** — vaborbactam a class A and C serine β-lactamase inhibitor. In combination with meropenem, it forms a potent drug targeting *Enterobacteriaceae* with MDR, including KPC [38].

**Imipenem/relabactam** — for the treatment of complicated UTI and intra-abdominal infections. Active against β-lactamase-producing strains of class A and C, such as ESBL, KPC and AmpC. Not active against *Acinetobacter spp*. [37].

**Aztreonam** — a drug from the monobactam group, activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*. Activity against strains producing MBL-type carbapenemases [39].

**Ceftazidime** — 3rd generation cephalosporin. Drug of choice for *Pseudomonas aeruginosa* if there is sensitivity to this antibiotic.

**Cefepime** — 4th generation cephalosporin, activity against *Pseudomonas aeruginosa* and AmpC-type β-lactamase-producing intestinal bacilli. It has no activity against ESBL(+) and carbapenemase-producing strains [14, 15, 37].

**Ceftaroline** — a fifth-generation cephalosporin, active against MRSA and penicillin resistant strains of *Streptococcus pneumoniae*. Also active against Gram-negative bacteria. Used in out-of-hospital pneumonia [40].

**Cefiderocol** — a new generation siderophore-based cephalosporin. Used in complicated UTIs, including pyelonephritis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterobacter cloacae*. Used for infections caused by XDR bacteria [41].

**Ceftolozane/tazobactam** — activity against ESBL-producing *Enterobacterales*. Used in complicated UTI and complicated abdominal infections, in HAPs and VAPs. Indicated for the treatment of severe bloodstream infections (BSIs) and skin and soft tissue infections caused by *Pseudomonas aeruginosa* with MDR [37].

**Ceftazidime/avibactam** — indications are complicated UTIs, HAPs, VAPs, complicated abdominal infections and BSIs secondary to the listed infections [37]. Active against *Pseudomonas aeruginosa* and *Enterobacterales*, including those producing AmpC, ESBL, KPC and OXA-48 enzymes.

**Colistin** — acts on *Enterobacterales*, especially *Escherichia coli, Klebsiella pneumonie* and *Enterobacter spp*. Resistance to *Serratia marcescens* and *Proteus spp.* strains. Activity against Gram-negative non-fermenting bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* Not active against Gram-positive bacteria [37, 42].

Table S2 provides an overview of the literature for selected antibiotic regimens used in multidrug-resistant bacterial infections. The efficacy of antibiotic therapy is confirmed by *in vitro studies*, case reports and *in vivo* results from randomised and retrospective studies.

Antibiotic recommendations according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) are recommendations for the treatment of infections caused by antibiotic-resistant Gram-negative bacteria [43]. Figures 1 and 2 present the most important therapeutic recommendations, with a concomitant indication of the reliability and strength of the recommendations.

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|---|
| 3GCephRE — BSI and other severe infections — carbapenems — imipenem, meropenem as targeted therapy |
| 3GCephRE — BSI without septic shock — ertapenem instead of imipenem or meropenem. |
| 3GCephRE — low risk, mild infections — piperacillin/tazobactam, amoxicillin/clavulanic acid or quinolones*. (+) GCP |
| 3GCephRE — after stabilisation achieved with carbapenems de-escalation to old generation βL+βLB, quinolones*, cotrimoxazole or other antibiotics based on bacterial sensitivity. (+) EO |
| 3GCephRE — tigecycline — is not recommended. |
| 3GCephRE — insufficient evidence for cefoperazone with sulbactam, ampicillin with sulbactam, ticarcillin with clavulanic acid, temocillin and mecillinam. |
| 3GCephRE — cefamycins and cefepime should not be used. |
| 3GCephRE — new βLzBβL reserved for XDR strains. (+) EO |
| CRE — severe infections — meropenem/vaborbactam or ceftazidime/avibactam if active *in vitro*. |
| Severe infections due to CRE MBL+ and/or CRE resistant to ceftazidime/avibactam and meropenem/vaborabactam — conditional recommendation for cefiderocol. |
| CRE — mild infections — old generation antibiotics with *in vitro* activity, individually selected, tailored to the source of infection. +GCP/conditional recommendation. In complicated UTI — aminoglycosides, including plazomycin, more so than tigecycline. |
| CRE — BSI, HAP, VAP — do not use tigecycline, if administration is necessary in PE the doctor may use a high dose of the antibiotic. |
| CRE — no rationale for or against the use of imipenem/relebactam and fosfomycin in monotherapies. |
| CRPA — mild infections, low risk — under antibiotic stewardship, suggested use of older generation drugs with *in vitro* activity, selected individually and depending on the source of infection. (+) EO |
| CRPA — severe, difficult-to-treat infections — ceftolozane/tazobactam (if *in vitro* activity). Insufficient evidence for the use of imipenem/relebactam, cefiderocol and ceftazidime/avibactam. |
| CRAB — sulbactam sensitivity in HAP and VAP — suggested ampicillin/sulbactam. |
| Gram-negative bacteria resistant to carbapenems — infections with PDR strains including those resistant to polymyxin — the antibiotic with the least (relative) resistance according to MIC. (+) EO |

**Figure 1.** Monotherapy
Antibiotic recommendations for the treatment of infections caused by Gram-negative bacteria resistant to commonly used antibiotics, according to ESCMID recommendations [43]. The recommendations apply to antibiotics used in monotherapy
3GCephRE — third-generation cephalosporins resistant Enterobacterales; βL+βLB — β-lactams with β-lactamase blockers; BSI — bloodstream infection; CRAB — carbapenems resistant Acinetobacter baumannii; CRE — carbapenems resistant Enterobacterales; CRPA — carbapenems resistant Pseudomonas aeruginosa; EO — expert opinion, if with (+) then as an additional recommendation; GCP — good clinical practice, if with (+) then as an additional recommendation; HAP — hospital-acquired pneumonia; MIC — minimum inhibitory concentration; PDR — pandrug-resistance; PE — pneumonia; UTI — urinary tract infection; VAP — ventilator-associated pneumonia; XDR — extensively drug-resistant

* See the safety note for quinolones and fluoroquinolones in section 8 discussing the principles of antibiotic treatment.
Strong recommendation, Conditional recommendation, Good clinical practice, No recommendation

It is probably no longer possible to stop the processes of increasing antibiotic resistance. In everyday medical practice, however, one can try to reduce its consequences on a local ward/hospital scale. The following can contribute to improving the situation:

Intensification of diagnostics to identify the pathogen responsible for the infection.

1. Collection of microbiological and/or serological tests identifying the pathogen prior to initiation of empirical antibiotic therapy.
2. Once the pathogen is identified, de-escalation or adjustment of empirical antibiotic therapy, if possible.
3. Use of sufficiently high doses of antibiotics in the shortest possible time.
4. Systematic evaluation of the effectiveness of the treatment with an initial treatment time appropriate to the expected effects (3 days).
5. Microbiological monitoring of treatment efficacy. In the case of MSSA bacteraemia, follow-up blood cultures on day 3 of antibiotic therapy are absolutely necessary.
6. Searching for the source of the infection and its location (e.g. IE, UTI, bacteraemia, catheter-related BSI, pneumonia, abscesses) enables and even indicates the need to implement additional treatment, not only with antibiotics.

| |
|---|
| CRE sensitive to ceftazidime/avibactam, meropenem/vaborbactam or cefiderocol — no recommendation for combination therapy in patients already treated with these antibiotics. |
| Severe infections due to CRE MBL (+) and/or CRE resistant to new antibiotics on monotherapy — aztreonam in combination with ceftazidime/avibactam is suggested. |
| Severe infections due to CRE susceptible *in vitro* only to polymyxins, aminoglycosides, tigecycline or fosfomycin or, in the case of unavailable new βL+βLB, treatment with more than one *in vitro* active antibiotic. No recommendation either for or against the use of a particular antibiotic combination. |
| Mild or low-risk CRE infection — under antibiotic stewardship consider monotherapy with an old-generation drug with *in vitro* activity individually selected taking into account the source of infection. (+) OE. |
| CRE — avoid combination therapy with carbapenems. Possible use of meropenem in combination therapy if new generation βL+βLB is not used and the MIC for meropenem is ≤ 8 mg/l. Meropenem is then recommended at a high dose and in a prolonged infusion. |
| CRPA infections — no evidence for or against combination treatment with new βL+βLB (ceftazidime/avibactam and ceftolozan/tazobactam) or cefiderocol. |
| Severe CRPA infections — when treated with polymyxins, aminoglycosides or fosfomycin, two *in vitro* active drugs are suggested. No recommendation either for or against specific drug combinations. |
| In all patients with CRAB infection — there is no recommendation for the combination of polymyxin with meropenem and polymyxin with rifampicin. |
| Severe and high-risk CRAB infection — suggested combination therapy, two antibiotics with *in vitro* activity from the group of available drugs (polymyxins, aminoglycosides, tigecycline, sulbactam in combinations). (+) OE. |
| In CRAB infection with MIC for meropenem ≤ 8 mg/L — a combination with a high-dose carbapenem in a prolonged infusion is to be considered. (+) OE |

**Figure 2.** Combination treatment
Antibiotic recommendations for the treatment of infections caused by Gram-negative bacteria resistant to commonly used antibiotics, according to ESCMID recommendations [43]. Recommendations on the use of antibiotics in combination therapy
CRE — carbapenem-resistant Enterobacterales, MBL — metallo-β-lactamases, CRPA — carbapenem-resistant Pseudomonas aeruginosa, CRAB — carbapenem-resistant Acinetobacter baumannii, βL+BβL — β-lactams with β-lactamase blockers, GCP — good clinical practice, EO — expert opinion, if with (+) then as an additional recommendation, MIC — minimum inhibitory concentration.
Conditional recommendation, Good clinical practice, No recommendation

7. Identification of carriers.
8. Eradication of nasal MSSA and MRSA carriage before cardiac and orthopaedic surgery — an independent risk factor for surgical site infection.
9. Use of isolation of patients with alert pathogens both causing infection and identified as carriers.
10. Systematic assessment of the epidemiological situation of the hospital/department.
11. Strict and rigorous adherence to hygiene and aseptic principles.

When using antibiotic therapy, it is important to remember a few general principles:

1. Adjusting the antibiotic dose according to the patient's weight, liver function, renal function, renal replacement therapy taking into account the type of renal replacement therapy — intermittent dialysis or continuous renal replacement therapy. The Stanford Health Care Antimicrobial Dosing Reference Guide website helps to determine antibiotic dosing in patients with renal failure and/or treated with renal replacement therapy (Stanford Health Care Antimicrobial Dosing Reference Guide http://portal.stanfordmed.org/depts/AntimicrobialStewardshipProgram, http://bugsanddrugs.stanford.edu ABX Subcommittee Approved: December 2022.).
2. Choosing an antibiotic that does not interfere with other medications being taken. An antibiotic with numerous interactions is, for example, linezolid.
3. Control of antibiotic blood levels where such control is possible and recommended e.g. during vancomycin treatment.
4. Frequent assessment of organ function parameters that may be affected by the antibiotic treatment, e.g. creatinine, GFR, transaminases, bilirubin, blood morphology parameters including platelet count and others.
5. Avoiding combining antibiotics with the same side effects, e.g. two nephrotoxic ones.
6. The choice of antibiotic therapy should take into account information from the patient's history regarding allergies and specific risk factors affecting the safety of antibiotic administration.
7. Not combining antibiotics from the same groups e.g. two β-lactams.

8. Avoiding antibiotics, which carry the risk of dangerous complications. Quinolones and fluoroquinolones are currently not recommended for this reason, according to a safety note posted in 2019 by the European Medicines Agency on the European Medicines Agency website, Science Medicines Health. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics 11 March 2019 EMA/175398/2019 Page 1–4 FluoroquinolonesQuinolones_Public Health Communication (europa.eu) and in the Polish version by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products on the URPLWMiPB website (Fluoroquinolones and quinolones for systemic and inhaled use: risk of disabling, prolonged and potentially irreversible adverse reactions and restrictions on use. | Office for the Registration of Medicinal Products, Medical Devices and Biocidal Products (urpl.gov.pl).

Due to the breadth of the topic, the article does not describe all mechanisms of multidrug resistance and it is impossible to provide a ready prescription for antibiotic therapy in the situation of every infection.

The information presented on antibiotics, their use, dosage, combinations and indications for their use applies to adults, does not apply to pregnant or breastfeeding women and does not take into account individual contraindications to specific antibiotics or specific indications for modifying their administration. It is essential to read the information in the SmPC before administering an antibiotic.

## Conclusions

Antibiotic resistance is a major clinical problem primarily due to the increasing number of severe infections caused by multidrug-resistant bacteria and the decreasing number of effective antibiotics. Bacterial infections with MDR often necessitate the use of combination therapy and/or result in the administration of antibiotics with increased toxicity with potentially many side effects. Antibiotic resistance is increasing morbidity and mortality from untreatable infections, but also increasing treatment costs.

The increasing number of patients requiring antibiotic therapy, the administration of broad-spectrum antibiotics, the unwarranted use of antibiotics to treat viral infections, inappropriate dosing and timing of treatment, and the prevalence of antibiotic use beyond medicine all contribute to antibiotic resistance.

A particular problem is the increasing number of infections caused by resistant bacteria among patients treated in ICUs and in immunocompromised patients. Another problem is the transmission of resistant bacteria to other patients treated in the same ward/hospital.


### Streszczenie

Wielolekooporność bakterii jest narastającym problemem klinicznym, który szczególnie dotyczy chorych leczonych w oddziałach intensywnej terapii. Mechanizmy oporności to produkcja enzymów inaktywujących antybiotyki, usuwanie antybiotyku z komórki bakteryjnej, zmniejszona przepuszczalność komórki bakteryjnej dla antybiotyku, zmiana miejsca docelowego działania antybiotyku, ochrona i nadprodukcja miejsca docelowego działania, wiązanie antybiotyku, a także obejście procesu wyhamowanego przez antybiotyk. Występowanie antybiotykooporności związane jest ze zmianami zachodzącymi w materiale genetycznym bakterii. W artykule przedstawiono przegląd piśmiennictwa opisującego skuteczność różnych antybiotyków w badaniach szczepów bakteryjnych *in vitro*, na podstawie opisów przypadków oraz rezultatów *in vivo* uzyskanych w badaniach randomizowanych i retrospektywnych. Zamieszczone zostały najważniejsze rekomendacje European Society of Clinical Microbiology and Infectious Diseases (ESCMID), dotyczące monoterapii i antybiotykoterapii skojarzonej zakażeń wywołanych bakteriami o potwierdzonej antybiotykooporności.



Słowa kluczowe: antybiotykooporność, antybiotyki, wielolekooporność, β-laktamazy

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AK 100%

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### Supplementary material
Table S2

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**Table S2.** Literature review on the treatment of infections caused by bacteria resistant to antibiotics routinely used to treat them.

| Bacteria | Resistance type | |
|---|---|---|
| *Acinetobacter baumannii* | MDR | Carbapenems + ampicillin/sulbactam better prognosis than the combination of carbapenem with amikacin or carbapenem alone — *in vivo* study [1]. |
| | MDR with sensitivity to colistin | Best synergism imipenem + colistin [2]. Meropenem + colistin inhibition of bacterial re-growth within 24 h [3]. |
| | Extended resistance to antibiotic therapy | Synergism for: colistin + rifampicin, colistin + meropenem, colistin + minocycline, minocycline + meropenem (*in vitro*) [4]. In bloodstream infections, compared to colistin monotherapy, the combinations: colistin + carbapenem and colistin + sulbactam were significantly more often effective in eradicating bacteria and were associated with lower in-hospital mortality (retrospective study) [5]. |
| | Resistance to carbapenems* | In skin and soft tissue infections, the efficacy of the ampicillin/sulbactam combination with meropenem — an *in vivo* study [6]. |
| | Resistance to carbapenems* and sensitivity to colistin | *In vitro* synergism of the meropenem-colistin combination in all isolates tested [7]. |
| | Resistance to carbapenems* | *In vitro/in vivo* — increased doses of meropenem in combination with polymyxin B — synergistic activity against carbapenem-resistant strains independent of the MIC for meropenem [8]. |
| | Resistance to carbapenems* | *In vitro* — carbapenem + plazomycin synergistic effects [9]. |
| | MDR | *In vitro/in vivo* ampicillin/sulbactam — significant reduction in mortality in bloodstream infections [10]. |
| *Enterobacterales* | Producing KPC | According to the IDSA, meropenem/vaborbactam, ceftazidime/avibactam and imipenem-cilastatin/relebactam are the choices, with cefiderocol as an alternative [11]. |
| | OXA-48-type carbapenemases | In a multicentre study, strains producing OXA-48, OXA-232, OXA-244 and OXA-181 enzymes showed sensitivity to ceftazidime/avibactam [12]. This is now the treatment of choice according to IDSA, with cefiderocol as an alternative [11]. |
| | MBL (+) | According to the IDSA of choice: ceftazidime/avibactam + aztreonam or cefiderocol [11]. |
| | Resistance to meropenem | The *in vitro* susceptibility of bacteria to cefiderocol was significantly higher irrespective of the location of infection compared to meropenem, colistin, ceftazidime/avibactam combination and ceftolozane/tazobactam [13]. |
| *Pseudomonas aeruginosa* | Invasive infections DTR-PA | Based on preclinical and clinical data: ceftolozane/tazobactam and ceftazidime/avibactam. Potential alternatives: imipenem-cilastatin/relebactam, cefiderocol and colistin-based therapy [14]. Combination therapy should not be a routine treatment but selected on an individual basis. In particular, fosfomycin should be considered as an additional drug [14]. |
| | MDR/XDR | Retrospective study: 100 patients with *P. aeruginosa* infections with MDR/XDR treated with ceftolozane/tazobactam (in 91% of patients as monotherapy) were compared with 100 patients treated with polymyxin or aminoglycoside (in 72% of patients in combination with another antibiotic) — no difference in-hospital mortality, but clinical cure effect significantly higher in the ceftolozane/tazobactam group ($P = 0.002$). At the same time, the rate of AKI was lower in the ceftolozane/tazobactam group (6% vs. 34%; $P < 0.001$) [15]. |
| *Stenotrophomonas maltophilla* | MDR — natural or acquired resistance mechanisms, bacterial biofilms on artificial materials | Recommended treatment regimens according to IDSA: 1). Two drugs from those listed i.e. TMP/SMX, minocycline, tigecycline, cefiderocol, or levofloxacin**, 2). If there are signs of significant clinical instability, intolerance or resistance to other antibiotics - alternatively a combination of ceftazidime/avibactam + aztreonam for consideration [11]. |

| | | |
|---|---|---|
| *Staphylococcus aureus* | MRSA (SSTIs) | Ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin and tedizolid are alternatives to glycopeptides for skin and soft tissue infection — the listed antibiotics should be selected individually depending on their availability and the patient's contraindications. Most large RCTs and review papers showed that the listed drugs were not inferior to vancomycin in the treatment of SSTIs and ABSSSIs caused by MRSA [16–21]. |
| | MRSA — uncomplicated SSTIs | TMP/SMX or clindamycin for consideration in out-of-hospital treatment or benign, uncomplicated skin infections (after drainage of abscesses if necessary) [22, 23]. |
| | MRSA — CAP | Ceftobiprole, ceftaroline, linezolid or vancomycin are recommended for the treatment of CAP caused by MRSA. The treatment is selected individually taking into account the toxicity profile and sensitivity of the bacteria [14]. |
| | MRSA-HAP not caused by mechanical ventilation | Linezolid, ceftobiprole or vancomycin. The treatment is selected individually taking into account the toxicity profile and sensitivity of the bacteria [24–26]. |
| | MRSA — VAP | Linezolid or vancomycin. The treatment is selected individually taking into account the toxicity profile and sensitivity of the bacteria [24–26]. |
| | MRSA-bacteremia | Daptomycin or vancomycin. The treatment is selected individually taking into account the toxicity profile and sensitivity of the bacteria [27]. Fosfomycin has very good activity against MRSA including those resistant or with reduced sensitivity to other anti-MRSA drugs including vancomycin, daptomycin and linezolid [28]. In combination with linezolid or daptomycin, fosfomycin shows synergistic activity against most strains and such combinations have potential clinical applications [28, 29]. |
| *Enterococcus* | *E. faecalis* UTI — penicillin or ampicillin resistance | Nitrofurantoin with preserved sensitivity, or tetracycline, in uncomplicated UTI — fosfomycin 1 x 3 g p.o. after removal of the urinary catheter, vancomycin with resistance to other drugs [30]. |
| | *E. faecium* UTI — penicillin or ampicillin resistance | Nitrofurantoin for retained susceptibility, tetracycline, and vancomycin for resistance to other antibiotics [30]. |
| | UTI VRE —resistance to penicillin or ampicillin | Linezolid, daptomycin, in uncomplicated UTI and caused by *E. faecalis* — fosfomycin 1 x 3 g p.o. after removal of the urinary catheter [30]. |
| | *E. faecalis* and *E. faecium* bacteremia — sensitisation or resistance to penicillin or ampicillin | Vancomycin, to consider the addition of gentamicin if prolonged bacteraemia [30]. |
| | VRE bacteremia — sensitisation or resistance to penicillin or ampicillin | Linezolid, daptomycin [30]. Linezolid — lower mortality than with daptomycin treatment (meta-analysis) [31]. |
| | IE — caused by *E. faecalis, E. faecium*, VRE-sensitisation to penicillin | |
| | 1. sensitivity to gentamicin | 1. *E. faecalis, E. faecium* - vancomycin + gentamicin [30, 31].<br>If VRE — linezolid + another antibiotic with activity against VRE or daptomycin + gentamicin [30]. |
| | 2. gentamicin resistance | 2. to consider combination with ceftaroline [30, 31]. |

ABSSSIs — acute bacterial skin and skin structure infections; AKI — acute kidney injury; BSI — bloodstream infection; CAP — community-acquired pneumonia; DTR-PA — difficult-to-treat resistance of *Pseudomonas aeruginosa* infections; ESBLs — extended spectrum β-lactamases; HAP — hospital-acquired pneumonia; IDSA — Infectious Disease Society of America; IE —infective endocarditis; KPC — *Klebsiella pneumoniae* carbapenemases; MBL — metallo-β-lactamases; MDR — multidrug resistance; MIC — minimal inhibitor concentration; MRSA — methicillin-resistant *Staphylococcus aureus*; MSSA — methicillin-susceptible *Staphylococcus aureus*; PE — pneumonia; RCTs — randomised controlled trials; SSTIs — skin and soft tissue infections; TMP/SMX — trimethoprim/sulfamethoxazole; UTI — urinary tract infection; VAP — ventilator-associated pneumonia; VRE — vancomycin-resistant enterococci; XDR — extensively drug-resistant.*Despite resistance to carbapenems, drugs in this group have been given in combination with another antibiotic to which sensitivity is retained. This drug combination is a way of circumventing resistance to carbapenem, **See the safety note for quinolones and fluoroquinolones included in section 8 discussing principles for antibiotic treatment.

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